PART I: DIELS-ALDER REACTIONS OF HETEROSUBSTITUTED DIENES AND DIENOPHILES. PART II: ENAMINES AND IMINIUM SALTS FROM AMIDO-ACIDS.

LILIANNA ZOFIA. PILLON

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PART I: DIELS-ALDER REACTIONS OF HETEROSUBSTITUTED DIENES AND DIENOPHILES

PART II: ENAMINES AND IMINUM SALTS FROM AMIDO-ACIDS

by

Lilianna Zofia Pillon

A DISSERTATION

Submitted to the Faculty of Graduate Studies through the Department of Chemistry in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy at The University of Windsor

Windsor, Ontario
1983
ABSTRACT

The Diels-Alder reaction of 3-carbomethoxy-2,5-dihydrothiophenes with butadiene or isoprene yielded bicyclic thiolanes. The isomeric distribution of the adducts was assigned using cmr data.

3-Acylamino-2,5-dihydrothiophenes were oxidized to sulfones and formed dienes by thermal sulfur dioxide elimination. Heating these sulfones in the presence of maleic anhydride yielded the Diels-Alder adducts in good yields.

The cycloaddition reaction of diethyl α-carbomethoxyvinylphosphonate with isoprene yielded the adduct in 95% yield and as one isomer. An attempt to prepare α-carbomethoxyvinylphosphonic acid diamide which could be used as a dienophile in the Diels-Alder reaction was unsuccessful.

C- and N-(ω-carboxyalkyl) lactams were prepared and distilled with soda-lime to form bicyclic enamines or imines. The method allows the preparation of bicyclic enamines with nitrogen at the bridgehead position as well as with nitrogen in the α-position. The formation of their iminium salts is also reported.
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>iv</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>PART I DIELS-ALDER REACTIONS OF HETEROSUBSTITUTED DIENES AND DIENOPHILES</td>
<td></td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>1 INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>2 RESULTS AND DISCUSSION</td>
<td>21</td>
</tr>
<tr>
<td>2,5-Dihydrothiophenes as Dienophiles</td>
<td></td>
</tr>
<tr>
<td>3-Acetamido-2,5-dihydrothiophenes as the Source of N-substituted</td>
<td></td>
</tr>
<tr>
<td>1,3-Dienes</td>
<td></td>
</tr>
<tr>
<td>Phosphorus-substituted Dienophiles</td>
<td></td>
</tr>
<tr>
<td>PART II ENAMINES AND IMINIUM SALTS FROM AMIDO-ACIDS</td>
<td></td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>1 INTRODUCTION</td>
<td>42</td>
</tr>
<tr>
<td>2 RESULTS AND DISCUSSION</td>
<td>51</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td>57</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>77</td>
</tr>
<tr>
<td>APPENDIX</td>
<td>83</td>
</tr>
<tr>
<td>VITA AUCTORIS</td>
<td>95</td>
</tr>
</tbody>
</table>
**LIST OF TABLES**

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pmr Data and Yields of the Diels-Alder Products</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>Cmr Data and Isomeric Distribution of Adducts 4-7</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Alkylation Products of N-Acetylcysteine</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>Yields and Pmr Data of Sulfoes and their Diels-Alder Derivatives</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>Yields and Pmr Data of Alkylation Products of N-Acetylhomocysteine</td>
<td>33</td>
</tr>
</tbody>
</table>
DIELS-ALDER REACTIONS OF HETEROSUBSTITUTED DIENES AND DIENOPHILES

CHAPTER 1

INTRODUCTION

The Diels-Alder reaction ([4+2] cycloaddition or diene synthesis) consists of the addition of a compound containing a double bond (usually activated by an additional electron-withdrawing substituent, e.g., a carbonyl group) to the 1,4-positions of a conjugated diene system, with the formation of a six-membered ring. The addition of butadiene to acrolein ([eq.1]) is a typical example.

\[ \text{diene} + \text{dienophile} \xrightarrow{\Delta} \text{adduct} \]

It is certainly justified to ask whether a reaction like the Diels-Alder cycloaddition, which was discovered more than 50 years ago, is still of general interest. The several hundred publications appearing each year on this topic give a positive answer. The preparative potential of this reaction has not yet been exhausted. The almost
unlimited possibilities of varying the diene- and dienophile-
components provides in many cases the simplest access to
cyclohexene and 1,4-cyclohexadiene derivatives. The
opportunity of using cyclic compounds, heterodienes, and
heterodienophiles opens up access to "one pot syntheses"
of monocyclic, bicyclic and polycyclic carbocycles and
heterocycles. The recent systematic studies of intra-
molecular Diels-Alder reactions have provided a new impact.

The versatility of the Diels-Alder reaction was
recognized primarily through the work of Diels and Alder,
whose series of papers on this subject began to appear in
1928. The development of the Diels-Alder reaction has been
of inestimable value not only in synthesis but also for
the light it has cast upon one mechanism of polymerization.
Polymerization of the diene sometimes accompanies or ex-
cludes the desired Diels-Alder reaction. Dienes with
doubly substituted carbon atoms in the terminal positions
of the conjugated system generally tend to produce polymers
rather than normal adducts. The use of purified maleic
anhydride in the Diels-Alder reaction is recommended. Free
maleic acid in the maleic anhydride may initiate the poly-
merization reaction of the diene. The use of polymerization
inhibitors such as hydroquinone, low temperatures, and
inert solvents (e.g., benzene, toluene, xylene) is sometimes
effective in suppressing polymerization of the diene.
The Diels-Alder reaction exhibits pronounced stereochemical selectivity, known as the Alder rules. These can be summarized as follows:

1. The addition of a dienophile to a diene is a cis addition: i.e., the dienophile stereochemistry is retained in the product.

2. In the reaction of maleic anhydride with a cyclic diene such as cyclopentadiene, two modes of addition are theoretically possible leading to the formation of an "endo" configuration or an "exo" configuration. Actually, in the case cited, the "endo" configuration is produced almost exclusively. The thermodynamically more stable "exo" compound is formed in yields of less than 1.5%. The products obtained from the cyclic diene furan and maleic anhydride and from diene addition reactions of fulvene do not obey the rule that the "endo" isomer predominates. The reason is that the initial "endo" adducts easily dissociate at moderate temperatures, allowing conversion of the kinetic "endo" adduct into the thermodynamically more stable "exo" isomer. Diels-Alder reactions are reversible, and on heating many adducts dissociate into their components, sometimes under quite mild conditions. It is not always the bonds formed
in the original diene addition which are broken in the retro reactions.³

The favoured "endo" orientation corresponds to the maximum accumulation of double bonds. It has been calculated⁹ that the attracting forces between the two molecules are greater in the "endo" orientation than in the "exo" orientation. However, when the dienophile has no activating unsaturation (e.g., allyl alcohol) it is no longer valid to speak of "maximum accumulation of double bonds." According to Alder¹⁰ the unshared electrons on an oxygen, nitrogen or halogen atom may be considered equivalent to unsaturation, and in a broader sense the presence of unshared electrons governs the spatial arrangement of the components before addition. This has been rationalised by Woodward and Hoffmann¹¹ as a stabilisation of the "endo" transition state by secondary orbital interaction. In a normal Diels-Alder reaction, that is one involving an electron-deficient dienophile and an electron-rich diene, the main interaction is that between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied orbital (LUMO) of the dienophile, and the smaller the energy difference between these
orbitals and the better overlap, the more readily the reaction occurs. However, it appears that these attractive forces are easily outweighed by steric factors and, in some cases, by changes in the experimental conditions.\textsuperscript{8}

3. Diels-Alder cycloadditions show a strong preference for the formation of specific regioisomers. Two structural isomers are possible when an unsymmetrical diene and an unsymmetrical dienophile interact.\textsuperscript{12} It has been frequently observed that mainly

\[ R\text{C}\equiv\text{C}+R'\text{C}\equiv\text{O} \rightarrow \text{R} \text{O} \]

\[ R\text{C}\equiv\text{C}+R'\text{C}\equiv\text{O} \rightarrow \text{R} \text{O} \]

"p-product" in the former case ([eq.2]) and mainly "o-product" in the latter case ([eq.3]) are formed. These observations were made for adducts from acrolein or acrylates and mono-substituted butadienes (R=methyl,\textsuperscript{13} acetoxy,}
alkyl, diethylamino, chloro, phenyl, cyano, carboxyl, and carboxymethyl).\textsuperscript{12}

A preparatively useful extension of the [4+2] cycloaddition was provided by the discovery of its catalysis by Lewis acids (e.g., AlCl\textsubscript{3}, SnCl\textsubscript{4}), which in many cases accelerates the rate of addition. In the presence of Lewis acids, "endo" products and the normally favoured regioisomers were frequently formed exclusively or to a higher extent than in their absence. The complexing of dienes and dienophiles by Lewis acids changes the energetic positions of intermediates and thus it effects the regiochemistry of the reaction ([eq.4]).\textsuperscript{14}

Many [4+2] cycloadditions are best described in terms of a symmetry allowed one-step mechanism (Scheme I).\textsuperscript{2} In principle, however, a two-step mechanism involving free radical or ionic intermediates cannot be
ignored. The experimental results suggest that the two-step mechanism is in most cases energetically more demanding, but in the case where the simultaneous bond formation may be hindered (e.g., steric or electronic effects) the two-step mechanism may be able to compete.

Since its discovery by Otto Diels and Kurt Alder in 1928, the Diels-Alder reaction has been of inestimable aid in the stereospecific synthesis of a number of natural products such as reserpine,\textsuperscript{15} minovine,\textsuperscript{16} and shikimic acid.\textsuperscript{17}

Dienophiles and dienes may be obtained in a number of ways. The more common ones (e.g., maleic anhydride, butadiene, isoprene) are commercially available, but many must be synthetically prepared. 2,5-Dihydrothiophenes are potentially very useful intermediates in a variety of organic syntheses and the corresponding sulfones have been used for separation and purification of conjugated dienes. The 2,5-dihydrothiophene-1,1-dioxides are dissociated to the 1,3-diene and sulfur dioxide under relatively mild thermal conditions.\textsuperscript{18} The thermal decomposition of 2,5-dihydrothiophene-1,1-dioxides also has been used for "in situ" generation of dienes in the Diels-Alder reaction.\textsuperscript{18} In addition, one example of a 2,5-dihydrothiophene has been used as a dienophile in the Diels-Alder reaction.\textsuperscript{19}

A search of the literature showed that there are a few methods of making 2,5-dihydrothiophenes.

McIntosh and co-workers\textsuperscript{20} have developed a deft
reaction involves the addition of an \( \alpha \)-mercaptoketone or aldehyde to a vinylphosphonium salt and then ring closure of the intermediate with elimination of a phosphine oxide ([eq. 5]). This synthesis is successful for alkylated

![Chemical Structure 5]

\[ \text{[5]} \quad \begin{align*} \text{CH}_2\text{CO} & \quad \text{SH} \quad + \quad \text{Br}^- \quad \text{PPh}_3 \quad \rightarrow \quad \text{S} \end{align*} \]

2,5-dihydrothiophenes. The preparation of 3-carboalkoxy-2,5-dihydrothiophenes offers more obstacles. McIntosh and Sieler\textsuperscript{21, 22} report 70-90% yields of 3-carbomethoxy-2,5-dihydrothiophenes from vinylphosphonates and mercaptoaldehydes ([eq. 6]).

![Chemical Structure 6]

\[ \text{[6]} \quad \begin{align*} \text{(EtO)}_2\text{O} & \quad \text{P} \quad \text{CO}_2\text{CH}_3 \quad + \quad \text{CHO} \quad \text{SH} \quad \rightarrow \quad \text{CO}_2\text{CH}_3 \end{align*} \]

\[ \text{R} = \text{H, Ph, n-C}_3\text{H}_7, \text{cyclo-C}_9\text{H}_{11} \]

Other methods for the formation of 2,5-dihydrothiophenes are known. The reduction of thiophene in liquid ammonia by sodium in the presence of methanol yields the mixture of 2,5-dihydrothiophene and 2,3-dihydrothiophene ([eq. 7]).\textsuperscript{23} The 2,5-dihydrothiophene must be isolated by careful
fractional distillation. During this distillation, some polymerization occurs and a relatively large high-boiling residue remains.

The addition of sulfur dichloride to conjugated dienes followed by elimination of the elements of chlorine yields the 2,5-dihydrothiophene with the overall yield for the two-step process of 12-13% ([eq. 8]).

The cyclization of a mercaptomuconate ([eq. 9]) yields 2,5-dihydrothiophenes in good yields but this method involves many steps.
2,5-Dihydrothiophene can be obtained in reasonable yield by reaction of cis-1,4-dichloro-butene-2 with anhydrous sodium sulfide ([eq.10]).\textsuperscript{26} The crude product

\[ \text{[10]} \quad \begin{array}{c}
\text{CH}_2\text{Cl} \\
\text{CH}_2\text{Cl}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{S} \\
\text{S}
\end{array} \quad + \quad \text{CH}_2=\text{CH}-\text{CH}-\text{CH}_2
\]

is a mixture of 2,5-dihydrothiophene and butadiene episulfide which cannot be effectively separated by distillation. The 2,5-dihydrothiophene can be purified only by oxidation to form the sulfoxide.

During the investigation of the reaction of vinylacetylene with sodium hydrosulfide by Trofimov and co-workers,\textsuperscript{27} it was found that the reaction yields 2,5-dihydrothiophene in 97\% yield ([eq.11]). The yield using this procedure is very good but it is limited to only one example, the unsubstituted 2,5-dihydrothiophene.

\[ \text{[11]} \quad \text{CH}_2=\text{CH} \quad \xrightarrow{\text{NaSH}} \quad \begin{array}{c}
\text{HS} \\
\text{HS}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{S} \\
\text{S}
\end{array}
\]

Recently thiophene and 2-ethylthiophene were reduced to the corresponding 2,5-dihydrothiophenes with zinc in trifluoroacetic acid ([eq.12]).\textsuperscript{28} This method appeared only as
[12] \[
\text{S} \quad \text{R} \\
\text{R}= \text{H, Et}
\]

\text{Zn} \quad \text{TFA}

\quad \text{R} \\
\text{S} \quad \text{R}

\quad \text{R} \\
\text{S} \quad \text{R}

a communication and it does not specify any details about the procedure and separation of the by-product, tetrahydrothiophene. It appears that the method developed by McIntosh and co-workers yields 2,5-dihydrothiophenes in the most effective way from readily available starting materials.

Stork and Stotter\textsuperscript{19} have shown that a substituted 3-carbomethoxy-2,5-dihydrothiophene has dienophilic character ([eq.13]) and desulfurization of the Diels-Alder adduct leads to precursors of the trans C/D hydrindan system of steroids.\textsuperscript{29} No other examples have been reported.

[13] \[
\text{R} \\
\text{R}_1 \\
\text{CO}_2\text{CH}_3
\]

\quad \rightarrow

\text{H}_3\text{CO}_2\text{C} \\
\text{R} \\
\text{H} \\
\text{S} \\
\text{R}_1 \\
\text{R}_2

1) \text{Ra-Ni} \\
2) \text{OMe}^- \\
3) \text{decarbox.}

R= \text{H, OC}_2\text{H}_5; \quad \text{R}_1=\text{CH}_2\text{CO}_2\text{CH}_3, \quad \text{R}_2=\text{H}
The possibility of removing sulfur from the Diels-Alder products to afford stereospecifically-substituted cyclohexene derivatives led us to explore the use of 3-carboxymethoxy-2,5-dihydrothiophenes as dienophiles in the Diels-Alder reaction (Chapter 2; Results and Discussion).

Nitrogen substituted 1,3-dienes have received little study. The most common examples are the sensitive N,N-di-substituted dieneamines which are afforded by condensation of an unsaturated carbonyl compound with a secondary amine. Acyclic dieneamides such as I are common in the literature but those such as II are virtually unexplored.

![Chemical Structures]

Only two reports exist for the synthesis of the 2-acetamido-\(^{34}\) and 2-benzamido-derivatives\(^{35}\) of butadiene. These are prepared by acylation of 2-amino-1,3-butadiene, which was formed from 2-amino-3-butyne by a pyrolysis reaction ([eq.14]).\(^{33}\)

\[
\begin{align*}
\text{CH}_2\text{CH}-\text{C=CH}_2 & \quad \text{CH}_2=\text{C-CH=CH}_2 & \quad \text{CH}_2=\text{C-CH=CH}_2 \\
\text{NH}_2 & \quad \text{NH}_2 & \quad \text{NHR} \\
3 & \quad \overline{1} & \quad \overline{1} \\
\end{align*}
\]

R = \text{-CCH}_3, \text{-CPh}
The 2-phthalimido-1,3-butadiene is reported in the literature but it is prepared by a multistep sequence in a low overall yield by pyrolysis of 2-phthalimido-1,3-butanol ([eq.15]).

\[ \text{R} \quad \begin{array}{c} \text{O} \\ \text{N} \text{C} \text{O} \end{array} \quad \text{CH}_2=\text{CH}-\text{C}=\text{CH}_2 \]

\[ \begin{array}{c} \text{O} \\ \text{N} \text{C} \text{O} \end{array} \quad \text{CH}_3-\text{CH}-\text{CH}-\text{CH}_2-\text{R} \]

\[ \Delta \]

\[ \text{a R}= \text{OH} \]
\[ \text{b R}= \text{OAc} \]

Overman and co-workers\(^ {31} \) have developed a new method for the synthesis of trichloroacetamido-1,3-dienes. In this short communication, Overman reports that the thermolysis of propargylic trichloroacetimidates affords a general, one-step route to a variety of 1- and 2-(trichloroacetamido)-1,3-dienes. Since the trichloroacetyl group can be removed by treatment with dilute base,\(^ {37} \) these 1,3-dienes hold particular synthetic interest as 1- or 2-amino-1,3-diene equivalents for the Diels-Alder reaction. Overman's work shows that generally the thermal rearrangement of a propargylic trichloroacetimidates forms only 1-(trichloroacetamido)-1,3-dienes (Scheme II).\(^ {32} \)
Dienes with the trichloroacetamido substituent at an internal diene carbon can be prepared by propargylic trichloroacetimidate rearrangement only in cases where the formation of a 1-(trichloroacetamido)-1,3-diene is not possible. Overman reports only two examples of the synthesis of 2-(trichloroacetamido)-1,3-dienes ([eq.16]).

\[ R = \text{H, } n-C_4H_9 \]  
\[ R = \text{H (14% yield)} \]  
\[ R = n-C_4H_9 (74\% \text{ yield}) \]
Only two reports of the Diels-Alder reaction with 2-acylamino-1,3-dienes have appeared. 2-Pthalimido-1,3-butadiene was chosen by Terada \textsuperscript{38} to study the role of such imido-groups in the Diels-Alder reaction. Overman \textsuperscript{31} reports very good yields of Diels-Alder products of 3-(tri-chloroacetamido)-1,3-octadiene with maleic anhydride, N-phenylmaleide, and acrolein.

In recent years the preparation and Diels-Alder chemistry of N-acylamino-1,3-dienes have been extensively developed by Oppolzer and co-workers \textsuperscript{39, 40} but their research deals only with 1-acylamino-1,3-dienes. Since, in our opinion, 2-acylamino-1,3-dienes had been under-exploited as components in the Diels-Alder reaction and since it appeared that thermolysis of 3-acylamino-2,5-dihydrothiophene sulfones would provide a simple access to these materials, we initiated the study of the preparation and Diels-Alder chemistry of 2-acylamino-1,3-dienes (Chapter 2; Results and Discussion). We were attracted to this diene class since they would be the synthetic equivalents for the unavailable parent 2-amino-1,3-dienes and also since they embodied the potential to control their Diels-Alder reactivity by modification of the acyl substituent on the nitrogen. Furthermore, the Diels-Alder products contain an enamide function which in principle can be alkylated, reduced or hydrolyzed.
The literature contains only a limited number of references of phosphorus-substituted dienophiles in the Diels-Alder reaction. Even as late as the 1960’s only a few examples were reported ([eq. 17]). The readily available diethyl vinylphosphonate has been reported to form adducts with butadiene, 2,4-hexadiene, 1,3-penta
diene, cyclopentadiene, and chlorocyclopentadiene in acceptable yields although the adducts were not fully characterized in all cases. The adducts of these reactions are claimed to be useful plasticizers with vinyl acetate, cellulose esters, polyvinyl chloride, useful for increasing film strength of lubricating oils, as well as insecti
cides. Interest has increased in these phosphorus-
substituted dienophiles in the last few years, although numerous unexplored areas remain.

Darling and co-workers report the cycloaddition reaction of diethyl vinylphosphonate with 1-diethylamino-
1,3-butadiene to give an adduct in 57% yield ([eq.18]).

\[
\text{[18]} \quad \begin{array}{c}
\text{NET}_2 \\
\text{N} \\
\text{O} \\
\text{CH}_3 \\
\text{C} \\
\text{O}
\end{array}
\quad \xrightarrow{\text{P(O)(OEt)}_2} 
\begin{array}{c}
\text{NET}_2 \\
\text{N} \\
\text{O} \\
\text{CH}_3 \\
\text{C} \\
\text{O}
\end{array}
\]

While cycloaddition reactions of the dienamine have been studied before, the hitherto unknown reaction of the vinylphosphonate illustrates the resistance of \(\beta\)-aminophosphonates to undergo Wittig elimination and also the directing effect of the phosphonate group to form only one isomer.

Neither isoprene nor acetoxybutadiene has been found to be selective with most dienophiles. A preponderance of one isomer may be obtained, but it is seldom formed exclusively. In reactions of 4-(diphenylphosphinyl)-3-buten-2-one with isoprene ([eq.19]) and acetoxybutadiene only one isomer was formed.\(^{48}\) The formation of only the isomer
shown in high yields (80%) in each case indicates an 
almost complete reversal of the usual directive effects 
of the acyl groups. Previous series of experiments 
placed the acyl group as the most influential in the 
orientation of the Diels-Alder cycloaddition. The data 
reported by Darling\(^\text{48}\) would suggest that the phosphinyl 
group is the most influential.

Rudinskas and Hullar\(^\text{49}\) report a cycloaddition re-
action of diethyl 2-formylphosphonate with isoprene but 
the position of the methyl group was not established.

Daniewski and Griffin\(^\text{50}\) report the formation and 
aromatization of Diels-Alder adducts of vinyl- and chloro-
vinylphosphonates. Reaction of diethyl vinylphosphonate 
with isoprene led to the formation of a mixture of two 
isomers (4:1) ([eq.\text{20}]). 1-Methoxybutadiene and diethyl 

\[
\text{[20]} \quad \begin{array}{c}
\begin{array}{c}
\text{R} = \text{H, CH}_3
\end{array}
\end{array}
\]

vinylphosphonate similarly gave an adduct which appeared 
to show two methoxyl singlets in pmr. Glpc analysis 
showed the presence of two materials with similar re-
tention times. These results show lack of orientational 
specificity in reactions of unsymmetrical dienes with the 
vinylphosphonate.
The results of the literature study indicate that vinylphosphonates can serve as effective dienophiles in Diels-Alder reactions with a variety of dienes. However, the very limited number of examples indicates that further work in this area is necessary, especially in the field of orientational specificity of dienophiles containing a phosphorous-substituent. In particular, the presence of a carbomethoxy group geminal to the phosphonate moiety should increase the dienophilic reactivity of the vinylphosphonate and perhaps improve the regioselectivity. The ready availability of the 2-carbomethoxyvinylphosphonates\textsuperscript{21} made this possibility attractive. Preparation of the related vinylphosphonic acid diamides and their use in the Diels-Alder reaction might lead to products which, on reduction of the carbomethoxy group, should lead to alkylidene cyclohexene derivatives ([eq.\textsuperscript{21}]).\textsuperscript{51}

\[
\text{[21]} \quad \text{CH}_3\text{OC} \quad \text{CH}_3\text{OC} \quad \text{CH}_3\text{OC} \\
\text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3
\]

Alicyclic phosphate esters are well known to be useful as insecticides.\textsuperscript{52} The Diels-Alder reaction of
readily available diethyl vinylphosphates with a variety of dienes would be an easy access to this class of compounds. The literature reports only one example of a Diels-Alder reaction of diethyl vinylphosphate with hexachlorocyclopentadiene ([eq. 22]). The adduct of this reaction was found to be an effective insecticide against 2-spotted mites, houseflies, and pea aphids. Since none of these systems (2,5-dihydrothiophenes as dienophiles, 3-acetamido-2,5-dihydrothiophenes as a source of N-substituted 1,3-dienes and Diels-Alder reactions of phosphorus-substituted dienophiles) have received much attention, it was felt that a detailed study of each should be conducted to develop their synthetic potential.
CHAPTER 2

RESULTS AND DISCUSSION

Important synthetic uses of cyclic sulfides include examples where the desired product retains sulfur in a ring (e.g., penicillins, cephalosporins, biotin, gliotoxin) as well as cases where the sulfur is destined for complete removal. Stork and Stotter\textsuperscript{19} report that 2,5-dihydrothiophenes have the ability to function as dienophiles for Diels-Alder reactions and further desulfurization of the bicyclic thiolane affords a substituted cyclohexene derivative of defined stereochemistry. In the context of natural product synthesis, cyclic sulfides have been used very often to solve problems of geometry or regiochemistry.\textsuperscript{54} Stork and Stotter's work appeared only as a single communication and no yields and experimental details were stated. A literature review showed that only this one example of the methyl ester of 2,5-dihydro-4-carboxyphenoxy-2-thiophene-acetic acid had been used as a dienophile in Diels-Alder reaction. To expand the knowledge in this area, we have investigated some additional examples of this reaction.

Two examples of 2,5-dihydrothiophenes \textsuperscript{3} were prepared (R=H and R=Ph) from methyl diethylphosphonoacetate (\textsuperscript{1}).\textsuperscript{55} Under proper conditions, interaction of phosphonate \textsuperscript{1} with aldehydes leads, not to a Wittig olefination reaction,\textsuperscript{56}
but to an aldol type condensation ([eq. 23]). Using literature methods, the phenylvinylphosphonate 2b and the unsubstituted phosphonate 2a were prepared in yields of 60-70%.

[23] \((\text{EtO})_2\text{PCH}_2\text{COOCH}_3 + \text{RCHO} \rightarrow (\text{EtO})_2\text{P-C-COOCH}_3\)

\(\begin{align*}
1 \\
2a & \text{ R=H} \\
2b & \text{ R=Ph}
\end{align*}\)

2,5-Dihydrothiophenes 3 were prepared employing the cyclization reactions of mercaptoacetaldehyde (in the form of its dimer) with vinylphosphonates 2 ([eq. 24]). The conjugate addition of thiolate ion to the double bond, followed by an intramolecular Wittig reaction of the ylide so formed, yielded 2,5-dihydrothiophenes 3 in yields 65-80%.

[24] \((\text{EtO})_2\text{PCH}=\text{CHSH} + \text{COCH}_3 \rightarrow \text{COCH}_3\)

\(\begin{align*}
a & \text{ R= H} \\
b & \text{ R= Ph} \\
3a & \text{ R= H} \\
3b & \text{ R= Ph}
\end{align*}\)

The \(\alpha\)-mercaptocarbonyl compounds generally exist as dimeric dihydroxy-1,1-dithianos, many of which are highly insoluble in the usual organic solvents (e.g., methylene chloride). In basic medium, after the addition of triethylamine, an equilibrium is established between monomer and dimer and the material becomes much more soluble.
The Diels-Alder reaction of 2,5-dihydrothiophenes \(^3\) with butadiene and subsequently isoprene ([eq.25]) yielded bicyclic thiolanes \(^4\)–\(^7\) (Table 1). The results obtained using a more reactive diene (cyclopentadiene) were complicated by severe isolation difficulties and rigorously defined products could not be isolated.

\[
\begin{align*}
\text{R}_1 = H, CH_3 && \text{R} = H, Ph
\end{align*}
\]

The purification of \(^4\)–\(^7\) was very laborious and possible only by preparative thin layer chromatography. The adducts \(^4\), \(^5\), \(^7\) were purified twice using chromatography. In case of \(^6\), the purification was repeated 3 times to completely separate the by-product, a polymer of isoprene. Attempts to improve the yields by employing catalysts such as aluminum chloride and tin (IV) chloride failed. Extensive polymerization of the diene was the major result of such modifications.

While both pmr and glc analysis of the adducts \(^4\)–\(^7\) indicated the presence of only one isomer, the cmr spectrum of \(^6\) showed the presence of two isomers in approximately a 3:2 ratio. Compounds \(^5\) and \(^7\) showed only one set of signals in their cmr spectra (Table 2). The stereochemistry of these adducts was assigned assuming steric control of the reaction.
Table 1

Pmr Data and Yields of the Diels-Alder Products

<table>
<thead>
<tr>
<th>Product</th>
<th>R₁</th>
<th>R</th>
<th>Pmr Data &lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield(%) &lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>5.6(bs,2H), 3.7(s,3H), 3.3-1.95(m,9H)</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>Ph</td>
<td>7.4(m,5H), 5.65(bs,2H), 4.3(s,1H), 3.65-1.0(m, 10H)</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>CH₃</td>
<td>H</td>
<td>5.3(bs,1H), 3.75(s,3H), 3.35-1.9(m,9H), 1.65(s,3H)</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>CH₃</td>
<td>Ph</td>
<td>7.3(m,5H), 5.2(bs,1H), 4.25(s,1H), 3.55-1.6(m, 13H)</td>
<td>29</td>
</tr>
</tbody>
</table>

<sup>a</sup>Spectra run in CDCl₃.

<sup>b</sup>A catalytic amount of hydroquinone was added to suppress the polymerization of the diene.
Table 2
Cmr Data and Isomeric Distribution
of Adducts 4-7

<table>
<thead>
<tr>
<th>Product</th>
<th>Structure</th>
<th>Cmr Dataa</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="#" alt="Structure 4" /></td>
<td>1 isomer (172.6, 141.1, 129.1, 127.7, 127.5, 124.9, 123.9, 60.9, 59.2, 51.4, 39.3, 35.1, 30.3, 26.1)</td>
</tr>
<tr>
<td>5</td>
<td><img src="#" alt="Structure 5" /></td>
<td>3:2 mixture (175.3, 175.2, 134.8, 131.0, 130.4, 124.2, 53.9, 53.1, 52.1, 42.3, 41.6, 39.5, 39.2, 38.7, 35.2, 32.7, 30.8, 28.6, 26.5, 26.2)</td>
</tr>
<tr>
<td>6</td>
<td><img src="#" alt="Structure 6" /></td>
<td>1 isomer (172.7, 141.2, 131.8, 130.1, 129.1, 127.7, 127.5, 60.6, 59.2, 51.4, 39.8, 38.8, 35.2, 30.7, 26.3)</td>
</tr>
<tr>
<td>7</td>
<td><img src="#" alt="Structure 7" /></td>
<td></td>
</tr>
</tbody>
</table>

aRun in CDCl₃.

bAssuming the formation of only one isomer the cmr study was omitted.
It is clear from these results that 2,5-dihydrothiophenes \( \text{3} \) can serve successfully as dienophiles in the Diels-Alder reaction but the practical application in synthesis must wait until an improvement in yields is realized. The phenyl substituent in \( \text{5} \) and \( \text{7} \) improved the regiochemistry of the Diels-Alder reaction by yielding only one isomer. The isomeric distribution in the mixture of \( \text{6} \) is in agreement with the experimental results of unsymmetrical dienes and dienophiles known in the literature.\(^5\)\(^7\)

2-Acylamino-1,3-Dienes

A new method of preparation of 2-acylamino-1,3-dienes and their use in the Diels-Alder reaction has been developed. This approach to the preparation of 2-acylamino-1,3-dienes and their use "in situ" in the Diels-Alder reaction was undertaken using 3-acylamino-2,5-dihydrothiophenes as starting materials ([26]).

\[ R_1 = H, \quad R_2 = \text{CCH}_3 \quad \text{or} \quad R_1, R_2 = \text{CCH}_3 \]
Field\textsuperscript{58} has reported the preparation of two examples of 3-acetamido-2,5-dihydrothiophenes ([eq.27]) using \(N\)-acetylcysteine and \(\alpha\)-haloketones as starting materials. The mechanism of this reaction has not been investigated in detail but Field suggests a possible mechanism. Using Field's method,\textsuperscript{58} two examples of 3-acylamino-2,5-dihydrothiophenes were prepared. The starting material \(N\)-acetylcysteine was commercially available but could be easily prepared from cystine.\textsuperscript{59} Alkylation of \(N\)-acetylcysteine with 2-chlorocyclohexanone, chloroacetone, and 3-chloro-3-methyl-butan-2-one in a basic ethanol solution proved to be facile and the expected products 8-10 were obtained in good yields (Table 3).

Compounds 8 and 9 were heated with acetic anhydride at 130-135°C for 1h to afford 3-acylamino-2,5-dihydrothiophenes 11 (52\%) ([eq.28]) and 12 (50\%) with a small amount of by-product 13 (15\%) ([eq.29]).
Table 3
Alkylation Products of N-Acetylcyesteine

<table>
<thead>
<tr>
<th>Alkylating Agent</th>
<th>Product</th>
<th>Structure</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-chloro- cyclohexanone</td>
<td>8</td>
<td><img src="image" alt="Structure" /></td>
<td>60.59</td>
</tr>
<tr>
<td>chloroacetone</td>
<td>9</td>
<td><img src="image" alt="Structure" /></td>
<td>68</td>
</tr>
<tr>
<td>3-chloro-3- methyl-butan-2-one</td>
<td>10</td>
<td><img src="image" alt="Structure" /></td>
<td>74</td>
</tr>
</tbody>
</table>
The reason for the incorporation of an extra acetyl unit in \( 12 \) during the cyclization reaction in acetic anhydride is unclear at this time. The cyclization of \( 10 \) in acetic anhydride afforded only the intermediate \( 14 \) ([eq. 30]) in low yield (25%). Compounds analogous to \( 14 \) have been shown by Field to be intermediates in the formation of \( 11 \). Attempts to decarboxylate \( 14 \) by heating with sodium hydride in toluene failed. Compound \( 14 \) was unchanged.

Prolonged heating only afforded more decomposition products. From these results it appears likely that the steric hindrance around the carbonyl group in \( 10 \) inhibits the formation of the desired 3-acylamino-2,5-dihydrothiophene.
The oxidation of 11 and 12 to sulphones 15 and 16, respectively ([eq. 31]) was carried out using m-chloroperbenzoic acid. Sulphones 15 and 16 are stable, crystalline compounds. However, when they are heated, rapid evolution of sulfur dioxide occurs. Heating the sulphones 15 or 16 in the presence of maleic anhydride yielded the adducts 17 or 19, respectively ([eq. 32]). Since adduct 17 was not very stable, it was hydrolyzed to diacid 18 before purification.
<table>
<thead>
<tr>
<th>Compound</th>
<th>mp. (°C)</th>
<th>Yield (%)</th>
<th>Pmr Data&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>157-159</td>
<td>68</td>
<td>7.85(bs,1H),4.2-3.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(m,3H),2.35(s,3H),2.3-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0(m,8H)</td>
</tr>
<tr>
<td>17</td>
<td>213-215</td>
<td>62</td>
<td>8.95&lt;sup&gt;b&lt;/sup&gt;(bs,1H),4.0-3.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(m,5H),2.35-1.0(m,11H)</td>
</tr>
<tr>
<td>16</td>
<td>151-152</td>
<td>42</td>
<td>3.9(bs,4H),2.4(s,6H),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.75(s,3H)</td>
</tr>
<tr>
<td>19</td>
<td>162-163</td>
<td>70</td>
<td>3.5(m,2H),2.6(m,4H),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.3(s,6H),1.7(s,3H)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Run in CDCl<sub>3</sub>.

<sup>b</sup>Run in DMSO.
The successful results with N-acetylcysteine suggested that perhaps other aminoacids could be used in this sequence of reactions to form other (e.g., six-membered) cyclic sulfides. N-Acetylhomocysteine, which was generated "in situ" from the N-acetylhomocysteine thiolactone (commercially available) reacted with chloroacetone and 3-chloro-3-methylbutan-2-one to form acids 20 and 21 in very good yields ([eq.33]). In the case of N-acetylhomocysteine the reaction was carried out in a basic solution of 2-propanol because in ethanol solution ethyl esters of 20 and 21 were produced (Table 5).
Table 5
Yields and Pmr Data of Alkylation Products
of N-Acetylhomocysteine

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Pmr Data(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acid 20</td>
<td>50(^a)</td>
<td>8.15 (bd, 1H), 4.25 (m, 1H), 2.4-1.55 (m, 4H), 2.25 (s, 3H), 1.8 (s, 3H), 1.35 (s, 6H)</td>
</tr>
<tr>
<td>ethyl ester of 20</td>
<td>81(^b)</td>
<td>6.3 (bd, 1H), 4.65 (m, 1H), 4.2 (q, 2H, J=7Hz), 2.25 (s, 3H), 2.0 (s, 3H), 2.4-1.7 (m, 4H), 1.4 (s, 6H), 1.25 (t, 3H, J=7Hz)</td>
</tr>
<tr>
<td>acid 21</td>
<td>84(^a)</td>
<td>8.05 (bd, 1H), 4.3 (m, 1H), 3.5 (s, 2H), 2.2 (s, 3H), 1.85 (s, 3H), 2.4-1.7 (m, 4H)</td>
</tr>
</tbody>
</table>

\(^a\) Reaction carried out in 2-propanol solution.

\(^b\) Reaction carried out in ethanol solution.

\(^c\) Run in DMSO.

\(^d\) Run in CDCl\(_3\).
The acids 20 and 21 were heated with acetic anhydride to form 6-membered cyclic sulfides. Compound 21 afforded a 6-membered enamide 22 in a good yield ([eq.34]). Purification of 22 was difficult, so crude 22 was oxidized to form a crystalline solid, which was purified and characterized as sulfone 23. The cyclization reaction of 20 did not yield the desired product, only compound 24 was isolated in 35% yield ([eq.35]). Prolonged heating or excess of acetic anhydride only produced more decomposition products.
It is apparent from these results and those of Field that in the absence of steric hindrance around the carbonyl group, good yields of 3-acetamido-2,5-dihydrothiophenones (11 and 12) are achieved and that the sulfone formation and subsequent decomposition leads to 3-acetamido-1,3-dienes. Also, the formation of 6-membered enamide 22 in a good yield proved that this method is more general than Field's reported. The isolation of small amounts of compound 13 and oxazolines 14 and 24 is in agreement with Field's proposed mechanism. Generally, all these results suggest that other aminoacids might be put to use to form substituted 5- and 6-membered cyclic enamides, especially if an enamide is desired for a subsequent step in a synthetic pathway. Also, in the light of Overman's results which have been previously referred to, the use of trifluoroacetic anhydride as the cyclizing agent may afford products which will possess some advantageous properties in the subsequent Diels-Alder reactions.
Phosphorus-substituted Dienophiles

The results of the literature survey indicate that vinylphosphonates can serve as effective dienophiles in Diels-Alder reactions with a variety of dienes. However, the very limited number of examples indicates that further work in this area is necessary, especially in the field of orientational specificity of dienophiles containing phosphorus-substituents.

It was interesting to attempt the Diels-Alder reactions using vinylphosphonates with a carbomethoxy group in the α-position to examine its directive effects with the unsymmetrical diene, isoprene ([eq.36]). The vinylphosphonate 2a has never been used before as a component of the Diels-Alder reaction. The cycloaddition reaction of 2a with isoprene yielded the adduct 25 in 95% yield and as one isomer. After hydrolysis the acid 26 was obtained in 90% yield which was decarboxylated to form 27. Compound 27 was prepared by Daniewski and Griffin\(^{50}\) ([eq.20]) as a mixture of two isomers (1:4) in a lower yield using an un-
substituted vinylphosphonate as the starting material. It is apparent from comparison of our results with those of Daniewski and Griffin that the presence of a carbomethoxy group in the α-position of a vinylphosphonate increases the dienophilic reactivity of vinylphosphonate and improves the regioselectivity. An attempt to use phenylvinylphosphonate 2b as the dienophile for the same reaction was not successful. Prolonged heating, higher temperatures or the addition of a Lewis acid (AlCl₃) afforded only higher yields of polyisoprene. Probably the steric hindrance of the double bond of the dienophile 2b decreases or stops completely the cycloaddition reaction.

In recent years, the construction of synthetic equivalents for unreactive dienophiles such as allenes has broadened the scope of the Diels-Alder reaction to include the production of alkylidene cyclohexenes not normally generated by this thermal system. The direct synthesis of 4-methylene-1-cyclohexene via a Diels-Alder reaction was possible only by modification of other Diels-Alder adducts. For example, α-bromoacrolein reacts with a variety of 1,3-dienes to form adducts which are converted to 4-methylene-1-cyclohexenes. A similar method is reported by Philips and Oku. None of these methods are entirely acceptable because of low yields or formation of product mixtures. The Diels-Alder product 25 ([eq.36]) from the vinylphosphonate 2a does not have any hydrogen left adjacent to the phosphorus atom and after dephosphorylation...
activated phosphonate 27 cannot undergo Wittig-type reactions. However, unactivated phosphonamides do undergo Wittig-type reactions \(^{51}\) and therefore it was decided to prepare the Diels-Alder product analogous to 25 using \(\alpha\)-carbomethoxy vinylphosphonic acid diamide ([eq.21]) instead of 2a ([eq.36]). The literature does not report any examples of \(\alpha\)-carboalkoxy vinylphosphonic acid diamides. It was decided to use methylphosphonic acid bis(dimethylamide) (28) as the starting material to prepare desired 29 ([eq.37]). The method of Kosolapoff\(^{51, 63}\)

\[
\begin{align*}
\text{[37]} & \quad \text{CH}_3\text{P}[[\text{N(CH}_3)_2]_2 \xrightarrow{0} \text{CH}_3\text{OCCH}_2\text{P}[[\text{N(CH}_3)_2]_2 + \left[\begin{array}{c}
0^+ \text{Li}^+
\end{array}\right] \\
28 & \quad 29 & \quad 30
\end{align*}
\]

was adapted for the synthesis of 28. We improved this method by using easily available dimethylamine hydrochloride and sodium hydroxide in water-ether solution instead of dry gaseous dimethylamine. The yield of 28 was 85%. The reaction of 28 with \(n\)-butyllithium and methyl chloroformate afforded the desired ester 29, but in a low yield (30%). The lithium salt 30 may be the major product of this reaction. The structure of 30 is not completely determined, because it could not be isolated from the reaction mixture. Careful acidification of the aqueous solution of 30 appeared to yield the acid 31, which was very sensitive to heat and at temperatures of 40-50° decomposed to form
a polymer ([eq.38]). The same products were obtained using n-butyl chloroformate. Compounds like 31 which contain two phosphorus-nitrogen bonds are known to polymerize easily under acidic conditions.64

\[
\begin{align*}
\text{[38]} & \quad 30 \xrightarrow{\text{HO}_2\text{CCH}_2\text{P(O)}[\text{N(CH}_3\text{)}_2\text{]}_2} \text{polymer} \\
& \quad 31
\end{align*}
\]

In a different approach to the preparation of a vinyl derivative of 28 ([eq.39]), compound 32 was afforded in a very good yield. The acylation reaction of 32 failed.

\[
\begin{align*}
\text{[39]} & \quad 28 \xrightarrow{\text{PhCHCH}_2\text{P(O)}[\text{N(CH}_3\text{)}_2\text{]}_2} \text{PhCH=CH-P(O)}[\text{N(CH}_3\text{)}_2\text{]}_2 \xrightarrow{\text{COCH}_3} 32
\end{align*}
\]

The treatment of 32 with n-butyllithium followed by acetic anhydride yielded only a mixture of starting materials. Under the same conditions acetyl chloride yielded dimethyl acetamide and decomposition products. It is known that acyl chlorides replace a dimethylamino group by chlorine in hexamethylphosphoramide.65

This project was not successful but these results have increased the information about the reactivity of derivatives of methylphosphonic acid bis(dimethylamide) with chloroformates and acetyl chloride. The reaction of chloroformates with the lithium salt of 28 is not to our knowledge known in the literature.

To our knowledge, there is only a single report in the literature of the use of the readily available vinyl-
phosphates as dienophiles in the Diels-Alder reaction. Whetstone and May\textsuperscript{52} report the reaction of diethyl-vinylphosphate with hexachlorocyclopentadiene to give an adduct in 65\% yield ([eq.22]). Other dienes have been used in this reaction, but the products were not characterized.\textsuperscript{53} It was interesting to try the Diels-Alder reaction using vinylphosphates as the dienophile because the phosphoryl group of an adduct could be removed by hydrolysis or reduction to afford synthetically useful products.

Diethyl isopropenylphosphate (33) was prepared using chloroacetone and triethylphosphite as the starting materials.\textsuperscript{66} The Diels-Alder reaction of 33 with isoprene yielded a mixture of decomposition products of the adduct 34 ([eq.40]) identified using IR, PMR and MS technique.

\begin{align*}
&\text{CH}_3\begin{array}{c}O \\
&\text{OP(OEt)}_2 \end{array} \quad \begin{array}{c}CH_3 \\
&\text{OP(OEt)}_2 \end{array} \quad \text{CH}_3 \\
\text{CH}_3 &\quad \text{CH}_3 &\quad \text{CH}_3
\end{align*}

Attempts to carry out the reaction under different conditions (time, temperature) to yield the adduct 34 before it decomposed failed.
It appears that, based on these very limited results, the use of vinylphosphates to prepare cyclohexenol derivatives via the Diels-Alder reaction is a problematical process.
ENAMINES AND IMINIUM SALTS

FROM AMIDO-ACIDS

CHAPTER I

INTRODUCTION

The preparation of optically active compounds is of primary importance for the synthesis of pharmacologically active compounds. An attractive approach to the preparation of these compounds is a "biomimetic" one in which a chiral catalyst induces significant chirality in reaction products. Despite considerable efforts, relatively few reactions of this type are known which proceed in reasonable chemical yields. Several teams have tried to accomplish kinetic racemate resolution and optical induction with optically active quaternary ammonium salts. However, the optical yields using these catalysts, having their chirality in the carbon skeleton of the salt, have been very low. Recently, Wynberg and co-workers have reported high optical yields of optically active Michael adducts from prochiral reactants using optically active catalysts derived from quinine and related alkaloids. The catalysts employed by Wynberg had chirality both in the carbon skeleton and the nitrogen atom of the salt. McIntosh initiated a study of the preparation of optically active catalysts where the effective existing chirality was centered on
the nitrogen atom. He pointed out that simple quaternary ammonium salts cannot be expected to cause significant asymmetric induction unless three of the four tetrahedral faces of the nitrogen are blocked. The difference in stability and population of the possible conformations in simple quaternary salts is small and each of these conformations might lead to a different stereochemical result. McIntosh designated the following structural criteria which a catalyst should possess in order to cause asymmetric induction in phase-transfer reactions.

1. They must have a chiral nitrogen atom.
2. They should be as rigid as possible to facilitate interpretation of stereochemical results.
3. Three of the faces of the nitrogen atom should be blocked.
4. Introduction of various substituents in stereochemically defined ways should be possible.

Ammonium salts meeting these requirements are not common but it has been suggested that 1-azoniapropellane salts may fulfill the criteria.

Recently, McIntosh has reported the successful synthesis of three examples of 1-azoniapropellane salts in racemic form (III-V) and their use as phase-transfer catalysts. The same method of preparation of III was reported recently by Alder. The salts III-VI effectively catalyzed the formation of aldehyde cyanohydrin ethers and
the reaction of 2-carbethoxy-cyclohexanone with methyl vinyl ketone.\textsuperscript{71, 72} 1-Azoniapropellane salts, whose structures are based on the propellane ring system with the quaternary nitrogen atom located at the bridgehead position and bearing ring substituents where necessary or having three rings of different sizes fulfill all four criteria. The synthesis of salt VI\textsuperscript{74} and closely related systems derived from lupinine\textsuperscript{75} has been known for many years. Molecules possessing the propellane structure are well known and their chemistry and structural features have been extensively reviewed by Ginsburg.\textsuperscript{76}

A most attractive feature of McIntosh's method for the preparation of salts III–V as well as a variety of derivatives substituted in the rings is the possibility of using a simple precursor – a bicyclic enamine (Scheme III).\textsuperscript{77}
To investigate the application of this method to the annulation of larger rings such as 7-membered rings in the azoniapropellanes, it is necessary to prepare the precursor dehydro-l-azabicyclo[5.4.0]undecane, which could be easily interconverted to the iminium salt ([eq. 41]).

[41]  \[
\begin{array}{c}
\text{N} \\
\text{X}
\end{array}
\rightarrow
\begin{array}{c}
\text{N}^+ \\
\text{X}^-
\end{array}
\]

In most cases, ketones are readily converted to enamines by condensation of the carbonyl compounds with a secondary amine and azeotropic removal of water.\textsuperscript{78} The addition of secondary amines to acetylenes, particularly the addition to acetylenic esters and sulfones, forms enamines.\textsuperscript{79} Enamines have also been obtained by addition of secondary amines to allenes.\textsuperscript{80} Recently, the Horner-Wittig reaction has been applied successfully to the synthesis of both aldehyde and ketone enamines.\textsuperscript{81} One of the most general methods for synthesis of bicyclic enamines is the oxidation of the tertiary amines with mercuric acetate which has been investigated by Leonard and co-workers.\textsuperscript{82} Leonard applied this method in the synthesis of dehydro-l-azabicyclo[5.4.0]undecane in 57% yield ([eq. 42]).\textsuperscript{82} In this case, the preparation of the starting
material, 1-azabicyclo[5.4.0]undecane$^8$ from diethyl acetonedicarboxylate involves too many steps and the overall yield is low. In addition, Leonard's method works well in cases where only one tertiary hydrogen atom adjacent to nitrogen exists. However, in cases where more than one hydrogen of this type exists, mixtures of enamines can be expected; i.e., the method is not regiospecific.

Another very useful process for the preparation of bicyclic amines has been described recently by Rapoport.$^8$ This involves decarboxylation of $\alpha$-aminoacids. This method is useful only in the case of 5- and 6-membered ring cyclizations. In the case of 7-membered rings the alkyl chain of the starting material ([eq.43]) cyclizes to diethyl cyclopentane-1,1-dicarboxylate. Rapoport$^8$
reports the possibility of reversing this process; that is closing a 6-membered ring onto an existing 7-membered ring, but again the preparation of the starting material, hexahydro-1H-azepine-2-carboxylic acid\textsuperscript{86} involves too many steps.

Miyano and co-workers\textsuperscript{87, 88} have reported the preparation of dehydropyrrolizidines by a simple two-step synthesis starting with readily available, \(\gamma\)-butyrolactone. The key step is a cyclization of an amido-acid by pyrolysis over soda-lime \(\gamma\) (eq. 44). The described sequence of reactions provides the most attractive method for the synthesis of dehydropyrrolizidines and their perchlorates in terms of the overall yield and the number of steps from readily available starting materials. Miyano's method\textsuperscript{87} of cyclization of amido-acids by pyrolysis is an extension of the work described by Murakoshi.\textsuperscript{89, 90} His work, which appeared largely in Japanese, indicates that 5-, 6-, and 7-membered rings can be formed, that the stereochemistry at

\[\text{Reaction 44}\]

\[\text{R} = \text{H}, \text{CH}_3\]
the C-N center is retained and that the presence of N-H bonds does not interfere with the cyclization. Furthermore, Murakoshi and co-workers\textsuperscript{89, 90} have shown that esters can be used in place of the acids.

In view of the simplicity of this method and the possibility of using different types of amido-acids which might undergo this reaction, it seemed to be the most attractive for preparing the desired dehydro-l-azabicyclo[5.4.0]undecane. Additionally, both C- and N-(ω-carboxy-alkyl)lactams, as well as ω-acylaminocarboxylic acids are potential substrates for the reaction. In each of these cases, the effect of ring size (both of the existing and cyclizing rings) and substituents on the nitrogen are possible variables.

Leonard and co-workers\textsuperscript{91} have reported that the dehydrogenation by mercuric acetate of 1-methyldecahydroquinoline does not yield a simple enamine derivative because of an hydroxylation reaction. To avoid the hydroxylation reaction, Leonard used aromatic amines as starting materials for the preparation of bicyclic enamines with the nitrogen in the α-position. He described\textsuperscript{92} the lithium-n-propylamine reduction of 1-methyltetrahydroquinoline ([eq.45]). Gray and Heitmeier\textsuperscript{93} reported the same reaction but claim that the product of this reaction is not an enamine derivative, but rather a mixture of double bond isomers.
Godefroi and Simanyi\textsuperscript{94} described a method of preparing 3,4,4a,5,6,7-hexahydro-2H-1-pyridine in 73% yield ([eq. 46]), which is based on the work of Cohen and Witkop.\textsuperscript{95} Mistryukov\textsuperscript{96} reported a modification of this method and a higher yield of the product (85%). A literature search showed that only the Cohen-Witkop method\textsuperscript{95} and its modifications\textsuperscript{96, 97} are known to afford good yields of bicyclic imines with the nitrogen in α-position. However, this method is limited to unsubstituted nitrogen precursors only.

Parcell and Hauck\textsuperscript{98} have reported the preparation of a N-methyl-enamine ([eq. 47]) in 74% yield, but this method
is successful only in a few cases. For example, the application of 3-bromopropylamine hydrobromide instead of N-methyl-3-bromopropylamine hydrobromide does not give the expected imine derivative.

In the last few years Mahajan and co-workers\textsuperscript{99} developed a method for preparing N-substituted bicyclic enamines by the cyclization of cycloalkanone esters in the presence of primary amines (eq.48) and subsequent reduction of the keto group using LiAlH\textsubscript{4}. However, the last step of this process, the reduction reaction, proceeds in low yields.\textsuperscript{100}

The lack of a simple and general method for preparing N-substituted and unsubstituted bicyclic enamines from easily available precursors focused our attention on the possibility of applying the soda-lime pyrolysis developed by Miyano and Murakoshi to the formation of these compounds with the nitrogen not only in the bridgehead position but also in the α-position.
CHAPTER 2

RESULTS AND DISCUSSION

A literature review showed that the cyclization reaction of amido-acids in the presence of soda-lime (a mixture of NaOH, CaCO$_3$, and CaO) had been widely investigated by Murakoshi$^{89, 90}$ and Miyano$^{87, 88}$ Their reports indicate that 5-, 6-, and 7-membered rings can be formed.

To start the investigation of the application of this method to the annulation of 7-membered rings, it was necessary to prepare N-(ω-carboxylalkyl)lactam 38. Compound 38 was prepared using ethyl 6-bromohexanoate (35) as the starting material ([eq.49]). Saturation of an ethanolic solution of ε-caprolactone with hydrogen bromide yielded 35 in 56% yield. The method of McIntosh$^{72}$ was

\[\text{[49]} \quad \text{Br(CH}_2\text{)}_5\text{COOEt} \quad \rightarrow \quad \text{\begin{tikzpicture} \draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle; \draw (0.5,0.5) circle (0.2cm); \end{tikzpicture}} \quad \rightarrow \quad \text{\begin{tikzpicture} \draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle; \draw (0.5,0.5) circle (0.2cm); \end{tikzpicture}} \quad \text{\begin{tikzpicture} \draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle; \draw (0.5,0.5) circle (0.2cm); \end{tikzpicture}} \quad \text{\begin{tikzpicture} \draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle; \draw (0.5,0.5) circle (0.2cm); \end{tikzpicture}} \quad \text{\begin{tikzpicture} \draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle; \draw (0.5,0.5) circle (0.2cm); \end{tikzpicture}} \]
adapted to afford compound 36. The bromoester 35 was heated under nitrogen with 2-methoxypyridine to yield 36 (64%). Crude 36 was hydrogenated over platinum oxide to form compound 37 in quantitative yield. The hydrolysis of 37 produced 38 in a very good yield. Compound 38 was pyrolyzed with soda-lime to give 39 in 49% yield ([eq.50]).

\[
\begin{align*}
\text{38} & \rightarrow \text{39} + \text{40} \\
\text{39} & \text{N+ C10} \quad 4 \\
\text{40} & \text{N} \\
\end{align*}
\]

The crude enamine 39 (one peak on glc) was acidified with ethanolic perchloric acid in ether to precipitate white crystals of the perchlorate 40. The yield of crystalline salt 40 was only 30%. Basification of the ether solution gave an oil whose ir spectrum showed a strong C=O and whose mass spectrum showed a peak at m/z=169. These data suggest the presence of the ring-opened aminoketone shown in ([eq. 50]). The difficulty in forming 7-membered rings is well known and has been reported by Rapoport. 84 However, the formation of the 7-membered ring of imine 41 (74%) ([eq.51]) from commercially available 6-acetamidohexanoic acid was more successful. Caprolactam (42) was also isolated in 24% yield. It is interesting that Murakoshi 90a reports imine 41 as the only product of the soda-lime
pyrolysis of ethyl 6-acetamidohexanoate. The imine 41 was precipitated as the salt of hexachloroplatinic acid 43 in a good yield.

Next, we turned our attention to C-(\(\omega\)-carboxyalkyl)-lactams. It was of interest to determine if cyclization would occur to give bicyclic fused systems in which the nitrogen was not at the bridgehead position. Two examples of C-(\(\omega\)-carboxyalkyl)lactams (46 and 50) were prepared. The starting material 3-carbethoxy-2-piperidinone was stirred under basic conditions with ethyl 4-bromobutyrate to form 44 in 54% yield. The diester 44 was hydrolyzed to form diacid 45, which was decomposed to form the lactam 46 ([eq. 52]). A similar sequence of reactions was repeated to form the N-methyl substituted lactam 50. The starting
material N-methyl-2-piperidone was converted to ethyl ester 49 (80%), which was hydrolyzed to give lactam 50 in 92% yield ([eq.53]). Compounds 46 and 50 were

\[
\begin{align*}
\text{CH}_3 & \quad \rightarrow \\
\text{N} & \quad \text{COOR} \\
\text{N} & \quad \text{CH}_3 \\
49 & \quad R = \text{Et} \\
50 & \quad R = \text{H}
\end{align*}
\]

pyrolyzed with soda-lime to yield crude enamines 47 (61%) and 51 (78%). The enamine 47 was treated with hexachloroplatinic acid to form yellow crystalline salt 48 ([eq.54]). Attempts to isolate the salt 52 were unsuccessful because of the extremely hygroscopic nature of this salt.

\[
\begin{align*}
\text{R} & \quad \rightarrow \\
\text{N} & \quad \left[ \begin{array}{c}
\text{N} \\
\text{R}
\end{array} \right] \\
47 & \quad R = \text{H} \\
51 & \quad R = \text{CH}_3 \\
48 & \quad R = \text{H} \\
52 & \quad R = \text{CH}_3
\end{align*}
\]

Our successful results with soda-lime pyrolysis of C-(ω-carboxyalkyl) lactams 46 and 50 taken together with the results of Miyano,\textsuperscript{87, 88} Murakoshi,\textsuperscript{89, 90} and concurrent results obtained by others in our group\textsuperscript{77} show that such
pyrolyses of amido-acids is a general method for the preparation of bicyclic enamines and is not restricted to compounds with nitrogen at the bridgehead position. Based on these results and others, a mechanism is suggested (Scheme IV) which is similar to that of the classical Ruzicka pyrolysis\textsuperscript{101} of dicarboxylic acids over barium, calcium or thorium oxide. Unlike previous methods, this process can be applied to nitrogen-substituted enamines as well as the nitrogen-unsubstituted enamines. The storage of enamines as iminium salts is necessary to avoid oxidation (atmospheric oxygen) and subsequent decomposition. Iminium salts, which are frequently used as intermediates in synthetic pathways, are easily converted to enamine derivatives under basic conditions.
Imines, enamines, and iminium salts play a central role in the chemistry of two important classes of nitrogen compounds in nature, aminoacids and alkaloids. Through the use of C=N, and H labels in plant feeding experiments, alkaloids have been shown to be derived either directly from aminoacids or from their decarboxylation products. Iminium salts and imines play a central role as intermediates in these biosynthetic pathways.
Structures of Compounds Described in Experimental Section

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EXPERIMENTAL

Melting points are corrected; boiling points are uncorrected. Infrared spectra were run on a Beckman IR-12 instrument. PMR spectra were run at 60 MHz and are reported in the following format: chemical shift (δ) (multiplicity; number of protons, coupling constant). CMR spectra were run at 22.64 MHz in the FT mode using a flip angle of 45° on a Bruker CXP-100 instrument. Mass spectra were obtained on a Varian MATCH-5DF instrument. Gas chromatographic analyses were performed using either 10% or 20% SE-30 on Chromosorb W columns, solvents were removed at reduced pressure and the drying agent was anhydrous magnesium sulfate. Preparative thin layer chromatography was performed on 2mm thick silica gel G.F. plates from Analtech Inc. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, U.S.A., and Guelph Chemical Laboratories Ltd., Guelph, Canada.

Methyl Diethylphosphonoacetate (I) was prepared by the method of House et al. in 70% yield; bp. 130-134°C/9.4 Torr.

Vinylphosphonates 2 were prepared by the method of McIntosh and Sieler; compound 2a (R=H) by method A in 67% yield, bp. 95-99°C/0.9 Torr and compound 2b (R=Ph) by method B in 60% yield, bp. 160-165°C/1 Torr.
3-Carbomethoxy-2,5-dihydrothiophenes 3 were prepared by the method of McIntosh and Sieler;\textsuperscript{22} compound 3a (R=H) in 65% yield, mp. 30-31°C and compound 3b (R=Ph) in 80% yield, mp. 65-66°C. The purification of 3a was modified from the literature procedure using 1:1 ether-petroleum ether as eluent and in the case of 3b methylene chloride as eluent.

General Procedure for the Diels-Alder Reactions of 3a and 3b.
A solution of 3 (2mmol), hydroquinone (0.01g) and the appropriate diene (20mmol) in 5mL of xylene was sealed in a tube and heated in an autoclave at 180°C. After 20h the sealed tube was opened, the crude mixture was concentrated and purified using thin layer chromatography (1:9 ether-petroleum ether). The reaction was monitored by glc analysis (200-250°C/20% SE-30).

**Compound 4**: colourless oil (38%); ir (CHCl\textsubscript{3}) cm\textsuperscript{-1}: 1710, 1640, 1180; pmr (see Table 1). Anal. calcd. (C\textsubscript{10}H\textsubscript{14}O\textsubscript{2}S): C 60.61, H 7.06. Found: C 60.85, H 7.10.

**Compound 5**: colourless oil (55%); ir (CHCl\textsubscript{3}) cm\textsuperscript{-1}: 1720, 1650, 1590, 1520, 1490, 1210; pmr (see Table 1); cmr (see Table 2). MS: 274(M\textsuperscript{+}), 183, 138, 135, 91. Anal. calcd. (C\textsubscript{16}H\textsubscript{18}O\textsubscript{2}S): C 70.08, H 6.56. Found: C 70.43, H 6.57.

**Compound 6**: yellowish oil (16%); ir (CHCl\textsubscript{3}) cm\textsuperscript{-1}: 1730, 1615, 1225; pmr (see Table 1); cmr (see Table 2). Anal. calcd. (C\textsubscript{11}H\textsubscript{16}O\textsubscript{2}S): C 62.27, H 7.54. Found: C 62.62, H 7.13.
**Compound 7**: colourless oil (29%); ir (CHCl₃) cm⁻¹: 3020, 1720, 1640, 1595, 1580, 1490, 1200; pmr (see Table 1); cmr (see Table 2). Anal. calcd. (C₁₇H₂₀O₂S): C 70.84, H 6.93. Found: C 70.40, H 7.14.

3-Chloro-3-methylbutan-2-one was prepared by the method of Wyman and Kaufman¹⁰³ in 60% yield, bp. 143-145°C.

**General Procedure for the Alkylation of N-Acetylcysteine.**

The procedure of Field¹⁵⁸ was followed.

**Compound 8**: yellowish crystals (60%), mp. 117-120°C.¹⁵⁸

**Compound 9**: yellow oil (68%); ir (neat) cm⁻¹: 3600-2600, 1720, 1565, 1425, 1380, 1250; pmr (DMSO). ppm: 8.2 (bd, 1H), 4.4 (m, 1H), 3.45 (s, 2H), 2.8 (m, 2H), 2.2 (s, 3H), 1.85 (s, 3H). MS: 219(M⁺), 201, 165, 159.

**Compound 10**: white crystals (74%), mp. 131-133°C; ir (KBr) cm⁻¹: 3300-2600, 1715, 1695, 1620, 1545, 1460, 1380, 1260; pmr (DMSO) ppm: 8.3 (bd, 1H), 4.3 (m, 1H), 2.5 (m, 2H), 2.2 (s, 3H), 1.85 (s, 3H), 1.35 (s, 2H); cmr (DMSO) ppm: 205.3, 171.6, 169.2, 52.2, 51.8, 30.3, 23.9, 23.6, 22.2. MS: 247(M⁺), 248, 202. Anal. calcd. (C₁₀H₁₇NO₄S): C 48.59, H 6.87. Found: C 48.45, H 6.63.

**General Procedure for the Alkylation of N-Acetylhomocysteine.**

The same procedure as for the alkylation of N-acetylcysteine was used except that the N-acetylhomocysteine thiolactone and α-chloroketones were dissolved in 2-propanol.
Compound 20: white crystals (50%), mp. 151-152°C; ir (KBr) cm⁻¹: 3600-3200, 1710, 1655, 1560, 1450, 1385, 1245; pmr (see Table 5); cmr (DMSO) ppm: 205.5, 173.1, 169.5, 52.4, 51.0, 31.0, 25.2, 24.1, 23.7, 22.4. MS: 261(M⁺), 218, 156, 143. Anal. calcd. (C₁₁H₁₉NO₄S): C 50.58, H 7.27. Found: C 50.31, H 7.04.

Compound 21: yellow oil (84%); ir (neat) cm⁻¹: 3400-2500, 1710, 1660, 1555, 1440, 1325, 1300, 1240; pmr (see Table 5); cmr (DMSO) ppm: 203.8, 173.1, 169.4, 58.1, 50.8, 41.3, 30.7, 27.8, 22.2. Anal. calcd. (C₉H₁₅NO₄S): C 46.36, H 6.43, N 6.00. Found: C 46.56, H 6.80, N 6.02.

General Procedure for the Cyclization of Acids 8-10, 20, and 21. Field’s method⁵⁸ was followed.

Compound 11: yellow solid (52%), mp. 135-138°C.⁵⁸

Compound 12: yellow oil (50%); unpurified 12 used to yield 16.

Compound 13: white crystals (15%), mp. 211-213°C; ir (KBr) cm⁻¹: 3400-2600, 1760, 1740, 1660, 1570, 1260; pmr (DMSO) ppm: 8.05 (s,1H), 3.6-2.9 (m,4H), 2.05 (s,3H), 1.9 (s,3H), 1.5 (s,3H); cmr (DMSO) ppm: 169.9, 169.6, 169.4, 87.1, 71.4, 36.1, 32.7, 25.5, 21.8, 18.9. MS: 261(M⁺), 157, 60. Anal. calcd. (C₁₀H₁₅NO₅S): C 45.99, H 5.74, N 5.36. Found: C 45.65, H 5.77, N 5.49.
Compound 14: yellow oil (25%); ir (CHCl₃) cm⁻¹: 3600-2700, 2990, 1715, 1465, 1440, 1375, 1270, 1110; pmr (CDCl₃) ppm:
2.35 (s, 3H), 2.3 (dd, 2H, J=2.2Hz), 1.5 (s, 6H), 1.45 (s, 3H).

Compound 22: the crude oil was oxidized directly to sulfone 23.

Compound 24: yellow oil (35%); ir (CHCl₃) cm⁻¹: 3500-2500, 1720, 1670, 1605, 1575, 1440, 1375, 1270; pmr (CDCl₃) ppm:
2.65-2.05 (m, 4H), 2.35 (s, 3H), 2.3 (s, 3H), 1.45 (s, 6H).
MS: 243(M⁺), 199, 185, 159. Anal. calcd. (C₁₁H₁₇NO₃S):

Oxidation of 11 to 15. The method of McIntosh and Sieler was followed.

Compound 15: yellow crystals (68%), mp. 157-159°C; ir (CHCl₃) cm⁻¹: 3420, 1700, 1670, 1500, 1310, 1115; pmr (see Table 4).
MS: 229(M⁺), 165. Anal. calcd. (C₁₀H₁₅NO₃S): C 52.40, H 6.55, N 6.11. Found: C 51.96, H 6.36, N 6.31. Sulfoines 16 and 23 were prepared in an analogous manner.

Compound 16: white crystals (42%), mp. 151-152°C; ir (CHCl₃) cm⁻¹: 1720, 1330, 1260, 1130, 1010; pmr (see Table 4); cmr (DMSO) ppm: 171.4, 135.0, 128.6, 59.3, 55.6, 25.3, 13.2.
MS: 231(M⁺), 188. Anal. calcd. (C₉H₁₃NO₄S): C 46.76,
**Compound 23:** yellow crystals (45%), mp. 181-182°C; ir (CHCl₃) cm⁻¹: 1710, 1580, 1420, 1370, 1325, 1295; pnmr (CDCl₃) ppm: 3.65 (s, 2H), 3.35-2.5 (m, 4H), 2.35 (s, 6H), 1.6 (s, 3H); cmr (CDCl₃) ppm: 171.9, 151.7, 127.8, 67.1, 53.7, 47.3, 29.1, 25.5. MS: 245 (M⁺), 202, 186. Anal. calcd. (C₁₀H₁₅NO₄S): C 48.99, H 6.12, N 5.71. Found: C 48.84, H 6.48, N 5.89.

**Diels-Alder Reaction of 15 and 16.** To a solution of 0.01 mol of sulfone 15 (or 16) and a small amount of hydroquinone in 50 mL of xylene was added 0.01 mol of maleic anhydride. The reaction mixture was heated at reflux overnight under nitrogen. The crude mixture was cooled and crystalline product precipitated.

**Compound 17:** yellow crystals (62%), mp. 213-215°C; ir (KBr) cm⁻¹: 3280, 1860, 1780, 1675, 1660, 1550, 1455, 1375; pnmr (see Table 4); cmr (DMSO) ppm: 173.3, 135.6, 110.2, 67.5, 45.4, 43.0, 42.4, 40.8, 39.9, 38.7, 37.8, 31.5, 29.5, 26.3. MS: 263 (M⁺), 261, 245, 222, 197.

**Compound 19:** white crystals (70%), mp. 162-163°C; ir (CHCl₃) cm⁻¹: 1860, 1790, 1720, 1445, 1430, 1375, 1270; pnmr (see Table 4); cmr (CDCl₃) ppm: 178.6, 178.2, 172.8, 172.5, 132.6, 128.8, 40.2, 39.8, 31.2, 29.6, 28.8, 26.7, 25.7. MS: 265 (M⁺), 223, 183. Anal. calcd. (C₁₃H₁₅NO₅): C 58.86, H 5.66, N 5.28. Found: C 58.52, H 5.56, N 5.68.
Hydrolysis of 17 to Diacid 18. 1.5g (0.006mol) of 17 was heated at reflux overnight with 40mL of 15% HCl. The reaction mixture was cooled and the diacid 18 precipitated as white crystals (54%), mp. 111-113°C; ir (KBr) cm⁻¹: 3200-2600, 1715, 1700, 1445, 1345, 1250; pmr (DMSO) ppm: 3.15-2.8 (m, 3H), 2.35-0.8 (m, 11H); cmr (DMSO) ppm: 182.2, 181.3, 173.1, 47.7, 45.3, 43.2, 42.3, 36.7, 31.1, 25.4, 25.1, 24.8. Anal. calcd. (Cl₂H₁₂O₅·H₂O): C 55.87, H 6.97. Found: C 56.06, H 7.22.

Diels-Alder Reaction of 2a with Isoprene. A mixture of 0.22g (0.001mol) of 2a and 0.1g (0.0015mol) of isoprene with a small amount of hydroquinone in 25mL of toluene was heated at reflux for 3h. The solvent was removed to yield 25 as a yellow oil (95%) which was pure to glc analysis. An analytical sample was purified using preparative thin layer chromatography (ether); ir (CHCl₃) cm⁻¹: 1730, 1650, 1460, 1380, 1270; pmr (CDCl₃) ppm: 5.3 (bs, 1H), 4.15 (qq, 4H, J = 7, 7Hz), 3.7 (s, 3H), 2.85-1.8 (m, 6H), 1.65 (s, 3H), 1.35 (t, 6H, J = 7Hz); cmr (CDCl₃) ppm: 171.2, 133.3, 118.7, 63.1, 62.8, 52.5, 50.7, 44.8, 28.4, 26.7, 25.9, 23.5, 16.6. Anal. calcd. (C₁₃H₂₃PO₅): C 53.82, H 7.92. Found: C 53.86, H 7.66.

Hydrolysis of 25. To a solution of 0.05g (0.00125mol) of NaOH in 5mL of absolute ethanol was added 0.28g (0.001mol) of crude ester 25. The mixture was heated at reflux for 3h
and the solvent was removed under reduced pressure. The residue was dissolved in water, acidified with hydrochloric acid and extracted with ether. The ether solution was dried and evaporated to yield white crystals of acid 26 (90%), mp. 134-135°C; ir (CHCl₃) cm⁻¹: 3500-2700, 1740, 1670, 1475, 1415, 1280, 1210; pmr (CDCl₃) ppm: 10.25 (bs, 1H), 5.25 (bs, 1H), 4.1 (qq, 4H, J = 7.7Hz), 2.7-1.85 (m, 6H), 1.6 (s, 3H), 1.3 (tt, 6H, J = 7.7Hz); cmr (CDCl₃) ppm: 172.7, 133.5, 118.2, 63.6, 63.4, 48.2, 46.8, 28.2, 26.8, 25.3, 23.4, 16.4. Anal. calcd. (C₁₂H₂₁PO₅): C 52.20, H 7.60. Found: C 52.16, H 7.57.

**Diethyl 4-Methyl-3-cyclohexen-1-ylphosphonate (27).** Heating 2.7g (0.01mol) of acid 26 at 200°C for 30 minutes yielded 27 as a yellow oil, which was purified using thin layer chromatography (ether) (70%); ir (CHCl₃) cm⁻¹: 3000, 1660, 1460, 1390, 1270, 1050; pmr (CDCl₃) ppm: 5.35 (bs, 1H), 4.15 (qq, 4H, J = 6.6Hz), 3.5 (m, 1H), 2.7-1.85 (m, 6H), 1.6 (s, 3H), 1.25 (tt, 6H, J = 6.6Hz); cmr (CDCl₃) ppm: 119.4, 118.7, 62.9, 61.4, 29.5, 28.2, 27.2, 26.6, 25.5, 23.4, 16.3. Anal. calcd. (C₁₁H₁₂PO₃): C 56.93, H 9.04. Found: C 57.09, H 9.23.

**Preparation of Methylphosphonic Acid Bis(dimethylamide).** To a cooled suspension of 32.6g (0.4mol) of dimethylamine hydrochloride in 125mL of diethyl ether was added 32g (0.4mol) of 50% NaOH and the mixture was stirred overnight.
at room temperature under nitrogen. The aqueous layer was separated and the organic fraction was dried over anhydrous magnesium sulfate for 15 min. The dried ether fraction was decanted, cooled to 0°C and 10g (0.075mol) of methylphosphonic acid dichloride was added. The resulting solution was stirred at 0°C for 1h and at room temperature for 3h. The precipitate of dimethylamine hydrochloride was removed by filtration and the filtrate evaporated. Distillation of the residue afforded 9.6g (85%) of methylphosphonic acid bis(dimethylamide), bp. 85-88°C/2.5 Torr.\textsuperscript{63}

\textit{a-Lithiomethylphosphonic Acid Bis(dimethylamide)} was prepared by the method of Corey and Kwiatkowski.\textsuperscript{51}

Reaction of \textit{a-Lithiomethylphosphonic Acid Bis(dimethylamide)}, with Methyl Chloroformate. To a stirred solution of 0.067mol of \textit{a}-lithiomethylphosphonic acid bis(dimethylamide) in 100mL of tetrahydrofuran was added 3.22g (0.035mol) of methyl chloroformate at -78°C and under nitrogen. Stirring was continued for 2h at -78°C and for 0.5h at room temperature. Water was added and the tetrahydrofuran evaporated. The aqueous solution was extracted with ether to remove the unreacted methylphosphonic acid bis(dimethylamide) and with chloroform to yield \textit{crude \textsuperscript{29}}. Distillation of \textsuperscript{29} afforded a pure colourless oil (30%), bp. 145-147°C/4 Torr; ir (CHCl\textsubscript{3}) cm\textsuperscript{-1}: 3000, 1735, 1460, 1290, 1200, 1170; pmr (CDCl\textsubscript{3}) ppm: 3.75 (s, 3H), 3.0 (d, 2H, J=18Hz), 2.65
(d,12H,J=10Hz); cmr (CDCl₃) ppm: 167.4, 52.0, 36.1, 31.2. MS: 208(M⁺), 177, 165, 150. Anal. calcd.

After neutralization of the aqueous solution with dilute hydrochloric acid, the water was evaporated at room temperature under reduced pressure to yield a crystalline residue, which was treated with a small amount of absolute ethanol. Crystals of lithium chloride were filtered off and the ethanol was evaporated to yield oily crystals of 31. Washing crude 31 with diethyl ether yielded pure white crystals of 31 (60%), mp. 48-50°C(dec.); ir (CHCl₃) cm⁻¹: 3600-3200, 2995, 1725, 1640, 1480, 1460, 1265, 1210; pmr (CDCl₃) ppm: 7.5 (bs,1H), 3.0 (d,2H,J=15Hz), 2.6 (d,12H,J=10Hz); cmr (CDCl₃) ppm: 178.6, 36.2, 35.5.

MS: 194(M⁺), 177, 167, 149. Correct analytical data could not be obtained because of the sensitive nature of this acid.

Preparation of 32 from α-Lithiomethylphosphonic Acid Bis(dimethylamide). The method of Corey and Kwiatkowski was adopted. To a solution of 0.067mol of α-lithiomethylphosphonic acid bis(dimethylamide) in tetrahydrofuran at -78°C was added 7.1g (0.067mol) of benaldehyde under nitrogen. After stirring at -78°C for 1.5h, 10mL of acetic anhydride was added. The reaction mixture was stirred at
room temperature for 1h, a small amount of water was added, and the mixture was extracted with methylene chloride to yield oily crystals of 32. Recrystallization from a pentane-ether solution afforded white crystals (87%), mp. 101-102°C; ir (CHCl₃) cm⁻¹: 3020, 3000, 1740, 1505, 1490, 1460, 1380, 1260, 1180; pmr (CDCl₃) ppm: 7.35 (m, 5H), 6.05 (m, 1H), 2.6 (d, 6H, J=10Hz), 2.45 (d, 6H, J=10Hz), 2.05 (s, 3H); cmr (CDCl₃) ppm: 193.4, 140.4, 128.6, 128.2, 126.7, 71.3, 35.8, 35.2, 22.4. MS: 298(M⁺), 254, 238, 212, 195. Anal. calcd. (C₁₄H₂₃N₂O₃): C 56.40, H 7.71, N 9.39. Found: C 56.16, H 7.84, N 9.20.

Attempted Transformations of 32. To a stirred solution of 0.5g (0.00167mol) of 32 in 10ml of dry tetrahydrofuran was added, while under nitrogen and at -78°C, 0.65ml (0.0017mol) of 2.6M solution of n-butyllithium in hexane. To this solution was added 0.2g of acetic anhydride. After stirring at -78°C for 1.5hr, 5ml of water was added, and the mixture was extracted with ether to afford the starting material. The same procedure was followed using acetyl chloride instead of acetic anhydride to afford dimethyl acetamide and decomposition products.

Diethyl Isopropenylphosphosphate (33) was prepared by the method of Griffin et al.⁶⁶ in 75% yield, bp. 85-87°C/2 Torr. The Diels-Alder reaction of 33 was carried out in a sealed tube in an autoclave in xylene at temperatures: 180°C/20h, 160°C/12h, 160°C/18h, and 160°C/72h with a small amount of hydroquinone. The crude mixture was purified using thin
layer chromatography (pentane). Two fractions, soluble
(dimethyl substituted, 1,3-cyclohexadiene\textsuperscript{104} and nonsoluble
(diethyl ester of phosphoric acid) in pentane were separated
and identified by comparison of their spectra with published
data.\textsuperscript{104}

\textbf{N-(5-Carboxypentyl-2-piperidinone (38).} Ethyl 6-bromo-
hexanoate (35) was prepared from \(\varepsilon\)-caprolactone by saturating
an ice-cold ethanolic solution of the lactone with hydrogen
bromide, allowing the mixture to stir at ambient temperature
overnight, pouring onto ice and extracting with dichloro-
methane. Distillation afforded a 44\% yield of the bromoester,
bp, 69-72°C/0.13 Torr.\textsuperscript{105} Alternatively, the bromoester could
be purified using silica gel chromatography and 3:1 petroleum
ether - ether as eluent. Using this procedure, the yield of
pure product was 56\%; ir (CHCl\(_3\)) cm\(^{-1}\): 2950, 2880, 1730,
1465, 1380; pmr (CDCl\(_3\)) ppm: 4.2 (q, 2H, J=8Hz), 3.5 (t, 2H, J=7Hz),
2.6-1.1 (m, 8H), 1.25 (t, 3H, J=8Hz); cmr (CDCl\(_3\)) ppm: 173.1,
60.1, 34.0, 33.2, 32.6, 27.7, 24.2, 14.3. MS: 223(M\(^+\)), 172,
150, 149, 143.

The bromoester 35 (6.5g, 0.06mol) was heated to 195°C under
a nitrogen atmosphere and 10g (0.045mol) of 2-methoxypyridine
was added dropwise by syringe over 4h. Methyl bromide was
evolved. The mixture was heated at 195°C for 3h and then
stirred at ambient temperature overnight.

Distillation gave a large forerun consisting largely of
N-methylpyridone (bp. 66-67°C/0.15 Torr). The desired product,
\textbf{N-(5-carbethoxypentyl)-2-pyridone 36} remained as the residue
after removal of this fraction. The crude material (6.9g, 64%) was used directly in the succeeding step; pmr (CDCl₃) ppm: 7.6 (m,2H), 6.8 (dd,1H, J=1.8Hz), 6.45 (dt,1H, J=1.6Hz), 4.15 (m,4H), 2.5-1.2 (m,8H), 1.25 (t,3H, J=7Hz).

The crude ester 36 (6.0g, 0.025mol) was dissolved in 30mL of ethanol and hydrogenated at one atmosphere pressure over platinum oxide. Hydrogen absorption was complete in 6h. Filtration and evaporation afforded 6.0g (100%) of N-(5-carbethoxypentyl)-2-piperidinone (37) as a clear liquid which was pure according to glc analysis; pmr (CDCl₃) ppm: 4.2 (q,2H, J=7Hz), 3.7-3.02 (m,4H), 2.6-2.1 (m,4H), 2.1-1.1 (m,10H), 1.25 (t,3H, J=7Hz).

The amidoester 37 (5.5g, 0.023mol) was dissolved in 25mL of ethanol and a solution of 1.85g (0.033mol) of KOH in 10mL of water was added. The mixture was stirred at ambient temperature overnight, evaporated, diluted with water and extracted with ether. The aqueous phase was acidified and extracted with chloroform (4x75mL). The extracts were dried and evaporated, the last traces of solvent being removed at 0.05 Torr. The white solid remaining (38) (3.5g, 71%) had mp. 72-74°C; ir (CHCl₃) cm⁻¹: 3500-2400, 1715, 1630, 1510, 670; pmr (CDCl₃) ppm: 10.7 (s,1H), 3.6-3.2 (m,4H), 2.5-2.0 (m,4H), 2.0-1.2 (m,10H); cmr (CDCl₃) ppm: 177.2, 170.5, 48.0, 47.3, 34.1, 32.0, 26.7, 26.4, 24.7, 23.6, 21.2. MS: 213(M⁺), 169, 127. Anal. calcd. (C₁₁H₁₉NO₃): C 61.95, H 8.98, N 6.57. Found: C 62.16, H 9.37, N 6.36.
3-(3-Carboxypropyl)-2-piperidinone (46). To a mixture of 6.9g of potassium t-butoxide (0.061mol) in 50mL of t-butyl alcohol was added 10.5g (0.061mol) of 3-carbethoxy-2-piperidinone. The solution was stirred at ambient temperature for 40 min and then ethyl 4-bromobutyrate (11.9g, 0.061mol) was added dropwise. After stirring overnight the solution was refluxed for 30 min, evaporated, diluted with chloroform, washed once with water, dried and evaporated. The residue was treated with petroleum ether and filtered to remove residual starting material. Evaporation of the filtrate gave 9.4g (54%) of a colourless oil [3-carbethoxy-3-(3-carbethoxypropyl)-2-piperidinone] (44) which was purified using silica gel chromatography (ether); ir (CHCl₃) cm⁻¹: 3420, 3015, 1730, 1670, 1470, 1380, 1360, 1250, 1200; pmr (CDCl₃) ppm: 7.7 (s, 1H), 4.2 (qq, 4H, J=7Hz), 3.6-3.2 (m, 2H), 2.5-1.7 (m, 10H), 1.25 (t, 3H, J=7Hz); cmr (CDCl₃) ppm: 172.2, 171.9, 170.1, 60.2, 59.2, 52.6, 41.1, 33.9, 33.5, 28.7, 19.1, 18.8, 13.1. MS: 285(M⁺), 241, 240, 171. Anal. calcd. (C₁₄H₂₃NO₅): C 58.96, H 8.06, N 4.91. Found: C 58.61, H 8.00, N 4.90.

The diester 44 (7.35g, 0.025mol) was heated at reflux with 30mL of 50% NaOH for 2h. The cooled solution was diluted with water, washed with chloroform, acidified and evaporated to dryness. The residue was slurried with absolute ethanol and filtered. The filtrate was evaporated to give 3-carboxy-3-(3-carboxypropyl)-2-piperidinone (45) (5.4g, 95%) as white crystals, mp: 181-183°C; ir (KBr) cm⁻¹: 3400-2600, 1720, 1650, 1620, 1470, 1440, 1300, 810; pmr (DMSO) ppm: 8:2 (bs, 1H), 2.7 (m, 2H), 2.3-1.2 (m, 10H).
The diacid 45 (5.0g, 0.021mol) was heated at 180-190°C for 5h. Carbon dioxide was evolved. The yellow oil was purified by silica gel chromatography (ethanol/methylene chloride) to give 3.6g (97%) of acid 46; ir (neat) cm⁻¹: 3500-2500, 1740, 1630, 1510, 1455, 1400, 1280, 1200, 1060, 880; pmr (D₂O) ppm: 3.4 (m,2H), 2.9 (m,3H), 2.6-1.9 (m,8H).

3-(3-Carboxypropyl)-1-methyl-2-piperidinone (50). Sodium hydride (0.021mol) which had been washed three times with hexane was added to a solution of 2.37g (0.021mol) of N-methyl-2-piperidinone in toluene (40mL) and the mixture was refluxed overnight. To the cooled mixture was added dropwise 4.3g (0.022mol) of ethyl 4-bromobutyrate and the mixture was refluxed overnight. The cooled solution was filtered and the residue washed with chloroform. The combined filtrates were evaporated to give 3.8g (80%) of the ethyl ester of 49 as a colourless oil, which was pure according to glc analysis; ir (neat) cm⁻¹: 2810, 1740, 1480, 1425, 1210, 1100; pmr (CDCl₃) ppm: 4.15 (q,2H,J=7Hz), 3.7 (t,1H,J=6Hz), 3.3 (m,2H), 2.95 (s,3H), 2.7-1.5 (m,10H), 1.25 (t,3H,J=7Hz). MS: 227(M⁺), 171, 158.

The ester 49 (3.4g, 0.017mol) was hydrolyzed using 25mL of 50% NaOH at ambient temperature for 3 days. The basic solution was washed once with chloroform, acidified, evaporated to dryness and worked up as described for 45.
to give 3.1g (92%) of 50 as a colourless oil which crystallized on standing to give oily crystals, mp. 40-43°C; ir (KBr) cm⁻¹: 3300-2500, 1735, 1660, 1470, 1435, 1230, 1200, 1100; pmr (CDCl₃) ppm: 4.1 (q, 2H, J=7Hz), 3.2 (m, 2H), 2.3 (m, 3H), 1.7 (m, 4H), 1.25 (t, 3H, J=7Hz); cmr (D₂O) ppm: 178.4, 160.1, 62.3, 58.2, 49.5, 34.1, 33.7, 25.7, 22.1, 18.0. MS: 172, 159, 144, 44 (100%).

**General Procedure for Soda-Lime Pyrolyses.** The procedure was the same in all cases. The acid was thoroughly mixed with twice its weight of finely ground soda-lime. The soda-lime used contained an indicator which turned blue in the presence of carbon dioxide. Frequently the mixture became sticky and turned blue as soon as mixing began. The pasty mass was transferred to a flask which was fitted with a short path distillation apparatus and heated with a free flame. The contents of the flask turned blue, evolved carbon dioxide and then turned white again. Water distilled, followed by organic material (head temperature 140-200°C). After all the material had distilled, the two-phase distillate was diluted with ether, the phases were separated and the aqueous phase extracted with ether. The combined ethereal extracts were dried and evaporated to give the crude enamine which was treated with either 70% perchloric acid in absolute ethanol (1:1) or 10% hexachloroplatinic acid hydrate in absolute ethanol.
From 38, the enamine 39 was obtained in 49% crude yield. Glc analysis showed the enamine to constitute approx. 70% of the mixture; ir (CHCl₃) cm⁻¹: 2960, 1640; pmr (CDCl₃) ppm: 4.55 (bs, 1H), 3.3 (m, 4H), 2.5-2.1 (m, 12H); cmr (CDCl₃) ppm: 115.7, 65.7, 49.6, 48.0, 37.1, 33.6, 29.8, 26.0, 23.1. The perchlorate 40 was obtained in 30% yield from this mixture, mp. 150-152°C (from ethanol after precipitation from ether with ethanolic perchloric acid); ir (CHCl₃) cm⁻¹: 2950, 1680, 1470, 1450, 1100; pmr (CDCl₃) cm⁻¹: 2950, 1680, 1470, 1450, 1100; pmr (CDCl₃) ppm: 3.6 (m, 4H), 2.55 (m, 4H), 1.5 (m, 10H); cmr (CDCl₃) ppm: 193.7, 59.7, 55.6, 37.2, 34.8, 29.1, 23.9, 21.3, 20.8, 16.7.


The mother liquors from 40 were made basic with a dilute NaOH and the organic fraction was separated, dried and solvent was removed. The crude oil, which rapidly darkened on contact with air, showed one peak (110°C, 10% SE-30) and was 90% pure according to glc analysis. The crude oil was purified using preparative thin layer chromatography (ether); ir (CHCl₃) cm⁻¹: 3400, 2960, 2940, 1710, 1500, 1460, 1265; pmr (CDCl₃) ppm: 7.2 (bs, 1H), 3.1-0.7 (m, 18H). MS: 169(M⁺), 112, 84, 55. The spectroscopic data for this product suggests the ring-opened aminoketone, which has not previously been reported.

From 6-acetamidohexanoic acid was obtained a mixture of a solid and liquid. The solid was removed by filtration of
an ether solution and shown to be 42 by mixed melting point and spectral comparison with an authentic sample. The remaining material was imine 41 (74%). The hexachloroplatinate had mp. 160-162°C (abs. ethanol); ir (KBr) cm⁻¹: 3480, 3230, 2960, 1720, 1590, 1485, 1390; pmr (DMSO) ppm: 7.5 (bs, 2H), 3.0-2.2 (m, 4H), 2.1 (s, 6H), 1.8-0.9 (m, 12H); cmr (DMSO) ppm: 43.3, 39.5, 39.3, 30.5, 27.5, 26.1, 23.5.

Anal. calcld. (C₁₄H₂₈N₂PtCl₆): C 26.68, H 4.16, N 4.44.
Found: C 26.11, H 4.87, N 4.56.

From 46, the crude enamine 47 was obtained in 61% yield. From this mixture, the hexachloroplatinate 48 was obtained in 15% yield as a yellow solid, mp. 162-163°C; ir (KBr) cm⁻¹: 3190, 2990, 1630, 1500, 1100; pmr (DMSO) ppm: 7.4 (s, 2H), 3.6 (m, 4H), 2.9 (m, 4H), 2.3-1.3 (m, 18H). FDMS: m/z=124. Correct analytical data could not be obtained because of the highly hygroscopic nature of this salt.

From 50, the enamine(s) 51 were obtained in 78% yield. Glc analysis showed this material to be 90% pure, but attempts to isolate salt 52 were unsuccessful because of its extremely hygroscopic nature; ir (CHCl₃) cm⁻¹: 2990, 2900, 1640, 1520, 1475, 1370, 1110; pmr (CDCl₃) ppm: 3.4 (m, 2H), 3.05 (s, 3H), 2.7-1.5 (m, 11H); MS: 137(M⁺).
REFERENCES


APPENDIX

Epoxidation of cis-1,4-Polyisoprene Using
tert-Butyl Hydroperoxide with
Molybdenum Catalysts

Report to Polysar Ltd. on the research project
carried out during the course of a Co-op project, June 1982
to September 1982. Reprinted by permission of Polysar Ltd.,
Sarnia, Ontario.
Introduction

The metal-catalyzed epoxidation of olefins with hydrogen peroxide was first observed in the 1930's. In those years very little was known about the chemistry of alkyl hydroperoxides, which certainly were not readily available at that time.\(^1\) The alkyl hydroperoxide chemistry flourished in the 1950's and a variety of tertiary alkanes and aralkanes were autoxidized in the temperature range of 50-150°C to give the corresponding hydroperoxides. In the early sixties Brill and Indictor\(^2\) were studying the reaction of tert-butyl hydroperoxide (TBHP) with olefins. They found that the reaction of 2,4,4-trimethylpent-1-ene with TBHP, at 25°C in the presence of catalytic amounts of hydrocarbon-soluble acetylacetonates of molybdenum, vanadium and chromium afforded the corresponding epoxide in high yields ([eq. 1]).

\[
[1] \quad (\text{CH}_3)_3\text{CO}_2\text{H} + (\text{CH}_3)_3\text{C} \xrightarrow{\text{cat.}} (\text{CH}_3)_3\text{C}^\text{O} + (\text{CH}_3)_3\text{COH}
\]

Hallcon and Atlantic Richfield\(^1\) also investigated the epoxidation of olefins with alkyl hydroperoxides and sought patent protection for their process. This process produced epoxides, in particular propylene oxide, by using
alkyl hydroperoxides in the presence of soluble compounds of molybdenum, vanadium, tungsten, titanium, zirconium, tantalum and other metals. Soluble molybdenum compounds gave the highest yields and selectivity. This finding was rapidly developed into a commercial process for the manufacture of propylene oxide.

When one considers the combined features of economics, selectivity and safety, TBHP emerges as one of the best sources of oxygen atoms for an epoxidation of olefins. TBHP is superior to better known sources of oxygen atoms such as hydrogen peroxide and peracetic acid. The key advantage of TBHP is its selectivity. In contrast to hydrogen peroxide and peracetic acid, TBHP is unreactive towards most organic compounds in the absence of catalysts. TBHP is less sensitive to contamination by metals than either peracetic acid or hydrogen peroxide, and on this basis is safer to handle. In dilute organic solutions TBHP has a high thermal stability (its half-life is 36 days at 115°C as a 0.2M solution in benzene). Hydrogen peroxide is, in principle, also very thermally stable, but it is more sensitive to decomposition catalyzed by trace metallic impurities than is TBHP. Peracetic acid is on every count less stable than TBHP.³

The formation of epoxides of cis-1,4-polyisoprene is well known by using m-chloroperbenzoic acid,⁴ performic acid (prepared in situ from hydrogen peroxide and a small
amount of formic acid), \(^5\) peracetic acid, perbenzoic acid and monoperphthalic acid. \(^6\) For large-scale epoxidations where cost and safety become important considerations, the attempt of the epoxidations of cis-1,4-polyisoprene by TBHP in the presence of molybdenum catalysts (e.g., \(\text{MoO}_3\) on silica and \(\text{Mo(CO)}_6\)) was necessary and important.

Epoxidation Using TBHP in the Presence of \(\text{MoO}_3\).

The reactions of TBHP in the presence of metal catalysts can be divided into two groups:

i) homolytic
ii) heterolytic.

Homolytic decomposition of TBHP ([eq. 2]) is catalyzed by transition metal complexes and involves t-butoxy and t-butyleroxy radicals as reactive intermediates, formed via the following reaction:

\[
[2] \quad 2 \text{RO}_2\text{H} \xrightarrow{\text{Catalyst}} \text{RO}_2^− + \text{RO}^− + \text{H}_2\text{O}
\]

In heterolytic reactions of TBHP the principal function of the metal catalyst is to withdraw electrons from the O-O bond, via coordination, thus making it more susceptible to heterolysis by attacking nucleophiles (e.g., olefins). The catalysts used for the selective heterolysis of TBHP by olefins are Lewis acids (e.g., complexes of metals in high oxidation states), but weak oxidizing agents (low oxidation potential in highest oxidation state). In the original investigations \(^1\) of this process, it was found
that hydrocarbon soluble complexes of molybdenum, such as Mo(CO)$_6$ were the most effective catalysts. Although insoluble catalytic precursors could be used, e.g., MoO$_3$, their reactivity was generally assumed to result from their dissolution in the presence of the TBHP. The reaction occurs in the liquid phase and involves homogenous catalysis. The suggested mechanism for the oxygen transfer step involves the metal peroxide as the active species.$^1$

\[
\begin{align*}
\text{CH}_2\text{CH}_2 + \text{OH} &\rightarrow \text{CH}_2\text{CH}_2\text{OH} \\
\rightarrow \text{RO}_2\text{H} &\rightarrow \text{OH} \\
\end{align*}
\]

Trifiro and co-workers$^1$ examined the activity of various molybdenum oxide-based catalysts in the epoxidation of cyclohexene with TBHP. Supporting MoO$_3$ (on silica) led to a significant increase in activity. In contrast, the activity of MoO$_3$ was destroyed when it was supported on γ-Al$_2$O$_3$ or on MgO. It was further shown that the activity
of the MoO₃ (on silica) catalyst was almost entirely due to rapid leaching of the molybdenum from the surface to give a soluble molybdenum catalyst. The function of the silica support is primarily to promote the dissolution of the catalyst by dispersing the MoO₃, and, hence, increasing the number of reactive centres available for interaction with the hydroperoxide.¹

A few attempts were undertaken to epoxidize the cis-1,4-polyisoprene with TBHP and MoO₃ (on silica) as a catalyst. The rate of epoxidation was rather low and slow. The unsaturation of the starting material and the product were tested by using the standard test method for iodine value of drying oils and fatty acids,⁷ the standard test method for epoxy content of epoxy resins,⁸ and pmr technique.⁵ In the case of a solid type of an epoxy product only pmr technique was used to count the percentage of epoxy content.
Experimental Results of Epoxidation of 
cis-1,4-Polyisoprene with TBHP/MoO₃ 
(on silica)

<table>
<thead>
<tr>
<th>Ratio of Olefin: TBHP</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Epoxy Content</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>room temp.</td>
<td>3h</td>
<td>0</td>
<td>starting material</td>
</tr>
<tr>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>41°C</td>
<td>20h</td>
<td>0</td>
<td>starting material</td>
</tr>
<tr>
<td>1:2</td>
<td>cyclohexane</td>
<td>81°C</td>
<td>4h</td>
<td>3.2%</td>
<td>colourless oil</td>
</tr>
<tr>
<td>1:2</td>
<td>cyclohexane</td>
<td>81°C</td>
<td>20h</td>
<td>7.7%</td>
<td>colourless oil</td>
</tr>
<tr>
<td>1:2</td>
<td>cyclohexane</td>
<td>81°C</td>
<td>40h</td>
<td>19.2%</td>
<td>colourless oil</td>
</tr>
</tbody>
</table>

aData. Bp. of dichloromethane is 41°C.

bBp. of cyclohexane is 81°C.

Epoxidation of cis-1,4-Polyisoprene with TBHP and Mo(CO)₆ as a Catalyst

Sheldon and Van Doorn⁹ made a detailed study of the epoxidation of cyclohexane with TBHP in the presence of a wide variety of catalysts. Soluble molybdenum complexes, such as Mo(CO)₆, were shown to be the most effective catalysts. The results were consistent with a reaction scheme involving competing metal-catalyzed epoxidation and metal-catalyzed homolytic decomposition of the hydroperoxide.
If the catalyst is added as a complex in a low oxidation state (e.g., Mo(CO)₆) it is initially oxidized by the hydroperoxide to its highest oxidation state ([eq. 3]), which is the active catalyst ([eq. 4]).

\[
\text{Catalyst activation: } \text{Mo(CO)}_6 + \text{RO}_2\text{H} \rightarrow \text{Mo}^{+6} \text{RO}_2\text{H} \\
[3]
\]

\[
\text{Complex formation: } \text{Mo}^{+6} + \text{RO}_2\text{H} \rightleftharpoons [\text{Mo}^{+6}\text{RO}_2\text{H}] \\
\text{Mo}^{+6}\text{RO}_2\text{H} + \begin{array}{c}
\text{CH}_2 \\
\text{CH}_2
\end{array} \rightarrow [\text{Mo}^{+6}\text{ROH}] + \begin{array}{c}
\text{CH}_2 \\
\text{CH}_2
\end{array} \\
[4]
\text{[Mo}^{+6}\text{ROH} + \text{RO}_2\text{H}] \rightleftharpoons [\text{Mo}^{+6}\text{RO}_2\text{H}] + \text{ROH}
\]

The attempt of the epoxidation of cis-1,4-polyisoprene with TBHP and Mo(CO)₆ as a catalyst was undertaken because of the unsatisfactory results with MoO₃ (on silica). The higher solubility of Mo(CO)₆ in hydrocarbons could improve the results of epoxidation. After a few attempts with Mo(CO)₆ as the catalyst, it was obvious that the results were very promising.
Experimental Results of Epoxidation of
cis-1,4-Polyisoprene with TBHP and
Mo(CO)₆ in Cyclohexane

<table>
<thead>
<tr>
<th>Ratio of Olefin: TBHP</th>
<th>Time of Reflux</th>
<th>Epoxy Content (%)</th>
<th>Yield (%)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:2</td>
<td>2h</td>
<td>15.1</td>
<td>70</td>
<td>colourless oil</td>
</tr>
<tr>
<td>1:2</td>
<td>4h</td>
<td>17.6</td>
<td>79</td>
<td>colourless oil</td>
</tr>
<tr>
<td>1:2.6</td>
<td>20h</td>
<td>65.6</td>
<td>97</td>
<td>white resin</td>
</tr>
<tr>
<td>1:1</td>
<td>20h</td>
<td>72.0</td>
<td>30</td>
<td>white resin</td>
</tr>
</tbody>
</table>

Experimental

The commercially available TBHP-90% (Aldrich) contains 5% H₂O and 5% tert-buetyl alcohol. Water is deleterious to the epoxidation, for it not only inhibits the reaction, but also gives rise to epoxide opening which produces diols as by-products. It was found that in this case epoxidation of cis-1,4-polyisoprene can be carried out efficiently by operating in nonreactive solvents (e.g., cyclohexane) and using 90% TBHP. In this study, isolene D-40 (Hardman Inc.) was used as a source of cis-1,4-polyisoprene. Isolene D-40 is a clear flowable reactive elastomer made from virgin polyisoprene. Chemically, it is a cis-1,4-polyisoprene of low molecular weight and it has a viscosity of 140,000 (Brookfield) at 25°C. It is more easily handled when warm, as its viscosity decreases
rapidly with an increase in temperature. The use of a small amount of anhydrous disodium hydrogen phosphate \( \text{Na}_2\text{HPO}_4 \) reduces the formation of by-products (at present there is no explanation of the effect of \( \text{Na}_2\text{HPO}_4 \)). The complete experimental details for the epoxidation of cis-1,4-polyisoprene are presented below.

A 500mL, 3 necked, round-bottomed flask was equipped with a magnetic stirring bar, a reflux condenser and a constant addition funnel. The flask was charged with 200mL of cyclohexane, 3.88g (0.057mol monomer unit) of cis-1, 4-polyisoprene, 0.1g of \( \text{Mo}(\text{CO})_6 \), and approximately 0.5g of \( \text{Na}_2\text{HPO}_4 \) (powder). The constant addition funnel was charged with a 50mL solution of 90\% TBHP (17mL of 90\% TBHP, 2.6mol) in cyclohexane. The stirred solution was brought to a gentle reflux and after 40 minutes, the TBHP solution was added dropwise. The reaction was monitored by using TLC plates (eluent, a mixture of diethyl ether and cyclohexane 1:1). The reaction mixture was then cooled to room temperature and about 50mL of 10\% \( \text{Na}_2\text{SO}_3 \) was added dropwise with stirring. The stirring was continued at room temperature until the organic phase gave a negative peroxide test using acidified starch-iodide test paper. The aqueous and organic phases were separated and the milky white organic layer was washed twice with 50mL portions of \( \text{H}_2\text{O} \) and once with 30mL of a saturated solution of \( \text{NaCl} \). The organic layer was then treated with 50mL of methanol to
afford a product which was washed twice with methanol and vacuum dried.

Summary

One of the major goals of petrochemical research is the development of processes for the conversion of olefin feedstocks into useful oxygen-containing derivatives such as epoxides, so this project shows promise for a new epoxidation approach. Epoxidized cis-1,4-polyisoprene can be used as an effective stabilizing and plasticizing agent for the production of various types of rubbers and plastics. Due to the problems involved in handling and storage of the peracids and hydrogen peroxide, which are commonly used to epoxidize cis-1,4-polyisoprene, this promising alternative using TBHP and Mo(CO)$_6$ in cyclohexane has a number of advantages. TBHP is readily prepared via autoxidation of cheap isobutane and is much less explosive than organic peracids. Reactions are performed in cyclohexane at moderate temperatures (81°C). Under these conditions and by using small amounts of Na$_2$HPO$_4$, there is no formation of by-products. In agreement with the findings of other workers, the best catalyst proved to be the homogeneous Mo(CO)$_6$. The rate of epoxidation is 65-72% (epoxy content) with yields 70-97%.

The results of this experimental work demonstrates that the epoxidation of cis-1,4-polyisoprene by using TBHP/MO(CO)$_6$ in cyclohexane can be extended to the in-
References


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