PART I: PHASE-TRANSFER REACTIONS OF ENONES. PART II: SYNTHETIC APPLICATIONS OF DIHYDROTHIOPYRANS.

DAVID WILLIAM. PILLON

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PART I: PHASE-TRANSFER REACTIONS OF ENONES

PART II: SYNTHETIC APPLICATIONS OF DIHYDROTHIOPYRANS

BY

DAVID WILLIAM PILLO

A DISSERTATION

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

Windsor, Ontario
1981
To my Mother and Father
ABSTRACT

Self-condensation of crotonaldehyde under base-catalyzed phase-transfer conditions leads to 4,6-dimethyl dihydropyran-carboxaldehyde or dihydro-o-tolualdehyde, depending only on the concentration of aqueous hydroxide used. Dihydro-o-tolualdehyde is formed when the hydroxide concentration is between 70% (17.5N) and 25% (6.25N). 4,6-Dimethyl dihydropyran-carboxaldehyde first appears at a hydroxide concentration 30% (7.5N) and it continues to be produced at concentrations as low as 5% (1.25N). The range, over which the product completely changes from one to the other, is small (30% NaOH to 25% NaOH). It appears that, as the hydroxide concentration decreases, the water concentration in the organic phase is sufficient to alter the action of the organic phase hydroxide from that of a base to that of a nucleophile. Mixed condensations using this phase-transfer technique are also reported. Self-condensation of senecioaldehyde under phase-transfer conditions leads to 4,6,6-trimethyl-1,3-cyclohexadienecarboxaldehyde. This product is used in an attempted synthesis of an isomer of β-damascenone.

Dihydrothiopyrans are reacted with methyl diethylphosphonoacetate in order to produce dienes suitable for use in Diels-Alder reactions. Several attempts using these dienes
with maleic anhydride in a Diels-Alder type reaction are reported.

A simple synthesis of N-chlorinated secondary amines, using commercial swimming pool bleach (~12.5% NaOCl), under phase-transfer conditions is reported.
Acknowledgements

This dissertation has been a time-consuming but always interesting project. Many people have assisted very ably and I wish to acknowledge their efforts.

First, I express sincere appreciation to my research advisor, Dr. John M. McIntosh, who gave me direction, guidance and encouragement at all times. I shall always be grateful to him.

Without the assistance of my labmates, this project would have been much more difficult. On many occasions, their suggestions and discussions were very helpful.

I further wish to thank Mr. Bob Charleton and Mr. Al Thibert for their technical assistance with the mass spectrometer and Mr. Mike Fuerth for his technical assistance with the NMR and IR instruments.

Finally, I am indebted to Mrs. June Stibbard for her patience and consideration while typing this dissertation.
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Phase-Transfer Reactions of Enones

Chapter 1

Introduction

Chemists often encounter the problem of bringing together two mutually insoluble reagents in sufficient concentration to produce a chemical reaction. The simplest solution to this problem is the use of a solvent which can dissolve both reagents. In some cases this may not be practical. For this reason the technique of phase-transfer catalysis\(^1\)\(^-\)\(^7\) has become a useful tool in organic chemistry. Under phase-transfer conditions the problems arising from heterogeneous reaction mixtures, where water-soluble reagents must react with water insoluble organic compounds, are avoided. The rates of such heterogeneous reactions are greatly enhanced by the addition of catalytic amounts of an agent which transfers the water soluble reagent across the interface into the organic phase where a homogeneous reaction can take place.

All phase-transfer catalyzed reactions involve at least two steps:

1) transfer of one reagent from its "normal" phase into the second phase and

2) reaction of the transferred reagent with the nontransferred reagent.
The mechanism of the phase-transfer catalysis can be depicted as in Scheme 1.

\[
\begin{align*}
\text{Aqueous Phase} & : Q^+X^- + \text{Nu}^- \leftrightarrow [Q^+\text{Nu}^-] + X^- \\
\text{Organic Phase} & : [Q^+X^-] + \text{NuB} \leftrightarrow [Q^+\text{Nu}^-] + \text{BX},
\end{align*}
\]

Scheme 1

The water soluble nucleophile, \( \text{Nu}^- \), is transferred as an ion pair, \( Q^+\text{Nu}^- \), into the organic phase when the phase-transfer catalyst, \( Q^+X^- \), is added. A homogeneous reaction will occur in the organic phase between the organic substrate, \( \text{BX} \), and the ion pair, \( Q^+\text{Nu}^- \), as shown in equation 1.

\[
Q^+\text{Nu}^- + \text{BX} \rightarrow \text{B-Nu} + Q^+X^- \quad (1)
\]

The cycle is completed with the return of the ion pair, \( Q^+X^- \), to the aqueous phase. The reaction will proceed until an equilibrium is reached or one of the reactants has been consumed. In order to have successful catalysis the partition coefficient:

\[
K = \frac{Q^+\text{Nu}^-_{\text{org.}}}{Q^+\text{Nu}^-_{\text{aq.}}}
\]

of the ion pair, \( Q^+\text{Nu}^- \), between the aqueous and organic phases should be larger than that of \( Q^+X^- \).

The most widely used phase-transfer catalysts are quaternary ammonium and phosphonium salts. Structural features influence the catalytic activity of quaternary
salts (e.g., $R_4N^+X^-$) to a significant degree.

The first requirement of the substituents $R$ is that they collectively have enough organic character to transfer the desired anion into the organic phase. Small changes in the carbon structure can have large effects on the partition coefficient. This was illustrated by Gibson and Weatherburn\(^9\) (Table I) who studied the effect of chain length on partition coefficients of triphenylalkylphosphonium salts between chloroform and water. The coefficient increased by a factor of about 2 for each $-\text{CH}_2- \, \text{group added in a given series.}$

The number of carbon atoms is not the only organic structure effect of quaternary cations in phase-transfer catalysis\(^5\). Salts having one long alkyl group and three methyl or ethyl groups or one pyridyl group attracted to the quaternary centre are good emulsifiers but are frequently poor phase-transfer catalysts. The reason for this is that these compounds are prone to form micelles and remain in the aqueous phase or may form a third phase if the organic phase is relatively nonpolar. This was shown to be the case by Herriott and Picker\(^7\) (Table II) who used several quaternary ammonium hydroxides to demonstrate the greater transferability of cations having all four groups as butyl or larger.
TABLE I - Effects of Chain Length on Partition Coefficients of Triphenylalkylphosphonium Salts between Chloroform and Water\textsuperscript{9}.

<table>
<thead>
<tr>
<th>Cation</th>
<th>Cl\textsuperscript{−}</th>
<th>Br\textsuperscript{−}</th>
<th>I\textsuperscript{−}</th>
<th>NO\textsubscript{3}\textsuperscript{−}</th>
<th>SCN\textsuperscript{−}</th>
<th>ClO\textsubscript{4}\textsuperscript{−}</th>
<th>ClO\textsubscript{3}\textsuperscript{−}</th>
<th>BrO\textsubscript{3}\textsuperscript{−}</th>
</tr>
</thead>
<tbody>
<tr>
<td>((C\textsubscript{6}H\textsubscript{5})\textsubscript{3}PCH\textsubscript{3})\textsuperscript{+}</td>
<td>0.01</td>
<td>0.10</td>
<td>1.7</td>
<td>0.11</td>
<td>1.5</td>
<td>2.7</td>
<td>0.18</td>
<td>0.03</td>
</tr>
<tr>
<td>((C\textsubscript{6}H\textsubscript{5})\textsubscript{3}PC\textsubscript{2}H\textsubscript{5})\textsuperscript{+}</td>
<td>0.02</td>
<td>0.17</td>
<td>3.6</td>
<td>0.25</td>
<td>3.1</td>
<td>6.5</td>
<td>0.40</td>
<td>0.05</td>
</tr>
<tr>
<td>((C\textsubscript{6}H\textsubscript{5})\textsubscript{3}PC\textsubscript{3}H\textsubscript{7})\textsuperscript{+}</td>
<td>0.04</td>
<td>0.52</td>
<td>6.9</td>
<td>0.53</td>
<td>6.3</td>
<td>12.0</td>
<td>0.84</td>
<td>0.11</td>
</tr>
<tr>
<td>((C\textsubscript{6}H\textsubscript{5})\textsubscript{3}P-n-C\textsubscript{5}H\textsubscript{11})\textsuperscript{+}</td>
<td>0.188</td>
<td>1.7</td>
<td>9.5</td>
<td>2.2</td>
<td>16.0</td>
<td>25.0</td>
<td>3.0</td>
<td>0.51</td>
</tr>
</tbody>
</table>
TABLE II - Effect of Quaternary Ammonium Salt Structure on Extraction of $Q^+OH^-$ into Benzene

<table>
<thead>
<tr>
<th>Cation</th>
<th>Number of C Atoms</th>
<th>Partition Coefficient $(OH^-)<em>{ben.} / (OH^-)</em>{aq.}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(CH_3)_4^+N^+$</td>
<td>4</td>
<td>0.0027</td>
</tr>
<tr>
<td>$C_6H_5CH_2^+(C_2H_5)_3$</td>
<td>13</td>
<td>0.041</td>
</tr>
<tr>
<td>$(C_3H_7)_4^+N^+$</td>
<td>12</td>
<td>0.11</td>
</tr>
<tr>
<td>$C_{16}H_{33}^+(CH_3)_3$</td>
<td>19</td>
<td>0.15</td>
</tr>
<tr>
<td>$C_5H_5^+N^+C_{12}H_{25}$</td>
<td>17</td>
<td>0.18</td>
</tr>
<tr>
<td>$C_{10}H_{21}^+(C_2H_5)_3$</td>
<td>16</td>
<td>0.26</td>
</tr>
<tr>
<td>$C_{12}H_{25}^+(C_2H_5)_3$</td>
<td>18</td>
<td>0.54</td>
</tr>
<tr>
<td>$(C_4H_9)_4^+N^+$</td>
<td>16</td>
<td>0.68</td>
</tr>
</tbody>
</table>

The anion also can affect the ability of a catalyst cation to transfer. Anions are hydrated to different degrees depending mostly on their charge to volume ratio and the more the anion is hydrated the more strongly it will be attracted to the aqueous phase. Studies\textsuperscript{10} indicate that the water of hydration is transferred to the organic phase (Table III).
TABLE III - Degree of Hydration $n$ of Several Anions

<table>
<thead>
<tr>
<th>Anion, $X^-$</th>
<th>$n$ in $\text{H}_2\text{O}$</th>
<th>(C$<em>8$H$</em>{17}$)$_4$N$^+$X$^-$</th>
<th>(C$<em>8$H$</em>{17}$)$_3$C$_3$H$_7$N$^+$X$^-$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl$^-$</td>
<td>2.3</td>
<td>3.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Br$^-$</td>
<td>1.7</td>
<td>2.4</td>
<td>1.6</td>
</tr>
<tr>
<td>OH$^-$</td>
<td>5.2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Also any organic structure of the anion would add to the total organic character of the cation-anion pair, increasing the partitioning of the ion pair into the organic phase.

The general criteria for selecting a quaternary catalyst are as follows:

1) The larger quaternary ions are more effective than smaller ones.

2) The catalytic efficiency increases as the length of the longest chain increases.

3) The more symmetrical ions are more effective than those with only one long chain.

Our laboratory became interested in phase-transfer catalysis due to work on the reaction of $\beta$-mercaptoaldehydes with conjugated carbonyl compounds. This reaction yielded substituted thiacyclohexene-carboxaldehydes (2) by a conjugate addition - aldol condensation sequence (Scheme 2).
Two problems were encountered with the use of \( \beta \)-mercaptocarbonyl compounds. One was thermal decomposition during purification by distillation and the other was their unpleasant odours. Replacement of the thiol proton with a suitable protecting group which would permit formation of the thiolate anion \textit{in situ} was an attractive solution to these problems. The use of thiol acetates was investigated for this purpose.

\( 3 \)-Thioacetoxy carbonyl compounds are readily made by addition of thiolacetic acid to \( \alpha,\beta \)-unsaturated aldehydes and ketones\(^\text{12}\).
Basic hydrolysis should yield the thiolate anion needed for the initiation of the cyclization reaction.

When 3-thioacetoxybutanal (3) was treated with alcoholic sodium hydroxide, neutralization yielded some 3-mercaptobutanal (1) but a large amount of crotonaldehyde (5) was formed also (Scheme 4). Acid-catalyzed methanolation did afford 1 but the problem of purification again arose.
Under phase-transfer conditions the absence of solvation forces increases not only the basicity but also the nucleophilicity of water-soluble nucleophiles. This has been shown by Starks. 1-Bromooctane and aqueous sodium cyanide were stirred at 100°C for two weeks with only the hydrolysis of sodium cyanide to sodium formate occurring. By adding a catalytic amount of quaternary salt, the desired substitution reaction was complete in less than two hours, octyl cyanide being formed in 95% yield. Hydrolysis of
esters by aqueous sodium hydroxide can also be accelerated by quaternary ammonium salts.

Due to the success of the phase-transfer technique in hydrolyzing esters, it was decided by our laboratory to apply this process to generating the thiolate anion (4) in the presence of an acceptor molecule to produce the desired thiacycloclohexenecarboxaldehydes. The application of this technique to the basic hydrolysis of 3-thioacetoxybutanal (3) in methylene chloride using 50% sodium hydroxide in the presence of crotonaldehyde (5) and a catalytic amount of tetrabutylammonium iodide (TBAI) afforded 4,6-dimethyl-5-thiacycloclohexene-1-carboxaldehyde (6) in 84% yield (Scheme 5)\textsuperscript{13}. Also the phase-transfer reaction of 3-thioacetoxypropanal (7) and acrolein (8) produced 5-thiacycloclohexene-1-carboxaldehyde (9) in 85% yield (Scheme 5)\textsuperscript{13}.
It has been previously found in this laboratory\textsuperscript{11} that when the reaction between 3-mercaptobutanal (3) and acrolein (8) was carried out in pyridine solution, two products, 4-methyl-5-thiacycloc hexene-1-carboxaldehyde (10) and its 6-methyl isomer (11) were obtained. This can be explained by anion transposition (Scheme 6)\textsuperscript{11}. 
Scheme 6
The absence of 6 and 9 in these reactions indicated that reversal of the conjugate addition was not competing with ring closure in the pyridine solution. Work on related systems\textsuperscript{14} indicated that side reactions like anion transposition are maximized when the rate of ring closure of carbanionic intermediates is slow. The large amount of energy associated with removing water molecules from the strongly hydrogen-bonded aqueous phase of a 50% aqueous sodium hydroxide-dichloromethane system, suggested that the solvation of the catalyst-hydroxide ion pair in the organic phase should be minimal. Therefore the rate of cyclization should be greatly enhanced.

To see if similar results would be obtained under phase-transfer conditions, the phase-transfer catalyzed reaction of 3-thioacetoxybutanal (3) and acrolein (8) was performed. Three products 6, 9 and 10 (Scheme 7)\textsuperscript{13} were formed. The assumption concerning anion transposition thus proved correct since no trace of 11 could be detected. The reverse condensation was attempted yielding three products 6, 9 and 11 but now excluding 10 (Scheme 7)\textsuperscript{13}. 
\[
\text{CHO} + \text{CHO} \xrightarrow{50\% \text{ NaOH}} \text{CH}_2\text{Cl}_2 / \text{TBAI} \rightarrow \begin{array}{c}
\text{CHO} + \text{CHO} \\
\text{CHO} + \text{CHO} \\
\text{CHO} + \text{CHO}
\end{array}
\]

Scheme 7
Scheme 8
The absence of the products of alternate ring closure seemed to discount direct anion equilibration in this reaction. A possible explanation was that the thiol ester reacted with base in the organic phase in an elimination-hydrolysis competition leading to crotonaldehyde and the desired thiolate anion (4). Condensation of 4 with acrolein led only to 10 while condensation of 4 with crotonaldehyde produced 6. The thiolacetate anion then added to acrolein, 12 was hydrolyzed and reacted with acrolein forming 9 (Scheme 8)\textsuperscript{13}.

In order for this postulate to be valid, thiolacetic acid must add to acrolein and crotonaldehyde under phase-transfer conditions. The reaction was run with 2 equivalents of acceptor, 1 equivalent of thiolacetic acid and 2 equivalents of 50% sodium hydroxide under standard conditions. In each case, the expected product 6 (81% yield) and 9 (41% yield) was formed (Scheme 9)\textsuperscript{13}.

\[2\text{CHO} + \text{CH}_3\text{COSH} \rightarrow \text{CHO} \]

\[2\text{CHO} + \text{CH}_3\text{COSH} \rightarrow \text{CHO} \]

Scheme 9\textsuperscript{13}
The simple and economically feasible procedure\textsuperscript{15} by which \textsuperscript{6} and \textsuperscript{9} were obtained (Scheme 9) prompted us to consider the use of the phase-transfer technique in synthesizing other heterocycles. The replacement of thiolacetic acid with acetic acid could lead to the preparation of dihydropyrans. Acceptor molecules such as crotonaldehyde (Scheme 10), acrolein, methyl vinyl ketone and 3-methyl-2-butenal could be used. The use of phase-transfer catalysis in this reaction is the subject of Chapter 2 of this thesis.

\[
\begin{align*}
2 \overset{\text{CHO}}{\longrightarrow} & + \overset{\text{CH}_3\text{COOH}}{\longrightarrow} & \overset{50\% \text{ NaOH}}{\text{CH}_2\text{Cl}_2/\text{TBAI}} & \overset{13}{\longrightarrow} \\
5 & & & \\
\end{align*}
\]

Scheme 10
Chapter 2

Results and Discussion

It had been previously found by this laboratory\textsuperscript{13} that under phase-transfer conditions and using sodium hydroxide, thiolacetic acid and crotonaldehyde (5) the condensation product 4,6-dimethyl-5-thiacyclohexene-1-carboxaldehyde (6) could be obtained in 81% yield (Scheme 9). The success of this procedure led us to consider the possibility of employing the phase-transfer technique in the synthesis of other heterocycles. It appeared that the use of acetic acid in place of thiolacetic acid would afford dihydropyrans. Under phase-transfer conditions only one product was formed in this instance. The spectral data immediately showed that the formation of the expected dimethyl dihydropyrancarboxaldehyde (13) had not taken place but instead dihydro-o-tolualdehyde (14) was formed in 45% yield (Scheme 11).
The aldehyde (14) has been obtained previously\textsuperscript{16,17} from 5, in varying yields under a variety of conditions the best of which is Grundmann's\textsuperscript{17} who obtained 14 in 75% yield by heating 5 with dibutylamine for 5.5 hours. It should be further noted that 13, 14 and a variety of open chain compounds have been isolated from the acid-catalyzed dimerization of crotonaldehyde\textsuperscript{18,19}.

It was quickly shown that the use of acetic acid was unnecessary in this reaction since the same product (14) was obtained in its absence. It was known that oxygen anions are both harder and poorer nucleophiles than the
analogous sulfur anions\textsuperscript{20} and this result seemed to
demonstrate this characteristic since the hydroxide ion was
functioning as a base instead of a nucleophile.

The formation of 14 was interesting from a synthetic
point of view. It can be transformed into o-tolualdehyde\textsuperscript{17},
o-methylalkylbenzenes\textsuperscript{16} and it could possibly be used as a
diene for Diels-Alder reactions. For these reasons, a
study was undertaken to determine the optimum yield of this
reaction by varying the reaction conditions.

The standard procedure for the phase-transfer reactions
was as follows.

1) Aqueous sodium hydroxide, methylene chloride and
   the catalyst were cooled under nitrogen to 0°C while
   being vigorously stirred.
2) To the stirred mixture was added dropwise over 20
   minutes the crotonaldehyde (1.4g, 0.02 mol.) in
   methylene chloride solution.
3) The mixture was then stirred for 2.5 hours at 0°C
   followed by refluxing for 20 minutes.

The effect of the reflux time was examined first and it
was found that a reflux time of over 20 minutes had no
effect on the reaction yield.

The effect of the structure of the quaternary ammonium
salt catalyst was investigated next. The reaction was
initially run using tetrabutylammonium iodide (0.1g, 0.00027
mol., 1.35 mole %). A yield of 43% of 14 (Table IV) was
obtained. It was thought that if one of the alkyl groups
of the cation was replaced by a larger alkyl group such as cetyl, then the resulting cation would have a greater degree of solubility in the organic phase\textsuperscript{21}. It has been shown\textsuperscript{22} that the Cannizzaro reaction of benzaldehyde under phase-transfer conditions is dependent on the catalyst structure. When a macrocyclic ether (18-crown-6) catalyst was used, the yield of benzoic acid was 90\%. However, when triethylbenzylammonium chloride was the catalyst only a trace of benzoic acid was formed. Also, the activity of the quaternary salt selected for use as a phase-transfer catalyst may depend greatly on the anion originally present. Many quaternary salts are commercially available in the iodide form but iodide ion associates much more strongly with quaternary cations in organic media than many other anions\textsuperscript{23}. If hydroxide ion transfer from the aqueous to the organic phase is desired, and 100 moles of sodium hydroxide is present for each mole of R\textsubscript{4}N\textsuperscript{+}I\textsuperscript{-} catalyst present, only about 0.002\% of the catalyst will be in the active R\textsubscript{4}N\textsuperscript{+}OH\textsuperscript{-} form in the organic phase\textsuperscript{23}. However, if R\textsubscript{4}N\textsuperscript{+}Cl\textsuperscript{-} had been used instead of the iodide form, approximately 50\% of the catalyst would be in the active R\textsubscript{4}N\textsuperscript{+}OH\textsuperscript{-} form in the organic phase\textsuperscript{23}. For these reasons, cetyltrimethylammonium bromide (CTMAB) and triethylbenzylammonium chloride (TEBAC) were selected as other possible catalysts. The reaction was repeated using the same catalyst concentrations (1.35 mole \%) under the standard reaction conditions. The results (Table IV) showed that all three catalysts were effective
although triethylbenzylammonium chloride (TEBAC) was the least active. In all cases the only organic-soluble product was 14.

The question arose to whether this reaction was really a phase-transfer catalyzed reaction or whether it was a micelle-catalyzed reaction. Many quaternary ammonium salts containing one or two large alkyl groups and two or three small groups such as cetyltrimethylammonium bromide (CTMAB) are good surfactants, which when added to a two-phase aqueous-organic system, normally form micelles. Such micelles usually take the form of small aggregations of about 10 - 50 organic molecules dispersed in the aqueous phase, wherein the nonpolar parts of the surfactant and other nonpolar organic molecules occupy the internal hydrophobic volume of the micelle, while the highly polar groups of the surfactant occupy the outer highly hydrophilic surface. Good phase-transfer catalysts are predominantly partitioned into the organic phase of a two-phase mixture unlike good surfactants which form emulsions or micelle dispersions in the aqueous phase. Since no emulsions could be detected in these reactions this would indicate that the catalyst was being partitioned into the organic layer. Phase-transfer catalyzed reactions are relatively insensitive to the concentration of the inorganic reagent (NaOH) in the aqueous phase whereas the micelle-catalyzed reactions are highly sensitive since the surfactant may be salted out of solution\(^5\). No indication of the catalyst being salted out
was observed in any of the reactions when the hydroxide concentration was varied.

The reactions were run under the standard conditions except the catalyst was omitted and only the starting aldehyde (5) was recovered indicating that the reaction did not take place at the interface between the two phases. For these reasons, it would appear that this reaction was indeed a true phase-transfer catalyzed process.

Finally the effect of changing the concentration of the sodium hydroxide was examined (Table IV). The reaction was performed under the usual conditions except 20% aqueous sodium hydroxide was used (Table IV, Run 5). In this case none of 14 was formed. Instead the sole product in the organic phase was identified as 13\(^{18,24}\) (as a 45:55 mixture of 13a and 13b, Scheme 12), the material originally expected.
Table IV - Self-Condensation of Crotonaldehyde

<table>
<thead>
<tr>
<th>run</th>
<th>normality</th>
<th>Vol., mL</th>
<th>mol</th>
<th>equiv.</th>
<th>catalyst</th>
<th>product</th>
<th>% yield</th>
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<td>1</td>
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<td>43</td>
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<td>4</td>
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<td>0.09</td>
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<td>37</td>
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<td>13</td>
<td>39</td>
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<td>7</td>
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<td>9</td>
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<td>0.01</td>
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<td>12</td>
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<td>5 + 3</td>
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<td>9.0</td>
<td>0.16</td>
<td>4</td>
<td>CTMAB</td>
<td>14</td>
<td>18</td>
</tr>
</tbody>
</table>

a All runs were performed using the standard phase-transfer conditions. For details, see Experimental, p. 52.

Vol. - volume (mL) of sodium hydroxide used.

mol. - number of moles of sodium hydroxide in the aqueous phase.

equiv. - number of equivalents of sodium hydroxide based on one equivalent of crotonaldehyde.

TBAI - tetrabutylammonium iodide.

TEBAC - triethylbenzylammonium chloride.

CTMAB - cetyltrimethylammonium bromide.
The two isomers were obtained in a total yield of 28%. Further runs were done at lower hydroxide concentrations to determine the maximum yield of the dihydropyran. It was found that the maximum (39% yield) was reached at 10.8% (2.7N, Table IV, Run 6), but 13 was also produced with the hydroxide concentration as low as 5% (1.25N, Table IV, Run 11). Since the runs at 20% and 10.8% aqueous sodium hydroxide contained different molar amounts of hydroxide ion, the reaction was repeated with equimolar amounts at the two concentrations (Runs 7 and 8, Table IV). Again the 10.8% sodium hydroxide concentration gave the superior yield. The range over which the product changed from 14 to 13 was relatively small, which is shown graphically by using the results of Table IV (Figure I). The first sign of 13 occurred at 7.5N (30% NaOH) and 14 was not detected below 6.25N (25% NaOH). To our knowledge, this is the first case of such a change in products caused only by varying the hydroxide concentration.

The other end of the hydroxide concentration range was also investigated. It was found that 14 was formed at concentrations as high as 17.5N (70% NaOH, Run 13, Table IV) although the yield (18%) was significantly less than for 12.4N (50%) aqueous sodium hydroxide (43% yield).

The recovery of 43% or less of the products and the absence of other products in the organic phase suggests all by-products were water soluble.

From the systematic investigation of the reaction variables, it was determined that the product make-up was
Figure 1 - Product Change in the Phase-Transfer Reaction of Crotonaldehyde.
affected only by the concentration of the hydroxide in the bulk aqueous phase and not by either the nature of the catalyst or the molar amount of hydroxide used.

Extensive investigation on the condensation of conjugated aldehydes and ketones under a variety of conditions has been carried out, mainly by Weimann\textsuperscript{25-28}. He has pointed out\textsuperscript{26} that four possible mechanisms exist. They are (Scheme 13):

1) an initial Michael addition of the $\gamma$-carbon atom of crotonaldehyde (5) with 5 followed by cyclization.

2) a similar condensation using the $\alpha$-carbon atom of 5 followed by cyclization at the $\gamma$-carbon.

3) a Diels-Alder reaction\textsuperscript{29} of 5 with the enolate of 5.

4) an Aldol condensation at the $\alpha$- or $\gamma$-position followed by a Cope-type rearrangement of the trienic product.

Another possible mechanism is the Michael addition of the oxygen atom of the enolate of 5 followed by rearrangement\textsuperscript{30} (Scheme 13). Although the reaction conditions used by Weimann are different (gas phase with alkaline earth oxide catalysts), the same mechanistic possibilities exist. The condensation of methyl vinyl ketone and mesityl oxide led to the isolation\textsuperscript{28} of an intermediate which could only be ascribed to the $\alpha$-Michael sequence, but in general they ascribe the majority of their results to the $\gamma$-Michael mechanism\textsuperscript{25}.

A study\textsuperscript{31} was undertaken to determine the operative
\[ \gamma-\text{Michael} \]
\[ OHC + \text{CHO} \rightarrow OHC \text{CHO} \rightarrow OHC \]

\[ \alpha-\text{Michael} \]
\[ OHC + \text{CHO} \rightarrow OHC \text{CHO} \rightarrow OHC \]

\[ \text{Diels-Alder} \]
\[ OHC + \text{CHO} \rightarrow OHC \text{CHO} \rightarrow OHC \]

\[ \text{Aldol-Cope} \]
\[ 2 \text{CHO} \rightarrow OHC \text{CHO} \rightarrow OHC \]

\[ \text{O-Addition} \]
\[ \text{CHO} + \text{CHO} \rightarrow \text{CHOCHO} \rightarrow \text{CHO} \]

Scheme 13
mechanism in the phase-transfer case by isolating the intermediates. Condensation of crotonaldehyde (5) with trimethylbenzylammonium fluoride (TMBAF) in THF\textsuperscript{32} gave 2-ethylidene-3-methylglutaraldehyde (15). Exposure of 15 to the usual phase-transfer conditions gave 14 (Scheme 14).

Scheme 14
This result appeared to rule out all but the $\alpha$-Michael mechanism.

Fluoride-catalyzed reactions of 5 with other acceptor molecules led to similar results\textsuperscript{31}. Thus compounds 16 and 17 were obtained from 5 and acrolein or methyl vinyl ketone respectively.
Although these experiments can account for the formation of $^{14}$ they do not explain the sudden change to $^{13}$ when sodium hydroxide concentration dropped below 30%. A possible explanation may involve the amount of water of hydration which may be carried into the organic phase by the catalyst $\text{Q}^+\text{OH}^-$. Starks$^{33}$ measured the hydration of quaternary salts by shaking the salt solution containing tritiated water with solutions of $\text{C}_{16}\text{H}_{33}\text{PBu}_3^+\text{X}^-$, where $\text{X}^- = \text{Cl}^-$, $\text{CN}^-$ and $\text{NO}_3^-$. These measurements were made at various concentrations of quaternary salt in toluene and 1-cyanoctane. This study demonstrated that the amount of water of hydration carried into the organic phase depends on the nature of the anion $\text{X}^-$, the catalyst $\text{Q}^+\text{X}^-$, and on the concentration of $\text{X}^-$ in the aqueous phase. As has been previously pointed out$^{13}$, the amount of energy associated with removing water molecules from the strongly hydrogen-bonded aqueous phase in concentrated hydroxide solutions implies that the solvation of the catalyst in the organic phase should be minimal and the solvation of the catalyst should increase as the sodium hydroxide concentration decreases. It is well known that basicity of anions is greatly increased by the absence of solvating effects in the reaction medium$^{34}$. It appears that at a sodium hydroxide concentration of 30% or less the water concentration in the organic phase is sufficient to alter the action of organic-phase hydroxide from that of a base to that of a nucleophile.

A study of mixed condensations using this phase-transfer
### Table V - Mixed Condensations

<table>
<thead>
<tr>
<th>Run</th>
<th>Reactants</th>
<th>OH(^-), N</th>
<th>Catalyst</th>
<th>Products (yield, %)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
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<td>10.5</td>
<td>TBAI</td>
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</tr>
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<td></td>
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<td></td>
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<tr>
<td>2</td>
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<td>CTMAB</td>
<td>(55) + 14 (34)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
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<td>3</td>
<td>5 + 21</td>
<td>10.5</td>
<td>CTMAB</td>
<td>14 (35)</td>
</tr>
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</tr>
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</tr>
<tr>
<td>5</td>
<td>18 + 22</td>
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<td></td>
<td></td>
<td>24 (70)</td>
</tr>
<tr>
<td>6</td>
<td>18 + 23</td>
<td>10.5</td>
<td>CTMAB</td>
<td>MeO&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26 (10)</td>
</tr>
</tbody>
</table>
technique was done with other \( \alpha, \beta \)-unsaturated carbonyl compounds. The reaction using acrolein (5) and crotonaldehyde (5) (Table V, Run 1) resulted in the recovery of only the self-condensation of crotonaldehyde (34\% yield). This suggests that acrolein may be too reactive to survive long enough to undergo condensation since it is known that acrolein polymerizes readily under alkaline conditions\(^{35}\). The reaction was also done using 5 with methyl vinyl ketone (18) (Table V, Run 2) leading to 14 (34\% yield) and 4-ethylidene-cyclohex-2-enone 20\(^{36}\) (55\% yield). The latter is derived by cyclization of 17. Senecioaldehyde (21) and 5 yielded only 14 while mesityl oxide (19) failed to condense with itself probably due to steric hindrance to the conjugate addition. The reactions of 18 with ethyl acrylate (22) (Table V, Run 5) and methyl acrylate (23) (Table V, Run 6) did not produce the desired cyclization product since the methyl group of 18 does not appear to be acidic enough to react as the donor. However, an addition product of the acrylate was isolated (24, 70\% yield; 25, 28\% yield) and in the reaction of 23 an addition product of 18 (26, 10\%) was also observed.

The phase-transfer catalyzed self-condensation of senecioaldehyde (21) was also attempted. The reactant 21 was prepared by the oxidation\(^{37}\) of 3-methyl-2-buten-1-ol\(^{38}\) with pyridinium chlorochromate. When the condensation was performed using the standard conditions, only the starting material 21 was recovered. In order to induce a reaction,
the reflux time was increased to 20 hours and a material other than 21 was isolated. From the previous study\textsuperscript{31} on the mechanism of these kinds of reactions it was our conclusion that they proceeded through $\alpha$-Michael addition followed by cyclization. If this were the case the product of the self-condensation of 21 should be 2,6,6-trimethyl-1,3-cyclohexadiene-carboxaldehyde (27, safranal) (Scheme 15).

![Chemical Reaction Diagram]

Scheme 15, $\alpha$-Michael

Spectral evidence rapidly showed that the reaction had taken a different course and the product formed, again uncontaminated by isomeric materials, was 4,6,6-trimethyl-1,3-cyclohexadiene-carboxaldehyde (28) (40\% yield), the $\gamma$-Michael product (Scheme 16).
Senecioaldehyde (21) was reacted with trimethylbenzylammonium fluoride (TMBAF) in THF in order to isolate the reaction intermediate. Unfortunately, no reaction occurred as only 21 was recovered.

The product 28, however, was of interest, since it could be a precursor for a compound 29 which is an isomer of \( \beta \)-damascenone (30)\textsuperscript{39, 40}. This material is a valuable perfume constituent and it was
felt that 29 might possess some utility in this area.

The proposed synthesis of 29 (Scheme 17) involved a Grignard reaction of 28 with allyl bromide followed by oxidation of the alcohol product with activated manganese dioxide and finally the isomerization of the double bond in the chain.

\[ \text{28} \xrightarrow{\text{Mg}} \text{29a} \]

\[ \text{29a} \xrightarrow{[O]} \text{29b} \]

\[ \text{Isomerization} \]

Scheme 17
The Grignard reaction was first attempted by preparing the allylmagnesium bromide\textsuperscript{39} and adding 28 to the mixture, however, it was found that the reaction proceeded more favourably by adding the Grignard reagent to the aldehyde 28 in a manner similar to De Meester and Fuson\textsuperscript{40}. The spectral data obtained on a chromatographed sample indicated the presence of 29a. Thus infrared absorption at 2440 cm\textsuperscript{-1} and NMR absorption between 6 and 5 ppm indicated the presence of an allylic alcohol. Oxidation of the alcohol was performed initially using pyridinium chlorochromate but these conditions appeared to be too vigorous as the reaction mixture became a black tar and none of the desired oxidation product could be isolated. Oxidation using manganese dioxide\textsuperscript{41} gave a material whose infrared spectrum indicated the presence of a carbonyl (1710 cm\textsuperscript{-1}) but no alcohol. However, due to the relative volatility of these compounds and the small scale on which these reactions were done, it was impossible to say with certainty what the exact structures were.
Synthetic Applications of Dihydrothiopyrans

Chapter 1

Introduction

The readily availability of molecules like 6 and 9 led us to consider how these might be used in synthesis. The synthesis of any molecule in a regio- or stereospecific manner usually depends on the availability of a number of smaller molecules which possess known stereochemistry. The synthesis of these "building blocks" is an active field of organic chemistry.

One reaction which utilizes the regio- and stereochemistry of the building blocks to a maximum degree is the Diels-Alder reaction. This consists of the addition of a compound containing a double or triple bond (the dienophile) to the 1,4-positions of a conjugated diene system (the diene), with the subsequent formation of a six-membered hydroaromatic ring. The configuration of the product conforms to general principles commonly known as the Alder rules.

Since its discovery by Otto Diels and Kurt Alder in 1928, the Diels-Alder reaction has been invaluable in stereospecific syntheses of a number of natural products such as reserpine, cortisone and yohimbine. Dienophiles may be obtained in a number of ways. Frequently these are commercially available or are easily prepared from
commercial starting materials. The major problem lies in the preparation of the required diene in a stereospecific and regiospecific manner.

Dienes have been prepared by a number of methods, such as the acid hydrolysis of allylic alcohols, the dehydration of allylic alcohols with $\text{H}_2\text{SO}_4$ and $\text{POCl}_3$, the base-catalyzed dehydrohalogenation of allylic halides and the elimination of sulfur dioxide from dihydrothiophene dioxides.

Another route to dienes is the Wittig reaction. In 1953, Wittig and Geissler found that the reaction of benzophenone with methylenetriphenylphosphorane gave 1,1-diphenylethylene and triphenylphosphine oxide in close to quantitative yield (Scheme 18).

$$\text{Ph}_3\text{P} = \text{CH}_2 + \text{Ph}_2\text{C}=\text{O} \rightarrow \text{Ph}_2\text{C} = \text{CH}_2 + \text{Ph}_3\text{P}=\text{O}$$

Scheme 18

This led to the development of a new method for synthesis of olefins, under the name Wittig reaction, which has become an important part of preparative organic chemistry. In this procedure the carbonyl group is replaced specifically.
by a carbon-carbon double bond without the formation of
regioisomeric olefins. The previous method of converting
carbonyl compounds to olefins using the Grignard reaction,
followed by dehydration of the alcohol, usually gives a
mixture of isomeric olefins.

The Wittig reaction has the advantage of being run
under mildly alkaline conditions. It is a valuable method
in preparing sensitive olefins such as carotenoids,
methylene steroids and other natural products.

In the years since the discovery of the Wittig reaction,
many olefins have been synthesized by this method. The
reaction is not limited to simple alkyl and aryl substituted
ethylene derivatives but may also be used in synthesizing
α, β-unsaturated carbonyl compounds and carboxylic esters
in addition to vinyl halides and vinyl ethers.

The usual Wittig reagents are prepared from alkyl
triphenylphosphonium salts. Another type of ylide, which
has been used in the Wittig reaction, is a phosphonate. It
is known that a carbanion located adjacent to a phosphorus
atom carrying a high degree of positive charge is stabilized
by overlap of the orbital carrying the lone pair of electrons
with a vacant 3d orbital of the phosphorus atom. In the
phosphonate carbanions, back donation from oxygen \( 31 \) will
decrease this stabilization and therefore, these anions are
more nucleophilic than phosphoranes.
The most extensive study of the utility of phosphonate
carbanions in the synthesis of olefins was conducted by
Wadsworth and Emmons\textsuperscript{57}, who found that phosphonate carbanions
containing electron-withdrawing groups reacted with aldehydes
and ketones under mild conditions to yield olefins. The
analogous reaction using triphenylphosphacyclidene phosphorane
with benzaldehyde required thirty hours refluxing in THF\textsuperscript{58}.
The evidence in the literature indicates that this Horner-
Emmons modification of the Wittig reaction only proceeds well
when electron-withdrawing substituents are adjacent to
phosphorus\textsuperscript{59}.

Further advantages of phosphonates other than increased
nucleophilicity over phosphoranes are:

1) Separation of the products from water soluble diethyl
phosphate is much easier than separation from
triphenylphosphine oxide.

2) Phosphonates are readily prepared using the Michaelis-
Arbuzov reaction\textsuperscript{60} and are cheaper than phosphonium
salts.

For these reasons, we decided to pursue the possibility
of using dihydrothiopyran carboxaldehydes in the Wittig
reaction producing dienes suitable for use in the Diels-
Alder type reactions (Scheme 19).

\[
\begin{align*}
\text{CHO} & + \text{Ph}_3\text{PCH}_2\text{R} \\
\text{or} & (\text{EtO})_2\text{POCH}_2\text{R}
\end{align*}
\]

Scheme 19

Although the position of the carbon-carbon double bond
in an olefin formed by a Wittig reaction may be predicted
with certainty, the stereochemistry of the olefin product is
sometimes less predictable\textsuperscript{61}. It was recognized by Bohlman
and co-workers\textsuperscript{62} that phosphorus alkylides do not necessarily
react non-stereoselectively, but may in fact preferentially
yield the thermodynamically less stable cis olefins in some
instances. The stereoselective synthesis of cis olefins
from alkylidene or aralkylidene triphenylphosphoranes and
aldehydes can be carried out in the presence of \( \text{I}^- \) (LiI),
forming a complex with the phosphorylides\textsuperscript{63,64}. Trans
olefins were selectively formed in the presence of an
electron acceptor group at the ylide carbon of the
phosphorylide molecule $^{63,64}$. Stable electron control in Wittig olefin synthesis may be accomplished in three different ways:

1) In salt-free solution the normal tendency of ylides is to combine with aldehydes to give betaine-like intermediates which are largely in the erythro configuration. If betaine formation can be made irreversible, high amounts of cis olefins will be obtained.

2) Several types of olefinic compounds, such as stilbenes and $\alpha,\beta$-unsaturated ketones and esters, are significantly more stable as trans isomers than as cis isomers. Wittig reactions will afford such products trans-stereoselectively if equilibration of the intermediate betaines through reversible decomposition to the reactants is rapid, relative to the irreversible decomposition to products.

3) In the presence of lithium salts, the adducts from triphenylphosphonium alkylides and aldehydes are thermodynamically much more stable in the threo configuration. Betaine equilibration is conveniently achieved by $\alpha$-metallation followed by reprotonation of the resultant $\beta$-oxido phosphorus ylides. After completion of the reaction sequence, almost pure trans olefins can be isolated.

Therefore, it was decided to look at the Wittig reaction with unstabilized and stabilized ylides.
Chapter 2

Results and Discussion

An investigation into the use of dienes derived from thiacyclopentenocarboxaldehydes in the Diels-Alder reaction was envisioned.

In order to do this, the thiacyclopentenocarboxaldehydes must first be converted into dienes. The reaction was originally done using an unstabilized phosphonium ylide but none of the desired diene could be detected (Scheme 20).

\[
\begin{align*}
\text{CHO} & \quad \text{Br}^- \\
\text{Ph}_3\text{PCH}_3 & \quad \rightarrow \\
\text{CH} = \text{CH}_2
\end{align*}
\]

Scheme 20

A possible explanation for the failure of this reaction could be the removal of an acidic proton on the 4,6-dimethyl-5-thiacyclopenten-1-enecarboxaldehyde by the base used. This could produce by rearrangement a thiolate anion (Scheme 21)
which could react further or reform the starting aldehyde.

\[
\begin{align*}
\text{B} & \text{H} \\
\text{CHO} & \rightarrow \\
\text{CHO} & \rightarrow \\
\text{S}^{-} & \\
\end{align*}
\]

Scheme 21

The use of the phosphonate variant of the Wittig reaction was investigated next with the hope that the increased nucleophilicity of the anion formed would permit the reaction to occur. The methyl diethylphosphonate \(^{(32)}\) was prepared from triethyl phosphite and methyl bromoacetate \(^{65}\). The condensation was tried using 50% sodium hydride in dry 1,2-dimethoxyethane in a method similar to Wadsworth and Emmons \(^{57}\). The two dihydropyrans used were 4,6-dimethyl-5-thiacyclopent-l-enecarboxaldehyde \((6)\) and 5-thiacyclopent-l-enecarboxaldehyde \((9)\) (Scheme 22).
The products 33 and 34 were obtained in 65% and 60% yields respectively. The dienes were initially reacted under reflux with maleic anhydride (35) in toluene with a catalytic amount of hydroquinone. Upon removal of the solvent, only starting material was found. It is known that Lewis acids can accelerate the rates of Diels-Alder reactions and therefore the same reactions with 33 and 34 and maleic anhydride were repeated using aluminum chloride and stannic chloride. However, neither Lewis acids proved useful in these cases (Scheme 23).
It is known that compounds like 35a are very poor Diels-Alder acceptors and it appears that this effect was operating here too with 33 and 34.
A Simple Preparation of N-Chloroamines

In connection with an ongoing research program, we required a synthesis of some 10-substituted quinolizidines (36).

It was felt a possible synthesis of these compounds would be the cyclization of 38 (Scheme 24).

Scheme 24
The route involving cyclization of 38 proved unsuccessful since the preparation of 37 was complicated and cyclization of 38 would be expected to be inhibited by the quaternary centre adjacent to nitrogen.

However, in attempts to prepare 37 it became necessary to synthesize N-chlorinated amines from which the imines could be made. The next step would be the C-alkylation of the imine (Scheme 25).

\[
\begin{align*}
\text{Pyridine} & \xrightarrow{\text{NaOCl}} \text{Pyridine-Cl} \\
\text{Pyridine-Cl} & \xrightarrow{\text{KOH}} \text{Pyridine} \\
\text{Pyridine} & \xrightarrow{\text{CO}_2\text{H}} \text{Pyridine-carboxylic acid}
\end{align*}
\]

Scheme 25

It was thought that a possible means of producing N-chloroamines could involve the phase-transfer technique. By using a sodium hypochlorite solution (commercial swimming pool bleach), methylene chloride as the organic phase and a quaternary ammonium salt as a catalyst, the N-chloroamines could be prepared. A study was undertaken to determine the utility of this process.

The phase-transfer preparation of N-chloroamines was
initially tried with piperidine (39). The reaction of 39 with aqueous sodium hypochlorite, methylene chloride and tetrabutylammonium iodide afforded the desired chloride product, N-chloropiperidine (40) in a 60% yield (Scheme 26).

\[
\text{piperidine} + \text{NaOCl} \quad \xrightarrow{\text{CH}_2\text{Cl}_2} \quad \text{N-chloropiperidine}
\]

Scheme 26

The purity of the product was determined by titration with standard sodium thiosulfate solution using a starch end point. The % chloride was found to be 78% which was equivalent to a 60% yield of the desired chloroamine (40). The use of sodium hypochlorite to convert secondary amines to chloroamines in aqueous media has previously been proven more convenient than by the use of N-chlorosuccinimide or dichloroamine T in methylene chloride. The advantage of our method is in the work-up which required only separation of the two phases, washing of the organic layer with water and evaporation of the solvent. The work-up for
the method of Edwards and co-workers\textsuperscript{70} involved extracting the aqueous sodium hypochlorite solution with pentane, followed by washing successively the organic extracts with water, dilute sulfuric acid, water and sodium carbonate. Further investigation was done (Table VI) to see if other secondary amines could also be N-chlorinated. As the results of Table VI show, this technique can be used in the preparation of secondary N-chloroamines.

Table VI - N-Chlorination of some Secondary Amines

<table>
<thead>
<tr>
<th>2\textsuperscript{o} Amine</th>
<th>Chloro-product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperidine</td>
<td>N-Chloropiperidine (40)</td>
<td>60</td>
</tr>
<tr>
<td>2-Carbomethoxy-piperidine</td>
<td>2-Carbomethoxy-1-chloropiperidine (41)</td>
<td>55</td>
</tr>
<tr>
<td>2,5-Pyrrolidinedione</td>
<td>1-Chloro-2,5-pyrrolidinedione (42)</td>
<td>40</td>
</tr>
<tr>
<td>Pyrrolidine</td>
<td>1-Chloropyrrolidine (43)</td>
<td>50</td>
</tr>
</tbody>
</table>

The yield for 42 (N-chlorosuccinimide) was slightly higher than the method found in the literature\textsuperscript{72} (40\% yield to 35\%). The product 43 also has been made before using N-chlorosuccinimide\textsuperscript{73} but the phase-transfer technique again worked in this case indicating that this method may have some use in the preparation of secondary N-chloroamines.
Experimental

Unless otherwise stated, nuclear magnetic resonance spectra (NMR) were obtained on a Jeolco C60HL spectrometer or a Varian EM-360 spectrometer and are reported in parts per million downfield ($\delta$) from TMS as an internal standard. Deuteriochloroform was the solvent unless otherwise indicated. The following codes were utilized: NMR (multiplicity, number of protons, coupling constant). Infrared spectra were recorded on a Beckman IR-12 and are reported in wave numbers (cm$^{-1}$) in the solvent indicated. Electron impact and field ionization mass spectra were recorded on a Varian MAT CH5-DF instrument. Glc analyses were carried out on F and M model 720 and Hewlett-Packard 5750 gas chromatographs using helium carrier gas at a flow rate of 1 mL sec$^{-1}$. Injection port temperature and detector temperature were 310$^\circ$C and 325$^\circ$C respectively. The following columns were used: A) $10' \times 0.375''$ o.d. SE-30 on Chromosorb W(NAW); B) $10' \times 0.125''$ o.d. SE-30 on Chromosorb W(NAW); C) $10' \times 0.25''$ o.d. 15% Carbowax 20M on Chromosorb W(NAW), 60-80 mesh. Preparative thin layer chromatography was performed on 2 mm. thick silica gel G. F. plates from Analtech Inc. Column chromatography was performed on Fisher acidic or neutral alumina (80-200 mesh) Brockman activity grade 1 and BDH silica gel 60(70-230 mesh ASTM).
Anhydrous sodium sulfate was used as a drying agent in all cases and solvents were removed in vacuo. Melting points were performed on a Fisher-Johns apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tennessee, U.S.A.

**Tetrabutylammonium Iodide** was purchased from Baker Chemical Company.

**Cetyltrimethylammonium Bromide** was purchased from Aldrich Chemical Company.

**Triethylbenzylammonium Chloride** was purchased from Aldrich Chemical Company.

**Crotonaldehyde (5)** was purchased from Aldrich Chemical Company and was distilled before being used.

**General Phase-Transfer Procedure**: A mixture of aqueous sodium hydroxide solution, 30 mL of dichloromethane and catalyst (0.00027 mol., 1.35 mol. %) was cooled to 0°C under nitrogen. To this mixture was added, dropwise with stirring and cooling, a solution of crotonaldehyde (5) (0.02 mol.) or, in the case of crossed condensations, a mixture of 0.01 mol. of each reactant, in 20 mL of dichloromethane. The addition required 20 minutes. Stirring was continued at 0°C for 2.5 hours and then the mixture was refluxed for 20 minutes. The organic phase was separated, diluted with 100 mL of ether, washed with water and dried. Evaporation of the solvents gave the product which was
analyzed by glc. The yields quoted in Tables IV and V were obtained by multiplying the weight of crude product by the integrated (disk integrator) area of the peak in the glc analysis. In each case, the NMR spectrum of the crude product showed no significant extraneous peaks.

6-Methylocyclohexa-1,3-dienecarboxaldehyde (14)\textsuperscript{17} was obtained as a clear oil; IR 3050, 2800, 1675, 700 cm\textsuperscript{-1}; NMR 9.47 (S, 1H), 6.69 (t, 1H, J = 5 Hz), 6.15 (m, 2H), 2.79 (m, 1H), 2.30 (m, 2H), 0.94 (d, 3H, J = 7 Hz); mass spectrum (FI), m/z 122 (M\textsuperscript{+}), 120, 92, 58, 52, 29.

5,6-Dihydro-2,6-dimethyl-2H-pyran-3-carboxaldehyde (13)\textsuperscript{18,19,24}.

This compound was obtained as a clear oil; IR 2690, 1695, 1255, 865 cm\textsuperscript{-1}. Glc analysis showed the presence of two isomers 13a and 13b in a ratio of 45:55. These were separated by preparative glc to give 13a; NMR 9.57 (S, 1H), 6.90 (m, 1H), 4.77-4.33 (m, 1H), 3.80-3.37 (m, 1H), 2.43-2.08 (m, 2H), 1.41 (d, 3H, J = 7 Hz), 1.30 (d, 3H, J = 7 Hz); m.p. (2,4-DNP) 178-179\textdegree C (lit\textsuperscript{18} m.p. 180\textdegree C); and 13b; NMR 9.60 (S, 1H), 6.92 (m, 1H), 4.90-4.50 (m, 1H), 4.16-3.63 (m, 1H), 2.53-2.15 (m, 2H), 1.42 (d, 3H, J = 7 Hz), 1.23 (d, 3H, J = 7 Hz); m.p. (2,4-DNP) 200-201\textdegree C (lit\textsuperscript{18} m.p. 204\textdegree C). The mass spectra (EI) of the two isomers were identical; m/z 140 (M\textsuperscript{+}), 125, 111, 83.

4-Ethylidenecyclohex-2-enone (20)\textsuperscript{36}:- This compound was obtained with 14 when the condensation of 5 and 18 was effected. These were separated by preparative glc to give 20 as an oil; IR 1675, 1635, 910, 845 cm\textsuperscript{-1}; NMR 6.95
(d, 1H, J = 10 Hz), 6.85 (m, 2H), 2.57 (m, 4H), 1.82 (d, 3H, J = 6 Hz); $^{13}$C NMR 199.4 (S), 149.4 (d), 133.9 (d), 132.4 (d), 125.3 (d), 36.5 (t), 23.3 (t), 14.3 (q); mass spectrum (FI), m/z 122 (M$^+$), 107, 94, 79, 66, 51.

"Anal. Calcd for C$_8$H$_{10}$O: C, 78.65; H, 8.25
Found: C, 78.82; H, 8.37"

Hydrogenation of 20 over a palladium catalyst at 1 atm led to the uptake of 2 equivalents of hydrogen. The product gave a semicarbazone melting point of 173-174°C (lit$^{74}$ 173-174°C).

Ethyl 3-ethoxypropanoate (24) was produced from the attempted condensation of 18 and 22. IR 2995, 1730, 1195, 1110 cm$^{-1}$, similar to IR for 24 in "The Aldrich Library of Infrared Spectra", 2nd ed., #298A; NMR 4.10 (q, 2H, J = 8 Hz), 3.70 (t, 2H, J = 6 Hz), 3.48 (q, 2H, J = 8 Hz), 2.55 (t, 2H, J = 6 Hz), 1.30 (t, 3H, J = 8 Hz), 1.15 (t, 3H, J = 8 Hz), similar to NMR for 24 in "The Aldrich Library of NMR Spectra", #51B; mass spectrum (FI), m/z 146 (M$^+$), 100, 58, 29.

4-Methoxy-2-butanone(25) was produced from the attempted condensation of 18 and 23. IR 2930, 1705, 1160, 1110 cm$^{-1}$; NMR 3.62 (t, 2H, J = 6 Hz), 3.32 (S, 3H), 2.65 (t, 2H, J = 6 Hz), 2.15 (S, 3H); mass spectrum (FI), m/z 102 (M$^+$), 87, 58, 43.

Methyl 3-methoxypropanoate(26) was produced from the attempted condensation of 18 and 23. IR 2850, 1720, 1240, 1050 cm$^{-1}$, similar to IR for 26 in "The Aldrich Library of Infrared Spectra", 2nd ed., #297G; NMR 3.70 (S, 3H), 3.65 (t, 2H, J = 6 Hz), 3.55 (S, 3H), 2.55 (t, 2H, J = 6 Hz);
mass spectrum (FI), m/z 118 (M^+), 103, 87, 43.

3-Methyl-2-buten-1-ol was prepared by the method of Riley et al. NMR 5.42 (t, 1H), 4.12 (d, 2H), 3.55 (s, 1H), 1.75 (s, 3H), 1.68 (s, 3H). b.p. 50-52°C (13 mm). Yield 70%.

3-Methyl-2-butenal(21): This compound was prepared using 3-methyl-2-buten-1-ol (2g.) by the method of Corey and Suggs. NMR 9.90 (d, 1H, J = 1 Hz), 5.80 (d, 1H, J = 1 Hz), 2.15 (d, 3H), 2.00 (d, 3H). Yield 78%.

4,6,6-Trimethyl-1,3-cyclohexadienecarboxaldehyde(28) The standard phase-transfer conditions employing 21 were used except the reflux time was increased to 21 hours. IR 2960, 2820, 1680, 1580; NMR 9.40 (s, 1H), 6.50 (d, 1H, J = 3 Hz), 5.90 (m, 1H), 2.10 (narrow m, 2H), 1.90 (narrow m, 3H), 1.20 (s, 6H); mass spectrum (FI), m/z 150 (M^+), 148, 120. m.p. (semicarbazone) 210-211°C (lit 76 m.p. 213°C).

Further transformations of 28 were attempted.

Preparation of the alcohol 29a was attempted with 28 and allylmagnesium bromide. To a stirred solution of 28 (1.1g, 0.007 mol.) in dry ether under nitrogen was added rapidly a solution of allylmagnesium bromide (1.16g., 0.008 mol.) in ether. The reaction mixture became cloudy and after 8 hours of stirring at room temperature, the gray slurry was poured into a cold saturated ammonium chloride solution. The ether layer was washed twice with water, dried (Mg SO₄) and the solvent was evaporated. IR 3440, 2990, 2940, 1450, 1390, 1080 cm⁻¹; NMR 5.65 (m, 2H), 5.00 (m, 3H), 3.70 (t, 2H), 2.25 (m, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.25
(s, 3H), 1.00 (s, 1H); mass spectrum (FI), m/z 174 (M+ - H2O). This compound was then oxidized with activated manganese dioxide but the spectral data did not allow conclusive identification of the product. IR 3020, 2970, 1710 cm⁻¹.

Methyl diethylphosphonoacetate(32) 65: This compound was prepared by the method of House et al. 65 b.p. 140°C (14 mm.). Yield 84%.

Methyl-3-[3-(2,6-dimethyl-3-thiacyclohexenyl)]-2-propenoate (33): Phosphonate 32 (3.15g, 0.015 mol.) was added dropwise to a slurry of 50% sodium hydride (0.015 mol.) in 40 mL of dry 1,2-dimethoxyethane. After the addition, the mixture was stirred for 1 hour at room temperature. 4,6-Dimethyl-5-thiacyclohex-1-ene carboxaldehyde (5) (2.34g, 0.015 mol.) in 1,2-dimethoxyethane was added dropwise to the solution. The mixture was heated with stirring at 50-60°C for 1 hour. The solution was cooled and taken-up in a large excess of water. The aqueous solution was extracted with two 100 mL portions of ether and the ether extracts were dried (Mg SO4). The organic solvents were evaporated yielding a yellow oil, (1.75g, 65%). NMR 7.20 (d, 1H, J = 16 Hz), 6.20 (m, 1H), 5.80 (d, 1H, J = 16 Hz), 3.75 (s, 3H), 3.25-2.70 (broad m, 2H), 2.50 (m, 2H), 1.47 (d, 3H, J = 7 Hz), 1.28 (d, 3H, J = 7 Hz). Glc revealed two isomers in a ratio of approximately 1:1.

Methyl 3-(3-thiacyclohexenyl)-2-propanoate(34): This compound was prepared in the same manner as 33. The product
34 was a yellow oil (1.35g, 60%). NMR 7.25 (d, 1H, J = 16 Hz), 6.25 (m, 1H), 5.75 (d, 1H, J = 16 Hz), 3.70 (s, 3H) 3.20 (m, 2H), 2.60 (m, 4H). Glc revealed two isomers in a ratio of approximately 1:1.

**Diels-Alder Reactions:** Each diene 33 and 34 (0.015 mol.) was added to maleic anhydride and a catalytic amount of hydroquinone. This mixture was refluxed in toluene under a nitrogen atmosphere for 18 hours. No cyclized product was isolated. The Diels-Alder reaction was also tried with aluminum chloride and stannic chloride (0.015 mol.). These Lewis acids catalyzed reactions also proved unsuccessful since only the starting materials were recovered.

**General Procedure for N-Chlorination of Secondary Amines:**

Sodium hypochlorite (150 mL) in the form of commercial swimming pool bleach (~12.5% NaOCl), 50 mL dichloromethane and 0.1g of tetrabutylammonium iodide were cooled to 0°C. The secondary amine was added rapidly and the mixture was kept at 0°C for an additional 3.5 hours. The organic phase was separated, washed with water and evaporated affording the desired N-chloroamine.

The purity of the N-chloroamines was determined by titrating with standard sodium thiosulfate solution. An accurately weighed sample of about 200 mg. was dissolved in water and a solution of approximately 1g. of potassium iodide in 10 mL of water was added. The solution was acidified with 10 mL of 10% sulfuric acid and was titrated with 0.1N thiosulfate to the starch end point.
Appendix

A reinvestigation of the phase-transfer catalyzed self-condensation of crotonaldehyde was initiated. The mechanism of this reaction shows that it is a base catalyzed reaction. In all reactions reported in this thesis, at least one molar equivalent of hydroxide was used. In order to study the effect of catalytic amounts of base, it was necessary to modify the standard phase-transfer conditions (see Experimental P. 52). The modified procedure was as follows.

1) The 10.8N sodium hydroxide solution (9 mL), methylene chloride (30 mL) and tetrabutylammonium iodide (TBAI) catalyst (1g, 0.0027 mol., 11.9 mole % instead of 0.1g) were vigorously stirred at room temperature for 45 minutes, with the idea that the catalyst (TBAI) would transfer some of the hydroxide ion to the organic phase.

2) The phases were separated and the organic layer was cooled to 0°C.

3) To the cooled methylene chloride phase was added the crotonaldehyde (1.4g, 0.02 mol.) in methylene chloride.

4) The mixture was stirred at 0°C for 2.5 hours and then fluxed for 20 minutes.

Three products were isolated (Scheme 27) by column chroma-


tography. The first product identified, 2-ethylidene-3-methylglutaraldehyde (15, 0.15 g, 11% yield) was the material isolated in the fluoride-catalyzed condensation of crotonaldehyde\textsuperscript{31}. The second material was the Michael-Aldol condensation product, dihydro-o-tolualdehyde (14, 0.21 g, 18% yield), which has been produced under the standard conditions (see p. 19) using 10.8N aqueous sodium hydroxide.

\[
\begin{align*}
2 \text{CHO} & \xrightarrow{\text{OH}^-} \xrightarrow{\text{CH}_2\text{Cl}_2} \text{CHO} \\
& + \text{CHO} \\
& + \text{CHO}
\end{align*}
\]

Scheme 27

The third compound was assigned the structure of 4-hydroxy-6-methyl cyclohexenecarboxaldehyde (44, 0.30 g, 22% yield) from its \textsuperscript{1}H NMR, \textsuperscript{13}C NMR, and IR spectra. The isolation of 44 was conclusive proof that the reaction proceeded through
an $\alpha$-Michael addition followed by an Aldol condensation. The modified procedure also demonstrated that the reaction was indeed base catalyzed since the maximum amount of hydroxide transferred is only 0.003 mol, and the total yield of the products was 0.005 mol.

Due to the success of the modified conditions in the crotonaldehyde case, it was decided to attempt the condensation of crotonaldehyde (0.7 g, 0.01 mol) and acrolein (1.1 g, 0.02 mol) using the same conditions. This reaction had failed using the earlier conditions (p. 31, Table V, Run 1). For this reaction the reflux time was increased to 3 hours. Glc analysis of the reaction mixture indicated the presence of two products. One of these, 2-ethylideneglutaraldehyde (16, 0.12 g, 9% yield), was the product of $\alpha$-Michael addition of crotonaldehyde to acrolein. This compound (16) had previously been isolated by the fluoride-catalyzed\(^{31}\) condensation of crotonaldehyde and acrolein. The second material was not available in sufficient quantity to allow clear spectral analysis. However, based on the available information, this compound could be 4-hydroxycyclohexene-carboxaldehyde (45, Scheme 28).
Finally, the reaction using 5.4N aqueous sodium hydroxide with crotonaldehyde was also performed using the modified procedure. In this case none of the 4,6-dimethyl dihydropyran carboxaldehyde was isolated. However, as the solution was allowed to cool to room temperature after the reflux period, a colourless precipitate formed. The solid was filtered, dried and the melting point (145-6°C) indicated that the solid was tetrabutylammonium iodide (actual mp 145-8°C). The recovery of 80% of added catalyst shows that the catalyst existed mostly as the iodide form and not as the hydroxide form in the organic phase. The reaction using 5.4N aqueous sodium hydroxide under the standard conditions (p. 20) may be taking place at the interface or via some other route in view of the fact that very little of the added catalyst is actually in the active form.
Experimental

The reactions were performed as outlined in the discussion section (p. 58).

All the products were separated by column chromatography utilizing BDH silica gel (70-230 mesh ASTM). The eluting solvent was 1:1:1 pentane-ether-methylene chloride.

6-Methylcyclohexa-1,3-dienecarboxaldehyde (14) was obtained as a clear oil; spectra identical with previous sample (p. 53).

2-Ethylidene-3-methylglutaraldehyde (15) was obtained as a yellow oil; spectra identical to an authentic sample.

4-Hydroxy-6-methylcyclohex-1-ene-carboxaldehyde (44) was obtained as a yellow oil; IR 3600, 3450, 3050, 2950, 1685 cm.\(^{-1}\); NMR 9.55 (S, 1H), 6.8 (t, 1H, J = 3 Hz), 3.85 (m, 1H), 2.7 (m, 2H), 2.15 (m, 2H), 1.85 (m, 2H), 1.15 (d, 3H, J = 3 Hz); \(^{13}\)C NMR, mixture of stereoisomers, 193.7, 148.1, 145.5, 66.2, 63.6, 40.2, 38.3, 35.9, 35.6, 28.2, 26.7, 19.8.

2-Ethylidene-glutaraldehyde (16) was obtained as a yellow oil; with spectra identical to an authentic sample.

4-Hydroxycyclohexene-carboxaldehyde (45): NMR 9.60 (s, 1H), 6.90 (m, 3H), 4.4 (d, 1H, J = 3 Hz), 2.00 (m, 4H), 1.40 (m, 2H).
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23. Ref. 5, p. 67-68.


42. O. Diels and K. Alder, Ann., 460, 98, (1928).
52. For a general review of the Wittig reaction, see A. Maercker, Org. Reactions, 14, 270, (1965).


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