The Abnormal Michael Reaction: Scope, Limitations, and Mechanism.

William George Haag III

Louisiana State University and Agricultural & Mechanical College

Follow this and additional works at: https://digitalcommons.lsu.edu/gradschool_disstheses

Recommended Citation

https://digitalcommons.lsu.edu/gradschool_disstheses/2126

This Dissertation is brought to you for free and open access by the Graduate School at LSU Digital Commons. It has been accepted for inclusion in LSU Historical Dissertations and Theses by an authorized administrator of LSU Digital Commons. For more information, please contact gradetd@lsu.edu.
HAAG, 3rd., William George, 1946-
THE ABNORMAL MICHAEL REACTION: SCOPE, LIMITATIONS, AND MECHANISM.

The Louisiana State University and Agricultural and Mechanical College, Ph.D., 1971
Chemistry, organic

University Microfilms, A XEROX Company, Ann Arbor, Michigan

© 1972

WILLIAM GEORGE HAAG, 3rd.

ALL RIGHTS RESERVED
THE ABNORMAL MICHAEL REACTION:
SCOPE, LIMITATIONS, AND MECHANISM

A Dissertation
Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy
in
The Department of Biochemistry

by
William George Haag, 3rd
B.S., Louisiana State University, 1968
December 1971
PLEASE NOTE:

Some pages may have indistinct print.

Filmed as received.

University Microfilms, A Xerox Education Company
ACKNOWLEDGMENT

The author would like to acknowledge Professor G.E. Risinger for his suggestions, discussion, and encouragement. His ever-present influence made completion of this paper possible.

An appreciative thanks is extended to Professors J. G. Traynham, R. S. Allen, E. S. Younathan, and A. D. Larson for their assistance and interest.

The author gratefully acknowledges his wife for her understanding and patience.

Financial support was provided by Louisiana State University and the National Science Foundation.
Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGMENT</td>
<td>ii</td>
</tr>
<tr>
<td>LIST OF SPECTRA</td>
<td>v</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>vii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>HISTORY</td>
<td>2</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>15</td>
</tr>
<tr>
<td>EXPERIMENTERAL</td>
<td>45</td>
</tr>
<tr>
<td>2-Cyclocododecenone</td>
<td>46</td>
</tr>
<tr>
<td>Condensation of 2-cyclocododecenone and diethyl methylmalonate</td>
<td>46</td>
</tr>
<tr>
<td>2-Cyclooctenone</td>
<td>47</td>
</tr>
<tr>
<td>Condensation of 2-cyclooctenone with diethyl methylmalonate</td>
<td>48</td>
</tr>
<tr>
<td>Reaction of diethyl methylmalonate and 2-cycloheptenone</td>
<td>48</td>
</tr>
<tr>
<td>Reaction of diethyl methylmalonate with 2-cyclohexenone</td>
<td>49</td>
</tr>
<tr>
<td>Reaction of diethyl methylmalonate with 2-cyclohexenone with a minimum of solvent</td>
<td>49</td>
</tr>
<tr>
<td>2-(3-Oxocyclohexyl)-2-cyclohexenone</td>
<td>50</td>
</tr>
<tr>
<td>Reaction of diethyl methylmalonate with 2-(3-oxocyclohexyl)-2-cyclohexenone</td>
<td>50</td>
</tr>
<tr>
<td>Reaction of diethyl methylmalonate and cinnamonicitrile</td>
<td>51</td>
</tr>
<tr>
<td>Diethyl α-cyano-β-phenyl-γ-methylglutarate</td>
<td>51</td>
</tr>
<tr>
<td>Reaction of diethyl methylmalonate and ethyl cinnamate</td>
<td>52</td>
</tr>
<tr>
<td>α-Methyl-β-phenylglutaric acid</td>
<td>52</td>
</tr>
</tbody>
</table>
Abnormal Michael reaction in the presence of ethyl formate 53
Abnormal Michael reaction in the presence of ethyl oxalate 53
Reaction of diethyl carbonate and diethyl β-phenylglutarate 54
Reaction of diethyl methylmalonate and ethyl cinnamate in the presence of catalytic amounts of base 54
p-Chlorophenacyl p-toluyl sulfone 54
β-β-Chlorophenyl-β-hydroxyethyl p-toluyl sulfone 55
p-Chlorostyryl p-toluyl sulfone 55
Reaction of diethyl methylmalonate and p-chlorostyryl p-toluyl sulfone 56
Reaction of ethyl α-methylcinnamate and diethyl α-ethoxycarbonyl-β-phenylglutarate 56
Reaction of ethyl cinnamate with sodium ethoxide 57
Reaction of diethyl malonate with cinnamonic acid under abnormal Michael reaction conditions 57
Reaction of diethyl malonate with cinnamonic acid under normal Michael reaction conditions 57
SPECTRA ........................................................................................................ 58
REFERENCES ............................................................................................. 79
VITA .............................................................................................................. 81
<table>
<thead>
<tr>
<th></th>
<th>Spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>2-cyclodecanone</td>
</tr>
<tr>
<td>2.</td>
<td>2-bromocyclododecanone</td>
</tr>
<tr>
<td>3.</td>
<td>2-cyclododecenone</td>
</tr>
<tr>
<td>4.</td>
<td>2-bromocyclooctanone</td>
</tr>
<tr>
<td>5.</td>
<td>cyclooctanone</td>
</tr>
<tr>
<td>6.</td>
<td>Compound 52, 2-cyclododecenone dimer</td>
</tr>
<tr>
<td>7.</td>
<td>diethyl α-ethoxycarbonyl-β-phenylglutarate</td>
</tr>
<tr>
<td>8.</td>
<td>ethyl α-ethoxycarbonyl-β-phenyl-γ-glutaromononitrile</td>
</tr>
<tr>
<td>9.</td>
<td>ethyl α-methylcinnamate</td>
</tr>
<tr>
<td>10.</td>
<td>diethyl β-phenylglutarate</td>
</tr>
<tr>
<td>11.</td>
<td>diethyl α-cyano-β-phenyl-γ-methylglutarate</td>
</tr>
<tr>
<td>12.</td>
<td>diethyl α-ethoxycarbonyl-β-phenyl-γ-methylglutarate,</td>
</tr>
<tr>
<td></td>
<td>diethyl α-ethoxycarbonyl-β-phenylglutarate mixture</td>
</tr>
<tr>
<td>13.</td>
<td>p-chlorophenyl p-toluy1 sulfone</td>
</tr>
<tr>
<td>14.</td>
<td>p-p-chlorophenyl-β-hydroxyethyl p-toluy1 sulfone</td>
</tr>
<tr>
<td>15.</td>
<td>p-chlorostyryl p-toluy1 sulfone</td>
</tr>
<tr>
<td>16.</td>
<td>diethyl α-methyl-β-p-chlorophenyl-γ-p-toluenesulfonylglutarate</td>
</tr>
<tr>
<td>17.</td>
<td>2-cyclohexenone</td>
</tr>
<tr>
<td>18.</td>
<td>2-(3-oxocyclohexyl)-2-cyclohexenone</td>
</tr>
<tr>
<td>19.</td>
<td>2-(ethoxycarbonyl-3-oxocyclohexyl)-2-cyclohexenone</td>
</tr>
<tr>
<td>NMR</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>2-cyclododecenone</td>
</tr>
<tr>
<td>2.</td>
<td>diethyl α-cyano-β-phenyl-γ-methylglutarate</td>
</tr>
</tbody>
</table>
3. diethyl α-ethoxycarbonyl-β-phenyl-γ-methylglutarate, diethyl α-ethoxycarbonyl-β-phenylglutarate mixture

4. 2-cyclohexenone

5. 2-(3-oxocyclohexyl)-2-cyclohexenone(45)

6. diethyl β-phenylglutarate

7. p-chlorophenacyl p-toluy1 sulfone.

8. β-p-chlorophenyl-β-hydroxyethyl p-toluy1 sulfone

9. p-chlorostyryl p-toluy1 sulfone

10. diethyl α-methyl-β-p-chlorophenyl-γ-p-toluenesulfonylglutarate

11. diethyl α-benzylidenegluturitate in ethyl cinnamate

MS

1. a) diethyl α-cyano-β-phenyl-γ-methylglutarate from ethyl cyanoacetate and ethyl α-methylcinnamate

   b) diethyl α-cyano-β-phenyl-γ-methylglutarate from abnormal Michael reaction

2. diethyl α-ethoxycarbonyl-β-phenyl-γ-methylglutarate, diethyl α-ethoxycarbonyl-β-phenylglutarate mixture

3. diethyl α-ethoxycarbonyl-β-phenylglutarate

4. ethyl α-ethoxycarbonyl-β-phenyl-α-glutaromononitrile
Abstract

The course of conjugate addition of diethyl methylmalonate depends upon reaction conditions, giving rearranged products in the presence of a full equivalent of base. With ethyl cinnamate, this rearranged product is diethyl α-ethoxycarbonyl-β-phenyl-γ-methylglutarate(36). The currently accepted view of the mechanism of this reaction involves conjugate addition followed by ethoxycarbonyl transfer via a cyclobutanone intermediate.

However, evidence to the contrary has been obtained. The study of ethyl cinnamate and its analogs suggests diethyl methylmalonate reacts with two molecules of the unsaturated component to give a ternary intermediate, which undergoes ethoxycarbonyl transfer via a cyclohexane intermediate. In the case of ethyl cinnamate, such a process followed by retrogression gives ethyl α-methylcinnamate and diethyl α-ethoxycarbonyl-β-phenylglutarate(49). These recombine via conjugate addition of compound 49 as an alkylmalonic ester to give the intermediate diethyl α-methyl-β,γ-diphenyl-γ,γ-diethoxycarbonylpimelate. This intermediate undergoes retrogression to give ethyl cinnamate and the rearranged product(36).

Furthermore, diethyl malonate does not undergo abnormal partition. A report to the contrary is discussed.
INTRODUCTION

The abnormal Michael reaction was to be studied as a model system for the biochemical conversion of methylmalonyl CoA into succinyl CoA. However, initial studies indicated the accepted mechanism for the abnormal reaction might not be correct. Thus, a determination of the mechanism of the abnormal Michael reaction was undertaken.
History

In 1887 Michael\textsuperscript{1} reported that base catalysed conjugate addition of diethyl malonate to $\alpha,\beta$-unsaturated esters gives substituted diethyl $\alpha$-ethoxycarbonylglutarates(1).

![Figure 1](image)

This reaction provides a general route to a wide variety of compounds as it has been shown that unsaturated ketones\textsuperscript{2} and nitriles\textsuperscript{3} also undergo conjugate addition. Monosubstituted malonic and cyanoacetic esters\textsuperscript{4} react in analogous fashion.

While studying alkali metal salts of $\alpha$-cyanoesters, Thorpe\textsuperscript{4} found that they do not undergo normal Michael condensation with unsaturated esters. For example, condensation of ethyl $\alpha$-cyanopropionate with ethyl $\beta$-methylcrotonate in the presence of one equivalent of sodium ethoxide gives diethyl $\alpha$-cyano-$\beta,\beta,\gamma$-trimethylglutarate(2) as shown in Figure 2.

Thorpe reported that compound(2) can be alkylated with sodium ethoxide and methyl iodide to give diethyl $\alpha$-cyano-$\alpha,\beta,\beta,\gamma$-tetramethylglutarate(4). Acid hydrolysis of (4) gives
Figure 2

α, β, β, γ-tetramethylglutaric acid(5). The product expected from a normal Michael condensation, diethyl α-cyano-α, β, β-trimethylglutarate(3), should not exhibit this reactivity toward alkylation, and based upon this experiment Thorpe concluded that the addition occurred as units of methyl and ethoxycarbonylcyanomethyl.

Unaware of Thorpe's work in England, Michael simultaneously reported similar results for conjugate addition of diethyl methylmalonate to ethyl crotonate in the presence of a full equivalent of sodium ethoxide. Unable to fully explain his results, Michael temporarily abandoned this facet of the reaction.
Returning to the problem in 1930, Michael and Ross found that the amount of ethoxide present determines the course of addition. From their results, Figure 3, they concluded that, with catalytic amounts of sodium ethoxide, the reaction takes the normal course, giving compound (6). However, in the presence of a full equivalent of base, the rearranged product (7) is produced.
They concluded that under normal conditions (i.e., room temperature, catalytic amounts of base) diethyl methylmalonate undergoes addition as units of proton and \( \alpha,\alpha \)-diethoxycarbonyl methyl, whereas refluxing the reactants with a full equivalent of base causes addition to occur as units of methyl and diethoxycarbonylmethyl.

Holden and Lapworth\(^8\) challenged this view and reported results that are inconsistent with this proposed mechanism. They pointed out that the products reported by Michael could arise through addition of diethyl methylmalonate as units of ethoxycarbonyl and \( \alpha \)-ethoxycarbonyl ethyl as well as via units proposed by Michael (Figure 4).

\[
\begin{align*}
\text{1 via Michael's mechanism} & \quad \text{2 via Holden's + Lapworth's mechanism} \\
\end{align*}
\]
Figure 5
They argued that differentiation between mechanisms is not possible with unsaturated esters, but unsaturated ketones should give different products indicative of the reaction course. As shown in Figure 5, diethyl methylmalonate and benzalacetophenone react under abnormal Michael reaction conditions to give ethyl α-methylcinnamate(8) and ethyl benzoylacetate(9). Holden argued these are formed from a retrograde Michael of diethyl α-benzoyl-β-phenyl-γ-methylglutarate(10), which could only arise from a transfer of an ethoxycarbonyl group.

Transfer of a methyl group would give ethyl α-ethoxycarbonyl-β-phenyl-γ-benzoylvalerate(11). Neither (11) nor any retrogression product was found in the reaction mixture.

Holden and Lapworth proposed a mechanism, shown in Figure 6, for the ethoxycarbonyl transfer which involves a Dieckmann cyclization

![Figure 6](image-url)
Figure 7
of the initially formed product (12). Ethanolysis of the cyclobutanone intermediate (13) gives the rearranged product (14).

Michael attacked this conclusion on the basis of the differing behaviors of benzalacetophenone and ethyl crotonate toward conjugate addition. He cited the relative ease with which benzalacetophenone enters into Michael reactions, forming trimolecular addition compounds (15, 16, 17, and 18) with diethyl malonate as shown in Figure 7. Compound (19) could be formed from benzalacetophenone and diethyl methylmalonate analogous to (18), and undergo ethanolysis to give ethyl α-methylcinnamate, benzalacetophenone and ethyl benzoylecetate. However, Michael stated that this mechanism was not applicable to ester systems, because no products analogous to (15-18) could be found in reactions of diethyl malonate and α,β-unsaturated esters.

Although Michael and Ross made repeated efforts to discount the mechanism advanced by Holden, their attempts failed to gain acceptance. Other workers attempted to clarify the problem, but offered little new insight toward a solution.

However, with the advent of isotopic labeling techniques, an ideal mechanistic probe for the abnormal Michael reaction became available. Simamura et al. reported that an ethoxycarbonyl group does indeed migrate during the course of the abnormal reaction. Other groups quickly verified this conclusion.

Alternate proposals for ethoxycarbonyl transfer have been made. Objection to cyclobutanone formation led Henecka to
propose that the reaction may actually proceed through a hemi-ketal anion (20) as shown in Figure 8. Bergmann reviewed a novel mechanism proposal that involves conjugate addition of catalyst followed by a Claisen condensation between components, shown in Figure 9, to give (21).
Compound (21) can eliminate ethanol to give (22) which undergoes an internal Michael reaction to give intermediate 13, Figure 6. Based upon the failure of 2-cyclohexenones to give rearranged products, Risinger and Durst\textsuperscript{24} advanced another alternative to the Holden-Lapworth mechanism. They proposed that the following scheme (Figure 10) might be involved.
On the basis of this mechanism, cinnamonitrile should fail to give rearranged products, since it would form a linear anion that could not participate in the transfer. This failure was reported to be the case. Also, in agreement with the proposal that \(\alpha\)-substituents should interfere with acylation by diethyl carbonate, ethyl cis-\(\alpha\)-phenylcinnamate gave diethyl carbonate, ethyl propionate and starting materials.

Though conclusive evidence for ethoxycarbonyl group transfer has been reported\(^{18-20}\), there are points concerning the abnormal Michael reaction still subject to question. The actual sequence of events leading to abnormal products is still unclear, though the proposal of Holden and Lapworth remains widely accepted. Also it has been assumed\(^2^5\) that the behavior of diethyl malonate is analogous to that of alkylmalonates and that under abnormal Michael reaction conditions, diethyl malonate would give rearranged products. This explanation was advanced by Johnson\(^2^6\) to account for the production of ethyl(3-keto-4-ethoxycarbonyl-1-methylcyclohexyl)acetate in the condensation\(^2^7\) of diethyl malonate with 3-methyl-2-cyclohexenone shown in Figure 11.

![Figure 11](image-url)
Johnson argued that (23) arises through the sequence shown in Figure 12, which involves an abnormal rearrangement from (24) to (25). A retrograde Dieckmann gives (26) which cyclizes to product (23). Although the subsequent isotope studies of Swan\textsuperscript{28} indicated that diethyl malonate and ethyl crotonate do not undergo abnormal condensation, Abramovitch\textsuperscript{29} suggested, as did Johnson, that malonic ester is capable of abnormal partition.

Figure 12
In conclusion, the course of conjugate addition of alkylmalonic esters is influenced by reaction conditions, giving rearranged products in the presence of a full equivalent of base. Furthermore, tracer studies show the reaction involves ethoxycarbonyl transfer. The mechanism proposed by Holden and Lapworth is widely accepted as fact, though some experimental evidence has been reported to the contrary. Finally, in light of conflicting reports, claims of abnormal partition of diethyl malonate must be considered as inconclusive.30
Discussion

Some of the most intriguing biochemical transformations are those involving the $B_{12}$ coenzymes (Figure 13). The $B_{12}$ dependent conversion of methylmalonyl CoA(27) into succinyl CoA(28) is difficult to explain because of the apparent lack of activation for the methyl group. This reaction is unprecedented in non-biological systems for which there exists no obviously analogous conversion.

However, the similarity between these conversions and the abnormal Michael reaction suggests that the latter may serve as a model for the metabolism of methylmalonic acid. One possible representation of this path is given in Figure 14.
Following conjugate addition to an activated double bond (29), CoA carbonyl transfer to this acceptor could proceed via an abnormal Michael reaction. The subsequent oxidation activates the methyl group,
allowing a second CoA carbonyl transfer to give the desired carbon skeleton. Reduction and retrogression produces succinyl CoA(28) and the regenerated acceptor. The exact nature of this acceptor is unknown; it may be part of the enzyme or of the B12 coenzyme. Functional groups X and Y need only stabilize electron density at their respective alpha positions.

Insight into complex biochemical systems has been obtained32 through the study of suitable model systems. The abnormal Michael reaction might serve as a model for these enzymatic reaction. If the cyclobutanone mechanism of Holden and Lapworth is correct, reactions between diethyl methylmalonate and α,β-unsaturated esters could serve as a beginning for such a model study.

However, previous results obtained in our laboratories indicate the currently accepted mechanism of the abnormal Michael reaction may be in error. Risinger and Durst, in a study24 of the synthetic utility of this reaction, failed in their attempts to prepare compound (32), Figure 15, via an abnormal reaction between
diethyl methylmalonate (31) and 3-methyl-2-cyclohexenone (30). They report both 2-cyclohexenone and cinnamonitrile fail to give rearranged products under similar conditions. This report places the Holden-Lapworth mechanism in doubt, as the cyclobutanone mechanisms cannot account for these failures. Therefore, the exact course of the abnormal Michael reaction had to be determined before study of this reaction as a model system for B12 catalyzed rearrangements could be undertaken.

Risinger and Durst suggest this reaction proceeds via enolate anion cleavage of the initial adduct. They attribute their failures to the inability of the enolate to assume the necessary syn configuration (33, Figure 16) with respect to the diethyl methylmalonate side chain. If the failure of the cyclohexenones was indeed due to the forced anti configuration of the enolate (34, Figure 16),
increasing the ring size should allow the enolate to assume the syn orientation, ultimately producing rearranged products. As cyclooctene is the smallest cycloalkene for which stable cis and trans isomers are known,\textsuperscript{33} one might expect 2-cyclooctenone to be the lowest homolog of the series shown in Figure 17 to produce rearranged products by formation of trans-enolates (i.e., \textsuperscript{35}).

\begin{align*}
\text{Figure 17}
\end{align*}
Since the rearranged products are $\beta$-ketoesters, alcoholic ferric chloride was used as a diagnostic test for their presence. This sensitive test for enolic materials showed this initial study of reaction dependence upon ring size did indeed give the predicted results (Table 1). Increasing the ring size from 2-cycloheptenone to 2-cyclooctenone allows the production of enolic materials. This indicates the proposal of Risinger and Durst may be correct.

![Figure 18](image)

**Table 1**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Enolate</th>
<th>(+)FeCl$_3$ products</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-cyclohexene</td>
<td>cis only</td>
<td>no</td>
</tr>
<tr>
<td>2-cycloheptene</td>
<td>cis only</td>
<td>no</td>
</tr>
<tr>
<td>2-cyclooctenone</td>
<td>cis or trans</td>
<td>yes</td>
</tr>
<tr>
<td>2-cyclodecenone</td>
<td>cis or trans</td>
<td>yes</td>
</tr>
<tr>
<td>2-cyclododecenone</td>
<td>cis or trans</td>
<td>yes</td>
</tr>
</tbody>
</table>

There are two possible structures for the rearranged product (Figure 18). In either case hydrolysis would give a $\beta$-keto acid
which could decarboxylate to the same product. Thus the keto function
must be removed to prevent the loss of carbon dioxide in order to
determine which product is formed.

The crude materials from 2-cyclooctenone and 2-cyclododecenone
were reduced by means of Clemmensen conditions\textsuperscript{34} for 12 hours which
hydrolyzes the esters as well as reduces the carbonyl functional
group. It was hoped that a Blanc\textsuperscript{35} degradation of the acid material
would determine which of the two isomers was present (Figure 19).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure19.pdf}
\caption{Figure 19}
\end{figure}

However, all attempts to isolate and identify the products of this
pyrolysis failed. Examination of the abnormal Michael reaction
products prior to reduction showed that the enolic material was present only in very low concentration. Apparently, the condensation reaction produced a complex mixture of products.

Therefore a complete examination of the abnormal Michael reaction at a very basic level appeared to be necessary before a study of this condensation as a model system can be made. Repeating the work of Risinger and Durst showed that, contrary to their report, diethyl methylmalonate does react with cinnamonic nitrile under abnormal conditions to give rearranged products in a 64% overall yield. Though polymerization of the nitrile is extensive, conducting the reaction at high concentrations and careful fractionation of the viscous reaction mixture gives ethyl α-methylcinnamate and a high boiling fraction (bp 198-202° @ 2 mm Hg) identified as diethyl α-cyano-β-phenyl-γ-methylglutarate (35). This compound is identical to that prepared from ethyl cyanoacetate and ethyl α-methylcinnamate.

\[ \text{CH}_3\text{CO}_2\text{C}_2\text{H}_5 + \text{CH}_3\text{CO}_2\text{C}_2\text{H}_5 \quad \rightarrow \quad \text{CH}_3\text{CO}_2\text{C}_2\text{H}_5 \]

\[ \text{CN} \quad \text{CO}_2\text{C}_2\text{H}_5 \quad \rightarrow \quad \text{CH}_3\text{CO}_2\text{C}_2\text{H}_5 \]

**Figure 20**
The IR spectrum of (35) (I.R. 11) has a strong ester carbonyl band and a weak nitrile absorbance. The NMR spectrum gives little information about its structure, as the signals for the ethyl groups mask those for the other protons (NMR 2). The complex nature of this spectrum is due to the fact that (35) is actually a mixture of isomers. The mass spectrum of (35) is by far the most valuable analysis of its structure (MS 1b). The molecular ion, m/e 303, undergoes two distinctive fragmentations, Figure 21, to give ions m/e 202 and m/e 102.

![Figure 21](image)

A method for determination of ion composition has been developed. By comparison of the relative intensities of an ion with that of ions one and two mass units higher, the empirical formula
of the ion can be computed if there are no interfering ions at these higher mass values. This system is based upon natural abundances of the isotopes of carbon, nitrogen and oxygen. Thus the ion (m/e 202) has an empirical formula of $\text{C}_{12}\text{H}_{22}\text{NO}_2$. However, interference prevents application of this technique to the determination of the formula of the ion with m/e 102.

The production of rearranged compounds from this system cast serious doubt upon the validity of the proposed enolate mechanism. However, the nitrile could participate in the ethoxycarbonyl transfer following addition of ethoxide (Figure 22).

Figure 22
Therefore, a reaction procedure was developed to test whether diethyl carbonate is an intermediate in this reaction. This method involves conducting the reaction in the presence of acylation agents more reactive than the carbonate ester. If diethyl carbonate is involved in an acylation step, these more reactive acylating agents should successfully compete with it and give correspondingly altered products. However, diethyl oxalate or ethyl formate did not interfere with the production of rearranged materials. Diethyl methylmalonate and ethyl cinnamate give diethyl malonate, ethyl α-methylcinnamate and diethyl α-ethoxycarbonyl-β-phenyl-γ-methylglutarate (36), Figure 23, under abnormal conditions. The presence of equimolar amounts of the oxalate or formate ester in the reaction mixture did not inhibit the formation of (36). Diethyl carbonate, therefore, cannot be an intermediate. Supporting this conclusion, diethyl carbonate and diethyl glutarate give only trace amounts of diethyl α-ethoxycarbonylglutarate.
under abnormal conditions. The reaction is, in all probability, intramolecular.

If the first step of the rearrangement involves enol participation, the only feasible mechanism to explain these results would be a sequential acyl transfer as shown in Figure 24.

\[ \text{CH}_3\text{COR} \]

\[ \text{H}^+ \]

To test this hypothesis, a reaction sequence was developed in which enol participation is unlikely. This test consisted of the addition of diethyl methylmalonate to an \( \alpha,\beta \)-unsaturated sulfone. Since sulfones are not good nucleophiles,\(^\text{37}\) one would not expect enol
participation in this sequence. Therefore, if this participation is the first step in the rearrangement, abnormal products should not form, since by the above argument, an intermediate such as (38), is unlikely. However, the abnormal modification of the Michael reaction was found to be independent of the carbonyl function. p-Chlorostyryl p-toluyll sulfone (39) and diethyl methylmalonate, under these conditions afforded the abnormal product, diethyl \( \alpha \)-p-toluenesulfonyl-\( \beta \)-p-chlorophenyl-\( \gamma \)-methylglutarate (40) (Figure 26) in a 45% yield.
The NMR spectrum of (40) shows two upfield triplets and an upfield doublet (1.19 ppm) (NMR 10). This doublet is the signal from the methyl group following rearrangement. This suggests rearrangement has probably occurred by an intramolecular path without participation of the enolate anion.

These findings can all be explained in terms of the original Holden-Lapworth mechanism except for those obtained from the cyclic systems. The failure of 2-cyclohexenone and 2-cycloheptenone to give rearranged products could be attributed to the ring strain in the 2-bicyclo[4.2.0]octanone (41) and 2-bicyclo[5.2.0]nonanone (42) intermediates being greater than that of the larger series (43).

\[ \text{R} = \text{C}_2\text{H}_5 \]

Figure 27

Although Allinger et al. have recently calculated strain energies for several bicycloalkane systems, they do not discuss bicyclo-[n.2.0]alkanones nor, apparently, are any other calculations available. One must therefore make a qualitative judgement about these systems based upon the available data. Eliel discusses various
bicycloalkane systems, citing examples of all bicyclo[n,2,0]alkanes from \( n = 1 \) to \( n = 7 \). Furthermore, Corey reports a synthesis of dl-caryophyllene that involves 7,7-dimethyl-2-bicyclo[4.2.0]octanone (44).

![Figure 28](image)

The similarity between (44) and the intermediate (41) from a Holden-Lapworth condensation with 2-cyclohexenone suggests failure is not due to ring strain.

This leaves one with a confused mechanistic picture. On the one hand, the reaction is apparently intramolecular as acylating agents do not interfere with production of rearranged materials. The enolate is apparently not involved as \( \alpha,\beta \)-unsaturated sulfones also give rearranged products. On the other hand, failure of cyclic systems is puzzling, as one would expect little difference between cyclic systems and simple activated ethylenes if the mechanism of Holden and Lapworth is correct.

Since the only evidence conflicting with the cyclobutanone mechanism is that obtained with cyclic systems, a detailed study of the
reaction of diethyl methylmalonate with 2-cyclohexenone was undertaken. The study of reaction dependence upon ring size confirmed the report by Risinger and Burst that 2-cyclohexenone fails to give enolic products with diethyl methylmalonate. However, in an attempt to force the production of rearranged materials by using more vigorous conditions, it was found increasing the concentrations of the reactants afforded enolic materials. Thus, refluxing the reactants in a solution of one equivalent of sodium in a minimum of absolute alcohol produced a yellow mixture giving a positive reaction with alcoholic ferric chloride.

However, all attempts to isolate abnormal Michael products from this reaction mixture failed. Distillation affords a compound corresponding to a dimer of 2-cyclohexenone, 2-(3-oxocyclohexyl)-2-cyclohexenone (45). Its NMR spectrum has a triplet at 6.71 ppm from the vinyl proton (NMR $\delta$). Two carbonyl absorptions indicate ketones; one is a simple ketone ($\delta_{82}$) and the other is an $\alpha,\beta$-unsaturated ketone ($\delta_{95}$).

Thick layer chromatography of the reaction mixture afforded an enolic material in addition to the dimer. This was subsequently identified as a 2-(ethoxycarbonyl-3-oxocyclohexyl)-2-cyclohexenone (46) (2,4-dinitrophenylhydrazone, M.P. 184°C., dec.). Compound (46) could be either of the two isomers, (46a or 46b), as they can be interconverted through the open chain intermediate (57) under the condition of the reaction (Figure 29).
Insufficient evidence has been obtained to differentiate between them. However, either apparently must arise via the intermediate (47) as shown in Figure 30.
If this ternary adduct, (47), is indeed the precursor of the products in the cyclic systems, perhaps a similar intermediate is involved in the production of rearranged materials from acyclic systems. Michael\textsuperscript{9} made such a proposal to explain the results obtained by Holden and Lapworth since he was able to isolate similar intermediates from the reaction of diethyl malonate and benzalacetophenone (Figure 7, page 8). In the case of ethyl cinnamate, such a ternary intermediate (48) could give rise to rearranged products by a similar sequence outlined in Figure 31. From this intermediate, ethoxycarbonyl transfer followed by retrogression would give ethyl α-methylcinnamate,
diethyl malonate, and ethyl cinnamate. Conjugate addition of malonic ester to ethyl \( \alpha \)-methylcinnamate would give the rearranged product (36). If this representation is correct, one would also expect the product from conjugate addition of diethyl malonate to ethyl cinnamate to be present in the reaction mixture. Though such compounds have not been

\[
\begin{align*}
\text{CO}_2R & + \\
\text{CO}_2R & \xrightarrow{\text{R} = \text{C}_2\text{H}_5} \\
\text{CO}_2R & \xrightarrow{\text{49}}
\end{align*}
\]

previously reported in these systems, the mass spectrum (MS 2) of the high boiling fraction from the reaction of ethyl cinnamate indicates that there is indeed a mixture of these two compounds formed under abnormal conditions. The molecular ion corresponding to the rearranged material (36, m/e = 350) is accompanied by a corresponding peak 1 unit mass units lower. This ion, m/e = 336, is from diethyl \( \alpha \)-ethoxycarbonyl-\( \beta \)-phenylglutarate (49). Pairs of ions corresponding to \((M-15)^+\), \((M-74)^+\), \((M-91)^+\), \((M-119)^+\), \((M-146)^+\), \((M-147)^+\), and \((M-148)^+\) are also present. The mass spectrum of (49), prepared from ethyl cinnamate and diethyl malonate indicates presence of (49) in the high boiling fraction.
Saponification and partial decarboxylation of the high boiling fraction gives an acid fraction from which the expected α-methyl-β-phenylglutaric acid can be crystallized. Thin layer chromatography of the mother liquor on silica indicates β-phenylglutaric acid is present by comparison with an authentic sample.

An analogous mixture is found in the condensation of diethyl methylmalonate and cinnamonic acid. The mass spectrum (MS 1b) of the rearranged product, diethyl α-cyano-β-phenyl-γ-methylglutarate (35), has a peak at m/e = 242, corresponding to the molecular ion of ethyl α-cyano-β-phenyl-γ-glutaracetonitrile (50). Compound (50) arises via a sequence analogous to that in Figure 31, shown below. Compound (50)

![Diagram](image-url)
is not present in material prepared via conjugate addition of ethyl cyanoacetate to ethyl α-methylcinnamate (MS 1a).

Though one may argue that these mixtures arise as shown in Figure 34 from a retrogression of the rearranged product formed via a cyclobutanone intermediate, evidence to the contrary has been obtained. While attempting to prepare the initial ternary adduct (48, Figure 31) by using milder conditions, it was found refluxing the components with catalytic amounts of base rather than the full equivalent classically employed produced rearranged materials as
before. A similar mixture of α-ethoxycarbonyl-β-phenylglutarate esters is formed, though diethyl malonate is absent. Since the retrograde Michael reaction is less likely under these mild conditions, the argument presented in Figure 34 seems unlikely. This is strongly supported by the fact that, though diethyl α-ethoxycarbonyl-β-phenylglutarate (49) undergoes retrogression (≈ 15%) under abnormal reaction conditions, it is stable to the milder reaction with catalytic amounts of base.

Since rearranged products are formed in the presence of catalytic amounts of base, complete retrogression of the ternary adduct after ethoxycarbonyl transfer also seems an unlikely route to rearranged products. A more likely explanation involves an initial retrogression to ethyl α-methylcinnamate and diethyl α-ethoxycarbonyl-β-phenylglutarate (49). These then recombine via conjugate addition to give the intermediate (51) which can undergo retrogression in either

![Diagram](image-url)
direction to give the resulting product mixture. In support of this proposal, a mixture of ethyl α-methylcinnamate and diethyl α-ethoxycarbonyl-β-phenylglutarate gives similar product mixtures in the presence of catalytic amounts of sodium ethoxide in refluxing absolute ethanol. Furthermore, the absence of diethyl malonate under these conditions suggested that the malonic ester arises via complete retrogression under the more vigorous abnormal Michael reaction conditions.

Seemingly, therefore, these product mixtures suggest the mechanism proposal involving ternary intermediates such as (48) (Figure 31) is involved in the acyclic systems as well as in the 2-cyclohexenone case. Furthermore, a mechanism involving the ternary intermediate explains the absence of abnormal Michael reaction products observed in the cyclic systems. These systems cannot undergo retrogression after ethoxycarbonyl transfer as do the acyclic analogs (Figure 36). The observed retrogression product is apparently formed

![Chemical Structures](image-url)
due to the relief of steric interference obtained upon elimination.
This reaction is analogous to that reported by Risinger and Durst. Ethyl cis-α-phenylcinnamate and diethyl methylmalonate give diethyl carbonate and ethyl propionate under abnormal conditions. As the α-substituent lowers the rate of formation of the ternary intermediate, rearranged products do not form. Therefore, the addition of diethyl methylmalonate followed by enolate cleavage of the adduct, as proposed by Risinger, becomes the predominant reaction. Following solvolysis of the resulting enol carbonate, the adduct undergoes elimination to give ethyl propionate and ethyl cis-α-phenylcinnamate. Similar results have been obtained upon reaction of diethyl methylmalonate with 2-benzylidene cyclohexanone. Apparently, enolate anion cleavage of the binary adduct becomes the predominant reaction only if the formation of the ternary adduct is prevented.

Since the above arguments imply these ternary intermediates give rise to rearranged products, determination of the path through which they are produced was attempted. Basically, there are two possible pathways for their production. Michael proposed a sequence of two simple conjugate additions as shown in Figure 37. The other

\[
\begin{align*}
\text{CH}_3\text{CO}_2\text{R} & \quad \text{CO}_2\text{R} \\
\text{CH}_3\text{CO}_2\text{R} & \quad \text{CO}_2\text{R} \\
\phi \text{CO}_2\text{R} & \quad \phi \text{CO}_2\text{R}
\end{align*}
\]

Figure 37
pathway consists of addition of diethyl methylmalonate to a previously formed dimer of the unsaturated component (Figure 38).

Since such a dimer was isolated from the reaction of diethyl methylmalonate with 2-cyclohexenone, the production of dimeric compounds was investigated as a possible key to the course of the abnormal Michael reaction. Base-catalyzed dimerization of other 2-cyclohexenones has been previously reported. Furthermore, 2-(3-oxocyclohexyl)-2-cyclohexenone (45) is produced by treating alcoholic solutions of 2-cyclohexenone with a trace of sodium ethoxide in the cold for long periods. The suggested mechanism for dimer formation is shown in Figure 39. This mechanism is, in all probability, correct, since 3-ethoxycyclohexanone is found along with (45) in the base-catalyzed dimerization. These findings prompted a re-examination of the condensation of diethyl methylmalonate with 2-cyclohexenone which revealed a
major product is a dimer of the ketone, \((C_{24}H_{38}O)\) compound (52), mp 144-145°C., apparently formed by an analogous dimerization and cyclization, followed by dehydration. Furthermore, ethyl crotonate gives a dimer, diethyl \(\alpha\)-ethyldene-\(\beta\)-methylglutarate as a minor product in the reaction with diethyl benzylmalonate. Dimeric compounds can apparently be found in other systems, as treatment of ethyl cinnamate with sodium ethoxide in refluxing absolute ethanol gives its corresponding dimer, diethyl \(\alpha\)-benzylidene-\(\beta\)-phenylglutarate (28) in about 10\% overall yield as estimated by NMR (NMR 11). The presence of these dimeric compounds suggested the mechanism involved is that in which dimerization occurs prior to addition of diethyl methylmalonate (Figure 38, page 39).
In support of this mechanism, reaction of diethyl methylmalonate with the 2-cyclohexenone dimer (45) gives the same 2-(ethoxycarbonyl-3-oxocyclohexyl)-2-cyclohexenone (46) as produced with 2-cyclohexenone. This compound must arise via addition of the methylmalonate anion to the dimer followed by subsequent ethoxycarbonyl transfer and elimination.

Therefore, the abnormal Michael reaction apparently follows the complex path presented above rather than the simple cyclobutanone mechanism proposed by Holden and Lapworth. Isolation of (46) from the 2-cyclohexenone reaction mixture suggested the reaction proceeds via a ternary adduct as is shown in Figure 30. The presence of mixtures in the high-boiling fractions from acyclic systems supports this hypothesis.

Unfortunately, the path by which these ternary adducts are formed has not been definitely established. The formation of dimers under abnormal conditions and the isolation of (46) from the reaction of the cyclohexenone dimer suggests this is the path which gives the ternary adducts.

The apparent driving force for this rearrangement is the production of a more stable carbanion following conjugate addition. However, if this is indeed the case, abnormal partition of diethyl malonate seems unlikely as a stable carbanion may be formed following addition by removal of the remaining acidic proton as in Figure 40.
To determine if diethyl malonate does indeed undergo abnormal partition, it was reacted with cinnamonicitrile under abnormal Michael reaction conditions as well as with catalytic amounts of base at room temperature. The high boiling fraction from both reactions was identified as ethyl α-ethoxycarbonyl-α-phenyl-δ-glutaromononitrile (53). The mass spectra of the high boiling material from both reactions were identical (M.S. 4). In view of these findings, it can be assumed that diethyl malonate does not undergo abnormal partition.

Therefore, the reaction of diethyl malonate and 3-methyl-2-cyclohexenone (Figure 11, p. 12) might be better explained by the scheme shown below (Figure 41). By the previous arguments, the first step should be conjugate addition followed by a tautomerization to give the more stable carbanion (54). This anion may undergo retrogression followed by a Claisen condensation to give compound (55).
Isomerization of the double bond followed by a retro-Dieckmann gives the acyclic compound, (56), which undergoes an internal Michael reaction to give product (23). This proposal seems more reasonable than that of Johnson in view of the evidence that diethyl malonate does not undergo abnormal partition.

In conclusion, the abnormal Michael reaction is apparently an extension of simple conjugate addition. The course of the reaction is determined by the relative rates of the various reaction pathways. Malonic ester undergoes addition readily and tautomerizes to the stable
carbanion. Alkylmalonic esters cannot form the stable carbanion following the addition and therefore may undergo retrogression. This allows formation of the dimer followed by addition which produces rearranged materials by the sequence presented above.
Experimental

In the following experiments the chemicals used were reagent grade unless otherwise designated. No further purification was necessary. Absolute ethanol was used in all cases unless otherwise designated.

Uncorrected melting points are reported which were taken on a Fisher-Johns Melting Point Apparatus.

The ultraviolet (UV) spectra were determined on a Cary, Model 14, double beam spectrophotometer; all were determined in 95% ethanol, wavelengths (\(\lambda\)) are reported in millimicrons (\(\text{mm}_{\mu}\)). Infrared (IR) spectra were determined on a Beckman, Model 10, or a Perkin-Elmer, Model 137, double beam spectrophotometer; wavelengths, \(\lambda\), are reported in microns (\(\mu\)). NMR spectra were determined on a Varian, Model A60A, NMR spectrometer at 60 MHz field strength. All chemical shifts are reported in parts per million (ppm) downfield (\(\delta\)) from tetramethylsilane (TMS) internal standard. Mass spectrograms were determined on a Varian, Model M-66, double-focusing mass spectrometer by Cheryl White, Louisiana State University - Baton Rouge, Department of Chemistry staff member.

Mr. Ralph Seab of the Louisiana State University - Baton Rouge, Department of Chemistry staff member performed all elemental analyses.
2-Cyclododecenone

Cyclododecanone (26.5 g., 0.146 mole) was dissolved in diethyl ether (250 cc., anhydrous) and aluminum trichloride (anhydrous, 0.2 g.) was added to the solution. Bromine (23.4 g., 0.146 mole, 7.5 cc.) was added dropwise under nitrogen at 0°-5°C. The initial bromine color was allowed to discharge before the remaining bromine was added. After addition was complete, the solution was stirred 5 min., then added to water (200 cc.) Separation of the layers and further extraction with water (2 x 50 cc.) gave a light yellow ethereal solution which was dried (CaCl₂) and concentrated to give a thick oil which was used directly for elimination (IR 2). The oil was taken up in 200 cc. of N,N-dimethylacetamide and refluxed 2½ hours with anhydrous calcium carbonate (20 g.) under nitrogen. The mixture was cooled and filtered, the filter cake was washed with diethyl ether and the filtrate was added to water (400 cc.) and extracted (5 x 100 cc.). The combined ether extracts were back-extracted with water (5 x 50 cc.) and dried (CaCl₂). Concentration and fractionation gave 2-cyclododecenone (14.9 g., 65% overall yield) bp 108°-111° @4 mm Hg; NMR 1; IR λₜₙₙₙₚ 5.85, 6.10 (µ). Condensation of 2-cyclododecenone and diethyl methylmalonate:

2-Cyclododecenone (14.0 g., 0.078 mole) and diethyl methylmalonate (13.5 g., 0.078 mole) were refluxed in a solution of sodium (1.8 g., 0.078 mole) in absolute ethanol (200 cc.) for 2½ hours under nitrogen. The resulting mixture was neutralized with ethanolic HCl
and concentrated. The thick oil was taken up in ether (200 cc.) and extracted with water (200 cc.). The water layer was washed twice with fresh ether, and the combined ether layers were dried over sodium sulfate and concentrated. This heavy oil was treated directly with amalgamated zinc (60 g.) and refluxed with 6 N HCl (400 cc.) overnight. This mixture was extracted with ether (3 x 200 cc.). The acidic fraction (25%) was converted to the barium salt and pyrolyzed in vacuo. Products could not be identified. The neutral fraction comprised most of the products (9.6 g.) from the reduction. Cooling the heavy oil before reduction gave a waxy solid. Recrystallization from petroleum ether (30-60°C.) afforded 2.5 g. of a white solid designated compound 52. mp 144-145°C., IR-\( \delta \), 5.97, 6.04, 6.10 \( \mu \). Mass Spectra \( m^+ \), m/e 342 
\[ C_{24}H_{38}O. \] UV \( \lambda_{\text{max}}^{\text{EtOH}} \) 245 \( \mu \).

2-Cyclooctenone

Cyclooctanone (13.0 g., 0.1 mole) was dissolved in diethyl ether (100 cc., anhydrous). Aluminum trichloride (anhydrous, 0.1 g.) was added under nitrogen. Bromine (16.2 g., 0.1 mole) was added dropwise to the cooled (0-5°C.) solution. The color discharged immediately. After addition was complete, the solution was stirred an additional five minutes. The etherial solution was washed with water (3 x 100 cc.), dried over sodium sulfate and concentrated to give 2-bromocyclooctanone (IR \( \delta \)) which was taken up in N,N-dimethylacetamide (100 cc.) and refluxed 24 hours with anhydrous calcium carbonate (10 g.) under nitrogen. The suspension was filtered, and the solid was washed with ether. The combined
filtrates were added to water (200 cc.) and extracted with diethyl ether (4 x 100 cc.). The combined ether layers were washed with water and dried over sodium sulfate. Concentration and fractionation gave 2-cyclooctenone (7.7 g., 62%) (bp 82-85° @ 4 mm Hg), \( \lambda_{\text{max}}^{\text{NaCl}} = 5.92 \mu \).

**Condensation of 2-cyclooctenone with diethyl methyldilalonate**

2-Cyclooctenone (16.0 g., 0.13 mole) and diethyl methyldilalonate (22.9 g., 0.13 mole) were refluxed in a solution of sodium (3.0 g., 0.13 mole) in absolute ethanol (200 cc.) under nitrogen for 24 hours. The solution was neutralized with ethanolic HCl and concentrated. The resulting mixture was taken up in diethyl ether (200 cc.) and washed with water (200 cc.). The water layer was washed twice with fresh ether and the combined ether layers were dried over sodium sulfate and concentrated. The heavy oil was treated directly with amalgamated zinc (60 g.) and refluxed with 6 N HCl (400 cc.) overnight. The mixture was extracted with ether (3 x 200 cc.). The acid fraction was converted directly to the barium salt and pyrolyzed. Products could not be identified. The neutral fraction comprised most of the products (8.4 g.) from the reduction.

**Reaction of diethyl methyldilalonate and 2-cycloheptenone**

Diethyl methyldilalonate (8.7 g., 0.05 mole) and 2-cycloheptenone (5.5 g., 0.05 mole) were refluxed in a solution of sodium (1.15 g., 0.05 mole) in absolute ethanol (300 cc.) for 24 hours under nitrogen. Neutralization gave a mixture containing no enolic products (-FeCl₃).
Reaction of diethyl methylmalonate with 2-cyclohexenone

Diethyl methylmalonate (8.7 g., 0.05 mole) and 2-cyclohexenone (4.8 g., 0.05 mole) were refluxed in a solution of sodium (1.15 g., 0.05 mole) in absolute ethanol (300 cc.) for 24 hours with N₂. Neutralization gave a mixture containing no enolic products (-FeCl₃).

Reaction of diethyl methylmalonate with 2-cyclohexenone with a minimum of solvent.

Diethyl methylmalonate (8.7 g., 0.05 mole) and 2-cyclohexenone (4.8 g., 0.05 mole) were refluxed in a solution of sodium (1.15 g., 0.05 mole) in approximately 25 cc. absolute ethanol for 24 hours under nitrogen. The reaction mixture was neutralized, giving a mixture containing enolic materials (+FeCl₃). The mixture was concentrated, taken up in ether (100 cc.), and washed with water (2 x 50 cc.). The ether was dried and concentrated to give a crude oil (10.4 g., 77%). Distillation of this oil gave diethyl methylmalonate (2.8 g., 32.1%) and 2-(3-oxocyclohexyl)-2-cyclohexenone. (1.1 g., 22.9%, bp 132-134°C @ 4 mm Hg), IR \( \lambda_{\text{max}}^{\text{NaCl}} \) 5.82, 5.95 \( \mu \), NMR \( \delta \), triplet (1); 6.7 ppm., UV \( \lambda_{\text{max}}^{\text{EtOH}} \) 233 \( \mu \). Chromatography of the crude oil (thick layer, silica elution with 3% ethyl acetate in heptane) followed by extraction of the enolic band (+FeCl₃) with methanol gave 2-(ethoxycarbonyl-3-oxocyclohexyl)-2-cyclohexenone (46), IR \( \lambda_{\text{max}}^{\text{NaCl}} \) 5.74 \( \mu \), 5.82 \( \mu \), 5.97 \( \mu \), UV \( \lambda_{\text{max}}^{\text{EtOH}} \) 235 \( \mu \), 2,4-dinitrophenylhydrazone M.P. 184°C. Anal. Calcd for C₂₁H₂₄N₄O₇: C, 56.76; H, 5.41; N, 12.61. Found: C, 56.58; H, 5.55; N, 11.97.
2-(3-Oxocyclohexyl)-2-cyclohexenone

2-Cyclohexenone (9.6 gr., 0.1 mole) was treated with a solution of sodium (0.23 gr., 0.01 mole) in ethanol (100 cc.) at 0°C for 72 hours. Neutralization and concentration gave a crude mixture which was taken up in diethyl ether (100 cc.) and extracted with water (2 x 50 cc.). The ether layer was dried (Na₂SO₄) and concentrated. The resulting oil was distilled giving 3-ethoxycyclohexanone (0.8 gr., 5.6%) and 2-(3-oxocyclohexyl)-2-cyclohexenone (3.2 gr., 33%) identical to that produced in the reaction between diethyl methylmalonate and 2-cyclohexenone.

Reaction of 2-(3-oxocyclohexyl)-2-cyclohexenone and diethyl methylmalonate

2-(3-Oxocyclohexyl)-2-cyclohexanone (7.7 gr., 0.08 mole) and diethyl methylmalonate (13.9 gr., 0.08 mole) were refluxed in a solution of sodium (1.8 gr., 0.08 mole) in absolute ethanol (20 cc.) for 24 hours. Neutralization and workup gave an oil (+ FeCl₃) which upon chromatography (silica, 3% ethyl acetate in heptane) gave a 3-(ethoxy-carbonyl-3-oxocyclohexyl)-2-cyclohexenone (1.8 gr., 8.4%) identical to that produced from 2-cyclohexenone (2,4-dinitrophenylhydrazone, mp 184°C dec).
Reaction of diethyl methylmalonate and cinnamonic acid

Cinnamonic acid (16.1 g., 0.125 mole) and diethyl methylmalonate (21.75 g., 0.125 mole) were refluxed in a solution of sodium (3.6 g., 0.125 in 100 cc. of absolute ethanol under nitrogen for 24 hours. Neutralization and concentration gave a yellow oil which was taken up in diethyl ether (200 cc.) and washed with an equal volume of water. The water layer was washed again with ether and the combined ether layers dried over sodium sulfate and concentrated. Distillation of the resulting oil in vacuo gave ethyl cyanoacetate (0.8 g., 0.007 mole), 5.6%, bp 45-55º @ 4 mm Hg), IR ν<sub>max</sub> N<sub>Ac</sub> 5.84, 6.10, MS, (M<sup>+</sup>) m/e = 190 and diethyl 2-cyano-3-phenyl-γ-methylglutarate (35), (20.0 g., 52.8%, bp 192-202º C), IR ν<sub>max</sub> N<sub>Ac</sub> 5.77, NMR δ 2, MS δ<sub>Ac</sub> (M<sup>+</sup>) m/e = 303 containing a trace amount of ethyl α-cyano-β-phenyl-γ-glutaramononitrile (M<sup>+</sup>, m/e 242).

Diethyl α-cyano-β-phenyl-γ-methylglutarate.

Ethyl cyanoacetate (8.5 g., 0.075 mole) and ethyl α-methyl-cinnamate (14.5 g., 0.075 mole) were refluxed in a solution of sodium (0.3 g., 0.013 mole) in absolute ethanol (100 cc.) under nitrogen for 6 hours. Neutralization and concentration gave an oil which was taken up in diethyl ether (30 cc.) and washed with an equal volume of water. The water layer was washed again with ether and the combined ether layers dried over sodium sulfate and concentrated. Distillation gave diethyl α-cyano-β-phenyl-γ-methylglutarate (12.2 g., 53.0%), I.R. ν<sub>Ac</sub> δ, NMR δ, MS δ.
Reaction of diethyl methylmalonate and ethyl cinnamate

Diethyl methylmalonate (8.7 g., 0.05 mole) and ethyl cinnamate (8.8 g., 0.05 mole) were refluxed in a solution of sodium (1.15 g., 0.05 mole) in absolute ethanol (200 cc.) under a nitrogen atmosphere for 24 hours. Neutralization and concentration gave a yellow oil which was taken up in diethyl ether (50 cc.) and extracted with water (50 cc.). The water was re-extracted and the ether layers combined, dried over sodium sulfate, and concentrated. Vacuum distillation gave diethyl malonate, (1.1 g., 13.1%, bp 68-70°C @ 1/4 mm Hg, IR $\lambda_{max}^{NaCl}$ 5.65, 5.71; NMR 3.32 ppm a singlet; ethyl $\alpha$-methylcinnamate (5.0 g., 51%, bp 130-133°C) diethyl $\alpha$-ethoxycarbonyl-$\beta$-phenyl-$\gamma$-methylglutarate (36) (2.6 g., 15.1%, bp 195-197°C @ 1/4 mm Hg), IR $\lambda_{max}^{NaCl}$ 5.68-5.81 $\mu$, M.S. 2 ($M^+$) m/e = 350 containing diethyl $\alpha$-ethoxycarbonyl-$\beta$-phenylglutarate, ($M^+$, m/e = 336).

$\alpha$-Methyl-$\beta$-phenylglutaric acid

Diethyl $\alpha$-ethoxycarbonyl-$\beta$-phenyl-$\gamma$-methylglutarate (2.0 g., .0057 mole) was refluxed in a solution of potassium hydroxide (1.1 g., .02 mole) in 50% ethanol (20 cc.) under nitrogen for 6 hours. The solution was neutralized and evaporated to dryness. The solid was extracted with hot CHCl₃ (50 cc.) and concentrated. The resulting solid was heated in an oil bath at 150°C until CO₂ evolution cease. The resulting gum slowly deposited crystals of $\alpha$-methyl-$\beta$-phenylglutaric acid (mp 120-1°C Lit mp 122°C). Thin layer
chromatography of the mother-liquor on silica (heptane, ethyl acetate::
5:1) gave a spot identical to one produced from an authentic sample
of β-phenylglutaric acid ($R_f = 0.16$).

Abnormal Michael reaction in the presence of ethyl formate

Diethyl methylmalonate (17.4 g., 0.1 mole), ethyl cinnamate
(17.6 g., 0.1 mole) and ethyl formate (7.4 g., 0.1 mole) were refluxed in a
solution of sodium (2.3 g., 0.1 mole) in absolute ethanol (300 cc.) under
nitrogen for 24 hours. Neutralization and concentration gave a yellow
mixture which was taken up in diethyl ether (100 cc.) and washed with
water (2 x 50 cc.). The ether layer was dried over sodium sulfate and
concentrated. Distillation gave diethyl malonate (0.7 g., \(4.5\%\), bp
65-70\(^\circ\)) ethyl α-methylcinnamate (9.2 g., \(48.4\%\), bp 125-135\(^\circ\) C @ 4 mm
Hg) and diethyl α-ethoxycarbonyl-β-phenyl-γ-methylglutarate (36)
(3.9 g., \(11.2\%\), bp 190-196\(^\circ\) C @ 4 mm Hg) containing diethyl
α-ethoxycarbonyl-β-phenylglutarate (49).

Abnormal Michael reaction in the presence of ethyl oxalate

Diethyl methylmalonate (17.4 g., 0.1 mole), ethyl cinnamate
(17.6 g., 0.1 mole) and ethyl oxalate (14.6 g., 0.1 mole) were refluxed in a
solution of sodium (2.3 g., 0.1 mole) in absolute ethanol (300 cc.)
under nitrogen for 24 hours. Normal work up yielded diethyl malonate
(1.0 g., \(6.2\%\), bp 64-69\(^\circ\) C @ 4 mm Hg), ethyl α-methylcinnamate
(8.7 g., \(45.7\%\), bp 128-135\(^\circ\) C) and diethyl α-ethoxycarbonyl-β-
phenyl-γ-methylglutarate (36) (4.2 g., \(12.0\%\), bp 192-197\(^\circ\) C) contain-
ing diethyl α-ethoxycarbonyl-β-phenylglutarate (49).
Reaction of diethyl $\beta$-phenylglutarate and diethyl carbonate

Diethyl $\beta$-phenylglutarate (3.2 g., 0.012 mole) and diethyl carbonate (1.4 g., 0.012 mole) were refluxed in a solution of sodium (0.3 g., 0.012 mole) in absolute ethanol (50 cc.) under a nitrogen atmosphere for 24 hours. Neutralization and concentration gave a clear oil which was taken up in diethyl ether (50 cc.) and extracted with water (50 cc.). Following re-extraction, the ether layers were combined, dried over sodium sulfate, and concentrated. Distillation of the resulting oil gave starting material, diethyl $\beta$-phenylglutarate, (2.9 g., 91% recovered; IR $\lambda_{\text{max}}^{\text{NaCl}}$ 5.74, NMR $\delta$) and a pot residue too small to distill.

Reaction of diethyl methylmalonate and ethyl cinnamate in the presence of catalytic amounts of base.

Ethyl cinnamate (17.4 g., 0.1 mole) and diethyl methylmalonate (17.6 g., 0.1 mole) were refluxed in a solution of sodium (0.34 g., 0.016 mole) in absolute ethanol (100 cc.) under nitrogen for 24 hours. Neutralization and normal work up gave ethyl $\alpha$-methylcinnamate (8.2 g., 44.1%, bp. 128-135°C @ 4 mm Hg) and diethyl $\alpha$-ethoxycarbonyl-$\beta$-phenylglutarate (49) (7.7 g., 22.1%, bp. 192-195°C).

p-Chlorophenacyl p-tolyl sulfone

p-Chlorophenacyl bromide (20 g., 0.084 mole) was added to a solution of sodium p-toluenesulfenate in 200 cc. of N,N-dimethylformamide at room temperature. The solution was stirred for 40 hours. Dilution with water (400 cc.) and filtration yielded the

**β-p-Chlorophenyl-β-hydroxyethyl p-toluyl sulfone**

p-Chlorophenacetyl p-toluyl sulfone (11.9 g., 0.0357 mole) was dissolved in N,N-dimethylformamide (50 cc.) and ethanol (50 cc.) was added. Sodium borohydride (1.0 g., 0.027 mole) was added to the cooled mixture with stirring. After 2 hours, the solution was diluted with an equal volume of water and refluxed for 30 minutes. Evaporation to half the volume and extraction with CHCl₃ gave white crystals. (10.2 g., 92%) recrystallized from benzene/heptane, mp 94-96°C, I.R. 14, N.M.R. 8.

**p-Chlorostyryl p-toluyl sulfone**

Dehydration was effected by refluxing the alcohol in a ten-fold (w/w) excess of phosphoric acid (85%) for 15 minutes. Dilution with ice/water slush (500 cc.) and extraction with benzene gave p-chlorostyryl p-toluyl sulfone in quantitative yield (14.8 g.). Recrystallization from chloroform/heptane gave white crystals, mp 147-148°C, I.R. 15, N.M.R. 2, U.V. λ max EtOH 283 mµ.
Diethyl \(\alpha\)-methyl-\(\beta\)-\(p\)-chlorophenyl-\(\gamma\)-\(p\)-toluenesulfonyleglutarate

Diethyl methylmalonate (1.74 g., 0.01 mole) and \(p\)-chlorostyryl \(p\)-toluyl sulfone (2.92 g., 0.01 mole) were refluxed in a solution of sodium (0.23 g., 0.01 mole) in absolute ethanol (130 cc.) under a nitrogen atmosphere for 24 hours. Neutralization and concentration gave a yellow oil which was taken up in diethyl ether (100 cc.) and extracted with water (100 cc.). The water was re-extracted and the ether layers combined, dried over sodium sulfate, and concentrated. Chromatography of the resulting oil on silica gave diethyl \(\alpha\)-methyl-\(\beta\)-\(p\)-chlorophenyl-\(\gamma\)-\(p\)-toluenesulfonyleglutarate (2.1 g., 45.1%, mp 166-167°C), I.R. 16, N.M.R. 10.

Reaction of ethyl \(\alpha\)-methylcinnamate and diethyl \(\alpha\)-ethoxycarbonyl-\(\beta\)-phenylglutarate

Ethyl \(\alpha\)-methylcinnamate (6.0 g., 0.032 mole) and diethyl \(\alpha\)-ethoxycarbonyl-\(\beta\)-phenylglutarate (10.7 g., 0.032 mole) were refluxed in a solution of sodium (0.1 g., 0.005 mole in ethanol (50 cc.) for 24 hours. Neutralization and work up yielded a mixture of ethyl cinnamate (25%) and ethyl \(\alpha\)-methylcinnamate (75%) (4.2 g., 70% bp 115-135°C) and a high boiling mixture of diethyl \(\alpha\)-ethoxycarbonyl-\(\beta\)-phenyl-\(\gamma\)-methylglutarate and diethyl \(\alpha\)-ethoxycarboxyl-\(\beta\)-phenylglutarate (8.1 g., 75.6%, bp 192-195°C).
Reaction of ethyl cinnamate with sodium ethoxide

Ethyl cinnamate (10.0 g., 0.057 mole) was refluxed in a solution of sodium (1.3 g., 0.057 mole) in absolute ethyl alcohol (100 cc.) for 24 hours. Neutralization and concentration gave a clear mixture which was taken up in diethyl ether (100 cc.) and washed with water (2 x 50 cc.). The ether layer was dried over sodium sulfate and concentrated to give a clear oil consisting of ethyl cinnamate and approximately 10% of its dimer (NMR ll).

Reaction of diethyl malonate with cinnamoylnitrile under abnormal Michael reaction conditions

Diethyl malonate (16.0 g., 0.01 mole) and cinnamoylnitrile (12.9 g., 0.1 mole) were refluxed in a solution of sodium (2.3 g., 0.1 mole) in absolute ethyl alcohol (100 cc.) for 24 hours under nitrogen. Neutralization and work up yielded diethyl α-ethoxycarbonyl-β-phenyl-ε-glutaromomonitrile (7.4 g., 25.6%, bp 175-182°C) (I.R. 8, λmax NaCl 5.25, 5.77; M.S. λ, M+, m/e = 289).

Reaction of diethyl malonate with cinnamoylnitrile under normal Michael reaction conditions.

Diethyl malonate (16.0 g., 0.1 mole) and cinnamoylnitrile (12.9 g., 0.1 mole) were mixed in a solution of sodium (0.37 g., 0.016 mole) in absolute ethanol (100 cc.) for 24 hours at room temperature. Neutralization and work up yielded diethyl α-ethoxycarbonyl-β-phenyl-ε-glutaromomonitrile (10.2 g., 35.4%, bp 176-182°C) identical to that prepared via abnormal conditions.
NMR 6
7.80 7.65 7.37
7.96
The diagram shows a mass spectrum (MS 2) with various peaks labeled with their respective masses. The molecular structure is also depicted, indicating the chemical bonds and substituents. The masses are as follows:

- R = CH₃: M⁻ m/e 358
- R = H: M⁻ m/e 338

Peaks labeled with masses include:
- 189
- 203
- 216
- 230
- 291
- 305
- 336
- 350

The diagram is annotated with MS 2 at the bottom.
References


23. Bergmann, loc. cit.


35. H.G. Blanc, Compt. rend., 144, 1356(1907).


VITA

William George Haag, 3rd was born November 11, 1946 in Lexington, Kentucky. The Haag family moved to Baton Rouge in 1952, where William entered Louisiana State University Laboratory School. In 1960 the Haag family traveled to the West Indies for a year. After graduating from University High School, William entered Louisiana State University in 1964. He received his B.S. in Biochemistry in 1968. He entered Louisiana State University Graduate School as a Graduate Teaching Assistant at that time. In 1970 he received a National Science Foundation Fellowship. He is presently a candidate for the Doctor of Philosophy in the Department of Biochemistry and has a minor in chemistry.

He is married and has one child.
Candidate: William George Haag, 3rd

Major Field: Biochemistry

Title of Thesis: The Abnormal Michael Reaction: Scope, Limitations, and Mechanism

Approved:

[Signature]
Major Professor and Chairman

[Signature]
Dean of the Graduate School

EXAMINING COMMITTEE:

[Signature]
James E. Traughber

[Signature]
R. M. Allen

[Signature]
E. S. Youngman

[Signature]
G. D. Lasso

Date of Examination:

_______________
August 5, 1971