MECHANISTIC STUDIES OF THE REACTION OF PHENYLcadMIUM REAGENT WITH ALPHA-BROMO ESTERS

SAMUEL JOSEPH COSTANZO

Follow this and additional works at: https://scholars.unh.edu/dissertation

Recommended Citation
https://scholars.unh.edu/dissertation/982

This Dissertation is brought to you for free and open access by the Student Scholarship at University of New Hampshire Scholars' Repository. It has been accepted for inclusion in Doctoral Dissertations by an authorized administrator of University of New Hampshire Scholars' Repository. For more information, please contact nicole.hentz@unh.edu.
INFORMATION TO USERS

This dissertation was produced from a microfilm copy of the original document. While the most advanced technological means to photograph and reproduce this document have been used, the quality is heavily dependent upon the quality of the original submitted.

The following explanation of techniques is provided to help you understand markings or patterns which may appear on this reproduction.

1. The sign or “target” for pages apparently lacking from the document photographed is “Missing Page(s)”. If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting thru an image and duplicating adjacent pages to insure you complete continuity.

2. When an image on the film is obliterated with a large round black mark, it is an indication that the photographer suspected that the copy may have moved during exposure and thus cause a blurred image. You will find a good image of the page in the adjacent frame.

3. When a map, drawing or chart, etc., was part of the material being photographed the photographer followed a definite method in “sectioning” the material. It is customary to begin photoing at the upper left hand corner of a large sheet and to continue photoing from left to right in equal sections with a small overlap. If necessary, sectioning is continued again – beginning below the first row and continuing on until complete.

4. The majority of users indicate that the textual content is of greatest value, however, a somewhat higher quality reproduction could be made from “photographs” if essential to the understanding of the dissertation. Silver prints of “photographs” may be ordered at additional charge by writing the Order Department, giving the catalog number, title, author and specific pages you wish reproduced.

University Microfilms
300 North Zeeb Road
Ann Arbor, Michigan 48106
A Xerox Education Company
COSTANZO, Samuel Joseph, 1941-
MECHANISTIC STUDIES OF THE REACTION OF
PHENYLACADMIUM REAGENT WITH α-BROMO ESTERS.

University of New Hampshire, Ph.D., 1972
Chemistry, organic

University Microfilms, A XEROX Company, Ann Arbor, Michigan
MECHANISTIC STUDIES OF THE REACTION OF
PHENYLCADMIUM REAGENT WITH α-BROMO ESTERS

by

SAMUEL JOSEPH COSTANZO

B. S., Niagara University, 1963
M. S., Boston College, 1966

A THESIS

Submitted to the University of New Hampshire
In Partial Fulfillment of
The Requirements for the Degree of
Doctor of Philosophy

Graduate School
Department of Chemistry
June, 1972
This thesis has been examined and approved.

Paul R. Jones, Thesis Director
Professor of Chemistry

Kenneth K. Andersen, Professor of Chemistry

Robert E. Lyle, Jr., Professor of Chemistry

Colin D. Hubbard, Assoc. Professor of Chemistry

R. Lee Byers, Assoc. Professor of Chemical Engineering

May 19, 1972
Date
PLEASE NOTE:

Some pages may have indistinct print.

Filmed as received.

University Microfilms, A Xerox Education Company
ACKNOWLEDGMENTS

First and foremost I wish to express my sincere appreciation to Dr. Paul R. Jones for his encouragement, guidance, and helpfulness during my studies at the University of New Hampshire. I thank him for exemplifying all that is good in the profession of teaching.

I wish also to thank the many fine people associated with the University Chemistry Department who have enriched, directly or indirectly, my work at this university.

Samuel J. Costanzo
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF ILLUSTRATIONS</td>
<td>viii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>ix</td>
</tr>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>II. HISTORICAL BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>III. EXPERIMENTAL</td>
<td>16</td>
</tr>
<tr>
<td>1. Instrumentation</td>
<td>16</td>
</tr>
<tr>
<td>2. Materials</td>
<td>16</td>
</tr>
<tr>
<td>3. Experimental Apparatus</td>
<td>17</td>
</tr>
<tr>
<td>4. Reaction of Phenylcadmium Reagent with Ethyl α-Bromopropionate</td>
<td>17</td>
</tr>
<tr>
<td>5. Refluxing of Phenylmagnesium and Phenylcadmium Solutions</td>
<td>18</td>
</tr>
<tr>
<td>6. Formation of S-(−)-Methyl Lactate</td>
<td>19</td>
</tr>
<tr>
<td>7. Formation of R-(+)-Methyl α-Bromopropionate</td>
<td>20</td>
</tr>
<tr>
<td>8. Reaction of Phenylcadmium Reagent with R-(+)-Methyl α-Bromopropionate</td>
<td>20</td>
</tr>
<tr>
<td>9. Amide Formation</td>
<td>23</td>
</tr>
<tr>
<td>10. Study of Racemization of R-(+)-Methyl α-Bromopropionate</td>
<td>26</td>
</tr>
<tr>
<td>a. On Standing</td>
<td>26</td>
</tr>
<tr>
<td>b. Gas Chromatography</td>
<td>26</td>
</tr>
<tr>
<td>c. Ratio of Peak Areas from Gas Chromatography and Rotation from Polarimeter</td>
<td>29</td>
</tr>
<tr>
<td>Reaction</td>
<td>Page</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>11. Reaction of Ethyl α-Bromopropionate with Phenylcadmium Reagent in the Presence of Cyclohexene</td>
<td>29</td>
</tr>
<tr>
<td>12. Electron Paramagnetic Resonance Studies of the Reaction between Ethyl α-Bromopropionate and Phenylcadmium Reagent</td>
<td>30</td>
</tr>
<tr>
<td>13. Reaction of Phenylcadmium Reagent with Ethyl α-Bromopropionate in the Presence of Azobisisobutyronitrile (AIBN)</td>
<td>31</td>
</tr>
<tr>
<td>14. Gas Chromatographic Analysis of AIBN Experiments</td>
<td>32</td>
</tr>
<tr>
<td>15. Reaction between Ethyl α-Bromopropionate and Phenylcadmium Reagent in the Absence of Oxygen and Light</td>
<td>32</td>
</tr>
<tr>
<td>16. Reaction of Ethyl α-Bromoisoobutyrate with Phenylcadmium Reagent</td>
<td>32</td>
</tr>
<tr>
<td>17. Reaction of Ethyl 2-Bromo-3-methylbutanoate with Phenylcadmium Reagent</td>
<td>33</td>
</tr>
<tr>
<td>18. Reaction of Ethyl Bromoacetate with Phenylcadmium Reagent</td>
<td>34</td>
</tr>
<tr>
<td>19. Reaction of Ethyl 2-Bromobutanoate with Phenylcadmium Reagent</td>
<td>35</td>
</tr>
<tr>
<td>20. Reaction of Phenylcadmium Reagent with 3-Bromocyclohexene</td>
<td>36</td>
</tr>
<tr>
<td>21. Reaction of Chloromethyl Methyl Ether with Phenylcadmium Reagent</td>
<td>37</td>
</tr>
<tr>
<td>22. Reaction of Benzyl Bromide with Phenylcadmium Reagent</td>
<td>38</td>
</tr>
<tr>
<td>23. Reaction of Allyl Bromide with Phenylcadmium Reagent</td>
<td>38</td>
</tr>
<tr>
<td>24. Attempted Reaction of Phenylcadmium Reagent with 1-Bromobutane</td>
<td>39</td>
</tr>
<tr>
<td>Attempted Reaction of Trimethylsilyl Chloride with Phenylcadmium Reagent</td>
<td>40</td>
</tr>
<tr>
<td>Attempted Reaction of Chlorocyanomethane with Phenylcadmium Reagent</td>
<td>40</td>
</tr>
<tr>
<td>Attempted Reaction of 1-Chloro-1-nitroethane with Phenylcadmium Reagent</td>
<td>41</td>
</tr>
<tr>
<td>Attempted Reaction of Ethylene Bromide with Phenylcadmium Reagent</td>
<td>41</td>
</tr>
<tr>
<td>Attempted Reaction of Bromoacetaldehyde Diethyl Acetal with Phenylcadmium Reagent</td>
<td>42</td>
</tr>
<tr>
<td>Attempted Reaction of tert-Butyl Chloride with Phenylcadmium Reagent</td>
<td>43</td>
</tr>
<tr>
<td>Attempted Reaction of Grignard and Cadmium Reagents with Styrene</td>
<td>43</td>
</tr>
<tr>
<td>Reaction of Phenylcadmium Reagent with Acetyl Chloride</td>
<td>44</td>
</tr>
<tr>
<td>Reactions with Ethylcadmium Reagent</td>
<td>44</td>
</tr>
<tr>
<td>Attempted Reaction of Ethyl Bromoacetate with Ethylcadmium Reagent</td>
<td>44</td>
</tr>
<tr>
<td>Reaction of Bromoacetophenone with Ethylcadmium Reagent</td>
<td>45</td>
</tr>
<tr>
<td>Reaction of Isopropylcadmium Reagent with Ethyl Bromoacetate</td>
<td>46</td>
</tr>
</tbody>
</table>

**IV. DISCUSSION AND RESULTS** | 48

**V. BIBLIOGRAPHY** | 73
### LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reaction of Organocadmium Reagents with α-Halo Esters</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Rotation of S-(-)-Methyl Lactate</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>Rotation of R-(+)-Methyl α-Bromopropionate</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>Rotation of Methyl Hydratropate</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Rotation of Methyl Hydratropate after GLPC Purification (A)</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>Rotation of Methyl Hydratropate after GLPC Purification (B)</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>Rotation of R-(+)-Methyl α-Bromopropionate after Standing Two Weeks</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>Reaction of Phenylcadmium Reagent with Various Organic Halides</td>
<td>67</td>
</tr>
</tbody>
</table>
LIST OF ILLUSTRATIONS

Chart 1: Preparation and Reaction of
R-(+)-Methyl α-Bromopropionate............ 58

Figure 1 .................................................. 14
ABSTRACT

MECHANISTIC STUDIES OF THE REACTION OF
PHENYLCADMIUM REAGENT WITH α-BROMO ESTERS

by

SAMUEL JOSEPH COSTANZO

When phenylcadmium chloride (0.02 mol) was allowed to react with R-(+)-methyl α-bromopropionate (0.04 mol) under reflux in 85 ml of anhydrous ether for 3 hr, the reaction proceeded with racemization to afford the displacement product (+)-methyl hydratropate. Aliquots from the reaction of (+)-ethyl α-bromopropionate with phenylcadmium reagent to give ethyl hydratropate gave rise to a strong electron paramagnetic resonance signal.

Product analysis of the reaction between phenylcadmium and several of the α-bromo esters was undertaken. The ethyl esters of α-bromoacetate, propionate, and butanoate gave the expected α-phenyl displacement product. However, ethyl α-bromoisobutyrate and ethyl α-bromoisovalerate appeared to give their coupling products, diethyl 2,3-diisopropylsuccinate and diethyl tetramethylsuccinate, respectively. All of the α-bromo esters also underwent some bromine-hydrogen exchange.

Phenylcadmium chloride gave a displacement product with 3-bromocyclohexene (81%), allyl bromide (39%), benzyl bromide (40%), and chloromethyl methyl ether (34%). Phenyl-
cadmium reagent did not react with 1-bromobutane, trimethylsilyl chloride, chlorocyanomethane, 1-chloro-1-nitroethane, ethylene bromide, bromoacetaldehyde diethylacetal, or tert-butyl chloride.
INTRODUCTION

Considerable work has been done on the mechanistic studies of Grignard reagents.\textsuperscript{1} It has been known for some time that cadmium reagents have a lower reactivity than Grignard reagents toward the carbonyl group.\textsuperscript{2} However, less work has been done on the mechanisms of cadmium reagents. Kauffman\textsuperscript{3} has studied the addition of organocadmium reagents to the carbonyl group of aldehydes and ketones, while Jarboe\textsuperscript{4} and Young\textsuperscript{5} have investigated the displacement of several leaving groups with organocadmium reagents.

In order to gain some insight into the mechanism of halogen displacement in \(\alpha\)-halo esters, stereochemical studies were initiated. Specifically the reaction of phenylcadmium reagent with optically active methyl \(\alpha\)-bromopropionate was studied.
HISTORICAL BACKGROUND

In their pioneering study of the reactivity of organocadmium reagents, Gilman and Nelson\(^2\) reported that these reagents exhibit a very low order of reactivity toward polar multiple bonds, but are very reactive toward acid chlorides. This would make organocadmium reagents of considerable value in the synthesis of ketones, especially ketones containing polar multiple bonds.

Although the displacement of halogens in acid chlorides has been the most important synthetic organocadmium reaction, other displacements have been studied as well. Some of these reactions are described below. Alkyl halides have been found to be unreactive toward displacement with organocadmium reagents. For example, no direct coupling was observed from the reaction of propylcadmium reagent with 2-iodooctane or octylcadmium reagent with allyl bromide in refluxing ether.\(^6\) In the work up of the 2-iodooctane reaction, only unchanged 2-iodooctane (76%) could be isolated. Further, in the reaction of allyl bromide with octylcadmium reagent, the only products isolated were octane (71%), possibly 1-octane, and a higher boiling fraction thought to contain 1-bromooctane and a very small amount of the displacement product.

Gilman and Nelson reported that both tert-butyl chloride and 3-chloro-3-ethyloctane were dehydrohalogenated by cadmium reagents. In the first case, where \(n\)-octylcadmium reagent was used, \(n\)-octane was also isolated in 76% yield. The dehydrohalogenation could have proceeded by an El mechanism; however, Cason and Fessenden\(^6\) postulated a cyclic transition state, because of the analogy with the intermediate involved in the conversion of a ketone to the enolate by a
Grignard reagent

The first displacement of an α-halo ether with an organocadmium reagent was accomplished by Summerbell and Bauer. From the reaction of 2,3-dichloro-1,4-dioxane with \( \text{n-butylcadmium chloride} \) in toluene for 4.5 hr, they obtained 2,3-di-\( \text{n-butyl-1,4-dioxane} \) in 44% yield. When methyl or propylcadmium was used, slightly lower yields were noted.

\[
\begin{align*}
\text{O} & \quad \text{Cl} \\
\text{O} & \quad \text{Cl}
\end{align*}
\]

\((\text{n-C}_4\text{H}_9)_2\text{Cd} \rightarrow \quad \text{O} \quad \text{C}_4\text{H}_9
\]

(1)

Another example of halogen displacement in an α-halo ether was observed by Hurd and Holysz. They carried out the following reaction.

\[
\begin{align*}
\text{Br} & \quad \text{CH} \\
\text{H-C-OCOCH}_3 & \quad \text{Ph}_2\text{Cd} \\
\text{I} & \quad \text{II}
\end{align*}
\]

(2)
Using tetraacetyl-α-D-glucopyranosyl bromide in benzene or tetraacetyl-α-D-mannopyranosyl bromide (I) in toluene and diphenylcadmium, they obtained a 20 and 29% yield, respectively, of the displacement product II. Using dibutyl and dibenzyl cadmium reagents, they obtained an acetal product instead. In order to rationalize the products formed, the authors presented an interesting mechanism, whereby an intermediate carbonium ion was formed. They further ascribed a higher electronegativity to the attacking phenyl, as compared to butyl or benzyl groups to explain the difference in products. No experimental confirmation for the mechanism was provided.

Cason and Fessenden were the first to report the reaction of an α-bromo ester with an alkylcadmium reagent. When they allowed ethyl α-bromoisobutyrate and butylcadmium reagent to react, they obtained ethyl 2,2,4-trimethyl-3-oxo-pentanoate (III) (72% yield). The same keto ester in slightly lower yield was isolated when dodecylcadmium was employed.
They explained the formation of this product by a condensation of the enolate of ethyl isobutyrate with \( \alpha \)-bromoiso­
butyrate, followed by dehalogenation of the bromo keto ester by the cadmium reagent. It is thought that the enolate is formed by way of a cyclic transition state.

The fact that the enolate is formed was substantiated by the reaction with other carbonyl compounds. For example, reaction of the ester with 2-octanone in the presence of cadmium reagent gave ethyl 2,2,3-trimethyl-3-hydroxynonanoate in 83% yield.

The displacement of halogen in an \( \alpha \)-halo ester by an organocadmium reagent was first effected by Gross and Freiberg.\(^9\) This displacement is at least partially due to the presence

\[
\begin{align*}
\text{Br} & - \text{C} - \text{COOC}_2\text{H}_5 + \text{RCdCl} \rightarrow \text{CH}_3 - \text{CH} - \text{C} - \text{C} - \text{COOC}_2\text{H}_5 \\
\text{CH}_3 & \\
\end{align*}
\]

\( (4) \)

III

\[
\begin{align*}
\text{CH}_3 & - \text{O} - \text{CH} - \text{COOC}_2\text{H}_5 + 2\text{PhCdCl} \rightarrow \text{CH}_3 - \text{O} - \text{CH} - \text{COOC}_2\text{H}_5 \\
\text{Cl} & \\
\end{align*}
\]
of the ether linkage, which is known to activate α-halogens to cadmium reagent displacement, inasmuch as the carbonyl group by itself does not activate the chloride toward displacement with alkyl or aryl cadmium reagents.\textsuperscript{10}

The displacement of halogens in α-halo esters was studied by Jones and Young.\textsuperscript{10} The results are listed in Table 1.

\[
\begin{align*}
R' & \quad R'' \\
R-C\text{-}COOC_2H_5 \quad + \quad R''\text{CdCl} & \quad \rightarrow \quad R-C\text{-}COOC_2H_5 \\
\text{R',R'} & \quad = \quad \text{H, CH}_3, \text{ COOC}_2H_5 \\
\text{R''} & \quad = \quad \text{C}_6H_5, \alpha\text{-C}_{10}H_7
\end{align*}
\]

Both bromoacetate and bromopropionate esters were converted to arylated esters in good yield. However, bromoisobutyrate did not form the displacement product in ether or THF, but was recovered unchanged. No trace of the Claisen product, ethyl 2,2,4-trimethyl-3-oxo-pentanoate (III) was found, as in the earlier work of Cason and Fessenden. When chloroesters were used, only starting material or dehalogenated coupling product could be isolated. By-products from the two cadmium reagents were biphenyl or binaphthyl in every case. With diethyl bromomalonate and phenylcadmium reagent, both malonic ester and bromobenzene were isolated in about equal amounts.

\[
\begin{align*}
\text{BrCH(COOEt)}_2 & \quad \overset{1. \text{ PhCdCl}}{\underset{2. \text{ H}^+}{\longrightarrow}} \quad \text{CH}_2(\text{COOEt})_2 \quad + \quad \text{PhBr} \\
75\% & \quad 75\%
\end{align*}
\]
Table 1

Reaction of Organocadmium Reagents with α-Halo Esters

<table>
<thead>
<tr>
<th>Ester</th>
<th>Cd Reagent</th>
<th>Solvent</th>
<th>Reaction Temp. (time, hr)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{R-C(R')XCOOEt}$</td>
<td>$\text{R''}$</td>
<td>Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>$\alpha$-$\text{C}_{10}\text{H}_7$</td>
<td>1</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>$\alpha$-$\text{C}_{10}\text{H}_7$</td>
<td>2</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>$\alpha$-$\text{C}_{10}\text{H}_7$</td>
<td>2</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>1</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>2</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>2</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>H</td>
<td>Br</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>2</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{CH}_3$</td>
<td>Br</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>2</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{CH}_3$</td>
<td>Br</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>2</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>2</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>H</td>
<td>Cl</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>2</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{CH}_3$</td>
<td>Br</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>2</td>
</tr>
</tbody>
</table>
Young\textsuperscript{5} has considered the possibility that these products result from an enolate intermediate similar to the one postulated by Cason and Fessenden\textsuperscript{6} for the reaction of ethyl α-bromoisobutyrate with butylcadmium reagent.

The displacement of α-halo ketones was also studied by Jones and Young.\textsuperscript{10} The reaction of phenacyl bromide with phenylcadmium reagent gave the displacement product deoxybenzoin in 3-31\% yield, along with the coupling products, bi-phenyl and 1,2-dibenzoylethane.

\[
\begin{align*}
\text{Ph-C-CH}_2\text{Br} + \text{PhCdCl} & \rightarrow \text{Ph-C-CH}_2\text{Ph} \\
\text{Ph-C-(CH}_2)_2\text{-C-Ph} & \rightarrow \text{Ph-Ph}
\end{align*}
\]

Methylcadmium reagent has been shown to react with naphthalic anhydride (IV) to give 8-acetyl-1-naphthoic acid (V) and 3,3-dimethylnaphthalide (VI).\textsuperscript{11} The formation of VI was rationalized as the displacement of an oxycadmium fragment in the initial cyclic adduct by methylcadmium reagent.
This mechanism was substantiated by the lack of reactivity of o-acetylbenzoic acid under comparable reaction conditions and the successful displacement at the 3-position in a series of 3-substituted phthalides.\textsuperscript{12} For example, 3-substituted phthalides VII have been shown to react with cadmium reagents, displacing the bromo, hydroxy, ethoxy, and acyloxy groups, to give the corresponding displacement product VIII. These reactions ranged from complete displacement with di-3-phthalidyl ether to no observable displacement with 3-acetoxyphthalide. It was then shown\textsuperscript{13} that there is a competition between displacement of "X" to give the phthalide VIII, and displacement of acyloxy with ring opening to give an o-substituted benzoic acid IX.

\[
\begin{align*}
\text{VII} & \quad + \quad R'\text{CdCl} \rightarrow \quad \text{VIII} \quad + \quad \text{IX} \\
R &= \text{H, CH}_3, \text{C}_6\text{H}_5; \quad R' = \text{CH}_3, \text{C}_2\text{H}_5; \\
X &= \text{Br, OH, OCH}_3, \text{OC}_2\text{H}_5, \text{OCO}^-, \text{CH-O}^-
\end{align*}
\]

These same authors have also shown that acyloxy displacements with organocadmium reagents are possible in acyclic
esters as well.

\[ \text{Ph-C} \equiv \text{O-CH-Ph} \xrightarrow{\text{PhCdCl}} \text{Ph-C} \equiv \text{OCH-Ph} \]

\( X = \text{Cl} \)  \( (29\%) \)

\( X = \text{OOCOCPh} \)  \( (13\%) \)

\[ \text{Ph-C} \equiv \text{O-CH-CH=CH-Ph} \xrightarrow{\text{PhCdCl}} (\text{Ph})_2\text{CHCH=CH-Ph} \]

It is of interest that the chloro group is displaced in preference to the benzoyloxy group. Further, these displacements may be considered as taking place at a benzylic carbon, since esters without the benzylic carbon moiety (chloromethyl and \( \alpha \)-chloroethyl) gave no evidence of displacement.

Cason and Schmitz\(^\text{14}\) have succeeded in replacing the chlorocarbonyl group of triphenylacetyl chloride by using organocadmium reagents. The product was generated in competition with ketone formation.

\[ (\text{Ph})_3\text{CCOCl} \xrightarrow{\text{R}_2\text{Cd}} (\text{Ph})_3\text{CR} + (\text{Ph})_3\text{CH} + (\text{Ph})_3\text{COR} \]

\( X \quad \text{XI} \quad \text{XII} \)

\| \text{\% Yields} \|
\| R \|
\| X \| \text{XI} \| \text{XII} \\
| CH\_3 | 0 | 11 | 73 |
| C\_2H\_5 | 11 | 13 | 39.5 |
| n-C\_4H\_9 | 11.5 | 17.5 | 46 |
Before the details of halogen displacement by cadmium reagent can be considered, the type of reaction must be known; i.e., does it involve an ionic or free radical displacement? Halogen displacement by an organometallic compound has been studied extensively in the case of the Wurtz reaction. This coupling may be visualized as following one of the two

\[
R - X + Na \xrightarrow{NH_3} R - R
\]

general pathways, free-radical or nucleophilic substitution.

\[
R^* + R^* \rightarrow R - R \quad (13)
\]

or,

\[
R^- + R-X \rightarrow R - R + X^- \quad (14)
\]

This latter possibility was studied by Cristol, Ragsdale, and Meek, using a Wurtz-like reaction. The reaction of phenyl- or methyllithium with n-butyl or tert-butyl chloride was found to be second-order, first-order in each reagent. The reactions with n-butyl chloride gave coupling and elimination, whereas with tert-butyl chloride, only elimination was observed. Because the reactivity of n-butyl chloride and tert-butyl chloride with phenyllithium was about the same, the results were explained in terms of a direct displacement (SN2) or elimination (E2) mechanism. The same authors, studying the reaction of α- and γ-methallyl chlorides with phenyllithium, obtained substantially identical mixtures comprising 90-95% crotylbenzene and 5-10% α-methallylbenzene. These results were interpreted as involving a carbonium ion intermediate.

In summary, Cristol, et al., state that it
appears that a displacement mechanism either of the $S_{N1}$ or $S_{N2}$ type is available for the reaction of organolithium compounds with alkyl halides, and also as well for the Wurtz reaction. By assuming a duality of mechanisms for such reactions, they attempted to rationalize the inconsistency of the results observed for the reactions of optically active halides with sodium, where some systems led to complete racemization and others led to Wurtz-type products with a limited amount of optical activity, and with inversion in the displacement of halogen by alkyl group.

Lane and Ulrich attempted to demonstrate that the Wurtz reaction proceeds through an ionic mechanism. They found that the action of ethyl sodium on (-)-2-bromo-octane (XIII) afforded a small amount of racemic 7,8-dimethyltetradecane (XIV); with (+)-2-chlorooctane (XV) they obtained a small amount of (+)-7,8-dimethyltetradecane (XVI). These two reactions were assumed to proceed by two different pathways. The first one was thought to involve an $S_{N1}$ mechanism:

(-)$-C_8H_{17}Br \xrightarrow{\text{slow}} Br^- + (\pm)-C_8H_{17}^+ \xrightarrow{\text{concerted}} (+)-C_8H_{17}^\text{Na}$

XIII

(\pm)-(C_8H_{17})_2 + meso-(C_8H_{17})_2

XIV

The second reaction was postulated as going by way of a concerted mechanism:

(+)$-C_8H_{17}Cl + (\pm)-C_8H_{17}^\text{Na} \xrightarrow{\text{concerted}} (+)-(C_8H_{17})_2$

XV

+ meso-(C_8H_{17})_2

XVI

(15) (16)
They then proposed that, if the Wurtz reaction goes by an ionic mechanism, it should be possible to observe similar results in a "true" Wurtz reaction. Indeed, the action of sodium on optically active 2-bromooctane gave inactive dimethyltetradecane (11%), while sodium and optically active 2-chlorooctane afforded active (-)-7,8-dimethyltetradecane (16%).

Postulating a four center transition state:

\[
\begin{array}{c}
\text{R} \\
\text{δ}^+ \quad \text{X} \quad \text{δ}^- \\
\text{δ}^- \\
\text{R} \quad \text{M} \quad \text{δ}^+
\end{array}
\]

these authors stated that, if bond making and bond breaking are synchronous, R will not only remain optically active but also retain its configuration. But if the newly formed carbon-carbon bond lags in its formation, the product will be optically inactive. When the stereochemistry of the above reaction was later studied\textsuperscript{25}, however, it was concluded that an inversion had taken place.

Furthermore, in the following similar reaction, the observed stereochemistry is in contradiction to the four-center transition state.\textsuperscript{26}

\[
(+)-2\text{-bromobutane} + C_4H_9Li \rightarrow (+)-3\text{-methylheptane (2%)} + (+)-3\text{-methylheptane (98%)}
\]

Direct S\textsubscript{N}2 displacement seems reasonable to account for the inversion pathway; however, the large amount of racemization may be due to a free-radical pathway.

The radical mechanism for the Wurtz reaction has been
postulated by several workers\textsuperscript{27,28} the main line of evidence being complete racemization of alkyl halides under Wurtz conditions, coupling of aryl halides, and the formation of ethane and ethylene from the reaction of ethyl iodide and sodium.

The fact that free radicals are present, at least to some degree in the Wurtz reaction, has been shown recently by Bryce-Smith.\textsuperscript{29} Isopropylbenzene was used to detect and estimate the presence of free radicals (see Figure 1 below). When various organometallics were used, the homolytic reaction appeared to occur in competition with heterolytic coupling and elimination reactions.

The ease of free-radical formation was dependent on the metals, which fit the following order: Mg \simeq Li > Na > K.

![Figure 1](image)

\[ M = \text{Li, K, Na, or Mg} \]

1. \( \text{RBr} + 2\text{Li} \rightarrow \text{RLi} + \text{LiBr} \)
2. \( \text{RLi} + \text{RBr} \rightarrow 2\text{R}^\cdot + \text{LiBr} \)
3. \( \text{PhCH(CH}_3)_2 + \text{R}^\cdot \rightarrow \text{PhC(CH}_3)_2 + \text{RH} \)
4. \( 2\text{PhC(CH}_3)_2 \rightarrow \text{Ph-C-C-Ph} \quad (\text{mp } 118^\circ) \)

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

It is reasonable that the carbon-cadmium bond, which is less polar than the carbon-magnesium bond, also might undergo homolytic cleavage.

Finally, the ionic mechanism has received strong support from the work of DeVries, Wepster, and Verkade.\textsuperscript{30} Optically active 1-phenylethyl chloride or bromide, when treated
with a solution of lithium, sodium, or potassium in liquid ammonia, yields optically active 2,3-diphenylbutanes admixed with the meso isomer. Values for the optical purity of 2,3-diphenylbutanes ranged from 3 to 30%.

These same authors found that racemic 1-phenylethyl chloride and a solution of sodium in liquid ammonia under varying conditions always afforded a mixture of 52% meso- and 48% racemic 2,3-diphenylbutane. But in the case where optically active 1-phenylethyl chloride was used, different results were obtained. This, of course, would not be expected for a free-radical intermediate. Although this work supports very strongly the suggestion that the Wurtz reaction proceeds by way of an ionic mechanism, it does not rule out the possibility that free radicals may also be present.
EXPERIMENTAL

Instrumentation. Infrared (IR) spectra were recorded with Perkin-Elmer Model 337 and Model 700 grating spectrophotometers. All spectra were run neat or as films. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian A-60 spectrometer and recorded in ppm downfield from tetramethylsilane used as an internal standard. Gas liquid phase chromatography (GLPC) was accomplished with a Varian Model 90-P gas chromatograph, with a recorder speed of one inch per minute. The columns were all 10 feet long and 1/4 inch in diameter. Peak areas were determined by using the product of the height times the width at half height, except in those cases noted, where a Sargent-Welch disc integrator was used. Yields were calculated by GLPC, using a measured amount of pure material and determining the peak area, and then comparing it with the corresponding peak area of the crude mixture. Rotations were obtained by using a Zeiss Polarimeter. Melting points, determined with a Hoover Melting Point Apparatus, are uncorrected.

Materials. Grignard reagents were prepared under anhydrous conditions using reagent-grade magnesium turnings and the appropriate halo compound. The solutions were refrigerated in serum-capped bottles, and their normality was obtained by titration with sec-butyl alcohol as titrant and 1,10-phenanthroline as indicator. Anhydrous cadmium chloride (reagent grade) was oven dried for at least 24 hr at 110°. The halogenated compounds were obtained from Aldrich Chemical Company, unless otherwise indicated.
**Experimental Apparatus.** Most of the reactions were run using a 3-necked, round-bottomed flask, fitted with a mechanical stirrer, reflux condenser, and pressure-equalizing addition funnel. Before each reaction the entire apparatus was flame-dried. Grignard reagents were transferred to the flask from the serum-capped bottles with a 20-ml syringe. Nitrogen was not used as an inert atmosphere, except where noted.

**Reaction of Phenylcadmium Reagent with Ethyl α-Bromopropionate.**

Phenylcadmium reagent (0.10 mol) in 100 ml of anhydrous ether was prepared from the Grignard reagent (22 ml, 0.10 mol) of bromobenzene, 4.71g (0.10 mol) of magnesium turnings, and 18.33g (0.20 mol) of anhydrous cadmium chloride. After a negative Gilman test, 6.5 ml (0.10 mol) of ethyl α-bromopropionate in 25 ml of anhydrous ether was added dropwise to the solution with stirring under reflux over a three-hour period. The reaction was then hydrolyzed with 10 ml of water, dried with MgSO₄, and the ether removed with a rotary evaporator. Some of the crude material was then injected into a glpc column (10% Carbowax, 150°, 50 ml/min helium) and the peaks collected directly onto salt plates, from which the infrared spectra were measured. The first peak (1.1 cm), too volatile to collect, was probably ether, inasmuch as an injection of pure ether emerged at this point on the chromatogram. The next peak appeared at 1.7 cm and the ir spectrum (No. 9476) indicated it to be ethyl propionate as shown by comparison with Sadtler spectrum No. 303. However, a few extra peaks present correspond to strong infrared absorbances of benzene (ir No. 9502). Further, the possibility that benzene and ethyl propionate were emerging from the column at the same place was confirmed by their identical retention times under the same column conditions. The next peak
observed (5.5 cm) was identified as ethyl α-bromopropionate (ir No. 9503). At 26.4 cm, ethyl hydratropate was observed by comparison of its ir spectrum (No. 9497) with an established spectrum (No. 8985) of this material. The final peak appearing at about 56 cm on the chromatogram was collected as a white solid in the collecting tube (the end of a disposable pipet). The melting point of this material, biphenyl, was 68-70°C [lit 70°]. The possibility that either phenol or bromobenzene was present was considered; a pure sample of each was injected on the glpc column under the above conditions. However, no peak corresponding to either was evident, the nearest being at 5.5 cm; the infrared spectrum did not indicate either compound to be present.

Refluxing of Phenylmagnesium and Phenylcadmium Solutions.

A solution of phenylmagnesium bromide (0.1 mol) in 150 ml of anhydrous ether was prepared in the usual manner, as was a solution of phenylcadmium reagent (0.10 mol) also in 150 ml of anhydrous ether. These solutions were allowed to reflux with stirring for twelve hours. Each reaction was then quenched with 120 ml of 10% NaHCO₃. Both solutions were decanted from the salt precipitates and then the precipitates were washed twice with 6 N HCl. Each aqueous solution was extracted three times with ordinary ether, and the extracts were combined with the corresponding original decantate. Both solutions were dried over MgSO₄, and the ether removed. After standing for a few hours, both solutions began to solidify, and a characteristic biphenyl odor was observed. In order to remove cadmium or magnesium salts, both samples were taken up in dry benzene, filtered, and the benzene allowed to evaporate. The Grignard reaction yielded 4.0g of biphenyl, while the phenylcadmium reaction yielded 2.3g of
biphenyl, mp 69-70°C [lit 70°C].

Formation of S-(-)-Methyl Lactate.

A 1-1 single-necked, round-bottomed flask was fitted with a Claisen head, an addition funnel, a magnetic stirrer, and a distillation condenser pointed downward. An alcoholic potassium hydroxide solution was prepared by dissolving 25g of potassium hydroxide in 40 ml of water and 125 ml of 95% of ethanol. This solution was placed in the flask, which was partially immersed in a water bath at 65°C. Diazald (108g, 0.5 mol) dissolved in 500 ml of anhydrous ether was then added dropwise. Diazomethane was liberated and was collected in a 250-ml, 3-necked, round-bottomed flask, immersed in an ice bath. One of the necks of the flask was connected to a 250-ml Erlenmeyer flask, partially submerged in an ice bath. This last flask contained 50 ml of anhydrous ether, and its purpose was to collect any diazomethane not condensed in the first flask. After all the ethereal Diazald was added to the alcoholic potassium hydroxide solution, an additional amount of dry ether was added, until the liquid coming into the 3-necked flask was colorless, instead of the usual light green color. Ether from the Erlenmeyer flask acting as a trap was then added to the 3-necked flask. The S-(+)-lactic acid (31.8g, 0.3 mol), dissolved in 75 ml of anhydrous ether, was added dropwise to the diazomethane solution, which was being stirred magnetically. After the greenish-yellow color had disappeared, the solution was stirred for an additional hour, after which the ether was removed on the rotary evaporator. The remaining product was vacuum distilled twice, and the product collected at 30-40°/6 mm. An infrared spectrum of the product (No. 8968) confirmed the identity of methyl lactate by comparison with a standard Sadtler spectrum (No. 24952). Five μl of the methyl lactate were injected into a gas
chromatograph, SAIB column, 170°, with a flow of 50 ml/min of helium. Only one peak was observed. The optical rotation of the S-(-)-methyl lactate is shown in Table 2.

Formation of R- (+)-Methyl α-Bromopropionate.

Optically active R- (+)-methyl α-bromopropionate was prepared according to the method of Gerrand and Richmond. A 250-ml, 3-necked round-bottomed flask was equipped with a reflux condenser, addition funnel, and stirrer and placed in an ice bath at -10°. Phosphorous tribromide was placed in the flask, and to it S-(-)-methyl lactate was added dropwise. The reaction was allowed to come to room temperature, and was stirred for an additional hour. The solution was then hydrolyzed by pouring it dropwise onto crushed ice. The bottom yellow layer containing the organic product was separated from the aqueous layer. The aqueous layer was then washed three times with small portions of anhydrous ether, and the washing combined with the organic layer. Finally, the organic layer was washed three times with water in order to remove any unreacted methyl lactate and any inorganic acids present. After drying with MgSO₄ and removal of the ether, the product was vacuum distilled, and the fraction, boiling at 30-32°/8 mm Hg, was collected. The infrared spectrum of this product (No. 8985) indicated that it was very similar to the ir spectrum of ethyl α-bromopropionate (No. 8995). A 2-μl sample of the product was passed through the glpc (SAIB, 170°, 50 ml/min of helium) and only one peak was obtained. The rotations of the product are shown in Table 3.

Reaction of Phenylcadmium Reagent with R- (+)-Methyl α-Bromopropionate.

A. In a 250-ml, 3-necked round-bottomed flask, equipped with a mechanical stirrer, reflux condenser, and
Table 2

Rotation of S-(-)-Methyl Lactate

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Blank Rotation</th>
<th>$\alpha^{26}\text{ (neat, } \ell = 1.0 \text{ dm)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>365</td>
<td>0.000°</td>
<td>-14.435°</td>
</tr>
<tr>
<td>405</td>
<td>0.000</td>
<td>-15.195</td>
</tr>
<tr>
<td>436</td>
<td>0.000</td>
<td>-14.505</td>
</tr>
<tr>
<td>546</td>
<td>0.000</td>
<td>-10.540</td>
</tr>
<tr>
<td>578</td>
<td>0.000</td>
<td>-9.670</td>
</tr>
</tbody>
</table>
Table 3

Rotation of R- (+)-Methyl α-Bromopropionate

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Blank Rotation</th>
<th>$\alpha^{26}_{\text{(neat, } \lambda = 1 \text{ dm)}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>365</td>
<td>0.000°</td>
<td>+273.035°</td>
</tr>
<tr>
<td></td>
<td>(0.270)</td>
<td>(270.355)</td>
</tr>
<tr>
<td>404</td>
<td>0.000</td>
<td>+183.235</td>
</tr>
<tr>
<td></td>
<td>(0.120)</td>
<td>(185.310)</td>
</tr>
<tr>
<td>436</td>
<td>0.000</td>
<td>+144.530</td>
</tr>
<tr>
<td></td>
<td>(0.070)</td>
<td>(146.350)</td>
</tr>
<tr>
<td>546</td>
<td>0.000</td>
<td>+76.755</td>
</tr>
<tr>
<td></td>
<td>(0.005)</td>
<td>(77.235)</td>
</tr>
<tr>
<td>578</td>
<td>0.000</td>
<td>+66.205</td>
</tr>
<tr>
<td></td>
<td>(0.000)</td>
<td>(66.750)</td>
</tr>
</tbody>
</table>

*Duplicate runs recorded.*
addition funnel, was placed 0.04 mol of phenylcadmium reagent in 75 ml of anhydrous ether. The phenylcadmium chloride solution was prepared by combining 0.04 mol of phenylmagnesium bromide and 7.35 g (0.04 mol) of anhydrous cadmium chloride. The solution was then stirred for one-half hour at room temperature, after which time a negative Gilman test indicated the absence of Grignard reagent. To the phenylcadmium reagent 3.34 g (0.02 mol) of (+)-methyl α-bromopropionate in 10 ml of anhydrous ether was added dropwise. The mixture was then allowed to reflux for three days. Thereupon, it was hydrolyzed with 10 ml of distilled water. Only one liquid resulted, along with a considerable amount of pasty, gray-white precipitate. This precipitate was washed three times with 25-ml portions of anhydrous ether and the washings combined with the liquid obtained from the reaction. The solution was dried over MgSO$_4$ and the ether removed on the rotary evaporator. The crude reaction mixture was then separated by vacuum distillation and the fraction, bp 55-60°C/1 mm, was collected. The ir spectrum of this product (No. 8992) indicated that it was methyl hydatropate. A chromatogram (SAIB, 170°, 50 ml/min of helium) showed that besides the methyl hydatropate, a small amount of biphenyl was also present. The optical rotations of this product are shown in Table 4. The sample was further purified by preparative glpc, (SAIB, 170°, 50 ml/min of helium) and the rotation again measured. The results are given in Table 5.

The amide of methyl hydatropate was prepared as follows. The sample of methyl hydatropate was saponified by refluxing with 12 ml of 10% potassium hydroxide for ten hours in a 25-ml, round-bottomed flask. The solution was then neutralized with dilute HCl until acid to litmus. Three ml of thionyl chloride were added and the solution stirred for 24 hr at room temperature. Excess concentrated ammonia
Table 4

Rotation of Methyl Hydratropate

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Blank Rotation</th>
<th>$\alpha^27$ (neat, $l=0.20$ dm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>365</td>
<td>0.000°</td>
<td>+0.200°</td>
</tr>
<tr>
<td>405</td>
<td>0.000</td>
<td>+0.160</td>
</tr>
<tr>
<td>436</td>
<td>0.000</td>
<td>+0.140</td>
</tr>
<tr>
<td>546</td>
<td>0.000</td>
<td>+0.075</td>
</tr>
<tr>
<td>578</td>
<td>-0.005</td>
<td>+0.060</td>
</tr>
</tbody>
</table>
# Table 5

Rotation of Methyl Hydratropate after GLPC Purification (A)

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Blank Rotation</th>
<th>$\alpha^{27}$\text{ (neat, } \ell = 0.10 \text{ dm)}</th>
</tr>
</thead>
<tbody>
<tr>
<td>365</td>
<td>0.000°</td>
<td>+0.100°</td>
</tr>
<tr>
<td>405</td>
<td>0.000</td>
<td>+0.065</td>
</tr>
<tr>
<td>436</td>
<td>0.000</td>
<td>+0.060</td>
</tr>
<tr>
<td>546</td>
<td>0.000</td>
<td>+0.035</td>
</tr>
<tr>
<td>578</td>
<td>0.000</td>
<td>+0.025</td>
</tr>
</tbody>
</table>
was added and the mixture stirred for one hour. A small amount of white precipitate resulted which was washed twice with deionized water, mp 91-92°, lit mp 92-92.5°.5

B. The above reaction was repeated using 4.10g (0.025 mol) of (+)-methyl α-bromopropionate and 0.050 mol of phenylcadmium reagent in 50 ml of anhydrous ether. After a three-hour reflux period and the usual workup, a crude reaction mixture was obtained. Methyl α-bromopropionate, after isolation by glpc, was identified by comparison of its ir spectrum (No. 10814) with a known spectrum (No. 8985). In a similar manner, the identity of methyl hydratropate was established by comparison of its ir spectrum (No. 10815) with a known ir spectrum (No. 8992). By means of preparative gas chromatography, as described above, enough methyl hydratropate was obtained to take its optical rotation. The results are given in Table 6. Methyl α-bromopropionate was more difficult to isolate, and studies done to determine if it racemized during reaction are described below.

Study of Racemization of R-(+)-Methyl α-Bromopropionate.

A. On standing. The (+)-α-bromopropionate ester was allowed to stand for two weeks at room temperature. The rotations of the material at the beginning and the end of this time period are given in Table 7. A racemization of 1-3% was observed.

B. Gas Chromatography. Because of the small amount of the (+)-α-bromopropionate ester isolated, the sample was diluted to 50:50 V/V mixture with carbon tetrachloride. The rotation of this solution in a 0.1-dm cell at room temperature was 4.595° at 365nm, with a blank reading of 0.025°. After the sample was reinjected through the glpc, and the ester collected, a 10:90 V/V mixture (ester:CCl₄) was
Table 6

Rotation of Methyl Hydratropate after GLPC Purification (B)

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Blank Rotation</th>
<th>$\alpha^{27}$ (neat, $l=0.10$ dm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>365</td>
<td>0.000°</td>
<td>+0.065°</td>
</tr>
<tr>
<td>405</td>
<td>0.000</td>
<td>+0.050</td>
</tr>
<tr>
<td>436</td>
<td>0.000</td>
<td>+0.050</td>
</tr>
<tr>
<td>546</td>
<td>0.000</td>
<td>+0.035</td>
</tr>
<tr>
<td>578</td>
<td>0.000</td>
<td>+0.020</td>
</tr>
</tbody>
</table>
Table 7

Rotation of R- (+)-Methyl $\alpha$-Bromopropionate
after Standing Two Weeks

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Blank Rotation</th>
<th>$\alpha^{27}$(neat, $\lambda = 0.10$ dm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>365</td>
<td>-0.005°</td>
<td>+7.710°</td>
</tr>
<tr>
<td>405</td>
<td>-0.005</td>
<td>+5.380</td>
</tr>
<tr>
<td>436</td>
<td>0.000</td>
<td>+4.170</td>
</tr>
<tr>
<td>546</td>
<td>0.000</td>
<td>+2.195</td>
</tr>
<tr>
<td>578</td>
<td>0.000</td>
<td>+1.890</td>
</tr>
<tr>
<td>Final</td>
<td></td>
<td></td>
</tr>
<tr>
<td>365</td>
<td>0.000</td>
<td>+7.605</td>
</tr>
<tr>
<td>405</td>
<td>0.000</td>
<td>+5.215</td>
</tr>
<tr>
<td>436</td>
<td>0.000</td>
<td>+4.110</td>
</tr>
<tr>
<td>546</td>
<td>0.000</td>
<td>+2.150</td>
</tr>
<tr>
<td>548</td>
<td>0.000</td>
<td>+1.845</td>
</tr>
</tbody>
</table>
prepared. The rotation under the above conditions was 0.520° 
($l = 0.1\text{dm}$).

C. Ratio of Peak Areas from Gas Chromatography and 
Rotation from Polarimeter. The crude product obtained from 
the reaction of (+)-methyl α-bromopropionate and phenyl-
cadmium reagent was placed in a 1-dm polarimeter tube and 
it's rotation obtained at room temperature. The rotations 
were 13.070° at 564 nm and 11.310° at 578 nm. This sample 
was then injected into the gas chromatograph (FFAP, 170°, 
50 ml/min of helium), and the peak due to methyl α-bromo-
propionate was found to be 142 units, using a disc integra-
tor. Next, to this sample of crude reaction mixture, pure 
R-(+)α-bromopropionate ester was added, and the optical 
rotations measured. Values of 22.390° (578 nm) and 19.495° 
(578 nm) were obtained when this sample was placed on the 
above glpc column. Under the same conditions, the peak area 
due to the bromo ester was found to be 233 units on the disc 
integrator.

The increase in peak area due to the R-(+)α-bromo-
propionate ester along with the increase in the optical 
rotation of this same ester were compared with the corre-
spending peak area and optical rotations of the original crude 
mixture. This allows the amount of racemization to be calcu-
lated. Specific details are listed in the Discussion Section.

Reaction of Ethyl α-Bromopropionate with Phenylcadmium Reagent 
in the Presence of Cyclohexene.

In a 250-ml, 3-necked round-bottomed flask were placed 
75 ml of anhydrous ether and 0.05 mol of phenyl Grignard 
reagent. To this solution 9.16g (0.05 mol) of anhydrous cad-
mium chloride were added and the mixture was stirred at room 
temperature for one-half hr. After a negative Gilman test,
7.6g (9.7 ml) of cyclohexene was added, followed by 6.5 ml (0.05 mol) of ethyl α-bromopropionate. The mixture was allowed to reflux for 16 hr, then hydrolyzed with 10 ml of water, dried with MgSO₄, filtered, and the ether removed. The crude sample was then injected into a gas chromatograph (SAIB, 170°, 50 ml/min of helium) and the chromatogram compared with one from a reaction mixture that was identical with the above, except that it did not contain any cyclohexene. Other than an additional cyclohexene peak, both chromatograms were very similar.


The reaction between phenylcadmium reagent (0.10 mol) and ethyl α-bromopropionate (0.05 mol) in 50 ml of anhydrous ether was studied by electron paramagnetic resonance (epr) spectroscopy. Aliquots of the reaction were taken at various time intervals and placed in a standard nmr tube. The following instrument settings were used while the spectra were run: Scan Range 406; Time Constant 0.30 sec; Field Set 73.023 G; Scan Time 0.5 min; Receiver Gain 3.2 x 10³; Temperature 30°C; Microwave Power 10 mV; Microwave Frequency 2.23 GHz. Before the experiment was started, several background spectra were taken. First of all, the epr spectrum from an empty nmr tube gave a very small signal. When a portion of the phenylmagnesium bromide reagent was placed in the nmr tube no absorbance was observed. Likewise, phenylcadmium reagent prepared in the usual way failed to give an epr signal by itself. When bromopropionate ester was added to the phenylcadmium reagent at room temperature, and an aliquot immediately removed and measured, a very strong epr signal was observed. The reaction mixture was stirred at room temperature for an
additional half-hour before the next spectrum was taken. The signal was still evident but of considerably diminished intensity. After the mixture had been refluxed for one-half hr, the resulting epr signal showed an extremely small absorbance, almost the same as for an empty nmr tube. Spectra were taken after further refluxing for additional time periods of one-half hr, six hr, and three days. The last spectrum did not show any absorbance. As a further control experiment, it was found that a 20% solution of ethyl α-bromopropionate in ether did not show any epr absorbance. In order to eliminate the possibility that peroxides in the ether could be causing free radicals in the reaction, the ether was tested with an iodine solution (2% KI plus a few drops of HCl). The test was negative.

**Reaction of Phenylcadmium Reagent with Ethyl α-Bromopropionate in the presence of Azobisisobutyronitrile (AIBN).**

The phenylcadmium reagent (0.10 mol) was prepared in the usual manner, and to this solution 0.5g of AIBN was added. The epr spectrum was then taken under the following conditions: Scan Range 40 G; Field Set 73.23; Time Constant 0.30 sec; Scan Time 0.5 min; Modulation Amplitude $3.2 \times 10^3$; Receiver Gain $3.2 \times 10^3$; Temperature 29°C; Microwave Power 12.1 mV; Microwave Frequency 9.24 GHz. A very small amount of absorbance was observed, similar to the epr absorbance for an empty nmr tube. Ethyl α-bromopropionate (0.05 mol) was added to the above cadmium solution at room temperature. An aliquot was then taken and the epr spectrum measured. No absorbance could be observed. Similar results were obtained after one-half hr and six hr of refluxing.
Gas Chromatographic Analysis of AIBN Experiments.

The above two reactions of phenylcadmium reagent with ethyl α-bromopropionate, with and without AIBN, were analyzed by glpc (SAIB, 170°, 50 ml/min of helium). The run that was made in the absence of AIBN produced the usual product, ethyl hydratropate, identified by its infrared spectrum. The usual side products were also present: ethyl α-bromopropionate, ethyl propionate, biphenyl and benzene. The reaction mixture containing AIBN did not produce any ethyl hydratropate or any other product, other than the usual side products, as indicated by gas chromatography under the above conditions.

Reaction between Ethyl α-Bromopropionate and Phenylcadmium Reagent in the Absence of Oxygen and Light.

The usual reaction between phenylcadmium reagent (0.10 mol) and ethyl α-bromopropionate (0.05 mol) was run under nitrogen and with the reaction vessel carefully wrapped in aluminum foil to exclude light. After three hours of refluxing, the mixture was hydrolyzed and worked up in the usual manner. The crude mixture was put through the gas chromatograph (SAIB, 170°, 50 ml/min of helium); a chromatogram identical to those from the normal runs was obtained.

Reaction of Ethyl α-Bromoisobutyrate with Phenylcadmium Reagent.

A. Phenylmagnesium bromide (0.10 mol) in 100 ml of anhydrous ether was placed in a 250-ml, 3-necked round-bottomed flask, equipped with a reflux condenser, electric stirrer and addition funnel. Phenylcadmium reagent was prepared in the usual manner by addition of anhydrous cadmium chloride (0.10 mol). After a negative Gilman test, the vessel was immersed in an ice bath and ethyl α-bromoisobutyrate (9.75g, 0.05 mol) was added dropwise. The mixture was stirred at ice-bath
temperature for three hours, after which time the reaction mixture was quenched with about 20 ml of water. The solution was dried with MgSO$_4$, filtered, and the ether removed. When the crude product was placed on a glpc column (SAIB, 170°, 50 ml/min of helium), several peaks were observed. At about 46.0 cm, the usual biphenyl peak was found (mp 69-70°C); a weaker peak at 22.0 cm was shown to be phenol by its ir spectrum (No. 9009); a peak at 30.0 cm was found to contain a carbonyl absorbance at 1730 cm$^{-1}$, but no aromatic bands in its ir spectrum (No. 9005). A small amount of this peak was collected by preparative glpc, bp 238-240°/760 mm (capillary tube micro-boiling apparatus). This is indicative of diethyl tetramethylsuccinate. Finally, the peak at 5.7 cm was found to contain both ethyl α-bromoisobutyrate and bromobenzene. (See ir Nos. 9099, 9132, 9134, 9100 and 9101).

B. The above reaction was repeated, but this time the mixture was stirred at room temperature for three hours, with results similar to those above.

C. The above reaction was again repeated, except that the reaction mixture was refluxed for three hours, again giving results similar to those above.

Reaction of Ethyl 2-Bromo-3-methylbutanoate with Phenyl-
cadmium Reagent.

A 250-ml, 3-necked round-bottomed flask, fitted with a mechanical stirrer, reflux condenser, and addition funnel was assembled. Ethyl ether (75 ml), together with 40 ml of 2.50 N phenyl Grignard reagent (0.10 mol), was placed in the flask. The cadmium reagent was prepared by adding 18.33g (0.10 mol) of anhydrous cadmium chloride. The mixture was stirred for one-half hr, after which time the Gilman test was negative. To this solution, ethyl 2-bromo-3-methylbutanoate was added
and the reaction mixture was stirred under reflux for three hours. After hydrolysis with 10 ml of water, the ether layer was dried with MgSO₄ and the solvent removed. The crude mixture, analyzed by glpc (Apiezon L, 150°, 50 ml/min of helium) gave several peaks. The first one at 2 cm was probably ethyl ether. The second at 2.9 cm was not collected but an odor of benzene was detected during the recording of it. The third peak at 3.6 cm was collected for an ir spectrum. The spectrum (No. 9876) was identical with that of ethyl isovalerate (Sadtler No. 7394). Enough of this compound was collected for an nmr spectrum (No. 8965, CC1), 0.90 (m), 1.21 (t), 2.08 (s), 4.08 (q). The fourth peak (10.5 cm) collected was not identified, but the ir spectrum (No. 9877) containing the C-H stretching from 3000-2850 cm⁻¹, did not have any carbonyl stretching. The fifth peak collected at 42.8 cm had an ir spectrum (No. 9878) similar to the one of ethyl isovalerate. This could possibly be the coupling compound, diethyl 2,3-diisopropylsuccinate. The nmr (No. 8964) was similar to that of ethyl isovalerate but more complicated. The last peak at 64.5 cm afforded the usual white crystals of biphenyl. A very small peak was found at 8.0 cm, the retention time found for the starting material, ethyl 2-bromo-3-methylbutanoate.

Reaction of Ethyl Bromoacetate with Phenylcadmium Reagent.

A 250-ml, 3-necked round-bottomed flask was set up with a mechanical stirrer, reflux condenser and addition funnel. A solution of 0.10 mol of phenylmagnesium bromide (62.2 ml of 1.60 N solution) diluted with 50 ml of anhydrous ether was placed in the flask; to this, 18.33g (0.10 mol) of anhydrous cadmium chloride was added. After the solution had been stirred for one-half hr, it gave a negative Gilman test. To this solution 5.7 ml of ethyl bromoacetate (8.35g, 0.05 mol)
was added dropwise and the solution allowed to reflux for 3 hr. After hydrolysis with 10 ml of water, the ether layer was dried with MgSO₄ and the solvent removed. The crude mixture was then placed on the gas chromatograph (Apiezon L, 140°, 54 ml/min of helium) and several peaks were observed. The first two peaks at 1.5 and 2.2 cm were not collected; the first was probably ether, and the second had a benzene odor. The third peak (3.9 cm) was weak, but its ir spectrum (No. 9858) matched that of commercial ethyl bromoacetate. The retention time for pure ethyl bromoacetate and Peak 3 were the same. An ir spectrum (No. 9850) obtained for Peak 4 (6.7 cm) matched that of commercial bromobenzene (No. 9849). However, it was later established that the Grignard reagent used in the reaction contained bromobenzene. Peak 5 (9.1 cm) gave an ir spectrum (No. 9851) which could not be identified. However, no carbonyl peak was present, and the same compound was obtained from the reaction mixture of ethyl α-bromobutyrate and phenylcadmium reagent. The sixth peak at 21.0 cm gave an infrared spectrum (No. 9852) which matched that of ethyl phenylacetate (Sadtler, No. 882). The last peak at 64 cm was collected as a white solid, mp 69-70°, indicating it to be biphenyl. At no point was ethyl acetate found. Even its very distinctive odor was not noted from any of the peaks that were eluted near the place where commercial ethyl acetate was found to appear.

Reaction of Ethyl 2-Bromobutanoate with Phenylcadmium Reagent.

To 0.1 mol of phenylcadmium reagent in 100 ml of anhydrous ether was added dropwise 6.85g (7.0 ml, 0.05 mol) of ethyl 2-bromobutanoate in 25 ml of anhydrous ether. The solution was then refluxed for 3 hr, hydrolyzed with 10 ml of water, the ether layer dried with MgSO₄, filtered and the
solvent removed. The crude mixture was then injected into a glpc column (Apiezon L, 120°, 52 ml/min of helium), and the resulting peaks characterized. The first two peaks were probably ether and benzene. The third peak found at 3.5 cm and collected on salt plates had an infrared spectrum (No. 9824) that matched that of commercial ethyl butanoate (No. 9790). At this point the temperature of the column was raised to 170°, and the fourth peak appeared at 9.3 cm. Its ir spectrum (No. 9825) was identical with that of commercial ethyl 2-bromobutanoate (No. 9795). The next peak at 11.6 cm was not identified, but it did not have any carbonyl stretching in its ir spectrum (No. 9826). This same spectrum was obtained from the reaction mixture of ethyl bromoacetate with phenylcadmium reagent, as noted earlier. The sixth peak (24.1 cm) isolated was substantial in size, and its ir spectrum (No. 9827) was identical with that of ethyl α-phenylbutanoate (Sadtler No. 236). The last peak (40.3 cm) was collected as a white solid, mp 69-70°C, indicating it to be biphenyl.

**Reaction of Phenylcadmium Reagent with 3-Bromocyclohexene.**

To 0.1 mol of phenylcadmium reagent in 75 ml of anhydrous ether, 8.05g (0.05 mol) of 3-bromocyclohexene was added slowly with stirring. The reaction mixture refluxed vigorously for about five minutes without an external source of heat. After the initial reaction subsided, the mixture was refluxed for four hours; thereupon it was hydrolyzed with 10 ml of water. The supernatant liquid was decantated from the usual grayish-white precipitate. The precipitate was extracted twice with 50-ml portions of anhydrous ether, and the washings were combined with original decantate. The solution was dried with MgSO₄, filtered, and the ether removed
on the rotary evaporator, leaving 7.00g (7.40 ml) of crude product. Glpc analysis (10% Carbowax, 150°, 50 ml/min helium) gave three peaks. The first was probably ether or water. The second peak had a retention time identical with that of the starting material. The third and strongest peak was collected at 23.4 cm. Its ir spectrum (No. A-1) indicated the presence of 3-phenylcyclohexene. Typical ir bands were found, C-H stretching, 3080 cm\(^{-1}\) (vinyl), 3050 cm\(^{-1}\) (aromatic), and 2850-2950 cm\(^{-1}\) (alkyl); C-C stretching, 1650 \(^{1}\) (vinyl), 1600, 1490 and 1450 \(^{1}\) (aromatic). The yield (81%) of 3-phenylcyclohexene was established by the method of peak enhancement.

The above reaction of 3-bromocyclohexene (0.05 mol) with phenylcadmium reagent (0.10 mol) was repeated and aliquots of the reaction mixture were removed at various time intervals, placed in an nmr tube, and the epr spectrum taken. Aliquots were taken immediately after mixing of the reagents at room temperature, after 5 min of stirring at room temperature, after 1/2 hr of refluxing, and after 4 hr of refluxing. None of the spectra indicated the presence of unpaired electrons.

Reaction of Chloromethyl Methyl Ether with Phenylcadmium Reagent.

A solution of 4.0g (0.05 mol) of chloromethyl methyl ether in 10 ml of anhydrous ether was added dropwise to a 0.1M solution of phenylcadmium reagent in 70 ml of anhydrous ether. The mixture was stirred under reflux for four hours; thereupon it was hydrolyzed with 10 ml of water. The solid grayish-white precipitate was washed twice with 25-ml portions of ether and the washings were combined with the original solution. Next, the solution was dried with MgSO\(_4\), filtered, and the solvent was removed. Some of the crude
mixture (6.00 ml) was placed on the glpc (Apiezon L, 160°, 54 ml/min helium) and three peaks were obtained. The first two were ether and benzene. The third peak at 7.5 cm was isolated; its ir spectrum (No. A-3) was identical with that of commercial benzyl methyl ether (Sadtler No. 17013). The yield, determined by the peak enhancement method, was 34%. No starting material or other byproducts were found.

Reaction of Benzyl Bromide with Phenylcadmium Reagent.

To 0.1 mol of phenylcadmium reagent in 75 ml of anhydrous ether, 8.55g (0.05 mol) of benzyl bromide was added dropwise with stirring at room temperature. The mixture was then refluxed for 10 hr. The mixture was hydrolyzed with 10 ml of water, and the solution was decanted from the grayish-white precipitate. The latter was washed twice with 25-ml portions of ether and the washings combined with the decantate. The solution was dried with MgSO₄, filtered, and the ether removed. A portion of the crude mixture was injected onto the gc (Apiezon L, 150°, 50 ml/min helium), and three peaks were observed. The first peak (1.8 cm), which appeared to contain more than one component, was not collected. The second peak at 2.4 cm was collected (ir No. A-5), but was not definitely identified. Possibly, it was either starting material (ir No. A-7) or toluene (ir No. A-9). The third peak collected at 15.3 cm (ir No. A-6) had the same infrared spectrum as diphenylmethane (Sadtler No. 3389). Its yield, as determined by the peak enhancement method, was 40%.

Reaction of Allyl Bromide with Phenylcadmium Reagent.

A solution of 6.05g (0.05 mol) of allyl bromide in 10 ml of anhydrous ether was added dropwise with stirring
to 0.1 mol of phenylcadmium solution diluted with 75 ml of dry ether. A slight amount of refluxing was noticed, which subsided after about five minutes. The reaction mixture was heated to reflux for an additional four hours. The mixture was hydrolyzed with 10 ml of water; the usual precipitate formed. The liquid was decantated from the solid, and the precipitate washed twice with 25-ml portions of ether. The washings were combined with the decantate, dried with MgSO₄, filtered, and the ether removed. This left 2.60 ml of crude product. A portion of the crude sample was then placed on the glpc, (10% Carbowax, 130°, 50 ml/min helium), and four major peaks were observed. The first peak was ether. The second peak at 2.4 cm had the same odor and retention time as allyl bromide. A peak at 10.7 cm was isolated and its ir spectrum (No. A-10) was identical with that of pure 3-phenylpropene (Sadtler No. 13701). A large peak was also observed at 16.1 cm, and its ir spectrum (No. A-11) was identical with that of bromobenzene (ir No. 9101). The yield of 3-phenylpropene was 39%, as determined by peak enhancement.

Attempted Reaction of Phenylcadmium Reagent with 1-Bromo-butane.

A. To a 0.1 mol solution of phenylcadmium reagent in 75 ml of anhydrous ether, 6.85g (0.05 mol) of 1-bromo-butane was added dropwise at room temperature. The solution was stirred under reflux for twelve hours. Thereupon, it was hydrolyzed with 10 ml of water, the liquid decanted, and the grayish-white precipitate washed twice with 25-ml portions of ether. The washings were combined with the original decantate, dried with MgSO₄, and the ether removed. The crude material was placed on a glpc (10% Carbowax, 100°, 50 ml/min helium) and three peaks were observed. The first
peak was probably the usual ether peak. The second peak at 5.6 cm gave an ir spectrum (No. A-14) that was identical with that of 1-bromobutane (No. A-15). The third peak at 7.0 cm gave an ir spectrum (No. A-16) which matched that of bromobenzene (No. 9101). No other peaks were observed.

B. The above reaction was repeated in the presence of AIBN for a reflux period of four hours with the same results.

**Attempted Reaction of Trimethylsilyl Chloride with Phenylcadmium Reagent.**

Trimethylsilyl chloride (10.8g, 0.10 mol) was added dropwise to 0.10 mol of phenylcadmium reagent in 75 ml of anhydrous ether. No heat evolution was noted. The solution was allowed to reflux for four hours, after which it was hydrolyzed with 10 ml of water and worked up in the usual manner. When a few µl of the crude mixture were injected into a glpc column (Apiezon L, 90°, 54 ml/min helium), three peaks resulted. The first peak at 2.3 cm could not be collected because of its high volatility. An infrared spectrum (No. A-18) of the second peak at 4.2 cm was identical with the spectrum of commercial trimethylsilyl chloride (No. A-19). The third peak at 6.2 cm gave a poor ir spectrum, but a very strong benzene odor was observed.

**Attempted Reaction of Chlorocyanomethane with Phenylcadmium Reagent.**

Chlorocyanomethane (3.88g, 0.05 mol) was added dropwise at room temperature under stirring to 0.10 mol of phenylcadmium reagent in 75 ml of anhydrous ether. No noticeable reaction was observed. The solution was heated for four hours under reflux and then hydrolyzed with 10 ml
of water. A brown viscous material was formed. The liquid portion was decanted; the residue was washed twice with 25-ml portions of ether and the washings combined with the decantate. The solution was dried with MgSO₄, filtered, and the solvent removed. A few microliters of the solution were placed on the glpc (10% Carbowax, 150°, 50 ml/min helium), with only two peaks resulting. The first one was very volatile and not isolated, while the second peak had a distinctive benzene odor. No peaks were found at 7.0 cm, the retention time for pure chlorocyanomethane. An ir spectrum (No. A-21) of the brown material contained very wide bands at 3500-2800 cm⁻¹ and 1750-1500 cm⁻¹.

Attempted Reaction of 1-Chloro-1-nitroethane with Phenylcadmium Reagent.

To 0.10 mol of phenylcadmium reagent in 75 ml of anhydrous ether at room temperature, 1-chloro-1-nitroethane (5.45g, 0.05 mol) was added dropwise with stirring. No significant reaction could be observed. The reaction mixture was then stirred for four hours under reflux, after which time it was hydrolyzed and worked up in the usual manner. A few microliters of the crude mixture were placed on a glpc column (Apiezon L, 150°, 54 ml/min helium) and three peaks were obtained. The first two peaks had the characteristic ether and benzene odors. The third peak at 5.4 cm was collected and its ir spectrum (No. A-23) was identical with that of starting material.

Attempted Reaction of Ethylene Bromide with Phenylcadmium Reagent.

Ethylene bromide (9.39g, 0.05 mol) was added dropwise to 0.10 mol phenylcadmium reagent in 75 ml of anhydrous
ether, with stirring at room temperature. Because no reaction could be noticed, the solution was stirred under reflux for four hours, hydrolyzed with 10 ml of water; a grayish-white precipitate resulted. The solution was decanted and the precipitate washed twice with two 25-ml portions of ether. The washings were combined with the decantate. The solution was dried with MgSO₄, filtered, and the ether removed to give a crude product. A 2-μl sample of this product was placed onto a glpc (10% Carbowax, 130°, 50 ml/min helium) and four peaks were observed. The first two peaks had the same retention time and odor of ether and benzene, respectively. At 10.2 cm a peak appeared which had the same retention time as ethylene bromide. Finally, a peak appeared at 15.8 cm and the ir spectrum (No. 10074) taken of this peak was identical with that of bromobenzene (ir No. 9101). However, it was found that the Grignard solution used to make up the phenylcadmium reagent contained bromobenzene.

Attempted Reaction of Bromoacetaldehyde Diethyl Acetal with Phenylcadmium Reagent.

To a solution of phenylcadmium reagent (0.10 mol) in 75-ml of anhydrous ether, bromoacetaldehyde diethyl acetal (9.85g, 0.05 mol) was added dropwise at room temperature. No reaction was noticed, and the mixture was stirred for four hours under reflux. The reaction mixture was then hydrolyzed with 10 ml of water, and a grayish-white precipitate was formed. The crude product was then isolated in a manner similar to the procedure described above, and a few ul were placed on the glpc (10% Carbowax, 100°, 50 ml/min helium). Three peaks appeared. The first two at 1.9 and 4.6 cm were probably ether and benzene, respectively. The third peak at 36.9 cm was isolated and its ir spectrum (No. A-28) matched that of pure bromoacetaldehyde diethyl acetal (No. A-25).
Attempted Reaction of tert-Butyl Chloride with Phenylcadmium Reagent.

To 0.1 mol of phenylcadmium reagent in 75 ml of anhydrous ether, tert-butyl chloride (4.6g, 0.05 mol) was added dropwise under stirring at room temperature. No reaction was noticed. The mixture was stirred under reflux for four hours, then hydrolyzed with 10 ml of water. A gray precipitate was formed and the decantate removed. The precipitate was washed twice with 25-ml portions of ether and combined with the decantate. The solution was then dried with MgSO₄, filtered, and the ether removed. A few μl of the crude product were put through the gas chromatograph (10% Carbowax, 100°, 50 ml/min helium) and three peaks were observed. The first at 2.3 cm was difficult to collect and no ir spectrum was taken. However, the retention time matched that of both ethyl ether and tert-butyl chloride. The second peak at 5.1 cm had the characteristic benzene odor. Finally, the last peak at 41.1 cm was collected on salt plates, and the ir spectrum (No. A-29) was identical with that of pure bromobenzene (No. 9101).

Attempted Reaction of Grignard and Cadmium Reagents with Styrene.

A solution of phenyl magnesium bromide (0.10 mol) in 50 ml of ether was prepared. About 10 ml of this solution was placed in a 5-in test tube, and then 10 ml of styrene added with vigorous shaking. No apparent reaction was observed. Next phenylcadmium reagent was prepared from the Grignard solution by adding cadmium chloride. After one-half hr of stirring, a negative Gilman test was observed. Ten ml of phenylcadmium solution were then placed in a 5-in test tube and mixed with 10 ml of styrene. Again, no polymerization reaction was noted. In a third test tube anhydrous
CdCl₂ was added to anhydrous ether and styrene, and vigorously mixed. The results were similar to those above, with no observable polymerization. Finally, 0.1 mol of phenylcadmium reagent in 50 of dry ether was prepared, and 25 ml of styrene added. After 12 hr of refluxing, no observable polymeric product could be detected.

Reaction of Phenylcadmium Reagent with Acetyl Chloride.

To 0.1 mol of phenylcadmium reagent in 75 ml of ether, 0.1 mol of acetyl chloride was added dropwise at room temperature with stirring. Immediately after mixing, an aliquot of the solution was removed, placed in an nmr tube and an epr spectrum taken. This was repeated 10 and 45 min after mixing. In none of these cases was an epr signal observed. The presence of acetophenone was evident by its characteristic odor.

Reactions with Ethylcadmium Reagent.

Attempted Reaction of Ethyl Bromoacetate with Ethylcadmium Reagent.

A. Ethylcadmium chloride (0.10 mol), prepared from a Grignard solution (0.10 mol 68.5 ml of 1.52 N EtMgBr) and anhydrous CdCl₂ (18.33g, 0.10 mol) was allowed to react with ethyl bromoacetate (0.05 mol) for twelve hours at room temperature with stirring. A reddish-brown polymer was formed. The mixture was then hydrolyzed with 10 ml of water, the liquid decanted, dried with MgSO₄, filtered, and the ether removed on the rotary evaporator. Portions of the crude product were then placed on the glpc (SAIB, Apiezon L, 10% Carbowax and STAP). The best conditions were: STAP, 65°C, 47 ml/min of helium. Only one peak resulted at 2.4 cm, which corresponded to ethyl ether. The peaks for ethyl acetate (13.7 cm) and ethyl bromoacetate (45.0 cm) were not observed.
An ir spectrum of the polymeric material did not give any characteristic peaks, only a very wide band between 2200 and 1400 cm⁻¹.

B. A similar reaction to that above was carried out in an ice bath, the results being the same. A polymer-like material was formed with no distinct ir spectrum. No other peaks from the decantate were observed by glpc.

**Reaction of 2-Bromoacetophenone with Ethylcadmium Reagent.**

To an ethylcadmium solution (0.10 mol) in 75 ml of anhydrous ether, 19.9g (0.10 mol) of 2-bromoacetophenone in 25 ml of dry ether was added dropwise at room temperature with stirring. Almost immediately, vigorous refluxing began and continued for over 10 min, after which the reaction mixture was heated to reflux for 4 hr. Then the mixture was hydrolyzed with 10 ml of water; a gray precipitate formed. The solution was decanted and the precipitate washed with two 25-ml portions of ether. The ether solution was combined with the decantate, dried with MgSO₄, filtered and the solvent removed. A few μl of the crude product were then injected into the gc, (SAIB, 150°, 50 ml/min helium), and four peaks were obtained. A 10% Carbowax column was also tried but resulted in a poor separation of peaks. The peak at 1.2 cm was too volatile to be collected for an ir spectrum. The second peak at 17.8 cm was collected, and the ir spectrum (No. A-30) indicated 1-phenyl-2-butanone, although a few bands in the fingerprint region were weak (see Sadtler 14 No. 14662). An nmr spectrum of the entire crude product (No. 9815) showed a singlet at 3.60 δ, which could correspond to the singlet for benzylic protons of 1-phenyl-2-butanone at 3.53 δ (see Sadtler nmr spectrum No. 547). Also, the nmr of the crude reaction mixture did not have a singlet at 4.43 δ indicative of nonaromatic protons of 2-bromoacetono-
phenone. The third peak at 21.6 cm was by far the largest. A sample of this peak was collected for an ir spectrum (No. A-31), which was in agreement with that of pure acetophenone (Sadtler No. 3226). In addition, the reaction mixture had an odor of acetophenone. The fourth peak (36.9 cm) was very weak, and it was difficult to collect enough for an ir spectrum. However, the spectrum that was taken (No. A-32) showed absorptions at 3050, 1600 and 1500 cm\(^{-1}\), indicative of aromaticity, and a carbonyl stretching band at 1730 cm\(^{-1}\). None of the ir spectra taken indicated 2-bromoacetophenone (Sadtler No. 4849) or butyrophenone (Sadtler No. 5772).

B. The above reaction was repeated and aliquots of the mixture were removed, placed in an nmr tube and an attempt made to observe an epr spectrum. Samples were taken immediately after mixing, 15 min after stirring at room temperature, 15 min after refluxing, and 4 hr after refluxing. None gave an epr spectrum.

**Reaction of Isopropylcadmium Reagent with Ethyl Bromoacetate.**

Isopropylmagnesium bromide (0.10 ml) was prepared from isopropyl bromide and magnesium ribbon in 150 ml of anhydrous ether. To this solution, 18.88g (0.10 mol) of anhydrous cadmium chloride was added and the solution was stirred for one-half hour, after which time a negative Gilman test was observed. Next, 0.10 mol of ethyl bromoacetate was added dropwise to the cadmium reagent at ice-bath temperature. The reaction was then stirred for two hours at ice-bath temperature, two hours at room temperature, and twelve hours at reflux. The reaction mixture was hydrolyzed with 10 ml of water; the organic layer was dried with MgSO\(_4\) and the ether removed. A sample of the crude reaction mixture was placed on the gc (SAIB). Four peaks, (A,B,C and D) were obtained.
These peaks were collected on salt plates and the infrared spectra taken. Peak "A" was difficult to collect and the ir (No. 8937) could not be identified. The spectrum from "B" was also weak, but the bands that appeared indicated ethyl bromoacetate. Commercial ethyl bromoacetate has the same retention time as "B". Compound "C" gave a distinctive infrared spectrum (No. 8939), showing a carbonyl stretching band at 1740 cm$^{-1}$. However, this spectrum did not match that of ethyl isovalerate given in the Sadtler Index (No. 7394). The ir spectrum of compound "D" proved to be identical with ethyl acetoacetate, Sadtler Index (No. 101).
DISCUSSION AND RESULTS

The possible mechanisms for the displacement of halogens will be discussed under the following groupings:

1. Analysis of the products from the reaction of α-bromo esters with phenylcadmium reagent
2. Stereochemistry and epr analysis of the displacement of bromine in α-bromopropionate ester with phenylcadmium chloride
3. Product analysis of the reaction of several halo compounds with phenylcadmium chloride
4. Reaction of alkylcadmium reagents with α-halo ketones

There are several ways in which a halogen may be displaced by an organometallic compound. Nucleophilic, electrophilic, free radical, and carbene mechanisms are all attractive possibilities, and it is also conceivable that two or more of these general types of mechanisms are operating simultaneously. Consider the following reaction:

\[ \text{CH}_3\text{-CHBr-COOEt} + \text{PhCdCl} \rightarrow \text{CH}_3\text{CH}_2\text{COOEt} + \text{CH}_2\text{CH(Ph)COOEt} \]

\[ + \text{Ph-Ph} + \text{Ph-H} \quad (1) \]

In order to explain these products, more than one mechanism may be necessary. The ethyl hydratropate could be accounted for by a direct nucleophilic displacement of the bromide atom by associated or dissociated phenyl reagent. This type of mechanism would not, however, provide for the
presence of ethyl propionate. In a similar reaction with butylcadmium reagent and α-bromo ester, Cason and Fessenden postulated enolate formation via a cyclic transition state to account for dehalogenated ester product. A similar intermediate may be drawn in the present case.

\[
\begin{align*}
\text{CH}_3 \text{CH}=\text{C} \text{Br} & \quad \xrightarrow{\text{C} \text{H}_3 \text{CH}=\text{C} \text{CdCl}} \quad \text{CH}_3 \text{CH}=\text{C} \text{OEt} + \text{PhBr} \\
\end{align*}
\]

However, the absence of any bromobenzene in the reaction mixture makes this seem less probable. The presence of benzene can be rationalized as resulting from the hydrolysis of the phenylcadmium reagent. The biphenyl product could arise by way of a free radical coupling of the cadmium reagent, independent of the displacement reaction. In fact, solutions of both 0.1 molar ethereal Grignard and cadmium reagents, which were hydrolyzed after 12 hr of refluxing, afforded both benzene and biphenyl. The Grignard solution gave 4.0 g of biphenyl, while the cadmium reagent solution gave only 2.3 g of biphenyl. A similar displacement reaction was observed from the reaction of ethyl bromoacetate with two molar equivalents of phenylcadmium reagent under reflux for three hours. As expected, both benzene and biphenyl were present in the product mixture, along with some starting material and the displacement product, ethyl phenylacetate. In addition to these products there was also obtained a small amount of some unidentified compound, whose infrared spectrum showed that it did not contain a carbonyl group.
In this reaction several attempts were made to detect the presence of ethyl acetate, but attempts to isolate enough sample for an ir spectrum were fruitless. Furthermore, even the very characteristic ethyl acetate odor could not be detected from any of the effluent peaks from the glpc near the place where ethyl acetate would have appeared if present.

In the reaction of phenylcadmium reagent with ethyl α-bromobutyrate, results analogous to the bromopropionate reaction were obtained. The components found were benzene, ethyl butyrate, starting bromoester, ethyl 2-phenylbutyrate, and biphenyl. A small amount of an unknown compound was also obtained, whose infrared spectrum was identical with that of the unknown in the reaction of phenylcadmium reagent with ethyl bromoacetate.

The reaction of ethyl 2-bromo-3-methylbutanoate with phenylcadmium reagent gave results somewhat different from those obtained above. In addition to benzene, biphenyl, ethyl isovalerate, and starting ester, a new product, which could be α,β-diisopropylsuccinate, was present. No displacement product, 2-phenyl-3-methylbutanoate, could be detected. Evidence for the succinate ester is found in the infrared and nmr data. First of all the ir spectrum for this compound is very similar to that of ethyl isovalerate. This would be expected because the coupling product is structurally similar to the isovalerate ester. The nmr spectrum (measured at 60 MHz) of the suspected succinate ester is in agreement with what is expected. In the nmr of ethyl isovalerate the methylene protons of the ethyl group appear as a quartet at 245 Hz, and the methyl protons appear as a triplet at 74 Hz. Now the coupling compound, ethyl diisopropylsuccinate, could exist as a dl pair and as a meso compound. The protons of the ethyl group should appear at slightly different positions in the
nmr. Thus, the ethyl moiety appears as a quartet at 247 Hz, and the methyl group appears as a triplet at 77 Hz, with a coupling constant of 6 cps. However, in addition to this, another weaker quartet appears at 244 Hz, and a corresponding triplet appears at 74 Hz with a coupling constant of 7 cps (see nmr spectrum No. 8964).

Convincing evidence for the presence of the enolate species in these reactions was found in the reaction of ethyl \(\alpha\)-bromoiso-butyrate with phenylcadmium reagent. The products of this reaction were not similar to any of the above reactions. The compounds identified, in addition to starting material, were benzene, biphenyl, phenol, ethyl tetramethylsuccinate, and bromobenzene. The presence of bromobenzene is consistent with enolate formation, as shown in Equation (2). The enolate may then displace bromide from the starting material to give ethyl tetramethylsuccinate.

In a similar reaction using butylcadmium reagent with ethyl \(\alpha\)-bromoiso-butyrate, Cason and Fessenden\(^6\) obtained the Claisen condensation product, ethyl 2,2,4-trimethyl-3-oxopentanoate, instead of the succinate product. The enolate formed in the present work may also condense in a Claisen-like manner:

1. \[ \text{Br-} \text{C COOEt} \xrightarrow{\text{RCdx slow}} \text{C-OEt} + \text{RX} \]

2. \[ \text{Br-} \text{C COOEt} \xrightarrow{\text{RCdX}} \text{Br-} \text{C COOEt} \]
By analogy with the generally accepted Claisen condensation mechanism, the reverse direction in Steps 2 and 3 is favored over the forward direction. A further analogy with the Claisen condensation of ethyl isovalerate, the last step probably drives the reaction to completion. This would be possible only if the R\(^-\) group is sufficiently nucleophilic to abstract bromine. Apparently this is the case with butylcadmium reagent but not with phenylcadmium reagent. The fact that Ph-H is a stronger acid than Et-H\(^{34}\) would indicate that R\(^-\) is a stronger nucleophile than Ph\(^-\). Therefore, since the reverse reactions are favored in Steps 2 and 3, the bromo keto ester should revert to starting material and enolate when phenylcadmium reagent is used. This makes the Claisen mechanism unlikely. It is still possible that the enolate displaces the bromide of the starting material to give tetramethylsuccinate in an irreversible step.

\[
(CH_3)_2 C(Br) COOEt + (CH_3)_2 C=O COOEt \rightarrow (CH_3)_2 C=O COOEt \quad \rightarrow \quad (CH_3)_2 C=O COOEt
\]
A similar reaction has been observed by Hudson and Hauser.\textsuperscript{33}

\[
\begin{align*}
\text{CH}_3 & \quad \text{NaCPh}_3 \quad 0.208 \text{ mole} \\
\text{H-} & \quad \text{C-} \quad \text{COOEt} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{0.208 mole} & \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{Br-C-} \quad \text{COOEt} \\
\text{CH}_3 & \quad \text{0.208 mole} \\
\end{align*}
\]

\[
\begin{align*}
(\text{CH}_3)_2- & \quad \text{C-} \quad \text{COOEt} \quad \text{(30\%)} \\
(\text{CH}_3)_2- & \quad \text{C-} \quad \text{COOEt}
\end{align*}
\]

If the formation of enolate is the rate-determining step in the keto ester product formation, it may be expected that the ester product and the aryl halide from arylcadmium reagent should be formed in stoichiometric amounts. In order to establish this quantitatively, three separate reactions of ethyl α-bromoiso-butyrate and phenylcadmium reagent were carried out under varying conditions: reflux, three days; room temperature, three hours; and ice-bath temperature, three hours. The reactions were worked up in the usual manner and portions put through the gc. Next, the area of the bromobenzene peak was divided by the area of the ester peak. This should be a constant in all three reactions if formation of the enolate is rate-determining. This was found to be the case.

Reflux, 3 days.

a. \[
\frac{\text{Area Ph-Br}}{\text{Area Ester Product}} = 0.25
\]

b. \[
\frac{\text{"}}{\text{0.28 ave.}} = 0.31
\]
Room Temperature, 3 hr

a. \( \frac{\text{Area Ph-Br}}{\text{Area Ester Product}} \) = 0.24

b. \( \frac{\text{Area Ph-Br}}{\text{Area Ester Product}} \) = 0.29

c. \( \frac{\text{Area Ph-Br}}{\text{Area Ester Product}} \) = 0.29

0.27 ave.

Ice-bath Temperature, 3 hr

a. \( \frac{\text{Area Ph-Br}}{\text{Area Ester Product}} \) = 0.27

b. \( \frac{\text{Area Ph-Br}}{\text{Area Ester Product}} \) = 0.34

c. \( \frac{\text{Area Ph-Br}}{\text{Area Ester Product}} \) = 0.26

0.29 ave.

As expected, the amount of starting material recovered diminished as time and temperature increased.

In the workup of the crude reaction mixture the ether was removed in a rotary evaporator using a water bath at approximately 40 °C. Bromobenzene may have been lost here; however, its vapor pressure at this temperature is only 10 mm Hg. Thus only an insignificant amount should have been lost by this process.

In summary, it appears that the ethyl esters of α-bromoacetic acid, α-bromopropionic acid and α-bromobutyric acid all undergo bromide displacement to give phenyl substituted products. All of these esters are also capable of hydrogen-bromine exchange. None of these esters gave any Claisen products, whereas ethyl 2-bromo-3-methylbutanoate
may give a coupling product. In none of these cases was there any evidence of bromobenzene, thus making a cyclic transition state such as shown in Equation (2) very unlikely.

By contrast, no displacement or dehalogenated product could be found from the reaction of ethyl α-bromoiso-butyrate, but a substantial amount of ethyl tetramethylsuccinate was formed, along with bromobenzene. These differences in behavior make it appear possible that the α-hydrogen is just as important as the α-bromine in the displacement mechanism.

In all the reactions where displacement occurred, the nature of the displacement step is still uncertain. Information of this type could best be obtained by studying the displacement at a chiral center. Jones and Jarboe\(^{36}\) reacted 3-(−)-menthoxyacetoxyphthalide with methylcadmium reagent and obtained (−)-R-3-methylphthalide.

\[
\begin{align*}
\text{CHOOCOCH}_2\text{O-(−)-menthyl} + \text{CH}_3\text{CdCl} & \rightarrow \text{CHOOCOCH}_2\text{O}\text{CH}_3 \\
\text{(-) I} & \rightarrow \text{(+)-(R)-II}
\end{align*}
\]

Although the configuration of I is uncertain, the formation of an optically active product rules out any mechanistic course where total racemization could take place.

It has been proposed that further insight into possible mechanisms could be gained by studying the reaction of ethyl α-bromopropionate with phenyl cadmium reagent. The absolute configurations for both starting bromopropionate
and the product, ethyl hydrotropate, are known.

A direct $S_N^2$ displacement would involve inversion of configuration. This could possibly involve a five-center transition state.

\[
\begin{align*}
\text{R} & \quad \text{Cd} \quad \text{X} \\
\text{C} & \quad \text{C} \quad \text{O} \\
\text{Br} & \quad \text{OE}\text{t}
\end{align*}
\]

There is also the possibility that the displacement may proceed through a four-center transition state, which would combine both electrophilic and nucleophilic attack.

\[
\begin{align*}
\text{Br} & \quad \text{Cd} \quad \text{X} \\
\text{C} & \quad \text{C} \quad \text{R} \\
\text{C} & \quad = \quad \text{O}
\end{align*}
\]

The four-center mechanism would, of course, give a product with retention of configuration. With these ideas in mind R-(+)-methyl $\alpha$-bromopropionate was prepared in the following manner.

\[
\text{S-(-)}\text{CH}_2\text{CH(OH)}\text{COOH} \xrightarrow{\text{CH}_2\text{N}_2} \text{S-(+)}\text{CH}_2\text{CH(OH)}\text{COOCH}_3 \xrightarrow{\text{PBr}_3} \text{R-(+)}\text{CH}_3\text{CHBr-COOCH}_3
\]

(7)
L- (+)-Lactic acid [S- (+)-], purchased commercially in crystalline form, was treated with diazomethane to give optically active methyl lactate. This step should involve retention at the asymmetric center. The OH group of the methyl lactate was displaced by bromine in a step that involves inversion at the asymmetric center to give (+)-methyl α-bromopropionate of 87% optical purity.

The next step was to react the optically active R- (+)-α-bromopropionate with phenylcadmium reagent and isolate methyl hydratropate.

\[
(+) \text{-CH}_3 \text{-CHBrCOOCH}_3 \xrightarrow{\text{PhCdCl}} (+) \text{-CH}_3 \text{CH(Ph)-COOCH}_3
\]

The resulting product, purified by vacuum distillation, exhibited only a negligible rotation. It was contaminated with a small amount of biphenyl, according to glpc analysis. After the product had been further purified by preparative gas chromatography (FFAP column), it again exhibited a very small rotation. Thus the reaction can be said to go essentially with racemization. The above sequence of reactions was repeated with identical results (see Chart 1).

In order to determine whether the α-bromopropionate ester undergoes racemization, the following control experiment was carried out. A portion of the crude mixture from the displacement reaction of R- (+)-α-bromopropionate ester with phenylcadmium reagent was set aside. This crude reaction mixture contained starting ester, methyl hydratropate, biphenyl, benzene and possibly a little ether. If the assumption is made that the methyl hydratropate is racemic (see above) and that all the other products are optically
CHART 1

Preparation and Reaction of 
R-(+) -Methyl α-Bromopropionate

\[
\begin{align*}
\text{CH}_3&\text{C} \equiv \text{COOH} \quad \xrightarrow{\text{CH}_2\text{N}_2} \quad \text{CH}_3&\text{C} \equiv \text{COOH} \\
\text{OH} & \quad & \text{PBr} \\
\end{align*}
\]

S-(+) -Lactic Acid 
S-(-) -Methyl Lactate

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{PhC}_6\text{dCl}} \quad \text{H} \quad \xrightarrow{\text{Ph}_2\text{C}} \quad \text{COOCH}_3 \\
\text{H} & \quad \quad \text{C} \equiv \text{CH}_3 & \quad \text{COOCH}_3 \\
\text{COOCH}_3 & \quad \quad \text{COOCH}_3 \\
\end{align*}
\]

R-(+) -Methyl \ 
α-Bromopropionate 
R- and S-Methyl Hydratropate

(9)
inactive, then the rotation exhibited by this mixture should be due solely to starting material. A portion of the crude mixture was placed in a 1-dm Zeiss polarimeter tube and the rotation measured (+13.070°). Next, 10 μl samples of the crude mixture were analyzed by glpc and the peak area of α-bromopropionate ester were measured by means of a disc integrator. The average area of the α-bromopropionate ester was 142 units. To the crude reaction mixture was added fresh (+)-methyl α-bromopropionate with 87% optical purity. The rotation of this sample, determined as above, was +22.390°. Then the sample was placed on the same gc column, under the same conditions as above, and the peak area of the α-bromopropionate amounted to 233 units. From these results the following calculations were made.

\[
\begin{align*}
233 \text{ units} & \quad -142 \text{ units} \\
91 \text{ units} & = \text{increase in area due to the added (+)-α-bromopropionate ester (87% optical purity).}
\end{align*}
\]

\[
(87\%)(91 \text{ units}) = 80 \text{ units due only to (+)-bromopropionate ester.}
\]

\[
\begin{align*}
22.390° & \quad -13.070° \\
9.320° & = \text{increase in rotation due to added (+)-bromopropionate ester.}
\end{align*}
\]

Therefore, the relationship between rotation and glpc area units is as follows:

\[
\frac{9.320°}{80.0 \text{ units}} = 0.1162°/\text{unit area}
\]

The rotation for the crude reaction mixture, in which the integrated area for α-bromopropionate ester represented 142 units, can be calculated as follows, provided no
racemization of the starting ester has occurred:

Calculated Rotation \((X°)\) = 142 units \(\times 0.87 \times 0.116°\) units

\(X°) = 14.33°\)

\[
\frac{13.07}{14.33} = 0.91
\]

% racemization = 9%

If displacement were 100% stereospecific, the calculated rotation of hydratropic ester would be 94.8° (maximum rotation) \(\times 0.87 \times 0.91 = 75°\).

It was found that \((+)-\)bromopropionate ester racemizes very slowly on standing. In a two-week period 1.3% racemization was observed. It may be concluded that the extent of racemization of starting material does not exceed 10%, and therefore the displacement with phenylcadmium reagent itself proceeds with essentially complete racemization.

The possibility that the product, methyl hydratropate, is formed stereospecifically and then racemized via a carb-anion intermediate is unlikely. The action of Grignard reagents on \((-)-\)methyl hydratropate \(^{37}\) did not affect the chiral center. Further, \((-)-\)hydratropic acid in the presence of lithium aluminum hydride \(^{38}\) or lithium alkyl \(^{39}\) did not affect the active center.

During the course of this investigation, very similar results were disclosed by Van Horn. \(^{40}\) Ethyl \(\alpha\)-bromopropionate in the presence of naphthylcadmium reagent gave the racemic displacement product. Van Horn also found that a sample of the optically active product, ethyl 2-naphthylpropionate, did not racemize in the presence of naphthylcadmium reagent.
Some of the starting α-bromo ester was also recovered from the reaction mixture without loss of optical activity.

These results make an $S_N^2$ or $S_E^2$ mechanism seem unlikely.

In order to explain the racemized product, an intermediate carbene was postulated. The carbene could form in the same manner as any α-elimination; i.e., by abstraction of a proton with a strong base and subsequent loss of halogen.

$$\text{PhCdCl} + \text{CH}_3-C-COOCH_3 \rightarrow \text{CH}_3-C-COOCH_3, \text{CdCl} + \text{C}_6\text{H}_6 \rightarrow \text{CH}_3-C-COOCH_3 + \text{CdClBr}$$

(11)

The carbene could then attack any nucleophile, such as the phenyl moiety in a second cadmium group.

$$\text{CH}_3-C-COOCH_3 \rightarrow \text{CH}_3-\text{C}-C-COOCH_3 \xrightarrow{\text{H}^+} \text{CH}_3-\text{CH(Ph)COOCH}_3$$

(12)

In order to test this possibility, the reaction was carried out in the presence of cyclohexene as a carbene trapping agent. Phenylcadmium reagent (0.10 mol) in the presence of 9.4 ml of cyclohexene was allowed to react with 0.05 mol of ethyl α-bromopropionate under reflux for 16 hr. The reaction mixture did not yield any new peaks except that of cyclohexene when passed through the gc, and an nmr spectrum of the crude product did not reveal any cyclopropyl protons at 12 Hz.

$$\text{cyclohexene} + \text{COOC}_2\text{H}_5 \xrightarrow{\text{H}} \text{cyclohexene with COOC}_2\text{H}_5$$

(13)
Because of the presence of biphenyl in the reaction mixture there appears to be a possibility that the reaction could go by a free radical mechanism. Therefore the usual reaction of phenylcadmium reagent with 0.05 mol of ethyl α-bromopropionate was repeated with a view to detecting any radical intermediates. Upon initial mixing of the reagents, an aliquot was removed, placed in an nmr tube and an electron paramagnetic resonance spectrum taken. A very definite signal was observed. While the mixture was allowed to reflux, aliquots were removed every few minutes and their epr spectra taken. After an hour the epr signal was weak; in 24 hr it had disappeared.

A possible radical mechanism is the following:

1. \[
\text{Br} \quad \text{H} \\
\text{CH}_3 \text{-C-COOC}_2 \text{H}_5 + \text{Ph}^- \rightarrow \text{CH}_3 \text{-C-COOC}_2 \text{H}_5 + \text{C}_6 \text{H}_6
\]

2. \[
\text{Br} \\
\text{CH}_3 \text{-C-COOC}_2 \text{H}_5 + \text{Ph}^- \rightarrow \text{CH}_3 \text{-C-COOC}_2 \text{H}_5 + \text{Br}^-
\]

3. \[
\text{CH}_3 \text{-C-COOC}_2 \text{H}_5 + \text{CH}_3 \text{-C-COOC}_2 \text{H}_5 \rightarrow \text{CH}_3 \text{-C-COOC}_2 \text{H}_5 + \\
\text{Br} \quad \text{Ph} \\
\text{CH}_3 \text{-C-COOC}_2 \text{H}_5
\]

This mechanism, involving an intermediate free radical, would explain the racemization results. Further, because the α-hydrogen is vital to this mechanism, it would explain why ethyl α-bromoisobutyrate did not give a displacement product with phenylcadmium reagent. Finally, the mechanism would
explain the appearance of a strong epr signal.

It is even possible that the displacement mechanism may involve a radical ion. Kornblum has postulated such a mechanism for some nucleophilic displacements. As an example, for the displacement in 2-(p-nitrophenyl)-2-chloropropane, the first step involves transfer of an electron from some electron source, \( A^- \); the radical ion then loses an anion with formation of a stabilized free radical.

\[
\begin{align*}
\text{CH}_3 & \text{C-Cl} \\
\text{NO}_2 & \\
\end{align*}
\xrightarrow{A^-} \left[ \begin{align*}
\text{CH}_3 & \text{C-Cl} \\
\text{NO}_2 & \\
\end{align*} \right] + A^-
\]

\( A^- \), acting as a nucleophile, may then attack the free radical to give another radical ion, which may in turn act as a source of electrons.
A similar mechanism may be written for the displacement of bromine by a phenyl group in the bromopropionate reaction.

This free radical intermediate, \( C^{(\cdot)} \), may be attacked in two different ways. Nucleophilic attack will generate a new radical ion, similar to the one just postulated. This radical ion could then lose an electron to produce the product and another radical ion, \( B^{(\cdot)} \). If, however, an electron
is transferred to the radical $\cdot C\, (\cdot)$, an enolate will be formed, which on protonation will afford ethyl propionate.

\[
\begin{align*}
&\text{Ethyl Hydratropate} \\
\rightarrow &\quad \text{Ethyl Propionate}
\end{align*}
\]

This mechanism is attractive because it does not require a cyclic transition state, as shown on page 5, which leads to bromobenzene as byproduct. It will be recalled that no bromobenzene could be found in the reaction mixture by glpc analysis.

In an attempt to increase the yield of product, a free radical initiator was added to the reaction mixture of phenylcadmium reagent and $\alpha$-bromopropionate. The initiator chosen was azobisisobutyronitrile (AIBN). As in the above
experiment, an aliquot of the reaction solution was removed immediately on mixing and an epr spectrum taken. Surprisingly, no signal appeared. All aliquots removed from the refluxing mixture over a six-hour period lacked an epr signal. Next, the reaction mixture was hydrolyzed and worked up in the usual manner. No displacement product was found by glpc analysis. On the contrary, the displacement product was found by glpc in a sample of the crude mixture which did exhibit an epr signal.

At first glance this result is somewhat surprising. If a free radical mechanism is indeed taking place, it would not seem reasonable that AIBN inhibit the reaction. However, if the pathway involves a radical ion, it may be possible that AIBN ties up the electrons, whatever their source, necessary for the first step of the radical ion mechanism.

In order to extend the scope of the displacement reaction of a halogen by phenylcadmium reagent, and possibly shed some light on likely mechanisms, a series of displacements was explored. (See Table 8)

It was found that allylic bromides are easily displaced. In the cases of 3-bromocyclohexene and allyl bromide, the phenyl displacement products were obtained in 81 and 39% yields, respectively. This appears to be the first displacement of an allylic bromide by an organocadmium reagent. Cason and Fessenden were unsuccessful in their attempt to displace bromine from allyl bromide with octylcadmium reagent.

The reaction with 3-bromocyclohexene was repeated and followed at various time intervals by epr spectroscopy. However, the spectra did not indicate the presence of free radicals.

As mentioned earlier, α-halo ethers undergo displacement reactions with both alkyl- and arylcadmium reagents.
### Table 8
Reactions of Phenylcadmium Reagent with Various Organic Halides

<table>
<thead>
<tr>
<th>Starting Halo Compound</th>
<th>Reflux Time (hr)</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Bromocyclohexene</td>
<td>3</td>
<td>3-Phenylcyclohexene</td>
<td>81</td>
</tr>
<tr>
<td>Chloromethyl methyl ether</td>
<td>4</td>
<td>Benzyl methyl ether</td>
<td>34</td>
</tr>
<tr>
<td>Benzyl bromide</td>
<td>4</td>
<td>Diphenylmethane</td>
<td>40</td>
</tr>
<tr>
<td>Allyl bromide</td>
<td>4</td>
<td>3-Phenylpropene</td>
<td>39</td>
</tr>
<tr>
<td>1-Bromobutane</td>
<td>12</td>
<td>(Starting Material)</td>
<td>0</td>
</tr>
<tr>
<td>1-Bromobutane (with AIBN)</td>
<td>12</td>
<td>(Starting Material)</td>
<td>0</td>
</tr>
<tr>
<td>Trimethylchlorosilane</td>
<td>4</td>
<td>(Starting Material)</td>
<td>0</td>
</tr>
<tr>
<td>Chlorocyanomethane</td>
<td>4</td>
<td>(Polymer)</td>
<td>0</td>
</tr>
<tr>
<td>1-Chloro-1-nitroethane</td>
<td>4</td>
<td>(Starting Material)</td>
<td>0</td>
</tr>
<tr>
<td>1,2-Dibromoethane</td>
<td>4</td>
<td>(Starting Material)</td>
<td>0</td>
</tr>
<tr>
<td>Bromoacetaldehyde, diethyl acetal</td>
<td>4</td>
<td>(Starting Material)</td>
<td>0</td>
</tr>
<tr>
<td>2-Chloro-2-methylpropane</td>
<td>4</td>
<td>tert-Butylbenzene (?) + bromobenzene</td>
<td>0</td>
</tr>
</tbody>
</table>
Therefore, it is reasonable to expect such a displacement with chloromethyl methyl ether and phenylcadmium reagent. This is exactly what was found, as benzyl methyl ether was produced in 34% yield. This product was isolated by gas chromatography, and no other side products were noticed. Therefore, it may be possible with a more careful workup to isolate the product in higher yield.

Benzylic halides also reacted with phenylcadmium reagent to give diphenylmethane in 40% yield. No side products could be found by glpc analysis. Thus the yield could be higher. This displacement was expected, since it has been previously observed that benzylic halogens are very susceptible to displacement by organocadmium reagents. 12

In view of the present work some generalizations can be drawn concerning the scope of halogen displacement by organocadmium reagents.

1. Phenylcadmium reagents react with α-bromo-esters that also contain α-hydrogens.

2. Allylic bromides undergo displacement with phenylcadmium reagent.

3. Both alkyl- and phenylcadmium reagents react with α-halo ethers.

4. Benzylic halogens are displaced with phenylcadmium reagents.

There are many halogen-containing compounds that do not undergo displacement with phenylcadmium reagent. Some of these will now be considered.

Cason and Fessenden 6 were unable to obtain the displacement product using 2-iodooctane and propylcadmium reagent, while recovering 76% of the starting material. With the view
that the phenylcadmium reagent might be more effective than the alkyl reagents for displacement, an experiment was conducted in which 1-bromobutane and phenyl reagent were heated for 12 hr under reflux. Only starting material was found by glpc analysis. The elimination product, if formed, was lost as a low-boiling material. When this reaction was repeated in the presence of a free radical initiator, AIBN, the same results were noted.

Only starting material was detected by glpc when 1,2-dibromoethane had been treated at reflux for 4 hr with phenylcadmium reagent.

Gilman and Nelson\textsuperscript{2} were the first to report the attempted replacement of halogen at a tertiary carbon atom. Both tert-butyl chloride and 3-chloro-3-propylheptane gave the elimination product with octylcadmium reagent.

In the present work, a reaction between tert-butyl chloride and phenylcadmium reagent was attempted. Analysis by glpc showed a small peak which was difficult to isolate, but which may have been tert-butylbenzene as judged by similar retention times with a known sample. A substantial amount of bromobenzene was found as well.

Although it has been shown that bromine can be displaced by phenylcadmium reagent if it is located on a carbon atom \(\alpha\)-to an ether linkage, displacement of halogens in the \(\beta\)-position has never been observed. Likewise, when bromoacetaldehyde diethyl acetal was treated with phenylcadmium reagent, only starting material was found from glpc analysis.

The reaction of phenylcadmium reagent with chlorocyanomethane gave only a polymer-like mass, while 1-chloro-1-nitroethane was unreactive, starting material being recovered.

Probably one common mechanism would not suffice to explain all the displacement reactions. Although the above work indicates that displacement involving \(\alpha\)-bromoesters
proceeds by a free radical mechanism, many of the other reactions could follow an ionic pathway. As already noted, one displacement reaction afforded an optically active product, and others such as the reaction of 3-bromocyclohexene with phenylcadmium reagent apparently generate no transient free radicals. As is discussed below, the reaction mixture of α-bromoacetophenone with ethylcadmium reagent also failed to give an epr signal. These facts, difficult to reconcile with a free radical mechanism, are rather indicative of an ionic or a concerted pathway.

If the possibility of a nucleophilic displacement is considered for many of the above reactions, it is reasonable to expect a certain order of reactivity:

for an $S_{N1}$ reaction,

$$ ROCH_2X > R_3CX > ArCH_2X > C=CH-CH_2-X > RCH_2X > ZCH_2X $$

(where $Z = RCO^-, HCO^-, ROCO^-$)

and for the $S_{N2}$ pathway,

$$ ArCH_2X > ZCH_2X > C=CH-CH_2-X > RCH_2X > R_3CX $$

Although no kinetic studies were carried out, the general ease with which products were formed may be considered. For example, the ready reaction of chloromethyl methyl ether with phenylcadmium reagent could be indicative of an $S_{N1}$ mechanism. However, the lack of any displacement product from tert-butyl chloride and trimethylsilyl chloride make it questionable if these cases follow an $S_{N1}$ pathway. In fact, the lack of reactivity at the tertiary carbon and silicon atoms would be consistent with an $S_{N2}$ mechanism.

In summary, the reactions of α-halo esters and ketones
with organocadmium reagents fit an $S_N^2$ or free radical mechanism rather than the $S_N^1$ pathway.

In all the above reactions, phenylcadmium was used as the reagent. To help establish the limits of organocadmium displacements, a few reactions with alkylcadmium reagents were tried. The reaction of ethylcadmium reagent with ethyl bromoacetate gave only a reddish-brown polymer. Upon attempted workup of the product, no ethyl acetate, ethyl bromoacetate, or ethyl butyrate could be found by glpc analysis. The reaction was carried out for 12 hr both at reflux and ice-bath temperature.

The reaction of ethyl $\alpha$-bromopropionate with ethylcadmium reagent, after 12 hr of refluxing, did not afford a polymer as in the above case; the only product identified after workup was ethyl propionate.

When isopropylcadmium reagent was allowed to react with ethyl bromoacetate under reflux for 12 hr, starting material and the Claisen condensation product, ethyl acetoacetate were the compounds found by glpc analysis. In a similar reaction with ethyl $\alpha$-bromoisobutyrate with butylcadmium reagent, Cason and Fessenden, also obtained the analogous Claisen product, ethyl 2,2,4-trimethyl-3-oxopentanoate.

One of the components from the reaction of $\alpha$-bromoacetophene with ethylcadmium reagent appeared to be 1-phenyl-2-butanone, although a few of the peaks in the fingerprint region of the spectrum were weak. An nmr spectrum of the crude product showed a singlet at 216 Hz, which could be due to the benzylic protons, next to the carbonyl group. The largest peak collected proved to be acetophenone, the product which could arise by way of the enolate. No starting material could be found in the reaction mixture by glpc analysis.
Furthermore, α-bromoacetophenone has a singlet at 266 Hz which was not observed in the nmr of the crude reaction mixture. It should be noted that no trace of the displacement product, butyrophenone, could be detected. The presence of 1-phenyl-2-butanone could be explained by attack at the carbonyl position, followed by concomitant rearrangement of phenyl and displacement of bromide.

When the above reaction was repeated and examined at several time intervals by epr, no evidence of free radicals was found.

These reactions indicate that alkyl cadmium reagents are of little synthetic value in displacing α-halo esters and ketones.
BIBLIOGRAPHY

40. A. R. Van Horn, private communication.