A STUDY OF THE MECHANISM OF THE DISPLACEMENT BY ORGANOCADMIUM REAGENTS IN 3-SUBSTITUTED PHTHALIDES: SCOPE AND STEREOCHEMISTRY

CARL JOSEPH JARBOE

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A STUDY OF THE MECHANISM OF THE DISPLACEMENT
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BY

CARL JOSEPH JARBOE

B.S., Lebanon Valley College, 1961

A THESIS
Submitted to the University of New Hampshire
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Doctor of Philosophy

Graduate School
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August, 1968
This thesis has been examined and approved.

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September 6, 1968
Date
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[Signature]

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TO THE ONLY GIRL IN THE WORLD

My future wife, Gail Frohock
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>LIST OF TABLES</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF COMPOUNDS</td>
<td>ix</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>HISTORICAL BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>DESCRIPTION OF EXPERIMENTS</td>
<td>8</td>
</tr>
<tr>
<td>1. Attempted Preparation of 3-Chloro-3-phenylphthalide</td>
<td>9</td>
</tr>
<tr>
<td>2. Attempted Preparation of 3-Methoxy-3-phenylphthalide</td>
<td></td>
</tr>
<tr>
<td>A.</td>
<td>9</td>
</tr>
<tr>
<td>B.</td>
<td>10</td>
</tr>
<tr>
<td>C.</td>
<td>10</td>
</tr>
<tr>
<td>3. Attempted Preparation of 3-Isobutoxy-3-phenylphthalide</td>
<td></td>
</tr>
<tr>
<td>A.</td>
<td>11</td>
</tr>
<tr>
<td>B.</td>
<td>11</td>
</tr>
<tr>
<td>C.</td>
<td>12</td>
</tr>
<tr>
<td>D.</td>
<td>12</td>
</tr>
<tr>
<td>4. Attempted Preparation of 3-t-Butoxy-3-phenylphthalide</td>
<td>13</td>
</tr>
<tr>
<td>5. Attempted Preparation of 3-(-)-Menthoxy-3-phenylphthalide</td>
<td></td>
</tr>
<tr>
<td>A.</td>
<td>13</td>
</tr>
<tr>
<td>B.</td>
<td>14</td>
</tr>
<tr>
<td>6. Attempted Preparation of 3-Phenoxy-3-phenylphthalide</td>
<td></td>
</tr>
<tr>
<td>A.</td>
<td>14</td>
</tr>
<tr>
<td>B.</td>
<td>15</td>
</tr>
<tr>
<td>C.</td>
<td>16</td>
</tr>
<tr>
<td>7. Attempted Preparation of 3-Ethoxy-3-phenylphthalide</td>
<td></td>
</tr>
<tr>
<td>A.</td>
<td>16</td>
</tr>
<tr>
<td>8. 3-Ethoxy-3-phenylphthalide.</td>
<td>17</td>
</tr>
<tr>
<td>9. o-(a-Ethyl-a-ethoxybenzyl)-benzoic acid.</td>
<td>18</td>
</tr>
<tr>
<td>10. Preparation of 3-Ethyl-3-phenylphthalide.</td>
<td>19</td>
</tr>
<tr>
<td>Table of Contents, continued</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>11. Reaction of ( \alpha-(\alpha\text{-Ethyl-}\alpha\text{-ethoxybenzyl})) -benzoic Acid and Concentrated Hydrochloric Acid</td>
<td>Page 20</td>
</tr>
<tr>
<td>12. (3\text{-Isopropoxy-3-phenylphthalide.} )</td>
<td>Page 20</td>
</tr>
<tr>
<td>13. (\alpha-(\alpha\text{-Ethyl-}\alpha\text{-isopropoxybenzyl})) -benzoic Acid</td>
<td>Page 21</td>
</tr>
<tr>
<td>14. Control Experiment between (3\text{-Isopropoxy-3-phenylphthalide and Aqueous Sulfuric Acid} )</td>
<td>Page 22</td>
</tr>
<tr>
<td>15. Reaction of (3\text{-Isopropoxy-3-phenylphthalide and Phenylcadmium Chloride.} )</td>
<td>Page 23</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>16. Phthalaldehydic Acid</td>
<td>Page 25</td>
</tr>
<tr>
<td>17. (3\text{-Ethoxyphthalide} )</td>
<td>Page 25</td>
</tr>
<tr>
<td>18. (\alpha-(\alpha\text{-Ethoxyethyl})) -benzoic Acid</td>
<td>Page 25</td>
</tr>
<tr>
<td>19. (3\text{-Methoxyphthalide} )</td>
<td>Page 26</td>
</tr>
<tr>
<td>20. (\alpha-(\alpha\text{-Methoxyethyl})) -benzoic Acid</td>
<td>Page 27</td>
</tr>
<tr>
<td>21. (Di-3\text{-Phthalidyl Ether} )</td>
<td>Page 28</td>
</tr>
<tr>
<td>22. Reaction of (Di-3\text{-phthalidyl Ether and Methylcadmium Chloride.} )</td>
<td>Page 28</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>23. (3-(p\text{-Chlorophenoxy})) -phthalide</td>
<td>Page 31</td>
</tr>
<tr>
<td>24. Reaction of (3-(p\text{-Chlorophenoxy})) -phthalide and Methylcadmium Chloride</td>
<td>Page 31</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>25. (3\text{-Phenoxyphthalide.} ) A</td>
<td>Page 32</td>
</tr>
<tr>
<td>26. Attempted Preparation of (3\text{-Phenoxyphthalide.} )</td>
<td>Page 33</td>
</tr>
<tr>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>27. (3\text{-Acetoxyphthalide.} )</td>
<td>Page 34</td>
</tr>
<tr>
<td>28. Reaction of (3\text{-Acetoxyphthalide and Methylcadmium Chloride.} )</td>
<td>Page 35</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Table of Contents, continued</td>
<td>Page</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>A. ........................................................................................................... 36</td>
<td></td>
</tr>
<tr>
<td>B. ........................................................................................................... 37</td>
<td></td>
</tr>
<tr>
<td>C. ........................................................................................................... 37</td>
<td></td>
</tr>
<tr>
<td>30. 3-(-)-Menthoxyphthalide. D. ........................................................................ 38</td>
<td></td>
</tr>
<tr>
<td>31. o-(a-(-)-Menthoxyethyl)-benzoic Acid.</td>
<td></td>
</tr>
<tr>
<td>A. ........................................................................................................... 38</td>
<td></td>
</tr>
<tr>
<td>B. ........................................................................................................... 40</td>
<td></td>
</tr>
<tr>
<td>32. 3-(-)-Menthoxyacetoxypthalide . .......................................................................... 41</td>
<td></td>
</tr>
<tr>
<td>33. Treatment of 3-(-)-Menthoxyacetoxypthalide with Methylcadmium Chloride. ................ 42</td>
<td></td>
</tr>
<tr>
<td>34. Unknown Component from Treatment of 3-(-)-Menthoxyacetoxypthalide with Methylcadmium Chloride . . 44</td>
<td></td>
</tr>
<tr>
<td>35. α-Phenylbutyryl Chloride . ............................................................................. 45</td>
<td></td>
</tr>
<tr>
<td>36. 3-α-Phenylbutyrylphthalide . ............................................................................... 45</td>
<td></td>
</tr>
<tr>
<td>37. Reaction of 3-α-Phenylbutyrylphthalide and Methylcadmium Chloride .................... 46</td>
<td></td>
</tr>
<tr>
<td>38. O-Methylmandelic Acid.</td>
<td></td>
</tr>
<tr>
<td>A. ........................................................................................................... 47</td>
<td></td>
</tr>
<tr>
<td>B. ........................................................................................................... 48</td>
<td></td>
</tr>
<tr>
<td>39. O-Methylmandelyl Chloride. . ............................................................................. 49</td>
<td></td>
</tr>
<tr>
<td>40. Attempted Preparation of 3-(O-Methylmandeloxy)-phthalide. ................................ 49</td>
<td></td>
</tr>
<tr>
<td>41. Attempted Separation of the Diastereomers of 3-(-)-Menthoxyacetoxypthalide . . . . 50</td>
<td></td>
</tr>
<tr>
<td>42. Determination of Grignard Reagent Concentration. ........................................... 50</td>
<td></td>
</tr>
<tr>
<td>RESULTS AND DISCUSSION . ..................................................................................... 65</td>
<td></td>
</tr>
<tr>
<td>SUMMARY. ................................................................................................. 86</td>
<td></td>
</tr>
<tr>
<td>BIBLIOGRAPHY ............................................................................................ 88</td>
<td></td>
</tr>
</tbody>
</table>
## LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Summary of Results</td>
<td>52</td>
</tr>
<tr>
<td>02</td>
<td>Rotation Data: 3-(-)-Menthoxyacetoxyphthalide, Reaction #1</td>
<td>55</td>
</tr>
<tr>
<td>03</td>
<td>Rotation Data: Recovered 3-(-)-Menthoxyacetoxyphthalide, Reaction #1</td>
<td>56</td>
</tr>
<tr>
<td>04</td>
<td>Rotation Data: 3-(-)-Menthoxyacetoxyphthalide, Reaction #2</td>
<td>57</td>
</tr>
<tr>
<td>05</td>
<td>Rotation Data: 3-Methylphthalide, Reaction #1, Fraction #1</td>
<td>58</td>
</tr>
<tr>
<td>06</td>
<td>Rotation Data: 3-Methylphthalide, Reaction #1, Fraction #1 (After 30 days in solution at ambient temperature)</td>
<td>59</td>
</tr>
<tr>
<td>07</td>
<td>Rotation Data: 3-Methylphthalide, Reaction #1, Fraction #2</td>
<td>60</td>
</tr>
<tr>
<td>08</td>
<td>Rotation Data: 3-Methylphthalide, Reaction #2, Fraction #2</td>
<td>61</td>
</tr>
<tr>
<td>09</td>
<td>Attempted Separation of the Diastereomers of 3-(-)-Menthoxyacetoxyphthalide</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>Preparation of 3-(-)-Menthoxyacetoxyphthalide</td>
<td>63</td>
</tr>
<tr>
<td>11</td>
<td>Titration of Ethereal Methylmagnesium Iodide</td>
<td>64</td>
</tr>
</tbody>
</table>
## LIST OF COMPOUNDS

<table>
<thead>
<tr>
<th>Compound Number</th>
<th>Compound Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>o-Benzoylbenzoyl Chloride</td>
</tr>
<tr>
<td>6</td>
<td>3-Methoxy-3-phenylphthalide</td>
</tr>
<tr>
<td>7</td>
<td>3-Isobutoxy-3-phenylphthalide</td>
</tr>
<tr>
<td>8</td>
<td>3-\text{-}Butoxy-3-phenylphthalide</td>
</tr>
<tr>
<td>9</td>
<td>3-Phenoxy-3-phenylphthalide</td>
</tr>
<tr>
<td>10</td>
<td>3-Ethoxy-3-phenylphthalide</td>
</tr>
<tr>
<td>11</td>
<td>3-Isopropoxy-3-phenylphthalide</td>
</tr>
<tr>
<td>12</td>
<td>3-Phenoxyphthalide</td>
</tr>
<tr>
<td>13</td>
<td>3-(-)-Menthoxyphthalide</td>
</tr>
<tr>
<td>14</td>
<td>3-(-)-Menthoxyacetoxyphthalide</td>
</tr>
<tr>
<td>15</td>
<td>3-(-)-Menthoxyacetyl Chloride</td>
</tr>
<tr>
<td>16</td>
<td>Di-3-Phthalidyl Ether</td>
</tr>
<tr>
<td>17</td>
<td>3-\text{-}a-Phenylbutyrylphthalide</td>
</tr>
<tr>
<td>18</td>
<td>3-(O-Methylmandeloxy)-phthalide</td>
</tr>
<tr>
<td>19</td>
<td>3-Ethyl-3-phenylphthalide</td>
</tr>
<tr>
<td>20</td>
<td>o-(\text{-}a-Ethyl-a-ethoxybenzyl)-benzoic Acid</td>
</tr>
<tr>
<td>21</td>
<td>o-(\text{-}a-Ethyl-a-isopropoxybenzyl)-benzoic Acid</td>
</tr>
<tr>
<td>22</td>
<td>3-Methoxyphthalide</td>
</tr>
<tr>
<td>23</td>
<td>3-Ethoxyphthalide</td>
</tr>
<tr>
<td>24</td>
<td>o, o'-Dicarboxy-bis-\text{-}a-phenethyl Ether</td>
</tr>
<tr>
<td>25</td>
<td>3-Methylphthalide</td>
</tr>
<tr>
<td>26</td>
<td>o-(\text{-}a-(-)-Menthoxyethyl)-benzoic Acid</td>
</tr>
<tr>
<td>27</td>
<td>3-Acetoxyphthalide</td>
</tr>
<tr>
<td>28</td>
<td>3-\text{-}P-Chlorophenoxy)-phthalide</td>
</tr>
</tbody>
</table>

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List of Compounds, continued

29  o-(α-Methoxyethyl)-benzoic Acid
30  (-)-Menthoxyacetone
31  l-(-)-Menthoxy-2-methyl-propan-2-ol
INTRODUCTION

The substitution reaction (Equation 1) between

\[
\begin{align*}
  & R \quad R' \\
  + \quad \text{R'}\text{CdCl} \quad \rightarrow \\
  & \text{R} \quad \text{R'}
\end{align*}
\]

organocadmium reagents (2) and 3-substituted phthalides (1) has been demonstrated\(^{17}\) and the scope\(^{17,19}\) of the reaction explored to a limited degree.

The goal of the present work was to gain evidence, shedding some insight into the mechanism of the reaction. The first objective was to extend the scope to the series with a phenyl group in the 3- position, in order to determine the influence of this group upon the reaction. The second objective was to identify and reexamine, by more exacting analytical methods, the products of some of the reactions in the series with a hydrogen in the 3- position. Thirdly, the stereochemistry of the reaction was to be explored by choosing appropriately constituted phthalides whose products could display optical activity.
HISTORICAL BACKGROUND

One of the early examples of a replacement by an organometallic reagent at a saturated carbon atom, exclusive of the well-known coupling reaction, was reported in 1936 when Summerbell and Bauer \(^{20}\) displaced the 2- and 3-chloro groups in 2,3-dichloro-1,4-dioxane with the n-butyl organometallic reagents of magnesium, zinc, and cadmium (Equation 2).

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
& \quad \text{M=Mg, Zn, Cd}
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
& \quad \text{M=Mg, Zn, Cd}
\end{align*}
\]

A similar result was later observed when Hurd and his collaborators \(^{21-23}\) replaced brominated sugars with magnesium, lithium, and cadmium organometallic reagents (Equation 3).

Both aryl and alkyl reagents of all three organometallics were used. The structure of the final product with the alkylcadmium reagent suggests participation of the ester carbonyl as a neighboring group (Equation 4). Chancel \(^{24}\) has reported

*After reacetylation in the case of Mg and Li

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exclusive replacement of the α-chloro group with methylzinc iodide (Equation 5) in a substrate containing both α- and β-chloro substituents. In the Boord olefin synthesis, the same result is obtained with alkyl and aryl magnesium halides.

In all the preceding work the replacement was that of a halogen attached to a saturated carbon next to an ether oxygen. The replacement also occurs on saturated carbon atoms adjacent to an ester oxygen. Chancel has reported an example of this type in the case of magnesium and zinc reagents.

When methylmagnesium bromide and substrate were employed in equimolar amounts, the α-bromide was replaced (Equation 6).

\[
\text{CH}_2(\text{Br})-\text{CH}(\text{Br})-\text{O}-\text{CO}-\text{CH}_3 + \text{CH}_3\text{MgBr} \rightarrow \text{CH}_2(\text{Br})-\text{CH}(\text{CH}_3)-\text{O}-\text{CO}-\text{CH}_3
\]

A similar result was obtained with methylzinc iodide (Equation 7) and 1-chloro-1-propyl acetate. When the analogous
replacement by cadmium reagents in the α-chloromethyl and α-chloroethyl esters of benzoic acid was attempted, no reaction was observed\(^{18,25}\) (Equation 8). However, if the α-carbon was

\[
\text{C}_6\text{H}_5\text{CO}-\text{O}-\text{CH}_2\text{Cl} + \text{C}_6\text{H}_5\text{CdCl} \rightarrow \text{No Reaction}
\]  

(8)

\[
\text{C}_6\text{H}_5\text{CO}-\text{O}-\text{CH(Cl)}-\text{CH}_3 + \text{C}_6\text{H}_5\text{CdCl} \rightarrow \text{No Reaction}
\]

made benzylic or allylic, replacement was effected\(^{18}\) (Equation 9).

\[
\text{C}_6\text{H}_5\text{COOCH(Cl)C}_6\text{H}_5 + \text{C}_6\text{H}_5\text{CdCl} \rightarrow \text{C}_6\text{H}_5\text{COOCH(C}_6\text{H}_5)_2
\]  

(9)

\[
\text{C}_6\text{H}_5\text{COOCH(Cl)CH=CHC}_6\text{H}_5 + \text{C}_6\text{H}_5\text{CdCl} \rightarrow (\text{C}_6\text{H}_5)_2\text{CHCH=CHC}_6\text{H}_5^*
\]

Substituents attached to a saturated carbon atom next to a carbonyl group also undergo replacement. Jones and Young\(^{26}\) (Equations 10, 12) and Gross and Freiberg\(^{27}\) (Equation 11) have

\[
\text{RR'C(Br)COOCH}_2\text{CH}_3 + \text{R"CdCl} \rightarrow \text{RR'R"COOCH}_2\text{CH}_3
\]  

(10)

\[
\text{R}=\text{H}; \text{R'}=\text{H}, \text{CH}_3; \text{R"}=\text{C}_6\text{H}_5, \alpha-\text{C}_{10}\text{H}_7
\]

\[
\text{ClCH(OC}_3\text{)}\text{COOCH}_3 + \text{C}_6\text{H}_5\text{CdCl} \rightarrow \text{C}_6\text{H}_5\text{CH(OC}_3\text{)}\text{COOCH}_3
\]

(11)

*Benzoyloxy is also replaced.*
reported this reaction with cadmium reagents.

The last example of a substrate for discussion is the 3-substituted phthalides. These are the cyclic analogs of the case containing a replaceable group on a benzylic carbon next to an ester oxygen. It is this reaction (Equation 1) which is the subject of the present investigation.

In this particular type of replacement, the reaction has previously been described as a "displacement", a term which will be used in the remainder of the present discussion. It should be noted, however, that the term carries no mechanistic implications.

It could be speculated that the first example of this type of reaction was observed by Nölting with diphenylmercury (Equation 13). It is now established that phthaloyl chloride exists in the solid state as the ring tautomer, and hence the reaction could be explained as a double displacement at the 3-carbon. Fuson has observed a similar displacement with diphenylcadmium (Equation 13).

A similar result was obtained by Jones and Hauser when 3-chloro-3-phenylphthalide was treated with a series of
alkyl- and arylcadmium reagents (Equation 14). All the evidence is consistent with the ring tautomeric structure for 3-chloro-3-phenylphthalide.\textsuperscript{40,41} Nightingale\textsuperscript{30} has reported using diethylcadmium in an analogous situation (Equation 15).

\begin{align*}
\text{C}_6\text{H}_5\text{Cl} + \text{R}_2\text{Cd} & \rightarrow \text{C}_6\text{H}_5\text{R} \quad \text{(14)} \\
\text{R} &= \text{C}_6\text{H}_5, \text{CH}_3, \text{n-C}_4\text{H}_9
\end{align*}

Boothe\textsuperscript{31} has demonstrated further the displacement characteristics of the reaction by using magnesium and sodium enolates with a 3-chloro-3-methylphthalide substrate (Equation 16).

\begin{align*}
\text{C}_6\text{H}_5\text{Cl} + (\text{C}_2\text{H}_5)_2\text{Cd} & \rightarrow \text{C}_6\text{H}_5\text{C}_2\text{H}_5 \\
\text{R} &= \text{C}_6\text{H}_5, \text{CH}_3, \text{n-C}_4\text{H}_9
\end{align*}

\begin{align*}
\text{CH}_3\text{Cl} + \text{MgR}_2 \\
\text{or NaR'} & \rightarrow \text{CH}_3\text{R} \quad \text{(or R')} \\
\text{R} &= \text{CH(COOEt)}_2 \\
\text{R'} &= \text{CH}_2\text{COOEt}
\end{align*}
The displacement reaction at the 3-position of a phthalide was mentioned as a possible mechanistic pathway by Jones and Congdon\textsuperscript{32} in an attempt to reconcile the work of Wang and coworkers\textsuperscript{33} and DeBenneville.\textsuperscript{34} Jones and Lavigne\textsuperscript{9} later demonstrated that, indeed, halogen and other groups could be displaced by the methylcadmium reagent (Equation 17).

\[
\text{R} = \text{H}; \text{X} = \text{Br}, \text{OC}_2\text{H}_5, \text{OCH}_3, \text{OH}, 3-\text{Phthalonyloxy} \\
\text{R} = \text{CH}_3; \text{X} = \text{OCONH}_3
\]

Jones and Crosby\textsuperscript{35} obtained similar results with phenylcadmium chloride (Equation 18).

\[
\text{X} = \text{Br}, 3-\text{phthalloyloxy}, \text{p-}(\text{Cl})\text{C}_6\text{H}_4\text{O}
\]

It was with this last work in mind that the present study was undertaken to establish concrete evidence for the mechanistic course of the reaction.
DESCRIPTION OF EXPERIMENTS

The infrared absorption spectra were determined with a Perkin-Elmer Model 21 infrared spectrophotometer with sodium chloride optics or a Perkin-Elmer Model 337 grating infrared spectrophotometer. The nuclear magnetic resonance spectra were determined with a Varian Model A-60 nuclear magnetic resonance spectrometer. Both infrared and nmr spectra are described by file number and major bands. Proton resonance signals are reported in ppm (δ) downfield from TMS. The number of protons a signal represents follows the multiplicity. Coupling constants (J) are in Hz.

Thin layer chromatography plates are indicated by file number. They are recorded as tracings, which include adsorbent, eluent, date, and spot composition.

Ir and nmr spectra and tlc tracings are on file in the Department of Chemistry, University of New Hampshire.

Optical rotations were measured on a Carl Zeiss photoelectric polarimeter or a Franz Schmidt & Haensch visual polarimeter.

Gas liquid phase chromatograms were obtained on a Varian Aerograph Model 90-P with a Servo-Riter II (Texas instruments) recorder.

Microanalyses were determined by Galbraith Laboratories, Knoxville, Tennessee, or on an F & M Model 185 Carbon Hydrogen Nitrogen Analyzer in the Department of Chemistry, University of New Hampshire. The boiling points and melting
points are in degrees centigrade and are uncorrected. The melting points were taken on a Thomas-Hoover Capillary Melting Point Apparatus.

Attempted Preparation of 3-Chloro-3-phenylphthalide.$^{25}$Anhydrous o-benzoylbenzoic acid (27 g, 0.12 mole) and 29 g (0.24 mole) of thionyl chloride were heated at 60° under dry nitrogen for 15 hr. Excess thionyl chloride was removed by heating to 96° under aspirator pressure. The remaining oil was placed in a desiccator ($P_2O_5$) at 34 mm pressure but failed to crystallize. An infrared spectrum (3960) of the oil exhibited a strong band at 1790 cm$^{-1}$.

Attempted Preparation of 3-Methoxy-3-phenylphthalide.$^{3}A$.--To 27 g (0.12 mole) of anhydrous o-benzoylbenzoic acid was added 29 g (0.24 mole) of thionyl chloride under a stream of dry nitrogen. The reaction was then heated at 64° for 14 hr. Excess thionyl chloride was removed by heating to 90-110° for 1.5 hr at aspirator pressure.

The reaction mixture was cooled to ice-bath temperature, and 7.23 ml (0.18 mole) of absolute methanol in 14.4 ml (0.18 mole) of dry pyridine added. When stored under dry nitrogen for 3 days, the mixture solidified. Ether failed to dissolve it but water was successful. The ether and water layers were separated and the aqueous layer extracted with 25 ml of ether. The combined ether layer was then extracted with four 25-ml portions of 1 N HCl, three 25-ml portions of saturated $Na_2CO_3$, and three 25-ml portions of saturated NaCl. It was dried ($Na_2SO_4$) and the ether removed.
Dry-ice cooling, subsequent warming to room temperature, and scratching produced crystallization. Repeated crystallizations from 95% ethanol yielded 8.9 g (31%) of a solid, mp 57-65°. The infrared spectrum (4201) indicated it to be a mixture of normal and pseudo esters.

**Attempted Preparation of 3-Methoxy-3-phenylphthalalide.**

o-Benzoylbenzoyl chloride was prepared from 1.75 ml (0.02 mole) of thionyl chloride and 5 g (0.02 mole) of anhydrous o-benzoylbenzoic acid. To the acid-chloride was added 25 ml (0.63 mole) of absolute methanol. Vigorous stirring was required to mix the two phases. After complete homogeneity, the reaction mixture was poured into 13 ml of 4 M sodium carbonate. The precipitate which formed immediately was collected by filtration.

The solid was dissolved in chloroform, the chloroform evaporated, and the oily residue crystallized slowly. The infrared spectrum (229) indicated a mixture of normal and pseudo esters.

**Attempted Preparation of 3-Methoxy-3-phenylphthalalide.**

o-Benzoylbenzoyl chloride was prepared as above. To the hot acid chloride was added a solution of 5.5 g (0.045 mole) of sodium carbonate, 13 ml (0.32 mole) of methanol, and 39 ml of water. The gummy solid produced was extracted with three 25-ml portions of chloroform. Evaporation of the chloroform deposited an oil which later solidified. The infrared spectrum (225) of the solid indicated a mixture of normal and pseudo esters.

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Attempted Preparation of 3-Isobutoxy-3-phenylphthalide. A.—

α-Benzoylbenzoyl chloride was prepared as above from 40 g (0.18 mole) of anhydrous α-benzoylbenzoic acid and 13 ml (0.18 mole) of thionyl chloride. To the cooled acid chloride was added 33 ml (0.35 mole) of isobutyl alcohol. The two phases were swirled to homogeneity, poured into 100 ml of 3.6 M Na₂CO₃, and allowed to stand for 3 hr.

A tacky precipitate formed which for the most part was washed through the filter with water. The residue was dissolved in 95% ethanol, and the solvent evaporated; the resulting oil was not examined further.

The aqueous filtrate was extracted with five 50-ml portions of chloroform. An oil resulted upon distillation of the solvent. An infrared spectrum (4930) indicated a mixture of normal and pseudo esters.

The aqueous filtrate was acidified with concentrated HCl, producing 12.3 g (24%) of a white solid, mp 122-126°. An infrared spectrum (163) confirmed its identity as α-benzoylbenzoic acid.

Attempted Preparation of 3-Isobutoxy-3-phenylphthalide. B.—

α-Benzoylbenzoyl chloride (0.089 mole) was prepared as in A above. To the warm acid chloride was added 8 ml (0.089 mole) of isobutyl alcohol. Upon cessation of the vigorous reaction, the viscous mixture was poured into 50 ml of 0.2 M Na₂CO₃ with stirring. A precipitate developed which was collected and washed with water. On the basis of its infrared spectrum (105), it appeared to be mostly pseudo ester. The filtrate
deposited crystals upon standing. These were collected and washed with 95% ethanol. The ethanol filtrate deposited crystals (2.3 g) which were collected. The infrared spectrum (96) of these was ambiguous.

The original filtrate consisted of oil and water. Stirring and dry-ice cooling failed to effect crystallization. By addition of 95% ethanol as an emulsifying agent, 23 g of a white solid was isolated. Most of the solid was insoluble in boiling 95% ethanol. Its infrared spectrum (97) indicated a predominance of the pseudo ester.

Attempted Preparation of 3-Isobutoxy-3-phenylphthalide. C.--

o-Benzoylbenzoyl chloride (0.049 mole) was prepared as in A above. The acid chloride was then poured, with stirring, into a two-layer system of 15 ml of 6 M Na₂CO₃, 4 ml (0.044 mole) of isobutyl alcohol, and 12.5 ml of dioxane. A white precipitate (9.7 g) was formed, whose infrared spectrum (180) was ambiguous. An additional amount (3.1 g) of solid was isolated from successive filtrates. The infrared spectrum (186) indicated a mixture of normal and pseudo esters.

Attempted Preparation of 3-Isobutoxy-3-phenylphthalide. D.--

o-Benzoylbenzoyl chloride (0.02 mole) was prepared as in A. The acid chloride was poured into a solution of 2 ml (0.02 mole) of isobutyl alcohol, 5 ml (0.07 mole) of pyridine, and 15 ml of dioxane. With stirring and heating the components became homogeneous.

The reaction mixture crystallized on a watch glass
after standing a few days. Infrared spectra (204, 205) indicated a mixture of normal and pseudo esters.

**Attempted Preparation of 3-t-Butoxy-3-phenylphthalide.**

An unknown amount of o-benzoylbenzoyl chloride was prepared as before. To the acid chloride was added t-butyl alcohol. Stirring, swirling, shaking, and finally heating were required to attain homogeneity. The reaction mixture was then poured into a cooled, saturated solution of NaHCO₃. The solid which formed was collected, washed with water, dried, and recrystallized (95% EtOH). The infrared spectrum (570) indicated a mixture of normal and pseudo esters.

The aqueous filtrate was acidified with concentrated HCl, producing 0.5 g of o-benzoylbenzoic acid (ir spectrum, 571).

**Attempted Preparation of 3-(−)-Menthoxy-3-phenylphthalide.**

o-Benzoylbenzoyl chloride was prepared by refluxing 10 g (0.044 mole) of anhydrous o-benzoylbenzoic acid and 3.3 ml (0.055 mole) of thionyl chloride 5 hr and then removing excess thionyl chloride. The acid chloride was added to a chilled solution of 13.8 g (0.089 mole) of (−)-menthol \[ [\alpha]^{22.5}_{D} = -52.1 \pm 0.9 \ (g 7.6, C_{2}H_{5}OH) \] in 25 ml of chloroform. The mixture became a homogeneous liquid when it reached room temperature.

After about 0.5 hr the mixture was poured into 25 ml of 0.089 M Na₂CO₃. The layers were separated. The aqueous layer was extracted with five 25-ml portions of chloroform.
The combined chloroform layer was washed with two 30-ml portions of 10% Na$_2$CO$_3$, the solvent evaporated and the residue recrystallized (EtOH), yielding 5.4 g of a white solid (mp 120-124°). The infrared spectrum (497, 515) indicated a mixture of normal and pseudo esters.

Acidification of the aqueous and Na$_2$CO$_3$ layers produced o-benzoylbenzoic acid (1.6 g; 16%).

**Attempted Preparation of 3-(−)-Menthoxy-3-Phenylphthalide. B.**—o-Benzoylbenzoyl chloride was prepared as before except at room temperature for 24 hr. The acid chloride, dissolved in 20 ml of anhydrous benzene, was added to a heterogeneous mixture of 1.8 M Na$_2$CO$_3$ and 6.9 g (0.044 mole) of (−)-menthol in 10 ml of benzene. The reaction mixture was stirred for 3 hr. A white solid was removed by filtration. The infrared spectrum (579) indicated the salt of an acid. It was suspended in water and the mixture acidified with 1 N HCl. The collected solid was not identified.

The layers were separated, the benzene layer extracted with three 10-ml portions of 10% Na$_2$CO$_3$, and the solvent evaporated. Recrystallization (ethanol-benzene) of the residue produced 0.74 g. The infrared spectrum (583) indicated a mixture of normal and pseudo esters.

**Attempted Preparation of 3-Phenoxy-3-Phenylphthalide.**—Anhydrous o-benzoylbenzoic acid (57 g; 0.25 mole), 117 g (1.3 mole) of practical grade phenol, and 150 ml of benzene were refluxed for 7 hr. To the reaction mixture were added 150 ml of benzene and 400 ml of distilled water.
The layers were separated and the benzene layer extracted with eight 50-ml portions of 5% Na$_2$CO$_3$. It was dried (Na$_2$SO$_4$) and the solvent removed. The residue, which could not be crystallized, was shown to be composed of organic and inorganic material.

$\alpha$-Benzoylbenzoic acid, 48 g (84%), was recovered from the Na$_2$CO$_3$ layer.

**Attempted Preparation of 3-Phenoxy-3-phenylphthalide.** $^5$B.

$\alpha$-Benzoylbenzoyl chloride (29 g; 0.12 mole) and 60 ml of dry benzene were mixed thoroughly. To this was added a solution of 17 g (0.18 mole) of reagent grade phenol in 45 ml of dry pyridine. The contents were refluxed under nitrogen for 1.5 hr.

Upon cooling a white solid formed, which was collected. The benzene filtrate was acidified with concentrated HCl producing a white solid which was combined with the original solid. The combined solid was extracted with ether in a Soxhlet apparatus for 8 hr.

The ether layer deposited a solid material. It was collected and recrystallized (benzene) to 4.3 g. The ether filtrate was washed with three 25-ml portions of 1 N HCl, three 25-ml portions of saturated Na$_2$CO$_3$, and two 25-ml portions of saturated NaCl. When it was dried (Na$_2$SO$_4$) and the ether removed, 0.7 g of solid remained. This was combined with the first solid and recrystallized from benzene, producing 4.5 g of white material, mp 163-170°. An infrared spectrum (4200) indicated a mixture of normal and pseudo esters.
The original benzene filtrate was washed with two 30-ml portions of concentrated HCl, three 30-ml portions of 10% Na₂CO₃, two 20-ml portions of 5% NaOH, and four 20-ml portions of water. The solution was dried (Na₂SO₄) and the benzene removed. Scratching caused the residue to solidify; upon recrystallization (95% EtOH) there was obtained 19.4 g of a white solid, mp 79-81⁰. An infrared spectrum (4080) indicated it to be phenyl o-benzoyl benzoate.

o-Benzoylbenzoic acid, 2.3 g (8.5%) was recovered from the Na₂CO₃ layer.

Attempted Preparation of 3-Phenoxy-3-phenylphthalide. C.—o-Benzoylbenzoyl chloride was prepared as before from 20 g (0.089 mole) of anhydrous o-benzoylbenzoic acid and 6.7 ml (0.093 mole) of thionyl chloride. To the acid chloride was added 12.6 g (0.13 mole) of melted phenol. An exothermic reaction resulted, which was controlled with an ice bath. The mixture was heated slightly to insure complete reaction and then poured into 50 ml of 0.2 M Na₂CO₃. When methanol was added to mix the layers, a white crystalline solid separated. Four more fractions of crystals were collected to give a total of 34.5 g. An infrared spectrum (4828) indicated the solid to be mostly normal ester.

o-Benzoylbenzoic acid was recovered (7 g; 35%) from the Na₂CO₃ layer.

Attempted Preparation of 3-ethoxy-3-phenylphthalide. A.—o-Benzoylbenzoyl chloride was prepared under dry nitrogen from 27 g (0.12 mole) of anhydrous o-benzoylbenzoic acid and
29 g (0.24 mole) of thionyl chloride. To the ice-cold acid chloride was added a solution of 14 ml (0.18 mole) of dry pyridine and 10 ml (0.18 mole) of absolute ethanol. The two-phase mixture became homogeneous when allowed to come to room temperature. An exothermic reaction resulted which required cooling. The flask was swept with dry nitrogen for 1 hr and the contents allowed to stand under nitrogen for 5 days.

The almost completely solidified reaction mixture was diluted with 75 ml of benzene. The residual undissolved solid was collected and washed with benzene. The combined benzene layers were washed with four 25-ml portions of 1 N HCl, four 25-ml portions of saturated NaHCO₃, three 25-ml portions of saturated NaCl, dried (Na₂SO₄), and the benzene distilled. Attempts to purify the solid obtained (31 g) by recrystallization and tlc failed.

By acidification of the sodium bicarbonate extract with concentrated HCl, 0.6 g (2%) of o-benzoylbenzoic acid, mp 126.5-128.0° (benzene) was recovered.

3-Ethoxy-3-phenylphthalide. 1 B.—To 40 g (0.18 mole) of anhydrous o-benzoylbenzoic acid was added dropwise 22 g (0.19 mole) of thionyl chloride. After addition, the reaction was warmed to insure complete reaction.

Excess thionyl chloride was removed by heating to 68° under aspirator pressure for 1.75 hr. The liquid residue was added dropwise to 15.8 g (0.34 mole) of cool, absolute ethanol. Immediately, 100 ml of 4.2 M Na₂CO₃ was added. The reaction commenced when the ice bath was removed.
The reaction mixture was filtered and the filtrate extracted with four 50-ml portions of chloroform. The chloroform layer was extracted with four 25-ml portions of 4.2 M Na$_2$CO$_3$. During this extraction, a yellow oily layer developed which was soluble in neither the chloroform nor the basic layer.

Crystals deposited in the chloroform layer were recrystallized from aqueous ethanol and repeatedly from 95% ethanol; 14.1 g (31%), mp 76-78° (lit. 51-53°).

A single carbonyl band in the infrared spectrum appeared at 1760 cm$^{-1}$. The nmr spectrum (CCl$_4$) exhibited a triplet at 1.19 (J=7) and a multiplet centered at 3.4.

o-(α-Ethyl-α-ethoxybenzyl)-benzoic acid.—The Grignard reagent was prepared from 2.72 g (0.11 mole) of magnesium, 12.2 g (0.11 mole) of ethyl bromide, and 125 ml of ether. To this was added portionwise, with stirring, 22.3 g (0.11 mole) of dry CdCl$_2$. The Gilman test being negative, the ether was distilled and gradually replaced by 125 ml of dry benzene. To the reagent was added, over 0.5 hr, 14.1 g (0.056 mole) of 3-ethoxy-3-phenylphthalide dissolved in 25 ml of dry benzene. The reaction mixture was refluxed for 6 hr.

Hydrolysis was carried out in 1.4 M H$_2$SO$_4$ containing ice. The hydrolyzed reaction mixture was filtered, the layers separated, and the aqueous layer extracted with four 30-ml portions of benzene. The combined benzene layer was extracted with five 50-ml portions of 10% Na$_2$CO$_3$, dried (Na$_2$SO$_4$), and the benzene removed. Analysis of the residue by ir and tlc.
indicated it could be a mixture of 3-ethyl-3-phenylphthalide
and 3-ethoxy-3-phenylphthalide.

Careful acidification of the Na₂CO₃ extracts was car-
ried out as before, producing white granules (13.9 g, 87%).
A portion (6.95 g) of the solid was recrystallized from ben-
zene and then ethanol, yielding 2.68 g (39% recovery), mp
156-159°, of 20.

Anal. Calcd for C₁₈H₂₀O₃: C, 76.03; H, 7.09; N.E. 284.
Found: C, 75.88; H, 6.90; N.E. 285, 289, 290, 291.

Infrared bands (334) are present at 2860-2960 cm⁻¹
(aliphatic C-H) and at 1700 cm⁻¹ (CO₂H). The nmr spectrum
(214) exhibited triplets (3 each) at 0.78 (J=7.5) and 1.23
(J=7) and quartets (2 each) at 2.41 (J=7.5) and 3.28 (J=7).

Preparation of 3-Ethyl-3-phenylphthalide. —The Grignard rea-
gent was prepared from 3.1 g (0.13 mole) of magnesium, 14 g
(0.13 mole) of ethyl bromide, and 125 ml of ether. To this
was added, over 0.5 hr, 9.5 g (0.042 mole) of o-benzoyl-
benzoic acid dissolved in 100 ml of ether. The reaction
mixture was stirred and refluxed for 1.5 hr.

The mixture was hydrolyzed with 300 ml of dilute HCl.
The layers were filtered and separated. The aqueous layer
was extracted with three 25-ml portions of ether. The com-
bined ether solution was washed with three 25-ml portions of
10% Na₂CO₃, two 25-ml portions of saturated sodium chloride,
dried (Na₂SO₄), and the ether removed. The oily residue was
recrystallized (95% EtOH), producing a small amount of white
crystals, mp 39-90° (lit. 47°). ⁴ The infrared spectrum (362)
exhibited a strong band at 1790 cm$^{-1}$.

Acidification of the 10% Na$_2$CO$_3$ layer produced no solid material.

Reaction of o-(a-Ethyl-a-ethoxybenzyl)-benzoic Acid and Concentrated Hydrochloric Acid.—A mixture of 0.66 g (0.0023 mole) of o-(a-ethyl-a-ethoxybenzyl)-benzoic acid and 40 ml of benzene was heated to effect solution. To this was added 10 ml of concentrated HCl and the mixture refluxed for 9 hr. Initially, HCl was given off rapidly.

The reaction mixture was filtered and the layers separated. The aqueous layer was extracted with three 5-ml portions of benzene. The combined benzene solution was extracted with four 15-ml portions of 10% Na$_2$CO$_3$, dried (Na$_2$SO$_4$), and the benzene distilled. Recrystallization (95% EtOH) of the viscous oil residue produced gray-white crystals, mp 42-75°. The infrared spectrum (440) showed a strong carbonyl band at 1770 cm$^{-1}$, indicative of a lactone.

Acidification of the Na$_2$CO$_3$ extract with concentrated HCl yielded 0.065 g of crude white crystals, mp 110-143°. The infrared spectra (442, 443) exhibited a strong band at 1690 cm$^{-1}$. They also contained bands at 930 cm$^{-1}$ and 960 cm$^{-1}$, not found in the spectrum (328) of o-(a-ethyl-a-ethoxybenzyl)-benzoic acid.

3-Isopropoxy-3-phenylphthalide.—In a manner analogous to that for the preparation of 3-ethoxy-3-phenylphthalide, 21 g (0.18 mole) of thionyl chloride was added dropwise to 40 g (0.18 mole) of anhydrous o-benzoylbenzoic acid, and the excess
thionyl chloride was removed.

To the slightly cooled acid chloride was added 68 ml (0.89 mole) of isopropyl alcohol while the components were swirled to insure complete mixing.

The reaction mixture was poured into 100 ml of 3.6 M Na₂CO₃. Recrystallization of the resulting white solid from 95% ethanol yielded 21.5 g (45%) of a white solid, mp 68-70°.

Anal. Calcd for C₁₇H₁₆O₃; C, 76.09; H, 6.01. Found: C, 76.02; H, 6.02.

The infrared spectrum contains a typical lactone carbonyl band at 1775 cm⁻¹. The nmr spectrum (CCl₄) exhibits a triplet (6) (apparently two overlapping doublets) at 1.16 (J=6) and a quintet (1) at 3.70 (J=6).

o-(α-Ethyl-α-isopropoxybenzyl)-benzoic acid.—The Grignard reagent was prepared from 2.72 g (0.112 mole) of magnesium turnings, 12.2 g (0.112 mole) of ethyl bromide, and 30 ml of ether. To the Grignard reagent was added portionwise, with stirring, 22.3 g (0.112 mole) of anhydrous CaCl₂ over a period of 15 min. The Gilman test being negative, the cadmium reagent was stirred an additional 10 min. The ether was replaced with 200 ml of dry benzene by distillation.

To the refluxing cadmium reagent was added dropwise, with stirring, over a period of 0.5 hr, 15.0 g (0.056 mole) of 3-isopropoxy-3-phenylphthalide in 25 ml dry benzene. The reaction mixture was refluxed and stirred for 6 hr. Hydrolysis was accomplished with an ice solution of 1.4 M H₂SO₄.
The hydrolyzed reaction mixture was filtered and the layers separated.

The aqueous layer was extracted with four 30-ml portions of benzene. The benzene layers were combined and extracted with six 50-ml portions of 10% Na$_2$CO$_3$, dried (Na$_2$SO$_4$), and the benzene removed. The residue was not examined further.

A white solid separated from the Na$_2$CO$_3$ extraction in four successive filtrates. These were suspended in distilled water and acidified dropwise with conc. HCl. The acidification had to be extremely slow as a gummy solid resulted from rapid acidification. The acid was dried (3.2 g, 19%) and re-crystallized from ethanol, mp 135-137°.

**Anal.** Calcd for C$_{19}$H$_{22}$O$_3$: C, 76.48; H, 7.43. Found: C, 76.31; H, 7.53.

The infrared spectrum contains typical aliphatic C-H absorption and a carbonyl band at 1690 cm$^{-1}$. The nmr spectrum (CHC$_3$) exhibits a triplet (3) at 0.77 ($\delta=7$), a doublet (6) at 1.05 ($\delta=6.5$), a quartet (2) at 2.45 ($\delta=7$), and an apparent septet (1) at 3.83 ($\delta=6.5$).

**Control Experiment between 3-Isopropoxy-3-phenylphthalalide and Aqueous Sulfuric Acid.**—To a solution of 3 g (0.01 mole) of 3-isopropoxy-3-phenylphthalalide in 50 ml benzene was added 12 ml of 1 M H$_2$SO$_4$. The mixture was stirred vigorously for 0.17 hr and allowed to stand for 0.7 hr. The layers were separated and the aqueous layer extracted with four 5-ml portions of benzene. The combined benzene solution was extracted with...
five 10-ml portions of 10% Na₂CO₃, dried (Na₂SO₄), and the benzene distilled. Some of the residual oil was spilled. The remaining 2.5 g crystallized, mp 68-70°. Infrared spectra (300, 301) were identical to that of 3-isopropoxy-3-phenylphthalide.

The Na₂CO₃ layer was acidified dropwise with concentrated HCl. After standing a few days, it was extracted with benzene; the benzene was dried (Na₂SO₄) and distilled. The resulting oil crystallized (mp 60-145°) upon trituration with chloroform. An infrared spectrum (302) indicated it was 3-isopropoxy-3-phenylphthalide. Total starting-material recovered was 83%.

**Reaction of 3-Isopropoxy-3-phenylphthalide and Phenylcadmium Chloride.**

A.—The phenylcadmium reagent was prepared in an analogous manner to the ethylcadmium reagent from 2.7 g (0.11 mole) of magnesium, 17.6 g (0.11 mole) of bromobenzene, 22.3 g (0.12 mole) of cadmium chloride, 150 ml of ether and 125 ml of benzene.

To the phenylcadmium reagent was added dropwise, over a period of 0.5 hr, 15 g (0.056 mole) of 3-isopropoxy-3-phenylphthalide in 75 ml of dry benzene. The mixture was stirred at reflux for 2 hr. The reaction mixture was cooled and poured into 0.7 M H₂SO₄ containing ice. The mixture was filtered and the liquid layers separated. The water layer was extracted with three 30-ml portions of benzene. The combined benzene solution was washed with four 50-ml portions of 10% Na₂CO₃, dried (Na₂SO₄), and the benzene distilled. The
aqueous layer was again extracted with benzene, the benzene
extracted with 10% Na₂CO₃, dried (Na₂SO₄), and the benzene
distilled. The two oily residues were combined. An infra-
red spectrum (4924) was similar to that (66) of 3-isopropoxy-
3-phenylphthalide.

The material filtered from the hydrolyzed reaction
mixture was washed with chloroform. The chloroform gave two
residues, A, 1.4 g, ir #68; B, 1.1 g, ir #67. The infrared
spectra were both similar to that of 3-isopropoxy-3-phenyl-
phthalide (66).

The solid remaining from above was combined with the
Na₂CO₃ extracts, and the mixture was acidified with concen-
trated HCl. This resulted in recovery of 9.2 g (73%) of
o-benzoylbenzoic acid, mp 124-127°C; 125-128°C. The infrared
spectra (4920, 4941) were identical to that (4718) of o-ben-
zoylbenzoic acid.

Reaction of 3-Isopropoxy-3-phenylphthalide and Phenyleadmmium
Chloride. B.—The reaction was carried out as described in A,
except that the reflux period was 16 hr. The reaction mix-
ture was cooled and poured into 1 M H₂SO₄ containing ice.
An additional 60 ml of 1 M H₂SO₄ was used to decompose par-
ticles in the reaction flask. The layers were filtered and
separated. The aqueous layer was extracted with four 30-ml
portions of benzene. The combined benzene solution was ex-
tracted with five 50-ml portions of 10% Na₂CO₃, dried (Na₂SO₄),
and the benzene distilled. The infrared spectrum (266) of
the residual oil exhibited a strong band at 1770 cm⁻¹. A tlc
plate (8) indicated a five-component mixture.

Upon acidification of the 10% \( \text{Na}_2\text{CO}_3 \) extract, 9.3 g (73%) of a white solid, mp 126.5-128.0° (benzene) was obtained. The infrared spectrum (4828) was identical to that of \( \alpha \)-benzoylbenzoic acid (4718). Mixture melting points of varying compositions with pure \( \alpha \)-benzoylbenzoic acid showed no depression.

**Phthalaldehydic Acid.**—The commercial sample (Dow Chemical Company, Midland, Michigan), was recrystallized from methylene chloride. It was in the form of a slightly off-white solid, mp 97-99°. The infrared spectrum (6794) exhibited a strong band at 1750 \( \text{cm}^{-1} \). The nmr spectrum (9597, acetone-\( \text{d}_6 \)) exhibited broad singlets at 6.86 and 7.14 and a multiplet at 7.76 (lit.,\(^{36} \text{D}_2\text{O}, \text{singlet at 6.75, multiplet at 7.6}).

**3-Ethoxyphthalide.**—Recrystallization of crude 3-ethoxyphthalide from petroleum ether (bp 100-115°): absolute ethanol (1:3), converted it to a white solid, mp 66.5-67.5°, (lit. 64-65°).\(^{10} \) The infrared spectrum (7361) contains a band at 1785 \( \text{cm}^{-1} \). The nmr spectrum (5003) exhibits a triplet (3) at 1.27, a quartet (2) at 3.86, a singlet (1) at 6.33 and a multiplet (4) at 7.47-7.90.

**\( \alpha \)-(\( \alpha \)-Ethoxyethyl)-benzoic Acid.**—Methylcadmium chloride was prepared in 125 ml of ether from 1.9 g (0.076 mole) of magnesium, 11 g (0.076 mole) of methyl iodide, and 14 g (0.076 mole) of cadmium chloride. To the cadmium reagent was added, over 1 hr, 6.8 g (0.038 mole) of 3-ethoxyphthalide\(^{10,11} \) in 70 ml of ether. The reaction mixture was stirred at reflux.
temperature for 4.5 hr.

The reaction mixture was poured into 48 ml of 6% H₂SO₄ containing ice. The reaction flask was rinsed with 2 g H₂SO₄ in 15 ml water. The layers were filtered and separated. The aqueous layer was extracted with five 40-ml portions of ether. The combined ether solution was washed with two 15-ml portions of saturated NaHSO₃, six 30-ml portions of saturated Na₂CO₃, one 30-ml portion of saturated NaCl, dried (MgSO₄), and the ether removed on the rotary evaporator. Nmr analysis (4668) of the oily residue with dioxane as an internal standard indicated 0.073 g (1.3%) of 3-methylphthalide.

From acidification of the Na₂CO₃ layer with concentrated HCl, 6.3 g (85%) of a white solid, mp 73.5-74.5°C, was collected.

**Anal.** Caled for C₁₁H₁₄O₃: C, 68.02; H, 7.27. Found: C, 67.97; H, 7.31.

The infrared spectrum (7414) contained a strong band at 1695 cm⁻¹. The nmr spectrum (4864) exhibited a triplet (3) at 1.17 (J=6.5), a doublet (3) at 1.45 (J=6.5), a quartet (2) at 3.39 (J=6.5), a quartet (1) at 5.42 (J=6.5) and a multiplet (4) at 7.10-8.17.

3-Methoxyphthalide — Phthalaldehydic acid (40 g, 0.27 mole) and 120 ml of methanol were refluxed for 4 hr. The reaction mixture was cooled, poured into 600 ml of water, and refrigerated for 1.5 days. A brown solid layer developed on the bottom of the beaker and white needles in the supernatant solution. All solid was collected, dissolved in n-hexane,
and the solution poured while hot into a separatory funnel. The brown-colored lower layer was removed, the upper clear layer put in a beaker and refrigerated. From this, 4.4 g (10%) of a white solid, mp 43-45° (lit. 44°),11 was collected. The infrared spectrum (1252) contains a band at 1782 cm⁻¹. The nmr spectrum (9596) exhibits a singlet (3) at 3.57, a singlet (1) at 6.29, and a multiplet (4) at 7.50-7.96.

**o-(α-Methoxyethyl)-benzoic Acid.**—Methylcadmium chloride was prepared in 130 ml of ether from 1.3 g (0.054 mole) of magnesium, 7.7 g (0.054 mole) of methyl iodide, and 9.9 g (0.054 mole) of cadmium chloride. To the cadmium reagent was added over 1 hr 4.4 g (0.027 mole) of 3-methoxyphthalide in 35 ml of ether. The reaction mixture was stirred at reflux temperature for 4 hr.

The reaction complex was poured into 9 ml of H₂SO₄ in 135 ml of water. The flask was rinsed with 3 ml of H₂SO₄ in 45 ml of water. The mixture was filtered and the liquid layers separated. The aqueous layer was extracted with five 50-ml portions of ether. The combined ether solution was washed with two 20-ml portions of saturated NaHSO₃, six 40-ml portions of saturated Na₂CO₃, two 40-ml portions of saturated NaCl, dried (MgSO₄), and the ether removed by rotary evaporation. Nmr analysis (4869) of the oily residue with dioxane as an internal standard indicated 0.062 g (1.6%) of 3-methyl-phthalide.

From acidification of the Na₂CO₃ layer with concentrated HCl, 4.4 g (91%) of a white solid, mp 111.0-111.5°,
was collected.

**Anal.** Calcd for C_{10}H_{12}O_{3}: C, 66.65; H, 6.71. Found: C, 66.65; H, 6.79.

The infrared spectrum (7415) contains a strong band at 1690 cm\(^{-1}\). The nmr spectrum (4865) exhibits a doublet (3) at 1.53 (J=6), a singlet (3) at 3.30, a quartet (1) at 5.37 (J=6), and a multiplet (4) at 7.19-8.20.

Di-3-Phthalidyl Ether. Phthalaldehydic acid (40 g, 0.27 mole) was heated at 232\(^\circ\) for 4 hr in a beaker covered with aluminum foil to keep a constant temperature and to collect sublimed material. By recrystallization from methylene chloride of the residual solid and sublimate, there was obtained 2.7 g (14\%) of a white solid, mp 213-217\(^\circ\) (lit. 221\(^\circ\)). The infrared spectrum (6793) contains a band at 1790 cm\(^{-1}\). The nmr spectrum (5055) exhibits a doublet (1) at 7.00 and a multiplet (4) at 7.60-7.90.

**Reaction of Di-3-Phthalidyl Ether and Methylcadmium Chloride.** A. Methylcadmium chloride was prepared in 43 ml ether from 0.47 g (0.019 mole) of magnesium, 2.7 g (0.019 mole) of methyl iodide and 3.5 g (0.019 mole) of cadmium chloride. To the cadmium reagent was added, over 0.5 hr, 2.7 g (0.0096 mole) of di-3-phthalidyl\(^\circ\) ether in 500 ml of hot toluene. The reaction mixture was stirred at 50\(^\circ\) for 4 hr.

The reaction mixture was poured into 288 ml of 6\% H\(_2\)SO\(_4\). The reaction flask was rinsed with 48 ml of 6\% H\(_2\)SO\(_4\). The mixture was filtered and the liquid layers separated. The water layer was extracted with five 60-ml portions of ether. The
combined ether solution was washed with two 30-ml portions of saturated NaHCO₃, six 50-ml portions of saturated Na₂CO₃, two 60-ml portions of saturated NaCl, dried (MgSO₄), and the ether removed on the rotary evaporator. The residue consisted of 1.4 g (52%) of a white solid. The infrared spectrum (7638) indicated it was starting material.

A large amount of solid material was collected from the hydrolyzed reaction mixture. It was taken up in acetone but partially decomposed when the solvent was removed by heating. The residue was extracted with boiling toluene and the toluene removed. The infrared spectrum (7641) of the residue indicated it was starting material.

The Na₂CO₃ layer was acidified with concentrated HCl. A white solid, mp 204-212°, was collected, 0.11 g (4%). The infrared spectrum (7639) exhibited a strong band at 1695 cm⁻¹. The nmr spectrum (5060) exhibited a triplet at 1.37, a multiplet at 5.00-5.60 and a multiplet at 7.10-8.00. It was not examined further.

**Reaction of Di-3-Phthalidyl Ether and Methylcadmium Chloride. B.**

Methylcadmium chloride was prepared in 100 ml of ether from 0.5 g (0.021 mole) magnesium, 2.92 g (0.021 mole) of methyl iodide, and 3.8 g (0.021 mole) of cadmium chloride. To the cadmium reagent was added all at once 2.9 g (0.010 mole) of di-3-phthalidyl ether. After being stirred at reflux for 0.75 hr, the reaction complex became so thick that stirring was no longer possible. It was allowed to stand at room temperature for 95.5 hr.
To the reaction mixture was added 32 ml of 6% H$_2$SO$_4$ containing ice. From the hydrolyzed mixture, 2.1 g (73%) of an off-white solid, mp 205-212$^\circ$, was collected. The infrared spectrum (7880) was identical to that of di-3-phthalidyl ether (6793). The liquid layers of the filtrate were separated and the aqueous layer extracted with five 50-ml portions of ether. The combined ether solution was washed with two 15-ml portions of saturated NaHSO$_3$, six 30-ml portions of Na$_2$CO$_3$, two 30-ml portions of saturated NaCl, dried (MgSO$_4$), and the ether removed.

The residue (0.6 g) was dissolved in chloroform and 0.03 g of a white solid collected upon partial evaporation of the solvent. The infrared spectrum (7886) was identical to that of di-3-phthalidyl ether (6793). Upon complete removal of the chloroform, 0.46 g of a sticky, colored solid remained. When this was put into boiling carbon tetrachloride and the solution cooled, 0.08 g of a white solid was obtained. This solid, combined with the 0.03 g above, accounts for 4% recovered starting material. The brown filtrate was concentrated. Its nmr spectrum (5378) indicated the presence of 3-methylphthalide.

Acidification of the Na$_2$CO$_3$ layer with concentrated HCl and refrigeration of the acidified solution produced 0.7 g (22%) of a white solid, mp 205-214$^\circ$.

**Anal.** Calcd for C$_{18}$H$_{18}$O$_5$: C, 68.78; H, 5.77. Found: C, 68.78; H, 5.92. The infrared spectrum (7881) contains one carbonyl band at 1690 cm$^{-1}$. The nmr spectrum (5372) exhibits
a triplet (6) at 1.46 (\(J=6\)), a septet (2) at 5.43 (\(J=6\)), and a multiplet (8) at 7.10-8.00.

3-(\(p\)-Chlorophenoxy)-phthalide\(^{12}\) -- 3-(\(p\)-Chlorophenoxy)-phthalide\(^{13}\) was recrystallized from isopropyl alcohol to long white needles, mp 162-163\(^\circ\) [lit. 157-158\(^\circ\) (benzene)].\(^{12}\) The nmr spectrum exhibited a singlet (1) at 6.87, a multiplet (4) centered at 7.27, and a multiplet (4) centered at 7.22.

**Reaction of 3-(\(p\)-Chlorophenoxy)-phthalide and Methylcadmium Chloride.** A. -- Methylcadmium chloride was prepared in 220 ml of ether from 2.0 g (0.081 mole) of magnesium, 12 g (0.081 mole) of methyl iodide, and 15 g (0.081 mole) of cadmium chloride. To the cadmium reagent was added all at once 10.6 g of 3-(\(p\)-chlorophenoxy)-phthalide\(^{12}\) in 375 ml of toluene. The reaction mixture was stirred at 40\(^\circ\) for 4.25 hr.

Hydrolysis was accomplished by pouring the reaction mixture into 240 ml of 6% \(\text{H}_2\text{SO}_4\), and the reaction flask was rinsed with 80 ml of 6% \(\text{H}_2\text{SO}_4\). The mixture was filtered and the liquid layers separated. The aqueous layer was extracted with five 60-ml portions of ether. The toluene and ether layers were combined and washed with two 30-ml portions of saturated \(\text{NaHSO}_3\), six 50-ml portions of saturated \(\text{Na}_2\text{CO}_3\), two 60-ml portions of saturated \(\text{NaCl}\), dried (\(\text{MgSO}_4\)), and the ether-toluene removed on the rotary evaporator. An nmr spectrum (4871) of the viscous residue (12.5 g) was not definitive except to indicate the absence of any 3-methylphthalide (singlet at 5.7).
The Na$_2$CO$_3$ layer was acidified with concentrated HCl, but no solid precipitated.

**Reaction of 3-(p-Chlorophenoxy)-phthalide and Methylcadmium Chloride.** B. — Methylcadmium chloride was prepared in 135 ml ether from 1.1 g (0.044 mole) of magnesium, 6.2 g (0.044 mole) of methyl iodide, and 8.0 g (0.044 mole) of cadmium chloride. To the cadmium reagent was added in one portion 5.7 g (0.022 mole) of 3-(p-chlorophenoxy)-phthalide. The reaction mixture was stirred at reflux temperature for 4 hr.

The mixture was poured into 50 ml of 6% H$_2$SO$_4$, and the reaction flask was rinsed with 27 ml of 6% H$_2$SO$_4$. The mixture was filtered and the liquid layers separated. The water layer was extracted with five 40-ml portions of ether. The combined ether solution was washed with two 15-ml portions of saturated NaHSO$_3$, six 25-ml portions of saturated Na$_2$CO$_3$, two 25-ml portions of saturated NaCl, dried (MgSO$_4$), and the ether removed on the rotary evaporator. A very viscous residue (5.6 g) resulted. Nmr analysis (5185) was ambiguous as in A.

Acidification of the Na$_2$CO$_3$ layer with concentrated HCl yielded no insoluble solid.

**3-Phenoxyphthalide.** A. — Phthalaldehydic acid (38 g; 0.25 mole) and 35 g (0.38 mole) of reagent grade phenol were refluxed in 100 ml of benzene for 7 hr. The benzene solution was extracted with twelve 50-ml portions of 5% Na$_2$CO$_3$, dried (Na$_2$SO$_4$), and the benzene distilled. The residue crystallized on a watch
Recrystallization (95% EtOH) produced two small fractions: A, mp 114-115°; B, mp 115-118°. These and other subsequent fractions were combined and recrystallized (95% EtOH) to give 2.0 g (3.6%) of a white solid, mp 115-117°.

**Anal.** Calcd for C$_{14}$H$_{10}$O$_3$: C, 74.33; H, 4.46. Found: C, 74.20; H, 4.51.

The infrared spectrum (3846) exhibited a strong band at 1770 cm$^{-1}$.

In the process of recrystallization there was isolated an ethanol-insoluble material (0.7 g), mp 214-230°, probably di-3-phthalidyl ether.$^6$

Acidification of the Na$_2$CO$_3$ extracts with concentrated HCl, evaporation to dryness, and redissolving in less water led to the recovery of 26 g (69%) of phthalaldehydic acid, mp 98-99° (benzene); mixture mp 97.0-98.5°.

**Attempted Preparation of 3-Phenoxyphthalide.** B.—To 42 g (0.35 mole) of ice-cold thionyl chloride was added 10 g (0.07 mole) of phthalaldehydic acid. The reaction mixture was allowed to warm to room temperature and stored overnight. It was heated to 78-80° under aspirator pressure for 3 hr.

To the remaining acid chloride was added 6.3 g (0.067 mole) of freshly fused phenol. A vigorous reaction ensued. When swirling produced no more evidence of reaction, the reaction mixture was poured into 0.2 M Na$_2$CO$_3$. A vigorous reaction followed. A total of 0.8 g (10%) of a white solid was collected. A portion of the white solid, soluble in hot 95% EtOH, could be recovered by allowing the ethanol filtrate to
cool. Infrared spectra (79,80) identified it as di-3-phthalidyl ether.

The remaining filtrate and ethanol-insoluble material were acidified with concentrated HCl. A negligible scum resulted in both cases.

Attempted Preparation of 3-Phenoxyphthalide. C.—3-Chlorophthalaldehyde was prepared as in B above from 20 g (0.13 mole) of phthalaldehydic acid and 10 ml (0.14 mole) of thionyl chloride. To the acid chloride was added 12.9 g (0.13 mole) of phenol. After addition of an unweighed excess of phenol, stirring, and heating, the mixture eventually became homogeneous. The reaction mixture was poured into 50 ml of 0.18 M Na₂CO₃.

A white, tacky solid resulted which required the addition of 50 ml more of water to make it filterable. Recrystallization (95% EtOH) yielded 0.6 g of a white solid. An infrared spectrum (4945) indicated phenyl o-formylbenzoate.

Acidification of the filtrate with concentrated HCl led to recovery of 1.8 g (9%) of phthalaldehydic acid (infrared spectrum #159).

3-Acetoxyphthalaldehyde.¹⁰—Phthalaldehydic acid (13.7 g, 0.091 mole), 7.5 g (0.092 mole) of anhydrous sodium acetate, and 74.0 g (0.73 mole) of acetic anhydride were refluxed for 3 hr. The hot solution was poured with rapid stirring into 150 ml of water containing ice. A white solid (15.9 g, 91%) was collected. After three recrystallizations from 95% EtOH,
there remained 4.4 g (25%) of a white solid, mp 64-65° (lit. 62-63°). The infrared spectrum (7360) contains a band at 1760 cm\(^{-1}\). The nmr spectrum (9595) exhibits a singlet (3) at 2.21, a singlet (1) at 7.40, and a multiplet (4) at 7.50-8.04.

**Reaction of 3-Acetoxyphthalide and Methylcadmium Chloride.**

Methylcadmium chloride was prepared in 50 ml of ether from 0.44 g (0.018 mole) of magnesium, 2.6 g (0.018 mole) of methyl iodide, and 3.3 g (0.018 mole) of cadmium chloride. To this was added, over a period of 50 min, 1.8 g (0.0091 mole) of 3-acetoxyphthalide. The reaction mixture was stirred at reflux temperature for 4 hr.

The complex was poured into 3 ml of H\(_2\)SO\(_4\) in 45 ml of water, the reaction flask being rinsed with 1 ml of H\(_2\)SO\(_4\) in 15 ml of water. The mixture was filtered and the liquid layers separated. The aqueous layer was extracted with five 40-ml portions of ether. The combined ether solution was washed with two 15-ml portions of saturated NaHSO\(_3\), six 30-ml portions of saturated Na\(_2\)CO\(_3\), two 30-ml portions of saturated NaCl, dried (MgSO\(_4\)), and the ether removed on the rotary evaporator. Because a dark color persisted, the residue was dissolved in 50 ml of ether, washed with four 5-ml portions of saturated NaHSO\(_3\), dried (MgSO\(_4\)), and the ether evaporated at room temperature. A recrystallization (absolute ethanol) was attempted with no success, so the ethanol was removed. Nmr analysis (4866) of the residue with dioxane as an internal standard indicated 0.30 g (30%) of 3-methylphthalide and

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0.41 g (42%) of starting material.

**Reaction of 3-Acetoxyphthalide and Methylcadmium Chloride.** B.—Methylcadmium chloride was prepared in 140 ml of ether from 1.1 g (0.046 mole) of magnesium, 6.5 g (0.046 mole) of methyl iodide and 8.4 g (0.046 mole) of cadmium chloride. To the cadmium reagent was added in one amount 4.4 g of 3-acetoxyphthalide. The reaction mixture was stirred under reflux for 4 hr.

The mixture was poured into 64 ml of 6% H₂SO₄ and the reaction flask rinsed with 16 ml of 6% H₂SO₄. The hydrolyzed mixture was filtered and the liquid layers separated. The water layer was extracted with five 50-ml portions of ether. The combined ether solution was washed with two 15-ml portions of saturated NaHSO₃, six 40-ml portions of saturated Na₂CO₃, two 40-ml portions of saturated NaCl, dried (MgSO₄), and the ether removed on the rotary evaporator. An amber oil (3.2 g) resulted. Nmr analysis (534A) indicated 1.8 g (57%) of 3-methylphthalide and 1.0 g (33%) starting material.

No solid precipitated after acidification of the Na₂CO₃ layer with concentrated HCl and refrigeration of the acidified solution.

**Attempted Preparation of 3-(−)-Menthoxyphthalide.** A.—Phthalaldehydic acid (15 g, 0.10 mole) and 16 g (0.10 mole) of (−)-menthol [ [α]²².₅ D = -52.1±0.9 (α 7.6, C₂H₅OH) ] were refluxed in 75 ml of benzene for 7.5 hr.

The reaction mixture was cooled and extracted with
four 50-ml portions of saturated NaHCO₃, dried (MgSO₄), the benzene distilled, and traces of benzene allowed to evaporate on a watch glass from the oil residue. The oil crystallized, producing a yellow tinted solid, 18 g (62%). The solid was recrystallized (95% EtOH), yielding 1.2 g (6.5% recovery), mp 104-111°. The infrared spectrum (5270) was consistent for 3-(-)-menthoxyphthalide.

From acidification of the NaHCO₃ extract with concentrated HCl, 3 g (10%) of phthalaldehydic acid was recovered, mp 97.5-99.0°.

Attempted Preparation of 3-(-)-Menthoxyphthalide. B.—Phthalaldehydic acid (9.6 g, 0.064 mole) and 10 g (0.064 mole) of (-)-menthol were refluxed in 50 ml of benzene for 27 hr. The benzene solution was cooled, extracted with three 25-ml portions of saturated NaHCO₃, dried (MgSO₄), the benzene distilled, and the last traces of benzene evaporated on a watch glass. The oil crystallized to 13 g (71%) of a yellow tinted solid. Four fractions totaling 10 g (77% recovery) of an off-white solid, mp 91-108°, were obtained by recrystallization from n-hexane. The infrared spectrum (5333) was consistent with 3-(-)-menthoxyphthalide. Acidification of the NaHCO₃ extract with concentrated HCl produced 1.1 g (11%) of phthalaldehydic acid, mp 97-99°.

Attempted Preparation of 3-(-)-Menthoxyphthalide. C.—Phthalaldehydic acid (25 g, 0.17 mole) and 26 g (0.17 mole) of (-)-menthol were refluxed in benzene for 48 hr. The mixture was worked
up as described in B.

The crude, solidified product (36 g, 74%) was recrystallized from n-hexane, producing, in five fractions, 19 g (53% recovery) of a white solid, mp 118-124°C. The infrared spectrum (5363) exhibited a strong band at 1760 cm\(^{-1}\).

From the acidified NaHCO\(_3\) extract 1 g (4%) of acid was recovered.

3-(-)-Menthoxyphthalide. D.--The reaction was carried out as in C above. The solidified benzene residue was recrystallized from isopropyl alcohol, yielding 27 g (55%) of a white solid. After recrystallization from the same solvent, the product (21 g) was in the form of a white solid, mp 95-122°C. This was recrystallized again from the same solvent to produce a white solid, mp 123.5-125.0°C.

**Anal.** Calcd for C\(_{18}\)H\(_{24}\)O\(_3\): C, 74.97; H, 8.39. Found: C, 74.86; H, 8.45.

The infrared spectrum (5373) exhibited a strong band at 1760 cm\(^{-1}\) and very strong aliphatic C-H absorption between 2800-3000 cm\(^{-1}\). The nmr spectrum (2209) exhibited a series of multiplets (19) from 0.70-4.00, a doublet (1) at 6.41 (\(J=6.0\)), and a multiplet (4) at 7.30-7.91.

\(\alpha\)-(-)-Menthoxyethyl)-benzoic Acid. A.--Methylcadmium chloride was prepared in an analogous manner to that for ethyl-cadmium chloride above from 3.2 g (0.13 mole) of magnesium, 19 g (0.13 mole) of methyl iodide, 24 g (0.13 mole) of cadmium chloride, 130 ml of ether, and 225 ml of benzene.
To the cadmium reagent was added, over a period of 0.5 hr, 19 g (0.065 mole) of 3-(−)-menthoxyphthalide in 60 ml of benzene. An additional 30 ml of benzene was added, and the reaction mixture was refluxed and stirred for 7.0 hr. It was stirred an additional 9 hr without external heating.

The cooled reaction mixture was poured into a mixture of 65 ml of 6% H₂SO₄ containing ice. The reaction flask was rinsed with 34 ml of 6% H₂SO₄. The mixture was filtered, the layers separated, and the aqueous layer extracted with four 40-ml portions of benzene.

The combined benzene solution was washed with four 50-ml portions of saturated NaHCO₃, two 50-ml portions of saturated NaCl, dried (MgSO₄), washed with two 30-ml portions of saturated sodium bisulfite and again dried (MgSO₄). From the benzene solution, 12.0 g (61%) of a white solid, mp 171-174°, was collected in six fractions. The infrared spectra (5924, 5950, 5996, 6000, 6002) showed a strong band at 1690 cm⁻¹. The benzene was removed from the final filtrate, producing 2.3 g (12%) of an impure solid. The infrared spectrum (6003) indicated it was similar to the preceding fractions.

A portion of the solid, mp 171-174°, was recrystallized (benzene), producing a white solid, mp 173.5-174.5°.

**Anal.** Calcd for C₁₉H₂₈O₃: C, 74.96; H, 9.27. Found: C, 75.11; H, 9.19.

The infrared spectrum (6079) exhibited a strong band at 1720 cm⁻¹ and strong aliphatic C-H absorption between 2850 cm⁻¹ and 3000 cm⁻¹. The nmr spectrum (3187) exhibited
a series of multiplets from 0.80-3.40, a doublet (3) at 1.55, a quartet (1) at 5.92, and two closely overlapping triplets at 7.97.

When the NaHCO₃ extract was acidified rapidly, with concentrated HCl, a gummy, amorphous solid separated. It was redissolved with solid NaHCO₃, and the solution was brought slowly to pH 6. An infrared spectrum (5771) of the precipitate (0.7 g) resembled that of the material from the neutral layer.

o-(a-(-)-Menthoxyethyl)-benzoic Acid. B.-Methylcadmium chloride was prepared from 3.6 g (0.15 mole) magnesium, 21 g (0.15 mole) methyl iodide, 195 ml ether, and 27 g (0.15 mole) cadmium chloride. To the cadmium reagent was added, over 2 hr, 21 g (0.074 mole) of 3-(-)-menthoxyphthalide in 200 ml ether. The reaction mixture was stirred at reflux temperature for 22 hr. It was stirred an additional 21 hr.

The reaction mixture was hydrolyzed by pouring it into 65 ml of 6% H₂SO₄ containing ice. The flask was rinsed with 35 ml of 6% H₂SO₄. The layers were filtered and separated. The aqueous layer was extracted with four 50-ml portions of ether. The combined ether solution was extracted with six 50-ml portions of saturated NaHCO₃, two 30-ml portions of NaHSO₃, two 50-ml portions of saturated NaCl, dried (MgSO₄), and the ether removed. A solid (22 g, 97%) remained. A portion of this was recrystallized from benzene, yielding a white solid, mp 164-172°. The infrared spectrum (6846) was

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identical to that of \( o-(\alpha-(\cdot)-\text{menthoxyethyl})-\text{benzoic acid} \) prepared in A.

The \( \text{NaHCO}_3 \) extract was acidified as before to \( \text{pH}=6 \) with concentrated \( \text{HCl} \). A white substance, basic to litmus, (3.8 g) was collected. It was suspended in water and acidified further producing another white solid. The infrared spectrum (6843) indicated it was \( o-(\alpha-(-)-\text{menthoxyethyl})-\text{benzoic acid} \).

\( 3-(-)-\text{Menthoxyacetoxyphthalide} \). Phthalaldehydic acid (28.7 g; 0.191 mole) was dissolved in 112 ml of anhydrous pyridine,* and 27.8 g (0.191 mole) of \( 3-(-)-\text{menthoxyacetyl chloride} \) was added over 0.5 hr. The reaction mixture was stirred magnetically at room temperature for 0.3 hr and then at \( 77^\circ \) for 1.0 hr.

The reaction mixture, when cool, was poured into 700 ml of cold water, the resulting mixture being stored in the refrigerator overnight. A colored solid (16.9 g) was collected.

This solid, in addition to 9.4 g from a similar experiment, was taken up in boiling 95% ethanol. Some insoluble material was removed by filtration and the filtrate cooled to room temperature. After removal of a second portion of yellow solid and refrigeration of the filtrate, 19.9 g of material was obtained. Two recrystallizations from 95% ethanol

*Commercial grade pyridine was stirred at reflux temperature for 58.5 hr over anhydrous barium monoxide. It was then stirred only for 49 hr.
yielded 13.4 g (33%) of a white solid, mp 85-86°.


\[
[a]^{24\text{D}} = -71.8\pm0.0 \ (e\ 2.2, \ C_2H_5OH); \ -70.7\pm0.0 \ (e\ 2.3, \ C_2H_5OH).
\]

The infrared spectrum (714) exhibited bands at 1775 and 1780 cm\(^{-1}\). The nmr spectrum (3500) exhibited a series of multiplets (19) at 0.50-3.50, a singlet (2) at 4.13, a singlet (1) at 7.38, and a multiplet (4) at 7.50-8.00.

Treatment of 3-(-)-Menthoxyacetoxyphthalide with Methylcadmium Chloride.---The Grignard reagent was prepared in 225 ml of ether from 1.8 g (0.072 mole) of magnesium turnings and 10.3 g (0.072 mole) of methyl iodide. To this reagent was added, portion-wise and with stirring, 13.2 g (0.072 mole) of anhydrous cadmium chloride. After 0.25 hr of additional stirring, a negative Gilman test\(^8\) was noted.

To the methylcadmium chloride was added dropwise, over a period of 50 min, 12.5 g (0.036 mole) of 3-(-)-menthoxyacetoxyphthalide \([ [a]^{24}\geq 578 = -71.8\pm0.0 \ (e\ 2.2, \ C_2H_5OH); \ -70.7\pm0.0 \ (e\ 2.3, \ C_2H_5OH) \] in 125 ml of ether. After the addition the mixture was stirred at reflux for 4.0 hr.

The reaction mixture was poured into 190 ml of 6% H\(_2\)SO\(_4\). The layers were separated and the aqueous layer extracted with five 40-ml portions of ether. The combined ether layer was extracted with two 15-ml portions of saturated NaHSO\(_3\), six 40-ml portions of saturated Na\(_2\)CO\(_3\), and two 40-ml portions of saturated NaCl. Acidification of the Na\(_2\)CO\(_3\)
extract produced no insoluble material.

The ether layer was dried (MgSO\textsubscript{4}) and the solvent removed. The neutral residue was fractionally distilled, producing 7.0 g of a colorless liquid, bp 78.5-96.5° (0.7 mm). This was subsequently shown to be a mixture of 3-methylphthalide and an unknown component.

The liquid was dissolved in 36 ml of ether and 12 ml of 10% NaOH added. This was allowed to stand at room temperature for 4 days with intermittent shaking. The layers were separated and the aqueous layer extracted with ten 10-ml portions of ether. The aqueous layer was acidified with concentrated HCl and heated on the steam bath slowly for 1 hr. It was extracted with eight 10-ml portions of ether. The combined ether layer was extracted with two 5-ml portions of saturated Na\textsubscript{2}CO\textsubscript{3}, dried (MgSO\textsubscript{4}), the solvent removed, and the residue distilled, producing two fractions (38%).

#1: 1.40 g, bp 101° (0.9 mm). The infrared spectrum (7666) showed a strong band at 1760 cm\textsuperscript{-1}. The nmr spectrum (5089) exhibited a doublet (3) at 1.67 (J=7), a quartet (1) at 5.71 (J=7), and a multiplet (4) at 7.40-8.00. [\alpha]\textsuperscript{24} 578 +1.99±0.00 (c 6.8, CH\textsubscript{3}OH); [\alpha]\textsuperscript{26} 578 +2.43±0.08 (c 6.8, CH\textsubscript{3}OH).

#2: 0.62 g, bp 102-103° (0.9 mm); the infrared spectrum (7667) exhibited a strong band at 1760 cm\textsuperscript{-1}. The nmr spectrum (5090) exhibited a doublet (3) at 1.61 (J=6.5), a quartet (1) at 5.60 (J=6.5) and a multiplet (4) at 7.30-7.90. [\alpha]\textsuperscript{25} 578 +2.29±0.00 (c 7.4, CH\textsubscript{3}OH), +2.27±0.07 (c 7.3, CH\textsubscript{3}OH).

The product from both fractions was comparable to an authentic sample of (+)-3-methylphthalide\textsuperscript{10} on the basis of
ir, nmr, and tlc.

Nmr analysis of the original neutral residue with dioxane as an internal standard indicated the presence of 36% of starting material. Recrystallization (95% EtOH) of the distillation residue, 36 g (29%), resulted in 0.5 g of white crystals, mp 84-85°C, \([\alpha]^2_0 578 -70.9\pm0.3 (c 2.5, C_2H_5OH); -69.2\pm0.1 (c 2.6, C_2H_5OH)\).

In a similar experiment from starting material with \([\alpha]^{24}_D -68.3\pm0.1 (c 2.2, C_2H_5OH); -69.6\pm0.1 (c 2.7, C_2H_5OH)\), the following results were observed: 0.34 g (13%), bp 80-83°C (0.6 mm). The infrared spectrum (7530) exhibited a band at 1760 cm\(^{-1}\). The nmr spectrum (4404C) exhibited a doublet (3) at 1.60 (\(J=7\)), a quartet (1) at 5.58 (\(J=7\)), and a multiplet (4) at 7.10-8.00.

\([\alpha]^{24}_0 578 +2.18\pm0.00 (c 5.4, CH_3OH); +1.56\pm0.10 (c 2.5, CH_3OH)\).

The residue from the fractional distillation consisted of 2.0 g (33%) of primarily starting material.

Unknown Component from Treatment of 3-(−)-Menthoxycetoxyphtalide with Methylcadmium Chloride.—The unknown component (above) was dissolved in 10 ml of ether, washed with two 2-ml portions of saturated NaCl, dried (MgSO\(_4\)), and the ether removed on the rotary evaporator. The residue was fractionally distilled resulting in 0.8 g of a colorless oil, bp 80-88°C (0.9 mm).

The infrared spectrum (7705) contains very strong aliphatic C-H bands at 2850-3000 cm\(^{-1}\). The nmr spectrum (4388)
exhibits the typical series of multiplets for the (-)-menthyl group from 0.50-3.50 plus a singlet (8) at 1.14, a singlet (2) at 2.10, and a series of signals from 2.90-4.10. Although tlc (87) indicated the oil was homogeneous, gas liquid phase chromatographic analyses on 10% Apiezon L, 10% FFAP and 10% STAP indicated it contains two major components in an approximately 4/1 ratio.

α-Phenylbutyryl Chloride.\textsuperscript{14}—Fused α-phenylbutyric acid\textsuperscript{*} (15.7 g, 0.098 mole) was added dropwise over 0.5 hr to 52.7 g (0.44 mole) of thionyl chloride. The reaction mixture was refluxed for 5 hr. Excess thionyl chloride was distilled at atmospheric pressure from the reaction mixture and remaining traces removed by heating to 100° at aspirator pressure. The residue was distilled under reduced pressure, producing 17 g (94%) of a faintly yellow liquid, bp 58-66° (0.5 mm). The infrared spectrum (7567) exhibited a strong band at 1800 cm\textsuperscript{-1}.

3-α-Phenylbutyrylphthalide.—α-Phenylbutyryl chloride (17 g, 0.092 mole) was added dropwise over 15 min to 14 g (0.092 mole) of phthalaldehydic acid in 150 ml of anhydrous pyridine.\textsuperscript{**} The reaction mixture was stirred at 70° for 8 hr. The mixture was filtered and the filtrate poured into 100 ml of cold water. From the water-pyridine mixture, refrigerated overnight, 4.8 g (18%) of crude solid was collected.

\textsuperscript{*Eastman 156}

\textsuperscript{**Commercial grade pyridine was stirred at reflux temperature for 58.5 hr over anhydrous barium monoxide. It was then stirred only for 49 hr.}
The solid was taken up in boiling methanol. Some insoluble material was removed by filtration and the filtrate cooled to room temperature. After removal of a second portion of solid and refrigeration of the filtrate, 2.5 g (9%) of a white solid, mp 78.0-79.0°, was collected.

**Anal.** Calcd for C\textsubscript{16}H\textsubscript{16}O\textsubscript{4}: C, 72.96; H, 5.44. Found: C, 72.90; H, 5.54.

The infrared spectrum (7577) exhibited strong carbonyl bands at 1755 cm\textsuperscript{-1} and 1780 cm\textsuperscript{-1}. The nmr spectrum exhibited a triplet (3) at 0.88, an octet (2) at 1.95, a triplet (1) at 3.51, a singlet (5) at 7.22, a singlet (1) at 7.32, and a multiplet (4) at 7.39-7.88.

**Reaction of 3-α-Phenybutyrylphthalide and Methylcadmium Chloride.**—Methylcadmium chloride was prepared in 19 ml of ether from 0.41 g (0.017 mole) of magnesium, 2.42 g (0.017 mole) of methyl iodide, and 3.1 g (0.017 mole) of cadmium chloride. To the cadmium reagent was added 2.5 g (0.0085 mole) of 3-α-phenylbutyrylphthalide in 60 ml ether, and the mixture was stirred under reflux for 4 hr.

It was poured into 35 ml of 6% H\textsubscript{2}SO\textsubscript{4}. The reaction flask was rinsed with 13 ml of 6% H\textsubscript{2}SO\textsubscript{4}. The mixture was filtered and the liquid layers separated. The aqueous layer was extracted with four 25-ml portions of ether. The combined ether solution was washed with two 15-ml portions of saturated NaH\textsubscript{2}SO\textsubscript{4}, six 15-ml portions of saturated NaHCO\textsubscript{3}, two 15-ml portions of saturated NaCl, dried (MgSO\textsubscript{4}), and the ether removed on the rotary evaporator. The residue, 1.4 g
crystallized spontaneously. The infrared (7597) and nmr (4672) spectra indicated that it was identical to the starting material (ir #7577).

Acidification of the NaHCO₃ washing with concentrated HCl resulted in the collection of 0.19 g (14%) of a white solid, mp 41-43°. It was identified by infrared (7485) and nmr (4870) spectra as α-phenylbutyric acid.

O-Methylmandelic Acid. — Ethyl mandelate (10 g, 0.056 mole) was dissolved in 20 ml of dry toluene. After 1.28 g (0.056 mole) of freshly cut sodium had been added, the mixture was stirred under reflux for 1.5 hr. During this time an additional 110 ml of toluene was required. Then the green-black mixture was stirred without heating for 7 hr. To the suspension, cooled to 0°, was added over 20 min 11.9 g (0.083 mole) of methyl iodide in 5 ml of anhydrous toluene. Stirring was maintained at ice-bath temperature for 15 min and at room temperature for 33.5 hr.

The mixture was filtered and the filtrate extracted with two 20-ml portions of water, dried (MgSO₄), and the toluene removed on the rotary evaporator. An infrared spectrum (7470) indicated free OH bands. Attempts were made to remove the starting material by dissolving in 50 ml ether and stirring with 0.5 equiv. calcium chloride for 15 min. The CaCl₂ was removed by filtration, the ether dried (MgSO₄), and removed. An infrared spectrum (7475) indicated a negligible amount removed. It was redissolved in 50 ml ether, 1.0 equiv. of CaCl₂ added; and the mixture was stirred for
12 hr. An infrared spectrum (7478) indicated removal of only a small amount of starting material. Nmr analysis (4873) indicated 33% conversion to ethyl O-methylmandelate. Ethyl O-methylmandelate exhibits a singlet at 3.30 and ethyl mandelate a broad singlet in the vicinity of 5.10 and 5.30.

O-Methylmandelic Acid. Ethyl mandelate (20 g, 0.11 mole) was dissolved in 36 ml of anhydrous toluene. To this was added 2.6 g (0.11 mole) of very thinly cut fresh sodium. The mixture was stirred for 4 hr. The solution was an amber color. Fresh sodium (1.5 g) and an additional 160 ml of toluene were added. Stirring was continued for 20 hr, and the excess sodium was removed by filtration through glass wool.

To the ice-cold sodium ethyl mandelate solution was added, over 40 min, 39.4 g (0.28 mole) of methyl iodide in 20 ml toluene. The solution was stirred for 24 hr. An orange precipitate was filtered from the solution and washed with toluene. The toluene was removed on the rotary evaporator. An infrared spectrum (7597) of the residual oil (10.3 g) indicated some remaining starting material. Upon standing, the oil deposited more solid, which was removed. The infrared spectrum (7611) of the filtrate (9.9 g) indicated it still contained starting material. Nmr analysis (5056) indicated 79% ethyl O-methylmandelate.

A solution of the neutral residue containing the ethyl O-methylmandelate in 40 ml dioxane and 106 ml of 6% H₂SO₄ was refluxed for 6.3 hr. When cool, the reaction mixture
was made basic with 10% NaOH. The aqueous solution was extracted with four 40-ml portions of ether and acidified with concentrated HCl. The acidic solution was extracted with three 40-ml portions of ether. The ether layer was then washed with two 20-ml portions of water, dried (MgSO$_4$), decolorized (Norite), and the ether removed on the rotary evaporator. A colored, oily residue (9.4 g) resulted. The infrared spectrum (7670) contains a band at 1740 cm$^{-1}$. The nmr spectrum (5099) exhibits a singlet (3) at 3.28, a singlet (1) at 4.80, an extremely weak singlet at 5.30, and a multiplet (5) at 7.10-7.60.

**0-Methylmandelyl Chloride.** Impure 0-methylmandelic acid (9.4 g, ≈0.057 mole) was added over 25 min to 32 g (0.27 mole) of thionyl chloride and the solution refluxed for 5 hr. The excess thionyl chloride was distilled at 76° and last traces removed by heating to 80° under aspirator pressure. Bumping was prevalent. The residue was distilled at reduced pressure resulting in a tinted oil, 3.2 g (31%), bp 37-88° (1 mm). The infrared spectrum (7682) exhibited strong bands at 1610 and 1725 cm$^{-1}$.

**Attempted Preparation of 3-(O-Methylmandeloxy)-phthalide.** Phthalaldehydic acid (2.6 g, 0.017 mole) was dissolved in 30 ml of anhydrous pyridine. To this was added over 5 min 3.2 g (0.017 mole) of 0-methylmandelyl chloride. The addition funnel was rinsed with 16 ml of pyridine. The reaction mixture was stirred at room temperature for 25 min, then
stirred at 82° for 1 hr. It was stirred again at room temperature for 23 hr.

The reaction mixture was poured into 75 ml of water. After addition of 150 ml more water, the solution was refrigerated overnight. A yellow solid (0.033 g) was collected. The infrared spectrum (7708) exhibited no OH band and strong bands at 1740 and 1790 cm⁻¹. The nmr spectrum exhibited no signals, presumably because of a low concentration of material. By evaporation of the filtrate under hood draft, 1.8 g (69%) of a white solid was collected. The infrared spectrum (7706) was identical to that of phthalaldehydic acid (6794).

Attempted Separation of the Diastereomers of 3-(−)-Menthoxyacetoxyphthalide. — 3-(−)-Menthoxyacetoxyphthalide (described in EXPERIMENTAL, p 41) was fractionally recrystallized from 95% ethanol, n-hexane, isopropyl alcohol, 1:1 n-hexane-isopropyl alcohol, 1:1 n-hexane-95% ethanol, 1:1 pentane-methanol, 1:1 n-hexane-methanol, methanol, and methanol saturated with n-hexane, in an attempt to separate it into its diastereomeric forms. In each successive recrystallization fresh solvent was used. In no case was the desired separation achieved. The results are recorded in Table 09, p 62.

Determination of Grignard Reagent Concentration. — The method of Watson and Eastham 42 was employed, in which a 5-ml aliquot of methylmagnesium iodide was mixed with about 10 drops of purified THF and a small amount of 1,10-phenanthroline as indicator. The red-purple suspension was then titrated with
1.00 M sec-butyl alcohol in xylene to a colorless end point. The results are tabulated in Table 11, p 64. An average Grignard conversion of 69.5±7.8% was obtained.
TABLE 01

Summary of Results

<table>
<thead>
<tr>
<th>R = C₆H₅</th>
<th>X = OCH(CH₃)₂</th>
<th>2 (R')</th>
<th>Mole ratio (1:2)</th>
<th>Solvent</th>
<th>Reflux time (hr)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>Recovered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅</td>
<td>1:2</td>
<td>C₆H₆</td>
<td>2.0</td>
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<td>---</td>
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<td>---</td>
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</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>C₂H₅</td>
<td>1:2</td>
<td>C₆H₆</td>
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<td>19</td>
<td>---</td>
<td>---</td>
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</tr>
<tr>
<td>C₂H₅</td>
<td>1:2</td>
<td>C₆H₆</td>
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<td>CH₃</td>
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<td>C₆H₆</td>
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<td>(C₂H₅)₂O</td>
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<td>97</td>
<td>---</td>
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</tbody>
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a⁰-Benzoylbenzoic acid recovered (73%). bUndetermined amount of starting material recovered.
<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>1 (R')</th>
<th>Mole ratio</th>
<th>Solvent</th>
<th>Reflux time (hr)</th>
<th>3 (%) Yield</th>
<th>4 (%) Yield</th>
<th>Recovered 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>OOC₂H₅</td>
<td>CH₃</td>
<td>1:2</td>
<td>(C₂H₅)₂O</td>
<td>4.5</td>
<td>85</td>
<td>1.3</td>
<td>—</td>
</tr>
<tr>
<td>H</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>1:2</td>
<td>(C₂H₅)₂O</td>
<td>4.0</td>
<td>91</td>
<td>1.6</td>
<td>—</td>
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<td>H</td>
<td>HOOC(₂H₅)₂O</td>
<td>CH₃</td>
<td>1:2</td>
<td>C₇H₈</td>
<td>4.0</td>
<td>4</td>
<td>—</td>
<td>52</td>
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*aReaction complex became solid; contents allowed to stand at room temperature for 4 days.*
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<th>X</th>
<th>2 (R')</th>
<th>Mole ratio</th>
<th>Solvent</th>
<th>Reflux time (hr)</th>
<th>3 (%)</th>
<th>4 (%)</th>
<th>Recovered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
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<td>CH₃</td>
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<td>(C₂H₅)₂O</td>
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<td>0</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>H</td>
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<td>CH₃</td>
<td>1:2</td>
<td>(C₂H₅)₂O</td>
<td>4.0</td>
<td>0</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>H</td>
<td>OCOCH₂O(-)Menthyl</td>
<td>CH₃</td>
<td>1:2</td>
<td>(C₂H₅)₂O</td>
<td>4.0</td>
<td>0</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>H</td>
<td>O₂C₆H₄Cl-</td>
<td>CH₃</td>
<td>1:2</td>
<td>C₇H₈</td>
<td>4.25</td>
<td>b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) α-Phenylbutyric acid recovered (14%). b) Nmr results were ambiguous.
TABLE 02
Rotation Data: 3-(-)-Menthoxyacetoxyphthalide

Reaction #1 (see EXPERIMENTAL, page 42)

<table>
<thead>
<tr>
<th>Sample #1</th>
<th>Sample #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>C- 2.22 g/100 ml; t, 24°</td>
<td>C- 2.30 g/100 ml; t, 24°</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>λ (mp)</th>
<th>α</th>
<th>[α]</th>
<th>α</th>
<th>[α]</th>
</tr>
</thead>
<tbody>
<tr>
<td>578</td>
<td>-1.595</td>
<td>71.8</td>
<td>-1.625</td>
<td>70.7</td>
</tr>
<tr>
<td>546</td>
<td>-1.801</td>
<td>81.1</td>
<td>-1.841</td>
<td>80.0</td>
</tr>
<tr>
<td>436</td>
<td>-3.015</td>
<td>135.8</td>
<td>-3.075</td>
<td>133.7</td>
</tr>
<tr>
<td>405</td>
<td>-3.583</td>
<td>161.4</td>
<td>-3.653</td>
<td>158.8</td>
</tr>
</tbody>
</table>

Av: \(71.8 \pm 0.0^\ast\)
Av: \(70.7 \pm 0.0^\ast\)
Av: \(81.1 \pm 0.0\)
Av: \(80.0 \pm 0.0\)
Av: \(-136 \pm 0\)
Av: \(-134 \pm 0\)
Av: \(-162 \pm 1\)
Av: \(-159 \pm 0\)

\(\ast\) Average deviation
TABLE 03

Rotation Data: Recovered 3-(-)-Menthoxycetoxyphthalide
(Recrystallized from 95% EtOH)

Reaction #1 (see EXPERIMENTAL, page 42)

<table>
<thead>
<tr>
<th>Sample #1</th>
<th>Sample #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>C - 2.50 g/100 ml; t, 32°</td>
<td>C - 2.59 g/100 ml; t, 32°</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>λ (mp)</th>
<th>α</th>
<th>[α]</th>
<th>α</th>
<th>[α]</th>
</tr>
</thead>
<tbody>
<tr>
<td>578</td>
<td>-1.780</td>
<td>-71.2</td>
<td>-1.795</td>
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<td></td>
<td>-1.765</td>
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<td>-1.790</td>
<td>-69.1</td>
</tr>
<tr>
<td></td>
<td>Av: -70.9±0.3*</td>
<td>Av: -69.2±0.1*</td>
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<td></td>
</tr>
<tr>
<td>546</td>
<td>-2.005</td>
<td>-80.2</td>
<td>-2.025</td>
<td>-78.2</td>
</tr>
<tr>
<td></td>
<td>-1.995</td>
<td>-79.8</td>
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<tr>
<td></td>
<td>Av: -80.0±0.2</td>
<td>Av: -78.1±0.1</td>
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</tr>
<tr>
<td>436</td>
<td>-3.320</td>
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<tr>
<td></td>
<td>Av: -133 ±0</td>
<td>Av: -130 ±0</td>
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<td></td>
</tr>
<tr>
<td>405</td>
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<td>-156.4</td>
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<tr>
<td></td>
<td>-3.910</td>
<td>-156.4</td>
<td>-3.955</td>
<td>-152.7</td>
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<tr>
<td></td>
<td>Av: -156 ±0</td>
<td>Av: -153 ±0</td>
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</table>

*average deviation
TABLE 04

Rotation Data: 3-(−)-Menthoxyacetoxyphthalide

Reaction #2 (see EXPERIMENTAL, page 42)

<table>
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<tr>
<th>Sample #1</th>
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<td>C- 2.73 g/100 ml; t, 24°</td>
<td>C- 2.18 g/100 ml; t, 24°</td>
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</table>

<table>
<thead>
<tr>
<th>α</th>
<th>[α] D</th>
<th>α</th>
<th>[α] D</th>
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</thead>
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<tr>
<td>-1.90</td>
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<td></td>
<td>-69.6±0.1*</td>
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<td>-68.3±0.1*</td>
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*average deviation
### TABLE 05

**Rotation Data: 3-Methylphthalide**

Reaction #1, Fraction #1 (see EXPERIMENTAL, page 42)

<table>
<thead>
<tr>
<th>λ (μm)</th>
<th>α₁</th>
<th>[α]</th>
<th>α₂</th>
<th>[α]</th>
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<tbody>
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<td>578</td>
<td>+.135</td>
<td>+1.99</td>
<td>+1.60</td>
<td>+2.35</td>
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<td></td>
<td>+.135</td>
<td>+1.99</td>
<td>+1.70</td>
<td>+2.50</td>
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<tr>
<td>Av:</td>
<td>+1.99±0.00*</td>
<td>Av:</td>
<td>+2.43±0.08*</td>
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<td>+2.50</td>
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<td>+4.64</td>
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<tr>
<td>Av:</td>
<td>+4.14±0.00</td>
<td>Av:</td>
<td>+4.49±0.15</td>
<td></td>
</tr>
<tr>
<td>365</td>
<td>+.360</td>
<td>+5.32</td>
<td>+3.65</td>
<td>+5.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+3.80</td>
<td>+5.59</td>
<td>+5.48±0.11</td>
</tr>
</tbody>
</table>

*average deviation
### TABLE 06

**Rotation Data: 3-Methylphthalide**

(After 30 days in solution at ambient temperature)

Reaction #1, Fraction #1 (see EXPERIMENTAL, page 42)

<table>
<thead>
<tr>
<th>Sample #1</th>
<th>Sample #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>C- 6.76 g/100 ml; t, 32°</td>
<td>C- 6.79 g/100 ml; t, 32°</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>λ (μm)</th>
<th>α</th>
<th>[α]</th>
<th>α</th>
<th>[α]</th>
</tr>
</thead>
<tbody>
<tr>
<td>578</td>
<td>+1.10</td>
<td>+1.63</td>
<td>+1.165</td>
<td>+2.43</td>
</tr>
<tr>
<td></td>
<td>+1.135</td>
<td>+1.99</td>
<td>+1.165</td>
<td>+2.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Av: +1.81±0.18*</td>
<td></td>
</tr>
<tr>
<td>546</td>
<td>+1.135</td>
<td>+1.99</td>
<td>+1.185</td>
<td>+2.72</td>
</tr>
<tr>
<td></td>
<td>+1.50</td>
<td>+2.22</td>
<td>+1.185</td>
<td>+2.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Av: +2.11±0.12</td>
<td></td>
</tr>
<tr>
<td>436</td>
<td>+1.230</td>
<td>+3.40</td>
<td>+1.280</td>
<td>+4.12</td>
</tr>
<tr>
<td></td>
<td>+1.240</td>
<td>+3.55</td>
<td>+1.280</td>
<td>+4.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Av: +3.48±0.08</td>
<td></td>
</tr>
<tr>
<td>405</td>
<td>+1.280</td>
<td>+4.14</td>
<td>+1.325</td>
<td>+4.78</td>
</tr>
<tr>
<td></td>
<td>+1.285</td>
<td>+4.21</td>
<td>+1.325</td>
<td>+4.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Av: +4.18±0.04</td>
<td></td>
</tr>
<tr>
<td>365</td>
<td>+1.350</td>
<td>+5.18</td>
<td>+1.405</td>
<td>+5.96</td>
</tr>
<tr>
<td></td>
<td>+1.360</td>
<td>+5.32</td>
<td>+1.405</td>
<td>+5.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Av: +5.25±0.07</td>
<td></td>
</tr>
</tbody>
</table>

*average deviation*
**TABLE 07**

Rotation Data: 3-Methylphthalide

Reaction #1, Fraction #2 (see EXPERIMENTAL, page 42)

<table>
<thead>
<tr>
<th>Sample #1</th>
<th>Sample #2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C- 7.43 g/100 ml; t, 25°</strong></td>
<td><strong>C- 7.26 g/100 ml; t, 25°</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>λ (μm)</th>
<th>α</th>
<th>[α]</th>
<th>α</th>
<th>[α]</th>
</tr>
</thead>
<tbody>
<tr>
<td>578</td>
<td>+.170</td>
<td>+2.29</td>
<td>+.170</td>
<td>+2.34</td>
</tr>
<tr>
<td></td>
<td>+.195</td>
<td>+2.62</td>
<td>+.190</td>
<td>+2.62</td>
</tr>
<tr>
<td></td>
<td>+.325</td>
<td>+4.37</td>
<td>+.305</td>
<td>+4.21</td>
</tr>
<tr>
<td>546</td>
<td>+.390</td>
<td>+5.25</td>
<td>+.390</td>
<td>+5.37</td>
</tr>
<tr>
<td>436</td>
<td>+.385</td>
<td>+5.18</td>
<td>+.365</td>
<td>+5.03</td>
</tr>
<tr>
<td>405</td>
<td>+.390</td>
<td>+5.25</td>
<td>+.390</td>
<td>+5.37</td>
</tr>
<tr>
<td>365</td>
<td>+.390</td>
<td>+5.25</td>
<td>+.395</td>
<td>+5.45</td>
</tr>
</tbody>
</table>

*average deviation

Rounded to 0.04
<table>
<thead>
<tr>
<th>λ (μm)</th>
<th>α</th>
<th>[α]</th>
<th>α</th>
<th>[α]</th>
</tr>
</thead>
<tbody>
<tr>
<td>578</td>
<td>+.117</td>
<td>+2.18</td>
<td>+.042</td>
<td>+1.66</td>
</tr>
<tr>
<td></td>
<td>+.117</td>
<td>+2.18</td>
<td>+.037</td>
<td>+1.46</td>
</tr>
<tr>
<td></td>
<td>Av: +2.18±0.00*</td>
<td>Av: +1.56±0.10*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>546</td>
<td>+.127</td>
<td>+2.37</td>
<td>+.047</td>
<td>+1.86</td>
</tr>
<tr>
<td></td>
<td>+.127</td>
<td>+2.37</td>
<td>+.047</td>
<td>+1.86</td>
</tr>
<tr>
<td></td>
<td>Av: +2.37±0.00</td>
<td>Av: +1.86±0.00</td>
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<td></td>
</tr>
<tr>
<td>436</td>
<td>+.215</td>
<td>+4.02</td>
<td>+.085</td>
<td>+3.38</td>
</tr>
<tr>
<td></td>
<td>+.215</td>
<td>+4.02</td>
<td>+.085</td>
<td>+3.38</td>
</tr>
<tr>
<td></td>
<td>Av: +4.02±0.00</td>
<td>Av: +3.38±0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>405</td>
<td>+.255</td>
<td>+4.75</td>
<td>+.105</td>
<td>+4.16</td>
</tr>
<tr>
<td></td>
<td>+.255</td>
<td>+4.75</td>
<td>+.100</td>
<td>+3.96</td>
</tr>
<tr>
<td></td>
<td>Av: +4.75±0.00</td>
<td>Av: +4.06±0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>365</td>
<td>+.320</td>
<td>+5.98</td>
<td>+.130</td>
<td>+5.15</td>
</tr>
<tr>
<td></td>
<td>+.130</td>
<td>+5.15</td>
<td>+.130</td>
<td>+5.15</td>
</tr>
<tr>
<td></td>
<td>Av: +5.15±0.00</td>
<td>Av: +5.15±0.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*average deviation
TABLE 09
Attempted Separation of the Diastereomers
of 3-(-)-Menthoxyacetoxyphthalide

<table>
<thead>
<tr>
<th>Recrystallization</th>
<th>No. of Recrystallizations</th>
<th>([\alpha]^{a}) (D)</th>
<th>Melting Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Original</td>
<td>Final</td>
</tr>
<tr>
<td>95% Ethanol</td>
<td>4</td>
<td>-70.8±0.6(^b)</td>
<td>-70.8±0.4(^b)</td>
</tr>
<tr>
<td>(n)-Hexane</td>
<td>2</td>
<td>-73.2±0.8</td>
<td>-71.7±0.2</td>
</tr>
<tr>
<td>Isopropyl Alcohol</td>
<td>1</td>
<td>-71.7±0.2</td>
<td>-71.4±0.3</td>
</tr>
<tr>
<td>1:1 (n)-Hexane-Isopropyl Alcohol</td>
<td>1</td>
<td>-71.5±0.2</td>
<td>-75.6±0.6</td>
</tr>
<tr>
<td>1:1 (n)-Hexane-95% Ethanol</td>
<td>1</td>
<td>-71.5±0.2</td>
<td>-77.6±0.5</td>
</tr>
<tr>
<td>1:1 Pentane-Methanol</td>
<td>1</td>
<td>-71.5±0.2</td>
<td>-75.2±0.5</td>
</tr>
<tr>
<td>1:1 (n)-Hexane-Methanol</td>
<td>1</td>
<td>-71.5±0.2</td>
<td>-79.7±0.4</td>
</tr>
<tr>
<td>1:1 (n)-Hexane-Methanol</td>
<td>4</td>
<td>-66.0±0.4</td>
<td>-73.4±0.5</td>
</tr>
<tr>
<td>Methanol</td>
<td>1</td>
<td>-71.5±0.2</td>
<td>-70.0±0.5</td>
</tr>
<tr>
<td>Methanol saturated with (n)-Hexane</td>
<td>2</td>
<td>-71.5±0.2</td>
<td>-71.0±0.7</td>
</tr>
</tbody>
</table>

\(^{a}\) All rotations were determined within the temperature range 26-31°.

\(^{b}\) Average deviation.
### TABLE 10
Preparation of 3-(−)-Menthoxyacetoxyphthalide

<table>
<thead>
<tr>
<th>Trial Number</th>
<th>Mole Ratio (16:28*)</th>
<th>Reaction Time (hr)</th>
<th>Reaction Temperature (°C)</th>
<th>% Yield Crude Material Collected From Aqueous Solution</th>
<th>% Yield After Recrystallization (95% EtOH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:2</td>
<td>6.25</td>
<td>115</td>
<td>54</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>4.0</td>
<td>115</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>1:1</td>
<td>10.0</td>
<td>115</td>
<td>58</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>1:1</td>
<td>1</td>
<td>75</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>1:2</td>
<td>42.5</td>
<td>28</td>
<td>27</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>1:1</td>
<td>1</td>
<td>73</td>
<td>38</td>
<td>30**</td>
</tr>
<tr>
<td>7</td>
<td>1:1</td>
<td>1</td>
<td>77</td>
<td>41</td>
<td>30**</td>
</tr>
</tbody>
</table>

*16 = 3-(−)-Menthoxyacetyl Chloride; 28 = Phthalaldehydic Acid

**The crude products from Trials # 6 and 7 were combined and recrystallized.
<table>
<thead>
<tr>
<th>Trial Number</th>
<th>Concentration (M)</th>
<th>% Conversion</th>
<th>% Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.764</td>
<td>72.7</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td>0.370</td>
<td>67.5</td>
<td>2.0</td>
</tr>
<tr>
<td>3</td>
<td>0.415</td>
<td>72.4</td>
<td>2.9</td>
</tr>
<tr>
<td>4</td>
<td>0.307</td>
<td>52.1</td>
<td>17.4</td>
</tr>
<tr>
<td>5</td>
<td>0.318</td>
<td>83.0</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Av: 69.5 ± 7.8
RESULTS AND DISCUSSION

Extending the scope of the reaction, re-examining some of the previous reactions, and determining the stereochemical course in one case, have provided evidence for the mechanism of the substitution reaction.

By substituting a phenyl group for a hydrogen in the 3-position, a new course\(^\text{18}\) for the reaction (Equation 19) has been uncovered. Previously, this reaction has led to a 3-substituted phthalide, the result of displacement of a group (X) in the 3-position. In the new course, the acyl group of the lactone ring has been displaced, resulting in ring opening with formation of a substituted benzoic acid.

An opportunity to investigate the scope of this new reaction in the phthalide series with a hydrogen in the 3-position was afforded by re-examining some earlier work.\(^\text{17}\)

Along with product identification, in one case stereochemistry has been used to great advantage. In this instance, where the reaction leads to a 3-substituted phthalide, the optical rotations of starting material and product have been determined. This information has provided evidence for the stereochemical pathway of the reaction.

The preparation of the 3-phenylphthalides proceeded
with limited success. In all cases, the appropriate alcohol was treated with \( \alpha \)-benzoylbenzoyl chloride (5). This method was used by Newman and McCleary\(^5\) and Jones and Desio\(^3\) to prepare pseudo methyl esters of \( \alpha \)-aroylbenzoic acids. Ample evidence\(^4\) exists in the literature supporting the cyclic structure for 5.

In the attempted preparation of 3-methoxy-3-phenylphthalide (6), methanol was added to 5 under three different sets of conditions: absolute methanol, methanol in pyridine, and methanol in sodium carbonate solution. In all cases, a mixture of normal and pseudo 6 was obtained. In the second and third attempts, it was anticipated the added base would neutralize excess acid, which was thought to catalyze rearrangement to the normal ester.

The preparation of 3-isobutoxy-3-phenylphthalide (7) was undertaken in a similar way. In the first two attempts isobutyl alcohol was added to 5. In the third and fourth attempts, 5 was added to isobutyl alcohol-6 M \( \text{Na}_2\text{CO}_3 \)-dioxane and isobutyl alcohol-pyridine-dioxane, respectively. Again, in all cases, a mixture of normal and pseudo esters was formed.

\( \text{t} \)-Butyl alcohol was added to 5 in an attempted preparation of 3-\( \text{t} \)-butoxy-3-phenylphthalide (8). A mixture of normal and pseudo 8 was formed.

In attempts to form diastereomeric 3-phenylphthalides, 5 was added first to (-)-menthol in chloroform; then 5 was added in benzene to (-)-menthol-\( \text{Na}_2\text{CO}_3 \)-benzene (heterogeneous). Normal and pseudo menthyl esters were formed in both cases.

The preparation of 3-phenoxy-3-phenylphthalide (2)
proved to be equally futile. In a first attempt, o-benzoylbenzoic acid and phenol were refluxed in benzene. Secondly, phenol in pyridine was added to a benzene solution of 5. Finally, melted phenol was added to 5. In each case a mixture of 10 and the normal phenyl ester formed or o-benzoylbenzoic acid was recovered.

The first successful preparation in the 3-phenyl-phthalide series was that of 3-ethoxy-3-phenylphthalide (10) by adding 5 dropwise to cooled, absolute ethanol and then immediately adding 4.2 M Na₂CO₃. Although both normal and pseudo esters were formed, 10 was separated by fractional crystallization with 95% ethanol. An unsuccessful attempt involved the addition of a 1:1 molar solution of ethanol-pyridine to 5.

The successful preparation of 3-isopropoxy-3-phenylphthalide (11) was effected by adding isopropyl alcohol to 5 and decomposing the mixture in 3.6 M Na₂CO₃. In this case, pseudo ester was formed exclusively. The cause of the failure of the pseudo esters of o-benzoylbenzoic acid to form might be a combination of the steric effect of the phenyl group and an acid-catalyzed isomerization to normal ester. The acid generated from o-benzoylbenzoyl chloride could catalyze rearrangement of the pseudo to the normal ester, if one assumes the pseudo ester is formed initially. The pseudo esters do tautomerize to normal ester in refluxing acidic media. In the two preparations which were successful, the reaction was quenched rapidly by addition of excess base.
The preparation of most of the unsubstituted 3-substituted phthalides proceeded by known methods.\textsuperscript{6,9-12} 3-Phenoxyphthalide (12) was successfully prepared by refluxing phthalaldehydic acid and phenol in benzene. The addition of phenol \textit{in situ} to 3-chlorophthalide failed to afford any 12.

A second attempt to form diastereomeric phthalides was successful when phthalaldehydic acid and (-)-menthol were refluxed in benzene; 3-(-)-menthoxyphthalide (13) was obtained in 55% yield.

However, it was subsequently shown that this compound did not undergo the displacement reaction with cadmium reagent as outlined in Equation 1. 3-(-)-Menthoxyacetoxyphthalide (14) proved to be a suitable substrate. It was prepared by adding 3-(-)-menthoxyacetyl chloride (15) to a molar equivalent of phthalaldehydic acid in dry pyridine. Table 10 (p 63) shows the effect of temperature and reaction time upon yield. The importance of using anhydrous pyridine must be emphasized. The reaction failed in three attempts until the pyridine had been stirred at reflux temperature for 58.5 hr over anhydrous barium monoxide before use.

The method of isolation of 14 from crude reaction material is also critical. The insoluble material must be removed when the crude material is boiled in 95% ethanol and when cooled to room temperature. The infrared spectra (7128, 7144) of these insoluble materials indicate they are aromatic compounds, one possibly being di-3-phthalidyl ether (16). The filtrate was then refrigerated; 14 crystallized and was
collected. Two more recrystallizations from 95% ethanol produced pure 14 (tlc 40).

In an attempt to find another diastereomeric phthalide, 3-α-phenylbutyrylphthalide (17) was prepared. The same precautions had to be observed concerning dry pyridine and product purification, as in the case of 14.

Finally, in order to study the effect on the displacement reaction of the α-oxygen of 3-(−)-menthoxyacetoxyphthalide, an attempt was made to prepare 3-(O-methylmandeloyl)-phthalide (18). The carbon analog of this material, 3-α-phenylbutyrylphthalide, did not undergo displacement. Thus if the role of an α-oxygen is critical, 18 should undergo displacement. When O-methylmandeloyl chloride was added to a molar equivalent of phthalaldehydic acid in pyridine, a solid, which could be the desired 18, was collected only in trace amount.

In all the reactions of the 3-substituted phthalides, one mole of cadmium chloride was added to one mole of Grignard reagent, producing "methylcadmium chloride". Invariably, excess cadmium chloride was present, for the Grignard conversion averaged 70% (see Table 11, p 64 and EXPERIMENTAL, p 50).

In some cases, benzene was used as the reaction solvent, because ether is known to undergo gradual cleavage by cadmium reagents. However, it was shown that ether was equally effective as solvent.

In most cases the substrates were added as ether solutions but when they were ether-insoluble they were added directly to the cadmium reagent as solids.
When 3-ethoxy-3-phenylphthalide (10) was treated with ethylcadmium chloride, the usual course for the reaction, which would lead to 3-ethyl-3-phenylphthalide (12), was not observed. By comparison, Lavigne had obtained a 9% yield of 3-methylphthalide from 3-ethoxyphthalide and methylcadmium chloride. Instead, 87% of o-(α-ethyl-α-ethoxybenzyl)-benzoic acid (20) was formed, resulting from displacement of the acyloxy group and cleavage of the lactone ring (Equation 20). Infrared and

\[
\text{\begin{array}{c}
\text{C}_6\text{H}_5 \text{OR} \\
\text{\text{O}} \\
\text{C}_6\text{H}_5 \text{OR}
\end{array}} + \text{C}_2\text{H}_5\text{CdCl} \rightarrow \text{\begin{array}{c}
\text{C}_6\text{H}_5 \text{OR} \\
\text{\text{C}_2\text{H}_5\text{COOH}}
\end{array}}
\]

\[R=C_2H_5, \text{CH(CH}_3)_2\]

thin layer chromatography indicated that some 10 might have been formed, but it could not be separated from starting material 11.

With 3-isopropoxy-3-phenylphthalide the same result was observed, o-(α-ethyl-α-isopropoxybenzyl)-benzoic acid (21) being formed in 19% yield. The neutral residue was not examined.

In two attempts to effect a similar displacement with phenylcadmium chloride on 3-isopropoxy-3-phenylphthalide, o-benzoylbenzoic acid was recovered (73%). This result indicates that, whatever the mechanism for the reaction, it is not a function of extended reaction time. In the second trial the time was increased eight-fold, with no effect on the outcome.
These results indicate that there might be a steric effect exerted by the alkoxy group in the three position. 3-Isopropoxy-3-phenylphthalide was only converted to product in 19% yield while 3-ethoxy-3-phenylphthalide was converted in 87% yield. The size of the cadmium reagent might also be critical. When the much larger phenylcadmium chloride was used with 3-isopropoxy-3-phenylphthalide, no product was observed, o-benzoylbenzoic acid being recovered in 73% yield. The hydrolysis of the ester must be the result of interaction with the phenylcadmium chloride, for when 3-isopropoxy-3-phenylphthalide was subjected to reaction hydrolysis conditions, it was recovered quantitatively.

In Lavigne's experiments on the reaction of methylcadmium chloride with various 3-substituted phthalides, it had been found that an unidentified product was isolable from the basic layer when the substrate was 3-methoxyphthalide (22), 3-ethoxyphthalide (23), and di-3-phthalidyl ether (16). All three of these compounds contain an alkoxy substituent in the 3-position analogous to the ethoxy and isopropoxy compounds (10, 11) in the phenyl series mentioned above. The reactions were repeated in the present investigation and the acid products identified. As suspected, there were indeed compounds of type 2 resulting from acyloxy displacement and ring opening (Equation 21). Small amounts of 3-methylphthalide were

\[
\text{\begin{align*}
\text{\begin{align*}
\begin{array}{c}
\text{H} \\
\text{OR}
\end{array}
\text{H} \quad + \quad \text{CH}_3\text{CdCl} \quad \rightarrow \quad \text{H} \\
\text{OR}
\end{align*}
\end{align*}
\text{CH}_3\text{COOH}
\end{align*}
\]

\[
\text{R=CH}_3, \text{CH}_2\text{CH}_3, \text{3-Phthalyloxy}
\]
also identified in all three cases.

The first reaction of methylcadmium chloride with di-3-phthalidyl ether (16) was carried out in a large volume of toluene, which was required to dissolve the starting material. In the second reaction, 16 was added as a solid to the cadmium reagent. It should be noted that the product, o, o'-dicarboxy-bis-α-phenethyl ether (24), is the result of displacement at both 3-positions of 16. No acid was detected which would be the result of displacement at only one 3-position.

Jones and Lavigne observed quite different results when 16 was treated with methylcadmium chloride. Indeed, they found that there was reaction at each 3-position, but it led to two moles of 3-methylphthalide (25) (Equation 22).

One more case of acyloxy displacement was found. When 3-(-)-menthoxyphthalide (12) was treated with methylcadmium chloride, o-(α-(-)-menthoxyethyl)-benzoic acid (26) was formed.
in high yield (Equation 23).

\[
\begin{align*}
0-(-)-\text{Menthyl} & + \text{CH}_3\text{CdCl} \rightarrow \text{CH}_3\text{COOH} \\
& \text{26}
\end{align*}
\]

Newman has observed a similar acyloxy displacement when 3-isopropoxyphthalide was treated with mesitylmagnesium bromide (Equation 24).

\[
\begin{align*}
\text{CH}_3\text{COOH} & + \text{C}_9\text{H}_11\text{MgBr} \rightarrow \text{C}_9\text{H}_11\text{COOH} \\
& \text{25}
\end{align*}
\]

In an attempt to demonstrate the previously observed displacement of the substituent in the 3-position, good leaving groups such as acyloxy and \( p \)-chlorophenoxy were incorporated into the phthalide series. The acyloxy groups chosen were acetoxy, \( \alpha \)-phenylbutyroxy, and (-)-menthoxyacetoxy. Jones and Lavigne had not observed any 3-methylphthalide (25) from 3-acetoxyphthalide. In contrast to this, yields of 25 amounting to 30 and 57% were observed. In the first case 27 was added to the cadmium reagent in ether solution, in the second case as a solid. The lower yield in the first
case is probably due to an extended work-up (see EXPERIMENTAL, p 35). In both Jones and Lavigne's\textsuperscript{17} and the present work, considerable starting material was recovered. The absence of any \( \text{25} \) in the work of Jones and Lavigne\textsuperscript{17} could be accounted for by the fact that distillation was required to detect \( \text{25} \). However, in the present work, when 3-(\( \alpha \)-phenylbutyryl)-phthalide (17) was treated with methylcadmium reagent (Equation 25), no

\[
\begin{array}{c}
\text{H} \\
\text{O} - \text{CO-CH}_6\text{H}_5\text{CH}_2\text{CH}_3 \\
\end{array} + 2 \text{CH}_3\text{CdCl} \rightarrow \text{17} + \text{CH}_3\text{CH}_2\text{CH}_6\text{H}_5\text{COOH} \quad \text{(25)}
\]

3-methylphthalide was detected by nmr analysis of the neutral residue. Also, starting material 17 and \( \alpha \)-phenylbutyric acid, resulting from hydrolysis of 17, were recovered. 3-(\text{-})(\text{-})-Menthoxyacetoxyphthalide gave 25 in yields of 38 and 13\%, determined, respectively, by nmr analysis and isolation.

3-p-Chlorophenoxyphthalide (28) was treated with methylcadmium chloride in two instances. In the first trial, a large excess of toluene was required to dissolve 28. In the second trial, 28 was added to the cadmium reagent as a solid. In both cases, a viscous polymeric material, difficultly soluble in carbon tetrachloride, was obtained. The only outstanding feature of the nmr spectra (4871, 5185) was a triplet at 1.03; the product was not investigated further.

The stereochemical study of the displacement proved to be the most rewarding. The reaction elected for study was
the displacement of 3-(−)-menthoxyacetoxyphthalide (14) by methylcadmium reagent (Equation 26). This reaction was 

![Chemical Structure](image)

(26)

chosen because the yields of 3-methylphthalide were reasonably good and the phthalide 14 would be optically active. The physical separation of 14 into its diastereomeric forms should proceed routinely, and Nagai\textsuperscript{44} had determined the absolute configuration of (−)-3-methylphthalide (25) to be S.

As Table 09, p 62 demonstrates, 14 could not be separated into its diastereomers by multiple recrystallizations with a variety of solvents, as deduced by lack of change in melting point and rotation. The rotation of 14 was then measured (Table 02, p 55), and it was treated with methylcadmium chloride. 3-Methylphthalide (25) possessing some degree of optical activity was obtained (Equation 27) in two separate experiments. The first fraction of 25 collected exhibited a specific rotation of about 2° at 578 μ and higher rotations at 546, 436, 405 and 365 μ (Table 05, p 58). The second fraction exhibited similar rotations (Table 07, p 60). The specific rotation of the first fraction was essentially unchanged after being allowed to stand in solution 30 days at room temperature (Table 06, p 59). Similar results

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were observed when the experiment was repeated (Tables 04, p 57 and 08, p 61). The starting material, 3-(-)-menthoxyacetoxyphthalide (14), was recovered with a rotation essentially unchanged (Table 03, p 56).

Whatever the diastereomeric composition of 14, the formation of optically active 3-methylphthalide (25) excludes total racemization as the stereochemical course of the reaction. Thus both a free radical homolysis and a carbonium ion mechanism are excluded as the sole reaction pathway. The possibility that 14 is a single diastereomer seems very remote, in spite of the fact that its rotation and melting point were unchanged after multiple recrystallizations from a variety of solvents. In addition, the rotation of recovered 14 was unaffected, and there was no resonance doubling of the diastereotopic hydrogen evident in the nmr spectrum. The phenomenon of resonance doubling would be expected in diastereomeric
phthalides, as indeed it is in the nmr spectra of 3-(−)-menthoxyphthalide (13) and di-3-phthalidyl ether (16).

The other possibility consistent with the observed results is that of an unequal mixture of diastereomers, each having a similar activation energy. This is represented in Figure 1. This would result in the same diastereomeric mixture for recovered product. The lack of resonance doubling in 14 could be accounted for by the large distance between the two asymmetric centers (the phthalide 3-carbon and the menthoxymethylene residue).

The two observations combined—formation of optically active product and recovery of starting material with unchanged rotation—rule out any case where 14 consists of equal amounts of the two diastereomers.

In the light of the above evidence, the first consideration of the mechanistic course for the displacement is whether it is a one-step (Equation 28) or multiple-step (Equation 29) process. The actual structure of the transition state will not be considered at this point. The fact that compounds

\[ \Delta G_a = \Delta G_b \]

\[ \Delta G = \Delta G_a = \Delta G_b \]

**FIGURE 1**
\[ \text{CH}_3 \text{CdCl} + \text{C}_6\text{H}_5\text{CH} \xrightarrow{\text{CH}_3\text{CdCl}} \text{C}_6\text{H}_5\text{CH} \xrightarrow{\text{Cl}\text{CdCH}_3} \text{C}_6\text{H}_5\text{CH} \]

(28)

\[ \text{CH}_3 \text{CdCl} + \text{C}_6\text{H}_5\text{CH} \xrightarrow{\text{CH}_3\text{CdCl}} \text{C}_6\text{H}_5\text{CH} \xrightarrow{\text{Cl}\text{CdCH}_3} \text{C}_6\text{H}_5\text{CH} \]

(29)

\[ \text{C}_6\text{H}_5\text{CH} \xrightarrow{\text{CH}_3\text{CdCl}} \text{C}_6\text{H}_5\text{CH} \]

(30)
such as \( o-(\alpha\text{-methoxyethyl})\text{-benzoic acid} \) (29) exist could be evidence for the multiple-step process. Acids such as 29 could correspond to the intermediate 30, unable to undergo further reaction. In all cases where acids were isolated, X was a poor leaving group. However, there is at present no evidence that 30 can be converted to phthalide with cadmium reagent. The one-step mechanism is not ruled out by the results. Displacement of acyloxy would then occur only in those cases where X is a poor leaving group, culminating in the same observed result as the multiple-step process.

Before considering the stereochemical result discussed above, a consideration of the transition state is necessary. Campbell and Kenyon\(^{47}\) have demonstrated the covalent nature of dimethylcadmium at 0\(^\circ\), as it failed to enolate an optically active acid chloride (Equation 30).

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CHCH}_3\cdot\text{COOH} & \xrightarrow{\text{SOCl}_2} \text{C}_6\text{H}_5\text{CHCH}_3\cdot\text{COCl} \\
\text{(CH}_3\text{)}_2\text{Cd} & \xrightarrow{0\,^\circ} \text{C}_6\text{H}_5\text{CHCH}_3\cdot\text{COCH}_3 
\end{align*}
\]

\( S- (+) \quad S- (+) \)

Sheverdina and Kocheshkov\(^{56}\) have demonstrated the monomeric nature of methylcadmium chloride in dilute solution, concentrations comparable to those used in this investigation (see Table 11, p 64). Klemm and Largman,\(^{48}\) Dauben and Collette,\(^{49}\) and Walravens and Martin\(^{50}\) have demonstrated the Lewis-acid nature of cadmium reagents. Cason\(^{51}\) has suggested cadmium coordination with anhydride oxygen (Figure 2), a possible factor in the transition state for a displacement reaction.
Magnesium halides, which are also present, could coordinate in a similar manner, but their effect has not been considered in previous discussions. An intermolecular mechanism, which could be operative in this reaction, would be extremely difficult to characterize. Hence, only the possibilities of an intramolecular mechanism will be considered. Coordination of cadmium reagent with the lactone-carbonyl would only be important in an intermolecular mechanism because of its distance from the reaction site. If the lactone oxygen were the principal site of coordination for the cadmium of the reagent, a four-center mechanism would probably prevail (Figure 3). The one- or
multiple-step mechanism could be accommodated by a transition state proceeding from this coordination complex. It could result in retention or inversion of configuration.

A second transition state might involve coordination with the 3-substituent oxygen in a four-center type complex (Figure 4). Both the one- and multiple-step mechanisms could be accommodated by this pathway as well. This would have to proceed with retention of configuration.

When the 3-substituent is an acyloxy group, a third mode of coordination is possible. In this case a six-membered transition state would be possible (Equation 30). Retention
or inversion of configuration could occur. Sawoda, Takehama, and Inouye\textsuperscript{52} have postulated a multicyclic transition state involving an ester carbonyl in the Simmons-Smith reaction (Equation 31).

\begin{equation}
\text{ICl}_2\text{ZnI} \rightarrow \text{[transition state]} \rightarrow \text{product}
\end{equation}

In 3-(\textendash\textendash)-menthoxycetoxypthalide (14), the substrate used for the stereochemical study, yet another transition state is possible. In this case it is a seven-membered ring (Figure 5) involving the $\alpha$-oxygen of the (\textendash\textendash)-menthoxycetoxypthalide.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Figure 5}
\end{figure}
group. Cason and Smith\textsuperscript{57} have suggested that, in the rearrangement of long chain carbomethoxy acid chlorides with di-n-butylcadmium, the reaction proceeds by way of a cyclic transition state and occurs when the ring is 6- or 7-membered but not in a case where a ring containing 8 atoms would be necessary.

Fieser molecular models demonstrate this to be completely plausible. In addition, the cadmium atom could be coordinated to the \((-\)-menthoxy ether linkage and the lactone oxygen at the same time (Figure 6). Newman\textsuperscript{58} has postulated

![Chemical Structure](image)

**FIGURE 6**

similar bicyclic transition states in analogous systems.

When \(3-(-\)-menthoxycetoxyphthalide\) was treated with methylcadmium chloride, an unidentified neutral material was also isolated (see EXPERIMENTAL, p 44) in good amount. Gas-liquid phase chromatography indicated this to be two components. The nmr spectrum of the material exhibited singlets at 1.14 and 2.10, but the ratio of their intensities could not be correlated with any single structure. It also exhibited
the typical series of multiplets characteristic of the (-)-menthyl group but no aromatic signal. By comparison, acetone exhibits its methyl signal at 2.17\textsuperscript{53} and methyl ethyl ketone at 2.13,\textsuperscript{53} Tertiary butyl alcohol and 1,3-butanediol exhibit methyl signals at 1.28\textsuperscript{54} and 1.23,\textsuperscript{54} respectively. The two compounds most consistent with the data are (-)-menthoxy-acetone (31) and 1-(-)-menthoxy-2-methyl-propan-2-ol (32).

\[ \text{CH}_3\text{-C-CH}_2\text{-O} \quad \text{OH} \quad \text{(CH}_3\text{)}_2\text{-C-CH}_2\text{-O} \]

These products could arise from the same transition state, pictured in Figure 6, that leads to 3-methylphthalide. Numerous reports of attack on carbonyl groups by cadmium reagents appear in the literature.

The transition state represented in Equation 32 could lead to retention or inversion of configuration. Because the

\[
\begin{align*}
\text{Retention} & \quad \text{Inversion} \\
\text{32}
\end{align*}
\]
absolute configuration of 3-(-)-menthoxyacetoxyphtalide is not known, the question of whether the reaction proceeds with net retention or inversion of configuration cannot be determined at this time.
SUMMARY

A series of 3-substituted phthalides with and without a 3-phenyl substituent have been treated with organocadmium chlorides. In addition to the displacement of the 3-substituent, that of the acyloxy group (with formation of a substituted benzoic acid) has been uncovered in some instances. One specific phthalide has been used to study the stereochemistry of the displacement.

A phenyl group in the 3-position of a phthalide seems to exert mainly a steric effect. In the corresponding unsubstituted phthalide series, the yields of product were much higher. In the phenyl series, if the group being displaced is bulky, the yield of product is decreased. With the same substrate, a relatively large reagent, such as phenylcadmium chloride, failed to react, whereas a smaller one, ethylcadmium chloride, led to product.

In both the 3-phenyl and 3-unsubstituted phthalide series, an alkoxy group in the 3-position leads to almost exclusive acyloxy displacement. An acyloxy group in the 3-position leads to product which can arise from direct 3-position displacement, acyloxy and subsequent α-benzylic displacement, or no displacement, depending on the nature of the 3-acyloxy group.

Although 3-(p-chlorophenoxy)-phthalide seemed to contain a relatively good leaving group, it led apparently to polymeric material rather than the expected displacement product.
In the stereochemical study, when optically active 3-(-)-menthoxyacetoxyphthalide (14) was treated with methylcadmium chloride, optically active 3-methylphthalide was obtained. In addition, 14 was recovered from the reaction with its rotation unchanged. These results exclude total racemization as the steric course of the reaction. In addition, the observations are consistent with 14 being either a single diastereomer or an unequal mixture of the two diastereomers, the latter being the more plausible.
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