Synthesis of C14-Labeled Bis (p-Chlorophenyl) Acetic Acid (DDA)

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by

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A Thesis presented to the Department of Chemistry of Union College in partial fulfillment of the requirements for the degree of Bachelor of Science with a Major in Chemistry.

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Approved By Alan L. Maycock

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Introduction

The past three decades has seen the widespread use of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) as an insecticide. As a persistent insecticide, its use has prompted a great amount of research into the fate of DDT in living organisms. A large number of metabolites of DDT has been found and many identified, although not all of the metabolites where found in all of the experimental bacterium, insects, or mammals.

Peterson and Rebison (1) and Wedemeyer (2) proposed metabolic pathways for DDT that are essentially the same. One pathway is: DDT to DDD \(^1\) to DDMU to DDMS to DDNU to DDOH to a hypothetical aldehyde to DDA to DBP. The alternative pathway is DDT to DDE (see Figure 1). The two major end products in mammals are DDA and DDE (1,2,4,5).

The metabolism of DDT in mammals occurs, in part, by bacteria in the gastro-intestinal tract (3). The products are then eliminated in the urine and feces of the animal (1,4,5). The National Institute of Health is now studying the transport of these metabolites in the kidney using radio-labeled samples. Thus, this research had the goal of synthesizing radio-labeled DDA.

The only radioactive compound available for the synthesis was C\(^{14}\)-labeled DDT (the C\(^{14}\) is statistically distributed in both p-chlorophenyl rings). Accordingly, the method employed had to use DDT as the

\(^1\) The abbreviations used are: DDD, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane; DDMU, 1-chloro-2,2-bis(p-chlorophenyl)ethylene; DDMS, 1-chloro-2,2-bis-(p-chlorophenyl)ethane; DDNU, unsym-bis(p-chlorophenyl)ethylene; DDOH, 2,2-bis(p-chlorophenyl)ethanol; DBP, 4,4'-di-chlorobenzophenone; DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene.
Figure 1. Metabolic Pathways of DDT.

\[
\begin{align*}
\text{R-Cl-C-R} & \xrightarrow{\text{-Cl}} \text{R-CH-Cl} \xrightarrow{+H} \text{R-CH-C-Cl}\xrightarrow{-\text{HCl}} \text{R-C-R} \\
\text{DDE} & \quad \text{DDD} & \quad \text{DDMU} \\
\text{Cl-C-Cl} & \xrightarrow{+H} \text{Cl-C-C-Cl} & \xrightarrow{-\text{HCl}} \text{Cl-C-C-Cl} \\
\text{DDT} & \quad \text{DDMS} & \quad \text{DDNU} & \quad \text{DDOH} \\
\text{H-C-Cl} & \xrightarrow{-\text{HCl}} \text{H-C-H} & \xrightarrow{+\text{H}_2\text{O}} \text{H-C-H} & \xrightarrow{[\text{O}]} \text{H-C-H} \\
\text{DDMS} & \quad \text{DDNU} & \quad \text{DDOH} & \text{[O]} \text{DDOH} \\
\text{R-CH-R} & \xrightarrow{(\text{O})} \text{R-CH-R} & \xrightarrow{-\text{CO}_2} \text{R-C-R} \\
\text{CHO} & \quad \text{DDA} & \quad \text{DBP} \\
\text{provable intermediate aldehyde} & & & \\
\text{R} & \equiv \text{p-chlorophenyl group}
\end{align*}
\]
starting material. Also, the quantity of radioactive DDT available was very small, necessitating a microsynthetic method to be devised.
Experimental

Organic Syntheses (6) provided a method for the preparation of DDA from DDT, with DDE as the intermediate. The method involves reacting DDT and KOH in a molar ratio of 0.14 to 1.12 in diethylene glycol and a small amount of water (see Table I for quantities of reactants and solvents). The batch is stirred and heated to 134-137° and maintained at that temperature for 6 hours. The batch is allowed to cool, and then poured into cold water. The mixture is filtered and the insoluble material washed with warm water. The filtrate is then boiled with Norit, filtered, and acidified with 20% sulfuric acid. The mixture is then cooled to 0-5°, filtered, washed with water, and dried at 100-110°. The product, DDA, melts at 163-165° (purified, 164-166°).

The method described above was for large reaction mixtures, and since the batch size for this project was considerably smaller (see Table I), several problems were encountered which required modification of the method. All the modifications were in the work-up of the mixture after reacting for 6 hours.

The first modification was as follows: the reaction mixture was extracted with chloroform (DDA is soluble in chloroform, DDT is not). The chloroform portion is extracted with alkaline water, which was then acidified with 20% sulfuric acid, filtered, and dried. For micro reactions, the water was stripped off at room temperature, and the solid sublimed at 100° and 0.750-0.200 mm pressure.

The second modification followed the procedure of the first modification with the following difference: after acidification, the DDA is extracted into chloroform, the chloroform stripped off, and
<table>
<thead>
<tr>
<th>Synth. No.</th>
<th>DDT (gm)</th>
<th>KOH (gm)</th>
<th>Diethylene glycol (ml)</th>
<th>H₂O (ml)</th>
<th>Temp. (°C)</th>
<th>Rxn. Time (hrs)</th>
<th>Yield (%)</th>
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<tr>
<td>lit.</td>
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<td>63.0</td>
<td>400</td>
<td>35</td>
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<td>6</td>
<td>69-73</td>
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<td>97-98</td>
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<tr>
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<td>6.3</td>
<td>40</td>
<td>15</td>
<td>96-99</td>
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<tr>
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<td>5.0</td>
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<td>96-102</td>
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<tr>
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<td>40</td>
<td>15</td>
<td>99-103</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
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<td>6.3</td>
<td>40</td>
<td>15</td>
<td>137-140</td>
<td>8.5</td>
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</tr>
<tr>
<td>F</td>
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<td>6.3</td>
<td>40</td>
<td>15</td>
<td>137-139</td>
<td>6</td>
<td>57</td>
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<td>G³,⁴</td>
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<td>0.032</td>
<td>0.2</td>
<td>0.02</td>
<td>136-139</td>
<td>6</td>
<td>-</td>
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<tr>
<td>H</td>
<td>0.103</td>
<td>0.126</td>
<td>0.8</td>
<td>0.1</td>
<td>133-135</td>
<td>6</td>
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<tr>
<td>I⁵</td>
<td>0.103</td>
<td>0.126</td>
<td>0.8</td>
<td>0.1</td>
<td>135-139</td>
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<tr>
<td>J⁶</td>
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<td>0.126</td>
<td>0.8</td>
<td>0.1</td>
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<tr>
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<td>0.1</td>
<td>136-140</td>
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<tr>
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<td>0.8</td>
<td>0.1</td>
<td>137-139</td>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>

¹Start extracting reaction mixture with chloroform.
²Start running reaction in oil bath instead of heating mantle.
Temperatures listed indicate temperature of oil bath.
³Start running microsyntheses - all subsequent batches are micro.
⁴No yields were measurable in reactions G-L.
⁵Start just acidifying reaction mixture.
the DDA sublimed.

The third modification is as follows: after allowing the reaction mixture to cool, it is acidified with 20% sulfuric acid, the solvent is stripped, and the solid material fractionally sublimed at 60° and 100° and reduced pressure.

The intermediate in the reaction, DDE, was readily isolated by heating the batch to reflux and then refluxing for 2 minutes. The mixture was then cooled, poured into cold water, washed and dried. The melting point was 83-86°, and a yield of approximately 90% was obtained.

All the procedures for the synthesis of DDA were repeated several times, both on a macro and micro scale.
Results and Discussion

The reason for the modifications of the synthesis was a result of the poor yield in reactions A, B, and C (see Table I). The expected yield was 69.73% (6); none of these syntheses gave a yield greater than 40%. Even with the first modification, however, the expected yield was never obtained (reactions C thru F). Also, the smaller in size the reaction mixture, the lower the yield that was obtained. This could be due to either incomplete reaction or to the loss of product during work-up procedures.

The problem of decreasing yield became most apparent in the attempted microsynthesis. No yield was measurable, even when any DDA was found present (taking the melting point of the sublimated material), but usually there was no DDA found. This can be attributed to several things. First, it was very difficult to obtain adequate stirring on the micro scale (25-100 mg.). Thus, poor yield could result from inadequate mixing of the reagents leading to incomplete reaction. Secondly, the stripping off of the water before sublimation somehow decomposed (or reacted with) the DDA that may have been formed. This was tested by adding sample DDA to the solution just before stripping off the solvent, and then having little or no DDA sublime. Also, even with the further extraction of DDA into chloroform (modification 2), a much smaller amount of DDA was sublimed than was started with.

The third modification (immediate acidification of the reaction mixture) was tried to eliminate handling of the mixture (and loss of product through extractions), but led to different results each time it was tried. The first time (reaction J), the sublimed material melted at approximately 90°, 110°, 155°, and some non-melting material.
(probably DDE, DDT, DDA, and inorganic material, respectively). In this case the sublimation was done only at 100°. The next two times (reactions K and L) this procedure was followed, too different things happened. In reaction K, a viscous, amber-colored mass with some white solid material in it resulted while attempting to sublime the batch. Reaction L ended with a brown oil, similar to the results of reactions G through J.

The question of whether DDA would sublime at all was raised earlier in the investigation. Starting with a sample of undissolved DDA and attempting sublimation, approximately 95% was sublimed.

One thing that should be noted, however, is that the reaction was somewhat inconsistent. Almost every batch gave results different from previous runs, a situation which made duplication of results (and problems) difficult, if not impossible.

-8-
Conclusions

In summary, the difficulties in the sublimation stage of the microsynthesis of DDA can be attributed to either incomplete reaction, loss of product during work-up, or decomposition or reaction of product while stripping off the solvent. It appears, however, that the inability to sublime DDA after reaction was due primarily to decomposition or reaction. This was concluded for the following reasons: 1) DDA itself sublimes well; 2) sample DDA added either after work-up or just dissolved in solvent cannot be sublimed (although in chloroform results are better than in water); and 3) the reaction appears to proceed well (in terms of color change and reaction with sulfuric acid). However, the possibility of an incomplete reaction is still strong for the reasons mentioned earlier.

Although this work failed to accomplish its goal (i.e., the synthesis of C14-labeled DDA), several questions have been raised. First, an alternative synthesis for DDA must be used, or alternative work-up procedures must be found. The need for radio-labeled DDA for tracing purposes still exists, and thus cannot be ignored. And second, it would be interesting to discover why DDA decomposes (or reacts) when a solvent is stripped off.
Bibliography


