An Approach to the Synthesis of Macrocyclic Beta-Diketones.

Carlton Jay Adams

Louisiana State University and Agricultural & Mechanical College

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The Louisiana State University and
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1971
Chemistry, analytical

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AN APPROACH TO THE SYNTHESIS OF MACROCYCLIC $\beta$-DIKETONES

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

by

Carlton Jay Adams
A.B., East Carolina University, 1959
M.S., Florida State University, 1962

January 1971
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The author is indebted to the National Science Foundation for financial support during the summers and for a Science Faculty Fellowship; and to the Dr. Charles E. Coates Memorial Fund of the Louisiana State University Foundation donated by George H. Coates for financial assistance pertinent to the publication of this Dissertation.
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ABSTRACT

Methods of synthesizing macrocyclic $\beta$-diketones have been proposed and investigated. These ligands were desired in order to study the volatile properties of their metal chelates. The general approach to the synthesis involved a "template" reaction, in which the $\beta$-diketone functional groups were held in place by a central metal ion while a ring closure was attempted.

Two synthetic schemes were investigated. The first scheme involved the reaction of 2,4-pentanedione with 1,6-dibromohexane in the presence of NaNH$_2$ in liquid NH$_3$ to form 2,4,13,15-hexadecanetetraone. The monomeric cyclic Be chelate of 2,4,13,15-hexadecanetetraone was prepared, but attempts to complete the macrocyclic structure by alkylating the methyl groups of this chelate with 1,6-dibromohexane in the presence of NaNH$_2$ were unsuccessful.

The second scheme proposed a novel synthesis of $\beta$-diketo-diesters as intermediates in the synthesis of macrocyclic $\beta$-diketones. Cyclopentanone or cyclohexanone, as starting material, was reacted with paraformaldehyde in the presence of base to produce bis(2-oxocyclopentyl)-methane and bis(2-oxocyclohexyl)methane, respectively. Treatment of these compounds with perbenzoic acid gave the new compounds bis(3-oxo-2-oxacyclohexyl)methane (m.p. 95-97°) and bis(3-oxo-2-oxacycloheptyl)-methane (not isolated), respectively. Refluxing these compounds with CH$_3$OH and HCl gave dimethyl 5,7-dihydroxyundecanedioate (m.p. 62-63°) and dimethyl 6,8-dihydroxytridecanedioate (m.p. 61-62°), respectively. These dihydroxy diesters have not been reported previously.
The oxidation of the dihydroxy diesters with chromic acid gave dimethyl 5,7-dioxoundecanedioate and dimethyl 6,8-dioxotridecanedioate (m.p. 30-31°). Addition of these new β-diketo diesters to Cu(II) ion yielded the copper chelate of dimethyl 5,7-dioxoundecanedioate (m.p. 111-113°) and the copper chelate of dimethyl 6,8-dioxotridecanedioate (m.p. 109-110°). The chelates were soluble in CH₂Cl₂, toluene, and xylene. They could not be sublimed under reduced pressure. The β-diketo diesters readily formed precipitates with Be(II), Cu(II), and Pd(II), and they formed red complexes with Fe(III). The Ni(II) and Co(II) complexes were isolated after extracting the aqueous solution with CH₂Cl₂. These chelates were not characterized further.

Treatment of dimethyl 6,8-dioxotridecanedioate with acid produced 6,8-dioxotridecanedioic acid. The β-diketo diacid formed precipitates readily with Be(II), Cu(II), Pd(II), and UO(II). The copper salt was characterized, and possible structures were proposed.

The copper chelate of dimethyl 6,8-dioxotridecanedioate was treated with sodium metal under conditions required for the acyloin condensation. The idea was to effect a ring closure by condensing the ester groups in the chelate. Only the starting chelate and polymeric material could be isolated. The copper chelate appeared stable under these conditions.

When the copper chelate of dimethyl 6,8-dioxotridecanedioate was treated with potassium tert-butoxide in refluxing toluene (Dieckmann condensation), only polymeric material, which could not be characterized, was isolated. The copper chelate appeared to be unstable under the reaction conditions.
An attempt was made to reduce the ester groups of the copper chelate of dimethyl 6,8-dioxotridecanedioate to hydroxy groups by treating the chelate with LiAlH₄. The chelate was apparently destroyed and the β-diketone groups were also reduced.
I. INTRODUCTION

One of the most remarkable properties of the metal chelates of the \( \beta \)-diketones is their volatility. The fact that many of these chelates can be sublimed at low temperatures has led to their separation by gas chromatography and fractional sublimation. In the classic monograph by Moshier and Sievers\(^1\) gas chromatographic procedures for many acetylacetone derivatives as well as for the trifluoro- and hexafluoroacetylacetones were reported. Berg and co-workers\(^2\)\(^-\)^\(^5\) have investigated the fractional sublimation of numerous metal \( \beta \)-diketonates and have effectively separated many by this method.

However, despite the success achieved in the separation of these metal chelates by gas chromatography and fractional sublimation, there are still some problems encountered which limit the success of these methods. For example, although many metal \( 1,3 \)-diketonates can be sublimed, the high temperature required for some is not suitable for conventional gas chromatography. Many of the lanthanide metal chelates are thermally unstable, and the presence of water has been postulated to cause the thermal instability.\(^6\)\(^-\)^\(^8\) Some metal ions do not form neutral chelates with the \( \beta \)-diketones, and the ionic chelates are inherently less volatile than the neutral chelates. Thus, the \( \beta \)-diketonates that are more likely to be separated by gas chromatography and fractional sublimation are those which are volatile, thermally stable, non-hydrated, and neutral. Any new ligand that would enhance these desired properties would have particular importance.

In general, metal ions react with the enol form of the \( \beta \)-diketone as shown in the following illustration.
2,4-Pentanedione (acetylacetone) is the simplest β-diketone, and most of the metal acetylacetonates are volatile to some extent. Since it was reasoned that the nature of the ligand shell would greatly influence such physical properties as volatility, many derivatives of 2,4-pentanedione have been synthesized. The effect of substitution on the 1, 3, and 5 carbon atoms of 2,4-pentanedione by various groups such as long chain alkyls, branched alkyls, aryl groups, and fluorinated groups have been studied. The most striking effect has been the introduction of fluorocarbon moieties in the ligand shell. Apparently, the highly electronegative fluorine groups act to repel other fluorine groups and many chelates of the fluorinated β-diketones have a much greater volatility than the nonfluorinated analogs. The most common examples are trifluoro- and hexafluoro-acetylacetone. (See Table I.)

In order to prevent the hydration of metal chelates, the introduction of branched chain alkyls on the 1 and 5 carbons of 2,4-pentanedione has been utilized. The concept here is that the branched chain alkyls provide steric hinderance and prevent the hydration of the complex. Thus, the compound 2,2,6,6-tetramethyl-3,5-heptanedione (dipivaloylmethane) has proved to be useful in the preparation of anhydrous chelates of the rare earth metals. Some of these rare earth complexes have been successfully separated by Berg and Sievers.
### TABLE I

**SOME 𝛽-DIKETONES SYNTHESIZED TO ENHANCE VOLATILITY OF CHELATES**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF₃-C-CH₂-C-CH₃</td>
<td>1,1,1-trifluoro-2,4-pentanedione (trifluoroacetylacetone)</td>
</tr>
<tr>
<td>CF₃-C-CH₂-C-CF₃</td>
<td>1,1,1,5,5,5-hexafluoro-2,4-pentanedione (hexafluoroacetylacetone)</td>
</tr>
<tr>
<td>CH₃-C-CH₂-C-C-CH₃</td>
<td>2,2,6,6-tetramethyl-3,5-heptanedione (dipivaloylmethane)</td>
</tr>
<tr>
<td>CF₃-CF₂-CF₂-C-CH₂-C-C-CH₃</td>
<td>1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione</td>
</tr>
<tr>
<td></td>
<td>1-(perfluoro-1-bicyclo[2.2.1]heptyl)-4,4,4-trifluorobutane-1,3-dione</td>
</tr>
<tr>
<td></td>
<td>1,1,1-trifluoro-4-(2-thienyl)-4-mercaptobut-3-en-2-one (thiothenoyltrifluoroacetone)</td>
</tr>
</tbody>
</table>
Sievers also reported the synthesis of 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione, which utilizes both the fluorocarbon moieties to increase the volatility and the branched chain alkyl to prevent the formation of hydrates. Indeed, this compound shows much promise in the separation of the rare earths by gas chromatography.

Belcher, et al., have recently reported the synthesis of a compound containing a bulky fluorinated group. This novel compound, L-(perfluoro-1-bicyclo[2.2.2]heptyl)-1,4,5-trifluorobutane-1,3-dione (see Table I) formed a sodium chelate that was remarkably stable; however, it was less volatile than the hexafluoroacetylacetone analog. They attempted to synthesize the completely fluorinated derivative of 2,2,6,6-tetramethyl-3,5-heptanedione.

Reed has studied the effect of substitution on the β-diketones from a different approach, in which the stereochemistry of the chelate ring and its electronic environment were directly altered. First, the effect of substituting a sulfur atom for an oxygen atom in the chelate ring was studied; and, second, the effect of introducing alkyl groups on the number 3 carbon of 2,4-pentanediione was determined. The synthesis of the new chelating agent, thiothenoyltrifluoroacetone was reported. In general, he found the monothio derivatives of the β-diketones and the methylene substituted derivatives to be less stable and less volatile, but more selective, than the β-diketone analogs. Nevertheless, Stephens, et al., have recently reported the gas chromatography of some transition metals of the monothioacetylacetonates.
In order to continue the search for new β-diketone ligands, it was envisioned that a macrocyclic ligand formed by joining both ends of two molecules of 2,4-pentanedione by straight chain hydrocarbon groups might prove to be interesting. The chelated metal ion conceivably would be enclosed in a hydrocarbon shell, and by varying the ring size, perhaps some selectivity could be introduced in the chelating reaction. Molecular models indicated that the ring size would have to be approximately 22 carbon atoms in order to accommodate a central metal ion without strain.

A review of the literature revealed that chelates of macrocyclic tetraketones have been synthesized. Coombs and Houghton synthesized the macrocyclic tetraketones I and II (Figure 1) in order to obtain a ligand that would form chelate compounds selectively with metal ions of a given ionic radius. Since they were concerned only with selectivity, they utilized aromatic groups as a means of constructing rigid molecules. Also, aromatic 1,3-diketones usually form stronger chelating agents than the aliphatic or partly aliphatic 1,3-diketones. Although they were successful in synthesizing the macrocyclic compounds, the initial object of synthesizing a specific chelating agent was not realized. No data were given on the volatilities of the chelates of these macrocyclic compounds. It is assumed that these macrocyclic chelates would not be particularly volatile for two reasons. First, it is known that the chelates of aromatic 1,3-diketones, such as dibenzoylmethane, are not as volatile as the chelates of the aliphatic 1,3-diketones and certainly not as volatile as the fluorinated derivatives. Second, the high molecular weight of these compounds tends to decrease the volatility further.
FIGURE I

I. $^{16,33}$-Diacetyl-16,17,33,34-tetrahydro-15,32$^\text{H}$-hexabenzo[ab,f,jk,pq,v,yz]cyclotriacontin-15,17,32,34-tetraone

II. $^{16,33}$-Diacetyl-5,10,16,17,22,27,33,34-octahydro-15,32$^\text{H}$-hexabenzo[c,gh,mn,r,vv,BC][1,6,16,21]tetrathiacyclotriacontin-15,17,32,34-tetraone

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Thus, non-aromatic macrocyclic \( \beta \)-diketones should offer a greater potential for increasing the volatility of chelates than the aromatic macrocyclic \( \beta \)-diketones.

This Dissertation is concerned with the synthesis of the following macrocyclic compounds: \( 1,3,12,14 \)-cyclodocosanetetraone (III) and \( 1,3,14,16 \)-cyclohexacosanetetraone (IV).

\[
\begin{array}{c}
\text{C-CH}_2\text{-C} \\
\text{CH}_2 \text{n} \\
\text{C-CH}_2\text{-C} \\
\text{0} \\
\text{0} \\
\text{0} \\
\text{0} \\
\end{array}
\]

Where \( n = 8 \) or greater

- \( n = 8 \), III
- \( n = 10 \), IV
II. APPROACH TO THE SYNTHESIS OF MACROCYCLIC COMPOUNDS

A survey of the literature revealed that macrocyclic compounds are usually synthesized by joining the ends of a suitably substituted chain in very dilute solution. Table II indicates the types of reactions that have produced macrocyclic compounds by this approach. For most preparative purposes the acyloin condensation has proved to be the most important reaction because high dilution is not required and the yields have been spectacular. (C\textsubscript{21}-acyloin, 96%).

More recently, several methods have been developed to generate large rings directly from readily available monomers. Sondheimer\textsuperscript{24} synthesized a number of unsaturated macrocyclic compounds by the oxidation of terminal diacetylenes with oxygen in the presence of cuprous chloride and ammonium chloride in aqueous ethanol. Dale\textsuperscript{25} and Wotiz\textsuperscript{26} independently prepared cyclic non-conjugated diynes and tetraynes from alka-\(\alpha\),\(\omega\)-diynes and \(\alpha\),\(\omega\)-dibromoalkanes in liquid ammonia. Corey\textsuperscript{27} prepared large-ring olefins by cyclization of allylic dibromides with nickel carbonyl. Wasserman\textsuperscript{28} recently reported the synthesis of macrocyclic compounds containing 120 carbons in the ring. This method involved reacting a small-ring olefin with a WCl\textsubscript{6}-EtAlCl\textsubscript{2}-EtOH catalyst. For example:

\[
2 \left(\text{CH}_2\right)\text{n} \xrightarrow{\text{Catalyst}} \left(\text{CH}_2\right)\text{n} \bigcirc \left(\text{CH}_2\right)\text{n} = \left(\text{CH}_2\right)\text{n} \bigcirc \left(\text{CH}_2\right)\text{n}
\]

The formation of larger rings from smaller rings is an exception to the usual procedure for the synthesis of macrocyclics.

Perhaps the latest novel synthesis of macrocyclic compounds has been reported by Story.\textsuperscript{29,30} This method involves the thermal
<table>
<thead>
<tr>
<th>No.</th>
<th>Reactant</th>
<th>Condensing Agent</th>
<th>Product</th>
<th>Ref.</th>
<th>% Yield (Approx.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>[C-CH&lt;sub&gt;2&lt;/sub&gt;-CO&lt;sub&gt;2&lt;/sub&gt;-Me]</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>[C-CH&lt;sub&gt;2&lt;/sub&gt;-CO&lt;sub&gt;2&lt;/sub&gt;-Me]</td>
<td>15</td>
<td>86</td>
</tr>
<tr>
<td>2.</td>
<td>[C≡C]</td>
<td>Cu(C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>[C≡C][C≡C-C≡C]</td>
<td>16,17</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>[CO&lt;sub&gt;2&lt;/sub&gt;H]</td>
<td>Ce Salt</td>
<td>[C=O]</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>4.</td>
<td>[COCl]</td>
<td>N(CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;OH&lt;sup&gt;-&lt;/sup&gt;</td>
<td>[C=O]</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>5.</td>
<td>[CO&lt;sub&gt;2&lt;/sub&gt;Et]</td>
<td>terBuOK</td>
<td>[C=O]</td>
<td>20</td>
<td>48</td>
</tr>
<tr>
<td>6.</td>
<td>[CN]</td>
<td>PhN(Me)Na</td>
<td>[C=NH]</td>
<td>21</td>
<td>70</td>
</tr>
<tr>
<td>7.</td>
<td>[CO&lt;sub&gt;2&lt;/sub&gt;Me]</td>
<td>Na</td>
<td>[CHOH]</td>
<td>22</td>
<td>96</td>
</tr>
</tbody>
</table>
decomposition of an appropriate cyclic peroxide by refluxing in a hydrocarbon solvent. A typical synthesis is shown in the following reaction:

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

A study of these general procedures for synthesizing large ring compounds reveals that none of the methods is directly suitable for synthesizing the desired compounds. The preparation of the macrocyclic tetraketones is complicated by the fact that β-diketone groups must be in the ring and they must be symmetrical. To alleviate this problem, one approach suggested was to synthesize a fused ring system and then to break the inner bonds judiciously to form the desired macrocyclic compounds. Indeed, Finnegan and Delacki\textsuperscript{31} have reported the synthesis of a 14-membered ring tetraketone by the oxidative cleavage of Diels-Alder adducts derived from cyclic acetylenes and dienes as shown in the following diagram.

Sondheimer\textsuperscript{32} has prepared dicycloocteno[1,2:4,5]benzene by the following reaction.

If the dicycloocteno[1,2:4,5]benzene were reduced \textit{via} the Birch reduction and then oxidized, the 18-membered ring tetraketone should be
obtained. Although these methods look promising for small-ring tetra-
ketones, the difficulty in preparing the starting materials for larger
ring synthesis, especially the dienes, would probably limit the success
of this reaction. Nevertheless, this route offers a possibility in the
synthesis of the macrocyclic tetraketones.

Coombs and Houghton\textsuperscript{14} presented an alternative scheme in the
synthesis of the macrocyclic $\beta$-diketones I and II (see page 6). The
cyclization involved a "template" reaction in which the $\beta$-diketone groups
were protected and held in place by chelating them with Mg(II) ion. The
ring closure was effected by condensing a bis(acid chloride) and magne-
sium chelate of the bis(methyl-$\beta$-diketone) in a solution of benzene and
diglyme for 14 days at high dilution (26\% yield).

The reaction involved an electrophilic attack on the central carbon in
the chelate ring under mild conditions.

The idea of building ring compounds around a central metal
atom is not new. Busch\textsuperscript{33} first illustrated this phenomenon by showing
that cis-oriented mercaptide groups react with difunctional active halogen
compounds to form new chelate rings, without cleaving the metal donor

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\includegraphics[width=\textwidth]{diagram.png}};
\end{tikzpicture}
\end{center}
atom bonds.

\[
\begin{array}{c}
\text{Ni} \\
\text{N} \\
\text{S} \\
\text{Ni} \\
\text{N} \\
\text{S}
\end{array}
+ \quad \begin{array}{c}
\text{Br} \\
\text{Br}
\end{array} \rightarrow \quad \begin{array}{c}
\text{Ni} \\
\text{N} \\
\text{S} \\
\text{Ni} \\
\text{N} \\
\text{S}
\end{array}
\]

Other template syntheses of macrocyclic ligands of this type have been reported but Coombs and Houghton appear to be the only ones to have utilized the chelates of the \(\beta\)-diketones in the synthesis of macrocyclic compounds.

After the rather limited synthetic possibilities were considered, it was concluded that the template idea would be the most direct and interesting approach. The success of any template synthesis would obviously depend upon the stability of the metal chelate under the reaction conditions required for ring closure. Collman reviewed the reactions of the chelates of the \(\beta\)-diketones, and reported that halogenation, nitration, thiocyanation, acylation, formylation, chloromethylation and aminomethylation take place on the central carbon of the chelate ring of the trisacetylacetonates of Cr(III), Co(III), and Rh(III). Several groups were displaced from the chelate rings under electrophilic conditions. The Cr(III), Co(III), and Rh(III) chelates were studied predominately because they provide the kinetically most stable complexes that are amenable to treatment in organic solvents.

As Collman has pointed out, acid lability of the acetylacetonates precludes any possible reaction in strongly acidic media. Therefore, reaction conditions are limited to slightly acidic, neutral, or basic media, and little or no work has been reported on the behavior...
of β-diketonates under strongly basic conditions. This lack of knowledge concerning the stability of various β-diketonates under different reaction conditions presents a serious handicap in proposing any synthetic scheme.

After much consideration, two different approaches were chosen for the synthesis of macrocyclic β-diketones. Scheme A and Scheme B are shown in Figures 2 and 3, respectively. Scheme A proposes the preparation of a bis-β-diketone, the formation of a cyclic beryllium bis-β-diketonate, and the reaction of this beryllium chelate to form the macrocyclic chelate. The bis-β-diketones have been prepared by Fernelius and by Hauser, who reported the higher yield. The method of Hauser involves the formation of a disodio salt of acetylacetone with NaNH₂ in liquid ammonia, followed by a two-fold alkylation with methylene halides.

In a later article, Hauser also reported that the bis-β-diketones were converted by means of 4 molar equivalents of NaNH₂ to the corresponding tetrasodio salts, which were alkylated with various halides to form the corresponding diterminal derivatives. Thus, the tetrasodio bis-β-diketones were treated with trimethylene bromide to give a poly(1,3-dione). The reaction led to the idea that a ring closure might be affected by holding the β-diketone groups in place by chelation and alkylating the methyl group with a methylene halide. The chelate must be stable under the necessary reaction conditions and the methyl carbon must remain the reactive site.

Holst prepared chelates of the bis-β-diketones with the following metal ions: Cu(II), Co(II), UO₂(II), and Mn(II). In no case did
FIGURE 2

Scheme A

\[
\begin{align*}
\text{CH}_3\text{-CH}_2\text{-C}-\text{CH}_3 + 2\text{NaNH}_2 & \rightarrow \text{CH}_3\text{-CH}_2\text{-C}-\text{CH}_3 + \text{(CH}_2)_n \text{NaNH}_2 \\
\text{CH}_3\text{-CH}_2\text{-C}-\text{CH}_3 + \text{Be}^{++} & \rightarrow \text{Be}^{++} + \text{(CH}_2)_n \text{Be}^{++} \\
\text{VI} + \text{Br}_2(\text{CH}_2)_6 & \rightarrow \text{Be}^{++} + \text{(CH}_2)_n \text{Be}^{++}
\end{align*}
\]

(V)

(VI)

(VII)
FIGURE 3

Scheme B

\[ \begin{align*}
\text{VIIIa} + \text{CH}_2\text{O} & \xrightarrow{\text{OH}^-} \text{VIIIa}^* \\
\text{VIIIa} + \text{COOH} & \xrightarrow{\text{IXa}} \text{IXa} \\
\text{IXa} + \text{CH}_3\text{OH} & \xrightarrow{\text{HCl}} \text{Xa} \\
\text{Xa} + \text{CrO}_3 & \xrightarrow{} \text{Xla} \\
\text{Xla} + \text{Cu}^{++} & \xrightarrow{} \text{XIIa}
\end{align*} \]
FIGURE 3 (Continued)

XIIa + Na $\xrightarrow{\text{xylene}}$ HO-C \(\overset{\text{Cu}^+}{\text{O}}\) C-OH

(XIIIa)

XIIIa $\xrightarrow{\text{reduction}}$ (XIVA)

XIIa $\xrightarrow{\text{KtBuO}}$ then decarboxylation (XVA)

b will refer to the cyclohexanone derivative.
the reaction of a bis-β-diketone with a metal ion yield a product which could be identified as a cyclic monomer. Apparently, due to the many conformations that the long bis-β-diketones can assume, the probability of an intermolecular reaction is much greater than an intramolecular reaction. However, Kluiber and Lewis prepared a number of cyclic beryllium bis-β-diketonates by first forming the polymer and then converting the polymer into the cyclic monomer by sublimation. It is interesting to note that the cyclic monomeric products were isolated when the β-diketone groups were separated by at least 6 carbon atoms, and the shorter the link, the less volatile the products. Thus, the information derived from molecular models that indicated the ring size should be approximately 22 carbons was confirmed.

The Be chelate was an obvious choice for the reaction for several reasons. First, the Be cyclic monomer had been prepared, whereas the preparation of other cyclic bis-β-diketonates had not been established. Second, since the reaction medium was ammonia, there was a possibility of ammonia complexing with the metal ion and destroying the chelate. Cotton pointed out, however, that Be forms stronger bonds with oxygen donors than with nitrogen donors. Third, nmr spectra can be obtained for Be chelates, and this tool offers the most logical means of characterizing the final product.

Scheme B proposes a novel multistep synthesis of β-diketone diesters as intermediates in the formation of the desired macrocyclic compounds. The idea was to chelate the diketone groups and effect a ring closure with a condensation of ester groups by either an acyloin condensation or a Dieckmann condensation. The size of the ring could

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be altered by varying the starting cyclanones. In order to form a ring size of 22 carbon atoms, via the acyloin condensation, cyclopentanone was required as the starting material. Cyclohexanone would produce a 26 carbon ring.

For the ring closure to be successful, the chelate ring must be stable and unreactive under strongly basic conditions. Unfortunately, the stability of the chelated β-diketonates under such conditions is not known; therefore, the choice of the metal ion cannot be based on past experience. According to molecular models, the square planar configuration is the most favorable for ring closure, although the tetrahedral configuration cannot be eliminated. It is obvious that the tris-complexes will not be suitable. This excludes the Cr(III), Co(III), and Rh(III) complexes, unless mixed ligands are utilized. The Cu(II) ion was chosen because it readily forms square planar complexes with the β-diketones, and it forms one of the most stable β-diketonates. However, this relative stability will probably be meaningless under the specific reaction conditions.
III. Experimental

A. Chemicals and Data Collection

When available, reagents and solvents were Analytical Reagent Grade materials that were usually used without further purification. The solvents used for the acyloin condensation and the Dieckmann condensation were dried over sodium and redistilled prior to use.

The nmr spectra were recorded on either the Varian A-60A or the Varian HA-100 spectrometer. The chemical shifts are given in parts per million (δ). The multiplicity notations used are: s, singlet; m, multiplet; b, broad. The sample concentrations were approximately 10% by volume. The solvents are noted in each case. The nmr spectra of new compounds are given in Appendix I.

The ir spectra were recorded by means of the Beckman IR-10 spectrophotometer. The band assignments are given in wave numbers. The ir spectra of new compounds are shown in Appendix II.

The mass spectra were recorded by Mrs. Gregory White of Coates Chemical Laboratories with the Varian M-66 Mass Spectrometer. The uv spectra were recorded with a Beckman DB spectrophotometer equipped with a Sargent Model SR6 recorder. Melting points were determined with a Thomas Hoover Melting Point Apparatus and are uncorrected. The carbon-hydrogen analyses were performed by Mr. Ralph Seab, Coates Chemical Laboratories. The copper analysis was performed with the Perkin-Elmer 303 Atomic Absorption Spectrophotometer.
B. Synthetic Scheme A

2,4,13,15-Hexadecanetetraone (V)

This intermediate was prepared according to the method of Hampton, Light, and Hauser.\textsuperscript{37} A 1 liter flask was equipped with a stirrer, a gas inlet tube, and a Dry Ice-acetone condenser. All glassware was dried overnight at 110° and flushed with dry N\textsubscript{2} during the reaction. The flask was immersed in a Dry Ice-acetone bath, and approximately 700 ml of NH\textsubscript{3} were collected. A minimum amount of clean Na was added to the liquid NH\textsubscript{3} to produce a permanent blue color. A few crystals of Fe(NO\textsubscript{3})\textsubscript{3} were added to catalyze the conversion of Na to NaNH\textsubscript{2}, and then 4.6 g (0.20 mole) of Na metal cut up in small pieces were added. When the Na has been completely converted to the NaNH\textsubscript{2}, the solution changed from a blue color to a gray suspension.

Ten grams (0.1 mole) of 2,4-pentanone in 20 ml of anhydrous ether was added dropwise from a pressure compensating funnel. The cooling bath was removed and 12 g (0.05 mole) of 1,6-dibromohexane in 20 ml of anhydrous ether was added over a period of 20 minutes. After 2 hours, 250 ml of ether was added and the reaction was stopped. The NH\textsubscript{3} was allowed to evaporate at room temperature. The resulting mixture was cooled in an ice bath, and 60 ml of HCl in 200 g of crushed ice was added. The mixture was filtered, and the solid residue was saved to combine with the extract. The ether layer was separated, and the aqueous layer was extracted twice with 100 ml portions of ether. The combined ether extracts were dried over MgSO\textsubscript{4}, filtered and concentrated. The residue was combined with the solid from the initial filtration. Recrystallization from ethanol gave 10 g (70\% yield) of product which
melted at 77-78° C. (Lit m.p. 78-79°): ir max (KBr) 1640, 1600, 1408, 1220, 786 cm⁻¹; nmr (CCl₄), 5.36 (s, enol), 3.45 (s, keto), 2.00 (s, CH₃) ppm.

Found: C, 67.92; H, 9.27.

Cyclic Beryllium Chelate of 2,4,13,15-hexadecanetetraone (VI)

This compound was prepared according to the method of Kluiber and Lewis.⁴⁰ 2,4,13,15-Hexadecanetetraone (0.8 g, 2.8 mmoles) and 0.5 g of BeSO₄·H₂O were added to 50 ml of distilled water and 10 ml of dioxane. The reaction mixture was adjusted to a pH of 8 with dilute NaOH, and the mixture was stirred overnight. The insoluble product was removed by filtration, washed with benzene and air dried. One gram of the product was sublimed for 24 hours at 200° C and 1 mm Hg. A white crystalline material (0.7 g), which melted at 135-138°, was collected. (Lit m.p. 138-140°): nmr (CCl₄), 5.48 (s, enol), 2.07 (s, CH₃) ppm.

Attempted Ring Closure with Be Chelate of 2,4,13,15-hexadecanetetraone

The procedure of Hauser, et al.,³⁸ was followed in this reaction. Approximately 100-150 ml of anhydrous NH₃ was collected in a 250 ml 3-necked flask, which was equipped with a stirrer, a gas inlet tube, and a pressure regulating funnel. The reaction vessel was flushed with N₂ during the reaction. A minimum amount of clean Na metal was added to produce a permanent blue color. After a few crystals of Fe(NO₃)₃ were added, 0.17 g (7.4 mmoles) of clean Na metal was added to the mixture.

When the Na metal had been converted to the NaNH₂, 0.5 g (1.7 mmoles) of Be chelate in 5 ml of anhydrous ether was added dropwise to
the reaction mixture. After 30 minutes, 0.45 g (1.9 mmole) of 1,6-
dibromohexane in 5 ml of anhydrous ether was added dropwise to the mix-
ture over a period of 20 minutes and was allowed to react for two hours.
Fifty ml of ether was added, and the NH₃ was allowed to evaporate. After
the addition of 50 ml of ice water, the mixture was neutralized with con-
centrated HCl. The ether layer was separated, and the aqueous layer was
extracted 3 times with ether. The combined ether extracts were dried
over MgSO₄ and concentrated, and the oily residue crystallized upon
cooling. The product was recrystallized with ethanol, and gave 0.45 g
of white solid. The substance melted at 133-135° and the nmr spectrum
(2.07 ppm, CH₃) indicated that the material was the starting material.
A mixture of the product with the starting material showed no depression
in the melting point. This reaction was repeated several times and in
all cases only the starting material could be isolated.

C. Synthetic Scheme B

Bis(2-oxocyclopentyl)methane (VIIIa)

This intermediate was prepared by the method of Colange, Dreux,
and Deplace, in which they isolated two crystalline forms. Accordingly,
168 g (2 moles) of cyclopentanone, and 10 g (0.33 mole) of paraformalde-
hyde were added to a 1 liter flask, which was fitted with a reflux con-
denser and a thermometer. The mixture was heated to 45° C, and 10 ml of
2 N KOH in methanol was added through the reflux condenser. After
boiling vigorously for 3 to 4 minutes, the solution was cooled rapidly
in an ice bath, neutralized with concentrated HCl, and filtered.
The filtrate was distilled under reduced pressure, and the product (10 g)
was collected at 140-150° at 3 mm Hg. Recrystallization of the solid from petroleum ether (b.p. 60-90°) at room temperature yielded 3.5 g of form A. The volume of the filtrate was reduced by one half, and the resulting solution was placed in the freezer for 24 hours. The solution yielded 3.4 g of form B.

Form A melted at 68-70° (Lit m.p. 70°): ir max. (KBr) 1730 (CO), 1450, 1405, and 1158 cm⁻¹; nmr (CCl₄) 2.4 to 1.4 ppm (m).

**Anal.** Calculated for C₁₁H₁₆O₂: C, 73.53; H, 8.88. Found: C, 73.1; H, 8.92.

Form B melted at 38° C (Lit m.p. 38°): ir max. (KBr) 1740 (CO), 1450, 1405, and 1158 cm⁻¹; nmr (CCl₄) 2.4 to 1.4 ppm (m).

**Anal.** Calculated for C₁₁H₁₆O₂: C, 73.53; H, 8.88. Found: C, 73.07; H, 8.99.

**Bis(2-oxocyclohexyl)methane (VIIIb)**

This compound was prepared according to the above procedure, and 2 moles of cyclohexanone was reacted with 10 g of paraformaldehyde. The product (15 g) distilled at 145-155° at 3 mm. Recrystallization from petroleum ether afforded 11 g of white solid, which melted at 56-58° (Lit m.p. 58°): ir max. (KBr) 1712 (CO), 1450 and 1405 cm⁻¹; nmr (CCl₄) 2.65 to 0.9 ppm (m).

**Anal.** Calculated for C₁₃H₂₂O₂: C, 74.95; H, 9.68. Found: C, 74.92; H, 9.50.

**Perbenzoic Acid**

Perbenzoic acid was prepared in CH₂Cl₂ solution by the general procedure of Braun. The concentration was determined by iodometric titration.
Bis(3-oxo-2-oxacyclohexyl)methane (IXa)

Procedures for the Baeyer-Villiger\textsuperscript{46} reaction were followed in this synthesis. Bis(2-oxocyclopentyl)methane (18 g, 0.1 M) in 50 ml of CH\textsubscript{2}Cl\textsubscript{2} was added dropwise to a cold stirred solution of 30.4 g (0.22 mole) of perbenzoic acid and 10 g of anhydrous NaHCO\textsubscript{3} in 350 ml of CH\textsubscript{2}Cl\textsubscript{2}. The reaction was stirred overnight at room temperature. The absence of the starting material was verified by tlc. Silica gel was used as the absorbent and ethyl acetate was used as the eluting solvent. Five grams of anhydrous MgSO\textsubscript{4} was added, and the solution was filtered and concentrated.

A portion of the mixture (0.30 g) was chromatographed on a silica gel column by eluting with 500 ml of a 20\% ethyl acetate-petroleum ether mixture. The first fractions contained 0.18 g of benzoic acid and were followed by 0.11 g of the bis(3-oxo-2-oxacyclohexyl)methane. Recrystallization of the latter product from CCl\textsubscript{4} yielded 0.09 g of white solid, which melted at 95-97° C: ir (CH\textsubscript{2}Cl\textsubscript{2}) 1735 (CO), 1072, and 1050 cm\textsuperscript{-1}; nmr (CDCl\textsubscript{3}) 4.90 to 4.31 (m, methine H), 2.72 to 1.5 (m) ppm; mass spectrum (70 eV) m/z (rel. intensity) 212 (0.7), 194 (15), 184 (16), 166 (9), 156 (37), 143 (29), 138 (11), 125 (22), 114 (55), 113 (13), 100 (19), 99 (100).

Anal. Calculated for C\textsubscript{11}H\textsubscript{16}O\textsubscript{4}: C, 62.25; H, 7.60

Found: C, 62.17; H, 7.62.

Dimethyl 5,7-dihydroxyundecanedioate (Xa)

The crude mixture from the preceding reaction containing the benzoic acid and bis(3-oxo-2-oxacyclohexyl)methane was dissolved in 250 ml of anhydrous methanol. The solution was saturated with HCl gas,
refluxed for 12 hours, cooled, and poured into 500 ml of saturated NaCl solution. The aqueous solution was extracted several times with 100 ml portions of CH₂Cl₂. The combined organic extracts were washed with 50 ml of 5% solution NaHCO₃, dried over MgSO₄ and concentrated. After the mixture was left under reduced pressure for 24 hours at room temperature, a yellow solid residue remained. Recrystallization from an ether-petroleum ether mixture gave 12 g (43% yield) of white solid, which melted at 61-63°C: ir max. (KBr) 3525 to 3250 (OH), 2960, 2940, 2920, 1735 (CO), 1440, 1415, 1382, 1350, 1320, 1285, 1230, 1195, 1175, 1120, 1100, 1032, 980, and 835 cm⁻¹; nmr (CDCl₃) 3.67 (s, CH₃CO), 3.09 (b, OH) 4.1 to 3.7 (m), 2.5 to 2.1 (m), and 2.0 to 1.2 (m) ppm.

**Anal.** Calculated for C₁₉H₂₄O₈: C, 56.50; H, 8.75.

Found: C, 56.45; H, 8.62.

**Bis(3-oxo-2-oxacycloheptyl)methane (IXb)**

A solution of 21 g (0.1 mole) of bis(2-oxocyclohexyl)methane (VIIIb) in 50 ml of CH₂Cl₂ was added to a cold, well-stirred solution of 30.4 g (0.22 mole) of perbenzoic acid and 10 g of anhydrous NaHCO₃ in 350 ml of CH₂Cl₂. The mixture was stirred overnight at room temperature, and 5 g of anhydrous MgSO₄ was added. The mixture was filtered, concentrated and subjected to nmr analysis: nmr (CDCl₃) 4.8 to 4.2 (m, methine H), 2.8 to 2.2 (m), and 2.1 to 1.2 (m) ppm. The compound was not isolated but used directly in the next synthesis.

**Dimethyl 6,8-dihydroxytridecanedioate (Xb)**

The crude solid mixture from the previous reaction was dissolved in 300 ml of anhydrous methanol and was saturated with HCl gas. After refluxing overnight, the mixture was poured into 500 ml of
saturated NaCl solution and extracted 4 times with 100 ml portions of CH_2Cl_2. The combined organic extracts were washed with 50 ml of 5% NaHCO_3, dried over MgSO_4 and concentrated. The resulting mixture was placed under reduced pressure overnight, and the product was recrystallized from an ether-petroleum ether mixture. A white solid (19.0 g, 63% yield), which melted at 61-62° C, was collected: ir max. (KBr) 3300 (OH), 2930, 1740 (CO), 1460, 1435, 1415, 1380, 1368, 1320, 1265, 1225, 1190, 1170, 1120, 1098, 1062, 1030, 980, and 870 cm^{-1}; nmr (CDCl_3) 3.67 (s, CH_3O-CO), 3.6 to 2.8 (b, OH), 4.1 to 3.8 (m), 2.5 to 2.1 (m), and 1.8 to 1.3 (m) ppm.

Anal. Calculated for C_{15}H_{28}O_{6}: C, 59.19; H, 9.27
Found: C, 58.93; H, 8.90.

**Cu Chelate of Dimethyl 5,7-dioxoundecanedioate (XIIa)**

The oxidation of 8-diols has been reported by Kaye and Mathews. A solution of 5.5 g (0.02 mole) of dimethyl 5,7-dihydroxyundecanedioate in 100 ml of acetone was cooled to 0-5° C in a 250 ml round bottom flask. The mixture was stirred and 22 ml of cold Jones reagent (8 N chromic acid) was added dropwise while the temperature was maintained below 5° C. The mixture was stirred for 1 hour, then 5 ml of isopropyl alcohol was added to decompose any excess chromic acid. The mixture was poured over 500 g of crushed ice which contained 3 ml of concentrated H_2SO_4. The aqueous layer was extracted several times with dichloromethane, and the combined organic extracts were washed with 100 ml of saturated NaCl solution, dried over MgSO_4 and concentrated. The residue was dissolved in 50 ml of methanol and added to 5 g of copper acetate in 250 ml of H_2O. The mixture was stirred overnight and was extracted several times with CH_2Cl_2. The combined organic extracts were dried and concentrated, affording
3.0 g of crude blue solid that was recrystallized from 95% ethanol. A
blue precipitate that melted at 111-113° was collected: ir max. (KBr)
1735 (ester CO), 1575, 1520, 1450, 1370, 1350, 1215, 1165, and 1165 cm⁻¹;
uv max. (C₂H₅OH) 296 μ (ε, 22,000).

**Anal.** Calculated for CuC₂₆H₃₈O₁₂: C, 51.52; H, 6.32.

Found: C, 51.68; H, 6.37.

**Dimethyl 5,7-dioxoundecanedioate (XIa)**

The copper chelate of dimethyl 5,7-dioxoundecanedioate (1 g)
was dissolved in 100 ml of 1 N HCl and was extracted 4 times with 25 ml
portions of CH₂Cl₂. The organic extracts were washed with H₂O, dried
over MgSO₄ and concentrated, giving 0.73 g of a clear liquid. The
material crystallized upon standing in the refrigerator but melted at
room temperature; ir max. (neat) 1735, 1710 (shoulder), 1615, 1440,
1370, and 1205 cm⁻¹; nmr (CDCl₃) 5.55 (s, enol form), 3.67 (s, CH₃-CO),
3.63 (s, keto) and 2.8 to 17. (m) ppm.

**Anal.** Calculated for C₁₂H₂₀O₈: C, 57.34; H, 7.40.

Found: C, 57.45; H, 7.24.

**Copper Chelate of Dimethyl 6,8-dioxotridecanedioate (XIIb)**

A solution of 11.5 g (0.038 mole) of dimethyl 6,8-
dihydroxytridecanedioate in 250 ml of acetone was cooled in an ice bath,
and Jones reagent (8 N chromic acid) was added dropwise with constant
stirring until the green color had changed to a dull brown color. The
mixture was stirred for 10 minutes and then was poured into 200 ml of
cold 1 N HCl. The product was extracted several times into CH₂Cl₂ and
the organic extracts were washed with 100 ml of saturated NaCl solution,
dried over MgSO₄ and concentrated. The residue was dissolved in 100 ml
of ethanol and was added to a solution of 4 g of copper acetate in 100 ml of distilled water. The mixture was stirred for one hour, 100 ml of water was added, and the mixture was filtered. The volume of mother liquid was reduced by one-half on the steam bath. The solution was cooled in an ice bath and the blue crystals were filtered. The combined solids were recrystallized from 95% ethanol, affording 3 g (30% yield) of blue needle crystals that melted at 109-110°: \textit{ir} max. (KBr) 2950, 1735 (ester CO), 1565, 1518, 1455, 1440, 1420, 1378, 1310, 1260, 1238, 1218, 1202, 1180, 1160, 1125, 1075, 975, and 775 cm\textsuperscript{-1}; \textit{uv} max. (C\textsubscript{2}H\textsubscript{5}OH) 296 μ (ε 25,000).

\textbf{Anal.} Calculated for CuC\textsubscript{30}H\textsubscript{46}O\textsubscript{12}: C, 54.41; H, 7.00. 

\textit{Found:} C, 54.38; H, 7.00.

\textbf{Dimethyl 6,8-dioxotridecanedioate (XIIb)}

Copper chelate of dimethyl 6,8-dioxotridecanedioate (1.0 g) was dissolved in 50 ml of dichloromethane and extracted with 25 ml of 1 N HCl. After the organic layer was dried and concentrated, 0.81 g of oily residue remained. The material crystallized upon cooling and was recrystallized from an ether-petroleum ether mixture. The white solid melted at 30-31°: \textit{ir} max. (KBr) 1740, 1710 (shoulder), 1615, 1440, 1370, and 1205 cm\textsuperscript{-1}; \textit{nmr} (CCL\textsubscript{4}) 5.41 (s, enol), 3.46 (s, keto), 3.67 (s, CH\textsubscript{3}0-C0), 2.4 to 2.1 (m), 1.8 to 1.4 (m) ppm.

\textbf{Anal.} Calculated for C\textsubscript{15}H\textsubscript{24}O\textsubscript{6}: C, 59.98; H, 8.05. 

\textit{Found:} C, 59.82; H, 8.02.

\textbf{6,8-Dioxotridecanedioic Acid (XVIib)}

A solution of 0.41 g of dimethyl 6,8-dioxotridecanedioate in 5 ml of methanol was added to 25 ml of distilled water containing 2 ml of concentrated HCl. The mixture was refluxed for 6 hours and about one-half of
the solvent was evaporated on a rotary evaporator. The solution was placed in a refrigerator and 0.25 g of white crystalline material, which melted at 103-105°, was collected: ir max. (KBr) 3300 to 2500 (broad), 1700, 1610, 1460, 1440, 1408, 1320, 1260, 1205, 1130, 930, and 775 cm⁻¹; nmr (CDCl₃) 9.0 to 8.0 (b, COOH), 5.51 (s, enol), 3.58 (s, keto), 2.7 to 2.1 (m), and 1.9 to 1.4 (m), ppm; uv max. (C₂H₅OH) 276 μ (ε, 18,000).

**Anal.** Calculated for C₁₃H₁₀O₈: C, 57.34; H, 7.40.
Found: C, 57.15; H, 7.40.

**Copper salt of 6,8-Dioxotridecanedioic Acid (XVIIb)**

6,8-Dioxotridecanedioic acid (100 mg) was added to 10 ml of a 5% solution of copper acetate. A blue precipitate was filtered, washed with ethanol and dried in the oven for 2 hours at 90° C. The compound melted at 250° with decomposition and was not soluble in the common organic solvents: ir max. (KBr) 1610 (shoulder), 1560, 1515, and 1410 cm⁻¹.

**Anal.** Calculated for Cu₃C₂₈H₃₄O₁₂·2H₂O: C, 40.81; H, 5.05; Cu, 24.91.
Found: C, 40.74; H, 5.36; Cu, 25.

**Attempted Ring Closure of the Copper Chelate of Dimethyl 6,8-tridecanedioate via the Acyloan Condensation**

The general procedure for the acyloan condensation as outlined by McElvain was followed in this reaction. Dry xylene (350 ml) was added to a 3 necked 1 liter flask which was fitted with a high speed stirrer and a reflux condenser. After 50 ml of xylene had been distilled through the condenser, the coolant was started flowing and the reaction vessel was placed under a N₂ atmosphere. The xylene was cooled
to room temperature and 0.304 g (13.2 mmol) of Na was added to the flask. Refluxing was continued and the Na was finely dispersed by rapid stirring.

A 250 ml pressure compensating funnel containing 1 g (1.5 mmol) of copper chelate in 200 ml of xylene was connected between the condenser and the N₂ line. The chelate solution was added dropwise to the stirred solution over a period of 5 hours. After reacting for an additional 2 hours, the mixture was cooled to room temperature and 50 ml of anhydrous methanol was added to destroy any excess Na. Water (500 ml) was added, and the mixture was filtered. A green oily solid (0.4 g) was collected that gave a broad IR absorption at 1740 cm⁻¹. The material appeared insoluble in the common organic solvents.

The xylene-water filtrate was separated, and the aqueous layer was extracted 4 times with 100 ml portions of CH₂Cl₂. The combined extracts were washed with 100 ml of saturated NaCl, dried and concentrated. The green oily residue (0.2 g) was placed on a thick layer chromatographic plate (silica gel) and was eluted with a 50% ethyl acetate-cyclohexane mixture. The chromatographic plate showed a continuous streaking at the bottom and a definite blue zone at Rf of 0.5. The blue zone was extracted with CH₂Cl₂ and 30 mg of blue solid was isolated. This material gave an IR spectrum identical to the starting copper chelate.

The lower portion of the plate was extracted with CH₂Cl₂ and finally with MeOH. The material was very difficult to remove from the silica gel and after continuous extraction overnight only 100 mg of oily material was collected. The IR spectrum presented a broad absorption
at 1740 cm⁻¹. The material was dissolved in 1 N HCl and extracted with CH₂Cl₂. The green color disappeared and the aqueous layer was made basic with NH₄OH. The characteristic blue color of the copper amine complex was observed. The nmr spectrum of the oil left in the organic layer gave absorption at 5.5 (s, enol) and 3.67 (CH₃O-CO) ppm. Attempts to resolve the apparent mixture by tlc failed.

The original aqueous layer was acidified with HCl and was extracted several times with CH₂Cl₂. The combined organic extracts produced approximately 0.4 g of yellow waxy material. The material was only partially soluble in CDCl₃, and the nmr spectrum gave absorptions at 5.5 (s, enol), and 3.67 (s, CH₃O-CO) ppm. Attempts to isolate any components by tlc failed.

**Attempted Ring Closure of the Copper Chelate of Dimethyl-6,8-tridecanedioate via the Dieckman Condensation**

The procedures set forth by Leonard and Schmelpfenig were followed in this reaction. A 1 liter, 3 neck flask was fitted with a high speed stirrer and a reflux condenser. Dry toluene (250 ml) was added to the flask, and 50 ml was distilled through the condenser. The coolant was allowed to flow through the condenser and a N₂ line was connected. Refluxing was discontinued, and 1.1 g (9.3 mmole) of potassium tert-butoxide was added to the flask.

A 250 ml pressure compensating addition funnel, which contained 0.6 g (0.96 mmole) of Cu chelate in 100 ml of dry toluene, was connected between the condenser and the N₂ line. The copper chelate solution was added dropwise over a period of 5 hours to the well-stirred refluxing mixture. During the addition, the reaction medium turned
orange. After reacting for an additional 8 hours, the mixture was allowed to cool and 0.5 ml of acetic acid (calculated amount to neutralize base) and 50 ml of water were added. The mixture was filtered and 0.1 g of brown tarry residue was collected. The filtrate was extracted 3 times with 50 ml portions of H₂O. The toluene was dried and concentrated, and no organic material was left in the flask.

The aqueous layer was extracted with CH₂Cl₂, but such an emulsion formed that the mixture was placed in a continuous extractor and extracted with CH₂Cl₂ for 3 days. The CH₂Cl₂ was concentrated, and 0.2 g of oily residue was collected that appeared to be insoluble in the common organic solvents. A gummy residue appeared to form at the interface of the two solvents in the continuous extractor.

The ir spectrum of the oily residue showed a broad absorption at 1740 cm⁻¹. The material was so insoluble that an nmr spectrum was not feasible. Attempts to isolate any soluble components by tlc failed.
IV. RESULTS AND DISCUSSION

A. Attempted Ring Closure via Scheme A (Page 14)

Hauser\(^{37,38}\) has pointed out that the terminal methyl groups of 2,4-pentanedione and the bis-β-diketones can be alkylated in the presence of 2 and 4 molar equivalents, respectively, of NaNH\(_2\) in liquid ammonia. Scheme A was based on the assumption that the cyclic Be chelate of the bis-β-diketones would behave in a manner similar to that of unchelated ligand, and that the terminal methyl groups could be alkylated by a methylene halide. Since the β-diketone groups would be chelated, this would enhance the probability of effecting a ring closure.

The preparation of 1,3,13,15-hexadecanetetraone (V) was accomplished by reacting 2,4-pentanedione with a 0.5 molar equivalent of 1,6-dibromohexane in the presence of 2 molar equivalents of NaNH\(_2\) in liquid ammonia. The nmr spectrum of V had singlets at 5.4 (enol form), 3.45 (keto form) and 2.00 ppm (CH\(_2\)) along with multiplets from 2.4 to 2.0 ppm and 1.8 to 1.0 ppm. The melting point (77°-78°) was consistent with that reported in the literature (78°-79°).\(^{37}\) Compound V was reacted with Be (II) ion to form the polymeric Be chelate, which, upon sublimation at 200° and 1 mm, produced the cyclic Be chelate of 1,3,13,15-hexadecanetetraone (VI) that melted at 135° (Lit m.p. 138°).\(^{40}\) The nmr spectrum was similar to that of compound V: 5.50 ppm (s, enol) and 2.02 ppm (CH\(_3\)).

Attempts to prepare the macrocyclic tetraketone VII from the cyclic Be chelate (VI) by reacting with 1,6-dibromohexane in the presence of NaNH\(_2\) in liquid ammonia yielded only starting material. That the product was starting material was confirmed by nmr analysis (s, 2.02 ppm,
CH$_2$) and the fact that a mixed melting point of starting material and product gave no depression.

Since the preparation of the cyclic Be chelate (VI) was time consuming, a more direct approach was taken to establish the conditions necessary for the direct alkylation of a simpler Be chelate. Attempts were made to react Be acetylacetonate directly with 1,6-dibromohexane and NaNH$_2$ in liquid ammonia. The amount of base was varied from 2 to 6 molar equivalents and the reaction time was varied from 2 to 24 hours. For each case, Be acetylacetonate was isolated in essentially quantitative yield. However, when 1,3,13,15-hexadecanetetraone (V) was reacted under the same conditions, polymeric material was obtained. This indicated that the Be chelate was unreactive toward the NaNH$_2$, or if the anion were formed, it failed to react with the 1,6-dibromohexane. Inasmuch as Scheme B offered a greater number of possibilities, no attempt was made to establish whether the anion was actually formed. The conclusions are that the Be chelate was indeed stable under the reaction conditions, but was unreactive.

B. Synthesis of $\beta$-Diketo Diesters via Scheme B (Page 15)

Scheme B proposes a novel synthesis of $\beta$-diketo diesters from readily available starting materials. The idea was to chelate these $\beta$-diketo diesters and attempt a ring closure by the acyloin condensation or the Dieckmann condensation. Bis(2-oxocyclopentyl)methane (VIIa) and bis(2-oxocyclohexyl)methane (VIIb) were prepared by a base catalyzed condensation of the appropriate cyclanone with paraformaldehyde, as reported by Colonge, et al.$^{44}$ These workers reported yields of 30% and 60% respectively, but such yields were never realized in this work. Apparently, the reaction gives a variety of products, and the yields of
VIIIa and VIIIb varied from 1 to 15%. The crude separation of the desired compounds was achieved by distillation under reduced pressure and was accompanied by the codistillation of other products. Recrystallization was at times troublesome because of these excess components.

One major component that was co-distilled with VIIIa was identified as 2-cyclopentylidenecyclopentanone:

\[
\begin{array}{c}
0 \\
\text{C} \\
\text{H} \\
\text{O}
\end{array}
\]

The oily residue that remained after recrystallization of VIIIa was distilled under reduced pressure on a spinning band column, and the product was collected at 79-80°C at 1 mm. The nmr spectrum contained a multiplet from 3.0 to 1.5 ppm. The carbon hydrogen analysis for C_{10}H_{14}O was calculated to be 79.94 for carbon and 9.39 for hydrogen; it was found to be 79.61 for carbon and 9.42 for hydrogen. The oxime derivative of 2-cyclopentylidenecyclopentanone melted at 122-124°C (Lit m.p. 123-124°C).

It was interesting to note that VIIIa was isolated in two crystalline forms. Form A melted at 68-70°C (Lit m.p. 70°C) and Form B melted at 38°C (Lit m.p. 38°C). These compounds are presumed to be diasteromers, as shown in the following illustration.

\[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{H} \\
\text{O}
\end{array}
\]

The nmr spectra (No. 1) of these two compounds are slightly different, and perhaps a detailed nmr analysis would indicate the structure of Form A and Form B. VIIIb apparently exists in only one crystalline form, even though diasteromers should be possible.
The second step in the synthesis involved the oxidation of VIIIa and VIIIb to form bis(3-oxo-2-oxocyclohexyl)methane (IXa) and bis(3-oxo-2-oxacycloheptyl)methane (IXb). The Baeyer-Villiger reaction is the classical method of forming a lactone from a cyclic ketone and has been reviewed by Hassall.\(^47\) The method involves the reaction of a ketone with a peroxide. Although a variety of peroxides has been utilized, Hassall pointed out that organic peroxides have proved more useful and convenient than the inorganic peroxides. Perbenzoic acid was used in this synthesis because it was easily made from available materials in the laboratory.

The question as to where the O atom would insert in the ring was of utmost importance in this synthesis. In order to obtain the desired end product, the bond must break between the more substituted carbon and the carbonyl carbon, as shown in the following diagram.

![Diagram](image)

According to results reported in the literature,\(^51-54\) a generalization can be made that tertiary groups migrate more readily than secondary groups to oxygen in this reaction. Fortunately, this proved to be the case in this synthesis, and the desired lactone was obtained.

VIIIa and VIIIb each were reacted with 2 molar equivalents of perbenzoic acid in CH\(_2\)Cl\(_2\). Some difficulty was encountered in the separation of IXa from the benzoic acid that was formed. Attempts to extract...
the benzoic acid with a solution of NaHCO$_3$ resulted in the partial hydrolysis of IXa. Pure IXa could not be isolated by this method. [Note: It was observed that partial esterification of IXa could be achieved by simply adding methanol to the crude benzoic acid-IXa mixture and concentrating.] IXa was isolated in sufficient quantity for characterization by column chromatography, but this method was impractical for preparative purposes due to the large amount of benzoic acid that was present.

Bis(3-oxo-2-oxacyclohexyl)methane (IXa) has not been reported previously. The nmr spectrum (No. 2) contained a multiplet from 4.90 to 4.31 ppm and integration of the peak indicated 2 protons. The multiplet was assigned to the methine proton and is consistent with that reported in the literature for C-CH-O-CO-R (4.8 ppm). The ir spectrum showed a carbonyl absorption at 1735 cm$^{-1}$. Nakanishi reported that the 6-membered ring lactone absorbed at 1735 cm$^{-1}$. The mass spectrum had a parent peak at 212 (mol. wt. 212.25). The carbon-hydrogen analysis was in accord with the above results. Also, the characterization of this compound was further substantiated by the products obtained in the following reactions.

Bis(3-oxo-2-oxacycloheptyl)methane (IXb) was not isolated, but the nmr analysis (No. 3) of the crude mixture was similar to that of IXa. The broad multiplet from 4.0 to 5.0 ppm was assigned to the methine protons.

Dimethyl 5,7-dihydroxyundecanedioate (Xa) and dimethyl 6,8-dihydroxytridecanedioate (Xb) were prepared by refluxing the crude mixture of benzoic acid and IXa and IXb, respectively, with CH$_3$OH and HCl. Attempts to separate the methyl benzoate from Xa by distillation under
reduced pressure failed, because Xa gave off CH₃OH and reverted back to the lactone structure. After the mixture was allowed to remain under reduced pressure overnight, Xa and Xb crystallized. Recrystallization from an ether-petroleum ether mixture gave 43% and 63% yields, respectively.

The new compounds Xa and Xb were characterized by their nmr spectra (Nos. 4 and 5), each of which contained a singlet at 3.67 ppm (CH₃O-CO), a multiplet from 4.1 to 3.8 ppm (CH-OH), and a broad absorption from 3.1 to 2.8 ppm (OH) that disappeared upon the addition of D₂O. The ir spectra (Nos. 2 and 3) each showed an OH stretch at 3300 cm⁻¹ and an ester carbonyl absorption at 1740 cm⁻¹. The carbon-hydrogen analysis substantiated that the compounds were the β-diol diesters.

The next step in the synthesis involved the oxidation of the β-diol diesters to the β-diketo diesters. Kaye and Mathews⁴⁷ previously reported the oxidation of β-diols by the Jones reagent to the β-diketones in 31-58% yields. Xa and Xb in acetone were oxidized on the addition of chromic acid and were isolated as the copper chelates. The copper chelate of dimethyl 5,7-dioxoundecanedioate (XIIa) was isolated in 20% yield, and the copper chelate of dimethyl 6,8-dioxotridecanedioate (XIIb) was isolated in 30% yield.

The ir spectrum of copper acetylacetonate has been studied by Nakamoto⁵⁷ and he assigned the observed bands by means of a normal coordinate analysis. Table III shows a comparison of the ir bands of copper acetylacetonate and XIIa and XIIb (see ir spectra Nos. 4 and 5). The characteristic bands that were assigned to the chelated ring system of copper acetylacetonate also occur in XIIa and XIIb. In addition, the

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<table>
<thead>
<tr>
<th>Assignment</th>
<th>Copper Acetyl-Acetonate</th>
<th>XIIa</th>
<th>XIIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nu(C\equiv C)$</td>
<td>1580</td>
<td>1575</td>
<td>1570</td>
</tr>
<tr>
<td>$\nu(C\equiv O)$</td>
<td>1554</td>
<td>1520</td>
<td>1520</td>
</tr>
<tr>
<td>$\nu(O\equiv O)$ Ester</td>
<td>---</td>
<td>1735</td>
<td>1735</td>
</tr>
<tr>
<td>$\nu(C\equiv O) + \delta(C-H)$</td>
<td>1465</td>
<td>1455</td>
<td>1450</td>
</tr>
</tbody>
</table>
ester carbonyl absorption occurs at 1735 cm\(^{-1}\). The uv spectra for the copper chelates also are compared with that of copper acetylacetonate, as shown in Table IV. The carbon-hydrogen analysis adds further evidence for the structure of XIIa and XIIb.

Attempts to sublime the copper chelates under reduced pressure resulted in the decomposition of the compound at 200° and 1 mm. This is not surprising, in view of the high molecular weight and the polar ester groups that exist in the molecule.

Dimethyl 5,7-dioxoundecanedioate (XIa) and dimethyl 6,8-dioxotridecanedioate (XIIb) were isolated by destroying the copper complexes XIIa and XIIb, respectively, with 1 N HCl and extracting with CH\(_2\)Cl\(_2\). The nmr spectra (No. 6) of XIa had singlets at 5.55 ppm (enol form), 3.63 ppm (keto form), and 3.67 ppm (CH\(_3\)-CO). The nmr spectra (No. 7) of XIIb had singlets at 5.41 ppm (enol form), 3.46 ppm (keto form), and 3.67 ppm (CH\(_3\)-CO). The ir spectra (Nos. 6 and 7) gave the characteristic 1735 cm\(^{-1}\) ester carbonyl absorption and the characteristic absorption of the \(\beta\)-diketones (1610 cm\(^{-1}\)).

Although XIa and XIIb have not been reported previously, Gelen, et al., have prepared the diethyl esters. This article was found after the above synthesis had been accomplished. A \(\beta\)-oxo diester was reacted with the appropriate acid chloride to produce the \(\beta\)-diketone diesters, as shown in the following equations:
<table>
<thead>
<tr>
<th>Complex</th>
<th>u.v. Max.</th>
<th>E Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper Acetylacetone</td>
<td>298</td>
<td>18,000</td>
</tr>
<tr>
<td>XIIa</td>
<td>296</td>
<td>22,000</td>
</tr>
<tr>
<td>XIIb</td>
<td>296</td>
<td>25,000</td>
</tr>
</tbody>
</table>
They reported an overall yield of 30-40%. The synthetic scheme proposed in the present work has the advantage that the starting materials, which are the cyclanones, are readily available and relatively inexpensive, but the yields for the oxidation of the β-diols were disappointing. It is felt, however, that these yields can be improved.

Dimethyl 6,8-dioxotridecanedioate (XIIb) was further characterized by hydrolysis to the diacid derivative, 6,8-dioxotridecanedioic acid (XVIb):

\[
\left[\text{CH}_3\text{O}-\text{C}-(\text{CH}_2)_4\text{C}\right]_2\text{CH}_2 + \text{H}_2\text{O} \xrightarrow{\text{H}^+} \left[\text{HO}-\text{C}-(\text{CH}_2)_4\text{C}\right]_2\text{CH}_2
\]

(XIIb) (XVIb)

The nmr spectrum of XVIb showed absorptions from 9.0 to 8.0 (b, COOH), 5.52 (s, enol form), 3.58 (s, keto form), from 2.8 to 2.1 (m) and from 1.9 to 1.4 (m) ppm. The ir spectrum gave a broad absorption around 3000 cm\(^{-1}\) (COOH), a carbonyl absorption at 1700 cm\(^{-1}\) and 1610 cm\(^{-1}\) (enol form). The carbon-hydrogen analysis supported the above data.

6,8-Dioxotridecanedioic acid (XVIb) was added to a solution of copper acetate and a blue solid was formed. The possible structures...
of the blue compound are intriguing and are projected in Figure 4. The ir spectrum had absorption at 1610 (shoulder), which is assigned to the CO antisymmetric stretch of the carboxylate anion, absorptions at 1570 and 1520 cm\(^{-1}\) (chelated diketone) and a strong absorption at 1400 (symmetric stretch of carboxylate anion). The compound decomposed at 250\(^\circ\) with no evidence of subliming. The elemental analysis indicated two waters of hydration.

The chelating abilities of XIA, XIB, and XVIIB with a number of metal ions were determined, and the results are summarized in Table V. The general procedure for forming the chelates was as follows: five drops of 1% \(\beta\)-diketone in ethanol were added to 5 drops of 10% metal salt solution, which was buffered with 3 to 5 drops of 10% NaC\(_2\)H\(_3\)O\(_2\) solution. The solution was allowed to stand for two hours. For those mixtures in which no reaction was observed, the solution was extracted with 10 drops of CH\(_2\)Cl\(_2\) and the organic layer was evaporated. Be(II), Cu(II), and Pd(II) immediately formed precipitates with these ligands. Fe(III) formed the characteristic red color of the enolic complexes, and UO(II) formed a yellow precipitate with XVIIIB. The Co(II) and Ni(II) chelates of XIA and XIB were detected only after extracting the aqueous solution with CH\(_2\)Cl\(_2\). Under the same conditions, 2,4-pentanedione formed precipitates with all these metal ions. This study indicates that ligands XIA, XIB, and XVIIB are more selective than 2,4-pentanedione.

C. Attempted Ring Closure via Scheme B

The acyloin condensation, which has been the most successful method for the preparation of macrocyclic compounds, has been reviewed by Ivan, and more recently by Finley. The method involves the
FIGURE 4

POSSIBLE STRUCTURES OF COPPER SALT OF 6,8-DIOXOTRIDECA-NEDIOIC ACID (XVIIb)
<table>
<thead>
<tr>
<th>Metal Ion</th>
<th>Dimethyl 5,7-dioxo-undecanedioate</th>
<th>Dimethyl 6,8-dioxo-tridecanedioate</th>
<th>6,8-Dioxotridecanedioic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Be(II)</td>
<td>white ppt</td>
<td>white ppt</td>
<td>white ppt</td>
</tr>
<tr>
<td>Ca(II)</td>
<td>NR†</td>
<td>NR†</td>
<td>NR†</td>
</tr>
<tr>
<td>Cd(II)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Co(II)</td>
<td>pink ppt‡</td>
<td>pink ppt‡</td>
<td>NR</td>
</tr>
<tr>
<td>Cr(III)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cu(II)</td>
<td>blue ppt</td>
<td>blue ppt</td>
<td>blue ppt</td>
</tr>
<tr>
<td>Fe(III)</td>
<td>red color</td>
<td>red color</td>
<td>red color</td>
</tr>
<tr>
<td>La(II)</td>
<td>NR</td>
<td>NR</td>
<td>white ppt</td>
</tr>
<tr>
<td>Mg(II)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mn(II)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ni(II)</td>
<td>green ppt‡</td>
<td>green ppt‡</td>
<td>NR</td>
</tr>
<tr>
<td>Pd(II)</td>
<td>yellow ppt</td>
<td>yellow ppt</td>
<td>yellow ppt</td>
</tr>
<tr>
<td>Pt(II)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>UO(II)</td>
<td>NR</td>
<td>NR</td>
<td>yellow ppt</td>
</tr>
<tr>
<td>Zn(II)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

† No observed reaction.
‡ Colored product observed only after extracting with CH₂Cl₂ and evaporating.
formation of an acyloin by reacting a long chain diester with finely dispersed Na metal in a solvent such as xylene. Although the mechanism is not well understood, the original one proposed by Prelog is currently accepted. This mechanism is projected in Figure 5 in which the chelated β-diketo diester is used as a model. If the projected mechanism is correct, and if the chelate remains stable, then the proposed reaction should occur. However, it should be mentioned that the ester groups on the same ligand are able to react with each other. This would form a cyclic compound, but with only one diketone group. Models indicated that this configuration would be more strained than the one projected in Figure 5.

The copper chelate of dimethyl 6,8-dioxotridecanedioate (XIIb) was added dropwise to a slurry of Na metal in boiling xylene. (The details are given in the Experimental Section on page 29.) After the addition of methanol and water to the reaction mixture, the total mixture was filtered, and 0.4 g of a green oily solid was collected. This material was insoluble in the common organic solvents and was assumed to be high molecular weight polymeric material.

The xylene-aqueous solution was separated and the aqueous layer was extracted several times with CH₂Cl₂. After the combined organic layers were concentrated, 0.2 g of green oily residue was collected. The residue was chromatographed on a thick layer plate (silica gel) and 30 mg of XIIb was isolated. Only 100 mg of oily residue could be extracted from the thick layer plate. The difficulty in extracting the residue indicated that it was polymeric. However, this material readily dissolved in 1 N HCl and the acid was extracted with CH₂Cl₂. The acid layer was made basic with NH₄OH, and the characteristic blue color of
1. The electrophilic carbon atoms of the diesters are attracted to the Na surface.
2. The lowest energy translational motion available is sliding on the metal surface.
3. The collisions of other molecules finally bring the terminal groups close enough for ring closure.
4. After ring closure, the electrophilic character is no longer sufficient to hold the cyclic system to the metallic surface.
the copper amine complex was observed. The organic layer was con­
centrated and subjected to nmr analysis. Absorptions were noted at 5.5 ppm
(enol) and 3.69 (CH$_3$OC). Attempts to resolve the apparent mixture by
tlc were not successful.

In summary, it was observed that: starting material (XIIb)
was recoverable after reaction; Cu(II) was present in the apparent poly­
meric material, and; an nmr analysis of the polymeric material after
removal of the Cu(II) ion verified the existence of the β-diketone
moity. Thus, it was evident that the Cu chelate was stable under the
reaction conditions.

Bloomfield$^{61}$ recently reported that the addition of trimethyl­
chlorosilane to the acyloin reaction resulted in an increase in yield.
The explanation was that the methoxide ion formed in the reaction re­
duces the yield by favoring the competing Dieckmann condensation, but
the trimethylchlorosilane acts as a base scavenger and isolates the
methoxide ion as it is formed. Unfortunately, when the acyloin reaction
was attempted with trimethylchlorosilane, the trimethylchlorosilane
formed a green insoluble complex with the copper chelate which solidi­
fied in the condenser. This compound was not characterized, but the
original diketone diester was isolated and recovered after destroying
the complex with acid.

It should be pointed out that the reaction conditions are
extremely critical for the acyloin condensation. A high speed stirrer
is required and unless the Na metal is very finely dispersed, the
reaction predominantly produces polymers. The reaction must be kept
under nitrogen as long as it remains basic, and all oxygen and water
must be excluded. Although every precaution was taken to meet these
requirements, the attempted ring closure via the acyloin condensation failed to produce the desired compound. However, the Cu chelate appeared to be stable under these conditions. Thus, either the desired reaction conditions were not achieved, or the possibility of polymer formation in this reaction far outweighed the formation of the desired macrocyclic compounds.

The Dieckmann condensation, reviewed by Schaefer and Bloomfield, has not been widely used for the preparation of large ring compounds, although Leonard and Schimelpfenig have used this method to produce macrocyclic compounds in fair yields. The ring closure was effected by reacting a long chain diester in high dilution with potassium tert-butoxide in refluxing xylene. It was reasoned that the chance for ring closure by a Dieckmann condensation might be increased if the chelated diesters were used rather than the unchelated esters, because the ester groups would be held relatively closer to each other in the chelate.

The copper chelate of dimethyl 6,8-dioxotridecanedioate (XIIb) was reacted with potassium tert-butoxide in refluxing toluene. (The experimental details are given on page 31.) After the base was neutralized with acetic acid and water, the total mixture was filtered and 0.1 g of tarry residue was collected. This residue was insoluble in the common organic solvents and apparently was polymeric material.

The toluene-aqueous layer was separated and the aqueous layer was extracted several times with CH₂Cl₂. The combined organic extracts were concentrated, and no detectable amount of organic material was left in the flask. The aqueous layer was extracted for 3 days with CH₂Cl₂.
and only 0.2 g of gummy residue was collected. The material appeared very insoluble in all the common organic solvents.

The material isolated from this reaction did not dissolve in acid, and attempts to identify Cu(II) ion in the residues were unsuccessful. The conclusion was that the Cu chelate was unstable in this basic medium and only polymeric material, which could not be characterized, was isolated. Obviously, the success of this reaction is dependent upon the stability of the chelate.

Although the ring closure was unsuccessful for the Dieckmann and acyloin condensation, the template idea is still intriguing and offers many possibilities. For example, if the ester groups were replaced with other functional groups, such as OH, halides, and CN, other types of ring closures could be attempted. An attempt was made to reduce the diesters in the copper chelate of dimethyl 6,8-dioxotridecanedioate to the diols with LiAlH$_4$ in anhydrous ether. However, the chelate was destroyed, and the diketone groups were apparently reduced to the diols. The fact that the diketone groups were destroyed was verified by nmr analysis which showed the absence of the absorption of the methoxycarbonyl protons (3.67 ppm) and the absence of the diketone protons (5.5 ppm). Absorptions at 3.7 to 2.9 (OH) ppm were observed. Because the chelate was destroyed, the compound was not further characterized. As Collman$^{35}$ has pointed out, the sensitivity to reduction of a chelated β-diketone is a serious limitation which must be kept in mind in planning synthetic schemes.
V. SUMMARY AND SUGGESTIONS FOR FUTURE WORK

A novel synthesis for the preparation of \( \beta \)-diketo diesters has been achieved. As a result of this work, several new compounds have been characterized. These are: \( \text{bis}(3\text{-oxo-2-oxacyclohexyl}) \) methane, \( \text{bis}(3\text{-oxo-2-oxacycloheptyl}) \) methane, dimethyl 5,7-dihydroxyundecanedioate, dimethyl 6,8-dihydroxytridecanedioate, dimethyl 5,7-dioxoundecanedioate and its copper chelate, dimethyl 6,8-dioxotridecanedioate and its copper chelate, and 6,8-dioxotridecanedioic acid.

Several methods for the synthesis of macrocyclic \( \beta \)-diketones have been investigated. These methods utilized the template effect in which the ring is built around various metal chelates of the \( \beta \)-diketones. First, the ring closure was attempted by reacting a cyclic Be bis-\( \beta \)-diketonate with a methylene halide in the presence of sodamide in liquid ammonia. The chelate was found to be stable but unreactive. If a reaction could be found in which the methyl groups of these chelates could be alkylated, then this method might be suitable for the preparation of macrocyclic \( \beta \)-diketones.

Second, the ring closure was attempted by reacting the copper chelate of a \( \beta \)-diketone diester in the presence of Na in xylene. Again the chelate appeared to be stable, but only polymeric material was formed. Third, the Dieckmann condensation was attempted on the copper chelate of the \( \beta \)-diketone diester. In this case, the copper chelate appeared to be unstable and only polymeric material was isolated.

Even though the macrocyclic compounds were not produced by these reactions, the fact that the chelates were apparently stable in
two cases previously mentioned substantiates the tremendous synthetic possibilities offered by the β-diketonates. A systematic study of the stability and reactions of these chelates under various conditions could lead to a very interesting and rewarding area of research. For example, methods of alkylating the methyl groups of acetylacetonates should be investigated. In addition, it should be possible to replace the ester functional groups of the β-diketo diesters with functional groups such as OH, Br, CN, NH₂. Other types of ring closures could then be attempted on these chelated compounds.

The β-diketones prepared in this work, and related ones which could be synthesized, might offer some potentially useful ligands. The analytical application of these ligands and their chelates in the area of extraction, gravimetry, surfactants, and others should be explored.
REFERENCES


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APPENDIX I: NMR SPECTRA
SPECTRUM NO. 1

Bis(2-oxocyclopentyl)methane

Form A: 70°C m.p.

Form B: 38°C m.p.

100 MHz NMR

Solvent: Benzene

Sweep Width: 250 cps
SPECTRUM NO. 2

Bis(3-oxo-2-oxacyclohexyl)methane

Sweep Width: 500 cps

Solvent: CDCl₃
SPECTRUM NO. 3

Bis(3-oxo-2-oxacycloheptyl)methane

Sweep Width: 500 cps
Solvent: CDCl₃
SPECTRUM NO. 4

Dimethyl 5,7-dihydroxyundecanedioate

Sweep Width: 500 cps

Solvent: CDCl₃
SPECTRUM NO. 5

Dimethyl 6,8-dihydroxytridecanedioate

Sweep Width: 500 cps
Solvent: CDCl₃
SPECTRUM NO. 6

Dimethyl 5,7-dioxoundecanedioate

Sweep Width:  500 cps
Solvent:  CDCl$_3$
SPECTRUM NO. 7

Dimethyl 6,8-dioxotridecanedioate

Sweep Width: 500 cps

Solvent: CCl₄
SPECTRUM NO. 8

6,8-Dioxotridecanedioic Acid

Sweep Width: 500 cps

Solvent: CDCl₃
APPENDIX II: IR SPECTRA
SPECTRUM NO. 1

Bis(3-oxo-2-oxacyclohexyl)methane (KBr)
SPECTRUM NO. 3

Dimethyl 6,8-dihydroxytridecanedioate (KBr)
SPECTRUM NO. 4

Copper Chelate of Dimethyl 5,7-dioxoundecanedioate (KBr)
SPECTRUM NO. 5

Copper Chelate of Dimethyl 6,8-dioxotridecanedioate (KBr)
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SPECTRUM NO. 7

Dimethyl 6,8-dioxoundecanedioate (Neat)
6,8-Dioxotridecanedioic Acid (KBr)

SPECTRUM NO. 8
\((\text{HOOC-}(\text{CH}_2)_4\text{C-})\text{CH}_2\)
VITA

Carlton Jay Adams was born in Pitt County, North Carolina, on July 16, 1937. After graduating from high school, he attended East Carolina University and was awarded the A.B. Degree in Chemistry in May, 1959. He received a teaching assistantship in chemistry at Florida State University, and completed the requirements for the M.S. Degree in Analytical Chemistry in August, 1962. He accepted a position as Instructor of Chemistry at Oxford College of Emory University, where he presently is teaching.

In June, 1964, he was appointed to the Summer Institute for College Chemistry Teachers at Louisiana State University and was reappointed for two consecutive summers. He was appointed to the College Teachers Research Participation Program in 1967, and was awarded a National Science Foundation Academic Year Extension Grant to continue research at Oxford College.

The following summer, he was awarded the National Science Foundation Science Faculty Fellowship for research and study at Louisiana State University under the direction of Dr. E. W. Berg. He is presently working toward the Doctor of Philosophy Degree in Analytical Chemistry.

Mr. Adams is married to the former Nancy Taylor Fleming of Richmond, Virginia, and they have two children.
Candidate: Carlton Jay Adams

Major Field: Chemistry

Title of Thesis: An Approach to the Synthesis of Macrocyclic β-Diketones

Approved:

Eugene W. Berg
Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

James H. Freyman

Robert V. Nauman

Philip W. West

Joel Selbin

Date of Examination:

December 7, 1970