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Synthesis of Hydroxy Tetronic Acid

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SYNTHESIS
OF
HYDROXY TETRONIC ACID

by
Phyllis Elaine Hoar

Submitted in partial fulfillment of the requirements for the Senior Scholars Program

Colby College
1967
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Tetronic acids are "five-membered cyclic systems, containing a lactone grouping and a carbonyl group in the position beta to the lactone" \( (1) \) p.1, the parent compound being:

\[
\begin{align*}
\text{keto form} & \quad \text{enol form} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{C}=\text{O} & \quad \text{C}=\text{O} \\
\text{O} & \quad \text{OH}
\end{align*}
\]

Substitution may occur on either the \( \alpha \) or the \( \gamma \) carbon, or both, thus permitting many possible tetronic acids. With Wolff's work in 1895 \( (2) \) on the hydrolysis and oxidation of tetronic acids, the structure of the tetronic acid system was finally established, after previous attempts by Michael \( (3) \), Net \( (4) \), and Pawlow \( (5) \).

Wedel \( (6) \) in 1883 was probably the first to synthesize the parent compound when he obtained an unknown acid and ethyl bromide upon the heating of the bromination product of acetoacetic ester in a sealed tube. Wolff \( (2) \) found that he was unable to cause the monobromo acetoacetic ester:
to undergo cyclization, while the desired cyclization could be obtained with the dibromo ester as follows:

\[
\begin{align*}
\text{CH}_2\text{C-CH}_2\text{COOC}_2\text{H}_5 \xrightarrow{\text{Br}_2} \text{CH}_2\text{C-CH-COOOC}_2\text{H}_5 \\
\end{align*}
\]

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

\[
\begin{align*}
\text{H} & \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{H} \\
\text{Br} & \quad \text{Br} & \quad \text{Br} & \quad \text{C}_2\text{H}_5 \\
\end{align*}
\]

\[
\begin{align*}
\text{120}^\circ-\text{130}^\circ \quad \text{reduced} \quad \text{pressure} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2 & \quad \text{C} \quad \text{C} \\
\text{H} \quad \text{Br} & \quad \text{Br} \\
\end{align*}
\]

\[
\begin{align*}
\text{Na amalgam} \quad \text{soda} \quad \text{CO}_2 \\
\end{align*}
\]

On the bromination of the acetoacetate ester, the bromine atom enters in the α-position and then rearranges to the γ-position in the presence of HBr and oxygen or peroxide(7). Although it is this bromine in the γ-position which is eliminated in the ethyl bromide during ring closure, there must be either another bromine atom or an ethyl or methyl group substituted on the α-carbon for the cyclization to occur. The α-substitution is favorable to the closure of the tetronic ring due to the steric effect caused by the substituted group. Evidently, without this steric effect, the ethyl group and γ-bromine do not come within bond-
Since Wolff's investigations, several other methods of synthesizing tetronic acids have been developed. In the early 1930's Micheel and Jung (8) were able to synthesize \( \alpha \)-hydroxy tetronic acid from the Claisen condensation product of ethyl benzoyl glycolate:

\[
\text{\( \phi = \text{C}_6\text{H}_5 \)}
\]

As was previously mentioned, Wolff (2) was able to establish the structure of tetronic acid through his hydrolysis and oxidation experiments:
Wolff found the mechanism of this oxidation interesting, but difficult to explain satisfactorily. Somehow, the H on the \( \alpha \) carbon must be oxidized to \( \overset{\text{\( \rightarrow \)}}{\text{\( >C=O \)}} \) and the CH\(_2\)-O-group reduced to CH\(_3\) to obtain the diacetyl product. Wolff was able to propose a mechanism for the oxidation through his experiments on bromo tetronic acid. He observed that treatment of \( \alpha \)-bromo-\( \alpha \)-methyl tetronic acid with base produced a new compound, probably \( \alpha \)-hydroxy-\( \alpha \)-methyl tetronic acid (not isolated) which yielded carbon dioxide and diacetyl upon acidification. Wolff also noticed that some HBr was given off from a water solution of the bromo derivative on standing. Wolff's explanation can be summarized as follows:
Wolff's explanation was a good proposal, but lacked sufficient proof as he did not deal with higher substituted acids. No further work was done to test his mechanism until the late 1940's with Helen Patterson. Upon oxidation of \( \alpha, \gamma \)-dimethyl tetronic acid she found that the expected diketone, 2,3-pentanedione, and \( \text{CO}_2 \) were produced. However, contrary to Wolff's theory of oxidation at the \( \alpha \) carbon and reduction at the \( \gamma \) carbon, the same products would result from reduction at the \( \alpha \) carbon and oxidation at the \( \gamma \) carbon. Therefore she oxidized \( \alpha \)-ethyl tetronic acid, and found upon identification, the products expected according to Wolff's theory: 2,3-pentanedione and \( \text{CO}_2 \).

Patterson's work supported Wolff's theory about the mechanism of oxidation. However, she realized that before any final mechanism could be proposed, further research was necessary. Fortenbough continued the investigation by attacking these fundamental problems: "(1) to show that in the oxidation of these tetronic acids there are two simultaneous and independent mechanisms, (2) to discover if the oxidation of the \( \alpha \) carbon and reduction of the \( \gamma \) carbon is a general reaction when these tetronic acids are oxidized with chromium trioxide and sulfuric acid, and (3) to investigate the mechanism of the reaction whereby carbon dioxide is eliminated." (1) pp. 8-9 From his investigations of differently substituted tetronic acids he was able to show that more than one theory is needed to explain the results.
The first\(^ {17}\) of several papers on the oxidation of tetronic acids, published by Reid, Fortenbaugh, and Patterson, deals mainly with the tetronic structure necessary for the formation of \(\alpha\)-diketones. There are three structural classes into which tetronic acids may be divided. One class consists of those with substitution on the \(\gamma\) carbon only; a second type consists of those with only \(\alpha\) carbon substitution; while in the third type there is substitution on both \(\alpha\) and \(\gamma\) carbons. Upon examination of the oxidation products of these three classes, it becomes apparent that the formation of \(\alpha\)-diketones is not a general reaction. First of all, there must be an enolizable hydrogen present for the formation of \(\alpha\)-diketones. On oxidation of \(\alpha\)-monosubstituted acids, \(\alpha\)-diketones will be formed regardless of the \(\gamma\) carbon substitution, with oxidation occurring at the \(\alpha\) carbon and reduction at the \(\gamma\) carbon. With monosubstitution on the \(\gamma\) carbon (and no \(\alpha\) substitution) oxidation occurs at the \(\gamma\) carbon and reduction at the \(\alpha\) carbon producing \(\alpha\)-diketones. As there is no enolizable hydrogen in the \(\alpha\)-disubstituted acid, the \(\alpha\)-diketone is not formed. In the case of \(\gamma\) disubstitution, a deep degradation occurs with no formation of \(\alpha\)-diketones.

They have established that hydrolysis occurs simultaneously with oxidation of tetronic acids. The \(\alpha\)-diketones are not formed from oxidation of hydrolysis products; for example:
The \( \alpha \)-diketone was isolated from the original hydrolysis mixture, but evidently it was not formed from the oxidation of the hydrolysis product, the ketol. Therefore, oxidation must occur before hydrolysis of the tetronic ring, and the hydrolysis product is not an intermediate in the oxidation reaction. Wolff's proposal of an \( \alpha \)-hydroxy tetronic acid as an intermediate still seems valid.

A second publication, by Reid and Fortenbough(18), deals with the problem of the mechanism of carbon dioxide elimination from the \( \alpha \)-hydroxy tetronic acid intermediate in the formation of the \( \alpha \)-diketone. They propose three possible mechanisms: 1) an intermediate diradical:

![Diagram of diradical mechanism]

which, upon hydrogen exchange with water molecules, forms the \( \alpha \)-diketone; 2) an ionic intermediate which upon decarboxylation forms the carbonium ion:
and 3) the hydrolysis of the lactone ring giving:

before decarboxylation.

By oxidation of tetronic acids containing neopentyl systems, they have been able to eliminate the carbonium ion possibility. If the carbonium ion existed, neopentyl rearrangements would have been found to occur during the oxidations of these acids. As no rearrangement was found to occur, the mechanism of the carbon dioxide elimination must be one of the other two possibilities, although not enough evidence was yet available to decide which of the two was correct.

The third of these mechanisms is favored in a third paper on the oxidation of tetronic acids\(^{(19)}\). Assuming that the \(\alpha\)-hydroxy tetronic acid can undergo normal acid catalyzed hydrolysis, the authors propose the following scheme for the oxidation:
As there was no clear-cut evidence for the dehydration of the ketodiol, experiments were carried out to test this step. The corresponding dibromoketones were used, due to the lack of methods for synthesizing the ketodiols. The α-diketones formed from the hydrolysis of the dibromoketones showed very close correspondence to those formed from the corresponding tetronic acids, but the suggested ketodiols were not isolated from the reaction mixtures. Before the ketodiol mechanism is accepted, however, further work is necessary.
PRESENT INVESTIGATION

As a result of all the research which has been done, much has been learned about the mechanism of oxidation of tetronic acids. The evidence strongly points to the existence of the intermediate

\[
\begin{array}{c}
\text{R} \\
\text{R'} \\
\text{R''}
\end{array}
\]

where \( R'' \) is not hydrogen.

in the oxidation of tetronic acids to \( \alpha \)-diketones. This intermediate, however, has never been conclusively isolated and proven to exist, although Densend\(^{(20)} \) isolated a yellow caramel smelling oil which he concludes is probably \( \alpha \)-hydroxy \( \alpha \)-ethyl tetronic acid from his experimental evidence. If this compound were definitely isolated and then made to undergo acid-catalyzed hydrolysis, the products obtained would either support the large mass of circumstantial evidence or refute it. Carbon dioxide and the appropriate \( \alpha \)-diketone as the hydrolysis products would indicate that this hydroxy compound is indeed the postulated oxidative intermediate. Hydrolysis of \( \alpha \)-hydroxy tetronic acid synthesized by Micheel and Jung\(^{(21)} \) would not help in this investigation, as, in addition to the hydroxy group, there must be another \( \alpha \)-substituted group for the formation of
\( \alpha \)-diketones as proposed by Reid and his associates.

Three proposed methods of synthesizing the postulated oxidative intermediate, where \( R'' = C_2H_5 \), and \( R! = R = H \), followed by determination of hydrolysis products, will now be discussed. According to the first scheme of synthesis, represented on page 12, the first step, \( I \rightarrow II \), involves the alkylation of ethyl acetocetate with ethyl iodide. Marvel and Hager\(^{(22)}\) give a detailed procedure for a similar reaction using ethyl acetoacetate and n-butyl bromide, which gives a yield of 69-72%. Patterson\(^{(16)}\) obtained a yield of 55.3\% using an adaptation of this procedure, combining acetoacetic ester and ethyl iodide. The mechanism of the alkylation may be represented as follows:

\[
\begin{align*}
CH_3&-CCH_2-COEt & CH_3&-C=CH-OEt \\
& & \xrightarrow{\text{EtI}} & \xrightarrow{\text{NaI}} \\
[CH_3&-CCH_2-COEt & CH_3&-C=CH-OEt] & \xrightarrow{\text{EtOH}} & \xrightarrow{\text{NaOEt}} \\
& \xrightarrow{\text{NaI}} & \xrightarrow{\text{EtI}} & \xrightarrow{\text{NaI}} & \xrightarrow{\text{EtI}} \\
CH_3&-C=CH-COEt & \text{NaOEt} & \text{NaI} & \text{EtI}
\end{align*}
\]

The ester II is then to be brominated as done by Patterson\(^{(16)}\), to yield the \( \alpha \)-bromo ester III. III will then be induced to
EXPERIMENTAL SCHEME 1

\[
\begin{align*}
\text{III} & \quad \text{Br}_2/\text{CHCl} \quad \text{Br}^+ \text{hydrolysis} \\
\text{IV} & \quad \text{Pb(OAc)}_4 \\
\text{V} & \quad \text{H}_2\text{O}, \text{NaHCO}_3 \\
\text{VII} & \quad \text{H}^+ \text{hydrolysis} \\
\end{align*}
\]
undergo ring closure by heating, with the elimination of ethyl bromide and the formation of α-ethyl tetronic acid, IV.

The next step in the scheme is the conversion of IV to the α-acetoxy-α-ethyl tetronic acid, V. It is hoped that this can be accomplished by oxidation of IV with lead tetraacetate in benzene as the solvent, in a method analogous to that used by Krampitz (23) in the oxidation of a similar compound, ethyl α-methyl acetoacetate. Krampitz was able to obtain a 39.3% yield of the α-acetoxy-α-methyl acetoacetic ester.

The step V→VI is the attempted hydrolysis of the acetoxy group with water and NaHCO₃, with the formation of the desired α-hydroxy-α-ethyl tetronic acid VI. The products of acid hydrolysis will hopefully be carbon dioxide and 2,3-pentanedione VII.

The second scheme of synthesis is represented on page 14. The first step, I→XI, is identical to that step in scheme I. The next step is the conversion of the ester II to the acetoxy ester IX. This may be accomplished in one of two ways. First, the labile hydrogen of the ester II is oxidized by lead tetraacetate in the method analogous to that used by Krampitz (23). The second method is analogous to that used by Nahm and Dirscherl (24) on ethyl α-methyl acetoacetate, where they were able to obtain an overall yield of 37.4%. Here the ester II is chlorinated with sulfuryl chloride, and the chloro compound VIII refluxed with potassium acetate.
EXPERIMENTAL SCHEME 2

\[ \text{CH}_3-\text{CH}_2-\text{OC}_2\text{H}_5 \quad \xrightarrow{\text{NaO}} \quad \text{II} \]
\[ \xrightarrow{\text{C}_2\text{H}_5\text{I}} \quad \text{- C}_2\text{H}_5\text{OH} \quad \text{- NaI} \]

\[ \text{CH}_3-\text{CH}_2-\text{OC}_2\text{H}_5 \quad \xrightarrow{\text{SO}_2\text{Cl}_2} \quad \text{CH}_3-\text{CH}-\text{OC}_2\text{H}_5 \quad \xrightarrow{\text{Pb(OAc)}_4} \quad \text{CH}_3-\text{CH}_2-\text{OC}_2\text{H}_5 \quad \xrightarrow{\text{Br}_2/\text{CHCl}_3} \quad \text{-HBr} \]

\[ \xrightarrow{\text{KOAe}, \text{AcOH}, \text{Ac}_2\text{O}} \quad \text{VIII} \]

\[ \xrightarrow{\text{KOAe}, \text{AcOH}, \text{Ac}_2\text{O}} \quad \text{V} \quad \xrightarrow{\text{H}_2\text{O}, \text{NaHCO}_3} \quad \text{VI} \quad \xrightarrow{\text{H}^+ \text{ hydrolysis}} \quad \text{VII} \quad \xrightarrow{+ \text{CO}_2} \quad \text{X} \]
in acetic acid and acetic anhydride to yield the \( \alpha \)-acetoxy ester IX. Either of these methods should work as well with the \( \alpha \)-ethyl ester as with the \( \alpha \)-methyl ester. The acetoxy ester IX is then to be brominated as done by Patterson(16), and, hopefully, the bromo compound X will be formed. X will then be induced to undergo ring closure by heating, with the elimination of ethyl bromide, and the formation of \( \alpha \)-acetoxy-\( \alpha \)-ethyl tetrronic acid V.

The third scheme, which is represented on page 16, starts out the same as the second scheme in the formation of the \( \alpha \)-acetoxy ester IX. Then, by the method of Böhme and Schneider(25), the \( \alpha \)-acetoxy ester is hydrolyzed to the \( \alpha \)-hydroxy ester by letting IX stand with 1 N \( \text{C}_2\text{H}_5\text{OH-HCl} \). In the bromination step it is hoped that the bromine will not replace the hydroxy group. The remaining steps are similar to those in schemes 1 and 2.
EXPERIMENTAL SCHEME 3

I $\xrightarrow{\text{NaOCH}_2\text{CH}_3}$ II

III $\xrightarrow{\text{SO}_2\text{Cl}_2}$ II

IV $\xrightarrow{\text{KOAc}, \text{AcOH}}$ V

VI $\xrightarrow{\Delta}$ VII

VII $\xrightarrow{\text{H}^+ \text{ hydrolysis}}$ VIII

IX $\xrightarrow{\text{HCl}}$ X

XI $\xrightarrow{\text{Pb(OAc)}_4}$ XII

XII $\xrightarrow{\text{Br}_2/\text{CCl}_4}$ XI

+ CO$_2$
DISCUSSION OF EXPERIMENTAL PART
(See pages 23-31)

The decision was made to attempt the synthesis of \( \alpha \)-hydroxy-\( \alpha \)-ethyltetronic acid by scheme 1 since there are fewer uncertain steps involved in this proposed method of synthesis than in the methods represented by schemes 2 and 3. In schemes 2 and 3 there is question in the steps involving both bromination and ring closure. During the heating of the cyclization step, there is a possibility of lactide formation as follows:

\[
\begin{align*}
R &= -H \text{ or } \text{--CH}_3 \\
\end{align*}
\]

which might greatly reduce the yield of the tetronic acid. The bromine might react also, and thus polymers would result.

Before the lead tetraacetate oxidation was attempted on the tetronic acid, it was decided to try to repeat the oxidation of ethyl \( \alpha \)-methylacetooacetate, which was commercially available, following Krampitz procedure.\(^{23}\) In addition to the fact that the apparatus used for the vacuum distillation was too large for the amount of material to be distilled,
the shaking of the benzene solution with water may have
caused hydrolysis of the acetoxy group of the ethyl α-methyl-
acetoacetate. This was indicated by the fact that the water
washes in run 1 never reached neutrality. In a similar case,-
Dimroth and Schweizer (26) have reported that in the shaking
of ethyl α-acetoxyacetoacetate with water, the acetoxy group
was hydrolyzed. For this reason the benzene solution in the
second run was not washed with water. The acetic acid, how­ever, which was thus allowed to remain in the benzene solu­
tion may have increased the amount of polymerization in the
residual solution of the distillation.

The weak yellow color of the distillate, which disappeared
on standing, may be an indication of the equilibrium of the
enol of the unreacted ester at a higher temperature. Dim­
roth and Schweizer (26) propose this idea in explaining the
disappearing yellow color observed when ethyl α-acetoxy-
acetoacetate, also an enol, is distilled.

Due to technical difficulties in the vacuum distillation,
it was then decided to try the lead tetraacetate oxidation
on some α-methyltetronic acid, in which case the distillation
would not be used to separate the acetoxy compound from the
original compound. The α-methyltetronic acid (synthesized
by Peter Densen) was available and should react in a manner
similar to α-ethyltetronic acid, which is proposed in scheme 1.

The fact that the α-methyltetronic acid was not appreci­
ably dissolved in the benzene during the addition of the lead
tetraacetate probably did not help the reaction to proceed very successively. Also, the temperature in the first run probably should have been lower, since, according to Criegee\(^{(27)}\) "The temperature is kept as low as possible since the selectivity of oxidation decreases rapidly with increasing temperature."

The brown oil-like drops in the distilling flask in the second run may have been some lead dioxide formed by the action of water on some unreacted lead tetraacetate. The ether fractions of the distillate probably contained some diacetyl, indicated by the slight yellow film on the bottom of a flask from which some of the ether distillate was evaporated. If much diacetyl was present from the oxidation of the \(\alpha\)-methyltetronic acid, it was lost through the water aspirator during the vacuum distillation.

As with the \(\alpha\)-acetoxy-\(\alpha\)-methylacetoacetic ester, water may cause hydrolysis of the acetoxy group in the oxidized tetronic acid. The large melting range of the \(p\)-bromophenacyl ester derivatives indicates that probably more than one acid was present in the distillate. There may have been some acetic acid present which was not removed in the previous vacuum distillation. Two other possibilities are glycollic and lactic acids, produced as shown below.
While the melting point of the derivative of the unknown melted at 107-114°, the p-bromophenacyl ester of glycollic acid melts at 138°C (28), and the same ester of lactic acid melts at 112.8°C (28). The unknown acid is not lactic acid alone, as is shown by the depression of the melting point of a 50-50 mixture of the derivatives of the two.

As the results obtained from the oxidation of the α-methyltetronic acid were inconclusive, it was again attempted to repeat the work of Krampitz on ethyl α-methylacetoacetate. The large amount of brown lead dioxide precipitate in runs 3 and 4 of the lead tetraacetate oxidation of the α-methylacetoacetic ester indicates the incompleteness of the oxidation reaction. The following reaction takes place:

\[
Pb(OAc)_4 + 2 \text{ HOH} \rightarrow \frac{\text{PbO}_2}{\text{brown}} + 4 \text{ HOAc}
\]

No lead dioxide would be formed if only lead diacetate, dissolved in the benzene, were present. According to Griegee, "When the reaction is run in benzene or other inert solvents, lead (II) acetate precipitates during the reaction. The precipitate is sticky at first and can occlude lead tetraacetate. This is avoided when crystallization is induced by seeding or scratching with a glass rod." Thus the incomplete reaction should be able to be avoided.

Difficulties were encountered in the vacuum distillations using the equipment in the "Chem Kits" due to the lack of a method of changing receiving flasks without equalizing the
pressure to atmospheric pressure, at which time the temperature of the vapor to be distilled falls. The longer heating period thus required to again raise the temperature probably caused more polymerization in the residual solution than there would have been otherwise.

Cavil and Soloman (29) propose the following mechanism for the oxidation of carbonyl compounds by lead tetraacetate:

\[
R\cdot CH\cdot COR' \xrightarrow{\text{Initiation}} R\cdot CH\cdot CR'\cdot OH \quad \text{(rate determining)}
\]

\[
\begin{align*}
\text{Initiation:} & \quad R\cdot CH\cdot CR'\cdot OH + Pb(OAc)_4 \rightarrow \text{complex} \\
\text{Propagation:} & \quad R\cdot CH\cdot CO.R' + Pb(OAc)_4 \rightarrow AcO\cdot CHR\cdot CO.R' \\
& \quad + Pb(OAc)_3 \\
\text{Termination:} & \quad (1) R\cdot CH\cdot CO.R' + OAc \rightarrow AcO\cdot CHR\cdot CO.R' \\
& \quad (2) 2 R\cdot CH\cdot COR' \rightarrow (R\cdot CO\cdot CHR.)_2
\end{align*}
\]

Dimers are isolated when the per cent of enol and the rate of enolization are appreciable, as in β-dicarbonyl systems. The dimer formed from ethyl α-methylacetooacetate would be:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{OC}_2\text{H}_5 & \quad \text{OC}_2\text{H}_5
\end{align*}
\]

Cocker and Schwarz (30) have isolated the dimer 3,4-diacetyl-2,5-hexanedione in the oxidation of acetylacetone with lead.
tetraacetate.

Criegee states that, "β-dicarbonyl compounds react very easily, commonly even at room temperature. Surprisingly, the yields of α-acetoxy compounds are not always good. The yields of dimers account for only a small part of the deficit, so that products of further oxidation must be formed." (27)p.311

The desired α-acetoxy-α-methyl acetoacetic ester finally was separated and identified as the semicarbazone.

As the yield of the acetoxy ester was small, it was decided to synthesize the same ester by the method of Nahm andDirscherl (24) mentioned previously. As the tetronic acid would not stand up to three days of refluxing, as required by this method, scheme 1 would have to be abandoned and either scheme 2 or 3 followed.
EXPERIMENTAL PART

1. Attempted oxidation of ethyl α-methylacetoacetate using Pb(OAc)$_4$

a. Run 1.

The procedure for the Pb(OAc)$_4$ oxidation is taken from that used by Krampitz.\(^\text{(23)}\) A 500 ml. three neck flask was set up connected with a mechanical stirrer, a reflux condenser with a CaCl$_2$ drying tube, and Gooch tubing for the addition of the Pb(OAc)$_4$. 28.9g. of 90% Pb(OAc)$_4$ was added in small portions from an erlenmeyer flask connected by the Gooch tubing to the flask containing a mixture of 24.6 ml. benzene and 47.4 gm. ethyl α-methylacetoacetate. The addition was made with vigorous mechanical stirring and it was attempted to keep the temperature below 35°C. After the addition was complete, the mixture was heated, with continued mechanical stirring, to 40°C. for 3 rather than 5 hours as done by Krampitz. During the addition of the Pb(OAc)$_4$, the mixture was a yellow color, but after the heating was begun the color disappeared and the white Pb(OAc)$_2$ was visible. After standing for 21 hours at room temperature, the mixture was filtered to remove the Pb(OAc)$_2$, and the precipitate was washed 5 times with 10 ml. portions of benzene. These washings were added to the original solution. In an attempt to remove any HOAc present, the benzene solution was washed with 10-20 ml. portions of water 30 times. The water never
did become neutral to bromthymol blue indicator. The benzene solution later was dried over MgSO₄, and then filtered. After the benzene had been distilled off at reduced pressure using a water aspirator and mercury manometer, 24.6 gm. unreacted ester came over at 81-89°C at 18-25 mm. pressure. The temperature of the distilling vapor then fell and could not be made to go up again, although the oil bath was raised to 170°C. When the unreacted ester first came over it was a light yellow color, but on standing it became colorless. The residual liquid was a dark brown color, probably due to the formation of a highly polymerized oil.

b. Run 2.

This run was similar to the first run with a few exceptions. 17.3 gm. ethyl α-methyl acetoacetate, 49 ml. benzene, and 57.8 gm. Pb(OAc)₄ were used, and the heating was continued for 5 hours this time. Also, the benzene solution was not washed with water due to possible hydrolysis of the acetonyl group, as was mentioned earlier. Following the removal of the benzene under reduced pressure distillation, difficulties arose due to the water aspirator. A few drops of distillate did come over at 34°C. and 20 mm., but then the pressure could not be made lower than 56 mm. Again the oil bath was raised to approximately 170°C, but still no distillate came over. The few drops at 34°C. and 20 mm. smelled like acetic acid and the boiling points correspond.
2. **Attempted oxidation of α-methyltetronic acid with Pb(OAc)$_4$**

a. Run 1.

19.4 gm. 90% Pb(OAc)$_4$ was added in small portions to a mixture of 31 ml. benzene and 5 gm. α-methyltetronic acid in a 200 ml. three neck flask to which a reflux condenser with CaCl$_2$ drying tube, a thermometer, and Gooch tubing, as before, were connected. Due to the smaller flask, it was necessary to use a magnetic stirrer, however it did not stir the mixture very effectively. The first part of the addition of the Pb(OAc)$_4$ was done in an ice bath, but the tetronic acid was not dissolved appreciably in the benzene, and the reaction was not exothermic, as was the case with the ethyl α-methylacetooacetate oxidation. Therefore the addition was continued at room temperature. The mixture was then heated for 2½ hours at approximately 50°C., although the temperature did reach 55°C. at one time. After standing overnight, the yellow precipitate was filtered from the benzene solution. A total of 130 ml. ether were used in five portions to extract any tetronic acid or oxidation products from the yellow precipitate, one 40 ml. portion being left standing with the precipitate overnight. The ether and benzene solutions were combined, and then the ether, benzene and acetic acid from the oxidation were evaporated off under reduced pressure with no heating. A few crystals precipitated from the syrupy light brown-yellow residual solution. These crystals were filtered off, but
there was not enough material for even a melting point. When the residual solution was shaken with an equal volume of water, large yellow globules separated from the water. A few of these yellow globules were removed and after standing in a flask overnight, they formed a colorless sticky film on the sides of the flask. Any lead present in the yellow mixture was precipitated with H₂S from an Aitch-tuess cartridge as black PbS. The water was then removed in a vacuum distillation at a temperature not above 30°C., leaving a yellow residual solution behind as the new residue. A very small amount of crystals similar to those from the previous residual solution also precipitated from this second residual solution. To the distillate, whose pH was 2 and which was obviously not pure water by the acrid smell, was added 10% NaOH until the solution was almost neutral, but still acidic. 0.5 gm. p-bromophenacylbromide and 10 ml. 95% ethanol were added and the mixture refluxed for 100 min. The recrystallized derivative melted at 99-110°C. (from ethanol).

b. Run 2.

In this run, similar but not identical to the first run, 38.6 gm. Pb(OAc)₄ was added to a mixture of 10 gm. α-methyl-tetronic acid and 62 ml. benzene at room temperature. Due to the larger amount of material it was again possible to use the 500 ml. three neck flask and the mechanical stirrer. In this run the mixture was heated to 40°C. for 5 hours. After the precipitate was filtered from the benzene solution,
it was washed with two 20 ml. portions of benzene, the first portion becoming a bright yellow color and the second remaining colorless. Then the precipitate was washed with ether as before. The yellow precipitate collected in this run formed irregular grainy balls while in the first run the precipitate formed a cake on the filter. When the benzene-ether solution was put in the distilling flask, a few brown oil-like drops were noticed at the bottom of the flask, possibly due to a few drops of water. In the vacuum distillation, it was attempted to collect the ether and benzene by using an ice bath around the receiving flask and not allowing the pressure to be reduced as low as possible. The first fraction (15.4 gm.) was collected at ~80 mm. and ~100°C, and smelled distinctly of ether. The second fraction (33.8 gm.) was collected at ~60 mm. and 100°C, while the third fraction (27.8 gm.) was collected at ~45 mm. and 100°C. All three fractions were clear, and the second and third smelled of benzene. Some of the distillate went down the drain as the pressure could not be controlled very accurately. The first fraction was left to evaporate in the air and a slight yellowish film was left on the bottom of the flask. An equal volume of a 50-50 water-ethanol solution was added to half of the residual solution from the preceding distillation. The lead was removed from this solution by precipitation as PbS with H2S. As before, the water (and ethanol) was removed by vacuum distillation. The pH of the distillate was 3 this time. Again
the p-bromophenacyl ester was made of the acidic material in the distillate. For comparison, the p-bromophenacyl ester was made of lactic acid and the melting point after two re-crystallizations from alcohol was 110-112°C (uncorr.). The melting point of the unknown derivative was 107-114°C (uncorr.). A mixture melting point of the two was 84-101°C (uncorr.).

Again, there were a few crystals which formed in the residual solution of the vacuum distillation. In this run, the yellow residual liquid appeared to consist of two liquid layers, one being thicker and more viscous than the other.

3. Oxidation of ethyl α-methyl acetoacetate with Pb(OAc)₄:
   a. Run 3.

   In the third run of this oxidation procedure, similar to the first two runs, 57 gm. 90% Pb(OAc)₄, 50 ml. benzene and 17.3 gm. ethyl α-methyl acetoacetate were used. After the mixture was heated, it was allowed to stand for 24 hours at room temperature. When it was attempted to wash the benzene solution with water, a brown precipitate of PbO₂ was formed. After being washed four times with 20 ml. portions of water, the benzene solution was filtered with suction to remove as much PbO₂ as possible and the solution was left to stand overnight while being dried with MgSO₄. The MgSO₄ was filtered from the solution and the benzene distilled off under reduced pressure. The first fraction (.71 gm.) after the benzene was removed came over at 30°C and 15 mm. The second fraction (4.21gm.) came over at 70-110°C and 10 mm., while
the third fraction (3.14 gm.) came over at 111° and 12 mm. A precipitate which was formed in the residual liquid during the distillation was filtered, recrystallized from ethanol, and found to melt at greater than 275°C. This precipitate was probably a lead salt. The first distillate fraction boiled at a point corresponding to the boiling point of acetic acid. It was attempted to make 2,4-dinitrophenylhydrazones of fractions 2 and 3 by the methods of both Feis-
er(31), and Shriner(32), but a crystalline precipitate could not be obtained by recrystallization from ethanol. For practice the 2,4-dinitrophenylhydrazone of ethyl acetoacetate was made by putting 0.4 gm. 2,4-dinitrophenylhydrazine, 12 drops ethyl acetoacetate, and 10 ml. 95% ethanol in a test tube and heating on a steam bath until the solid dissolved. A yellow precipitate formed which was recrystallized from ethanol and found to have a melting point of 94-94°, which corresponds to the literature values of 95° and 96°(33).

0.4 gm. 2,4-dinitrophenylhydrazine, 12 drops distillate fraction 3, 10 ml. methanol, and 1 drop HCl were left standing in a test tube for a week, but no derivative formed. No heat was used because, according to Nahm and Dirscherl(24) in that case one obtains the derivative of acetylacetoin, rather than the derivative of the \(\alpha\)-acetoxy-\(\alpha\)-methylacetoacetic ester. If the third fraction of distillate is the acetoxy ester, the yield was 3.14 gm. or 13% of the theoretical value. The boiling point, 111°C at 12 mm. does correspond to that of
the compound in run 4 which was shown to be the desired acetoxy ester. This temperature is below that given by Nahm and Dirscherl(24) as 80-81°C at 1 mm., but is included in the range of 79-81°C at 10-1 mm. given by Krampitz(23).

b. Run 4.

In a fourth run 84.8 gm. 90% Pb(0Ac)₄, 28.8 gm. ethyl α-methylacetoacetate, and 99 ml. benzene were used. 25 ml. portions of benzene and 25 ml. portions of water were used for wash solutions. When the benzene solution was washed with water, brown PbO₂ again precipitated. There was so much PbO₂ that it was necessary to filter the water-benzene mixture several times before the two layers could be separated. The water wash solution was left standing in a separatory funnel, and over a period of two weeks tiny white needles precipitated. These needles were filtered and found to contain lead by precipitation of PbS with H₂S. Also these needles did not dissolve in water, NaOH or ethanol. After the solution was heated to remove the ethanol, the precipitate dissolved in conc. HNO₃. The precipitate was regenerated by the addition of 10% NaOH. On the heating, brown material appeared, indicating decomposition of organic material.

After the benzene was removed by reduced pressure, the first fraction of distillate (10.87 gm.) came over from 28°C and 25 mm. to 110°C and 12 mm. The second fraction (2.28 gm.) came over at 115°C. and 13 mm. One gm. of this second fraction
was put in a test tube, 2 ml. water added, and just enough ethanol added to dissolve the ester (2 ml.), 1.0 gm. semicarbazide and 1.5 gm. NaOAc were added and the mixture shaken vigorously. The test tube was put in a boiling water bath, then filtered to remove the undissolved semicarbazide, and put back in the boiling water bath and allowed to cool to room temperature. The derivative was recrystallized once from ethanol and had a melting point of 131-134°C. The literature value is 135°C.\(^{(23)}\) 2.28 gm. of the acetoxy ester, boiling point 115°C at 13 mm. is a yield of 5.6% of the theoretical value.
CONCLUSION

Unless the yield of the \( \alpha \)-acetoxy-\( \alpha \)-methyl acetoacetic ester can be improved, the proposed schemes should be abandoned in the search for a method of synthesizing an \( \alpha \)-hydroxy-\( \alpha \)-alkyltetronic acid. Although the \( \alpha \)-acetoxy ester is not actually involved in the first proposed scheme, it would appear that the difficulties involved in the lead tetraacetate oxidation of the ester ought to be overcome, before the further difficulties of the tetronic acid oxidation are added. Given more time, the yields of the \( \alpha \)-acetoxy ester most likely could be improved. By following the suggestions of Criegee (see page 20), one may be able to cause all the lead tetraacetate to react and thus increase the yield. Then both the temperature and the period of heating should be varied in several experiments to determine the best reaction conditions for the oxidation of the \( \alpha \)-substituted tetronic acid. A method will also be needed to effectively separate the \( \alpha \)-acetoxy tetronic acid from the unreacted acid. Column chromatography may be a useful method for this separation, however much trial and error is involved in finding efficient solvents, eluants and column materials.

If the lead tetraacetate oxidation can not be improved, scheme 2 or 3 could be followed by way of the \( \alpha \)-chloro ester. After all the problems have been worked out with regard to the \( \alpha \)-methyl ester and the \( \alpha \)-methyltetronic
acid, then the syntheses of the α-ethyl homologues could be attempted, as proposed earlier.
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ADDENDUM

EXPERIMENTAL PART

1. Chlorination of ethyl $\alpha$-methylacetoacetate.

The procedure followed was taken from the method of Nahm and Dirscherl (24). 80.0 gm. ethyl $\alpha$-methylacetoacetate was put in a 200 ml. three neck flask equipped with a thermometer, a reflux condenser with CaCl$_2$ drying tube, and a separatory funnel with CaCl$_2$ drying tube containing 80.0 gm. SO$_2$Cl$_2$. The flask was cooled in an ice bath and a magnetic stirrer was used during the addition. After one third of the SO$_2$Cl$_2$ had been added, the addition was stopped because it was observed that the volume had increased and the solution was fairly yellow, indicating that much of the SO$_2$Cl$_2$ had not reacted. Therefore the stirring was continued with no further addition while the temperature was gradually raised to room temperature. The HCl gas came off very slowly at 0°C. and did not come off vigorously even at higher temperatures.

After sitting over the weekend, the solution was cooled to approximately 15°C., the stirrer started, and the addition of the remaining SO$_2$Cl$_2$ was continued. The temperature was kept at 15°C. at first because at lower temperatures the HCl evolution was very small. Gradually the temperature was lowered to 5°C. without decreasing the HCl evolution. After the addition was complete, the stirring was continued until there was no more HCl evolution. The product was separated by vacuum distillation. 57.9 gm. product distilled at 81°C.-85°C. at
14-16 mm. representing a yield of 58.4%. 31.5 g. unreacted ester came over at 87⁰-90⁰C. at 16 mm. A positive Beilstein test was found for both fractions. The first fraction was redistilled at 71⁰C. and 9-12 mm. to 79⁰C. and 14 mm. to yield 46.9 gm. of the α-chloro ester.

2. Attempted preparation of ethyl α-acetoxy-α-methylacetoacetate from the α-chloro ester.

The method of Nahm and Dirichtl(24) was continued. 40.5 gm. ethyl α-chloro-α-methylacetoacetate, 37.5 gm. KOAc, 37.5 ml. glacial HOAc, and 12.5 ml. Ac₂O were put in a 250 ml. flask equipped with a thermometer and a reflux condenser with CaCl₂ drying tube. With an electric heater (controlled by a rheostat) the mixture was heated so that it was refluxing (155⁰C). After 30 min. the mixture began to turn brown. Due to an improperly wired light switch, the mixture did not reflux over a weekend as planned. A brown tarry mass was found in the flask, but the mixture was still refluxed for three days. When cooled to room temperature, no liquid was visible in the flask. On heating under reduced pressure, no material was found to distil. It was attempted to extract some material from the tarry solid with three 25 ml. portions of ether and then with three 25 ml. portions of salted distilled water. This water was then washed with 25 ml. ether and the ether solutions combined. The ether solution was the washed with 25 ml. salted distilled water and dried over MgSO₄. The ether solution was dark brown in color, and upon evaporation in air,
approximately 5 gm. dark brown tarry material remained. No ethyl \( \alpha \)-acetoxy-\( \alpha \)-methylacetoacetate was obtained.

**DISCUSSION OF RESULTS**

During the addition of the \( \text{SO}_2\text{Cl}_2 \) in the chlorination procedure, the HCl at first produced was probably dissolved in the ester and catalyzed further enolization of the unreacted ester. Then, due to the larger amount of enolization, the reaction proceeded more rapidly, and thus the temperature could be lowered without decreasing the HCl evolution. The KOAc used in the refluxing step was not freshly fused although it was from a tightly sealed, unopened bottle. This KOAc may have been the cause of formation of the brown tarry material. Further work is necessary to determine whether the procedure of Nahm and Dirscherl is useful for the preparation of the \( \alpha \)-acetoxy-\( \alpha \)-methylacetoacetate ester required in proposed schemes 2 and 3.

If the results of neither the lead tetraacetate oxidation of Krampitz\(^{(23)}\) nor procedure of Nahm and Dirscherl\(^{(24)}\) can be improved, the proposed synthetic schemes should be abandoned and a completely new approach taken toward the synthesis of an \( \alpha \)-hydroxy-\( \alpha \)-alkyltetronic acid.
ABSTRACT

A Historical Introduction is given as background material to the problem of the existence of an $\alpha$-hydroxy-$\alpha$-substituted tetronic acid as the intermediate in the oxidation of tetronic acids to $\alpha$-diketones. Three schemes are proposed by which this intermediate may be synthesized, starting with ethyl acetoacetate. In the first scheme the $\alpha$-substituted tetronic acid is oxidized by lead tetraacetate to the $\alpha$-acetoxy-$\alpha$-substituted compound. In the second and third schemes, the lead tetraacetate oxidation can be applied to the $\alpha$-substituted acetoacetic ester, or the $\alpha$-substituted acetoacetic ester can be chlorinated with sulfonyl chloride and then converted to the $\alpha$-acetoxy ester.

Experimental work dealing with the lead tetraacetate oxidation is described, and the difficulties encountered discussed. The yields of ethyl $\alpha$-acetoxy-$\alpha$-methylacetoacetate were low and thus more work is necessary before the proposed synthetic procedures are tested further.