THESIS

entitled

"dβY-TRIMETHYL-GLUTAMIC ACID."

Presented for the Degree

of

Master of Science and Honours

in the

University of New Zealand

1947

Code Word: Paul R. Jacobson
# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical Introduction</td>
<td>1</td>
</tr>
<tr>
<td>The Present Investigation</td>
<td>20</td>
</tr>
<tr>
<td>Summary</td>
<td>36</td>
</tr>
<tr>
<td>Experimental Section</td>
<td>38</td>
</tr>
</tbody>
</table>
THEORETICAL SECTION

Over a number of years many attempts have been made to synthesize \(\delta\beta\)-trialkyl-glutaconic acids (1)

\[
\begin{align*}
R & \quad R \\
H\text{OOC-C} & \quad C - \text{CH-GOOH}
\end{align*}
\]

No method has given very satisfactory results. In many cases the yields have been very poor and in no case has the constitution of the product been demonstrated conclusively.

These methods are discussed below.

A. The methylation of \(\delta\beta\)-dimethyl-glutaconic ester.

Thorpe and Wood (J. C. S. 1913, 103, 1759) prepared a "labile" ethyl \(\delta\beta\)-dimethyl-glutaconate (3) by treating ethyl isodehydracetate (2) with alcoholic sodium ethoxide and methyl iodide

\[
\begin{align*}
\text{C=O} & \quad \text{CH}_3 \\
\text{H-C} & \quad \text{C-GOOEt} \\
\text{CH}_3 & \quad \text{G} \quad \text{CH}_3 & \quad \text{NaOEt} & \quad \text{CH}_3 \text{I} & \quad \text{G-GOEt-CH}_2-\text{C} = \text{C-G-GOEt} \\
\text{CH}_3 & \quad \text{G} & \quad (2) & \quad (3)
\end{align*}
\]

The ester obtained was methylated by alcoholic sodium ethoxide and excess methyl iodide. The product was hydrolysed giving an acid of melting pt. 127\(^\circ\) C.
which the authors considered to be $\alpha\beta$-trimethyl-glutaconic acid (4)

\[
\begin{align*}
\text{COOEt-CH}_2\text{-C}=\text{O-} & \text{COOEt} \\
\text{CH}_3\text{CH}_3 & \to \\
\text{NaOEt} & \text{CH}_3\text{CH}_3 \text{CH}_3 \\
\text{CH}_3 & \text{CH}_3 \\
\end{align*}
\]

Packer and Sargent (J.C.S. 1933, 136, 556) could not methylate "labile" ethyl$\alpha\beta$-dimethyl-glutaconate by Thorpe and Wood's method, but effected methylation only by using sodium dispersed in ether and methyl iodide. The product was mainly ethyl$\alpha\beta$-trimethyl-glutaconate (5) and no evidence could be found for any ethyl $\alpha\beta$-trimethyl-glutaconate in the product.

\[
\begin{align*}
\text{COOH - C - C = CH-COOH} \\
\text{CH}_3 \\
\end{align*}
\]

This result is consistent with the report of Feist and Beyer (Annalen 1936, 545, 117) that they were unable to methylate ethyl$\alpha\beta$-dimethyl-glutaconate, and also with the work in this field of Kon and Watson.

These two workers showed (J.C.S. 1932, 135, 1) by ozonolysis that the "labile" ethyl$\alpha\beta$-dimethyl-glutaconate was a mixture of two tautomeres (6) and (7), mainly (6).
It would thus be expected to give mainly dL-trimethyl glutaric acid on methylation as demonstrated by Packer and Sargent.

In the same paper Kon and Watson showed that the "normal" Lβ-dimethyl-glutaric acid obtained by hydrolysis of "labile" ethyl Lβ-dimethyl-glutarate was almost pure cis Δαβ acid (8), and that

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

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

the silver salt of this acid on treatment with methyl iodide gave almost pure Δνβ ester (9).

Hutchison (M.Z. University Thesis, 1935, unpublished) prepared this Δαβ form of methyl dβ-dimethyl-glutarate (9) by the above method and methylated it by using potassium dispersed in ether and methyl iodide, hoping to get methyl dβ-trimethyl-glutarate. The product on hydrolysis gave a mixture of acids from which small quantities of two acids were isolated by fractional crystallisation from water. The first to separate
(m.p. 118⁰C) he assumed to be $\alpha\beta$-trimethyl-glutaconic acid as its melting point was depressed by both trans $\alpha\beta$-trimethyl-glutaconic acid, and cis $\Delta^\alpha\beta$-dimethyl-glutaconic acid. The second acid was identical with trans $\alpha\beta$-trimethyl-glutaconic acid. It seemed, therefore, that under the conditions of methylation, much of the $\Delta^\alpha\beta$-methyl $\alpha\beta$-dimethyl-glutaconate (9) had undergone conversion to the $\Delta^\alpha\beta$ tautomeride (10):

$$
\text{CH}_3 \text{CH}_3 \quad 1
\text{MeOOC} - \text{CH} - \text{C} = \text{CH} - \text{COO} \text{Me} \quad (10)
$$

B. The methylation of cyano-dimethyl-glutaconic ester.

Rogerson and Thorpe (J.C.S. 1935, 87, 1792) condensed ethyl cyanoacetate and ethyl methylacetacetate with sodium ethoxide in alcohol to give the sodio derivative of ethyl-$\alpha$-cyano-$\beta\alpha$-dimethyl-glutaconate (11):

$$
\text{COOEt} - \text{CH} = \text{C} - \text{COOEt} \quad \text{NaOEt} \quad \text{COOEt} - \text{CH} - \text{C} = \text{C} - \text{COOEt} \quad (11)
$$

On treating the sodio derivative of this ester with methyl iodide a product was obtained which they considered to be ethyl-$\alpha$-cyano-$\alpha\beta$-trimethyl-glutaconate (12):

$$
\text{COOEt} - \text{C} - \text{C} = \text{C} - \text{COOEt} \quad (12)
$$
Actually two products are possible on methylation, because ethyl α-cyano-βγ-dimethyl-glutaconate may have either the $\Delta^{αγ}$ structure (11) or the $\Delta^{αδ}$ structure (13)

$$
\text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3
\text{COOEt} - \text{C} - \text{C} - \text{CH} - \text{COOEt}
$$

Kon and Hanji (J.C.S. 1951, 134, 571) showed by ozonolysis that the ester from the condensation quoted is mainly the $\Delta^{αγ}$ form (11) with a small amount of $\Delta^{αδ}$ form (13). Methylation should therefore give mainly ethyl α-cyano-βγ-trimethyl-glutaconate (12) as claimed by Rogerson and Thorpe, together with a little ethyl γ-cyano-βδ-trimethyl-glutaconate.

Acid hydrolysis of the methylated product gave a pyridine derivative and a glutaric acid, while alkaline hydrolysis gave the pyridine derivative only. The authors considered the pyridine derivative to be 3:4:5-trimethyl-2:6-dihydroxy-pyridine (14), but no conclusive proof of its constitution was given.

$$
\text{CH}_3
\|\|\|\|\|\|\|\|\|\|
\text{CH}_3 - \text{C} - \text{C}-\text{OH}_2
\text{HO} - \text{C} - \text{C}-\text{OH}
$$

The acid obtained melted at 129°C and was considered
to be \( \alpha \beta \)-trimethyl-glutaconic acid. On boiling
with acetic anhydride it readily gave an anhydride
melting at 119°C which Thole and Thorpe (J.C.S. 1911,
92, 2221) showed to be a hydroxy-anhydride with the
same properties as others of the series, and which they
assumed to be (15)

\[
\begin{align*}
\text{CH}_3 & \quad \text{OH} \\
\text{CH}_3 & \quad \text{C} = \text{O} \\
\text{C} & \quad \text{G} - \text{CO} \\
\text{CH}_3 & \\
\end{align*}
\]

A normal anhydride, assumed to be (16) was
obtained by boiling the acid with acetyl chloride. The
only evidence for the methyl groups being in the
positions was the preparation of the two anhydrides.

Sargent (N.Z. University Thesis 1931, unpublished)
tried to repeat this work of Rogerson and Thorpe, but
could not effect methylation. Hydrolysis of the
product yielded only \( \alpha \beta \)-dimethyl-glutaconic acid and
the corresponding pyridine derivative.

C. The condensation of malonic ester with a substituted
chloroform and subsequent methylation.

By methylation of the sodio derivative of \( \alpha \beta \)-
dicarboxyloxy-glutaconic ester (17) made by the method
of Conrad and Gutzzeit (Annalen 1883, 222, 259) from chloroform and malonic ester, Thole and Thorpe (J.C.S. 1911, 99, 2191) obtained ethyl 6,6'-dimethyl-glutaconate (18).

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{Na} \\
\text{CO}_2\text{Et} & \quad \text{Na}
\end{align*}
\]

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{H} \\
\text{CO}_2\text{Et} & \quad \text{Na}
\end{align*}
\]

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{H} \\
\text{CO}_2\text{Et} & \quad \text{Na}
\end{align*}
\]

By using a substituted chloroform it should be possible to prepare a 6,6'-trialkyl-glutaconic ester by a similar series of reactions.
Thompson (M.Z. University Thesis, 1930, unpublished) attempted to condense phenyl-chloroform with malonic ester, but obtained none of the $\beta$-phenyl-dicarboxethoxy-glutaconic ester (19) expected as product.

\[
\begin{align*}
\text{COOEt} & \quad \text{H} \\
\text{COOEt} & \quad \text{C} = \text{O-CH} \\
\text{COOEt} & \quad \text{C} = \text{O-CH} \\
\end{align*}
\]

He obtained an undistillable oil which gave benzoic acid on hydrolysis, and on oxidation. Kon (J.C.S. 1932, 135, 2447) attempted the same condensation with the same result. Adams (M.Z. University Thesis, 1936, unpublished) condensed methyl-chloroform with malonic ester and sodium ethoxide, but could not obtain any $\beta$-methyl-$\alpha$-dicarboxethoxy-glutaconic ester.

D. Reformatsky condensation of an $\alpha$-bromo ester with a mono-alkylacetoacetic ester.

Perkin and Thorpe (J.C.S. 1897, 21, 1178) made ethyl $\beta$-hydroxy-$\beta$-trimethyl-glutarate (20) by two different Reformatsky syntheses, and dehydrated this ester, hydrolysing the product to give $\delta\beta$-trimethyl-glutaconic acid (21).
This work suggests a method for the synthesis of 3-methyl-α,β-dialkyl-glutamic acids (22), namely by Reformatsky condensation of an α-bromo-ester and a monoalkyl-acetoacetic ester as follows:

\[
\text{COO}_{\text{Et}} \cdot \text{CHBr} + \text{O=CH-CH-GOOGt} \xrightarrow{\text{Mg}} \text{R} \cdot \text{CH}_{3} \cdot \text{R} \xrightarrow{-\text{H}_{2}\text{O}} \text{COO}_{\text{Et}} \cdot \text{CH-CH-GOOGt} \]

(23)
In order to test the method, Mapstone (K.Z. University Thesis, 1947, unpublished), carried out the following synthesis using bromo-acetic ester and acetoacetic ester with magnesium in benzene. This synthesis is represented above where \( R = K = H \). He obtained only a very poor yield (1% theoretical) of the hydroxy ester, but isolated \( \beta \)-methyl-glutaconic acid (22, \( R = K = H \)) by its dehydration and hydrolysis. He attributed the low yield to reaction of the enolic form of the monoalkyl-acetoacetic ester with the intermediate organometallic compound \( \text{CH}_2\text{COET-Mg-Br} \).

E. Reformatsky condensation of an acyl-alkyl-
malonic ester and an \( \alpha \)-bromo ester.

Mapstone suggested replacing the monoalkyl-
acetoacetic ester in the above synthesis by an acyl-
alkyl-malonic ester (24) because the latter has no
mobile hydrogen and hence no enolic form to react with
the organometallic compound. He proposed this
synthesis:

\[
\begin{align*}
\text{COOET} & \quad \overset{\text{Zn or Hg}}{\underset{\text{Br-CH-COOET}}{\xrightarrow{\text{COET}}} \quad \text{COET}} \\
\text{COOET} & \quad \overset{-\text{H}_2\text{O}}{\underset{\text{NaOEt}}{\xrightarrow{\text{COET}}}} \\
\text{COOH} & \quad \overset{\text{hydrolysis}}{\underset{\text{COET}}{\xrightarrow{\text{COET}}}}
\end{align*}
\]
(1) Sinclair (N.Z. University Thesis 1941, unpublished), in order to test this method, tried to carry out the following synthesis of $d\beta$-dimethyl-glutaconic acid, samples of which were available for comparison:

$$
\begin{align*}
\text{COOEt} & \xrightarrow{\text{NaOEt}} \text{COOEt} \quad \text{CH}_3 \quad \text{Na} \quad \text{CH}_3 \quad \text{in ether} \quad \text{COOEt} \quad \text{CH}_3 \quad \text{CH}_3 \\
\text{COOEt} & \xrightarrow{\text{CH}_3 \quad \text{I}} \quad \text{COOEt} \quad \text{CH}_3 \quad \text{COCl} \quad \text{COOEt} \\
\text{COOEt} & \xrightarrow{\text{C} \quad \text{C} = \text{O} \quad \text{S}_2 \text{O}_5} \quad \text{COOEt} \quad \text{C} \quad \text{C} = \text{CH}_2 \quad \text{COOEt} \\
\text{COOEt} & \xrightarrow{\text{cold NaOEt}} \quad \text{COOEt} \quad \text{CH}_3 \quad \text{CH}_3 \\
\text{COOEt} \quad \text{CH}_3 \quad \text{CH}_3 & \xrightarrow{\text{hydrolysis}} \quad \text{COOH} \quad \text{CH}_3 \quad \text{CH}_3 \\
\end{align*}
$$

He obtained a 21% yield of an ester which he considered to be the required $\alpha$-carbethoxy- $d\beta$-dimethyl- $\beta$-hydroxy-glutaric ester (25), but, using a variety of conditions, he was unable to dehydrate it to the carbethoxy-glutaconic ester.

(2) Greenwood (N.Z. University Thesis 1942, unpublished) repeated the work of Sinclair and obtained an ester of the same boiling range which he showed was not $\alpha$-carbethoxy $d\beta$-dimethyl-$\beta$-hydroxy-glutaric ester, but was impure $\alpha$-carbethoxy-$\alpha$-methyl-succinic ester (26). On hydrolysis
and heating, the ester gave impure methyl-succinic acid.

\[
\text{COOEt} - \text{CH}_2 - \text{O} - \text{COOEt} \\
\begin{align*}
\text{COOEt} \\
\end{align*}
\]

Greenwood suggested that the product obtained was due to the condensation of bromo-acetic ester with itself in the presence of magnesium to give EtO-Mg-Br which reacted with acetyl-methyl-malonic ester to give \(\alpha\)-carbethoxy-\(\alpha\)-methyl-succinic ester (26).

(3) Bailey (N.Z. University Thesis 1944, unpublished) attempted the same synthesis, but used zinc instead of magnesium, hoping thus to avoid the condensation of bromo-acetic ester with itself. However, he obtained none of the required product, the main products being acetoacetic ester, methyl-malonic ester and methyl ethyl ketone from side reactions. He concluded that such a reaction was unsuitable for the synthesis of \(\alpha\beta\gamma\)-trimethyl-glutaconic acid.

F. The condensation of an \(\alpha\)-alkyl-\(\beta\)-chloro-\(\gamma\)-crotonic ester with the sodio derivative of an alkyl-malonic ester.

This is an extension of the method of synthesis of Fichter and Schwab (Annalen 1936, 548, 251) of \(\beta\)-methyl-glutaconic acid. Fichter and Schwab condensed ethyl
β-chloro-crotonate (27, trans) and ethyl β-chloro-
aldehyde (27, cis) respectively with sodio-malonic
ester, hoping to obtain by hydrolysis of the esters
produced, the two stereoisomeric β-methyl-glutaconic
acids (28).

\[
\begin{align*}
\text{GOOEt} & \rightarrow \text{CHNa} \quad \text{CH}_3 \\
\text{GOOEt} & \rightarrow \text{GOOEt} \quad \text{CH}_3 \quad \text{GOOEt} \\
\text{(27)} & \quad \text{(28)} \\
\end{align*}
\]

combined hydro-
ysis and decarb-
ethoxylation

\[
\begin{align*}
\text{CH}_3 \\
\text{(29)} \quad \text{GOOEt} - \text{CH}_2 = \text{C} - \text{CH} - \text{GOOEt} \\
\end{align*}
\]

They claimed that both condensations gave the same
α-carbethoxy-β-methyl-glutaconic ester (28) boiling at
163-165 °C at 12 mm. They hydrolysed this ester with
baryta to give a mixture of the two stereoisomeric
β-methyl-glutaconic acids which were separated by frac-
tional crystallisation. Gidvani, Kna and Wright
(J.C.S. 1932, 125, 1927) repeated these condensations
and obtained two tricarboxylic esters showing small but
definite differences in physical properties.

That from the (trans) β-chlorocrotonic ester had:
b.p. 169-173 °C at 13 mm., \(d_4^{20} = 1.0937\), \(n_D^{20} = 1.4535\)
That from the (cis) iso-β-chlorocrotonic ester had:
b.p. 164-165 °C at 12 mm., \(d_4^{20} = 1.0884\), \(n_D^{20} = 1.4579\).
These two stereoisomeric tricarboxylic esters were hydrolysed by keeping with cold 5% KOH for three days, enough alcohol being added to give a homogeneous solution.

From the trans-tricarboxylic ester trans-\(\beta\)-methyl-glutaconic acid \((29,\text{trans})\) was obtained, and from the cis-tricarboxylic ester cis-\(\beta\)-methyl-glutaconic acid \((29,\text{cis})\) was obtained, of melting points 149°C and 118°C respectively.

By condensing together an \(\alpha\)-alkyl-\(\beta\)-chloro-crotonic ester and the sodio derivative of an alkyl-malonic ester, it should be possible to obtain an \(\alpha\)-carbethoxy-\(\alpha\)-\(\beta\)-dialkyl-\(\beta\)-methyl-glutaconic ester, which on hydrolysis should yield \(\beta\)-methyl-\(\alpha\)-\(\beta\)-dialkyl-glutaconic acid.

As neither Fischer and Schwab, nor Kon and his co-workers, describe the method used to separate the chlorocrotonic esters or the conditions and yields for the main condensation, Blakley (N.Z. University Thesis 1946, Unpublished), before attempting the synthesis of \(\alpha\)-\(\beta\)-trimethyl-glutaconic acid by this method, first synthesised a mixture of the \(\beta\)-methyl-glutaconic acids by the method of Fischer and Schwab, without separating the chlorocrotonic esters. He found that by carrying out the condensation in ethyl alcohol he obtained only an 18% yield of the condensation product \((28)\), but in ether
the yield was increased somewhat, to 22.6%.  

On the basis of this experience, he set about the synthesis of \( \alpha \beta \gamma \)-trimethyl-glutaconic acid by condensing sodio-methyl-malonic ester (30) and \( \alpha \)-methyl-\( \beta \)-chlorocrotonic ester (31) in ether and hydrolysing the \( \alpha \)-carbethoxy-\( \alpha \beta \gamma \)-trimethyl-glutaconic ester (32) so produced, as set out in the scheme below.

\[
\begin{align*}
\text{CH}_3C=O-\text{CH}_2-\text{CO}_2\text{Et} & \xrightarrow{\text{NaOEt}, \text{CH}_3\text{Br}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{Et} \\
\text{Cl}-\text{O}=\text{C}-\text{CO}_2\text{H} & \xrightarrow{\text{H}_2\text{O}, \text{EtOH}, (\text{HCl})} \text{CH}_3\text{CH}_3\text{Cl} \\
\text{CH}_3\text{CH}_3\text{Cl} & \xrightarrow{\text{Ether}, \text{Na}_2\text{CO}_2\text{Et} \text{ (b.pt)}} \text{CH}_3\text{CH}_3\text{CO}_2\text{Et}
\end{align*}
\]

Blakley ultimately obtained a small quantity of the \( \alpha \beta \gamma \)-trimethyl-glutaconic ester (33), which gave the correct results on combustion analysis, and, on hydrolysis of the ester, a quantity of acid which was too small for
analysis or further characterisation, but which he believed to be \( \alpha\beta\gamma \)-trimethyl-glutaconic acid (54).

The method of making \( \alpha \)-methyl-\( \beta \)-chboro-crotonic ester was that of Koll (Annalen 1889, 242, 308). Methyl-acetoacetic ester was dropped on to phosphorus pentachloride, the acid chloride formed decomposed by water and the products separated by steam distillation and ether extraction. The \( \alpha \)-methyl-\( \beta \)-chloro-crotonic acid was esterified by the Fischer-Speier method.

The yield of \( \alpha \)-methyl-\( \beta \)-chboro-crotonic acid from the chlorination varied from 30.1% to 41.8% of theoretical and that of the ester from its acid from 41.5% to 48.4% of theoretical, making the overall yield of \( \alpha \)-methyl-\( \beta \)-chboro-crotonic ester from methyl-acetoacetic ester only about 16% of theoretical.

In the main condensation of \( \alpha \)-methyl-\( \beta \)-chboro-crotonic ester with sodio-methyl-malonic ester, the yield of tricarboxylic ester (52) was poor, being about 17%. Blakley attempted the combined hydrolysis and decarboxylation of this ester, using both acid and alkali, (following Fichter and Schwab, and Kon et al.) but none of the desired \( \alpha\beta\gamma \)-trimethyl-glutaconic acid could be crystallised from the oily product formed.

Thole and Thorpe long ago (J.C.S. 1911, 92, 2191)
observed that many compounds of the type of the carbethoxy-glutaconic esters, where a mobile hydrogen atom has been replaced by an alkyl group, can be made to replace a carbethoxy group by a hydrogen atom when treated with cold sodium ethoxide, thus acquiring tautomeric mobility. The actual product of the reaction is the yellow or orange sodium derivative of the glutaconic ester, the carbethoxy group being eliminated as ethyl carbonate. Thorpe et al. frequently used this reaction to eliminate a carbethoxy group before carrying out the hydrolysis of the ester, as they found that better yields of the glutaconic acids were obtained in this way.

Blakley, therefore, treated his carbethoxy ester with cold sodium ethoxide, but little or no reaction appeared to occur in this case. This was unexpected although both Thorpe (J.C.S. 1915, 192, 1569) and Kon (J.C.S. 1932, 135, 2447) found that the two forms of \( \alpha \)-carbethoxy-\( \beta \)-phenyl-\( \alpha \)-methyl-glutaconic ester failed to react with cold sodium ethoxide. Kon accounted for this on an electronic basis, thus:

Elimination of the carbethoxy group is due to the strong demand for electrons of the two electrophilic carbethoxy groups attached to the same carbon atom.
As a result, an ethoxide ion becomes attached by a
dative bond to the carbon atom of a C=O group, and
the subsequent electronic rearrangements (shown
diagrammatically below) result in the splitting off
of ethyl carbonate.

\[
\begin{align*}
&\text{CO}_2\text{Et} - \text{C} = \text{C} - \text{C} = \text{C} - \text{CO}_2\text{Et} \\
&\text{EtO} - \text{C} = \text{O} - \text{OEt} \\
&\text{Na}^+ \quad \text{OEt} \\
&\text{Na}^+ \quad \text{OEt}
\end{align*}
\]

In the case of \(\alpha\)-carbethoxy-\(\beta\)-phenyl-\(\alpha\)-methyl-
glutaconic ester, Kon suggested that the electron
demand of the carbethoxy groups can be met by electron
displacements involving the phenyl group, which becomes
electron donating. Thus the co-ordination of the
ethoxide ion, necessary for the elimination of the
carbethoxy group, occurs less readily. Blakley
concluded that in \(\alpha\)-carbethoxy-\(\alpha\)(\(\beta\))-trimethyl-
glutaconic ester the cumulative electron donating effect of the
three methyl groups produced a similar effect.
Blakley then treated his carboxy ester with sodium ethoxide at successively higher temperatures, hoping the reaction might thus be induced. After treatment at 80°C he found that a bright orange colour developed and from the reaction mixture he isolated an ester boiling about 200 lower than the carboxy ester. This was redistilled under reduced pressure, when a liquid distilling at 143°C-148°C at 19 mm. was obtained. Microcombustion analysis gave 

\[ C = 63.04\%, \quad H = 8.86\% \]

The theoretical values for ethyl-(\(\beta\))-trimethyl-glutaconate are 

\[ C = 63.13\%, \quad H = 8.85\% \]

Hydrolysis of the small amount of ester remaining by refluxing with aqueous-alcoholic HCl gave a viscous oil from which a small amount of colourless crystalline solid separated on standing. This gave an acid reaction with bicarbonate, and Blakley considered that it was probably \(\alpha(\beta\delta)-\)trimethyl-glutaconic acid, but there was not enough for purification and melting point determination or quantitative analysis.
THE PRESENT INVESTIGATION.

The object of the present investigation was to repeat Blakley's work, endeavouring to improve yields wherever possible, and to obtain sufficient product to analyse and characterise.

Methyl-malonic ester was made by methylating malonic ester in alcohol with sodium ethoxide and methyl bromide, and methyl-acetoacetic ester by methylating acetoacetic ester in a similar way.

An attempt was made to chlorinate methyl-acetoacetic ester directly to α-methyl-β-chloro-crotonic ester, using mild conditions and so avoiding attack on the carboxyxy group. The following conditions were used:

1. With PCl₃ in benzene at room temperature.

The ester reacted slowly. On extraction and fractional distillation all the products distilled between 68° and 75° at 14 mm. and no portion of the distillate had the properties expected of α-methyl-β-chloro-crotonic ester. On redistillation with a longer column, the result was the same.

2. With PCl₃ in benzene at 0°C.

After 12 hours little reaction had occurred and on working up, unchanged ester was obtained, together
with a small fraction with properties similar to those of the product obtained in (1) above.

3. With PC15 in ether at 0°C.

It was thought that a solvent more capable of catalysing the tautomerism of methyl-acetooxacetic ester might give better results since only the enol form is involved in the production of the desired product and so ether was tried, at 0°C, but the result was the same as in (2) above.

4. With PC15 in ether initially at 0°C and then warmed to room temperature.

The result was the same as in (1) above.

5. With PC15 in ether under reflux.

Reaction was complete in 40 minutes and the products were the same as in (1) and (4) above.

An attempt was made to separate the chlorinated products in the mixture obtained in (1), (4), and (5) above, by more efficient fractional distillation under reduced pressure. As no high efficiency columns were available, an asbestos lagged column packed with glass helices was used. The distilling range was widened a little on distillation and redistillation, but separation of any α-methyl-β-chloro-crotonic ester could not be effected. Fractional distillation at atmosphere
pressure was also tried but, as expected, was unsuccessful and caused considerable decomposition.

The possible products of the chlorination reaction, other than $\alpha$-methyl-$\beta$-chloro-crotonyl chloride, are:

$$\begin{align*}
\text{CH}_3 \\
\text{CH}_3 - C = C - \text{CO}_2\text{Et} \\
\quad \text{Cl} \\
\text{CH}_3 \\
\text{CH}_3 - C = C - \text{CO}_2\text{Et} \\
\quad \text{O} \\
\quad \text{Cl} \\
\text{CH}_2\text{Cl} \\
\text{CH}_3 - C = \text{CH} - \text{CO}_2\text{Et} \\
\quad \text{O} \\
\quad \text{Cl} \\
\text{CH_3Cl} \\
\text{CH}_3 - C = \text{CH} - \text{CO}_2\text{Et} \\
\quad \text{O} \\
\quad \text{Cl} \\
\end{align*}$$

It is notable that the wanted $\alpha$-methyl-$\beta$-chloro-crotonic ester is the only one of these which has no keto (or keto-enol) grouping. It seemed possible therefore, that some reaction of the keto group might be used to remove the other substances, so that this might be
recovered from the residue. Reaction with phenyl-hydrazone was tried for this purpose. At room temperature, using excess of phenylhydrazone, practically everything in the mixture was found to react with the phenylhydrazone. Reaction at 0°C for a short time was then tried, but the usual mixture of chlorinated products was recovered from the residue. It was concluded that the chlorine of α-methyl-β-chlorocrotonic ester was about as labile to phenylhydrazone as were the keto groups of the other compounds.

Other chlorinating agents were then tried for the chlorination as follows:

6. \( \text{PCl}_3 \) in ether.

No reaction occurred, even under reflux, and only unchanged ester was recovered.

7. \( \text{PCl}_3 \) and methylacetoacetic ester refluxed together.

The solution darkened, but only unchanged ester was recovered.

8. \( \text{SOCl}_2 \) in ether.

The result was the same as in (2) above.

9. \( \text{SOCl}_2 \) and methylacetoacetic ester refluxed together.

About a third of the ester was found to be chlorinated to the usual mixture, the rest being unchanged.

After these unsuccessful attempts at a new method
of chlorination, the method of Koll, as described in the Theoretical Introduction, was used.

Blakley had obtained a rather poor yield (45%) in the last step of this synthesis, namely, the Fischer-Speier esterification of the acid. There seemed no reason why unchanged acid could not be recovered and esterified again. This was done, and by this means the overall yield of ester from acid was raised to 32% of theoretical.

As Blakley had found that the condensation of \( \alpha \)-methyl-\( \beta \)-chloro-crotonic ester and sodio-methylmalonic ester in ether as a medium gave only a 17% yield, and as in the simpler case of the condensation of \( \beta \)-chloro-crotonic ester and sodio-malonic ester ethanol was less efficient even than ether, it was decided to try tert.-butyl alcohol as the solvent in the present work. This alcohol has been used as a medium for condensations involving sodio derivatives by many workers in recent years with success, as alcoholysis occurs less readily than in ethanol or methanol. Blakley did not use this solvent because insufficient was available in this laboratory in 1946.

Sodium was dissolved in the tert.-butyl alcohol, methyl-malonic ester added to give the sodio derivative,
and \( \alpha \)-methyl-\( \beta \)-chloro-crotonic ester finally added. After refluxing the mixture there was isolated from the products a viscous liquid distilling at 166-171\(^{\circ}\)/ 13 mm. with \( \alpha \_D^{20} 1.4570 \), having a neutral reaction, decolourising bromine and permanganate, and giving no test with ferric chloride. This was evidently the required product, \( \alpha \)-carbethoxy-\( \alpha \_\alpha \)-trimethyl-glutaconic ester. Several batches were made, and yields of up to 70-2\% of theoretical were obtained, i.e. about four times as high as the yield previously obtained using ether as the medium. The higher yield was probably due mainly to the higher temperature employed, and to reduced alcoholysis.

The decarbethoxylation of this ester to the trimethyl-glutaconic ester, by treating with a sodium alkoxide in hot alcoholic solution, was next investigated. Sodium ethoxide in ethyl alcohol and sodium tert.-butoxide in tert.-butyl alcohol were both tried in two separate decarbethoxylation. In each case, there was isolated from the products, an ester boiling about 40\(^{\circ}\) lower than the carbethoxy ester. This ester distilled at 135\(^{\circ}-\)194\(^{\circ}\)C at ½ mm. and was a colourless, fairly mobile liquid of \( \alpha \_D^{20} 1.4577 \).

This ester was hydrolysed by refluxing with hydrochloric acid, giving an acid in the form of an oil which
took over three weeks to crystallise. The solid acid, which did not crystallise well, had a typical "glutaconic acid smell" and behaved chemically as an unsaturated acid. It was practically insoluble in petroleum ether, sparingly soluble in cold water and cold benzene, and readily soluble in alcohol, ether, hot water and (to a lesser extent) hot benzene. Recrystallisation from water gave a melting point of 106-109°C (°) and after four recrystallisations from benzene, a constant melting point of 112°C was obtained. The melting point of this acid was depressed by all the following methyl-substituted glutaconic acids:

trans - Dβ - trimethyl -  
trans - Dγ - trimethyl -  
trans - aγ - dimethyl -  
cis - Oγ - Dβ - dimethyl -  
trans - β - methyl -  
cis - β - methyl -  

Boiling the recrystallised acid with hydrochloric acid rapidly lowered the melting point, indicating that strong acids cause rapid interconversion of the stereo-isomeric forms of the acid and give rise to an equilibrium mixture with a low melting point.

The equivalent weight of the recrystallised acid was

(*) All melting points recorded in the present work are uncorrected.
determined on a micro scale by titration with standard carbonate-free alkali and was found to be 86. The theoretical equivalent weight for a trimethyl-glutaconic acid is 86.

In view of these results and of the method of synthesis, there seemed no doubt that the acid obtained was the desired one.

The rest of the α-carbethoxy-αβ-trimethyl-glutaconic ester was decarbethoxylated in similar fashion, using the alkoxide solutions under varying conditions of temperature and duration of heating. The best yield (75.9% of theoretical) was obtained by treatment with sodium ethoxide in ethyl alcohol for 1 1/2 hours at 80°C. It had been expected that side reactions with the ethoxide solution would occur to a significant extent under such drastic conditions, but on distilling the products of reaction, two sharply defined fractions only, were obtained. One was the trimethyl-glutaconic ester and the other, in the case where sodium ethoxide was used, was identified by its smell and physical properties as di-ethyl carbonate. When sodium tert.-butoxide was used, this was replaced by a similar substance, presumably ethyl tert.-butyl carbonate. However, in all cases, a brown residue was left in the distilling flask. As very
little decomposition occurred on distilling the carbethoxy ester under the pressures used, this residue apparently arose from the occurrence of side reactions, probably involving polymerisation.

The $\alpha\beta\gamma$-disposition of the three methyl groups in the trimethyl-glutaconic ester was confirmed by a study of its oxidation products.

For $\alpha\beta\gamma$-trimethyl-glutaconic ester, oxidative fission would be expected to take the following course:

\[
\begin{array}{c}
\text{COOEt} \\
| \\
| \\
| \\
H-C-Me \\
| \\
| \\
| \\
\text{G-Me} \\
| \\
| \\
| \\
\text{G-Me} \\
| \\
| \\
| \\
\text{COOEt} \\
\end{array}
\quad \rightarrow 
\begin{array}{c}
\text{COOEt} \quad \text{monomethyl-acetoacetic ester} \\
| \\
| \\
| \\
H-C-Me \quad \text{ester} \\
| \\
| \\
| \\
\text{G=C} \\
| \\
| \\
| \\
\text{Me} \\
| \\
| \\
| \\
\quad \rightarrow 
\begin{array}{c}
\text{Me} \quad \text{pyruvic ester} \\
| \\
| \\
| \\
\text{G=C} \\
| \\
| \\
| \\
\text{COOEt} \\
\end{array}
\]

the pair of products being distinct from the pairs obtained by oxidising the other trimethyl-glutaconic esters.

On oxidising some of the ester with 5% neutral permanganate and extracting and distilling the products, the main fraction obtained was a colourless mobile liquid smelling like acetoacetic ester and its methyl derivatives.
Its general physical and chemical properties and the formation of $\alpha$-methyl-$\beta$-chloro-erotic acid of m.p.t. 67° by chlorination, showed that it was mono-methyl-acetoacetic ester. No pyruvic ester was detected because this substance is rapidly oxidised by excess neutral permanganate.

More of the ester was oxidised at 0°C by very dilute neutral permanganate, using insufficient permanganate for complete oxidation. Distillation of the products again gave mono-methyl-acetoacetic ester as the main product, but a very small fraction distilled over a range of temperature which included the boiling range of pyruvic ester. Using a micro technique, this fraction was hydrolysed by caustic soda and the resultant solution, in company with a separate reference solution of pyruvic acid, gave several positive chemical tests for pyruvic acid, including the highly specific colour reactions with sodium nitroprusside and with $\beta$-naphthol in sulphuric acid. It was therefore concluded that pyruvic ester was one of the products of oxidation of the trimethyl-glutaconic ester, the other being mono-methyl-acetoacetic ester, just as expected for the $\alpha\beta\gamma$-configuration.

In the hydrolysis of the $\alpha\beta\gamma$-trimethyl-glutaconic ester by hydrochloric acid, besides the acid, a little
anhydride was formed. This anhydride was easily reconverted to the acid by dissolution in hot sodium carbonate solution followed by acidification. Including this, the overall yield of acid from ester in the hydrolysis was 95% of theoretical.

The initial crystallisation of the acid occurred more readily from aqueous than from non-aqueous solution, but hot water appeared to cause interconversion of the isomeric forms of the acid, which was undesirable because it was intended to attempt the separation of the latter. For these reasons and also because other glutaric acids appear to be somewhat volatile in steam at the temperature of boiling water, e.g. see Sargent (N.Z. University Thesis 1931, unpublished), it appeared that the best method of crystallising the acid was by removal of water from the aqueous solution at as low a temperature as possible under reduced pressure. Successive crops of crystals were precipitated by this means.

After further purification by recrystallisation from benzene, the acid gave on combustion analysis

\[ \text{C=55.73\%} \quad \text{H=6.88\%} \]

\[ C_8 H_{12} O_4 \text{ requires C=55.80\%} \quad \text{H=7.94\%} \]

A molecular weight determination was made by the
Rast semi-micro method. The molecular depression constant value used was determined from the melting point depression caused by a known concentration of \( \alpha\beta\)-trimethyl glutaric acid in the camphor. This reference solute was chosen in order to counteract, as far as possible, any errors due to the ionisation (and possibly other properties) of the acid under test. Two complete determinations were carried out, giving for the molecular weight of the acid:

(a) 179 and (b) 173

\( C_8 H_{12} O_4 \) requires 172.

Rogerson and Thorpe (J.C.S. 1935, 87, 1672), describe the preparation of 3:4:5-trimethyl-2:6-dihydroxy-pyridine (35) both by the distillation of the ammonium salt of \( \alpha\beta\)-trimethyl-glutaric acid and by the hydrolysis of \( \alpha\)-cyano-\( \alpha\beta\)-trimethyl-glutaric ester, but give no conclusive proof of the constitution of the product. According to these authors, this pyridine derivative has melting point 160\(^\circ\)C and its dibenzoyl derivative has melting point 188\(^\circ\)C.

In the present investigation the ammonium salt was made by the removal of water from a solution of the acid in strong ammonia solution, in a vacuum desiccator,
(boiling the water off caused considerable hydrolysis). The dry salt was distilled at 590 m.m. pressure, and a yellow oil, which solidified immediately, distilled at about 260°, as described by Rogerson and Thorpe. This substance had the general properties to be expected of a hydroxy-pyridine derivative. After repeated recrystallisation from absolute alcohol it had melting point 183.5°C.

\[ \text{CH}_3 \text{CH}_3 \]
\[ \text{HO}^+ \text{N} \]

(35)

\[ \text{CH}_3 \text{CH}_3 \]
\[ \text{PhOCO} \text{O.CO.P} \]

(36)

A further small quantity was made in the same way and was benzoylated by the Schotten-Baumann method. The benzoyl derivative, assumed to be the dibenzoyl derivative (36), after repeated recrystallisation from glacial acetic acid, had melting point 186°C.

Thole and Thorpe (J.C.S. 1911, 22, 2221.) stated that on boiling \( \text{Ph} \)trimethyl-glutaconic acid with acetic anhydride, a hydroxy-anhydride with the same general properties as other members of the series was obtained, with melting point 119°C. According to these authors a normal anhydride, which was a liquid, was
obtained by boiling the acid with acetyl chloride. However, no conclusive proofs of the constitutions of the acid or the anhydrides were given.

In the present investigation some acid was boiled with acetic anhydride and some with acetyl chloride, as described by the above authors, but the same anhydride was obtained in each case. Boiling with acetyl chloride containing a small proportion of phosphorus trichloride also gave the same result. This anhydride was a crystalline normal anhydride (37), with none of the properties typical of hydroxy-anhydrides.

Solution in hot sodium carbonate followed by acidification gave back the trimethyl-glutaconic acid. Repeated recrystallisation of the normal anhydride from benzene-petroleum ether mixtures gave melting point 119.5°C.

On distillation under reduced pressure, the normal anhydride was converted into another quite distinct anhydride, which appeared to be the hydroxy-anhydride (38) as it reacted with cold sodium bicarbonate and was
slowly hydrated by cold water, although it appeared not to give a red colour with ferric chloride. It was converted back to trimethyl-glutaconic acid in the same way as the other anhydride. Solution in cold alkali followed by immediate acidification gave a mixture of the acid and of unchanged anhydride, as with certain other hydroxy-anhydrides in the glutaronic series. Repeated recrystallisation of this hydroxy-anhydride from benzene gave melting point 116°.

From the solution obtained by dissolving the hydroxy-anhydride in distilled water, there was isolated a small quantity of cis-acid (m.p.t. 115°). Pure cis-acid was prepared by careful fractional crystallisation, in the cold, of the crude acid. It had melting point 117° and was identical with that made by the hydration of the hydroxy-anhydride with cold water. The recrystallised cis-acid on combustion analysis, gave

\[ \begin{align*} 
\text{C}_8\text{H}_{12}\text{O}_4 \text{ requires } & C=55.80\% \text{ H}=7.04\% \\
\text{observed } & C=55.62\% \text{ H}=7.06\% 
\end{align*} \]

The separation of the pure trans-acid from the crude acid by recrystallisation in the cold was attempted, but was found more difficult than the separation of pure cis-acid. The acid crystallised very slowly from the mixed organic solvents used and the rise of melting
point with each recrystallisation was small. The highest melting point attained in two series of recrystallisations was 131-133°. Time did not permit further work with a larger quantity of crude acid.

Rogerson and Thorpe (loc.cit.) and Thorpe and Wood (J.C.S. 1913, 192, 1759) quoted the melting point of their αβγ-trimethyl-glutaconic acid as 127° after recrystallisation from water.
SUMMARY

1. A new synthesis of \( \alpha\beta\gamma \)-trimethyl-glutaconic acid has been carried out and the optimum conditions established for the reactions involved.

2. The composition and constitution of the \( \alpha\beta\gamma \)-trimethyl-glutaconic acid produced have also been demonstrated by the determination of its equivalent weight, molecular weight and chemical composition, and by a study of the oxidation products of its parent ester.

3. The geometrical isomerism of the acid has been demonstrated and the normal and hydroxy-anhydrides prepared and examined. 3:4:5-Trimethyl-2:6-dihydroxy-pyridine has been prepared by the distillation of the ammonium salt of the acid.

A brief diagrammatic outline of the synthesis, and of the preparation of derivatives, is shown on the next page. The approximate yields which were attained in various steps are indicated.
INDEX TO EXPERIMENTAL SECTION.

I. Purification and/or Preparation of Chemicals. ........................................ 40
II. Methylation of Malonic Ester. ............................................................... 43
III. Methylation of Acetoacetic Ester. ......................................................... 46
IV. Attempted Chlorination of Methyl-Acetoacetic Ester .............................. 48

By PCl5 in benzene.
(1) At room temperature .................................................................................. 48
(2) At 0°C ......................................................................................................... 49

By PCl5 in ether.
(3) At 0°C .......................................................................................................... 50
(4) At room temperature .................................................................................... 51
(5) Under reflux. ............................................................................................... 51

Attempted separation of chlorination products
(a) by more efficient fractional distillation, .................................................. 52
(b) by reaction with phenylhydrazine. ............................................................. 54

By PCl3
(6) In ether under reflux .................................................................................... 55
(7) Alone under reflux ....................................................................................... 55

By SOCl2
(8) In ether under reflux .................................................................................... 55
(9) Alone under reflux ....................................................................................... 56

V. Preparation of α-methyl-β-chloro-crotonic acid. ........................................ 57
VI. Esterification of α-methyl-β-chloro-crotonic acid. ....................................... 59
VII. Condensation of sodio-methylmalonic ester and α- ................................ 61
methyl-β-chloro crotonic ester.

VIII. Decarbethoxylation of the ester from the condensation, and hydrolysis of the ester produced. 65

IX. Preliminary investigation of the acid from the hydrolysis, and microdetermination of its equivalent weight. 72

X. Oxidative fission of the ester from the decarbethoxylation. 75

XI. Analysis and molecular weight determination of the acid. 78

XII. The distillation of the ammonium salt of the acid. 80

XIII. The preparation of the anhydrides of the acid. 83

XIV. The separation of the cis-form of the acid by two methods, and its analysis. 86

XV. The attempted separation of the trans-form of the acid. 88

+++++++
I. PURIFICATION OF CHEMICALS.

Ethyl alcohol.

Commercial absolute alcohol was refluxed over quicklime for six hours, then over aluminium amalgam for two hours, and distilled through an efficient fractionating column. The product had $n_D^{18\circ} 1.3622$. Lorenz gives for pure alcohol $n_D^{18\circ.35} 1.36242$ (Annalen der Physik 11, 70, 80). For use in the methylation of malonic and acetoacetic esters, alcohol was purified as required and distilled into the actual reaction vessel.

Ether.

Ether was shaken with acid ferrous sulphate solution (conc. $\text{H}_2\text{SO}_4$, 7.5 gms., water 135 c.c., $\text{FeSO}_4$ 60 gms. to 2.5 litres of ether) to remove peroxides, washed with dilute alkali and then water. It was dried over calcium chloride, distilled through a long fractionating column from caustic potash sticks, and stored in a dark cupboard. Part of it was kept over sodium wire.

Malonic ester.

The B.D.H. product was distilled from a Claisen flask with fractionating column and the fraction boil-
ing at 95°C at 16 mm. kept. This had \( n_D^{20} = 1.4144 \). Smythe and Walls give \( n_D^{20} = 1.4145 \) for the pure ester. (J.C.S. 1931, 529)

**Acetic acid ester.**

The B.D.H. product and some of doubtful manufacture were distilled from a Claisen flask with fractionating column and the fraction boiling 73-78°C at 15 mm. kept. The distillate had \( n_D^{16.6} = 1.4201 \). Brühl (Zeitsch. anorg. allg. chem. 13, 293; 1, 80) gives \( n_D^{16.6} = 1.42092 \) for the pure ester.

**Phenylhydrazine.**

This was made from the hydrochloride (The Fisher Scientific Co.'s product) by treating with caustic potash, extracting with benzene and fractionating in vacuo. The fraction distilling at 115-119°C/14 mm. was kept in a bottle with ground-in stopper, in a dark cupboard.

**Tertiary butyl alcohol.**

The Shell Oil Company's product was refluxed with quicklime for 5 hours and with calcium borings for 2 hours, then distilled through a good column. It distilled at 82.7°C at 760.4 mm., there being practically no forerun or residue. Various workers give boiling
points from 82.55° to 82.94° for the pure alcohol. The distillate had $n_D^{20} = 1.3878$. Brühl (Zeitsch. an. allg. chem. 13, 203:1:30) gives $n_D^{20} = 1.38779$ for the pure alcohol. The melting point of this alcohol is 25.5°, so it was necessary, when working with it, to provide all condensers with a supply of water warmed to slightly above this temperature, and to keep adapters and similar components slightly warmed by nearby flames. Otherwise, solidification and blockages occurred.
II. METHYLATION OF MALONIC ESTER.

(Fresh cut sodium (69 gms.) was added to anhydrous ethyl alcohol (1.51.) in a 3 litre flask fitted with a reflux condenser and delivery tube. When all the sodium had dissolved, malonic ester (480 gms.) was added.

Methyl bromide was made as follows. 98% H₂SO₄ (758 gms.) was added slowly with shaking to methanol (627 gms. technical grade) cooled in ice. Sodium bromide (338 gms.) was suspended in half this mixture in a 2 litre round bottom flask fitted with dropping funnel, delivery tube and thermometer. Evolution of methyl bromide commenced on heating to about 50°C on a water bath and the rest of the acid mixture was added to the funnel while the temperature was slowly raised. The gas was passed through a tower of KOH flakes and sticks (no pellets were available).

The methyl bromide was bubbled through the alcoholic solution, and when all this gas had been passed in (11-12 hours) the malonic ester solution was boiled for half an hour, neutralised with glacial acetic acid and cooled. The sodium bromide was
filtered off and washed with anhydrous alcohol, the washings being added to the main solution. Most of the alcohol was distilled off at atmospheric pressure and the residue shaken with a solution made by dissolving the sodium bromide in 600-700 ccs. of water plus 10 ccs. of conc. HCl. The aqueous layer was separated and extracted twice with ether. The combined ester and ether extracts were dried quickly with CaCl₂, and ether distilled off and the ester shaken for 60 seconds with a cold solution of NaOH (10 gms.) in water (30 ccs.) to remove malonic ester. The ester was then washed with dilute acid and water and dried by CaCl₂. Distillation under reduced pressure gave 254.9 gms. of ester distilling at 92-95° at 15 mm. This had nD¹⁸·⁷ 1.4134. Von Auwers (Berichte 46, 594) gives nD¹⁸·⁷ 1.41369 for pure methyl-malonic ester. **Yield: 48.8% theoretical.**

In a second preparation, the same quantities were used. In this second preparation and in the methylations of acetoacetic ester, the methyl bromide was passed into the alcoholic solution by a perforated tube inside a larger one, up and down which it could be moved by sliding in a rubber joint. At intervals it was slid down to knock out sodium bromide incrus-
tation which collected at the outlet of the wider tube, thus avoiding the blockages which caused considerable trouble in the first preparation.

Also a reflux condenser was inserted between the generator and the tower as there was some tendency for methanol to distil into the latter. Amount produced: 372.5 gms. distilling at 93-95° at 15 mm. with np\textsuperscript{13} 1.4136. \textbf{Yield: 71.3\% theoretical.}

After boiling with a little sodium to remove methyl bromide, and distilling, the alcohol used in these experiments was used again in the methylation of acetocetic ester.
III. METHYLATION OF ACETOACETIC ESTER.

(Frank C. Gilman and J. H. Hussey, J. Am. Chem. Soc. 55, 727, 1933)

Fresh cut sodium (46 gms.) was dissolved in anhydrous alcohol (1 l.) in a 2 litre round bottomed flask fitted up as described in II above. Acetoacetic ester (260 gms.) was added and the solution heated to gentle boiling. Methyl bromide generated as described in II above, was bubbled through the gently boiling solution for 11-12 hours. The mixture was then refluxed on a water bath for about 6 hours, when the solution was neutral. The mixture was cooled, the sodium bromide filtered off and washed with alcohol, the washings being added to the main solution. Most of the alcohol was distilled off at atmospheric pressure, and the oil washed with water which was then extracted 3 times with ether.

Kon (J.C.S. 1931, 134, 571) considers it essential to purify the methylacetoacetic ester from traces of acetoacetic ester by shaking with dilute aqueous ammonia, so the combined ester and ether extracts were shaken 3 times with 2N aqueous ammonia. They were dried overnight with anhydrous sodium sulphate,
the ether distilled off and the residue fractionated under reduced pressure. The part boiling at 81°-
84.5° at 16 mm. was kept. This had $n_d^{17.8} 1.4298$.
Von Auwers (Ber. 46, 504) gives $n_d^{17.8} 1.429$ for pure methyl-acetoacetic ester. Yield: 161.8 gms. (56.1% theoretical).

After the passage of methyl bromide the alcoholic solution in the above preparation was deeply coloured, and on washing the oil with water, quite a lot of dark tarry material appeared in a flocculent form and made separation and ether extraction slow and difficult. In subsequent batches, therefore, the residue from the distilling off of the alcohol was distilled under reduced pressure when the ester came over colourless, leaving a tarry residue. This colourless distillate was much more convenient to wash and extract.

Two more batches were made using the same quantities. The products were:

177.1 gms. with $n_d^{17.8} 1.4299$

and 182.2 gms. with $n_d^{17.8} 1.4292$

Yields: 61.4% theoretical and 63.1% theoretical.
IV. ATTEMPTED PREPARATION OF $\alpha$-METHYL-$\beta$-CHLORO CROTIC ESTER BY THE CHLORINATION OF METHYL-
ACETOACETIC ESTER.

By PC15 in Benzene.

(1) At room temperature.

20 gms. of methyl-acetoacetic ester was dissolved in 36 gms. of benzene in a small bolt-head flask fitted with a reflux condenser. 14.6 gms. of PC15 was added in small portions, while the flask was kept cool by tap water. After half an hour a slow evolution of gas commenced, and after about 4 hours, all the PC15 had dissolved. The mixture was shaken with 3 volumes of water and the water layer drawn off and extracted several times with benzene. After drying with a little CaCl2, the benzene was distilled off over a water bath and the residue fractionated under reduced pressure. The following fractions were taken:

Up to 68°/14 mm. few drops

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Weight (gms.)</th>
<th>$n_D^{20}$</th>
<th>$\rho_{20}^{4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>68-70°/14 mm.</td>
<td>5</td>
<td>1.4436</td>
</tr>
<tr>
<td>B</td>
<td>70-75°/14 mm.</td>
<td>8</td>
<td>1.4429</td>
</tr>
<tr>
<td>C</td>
<td>73-75°/14 mm.</td>
<td>7</td>
<td>1.4425</td>
</tr>
</tbody>
</table>

Only a small tarry residue remained. On ether extraction, extraction with sodium carbonate, acid-
ification and ether extraction, a small amount of solid acid was isolated from this residue.

The above fractions were each refractionated, giving the following fractions.

(A) 67°-69°/14 mm. 1 gm. \( n_D^{20} = 1.4431 \)  \( \text{FeCl}_3 \) test: enol present.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Weight</th>
<th>( n_D^{20} )</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>2 gm.</td>
<td>1.4428</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>0.5 gm.</td>
<td>1.4425</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>1 gm.</td>
<td>1.4428</td>
<td></td>
</tr>
</tbody>
</table>

(B) 68°-70°/14 mm. 2 gm. \( n_D^{20} = 1.4429 \)

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Weight</th>
<th>( n_D^{20} )</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>1.5 gm.</td>
<td>1.4420</td>
<td></td>
</tr>
<tr>
<td>71.5-72.5°</td>
<td>2 gm.</td>
<td>1.4418</td>
<td></td>
</tr>
<tr>
<td>72-75°</td>
<td>1.5 gm.</td>
<td>1.4430</td>
<td></td>
</tr>
</tbody>
</table>

(C) 68°-70°/14 mm. 1.5 gm. \( n_D^{20} = 1.4425 \)

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Weight</th>
<th>( n_D^{20} )</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>70.5-72°</td>
<td>1.5 gm.</td>
<td>1.4421</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>2 gm.</td>
<td>1.4427</td>
<td></td>
</tr>
<tr>
<td>73.5-75°</td>
<td>1 gm.</td>
<td>1.4417</td>
<td></td>
</tr>
</tbody>
</table>

(All these refractive indices are much lower than that of \( \alpha \)-methyl-\( \beta \)-chloro-crotonic ester).

(2) \( \text{At } 0^\circ\text{C.} \)

To 20 gms. of methyl-acetoacetic ester in 30 gms. of benzene cooled in ice, 14.6 gms. of \( \text{PCl}_3 \) was
added in portions. There were no visible signs of reaction and after 12 hours not much PCl₅ seemed to have reacted. The liquid was extracted and distilled as in (a) above, and the following fractions taken, all at 14 mm.

(A) 67-70° 5 gm. n₂₀ 1.4431 FeCl₃ test: enol present.
(B) 70-75° 5 gm. n₂₀ 1.4413 * * * *
(C) 75-78° 2 gm. n₂₀ 1.4309 * * * *
(D) 78-81° 16 gm. n₂₀ 1.4213 * * * *

Fraction (D) was refractionated and the following fractions taken:

70-78° 5 gm. n₂₀ 1.4251 FeCl₃ test: enol present.

78-81.5° 15 gm. n₂₀ 1.4205 * * *

The latter fraction was returned to the methyl-acetoacetic ester bottle.

By PCl₅ in Ether.

(3) At 30°C.

To 20 gms. methyl-acetoacetic ester in 50 gms. of ether was added gradually 14.6 gms. PCl₅, the whole being cooled in ice. Reaction appeared very slow and after 9 hours little PCl₅ had reacted. On working
up the mixture as before, the following fractions were taken at 14 mm.

67-78° 1 gm. \( n-D 1.4393 \) FeCl₃ test: enol present.
78-81.5° 1' gm. \( n-D 1.4207 \)

The latter fraction was returned to the methyl-aceto-acetic ester bottle.

(4) **At room temperature.**

To 20 gms. methyl-acetoacetic ester in 50 gms. of ether, was added gradually 14.6 gms. FeCl₃, the whole being cooled in ice. The solution was then allowed to warm up to room temperature. After about 4 hours all the FeCl₃ had dissolved. The products were worked up as before, and the following fractions taken at 14 mm.

(A) 68-70.5° 3 gms. \( n-D 1.4438 \) FeCl₃ test: enol present.
(B) 70.5-73° 7 gms. \( n-D 1.4439 \)
(C) 73-75.5° 9 gms. \( n-D 1.4427 \)

(5) **Under reflux.**

10 gms. of methyl-acetoacetic ester was dissolved in 25 gms. of ether, 7.3 gms. of FeCl₃ added and the mixture refluxed. All the FeCl₃ dissolved in 40 minutes. The products were worked up in the usual way and the following fractions taken at 14 mm. pressure:
(A) 67.5-69° 1 gm. n_{D}^{20} 1.4440 FeCl₃ test: enol present.
(B) 69.5-70° 1.5 gm. n_{D}^{20} 1.4437
(C) 70.5-72° 2 gm. n_{D}^{20} 1.4431
(D) 72.5-73.5° 1.5 gm. n_{D}^{20} 1.4423
(E) 73.5-75° 1 gm. n_{D}^{20} 1.4405
(F) 75-78° a little
(G) 78-80.5° 1 gm. n_{D}^{20} 1.4219

(G) was presumably mainly methyl-acetoacetic ester.

**Attempted Separation of Products of the above Chlorinations.**

First, by more efficient fractional distillation.

The chlorinated mixture was mixed with a higher boiling substance (malonic ester) to avoid leaving a large amount of it in the apparatus at the end of the distillation. It was then distilled slowly (50-70 sec. per drop) through 35 cms. of glass helices in an asbestos lagged column. The following fractions were taken at 14 mm.:

(A) 65-68° 9 gm. n_{D}^{20} 1.4445 FeCl₃ test: enol present.
(B) 68-71° 8 gm. n_{D}^{20} 1.4421
(C) 71-74° 5 gm. n_{D}^{20} 1.4451
(D) 74-78° 9 gm. n_{D}^{20} 1.4399
Each of these fractions was refractionated in a similar manner, and the following fractions were taken:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Temperature</th>
<th>Mass (g)</th>
<th>Density (g/mL)</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>64 - 70°</td>
<td>2</td>
<td>1.4063</td>
<td>FeCl₃ test: enol absent.</td>
</tr>
<tr>
<td>A.</td>
<td>68 - 72°</td>
<td>1.5</td>
<td>1.4043</td>
<td>enol present</td>
</tr>
<tr>
<td>A.</td>
<td>72 - 75°</td>
<td>2</td>
<td>1.4367</td>
<td></td>
</tr>
<tr>
<td>A.</td>
<td>75 - 77.5°</td>
<td>2</td>
<td>1.4438</td>
<td></td>
</tr>
<tr>
<td>B.</td>
<td>66.5 - 68°</td>
<td>5</td>
<td>1.4212</td>
<td></td>
</tr>
<tr>
<td>B.</td>
<td>68 - 72°</td>
<td>1.5</td>
<td>1.4411</td>
<td></td>
</tr>
<tr>
<td>B.</td>
<td>72 - 75°</td>
<td>2</td>
<td>1.4387</td>
<td></td>
</tr>
<tr>
<td>B.</td>
<td>75 - 78°</td>
<td>2.5</td>
<td>1.4324</td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td>65 - 68°</td>
<td>5</td>
<td>1.4273</td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td>68 - 72°</td>
<td>1</td>
<td>1.4456</td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td>72 - 74°</td>
<td>1</td>
<td>1.4468</td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td>74 - 78.5°</td>
<td>1.5</td>
<td>1.4525</td>
<td></td>
</tr>
<tr>
<td>D.</td>
<td>65.5 - 68°</td>
<td>1.5</td>
<td>1.4281</td>
<td></td>
</tr>
<tr>
<td>D.</td>
<td>68 - 73°</td>
<td>1.5</td>
<td>1.4497</td>
<td></td>
</tr>
<tr>
<td>D.</td>
<td>73 - 76°</td>
<td>2</td>
<td>1.4459</td>
<td></td>
</tr>
<tr>
<td>D.</td>
<td>76 - 78.5°</td>
<td>2.5</td>
<td>1.4336</td>
<td></td>
</tr>
</tbody>
</table>

Fractional distillation at atmospheric pressure was tried next using a similar column. The following fractions were taken:
A large amount of darkly residue was left, indicating considerable decomposition.

**Second, by condensation with phenylhydrazine.**

5 gms. of acetoneacetic ester was treated with 4.2 gms. of phenylhydrazine and a drop of glacial acetic acid. A yellow precipitate formed at room temperature and increased on warming.

The chlorinated mixture (5 gms.) was then treated with phenylhydrazine (4 gms.). A copious precipitate formed rapidly at room temperature. After standing half an hour, the mixture was filtered, shaken with dilute acetic acid, and ether extracted. The extracts were dried and distilled. Only a very small fraction distilled between 60° and 85° at 1 atm. This had nd20 1.3938, much lower than that of the desired product.

5 gms. of the chlorinated mixture was then treated with 3.5 gms. of phenylhydrazine at 0°C. After 10 minutes
the products were worked up as before and a fraction taken at 66-79°/14 mm. with \( n_D^{20} 1.4423 \) and giving an enol test with ferric chloride.

By PCl₃

(6) In ether.

To 15 gms. of methyl-acetoacetic ester in 20 gms. of ether was added 4.7 gms. of PCl₃. After two hours, no sign of reaction was apparent, so the mixture was refluxed for 4 hours. On extraction and distillation all the product distilled at 79-81°/14 mm. and had \( n_D^{20} 1.4198 \). It was returned to the methyl-acetoacetic ester bottle.

(7) Refluxing together.

15 gms. of methyl-acetoacetic ester and 4.7 gms. PCl₃ were refluxed together for one hour. The mixture became very dark. On extraction and distillation all the distillate boiled 77°-81° at 14 mm. and had \( n_D^{20} 1.4190 \). This was returned to the methyl-acetoacetic ester bottle after Lassaigne's test for Cl was found to be negative.

(8) In ether.

By SOCl₂

To 15 gms. of methyl-acetoacetic ester in 20 gms. of ether was added 6.2 gms. SOCl₂ and as the solution
showed no signs of reaction, the mixture was refluxed for 5 hours. On working up as before the following fractions were taken at 14 mm.
(a) 70°-77° few drops.
(b) 77°-81° 15.5 gms. \( n_D^{20} 1.4212 \).
Lassaigne test for Cl - weakly positive.
This was used again as methyl-acetoacetic ester.

(9) Refluxing together.

15 gms. of methyl-acetoacetic ester and 6.2 gms. of \( S OCl_2 \) were refluxed together for 1½ hours, by which time the mixture was very dark.

On working up the mixture the following fractions were taken at 14 mm.
(a) 67°-76° 4.5 gms. \( n_D^{20} 1.4429 \)
(b) 76°-79° few drops
(c) 79°-81.5° 8.5 gms. \( n_D^{20} 1.4218 \)
(c) was redistilled and the portion boiling 79.5°-81.5° at 14 mm. (7.5 gms.) kept as methyl-acetoacetic ester.
V. PREPARATION OF \( \alpha \)-METHYL \( \beta \)-CHLOROCROTONIC ACID.

Methyl-acetoacetic ester (100 gms.) was added cautiously by a dropping funnel to PCl\(_5\) (146 gms.) in an ice-cooled round-bottomed flask fitted with reflux condenser. A vigorous reaction ensued, about half the PCl\(_5\) dissolving. The flask was warmed slowly to about 65\(^{\circ}\)C when the rest reacted.

The acid chlorides formed were decomposed by cautiously adding water, by a dropping funnel, to the flask cooled in ice. The products were then steam distilled, a yellowish oil and then the white crystalline acid distilling. The distillate was neutralised by sodium carbonate and ether extracted. The extracts were dried and the ether distilled off leaving a strongly smelling yellow oil, which is, according to Roll, a mixture of mono- and di-chloromethyl aceto acetic esters. (Annalen 1889, 249, 308). The aqueous layer was acidified with excess HCl and ether extracted three times. On distilling off the ether, a white crystalline solid was left. This was purified by dissolving in a little alcohol, and precipitating by the addition of water. After drying in a vacuum desiccator the acid weighed 29.4 gms. Yield: 31.5\% theoretical.
Two more batches were made, the second giving 30.2 gms. of acid from the same quantities (32.3% theoretical) and the third giving 64 gms. from 218 gms. of methyl-acetoacetic ester and 318.3 gms. of PCl₅ (32.2% theoretical).

After three recrystallisations from aqueous alcohol, the melting point was 67.5°C.
VI. THE ESTERIFICATION OF $\alpha$-METHYL-$\beta$-CHLORO CROTONIC ACID.

50 gms. of $\alpha$-methyl-$\beta$-chloro-crotonic acid was dissolved in 50 ccs. of anhydrous ethyl alcohol. HCl gas dried by $\mathrm{H}_2\mathrm{SO}_4$ was bubbled through the gently boiling solution for 2½ hours. The mixture was cooled and poured into 500 ccs. of water in a separating funnel. Sodium carbonate solution was added until slightly alkaline and the solution ether extracted. After drying by anhydrous sodium sulphate, the ether was distilled off and the residue fractionally distilled at reduced pressure. The fraction boiling, 72-74°C at 14 mm. had $n_\text{D}^{20}$ 1.4571. This was kept. Yield: 31.5 gms. (52.2% theoretical).

In a second batch, 64.1 gms. of acid gave 37.2 gms. ($43.15$ theoretical) boiling 72-74°C at 14 mm. with $n_\text{D}^{20}$ 1.4566.

The alkaline aqueous layers were acidified and ether extracted, yielding 54.9 gms. of acid. This was esterified as before giving 22.1 gms. ($43.7\%$ theoretical) of ester with $n_\text{D}^{20}$ 1.4568 distilling 70-74°C at 14 mm.

28.9 gms. of acid were recovered from this esterification in the same way and esterified giving 15.1 gms. ($43.3\%$ theoretical) of ester, b. pt. 70-74°C at
14 mm., \( n^0_{D} = 1.4563 \).

Overall Yield: 112.8 gms. of ester from 114.0 gms. of acid, = 81.9\% of theoretical.
VII. THE CONDENSATION OF \(\alpha\)-METHYL-\(\beta\)-CHLOROCROTONIC ESTER AND SODIOMETHYLMALONIC ESTER.

Freshly cut sodium (4.7 gms.) was added to anhydrous tertiary butyl alcohol in a round-bottomed flask fitted with ground-in water condenser. The condenser was supplied with water warmed to 28°-29° to avoid solidification of the alcohol in it. In order to get the sodium dissolved in a reasonable time, it was found necessary to cut it in thin shavings, to use a large excess of the alcohol, and to reflux the mixture vigorously. After making up the alcohol to about 350 cc., three hours' refluxing dissolved the metal. After cooling somewhat, 36.5 gms. of methylmalonic ester were added, giving a white suspension of the sodium derivative. 33.5 gms. of \(\alpha\)-methyl-\(\beta\)-chlorocrotonic ester were then added. The mixture became light yellow in colour and opaque, almost immediately. It was refluxed for one hour, transferred to a Kon flask, and most of the tertiary butyl alcohol evaporated off with gentle warming under reduced pressure. The mixture was then shaken with 3 to 4 volumes of water, and ether extracted three times.

The combined ether extracts were dried by anhydrous sodium sulphate (overnight) and the ether distilled off
at atmospheric pressure. The remaining liquid was fractionally distilled under reduced pressure, when the following fractions were taken:

(1) 65-73°/13 mm. - α-methyl-β-chloro-crotonic ester.
(2) 73-80°/13 mm. - few drops.
(3) 80-94°/13 mm. - methyl-malonic ester.
(4) 94-104°/13 mm. - by products (5 gms.) (probably alcoholysis products).
    104-166°/13 mm. - nothing.
(5) 166-171°/13 mm. - condensation product (35.6 gms.)

A tarry residue was left in the flask.

Fraction (5) was a viscous liquid with a slight yellowish tinge, having n°20 1.4560. It decolourised a solution of bromine in CCl₄, and dilute permanganate solution, and gave no visible reaction with sodium bicarbonate or ferric chloride. Yield: 57.4% theoretical.

A second batch was made using the same quantities and proceeding as before except that the reagents were refluxed together for 1½ hours instead of 1 hour. The following fractions were taken:

(1) 65-73°/13 mm. - α-methyl-β-chloro-crotonic ester.
    73-80°/13 mm. - nothing.
(2) 80-94°/13 mm. - methyl-malonic ester.
(3) 94-105°/13 mm. - by products.
105-166°/13 mm. - nothing.

(4) 166-171°/13 mm. - condensation product (40.3 gms.)

Fraction (4) was a viscous colourless liquid with \( n_D^{20} \) 1.4561. Yield: 65% theoretical.

A third batch was made, again using the same quantities, but this time refluxing for 1½ hours. The following fractions were obtained:

(1) 68-73°/13 mm. - \( \alpha \)-methyl-\( \beta \)-chloro-crotonic ester (few drops only).

73-84°/13 mm. - nothing.

(2) 84-94°/13 mm. - methylmalonic ester (very little)

(3) 94-105°/13 mm. - by products.

105-168°/13 mm. - nothing.

(4) 168-172°/13 mm. - condensation product (43.5 gms.)

Fraction (4) was a viscous colourless liquid with \( n_D^{20} \) 1.4555. Yield: 72.2% theoretical.

The fractions corresponding to \( \alpha \)-methyl-\( \beta \)-chloro-crotonic ester obtained in the above experiments were combined and redistilled giving 14.1 gms. of liquid distilling at 70-73°/13 mm. with \( n_D^{20} \) 1.4569.

This, with a few grams not used previously, made up 17.8 gms. which was condensed with sodio-methyl-malonic ester as above, refluxing for 1½ hours.

21.2 gms. of viscous yellowish liquid distilled at
166-171°/13 mm., with nD\textsubscript{20} 1.4563.

**Yield:** 64.3\% of theoretical.

In all the above distillations some decomposition was indicated by a tarry residue left behind.
A. Sodium (1.8 gms.) was dissolved in anhydrous ethyl alcohol (25 cc.), 20 gms. of the ester from the condensation added and the mixture warmed to 80 in a bath. A deep orange colour developed and the mixture was maintained at 80 for one hour. No solid material separated. The mixture was shaken with 3 volumes of water and ether extracted three times.

The ether extracts were dried with anhydrous sodium sulphate, the ether distilled off at atmospheric pressure, and the residue distilled under reduced pressure. A small Glaisher flask with a short vacuum jacketed fractionating sidearm, and all glass fittings, was used. The following fractions were taken:

1. About 20-30°/13 mm. (therm. stem obscured) - few drops, smelling of Et₂CO₃
2. 116-120°/13 mm. 3.5 gms.
3. 120-135°/13 mm. 4.0 gms.
4. 135-145°/13 mm. 1.0 gms.
5. 145-158°/13 mm. 6 gms.
6. 158-169°/13 mm. 1 gms.

Some tarry residue was left in the flask, indicating decomposition.
Fractions (2), (3), and (4) were colourless, fairly mobile liquids with $n_D^0$ 1.4576, 1.4570 and 1.4568 respectively. Fractions (5) and (6) were yellowish viscous liquids with $n_D^0$ 1.4563 and 1.4560 respectively.

The thermometer socket in the flask used was rather high in relation to the side arm and the efficiency of the column questionable, so it was suspected that the true boiling ranges of fractions (2) to (4) and (5) to (6) were narrower and higher than those recorded by the thermometer. It was felt that a sharp cut ought to have been made between (4) and (5) since (5) and (6) were presumably unchanged carboxy ester.

Fractions (2), (3) and (4) were separately refluxed with 10 vols. of 5N HCl and 1 vol. of alcohol. (2) and (3) dissolved completely after 8 or 9 hours, but after refluxing (4) for 14 hours, there still remained a small amount of brown oil which was removed by filtration through glass wool while hot.

The solutions were made alkaline with sodium carbonate, washed with ether to remove non-acidic impurities and recrystallised slightly with HCl. Each solution was ether extracted five times and the ether evaporated off, leaving in each case a clear light brown oil. These were put in a vacuum desiccator.
B. Sodium (0.9 gms.) was dissolved in the minimal quantity of tertiary butyl alcohol (about 70 cc.), and 10 gms. of carbethoxy ester added. On warming to 35° in a bath an orange colour developed. After one hour at this temperature, most of the tert.-butyl alcohol was removed under reduced pressure at a slightly lower temperature. The mixture was then shaken with water and worked up as in A above. A small Kon flask with ordinary rubber stoppers, but a longer column, was used this time for the distillation. A mercury diffusion pump was available so it was used in order to minimise decomposition.

Some of the carbethoxy-ester was distilled in a trial run and came over at 141-146°/1/2 mm. with practically no decomposition. The reaction products were then distilled giving the following fractions:

Up to 100°/2 mm. — few drops
(1) 100–130°/2 mm.— 2.5 gms.
     104–142°/2 mm.— nothing.
(2) 142–146°/2 mm.— 6 gms.

Fraction (1) was a colourless, fairly mobile liquid with nD20 1.4577. Fraction (2) was a colourless viscous liquid with nD20 1.4559, evidently unchanged carbethoxy —
ester. A brownish residue was left in the flask.

Fraction (1) was hydrolysed by boiling with HCl.
and the resultant acid extracted as described in A
above.

The acid was slow to crystallise. Slow evap-
oration of solvent from solutions in ether, benzene and
water was tried without success, but after about three
weeks the oils deposited white crystals and in a few
days they were almost completely solid. This solid
acid was investigated as described in the next section
(section IX). The rest of the carbethoxy-ester was
decarbethoxylated as follows:

0. Carbethoxy ester (25 gms.) was treated with
sodium tertiary butoxide in tertiary butyl alcohol
as in B. above, but heating the mixture to 40° for
1½ hours. The products gave the following fractions:

(1) Gentle warming ½ mm. - liquid volatile at this
pressure.
Up to 102°½ mm. - few drops.

(2) 102° - 105°½ mm. - 7·2 gms. (trimethyl-glu-
taconic ester)
105° - 142°½ mm. - nothing.

(3) 142° - 146°½ mm. - 12 gms. (carbethoxy-glu-
taconic ester).

A brown residue was left in the flask.

Fraction (1) was presumably ethyl, tertiary butyl
carbonate. Fraction (2) was a colourless liquid with \( n^0_{D} = 1.4575 \). Fraction (3) was a colourless viscous liquid with \( n^0_{D} = 1.4558 \).

D. Just the same as C above, except that the mixture was heated to 40° for 1 hour then to 70° for \( \frac{1}{2} \) hour.

The following fractions were obtained:

1. As in C above.
   
   Up to 101°/\( \frac{1}{2} \) mm. — nothing.
   
   (2) 101° - 104°/\( \frac{1}{2} \) mm. — 9.6 gms. with \( n^0_{D} = 1.4581 \).
   
   104° - 106°/\( \frac{1}{2} \) mm. — nothing.
   
   (3) 106° - 108°/\( \frac{1}{2} \) mm. — 9 gms. with \( n^0_{D} = 1.4555 \).

The fractions resembled those obtained in C above.

A brown residue was left in the flask.

E. Carbethoxy-eater (25 gms.) was treated with sodium ethoxide in ethyl alcohol just as in A above, except that the mixture was heated at 80° for 1\( \frac{1}{4} \) hours.

The following fractions were taken:

1. Gentle warming/\( \frac{1}{2} \) mm. — 5 or 6 c.c.s. of liquid.
   
   Up to 99°/\( \frac{1}{2} \) mm. — few drops.
   
   (2) 99° - 104°/\( \frac{1}{2} \) mm. — 12°/4 gms. liquid with \( n^0_{D} = 1.4577 \).
   
   104° - 106°/\( \frac{1}{2} \) mm. — nothing.
   
   (3) 106° - 108°/\( \frac{1}{2} \) mm. — 4°/4 gms. with \( n^0_{D} = 1.4553 \).

Fractions (2) and (3) resembled those obtained in D, C, and E above. Fraction (1) was volatile at the pressure
used and much of it escaped into the pump. This was
minimised in later distillations by cooling the
receiver in ice and salt.

Fraction (1) distilled at 125-127° at atmospheric
pressure, had the smell of ethyl carbonate, and had
\( n_D^{20} = 1.3850 \). Auwers (S.C. Belg. 56, 1672) gives \( n_D^{20} = 1.3852 \).

A brown residue was left in the distilling flask.

Yield of trimethyl-glutaconic ester: 67.7% theoretical.

8. Just as in 6. above, except that the heating at
80° was prolonged to 1½ hours. Fractions obtained:

(1) Gentle warming /½ mm. - 6 or 7 cms. of ethyl
    carbonate.
    Up to 100°/½ mm. - nothing.
(2) 100° - 134°/½ mm. - 13.2 gms. with \( n_D^{20} = 1.4559 \).
    Above 134°/½ mm. - only a few drops.

A brown residue was left in the flask.

Yield of trimethyl-glutaconic ester - 75.9% of theoretical.

9. The high boiling (carbethoxy-ester) fractions from
the above distillations were combined (33 gms.) and
were just as in 8. above, yielding 17.8 gms. of ester
distilling at 102-104°/½ mm.

Yield: - 73.7% of theoretical.

A portion of the trimethyl-glutaconic ester obtained
was used for the oxidation experiments described later
(section X.).
The ester was hydrolysed by 5M HCl (10 volumes) plus a little alcohol. The ester dissolved completely in about 10 hours, giving a colourless solution. After boiling for a further hour, the mixture was cooled and extracted five times with ether. After distilling off the ether, the residue was treated with sodium carbonate. The acid dissolved readily in the cold, giving a yellow solution of the sodium salt. A small amount of a viscous brown liquid remained undissolved. This was presumed to be anhydride and on boiling with sodium carbonate solution dissolved to give a yellow solution. This solution and the main sodium salt solution washed with ether, were each acidified slightly, ether extracted five times and the ether evaporated off, leaving the acid. The acid made from the anhydride had melting point 103-105°C. The acid produced directly by hydrolysis of the ester had melting point 96-98°C. Their "mixed" melting point was 101-103°C indicating that they were identical.

Yield: 38.1 gms. of acid from 54.2 gms. of ester, i.e. 93.2% of theoretical.
IX. PRELIMINARY INVESTIGATION OF THE ACID FROM THE HYDROLYSIS. THE MICRODETERMINATION OF ITS EQUIVALENT WEIGHT.

This was carried out as soon as the acid made from the first (A) batch of decarboxylated easter had crystallised, and before treating the rest of the material.

The general properties and a series of mixed melting point determinations indicated that the acids from the hydrolysis of each of the easter "fractions" (2), (3), and (4) (see section VIII above) were identical.

The acid had a typical glutaric acid smell. It effervesced with sodium bicarbonate and gave a sodium salt whose aqueous solution was pale yellow. It decolourised both bromine and permanganate solutions. The acid was very soluble in alcohol and ether, practically insoluble in petroleum ether (60-80°C) and sparingly soluble in cold water and benzene. These latter two both dissolved the acid when hot, though less readily in the case of benzene.

After several recrystallisations from water, the acid had melting point 196-199°C. Recrystallisation from dilute HCl gave a lower melting point, and the melting point of the water-recrystallised acid was lowered by boiling with HCl. It was found impossible to
recrystallise the acid from benzene unless it had been recrystallised previously from water. It was also found impossible to recrystallise from water if the hot solution was too concentrated. Recrystallisation from benzene to constant melting point (4 recrystallisations) gave melting point 111-112°C. This recrystallised product was then used in "mixed" melting point determinations with the following substituted glutaric acids, pure samples of which were available:

trans-\(d\text{ol}-c\text{trimethyl-}
trans-\(d\text{ol}-c\text{trimethyl-}
trans-\(d\beta\)-dimethyl-
\(c\text{is-}\Delta^\gamma\)-\(d\beta\)-dimethyl-
trans-\(\beta\)-methyl-
\(c\text{is-}\beta\)-methyl-

The melting point was depressed in each case.

The equivalent weight of the acid was determined as follows:

Acid recrystallised to constant melting point from benzene was titrated with dilute (approx. \(\frac{1}{50}\)) carbonate-free alkali standardised against potassium hydrogen phthalate, using a micro burette and using phenolphthalein as indicator. A current of carbon dioxide-free air was bubbled through the aqueous suspension of acid used by
means of a fine glass capillary. This stirred the solution and "blanketed" its surface against carbon dioxide *0.361 gms. acid * 2.01 ml. of 0.204N. alkali

* equivalent weight of acid = 88.0.
X. OXIDATION OF THE ESTER FROM THE DECARBOXYLATION.

(a) With 5% neutral permanganate.

The ester (2 gms.) was treated with 5% neutral potassium permanganate. This was added in 10 c.c. portions. Reduction of the permanganate proceeded fairly rapidly in the cold and the ester required about 90 c.c. for complete oxidation. After shaking for some time the precipitate of manganese dioxide coagulated and settled out. The mixture was filtered and the filtrate thoroughly ether extracted. After drying, the ether was distilled off and the residue fractionated under reduced pressure.

The following fractions were taken:

1) Up to $45^\circ/13$ mm. — very little.
   $45^\circ - 71^\circ/13$ mm. — nothing.
2) $71^\circ - 79^\circ/13$ mm. — main fraction.
   over $79^\circ/13$ mm. — a little.

1) was a colourless liquid which did not respond to tests for pyruvic ester.

2) was a colourless liquid with the characteristic smell of acetoacetic ester and its methyl derivatives. It gave a positive enol test with FeCl$_3$ and had $n^0_{D} = 1.4206$. It was chlorinated with POCl$_3$ as described previously in the preparation of $\alpha$-methyl-$\beta$-chloro-crotonic acid and
the acid formed on hydrolysis extracted as described therein. On recrystallisation from aqueous alcohol this acid had m.pt. 67°. It was therefore considered that substance (2) was mono-methyl-acetoacetic ester.

(b) With very dilute neutral permanganate at 0°C.

Ester (2 gms.) was added to distilled water (190 c.c.), the containing flask cooled in ice, and 5% neutral permanganate insufficient for complete oxidation (70 c.c.) added in small portions. Reaction was fairly slow although accelerated by shaking. The products were worked up as in the previous permanganate oxidation and the following fractions taken:

(1) Up to 64°/13 mm. - a little.

64° - 74°/13 mm. - almost nothing.

(2) 74° - 78°/13 mm. - methylacetoacetic ester.

When fraction (2) had come over the distillation was discontinued. (2) was the same as before. (1) was a rather pungent liquid. It was boiled with caustic soda for a short time in a little reflux tube with a wet rag wrapped round the top. When the tube was cool it was centrifuged to bring drops on the tube walls to the bottom, illing through near the bottom, and the following tests were performed on its contents. In each case a parallel test was done with a sample of pyruvic acid.
solution for comparison.

(a) With Br₂ water - test liquid and pyruvic acid both
decolourised it.

(b) With permanganate - both decolourised it.

(c) With sodium nitroprusside and caustic soda - both
gave the same scarlet colour, changing to dirty greyish-
brown on addition of acetic acid.

(d) With β-naphthol and conc. H₂SO₄ - both gave a red
colour which changed on warming to violet blue and then
to brown.

(e) With phenylhydrazine acetate - both became opaque.

Because of the small quantity of test solution,
most of these tests were carried out on a glass plate,
using drops of reagent and of test solution picked up
by fine capillary tubes. A lens was used for observation.

It was concluded that (1) was pyruvic ester.
XI. THE ANALYSIS AND MOLECULAR WEIGHT DETERMINATION OF THE ACID.

The acid obtained by hydrolysis of the trimethyl-glutaconic ester (as described in section VIII above), was dissolved in a large quantity of hot water. (Unless a large quantity was used, the acid tended to separate as an oil on cooling). The inside of the containing vessel was scratched and the solution left to cool spontaneously. In 1-2 days a crop of white, not very well formed, crystals separated, and were filtered off at the pump. The rest of the acid was crystallised out in batches by evaporating off water at 25-30 under reduced pressure as described in section XIV below. Meanwhile, the first crop of solid acid, after being recrystallised several times from benzene, was used for a combustion analysis and a molecular weight determination as follows:

(a) On combustion 16.56 gms. of the acid gave 1.026 gm. H₂O and 0.531 gm. CO₂

\[ C = 55.73\% \quad H = 6.88\% \]

C₃H₁₂O₃₄ requires C = 55.83%, H = 7.94%.

(b) A West molecular weight determination was carried out in the usual way on a semi-micro scale. The molecular depression constant was determined by using dix-trimethyl-glutaconic acid as solute in the camphor. As the
solubility of both acids in camphor was not very high; a somewhat higher proportion of camphor than usual was employed. Two complete determinations were carried out:

1. Melting point of camphor = 171.7°C
   Melting point of solution of 0.201 gms. of \( \alpha\beta\gamma \)-trimethylglutamic acid in 3.994 gms. of camphor = 161.9°C i.e. depression of melting point = 9.7°C
   * Molecular depression constant = 36.6

2. Melting point of camphor = 171.7°C
   Melting point of solution of 0.176 gms. of \( \alpha\beta\gamma \)-trimethylglutamic acid in 3.592 gms. of camphor = 161.6°C i.e. depression of melting point = 9.1°C
   * Molecular weight of \( \alpha\beta\gamma \)-trimethylglutamic acid = 172.

(2) Melting point of camphor = 171.7°C
   Melting point of solution of 0.163 gms. of \( \alpha\beta\gamma \)-trimethylglutamic acid in 3.658 gms. of camphor = 162.3°C i.e. depression of melting point = 9.4°C
   * Molecular depression constant = 36.3

   Melting point of solution of 0.164 gms. of \( \alpha\beta\gamma \)-trimethylglutamic acid in 3.716 gms. of camphor = 161.2°C i.e. depression of melting point = 9.5°C
   * Molecular weight of \( \alpha\beta\gamma \)-trimethylglutamic acid = 173

\( \text{C}_8\text{H}_{12}\text{O}_4 \) requires molecular weight = 172.
XII. THE DISTILLATION OF THE AMMONIUM SALT OF THE ACID.

The acid was dissolved in sufficient 10% ammonia solution to give an alkaline solution and the solution evaporated on the steam bath. Before the water had all been removed, the solution had become acid, indicating hydrolysis. Sufficient 880 ammonia was then added to make the solution just alkaline. The solution was placed in a vacuum desiccator over caustic soda and a vacuum of about 31 mm. applied. During the next two days, the desiccator was re-evacuated to this pressure twice, thus removing excess ammonia, and at the end of this time, a hard, glassy mass of ammonium salt remained. It was pink in colour.

A small amount of this ammonium salt was put in the bulb of a tiny retort fitted with a thermometer, and distilled at 500 mm. pressure. The following fractions were taken.

(a) Up to 90° - a fairly large amount of water, NH₃ and CO₂
(b) 90 -110° - a small amount of white solid.

110 -260° - nothing.

(c) 260 -270° - a yellowish oil which solidified in the arm of the retort.

Fraction (b) turned blue on standing in the open for a short time. It was not investigated further.
The yield of fraction (c) was not very good because a considerable amount of decomposition occurred during its evolution, leaving a black tar in the bottom of the retort and a greenish coating on the sides of the bulb.

This fraction crystallised from absolute alcohol in the form of small, colourless, lustrous plates. The recrystallised material contained nitrogen as shown by a Lassaigne test. It gave a transient red colour with alcoholic ferric chloride and reduced ammoniacal silver oxide to a silver mirror on warming. It was readily soluble in alkali, being reprecipitated on the addition of acetic acid. It dissolved in concentrated HCl and the solution deposited well-formed needles on standing over sulphuric acid in a vacuum desiccator. These, on addition of water, gave back the original substance.

Three recrystallisations from alcohol gave melting point 183.5°.

A further small quantity of ammonium salt was distilled and the same product obtained. This was benzoylated in the usual Schotten-Baumann manner, by shaking with benzoyl chloride and 10% caustic soda. The benzoyl derivative which precipitated crystallised from glacial acetic acid in the form of small colourless
shiny needles. It was insoluble in alkali, but soluble in strong acid. Four recrystallisations from glacial acetic acid gave melting point 186°.
XIII. THE PREPARATION OF THE ANHYDRIDES OF THE ACID.

(1) The Preparation of the Normal Anhydride.

(a) By boiling the acid with acetic anhydride.

The acid was boiled with excess of acetic anhydride for one hour. The removal of acetic anhydride from the product was very slow in an evacuated desiccator containing caustic soda so the acetic anhydride was distilled off under high vacuum, as much being removed as possible without undue warming. Dry alcohol (and finally ether) was added and the evaporation repeated, to remove as much acetic anhydride as possible.

An almost colourless crystalline residue remained. It was found that washing this with a small amount of cold benzene removed the anhydride in solution, leaving any unchanged acid almost wholly undissolved. The high solubility of the anhydride in cold benzene thus enabled ready purification of the anhydride, the yield of which was good.

The anhydride was very soluble in alcohol and almost insoluble in petroleum ether. It crystallised as well-formed colourless needles. It dissolved in hot water and was precipitated unchanged on cooling. It showed no colour change with ferric chloride and no effervescence with sodium bicarbonate.
On boiling with aqueous sodium carbonate, it dissolved entirely, giving a pale yellow solution. On acidification and ether extraction, an acid was obtained. This was recrystallised from dilute hydrochloric acid and then benzene. Its melting point was 110°-111°C and its mixed melting point with the original acid of m.pt. 111°-112°C, was 110°-111°C. This, with its general properties, indicated that it was identical with the original acid.

After 4 recrystallisations from benzene-petroleum ether mixtures, the normal anhydride had m.pt. 119-5°.

(b) By the action of acetyl chloride on the acid.

The acid was boiled with excess of acetyl chloride for half an hour and excess of the chloride removed by standing in a vacuum desiccator over caustic soda. The anhydride obtained was identical in all its properties with that described in (a) above and did not depress the melting point of the latter. The yield was considerably lower than in (a) above.

(c) By the action of acetyl chloride containing a little PC13 on the acid.

After boiling for half an hour, the same anhydride was obtained, in good yield. After the removal of the acetyl chloride, the residual syrup of phosphorous acid, etc. was removed by washing with water, followed by drying.
(2) **The Preparation of the Hydroxy-Anhydride by the Distillation of the Normal Anhydride.**

The anhydride obtained above was distilled under reduced pressure. An almost colourless oil distilled at 159-160°/12 mm. After standing for about 24 hours, with scratching, it solidified completely.

This solid was highly soluble in alcohol, fairly soluble in hot benzene, and almost insoluble in petroleum ether and cold benzene. It was soluble in hot water and dissolved very slowly in cold water. It recrystallised from benzene as small shiny crystals of indeterminate shape.

In aqueous sodium bicarbonate, it dissolved with a steady evolution of bubbles, but it did not appear to give a colour change with ferric chloride. On dissolving it in cold caustic soda and acidifying immediately, ether extraction gave what appeared to be a mixture of the same anhydride and the original acid. After warming the yellowish solution of the anhydride in caustic soda, acidifying and ether extracting, an acid was obtained. This was recrystallised from dilute HCl and benzene. Its melting point was 109°-110°C, and its mixed melting point with the original acid, of m.pt. 111°-112°C, was 110°-112°C. This, together with its general properties, indicated that it was identical with the original acid.

After four recrystallisations from benzene, this hydroxy-anhydride had **melting point 116°C**.
XIV. THE PREPARATION OF THE CIS-FORM OF THE ACID BY TWO
METHODS, AND ITS ANALYSIS.

The aqueous solution of the acid was concentrated in steps by distilling off water at 25-30° under reduced pressure. After each distillation, the remaining solution was stood in the cold for some time, and the solid filtered off.

After about three quarters of the water had been removed and the solids filtered off, a further very small quantity was removed and the solution stood aside. After several days, a quantity of large transparent crystalline plates separated out. These were filtered off and purified by solution in cold benzene and precipitation by addition of petroleum ether. This was repeated three times, giving the constant melting point 117°. This purified material was considered to be pure cis-acid.

Cis-acid was also prepared by the hydration of the hydroxy-anhydride, as follows:

This anhydride was added to excess of cold distilled water and stood overnight. Next morning it had all dissolved. The solution was extracted with pure ether and the ether evaporated off. The residue was recrystallised from cold benzene by the addition of petroleum ether. After three such recrystallisations transparent crystalline plates were
obtained, with melting point 115°. With the cis-acid of 
melting point 117°, it gave the mixed melting point 117°.

On combustion analysis of the recrystallised cis-acid, 
1598 gms. gave 3259 gms. of CO₂ and 1099 gms. of H₂O.

\[ \text{C} = 55.62\%, \quad \text{H} = 7.26\% \]

C₇H₁₂O₄ requires C = 55.87%, H = 7.04%.
XV. THE ATTEMPTED SEPARATION OF THE TRANS-FORM OF THE ACID.

In an attempt to separate the pure trans-acid, the first crop of crystals obtained on removing water from the aqueous solution was recrystallised from cold benzene by the addition of petroleum ether. This was a slow process because the supersaturated solutions crystallised very slowly, even on concentration by evaporation in vacuo. Two to three days were required for each recrystallisation, and solid acid was deposited on the sides of the vessel above the level of the solution by solution which "crept" up the sides. After four recrystallisations, when practically no crystalline material was left, the melting point had risen to 126°-129°. The same process was repeated with a larger quantity, when five recrystallisations gave melting point 131°-133°. Purification to constant melting point was not achieved.