THESIS

entitled

"DIBENZYL GLUTARIC ACID"

Presented for the Degree

of

Master of Science and Honours

in the

University of New Zealand

1942

V. R. STONE
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I. INTRODUCTION

A. THE STRUCTURE OF THE GLUTARONIC ACIDS

The glutaric acids constitute a group of unsaturated dibasic acids in which geometrical isomerism coexists with that of tautomeric mobility; the latter reaches its maximum in glutaric acid itself where the three carbon system is activated by two terminal keto-enol systems so the whole is really a heptad system.

\[ \overset{\text{\H}}{\overset{\text{\H}}{C}} - \overset{\text{\H}}{\overset{\text{\H}}{C}} - \overset{\text{\H}}{\overset{\text{\H}}{C}} = \overset{\text{\H}}{\overset{\text{\H}}{C}} - \overset{\text{\H}}{\overset{\text{\H}}{C}} - \overset{\text{\H}}{\overset{\text{\H}}{C}} \]

In glutaric acid the mobility is such that only one form of the acid, the trans, is stable, although the cis form has been obtained by careful hydration of the anhydride, (Malachowski, Ber. 1929, 623, 1323). Introduction of electron releasing groups on the \(\alpha\), and/or \(\beta\), and/or \(\gamma\) reduces this mobility so that in some cases most of the theoretically possible forms have been isolated.

Modern theory demands that unsymmetrically substituted glutaric acids should exist in six forms, cis \(\Delta^\alpha\), trans \(\Delta^\alpha\), d- and l- trans \(\Delta^\beta\) and d- and l- cis \(\Delta^\gamma\) due to structural and geometrical and optical isomerism. The optical active forms have not been isolated. However, in symmetrically substituted acids the theoretically possible number of forms is four, d- and l- cis and d- and l- trans, these being due
to geometrical and optical isomerism; no structural isomerism resulting from the position of the double bond occurs.

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{HOOC} & \quad \text{O} \quad \text{C} \quad \text{= C} \quad \text{= COOH} \quad \text{H} & \quad \text{H} \\
\text{R} & \quad \text{R} \\
\text{HOOC} & \quad \text{O} \quad \text{C} \quad \text{= C} \quad \text{= C} \quad \text{= COOH} \\
\text{R} & \quad \text{R}
\end{align*}
\]

dl cis and trans "dialkyl glutaric acid.

Due to the mobility of the system, the existence of geometrical and optical isomerism in the glutaric acids was not recognised at first. The evidence lead early workers to believe that glutaric acids and their alkyl substituted derivatives possessed some molecular symmetry; and that where two forms of a glutaric acid could be obtained they were structural and not cis and trans geometrical isomers. (Thole and Thorpe, J.C.S. 1911, 92, 2187, 2208). Bland and Thorpe (J.C.S. 1912, 101, 871) postulated the existence, in every mobile acid of the system, of two forms, one a stable symmetrical form called the normal form, and the other a labile form, which had a cis configuration according to these workers.

\[
\begin{align*}
\text{COOH} & \quad \text{COOH} \\
\text{C} \quad \text{H} & \quad \text{H} \quad \text{C} \quad \text{H} \\
\text{H} \quad \text{C} \quad \text{H} & \quad \text{H} \quad \text{C} \quad \text{H} \\
\text{COOH} & \quad \text{COOH}
\end{align*}
\]

normal form \quad \text{labile form}
However, with the preparation of substituted derivatives in which the mobility was reduced, more than two forms were isolated and the early theory had to be continually modified. The above workers (J.C.S. 1912, 101, 1557) later concluded that the labile form could exist in either cis or trans forms where they were stabilised by suitable substituent groups.

Feist (Ann. 1922, 428, 25) failed to recognise the full significance of this as evidence for a tautomeric mixture of the $\Delta^\alpha$ - $\Delta^\beta$ forms and continued to argue that the two forms of many $\alpha$-$\beta$ substituted glutaric acids were simple geometrical isomers, not structurally different. Thorpe did not accept such a view and regarded Feist's results as evidence in favour of structural isomerism.

Later workers, Ken and Watson (J.C.S. 1932, 135, 1), repeated Feist's work on the ozonolysis of $\beta$-methyl-$\alpha$-benzyl-glutaric esters prepared by special methods from pure isomeric acids and showed that under suitable conditions four esters could be prepared, which, from their products of ozonolysis could be shown to correspond to cis $\Delta^\alpha$-$\Delta^\beta$, cis $\Delta^\beta$, trans $\Delta^\alpha$ and trans $\Delta^\beta$, thus confirming the four theoretically possible structures.

Packer and Thorpe (J.C.S. 1926, 122, 1499) pointed out theoretically how the tautomeric mobility may involve a change from the cis to the trans acid and vice versa, and that in symmetrically substituted acids such as $\alpha$-$\gamma$-dimethyl- and
αβγ-trimethyl-glutaconic acids the theoretically possible cis and trans forms should be capable of resolution into optically active forms. The resolution of trans αβγ-dimethyl-glutaconic acid was effected by McCombs, Packer and Thorpe (J.C.S. 1931. 134, 547), and this lead to the complete abandonment of the theory of the normal configuration, it being realised that the apparent symmetry was due to the mobility of the hydrogen atom in the three-carbon system. They deduced that if the stable form of αβγ-dimethyl-glutaconic acid has the classical structure

\[
\text{HOOC} - \text{CH} - \text{CH} = \text{C} - \text{COOH} \\
\text{CH}_3 \quad \text{CH}_3
\]

(in which case it would most probably be the trans form) it should be capable of resolution into active forms whereas if it has the symmetrical "normal" structure previously assigned to it, it should not be capable of resolution.

Evans, Ryder and Briscoe (J.C.S. 1939. 142, 1673) working on isotopic exchange reactions (deuterium) concluded that the tautomerism exhibited by glutaconic acid has an ionic mechanism, the anion has an independent existence. They represented the anion formed in alkaline solution as mesomeric as follows:-
It follows from this that recombination of the proton with the kinetically free mesomeric ion must take place with equal readiness at $O_\kappa$ and $O_\gamma$, i.e. half the reassociation will occur at $O_\kappa$ and half at $O_\gamma$.

The great mobility of the cis acid is no doubt due to the instability and higher energy content of the cis ion. It is suggested that ionization of the hydrogen of the methylene group is responsible and this occurs through the agency of hydrogen bond formation which is sterically possible only in
the case of the cis acid.
B. **SYMMETRICALLY SUBSTITUTED GLUTARONIC ACIDS**

The only symmetrically substituted glutaronic acids, other than the $\beta$-alkyl or aryl, which have been prepared are

1. $\alpha\gamma'$-dimethyl glutaronic acid
2. $\alpha\beta\gamma'$-trimethyl glutaronic acid.

(i) $\alpha\gamma'$-dimethyl-glutaronic acid.

Thole and Thorpe (J.C.S. 1911, 22, 2191) obtained $\alpha\gamma'$-dimethyl-glutaronic acid by successive methylation of the sodio derivative of ethyl $\alpha\gamma'$-dicarboxyglutaronate made by the method of Conrad and Guthzeit (Ann. 1883, 222, 259) from chloroform and malonic ester.
By using a substituted chloroform it should be possible to prepare an αβγ-trimethyl glutaric acid ester by a similar series of reactions. However, Adams (N.Z. University Thesis, 1936, unpublished) could not obtain any β-methyl-αγ-dicarboxyglutaric acid ester by condensing methyl chloroform with malonic ester and sodium ethoxide.

Thole and Thorpe (ibid) found the best way to prepare ethyl-αγ-dicarboxyglutaric acid-methyl-gluconate was merely to heat a solution of the yellow solid derivative of ethyl αγ-dicarboxyglutaric acid, which had been prepared by condensing malonic acid (2 mols) with chloroform (1 mol) using sodium ethoxide as condensing agent, in alcohol with a slight excess of methyl iodide for five hours. The colourless solution was poured into water and extracted by ether; the ether extract, after being washed with water and shaken with 10% potassium hydroxide solution until the extract ceased to be
yellow, was dried and evaporated. The residual oil on distillation under reduced pressure yielded pure ethyl dicarbethoxy-\(\alpha\)-methyl glutaconate.

The elimination of one carbethoxy group from ethyl dicarbethoxy \(\alpha\)-methyl glutaconate and subsequent methylation was effected in alcoholic solution, without isolating the intermediate compound, sodium ethyl \(\alpha\)-carbethoxy-\(\alpha\)-methyl-glutaconate, by treating with an equivalent amount of sodium ethoxide, adding an excess (20\%) of methyl iodide and warming on a water bath until the yellow colour of the solution was discharged. Water was then added and the ethyl ester isolated in the same manner as described above.

The conversion of ethyl \(\alpha\)-carbethoxy-\(\alpha\)-\(\alpha\)-dimethyl-glutaconate into ethyl \(\alpha\)-\(\alpha\)-dimethyl-glutaconate, i.e. the elimination of a carbethoxy group was effected by treating with an equivalent amount of sodium ethoxide in an alcoholic solution in the cold. The oil obtained after evaporating the dried ethereal extract was distilled and gave practically a quantitative yield of ethyl \(\alpha\)-\(\alpha\)-dimethyl-glutaconate.

Hydrolysis of the ester by heating with ten times its volume of 10\% hydrochloric acid until all the oil had passed into solution gave a 90\% yield of \(\alpha\)-\(\alpha\)-dimethyl-glutaconic acid of melting point 147\(^\circ\)C. The constitution of the acid was proved, both by the formation of methyl malonic acid from it on oxidation with alkaline permanganate and by direct comparison with a specimen of \(\alpha\)-\(\alpha\)-dimethyl-glutaconic acid prepared by
Reformatsky's method from ethylβ-hydroxy-αγ-dimethylglutamate.

Thole and Thorpe (J.C.S. 1911. 22, 2217) describe the preparation of the hydroxy-anhydride of αγ-dimethyl-glutaconic acid by the action of acetyl chloride on the acid. Packer (personal communication) tried to repeat this work of Thole and Thorpe (ibid) but obtained as the main product, a complex anhydro-condensation product, along with the hydroxy anhydride (7 per cent yield). Feist (Ann. 370, 32) was also unable to obtain any simple normal or hydroxy anhydride of αγ-dimethyl-glutaconic acid in his experiments but obtained instead the complex anhydro-condensation product by the action of phosphorus pentachloride on the acid. He assigns the constitutional formula

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH} \\
\text{CH} \\
\end{array}
\begin{array}{c}
\text{C} - \text{CO} - \text{C} - \text{C} - \text{CO} \\
\text{CH} \\
\text{CH}_3 - \text{CH} - \text{CO} - \text{C} \\
\end{array}
\]

Thole and Thorpe (ibid) claimed to have prepared cis αγ-dimethyl-glutaconic acid from the corresponding hydroxy anhydride in the presence of excess strong alkali, as well as by the aid of an "anticatalyst". They used casein as their anticatalyst. Packer (private communication) repeated Thole and Thorpe's work, but with negative results.
The Resolution of $\alpha\beta$-dimethyl-glutaconic acid.

The resolution of the symmetrically substituted $\alpha\beta$-dimethyl-glutaconic acid was effected by McCombs, Packer and Thorpe (J.C.S. 1931. 134, 559) by first order asymmetric transformation of the strychnine salt from an acetone chloroform solution. The $\perp$ trans-strychnine hydrogen salt was much less soluble in the above solvents than the corresponding $d$-acid salt and readily crystallised out on mixing a solution of the acid in acetone with a solution of strychnine in chloroform. The pure $\perp$-acid was obtained by repeated precipitation of the $\perp$-acid strychnine salt, but the $d$-acid could not be obtained from the solution as considerable racemisation occurred, the acid recovered showing a rotation corresponding to 75% $d$- and 25% $\perp$- forms.

These workers investigated the resolution of $\alpha\beta$-dimethyl glutaconic acid by the action of the following bases, quinine, brucine, chinconine, quinidine and $d$-$\alpha$-phenylethylamine, but these reagents gave salts which would not crystallise or were otherwise unsuitable for the resolution of the acid.

Other attempts to resolve open chain glutaconic acids had previously been made with negative results: e.g. Glutaconic acid (Thorpe and Wood, J.C.S. 1913. 103, 277) also by McCombs, Packer and Thorpe (ibid). The only other glutaconic acid to be resolved was the cyclic "glutaconic"
acid, 3 methyl-cyclo-propene - 1,2 dicarboxylic acid. Feist
(Am. 1924, 436, 135).
(11) \( \alpha\beta \gamma \)-trimethyl-glutaconic acid.

Over a number of years many attempts have been made to synthesise \( \alpha\beta \gamma \)-trimethyl-glutaconic acid. Most methods have in general given only poor yields and in many cases the constitution of the product has not been demonstrated conclusively.

These methods are discussed below:

A. Thorpe and Wood (J.C.S. 1913, 103, 1759) prepared what they considered to be \( \alpha\beta \gamma \)-trimethyl-glutaconic acid by the methylation of ethyl \( \alpha\beta \)-dimethyl-glutaconate (II) with sodium ethoxide and excess methyl iodide.

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

(II)

The ester was hydrolysed giving an acid of melting point 127\(^\circ\)C, which the authors considered to be \( \alpha\beta \gamma \)-trimethyl-glutaconic acid (III).

\[
\begin{align*}
\text{CH}_3\text{CH}_3\text{CH}_3 & \quad \text{CH}_3\text{CH}_3\text{CH}_3 \\
\text{EtOOC} - \text{CH} - \text{CH} = \text{C} - \text{COOEt} & \quad \text{HOOC} - \text{CH} - \text{C} = \text{C} - \text{COOH} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

(III)

Packer and Sargent (J.C.S. 1933, 136, 556) could not methylate
ethyl αβ-dimethyl-glutaconate by Thorpe and Wood's methods, but succeeded in affecting methylation by using methyl iodide with sodium dispersed in ether. By this method however the methyl group went into the α position to give trans αβ-trimethyl-glutaconic acid (IV) and no evidence could be found for any αβ'-trimethyl-glutaconic acid in the product.

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

(IV)

Feist and Beyer (Annalen 1906, 245, 117) were also unable to methylete αβ-dimethyl glutaconate which is also consistent with work in this field by Kon and Watson (J.C.S. 1932, 132, 1) who showed by crystallization that the ethyl αβ-dimethyl-glutaconate was a mixture of two tautomers, namely ethyl Δαβ (V) and ethyl Δβ (VI) αβ-dimethyl-glutaconate, the latter predominating.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{EtOO} & \quad \text{C} = \text{C} - \text{CH}_2 - \text{COEt} \\
& \quad \text{CH}_3 \quad \text{CH}_3 \\
& \quad \text{EtOO} - \text{CH} - \text{C} = \text{CH} - \text{COEt} \\
\end{align*}
\]

(V) (VI)

This would be expected to give mainly αβ'-trimethyl-glutaconic ester on methylation, as demonstrated by Packer and Sargent.

Hutchison (N.Z. University Thesis, 1935, unpublished) prepared the Δαβ form of methyl αβ-dimethyl glutaconate by the method of Kon and Watson and methylated it by using
potassium dispersed in ether and methyl iodide, hoping to get methyl $\text{C}_3\text{H}_5$-trimethyl-glutaconate. The product on hydrolysis gave a mixture of acids from which small quantities of two acids were isolated by fractional crystallisation. The first to separate he assumed to be $\alpha\beta\gamma$-trimethyl-glutaconic acid as its melting point was depressed by $\alpha\alpha\beta$-trimethyl-glutaconic acid. The second was identical with $\alpha\alpha\beta$-trimethyl-glutaconic acid. It seemed therefore that under the conditions of methylation, much of the methyl $\Delta^\beta$-dimethyl-glutaconate had undergone conversion to the $\Delta^\beta\gamma$ tautomeride.

B. Methylation of Cyanoc(dimethyl glutaconic ester.

Rogerson and Thorpe (J.C.S. 1905, 27, 1702) condensed ethyl cyanocacetate and ethyl-methylacetocacetate with sodium ethoxide in alcohol to give the sodic derivative of ethyl-$\alpha$-cyanoc-$\beta\gamma$-dimethyl-glutaconate (VII).

$$\text{CN} \quad \text{CH}_3 \quad \text{CN} \quad \text{CH}_3 \quad \text{NaOEt} \quad \text{CN} \quad \text{CH}_3 \quad \text{CH}_3$$

$$\text{EtOOC} - \text{CH} + \text{C} = \text{C} - \text{COOEt} \rightarrow \text{EtOOC} - \text{CH} - \text{C} = \text{C} - \text{COOEt}$$

(VII)

Methylation of this product, followed by acid hydrolysis, gave a glutaconic acid which these workers considered to be $\alpha\beta\gamma$-trimethyl-glutaconic acid. The acid obtained melted at 127°C.

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

C. Reformatsky condensation of an \( \alpha \)-bromo ester with a mono alkyl acetacetic ester.

Perkin and Thorpe (J.C.S. 1897, 21, 1178) made ethyl \( \beta \)-hydroxy-\( \alpha \beta \)-trimethyl glutarate by two different Reformatsky condensations and dehydrated this ester, hydrolysing the product to give \( \alpha \beta \)-trimethyl glutaric acid (VIII).

\[
\begin{align*}
\text{CH}_3\text{CH}_3\text{OH} & \quad \text{CH}_3\text{CH}_3 \\
\text{OOC} - \text{C} - \text{C} - \text{O} - \text{COOEt} & \xrightarrow{\text{H}^+} \text{OOC} - \text{C} - \text{C} = \text{CH} - \text{COOEt} \\
\text{CH}_3\text{CH}_3\text{H} & \quad \text{CH}_3 \\
\text{Et} & \quad \text{Et}
\end{align*}
\]

Hydrolysis

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

(VIII)

This work suggests a method for the synthesis of \( \alpha \beta \)-dialkyl \( \beta \)-methyl glutaric acids. Mapstone (M.Z. University Thesis, 1940, unpublished) suggested the following synthesis -
The acyl alkyl malonic ester was used because it has no mobile hydrogen and hence no enolic form to react with the organometallic compound. Individual work by Sinclair (M.Z. University Thesis, 1943, unpublished), Greenwood (M.Z. University Thesis, 1942, unpublished) and Bailey (M.Z. University Thesis, 1944, unpublished) showed that the method was unsuitable for preparing α,α-dimethyl glutaric acid mainly because the bromo acetic ester condensed with itself to give a product which reacted with the acetyl methyl malonic ester to give α-carbethoxy α-methyl-succinic acid. The latter worker concluded that such a method was unsuitable for the synthesis of αβ,β-trimethyl-glutaric acid.
D. The Condensation of an $\alpha$-alkyl-$\beta$-chlore-crotonic ester with the sodio derivative of an alkyl-malonic ester.

This is a modification of the method of synthesis of Fichter and Schwab (Ann. 1906, 348, 251) of $\beta$-methyl-glutaconic acid. These workers condensed ethyl $\beta$-chlore-crotonate trans and cis respectively with mono-sodio-malonic ester, hoping to obtain on hydrolysis of the esters produced, the two stereoisomeric $\beta$-methyl-glutaconic acids (IX).

$$\text{EtOOC} \text{CHBr} + \text{Cl} - \text{C} = \text{CH} - \text{COOEt} \rightarrow \text{EtOOC} \text{CH} - \text{C} = \text{CH} - \text{COOEt}$$

$$\text{EtOOC} \text{CHBr} + \text{Cl} - \text{C} = \text{CH} - \text{COOEt} \rightarrow \text{EtOOC} \text{CH} - \text{C} = \text{CH} - \text{COOEt}$$

They claimed that both condensations gave the same ethyl-$\alpha$-carbethoxy-$\beta$-methyl glutaconate. They hydrolysed this ester with baryta and obtained a mixture of the two stereoisomeric $\beta$-methyl-glutaconic acids which were separated by fractional crystallisation. Sidvani, Kon and Wright (J.C.S. 1932, 135, 1027), repeated these condensations and obtained two tricarbethoxy esters showing small but definite differences in physical properties. Hydrolysis with 5% cold aqueous potassium hydroxide solution containing a little alcohol
resulted in the trans-β-methyl (m.p. 149°C.) and cis-β-methyl (m.p. 118°C.) glutaric acids being obtained from the trans-tricarbethoxy ester and cis-tricarbethoxy esters respectively.

Blakely (N.Z. University Thesis, 1946, unpublished) investigated the possibility of synthesising αβγ-trimethylglutaconic acid by condensing mono-sodic-methyl-malonic ester with α-methyl-β-chloro crotonic ester and hydrolysing the α-carbethoxy-αβγ-trimethyl glutaric acid ester so produced.

\[ \text{EtOOC} \quad CH_3 \quad CH_3 \quad CH_3 \quad C - CH = CH - COOEt \quad \text{Ether} \]

\[ \text{EtOOC} \quad \text{EtOOC} \quad CH_3 \quad CH_3 \quad CH_3 \quad G - C = C - COOEt \quad \text{EtOOC} \quad \text{NaOEt} \]

\[ \text{HOOC} - CH - C = C - COOH \quad \overset{\text{Hydrolysis}}{\longrightarrow} \quad \text{EtOOC} - CH - C = C - COOEt \]

\[(XI) \quad (X)\]

Blakely ultimately obtained a small quantity of ethyl αβγ-trimethyl-glutaconate (X) which on combustion analysis gave correct results. Hydrolysis of the ester gave a quantity of acid which was too small for analysis or further characterisation, but which he believed to be αβγ-trimethyl-glutaconic acid (XI).
repeated Bjelkely's synthesis and obtained a 30gm. yield of acid which he showed to be the required \( \alpha\beta\gamma \)-trimethyl-glutaconic acid (m.p. 111-112°C.) The same worker prepared the normal anhydride of the above acid by boiling it with acetic anhydride. He assumed it was the normal anhydride for it showed no colour change with ferric chloride solution and no effervescence with sodium bicarbonate. The normal anhydride had a melting point 119.5°C. Jacobsen prepared the hydroxy anhydride by distillation of the normal anhydride. In aqueous sodium bicarbonate solution it dissolved with a steady evolution of bubbles, but it did not appear to give a colour change with ferric chloride solution. The hydroxy-anhydride had a melting point 116°C.

Jacobsen (ibid) prepared the cis-\( \alpha\beta\gamma \)-trimethyl-glutaconic acid by two methods.

(i) Concentration of an aqueous solution of the acid under reduced pressure. Repeated precipitation of the solid acid, thus obtained, from benzene-petroleum ether, gave an acid of constant melting point 117°C.

(ii) Hydration of the hydroxy-anhydride. The anhydride was stood in cold distilled water over-night. The solution was extracted with ether and the ether evaporated off. The residue was recrystallised from benzene and petroleum ether. Three recrystallisations gave a constant melting point
of 115°C. With the acid of melting point 117°C, it gave a mixed melting point of 117°C.

These two acids Jacobsen considered to be the cis-form of \( \alpha\beta\gamma \)-trimethyl-glutaconic acid. Combustion analysis of the cis-acid gave:

\[
C = 55.62\% \quad H = 7.06\%
\]

\( C_6H_{12}O_4 \) requires \( C = 55.80\% \), \( H = 7.08\% \)

Nottingham (N.Z. University Thesis, 1948, unpublished) repeated the above synthesis of \( \alpha\beta\gamma \)-trimethyl-glutaconic acid. He showed the presence of asymmetry within the molecule by partial resolution of the acid into the \( d \)- and \( l \)-forms. These optically active acids obtained were probably not pure enantiomorphs.
THE PRESENT INVESTIGATION

The main object of the present work was to synthesise αβ-dibenzyl-glutaconic acid, by a method parallel to that used by Thole and Thorpe (ibid) to prepare αβ-dimethyl-glutaconic acid, and to examine its properties. It was hoped in particular to isolate it in both trans and cis forms and if possible to resolve both these geometrical isomers into optically active forms. Time did not permit the whole of this programme to be carried out.

A. The Synthesis of αβ-dibenzyl-glutaconic Acid.

The proposed steps in the synthesis were:
\[
\text{EtOOC} \xrightarrow{\text{Na}} \text{Cl} \xrightarrow{\text{H}} \text{Na} \xrightarrow{\text{COOEt}} \text{EtOOC} \\
\text{EtOOC} \xrightarrow{\text{Na}} \text{Cl} \xrightarrow{\text{Cl}} \text{Na} \xrightarrow{\text{COOEt}} \text{EtOOC}
\]

Sodium derivative of ethyl \(\alpha\)'-dicarbethoxy glutarconate.

\[
\text{EtOOC} \xrightarrow{} \text{COOEt} \xrightarrow{\text{C_6H_5CH_2Cl}} \text{EtOOC}
\]

Ethyl \(\alpha\)-benzyl-\(\alpha\)'-dicarbethoxy-glutarconate.

\[
\text{EtOOC} \xrightarrow{\text{C = CH \xrightarrow{\text{C}} \text{COOEt}}} \text{EtOOC}
\]

Ethyl \(\alpha\)'-dibenzyl-\(\alpha\)-carbethoxy-glutarconate.

\[
\text{EtOOC} \xrightarrow{\text{CH_2C_6H_5 \xrightarrow{\text{CH_2C_6H_5}}} \text{NaOEt}} \xrightarrow{\text{C_6H_5CH_2Cl}} \text{EtOOC}
\]

Ethyl \(\alpha\)'-dibenzyl-\(\alpha\)-glutarconate.

\[
\text{EtOOC} \xrightarrow{\text{CH_2C_6H_5 \xrightarrow{\text{CH_2C_6H_5}}} \text{NaOEt}} \xrightarrow{\text{Hydrolysis}} \text{EtOOC}
\]

\(\alpha\)'-dibenzyl-glutaconic acid.
(i) The preparation of the sodio derivative of ethyl-αγ-dicarbethoxy-glutaconate.

This, the yellow sodium compound of Conrad and Guthzeit (Ann. 1883, 222, 257) was prepared by the method described by Kohler and Reid (J.A.C.S. 1925, 47, 2607), except that vigorous shaking by hand was used instead of a mechanical stirrer. This method was found by Packer and Thorpe (ibid) to give yields equivalent to that of Ingold and Perrin, (J.C.S. 1921, 112, 1591) provided the chloroform was added as rapidly as possible, consistent with keeping the reaction under control by cooling the upper part of the flask. It was discovered accidentally that addition of water to the mother liquor increased the yield of the yellow sodium compound. Evidently the yellow sodio compound is less soluble in water than in alcohol. The addition of water to this sodio compound is peculiar for most sodio organic compounds decompose under the same treatment.

(ii) Ethyl α-benzyl-αγ-dicarbethoxy-glutaconate.

An alcoholic solution of the yellow sodio derivative of αγ-dicarbethoxy-glutaconic ester was refluxed with benzyl chloride (1 mol. + 50% excess) on a water bath till the reaction mixture was neutral. Twelve hours were required which is a much longer time than that required for the
substitution of a methyl group, this being in accord with observations by Thole and Thorpe (J.C.S. 1911. 22, 2192). From the reaction mixture there were isolated well formed crystals which on recrystallisation from aqueous alcohol gave a melting point of 77.5°C. Ruhemann (Trans. 1893. 63, 259) and Conrad and Guthsart (Ann. 1883. 222, 261) give a melting point of 78°C. for the same compound. Purification of the crystals by distillation under reduced pressure was attempted but each time decomposition of the compound took place even at a temperature of 250°C - 255°C and 18-19 mm pressure. Thole and Thorpe (ibid) claimed to have distilled the same compound, ethyl α-benzyl-α-y-dicarboxy glutarate at a temperature of 253°C. and 18 mm. pressure. However, Kon, Giavani and Wright (J.C.S. 1932. 135, 1039) prepared the same ester but were unable to distil it without decomposition even at a pressure of 2 mm.

The same benzylation was attempted using tertiary butyl alcohol as the reaction medium, but the yellow colour of the sodium compound persisted even after 24 hours' refluxing. The sodic compound and the benzyl chloride were recovered unchanged by distilling off the alcohol under reduced pressure.

(iii) Ethyl α-y-dibenzyl-α-carboxy-glutarate.

The decarboxylation of ethyl α-benzyl-α-y-dicar-
bethoxy glutaconate and its conversion to ethyl \( \alpha'\gamma\)-dibenzyl-\( \alpha\)-
carbethoxy glutaconate was done in one step, there being no
need to isolate the intermediate sodium derivative.

\[
\begin{array}{c}
\text{C}_6\text{H}_5 \\
\text{CH}_2 \\
\text{EtOOC} - \text{C} - \text{OH} - \text{C} - \text{COOEt}
\end{array}
\]

\[\text{Na}^+\]

An alcoholic solution of sodium ethoxide was added to a
warm (approximately 35\(^{\circ}\)C.) solution of ethyl \( \alpha\)-benzyl-\( \alpha'\)
dicarbethoxy-glutaconate in alcohol, both a bright orange
colour and a relatively strong odour of ethyl carbonate
developed almost immediately. Benzyl chloride (1 mol + 25%
excess) was added and the mixture refluxed on a water bath
for 35 hours, after which the yellow colour of the sodium
compound had disappeared and the solution was neutral to
lithium. An ester was isolated which distilled at 246-248\(^{\circ}\)C/
17·5 mm. or 218-220\(^{\circ}\)C./0·5 mm. It was a pale yellow oil,
fairly mobile with \( n^2_{D} 1·5275. \)

(iv) Ethyl \( \alpha'\gamma\)-dibenzyl-glutaconate.

The decarbethoxylation of ethyl \( \alpha'\gamma\)-dibenzyl-\( \alpha\)-
carbethoxy-glutaconate to ethyl \( \alpha'\gamma\)-dibenzyl-glutaconate was
accomplished by cold sodium ethoxide. In terms of electronic
mechanisms it appears that the electron demand of the carbethoxy
groups is not met by electron displacements involving the
benzyl group. The ethoxide ion attacks the carboxethoxy group which subsequently breaks off as ethyl carbonate.

The ester isolated distilled at a temperature of 239-241°C./17.5 mm. or 204-208°C./0.5 mm. and had a $^o_D$
1.5299. It was a pale yellow oil more viscous than ethyl $\alpha\gamma$-dibenzyl-$\alpha$-carboxethoxy-glutaconate.

Thole and Thorpe (J.C.S. 1911. 29, 2191) observed that many compounds of the type of the carboxethoxy-glutaconic esters where no mobile hydrogen is present but where the mobile glutamic acid can be generated by the elimination of a carboxethoxy group and so retain a mobile hydrogen atom when treated with cold sodium ethoxide. The actual product of the reaction is the yellow sodium derivative of the glutamic ester, the carboxethoxy group being eliminated as ethyl carbonate. Experiment showed that the reaction proceeded quantitatively. Similarly, substitution of the sodium by another $R$ group and then treatment with sodium ethoxide would yield a compound thus:

\[
\text{EtOOC} - \text{C} = \text{C} - \text{R} \rightarrow \text{COOEt}
\]

Kon (J.C.S. 1932. 135, 2447) accounted for this phenomenon on an electronic basis. He said the elimination of the carboxethoxy group is due to the strong demand for electrons of the two electrophilic carboxethoxy groups attached to the same carbon atom.
As a result an ethoxide ion attacks the carbon atom of a carbonyl group, and the subsequent electronic rearrangements result in the splitting off of ethyl carbonate.

\[
\text{EtO} - \text{C} = \text{O} \quad \text{CH} = \text{O} = \text{COOEt}
\]

\[
\text{EtO} = \text{C} = \text{CH} = \text{O} = \text{COOEt} \quad \text{Na}^+
\]

\[
\text{EtO} - \text{C} = \text{C} = \text{CH} = \text{C} = \text{COOEt} \quad \text{(XII)}
\]

\[
\text{EtO} = \text{C} = \text{O} = \text{CH} = \text{C} = \text{COOEt} + (\text{EtO})_2\text{CO}
\]

\[
\text{H}_2\text{O}
\]

\[
\text{RtO} = \text{C} = \text{C} = \text{CH} = \text{C} = \text{COOEt} + \text{NaOH}
\]

Since the formation of the intermediate (XII), shown above, would involve a high energy of activation and also loss of the resonance energy of the original ester, the
elimination of the carbethoxy-group is best represented in terms of the molecular orbital theory.

\[
\begin{align*}
\text{EtOOC} & \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{EtCOEt} \\
\text{EtO} & \quad \text{C} \quad \text{C} \quad \text{C} \\
& \quad \text{C} \quad \text{C} \\
& \quad \text{C} \quad \text{C} \\
& \quad \text{C} \quad \text{C} \\
\end{align*}
\]

i.e.

\[
\begin{align*}
\text{EtOOC} & \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{EtCOEt} \\
\text{EtO} & \quad \text{C} \quad \text{C} \quad \text{C} \\
& \quad \text{C} \quad \text{C} \\
& \quad \text{C} \quad \text{C} \\
& \quad \text{C} \quad \text{C} \\
\end{align*}
\]

The 2p orbitals of the incoming-ethoxide and \( R'' - \text{EtCOEt} \) groups will then overlap with the \( \text{C} = \text{O} \) \( \pi \)-orbital to form a mesomeric system. In the transition state, which will be planar, the ethoxide and \( R'' \) groups are linked by partial double bonds to the central carbon atom.

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

Where \( R'' = \)

\[
\begin{align*}
\text{EtO} & \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \\
& \quad \text{C} \quad \text{C} \\
& \quad \text{C} \quad \text{C} \\
& \quad \text{C} \quad \text{C} \\
& \quad \text{C} \quad \text{C} \\
\end{align*}
\]
The case with which this elimination of a carbethoxy group takes place depends on the nature of the substituent groups in the molecule. Thus \( \alpha\)-methyl-\( \beta\)-phenyl-\( \alpha\)-carbethoxy-glutaconate (XIII)

\[ \text{EtOOC} - \text{C} = \text{C} - \text{CH} - \text{COOEt} \] (XIII)

\[ \text{COOEt} \]

does not react with alcoholic sodium ethoxide. Ken suggests the electron demand of the carbethoxy groups can be met by electron displacements involving the phenyl group which has a fairly high +I effect, so that attack by the ethoxide ion, necessary for the elimination of the carbethoxy group as ethyl carbonate occurs less readily. In the case of \( \alpha\beta\gamma\)-trimethyl-glutaconic acid alcoholic sodium ethoxide in the cold does not produce elimination of a carbethoxy group and heating at 30°C for 1½ hours is necessary. Blakely (N.Z. University Thesis, unpublished) concluded that in \( \alpha\)-carbethoxy-\( \alpha\beta\gamma\)-trimethyl-glutaconic ester (XIV) the cumulative electron donating (+I) effect of the three methyl groups produces a similar effect as in the case of \( \alpha\)-carbethoxy-\( \alpha\)-methyl-\( \beta\)-phenyl-glutaconic ester.

\[ \text{EtOOC} - \text{CH}_3 \text{CH}_3 \text{CH}_3 \]
\[ \text{C} - \text{C} = \text{C} - \text{COOEt} \] (XIV)

\[ \text{EtOOC} \]
(v) Hydrolysis of the ester to \(\alpha\beta\)-dibenzyl-glutaconic acid.

Aqueous alcoholic hydrochloric acid is the reagent which has been used most frequently to effect the hydrolysis of glutaconic esters to the corresponding acids. The main exception to this are the \(\beta\)-phenyl-glutaconic esters which are decomposed by hydrochloric acid but can be hydrolysed successfully by alkali. Attempts were made to hydrolyse ethyl \(\alpha\beta\)-dibenzyl-glutaconate to \(\alpha\beta\)-dibenzyl-glutaconic acid, by refluxing with 5N aqueous alcoholic hydrochloric acid, but with no success. Aqueous acetone, as solvent, was also tried but once again failed to give the required glutaconic acid.

Alkaline hydrolysis was resorted to; the successful method being the use of alcoholic sodium hydroxide. On refluxing the ester with the alkaline solution a voluminous precipitate of the sodium salt was readily obtained. This was washed with alcohol, the alcohol removed, then dissolved in water which was acidified with the calculated amount of dilute hydrochloric acid. The acid separated as an oil, crystallisation of which, after separating, washing and drying, was best effected by keeping at 30\(^\circ\)C. for 36 hours, then plunging into a freezing mixture of "dry" ice and alcohol; scratching the inside of the container aided crystallisation. Crystals of acid from a small scale hydrolysis were used to "seed" the oil obtained from the main hydrolysis. The acid
obtained was readily soluble in alcohol, ether, benzene, acetone and chloroform, but only sparingly soluble in water. Recrystallisation three times from aqueous alcohol gave an acid of constant melting point 139° -139.5°C.

Combustion analysis gave

\[ \text{H} = 5.85\% \quad \text{C} = 73.65\% \]

\[ \text{C}_{19}\text{H}_{18}\text{O}_4 \text{requires} \quad \text{H} = 5.8\% \quad \text{C} = 73.5\% \]

Molecular weight determination by Reast method using first naphthalene and secondly glutamic acid as solvent in the borneol gave 298 and 305 respectively.

\[ \text{C}_{19}\text{H}_{18}\text{O}_4 \text{requires} \quad 310. \]

Equivalent weight by titration with carbonate-free alkali was found to be 156.5, the theoretical value is 155. In view of these results and the method of synthesis, there seemed no doubt that the acid obtained was the one desired.

(vi) Preparation of Derivatives.

The following derivatives were prepared:

a. \( p \)-toluidide
b. anilide
c. an addition compound with benzyl thiuronium chloride
d. phenyl hydrazide
e. normal anhydride.
a. The p-toluidide was prepared directly from the acid and also via the acid chloride. A poor yield, but sufficient for recrystallisation, was obtained in both cases. Recrystallisation was effected from hot water. The melting points of the p toluidides were 77°C. and 75°C. respectively. A mixed melting point was 76°C-77°C.

b. The anilide was prepared by the same methods used for preparing the p-toluidide. The melting points of the recrystallised anilides were 86°C. and 86.5°C- 87.5°C. respectively. A mixed melting gave 86°C-87°C.

c. The addition compound was formed between α,β-dibenzyl-glutaconic acid and benzyl-thiuronium chloride. A neutral compound was formed which had a melting point of 156°C-157°C. after three recrystallisations from aqueous alcohol.

d. A phenyl hydrazide was prepared by the direct action of a solution of phenyl-hydrazine in benzene on α,β-dibenzyl-glutaconic acid. The hydrazide separated and was recrystallised from benzene. The recrystallised hydrazide had a melting point of 92°C.

e. Refluxing some of the acid separately with acetic anhydride and acetyl chloride resulted in a crystalline normal anhydride (XV)
This anhydride showed none of the properties typical of hydroxy anhydrides (XVI) such as coloration with ferric chloride solution and effervescence with sodium bicarbonate solution. Thole and Thorpe (J.C.S. 1911. 29, 2208) prepared hydroxy anhydrides of unsymmetrically substituted glutaconic acids by merely distilling the normal anhydride under reduced pressure. The writer attempted to do the same with \( \alpha \gamma \)-dibenzyl-glutaconic acid anhydride but only obtained tarry decomposition products. Repeated recrystallisation of the normal anhydride from benzene gave a constant melting point of 136°C. Solution in boiling aqueous sodium carbonate followed by acidification gave back the original \( \alpha \gamma \)-dibenzyl-glutaconic acid.

(vii) **Preparation of cis-\( \alpha \gamma \)-dibenzyl-glutaconic acid.**

The preparation of the cis form of \( \alpha \gamma \)-dibenzyl glutaconic acid was attempted by the method of Malachowski (Ber. 1929. 62, 1323), namely, the anhydride was gradually added to a small
volume of water at $10^o-12^o C$. On dissolution it was evaporated as quickly as possible under reduced pressure. The solid remaining had the properties consistent with $\alpha \beta$-dibenzyl-glutaconic acid in that it decolorised bromine water and dilute permanganate solution and it effervesced with sodium bicarbonate solution. An equivalent weight determination, by titration, gave a result of 152. But, however, its melting point was $124.5^o-125^o C.$ and a mixed melting point with the original acid gave $124.5^o-122.5^o C.$
B. The Interconversion of Cis and Trans Isomers

In the hydrolysis of ethyl \(\alpha\beta\)-dibenzyl-glutaconate to the acid, the ester was refluxed with aqueous alcoholic sodium hydroxide for 1\(\frac{1}{2}\) hours and the crude acid obtained had a melting point of 136\(^{\circ}\)C - 138\(^{\circ}\)C, and on recrystallisation, a constant melting point of 139\(^{\circ}\)C - 140\(^{\circ}\)C, which is remote from the melting point of the cis acid (m.p. 124\(^{\circ}\)C) obtained by hydration of the anhydride. This suggests that the acid obtained on hydrolysis was mainly, if not wholly, the trans form. This is similar to the case of \(\alpha\beta\)-dimethyl-glutaconic acid. McCombs, Packer and Thorpe (J.C.S. 1932, 135, 547) showed that concentrated caustic potash on the trans \(\alpha\beta\)-dimethyl-glutaconic acid does not produce any of the cis isomeride.

Thorpe and Wood (J.C.S. 1932, 135, 2434) studied the effect of alkali and acid on the cis- and trans- \(\alpha\)-benzyl-\(\beta\)-methyl-glutaconic acids, and found that dilute acid had no apparent effect on the interconversion, whereas concentrated hydrochloric acid readily converts the trans- \(\Delta^\alpha\beta\) and the trans- \(\Delta^\delta\beta\) acids into the cis- \(\Delta^\alpha\beta\) form. On the other hand, alkali even in low concentration causes the reverse change of the cis- \(\Delta^\alpha\beta\) to the trans- \(\Delta^\delta\beta\) acid.

According to modern views the interconversion of cis and trans isomers is considered to take place through an intermediate mesomeric ion by migration of a proton as
described in the introductory section on the Structure of Glutaconic Acids. This common mesomeric ion (in alkaline solution)

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

would be expected to have a more or less planar structure, due to partial double bond character imposed on it by mesomerism.

A study of the Fischer-Hirschfelder models of \(\alpha\beta\)-dibenzyl-glutaconic acid shows that only the trans-modification of the acid can the five carbon atoms of the glutaconic chain assume a planar configuration without any undue strain. This is true for any \(\alpha\beta\)-disubstituted glutaconic acid for the substituent groups are too far apart to interfere with each other.

In the cis-form of the acid (from the models) the constituent atoms are packed more tightly together thus limiting any adjustment of bond angles. Also the five carbon atoms of the glutaconic chain can have a planar arrangement; although the carboxyl groups at the ends of the system cannot lie in
the same plane without strain.

From the above considerations it would appear that the trans- form of $\beta$-dibenzyl-glutaconic acid should be more stable than the cis-, as experimental results have shown.
C. The Optical Isomerism of \( \alpha\gamma \)-dibenzyl-glutaconic Acid.

Since \( \alpha\gamma \)-dibenzyl-glutaconic acid contains an asymmetric carbon atom

\[
\begin{align*}
\text{CH}_2\text{C}_6\text{H}_5 & \quad \text{CH}_2\text{C}_6\text{H}_5 \\
\text{HOOC} & - \text{CH} = \text{CH} \quad \text{C} - \text{COOH} \\
\text{H} &
\end{align*}
\]

it should be capable of resolution into optical active forms. Of the methods available for resolution of optical racemic compounds the one chosen was that used by McConbe, Packer and Thorpe (ibid) for the resolution of \( \alpha\gamma \)-dimethyl-glutaconic acid. Time was not available for complete investigation of resolution but the methods attempted were:

Strychnine in chloroform.

A solution of strychnine in chloroform was added to an equimolecular quantity of trans \( \alpha\gamma \)-dibenzyl-glutaconic acid dissolved in acetone. In these experiments it was found that the quantity of chloroform for solution of the strychnine had to be kept to a minimum otherwise crystallisation of the strychnine salt would not take place. The method of decomposition of the alkaloid salt and recovery of the acid was that used by McConbe, Packer and Thorpe (ibid) with \( \alpha\gamma \)-dimethyl-glutaconic acid. The alkaloid salt was decomposed
by dilute ammonium hydroxide, thus forming the ammonium salt, the alkaloid extracted with chloroform, the solution then acidified to obtain the glutaconic acid, the acid being extracted by ether. Since \( \alpha\gamma \)-dibenzyl-glutaconic acid is only sparingly soluble in water, ethyl alcohol was used as the solvent for measurement of rotation. This acid was dextrorotatory \([\alpha]_D^{14} = 44^\circ\). The mother liquor, from which the strychnine salt had crystallised, after removal of the crystals was evaporated to dryness and the glutaconic acid recovered as before. The amount of acid so recovered was very much less than of the d- acid. Probably incomplete first order asymmetric transformation had taken place.

The melting points of the acids recovered were:

- Dextrorotatory acid, 138\(^\circ\)C.
- Mixed melting point with trans-dl- \( \alpha\gamma \)-dibenzyl-glutaconic acid, 134.5\(^\circ\)C.
- Melting point of the second "optically active" acid 134\(^\circ\)C. and a mixed melting point with the dl-trans acid 137\(^\circ\)C.
SUMMARY

1. The synthesis of trans-\(\alpha\beta\)-dibenzyl-glutaconic acid has been accomplished by modifications of Thole and Thorpe's method of \(\alpha\beta\)-dimethyl glutaconic acid.

2. The acid has been characterised by the formation of derivatives such as anilide, \(p\)-toluidide, phenyl hydrazide and an addition compound with benzyl thiononium chlorides.

3. The geometrical isomerism of the acid has been demonstrated by the formation of the cis acid by hydration of the normal anhydride.

4. The optical isomerism of the acid has also been demonstrated by partial resolution.
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EXPERIMENTAL SECTION

A. PURIFICATION OF CHEMICALS

Ethyl Alcohol.

Commercial ethyl alcohol was refluxed over fresh quicklime for six to eight hours. 200 ml. of this dehydrated alcohol, magnesium turnings (10 gms.) and iodine (1 gm.) were refluxed until all the magnesium was converted to the ethylate. "absolute" alcohol (1800 ml.) was then added and the mixture refluxed for 30 mins. The alcohol was distilled off directly into the vessel in which it was stored. For condensation reactions the alcohol was purified as required and distilled into the reaction vessel. After purification the alcohol had a density of 0.7928 at 16°C. Osborne, McKelvy and Bearce give a value of 0.79360 at 15°C.

Ether.

Ether was shaken with an acid ferrous sulphate solution (conc. H₂SO₄, 7·5 gms., water 135 ml., Ferrous sulphate 60 gms., to 2·5 litres of ether) to remove peroxides, washed with dilute alkali and then with water. It was dried over anhydrous magnesium sulphate, and distilled through a long fractionating column from caustic potash sticks. The product was stored in a dark bottle and kept in a cupboard. Part was
kept over sodium wire.

Chloroform.

Chloroform was stood overnight overnight over calcium chloride and then distilled through an efficient fractionating column. The product had a $n_D^{15} 1.4434$.

Malonic Ester.

Malonic ester was shaken with sodium carbonate solution, washed with water, most of the water was removed by solid potassium carbonate, and the product dried over phosphorus pentoxide (Young and Thomas, J.C.S. 1893. 63, 1191) then distilled under reduced pressure. The fraction distilling at 89°/14 mm. was collected. The product had a $n_D^{18} 1.443$. Smythe and Walls (J.C.S. 1931. 134, 529) give $n_D^{20} 1.4445$ for the pure ester.

Benzyl Chloride.

The B.D.H. product was distilled through a small fractionating column and the fraction distilling at 179°C. collected. For benzylations the benzyl chloride was distilled as required.
SYNTHESIS OF DIBENZYL-GLUTACONIC ACID

dibenzylglutaconic was prepared by the method Thole and Thorpe (J.C.S. 92, 2187) used for preparing dimethyl glutaconic acid, namely, by the following series of reactions:

Malonic ester, chloroform and sodium ethoxide

\[ \rightarrow \text{ethyl sodic-}\alpha\gamma\text{-dicarbethoxyglutaconate} \]

\[ \rightarrow \text{ethyl } \alpha\text{-benzyl dicarbethoxyglutaconate} \]

\[ \rightarrow \text{ethyl } \alpha\gamma\text{-dibenzylcarbethoxyglutaconate} \]

\[ \rightarrow \text{ethyl } \alpha\gamma\text{-dibenzylglutaconate } \rightarrow \alpha\gamma\text{-dibenzylglutaconic acid.} \]

I. Ethyl sodic $\alpha\gamma$ dicarbethoxy glutaconate.

This, the yellow sodium compound of Conrad and Guthzeit (Ann. 222, 259) was prepared by a modification of the method described by Kohler and Reid (J.A.C.S. 47, 2803).

1500 mls. absolute alcohol were added to a 3 litre flask fitted with a double-surface condenser of large bore, then 69 gms. of freshly cut sodium were added gradually. When all the sodium had dissolved 240 gms. of malonic ester were added and then while the mixture was still hot, as rapidly as possible without losing control of the reaction, 89 gms. of chloroform were added. The reaction mixture was
now shaken vigorously by hand. Vigorous reaction took place which was controlled by cooling the upper part of the flask. When the reaction had subsided a further 29 gm. of the chloroform was added and the whole heated on a water bath for ½ hour. The reaction mixture was filtered while still hot through a large Buchner funnel (to remove the precipitated sodium chloride) and the filtrate transferred to a large beaker. The sodium chloride and flask were washed with several lots of hot alcohol, the washings collected separately. The filtrate and washings were cooled on ice for one hour with frequent stirring (to prevent supersaturation). The yellow sodium compound was filtered off and dried on a porous plate over calcium chloride in a vacuum desiccator.

The combined mother liquors were evaporated under reduced pressure to about 1/6 their volume, when more sodium compound separated on cooling over ice.

**Yield:**  
First crop of crystals 105 gms.  
Second " " 17 gms.  
Total 122 gms.  
or 46% of theoretical.

Another two batches were worked up (i.e. a total of 720 gm. malonic ester).

**Yields:**  
Second batch 127 gms. or 46% of theoretical.  
Third batch 145 gms. or 55% of theoretical.
During the recovery of the sodium compound, of the third batch, from the mother liquor, some of the latter accidently came in contact with a small amount of water. After a few hours well-formed crystals were precipitated in quantity sufficient to merit investigation. Working with five millilitre quantities of the mother liquor it was found that an equal proportion of water gave a maximum yield of the yellow sodium compound. The whole of the mother liquor on the same treatment gave a yield of the yellow sodium derivative of $\alpha\beta$-dicarbethoxy-glutaconic ester of 55%, or an increase of 7-9% over the first two batches. These crystals were proved to be the required product by conversion to ethyl $\alpha$-benzyl-$\alpha\beta$-dicarbethoxy glutaconate, as described below, and doing a series of mixed melting points with the same compound derived from crystals of the yellow sodium compound from the first two batches.

(II) Benzylolation of yellow sodium compound to give ethyl $\alpha$-benzyl-dicarbethoxyglutaconate.

Yellow sodium compound (105 gms.) was dissolved in absolute alcohol (240 gms.) contained in a 750 ml. flask fitted with a double surface condenser. When the mixture was homogeneous 57 gms. ($1\frac{1}{2}$ mole) of benzyl chloride were added and the whole refluxed on a water bath till the reaction mixture
was neutral to litmus (12 hours). The solution remained a pale brown colour; this was poured into about 1.5 litres of water and extracted three times with ether. The yellow ethereal solution was washed four times with water and then alternately with 10% potassium hydroxide soln. and water till the washings ceased to be yellow (four such washings were needed). The extract was then washed with three lots of water, dried with anhydrous magnesium sulphate and evaporated, a white crystalline compound remained. These impure crystals were recrystallised from aqueous alcohol three times.

Yield: 89 gms. or 71% theoretical.

M.P. = 77.5° (uncorrected)

Second batch: 91 gms. or 72% theoretical.

III. Conversion of ethyl \( \alpha \)-benzyl-\( \alpha \)\( \gamma \)-dicarboxyglutaconate to ethyl \( \alpha \)\( \gamma \)-dibenzyl-\( \alpha \)-carboxyglutaconate, i.e. elimination of a carboxy group by sodium ethoxide and subsequent benzylation.

Freshly cut sodium (4.1 gms.) was added to absolute alcohol (55 mls.) in 500 ml. flask fitted with a double surface reflux condenser. In a separate flask, ethyl \( \alpha \)-benzyl-\( \alpha \)\( \gamma \) dicarboxyglutaconate (75 gms.) was dissolved in absolute alcohol, refluxed gently till all had dissolved (10 mins.) and this was allowed to cool to a temperature (\( 35^\circ \)) just above solidification and then added to the sodium ethoxide solution.
A bright orange colour and a strong odour of ethyl carbonate developed, (there was no appreciable rise in temperature). After twelve hours, benzyl chloride (25.6 gm. i.e. 1 mol + 25% excess) was added and the whole refluxed. After 24 hours the orange colour still persisted slightly so another 3 gm. of benzyl chloride was added and refluxing continued for 11 hours. After the 35 hours the orange colour had vanished and the solution was neutral to litmus. The mixture was then shaken with six to eight volumes of water and ether extracted four times. The aqueous layer was acidified and what little oil separated (1 ml.) was added to the other extract which was washed with water (four lots) and then alternately with 10% aqueous potassium hydroxide and water till the washings ceased to be yellow; six such washings were needed. Finally the extract was washed with water, dried with anhydrous magnesium sulphate, the ether distilled off, and the remaining liquid fractionally distilled under reduced pressure.

The following fractions were taken:

1. $34^\circ$ - $43^\circ/20$ mm. 15 gms. mainly ethyl carbonate.
2. $75^\circ$ - $128^\circ/20$ mm. 10 gms. mainly benzyl chloride.
3. $218^\circ$ - $230^\circ/20$ mm. 25.5 gms. mainly dibenzyl ester.
4. $238^\circ$ - $262^\circ/19.5$ mm. 4.3 gms. mainly dibenzyl ester.

Redistilled (3) and (4)
Fractions taken were:

(3) 246°-248°/17·5 mm.  22·5 gns.
(4) 254°-257°/20 mm.  36·5 gns.

Yield = 59·0 gns. or 77·5% theoretical.

A second batch was worked up as above and distilled at a lower pressure. A Todd mercury diffusion pump being used backed by an ordinary water-pump. In order to decrease the volume of the distillation apparatus and thereby increase the efficiency of the mercury pump, the distillation was carried out in two portions using a small (50 ml.) claissen flask. The following fractions were taken:

A. (1) 46°-68°/10 mm.
    (ii) 68°-98°/4 mm.
    (iii) 108°-130°/4 mm.
    (iv) 180°-205°/0·5 mm.
    (v) 206°-222°/0·5 mm.
    (vi) 222°-232°/0·5 mm.

    Residues in flask

B. (1) 47°-68°/10 mm.
    (ii) 70°-98°/4 mm.
    (iii) 100°-160°/4 mm.

    7 gns. ethyl carbonate.
    nothing.
    5 gns. mainly benzyl chloride
    nothing.
    22·4 gns. ester
    5·3 gns. probably ester.

    2·6 gns. tarry.

    6 gns. ethyl carbonate.
    nothing
    4·7 gns. mainly benzyl chloride.
(iv) $180^\circ - 200^\circ / 0.5$ mm. 

(v) $204^\circ - 220^\circ / 0.5$ mm. 

(vi) $222^\circ - 235^\circ / 0.5$ mm. 

nothing

$26.6$ gms. ester

$4.0$ gms. probably ester.

Residue in flask

$2.2$ gms. tarry opd.

Fractions A(v) and B (v), and A(vi) and B(vi) were combined and redistilled

(v) $216^\circ - 226^\circ / 0.5$ mm. 

$212^\circ - 222^\circ / 0.5$ mm. 

$4.54$ gms.

$8.5$ gms.

Yield = $53.9$ gms. or $69\%$ of theoretical.

IV. Conversion of $\alpha\beta'$-dibenzyl-$\alpha$-carbethoxy-glutaconate to $\alpha\beta'$-dibenzyl-glutaconate.

Freshly cut sodium (2.15 gms.) was dissolved in absolute ethyl alcohol (56 cc.) and allowed to cool, $40$ gms. of $\alpha\beta'$-dibenzyl-$\alpha$-carbethoxy-glutaconate dissolved in absolute ethyl alcohol (24 cc.) was added to the sodium ethoxide solution. A deep orange colour developed immediately and the odour of ethyl carbonate became quite evident. After $\frac{1}{2}$ hour the mixture was added to one litre of water and ether extracted three times; the extract was a bright orange colour.
The aqueous solution was acidified with dilute hydrochloric acid, when about one gram of oil separated which was added to the ether extract. This extract was washed four times with water and then alternately with 10% potassium hydroxide solution and water till the washings ceased to be yellow; five such washings were needed. The ethereal extract was dried over anhydrous magnesium sulphate, the ether distilled off at atmospheric pressure, and the residue distilled under reduced pressure.

- 55°/ 17.5 mm. Ethyl carbonate.
- 235°-238°/ 17.5 mm. 28 gms.

Yield = 28 gms. or 84% theoretical.

A second batch of the ester was decarbethoxylated in a similar manner.

B. (i) 68°-89°/ 6 mm. 1.0 gms. mainly ethyl carbonate.
- (ii) 192°-218°/ 0.5 mm. 29 gms. ester.
- (iii) 216°-230°/ 0.5 mm. 3.0 gms. probably ester.

Yield = 29 gms. or 37% theoretical.

V. Hydrolysis of ethyl αβ-dibenzyl-glutarate to trans αγ-dibenzyl-glutaric acid.

(i) Attempted hydrolysis by aqueous alcoholic hydrochloric
acid:

(a) Ethyl αβ-dibenzyl-glutaconate (2 gm.) was added to ten volumes of 5N HCl plus two c.c. alcohol. The mixture was refluxed for 9 hours, the ester failing to dissolve. The mixture was extracted with ether four times, the extracts washed with water, dried with anhydrous magnesium sulphate and the ether distilled off. A brown viscous oil remained which showed no acid reaction when treated with sodium bicarbonate solution.

(b) A similar experiment was carried out except that refluxing was continued for 48 hours. The ester again failed to dissolve and the material extracted by ether again showed no acid reaction.

(c) A similar experiment to (b) was carried out except acetone was used instead of alcohol to aid dissolution. Once again a non-acidic oil remained.

(ii) Alkaline Hydrolysis:

(a) Barium hydroxide.

Five grams of the ester were refluxed for 7 hours with barium hydroxide (2 gm.), water 7 c.c. and 1 c.c. alcohol. The reaction mixture was ether extracted to remove any unchanged ester and the solid was dissolved in water, acidified and ether extracted three times. The ether extracts
were dried with anhydrous magnesium sulphate and the ether
distilled off; 0.4 g.m. of an oil showing acid properties
remained. The oil failed to crystallise even by scratching
the container with a glass rod. Yield 9.5% theoretical.

(b) Potassium Hydroxide solution containing a little alcohol

Five grams of the ester were dissolved in 10 c.c.s.
of 10% potassium hydroxide solution and were left for 10 days
at room temperature. A small precipitate was formed which
dissolved in water to give an alkaline solution; this, on
acidifying and subsequent ether extraction, yielded an oil
showing acid properties. Yield = 0.5 g.m. or 11.8% theoretical.

(c) With alcoholic sodium hydroxide containing a little
water.

Five grams of the ester were dissolved in 5 mls.
of alcohol and this solution added to 0.5 gms. freshly cut
sodium dissolved in 20 mls. of alcohol to which had been added
4 mls. of water. The whole was refluxed on a water bath
for 1½ hours. A white, flocculent precipitate of the sodium
salt was formed, and more separated on diluting with alcohol,
indicating the sodium salt was not very soluble in alcohol.
The precipitate was filtered off, washed with alcohol and dried
at 80°C. An aqueous solution of the sodium salt was carefully
acidified with very dilute hydrochloric acid, vigorous
effervescence occurring. The solution was extracted with
ether four times. The ether extracts were washed with small amounts of water, dried over anhydrous magnesium sulphate and the ether distilled off, leaving an acidic oil.

Scratching the inside of the containing vessel failed to crystallise the oil, so it was left for 36 hours at a temperature of 30°C and then plunged into a freezing mixture of 'dry' ice and alcohol and left for 10 minutes. The oil was then allowed to come to room temperature when scratching the reaction vessel caused crystallisation. Yield 1.5 gms. or 35.5% theoretical.

Crystals of the acid were used to "seed" the oil from experiments (ii) (a) and (b).

The main part of the ester was then hydrolysed in precisely the same manner. Yield from 36 gms. of ester = 11.2 gms. or 37% theoretical.

The dibenzyl glutaronic acid was not very soluble in water, but dissolved readily in the cold in ethyl alcohol, acetone, benzene, ether and chloroform. Recrystallisation was therefore carried out from aqueous alcohol. The acid was dissolved in hot alcohol and water was added till the liquid became cloudy, a few ml's. of alcohol were added and the solution allowed to cool spontaneously. The crystals formed were filtered off and recrystallised until a constant melting point was obtained.
Melting point of unrecrystallised acid = 136°-138°C.
Melting point of recrystallised acid = 139°-139.5°C.

The general properties and a series of mixed melting point determinations indicated that the acids from each of the alkaline catalysed hydrolysis were identical. The acid effervesced with aqueous sodium bicarbonate solution and gave a sodium salt whose aqueous solution was pale yellow. It decolorised both bromine water and dilute permanganate solution.
C. INVESTIGATION OF αβ-DIBENZYL-GLOTACONIC ACID

(a) Combustion analysis.

(i) 14.70 gms. of the acid gave 0.07554 gms. H₂O and
    0.33783 gms. CO₂.

    \( H = 5.759\% \quad C = 73.81\% \)

(ii) 17.4 gms. of the acid gave 0.09080 gms. H₂O and
     0.47221 gms. CO₂.

    \( H = 5.85\% \quad C = 73.65\% \)

\( C_{19}H_{18}O_{4} \) requires \( \quad H = 5.8\% \quad C = 73.53\% \)

(b) Equivalent Weight.

The acid was titrated with dilute (approximately 100/N) carbonate free alkali standardised against potassium hydrogen phthalate, using a semi-micro burette and phenolphthalein as indicator.

\( 0.00361 \) gms. acid = 2.35 mls. 0.09971N NaOH

\( \therefore \) Equivalent weight of acid = 156.5
Theoretical value = 155

(c) Molecular Weight.

A Rast molecular weight determination was carried out, using borneol as solvent, in the usual way on a semi-micro scale. The molecular depression constant was determined by using firstly naphthalene and secondly glutaric acid
unsubstituted as solutes in the borneol.

(i) With naphthalene as solute for determination of the cryoscopic constant.

Melting point of borneol (mean value) = 204°C.
Weight of naphthalene used = 0.20028 gm.
Weight of borneol used = 2.08702 gm.
Melting point of mixture (mean value) = 175°C.

\[ \text{\textcdot \cdot Depression of melting point} = 29 \]

\[ \text{\textcdot \cdot Molecular depression constant for 1000} \text{ gm.} = 385 \]

Weight of \( \alpha\gamma \)-dibenzyl glutaconic acid used = 0.02065
Weight of borneol used = 0.19772
Melting point of mixture = 192°C.

\[ \text{\textcdot \cdot Depression of melting point} = 13^\circ \]

Molecular weight of \( \alpha\gamma \)-dibenzyl-glutaconic acid = 298

(ii) Glutaconic acid as solute for determination of cryoscopic constant.

Melting point of borneol = 204°C.
Weight of glutaconic acid used = 0.0093 gm.
Weight of borneol used = 0.21096 gm.
Melting point of mixture (mean value) = 190°C.

\[ \text{\textcdot \cdot Depression of melting point} = 14^\circ \]

\[ \text{\textcdot \cdot Molecular depression constant} = 414 \]
Weight of $\alpha\beta$-dibenzyl-glutaconic acid = 0.02090 gms.
Weight of borseul used = 0.19600 gms.
Melting point of mixture (mean value) = 169.5°C.
  * Depression of melting point = 14.5°C
  * Molecular weight of $\alpha\beta$-dibenzyl-glutaconic acid = 305

$C_{19}H_{18}O_4$ requires molecular weight 310.

(d) Preparation of derivatives of $\alpha\beta$-dibenzyl glutaconic acid.

(i) p-toluidide.

$\alpha\beta$-dibenzyl-glutaconic acid (0.5 gms.) and p-toluidine (1.5 gms.) were refluxed with alcohol (1.5 mls.) for 30 minutes, 5 mls. of alcohol were added and the reaction mixture brought to the boil then poured into 20 mls. of hot water. This solution was concentrated to 10 - 12 mls. and on cooling a crystalline mass precipitated which was collected on a button filter and recrystallised from hot water. Pale yellow crystals resulted, melting point 77°C. Yield, poor.

(ii) Anilide.

The same method was employed as for the p-toluidide. Pale yellow crystals were obtained with a melting point of 86°C. after recrystallisation. Yield, poor.

(iii) p-toluidide via acid chloride.

A mixture of $\alpha\beta$-dibenzyl glutaconic acid (0.2 gms.) and thionyl chloride was heated gently under reflux for 1½ hours.
on a water-bath. The excess thionyl was distilled off and the residue used as crude acid chloride. A solution of p-toluidine (0.5 g.) in benzene was slowly added, stirring vigorously and cooling in a bath of cold water. The reaction was completed by heating for a few minutes, then allowing to cool. The benzene solution was washed with water, dilute hydrochloric acid and finally with water. The solvent was removed from the filtered solution and the solid recrystallised from ethyl alcohol. Poor yield. Melting point 75°C. Melting point when recrystallised 76° - 77°C.

(iv) Anilide via acid chloride.

The experiment was carried out as for the p-toluidides. The melting point was 86.5° - 87.5°C. A mixed melting point with the anilide prepared in (ii) gave 86° - 87°C.

(v) Addition compound of the acid and benzyl thiononium chloride.

A few drops of methyl orange were added to an aqueous alcoholic solution of α,β-dibenzyl glutaric acid (1.65 g.). Sodium hydroxide (N) was added until the solution was just alkaline, the solution acidified with dilute hydrochloric acid, and the mixture added to a solution of benzyl thiononium chloride (2.0 g.) in 6 ml. of water. At this point the mixture was cooled in ice water till the salt had
precipitated completely, the solution was then filtered and
the precipitate recrystallised from aqueous alcohol. The
resulting salt was a white crystalline compound showing no
acidic properties, indicating the acid had reacted with two
mols. of benzyl thiuronium chloride. Melting point after
three recrystallisations was 156°C-157°C. The yield was only
fair.

(vi) Phenyl hydrazide.

A mixture of αβ-dibenzyl-glutaconic acid
(16 gms.) and phenyl hydrazine (26 gms.) dissolved in benzene
(5 ml.) was heated gently under reflux during half an hour.
After cooling a solid separated, which was filtered off,
washed with benzene and recrystallised from the same solvent.
After three recrystallisations the compound showed no change
in melting point which was constant at 92°C. The yield was
good.

(vii) The preparation of the anhydride of the acid.

(a) Normal anhydride by means of acetic anhydride.

The acid (25 gms.) was heated under reflux
over a small bunsen flame with acetic anhydride (4 ml.) for
two hours. The excess acetic anhydride was removed under
reduced pressure as much being removed as possible without
undue heating. Dry alcohol and ether were successively added
and evaporated to remove the residual acetic anhydride. A pale yellow oily residue remained which failed to crystallise. This was left for 24 hours in a vacuum desiccator. The side of the vessel was then scratched with a glass rod when the oil set to a pale crystalline mass. The anhydride was recrystallised from benzene. It showed no colour change with ferric chloride solution and no effervescence with sodium bicarbonate solution. Melting point of the recrystallised product 136°C. Yield was poor.

(b) Normal anhydride by means of acetyl chloride.

The acid (0.25 g.) was heated with an excess of acetyl chloride for one hour. The excess chloride removed under reduced pressure and then standing over caustic soda in a vacuum desiccator. The anhydride formed was identical in its properties with that formed in (a) above. The yield was slightly better. The melting point and a mixed melting point with that obtained from (a) were 135°-136°C. and 136°-136.5° respectively.

A small quantity of the normal anhydride was dissolved in boiling sodium carbonate solution which was then acidified and extracted with ether. The ether extract was washed with water, dried with anhydrous magnesium sulphate and the solvent evaporated. αα'-dibenzyl-glutaconic acid was obtained which was recognised by a mixed melting point with some of the
original acid.

Hydroxy anhydride.

An attempt was made to produce the hydroxy-anhydride by distillation of the normal anhydride under reduced pressure, but the latter decomposed to give a tarry product.
THE PREPARATION OF THE CIS FORM OF THE ACID

α-Dibenzyl-glutaconic acid (0.2 g) was converted to the normal anhydride as described above.

The anhydride (15 g) was gradually added to a small quantity of water (4 ml) at 10-12°C. in which it dissolved; it was evaporated as quickly as possible under high vacuum at room temperature. After all the water was taken off (½ hour) a white crystalline solid remained which showed acid properties towards sodium bicarbonate solution.

This new acid was recrystallised from any other twice and gave a melting point of 124.5-125°C. When mixed with the acid obtained from hydrolysis of the ester it lowered the melting point of the same to 121.5-122.5°C. An aqueous solution of the new acid was left for 4 days in a vacuum desiccator, then the water taken off under vacuum. The melting point of the acid now had risen to 138°C thus indicating it had reverted to the trans form.

Not enough of the new (cis) acid was available for analysis, but an equivalent weight determination was carried out in a similar manner as for the original acid, the results as follows:

\[
\begin{align*}
0.00298 \text{ gm. acid} & = 1.97 \text{ ml. } 0.0097\text{N NaOH} \\
\therefore \text{ Equivalent weight of acid} & = 152. \\
\text{Theoretical value} & = 155.
\end{align*}
\]
E. THE PARTIAL RESOLUTION OF TRANS αβ-DIBENZYL-GLUTARIC ACID.

(1) The action of strychnine on trans-dl-αβ-dibenzyl-glutamic acid.

To a solution of dl-trans-αβ-dibenzyl-glutaric acid (3.1 g.) in acetone (5 ml.), strychnine (3.4 g.) (i.e. one equivalent) dissolved in 2 ml. of chloroform was added. Strychnine hydrogen "d" αβ-dibenzyl glutarate rapidly precipitated out from the solution from which it was removed by filtration after cooling in ice for one hour. This crystalline solid was washed with acetone and ether, dried in air and used for the preparation of "d" acid whilst the filtrate was utilised in an attempt to prepare the l-aid on which no experiments were done to determine its optical activity mainly because of lack of material since first order asymmetric transformation had probably taken place.

(a) "d" αβ-dibenzyl-glutaric acid.

The strychnine salt was decomposed with a slight excess of dilute ammonium hydroxide and the solution extracted four times with chloroform to remove the strychnine liberated. The solution was then acidified with a slight excess of hydrochloric acid and extracted three times with ether. The ether extract was washed twice with small quantities of water to remove any hydrochloric acid, dried over anhydrous
magnesium sulphate and the ether removed under vacuum at room temperature. The solid acid (m.p. 137°C.) was reprecipitated as the strychnine acid salt and the procedure described above repeated. The melting point (138°C.) was not appreciably altered. This trans-α-α'-dibenzyl-
gluconic acid so obtained had \( [\alpha]_D^{14} = +14.2^\circ \), where \( \theta = +.54 \) for a solution containing 1.9gna. per 100 ml. and using a 2-decimeter polarimeter tube and ethyl alcohol as solvent. This gives an \( [\alpha]_D^{14} = +4.4^\circ \).

After filtering off the strychnine salt of the d-acid, the filtrate was evaporated under vacuum at atmospheric temperature and the residue dissolved in a slight excess of dilute ammonium hydroxide. This was extracted three times with chloroform to remove any strychnine. The solution was acidified with dilute hydrochloric acid and extracted three times with ether. The ethereal solution after washing with a little water and drying with anhydrous magnesium sulphate was evaporated to dryness under vacuum at room temperature. There was insufficient acid to measure its optical rotation. The melting point of the acid was 134°C. and a mixed melting point with the trans-dl-acid gave 131°C.