

T H E S I S

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T H E S Y N T H E S I S O F

$\alpha\beta\gamma$ -TRIMETHYLGLUTACONIC ACID

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C O N T E N T S

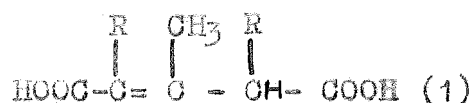
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T H E O R E T I C A L S E C T I O N

The condensation of ethyl β -chloro α -methylcrotonate with the sodio-derivative of ethyl ^{methyl}malonate was attempted as part of a projected synthesis of $\alpha\beta\gamma$ -trimethylglutaconic acid, and to test a new general method for the synthesis of β -methyl- $\alpha\gamma$ -dialkylglutaconic acids (1)

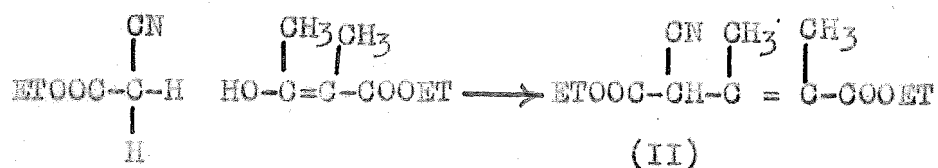


Many attempts have been made over a number of years to synthesise $\alpha\beta\gamma$ -trialkylglutaconic acids but no method has given very satisfactory results. In many cases the yields have been very poor and in no case has the constitution of the product been demonstrated conclusively.

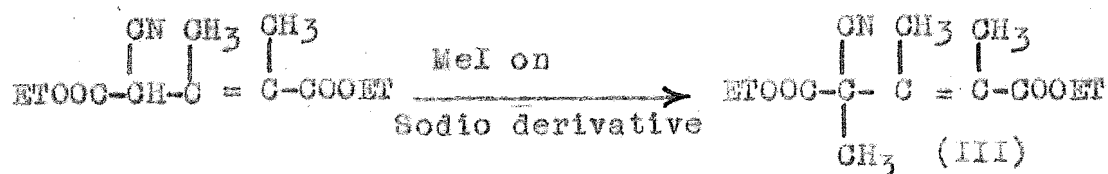
In the following sections the methods which have been used are discussed.

A. Methylation of cyano- dimethylglutaconic acid.

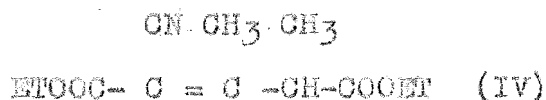
Rogerson and Thorpe (J.C.S. 1905, 87, 1702) condensed methylacetoacetic ester with the sodio-derivative of ethyl cyanoacetate in alcoholic solution to give the sodio derivative of α -cyano- $\beta\gamma$ -dimethylglutaconate which Thorpe formulated as (II)



On treating the sodio derivative of this ester with methyl iodide a product was obtained which was considered to be ethyl α -cyano- $\alpha\beta\gamma$ -trimethylglutaconate (III)



Two products are possible on methylation, however, since ethyl α -cyano- $\beta\gamma$ -dimethylglutaconate may have either the $\Delta^{\beta\gamma}$ structure (II) or the $\Delta^{\alpha\beta}$ structure (IV)

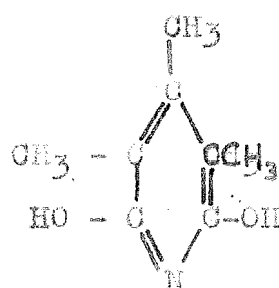


Kon and Nanji (J.C.S. 1931, 134, 571) showed by oxidation with ozone that the ester obtained by the condensation consists mainly of the $\Delta^{\beta\gamma}$ form (II) together with a little of the $\Delta^{\alpha\beta}$ tautomeride (IV). Hence methylation should give ethyl α -cyano- $\alpha\beta\gamma$ -trimethylglutaconate (III) as claimed by Rogerson and Thorpe.

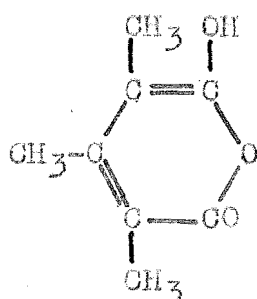
Acid hydrolysis of the methylated ester obtained gave a pyridine derivative and a glutaconic acid, while alkaline hydrolysis gave the pyridine derivative alone. The pyridine derivative was considered to be 3:4:5-trimethyl-2:6-dihydroxy pyridine (V) but no conclusive proof of its constitution was given. The acid obtained melted at 127° C and was considered to be $\alpha\beta\gamma$ -trimethylglutaconic acid. On boiling with acetic anhydride it readily gave an anhydride (m.p. 119° C) which was

shown by Thole and Thorpe (J.C.S. 1911, 29, 2221) to be a hydroxy anhydride having the same properties as other members of the series, and was assumed to be (VI).

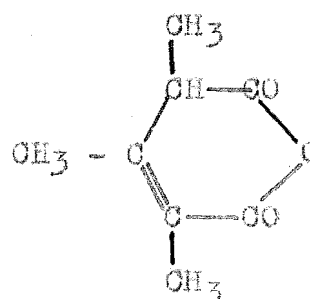
A normal anhydride, supposed to be (VII) was obtained by the action of boiling acetyl chloride on the acid. The only evidence for the α, β, γ positions of the methyl groups was the preparation of the two anhydrides.



(V)



(VI)

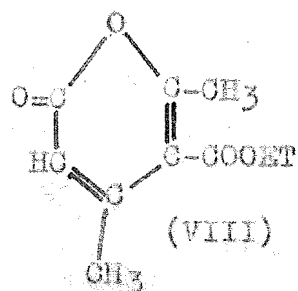


(VII)

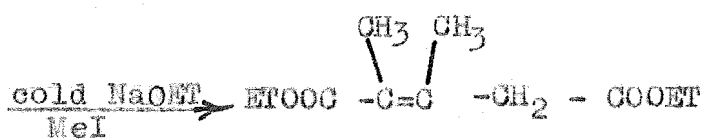
Sargent (N.Z. University Thesis 1931, unpublished) attempted to repeat this work of Rogerson and Thorpe but was unable to effect methylation. Hydrolysis of the product yielded only $\alpha\beta$ -dimethylglutaconic acid and the corresponding pyridine derivative.

B. The Methylation of $\alpha\beta$ -dimethylglutaconic ester.

Thorpe and Wood (J.C.S. 1913, 103, 1759) prepared a "labile" ethyl $\alpha\beta$ -dimethylglutaconate (IX) by the action of alcoholic sodium ethoxide and methyl iodide on ethyl isodehydracetate (VIII).

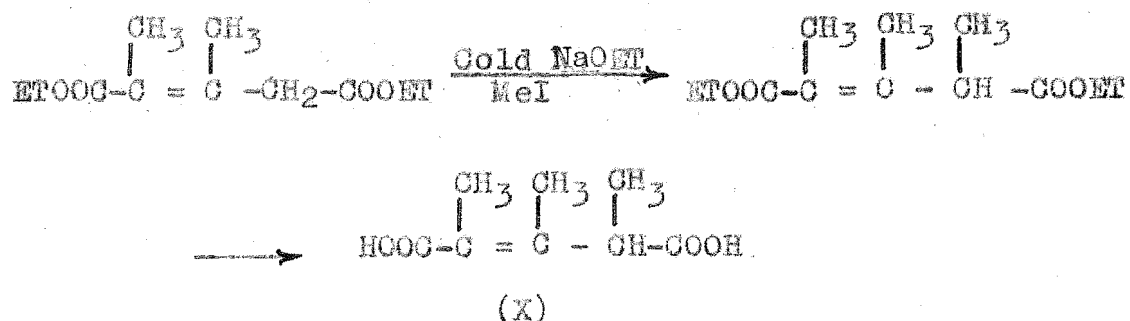


(VIII)

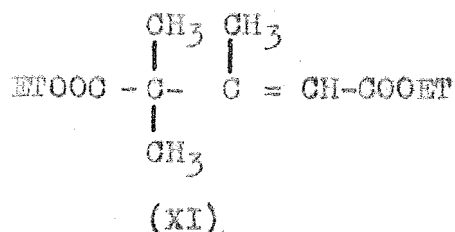


(IX)

The ester obtained was methylated, and the product hydrolysed to give an acid, m.p. 127° C., which was considered by the authors to be $\alpha\beta\gamma$ -trimethylglutaconic acid (X)

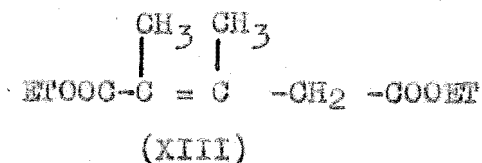
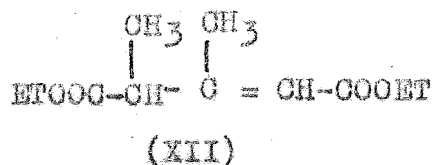


Paeker and Sargent (J.C.S., 1933, 136, 556) were unable to methylate "labile" ethyl $\alpha\beta$ -dimethylglutaconate by Thorpe's method but succeeded by using sodium dispersed in ether and methyl iodide. The product however, was mainly ethyl $\alpha\alpha\beta$ -trimethylglutaconate (XI) and no evidence was obtained for any ethyl $\alpha\beta\gamma$ -trimethylglutaconate (X) in the product.



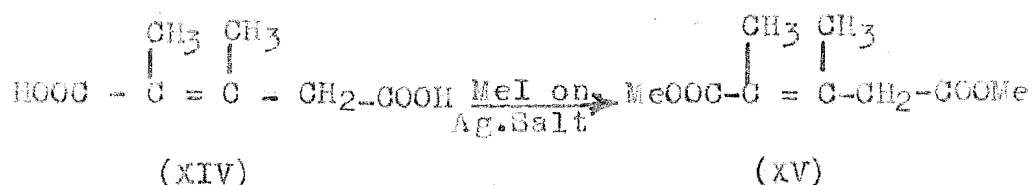
This is in accord with the report of Feist and Beyer (Annalen 1906, 345, 117) that they were unable to methylate ethyl $\alpha\beta$ -dimethylglutaconate.

Kon and Watson (J.C.S., 1932, 135, 1) showed by ozonolysis that the "labile" ethyl $\alpha\beta$ -dimethylglutaconate was a mixture of tautomerides (XII) and (XIII) mainly (XII)



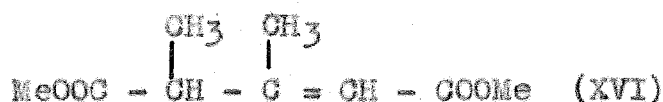
The main product of methylation would therefore be expected to be $\alpha\alpha\beta$ -trimethylglutaconate as shown by Packer and Sargent.

Kon and Watson (loc.cit) also showed that Thorpe's "normal" $\alpha\beta$ -dimethylglutaconic acid obtained by acid hydrolysis of "labile" ethyl $\alpha\beta$ -dimethylglutaconate, was practically pure cis $\Delta^{\alpha\beta}$ acid (XIV). They also showed that the silver salt of this acid could be esterified to give almost pure $\Delta^{\alpha\beta}$ ester (XV.) Hutchison (N.Z.University Thesis 1935, unpublished) prepared the $\Delta^{\alpha\beta}$ form of methyl $\alpha\beta$ -dimethylglutaconate (XV) by this method hoping to obtain methyl $\alpha\beta\gamma$ -trimethylglutaconate on methylation.



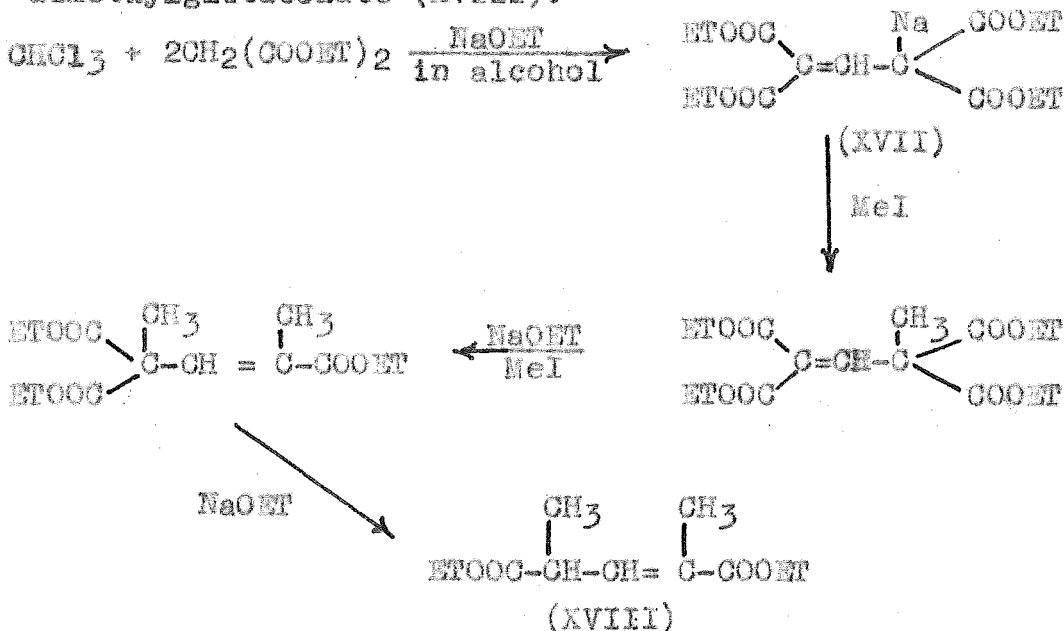
The ester was methylated by treatment with dispersed potassium in ether followed by methyl iodide, and on hydrolysis gave a mixture of acids from which small quantities of two acids were isolated by fractional crystallisation from water. The first to separate (m.p. 118° C) he assumed to be $\alpha\beta\gamma$ -trimethylglutaconic acid as its melting point was depressed by both trans $\alpha\alpha\beta$ -trimethylglutaconic acid and cis $\Delta^{\alpha\beta}$ -dimethylglutaconic acid. The second acid was identical with trans $\alpha\alpha\beta$ -trimethylglutaconic acid prepared by methylation of trans ethyl $\Delta^{\alpha\beta}$ -dimethylglutaconate and hydrolysis of the product. Apparently

therefore, under the conditions of methylation much of the $\Delta^{\alpha\beta}$ methyl $\alpha\beta$ -dimethylglutaconate (XV) had undergone conversion to the $\Delta^{\alpha\beta}$ tautomeride (XVI).



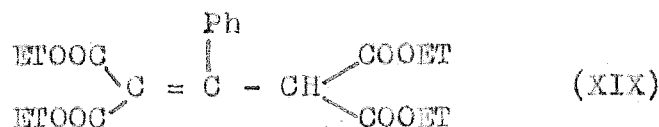
C. The Condensation of Malonic ester with a substituted
Chloroform and subsequent Methylation.

Thole and Thorpe (J.C.S., 1911, 99, 2191) prepared the sodio derivative of $\alpha\gamma$ -dicarbethoxyglutaconic ester (XVII) by the method of Conrad and Gutzeit (Annalen 1883, 222, 259) from chloroform and malonic ester in the presence of sodium ethoxide. The product was then methylated in stages to give ethyl $\alpha\gamma$ -dimethylglutaconate (XVIII).



Thompson (N.Z. University Thesis 1930, unpublished) therefore attempted to condense phenylchloroform with malonic ester in the presence of sodium ethoxide in order to obtain β -phenyl- $\alpha\gamma$ -

dicarbethoxyglutaconic ester (XIX), but obtained none of the desired product.

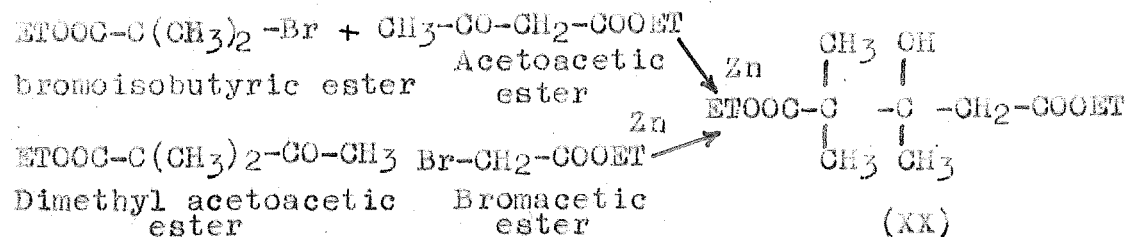


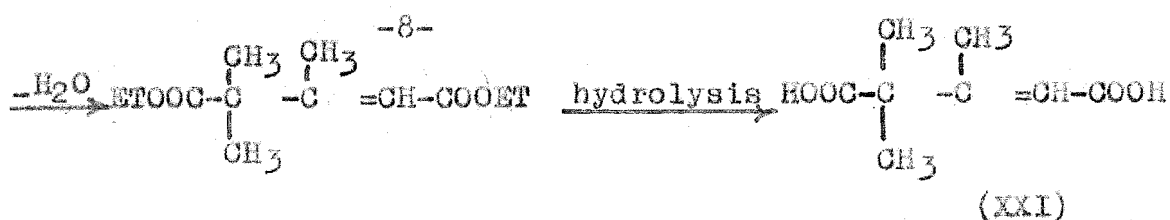
He obtained an undistillable oil which on hydrolysis and on oxidation gave benzoic acid. Kon (J.C.S. 1932, 135, 2447) later attempted the same condensation and also obtained an undistillable oil as the only product.

Adams (N.Z. University Thesis 1936, unpublished) attempted to prepare β -methyl- $\alpha\gamma$ -dicarbethoxyglutaconic ester by a similar method using methylchloroform but was also unable to obtain the desired product. The preparation of methyl chloroform in quantity also presents considerable difficulty.

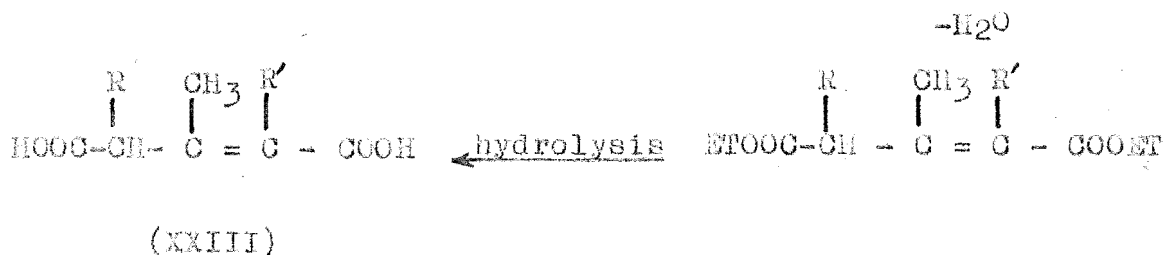
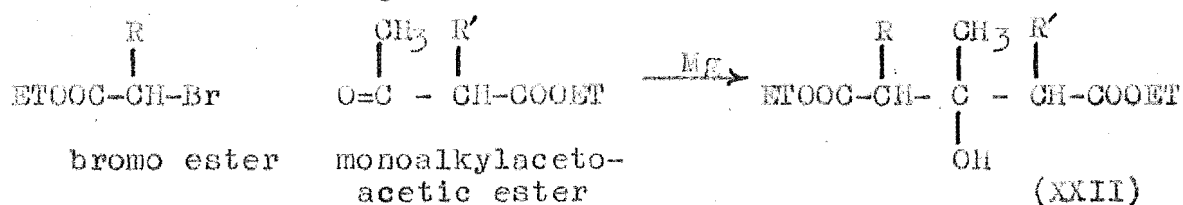
D. Reformatsky condensation of an α -bromo ester and mono-alkylaceto-acetic ester.

Perkin and Thorpe (J.C.S. 1897, 71, 1178) prepared ethyl β -hydroxy- $\alpha\beta$ -trimethylglutarate (XX) by two different Reformatsky syntheses, and dehydrated this substance, hydrolysing the product to give $\alpha\beta$ -trimethylglutaconic acid (XXI).





Hence condensation of an α -bromo ester and a monoalkyl-acetoacetic ester by the Reformatsky method should give a β -methyl- $\alpha\gamma$ - dialkylglutaconic acid (XXIII.)

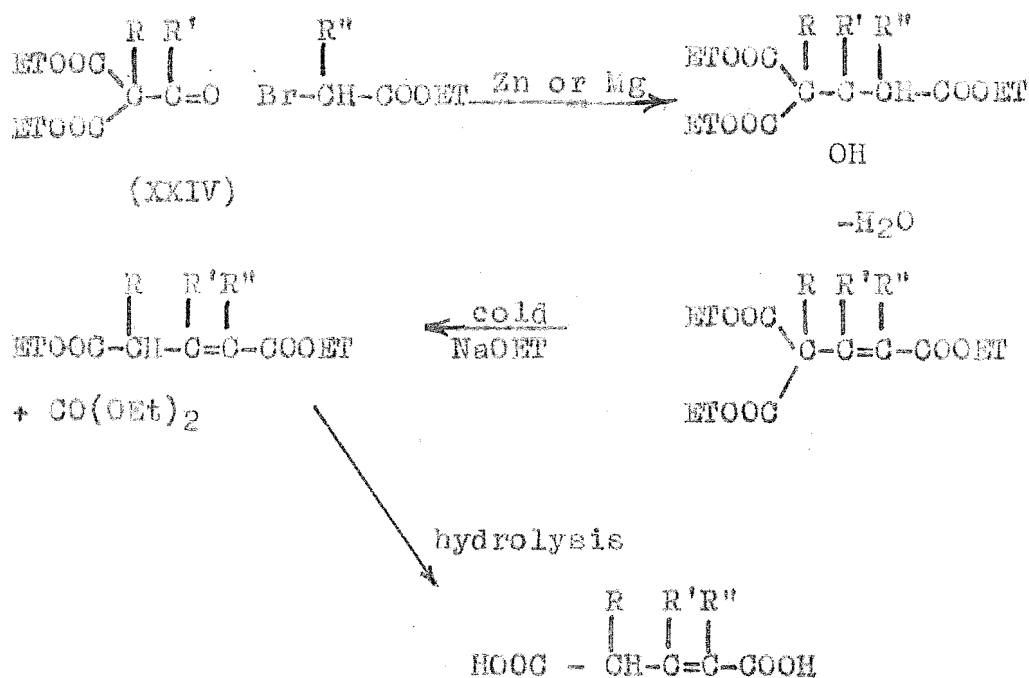


Mapstone (N.Z. University Thesis 1940, unpublished) in an exploratory synthesis condensed bromoacetic ester and acetoacetic ester in the presence of magnesium in benzene. His synthesis is represented above where $\text{R} = \text{R}' = \text{H}$. He obtained only a very poor yield of the hydroxy ester (XXII, $\text{R}=\text{R}'=\text{H}$), but by its dehydration and the hydrolysis of the glutaconic ester so obtained, he isolated β -methylglutaconic acid (XXIII, $\text{R}=\text{R}'=\text{H}$). The very poor yield (1% theoretical) he attributed to reaction of the acid enolic form of the monoalkylacetoacetic ester with the intermediate organometallic

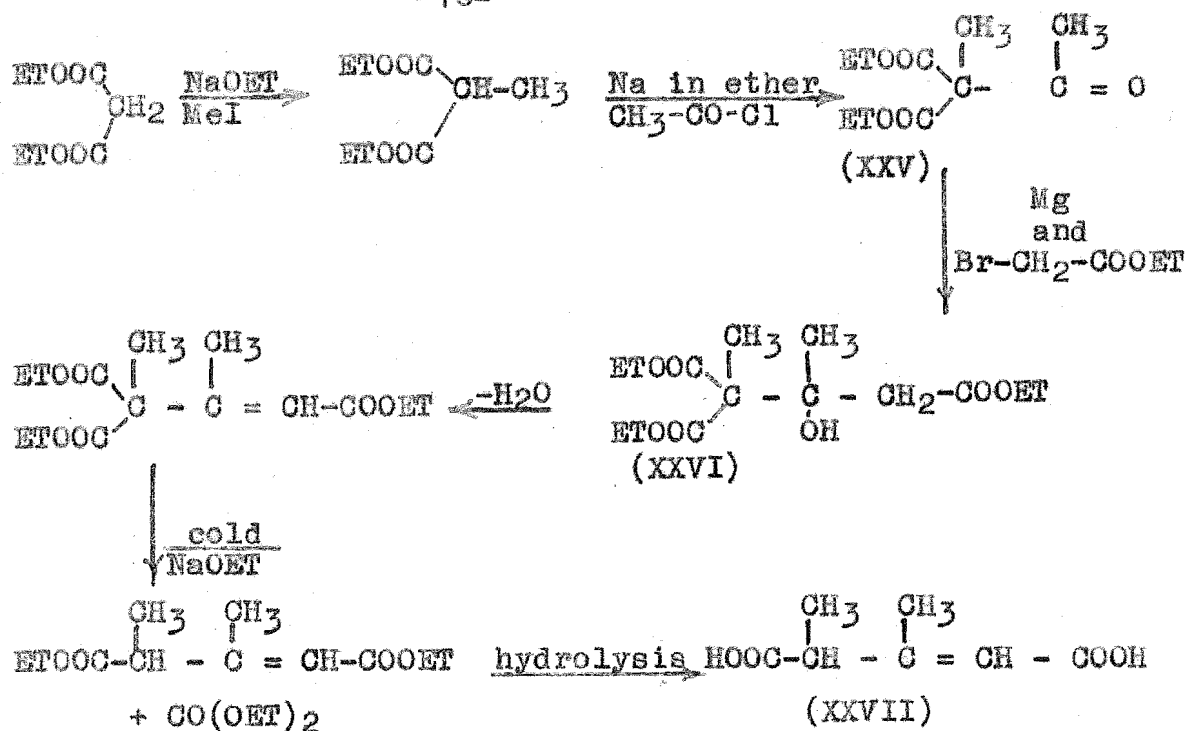
compound $\text{Br.Mg.CH}_2\text{COOEt}$.

E. Reformatsky Condensation of an Acyl-Alkylmalonic ester and α -bromo ester.

Mapstone suggested replacing acetoacetic ester in the Reformatsky condensation by an acyl-alkylmalonic ester (XXIV) since the latter has no mobile hydrogen and the possibility of the enolic form reacting is prevented. The proposed synthesis was as follows:

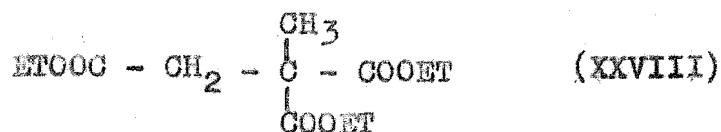


(a) Sinclair (N.Z. University Thesis 1941, unpublished) in order to test this method attempted to prepare α/β -dimethylglutaconic acid (XVII) samples of which were available for comparison, by the condensation of ethyl acetyl-methylmalonate (XV) and ethyl bromacetate in the presence of magnesium. His proposed synthesis was as follows:



Sinclair obtained a 21% yield of an ester which he concluded was the required product (XXVI) but which he was unable to dehydrate.

(b) Greenwood (N.Z. University Thesis 1942, unpublished) repeated Sinclair's work and obtained an ester of the same boiling range which he showed to be not the expected α -carbethoxy- $\alpha\beta$ -dimethyl- β -hydroxyglutaric ester (XXVI) but instead impure α -carbethoxy- α -methyl-succinic ester (XXVIII). The ester on hydrolysis and heating gave an acid which was shown to be impure methyl succinic acid.



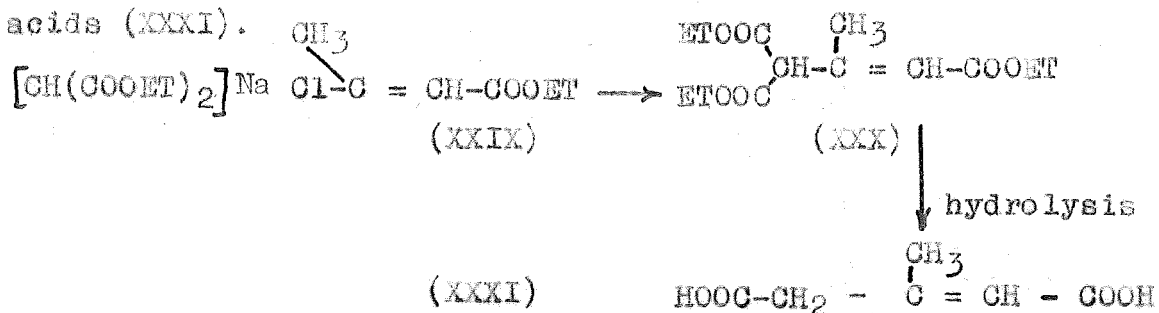
Greenwood suggested that the product obtained was due to the

condensation of bromacetic ester with itself in the presence of magnesium to give $\text{Mg}(\text{OEt})\text{Br}$ which then reacted with the acetyl-methylmalonic ester to give the α -carbethoxy- α -methyl succinic ester.

(c) Bailey (N.Z. University Thesis 1944, unpublished) attempted to carry out the Remormatsky condensation of bromacetic ester and acetyl-methylmalonic ester in the presence of Zn, hoping that under these conditions there would be no condensation of bromacetic ester with itself. He obtained none of the desired product however, the main products being acetoacetic ester, methylmalonic ester and methyl ethyl ketone formed by side reactions. Bailey concluded that such a reaction was unsuitable for the synthesis of trialkylglutaconic acids.

F. The Present Investigation:

The object of the present investigation was to test a method of synthesis of $\alpha\beta\gamma$ -trialkylglutaconic acids suggested by the work of Fichter & Schwab (Annalen, 1906, 348, 251). These workers condensed ethyl β -chlorocrotonate (XXIX, trans) and ethyl β -chloroisocrotonate (XXIX, cis) respectively with sodiomalonic ester, hoping to obtain by hydrolysis of the resulting esters the two stereoisomeric β -methylglutaconic acids (XXXI).



They claimed however to obtain the same ethyl α -carbethoxy- β -methylglutaconate (XXX) boiling at 163-165°C. at 12 mm., in both cases. This ester they hydrolysed with baryta to give a mixture of the stereoisomeric β -methylglutaconic acids which were separated by fractional crystallisation.

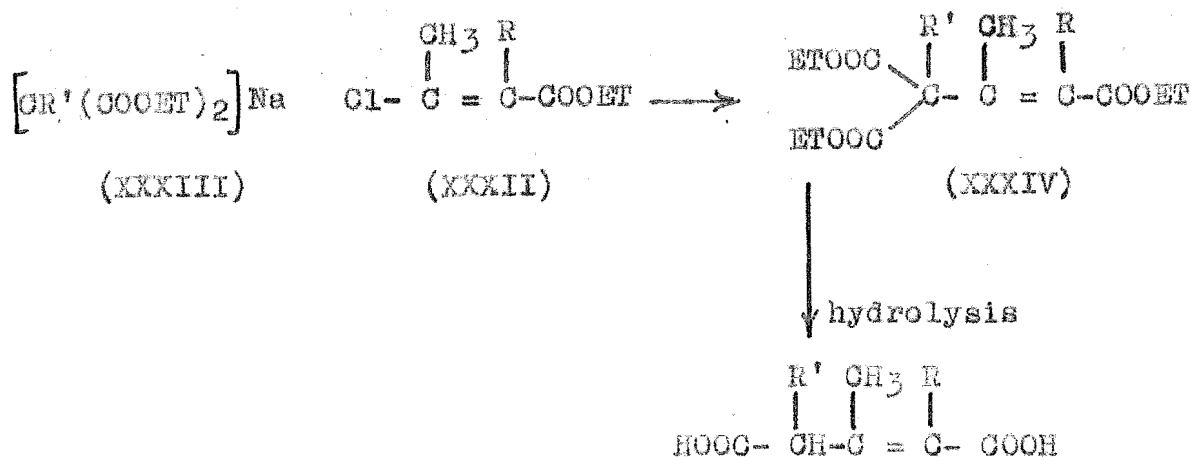
Gidvani, Kon and Wright (J.O.S. 1932, 135, 1027) repeated these condensations and obtained two tricarboxylic esters which showed small but distinct differences in physical properties. Ethyl β -chlorocrotonate (trans) yielded the trans-tricarboxylic ester, b.p. 169-170°C. at 13 mm., d_4^{20} 1.0937, n_D^{20} 1.4595. Ethyl β -chloroisocrotonate (cis) yielded the cis-tricarboxylic ester b.p. 164-165°C. at 12 mm., d_4^{20} 1.0884, n_D^{20} 1.4579.

The two stereoisomeric esters were hydrolysed by keeping for three days with cold 5% KOH aq., enough alcohol being added (with care to avoid all rise in temperature) to give a homogeneous solution. The alcohol was then evaporated off under reduced pressure at room temperature, and the acids liberated in presence of ether by means of dilute HCl. Under these mild conditions the trans-tricarboxylic ester yielded trans- β -methylglutaconic acid (XXXI) m.p. 149°C and the cis ester gave cis- β -methylglutaconic acid m.p. 118°C.

Neither Fichter and Schwab nor Kon and workers give any indication of the method used to separate the chlorocrotonic esters, or of the experimental conditions under which the condensation was carried out.

By condensing together an β -chloro- α -alkylcrotonate (XXXII)

with the sodio derivative of an alkylmalonic ester (XXXIII) it should therefore be possible to obtain an ethyl α -carbethoxy- $\alpha\gamma$ -dialkyl- β -methylglutaconate (XXXIV) from which an $\alpha\gamma$ -dialkyl- β -methylglutaconic acid should be obtained on hydrolysis.



Separation of the stereoisomeric alkylchlorocrotonates and condensation separately with the alkylmalonic ester should lead to the formation of the two stereoisomeric glutaconic acids. However in the present exploratory synthesis mixtures of the alkylchlorocrotonates were used.

As a preliminary step the synthesis of β -methylglutaconic acid was carried out by the method of Fichter and Schwab.

A mixture of ethyl chlorocrotonate and ethyl chloro*iso*-crotonate was prepared by the method of Thomas - Mamert (Bulletin de la Societe Chimique de France (3), 13, 71).

Acetoacetic ester in benzene solution was treated with phosphorus pentachloride and the product extracted and distilled to give a liquid b.p. 156°C at 762 mm. The boiling point of ethyl chlorocrotonate is given as 179-180° and that for ethyl chloro*iso*-crotonate as 157-158° at 740 mm. by Autenrieth (Berichte 29, 1655).

If the mixture of esters consists mainly of the chloroisocroton-ate as described by Gidvani, Kon and Wright (loc.cit.) the boiling point observed is about the expected value.

An attempt was made to condense a portion of this mixture of esters with ethyl malonate in the presence of alcoholic sodium ethoxide, with refluxing on a steam bath for an hour. On extraction and distillation a liquid was obtained which distilled at 160-175°C and 15 mm., having n_D^{20} 1.4540, and which was therefore regarded as ethyl α -carbethoxy- β -methylglutaconate (XXX). This ester was treated with cold 5% aqueous alcoholic KOH for 3 days by the method of Kon and the product extracted in the usual manner.

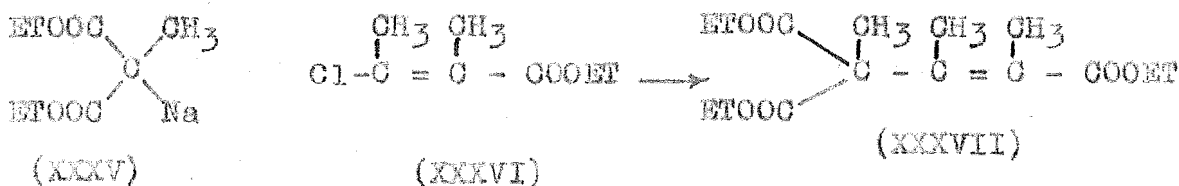
This gave a small amount of a mobile, pungent-smelling liquid which gave an acid reaction to litmus, but yielded no crystalline product. Presumably only partial hydrolysis had been effected and the liquid was therefore further hydrolysed by refluxing with aqueous, alcoholic HCl, giving a small amount of a crystalline acid, m.p. 148°C. (Trans- β -methylglutaconic acid has m.p. 149°C.)

The very poor yield of acid indicated that alcohol was not a good medium for the condensation, probably due to alcoholysis, and pointed to the use of an inert solvent.. Tertiary butyl alcohol would probably give best results but as no supplies of this were available, anhydrous ether was used. Sodium was dispersed in ether and ethyl malonate added, forming the sodio derivative, which was then treated with the mixture of chlorocrotonic esters. A liquid was obtained from the

products, which distilled at 165-185°C at 17 mm. and had n_D^{20} 1.4572. (Kon gives for ethyl cis- α -carbethoxy- β -methylglutaconate n_D^{20} 1.4579. Since the chlorocrotonic esters consist mainly of the cis isomer, condensation should yield mainly the cis-carbethoxy ester.)

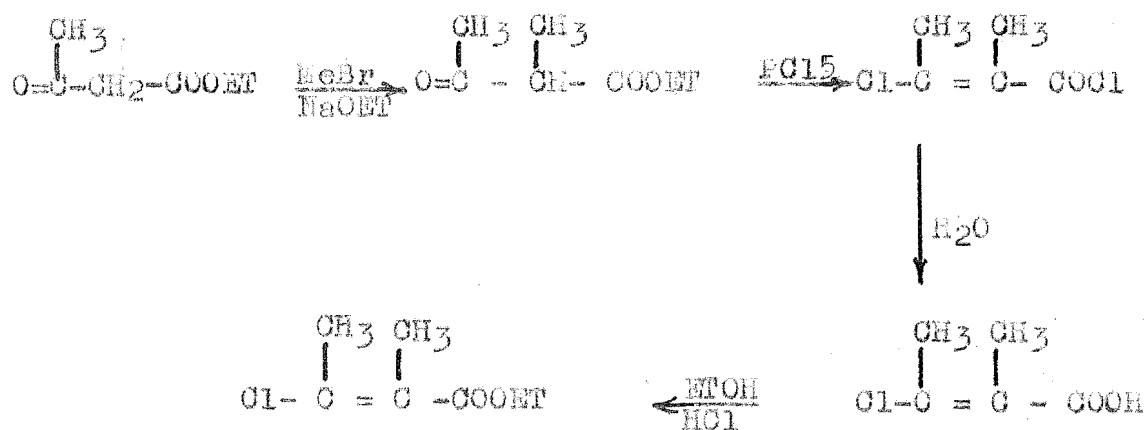
The ester was hydrolysed with 2N aqueous alcoholic KOH under reflux and the acid isolated as a white crystalline solid m.p. 112.2°C. A reference sample of β -methylglutaconic acid previously synthesised from isodehydracetic ester, and given the same hydrolysis treatment as the preparation so as to yield a similar mixture of cis and trans forms, had m.p. 111.7-112.2°C. and had a mixed m.p. with the preparation 111.2-112.7°C. The acid had equivalent weight 74.8. (Theoretical value for β -methylglutaconic acid is 72.)

As the yield of ester (XXXIV, R=R'=H) was considerably improved by the use of anhydrous ether as the condensing medium (22.6% theoretical) it was decided that this medium should be used for the condensation of ethyl α -methyl- β -chlorocrotonate (XXXVI) and sodiomethylmalonate (XXXV). The proposed synthesis is represented:



As no recent reference could be found to the preparation of ethyl α -methyl- β -chlorocrotonate in the literature the method used was that described by Koll (Annalen 1889, 249, 308).

Methylacetoacetic ester (XXXVIII) was prepared by a method similar to that described in Organic Synthesis, Collective Vol.1. p.243., by the action of methyl bromide on alcoholic acetoacetic ester (XXXVII) in the presence of sodium ethoxide. The methylacetoacetic ester was then dropped onto the theoretical quantity of phosphorus pentachloride when a vigorous reaction occurred. According to Koll a higher yield of acid is obtained under these conditions. When the reaction had ceased the acid chloride formed was decomposed with water and the products separated by steam distillation and ether extraction.



The α -methyl- β -chlorocrotonic acid was obtained as a white crystalline solid, soluble in alcohol but insoluble in cold water. After dissolving in alcohol and precipitating with water several times the solid was dried on a porous plate in vacuo to give crystals melting at 67.7°C. Demarcay (Compte r., 84, 1087) gives 67°C as the melting point of this acid.

The acid was esterified by heating an alcoholic solution of the ester under reflux and passing through the mixture a stream of dry HCl gas. Extraction and distillation gave the

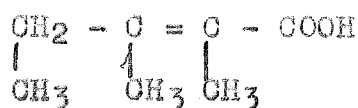
ester, distilling at 73-74°C at 14 m.m., n_D^{20} 1.4569, b.p. 173-174°C (Various workers give boiling points 171-172, 173-175, 178-180°C. for ethyl α -methyl- β -chlorocrotonate.)

Ethyl methylmalonate was prepared by methylation of malonic ester by methyl bromide.

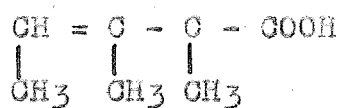
Condensation of the ethyl methylmalonate and ethyl α -methyl- β -chlorocrotonate was effected by dispersing sodium in anhydrous ether, adding the methylmalonate to give its sodio-derivative and then finally by adding the chloro ester. From the products there was isolated a liquid distilling at 172-174°C. at 15 m.m., a boiling point of the same order as those for other tricarboxylic glutaconic esters. The condensation was repeated and gave a viscous yellow liquid distilling at 165-172°C. at 14 m.m., n_D^{20} 1.4538, $D_4^{14.5}$ 1.366.

It decolourised both bromine and permanganate indicating an olefinic linkage, gave a neutral reaction, and was unaffected by ferric chloride. Combustion analysis gave C = 58.5%, H = 7.84% (theoretical for ethyl α -carbethoxy- $\alpha\beta\delta$ -trimethylglutaconate is C = 60.0%, H = 8.00%.) Although the combustion data do not agree very closely, the discrepancy is small enough to be attributed to the presence of impurities. The flask in which redistillation was performed, prior to analysis, had only a small fractionating surface making separation of fractions difficult. The molecular weight of the ester determined cryoscopically in benzene was 303 (molecular weight of ethyl α -carbethoxy- $\alpha\beta\delta$ -trimethylglutaconate is 300.)

Attempts were made to hydrolyse the ester obtained using various concentrations of both alkali and acid. Refluxing with 2 N potassium hydroxide or with alcoholic hydrochloric acid resulted in the formation of viscous brown liquids from which no crystalline material could be obtained. These oily liquids had an acid reaction to bicarbonate and equivalent weights about 122 (theoretical for $\alpha\beta\gamma$ -trimethylglutaconic acid is 86.) Their formation might be due either to partial hydrolysis, or to loss of carbon dioxide from two carboxyl groups giving an $\alpha\beta$ -dimethylpentenoic acid. However the physical constants reported by Kon (J.C.S. 1928, 131, 2519) for these two acids (XL) and (XLI) do not give any agreement with those observed for the products of hydrolysis.



(XL)



(XLI)

Refluxing with alkali and with acid produced in every case brown gums and solids together with acidic liquids. These may possibly have been polymerisation products of the glutaconic acid, since other members of the series are known to polymerise on treating with suitable reagents. Such a process would lead to high values of the equivalent weight such as those obtained experimentally.

Treatment of the ester by 5% potassium hydroxide after the method of Kon (loc.cit.) yielded an acidic brown liquid of

equivalent weight 212 (theoretical for $\alpha\beta\gamma$ -trimethylglutaconic acid is 86.) Half of this liquid was subjected to repeated acid hydrolysis but the only products were again oily brown liquids. From the other half of the liquid there separated on standing a very small amount of a neutral white solid m.p. 35-50°C but this was not further investigated.

From the reports in the literature of the hydrolysis of similar compounds, hydrolysis of ethyl α -carbethoxy- $\alpha\beta\gamma$ -trimethylglutaconate would not be expected to be difficult. Hydrolysis of the tricarboxylic ester proceeds readily in the case of the β -methyl ester and $\alpha\gamma$ -dimethyl ester. Yet in spite of a long series of attempts to effect hydrolysis using various reagents which have been successful for similar compounds, no crystalline acid could be obtained. The equivalent weight for some of the liquids was about 105 which is approaching the value for $\alpha\beta\gamma$ -trimethylglutaconic acid (86), but these liquids could not be induced to crystallise. All attempts to bring about crystallisation by keeping at 0° C for some weeks and by slowly evaporating off the solvent from solutions in water and in benzene produced only minute amounts of solid.

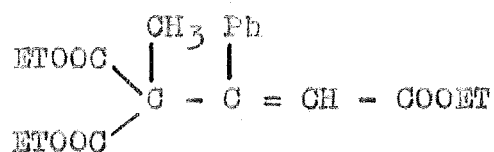
Thole and Thorpe (J.C.S. 1911, 99, 2191) observed that compounds of the type of the carbethoxy-glutaconic esters, where the mobile hydrogen atom has been replaced by an alkyl group, tend to replace a carbethoxy group by hydrogen in the presence of cold sodium ethoxide, and so acquire tautomeric mobility. The carbethoxy group reacts with the sodium

ethoxide to form ethyl carbonate and the yellow or orange sodio-derivative of the glutaconic ester is produced if it is stable in the presence of alcohol.

The ester obtained from the condensation was accordingly treated with an equivalent amount of cold sodium ethoxide. However, on distilling the products no fraction was observed corresponding to ethyl carbonate and the main fraction distilled over at the same temperature as before treatment of the liquid. Combustion analysis gave C= 59.0%, H= 7.99% showing that the ester was unchanged. Acid hydrolysis of the liquid again yielded brown viscous liquids from which very small amounts of crystalline solid separated. The solid material seemed to vary considerably in composition and equivalent weight.

Thorpe (J.C.S. 1913, 103, 1569) claimed to have prepared two forms of ethyl α -carbethoxy- β -phenyl- α -methylglutaconate (XLII) neither of which gave a sodio-derivative with sodium ethoxide. The same result was obtained by Kon (J.C.S. 1932, 135, 2447) who reports that the ester was recovered unchanged after treating with sodium ethoxide for several days. Kon accounts for the exceptional stability of this compound on the basis of the electronic theory. Elimination of the carbethoxy group is due to the inability of the system to meet the demand for electrons of the two negative groups in the α -position. If a suitable source of electrons such as ethoxide ions is available in the surrounding medium one of the negative groups

becomes attached to the latter with the production of a molecule of ethyl carbonate. In the case of α -carbethoxy- β -phenyl- α -methylglutaconic ester the electron demand of the carbethoxy groups can be met by electron displacements involving the phenyl group which becomes electron donating. Thus the acquisition of the necessary electron from the ethoxide ion which would result in the elimination of the carbethoxy group is prevented. A similar state of affairs exists in the α -carbethoxy- $\alpha\beta\delta$ -trimethylglutaconic ester. Although the methyl group has a less powerful electron donating effect than the phenyl group the cumulative effect of the three groups may be sufficient to meet the electron requirements of the carbethoxy groups by electron displacements.



(XLII)

In the case of a particularly stable ester, treatment with sodium ethoxide at a higher temperature might be more effective in removing the carbethoxy group. The liquid ester was therefore treated with sodium ethoxide at successively higher temperatures in the hope that the reaction would proceed under these conditions. Only when the liquid mixture was heated to 80° C was there any evidence of reaction. A bright orange colour developed, pointing to the formation of the sodio-derivative of the glutaconic ester, and there

was isolated from the reaction mixture a fraction boiling at a temperature about 20°C lower than that for the original ester. Removal of a carbethoxy group from similar esters lowers the boiling point by about this amount. The fraction also had a lower value of refractive index than the original ester. No ethyl carbonate was detected but the quantities used were small and such a comparatively volatile substance could easily escape detection without special precautions. Treatment with sodium ethoxide thus at a higher temperature involved considerable destruction of material.

The new liquid ester of lower boiling point was re-distilled under reduced pressure in a small Widmer flask with a vacuum-jacketed fractionating column when 0.49 gms. of liquid distilling $143\text{--}148^{\circ}\text{C}$ at 19 mm was obtained. Micro-combustion analysis gave $\text{C} = 63.04\%$, $\text{H} = 8.86\%$ (theoretical values for ethyl $\alpha\beta\gamma$ -trimethylglutaconate are $\text{C} = 63.13\%$, $\text{H} = 8.83\%$.) This close agreement undoubtedly proves the identity of the product and the difficulty experienced in obtaining it from the carbethoxy ester must be due to the stability of the latter.

Hydrolysis of the small amount of ester remaining (about 0.2 gms.) by refluxing with aqueous alcoholic hydrochloric acid, gave on ether extraction of the products, a viscous oil from which there separated on standing a white crystalline solid. This had an acid reaction to bicarbonate, but there was not a large enough quantity to purify by recrystallisation sufficiently to determine the melting point, or to make any quantitative analyses. This acid was probably $\alpha\beta\gamma$ -trimethylglutaconic acid

but a larger quantity must be prepared before its properties can be investigated and analysis can be made.

S U M M A R Y.

1. The synthesis of β -methylglutaconic acid by condensation of β -chlorocrotonic ester and ethyl sodiomalonate has been repeated. The yield of acid was small but was best when ether was used as the condensing medium.
2. A new synthesis of β -methyl- $\alpha\gamma$ -dialkylglutaconic acids has been tested by the condensation of α -methyl- β -chlorocrotonate and ethyl sodiomethylmalonate.
3. The product of the condensation has been shown to possess the properties expected for ethyl α -carbethoxy- $\alpha\beta\gamma$ -trimethylglutaconate.
4. Hydrolysis of the ester obtained has been attempted using a variety of conditions but produced no crystalline acid.
5. Treatment of the ester with sodium ethoxide has been shown to be effective only on heating and produces an ester corresponding in properties to ethyl $\alpha\beta\gamma$ -trimethylglutaconate.
6. The hydrolysis of this ester produces a crystalline acid which is probably $\alpha\beta\gamma$ -trimethylglutaconic acid, but ^{which} was not obtained in sufficient quantity to analyse.

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I. PURIFICATION OF CHEMICALS

Ethanol. 5 litres of 'absolute' alcohol was refluxed over quicklime for six hours. Half this quantity was refluxed with aluminium amalgam for two hours and then distilled off through an efficient fractionating column, the product having n_D^{20} 1.3612. To the second portion 5 gms. of sodium was added and the alcohol distilled off, the last 25% being rejected. The product had n_D^{20} 1.3610. Lorenz gives for pure alcohol $n_D^{13.35}$ 1.36242 (Annalen der Physik 11, 70; 80.)

Ether. 2.5 litres of ether was shaken with a solution of ferrous sulphate (conc. H_2SO_4 7.5 gms., water 135 c.c., $FeSO_4$ 60 gms.) 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. A portion was stood over sodium wire.

Acetoacetic ester. The B.D.H. product was distilled from a fractionating Claisen flask under reduced pressure, and the fraction distilling 72-77°C./ 14 m.m. collected.

II. PREPARATION OF ETHYL β -CHLOROCROTONATE
AND ETHYL β -CHLORISOCROTONATE.

Acetoacetic acid (100 gms.) was thoroughly mixed with benzene (100 gms.) in a round-bottomed flask fitted with a reflux condenser. Phosphorous pentachloride (137 gms.) was added in small portions and when the reaction was complete the liquid was shaken with four volumes of water, the benzene layer removed and the aqueous layer extracted several times with benzene. The benzene was distilled off from the combined extracts over a water bath.

Distillation from a Claisen flask under reduced pressure gave 56.3 gms. of liquid bp. 156° at atmospheric pressure. Yield: 49.1% theoretical.

III. PREPARATION OF β -METHYLGLUTACONIC ACID

(A) By Condensation of ethyl sodiomalonate and chloro-crotonic ester in alcohol.

To sodium (2.3 gms.) dissolved in alcohol (27.6 gms.), ethyl malonate (16 gms.) was added giving a suspension of the white sodio-derivative. The chlorocrotonic esters (14.9 gms.) were added and the mixture refluxed on a steam bath for an hour.

The reaction mixture was shaken with 3-4 volumes of water and extracted several times with ether. The combined ether extracts were dried over CaCl_2 , the ether distilled off over a water bath, and the remaining liquid distilled under reduced pressure.

5 gms. of liquid (18% theoretical) was obtained distilling $160-175^\circ \text{C}/14 \text{ m.m.}$, $n_D^{20} 1.4540$.

The liquid was treated with 5% potassium hydroxide, enough alcohol being added to give a homogeneous solution, and the mixture left for three days at room temperature. The alcohol was then evaporated off at room temperature, the solution extracted once with ether to remove unhydrolysed ester, acidified with dilute hydrochloric acid and extracted several times with ether. On evaporating off the ether from the dried ether extracts there remained a few c.cs. of a mobile pungent-smelling liquid with an acid reaction to litmus.

This liquid was refluxed for several hours with alcoholic hydrochloric acid (conc. HCl 22.5 c.c., H_2O 15 c.c., alcohol 12.5 c.c.). The solution was then diluted, the alcohol evaporated off at room temperature and reduced pressure, and the solution extracted several times with ether. The ether extracts

on drying and removing the ether by distillation over a water bath, yielded a white crystalline solid m.p. 148° C.

(B) By condensation of ethyl sodiomalonate & chlorocrotonic ester in ether.

Freshly cut sodium (5.77 gms.) was dispersed by shaking under boiling xylene, and the xylene subsequently displaced by ether (80 c.c.). Ethyl malonate (40.2 gms.) was added and the mixture refluxed in a round-bottomed flask fitted with a double-surface condenser, over a steam bath for 2 hrs., when most of the sodium had dissolved.

β -chlorocrotonic ester (37.4 gms.) purified by re-distillation was added in portions, the volume of ether being simultaneously increased to 250 cc. to maintain a suitable concentration of materials. The mixture was refluxed over a steam bath for 6 hrs., and then shaken with 2-3 volumes of water. The aqueous layer was acidified by dil. HCl, separated from the ether layer, and extracted with ether several times. From the combined ether extracts, after drying with calcium chloride the ether was removed on a water bath, and the remaining liquid distilled under reduced pressure. The fraction distilling 165-185° C/17 m.m. was collected separately. A large fraction corresponding to unchanged reactants distilled below this range, but there was only a very small and highly coloured residue left at 185° C..

The liquid distilling at 165-185° C (15.45g.) was refluxed with three times the theoretical amount of 2 N potassium

hydroxide and a little ethanol, until the oil had disappeared (2 hrs.). The alcohol was removed at room temperature and reduced pressure; the solution diluted with two volumes of water, acidified and extracted three times with ether. On distilling off the ether only a small amount of material remained, since β -methylglutaconic acid has a high solubility in water. More thorough extraction of the aqueous solution yielded a white crystalline solid which was dried on a porous plate in vacuo to give 3.31 g. of crude acid (9.1% theoretical.) The product was purified by repeated recrystallisation from benzene solution, when it gave m.p. 112.2°C. A reference sample of β -methylglutaconic acid synthesised from isodehydracetic ester, and given the same hydrolysis treatment as the preparation so as to yield a similar mixture of cis and trans isomers, had m.p. 111.7-112.2°C and a mixture of this with the prepared acid had m.p. 112.2-112.7°C.

The equivalent weight of the acid was determined by titrating a small amount dissolved in water with carbonate-free alkali standardised against benzoic acid, using phenol phthalein as indicator, care being taken to avoid absorption of CO₂ from the air. This gave equivalent weight 74.8 (theoretical value for β -methylglutaconic acid is 72.)

IV.

METHYLATION OF ETHYL MALONATE.

(Organic Syntheses, Vol.II, p.279)

Freshly cut sodium (69 gms.) was added to absolute ethyl alcohol (1.5 l.) in a 3 l. round-bottomed flask fitted with a reflux condenser and delivery tube. When all the sodium had dissolved ethyl malonate (480 gms.) was added.

Methyl bromide was generated as follows. 98% H_2SO_4 (758 gms.) was added slowly with shaking to ordinary methanol (627 gms.) cooled by an ice bath. Sodium bromide (938 gms.) was suspended in half this mixture in a 2 l. round-bottomed flask fitted with a dropping funnel and delivery tube. Evolution of methyl bromide was started by heating the flask by a water bath to 50°C . and the rest of the acid mixture was added slowly from the dropping funnel as the reaction proceeded, the temperature being slowly raised at the same time. The evolved gas was dried by KOH pellets.

The methyl bromide was bubbled into the alcoholic ethyl malonate solution until evolution of gas had ceased, and the malonic ester solution then boiled for an additional half-hour, neutralised with glacial acetic acid, and cooled. The sodium bromide was filtered off and washed with alcohol. After the removal of the bulk of the alcohol by distillation at atmospheric pressure, the residue was shaken with a solution obtained by dissolving the sodium bromide in 600-700 cc. of water containing 10 cc. of conc. HCl. The aqueous lower layer was separated from the ester and extracted twice with ether.

The combined ester and ether extracts were dried quickly with CaCl_2 , the ether distilled off, and the ester shaken for 1 min. with a cold solution of 10 gms. of NaOH in 30 cc. of water to remove unchanged ethyl malonate. The alkali was removed, and the ester washed with dilute acid and dried with CaCl_2 . Distillation in vacuo yielded 275.3 gms. distilling at $93-95^\circ\text{C}$. at 15 m.m. This had $n_D^{18.7}$ 1.4136. Von Auwers (Berichte 46, 504) gives for ethyl methylmalonate $n_D^{18.7}$ 1.41369. Yield: 52.7% theoretical.

A second preparation using similar quantities gave 351.6 gms. of fraction distilling at $93-95^\circ\text{C}$ at 15 m.m. with $n_D^{18.7}$ 1.4135. Yield: 67.3% theoretical.

V. METHYLATION OF ETHYL ACETOACETATE

(Organic Syntheses, Vol. I, p. 243)

Freshly cut sodium (69 gms.) was added to absolute alcohol (1.5 l.) in a 3 l. round-bottomed flask fitted with a delivery tube and reflux condenser. When all the sodium had dissolved ethyl acetoacetate (390 gms.) was added and the solution heated to gentle boiling. Methyl bromide generated in exactly the same manner as described in IV above was bubbled into the boiling solution for a period of about 10 hrs..

After the methyl bromide had all been added the mixture was refluxed on a water bath for 4 hrs., when the solution was faintly alkaline to moist litmus paper. The mixture was cooled and the solution decanted from the sodium bromide which was washed with 100 cc. of absolute alcohol and the washings added to the main solution. After the alcohol had been distilled off over a water bath through a short fractionating column, the residual oil was shaken with water, the oil layer separated off and the water layer extracted three times with ether.

Kon (J.O.S. 1931, 134, 571) considers it essential to purify the ethyl methylacetoacetate from traces of the parent ester by repeated shaking with dilute aqueous ammonia. Accordingly the ethereal extracts were washed three times with 25 ammonia, dried overnight by anhydrous sodium sulphate, the ether removed over a water bath, and the residue distilled in vacuo. The portion boiling at 79-83° C. at 15 mm. was collected separately. For successive similar preparations the yields of

this fraction were: 251.5 gms. with n_D^{20} 1.4188, 242.3 gms.
with n_D^{20} 1.4197, 240.3 gms. with n_D^{20} 1.4198. Von Auwers
(Berichte 46, 504) gives for ethyl methylacetoacetate $n_D^{17.8}$ 1.420.
Yields: 58.2%, 56.1%, 55.5% theoretical respectively.

VI. PREPARATION OF α -METHYL- β -CHLOROCROTONIC ACID.

Ethyl methylacetoacetate (50 gms) was added slowly from a dropping funnel to solid phosphorous pentachloride (73 gms.) in a round-bottomed flask fitted with a reflux condenser and cooled in ice water. When all the ester had been added about half the pentachloride remained unreacted, so the mixture was warmed to room temperature and finally heated slowly to 70° C. when the remainder of the pentachloride reacted.

The acid chlorides formed were decomposed by addition of water to the mixture cooled by ice water, and the products steam distilled. A yellowish oil distilled first and then the white crystalline acid. The distillate was neutralised with sodium carbonate and extracted with ether. On drying the ethereal extracts and distilling off the ether there remained a strongly smelling yellow oil which according to Koll (Annalen 1889, 249, 308,) consists of the mono- and di-chloromethyl-acetoacetic esters.

The aqueous solution remaining after ether extraction was acidified with excess HCl and ether extracted several times. On distilling off the ether from the dried ethereal extracts there remained a white crystalline solid (6.6 gms.) which was dried on a porous plate in vacuo. The product was purified by dissolving in alcohol in which it was readily soluble, and then precipitating by addition of water. After careful drying in vacuo the product had m.p. 67.7°C. The presence of chlorine in the acid was shown by the Lassaigne test. Yield: 35.5% theoretical.

In succeeding preparations quantities were as follows:

200 gms. ethyl methylacetoacetate, 292 gms. PCl_5 , giving 58.2 gms. of acid; 456.9 gms. ethyl methylacetoacetate, 667.3 gms. PCl_5 giving 128.45 gms. of acid. Yields 41.8%, 30.1% theoretical.

The solution of the acid in alcohol had no reaction with ferric chloride, but an alcoholic solution of the chloromethylacetoacetic esters simultaneously formed gave a brown colouration with ferric chloride indicating the presence of an enolic hydroxyl group.

VII. ESTERIFICATION OF α -METHYL- β -CHLOROCROTONIC ACID.

α -methyl- β -chlorocrotonic acid (58.2 gms.) was dissolved in ethyl alcohol (58.2 c.c.) and heated to boiling in a round-bottomed flask fitted with a reflux condenser and delivery tube. Hydrogen chloride gas dried by sulphuric acid was bubbled through the gently boiling solution for 2 hrs.. The mixture was then cooled and the liquid poured into water (580 c.c.) in a separating funnel. The solution was neutralised with sodium carbonate and extracted three times with ether. After distilling off the ether from the dried ethereal extracts, the remaining liquid was distilled under reduced pressure and the fraction boiling at 73-74° C at 14 m.m. collected separately. This fraction (34.0 gms.) had n_D^{20} 1.4569, b.p. 74.7, 173-4° C. Koll (loc.cit.) gives 171-2° C as the b.p. of ethyl α -methyl- β -chlorocrotonate. Yield 48.4% theoretical.

A second preparation yielded 64.6 gms. of ester from 128.45 gms. of acid. The liquid distilled at 65-74° C at 14 m.m. and had n_D^{20} 1.4554. Yield 41.5% theoretical.

VIII. REACTION OF ETHYL α -METHYL- β -CHLOROCROTONATE
AND ETHYL SODIOMETHYLMALONATE.

(A) With heating under reflux.

Sodium (4.7 gms.) freshly cut under xylene, was dispersed by placing in xylene in a small round-bottomed flask and heating the xylene to boiling over a small flame. As soon as the xylene vapour had displaced all air from the flask, the flask was closed with a tight stopper and shaken vigorously once, when the sodium was dispersed to fine globules. Under these conditions it was found that the sodium coagulated on cooling and it was found necessary to admit some air during shaking to prevent coagulation. The xylene was then displaced by sodium-dried ether (200 c.c.) and ethyl methylmalonate (35.9 gms.) added. A vigorous action occurred and most of the sodium dissolved. When the remaining sodium had practically ceased to react ethyl α -methyl- β -chlorocrotonate (33.5 gms.) was added and the mixture refluxed over a steam bath. As a small amount of sodium still remained undissolved a small excess of ethyl methylmalonate was added. After refluxing for 4 hrs. the mixture was cooled and shaken with four volumes of water. The aqueous solution was extracted several times with ether, the ethereal extracts dried by calcium chloride and the ether distilled off at atmospheric pressure. The remaining liquid was distilled under reduced pressure from a Claisen flask, giving the fractions:

- (a) 80-100° C/15 m.m. - large fraction, unreacted materials.
- (b) 100-172° C/15 m.m. - very little.
- (c) 172-174° C/15 m.m. - 10.1 gms.

Fraction (c) was a viscous, yellowish liquid with n_D^{20} 1.4527. Yield 16.3% theoretical.

(B) With Long Standing at Room Temperature.

Sodium (9.1 gms.) dispersed in ether was treated with ethyl methylmalonate (68.9 gms.) to give the sodio-derivative as described under VIII A. Ethyl α -methyl- β -chlorocrotonate (64.4 gms.) was added, and the mixture stood for 20 hrs. at room temperature. The reaction mixture was worked up as described in the previous condensation and distillation of the product under reduced pressure gave the following fractions:

- (a) 40-70° C/13 m.m. - a little.
- (b) 70-106° C/13 m.m.- a large fraction, unreacted materials
- (c) 106-165° C/13 m.m.- a little.
- (d) 165-172° C/14 m.m.- 21.6 gms. (18.2% theoretical.)

During distillation of the last fraction there were signs of decomposition. There was a small amount of dark residue which solidified on cooling. Fraction (d) was a viscous yellow liquid n_D^{20} 1.4538, $D_4^{14.5}$ 1.366. It decolourised a solution of bromine in carbon tetrachloride and rapidly decolourised dilute aqueous alcoholic potassium permanganate. It gave no reaction with sodium bicarbonate solution or with aqueous alcoholic ferric chloride.

Redistillation of fraction (d) from a 10 c.c. Claisen flask at reduced pressure gave a liquid distilling 163-167°C. at 7 m.m. Combustion analysis of the redistilled ester gave C= 58.5%, H= 7.84%. The molecular weight was determined by measuring the change in freezing point as obtained from cooling curves of pure benzene after the addition of a weighed amount of ester. This gave a molecular weight of 303 for the ester.

Fraction (b) was redistilled to give 54.0 gms. of liquid distilling at 65-74°C at 14 m.m. and consisting mainly of unreacted ethyl α -methyl- β -chlorocrotonate. This was added to the sodio-derivative of ethyl methylmalonate which was formed as described above. The reaction mixture was left for a week at room temperature and then extracted as previously described. Distillation of the product in vacuo gave the following fractions:

- (a) 45-68° C./15 m.m. - a few gms.
- (b) 68-80° C/15 m.m. - 21.9 gms.
- (c) 80-164°C/15 m.m. - 40.2 gms.
- (d) 164-178°C/15 m.m. - 7.1 gms. (7.1% theoretical.)

A small brown solid residue remained.

IX. ATTEMPTS TO HYDROLYSE ESTER FROM CONDENSATION.

- (A) By refluxing with potassium hydroxide followed by refluxing with acid.

The ester (10.1 gms.) obtained as described in VIII(A) above, was refluxed with three times the amount of 2N potassium hydroxide theoretically required for hydrolysis to $\alpha\beta\gamma$ -trimethylglutaconic acid, for 2 hrs. As a considerable amount of oil remained after this treatment a small amount of ethanol was added and the liquid refluxed for a further 2 hrs. The alcohol was then removed at room temperature and reduced pressure and the solution extracted by ether to remove unhydrolysed material. After drying the ether extracts with calcium chloride the ether was distilled off through a long fractionating column over a water bath, giving a very small amount of unhydrolysed oil.

The aqueous solution remaining after extraction by ether was acidified with excess hydrochloric acid and extracted three times with ether. On drying the combined ether extracts with calcium chloride and evaporating off the ether over a water bath a brown viscous liquid remained. No solid material could be crystallised from this liquid by long standing, or by slowly evaporating the solvent from solutions of it in benzene and in water.

As it appeared that hydrolysis was incomplete the liquid was refluxed for some hours with hydrochloric acid (conc. HCl 45 c.c., H₂O 15 c.c., ethanol 25 c.c.).

The solution was extracted as before again giving a brownish oily liquid (2.4 gms.) which could not be crystallised on long cooling by a freezing mixture or on treating with benzene or water. The Lassaigne sodium test for chlorine showed that only a trace of the latter was present. Titration with standard alkali gave an equivalent weight of 170.

On treating the oil for some time with excess 4N sodium hydroxide the bulk of the material dissolved, leaving a gummy material which was filtered off. The alkaline solution was ether extracted to remove ether soluble impurities, acidified with excess hydrochloric acid, and again extracted with ether. From the ether extracts there was obtained in the usual manner an oily liquid of equivalent weight 122, n_D^{20} 1.4683, D_4^{15} 1.161.

(B) By Treating with Dilute Alkali at Room Temperature.

A 5% solution of potassium hydroxide (281 c.c.) was added to the ester (5.01 gms.) obtained by the condensation described under VIII (B), and sufficient ethanol added to make the liquids miscible. A bright yellow colour was developed by the solution. After standing for five days at room temperature, and then removing the alcohol at room temperature and reduced pressure, the mixture was extracted as described in the previous section, giving a dark brown liquid with a strong sweet smell. This liquid (2.97 gms.) was immiscible with water, and gave effervescence with bicarbonate indicating that it was acidic.

Titration with standard alkali gave an equivalent weight of 212.

About half of this liquid material was boiled for one hour with hydrochloric acid (conc. HCl 20 c.c., H₂O 40 c.c.) The bulk of the oil had dissolved after 15 min., but a brown solid material remained. On extracting the cold solution six times with ether, drying the extracts with calcium chloride, and evaporating off the ether over a water bath, a small amount of viscous liquid was obtained from which a minute quantity of white solid crystallised. The material was insoluble in water but completely soluble in alkali and had equivalent weight 105.

The liquid was boiled for a further hour with hydrochloric acid (conc. HCl, 26 c.c., H₂O 52 c.c.) under reflux. A small quantity of brown solid which remained undissolved was filtered off and the solution extracted as above giving a little viscous

greenish liquid from which minute amounts of solid crystallised. This had equivalent weight 101.

On boiling the material for a further hour with concentrated hydrochloric acid, filtering, and extracting as before, a small amount of viscous green liquid was obtained with equivalent weight 121. Only a small fraction of this was alkali soluble.

From the second half of the liquid with equivalent weight 212 there crystallised after standing for many weeks a very small amount of solid. This was separated from the liquid on a porous plate. It was a white solid, readily soluble in water, neutral, and melting 35-50° C. It decolourised dilute permanganate solution but did not react with ferric chloride solution.

X. TREATMENT OF ETHYL α -CARBETHOXY- $\alpha\beta\gamma$ -TRIMETHYLGLUTACONATE

(A) First Treatment with Sodium Ethoxide at Room Temperature.

The ester (7.5 gms.) was dissolved in alcohol (4.68 c.c.) and treated with a cold solution of sodium ethoxide made by dissolving sodium (0.59 gms.) in absolute alcohol (7.05 c.c.) Only a faint yellow colour was produced. The mixture was allowed to stand for 1 hr. 20 min. and then poured into water (100 c.c.) and extracted three times with ether. The ethereal solutions were dried with calcium chloride, the ether distilled off over a water bath through a long fractionating column, and the remaining liquid distilled under reduced pressure. The following fractions were taken:

(a) 60-164° C/16 m.m. - 1.2 gms.

(b) 164-170° C/16 m.m. - 3.9 gms.

No fraction was observed corresponding to ethyl carbonate.

There was very little residue. Fraction (b) was a liquid with n_D^{20} 1.4568, $D_4^{14.5}$ 1.098.

Hydrolysis. Fraction (b) was refluxed with ten times its volume of hydrochloric acid (1 conc HCl:2H₂O) for six hours but there still remained a large fraction of oily liquid which appeared unchanged except that a dark brown colour had been developed. The mixture was extracted six times with ether, the ethereal extracts washed once with water, dried by calcium chloride, and the ether evaporated off. A brown viscous liquid (2.9 gms.) was obtained, which effervesced with bicarbonate indicating the presence of acidic groups.

This liquid was refluxed for a further hour with concentrated hydrochloric acid. Considerable darkening in colour was observed and some of the oil still remained undissolved. The cold solution was extracted six times with ether, and the ethereal solution extracted twice with 5N sodium hydroxide. The remaining ether solution in the usual manner yielded 0.7 gms. of a viscous brown liquid A. The alkali extracts were acidified with excess acid and on ether extraction yielded 1.52 gms. of brown liquid B.

On standing for some days a very small amount of material crystallised from A. The mixture was refluxed for a further two hours with concentrated hydrochloric acid and on ether extraction gave a dark viscous liquid. Extraction of this with 5N alkali precipitated a light brown solid which was filtered off. The solid was insoluble in water, had no acid reaction to bicarbonate and decolourised permanganate. The remaining aqueous solution reduced permanganate, and on acidifying and ether extracting gave a brownish liquid which with bicarbonate effervesced and gave a light brown solid insoluble in water.

The liquid B crystallised to a small extent on standing at 0°C for some time. The crystalline material on separation from the oil, washing with water, and drying in vacuo, proved to be heterogeneous since it melted 98.7-116°C. and on titration with alkali gave widely varying equivalent weights. It was incompletely soluble in alkali. On treating the remaining liquid with water more solid material was precipitated and filtered off.

The remaining aqueous solution was acid to litmus and reduced permanganate. On ether extraction it yielded a viscous liquid with equivalent weight 112. A small amount of crystalline material which separated was dried and titrated with alkali giving equivalent weight 118.

(B) Second Treatment with Sodium Ethoxide at Room Temperature.

Redistilled ester (5.07 gms.) dissolved in alcohol (3.3 c.c.) was treated with the solution obtained by dissolving sodium (0.42 gms.) in alcohol (6 c.c.) The mixture was left for one hour at room temperature and then extracted as previously. On distilling under reduced pressure the following fractions were obtained:

(a) 150-163°C/ 9m.m. - a few drops.

(b) 163-170°C/ 9m.m. - 2.5 - 3 gms.

A brown solid residue remained. No low boiling fraction was observed. Combustion analysis of fraction (b) gave C= 59.0%, H= 7.99%. The ester gave no reaction with alcoholic ferric chloride and reacted with metallic sodium with slow effervescence.

On acidifying the aqueous solution from which the ester had been ether extracted, and again extracting with ether there was obtained more liquid (about 1 gm.) boiling at 165-170°C/16 m.m

(C) Treatment with Sodium Ethoxide At 40-50°C.

The ester (1.34 gms.) was treated with a solution of sodium (0.11 gms.) in alcohol (3 c.c.) for 1 hr.20 mins. at 40-50°C.

A slight yellow colour was developed by the mixture. The liquid was extracted as before and on distillation gave the fractions:

- (a) 30-40°C/atmospheric pressure - 3 cc. (ether)
- (b) 40-65°C/atmospheric pressure - 1 cc. (alcohol, ether)
- (c) 65-75°C/atmospheric pressure - none
- (d) 140-162°C/12 m.m. - 2 or 3 drops
- (e) 162-167°C/12 m.m. - 0.7 gms.

A very small amount of brown residue remained.

(D) Treatment with Sodium Ethoxide at 65-70°C.

The ester (1.00 gm.) was treated with a solution of sodium (0.09 gms.) in alcohol (1.5 cc.) in a test tube fitted with a reflux condenser, for 1½ hrs. at 65-70°C. A bright orange colour developed and there were signs of solid material separating. On extraction and distillation, the following fractions were obtained:

- (a) 15-60°C/atmospheric pressure - large fraction (ether)
- (b) 60-70°C/atmospheric pressure - 2-3 drops
- (c) 127-155°C/ 10 mm. - about 0.5 gms.
- (d) 155-165°C/ 10 mm. - about 0.5 gms.

(E) Treatment with Sodium ethoxide At 66-72°C.

The ester (3.45 gms.) was treated with sodium (0.29 gms.) dissolved in alcohol (5.8 c.c.) for 1 hr.15 min. at 66-72°C. A bright orange colour developed and a solid separated out. Extraction and distillation of the product gave the fractions:

- (a) 30-60°C/754 m.m. - about 1 cc. (ether)
- (b) 60-80°C/754 m.m. - little, (ether & alcohol)
- (c) 120-155°C/14 m.m. - 1.14 gms.
- (d) 160-166°C/14 m.m. - none
- (e) 166-172°C/14 m.m. - 1.46 gms.

Fraction (c) had n_D^{20} 1.4530, fraction (e) had n_D^{20} 1.4578

(F) Treatment with Sodium ethoxide at 80°C.

The higher boiling fractions from previous treatments were combined (2.6 gms.) and treated with the solution obtained by dissolving sodium (0.22 gms.) in alcohol (4.4 cc.) for $1\frac{1}{4}$ hrs. at 80°C. A bright orange colour was again observed.

Extraction and distillation gave the fractions:

- (a) 30-70°C/741 m.m. - (ether)
- (b) 70-100°C/741 m.m. - a little (ether & alcohol)
- (c) 100-140°C/741 m.m. - 0.49 gms. (no smell of Et_2CO_3)
- (d) 120-160°C/13 m.m. - 2.07 gms.
- (e) 160-170°C/13 m.m. - 1.52 gms.

Fraction (d) was redistilled from a Widmer flask with vacuum-jacketed fractionating column giving the fractions:

- (i) 110-136°C/19 m.m. - 0.24 gms.
- (ii) 136-143°C/19 m.m. - none
- (iii) 143-148°C/19 m.m. - 0.49 gms.
- (iv) 148-160°C/19 m.m. - 0.37 gms.
- (v) 160-165°C/19 m.m. - none
- (vi) 165-168°C/19 m.m. - 0.14 gms.

Undistilled liquid remaining - 0.44 gms.

The temperatures were recorded in the bath since the flask had no provision for a thermometer. Fraction (iii) gave micro-combustion analysis C = 63.04%, H= 8.86%. During the collection of fraction (iii) the refractive index changed from n_D^{20} 1.4419 to n_D^{20} 1.4537.

Hydrolysis. The remainder of this fraction (about 0.2 gms.) was boiled with a few c.cs. of aqueous alcoholic hydrochloric acid for one hour. On extracting with ether in the usual manner a small amount of viscous liquid was obtained from which there separated on standing for several days a small quantity of white crystalline solid. The crystals caused sodium bicarbonate solution to effervesce freely indicating that the substance was an acid. Attempts were made to recrystallise from benzene, petroleum ether, alcohol ether and water respectively, but with such small quantities of material it was found impossible to crystallise the pure solid free from the viscous liquid which accompanied it. After recrystallising once from benzene the crystals melted 65-85°C. Insufficient solid was obtained for analysis.