T H E S I S

entitled

AN ATTEMPTED NEW METHOD FOR THE SYNTHESIS OF $\alpha\beta$-DIALKYL AND $\alpha\beta\gamma$-TRIALKYL-GLUTACONIC ACIDS.

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Codeword:.....

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

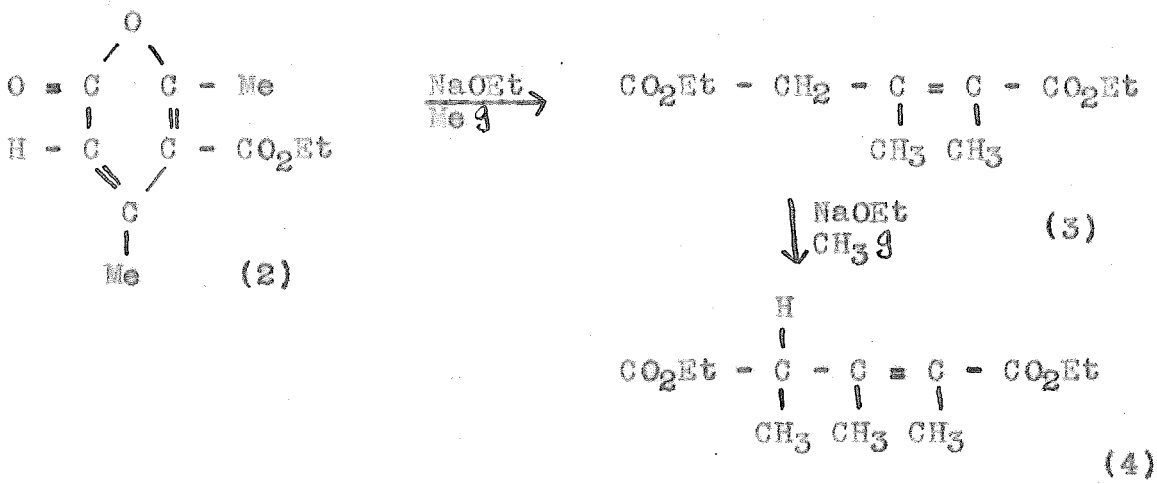
Various methods for the synthesis of $\alpha\beta\gamma$-trialkyl-glutaconic acids (I) have been tried in the past, but none of these either gives satisfactory yields, or is such as to establish positively the constitution of the product.

(1)

These methods are discussed below.

A. The Methylation of ethyl $\alpha\beta$ - dimethyl - glutaconate.

Thorpe and Wood (J.C.S. 1913, 103, 1759) methylated the so-called "labile" ethyl $\alpha\beta$ - dimethyl-glutaconate (3), prepared by the action of alcoholic sodium ethoxide and methyl iodide on ethyl isodehydracetate (2), by treating it with alcoholic sodium ethoxide and excess methyl iodide, methylation being complete at the end of three hours at room temperature.



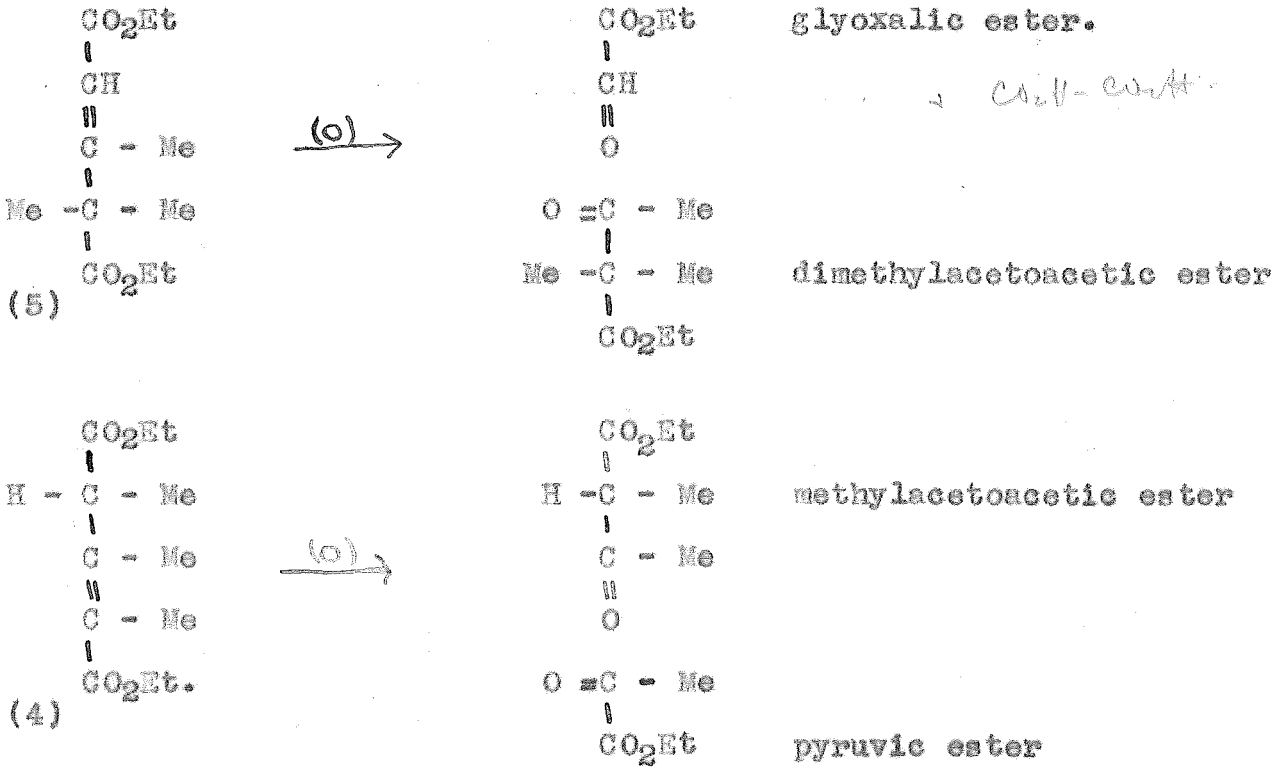
(2)

(3)

(4)

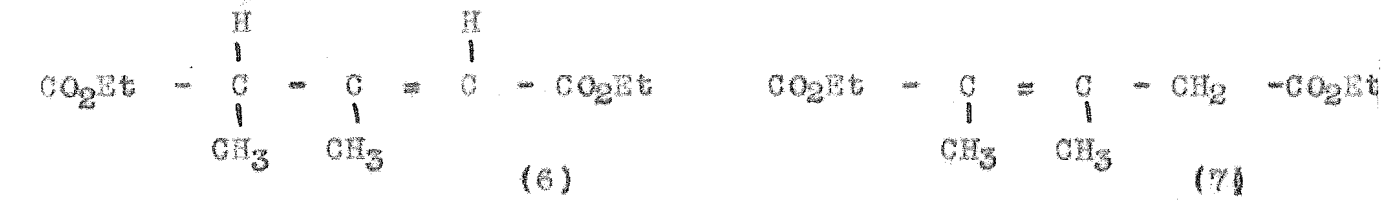
The trimethyl ester (4) on hydrolysis gave an acid, m.p. 127°, which was considered by the authors to be $\alpha\beta\gamma$ - trimethyl-glutaconic acid. On the other hand, Feist and Beyer (Annalen 1906, 345, 117) were unable to methylate ethyl $\alpha\beta$-dimethyl-glutaconate.

Packer and Sargent (J.C.S., 1933, 136, 556) were also unable to methylate "labile" ethyl $\alpha\beta$-dimethyl-glutaconate (3) to any extent using methyl or ethyl-alcoholic sodium methoxide or ethoxide under a variety of conditions. By using dispersed sodium in ether and isolating the sodio derivative of the ethyl $\alpha\beta$-dimethyl-glutaconate, methylation was readily effected by methyl iodide, but the resultant ester was mainly ethyl $\alpha\alpha\beta$-trimethyl-glutaconate (5). As no ethyl pyruvate could be detected amongst the products of oxidation with neutral $KMnO_4$, it is likely that no appreciable quantity of ethyl $\alpha\beta\gamma$-trimethyl-glutaconate was formed.



Alkaline Hydrolysis of the ethyl $\alpha\alpha\beta$-trimethyl-glutaconate gave a product which was identical with trans $\alpha\alpha\beta$-trimethyl-glutaconic acid prepared by a method that left no doubt as to its constitution. This method, due to Perkin and Thorpe (J.C.S. 1897, 71, 1178), is described later (p. 8).

The "labile" $\alpha\beta$-ester of Thorpe has been shown by Kon and Watson (J.C.S. 1932, 135, 1) by ozonolysis of ethyl $\alpha\beta$-dimethyl-glutaconate to be a mixture of the tautomerides (6) and (7).



(6) (7)

They called (6) ethyl $\beta\gamma$-dimethyl-glutaconate, and (7) ethyl $\alpha\beta$-dimethyl-glutaconate. The ester prepared by the methylation of isodehydracetic ester was shown to be mainly the $\beta\gamma$ isomeride (6) which on methylation gives rise to the ethyl $\alpha\alpha\beta$-trimethyl-glutaconate as shown by Packer and Sargent. The ester obtained from $\alpha\beta$-dimethyl-glutaconic acid by esterification through the silver salt was shown to be practically pure ethyl $\alpha\beta$-dimethyl glutaconate (7) and methylation of this should therefore give rise to ethyl $\alpha\beta\gamma$-trimethyl-glutaconate.

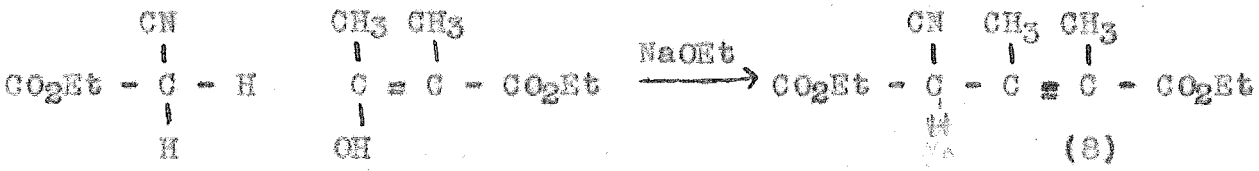
Hutchinson (N.Z. University Thesis 1935. Unpublished) prepared ethyl $\alpha\beta$-dimethyl-glutaconate (7) by the method of Kon and Watson, i.e., by esterfication of the $\Delta^{\alpha\beta}$ form of $\alpha\beta$-dimethyl-glutaconic acid through the silver salt, and methylated it by treatment with dispersed potassium in ether followed by methyl iodide. On hydrolysis he obtained a mixture of acids from which small quantities of two pure acids were isolated by fractional crystallisation from water. The first to separate (m.p. 118°) he assumed to be the $\alpha\beta\gamma$-trimethyl glutaconic acid as its melting point was depressed by both trans $\alpha\alpha\beta$-trimethyl-glutaconic acid and cis. $\Delta^{\alpha\beta}$-dimethyl-glutaconic acid. The trans $\alpha\alpha\beta$-acid was prepared by Perkin and Thorpe's method (loc. cit.) and the cis- $\alpha\beta$-acid by acid hydrolysis of the "labile" $\alpha\beta$ ester.

The second acid obtained (m.p. 143° - 147°C.) was identical with trans $\alpha\alpha\beta$-trimethyl-glutaconic acid.

Apparently therefore, under the conditions of methylation much of the ethyl $\alpha\beta$-dimethyl-glutaconate (7) had undergone conversion to ethyl $\beta\gamma$-dimethyl-glutaconate (6). It seems improbable then that this method can be applied to the preparation of $\alpha\beta\gamma$-trialkyl-glutaconic acids in quantity, and in any case the constitution of Hutchinson's acid is still open to question.

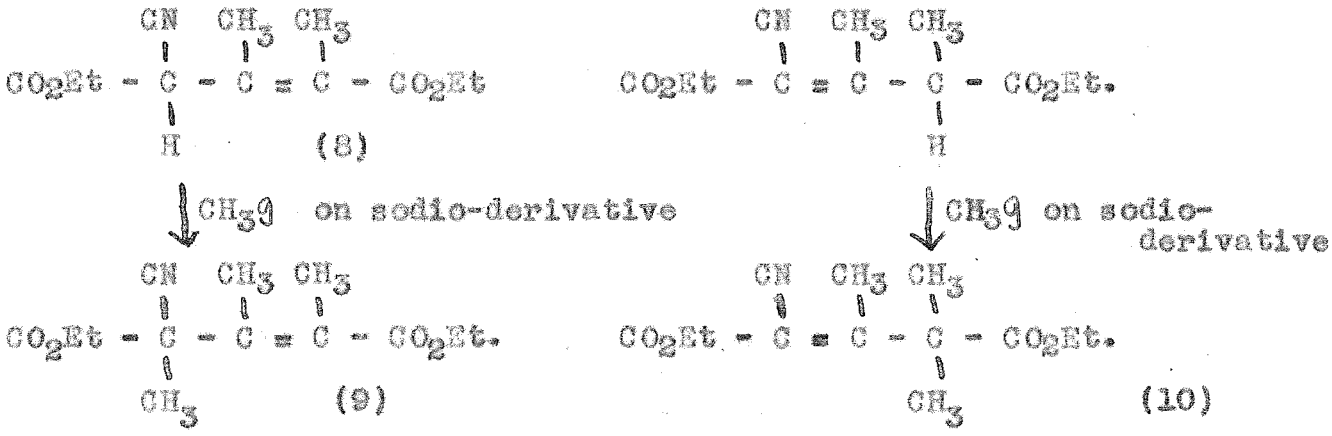
B. Methylation of cyano - dimethyl - glutaconic ester.

Rogerson and Thorpe (J.C.S. 1905, 87, 1702) described the condensation of ethyl cyanoacetate and methyl acetoacetic-ester in the presence of alcoholic sodium ethoxide to give ethyl α-cyano - $\beta\gamma$-dimethyl glutaconate (8) as its sodio derivative.

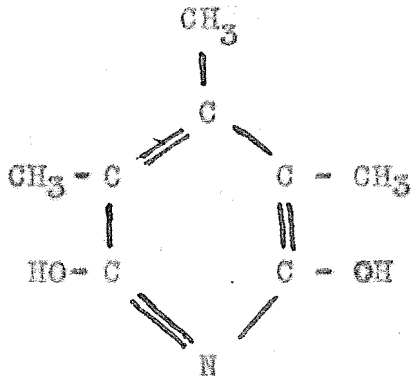


(8)

This ester on treatment with methyl iodide was believed to yield ethyl α-cyano-$\alpha\beta\gamma$-trimethyl-glutaconate (9). Actually two products are possible as ethyl α-cyano-$\beta\gamma$-dimethyl-glutaconate (8) is tautomeric.



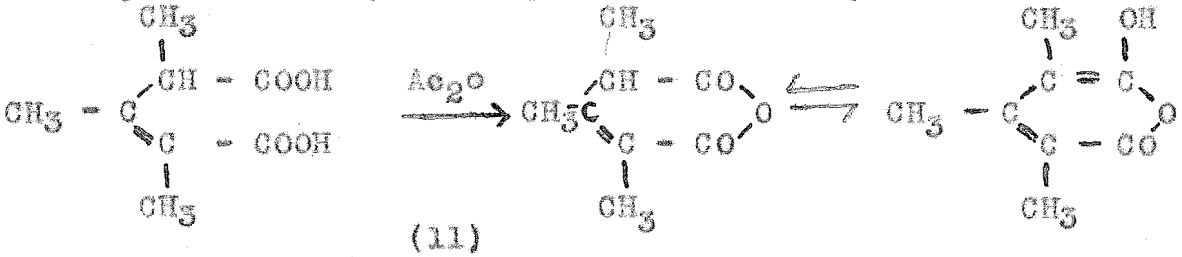
Hydrolysis of the ester they obtained yielded what the authors considered to be 3:4:5 -trimethyl - 2:6 -dihydroxy pyridine (27) and $\alpha\beta\gamma$-trimethyl glutaconic acid.



(27)

The structure of the pyridine derivative would fix the structure of the ester and hence also the acid, but no conclusive evidence as to its constitution was advanced, its identification as a trimethyl-dihydroxy-pyridine depending entirely on combustion analysis of the compound.

The acid obtained from the mother liquors after separation of all the pyridine derivative melted at 127°C. and readily gave an anhydride (11) by boiling with acetic anhydride.



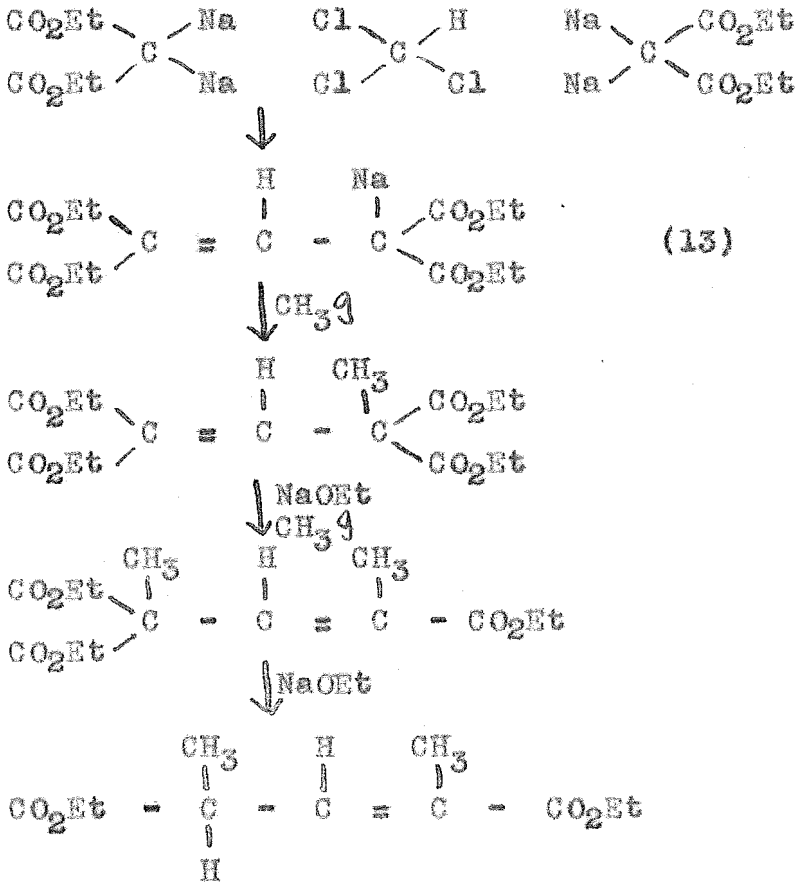
(11) (12)

This anhydride (11) has a mobile hydrogen atom and should give rise to the hydroxy anhydride (12), like other acids of the glutaconic series having a mobile hydrogen still present. In the description of the anhydride Rogerson and Thorpe make no mention of properties characteristic of (OH) group.

Sargent (N.Z. University Thesis 1931, Unpublished) attempted to prepare $\alpha\beta\gamma$-trimethyl-glutaconic acid by the method of Rogerson and Thorpe (loc. cit.) but was unable to effect methylation, and hydrolysis of the resultant ester yeilded only $\alpha\beta$-dimethyl-glutaconic acid, and the corresponding pyridine derivative.

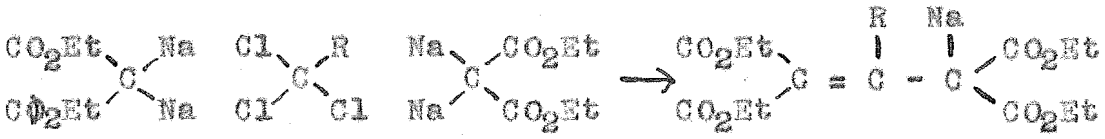
C. <u>The Condensation of Malonic ester with a substituted Chloroform and subsequent Methylation.</u>

By methylation of the sodio derivative of $\alpha\gamma$-dicarbethoxy glutaconic ester (13) prepared by method of Conrad and Gutzeit (Ann. 222, 256, 1883) from chloroform and malonic ester in the presence of sodium ethoxide, Thole and Thorpe (J.C.S. 1911, 99, 2191) obtained ethyl $\alpha\gamma$-dimethyl-glutaconate (14).



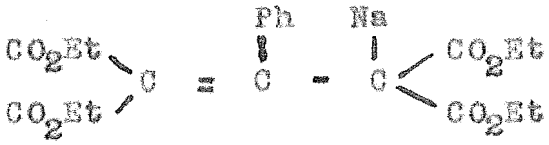
(13)

By using a substituted chloroform it should be possible to prepare an $\alpha\beta\gamma$-tri-alkyl-glutaconic ester by carrying



out the same series of reactions as above.

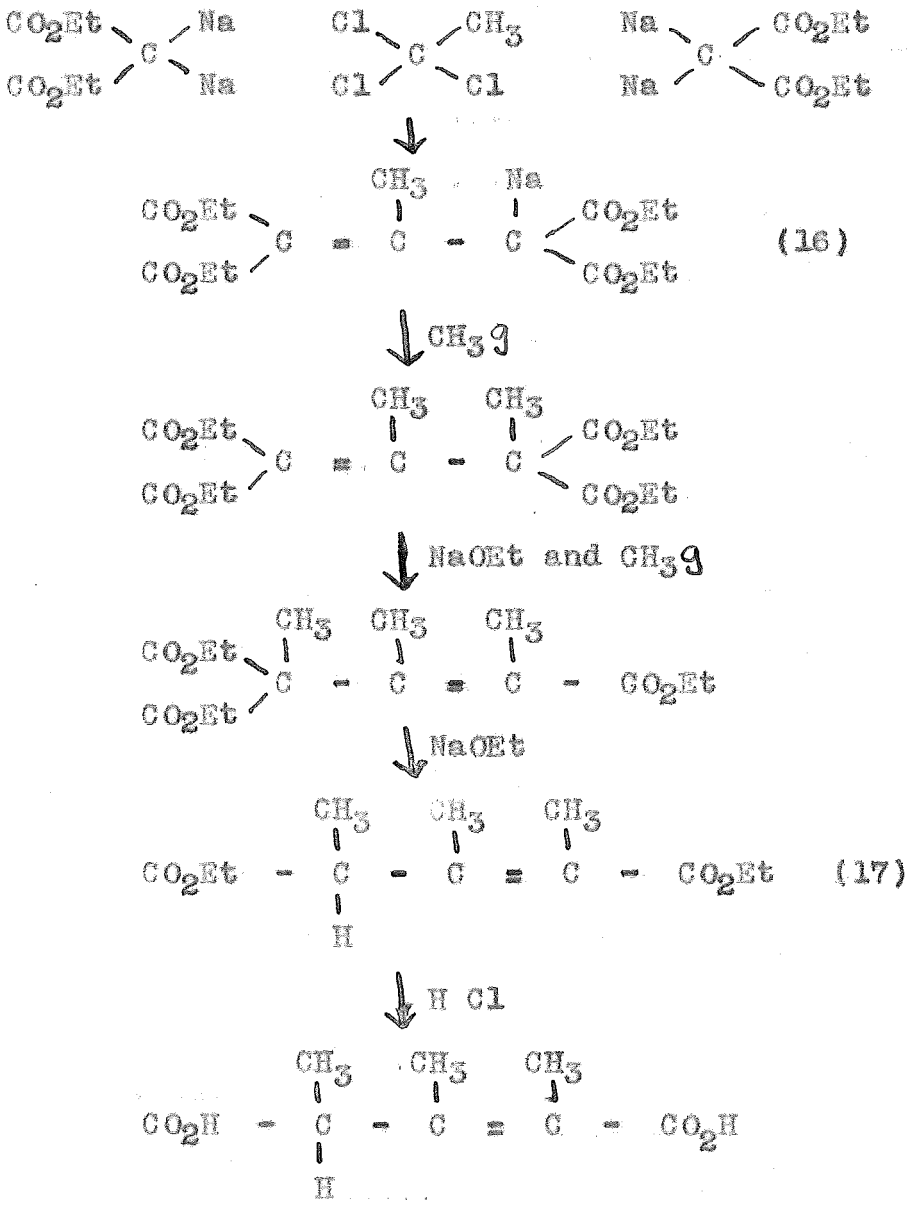
Thompson (N.Z. University Thesis, 1930, Unpublished) attempted to condense phenyl-chloroform with malonic ester in the presence of sodium ethoxide.



(15)

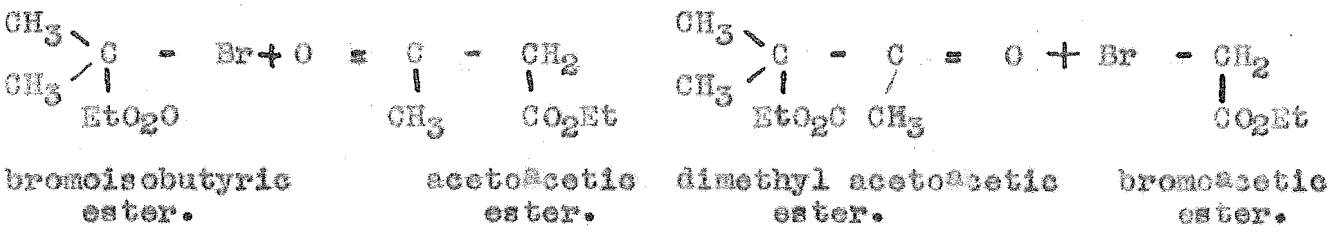
but obtained none of the expected product, β-phenyl-$\alpha\gamma$-dicarbethoxy-glutaconic ester. (15)

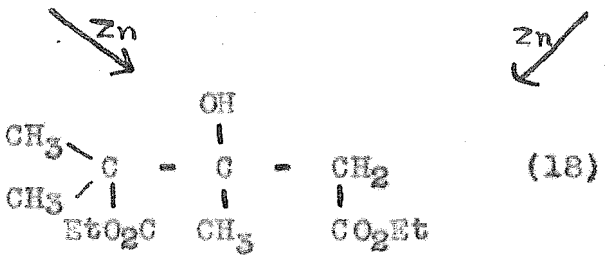
Adams (N.Z. University Thesis 1936, Unpublished) condensed methyl chloroform with malonic ester and sodium ethoxide but hydrolysis of the product yielded only malonic acid derived from unchanged malonic ester. Had he obtained β-methyl-$\alpha\gamma$-dicarbethoxy-glutaconate (16) further methylation by Thole and Thorpe's method would have yielded $\alpha\beta\gamma$-trimethyl-glutaconate (17).

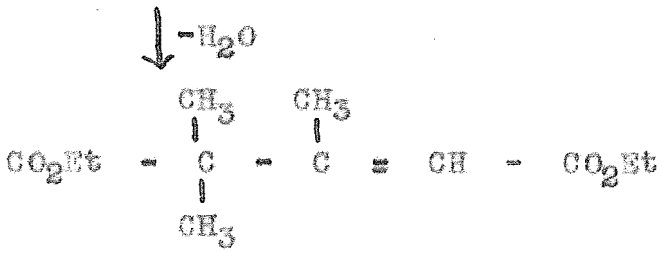


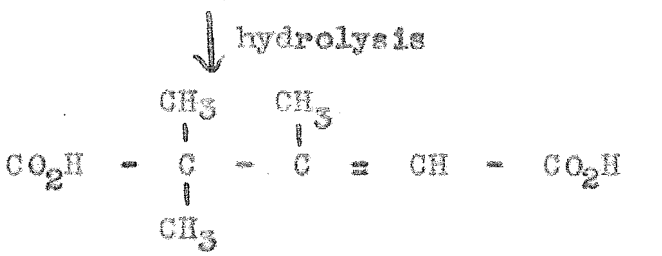
D. Other possible methods of synthesis.

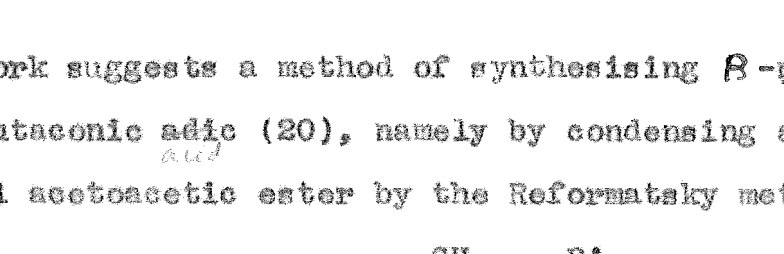
A new line of attacking the problem is suggested by Perkin and Thorpe's (J.C.S., 1897, 71, 1178) preparation of ethyl β-hydroxy αα β-trimethyl-glutarate (18) by two different Reformatsky synthesis, and the subsequent dehydation and hydrolysis to αα β-trimethyl-glutaconic acid (19).



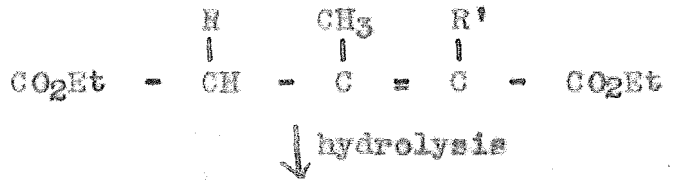


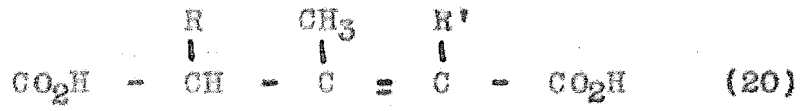






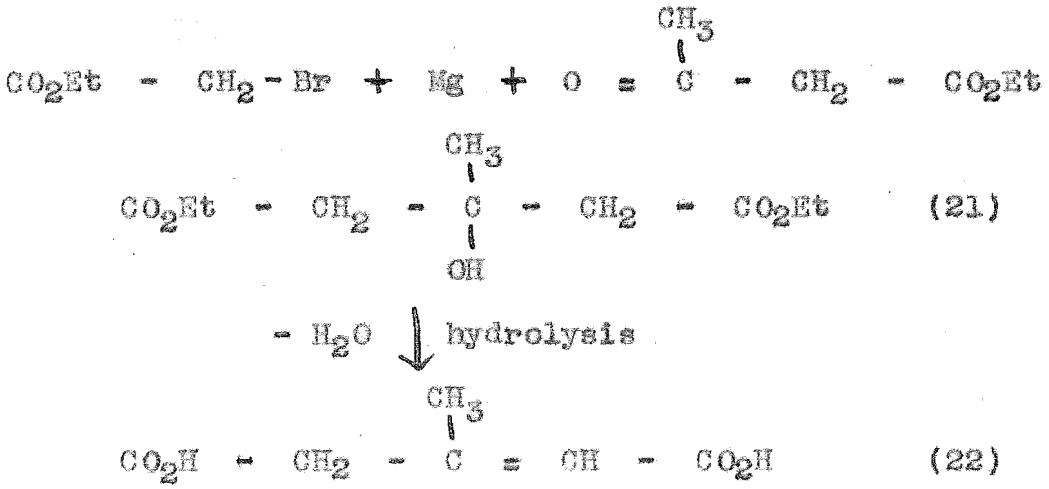
This work suggests a method of synthesising β-methyl α γ-dialkyl-glutaconic adic (20), namely by condensing an α-bromoester and a monoalkyl acetoacetic ester by the Reformatsky method.





(20)

Mapstone (N.Z.University Thesis, 1940. Unpublished) in order to test the method, carried out a synthesis using bromacetic ester and acetoacetic ester in the presence of magnesium.

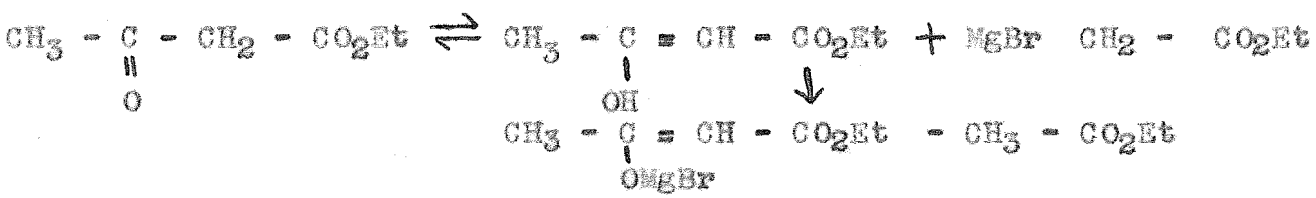


(21)

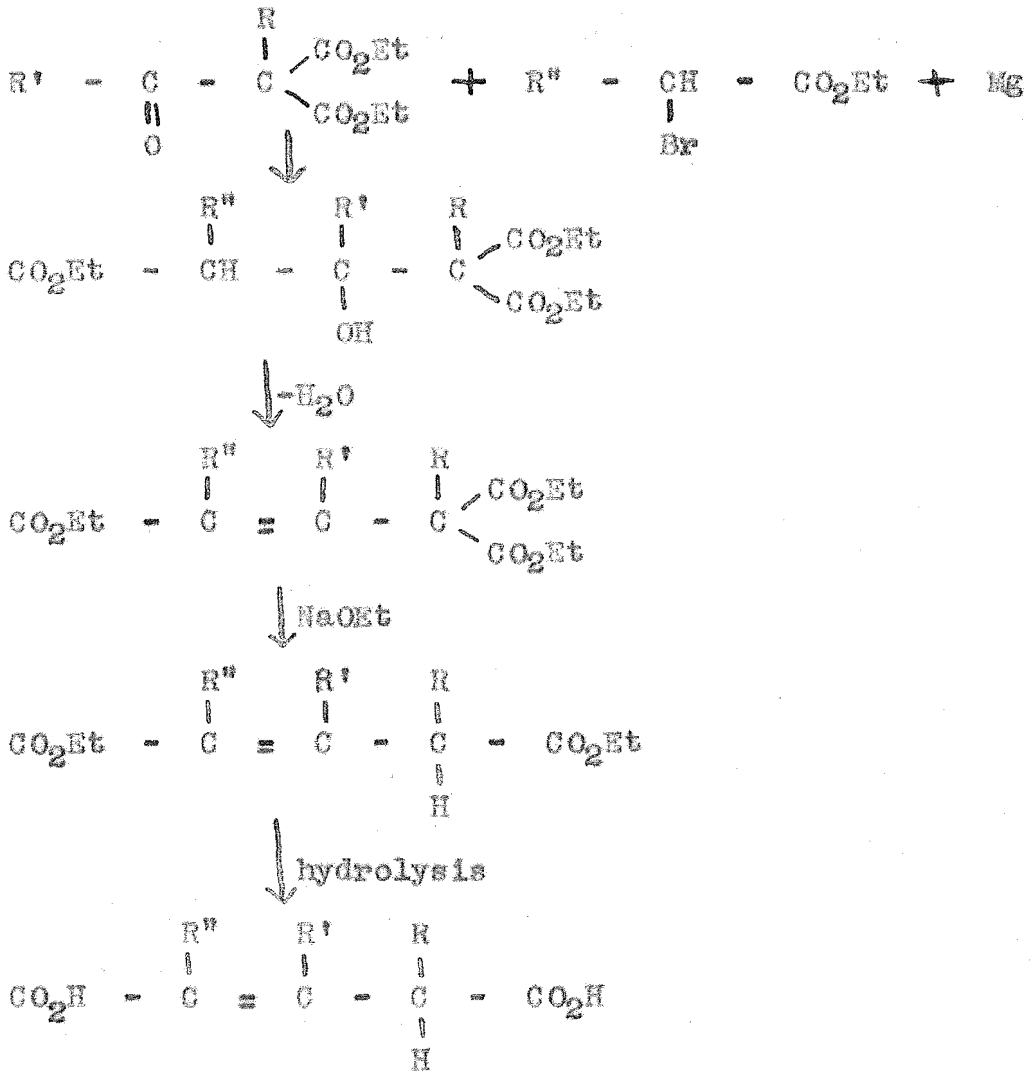
(22)

He obtained only a very poor yield of the hydroxy-ester (21) but by its dehydration and the hydrolysis of the glutaconic ester so obtained he isolated a small quantity of β -methyl-glutaconic acid (22).

The low yield obtained in the Reformatsky condensation may be due to the fact that acetoacetic ester and its monoalkyl derivatives possess a mobile hydrogen atom, and hence give rise to an equilibrium mixture of ketonic and enolic forms. The organo-metallic compound derived from the α-bromoester may possibly react preferentially with the acidic enolic form, resulting in its own destruction as well as in the removal of the ketonic form.



Mapstone suggested a method of overcoming this difficulty by using an alkyl-acyl-malonic ester instead of acetoacetic ester. As it has no mobile hydrogen, the possibility of the enolic form reacting is prevented. A second advantage is that the substituent group on the β-carbon atom may be varied. The steps of the proposed synthesis can be represented as following, and the simplest example is the synthesis of αβγ-trimethyl-glutaconic acid where R = R' = R" = CH_3.



E. Present Investigation.

The present investigation was carried out to test Mapstone's proposed method. However, no attempt was made to

prepare $\alpha\beta\gamma$-trimethyl-glutaconic acid, as an authentic sample of $\alpha\beta$-dimethyl-glutaconic acid (prepared by the methylation and hydrolysis of isodehydracetic ester) was available in the laboratory, for purposes of comparison. Also no α-bromo-propionic ester was available and the yields by ordinary methods of preparation from the available materials are known to be poor.

Two methods are available for the preparation of acetyl-methyl-malonic ester (23).

(i)

$$CH_2(CO_2Et)_2 \xrightarrow[CH_3I]{NaOEt} CH(CH_3)(CO_2Et)_2 \xrightarrow[CH_3COCl]{Na\ in\ ether} C(CH_3)(CO_2Et)_2(CO)CH_3 \qquad (23)$$

By methylating malonic ester with sodium ethoxide and methyl iodide and acetylating the methyl-malonic ester with sodium dispersed in ether and acetyl chloride.

(ii)

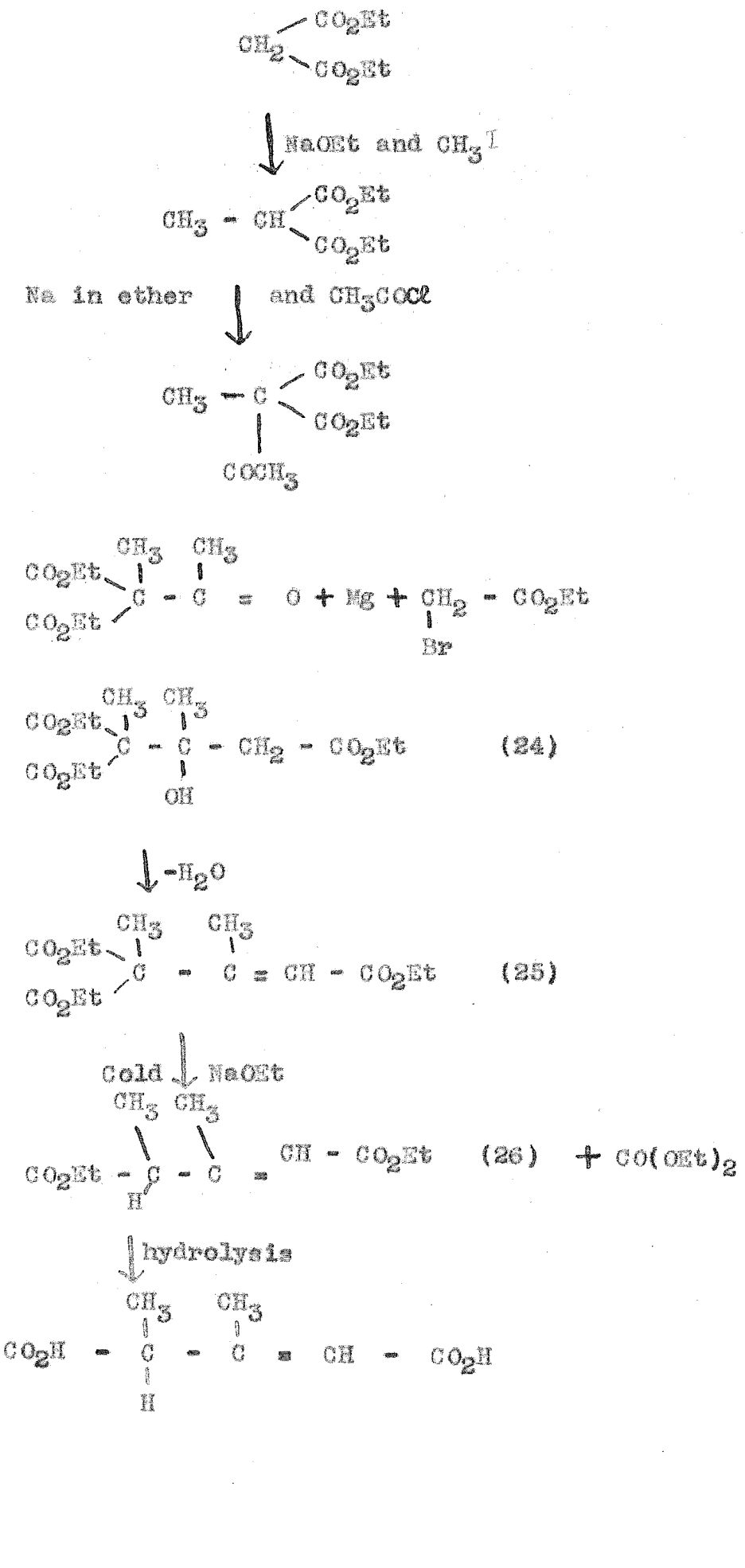
$$CH_3 - CO - CH_2 - CO_2Et \xrightarrow[CH_3I]{NaOEt} CH_3 - CO - CH(CH_3) - CO_2Et$$

$$CH_3 - CO - CH(CH_3) - CO_2Et \xrightarrow{NaOEt} CH_3 - CO - C(CH_3)(CO_2Et)^- Na^+$$

$$CH_3 - CO - C(CH_3)(CO_2Et)^- Na^+ + Cl.CO_2Et \longrightarrow CH_3 - CO - C(CH_3)(CO_2Et)_2 \qquad (23)$$

By methylating aceto-acetic ester with sodium ethoxide and methyl iodide and treating the methyl-acetoacetic ester with sodium ethoxide and chloroformic ester.

As the first method is simpler and has been described in the literature, it was used. The outline of the whole proposed synthesis is as follows:-


CO2Et
CH2
CO2Et
NaOEt and CH3I
CH3 - CH
CO2Et
CO2Et
Na in ether
and CH3COCl
CH3 - C
CO2Et
CO2Et
COCH3
CH3 CH3
CO2Et
C - C = O + Mg + CH2 - CO2Et
CO2Et
Br
CH3 CH3
CO2Et
C - C - CH2 - CO2Et (24)
CO2Et
OH
-H2O
CH3 CH3
CO2Et
C - C = CH - CO2Et (25)
CO2Et
Cold
NaOEt
CH3 CH3
CO2Et - C - C = CH - CO2Et (26) + CO(OEt)2
H
hydrolysis
CH3 CH3
CO2H - C - C = CH - CO2H
H

The removal of a carbethoxy group from ethyl α carbethoxy - $\alpha\beta$ dimethyl-glutaconate (25) by the action of cold sodium ethoxide is based upon the observation by Thole and Thorpe (J.C.S. 1911, 99, 2191) 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 to form ethyl carbonate and the sodio derivative of glutaconic ester, which possesses a characteristic yellow colour. This reaction has been very successfully used by Thole and Thorpe (loc.cit.) in the preparation of $\alpha\gamma$ -dimethyl-glutaconic acids (see p. 6).

In outline the procedure adopted was as follows:- Malonic ester was methylated by the action of sodium ethoxide and methyl iodide and the product fractionally distilled. The methyl-malonic-ester so obtained was treated with dispersed sodium in ether, and after the sodium had reacted, with acetyl chloride, following the method used by Michael (Am. Chem. J. 1892 Vol. 14 No. 7, P. 481). A considerable amount of the sodio derivative was precipated and the solution acquired a pink tinge. Reaction with acetyl chloride tended to become vigorous, so the flask was cooled in ice water. The ester obtained was fractionally distilled twice.

Bromacetic ester, prepared by the action of alcohol on brom-acetyl bromide formed from acetic acid, red phosphorus and bromine, was condensed with the acetyl-methyl-malonic ester in the presence of dry magnesium using benzene as a solvent. The reaction commenced after warming on the steam bath for a quarter

of an hour and continued so vigorously that the flask had to be cooled under running water to keep the reaction under control. After warming on the steam bath for twenty minutes, reaction was complete and the product was decomposed with dilute sulphuric acid, separated, washed, dried and distilled. Two to three drops of the ester were dissolved in a few drops of sodium dried ether and a small pellet of sodium added. A steady stream of hydrogen bubbles escaping from the surface of the sodium indicated the presence of the (OH) group.

Combustion analysis gave:-	C	=	55·43%	H	= 7·99%
Hydroxy ester (24) requires:-	C	=	55·22%	H	= 7·95%

Experiments on the dehydration of the hydroxy ester. The next stage in the process — dehydration of the ethyl α-carbethoxy $\alpha\beta$-dimethyl β-hydroxy glutarate presented unexpected difficulties. In a small scale preliminary experiment the dehydration appeared to proceed satisfactorily by refluxing with phosphorus oxychloride in benzene for half an hour on the boiling water bath. The boiling point of the resultant ester was 15 - 20° below that of the hydroxy-ester although with the small quantity available, an accurate value of the b.p. was difficult to obtain The addition of sodium ethoxide produced a yellow colouration with the dehydrated ester due to the formation of a yellow sodio derivative and the odour of ethyl carbonate was detectable. This indicated that dehydration had occurred as expected.

Attempted dehydration, under the same conditions, of the total yield of hydroxy ester (22 gm.) was carried out, but on distillation the resultant ester was found to have the same

boiling point (140 - 141°/13 m.m.) as before treatment.

Combustion analysis gave:	C	=	55·2 %	H	= 7·75%
Hydroxy ester (24) requires:	C	=	55·22%	H	= 7·95%
Dehydrated ester (25) requires:	C	=	58·73%	H	= 7·69%

The yield of ester (16 gm.) indicated that a considerable loss of material was entailed by this treatment.

As dehydration had not occurred it was thought that phosphorus oxychloride might have acted as a chlorinating agent and replaced the (OH) group. A Lassaigne test gave indication of some halogen so a quantitative estimation was carried out by Robertson's method (J.C.S. 1915, 107, 902) but the amount of halogen was below 0·3%. As treatment with phosphorus oxychloride in benzene has proved ineffective, phosphorus oxychloride in the higher boiling toluene was tried. Accordingly the ester was refluxed with phosphorus oxychloride in toluene for three quarters of an hour. The resulting ester distilled over at 143 - 146°/17 m.m. Yield Ca. 8 gm.

Combustion analysis gave:	C	=	55·69%	H	= 7·99%
Hydroxy ester (24) requires:	C	=	55·22%	H	= 7·95%
Dehydrated ester (25) requires:	C	=	58·73%	H	= 7·69%

As there appeared to be some dehydrated ester (α-carbethoxy-$\alpha\beta$-dimethyl-glutaconic ester) present, all the ester obtained above (7·7 gm.) was treated with the required quantity of cold sodium ethoxide and allowed to stand for 1 hour. A light yellow colour formed indicating the presence of some unsaturated ester. The sodio derivative was decomposed with water and the ester separated in the usual way. On distillation from a small Claisen flask a

small portion came over between 60° - 120°/ 760 m.m., consisting mainly of ethyl carbonate, followed by a fraction at 120° - 122° / 14 m.m., and another at 141° - 143°/ 14 m.m. The lower boiling fraction (2 gm.) was assumed to be ethyl $\alpha\beta$-dimethyl glutaconate (A) (see p. 18) and the higher boiling fraction (3·8 gm.) unchanged ethyl α-carbethoxy $\alpha\beta$-dimethyl-β hydroxy-glutarate. Further attempts at the dehydration of this hydroxy ester fraction were made as follows:-

(a) Distillation from anhydrous zinc chloride. I.C.C. of the hydroxy-ester recovered in the previous experiment was distilled from a small Claisen flask from half its weight of anhydrous zinc chloride. Only some of the ester distilled leaving a brown residue in the flask. Probably the zinc chloride acted as a condensing agent at the temperature of the bath (160°C.) The ester (B) (see p. 19) boiled at 134° - 136°/ 14 m.m.

(b) Refluxing with phosphorus pentoxide in toluene. In a paper on the dehydration of β-hydroxy esters, Kon and Nargund (J.C.S. 1932, 135, 2461) found that phosphorus pentoxide refluxed for three hours with the ester dissolved in three times its volume of benzene, was an effective dehydrating agent, and state that it was a better dehydrating agent for their esters (esters of β-hydroxy monobasic acids) than phosphorus oxychloride. However, refluxing the ester (3 gm.) for three quarters of an hour with the theoretical quantity of phosphorus pentoxide in dry toluene yielded the ester unchanged as shown by analysis.

Found:	C = 55·3 %	H = 7·71%
Hydroxy ester (24) requires:	C = 55·22%	H = 7·95%

This result does not agree with the experience of Kon and Nargund.

(c) Treatment with potassium bisulphate. The ester (1·8 gm.) was heated with double its weight of potassium bisulphate for three hours at 170° - 180° but no appreciable change in the boiling point of the ester occurred. Kon and Nargund, using half the quantity of this reagent under the same conditions obtained 60 - 70% yields of dehydrated ester.

(d) Refluxing with considerable excess of Phosphorus oxychloride. Finally, as all the usual methods of dehydration had been tried and found ineffective, and as treatment with phosphorus oxychloride produced partial conversion of hydroxy ester (24) to unsaturated ester (25) it was decided to use this reagent under severer conditions. The ester (1·9 gm.) was refluxed with five times its volume of phosphorus oxychloride in toluene for two and a half hours. This treatment was too severe and distillation yeilded no product corresponding to α-carbethoxy $\alpha\beta$-dimethyl-glutaconic ester or α-carbethoxy $\alpha\beta$-dimethyl-β-hydroxy-glutaric ester. Thus no hydroxy ester remained for further experiments.

Hydrolysis of Ester (A).

The low boiling fraction (120° - 122°/14 m.m.) ester (A), thought to be ethyl $\alpha\beta$-dimethyl-glutaconate was hydrolysed by boiling with 5N. HCl, and after concentration of the resultant solution crystals separated out. They were recrystallised twice from ether petrol-ether mixture and dried on a porous plate. They melted at 109°C. The total quantity of acid (C) so obtained was little more than ·1 gm. For purposes of comparison, and because the cis and trans forms of glutaconic acids with a mobile hydrogen

are interconvertible in boiling HCl solutions, an authentic sample of αβ-dimethyl glutaconic acid was refluxed for three hours with 5N. HCl and recrystallised under the same conditions. The resultant crystals melted at 118° - 119°C. A mixture of the two acids melted at 89 - 91°C. proving that they were not identical.

Combustion analysis of acid (C) (whole of above quantity used) gave: C = 45·06% H = 6·12% (O = 48·82%)

αβ-dimethyl-glutaconic acid requires: C = 53·16% H = 6·33% (O = 40·51%)

α-carboxyl -αβ-dimethyl-β-hydroxy-glutaric acid requires: C = 43·64% H = 5·46% (O = 50·91%)

A mixture of αβ-dimethyl-glutaconic acid (three parts) and α-carboxyl αβ-dimethyl β- hydroxy-glutaric acid (17 parts) requires: C = 45·06% H = 5·60% (O = 49·3%)

Hydrolysis of ester (B) obtained by distilling the hydroxy ester with zinc chloride.

This ester (p. 17) was hydrolysed with 5N. HCl and the acid (D) formed crystallised out on concentrating the solution. It was recrystallised from ether-petrol-ether mixture and melted at 108·5° - 109°C. With a sample of acid (C) it gave a mixed m.p. 108 - 108·5°C. This establishes the identity of the two acids obtained by hydrolysis of ester (A) and ester (B). Titration of acid (D) with alkali gave an equivalent weight of 72·5, the value for tribasic α-carboxyl-αβ-dimethyl- β - hydroxy glutaric acid being 73·3, and that for the dibasic αβ-dimethyl-glutaconic acid 79. This supports the conclusion drawn from combustion analysis that the acid obtained consisted mainly of α-carboxy- αβ dimethyl-~~glutaconic~~ β-hydroxy-glutaric acid, but further work is required to establish this beyond all doubt.

A satisfactory method for the dehydration of the hydroxy-

ester (24) was therefore not discovered in the present investigation, and until this is found the proposed method for the synthesis of $\alpha\beta\gamma$-trialkyl-glutaconic acid is not practicable.

S U M M A R Y.

1. A new proposed method for the preparation of αβγ-trialkyl-glutaconic acids has been investigated.

2. The method has been tested in an attempted synthesis of αβ-dimethyl-glutaconic acid.

3. The condensation between acetyl-methyl-malonic ester and bromacetic ester by the Reformatsky method, took place with the formation of α-carbethoxy -αβ-dimethyl-β-hydroxy glutaric ester, but a satisfactory method for dehydrating this hydroxy ester was not found.

INDEX TO EXPERIMENTAL SECTION.

I. PURIFICATION OF CHEMICALS.

Alcohol. Reputed "absolute" alcohol was refluxed over fresh quick-lime (·4 K gn. per litre) for 8 hours and distilled through a long fractionating column b.p. 78·30 - 78·37°C. This method (Weissberger and Proskauer. Organic Solvents) gives a product of 99·9% purity.

Ether. Two litres of ether were shaken up with a solution of ferrous sulphate (Conc. H_2SO_4 6 gm., water 110 C.C., $FeSO_4$ 60 gm.) 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 of this ether was stood over sodium wire.

Methyl Iodide. Hopkin and Williams product was used without further purification.

Malonic ester. B.D.H. product gave n_D^{20} 1·4143 (compare Smythe and Walls (J.C.S. 1931, 529) n_D^{20} 1·4145). It was therefore used without further purification.

Acetyl Chloride. Hopkin and Williams product was redistilled and the fraction b.p. 54 - 55° was taken as pure.

Xylene. The xylene supplied was slightly discoloured, so it was redistilled and stored over sodium wire. On standing it became discoloured so was refluxed for two hours over sodium amalgam, redistilled and kept over sodium wire.

II. METHYLATION OF MALONIC ESTER.

71·8 gm. of freshly-cut sodium were dissolved in 1000 c.c. of absolute ethyl alcohol in a 3-litre flask fitted with a double surface condenser. 500 gm. of malonic ester were slowly added with the production of a yellow colouration, but no separation of sodio-derivative occurred. 565 gm. of methyl iodide were slowly run into the flask from a dropping funnel, the flask being constantly shaken. It was then heated on a boiling water bath for 2½ hours till the liquid was neutral to litmus, during which time separation of sodium iodide took place. As much alcohol as possible was removed under reduced pressure and the liquid poured into twice its volume of water, and extracted three times with ether. The brown colouration due to the presence of iodine was removed by shaking with sodium sulphite solution; the ether layer was then washed twice with water and dried over night over anhydrous sodium sulphate. Ether was removed by distillation through a long fractionating column at ordinary pressure, and the remaining liquid transferred to a 1 litre Claisen flask with a fractionating side arm (Kon flask) and distilled under reduced pressure. The following fractions were taken:-

89° - 91°/ 18 m.m. unchanged malonic-ester.
91° - 91·5°/18 m.m. methyl-malonic ester.
91·5° - 93°/18 m.m. heavy fraction.

A second batch of the same quantities was worked up in the same way. The following fractions were taken:-

89 - 91°/19 m.m. unchanged malonic ester.

91° - 91·8°/19 m.m.	methyl-malonic ester.
91·8° - 93°/19 m.m.	heavy fraction.

The corresponding fractions of each batch were mixed and redistilled. Low boiling fraction yielded the following fractions:-

89° - 91·5°/20 m.m.	main fraction; mainly malonic ester.
91·5° - 92·5°/20m.m.	methyl-malonic ester.
above 92·5°/20m.m.	very little.

High boiling fraction on redistillation boiled mainly above 93°C./19 m.m.

Yield of methyl malonic ester ex. 1000 gm. of malonic ester was 660 gm.

The boiling point of the main product determined under atmospheric pressure (755 m.m.) was 200°C., compared with 198°C. for pure malonic ester under the same conditions.

III. ACETYLATION OF METHYL-MALONIC ESTER.

23 gm. of freshly-cut sodium were dispersed under boiling xylene and the xylene replaced, after several washings, with 550 gm. of sodium-dried ether. A double surface condenser was fitted to the 1500 c.c. flask and 174 gm. (1 mol.) of methyl-malonic ester slowly added. Rapid evolution of hydrogen occurred with the separation of a white sodio-derivative. As the ester was being added the solution became pink, but when addition was complete, it turned yellow. The flask was allowed to stand at room temperature for 3 hours being repeatedly shaken. After evolution of hydrogen had entirely ceased, the flask was cooled in ice water and 78 gm. of redistilled acetyl chloride added very slowly. Vigorous reaction occurred, and as the sodio-derivative disappeared sodium chloride separated out. The flask was stood in ice water for 14 hours, at the end of which time it showed an acid reaction. 800 c.c. of water were added and the ethereal layer separated and washed twice with water, (alkali could not be used as the acetyl derivative is readily decomposed even in ethereal solution, by aqueous alkali) and dried for a day over anhydrous sodium sulphate.

Ether was removed on the steam bath by distillation through a long column at atmospheric pressure, and the residual liquid transferred to a Claisen flask and subjected to distillation under reduced pressure.

The following fractions were taken:-

Up to 95°C./12 m.m.	mainly methyl-malonic ester.
95° - 120°C./12 m.m.	Methyl malonic ester and some acetyl-methyl-malonic ester.

120° - 134°C./12 m.m. 52 gm. acetyl-methyl-malonic ester.

On redistillation of (2) a fraction b.p. 93° - 95°C./12 m.m. was obtained followed by a rapid rise in temperature to 118° and another fraction b.p. 118° - 125°C./12 m.m. - 18 gm. so recovered were added to (3).

Redistillation of (4) gave 5 gm. of a fraction b.p. 129° - 132°C./12 m.m. This was added to (3).

Total yield:- 75 gm. i.e. 33% theoretical.

IV. PREPARATION OF BROMACETIC ESTER.

90 gm. of glacial acetic acid with 11·7 gm. of red phosphorus were placed in a flask fitted with a condenser and dropping funnel. Reaction was carried out in a fume cupboard as bromacetic ester is a tear-gas. A tube from the condenser was led into a flask containing water so that the end of the tube was just above the surface of the water. 150 gm. of bromine were added slowly from the tap-funnel, the flask being agitated and cooled in a stream of water. It was then warmed on a water bath at 60° - 65°C. while a further 255 gm. of bromine were added. When all the bromine was added the flask was heated on a boiling water bath till no more hydrogen bromide was evolved. After cooling in ice water, 105 gm. of alcohol were added in small portions with constant stirring. 18 gm. of sulphuric acid were then added and the flask heated on a boiling water bath for 2 hours. At the end of this time the flask was again cooled, and the reaction product poured into cold water. The oily layer was separated, washed three times with water, dried over anhydrous calcium chloride, and distilled. The fraction boiling at 167° - 168°C./760 m.m. was taken as pure ester.

Yield:- 153 gm. 61% of theory.

V. THE CONDENSATION OF ACETYL-METHYL-MALONIC ESTER AND BROMACETIC ESTER BY THE REFORMATSKY REACTION TO GIVE ETHYL α-CARBETHOXY - $\alpha\beta$ - DIMETHYL - β - HYDROXY-GLUTARATE.

9·7 gm. of clean, dry magnesium turnings were placed in a litre flask, fitted with a double surface condenser, and 80 c. c. of sodium dried benzene added; then 75 gm. of acetyl-methyl-malonic ester (10% excess of theoretical) and 54 gm. of bromacetic ester were added. The measuring cylinder was rinsed out with 30 c.c. of benzene and the rest of the benzene (30 c.c.) added. The flask was heated for a quarter of an hour on a steam bath till reaction began, and as it became violent the flask was cooled in ice water. When most of the magnesium had disappeared, it was heated on the steam bath for a further twenty minutes, at the end of which time reaction was complete. The flask was removed from the water bath, cooled in ice water, ice added, and 200 c.c. of ice-cold 25% sulphuric acid added a little at a time with constant shaking, till all the solid product of the reaction had dissolved. The benzene layer was separated, washed twice with 25% sulphuric acid and twice with water. The next washing with 10% caustic soda solution formed an emulsion which had to be broken down with ether. The aqueous layer was separated and twice extracted with ether, the ethereal layer being returned to the benzene solution. Washing with caustic soda was repeated, followed by four washings with water. The first washings with water formed an emulsion and so the aqueous layer was ether extracted as before, and the extracts were returned to the benzene solution.

The benzene-ether solution was dried over anhydrous sodium sulphate for a day, filtered, and the ether and benzene distilled off under reduced pressure. The resultant liquid was transferred to a small Kon flask and distilled under reduced pressure.

First Fraction:	40° - 80°C./12 m.m.	very little.
Second Fraction:	80° - 125°C./ 12 m.m.	large portion mainly methyl-malonic ester.
Third Fraction.	125 - 145°C./12 m.m.	
mainly at:	140° - 145°C./12 m.m.	the required product.

Redistillation of Second Fraction.

First Fraction up to	90°C./12 m.m.	methyl malonic ester.
Second Fraction:	(slow rise to 125°C./12m.m.)	very little.
Third Fraction:	130° - 140°C./12 m.m.	small fraction of hydroxy-ester.

Yield:- 22 gm. (21% of theoretical).

VI. THE ATTEMPTED DEHYDRATION OF ETHYL α-CARBETHOXY - $\alpha\beta$ - DIMETHYL- β -HYDROXY-GLUTARATE.

(a) With phosphorus oxychloride in benzene.

To 22 gm. of hydroxy ester dissolved in 40 c.c. of benzene were added 15 c.c. of phosphorus oxychloride, and the whole was refluxed on a boiling water bath for three quarters of an hour in a 250 c.c. flask with a reflux condenser fitted with a ground-glass joint. When cold, the benzene solution was poured into 150 c.c. of cold water, separated, and washed twice with water, the washings being ether extracted and ether extracts added to the benzene solution. It was then washed twice with 10% caustic soda solution and the aqueous layer extracted with ether as before. The ether extracts were added to the main benzene solution and the whole washed four times with water. The first washing had also to be ether extracted.

The ether and benzene were removed under reduced pressure and on distillation from a 100 c.c. Kon flask the product yielded only one main fraction, b.p. 135° - 141°C./13 m.m. mainly at 140°C./13 m.m.

Recovered hydroxy ester 16 gm.

(b) With phosphorus oxychloride in Toluene.

12 gm. of redistilled hydroxy ester from (a), in 20 c.c. of dry toluene were refluxed with 8 c.c. of phosphorus oxychloride for three quarters of an hour. The solution became dark coloured and some HCl fumes were evolved. The toluene solution was poured into cold water, separated, washed twice with water and twice with 10% caustic soda solution. Emulsions formed were broken down by extraction with ether as described previously, the ether extracts

being added to the main toluene solution. This solution was washed three times with water and distilled under reduced pressure. Most of the ether was removed first and the toluene distilled off below 30°C./24 m.m. Only one other fraction was obtained, b.p. 143° - 146°C./17 m.m. (bath 160°): Yield 8 gm. This still consisted mainly of the hydroxy-ester, but as it was thought to contain some ethyl α-carbethoxy-$\alpha\beta$-dimethyl-glutaconate, it was treated with cold alcoholic sodium ethoxide, as described in VII below. The still undehydrated hydroxy ester recovered after this treatment with sodium ethoxide was used in the following attempted dehydrations.

(c) By distillation from anhydrous zinc chloride.

1 c.c. of hydroxy ester was distilled from $\frac{1}{2}$ gm. of anhydrous zinc chloride in a 5 c.c. Claisen flask. Only about half the ester distilled and this came over at 134° - 136°/14m.m. but no reliance can be placed on these figures as the rate of distillation was irregular. A brown tarry residue remained in the flask and no further distillate could be obtained from it. The product, referred to as ester (B) in the theoretical section, was hydrolysed as described in IX below.

(d) Phosphorus pentoxide in toluene.

3 gm. of the hydroxy ester, dissolved in 10 c.c. of dry toluene were refluxed for three quarters of an hour with ·7 gm. of phosphorus pentoxide. The resultant liquid was poured into cold water, separated, washed twice with water, twice with 10% caustic soda and finally three times with water. Emulsions formed were broken down with ether. Ether and toluene were

removed under reduced pressure and the resultant liquid distilled at 139° - 140°C./14 m.m. Recovered 2 gm. No dehydration had apparently occurred.

(e) By treatment with anhydrous potassium bisulphate.

1·8 gm. of hydroxy ester recovered in (d), and 3·5 gm. of potassium bisulphate freshly crushed in a mortar, were heated in a glycerine bath for 3 hours, at 170° - 180°C. Water was then added and the ester extracted with ether. After removal of the ether under reduced pressure, the unchanged ester distilled at 140°C./13 m.m. Recovered 1·7 gm. Dehydration had apparently not occurred.

(f) With excess phosphorus oxychloride in toluene.

1·7 gm. of hydroxy ester dissolved in 10 c.c. of dry toluene were refluxed with 10 c.c. of phosphorus oxychloride for 2½ hours. The cold solution was poured into water separated, washed twice with water and twice with 10% caustic soda. The aqueous and alkaline washings were extracted with ether, and the ether extracts added to the main solution, which was then washed three times with water. The first washing had also to be extracted with ether. The ether-toluene solution was dried over anhydrous sodium sulphate. The ether and most of toluene were distilled off at atmospheric pressure and the residual liquid transferred to a small Claisen flask. The major portion of the liquid distilled between 20° - 40°C./14 m.m. and consisted mostly of toluene. A few drops of liquid were collected at a higher temperature but there was insufficient to purify or treat further. The whole of the hydroxy ester had been destroyed.

VII. TREATMENT OF SUPPOSED MIXTURE (from VI b, above) OF ETHYL α-CARBETHOXY-$\alpha\beta$-DIMETHYL-β-HYDROXY GLUTARATE AND ETHYL α-CARBETHOXY-$\alpha\beta$-DIMETHYL-GLUTACONATE WITH COLD SODIUM ETHOXIDE TO CONVERT THE LATTER ESTER INTO ETHYL $\alpha\beta$-DIMETHYL-GLUTACONATE.

7·7 gm. of ester in 5 c.c. of absolute alcohol were added to a cold solution of ·6 gm. of sodium in 7·5 c.c. of absolute alcohol. A yellow colouration was produced and the solution was allowed to stand for 1 hour at room temperature. It was poured into cold water (70 c.c.) and extracted three times with ether. Then the aqueous solution was made just acid with dilute HC and again ether extracted. The ethereal solution was dried over anhydrous sodium sulphate over night.

After filtering off the sodium sulphate, the ether was removed under atmospheric pressure and a small fraction obtained between 60° - 120°C./760 m.m., which consisted mainly of ethyl carbonate. Distillation under reduced pressure yielded two fractions:-

First Fraction, ester (A)	120° - 122°C./14 m.m. (bath 140°C.)	1·5 gm
Second Fraction	141° - 143°C./14 m.m. (bath 160°C.)	3·8 gm

The first fraction, ester (A) of the theoretical section, thought to be ethyl $\alpha\beta$-dimethyl-glutaconate was hydrolysed under VIII below.

The second fraction consisted of unchanged hydroxy ester and was used in dehydration experiments described under VI (c), (d), (e), (f).

VIII. HYDROLYSIS OF ESTER (A) TO ACID (C).

1·5 gm. of ester (A) from VII were hydrolysed by boiling with 15 c.c. of 5N. HCl for 8 hours. The resulting solution was evaporated down in a vacuum desiccator, and after standing a day, crystals separated. These were dissolved in ether and recrystallised twice from ether by the addition of petrol-ether (b.p. 40° - 60°C.) This was found to be the best method, as from ether alone the acid tended to separate out as an oil. The crystals were dried in a desiccator. Yield ·14 gm. m.p. 109°C. A mixed melting point with authentic $\alpha\beta$-dimethyl-glutaconic acid (m.p. 118° - 119°C.) previously boiled with 5N. HCl for 3 hours, gave m.p. 89 - 91°C.

The product of hydrolysis was therefore not $\alpha\beta$-dimethyl-glutaconic acid and for purposes of reference is called (C).

IX. HYDROLYSIS OF ESTER (B) TO ACID (D).

The ester, obtained from VI C, was hydrolysed by boiling with 10 times its volume of 5N. HCl for 4 hours. The solution was evaporated down and the oil which separated, crystallised on standing. The crystals were drained on a porous tile and the acid recrystallised from ether-petrol-ether mixture, m.p. 108·5 - 109°C.

A mixed melting point determination with acid (C) gave m.p. 108° - 108·5°C., thus establishing the identity of acids (C) and (D).

X. DETERMINATION OF THE EQUIVALENT WEIGHT OF ACID (D) BY TITRATION WITH ALKALI.

An approximately 1/50 N. caustic soda solution was made up and standardised against succinic acid, using phenolphthalein as an indicator. Acid (D) was titrated with this, using phenolphthalein as an indicator. On account of the small quantities a micro-burette was used.

7·67 c.c. of ·0196 N. NaOH neutralised ·0109 gm. of acid (D)

1000 c.c. of 1 N. NaOH require $\frac{\cdot 0109}{1} \times \frac{1000}{7 \cdot 67} \times \frac{1}{\cdot 0196}$

= 72·5 gm. of acid (D)

Equivalent weight of acid (D) = 72·5

Equivalent weight of the tribasic α-carboxyl-$\alpha\beta$-dimethyl-hydroxy-glutaric acid is 73·3.