THESIS

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THE METHYLATION OF $\alpha$-$\beta$-DIETHYLGLUTARIC ESTER

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CODENWOD: APOSTLE.
SYNOPSIS

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THEORETICAL SECTION.

For a considerable number of years the glutaronic acids and their derivatives have been the subject of much discussion and not a little controversy. The interest attaching to these substances lies in the fact that they exhibit geometrical isomerism together with tautomeric mobility which is associated with the three carbon system and activated by two terminal carboxyl groups.

On the one hand Feist considered that all the properties of these compounds could be completely explained on the basis of a simple geometrical isomerism of the maleic acid - fumaric acid type, while on the other hand, Thorpe postulated a "normal" or symmetrical structure to account for the properties of certain derivatives of glutaric acid, and he subsequently applied it to all the glutaric compounds.

At this point it may be of interest to outline the "normal" theory and to give Thorpe's principal reasons for its introduction. In order to account for two peculiar properties of glutaric acid itself, namely, the identity of the α and γ positions and the occurrence of the acid in one form only, Perkin and Tattersall (J.C.S. 1903, 87, 361) suggested that the structure of the molecule might be represented by some such configuration as the following:

\[
\text{CO}_2\text{H} - \text{C} = \text{C} - \text{C} - \text{CO}_2\text{H} \quad (1)
\]

\[
\text{H} \quad \text{H} \quad \text{H}
\]
which was regarded as a stable structure. Later, Thorpe and other workers assigned this configuration to the stable modifications of all the alkyl glutaconic acids which possessed a mobile hydrogen atom (H). There was no doubt that those substituted acids which contained two alkyl groups on the carbon atom, were capable of existence in well defined cis- and trans- forms. The ease of dehydration of most "normal" forms was accounted for by assigning to them a cis- "normal" configuration.

Recently however, experimental evidence has been accumulating which makes it necessary to abandon the "normal" theory. Malachowski, (Ber., 1929, 62, 13, 1323; J.C.S. Abstracts, 1929, 794) has been able to prepare the second or cis- form of glutaconic acid. McGombs, Packer and Thorpe, (J.C.S. 1931, 134, 549.) have resolved "normal" or trans- \( \alpha \gamma \) - dimethyl-glutaconic acid into optically active forms. If the "normal" theory is postulated for glutaconic acid and its symmetrically substituted derivatives, it would be expected that such compounds would possess a plane of symmetry and would be incapable of resolution into optically active enantiomorphs. Moreover, Thorpe himself, (Presidential Address, J.C.S. 1931, 134, 1014) says, "If one accepts the modern view that tautomeric change is due to ionisation then it follows that the cis- and the trans- forms of a mobile glutaconic acid have the same ion and rapid interchange between the two forms can be readily understood. It would appear therefore that the "normal"
form as such has no existence, though it may occur as the common ion."

The position of the "normal" theory at the present time having thus been stated, it is now necessary to determine its bearing upon the results of the present research. Bland and Thorpe (J.C.S. 1912, 101, 1557.) described a new method for the preparation of the esters of the "labile" glutaronic acids. It consisted in the hydrolysis and methylation of ethyl isodehydracetae with sodium ethoxide and methyl iodide to form "labile" ethyl $\alpha\beta$ - dimethylglutaconate which was formulated as,

$$\begin{align*}
\text{CO}_2\text{Et} & \rightarrow \text{C} = \text{C} \rightarrow \text{CH}_2 \rightarrow \text{CO}_2\text{Et}, \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}$$

(2)

Thorpe and Wood, (J.C.S. 1913, 103, 1759.) described the methylation of "labile" ethyl $\alpha\beta$ - dimethylglutaconate in the presence of sodium ethoxide and methyl iodide, to form ethyl $\alpha\beta\gamma$ - trimethylglutaconate and the reaction was "complete at the end of three hours at the temperature of running water". The ester was converted into $\alpha\beta\gamma$ - trimethylglutaconic acid (m.p. 127° C.), on hydrolysis, the conditions of which, however, were not given. This was remarkable as Feist and Beyer had stated previously (Ann. 1906, 345, 117.) that they could not introduce a methyl group into the molecule.
\[ \text{CO}_2\text{Et} - \text{CH} - \text{C} = \text{CH} - \text{CO}_2\text{Et} \quad \text{or} \quad \text{CO}_2\text{Et} - \text{C} = \text{C} - \text{CH}_2 - \text{CO}_2\text{Et} \]
\[ \text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3 \]

with the aid of Sodium ethoxide and methyl iodide. The observations of Feist and Beyer were confirmed in these laboratories by Packer (work unpublished) who, following very carefully the instructions given by Thorpe and Wood (loc. cit.) was unable to isolate any trimethyl derivative from repeated attempts to methylate ethyl \( \alpha \beta \) - dimethylglutaconate in the presence of sodium ethoxide and methyl iodide. The same worker then tried the methylation under a variety of conditions viz., with methyl iodide and (i) dispersed sodium in benzene and ether; (ii) alcoholic sodium ethoxide under increased pressure, (10 atmos.); (iii) with dimethyl sulphate in ethyl alcohol; (iv) with methyl alcohol substituted for ethyl alcohol in Thorpe's method. In each case, \( \alpha \beta \) - dimethylglutaconic acid was the only product isolated by hydrolysis of the resultant ester.

Finally, however, a successful means of methylation was discovered, consisting in the isolation of the sodio-derivative of ethyl \( \alpha \beta \) - dimethylglutaconate followed by treatment with methyl iodide.

The present investigation was undertaken with the object of determining the course of the methylation and in the hope of preparing \( \alpha \beta \gamma \) - trimethylglutaconic acid by this means. Briefly the procedure was as follows. Finely dispersed sodium was suspended in dry ether and the equivalent quantity of \( \alpha \beta \) - ester dissolved in ether was added. The reaction did not always
commence immediately but when once started became very vigorous and the orange yellow sodio - derivative of ethyl $\alpha\beta$ - dimethylglutaconate separated. When all the sodium had apparently dissolved, methyl iodide was added and the contents of the flask became quite hot followed by the separation of sodium iodide. On several occasions when the methylation was being carried out it was noticed that bubbles of gas were evolved. The gas was presumably ethane formed by interaction between the methyl iodide and tiny particles of sodium on which the ester had been unable to act.

There are two possible products of this methylation and the nature of the product will depend upon the particular structure of the parent dimethyl ester, according to the scheme given on Page 6.

From the structure (3) which Thorpe assigned to labile ethyl $\alpha\beta$ - dimethylglutaconate, one would expect the product of methylation to be ethyl $\alpha\beta\gamma$ - trimethylglutaconate (5) whereas the ester (4) should yield ethyl $\alpha\kappa\beta$ - trimethylglutaconate (6).

The trimethylglutaconic ester was hydrolysed by two methods,

(i) 10% hydrochloric acid,
(ii) 20% potassium hydroxide

and the products are described separately below.

(i) Acid hydrolysis - yielded a substance melting at 96° – 100° C. on recrystallisation from water. The combustion figures were those for the trimethylglutaconic acid so that any unchanged
THE METHYLATION OF αβ - DIMETHYLGLUTAMIC ESTER

(4) \( \text{CO}_2\text{Et} - C - C = C - \text{CO}_2\text{Et} \rightleftharpoons \text{CO}_2\text{Et} - C - C - \text{CO}_2\text{Et} \)

\( \Delta \) form cis - or trans - \( \text{Normal form} \)

(5) \( \text{CO}_2\text{Et} - C - C = C - \text{CO}_2\text{Et} \)

\( \Delta \) form cis - or trans -

(6) \( \text{CO}_2\text{Et} - C - C = C - \text{CO}_2\text{Et} \)

ααβ - ester cis - or trans -

αβγ - ester cis - or trans -
dimethyl ester must have been eliminated during refractionation. Recrystallisation from various solvents, e.g., benzene, ether, mixtures of ether and petrol ether, caused partial separation of the original acid into two components one of which melted at 120°-130° C, and the other at 100° - 107° C. It was concluded from the preliminary experiments that the product of acid hydrolysis was a mixture of acids. The yield of crystalline product by the original method was less than 10% of the theoretical due undoubtedly to volatility of the acid or its anhydride during concentration of the product at 100° C. (See Experimental Section page 22 and compare Linstead and Mann J.C.S. 1931, 134, 726 - 727.) However this fact was not discovered until the bulk of the trimethyl ester had been hydrolysed using that method with the result that the work had to be continued with a considerably smaller amount of acid than originally anticipated and for that reason it was impossible to carry out a successful fractional crystallisation of the mixture although partial separation could be effected as stated above.

When the trimethylglutaconic ester was hydrolysed with hydrochloric acid, viscous brown globules of material separated in the cold at the bottom of the flask. This substance was assumed to be anhydride but all attempts to crystallise it as such were unsuccessful and when left to stand for some days in dilute hydrochloric acid it crystallised to give a trimethyl acid verified by analysis and melting at 96° - 98° C.

It was thought that some evidence for the constitution of the product of hydrolysis would be offered by anhydride formation as the anhydride of \( \text{cis} - \alpha \alpha \beta \) - trimethylglutaconic acid melts
at 107° C. (Perkin and Thorpe J.C.S. 1897, 71, 1185.) while the hydroxy-anhydride of $\alpha\beta\gamma$-trimethylglutaconic acid melts at 119° C. (Rogerson and Thorpe, J.C.S., 1905, 87, 1705; Thole and Thorpe, J.C.S. 1911, 99, 2221.) and has the peculiar properties associated with the mobile hydrogen atom. The method originally used for the preparation of the anhydride was that described for $\alpha\beta\gamma$-trimethylglutaconic acid by Thole and Thorpe (loc. cit.). Using redistilled acetyl chloride, the product distilled at 140° C./16 mm. (approx.) and gave a 6-7% yield. By adding 5% of phosphorus trichloride to the acetyl chloride the yield was increased to 50% of the theoretical (c.f. Thole and Thorpe loc. cit. p. 2216.). On recrystallisation from ether the product remained as glistening plates, m.p. 106° - 107° C. Found C. = 62.2 H = 6.71; 

$\text{C}_8\text{H}_{10}\text{O}_3$ requires 

C. = 62.3 H = 6.5 per cent.)

The anhydride showed none of the properties associated with the mobile hydrogen atom, e.g. coloration with $\text{FeCl}_3$ and was therefore obviously not the hydroxy-anhydride of $\alpha\beta\gamma$-trimethylglutaconic acid while the melting point and combustion figures prove that it must be the anhydride of $\text{Gle} - \alpha\alpha\beta - \text{trimethylglutaconic acid}.$

\[
\begin{array}{ccc}
\text{CH} & \text{C} & \text{O} \\
\text{CHMe} & \text{CMe}_2 & \text{O} \\
\end{array}
\]

\((7)\)

It is remarkable however that an attempt to hydrate the above
anhydride to cis-\(\alpha\alpha\beta\) - trimethylglutaconic acid by the method of Perkin and Thorpe (J.C.S. 1897, 71, 1186) yielded a mixture of acids m.p. 82° - 92° C, which was obviously not the pure cis - acid anticipated. The quantity was insufficient for isolation of the pure cis - form by recrystallisation.

(ii) Alkaline hydrolysis gave two products.

(a) from the part of the ester which was easily hydrolysed.

This was gummy and resisted attempts at crystallisation.

(b) from the part of the ester which was difficult to hydrolyse. This crystallised easily from the ester extract and after recrystallisation from water melted at 147° - 148° C. (Found C 56.11, H = 7.34; \(\text{C}_8\text{H}_{12}\text{O}_4\) requires C 55.8, H = 7.04 per cent.)

This was trans-\(\alpha\alpha\beta\) - trimethylglutaconic acid, identified by a mixed melting point with a specimen prepared by a method which leaves no doubt as to the constitution of the final product.

(Perkin and Thorpe J.C.S. 1897, 71, 1182, 1) This method consisted essentially in the condensation of dimethylacetoacetic ester with bromoacetic ester in the presence of magnesium, to form ethyl \(\beta\) - hydroxy \(\alpha\alpha\beta\) - trimethylglutarate,

\[
\text{Me} \quad \text{Me} \quad \text{H} \\
\text{CO}_2\text{Et} - \text{C} - \text{C} - \text{C} - \text{CO}_2\text{Et} \\
\text{Me} \quad \text{OH} \quad \text{H}
\]

which on hydrolysis with concentrated hydrochloric acid, eliminated a molecule of water and yielded on recrystallisation from
water pure trans - ααβ - trimethylglutaconic acid. m.p. 148° C. The condensation did not proceed as vigorously as described by Perkin and Thorpe (loc. cit.). In fact heating on the steam bath for a considerable length of time was necessary in order to obtain a sufficient yield of product to work with, and the addition of a crystal of iodine did not accelerate the action although this substance will usually catalyse a Reformatsky reaction.

According to Rogerson and Thorpe, (J.C.S. 1906, 87, 1672.) distillation of the ammonium salt of αβγ - trimethylglutaconic acid yields 3:4:5: trimethyl 2:6 dihydroxy-pyridine by the following reaction:-

\[\text{Me} \quad \text{Me} \quad \text{Me} \]
\[\text{Me}_2\text{C} \quad \text{C}_2\text{HMe} \quad \text{C}_2\text{H}\]
\[\text{CO}_2\text{H} \quad \text{CO}_2\text{H} \quad \rightarrow \]
\[\text{Me} \quad \text{Me} \quad \text{Me} \]
\[\text{Me}_2\text{C} \quad \text{C}_2\text{HMe} \quad \text{C}_2\text{H}\]
\[\text{CO} \quad \text{CO} \quad \rightarrow \]
\[\text{NH} \quad \text{HO}_2\text{C} \quad \text{N} \]
\[\text{CHMe} \quad \text{CMe} \quad \text{OH} \]

whereas ααβ - trimethylglutaconic acid only gives the imide

\[\text{Me} \quad \text{Me} \quad \text{Me} \]
\[\text{CHMe}_2 \quad \text{CH} \quad \text{CH}\]
\[\text{CO}_2\text{H} \quad \text{CO}_2\text{H} \quad \rightarrow \]
\[\text{Me}_2\text{C} \quad \text{C}_2\text{HMe} \quad \text{C}_2\text{H}\]
\[\text{CO} \quad \text{CO} \quad \rightarrow \]
\[\text{Me}_2\text{C} \quad \text{C}_2\text{HMe} \quad \text{C}_2\text{H}\]
\[\text{CO} \quad \text{CO} \quad \rightarrow \]
\[\text{NH} \quad \text{HO}_2\text{C} \quad \text{N} \]
\[\text{M} \quad \text{N} \quad \text{OH}\]

because in this case the necessary mobile hydrogen atom (\(\text{H}^\ast\)) is absent.
The product of acid hydrolysis (m.p. 90°–93° C) was converted into its ammonium salt and distilled under reduced pressure. Considerable decomposition took place and the bulk of the distillate came over at 81°–82° C/500 mm. and consisted of a blue compound which was greenish blue in aqueous solution and dark green in alcoholic solution both being changed to a bright yellow on the addition of dilute hydrochloric acid. The final portion of the distillate, 125° C/500 – mm. – 125° C/30 mm. consisted of a small amount of yellow substance which was not further investigated. The absence of 3:4:5 trimethyl 2:6 dihydroxypyridine indicated that the amount of \( \alpha\beta\gamma \) - trimethylglutaconic acid, if any, in the mixture was exceedingly small.

The formation of the blue compound was interesting, for Rogerson and Thorpe (loc. cit. page 1697) state that the pyridine derivative of \( \alpha\beta \) - dimethylglutaconic acid forms with phthalic anhydride, phthaleins which possess intense blue colorations. Although there is no evidence for assigning any particular constitution to the above substance, it is suggested that it may have been formed by condensation between the pyridine derivative formed from any \( \alpha\beta \) - dimethylglutaconic acid present and the anhydride of \( \alpha\alpha\beta \) - trimethylglutaconic acid which would be present during the distillation, by analogy with compounds of the succinyl-fluorescein type. In such reactions the amount of any one of the reactants present, may be very small and still yield the coloured product.

Finally, an attempt was made to prepare \( \alpha\beta\gamma \) - trimethylglutaconic acid by the original method of Rogerson and Thorpe
(J.C.S. 1905, 87, 1699, 1703,) which consisted in the condensation of methylacetocetic ester with cyanacetic ester in the presence of sodium ethoxide, the resulting sodium-derivative being methylated without the separation and distillation of the dimethylglutaconic ester. The first part of the reactions proceeded readily but the introduction of a methyl group into the product with the aid of methyl iodide could not be carried out. Korn and Nanji (J.C.S. 1931, 134, 560) have been able to improve the yield of condensation product by various methods, chiefly by using potassium instead of sodium but they did not attempt further methylation of the condensation product to form ethyl $\alpha$-cyano-$\alpha\beta\gamma$-trimethylglutaconate. However at the time the present work was under taken these methods had not been published and the matter was not further investigated. The ester obtained was hydrolysed and yielded only $\alpha\beta$-dimethylglutaconic acid together with the corresponding pyridine derivative.

Further light was thrown on the constitution of the product of methylation of ethyl $\alpha\beta$-dimethylglutaconate by oxidation with neutral potassium permanganate though the results are inconclusive.

The possible products of oxidation are:
The only product which was isolated was dimethylacetoacetic ester while none of the distinctive colour reactions for ethyl pyruvate were observed which results support the view that the ester formed on methylation has the structure (8) and contains no appreciable quantity of (9).

Further, if the product of methylation were $\alpha\beta\gamma$ - trimethylglutaric acid, with the structure (9) the molecule of the resulting $\alpha\beta\gamma$ - trimethyl - acid would possess an asymmetric carbon atom, and theoretically should be capable
of resolution into optically active forms. Another worker in this laboratory (M.Sc. thesis, 1931.) made attempts to effect resolution through various alkaloid salts, but obtained only negative results. In order to account for the isolation of both the anhydride and the trans - form of the acid, it is necessary to postulate that the ester formed on the methylation of ethyl αβ - dimethylglutaconate is a mixture of s _i _s - and trans - forms, as outlined in the scheme on page 6.

The product of methylation has thus been shown to be ethyl αβ - trimethylglutaconate (s _i _s - and trans - forms) and in order to explain why the third methyl group enters on the α - rather than on the γ - carbon atom, it is necessary to postulate that ethyl αβ - dimethylglutaconate reacts in the following form (10) under the conditions employed.

\[
\begin{align*}
\text{(10) } \text{CO}_2\text{Et} - C \xrightleftharpoons{\text{Me}} - C \xrightleftharpoons{\text{Me}} - \text{CO}_2\text{Et} & \rightarrow \text{CO}_2\text{Et} - C \xrightleftharpoons{\text{Me}} - C \xrightleftharpoons{\text{Me}} - \text{CO}_2\text{Et} \\
\Delta^2,3 \text{ form} & \rightarrow \Delta^1,2 \text{ form}
\end{align*}
\]

On the other hand, Thorpe stated that he was able to methylate it by means of sodium ethoxide and methyl iodide to ethyl αβγ - trimethylglutaconate, from which fact one is lead to assign to it the \( \Delta^1,2 \) structure (11).

Thus it seems probable that ethyl αβ - dimethylglutaconate as ordinarily prepared, is a mixture of the \( \Delta^1,2 \) and \( \Delta^2,3 \) forms, and that equilibrium between these forms is readily established in the presence of polar catalysts. (c.f. Hugh and
Kon J.C.S. 1930, 133, 775) These conclusions are in accord with the recent work of Kon and Nanji (J.C.S. 1931, 134, 560.) who have shown that the cyanoglutaconic esters react in the two forms,

\[
CO_2Et - CH - C = CH - CO_2Et \quad (\alpha \beta)
\]

\[
CO_2Et - CH - C = CH - CO_2Et \quad (\beta \gamma)
\]

which are interconvertible in the presence of suitable catalysts forming equilibrium mixtures, notably when they are liberated from their sodio-derivatives by water or acid.
SUMMARY.

(a) A new method for the methylation of ethyl $\alpha\beta$-dimethylglutaconate is described.

(b) The product was ethyl $\alpha\alpha\beta$-trimethylglutaconate, as shown by oxidation, and was converted into a mixture of cis- and trans-$\alpha\alpha\beta$-trimethylglutaconic acids on hydrolysis.

(c) The cis-acid was converted into its anhydride and identified by that means.

(d) The trans-acid was identified by analysis, melting point, and by direct comparison with a sample of trans-$\alpha\alpha\beta$-trimethylglutaconic acid prepared by the method of Perkin and Thorpe.

(e) Under the conditions employed, the amount of $\alpha\beta\gamma$-trimethylglutaconic acid in the mixture was negligible.

(f) An attempt to prepare $\alpha\beta\gamma$-trimethylglutaconic acid by the method of Rogerson and Thorpe yielded only $\alpha\beta$-dimethylglutaconic acid and 4:5 dimethyl-2:6-dihydroxypyridine.

(g) An explanation of the course of methylation is put forward on the basis of the present theory of tautomeric mobility in the glutaconic system.
PART 1.

Purification etc. of Chemicals Used.

(a) **Alcohol** Merck's good "absolute alcohol" was refluxed over fresh quicklime for 12 - 14 hours and then distilled from metallic calcium directly before use. Any sample giving a colour with permanganate was rejected.

(b) **Ether** Hopkin and Williams' "technical" product, (e.g., 730) was stood over caustic soda sticks, distilled, and kept over sodium wire.

(c) **Acetoacetic ester.** Hopkin and Williams' distilled reagent was fractionated under reduced pressure and the portion distilling at 76° - 78°/20 mm. was taken as pure.

(d) **Cyanoacetic ester.** B. D. H. product was distilled under reduced pressure and the pure ester came over at 102°/21 mm., the first and last fractions being rejected.

(e) **Xylene.** This was B. D. H. redistilled product and was kept over sodium wire.

(f) **Methyl Iodide.** This was prepared by the usual method from methyl alcohol, red phosphorus and iodine. The product distilled at 44°C/760 mm. and was stored in a dark tightly stoppered bottle away from light.
PART II.

\( \alpha \beta \) - TRIMETHYLGLUTARIC ACID - ITS PREPARATION BY THE
METHYLATION OF \( \alpha \beta \) - DIMETHYLGLUTARIC ESTER AND THE PRE-
PARATION OF SOME OF ITS DERIVATIVES.

A. THE PREPARATION OF \( \alpha \beta \) - DIMETHYLGLUTARIC ESTER.

(a) Preparation of iso-dehydracetic ester.

(Coss, Ingold and Thorpe, J.C.S. 1923, 123, 348)

Acetoacetic ester (2000 g, Hopkin and Williams' redistilled product) was cooled in an efficient freezing mixture at \(-16^\circ\text{C}\) and treated for \(7\) - 8 hours with a rapid stream of dry hydrogen chloride. The liquid which had turned red was protected from moisture by means of a CaCl₂ tube, and stored in a dark place for one week. Dry hydrogen chloride was again passed rapidly through the liquid as before for about 8 hours when it was left for a further week away from the light. The product was then divided into two equal portions and each washed with one litre of distilled water followed by 500 c.c. of a N solution of sodium carbonate. The aqueous washings were evaporated to an oil on the water bath, washed out of the evaporating basin with a little ether and stood 24 hours in a vacuum desiccator over potash. The sodium carbonate washings were acidified with dilute hydrochloric acid and extracted with ether. This extract, together with the acid-free residue from the aqueous washings was added to the washed ester dissolved in 500 c.c. of ether, and the whole stood over anhydrous sodium sulphate. The ether was removed at atmospheric
pressure and the residual ester distilled under reduced pressure, the following fractions being collected:

(i) up to $70^\circ/40$ mm., 30 c.c. dark red liquid - pungent smell.

(ii) $70^\circ/40$ mm. - $120^\circ/30$ mm, 35 c.c. mainly unchanged acetoacetic ester.

(iii) $120^\circ/30$ mm. - $160^\circ/20$ mm. mixture of esters.

(iv) $160^\circ/20$ mm. - $180^\circ/20$ mm. main product 910 g.

On refractionation, ethyl isodehydracetate was obtained as a heavy yellow oil b.p. $160^\circ/20$ mm. - $180^\circ/20$ mm.

Yield 950 g. = 63% of theory.

(b) Preparation of "labile" ethyl $\alpha\beta$ - dimethylglutaconate.

Ethyl isodehydracetate (300 g.) in absolute ethyl alcohol (300 g.) was added slowly through a double surface condenser to an ice-cold solution of sodium ethoxide formed by dissolving sodium (36 g.) in absolute alcohol (413 g.). Methyl iodide was poured in and the mixture stood at 5$^\circ$C. for 2 hours and after a considerable time sodium iodide began to separate out. The mixture was then heated on the water bath for one hour. The ester was separated by pouring into water and extracting with ether. On distillation under reduced pressure the following fractions were collected:
(i) 128°/31 mm. - 133°/29 mm. Red in colour, changed to dirty brown in receiver.

(ii) 132°/20 mm. - 136°/19 mm. Lighter in colour than (i) - main fraction.

(iii) Residue, small and tarry.

On fractionation of the products labile ethyl $\alpha\beta$-dimethylglutaconate came over as a colourless mobile oil, b.p. 130° - 134°/18 mm.

Yield ex. 950 g. ethyl isodehydracetate, 646 g. = 68% of theory.

B. METHYLATION OF ETHYL $\alpha\beta$-DIMETHYLGLUTACONATE TO ETHYL $\alpha\alpha\beta$-TRIMETHYLGLUTACONATE.

Sodium (5.75 g.) was finely dispersed under boiling xylene (100 c.c.). It was found necessary to repeat the dispersion if any large globules were present, for fineness of grain appeared to be an important factor in ensuring complete solution of the sodium in the ester. The ester (53.5 g.), dissolved in an equal volume of dry ether was added gradually and the reaction controlled if necessary by cooling with water. Frequent shaking was necessary in order to prevent the sodium-derivative from setting to a hard mass in the bottom of the flask and surrounding small particles of undissolved sodium. When solution was complete, the sodium-derivative formed a viscous orange-yellow mass. The flask was stood in warm water for some time and then 15 c.c. of methyl iodide were added in two portions. Vigorous reaction with copious
precipitation of sodium iodide set in after about 10 minutes. Excess methyl iodide was added and the flask transferred to the water bath for 3/4 hour until the contents of the flask were neutral to litmus. The product was then poured into water, extracted twice with ether, washed with water, sodium thiosulphate water, sodium carbonate, water and finally dried over anhydrous sodium sulphate. After removal of the ether at atmospheric pressure, the residue was distilled under reduced pressure.

The following fractions were collected:

(i) up to 60°/17 mm. vapour which did not all condense - mainly ether.
(ii) 60°/17 mm. 136°/16 mm. 5 c.c. red liquid.
(iii) 126°/19 mm. 136°/19 mm. main fraction.

After refractionation ethyl \(\alpha\)-trimethylglutaconate distilled as a colourless oil at 136°/20 mm. - 138.5°/20 mm.

\[1.044 \text{ g. gave} \quad 0.9715 \text{ g. H}_2\text{O} \quad 0.3409 \text{ g. CO}_2\]

\[H = 8.73\% \quad C = 62.94\%\]

\[\text{C}_2\text{H}_2\text{O}_4 \text{ requires} \quad H = 8.8\% \quad C = 63.16\%\]

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**C. HYDROLYSIS OF ETHYL \(\alpha\)-TRIMETHYLGLUTACONATE TO \(\alpha\)-TRIMETHYLGLUTACONIC ACID.**

(a) Acid hydrolysis. The ester was hydrolysed with ten times the volume of 10% hydrochloric acid. The time taken for complete solution of the ester varied slightly, the average being 14\(\frac{1}{2}\) hours. On cooling, a certain amount of a viscous syrup,
presumably anhydride, separated out in the bottom of the flask. Several methods were adopted for extraction of the acid.

(i) **Evaporation on the steam bath.**

The excess HCl was removed in a vacuum desiccator over KOH and the product remained as a viscous oil which crystallised very slowly on standing with frequent scratching. The addition of benzene to an aqueous solution of the oil was found to facilitate crystallisation but the yield of acid by this method was so low that it was decided to try other means of extraction.

(ii) **Removal of water under reduced pressure at 35°–30° C.**

This method yielded more of the oily product and it was concluded therefore that the losses in method (i) were due to volatility of the acid or its anhydride at the temperature of the steam bath.

(iii) **Extraction with ether.**

The solvent was removed at room temperature under reduced pressure and the residual oil crystallised fairly readily on standing. In a typical experiment the yield of crystalline product was 54% of theory while there remained a considerable amount of oily material which would not crystallise.

In each case, the crystalline product on recrystallisation from water melted at 96°–100° C.
.1674 g. gave  .1028 g. H₂O  .3424 g. CO₂
H = 6.87%  C = 55.80%

C₈H₁₂O₄ requires  H = 7.04%  C = 55.80%

(b) **Alkaline hydrolysis.** The ester was hydrolysed by boiling with five times its volume of 20% potassium hydroxide for 13½ hours. At the end of this time, the considerable quantity of ester which remained unhydrolysed was extracted with ether and boiled for a further 5 hours with alkali. The products of alkaline hydrolysis were separately acidified with dilute hydrochloric acid, extracted with ether, and yielded the following substances:

(i) **From ester easily hydrolysed.** The product was gummy and would not crystallise though in one experiment where the whole of the ester was hydrolysed without separation, the crystalline product melted at 107°–111° C.

(ii) **From ester difficult to hydrolyse.** The product separated easily in a crystalline condition on removal of the solvent. Recrystallised from water it melted sharply at 147°–148° C.

.0777 g. gave  .0511 g. H₂O  .1598 g. CO₂
H = 7.34%  C = 56.11%

C₈H₁₂O₄ requires  H = 7.04%  C = 55.8%

This was trans-αβ - trimethylglutaconic acid and was identified by a mixed melting point with a pure specimen.
prepared for the purpose by the method of Perkin and Thorpe.
(see Part IV. p. 35)

D. PROPERTIES AND PREPARATION OF DERIVATIVES OF TRIMETHYLGLUTARIC ACID.

(a) Effect of heat and solvents on the acid.

A small amount of trimethyl acid from acid hydrolysis (m.p. 97° - 98° C) was dissolved in benzene and the solvent completely removed on the hot plate, the residual oil being heated for some time and then dissolved in a very small volume of benzene and crystallisation induced by scratching. Recrystallised from benzene it melted at 144° - 147° C.

0.0501 g. gave 0.0319 g. H₂O 1.309 g. CO₂

H = 7.12%  C = 56.49%

C₆H₁₂O₄ requires H = 7.04%  C = 55.8%

The experiment was repeated several times and the only explanation which can be offered is that either under the influence of heat, rearrangement has taken place within the molecule or that the cis - form of the acid has volatilised leaving the stable trans - form and thus accounting for the remarkable elevation of the melting point.

The acid (m.p. 97° - 98° C) was sparingly soluble in cold water and benzene, both dissolving it in the hot, though less readily in the latter case. It was extremely
soluble in acetone and ether. 2 g. of acid was dissolved in ether, and petrol ether (b.p. 50° – 60°) was added. Crystals (m.p. 103° – 111° C.) were deposited on the sides of the tube while the acid recovered from the mother liquor melted at 109° – 115° C. 1.3 g. of acid (m.p. 97° – 99° C.) were digested with 30 c.c. of benzene in a thermostat at 50°C. for some time; the mother liquor poured off and replaced by fresh solvent. The undissolved acid melted at 129° – 130° C. but the amount was too small for further investigation.

The above two experiments are typical of many made with different solvents and mixtures of solvents in an endeavour to separate the constituents of the mixture, but as stated previously, complete separation could not be effected by this means.

(b) Preparation of the anhydride of $\alpha\beta$-trimethylglutaconic acid.

Although the oily material which separated after hydrolysis with hydrochloric acid was probably anhydride, every attempt to crystallise it as such was unsuccessful. Other methods for its preparation were therefore adopted.

(i) Using acetyl chloride $\alpha\beta$-trimethylglutaconic acid (3 gms.) with acetyl chloride (H. and W. redistilled, 7 g.) was boiled in a reflux apparatus for one hour. The dehydrant was removed at 30°C. under reduced pressure and the residue taken up in ether. The ether solution was washed with ice-cold saturated sodium bicarbonate solution,
to remove acid impurities, dried over CaCl₂ and distilled under reduced pressure. At 140⁰/16 mm. (approx.), a colourless distillate came over and solidified in the receiver. It was removed and dried on the tile, where it remained as glistening plates. Recrystallised from ether it melted at 106⁰-107⁰ C.

\[
\begin{align*}
0.0730 \text{ g.} & \quad \text{gave} & \quad 0.0438 \text{ g.} \quad \text{H₂O} & \quad 0.1663 \text{ g.} \quad \text{CO}_2 \\
& & & \\
\text{H} = 6.71\% & & \text{C} = 62.30\% \\
\text{C₆H₁₀O₃ requires} & & \text{H} = 6.5\% & & \text{C} = 62.33\%
\end{align*}
\]

Under the conditions employed in the above experiment, the yield of anhydride was 6 - 7% of the theoretical.

(ii) Using acetyl chloride and phosphorus trichloride. \(\alpha\alpha\beta\) - Trimethylglutaric acid (1.4 g.) was boiled with acetyl chloride (20 g.) and phosphorus trichloride (1 g.) for half an hour, and the same procedure followed as in (i) except that the ether extract was not distilled. The solvent was removed at room temperature and the anhydride separated as fine needles. By this means, the yield was increased to 50% of the theoretical.

(c) Properties of the anhydride.

(i) Insoluble in cold water - soluble in hot water but separates unchanged on cooling.

(ii) No action with sodium bicarbonate solution in the cold but in the hot CO₂ is evolved slowly with the formation of the sodium salt of \(\alpha\alpha\beta\) - trimethylglutaric acid.
(iii) No colour change with ferric chloride indicating the absence of hydroxy-anhydride of trimethylglutaconic acid.

(iv) The addition of silver nitrate solution causes a transient white precipitate followed by darkening.

(d) Attempt to prepare cis-\(\alpha\alpha\beta\) trimethylglutaconic acid by hydration of the anhydride.

Pure anhydride (m.p. 107° C.) was heated for ten minutes over boiling water with excess 20% potassium hydroxide solution. The solution assumed the pale yellow colour characteristic of the potassium salt. It was cooled to 0° C. in a freezing mixture and acidified slowly with dilute hydrochloric acid followed by extraction three times with ether. When the solvent was removed, white crystals separated melting at 82° - 92° C. This was obviously not the pure cis-acid which is recorded as melting at 133° C. (Perkin and Thorpe J.C.S. 1897, 71, 1186; Thorpe and Wood J.C.S. 1913, 103, 1759.)

(e) Distillation of ammonium \(\alpha\alpha\beta\) - trimethylglutaconate.

\(\alpha\alpha\beta\) - Trimethylglutaconic acid was dissolved in 50 c.c. of 10% ammonium hydroxide solution and the solution evaporated to dryness on the water bath. There remained a syrup which would not crystallise so this was boiled again to dryness with 50 c.c. of ammonia solution. The final traces of moisture were removed in a vacuum desiccator over CaCl₂.
During distillation the pressure was kept at 500 ± 2 mm, and the following fractions were collected:

(i) up to 81°/500 mm, considerable quantities of H₂O, NH₃ and CO₂ evolved.

(ii) 82°/500 mm, distillate blue in colour and continued to come over up to 126°/500 mm.

**Substance A.**

(iii) 128°/500 mm. - 135°/30 mm, small amount of a yellow distillate followed by evolution of white fumes and only a charred mass remained in the flask.

**Substance B.**

Substance A, was greenish blue in aqueous, and dark green in alcoholic solution, both being changed to a bright yellow by the addition of dilute hydrochloric acid. Substance B, was yellow, amorphous, sparingly soluble in benzene to give a bright yellow solution. The addition of FeCl₃ gave a transient red colour which changed to a permanent brown. It was slightly soluble in water to give a yellow solution to which the addition of FeCl₃ caused no change of colour in the cold, but on boiling, a dark purple colour appeared and at the same time a curdy precipitate
was formed.
Neither Substance A nor Substance B was investigated further. The formation of 3:4:5 - trimethyl - 2:6 - dihydroxy pyridine at 260°/500 mm. as described by Rogerson and Thorpe (J.C.S. 1905, 87, 1705.) was not observed.

E. Oxidation of ethyl $\alpha$-$\alpha$-$\beta$-trimethylglutaconate by potassium permanganate.

The ester (5 g.) was treated with a 5% neutral solution of potassium permanganate in 30 c.c. lots and the solution warmed after each addition. It required for complete oxidation, 220 c.c. The precipitate of manganese dioxide was filtered off and the filtrate extracted four times with ether and fractionally distilled under reduced pressure. The following fractions were collected:

(i) up to 80°/27 mm. colourless pungent liquid.
(ii) 80°/27 mm. – 90°/27 mm.
(iii) 90°/27 mm. – 140°/27 mm. unchanged ester.

Examination of fraction (i). It gave no colour with FeCl$_3$. With phenylhydrazine acetate, it gave an opaque solution after heating for 35 minutes at 95° C., but the precipitate was too small to isolate. It did not give the characteristic test for ethyl pyruvate with sodium nitroprusside solution.
Examination of fraction (ii). It had the characteristic smell of acetoacetic ester and its methyl derivatives, and gave no colouration with FeCl₃ solution.

\[ \text{.1814 g. gave } .1436 \text{ g. } \text{H}_2\text{O} \quad .4041 \text{ g. } \text{CO}_2 \]

\[ \text{H = 8.85\%} \quad \text{C = 60.76\%} \]

C₈H₁₄O₃ requires \[ \text{H = 8.86\%} \quad \text{C = 60.76\%} \]

The substance was therefore dimethylacetoacetic ester.
PART III.

ATTEMPTED PREPARATION OF \( \alpha\beta\gamma \) - TRIMETHYLGLUTARONIC ACID BY
THE METHOD OF ROGERS AND THORPE (J.C.S., 1905, 87, 1699).

A. METHYLATION OF ACETOACETIC ESTER.

Acetoacetic ester (130 g.) was added to a solution of
sodium (23 g.) in absolute ethyl alcohol (250 c.c.). No
separation of sodium derivative took place. Methyl iodide
was added in two lots (30 c.c. and 35 c.c.) but no reaction
was observed so the experiment was stood overnight after
which it was heated for one hour at 70\(^{0}\) C. on the water
bath, when the contents of the flask became neutral to litmus.
The crude ester was poured into water and extracted with ether
in the usual manner. On fractional distillation methylacetoxe-
acetic ester came over at 78\(^{0}\)C/16 mm.

Yield 80.7 g. = 56% of theory.

\[ \text{.2238 g. gave} \quad .1695 \text{ g. H}_2\text{O} \quad .4763 \text{ g. CO}_2 \]

\[ \text{H : 8.47\%} \quad C : 58.06\% \]

\[ \text{C}_7\text{H}_4\text{O}_3 \text{ requires} \quad \text{H : 8.33\%} \quad C : 58.33\% \]

B. CONDENSATION OF METHYLAECETOACETIC ESTER WITH CYANACETIC
ESTER AND ATTEMPTED METHYLATION OF THE PRODUCT.
Sodium (7.7 g.) was dissolved in absolute alcohol (92 g.) and the solution after cooling mixed first with cyanacetic ester (37.7 g.) which caused the separation of the orange-coloured sodio-derivative of that ester. On adding methyl acetoacetic ester (48 g.) and heating on the water bath for 30 minutes, the above sodio-derivative slowly dissolved to give a wine-red solution which precipitated the gelatinous sodio-derivative of the condensation product. Methyl iodide (48 g.) was then gradually added and the whole left overnight. Even after heating 6½ hours the sodio-derivative was still apparently unattacked, and the solution was definitely alkaline to litmus. The crude product was poured into water and extracted as previously described. The following fractions were collected on distillation under reduced pressure:

(i) up to 85°/15 mm. unchanged methylacetoacetic ester 28.1 g.

(ii) 85°/15 mm. - 100°/18 mm. unchanged cyanacetic ester, 8.5 g.

The temperature then rose rapidly to

(iii) 150°/20 mm. - 165°/16 mm 14.5 g.

After refractionation, the ethyl $\alpha$-cyano-1/$\beta$V-dimethyl-glutaconate boiled at 156.5°/17 mm.
C. HYDROLYSIS OF ETHYL $\alpha$-CYANO-$\beta^+$-DIETHYLGlutaconate
TO $\alpha^\beta$-DIETHYLGUTACONIC ACID AND 4:5-DIMETHYL-2:6-
DIHYDROXY-PYRIMINE WITH HYDROCHLORIC ACID.

The ester (5 g.) was boiled with 50 c.c. of 10% hydro-
chloric acid for 14 hours when solution appeared to be complete.
The product was extracted with ether and the following substances
isolated.

(a) Ether extract yielded an acid which on recrystallisa-
tion from ether melted at 138° C. Mixed with pure $\alpha^\beta$-acid
(m.p. 144° - 145° C.), it melted at 138° - 139° C. Mixed with
pure trans-$\alpha\alpha^\beta$-acid (m.p. 147° - 148° C.) it melted at
114° - 115° C.

0.1301 g. gave 0.0771 g. H₂O 0.2547 g. CO₂
H = 6.63% C = 53.4%

C₇H₁₀O₄ requires H = 6.3% C = 53.2%

The substance was, therefore, slightly impure $\alpha^\beta$-dimethyl-
glutaconic acid.

(b) Aqueous Residue. This was evaporated to dryness
and yielded on recrystallisation from benzene a substance
melting at 180° - 190° C. It contained nitrogen by the
Lassaigne test and gave a cloudy precipitate with FeCl₃.
It was obviously the 4:5-dimethyl-2:6-dihydroxypyridine
obtained by Rogerson and Thorpe and was therefore not further
investigated.
No \( \alpha\beta\gamma \) - trimethylglutaconic acid could be isolated, a fact which was verified by repeating the above experiment.
PART IV.
PREPARATION OF TRANS-\(\alpha\alpha\beta\) -TRIMETHYLGluTARONIC AcID BY THE
METHOD OF PERKIN AND THORPE  
[J. C. S., 1897, 71, 1178.]

A. PREPARATION OF DIMETHYLAcETOACETIC ESTER.

Monomethylacetoacetic ester (80.7 g.) prepared by the
method described in Part III A was added gradually to a solu-
tion of sodium (12.9 g.) in absolute ethyl alcohol (300 c.c.)
cooled in a freezing mixture. The sodium derivative of mono-
methylacetoacetic ester separated and after removing the flask
from the freezing mixture, methyl iodide (15 c.c.) was added.
No apparent reaction took place so the flask was stood half
an hour at room temperature and then excess methyl iodide
(35 c.c.) was added. After standing for one day sodium
iodide began to separate and on warming in water at 40° C.
for some time, the solution became neutral to litmus. Extrak-
tion was carried out as for the monomethyl ester, and on
distillation dimethylacetoacetic ester was obtained as a
colourless liquid b.p. 79°0/19 mm.

Yield 65 g. = 73.5% of theory.

B. CONDENSATION OF DIMETHYLAcETOACETIC ESTER IN
THE PRESENCE OF MAGNESIUM TO FORM ETHYL \(\beta\) -
HYDROXY-\(\alpha\alpha\beta\) -TRIMETHYLGluTARATE.
Dimethylacetoacetic ester (50 g.) was mixed with bromacetic ester (50 g.) in a reflux apparatus on the water bath until the mixture had reached a temperature of 90°–95° C. Following the instructions of Perkin and Thorpe (loc. cit.), a small quantity of clean dry zinc (1 g.) was added, but as no reaction took place, the mixture was heated on the bath for a further 1½ hours. It was then decided to try the effect of adding a crystal of iodine but although a slight change in the viscosity of the mixture was noticed, no vigorous reaction as anticipated took place. At this stage it was considered that magnesium might form a more satisfactory condensing agent than zinc, and this metal was accordingly substituted. Five grams of magnesium powder were added and the mixture was heated for 12 hours. An excess of magnesium was then added and the whole heated for 8 hours, when the contents of the flask became very viscous and 50 c.c. of dry benzene were added. After heating for a further 8½ hours, the reaction appeared to be complete.

The product, a brown viscous magnesium compound containing large quantities of unchanged metal, was treated with dilute sulphuric acid (1:10), extracted with ether, the extract washed 6 times with dilute sulphuric followed by water, and dried over anhydrous potassium carbonate. The product was distilled under reduced pressure and the following fractions were collected:
(i) up to $30^\circ/300$ mm. ether and benzene.

(ii) $30^\circ/300$ mm. - $70^\circ/46$ mm. 30 c.c. colourless liquid benzene and bromoacetic ester

(iii) $70^\circ/46$ mm. - $95^\circ/19$ mm. 40 c.c. bromoacetic ester and dimethyl-acetoacetic ester.

(iv) $95^\circ/19$ mm. - $182^\circ/23$ mm. crude condensation product - first portion yellow last portion brown and viscous.

On refractionation, ethyl $\beta$ - hydroxy $\alpha\alpha\beta$ - trimethylglutarate boiled at $142^\circ/17$ mm. - $151^\circ/18$ mm.

Yield, 10.1 g. = 12% of theory.

$G_e$ HYDROLYSIS OF ETHYL $\beta$ - HYDROXY $\alpha\alpha\beta$ - TRIMETHYLGLUTARATE WITH CONCENTRATED HYDROCHLORIC ACID TO FORM TRANS $\alpha\alpha\beta$ - TRIMETHYLGLUTARONIC ACID.

5.15 g. of ester were boiled with 60 c.c. of conc. hydrochloric acid for $3\frac{1}{2}$ hours, when hydrolysis was complete. The excess water was evaporated from the water bath and when the hydrogen chloride had been removed in a vacuum desiccator, crystals separated. On recrystallisation from water they melted at $147.8^\circ - 148.3^\circ$ C. (corr.). This was the trans $\alpha\alpha\beta$ - trimethylglutaronic acid.

$0.0382$ g. gave $0.0624$ g. $H_2O$ $0.2011$ g. $CO_2$

$H = 7.10\%$ $C = 55.86\%$

$C_6H_{12}O_4$ requires $H = 7.04\%$ $C = 55.80\%$

"Mixed melting point" determinations were made with this, and
the following acids:

(a) trans $\alpha\beta\beta$ - acid from $147.8^\circ - 148.3^\circ$ (corr.)

alkaline hydrolysis.

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(b) Pure $\alpha\beta$ - dimethyl - $144^\circ - 145^\circ$ (corr.)

glutaconic acid.