

CLXXXVIII.—*The Chemistry of the Glutaconic Acids.*
Part X. The Alkylation of the Ethereal Salts.

By JOCELYN FIELD THORPE and ARTHUR SAMUEL WOOD.

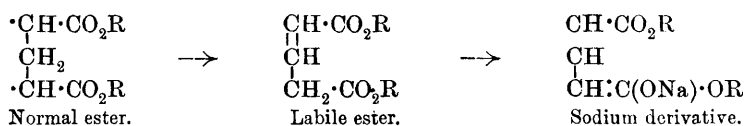
DURING the course of the experiments described in the preceding parts of this series evidence has accumulated which shows the mechanism by which esters of the glutaconic acids can be transformed into their alkyl derivatives, and from this evidence the following generalisations can be derived:

(1) *The formation of the sodium derivative of an ester of a glutaconic acid, and hence the formation of an alkyl derivative, takes place through the labile form of the ester alone.*

(2) *The normal esters, as such, do not react with sodium ethoxide.*

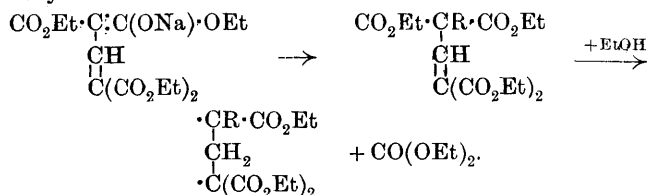
(3) *The formation of a sodium derivative of a normal ester is therefore dependent on the tendency for the ester to pass into the labile modification under the experimental conditions employed.*

These generalisations may be expressed by the following formulæ:



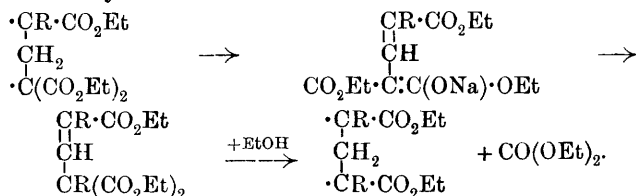
For the purpose of showing that the different types of ester conform to these generalisations, it is advisable to divide them into three classes:

(a) *The Tetracarboxylic Esters.*—The only ester of this kind is ethyl dicarbethoxyglutaconate. The well-known yellow sodium derivative of this ester yields the *C*-alkyl derivative with alkyl iodides. In this alkyl derivative the "labile" structure must necessarily be fixed; it therefore reacts with alcoholic sodium ethoxide, yielding ethyl carbonate and the normal ester of the tricarboxylic acid:



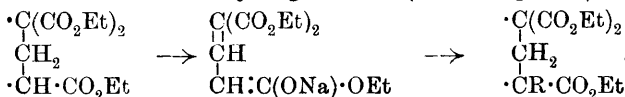
(b) *The Tricarboxylic Esters.*—The formation of a sodium derivative from an ester of this type, formed as shown above, involves

the replacement of the mobile hydrogen atom; the sodium atom therefore takes up the most negative position in the system (compare T., 1912, **101**, 250), and yields the corresponding alkyl derivative with alkyl iodides:

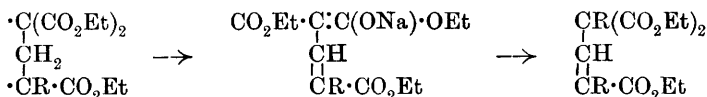


In this alkylated ester the "labile" structure is also fixed, and it therefore reacts with sodium ethoxide, yielding the dicarboxylic ester and ethyl carbonate.

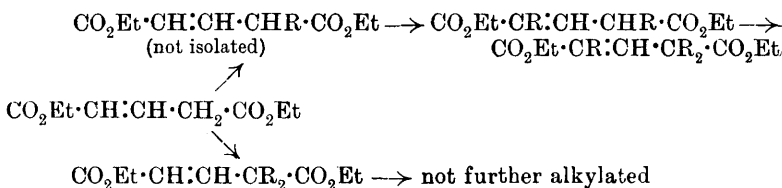
On the other hand, the alkylation of an unsubstituted tricarboxylic ester leads to the replacement of the hydrogen atom at the other end of the chain, the compound forming a sodium derivative, which retains the mobile hydrogen atom (*loc. cit.*, p. 252):



This compound then reacts with sodium ethoxide, without the elimination of ethyl carbonate, and from this the dialkyl derivative can be formed:

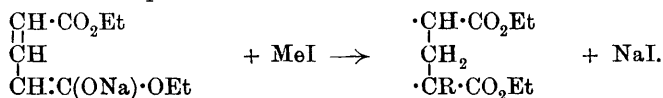


The Dicarboxylic Esters.—The systematic alkylation of ethyl glutaconate, the simplest member of this series, has been investigated by Blaise (*Compt. rend.*, 1903, **136**, 381, 692, 1140; *Bull. Soc. chim.*, 1903, [iii], **29**, 1015), whose results may be shown as follows:

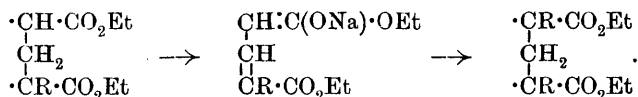


The formation of the $\alpha\alpha$ -dimethyl derivative in this manner is certainly remarkable, especially when it is remembered that, in the original preparation of this substance, Henrich (*Monatsh.*, 1899, **20**, 539) used equimolecular quantities of the ester, sodium ethoxide, and methyl iodide.

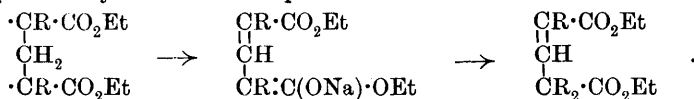
Our own experiments show that when the pure sodium derivative of ethyl glutaconate is treated with methyl iodide in dry ethereal solution, its conversion into the monomethyl derivative in accordance with the equation



is complete, and that when the ester of α -methylglutaconic acid, formed in this manner, is again alkylated the product is composed entirely of the $\alpha\gamma$ -dialkyl derivative:



When this normal ester is again treated with sodium ethoxide and an alkyl iodide, the mobile hydrogen atom is displaced and the $\alpha\alpha\gamma$ -trimethyl derivative is produced:

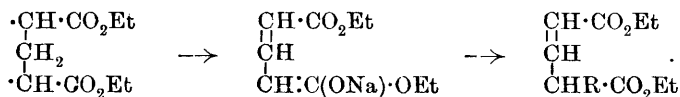


It follows, therefore, that the behaviour of these compounds can be expressed by the generalisation:

(4) *The formation of a sodium derivative from a normal ester of a mono-alkylated dicarboxylic acid involves the passage of the mobile hydrogen atom to the carbonyl system not affected by the substituting group. The second alkyl group therefore enters on the carbon atom of the three-carbon system most remote from that bearing the existing alkyl group.*

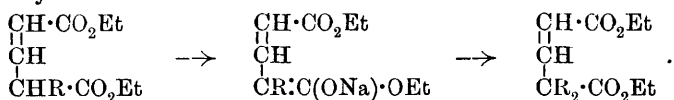
The formation of ethyl $\alpha\alpha$ -dimethylglutaconate in the manner described by Henrich and by Blaise must be regarded as an abnormal reaction, for which, however, an explanation is readily forthcoming.

Our experiments show that the transformation of ethyl glutaconate into its sodium derivative by the action of an equivalent amount of sodium ethoxide in alcohol is far from complete, and that nearly half the ester remains unaltered in solution, there being, of course, an equivalent quantity of free sodium ethoxide also present. The first action of methyl iodide leads, then, to the formation of the labile methyl ester:

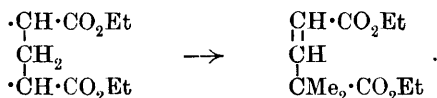


but the presence of sodium ethoxide prevents this labile ester from

passing into its normal form, and it is therefore again transformed into a sodium derivative, from which methyl iodide forms the dimethyl derivative:



The truth of this explanation is shown by the fact that when ethyl glutaconate is methylated in the presence of more than twice the equivalent amount of sodium ethoxide, its transformation into the $\alpha\alpha$ -dimethyl derivative is complete:

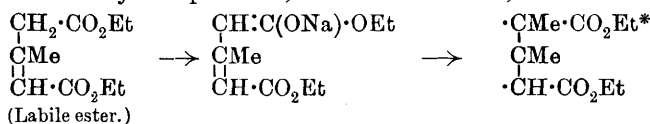


This further generalisation is therefore necessary:

(5) *Those esters which contain two or three potentially mobile hydrogen atoms can be made to yield dialkyl derivatives having the alkyl groups on the same carbon atom by alkylating them under conditions which prevent the passage of the labile alkyl derivative, which is first formed, into its normal isomeride. This can be effected by the presence of excess of sodium ethoxide throughout the alkylation.*

The normal esters of the alkylglutaconic acids mentioned above, which have the alkyl groups on the terminal atoms of the three-carbon system, have the movable hydrogen atom in so mobile a condition that it is probably impossible to isolate the corresponding labile esters in a pure condition, and no evidence can therefore be derived from them respecting the behaviour of the two forms on alkylation. It is only by the entrance of an alkyl group on the central carbon atom of the system that sufficient stability is conferred on the two modifications to enable them to supply definite evidence on this point.

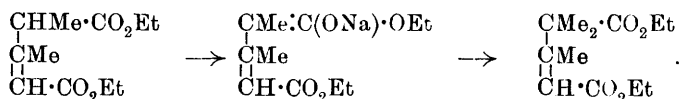
It has already been shown (T., 1912, 101, 1557) that it is an easy matter to prepare both the normal and labile esters of β -methylglutaconic acid in a pure condition, and experiment proves that, whereas the labile ester is completely converted into the dimethyl derivative by alcoholic sodium ethoxide and methyl iodide at the ordinary temperature, the normal ester, under the same



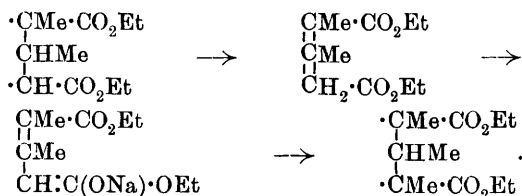
* The product formed in this reaction is a mixture of the normal and labile esters.

experimental conditions, is quite unchanged. The normal ester can, however, be alkylated in a sealed tube at 120°, as shown by Feist and Beyer (*Annalen*, 1906, **345**, 123), because, under these conditions, the ester is converted into the sodium derivative of the labile form.

The formation of the sodium derivative from the labile ester is evidently complete under these conditions, because, unlike ethyl glutaconate in similar circumstances, no formation of the $\alpha\alpha\beta$ -trimethyl derivative was noticed. The labile ester may, nevertheless, be made to conform to the generalisation (5) by alkylating it in the presence of excess of sodium ethoxide when ethyl $\alpha\alpha\beta$ -trimethylglutaconate is formed, thus:



The further alkylation of normal ethyl $\alpha\beta$ -dimethylglutaconate (prepared from the normal acid) requires a high temperature, and then yields the $\alpha\beta\gamma$ -trimethyl derivative. The methylation of the labile ester (T., 1912, **101**, 1567) can, however, be effected at the ordinary temperature:



The production of the tetramethyl derivative from the trimethyl ester could not be effected.

It should also be mentioned that in certain cases even the labile form of a substituted ester may fail to yield a sodium derivative. This only happens when the entrance of substituting groups on the carbon atoms of the three-carbon system completely inhibits the movement of the hydrogen atom. The only case of this kind which has yet come under our notice is that of ethyl α -carbethoxy- β -phenyl- α -methylglutaconate (this vol., p. 1574), which can be isolated in the two forms:



neither of which reacts with alcoholic sodium ethoxide.

The final generalisation is therefore as follows:

(6) *Esters, although they may have the labile structure, will not*

react with sodium ethoxide if the nature of the groups carried by the carbon atoms of the three-carbon system is such as to prevent the movement of the hydrogen atom within the molecule.

EXPERIMENTAL.

The Sodium Derivative of Ethyl Glutaconate.

We find that this substance can be prepared in a condition sufficiently pure for analysis by adding dry ether to the solution obtained by mixing the ester with an equivalent amount of sodium ethoxide dissolved in alcohol. The yellow, crystalline precipitate is further purified by washing with dry ether. (Found, Na=10.91. $C_9H_{13}O_4Na$ requires Na=11.06 per cent.)

During this preparation it was evident that the conversion of the ester into its sodium derivative is only partial; for example, when 18.6 grams of ethyl glutaconate are added to a solution of 2.3 grams of sodium dissolved in 25 grams of alcohol and the yellow sodium derivative is completely precipitated by dry ether, 8.7 grams of unaltered ester can be recovered from the filtrate.

The Methylation of the Sodium Derivative.

The transformation of the yellow sodium compound into ethyl α -methyl glutaconate can be effected by suspending the pure salt in dry ether, adding the requisite amount of methyl iodide, and then shaking the well-cooled mixture until the yellow colour has disappeared. The product distils at $244^\circ/754$ mm. (Found, C=59.86; H=8.12. $C_{10}H_{16}O_4$ requires C=60.0; H=8.0 per cent.) The ester gave α -methylglutaconic acid, melting at 145 — 146° , on hydrolysis.

The Methylation of Ethyl α -Methylglutaconate.

The methylation was effected by means of an equivalent amount of sodium ethoxide and methyl iodide in alcohol at 12 — 14° . It was found, however, by an analysis of the product, that quite half of the monoalkyl ester remained unchanged under these conditions. The methylation was therefore repeated three times, steps having been taken in the first instance to show that the dimethyl derivative did not undergo further methylation under the experimental conditions employed. *Ethyl $\alpha\gamma$ -dimethylglutaconate*, $CO_2Et \cdot \dot{C}Me \cdot CH_2 \cdot \dot{C}Me \cdot CO_2Et$, is a mobile oil boiling at $179^\circ/80$ mm.:

0.1901 gave 0.4296 CO_2 and 0.1421 H_2O . C=61.63; H=8.31.

$C_{11}H_{18}O_4$ requires C=61.7; H=8.4 per cent.

This ester has been described in Part I. of this series (T., 1911, 99, 2203), but it is evident from the analysis given there that the compound is the methyl ethyl ester, and that the name "*Methyl Ethyl α -Dimethylglutaconate*" should be placed at the head of the paragraph.

It is probable that the ester prepared above is pure, and does not contain any appreciable amount of the methyl ethyl ester of the trimethylated acid. α -Dimethylglutaconic acid melting at 147° was the only substance which could be isolated from it on hydrolysis.

The Methylation of Ethyl Glutaconate in the Presence of Excess of Sodium Ethoxide.

In carrying out this experiment, 18.6 grams of ethyl glutaconate were added to a solution containing 5.6 grams of sodium dissolved in 65 grams of alcohol, and after excess of methyl iodide had been added the whole was shaken under running water until all colour had disappeared. The product boiled at 163°/50 mm. (Found, C=61.59; H=8.45. $C_{11}H_{18}O_4$ requires C=61.7; H=8.4 per cent.) The ester on hydrolysis yielded a mixture of acids, from which *cis*- $\alpha\alpha$ -dimethylglutaconic acid melting at 135° was readily isolated. From the residues a small quantity of the *trans*-acid melting at 172° was isolated by the aid of acetyl chloride, but no other acid could be separated.

The Methylation of Normal and Labile Ethyl β -Methylglutaconate.

(1) *With an Equivalent Amount of Sodium Ethoxide.*—Twenty grams of the labile ester were added to an alcoholic solution containing 2.3 grams of sodium, and, after excess of methyl iodide had been added, the mixture was shaken under running water until all colour had disappeared. Ethyl $\alpha\beta$ -dimethylglutaconate, $CO_2Et \cdot CMe \cdot CMe \cdot CH \cdot CO_2Et$,* which was isolated in the usual manner, is a mobile liquid melting at 176°/76 mm. (Found, C=61.67; H=8.39. $C_{11}H_{18}O_4$ requires C=61.7; H=8.4 per cent.)

The ester yields $\alpha\beta$ -dimethylglutaconic acid, melting at 148°, on hydrolysis.

The normal ester when treated in the same manner is recovered unchanged, although methylation is effected in a sealed tube at 120° in the manner described by Feist and Beyer (*loc. cit.*).

(2) *With Excess of Sodium Ethoxide.*—In this experiment the same amount of labile ester was used, but it was mixed with an

* See footnote, p. 1755.

alcoholic solution of 5.6 grams of sodium and an equivalent quantity of methyl iodide was added. The heat of the reaction was controlled by running water, the product being isolated as soon as all colour had disappeared. *cis*-Ethyl $\alpha\alpha\beta$ -trimethylglutaconate, $\text{CO}_2\text{Et}\cdot\text{CMe}_2\cdot\text{CMe}\cdot\text{CH}\cdot\text{CO}_2\text{Et}$, is a mobile liquid boiling at $164^\circ/45$ mm.:

0.1765 gave 0.4081 CO_2 and 0.1407 H_2O . $\text{C}=63.07$; $\text{H}=8.86$.

$\text{C}_{12}\text{H}_{20}\text{O}_4$ requires $\text{C}=63.2$; $\text{H}=8.8$ per cent.

When the ester is hydrolysed by dilute hydrochloric acid the anhydride of *cis*- $\alpha\alpha\beta$ -trimethylglutaconic acid melting at 107° separates when the clear solution is cooled (Found, $\text{C}=62.21$; $\text{H}=6.59$. $\text{C}_8\text{H}_{10}\text{O}_3$ requires $\text{C}=62.3$; $\text{H}=6.5$ per cent.) (compare Perkin and Thorpe, T., 1897, **71**, 1184).

The anhydride was identified by conversion into the acid melting at 133° by the action of cold dilute alkali. No trace of the *trans*-acid melting at 148° could be found accompanying this compound, and this fact is in complete accordance with our view that both the normal and labile modifications of the acids of this series have the *cis*-configuration (T., 1912, **101**, 1740). It is therefore certain that the above ester is the *cis*-modification, and that the ester previously prepared (T., 1897, **71**, 1183) is the *trans*-isomeride.

The Methylation of the Normal and Labile Esters of Ethyl $\alpha\beta$ -Dimethylglutaconate.

The manner in which these esters can be prepared has been described (T., 1912, **101**, 1567). When the labile ester (21.4 grams) is added to a solution containing 2.3 grams of sodium in alcohol and is mixed with excess of methyl iodide, the methylation is complete at the end of three hours at the temperature of running water. The product is ethyl $\alpha\beta\gamma$ -trimethylglutaconate,



a mobile oil boiling at $164^\circ/50$ mm. (Found, $\text{C}=63.13$; $\text{H}=8.91$. $\text{C}_{12}\text{H}_{20}\text{O}_4$ requires $\text{C}=63.2$; $\text{H}=8.8$ per cent.) (compare T., 1905, **87**, 1707). The ester is converted into $\alpha\beta\gamma$ -trimethylglutaconic acid, melting at 127° , on hydrolysis.

The normal ester remains unaltered after treatment in the same manner, but is converted into the trimethyl derivative when the mixture as above is heated in a sealed tube at 120° for five hours.

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