alysis was dried to constant weight at 110°. The melting point was 91–92°. The yield was 0.5 g.

Anal. Subs., 0.0734, 0.0638: H_2O, 0.0055, 0.0044. Calcd. for $C_{12}H_{14}O_5 \cdot H_2O$: H_2O, 7.04. Found: 7.4, 6.9. Subs., 0.0594, 0.0679; CO_2, 0.1318, 0.1515; H_2O, 0.0316, 0.0351. Subs., 0.0200, 0.0199: AgI, 0.0392, 0.0391. Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88; $2CH_3O$, 26.05. Found: C, 60.49, 60.84; H, 5.91, 5.74; CH_3O, 25.89, 25.95. *Titration.* Subs., 0.0201: 1.72 cc. *N*/20 KOH. Calcd. mol. wt.: 238. Found: 234. 0.1982 g. of subs. in 10.6 cc. of ethyl alcohol showed no appreciable rotation in a 2-dm. tube.

Summary

Methylderritolic acid yields on alkaline peroxide oxidation a monocarboxylic acid of formula $C_{11}H_{14}O_5$ having the properties of a trimethoxyphenylacetic acid which yields the next lower homolog by permanganate oxidation. The new acid corresponds in its empirical formula to a trimethoxybenzoic acid but does not agree in its properties with any of the four known compounds of this type. It therefore probably corresponds to either the 2,3,5- or 2,3,6-derivative, both of which are unknown.

Dihydrorotenolic acid on peroxide oxidation yields a monocarboxylic acid of formula $C_{12}H_{14}O_5$ containing the two methoxyl groups of rotenol.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ON THE COURSE OF ADDITION OF SODIUM ENOL ALKYL MALONIC ESTERS TO ALPHA, BETA-UNSATURATED ESTERS

BY ARTHUR MICHAEL AND JOHN ROSS

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In the first account of the addition of sodium enol malonic ester to esters of α,β-unsaturated acids[1] the reaction was expressed as though the parts of the addendum were Na and $-CH(COOEt)_2$

$$\begin{array}{c} RCH{=}CHCOOEt \\ + \\ NaCH(COOEt)_2 \end{array} \longrightarrow \begin{array}{l} RCHCHNaCOOEt \\ \;| \\ HC(COOEt)_2 \end{array}$$

In agreement with this view, the many cases of α,β-olefinic carboxylic esters that have since been examined by reaction with sodium enol malonic ester gave products that indicated that the malonic residue had united with the β-carbon atom. After the enol structure was assigned to the sodium derivative of malonic ester[2] the above reaction continued to be written as though the sodium atom migrated in the reaction.[3] This mecha-

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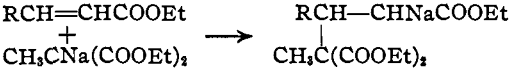
[1] Michael, *J. prakt. Chem.*, **35**, 349 (1887).

[2] Michael, *ibid.*, **37**, 496 (1889).

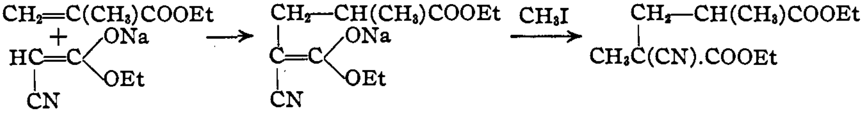
[3] Although usually written as though the sodium atom becomes attached to the α-carbon atom of the unsaturated ester, attention had been called to the fact that the structure of such an addition compound would be unstable and would rearrange from the $-CHNaCOOEt$ to the $-CH{=}C(ONa)OEt$ form [Michael, *Ber.*, **33**, 3731 (1900)].

nism for the reaction received apparent support when it was shown that addition products could be obtained using sodium enol alkyl malonic esters in the place of sodium enol malonic ester.[4]



$$\begin{array}{c}\mathrm{RCH{=}CHCOOEt}\\ +\\ \mathrm{CH_3CNa(COOEt)_2}\end{array} \longrightarrow \begin{array}{l}\mathrm{RCH{-}CHNaCOOEt}\\ \quad\ \ |\\ \mathrm{CH_3C(COOEt)_2}\end{array}$$

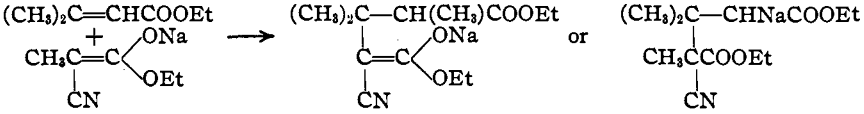
J. F. Thorpe[5] examined the reaction of the sodium derivatives of cyanacetic and of α-cyanopropionic esters and concluded that the above manner of expressing the addition of sodium enol malonic esters to α,β-unsaturated esters was erroneous. He showed that the addition of sodium enol cyanacetic ester to α-methylacrylic ester proceeded as follows, since upon treating with methyl iodide the addition compound gave α,γ-dimethyl-γ-cyano glutaric ester



$$\begin{array}{l}\mathrm{CH_2{=}C(CH_3)COOEt}\\ \quad +\ \ \mathrm{{}^{\nearrow}ONa}\\ \mathrm{HC{=}C{<}}\\ \ \ |\quad\ \ \mathrm{{}^{\searrow}OEt}\\ \mathrm{CN}\end{array} \longrightarrow \begin{array}{l}\mathrm{CH_2{-}CH(CH_3)COOEt}\\ |\quad\ \ \mathrm{{}^{\nearrow}ONa}\\ \mathrm{C{=}C{<}}\\ |\quad\ \ \mathrm{{}^{\searrow}OEt}\\ \mathrm{CN}\end{array} \xrightarrow{\mathrm{CH_3I}} \begin{array}{l}\mathrm{CH_2{-}CH(CH_3)COOEt}\\ \quad\ \ |\\ \mathrm{CH_3C(CN).COOEt}\end{array}$$

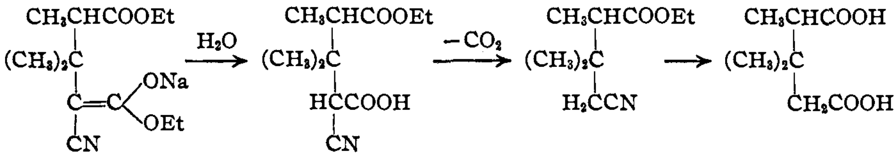
Thorpe regarded this as evidence that the sodium showed no tendency to leave the oxygen in the more acidic cyanacetic ester residue in order to add to the α-carbon atom attached to only one carbethoxyl group, and concluded that the reaction took place with migration of hydrogen but not of sodium.

In the addition of sodium enol α-cyanopropionic ester to β,β-dimethyl acrylic ester, the following possibilities were considered



$$\begin{array}{l}\mathrm{(CH_3)_2C{=}CHCOOEt}\\ \quad +\ \ \mathrm{{}^{\nearrow}ONa}\\ \mathrm{CH_3C{=}C{<}}\\ \quad |\quad\ \ \mathrm{{}^{\searrow}OEt}\\ \mathrm{CN}\end{array} \longrightarrow \begin{array}{l}\mathrm{(CH_3)_2C{-}CH(CH_3)COOEt}\\ \quad\ \ |\quad\ \ \mathrm{{}^{\nearrow}ONa}\\ \quad\ \ \mathrm{C{=}C{<}}\\ \quad\ \ |\quad\ \ \mathrm{{}^{\searrow}OEt}\\ \quad\ \ \mathrm{CN}\end{array} \ \text{or}\ \begin{array}{l}\mathrm{(CH_3)_2C{-}CHNaCOOEt}\\ \qquad\ |\\ \mathrm{CH_3CCOOEt}\\ \qquad\ |\\ \qquad\ \mathrm{CN}\end{array}$$

The acid cyano ester obtained upon acidifying the product lost carbon dioxide upon distillation to give a cyano ester. This upon hydrolysis yielded α,β,β-trimethylglutaric acid and it was, therefore, concluded, that the methyl group had migrated to the α-carbon atom in the initial addition. These reactions were expressed as follows



$$\begin{array}{l}\mathrm{CH_3CHCOOEt}\\ \quad\ |\\ \mathrm{(CH_3)_2C}\\ \quad\ |\quad\ \ \mathrm{{}^{\nearrow}ONa}\\ \quad\ \mathrm{C{=}C{<}}\\ \quad\ |\quad\ \ \mathrm{{}^{\searrow}OEt}\\ \quad\ \mathrm{CN}\end{array} \xrightarrow{\mathrm{H_2O}} \begin{array}{l}\mathrm{CH_3CHCOOEt}\\ \quad\ |\\ \mathrm{(CH_3)_2C}\\ \quad\ |\\ \mathrm{HCCOOH}\\ \quad\ |\\ \quad\ \mathrm{CN}\end{array} \xrightarrow{-\mathrm{CO_2}} \begin{array}{l}\mathrm{CH_3CHCOOEt}\\ \quad\ |\\ \mathrm{(CH_3)_2C}\\ \quad\ |\\ \mathrm{H_2CCN}\end{array} \longrightarrow \begin{array}{l}\mathrm{CH_3CHCOOH}\\ \quad\ |\\ \mathrm{(CH_3)_2C}\\ \quad\ |\\ \mathrm{CH_2COOH}\end{array}$$

Michael[6] examined the addition of sodium enol methylmalonic ester to crotonic ester and obtained an ester (a) which upon treatment with methyl

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[4] Auwers, *Ber.*, **24**, 307, 1923, 2887 (1891).

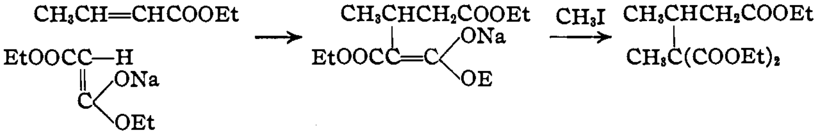
[5] Thorpe, *J. Chem. Soc.*, **77**, 923 (1900).

[6] Michael, *Ber.*, **33**, 3731 (1900).

iodide gave a quantitative yield of a trimethylcarboxyglutaric ester. Methylation of the sodium derivative of β-methyl-γ-carboxyglutaric ester (prepared by addition of sodium enol malonic ester to crotonic ester) gave a dimethyl γ-carboxyglutaric ester (b), which had quite different properties from the isomeric ester (a). The ester (a) not only boiled 6° lower than the ester (b) but upon attempted methylation with sodium ethoxide and methyl iodide the ester (b) gave crotonic and dimethylmalonic esters. Evidently ester (a) forms a stable sodium derivative whereas ester (b) does not, but undergoes retrogression into crotonic and sodium enol methyl malonic esters.[7] From their methods of preparation the two esters should have been identical and Michael was unable to explain the appearance of different compounds. Thorpe's research appeared at about the same time but neither chemist was aware of the other's work.

In view of these anomalous results it was decided to reëxamine the addition of sodium alkyl malonic esters to α,β-unsaturated esters and determine the constitution of the two isomeric esters (a) and (b). It was thought that this might lead to an explanation of the reactions by which they were formed.

When the product of addition of sodium enol malonic ester to crotonic ester is treated with methyl iodide, β,γ-dimethyl-γ-carboxyglutaric ester is formed



This is a proof that when sodium enol malonic ester is used in these addition reactions, then the sodium remains combined with the oxygen in the malonic residue. In other words, the addendum components are H and —C(COOEt)=C(ONa)OEt, a parallel mechanism shown by Thorpe to occur with sodium enol cyanacetic ester addition. It has also been shown that it is hydrogen that migrates in the reactions of sodium enol malonic, sodium enol alkyl malonic esters[8] and diethylaminocrotonic ester[9] toward phenyl isocyanate.

If the above conception of the mechanism of this reaction offers any parallel in the case of the addition of sodium enol alkyl malonic esters to such α,β-unsaturated esters, the course of the reaction would depend upon the chemical hindrance to separation of the components of the addendum, that is, upon the separation of the alkyl group from the directly attached carbon atom. This might be rendered possible by the positive character

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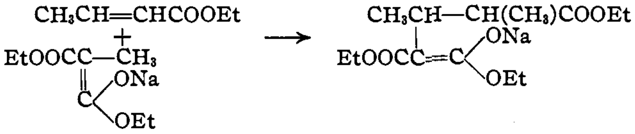
[7] This was the first proof of the possible retrogression of these addition reactions; the subject was later more fully investigated by Ingold, *J. Chem. Soc.*, **119**, 1976 (1921).

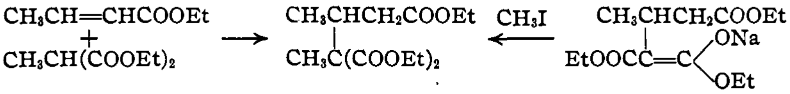
[8] Michael, *Ber.*, **37**, 32 (1905).

[9] Michael and Cobb, *Ann.*, **363**, 14 (1905).

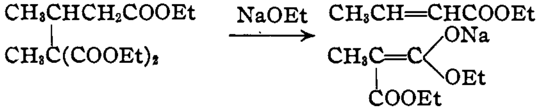
of the alkyl group and the strong positive influence of the slightly neutralized sodium atom in loosening the affinity between the respective carbon atoms. The addendum to the ethylenic linkage would then be alkyl and —C(COOEt)=C(ONa)OEt. With sodium enol methylmalonic ester and crotonic ester the reaction would be as follows



Upon examining the conditions of addition of methylmalonic to crotonic ester, it was found that the course of the reaction varied according to the amount of sodium ethoxide used. When the addition was carried out in the presence of a small quantity of sodium ethoxide, then the addendum functioned as H and —C(CH$_3$)(COOEt)$_2$. With one-sixth of a molecular equivalent of sodium ethoxide, almost the theoretical yield of β,γ-dimethyl-γ-carboxyglutaric ester was obtained. This ester is also 60% of the product of methylation of the sodium derivative of β-methyl-γ-carboxyglutaric ester with methyl iodide. These reactions may be represented thus

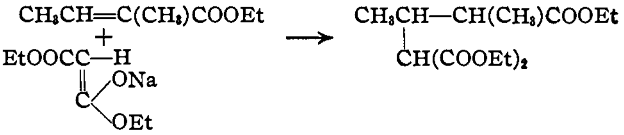


In each case the structure of the ester was proved by saponifying and isolating the β,γ-dimethyl-γ-carboxyglutaric acid, m. p. 167°. Furthermore, it was shown that β,γ-dimethyl-γ-carboxyglutaric ester would not form a sodium derivative. Upon attempted methylation by treatment in the cold with sodium ethoxide and methyl iodide, fission occurred into crotonic and sodium enol methylmalonic esters.



The sodium enol methyl malonic ester was converted by the methyl iodide into dimethylmalonic ester.

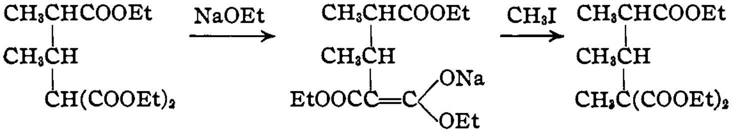
When methylmalonic ester and crotonic ester were condensed using a molecular equivalent of sodium ethoxide, no β,γ-dimethyl-γ-carboxyglutaric ester was formed. Instead, a 60% yield of α,β-dimethyl-γ-carboxyglutaric ester was obtained. Hence it is concluded that under these conditions the reaction takes place with migration of the methyl group. The direct proof of this migration of the methyl group was obtained by comparison of the α,β-dimethyl-γ-carboxyglutaric acid, m. p. 145°, obtained on saponification of the above ester, with the acid synthesized by the addition of sodium enol malonic ester to tiglic ester as follows.



$$\begin{array}{l} CH_3CH{=}C(CH_3)COOEt \\ \quad + \\ EtOOCC{-}H \\ \quad \| \\ \quad C(ONa)(OEt) \end{array} \longrightarrow \begin{array}{l} CH_3CH{-}CH(CH_3)COOEt \\ \quad | \\ \quad CH(COOEt)_2 \end{array}$$

However, the yields are small by this method (about 15%). Blaise[10] prepared α,β-dimethyl-γ-cyanoglutaric ester by addition of sodium enol cyanacetic ester to tiglic ester and obtained a better yield (65%). He also obtained α,β-dimethyl-γ-carboxyglutaric acid from the above cyano ester, but described it as a thick sirup. Repeating his synthesis, a crystalline acid was obtained which was identical with the acid prepared by the other methods.

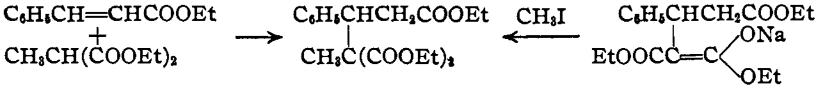
The α,β-dimethyl-γ-carboxyglutaric ester readily gave a sodium derivative which with methyl iodide gave the theoretical yield of α,β,γ-trimethyl-γ-carboxyglutaric ester



$$\begin{array}{l} CH_3CHCOOEt \\ | \\ CH_3CH \\ | \\ CH(COOEt)_2 \end{array} \xrightarrow{NaOEt} \begin{array}{l} CH_3CHCOOEt \\ | \\ CH_3CH \\ | \\ EtOOCC{=}C(ONa)(OEt) \end{array} \xrightarrow{CH_3I} \begin{array}{l} CH_3CHCOOEt \\ | \\ CH_3CH \\ | \\ CH_3C(COOEt)_2 \end{array}$$

When β,γ-dimethyl-γ-carboxyglutaric ester was treated with one molecular equivalent of sodium ethoxide, about half underwent retrogression into crotonic and methylmalonic esters. The remainder was converted into α,β-dimethyl-γ-carboxyglutaric ester, while a small amount (about 5%) of the ester was recovered unchanged. Since the addition is readily reversible, the change from β,γ-dimethyl-γ-carboxyglutaric ester to α,β-dimethyl-γ-carboxyglutaric ester undoubtedly went through this stage, the methyl migrating by virtue of the type of addition that occurs between the sodium enol methylmalonic and crotonic esters.

Parallel results were obtained in the addition of sodium enol methyl malonic ester to cinnamic ester. When the condensation was carried out using one-fifth of a molecular equivalent of sodium ethoxide, γ-methyl-β-phenyl-γ-carboxyglutaric ester was produced, showing that the parts of the addendum under these conditions are H and $-C(CH_3)(COOEt)_2$. The same ester was obtained by treatment of the sodium derivative of β-phenyl-γ-carboxyglutaric ester with methyl iodide



$$\begin{array}{l} C_6H_5CH{=}CHCOOEt \\ \quad + \\ CH_3CH(COOEt)_2 \end{array} \longrightarrow \begin{array}{l} C_6H_5CHCH_2COOEt \\ | \\ CH_3C(COOEt)_2 \end{array} \xleftarrow{CH_3I} \begin{array}{l} C_6H_5CHCH_2COOEt \\ | \\ EtOOCC{=}C(ONa)(OEt) \end{array}$$

These esters were identified by the acids obtained from them upon saponification. Two apparently stereomeric forms of γ-methyl-β-phenyl-γ-carboxyglutaric acid were obtained, m. p. 148 and 188°, respectively. The

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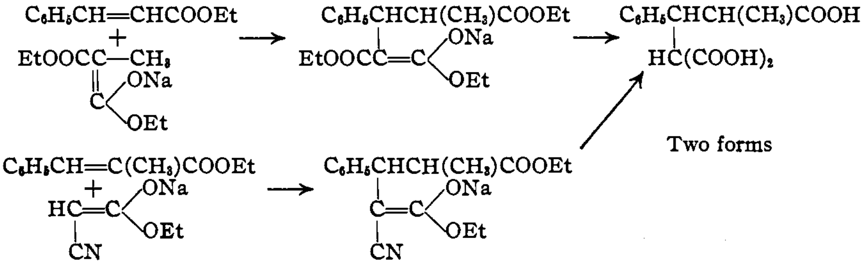
[10] Blaise, *Bull. soc. chim.*, [3] **29**, 332 (1903).

acid of m. p. 148° is a labile form and under certain conditions changes into the stable form, m. p. 188°. However, the acid of m. p. 148°, crystallized in large prisms, could be kept apparently for an indefinite period (a specimen over six months old shows no signs of change). Such isomerism in an acid of the glutaric series, asymmetric about one carbon atom only, is anomalous since a meso as well as a racemic form is not possible.

When methyl malonic ester was added to cinnamic ester, using one molecular equivalent of sodium ethoxide, the addition product consisted entirely of α-methyl-β-phenyl-γ-carboxyglutaric ester. Upon saponification and separation of the isomeric acids produced from this ester, two apparently stereomeric forms of α-methyl-β-phenyl-γ-carboxyglutaric acid were obtained. These were identified by direct comparison with the isomeric acids synthesized from the condensation product of sodium enol cyanacetic ester with α-methylcinnamic ester. The α-methyl-β-phenyl-γ-carboxyglutaric acid was obtained by hydrolysis of the cyano ester with caustic potash.



From these experiments it is apparent that sodium enol methylmalonic ester will suffer fission in the presence of an α,β-unsaturated ester so that the addendum to the ethylenic carbon atoms becomes CH_3 and —C(COOEt)-=C(ONa)OEt. When small amounts of sodium ethoxide are used to bring about the addition of methylmalonic ester to unsaturated esters, an entirely different mechanism is involved and the sodium enol methylmalonic ester cannot be considered to react as such; it is even doubtful whether it is formed. The small amount of sodium methoxide merely serves as a catalyst in the same manner as certain nitrogen bases, *e. g.*, piperidine, diethylamine,[11] used to produce similar additions of malonic to unsaturated esters.

A reacting system will proceed along the course whereby the maximum possible degradation of energy under the conditions of the experiment will be realized. This is illustrated by the conversion of maleic into fumaric acid by the catalytic action of a small amount of hydrobromic acid.[12] It may be assumed that a polymolecule of hydrobromic and maleic acid

[11] Knoevenagel and Mottek, *Ber.*, 37, 4464 (1904).

[12] Michael, *Am. Chem. J.*, 39, 3 (1908).

is first formed, evidently possessing greater free chemical energy than maleic acid, which enables it upon decomposition to form fumaric acid with liberation of heat and hydrogen bromide. Such a transformation proceeds until almost all the maleic acid is converted into fumaric acid. Thus a far greater degradation of energy is realized in the formation of fumaric acid than would be achieved in the formation of a small amount of bromosuccinic acid. When a considerable quantity of hydrobromic acid reacts with maleic acid, a mixture of bromosuccinic with fumaric acid is obtained.

Similarly, small amounts of sodium ethoxide may form polymolecules of high free chemical energy content but low stability, with the alkyl malonic ester present. The maximum degradation of energy is accomplished by causing simple addition of the alkyl malonic ester to the unsaturated ester, rather than the formation of some sodium enol alkyl malonic ester and addition of this to the unsaturated ester with migration of alkyl group to form a small amount of the sodium enol derivative of the tricarboxylic ester.

However, when a molecular equivalent of sodium ethoxide is used, the neutralization of the sodium in the sodium enol alkyl malonic ester becomes the deciding energy factor upon the course of the reaction. This is realized by the migration of the alkyl radical and the consequent formation of a better neutralized sodium enol derivative.

As a consequence of the above results, it is very probable that the addition products obtained previously using sodium enol alkyl malonic esters are compounds in which the alkyl group has migrated from the malonic residue. Some of these compounds are under reëxamination.

Experimental

β-Methyl-γ-carboxyglutaric ester was prepared by condensing sodium enol malonic ester with crotonic ester by Auwers.[13] A better yield was obtained by using a small amount of sodium ethoxide as condensing agent.

0.75 g. of sodium was dissolved in 10 cc. of absolute ethyl alcohol, 32 g. of malonic ester added and the mixture diluted with 300 cc. of dry ether; 23 g. of crotonic ester was added and the liquid refluxed for five hours on the water-bath. After cooling, a solution of 2 g. of acetic acid in 20 cc. of water was added with rapid shaking. The ethereal extract was washed with 10% sodium carbonate solution. The neutral ester had b. p. 144° (3 mm.); yield, 95%.

β-Methyl-γ-carboxyglutaric acid was obtained upon saponification of the above ester with 10% caustic soda. It crystallized in large prisms from a mixture of acetone and chloroform, m. p. 139°.

Anal. Calcd. for $C_7H_{10}O_6$: C, 44.21; H, 5.26. Found: C, 44.54; H, 5.36.

Methylation of β-Methyl-γ-carboxyglutaric Ester.—Two and three-tenths grams of sodium was pulverized and dissolved in 4.6 g. of ethyl alcohol in absolute ether solution by standing overnight;[14] 27.4 g. of β-methyl-γ-carboxyglutaric ester was added to the suspension of sodium ethoxide with cooling in ice and shaking. In a few minutes the

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[13] Auwers, *Ber.*, **24**, 2888 (1891); Michael. *ibid.*, **33**, 3748 (1900).

[14] Brühl, *ibid.*, **37**, 2067 (1904).

sodium ethoxide went into solution and 15 g. of methyl iodide was added. After standing for six hours in ice water, the product was worked up in the usual fashion; 28 g. of ester, b. p. 160° (9 mm.), was obtained, representing almost the theoretical yield of dimethyl-γ-carboxyglutaric ester.

Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.33; H, 8.33. Found: C, 58.2; H, 8.5.

β,γ-Dimethyl-γ-carboxyglutaric acid was obtained upon saponification of the above ester with caustic soda. It crystallized from acetone–chloroform mixture in characteristic nodules, m. p. 167°. Thorpe and Young[15] prepared this acid by methylation of β-methyl-γ-cyanoglutaric ester and give the melting point as 165°.

Anal. Calcd. for $C_8H_{12}O_6$: C, 47.07; H, 5.88. Found: C, 47.05; H, 5.9.

This acid, m. p. 167°, formed approximately 65% of the acid material. From the mother liquor a quantity of a sirupy acid was obtained, probably α,β-dimethyl-γ-carboxyglutaric acid.

Attempted **Methylation** of **β,γ-Dimethyl-γ-carboxyglutaric Ester.**—One and one-tenth grams of sodium was converted into anhydrous sodium ethoxide, and 12 g. of β,γ-dimethyl-γ-carboxyglutaric ester was added to the ether suspension cooled in ice. Although shaken for thirty minutes, not all the sodium ethoxide dissolved; 7.5 g. of methyl iodide was added and in a few minutes sodium iodide separated. The mixture was permitted to stand for six hours at room temperature. The material was then worked up in the usual way and the neutral products on distillation gave the following two main fractions: b. p. 80–100° (12 mm.), 8.0 g. of crotonic ester, dimethylmalonic ester; b. p. 160–162° (10 mm.), 3.5 g. of unchanged ester. Upon saponification, the last fraction gave entirely β,γ-dimethyl-γ-carboxyglutaric acid, m. p. 167°, showing that the only change that took place was the fission of the main part of the ester into crotonic and sodium enol methylmalonic esters.

Addition of **Methylmalonic** Ester to Crotonic Ester.—The methylmalonic ester used in the following experiments was prepared by methylation of sodium enol malonic ester and was purified from malonic ester by shaking out the latter with 25% caustic potash in the cold.[16]

(a) Using a Small Amount (One-Sixth **Molecule**) of Sodium **Ethoxide.**—0.75 g. of sodium was dissolved in 10 cc. of ethyl alcohol, 35 g. of methylmalonic ester was added, followed by 23 g. of crotonic ester and 300 cc. of dry ether. The whole was refluxed for five hours, then cooled and 2 g. of acetic acid in 20 cc. of water added. The ethereal solution was washed with 10% sodium carbonate. A yield of 49 g. of ester, b. p. 155° (2 mm.), was obtained. Saponification of this ester gave a mixture of acids which consisted of approximately 90% β,γ-dimethyl-γ-carboxyglutaric acid, m. p. 167°, together with 10% of α,β-dimethyl-γ-carboxyglutaric acid.

(b) Using One **Molecular** Equivalent of Sodium **Ethoxide.**—Four and six-tenths g. of sodium was converted into anhydrous sodium ethoxide; 35 g. of methylmalonic ester was added to the ethereal suspension, followed by 23 g. of crotonic ester and 300 cc. of ether. The mixture was refluxed for five hours, cooled, poured into 100 cc. of water containing 12 g. of acetic acid and worked up in the usual manner. On distillation 20 g. of unchanged esters, b. p. 60–100° (12 mm.), was first obtained, followed by 32 g. of ester, b. p. 148–150° (3 mm.), which proved to be α,β-dimethyl-γ-carboxyglutaric ester; yield, 60%.

Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.33; H, 8.33. Found: C, 58.25; H, 8.4.

α,β-Dimethyl-γ-carboxyglutaric acid was obtained by saponification of the above

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[15] Thorpe and Young, *J. Chem. Soc.*, **83**, 358 (1903).

[16] Michael, *J. prakt. Chem.*, **72**, 537 (1905).

ester with caustic soda. It was obtained as a sirup which in a desiccator became a solid. This was broken up, rubbed with chloroform and recrystallized from a mixture of ether and ligroin, m. p. 145°.

Anal. Calcd. for $C_8H_{12}O_6$: C, 47.07; H, 5.88. Found: C, 47.13; H, 5.99.

This acid was identified as α,β-dimethyl-γ-carboxyglutaric acid by mixed melting point with the acid prepared from the condensation product of sodium enol malonic ester with tiglic ester.

Upon distillation of this acid, m. p. 145°, a mixture of *cis* and *trans* α,β-dimethylglutaric acids was produced. This was separated by conversion of the *cis* acid into the anhydride and thence into the imide by treatment with dry ammonia gas at 130°. The *trans* acid was extracted with sodium carbonate from the reaction mixture, leaving the pure imide, m. p. 113°. Hydrolysis of the imide with caustic soda gave the *cis* α,β-dimethylglutaric acid, m. p. 87°. The *trans* acid was a liquid.[17]

Similarly, distillation of β,γ-dimethyl-γ-carboxyglutaric acid, m. p. 167°, gave *cis* and *trans* α,β-dimethylglutaric acids, which were separated through the imide. These were shown to be identical with the *cis* and *trans* α,β-dimethylglutaric acids obtained from α,β-dimethyl-γ-carboxyglutaric acid.

Methylation of α,β-Dimethyl-γ-carboxyglutaric Ester.—One and two-tenths grams of sodium was converted into anhydrous sodium ethoxide and 14.5 g. of α,β-dimethyl-γ-carboxyglutaric ester was added to the ether suspension, cooled in ice water. The sodium ethoxide readily dissolved, 8 g. of methyl iodide was added and the mixture left to stand for six hours. The product was then worked up in the usual way; 14 g. of α,β,γ-trimethyl-γ-carboxyglutaric ester, b. p. 164° (3 mm.), was obtained.

Anal. Calcd. for $C_{15}H_{26}O_6$: C, 59.6; H, 8.61. Found: C, 59.4; H, 8.6.

α,β,γ-Trimethyl-α-carboxyglutaric acid was obtained from the above ester by saponification with caustic soda. The acid was obtained as a sirup which could not be crystallized.

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.53; H, 6.45. Found: C, 49.83; H, 6.52.

Upon distillation the acid gave the *cis* and *trans* forms of α,β,γ-trimethylglutaric acid.

Action of Sodium Ethoxide upon β,γ-Dimethyl-γ-carboxyglutaric Ester.—Fourteen and five-tenths grams of the ester was refluxed for six hours with an ethereal suspension of sodium ethoxide prepared from 1.2 g. of sodium by Brühl's method. After cooling, the product was poured into a solution of 4 g. of acetic acid in water, and the mixture worked up in the usual manner; 7 g. of the neutral ester boiling below 150° (15 mm.) consisted of crotonic and methylmalonic esters; 6 g. of ester boiled at 160–163° (15 mm.). This ester was saponified and found to consist mainly of α,β-dimethyl-γ-carboxyglutaric acid, m. p. 145°. A small amount (0.5 g.) of β,γ-dimethyl-γ-carboxyglutaric acid, m. p. 167°, separated from this material was formed from unchanged ester.

Addition of Malonic Ester to Tiglic Ester.—Twelve grams of malonic ester was added to sodium ethoxide prepared by Brühl's method from 1.8 g. of sodium; 9 g. of tiglic ester, b. p. 158° (760 mm.), was added and the ethereal solution heated on a water-bath for five hours. Working up the products in the usual manner gave a yield of 3 g. of α,β-dimethyl-γ-carboxyglutaric ester, b. p. 150° (3 mm.).

Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.33; H, 8.33. Found: C, 58.1; H, 8.4.

α,β-Dimethyl-γ-carboxyglutaric acid was obtained from the above ester by saponification with caustic soda. It crystallized in well-defined prisms, m. p. 145° with decomposition.

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[17] Thorpe, *J. Chem. Soc.*, **83**, 358 (1903).

Anal. Calcd. for $C_8H_{12}O_6$: C, 47.07; H, 5.88. Found: C, 47.15; H, 5.8.

Larger quantities of this acid were prepared from the product of addition of sodium enol cyanacetic ester to tiglic ester.[18] The yield of α,β-dimethyl-γ-cyanoglutaric ester was 65% and it boiled at 143° (3 mm.). α,β-Dimethyl-γ-carboxyglutaric acid, obtained from the cyano ester by hydrolysis with caustic potash, was identical with the substance prepared by the other two methods.

α,β,γ-Trimethyl-γ-cyanoglutaric Ester.—Twelve grams of α,β-dimethyl-γ-cyanoglutaric ester was added to sodium ethoxide prepared from 1.2 g. of sodium and to the cooled ether solution 8 g. of methyl iodide was added. After standing for six hours. the mixture was worked up as usual. α,β,γ-Trimethyl-γ-cyanoglutaric ester distilled at 160° (2 mm.).

Anal. Calcd. for $C_{13}H_{21}O_4N$: C, 61.2; H, 8.24. Found: C, 60.9; H, 8.3.

α,β,γ-Trimethyl-γ-**carboxyglutaric** acid was obtained by hydrolysis of the above ester with a 20% caustic potash solution. The acid was obtained as a sirup.

Anal. Calcd. for $C_8H_{14}O_6$: C, 49.53; H, 6.45. Found: C, 49.6; H, 6.6.

F. E. Ray[19] prepared this acid from the ester obtained upon methylation of α,β-dimethyl-γ-cyanoglutaric ester, and described it as a solid, m. p. 144–145°. (It may be noted that 145° is the melting point of α,β-dimethyl-γ-carboxyglutaric acid.)

α,β,γ-Trimethylglutaric Acid.—α,β,γ-Trimethyl-γ-carboxyglutaric acid was heated at 160° in a distilling flask for thirty minutes, when the evolution of carbon dioxide ceased. The residue was then distilled, coming over at 170–180° (15 mm.) and partially solidifying in the receiver. This distillate was a mixture of *cis* and *trans* acids which were separated by the conversion of the *cis* form into the imide in the following way. The mixture, in a small distilling flask, was converted into the anhydride by several treatments with acetyl chloride. The acetic acid formed was removed under reduced pressure and dry ammonia gas passed through the sirupy mass at 130° for one hour. The cooled contents was dissolved in dilute hydrochloric acid. The acid solution was extracted with ether and the extract washed with aqueous sodium carbonate to remove the *trans* acid. Upon concentration of the ether solution the imide crystallized out.

α,β,γ-**Trimethylglutarimide** was recrystallized from a mixture of ether and ligroin, m. p. 90°.

Anal. Calcd. for $C_8H_{13}O_2N$: C, 61.94; H, 8.38. Found: C, 61.8; H, 8.2.

Cis-α,β,γ-**trimethylglutaric** acid was obtained from the α,β,γ-trimethylglutarimide by hydrolysis with 20% caustic soda. It crystallized from an ether and ligroin mixture in large prisms which, after the fourth crystallization, softened at 115° and melted at 125°.

Anal. Calcd. for $C_8H_{16}O_4$: C, 55.2; H, 8.06. Found: C, 55.6; H, 8.3.

Cis-α,β,γ-**trimethylglutaric anhydride** was a liquid. It was prepared from the above acid by treatment with acetyl chloride.

Trans-α,β,γ-trimethylglutaric acid was obtained by acidification of the sodium carbonate extract in the above separation from the *cis* imide. It remained a liquid and resisted all attempts to obtain a crystalline form.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.2; H, 8.04. Found: C, 55.0; H, 8.2.

F. E. Ray[19] described an α,β,γ-trimethylglutaric acid melting at 134°. He did not attempt to separate his product into the *cis* and *trans* forms, but obtained his acid by a series of crystallizations.

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[18] Blaise. *Bull. soc. chim.*, [3] **29**, 332 (1903).

[19] Ray, THIS JOURNAL, **50**, 558 (1928).

β-Phenyl-γ-carboxyglutaric ester was prepared by addition of malonic ester to cinnamic ester using a small amount of sodium ethoxide; yield, 70%; b. p. 187° (4 mm.).[20]

β-Phenyl-γ-carboxyglutaric acid was obtained by saponification of the above ester with 10% caustic soda. This acid crystallizes from a mixture of chloroform and ligroin in fine needles, m. p. 137°.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.15; H, 4.76. Found: C, 56.9; H, 5.0.

Methylation of β-Phenyl-γ-carboxyglutaric Ester.—Thirty-four grams of the above ester was added to anhydrous sodium ethoxide prepared from 2.3 g. of sodium in ether; 15 g. of methyl iodide was added, the mixture allowed to stand in ice water for six hours, and the material worked up in the usual manner. On distillation of the neutral product, 17 g. boiled from 80–140° (3 mm.) and consisted of cinnamic and dimethylmalonic esters and 12 g. of γ-methyl-β-phenyl-γ-carboxyglutaric ester boiled at 194° (3 mm.).

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.13; H, 7.43. Found: C, 65.0; H, 7.6.

γ-Methyl-β-phenyl-γ-carboxyglutaric acid was obtained from the above ester by saponification with caustic soda. On crystallization from a mixture of chloroform, acetone and ligroin, the acid first deposited fine needles which melted at 188° with decomposition.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.26. Found: C, 58.4; H, 5.4.

The mother liquor then deposited a second acid crystallizing in large prisms, m. p., 148°.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.26. Found: C, 58.3; H, 5.1.

These two acids are isomeric forms of γ-methyl-β-phenyl-γ-carboxyglutaric acid. The fine crystals of the acid, m. p. 148°, upon standing on a porous tile became converted into a form of m. p. 188° in the course of several hours. Large, well developed crystals of the low-melting form could be kept in a corked vessel for several months without change.

Carter and Lawrence[21] described γ-methyl-β-phenyl-γ-carboxyglutaric acid which they prepared by methylation of β-phenyl-γ-cyanoglutaric ester and saponification of the resulting γ-methyl-β-phenyl-γ-cyanoglutaric esters (which they obtained in two stereoisomeric forms) with caustic potash. They found that each of these stereoisomeric cyano esters gave the same γ-methyl-β-phenyl-γ-carboxyglutaric acid, m. p. 148°. Since they did not report obtaining any of the form of m. p. 188°, their synthesis was repeated. It was found that hydrolysis with alkali of each of the two γ-methyl-β-phenyl-γ-cyanoglutaric esters gave the acid of m. p. 148°, but this could be converted into the form of m. p. 188°.

Addition of Methylmalonic Ester to Cinnamic Ester

(a) **Using a Small Amount of Sodium Ethoxide.**—One-half gram of sodium was dissolved in the minimum of ethyl alcohol, 20 g. of methylmalonic ester added, then 200 cc. of dry ether and finally 20 g. of cinnamic ester. The mixture was refluxed on the water-bath for five hours, cooled and a solution of 2 g. of acetic acid in 20 cc. of water added. The product was worked up in the usual way; 16 g. of ester boiling at 80–140° (3 mm.) consisted of apparently unchanged esters; 20 g. boiling at 194–195° (3 mm.) proved to be γ-methyl-β-phenyl-γ-carboxyglutaric ester, since upon saponification it gave the corresponding acid.

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[20] Michael, *J. prakt. Chem.* 35, 350 (1887).

[21] Carter and Lawrence, *Proc. Chem. Soc.*, 178 (1900).

(b) **Using One Molecular Equivalent of Sodium Ethoxide.**—Twenty grams of methylmalonic ester was added to a suspension of sodium ethoxide prepared from 2.6 g. of sodium in dry ether; 20 g. of cinnamic ester was added and the mixture refluxed on the water-bath for six hours. After cooling, 7 g. of acetic acid in 50 cc. of water was added, and the ethereal extract worked up in the usual way. The neutral esters were fractionated and 16 g., b. p. 185–188° (3 mm.), was obtained.

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.13; H, 7.43. Found: C, 64.9; H, 7.51.

α-Methyl-β-phenyl-γ-carboxyglutaric acids were obtained from the above ester upon saponification with caustic soda, thus proving its structure. The acid first deposited from solution in a mixture of chloroform, acetone and ligroin had a melting point of 171°. The mother liquor deposited a second acid, which crystallized in fine needles, m. p. 145°. These two acids, present in approximately equal amounts, were shown by analysis and mixed melting point to be identical with the corresponding acids synthesized from α-methylcinnamic ester.

Addition of Sodium Enol Cyanacetic Ester to α-Methylcinnamic Ester.—Three and six-tenths grams of sodium was dissolved in 50 cc. of alcohol and 17 g. of cyanacetic ester added, followed by 29 g. of α-methylcinnamic ester. The mixture was heated on the water-bath for twenty-four hours. After cooling, the product was poured into a solution of 10 g. of acetic acid in 200 g. of water, and the esters were extracted with ether. On fractionation of the neutral esters, 26 g. of α-methyl-β-phenyl-γ-cyanoglutaric ester, b. p. 185–187° (3 mm.), was obtained as a thick liquid.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.33; H, 6.93. Found: C, 67.15; H, 7.1.

α-Methyl-β-phenyl-γ-carboxyglutaric acids were obtained by hydrolysis of the above ester with caustic potash. Upon fractional crystallization, the first acid was deposited as large prisms, m. p. 171°, with decomposition.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.49; H, 5.26. Found: C, 58.49; H, 5.5.

From the mother liquor a second acid was deposited as fine needles, m. p. 145° with decomposition.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.49; H, 5.26. Found: C, 58.30; H, 5.4.

Summary

1. It has been shown that the course of addition of methylmalonic ester to crotonic and cinnamic esters varies with the amount of sodium ethoxide used.

2. In the presence of small amounts of sodium ethoxide the addition proceeds with H and $—C(CH_3)(COOEt)_2$ as addendum components.

3. In the presence of a molecular equivalent of sodium ethoxide the addition proceeds with CH_3 and $—C(COOEt)=C(ONa)OEt$ as addendum components.

4. These results have rigorously proved the correctness of Thorpe's conclusions: that the addition of sodium enol cyanacetic ester to α-methylacrylic ester takes place with migration of the hydrogen atom and that the addition of sodium enol α-cyano propionic ester to β,β-dimethylacrylic ester takes place with migration of the methyl group.

5. The mechanism of these reactions is discussed and explanations of the results are suggested.

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