The Michael Addition of Diethyl Methylmalonate to Ethyl Crotonate-(carbonyl C^{14}). A Contribution to the Elucidation of the Mechanism of the Abnormal Addition

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In the course of a paper on the constitution of ethyl sodiocyanacetate and of ethyl sodiomethylcyanacetate, Thorpe[1] has put forth a view that these sodio compounds, $RC(CN):C(ONa)OC_2H_5$ (R=H or alkyl), add to the double bond of α,β-unsaturated carboxylic esters with R- and $-C(CN):C(ONa)OC_2H_5$ acting as addendum components. More recently, Michael and Ross[2] have shown that diethyl methylmalonate in the presence of one sixth equivalent of sodium ethoxide adds to ethyl crotonate to yield diethyl α-ethoxycarbonyl-α,β-dimethylglutarate, whereas, with one equivalent of sodium ethoxide, the product is diethyl α-ethoxycarbonyl-β,γ-dimethylglutarate in accordance with Thorpe's view. A product of the former type in the Michael addition is often referred to as normal by later workers and one of the latter type as abnormal.

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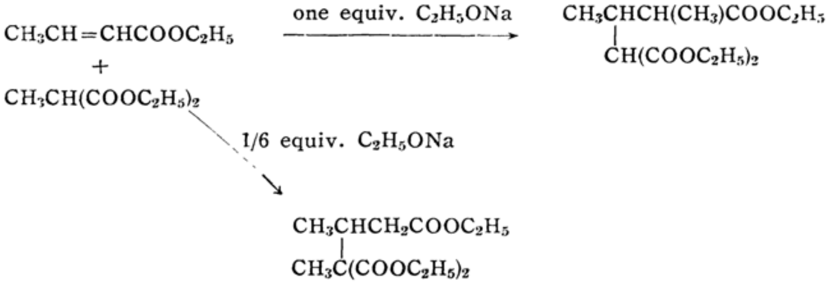
[1] J. F. Thorpe, *J. Chem. Soc.*, **77**, 923 (1900).

[2] A. Michael and J. Ross, *J. Am. Chem. Soc.*, **52**, 4598 (1930).

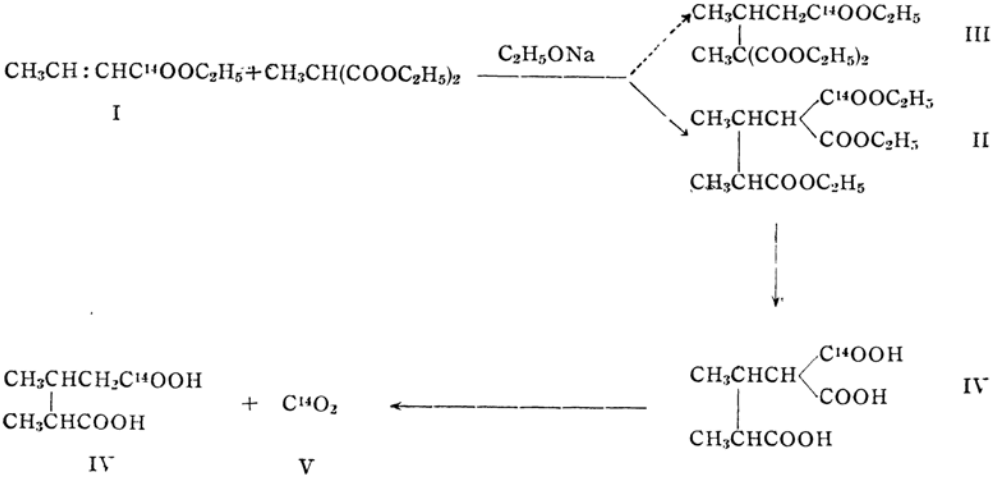


$$CH_3CH{=}CHCOOC_2H_5 + CH_3CH(COOC_2H_5)_2 \xrightarrow{\text{one equiv. } C_2H_5ONa} CH_3\underset{CH(COOC_2H_5)_2}{CH}CH(CH_3)COOC_2H_5$$

$$CH_3CH{=}CHCOOC_2H_5 + CH_3CH(COOC_2H_5)_2 \xrightarrow{\text{1/6 equiv. } C_2H_5ONa} CH_3\underset{CH_3C(COOC_2H_5)_2}{CH}CH_2COOC_2H_5$$

It has then been suggested by Holden and Lapworth[3] that the abnormal addition product with a structure expected from Thorpe's theory could result equally well by migration, during the addition process, of an ethoxycarbonyl group from the malonic ester part of the adduct; however, they were unable to produce any convincing experimental evidence in favour of the theory. Gardner and Rydon[4] have subsequently shown that all the then available observations can be accounted for on the basis of the Holden-Lapworth mechanism; but it has been viewed with some suspicion because of the strained four-membered cyclic structure postulated as an intermediate. It has now been definitely established by a tracer method with carbon-14 that, in the Michael addition of diethyl methylmalonate to ethyl crotonate with one equivalent of sodium ethoxide, it is an ethoxycarbonyl group which migrates to yield the abnormal addition product.

Labelled ethyl crotonate was condensed with diethyl sodiomethylmalonate, and the resulting diethyl α-ethoxycarbonyl-β,γ-dimethylglutarate hydrolyzed with sodium hydroxide to the corresponding tricarboxylic acid, which was subsequently decarboxylated by heating at 170–180°. The carbon dioxide evolved was found to contain about 42 % of the radioactive carbon of the original ethyl crotonate. This observation demonstrated beyond doubt that in the course of the condensation migration of an ethoxycarbonyl group took place from the methylmalonate moiety to the carbon atom α to the labelled ethoxycarbonyl group giving a product (II) with a malonic ester grouping labelled with C^{14}. If a methyl group had become attached to the carbon atom α to the labelled ethoxycarbonyl group as postulated by Thorpe[1] and Michael and Ross[2], the resulting condensation product could have contained no labelled malonic ester grouping, and the subsequent hydrolysis followed by pyrolysis could have consequently given no radioactive carbon dioxide. The sequence of the reactions followed is shown as follows and the measured activities of the products at each stage of the reactions given in Table I.



$$\underset{\text{I}}{CH_3CH:CHC^{14}OOC_2H_5 + CH_3CH(COOC_2H_5)_2} \xrightarrow{C_2H_5ONa} \underset{\text{III}}{CH_3\underset{CH_3C(COOC_2H_5)_2}{CH}CH_2C^{14}OOC_2H_5} \text{ or } \underset{\text{II}}{CH_3\underset{CH_3CHCOOC_2H_5}{CH}CH\begin{smallmatrix}C^{14}OOC_2H_5\\COOC_2H_5\end{smallmatrix}}$$

$$\text{II} \longrightarrow \underset{\text{IV}}{CH_3\underset{CH_3CHCOOH}{CH}CH\begin{smallmatrix}C^{14}OOH\\COOH\end{smallmatrix}} \longrightarrow \underset{\text{IV}}{CH_3\underset{CH_3CHCOOH}{CH}CH_2C^{14}OOH} + \underset{\text{V}}{C^{14}O_2}$$

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[3] N. E. Holden and A. Lapworth, *J. Chem. Soc.*, **1931**, 2368.

[4] J. A. Gardner and H. N. Rydon, ibid., **1938**, 48.

TABLE I

MOLAR ACTIVITIES* OF THE REACTION PRODUCTS

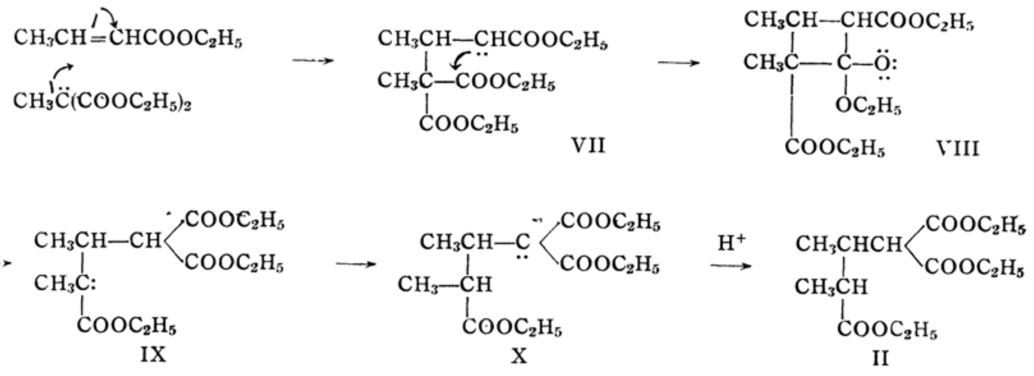
	Expt. 1 mc./mol.	Expt. 2 mc./mol.
Ethyl crotonate (I)	0.0805 ± 0.0013	0.0285 ± 0.0006
Diethyl α-ethoxycarbonyl-β,γ-dimethylglutarate (II)	0.123 ± 0.003	0.0415 ± 0.0018
α-Carboxy-β,γ-dimethylglutaric acid (IV)	0.120 ± 0.003	0.0399 ± 0.0013
Carbon dioxide from decarboxylation (V)	0.0335 ± 0.0007	0.0120 ± 0.0004
Carbon dioxide from combustion of the residue (VI)	——	0.0043 ± 0.0002

* Indicated deviations are standard errors.

In the course of the investigation some difficulty arose with regard to some molar activity values. Molar activities of diethyl α-ethoxycarbonyl-β,γ-dimethylglutarate (II) and the corresponding free tricarboxylic acid were unusually high compared with the theoretical values of 0.0805 and 0.0285 expected from the activities of the starting materials. This anomaly is probably attributable to the contamination with labelled diethyl α-ethylidene-β-methylglutarate, which may have been formed by the dimerization of the labelled ethyl crotonate in the presence of basic reagents⁵⁾. It seems that the fractionation was not carried out effectively owing to the smallness of the quantity of the material to be handled. On the basis of the measured molar activities, the contents of the dimer of ethyl crotonate in the condensation products are calculated to be 49 and 39 mole% for Expts. 1 and 2, respectively. The alkaline hydrolysis of the condensation product did not give crystalline acid; this is due to the presence of diastereomeric forms of the tricarboxylic acid (IV) in addition to the acid from the above dimer. The observed neutralization equivalents of the products (72.7 and 73.9 for Expts. 1 and 2, respectively) were higher than the theoretical value of 68.1 for α-carboxy-β,γ-dimethylglutaric acid; the differences are accounted for quantitatively by correcting for the presence of the crotonic acid dimer. Further, the activity of the carbon dioxide obtained by oxidation of the residue from the decarboxylation was found to be 0.0043 mc./mol., which agrees well with 0.0044 mc./mol. calculated from the composition of the condensation product.

It is generally recognized that the C^{12}-carboxyl group is eliminated as carbon dioxide from malonic and substituted malonic acids several per cent more frequently than the C^{14}-carboxyl group.⁶⁾ On the tentative assumption that the difference in the reaction rate is ten par cent, the molar activity of the carbon dioxide evolved from α-carboxy- β,γ-dimethylglutaric acid in, for example, Expt. 2 should be 0.0285/(1.10+1.0) = 0.0136 mc./mol. The observed value of 0.0120 mc./mol. appears therefore to be too low. This is probably attributed to the possible presence of a small quantity of the unrearranged normal product (III).

An essential part of the mechanism of the Michael addition with migration of an ethoxycarbonyl group may be formulated as follows:



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5) H. v. Pechmann, *Ber.*, **33**, 3323 (1900); A. Michael and J. Ross, *J. Am. Chem. Soc.*, **53**, 1150 (1931).

6) G. A. Ropp, *Nucleonics*, **10**, No. 10, 22 (1952)

The carbonyl oxygen of the migrating ethoxycarbonyl group plays a role in helping the carbonyl carbon to accept a lone pair of electrons from the carbon atom α to the ethoxycarbonyl group on the original ethyl crotonate resulting in a four-membered cyclic structure provisionally shown as VIII. Objection might be raised to such a structure which may suffer from a considerable strain, but the four-membered cyclic compounds are not so strained that their existence should be rendered impossible. It may be considered that structure VIII represents a transitional state of the rearrangement rather than a more or less stable intermediate, the acceptance of the lone pair being synchronized with the release of the electron pair which has originally linked the migrating group with the α carbon atom of the original diethyl methylmalonate, giving rise to IX. The migration of the ethoxycarbonyl group is followed by a transfer of a proton in the reverse direction to it, X thus being formed, in which a carbanion group is more stabilized than in IX. It is possible that the transfer of the proton may be simultaneous with the migration of the ethoxycarbonyl group. This is a natural consequence of the difference in acidity between a CH group activated by one ethoxycarbonyl group and one activated by two such groups, the acidity of the former being less strong than the latter. Finally, X gives the rearranged product (II) on working up with aqueous acid.

If there is, in the reacting mixture, a stronger acid which can donate a proton to a lone pair of electrons shown in structure VII, the migration of an ethoxycarbonyl group will not take place. This is indeed the case with the Michael condensation with one sixth equivalent of sodium ethoxide[2]; diethyl methylmalonate which had not completely been converted to the sodio compound served as a proton donor. Tsuruta, Yasuhara and Furukawa[7] investigated the effect of variation of experimental conditions, specially of the amount of sodium ethoxide in the Michael addition of diethyl ethylmalonate to diethyl fumarate on the relative yield of the normal and abnormal products and pointed out a competition between the reaction of the initially formed adduct anion (similar to VII) with a proton donor giving the normal product and the isomerization of the adduct anion leading to the abnormal product; but the mechanism of the latter reaction was obscure to them.

As regards what types of reactants will show abnormality and what types will be normal, the theory of the abnormal addition discussed above predicts that condensation of unsaturated compounds of the type $CR_2:CHCOOC_2H_5$ with alkylmalonic ester and similar compounds can be abnormal, and that those of unsaturated substances of the type $CR_2:CRCOOC_2H_5$ with malonic esters will be normal.

Experimental

Crotonic Acid-(carboxyl-C^{14}) This acid was synthesized by the carbonation with radioactive carbon dioxide of allymagnesium bromide prepared according to Shoemaker and Boord[8] followed by the isomerization with hot 50 % sulfuric acid[9] according to the following scheme.

$$CH_2:CHCH_2MgBr + C^{14}O_2 \longrightarrow CH_2:CHCH_2C^{14}OOH$$

$$CH_2:CHCH_2C^{14}OOH \longrightarrow CH_3CH:CHC^{14}OOH$$

Starting from 393 mg. of active barium carbonate containing 0.12 mc. of C^{14} and diluting the resulting crude labelled crotonic acid with a total of 2.0 g. of pure unlabelled crotonic acid as a carrier for ease of manipulation, 0.48 g. of labelled crotonic acid with constant activity of 0.245 ± 0.0043 mc./mol., m. p. 70.5–72.0°, was obtained after crystallization four times from petroleum ether. On the basis of the molar activity of the crotonic acid the overall yield of the above synthesis is estimated at 4.9 % based on the carbon dioxide used. The poor yield is attributed to the carbonation step, as the isomerization appears to be effected with an almost quantitative yield of 98% according to the literature.[9]

Another approach to labelled crotonic acid followed consisted in the action of labelled potassium cyanide on allyl bromide at 100° in a sealed tube, and the subsequent hydrolysis and simultaneous isomerization to crotonic acid by heating the resulting ally cyanide with 50 % sulfuric acid on a water bath.

$$CH_2:CHCH_2Br + KC^{14}N \longrightarrow CH_2:CHCH_2C^{14}N$$

$$CH_2:CHCH_2C^{14}N \longrightarrow CH_3CH:CHC^{14}OOH$$

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[7] T. Tsuruta, Y. Yasuhara and J. Furukawa, *J. Org. Chem.*, **18**, 1246 (1953).

[8] B. H. Shoemaker and C. E. Boord, *J. Am. Chem. Soc.*, **53**, 1505 (1931).

[9] E. J. Boorman and R. P. Linstead, *J. Chem. Soc.*, **1933**, 577.

This method gave an overall yield of 25 % based on the cyanide used.

Ethyl Crotonate-(carbonyl-C^{14}) The synthetic procedure was similar to that for ethyl acetate by Ropp.[10] Crotonic acid-(carboxyl-C^{14}) (1. 1 g.) was neutralized with aqueous sodium hydroxide, the resulting solution evaporated to dryness on a water bath, and the remaining labelled sodium crotonate desiccated at 120° under 5×10^{-4} mm.Hg. This was heated for one hour at 180–210° with 3.8 cc. of ethyl phosphate, b. p. 104–5° at 20 mm. Hg, prepared according to the method of Dutton and Noller.[11] Distillation of the reaction mixture at 2×10^{-4} mm. Hg gave 1.3 g. of ethyl crotonate-(carbonyl-C^{14}). This procedure yielded pure specimen of ethyl crotonate, n_{D}^{20}1.4247, in a preliminary experiment with unlabelled crotonic acid.

The Michael Addition Two similar runs were carried out, one of which (Expt. 2) is described as an example. Sodium (0.5 g.) was melted by heating in xylene and powdered by shaking, the xylene decanted, the sodium washed with ether, and 100 cc. of ether and 1.3 g. of absolute ethyl alcohol added to prepare sodium ethoxide. To this mixture 3.8 g. of diethyl methylmalonate prepared from methyl iodide and diethylsodiomalonate in alcohol according to the usual practice, b. p. 114.0–114.5° at 46 mm Hg, was added. Ethyl crotonate-(carbonyl-C^{14}) (2.21 g., 0.0285 mc./mol.) in 50 cc. of ether was then added dropwise to the stirred mixture and the mixture was refluxed for 5 hours. Acetic acid (1.6 g.) in 12.5 cc. of water was added with stirring, the ethereal layer separated, dried with anhydrous sodium sulfate, the ether removed on a water bath and the residue subjected to distillation under diminished pressure, giving 1.7 g. of a fraction (II) boiling at 130–131° at 3 mm. Hg. The condensation product was heated with 1.0 g. of sodium hydroxide in a mixture of 5 cc. each of water and alcohol for two hours and a half on a water bath, the alcohol removed, the residue diluted with water to 80 cc. and filtered through a column of Amberlite IR 120. A fraction with *p*H 2.2 was collected and evaporated to dryness over sulfuric acid in a vacuum desiccator, giving 1.1 g. of acid (IV) (neutralization equivalent, 73.9; activity, 0.0399 ± 0.0013 mc./mol.).

Decarboxylation of α-Carboxy-β,γ-dimethylglutaric Acid The above acid (170 mg.) was heated gradually to 180° in an evacuated vessel, and the vessel was kept at that temperature for one hour. The carbon dioxide evolved was condensed in a trap cooled with liquid air attached to the reaction vessel. When the decarboxylation was over, the condensed carbon dioxide was transferred, also in vacuum, to aqueous sodium hydroxide contained in another flask. Ammonium chloride was added to the sodium hydroxide solution, barium carbonate precipitated by adding barium chloride solution, collected on a filter paper and assayed for radioactivity (Found: 0.0120 ±0.0004 mc./mol.). The same result was obtained, if the decarboxylation and absorption of carbon dioxide by aqueous sodium hydroxide was carried out in an apparatus for Van Slyke-Folch oxidation[12], thus eliminating the operation of condensing carbon dioxide by liquid air.

Radioactivity Determinations Radiocarbon assays were carried out by oxidizing samples according to Van Slyke and Folch[13], and converting the resulting carbon dioxide to barium carbonate, which was counted with a Geiger-Müller counter on an "infinitely thick" layer with a surface area of 4.9 cm², the counts being all corrected for background and compared with the count of a standard barium carbonate with known molar activity.

Summary

The Michael addition of diethyl methylmalonate to ethyl crotonate-(carbonyl-C^{14}) was carried out with one equivalent of sodium ethoxide; the addition product, diethyl α-ethoxycarbonyl-β,γ-dimethylglutarate, was hydrolyzed and the resulting acid decarboxylated by heating. The evolved carbon dioxide contained 42 % of the radiocarbon of the original ethyl crotonate. Thus it was demonstrated that the migration of an ethoxycarbonyl group took place in the course of the reaction from the methylmalonate moiety to the carbon atom α to the labelled ethoxycarbonyl group. The mechaism of the reaction is discussed.

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[10] G. A. Ropp, *J. Am. Chem. Soc.*, **72**, 2299 (1950).

[11] R. G. Dutton and C. R. Noller, "Organic Syntheses," **16**, 9 (1936).

[12] M. Calvin et al., "Isotopic Carbon", John Wiley & Sons, Inc., New York, 1949, p. 93.

[13] D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 509 (1940).