The Michael Addition of Diethyl Malonate to Ethyl Crotonate-(carbonyl-C^{14})[1]

By Osamu SIMAMURA and Naoki INAMOTO

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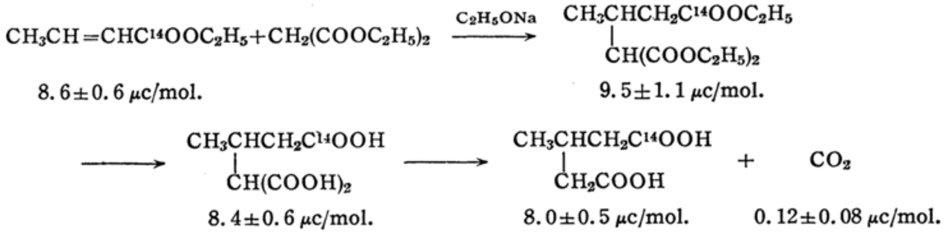
Michael and Ross have shown[2] that whereas diethyl methylmalonate adds to ethyl crotonate in the presence of one sixth equivalent of sodium ethoxide to yield diethyl α-ethoxycarbonyl-α, β-dimethylglutarate (normal product), the product is, with one equivalent of sodium ethoxide, diethyl α-ethoxycarbonyl-β, γ-dimethylglutarate (abnormal product). In a previous work[3] it has been established by a tracer technique with radioactive carbon-14 that the abnormal product is formed by the migration of an ethoxycarbonyl group from the diethyl methylmalonate moiety to the α-carbon atom of the crotonate in the course of the addition reaction. A mechanism of the formation of the normal or abnormal product according to experimental conditions has been put foward and the structural features which lead to the migration of the ethoxycarbonyl group have been discussed.

Work has now been extended to the Michael addition between diethyl malonate and ethyl crotonate-(carbonyl-C^{14}). In this case, the migration of an ethoxycarbonyl group from diethyl malonate should result in structurally the same product as the one formed without the migration. But, similarly to the case with diethyl methylmalonate described previously, the tracer method would reveal any migration which might take place.

Labelled ethyl crotonate (activity 8.6±0.6 μc/mol.) was refluxed with diethyl sodiomalonate in ether and the resulting diethyl α-ethoxycarbonyl-β-methylglutarate was hydrolyzed with sodium hydroxide to the corresponding tricarboxylic acid (activity 8.4±0.6 μc/mol.). The decarboxylation of this acid by heating at 165° gave carbon dioxide which was found to be only slightly active, and β-methylglutaric acid with an activity of 8.0±0.5 μc/mol. The sequence of the reactions carried out is shown below and the measured activities (with standard errors) of the products at each step are also given under the formulae.

If the migration of an ethoxycarbonyl group had taken place freely in the course of the Michael addition from an adding molecule of diethyl malonate to the carbon atom α to the labelled ethoxycarbonyl group of ethyl crotonate, the tricarboxylic acid



$$CH_3CH{=}CHC^{14}OOC_2H_5 + CH_2(COOC_2H_5)_2 \xrightarrow{C_2H_5ONa} \begin{array}{l} CH_3CHCH_2C^{14}OOC_2H_5 \\ \quad | \\ \quad CH(COOC_2H_5)_2 \end{array}$$

8.6±0.6 μc/mol. 9.5±1.1 μc/mol.

$$\longrightarrow \begin{array}{l} CH_3CHCH_2C^{14}OOH \\ \quad | \\ \quad CH(COOH)_2 \end{array} \longrightarrow \begin{array}{l} CH_3CHCH_2C^{14}OOH \\ \quad | \\ \quad CH_2COOH \end{array} + CO_2$$

8.4±0.6 μc/mol. 8.0±0.5 μc/mol. 0.12±0.08 μc/mol.

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[1] Presented at the Meeting of the Kanto Section of the Chemical Society of Japan, in Tokyo, Sept. 18, 1954.

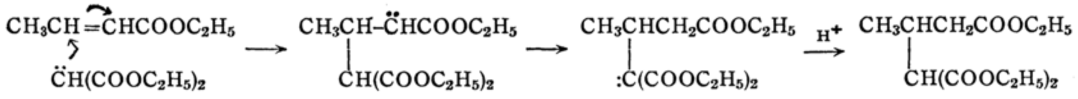
[2] A. Michael and J. Ross, *J. Am. Chem. Soc.*, 52, 4598 (1930).

[3] O. Simamura, N. Inamoto and T. Suehiro, This Bulletin, 27, 221 (1954).

Added in proof—D. Samuel and D. Ginsburg, *J. Chem. Soc.*, **1955**, 1288, have come to the same conclusion by the use of O^{18} as tracer.

obtained by hydrolysis of the addition product would have included a labelled malonic acid grouping, and therefore the carbon dioxide evolved on decarboxylation would have contained half the amount of the radioactivity in the original ethyl crotonate. Most of the activity being actually found in β-methylglutaric acid, it was demonstrated that such a migration of the ethoxycarbonyl group occurred only to an extremely limited extent and the addition proceeded almost normally.

According to the theory set forth previously, the non-migration of the ethoxycarbonyl group in the present case is due to the presence of an acidic hydrogen atom on the carbon with two activating ethoxycarbonyl groups in an adduct anion (I) initially formed from diethyl sodiomalonate and ethyl crotonate. This hydrogen atom immediately migrates to the carbon atom carrying a lone pair of electrons, giving rise to an isomeric anion (II), which is more stable than structure (I) owing to the conjugation of the lone pair of electrons thus produced with two ethoxycarbonyl groups. In the process of working up of the reaction mixture, anion (II) picks up a proton from the aqueous medium to give the final product (III). The present result demonstrates that the migratory aptitude of a proton to an atom with a lone pair of electrons exceeds by far that of an ethoxycarbonyl group.



$$\begin{array}{l} CH_3CH{=}CHCOOC_2H_5 \\ \ddot{C}H(COOC_2H_5)_2 \end{array} \longrightarrow \begin{array}{l} CH_3CH{-}\ddot{C}HCOOC_2H_5 \\ \quad | \\ CH(COOC_2H_5)_2 \end{array} \longrightarrow \begin{array}{l} CH_3CHCH_2COOC_2H_5 \\ \quad | \\ :C(COOC_2H_5)_2 \end{array} \xrightarrow{H^+} \begin{array}{l} CH_3CHCH_2COOC_2H_5 \\ \quad | \\ CH(COOC_2H_5)_2 \end{array}$$

(I) (II) (III)

Added in Proof—After the submission of this article our attention has been drawn to the work of G. A. Swan, *J. Chem. Soc.*, 1955, 1039, who reported the results of similar experiments, which are in full accord with ours.

Experimental

Materials.—Ethyl crotonate-(carbonyl-C^{14}) was prepared as reported previously[3]. Diethyl malonate was purified by fractional distillation under diminished pressure.

The Michael Addition.—Sodium (0.24 g.) was melted by heating in xylene and powdered by shaking, the xylene decanted, the sodium washed with ether, and 50 cc. of ether and 0.5 g. of absolute ethyl alcohol added to prepare sodium ethoxide. To this mixture 1.52 g. of diethyl malonate was added. Ethyl crotonate-(carbonyl-C^{14}) (1.09 g., 8.6±0.6 μc/mol.) in 30 cc. of ether was then added to the stirred mixture and the mixture was refluxed for five hours. Acetic acid (0.7 g.) in 14 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 0.9 g. of diethyl α-ethoxycarbonyl-β-methylglutarate boiling at 127∼128° at 4 mmHg. This was heated with 0.6 g. of sodium hydroxide in a mixture of 6 cc. each of water and alcohol for three hours on a boiling water bath. The alcohol was removed from the reaction mixture and the residue diluted with water to 40 cc. and passed through a column of Amberlite IR 120. A fraction with pH 2.2 was collected and evaporated to dryness over concentrated sulfuric acid in a vacuum desiccator, giving 0.6 g. of crude acid. This acid was recrystallized four times from ether and benzene, yielding 0.4 g. of α-carboxy-β-methylglutaric acid, m.p. 138–139°C (Found: neutralization equivalent 63.4; activity 8.4±0.6 μc/mol.).

Decarboxylation of α-Carboxy-β-methylglutaric Acid.—The decarboxylation of the labelled α-carboxy-β-methylglutaric acid described above and the absorption of the evolved carbon dioxide by aqueous sodium hydroxide were carried out in an apparatus similar to that for the Van Slyke-Folch oxidation[4]. The labelled acid (173 mg.) was placed in one limb of the apparatus and aqueous sodium hydroxide in another. The apparatus was evacuated and the limb containing the acid was heated gradually to 165°C and kept at that temperature for one hour. When the reaction was completed, ammonium chloride was added to the sodium hydroxide solution, and barium carbonate was precipitated by barium chloride, collected on a filter paper and assayed for radioactivity (Found: 0.12±0.08 μc/mol.). The residue from the decarboxylation was recrystal-

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

lized three times from benzene, giving 60 mg. of β-methylglutaric acid, m.p. 86–87°C (Found: activity 8.0±0.5 μc/mol.).

Radioactivity Determinations. — Radiocarbon assays were carried out by oxidizing samples according to Van Slyke and Folch[5], and converting the resulting carbon dioxide to barium carbonate, which was counted with an end-window Geiger-Müller counter on an "infinite thick" layer, the counts being all corrected for background and compared with the count of a standard barium carbonate with a known molar activity.

Summary

The Michael addition of diethyl malonate to ethyl crotonate-(carbonyl-C^{14}) was carried out with one equivalent of sodium ethoxide. The addition product, diethyl α-ethoxycarbonyl-β-methylglutarate, was hydrolyzed to the corresponding acid. It was decarboxylated by heating to give β-methylglutaric acid, which was found to contain most of the radioactivity originally present in the ethyl crotonate. Thus, it was demonstrated that the migration of an ethoxycarbonyl group did not take place in contrast to the case with diethyl methylmalonate. The mechanism is discussed.

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Department of Chemistry,
Faculty of Science,
Tokyo University,
Tokyo

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