XXXVIII.—*The Reactions of Malonic Esters with Formaldehyde. Part I.*

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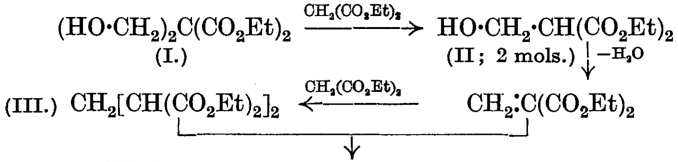
DURING the course of a research requiring large quantities of ethyl methylenedimalonate, it was found that the product prepared by Knoevenagel's method (*Ber.*, 1894, **27**, 2345) varied considerably in yield and contained a substance which decomposed with evolution of formaldehyde during distillation. Although Gault (*Bull. Soc. chim.*, 1912, [iv], **11**, 381) showed that better yields could be obtained by employing an excess of ethyl malonate, it was felt that a more thorough investigation of the reaction would be justified.

Ethyl malonate condenses with formaldehyde in the presence of dilute sodium hydroxide solution to give a solid addition compound, *ethyl di(hydroxymethyl)malonate* (I). The presence of two hydroxyl groups was proved by the preparation of a *diphenylcarbamate* and a neutral *sulphite*. Further, the ester (I) was converted into *α-iodomethylacrylic acid*, $CH_2{:}C(CH_2I){\cdot}CO_2H$, by the action of hydriodic acid, and this unsaturated acid, which gave the iodoform reaction, was reduced to *iso*butyric acid by the action of hydriodic acid and red phosphorus. The readiness with which ethyl di(hydroxymethyl)malonate loses formaldehyde forms an interesting comment on a paper by Earl, Ellsworth, Jones, and Kenner (J., 1928, 2697).

When formaldehyde was condensed with a larger excess of ethyl malonate in the presence of dilute sodium hydroxide solution, a saturated compound, probably ethyl hydroxymethylmalonate (II), was produced as an oil: this could not be distilled owing to the ease with which it lost water to give ethyl methylenemalonate. This substance is responsible for the more complex condensation products obtained by the action of formaldehyde on ethyl malonate: the production of ethyl methylenedimalonate (III) and ethyl pentane-ααγγεε-hexacarboxylate (IV) (compare Bottomley and Perkin, J., 1900, **77**, 294) is explained as follows:



$$\begin{tikzcd} \underset{\text{(I.)}}{(HO{\cdot}CH_2)_2C(CO_2Et)_2} \arrow[r, "CH_2(CO_2Et)_2"] & \underset{\text{(II; 2 mols.)}}{HO{\cdot}CH_2{\cdot}CH(CO_2Et)_2} \arrow[d, "-H_2O"] \\ \text{(III.) } CH_2[CH(CO_2Et)_2]_2 & CH_2{:}C(CO_2Et)_2 \arrow[l, "CH_2(CO_2Et)_2"'] \end{tikzcd}$$

$$\text{(IV.) } CH(CO_2Et)_2{\cdot}CH_2{\cdot}C(CO_2Et)_2{\cdot}CH_2{\cdot}CH(CO_2Et)_2$$

The above reactions take place independently under the conditions employed in the condensation of formaldehyde and ethyl malonate.

For instance, ethyl di(hydroxymethyl)malonate reacts with ethyl malonate in the presence of piperidine, triethylamine, or potassium hydroxide (*a*; p. 260) to give a mixture of (III) and (IV), and the yield of the latter is decreased when a larger excess of ethyl malonate is used (*b*; p. 260): experiment (*c*) (p. 260) shows that the last result is not due to the action of ethyl malonate on (IV). Further, ethyl methylenemalonate condenses readily with ethyl malonate and with ethyl methylenedimalonate (III) in the presence of piperidine to give (III) and (IV) respectively.

Although ethyl hydroxymethylmalonate (II) is incapable of isolation in the pure state, its alkyl substitution products, for example, *ethyl* (*hydroxymethyl*)*ethylmalonate*, can be distilled in a vacuum without decomposition.* This ester reacts with ethyl malonate in the presence of piperidine to give ethyl methylenedimalonate and ethyl ethylmalonate, but no facile reaction occurs between ethyl (hydroxymethyl)ethylmalonate and ethyl ethylmalonate.

EXPERIMENTAL.

Ethyl Di(*hydroxymethyl*)*malonate* (I).—Ethyl malonate (100 g.), 40% formalin (180 g.), and a few drops of B.D.H. Universal Indicator were mixed and 10% sodium hydroxide solution was gradually added. Reaction began at p_H 7·5 and was rapid at p_H 8·5. Owing to slight hydrolysis of the ester the p_H was apt to fall, and sodium hydroxide was added during 48 hours to maintain it between 8 and 9. The mixture became homogeneous and the temperature was kept below 50°. The mixture was then diluted with water (2 vols.), shaken with the smallest quantity of ether necessary to remove insoluble impurities, saturated with sodium chloride, and extracted five times with ether. The dried extracts, on removal of the ether, left a residue, which was heated in a vacuum at 50—60°. The glycerol-like substance remaining solidified after some months or more quickly on generous seeding. After being drained on porous plate and recrystallised from benzene–petroleum (b. p. 100—120°) or, better, from ether–amyl ether, *ethyl di*(*hydroxymethyl*)*malonate* was obtained in colourless elongated prisms, m. p. 52—53° (Found: C, 49·1, 48·9; H, 7·1, 7·2; OEt, 40·1. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3; OEt, 40·9%). This ester has an intensely bitter taste and is very soluble in water, alcohol, ether, and benzene and slightly soluble in light petroleum and amyl ether. It is decomposed by heat into formaldehyde, water, alcohol, carbon dioxide, small

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* Such condensations appear to be general and experiments with formaldehyde and ethyl butane-$\alpha\alpha\beta$-tricarboxylate are in progress with a view to the synthesis of pilocarpic acid (Jowett, J., 1901, **79**, 1331).

quantities of ethyl acrylate and ethyl methylenemalonate and a large quantity of high-boiling tar.

The *diphenylcarbamate*, prepared by the action of phenylcarbimide (5 g.) on ethyl di(hydroxymethyl)malonate (5 g.) during one week at the room temperature, crystallised from alcohol in needles (8 g.), m. p. 161° (Found: C, 60·0; H, 5·8; N, 6·3. $C_{23}H_{26}O_8N_2$ requires C, 60·3; H, 5·7; N, 6·1%). *Ethyl di(hydroxymethyl)-malonate sulphite*, prepared by the action of thionyl chloride (11·8 g.) on ethyl di(hydroxymethyl)malonate (22 g.) in anhydrous ether for 6 hours, distilled as a colourless oil (19 g.), b. p. 166°/20 mm. (Found: C, 40·6; H, 5·3. $C_9H_{14}O_7S$ requires C, 40·6; H, 5·2%).

α-Iodomethylacrylic Acid.—Ethyl di(hydroxymethyl)malonate (10 g.) and hydriodic acid (*d* 1·71; 66 g.) were boiled for 45 minutes, ethyl iodide and carbon dioxide being evolved. After cooling and standing for 1 hour, the solid (7 g., m. p. 95—100°) was collected, washed with a little water, and rapidly recrystallised from boiling water; it separated in cream-coloured plates, m. p. 104—106° (slight decomp.). A somewhat purer specimen (m. p. 106—107°) of the same substance was obtained by subjecting ethyl di(hydroxymethyl)malonate to a preliminary hydrolysis with 3% sulphuric acid at 120—140°, and treating the crude acid (which rapidly polymerises) with cold hydriodic acid (Found: C, 22·6; H, 2·4; *M*, ebullioscopic in ether, 220. $C_4H_5O_2I$ requires C, 22·6; H, 2·4%; *M*, 212). *α-Iodomethylacrylic acid* rapidly turns brown on exposure to light and air.

Reduction of α-Iodomethylacrylic Acid.—Ethyl di(hydroxymethyl)-malonate (25 g.) was converted into iodomethylacrylic acid by heating with hydriodic acid as described above. Red phosphorus (7 g.) and hydriodic acid (30 g.) were then added and the mixture was boiled for 10 hours. After dilution with an equal volume of water, the mixture was steam-distilled; the distillate was neutralised with sodium hydroxide and evaporated to dryness. Excess of 50% sulphuric acid was added; the liberated acid, isolated by extraction with ether, boiled at 150—160°. It was converted into the chloride by the action of the theoretical quantity of boiling thionyl chloride for 20 minutes, and the product poured into an excess of aniline (6 g.). After being heated on the water-bath for 20 minutes, the product was poured into an excess of dilute hydrochloric acid; the solid obtained, after recrystallisation from dilute alcohol, melted at 103—105°, alone or in admixture with authentic *iso*butyranilide.

Ethyl (Hydroxymethyl)malonate (II).—Formalin (10 g.), ethyl malonate (60 g.), and enough alcohol to give a homogeneous mixture were mixed with a few drops of B.D.H. Universal Indicator, and sodium hydroxide solution added to produce p_H 9. After 24 hours, the mixture was rendered faintly acid, diluted with water, and extracted with ether. After drying and removal of the solvent, the excess of ethyl malonate was distilled off in a vacuum, leaving ethyl (hydroxymethyl)malonate as an oil, which was almost without action on dilute potassium permanganate solution. Treated with phenylcarbimide, the ester gave diphenylurea, m. p. 238°.

Condensation of Ethyl Di(hydroxymethyl)malonate with Ethyl Malonate.—(*a*) Ethyl di(hydroxymethyl)malonate (10 g.), ethyl malonate (20 g.), and piperidine, triethylamine or alcoholic potassium hydroxide (a few drops) were heated for 6 hours in the water-bath. On cooling and standing over-night, crystals separated. The whole was then fractionated, giving: (i) ethyl methylenedimalonate (10 g.), b. p. 140—180°/5 mm., which on hydrolysis gave glutaric acid, m. p. 95—97°, not depressed by admixture with an authentic specimen; (ii) ethyl pentane-$\alpha\alpha\gamma\gamma\varepsilon\varepsilon$-hexacarboxylate (10 g.), b. p. 180—240°/5 mm., which solidified and, after being drained and recrystallised from alcohol, melted at 52—53° (Found: C, 54·9; H, 7·0. Calc. for $C_{23}H_{36}O_{12}$: C, 54·8; H, 7·1%).

(*b*) A similar experiment with 60 g. of ethyl malonate instead of 20 g. yielded ethyl methylenedimalonate (27 g.) but no pentane derivative (IV).

(*c*) The condensation (*a*) was repeated, but, after the preliminary heating, the product was mixed with ethyl malonate (35 g.) and a few drops of piperidine and heated for a further 6 hours. Ethyl pentane-$\alpha\alpha\gamma\gamma\varepsilon\varepsilon$-hexacarboxylate (10 g.) was isolated after removal of the excess of ethyl malonate.

Ethyl (hydroxymethyl)ethylmalonate, prepared by condensing ethyl ethylmalonate (20 g.) and formalin (30 g.) for 48 hours under the conditions employed for the condensation of formalin with ethyl malonate, was obtained as an oil (15 g.), b. p. 105—107°/4 mm. (Found: C, 54·8; H, 8·3. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%). The *phenylcarbamate* crystallised from dilute methyl alcohol in plates, m. p. 63—64° (Found: C, 60·5; H, 6·9. $C_{17}H_{23}O_5N$ requires C, 60·5; H, 6·8%).

Ethyl (hydroxymethyl)ethylmalonate (2 g.), ethyl malonate (5 g.), and piperidine (1 drop) were heated on the water-bath for 5 days. Distillation then yielded ethyl ethylmalonate, b. p. 90—100°/12 mm., and ethyl methylenedimalonate, b. p. 190—200°/12 mm., which was hydrolysed to glutaric acid, m. p. 94—96°.

No apparent reaction took place on the water-bath between ethyl (hydroxymethyl)ethylmalonate and ethyl ethylmalonate in the presence of piperidine. At 130—140°, alcohol was eliminated, but nothing further could be isolated from the product.

Condensation of Ethyl Methylenemalonate with Ethyl Malonate and with Ethyl Methylenedimalonate.—Ethyl methylenemalonate (freshly distilled) (2 g.) and ethyl malonate were mixed and methyl-alcoholic potassium hydroxide (1 drop) was added; considerable heat was evolved. After standing in the cold for 1 hour, the product was unreactive to dilute potassium permanganate solution and on distillation gave ethyl methylenedimalonate (3 g.), as proved by conversion into glutaric acid.

Under the same conditions, the condensation with ethyl methylenedimalonate was complete after 1 hour's heating on the water-bath; the mixture solidified on cooling and was proved to be ethyl pentane-ααγγεε-hexacarboxylate by the mixed m. p. method.

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