[CONTRIBUTION FROM THE GATES CHEMICAL LABORATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 218]

THE CONDENSATION OF ACETALDEHYDE WITH METHYLMALONIC ESTER. METHYLATIONS WITH METHYL BROMIDE

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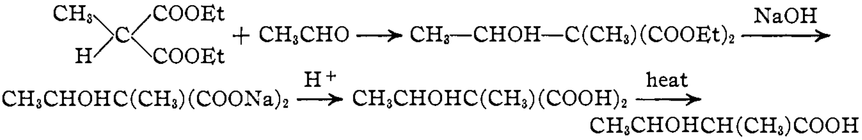
RECEIVED APRIL 3, 1929 PUBLISHED AUGUST 7, 1929

In developing a method for synthesizing the isomeric 2-butenes, it was thought that the decomposition of β-hydroxy-α-methylbutyric acid might give a yield of the unsaturated angelic and tiglic acids higher than that which was obtained by the decomposition of α-hydroxy-α-methylbutyric acid. The attempt was therefore made to synthesize the β-hydroxy acid from methylmalonic ester through the following steps



$$\begin{matrix}CH_3 & & COOEt\\ & C & \\ H & & COOEt\end{matrix} + CH_3CHO \longrightarrow CH_3—CHOH—C(CH_3)(COOEt)_2 \xrightarrow{NaOH}$$

$$CH_3CHOHC(CH_3)(COONa)_2 \xrightarrow{H^+} CH_3CHOHC(CH_3)(COOH)_2 \xrightarrow{heat} CH_3CHOHCH(CH_3)COOH$$

It soon became evident that the method was less satisfactory than the one finally adopted,[2] in which the α-hydroxy acid was obtained from methylethyl ketone.

It is the purpose of this paper to describe the synthesis of the diethyl ester of 3-hydroxybutane-2,2-dicarboxylic acid by the condensation of acetaldehyde with methylmalonic ester.

Discussion

The use of methyl iodide for the quantity production of methylmalonic ester is an expensive procedure. We have found methyl bromide to be a satisfactory methylating agent with both malonic ester and acetoacetic ester. From the standpoint of cost it possesses a distinct advantage over methyl iodide, and for one who must prepare his own reagent in quantity it possesses in addition the decided superiority of greater convenience, since the bromide can be prepared, purified and used in one operation. The yields obtained are, in the case of malonic ester, as satisfactory as any described in the literature and in the case of acetoacetic ester are somewhat better.

The condensation of acetaldehyde with methylmalonic ester was carried out by heating the reactants with acetic anhydride for fifty hours in sealed tubes at 104°. This reaction is undoubtedly similar to the one between acetaldehyde and malonic ester[3] in which ethylidene malonic

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[1] Du Pont Fellow in Chemistry, 1928–1929.

[2] Young, Dillon and Lucas, THIS JOURNAL, **51**, 2528 (1929).

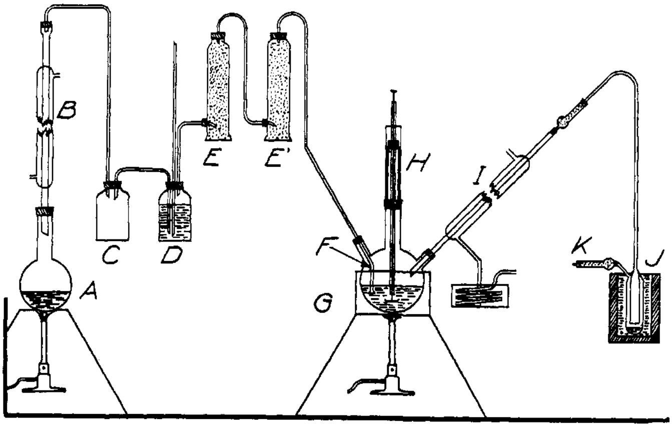
[3] Komnenos, *Ann.*, **218**, 156 (1883).

ester is produced by the loss of water, involving the α-hydrogen atom. The condensation product from methylmalonic ester does not contain an α-hydrogen atom and thus an ethylidene derivative is not produced. However, a small amount of unsaturated ester results from the loss of water, involving a γ-hydrogen atom.

The condensation mixture was fractionally distilled at reduced pressure. Molecular weight determinations on the various higher fractions by the micro-method of Smith and Young[4] made it possible to tell which fractions contained the desired hydroxy ester. This procedure is a valuable aid in determining the approximate composition of various fractions.

Experimental

Methyl Bromide as a Methylating Agent.—The methyl bromide, generated in a 2-liter flask, *A* (see figure), from 215 g. (6.7 moles) of methanol, 266 g. (2.6 moles) of sodium bromide, 695 g. (7.0 moles) of 95% sulfuric acid and 230 g. of water according to the directions of Bygden,[5] was purified by passing it through concentrated sodium hydroxide, *D*, soda lime, *E*, calcium chloride, *E'*, and led through the large tube *F*, flared at the lower end to a diameter of 22 mm., into the three-necked, 3-liter flask, *G*. This contained a solution of sodium malonic ester prepared from 350 cc. of absolute ethanol, 25 g. (1.1 moles) of metallic sodium and 160 g. (1.0 mole) of malonic ester (Eastman). The flask *G* was surrounded by a water-bath at 80–85° and the solution was agitated with a mechanical stirrer, *H*. A reflux cooler, *I*, condensed the alcohol



A, methyl bromide generating flask, 2-liter; *B*, reflux cooler; *C*, safety bottle; *D*, concentrated sodium hydroxide; *E*, soda lime tower; *E'*, calcium chloride tower; *F*, flared inlet tube; *G*, flask, 3-liter, containing sodium malonic ester in ethanol; *H*, mechanical stirrer (mercury seal); *I*, reflux cooler; *J*, tube at −15°; *K*, calcium chloride tube.

Fig. 1.

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[4] Smith and Young, *J. Biol. Chem.*, **75,** 289 (1927).

[5] Bygden, *J. prakt. Chem.*, **104,** 285–288 (1922).

vapor, and any unreacted methyl bromide was condensed in the tube *J*, kept at −30° by an ice–hydrochloric acid mixture and provided with a calcium chloride tube, *K*. The generation of the methyl bromide was regulated by the rate of heating of the flask *A* and was made as fast as was consistent with effective purification. Soon after the gas flow was started sodium bromide precipitated in the reaction mixture and during an hour and one-half no trace of methyl bromide condensed in the tube *J*. Shortly after this a liquid began to collect in *J*. The reaction mixture was then tested with litmus and found to be neutral. The alcohol was distilled by heating the flask in an oil-bath at 125–130°, the least quantity of water was added for dissolving the salt, the resulting oil layer separated and the aqueous phase was extracted three times with 50 cc. of ether. The ether extracts and the crude ester were combined and dried overnight with anhydrous sodium sulfate. The ether was removed from the dried solution by heating over a water-bath at 50–80°, and the residue of crude methyl malonic ester was fractionally distilled through a 30-cm. bead column at reduced pressure, the main fraction boiling at 113.5–114° at 46–48 mm. The yield was 80%. Since the boiling points of malonic, methylmalonic and dimethylmalonic esters lie within three and one-half degrees of each other,[6] the purity of the product obtained by the procedure outlined could not be told by its boiling range. Nevertheless, it was largely the desired methylmalonic ester, as shown by conversion to the free acid and decomposition of this to the monobasic acid. Now the melting point of 125.5–126.5° obtained for the dibasic acid does not distinguish between malonic and methylmalonic acids,[7] but the boiling point of the monobasic acid, 140–141°, indicated that the latter was largely propionic acid. The absence of acetic acid in this product, and therefore of malonic ester in the methylated ester, was likewise indicated by the successive values of 14.0 and 12.5 obtained for the Duclaux numbers.[8] These values were a trifle high for propionic acid, indicating the presence of a small quantity of *iso*butyric acid.

The methylmalonic ester prepared above had properties identical with the product obtained when methyl iodide was used, following the method of Conrad.[9] The melting points of the methylmalonic acids and the Duclaux numbers of the monobasic acids obtained by both methods were identical. It is thus evident that methyl iodide may be replaced by methyl bromide in a malonic ester synthesis.

Methyl bromide was likewise used in the synthesis of methylacetoacetic ester with satisfactory results. The product, obtained in 83% yields, was identical with that obtained by the use of methyl iodide.

Diethyl Ester of 3-Hydroxybutane-2,2-dicarboxylic Acid.—A mixture of 40 g. (0.23 mole) of methylmalonic ester, 47.0 g. (0.46 mole) of acetic anhydride and 21.0 g. (0.48 mole) of acetaldehyde (freshly prepared by the depolymerization of paraldehyde) was divided into portions of 35 cc. each, sealed in tubes and heated at 140° for fifty hours. The tubes were opened and the combined reaction mixture was fractionally distilled at reduced pressure. The fractions obtained are shown in Table I.

By running molecular weight determinations on several of the higher fractions by the camphor method of Smith and Young,[4] it was possible to identify the fractions containing the desired hydroxy ester, which has a molecular weight of 218. Two more fractionations of distillates 5, 6, 7 and 8 gave a fraction boiling at 94–98° at 2 mm. This material, after washing with sodium carbonate solution, distilled at 100–106° under 3–5 mm. pressure and weighed 17 g. The yield was 63%, based on the methylmalonic ester

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[6] Meyer and Bock, *Ann.*, **347**, 94 (1906).

[7] Salzer, *J. prakt. Chem.*, **61**, 166 (1900); ref. 6, p. 100.

[8] Kamm, "Qualitative Organic Analysis," John Wiley and Sons, Inc., New York, **1923**, p. 139.

[9] Conrad, *Ann.*, **204**, 134 (1889).

TABLE I

FRACTIONATION OF CONDENSATION PRODUCT FROM METHYLMALONIC ESTER AND ACETALDEHYDE

	Temp., 0°C.	Press., mm.	Weight, g.	Mol. wt.	Remarks
1	20–95	50	37	...	Acetic acid, acetic anhydride
2	95–112	50	18	...	Methylmalonic ester, mostly 110–112°
3	80–90	17–18	3	...	Mixtures
4	90–97	17–18	5.5	...	Mixtures
5	97–104	17–18	4.5	195	Probably the unsaturated ester[a]
6	100–110	8	3.5	200	Probably the unsaturated ester[a]
7	110–125	8	8	218	Desired product.
8	91–104	1–2	10	236	Desired product, but less pure
9	104–130	1–2	1	...	....
10	Residue	...	6.6	...	....

[a] Gave usual tests for unsaturation.

reacted. The results of molecular weight determinations by the camphor method on this purified product were 215 and 221 (theoretical, 218). The density, d^{21}_4 was 1.0732.

Anal. Subs., 0.2180, 0.2101: H_2O, 0.1510, 0.1467; CO_2, 0.4405, 0.4247. Calcd. for $C_{10}H_{18}O_5$: H, 8.31; C, 55.0. Found: H, 7.76, 7.81; C, 55.1, 55.1.

Attempts to saponify the ester with alcoholic potassium hydroxide gave a reddish brown precipitate of high molecular weight. We were unsuccessful in obtaining a derivative with acid chlorides, the reaction yielding instead an unsaturated compound, probably the unsaturated ester. Apparently with acid chlorides water is eliminated very easily as might be expected from derivatives of β-hydroxy esters, although with acetic anhydride at 104°, a condition prevailing in the condensation reaction, dehydration was not an important factor, for the fraction of unsaturated ester did not exceed 10%. The presence of the hydroxyl group was demonstrated, since on addition of sodium hydrogen was evolved and a solid was formed. In order to establish completely the identity of the diethyl ester of 3-hydroxybutane-2,2-dicarboxylic acid, it was converted into the diamide.

Diamide of 3-Hydroxybutane-2,2-dicarboxylic Acid.—When 7.0 g. of the hydroxy ester was shaken with concentrated ammonium hydroxide the oil slowly went into solution during the course of eight days. From the aqueous solution evaporation yielded a white solid, readily soluble in water and sparingly soluble in absolute alcohol. Recrystallization from hot absolute alcohol gave 3 g. of pure white prisms melting at 209.5° (corr.) with decomposition. From 0.1042 g. there was obtained 16.40 cc. of nitrogen by the Dumas method, corresponding to 17.82%, whereas the theoretical value calculated from $C_6H_{12}O_3N_2$ is 17.48%.

The authors are indebted to Mr. R. T. Dillon for the analysis of the diamide.

Summary

Methyl bromide may satisfactorily replace methyl iodide in the preparation of the methyl derivatives of malonic ester and acetoacetic ester.

Acetaldehyde in the presence of acetic anhydride condenses with the ethyl ester of methylmalonic acid to produce the diethyl ester of 3-hydroxybutane-2,2-dicarboxylic acid.

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