[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KANSAS STATE COLLEGE]

Vicinal Tricarbonyl Compounds. II. Condensation of Ethyl 3-Phenyl-2,3-dioxopropanoate with Malonic Acid[1]

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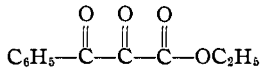
Ethyl 3-phenyl-2,3-dioxopropanoate has been found to undergo a Knoevenagel–Doebner type condensation with malonic acid. Studies of the product indicated that condensation occurred at the central carbonyl group of the tricarbonyl compound with loss of one molecule of carbon dioxide.

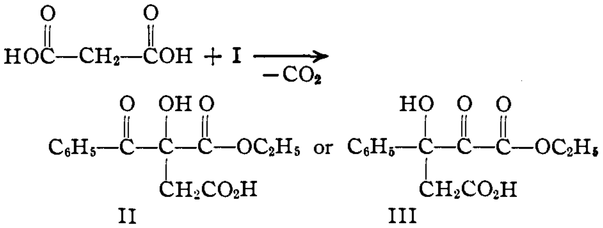
In a previous paper,[2] an investigation of the condensation of malonic acid and of *p*-nitrophenylacetonitrile with 1,3-diphenylpropanetrione-1,2,3 was reported. Similar studies have been extended to ethyl 3-phenyl-2,3-dioxopropanoate (I), another member of the vicinal tricarbonyl compound class. Older studies[3] of condensation reactions of this type of compound have been reported, but structures of the products were postulated solely on the basis of carbon–hydrogen analytical results. The purpose of the current investigation was to determine which of the three carbonyl groups was attacked by the carbanion formed from the active methylene component. Such information may be of value in defining the electronic structures of the tricarbonyl compounds. Malonic acid was selected as the addendum because of anticipated ease of manipulation and structure studies of a condensation product.



$C_6H_5-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-OC_2H_5$

I

Malonic acid readily condensed with I in the presence of pyridine and piperidine to give a solid acid in 40% yield. Tests indicated that carbon dioxide was evolved during the condensation. Carbon-hydrogen analysis of the product indicated a composition corresponding to the formula $C_{13}H_{14}O_6$. This represents one-to-one condensation with loss of carbon dioxide. A Knoevenagel–Doebner type condensation might be expected at either of the two ketonic carbonyl groups; therefore, this reaction may be represented as follows to give one of two possible structures, (II) or (III).

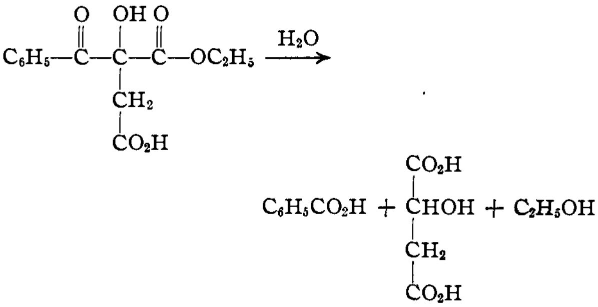


$$HO\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}OH + I \xrightarrow[-CO_2]{}$$

$$\underset{\text{II}}{C_6H_5-\overset{\overset{O}{\|}}{C}-\underset{CH_2CO_2H}{\overset{OH}{C}}-\overset{\overset{O}{\|}}{C}-OC_2H_5} \quad \text{or} \quad \underset{\text{III}}{C_6H_5-\underset{CH_2CO_2H}{\overset{HO}{C}}-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-OC_2H_5}$$

The product was analyzed for functional groups, and the results indicated two active hydrogens and one ketonic carbonyl group in each molecule. Also, three mole portions of Grignard reagent added to one mole portion of the product, which indicated the presence of a ketone and an ester function. These data would be observed for a compound of either structure II or III.

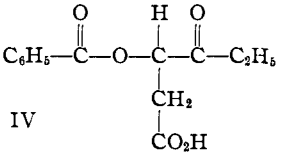
The fading end-point observed during attempted determinations of the neutral equivalent demonstrated a sensitivity toward base, and saponification equivalent values indicated that the product gives rise to three carboxyl groups. Two acid fragments, benzoic acid and malic acid, were identified in high yield as products of saponification. Structure II best fits these data, and the saponification apparently occurred as



$$C_6H_5-\overset{\overset{O}{\|}}{C}-\underset{\underset{CO_2H}{|}}{\underset{CH_2}{\overset{OH}{C}}}-\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow{H_2O} C_6H_5CO_2H + \underset{\underset{CO_2H}{CH_2}}{\overset{CO_2H}{CHOH}} + C_2H_5OH$$

The carbon–carbon cleavage of the molecule may be due to its β-ketoacid structure. It is very difficult to visualize how benzoic and malic acids could arise from the saponification of a compound with a structure such as III.

The facile formation of benzoic acid (as shown by the complete saponification of II at room temperature in dilute alkali) suggested a third possibility (IV) as the structure of the condensation product.



$$C_6H_5-\overset{\overset{O}{\|}}{C}-O-\underset{\underset{CO_2H}{CH_2}}{\overset{H}{C}}-\overset{\overset{O}{\|}}{C}-C_2H_5$$

IV

This could arise, perhaps, by a rearrangement similar to that observed by Kohler and Erickson.[4] They isolated the benzoate of benzoin from the reaction of the nucleophilic phenyl magnesium bromide with 1,3-diphenylpropanetrione-1,2,3. However, IV would contain only one active hydrogen, would add four molecules of Grignard, and would have no ketonic carbonyl group; all of these values are contrary to those experimentally obtained with the condensation product. In the light of these data the condensation product is assigned structure II. Complete verification, of course, will depend upon an independent synthesis of II.

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[1] Abstracted in part from the M.S. thesis submitted by Glenn V. Hudson to the Graduate Faculty of Kansas State College, August, 1950. Contribution No. 433 from the Department of Chemistry. Supported in part by a grant-in-aid from the Frederick Gardner Cottrell funds of Research Corporation.

[2] D. B. Sharp and H. A. Hoffman, THIS JOURNAL, **72**, 4311 (1950).

[3] See literature cited in ref. 2.

[4] E. P. Kohler and J. L. E. Erickson, THIS JOURNAL, **53**, 2301 (1931).

The results obtained thus far tentatively support the contention that the central carbonyl group (number 2 carbon) is the more active ketone group of the two present in I. More positive assertions regarding the relative reactivities of the two ketonic carbonyl groups must be reserved until further data are obtained, particularly since the solid condensation product was obtained in only 40% yield.

Further investigations along these lines are being pursued in this Laboratory.

Experimental[5]

Materials.—Ethyl benzoylacetate (Eastman Kodak Co. 2731), nitrogen dioxide (Matheson Co.) and malonic acid (Eastman 695) were used without further purification. Piperidine (Eastman P687) and pyridine (General Chemical Co. 2.65) were dried and distilled before use.

Ethyl 3-Phenyl-2,3-dioxopropanoate (I). A. Preparation.—This compound was prepared by direct oxidation of ethyl benzoylacetate by nitrogen dioxide. Vapors of nitrogen dioxide (92 g.) were bubbled through a cooled (3–5°) solution of ethyl benzoylacetate (100 g.) in ether (200 ml.) and acetic anhydride (30 g.). After the addition of nitrogen dioxide was complete the solution was allowed to warm slowly to room temperature and stand overnight. The ice-bath was allowed to remain about the flask containing the final mixture in order to ensure a gradual warming. When the ice-bath was removed immediately after completion of the nitrogen dioxide addition, a violent decomposition of the reaction mixture occurred. The ethereal solution was washed repeatedly with a one-to-one mixture of 20% potassium carbonate and saturated sodium chloride solution. The ether was removed at room temperature and the residue was distilled under reduced pressure. A crude fraction was collected over the range 90–190°. Benzoic acid was a by-product which gave some trouble in all initial distillations due to plugging of the still-head. The crude distillates of five such reactions were combined and fractionated through a 24 inch, 20 mm. i.d. column filled with $^3/_8$ inch glass helices. The ethyl 3-phenyl-2,3-dioxopropanoate was a yellow oil (85 g., 16% yield based on total starting material); b.p. 86–89° at 0.2 mm. (reported,[6] 150–153° at 13 mm.).

B. **Condensation with Malonic Acid.**—Compound I (3.0 g.) and malonic acid (1.51 g.) were dissolved in pyridine (4.4 g.), piperidine (0.1 g.) was added, and the solution was heated for three hours on a steam-bath. Carbon dioxide evolved during the early part of the reaction. The solution was cooled and then was poured into a mixture of ice and hydrochloric acid, the latter in excess over the amount necessary to combine with all of the pyridine and piperidine. The acid solution was extracted with several portions of ether and the combined ether extracts were evaporated at room temperature. The residue was dissolved in sodium carbonate (10%), the solution was extracted with ether and the extracts were discarded. The aqueous solution was acidified with hydrochloric acid and was extracted with ether. The ether was removed by evaporation and the residue was extracted with several small portions of hot cyclohexane. The solid which separated when the cyclohexane solution cooled was recrystallized from a mixture of chloroform and petroleum ether. The product was a white crystalline solid (1.57 g., 40%), m.p. 101–102°.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.31. Found: C, 58.54; H, 5.25.

Condensation Product. A. Functional Group Analyses.—The methods described by Siggia[7] were employed for the determination of active hydrogen and addition of Grignard reagent (Zerewitinoff), and for analysis of ketonic carbonyl groups (hydroxylamine hydrochloride method). Consistent saponification equivalents were obtained at room or reflux temperatures by standard procedures. The determination of neutral equivalent was precluded by a fading end-point.

Anal. Calcd. for $C_{13}H_{14}O_6$: sapn. equiv., 133 (dibasic), 88.9 (tribasic); active hydrogen,[7] 2; addn. of Grignard,[7] 3; no. of carbonyl groups,[7] 1. Found: sapn. equiv., 88.7, 88.0, 88.2, 87.7; active hydrogen, 2.19, 2.10; addn. of Grignard, 3.1; no. of carbonyl groups, 0.98.

B. **Saponification Products.**—A sample (1.781 g.) of condensation product was heated in excess alkali for three hours. The alkaline solution was acidified to *p*H 2 and extracted with ether. The ether was evaporated and the residue was identified as benzoic acid (0.829 g., 100%); m.p. 119–121° and mixed m.p. 122–124° with authentic benzoic acid. The acidic aqueous solution gave positive results for the qualitative tests described by Huntress and Mulliken[8] for malic acid. The malic acid in the major portion of the acid solution was converted to fumaric acid.[8] Excess sodium hydroxide was added to the acid solution, the mixture was evaporated to dryness and was baked at 130° for three hours. Concentrated sulfuric acid was added to the residue and the solid was removed by filtration. This material was extracted with hot alcohol, the alcohol was removed and the white solid was purified by sublimation at reduced pressure. The fumaric acid (0.560 g., 72%) had a m.p. of 284–286°: (sealed tube) and mixed m.p. 283–285° (sealed tube) with authentic fumaric acid.

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[5] Each m.p. was corrected for emergent stem.

[6] A. Wahl, *Compt. rend.*, **144**, 212 (1907).

[7] S. Siggia, "Quantitative Organic Analysis via Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 17, 41.

[8] E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 100.