[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Reactions of Certain Gamma Ketonic Acids. II. Hydroxyl Derivatives

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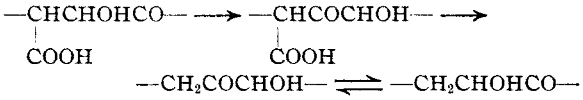
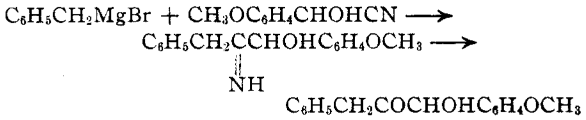
In the preceding paper[2] it was reported that bases rapidly eliminated carbon dioxide from a beta hydroxy gamma ketonic acid and converted it into a mixture of hydroxy ketones. It was assumed that the conversion occurs in a series of steps which may be represented as follows



$$\underset{\mathrm{COOH}}{\mathrm{—CH}}\mathrm{CHOHCO—} \longrightarrow \underset{\mathrm{COOH}}{\mathrm{—CH}}\mathrm{COCHOH—} \longrightarrow \mathrm{—CH_2COCHOH—} \rightleftharpoons \mathrm{—CH_2CHOHCO—}$$

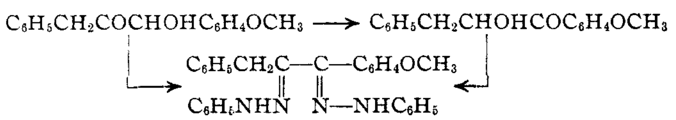
This series of changes represents a plausible explanation of the observations but since the conversion occurred with quite unexpected ease it was desirable to examine this mechanism with more appropriate material. We therefore studied the action of bases on alpha phenyl beta hydroxy beta anisoyl propionic acid in which the two hydrocarbon residues are not the same.

This acid was cleaved by bases quite as readily as was the corresponding compound in which both hydrocarbon residues were phenyl. Its clear colorless solution in a slight excess of cold dilute sodium hydroxide immediately became yellow and soon began to deposit a hydroxy ketone, the structure of which was established with certainty by a synthesis in accordance with the scheme



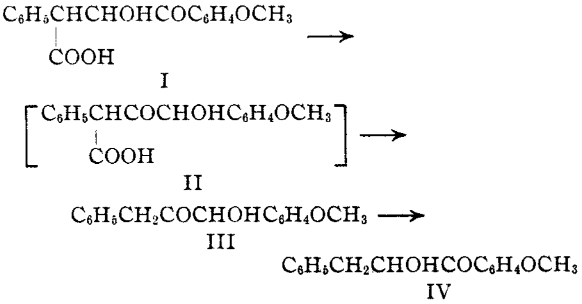
$$\mathrm{C_6H_5CH_2MgBr + CH_3OC_6H_4CHOHCN} \longrightarrow \mathrm{C_6H_5CH_2}\underset{\overset{\|}{\mathrm{NH}}}{\mathrm{C}}\mathrm{CHOHC_6H_4OCH_3} \longrightarrow \mathrm{C_6H_5CH_2COCHOHC_6H_4OCH_3}$$

At the ordinary temperature this hydroxy ketone is the only product of the reaction. Although formed in an alkaline solution it is not stable in the presence of alkali. When it is heated with dilute sodium hydroxide, and even when it is allowed to remain in contact with it for a long time at the ordinary temperature, it passes completely into a lower melting isomer in which the order of the hydroxyl and carbonyl groups must be reversed because phenylhydrazine converts both compounds into the same osazone



$$\mathrm{C_6H_5CH_2COCHOHC_6H_4OCH_3} \longrightarrow \mathrm{C_6H_5CH_2CHOHCOC_6H_4OCH_3};\quad \text{both} \longrightarrow \mathrm{C_6H_5CH_2}\underset{\overset{\|}{\mathrm{C_6H_5NHN}}}{\mathrm{C}}\mathrm{—}\underset{\overset{\|}{\mathrm{N—NHC_6H_5}}}{\mathrm{C}}\mathrm{—C_6H_4OCH_3}$$

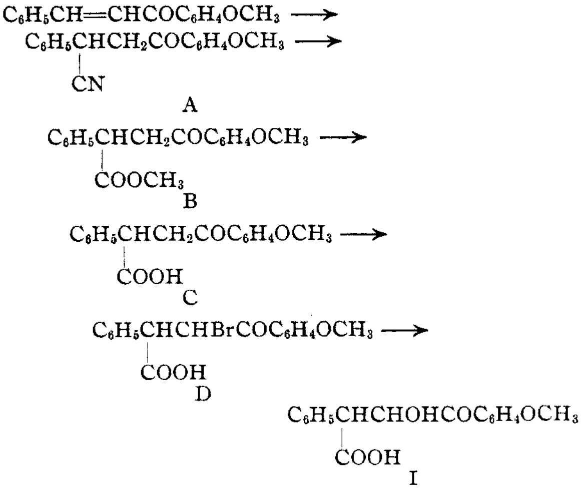
Since the lower melting hydroxy ketone is not affected by bases, it is evident that the higher melting isomer is the primary cleavage product. And since the order of the hydroxyl and carbonyl groups in this compound is the reverse of that in the hydroxy acid, it is equally evident that the first step in the process must be the transposition of these groups. Our results, therefore, definitely establish the mechanism which was proposed in the earlier paper



$$\underset{\mathrm{I}}{\mathrm{C_6H_5}\underset{\mathrm{COOH}}{\mathrm{CH}}\mathrm{CHOHCOC_6H_4OCH_3}} \longrightarrow \underset{\mathrm{II}}{\left[\mathrm{C_6H_5}\underset{\mathrm{COOH}}{\mathrm{CH}}\mathrm{COCHOHC_6H_4OCH_3}\right]} \longrightarrow \underset{\mathrm{III}}{\mathrm{C_6H_5CH_2COCHOHC_6H_4OCH_3}} \longrightarrow \underset{\mathrm{IV}}{\mathrm{C_6H_5CH_2CHOHCOC_6H_4OCH_3}}$$

Experimental Part

The hydroxy ketonic acid was prepared by means of a series of reactions similar to those employed in the earlier work. The successive steps can be represented as follows



$$\mathrm{C_6H_5CH{=}CHCOC_6H_4OCH_3} \longrightarrow \underset{\mathrm{A}}{\mathrm{C_6H_5}\underset{\mathrm{CN}}{\mathrm{CH}}\mathrm{CH_2COC_6H_4OCH_3}} \longrightarrow \underset{\mathrm{B}}{\mathrm{C_6H_5}\underset{\mathrm{COOCH_3}}{\mathrm{CH}}\mathrm{CH_2COC_6H_4OCH_3}} \longrightarrow \underset{\mathrm{C}}{\mathrm{C_6H_5}\underset{\mathrm{COOH}}{\mathrm{CH}}\mathrm{CH_2COC_6H_4OCH_3}} \longrightarrow \underset{\mathrm{D}}{\mathrm{C_6H_5}\underset{\mathrm{COOH}}{\mathrm{CH}}\mathrm{CHBrCOC_6H_4OCH_3}} \longrightarrow \underset{\mathrm{I}}{\mathrm{C_6H_5}\underset{\mathrm{COOH}}{\mathrm{CH}}\mathrm{CHOHCOC_6H_4OCH_3}}$$

The first step in this series, the addition of hydrocyanic acid to benzalacetylanisole, is much more difficult than it is in the case of benzalacetophenone—largely, doubtless, because the addition product is much more soluble than the unsaturated ketone in aqueous alcohol.

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(1) Fellow of the Harvard Club of France, 1928–1929.

(2) Kohler and Kimball, THIS JOURNAL, **56**, 729 (1934).

By operating at a somewhat higher temperature and employing both more concentrated solutions and a large excess of cyanide, we finally obtained fairly consistent yields. Our procedure was as follows.

A suspension of 25 g. of the unsaturated ketone in 500 cc. of alcohol, to which had been added in succession 15 cc. of glacial acetic acid and a solution of 40 g. of potassium cyanide in 75 cc. of hot water, was rapidly heated to the boiling point and kept there for about seventeen minutes. The resulting brown solution was cooled as rapidly as possible by decanting it into a beaker surrounded with ice and salt. The cooled solution was gradually diluted with 500 cc. of water and set aside until precipitation was complete. The nitrile after recrystallization from alcohol melted at 68°. The average yield was 60%.

Anal. Calcd. for $C_{17}H_{15}O_2N$: C, 77.0; H, 5.7. Found: C, 77.0; H, 5.8.

Most of the remaining steps in the series presented no unusual difficulties. The essential properties of the products are shown in the table.

Formula	M. p., °C.	Calcd., % C	Calcd., % H	Found, % C	Found, % H	Yield, %
A	68	77.0	5.7	77.0	5.8	60
B	97	72.5	6.1	72.2	6.1	75
C	141	71.8	5.6	71.6	5.6	92
D	158	56.2	4.2	56.0	4.2	78
I	159	68.0	5.3	68.1	5.5	50

In order to avoid the possibility of transposing the hydroxyl and carbonyl groups the bromo acid was converted into the hydroxy acid by boiling it with water. This method results in a very pure acid but the yield is not high because a part of the bromo acid, as usual, loses carbon dioxide and hydrogen bromide, and thus reverts to the unsaturated ketone. The stability of the hydroxy acid at the relatively high melting point is adequate proof of the relative positions of the hydroxyl, carbonyl and carboxyl groups.

Action of Cold Alkalies: α-Phenyl-γ-hydroxy-β-oxo-γ-(*p*-methoxyphenyl)-propane, III.—A solution of 15 g. of the hydroxy acid in slightly more than one equivalent of 1% aqueous sodium hydroxide was left to itself for a day. It precipitated a colorless solid which melted at about 115°. The solid was thoroughly washed with water and recrystallized from alcohol from which it separated in fine needles melting at 119°. The yield was 10.5 g.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.0; H, 6.2. Found: C, 74.8; H, 6.3.

The same hydroxy ketone can be obtained more easily by dissolving the bromo acid in slightly more than two equivalents of cold dilute sodium hydroxide. When it was digested with a solution of phenylhydrazine in glacial acetic acid, it formed a phenylosazone which melted at 156° and which was identified with a product previously obtained by Jörlander[3] by similar treatment of benzyl anisyl diketone.

Synthesis of the Hydroxy Ketone.—The cyanhydrin of anisic aldehyde was prepared by first converting the aldehyde into the bisulfite compound and adding this to a cold solution containing 1.5 equivalents of potassium cyanide. The mixture was set aside for an hour, then filtered. After washing with bisulfite solution and water, the product was sufficiently pure for use. The yield was almost quantitative.

An ethereal solution of the cyanhydrin was added very slowly and with vigorous stirring to a solution of benzylmagnesium chloride which contained 2.5 equivalents of the reagent and which was cooled in a freezing mixture. After the vigorous reaction subsided, the mixture was boiled for an hour, then cooled and added slowly to iced hydrochloric acid. The product separated as a solid (15 g. from 20 g. of the cyanhydrin) which melted at 119° and which was identical with the hydroxy ketone obtained from the acid.

IV, α - Phenyl - β - hydroxy - γ - oxo - γ - (*p* - methoxyphenyl)-propane.—A suspension of 6 g. of the higher melting hydroxy ketone in 50 cc. of a 2% solution of sodium hydroxide was heated on a steam-bath. Samples removed at intervals showed that the ketone was changing and that after an hour it had been completely converted into a lower melting product which, after recrystallization from alcohol, melted at 62°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.0; H, 6.2. Found: C, 74.8; H, 6.3.

This same hydroxy ketone is formed when solutions of the beta bromo acid or the beta hydroxy acid in dilute sodium hydroxide are heated for the same length of time, but in these cases one of the products is an unidentified acid which remains in the alkaline solution. When the hydroxy ketone was warmed with a solution of phenylhydrazine in acetic acid it formed the same phenylosazone that had been obtained from its higher melting isomer.

Oximes.—An alcoholic solution of the lower melting hydroxy ketone containing excess of alkali and hydroxylamine was boiled for an hour, then cooled, saturated with carbon dioxide and allowed to evaporate. It left an oil which solidified when treated with petroleum ether and a little alcohol. By systematic fractional crystallization from benzene the solid was separated into approximately equal quantities of two isomers melting, the one at 135° and the other at 118°.

Anal. Calcd. for $C_{16}H_{17}O_3N$: C, 70.8; H, 6.3. Found: (135°) C, 70.7; H, 6.3; (118°) C, 70.8; H, 6.5.

α - Phenyl - α - hydroxy - β - oxo - γ - (*p* - methoxyphenyl)-propane, $C_6H_5CHOHCOCH_2C_6H_4OCH_3$.—In order to secure more material for the purpose of relating the behavior of these hydroxy ketones toward alkalies with their structure, we prepared a third isomer by the action of *p*-methoxybenzylmagnesium chloride on the cyanhydrin of benzaldehyde. The ketone crystallized in needles and melted at 126°. It was not altered by prolonged boiling with 2% aqueous sodium hydroxide.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.0; H, 6.2. Found C, 74.8; H, 6.4.

Summary

In this paper the mechanism is established by which bases convert an hydroxy ketonic acid into the corresponding hydroxy ketone.

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[3] Jörlander, *Ber.*, **50**, 406 (1917).