DERIVATIVES OF CITRACONIC ACID. I. THE SYNTHESIS OF METHYLTARTARIC ACID AND THE DECOMPOSITION OF DIHYDROXYMALEIC ACID[1]

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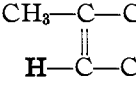
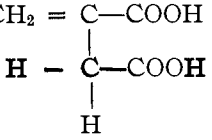
Foreword

The reaction of Fenton employed in the oxidation of hydroxy and polyhydroxy acids to their ketonic derivatives makes use of hydrogen peroxide as the oxidizing agent and minute quantities of ferrous sulfate as catalyst. Although acids such as acetic, malonic, oxalic, succinic or maleic undergo no definite change when subjected to the Fenton reaction, tartaric, lactic and many other hydroxy acids are readily converted to their ketonic derivatives. One of the classic examples of the application of this principle is to be found in those remarkable researches of Fenton dealing with the oxidation of tartaric acid to dihydroxymaleic acid. He found that this latter compound, when warmed with water, loses quantitatively two molecules of carbon dioxide to yield glycolic aldehyde:[2] $HOOCCOH:COH\text{-}COOH = CH_2OHCHO + 2CO_2$. Although the literature following Fenton's first paper has been enriched by many investigations embodying his principle, little attention has been paid to the mechanism of decomposition of dihydroxymaleic acid. The purpose of this research is therefore twofold; first, of establishing a method for the preparation of methyltartaric acid, and second, through a study of its behavior toward the Fenton reagent, of throwing some light on the mode of decomposition of dihydroxymaleic acid.

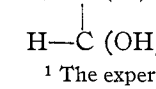
The distillation of citric acid yields, among other products, citraconic[3]



and itaconic[4] acids



When citraconic acid is treated with hypochlorous acid, chlorocitramalic acid,



, is formed,[5] a compound that one might readily

[1] The experimental work carried out in connection with this research was performed in the laboratories of Professor Richard Willstätter at the Bayerische Akademie der Wissenschaften, Munich, Germany.

[2] Fenton, (a) *J. Chem. Soc.*, **65**, 899 (1894); (b) **67**, 48, (c) 774 (1895); **69**, 546 (1896); (d) **71**, 375 (1897); (e) **73**, 71 (1898); (f) **81**, 426 (1902); (g) *Proc. Cambridge Phil. Soc.*, **11**, 109 (1901); (h) **11**, 358 (1902).

[3] Lassaigne, *Ann. chim.*, [2] **21**, 100 (1822). Crasso, *Ann.*, **34**, 53 (1840).

[4] Gottlieb, *Ann.*, **77**, 265 (1851). Swarts, *Jahresber.* **1873**, 579.

[5] (a) Gottlieb, *Ann.*, **160**, 101 (1864). (b) Carius, *Ann.*, **126**, 205 (1863); **129**, 159 (1864).

expect to suffer hydrolysis to methyltartaric acid,

CH_3—C(OH)—COOH. A search of the literature for an accurate account
  |
H—C(OH)—COOH

of the preparation of methyltartaric acid discloses indeed little. Carius[5b] claimed to have obtained the desired product by treating the chloro acid with barium hydroxide, but both Morowski[6] and Sherks[7] have demonstrated that not methyl tartaric acid but oxycitraconic acid, CH_3C(COOH)CH.COOH, was actually produced under such treatment.
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Indeed, it was only by a treatment involving great decomposition that Morowski was able to prepare minute quantities of methyltartaric acid from chlorocitramalic acid.

Discussion

Despite Morowski's unsuccessful attempts at preparing pure methyltartaric acid from chlorocitramalic acid, or its salts, the hydrolysis of the latter was re-investigated with numerous hydrolytic agents. It was found, however, that at temperatures where the decomposition of the parent substance was held in check[8] alkaline hydrolytic agents yielded almost quantitatively the oxycitraconate, and at elevated temperatures a similar reaction occurred together with decomposition. When treated with water alone at elevated temperatures (100–120°), although methyltartaric acid was indeed formed from chlorocitramalic acid or its salts, as a preparative scheme the method had to be abandoned, for not only was decomposition great, but the end-product was so contaminated that it took actually weeks for crystallization to follow.

A study of the hydrolysis of oxycitraconic acid was therefore resorted to with the aim in view of hydrolyzing it more successfully than did Morowski. Oxycitraconic acid is remarkable both in its instability at elevated temperatures, at which the molecule suffers a marked decomposition, and in the great stability of its ethylene oxide ring under controlled conditions. Only after a wide variety of experiments had been carried out with various hydrolytic agents was it found possible to convert the acid almost quantitatively into the desired product, methyltartaric acid. The reaction probably involves the formation of an unstable sulfuric

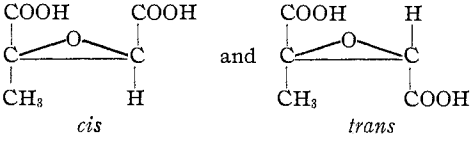
[6] Morowski, *J. prakt. Chem.*, [2] **10**, 68 (1874); [2] **11**, 430 (1875).

[7] Sherks, *Ann.*, **228**, 233 (1885).

[8] Chlorocitramalic and oxycitraconic acids, as well as their salts, are both sensitive towards heat. They both decompose to yield propionic aldehyde and carbon dioxide (Ref. 7, p. 238). In the case of chlorocitramalic acid, oxycitraconic acid is probably first formed, which decomposes to propionic aldehyde and carbon dioxide. The mechanism of the decomposition has never been satisfactorily explained.

ester which may readily suffer hydrolysis by alkali or water.

$CH_3.C(COOH)OCH.COOH + H_2SO_4 = HOSO_3C(COOH)(CH_3).CHOH.COOH + HOOCC(OH)CH_3.CHOH.COOH + H_2SO_4$. Oxycitraconic acid may be said to exist in two forms,



It was found that the oxycitraconic acid produced by the hydrolysis of chlorocitramalic acid resisted all attempts a forming an anhydride, and that the acid thus prepared in all probability exists in the *trans* form.

The oxidation of methyltartaric acid with hydrogen peroxide should yield methyl-hydroxy-keto-succinic acid, $HOOC.CH.(OH).C(CH_3)(OH).COOH \longrightarrow HOOC.CO.C(CH_3)(OH).COOH$, just as the oxidation of tartaric acid yields dihydroxymaleic acid (or hydroxy-keto-succinic acid, HOOC.CO.CHOH.COOH). And, just as the decomposition of the latter compound yields glycolic aldehyde, so should the homolog, hydroxy-methyl-keto-succinic acid, decompose to yield lactaldehyde and carbon dioxide. Though, on account of its remarkable instability, it was found impossible to isolate either a salt or a hydrazone of hydroxy-methyl-keto-succinic acid, there is, nevertheless, justification for a study of the decomposition of this product in the presence of unchanged and inert methyltartaric acid, for the isolation of derivatives of its predicted degradation products have left the formation and transient presence of hydroxy-methyl-keto-succinic acid beyond question.

There remains still a most important point for discussion, a point bearing both on the oxidation products of tartaric and methyltartaric acids. The first mechanism for the decomposition of dihydroxymaleic acid, the oxidation product of tartaric acid, was restricted to the decomposition of trihydroxysuccinic acid produced by the hydration of dihydroxymaleic acid.[9] The explanation was based on the stability of benzene and chloroform solutions of the parent substance. This hypothesis was later supplemented[10] when it was found that the addition of small amounts of anhydrous pyridine to a benzene suspension of dihydroxymaleic acid caused a rapid and quantitative decomposition, by the contention that decomposition was restricted to the dihydroxymaleate ion. Locke[11] has demonstrated the inadequacy of Fenton's later contention.

The products from the oxidation of tartaric acid and its homolog have

[9] Ref. 2 c, p. 777.

[10] Fenton, *J. Chem. Soc.*, **87**, 818 (1905).

[11] Locke, THIS JOURNAL, **46**, 1426 (1924).

points quite in common. Both show an analogous instability in aqueous solution where a rapid and quantitative loss of two molecules of carbon dioxide is suffered; in the first case, glycollic aldehyde is ultimately obtained, in the latter, either lactaldehyde or an isomer. These products of oxidation differ, however, in that the oxidation of methyltartaric acid yields the methyl homolog of hydroxy-keto-succinic acid (dihydroxymaleic acid), a compound incapable of suffering isomeric change, whereas hydroxy-keto-succinic acid may readily pass into its tautomeric form. In view of this astonishing similarity between the mode of decomposition of these two acids which ordinarily are represented as so dissimilar in structure, it is suggested that dihydroxymaleic acid does not, in the course of its decomposition, follow the accepted mechanism: $HOOC.C(OH):C(OH).COOH \longrightarrow 2\ CO_2 + HCOH.CHOH \longrightarrow CH_2OH.CHO$, but must pass first into its tautomeric form: $HOOC.C(OH):C(OH).COOH \longrightarrow HOOC.CO.CHOH.COOH$, and then decompose according to the equation, $HOOC.CO.CHOH.COOH \longrightarrow 2\ CO_2 + CHO.CH_2OH$, a mechanism now compatible with that of the decomposition of its non-tautomerizing homolog, hydroxy-methyl-keto-succinic acid: $HOOC.CO.C(CH_3)\ OH.COOH \longrightarrow 2\ CO_2 + CH_3.CHOH.CHO$.

The assumption of such an isomeric change in dihydroxymaleic acid is by no means out of the question. Fenton[12] who first assumed the formula of dihydroxymaleic acid to be $HOOC.C(OH) = COH.COOH$ later showed that the formation of pyrazine-2,5-dicarboxylic acid by heating the sodium salt of dihydroxymaleic acid with phenylhydrazine acetate, the formation of the osazone of glyoxal-carboxylic acid on treating dihydroxymaleic acid with phenylhydrazine acetate at elevated temperatures, as well as the formation of the ethyl ester of phenylhydrazone-ketophenyl-pyrozolone-carboxylic acid, $C_2H_5OOC.C:N—N(C_6H_5)COC:N\ NHC_6H_5$ from phenylhydrazine acetate and ethyl dihydroxymaleate, again at elevated temperatures, could be explained only on assuming the ketonic structure for the dihydroxymaleate.

Whether the loss of two molecules of carbon dioxide suffered on heating aqueous solutions of both hydroxy-keto- and methyl-hydroxy-keto-succinic acids is entirely simultaneous or one of succession is a question which at this time cannot be answered. That the decomposition of the carboxyl adjacent to the carbonyl group in hydroxy-keto-succinic acid (and hence in its homolog) cannot be the initial loss was demonstrated by Nef[13] when he showed that tartronic semi-aldehyde was stable. On the other hand, an initial loss of the carboxyl group beta to the carbonyl in hydroxy-methyl-keto-succinic acid cannot well be assumed unless it is followed by com-

[12] Ref. 10, p. 806.

[13] Nef, *Ann.*, **376**, 115 (1910).

plete rearrangement of the resultant product, $CH_3.CHOH.CO.COOH$, to $CH_3.CO.CHOH.COOH$, a reaction difficult to comprehend.[14]

In conclusion the author wishes to express his deep and sincere gratitude to Professor Richard Willstätter who guided him with many fruitful and valuable suggestions throughout the experimental work carried on in connection with this research.

Experimental Part

The Preparation of Citraconic Anhydride.—Citraconic anhydride was prepared according to the method of Gottlieb[4] but using, instead of the crystalline, the anhydrous acid, and instead of numerous receivers cooled with ice, a long air condenser. In this manner a more concentrated distillate was obtained and only one further fractional distillation was necessary to obtain pure citraconic anhydride. From 1 kg. of citric acid about 175 g. of citraconic anhydride can be obtained.

The Addition of Hypochlorous Acid to Citraconic Acid.—Gottlieb[4] previously prepared chlorocitramaleic acid by bubbling chlorine through a 2 % solution of sodium citraconate. It was found, however, that much better yields could be obtained by the addition of free hypochlorous acid to sodium citraconate.

Hypochlorous acid was prepared by the addition of boric acid in excess to a suspension of "chloride of lime" followed by distillation in a vacuum. About 50% of the available hypochlorous acid was obtained in the first quarter fraction. The acid was cooled to 0° and slowly added to an ice-cold 4% solution of sodium citraconate. The acid was added in molecular proportions at such a rate that at no time did it exist in excess within the reaction mixture. A 50% solution of barium acetate was added in excess after the reaction had reached completion. At the end of 24 hours the beautiful crystals of barium chlorocitramalate were filtered from the mother liquors. The method gave repeatedly yields of 45–50%, whereas the method of Gottlieb gave yields of 30%.

Anal. Calcd. for $H_5C_5O_5ClBa.4H_2O$: Cl, 9.14. Found: 9.03, 9.10.

The Hydrolysis of Chlorocitramalic Acid.—Carius[5] prepared what was thought to be methyltartaric acid by heating mixtures of chlorocitramalic acid and barium hydroxide, and obtained a non-crystalline product. Morowski[6] found that the acid, or its salt, when heated with water in a sealed tube for ten hours at 120° gave small quantities of methyltartaric acid. He also suggested the heating of the barium salt with water at 100° as a method for the preparation of the desired acid.

The suggestion of Carius is out of the question, whereas the latter method of Morowski yields a neutral solution, a result which leaves but one interpretation, namely, that half of the original salt must have suffered a decomposition and that the other half actually was hydrolyzed to methyltartaric acid. A loss of 50% precluded the adoption of Morowski's

[14] In view of the fact that the intermediary products of decomposition of hydroxy-keto-succinic acid (dihydroxymaleic acid) are, as we know them, stable, there can be no great difference in the rate of elimination of each carbon dioxide molecule. This difference is apparently so small that it seems quite impossible to measure it.

suggestion as that of a practicable means for preparing methyltartaric acid. It was found, however, that barium chlorocitramalate could be hydrolyzed at temperatures lower than that of the boiling point of water. With the hope that decomposition of the salt could be avoided or minimized at reduced temperatures a study was made in which a sample of the salt was completely hydrolyzed at a specific low temperature, and its neutrality, as well as the weight of the newly formed methyltartaric acid, determined. The results of the experiments demonstrated conclusively that the hydrolysis of barium chlorocitramalate in water is accompanied by a simultaneous decomposition regardless of the temperature. The methyltartaric acid obtained by the above procedure crystallized only after weeks of standing.

A series of experiments was carried out in which a variety of weak bases was used in an effort to hydrolyze chlorocitramalic acid to methyltartaric acid. Sodium carbonate, sodium bicarbonate, magnesium oxide, dil. barium hydroxide and barium carbonate were tried, with the result that in each case an almost quantitative formation of oxycitraconate, and not the methyltartrate, resulted. In the case of barium carbonate no hydrolysis took place. The experiments were all carried out at room temperature, for higher temperatures involve a decomposition of the acid and have no effect on the mode of hydrolysis. The end-product was easily isolated through its solubility in ether. The results, in fact, of all of the experiments attempted in trying to hydrolyze chlorocitramalic acid, as well as its barium salt, directly to methyltartaric acid, indicated concisely that any attempt in this direction is practically futile.

The Preparation of Barium Oxycitraconate.—Both Morowski[6] and Sherks[7] have demonstrated that when barium chlorocitramalate is heated with diluted, boiling barium hydroxide solution, barium oxycitraconate can be obtained. Their method involves, however, an appreciable loss of material through decomposition.

It was found that barium oxycitraconate could be prepared both quantitatively and free from barium carbonate by treating barium chlorocitramalate with a 10% excess of 3% barium hydroxide at 35° until hydrolysis was complete.

Anal. Calcd. for $C_5H_4O_5Ba.4H_2O$: Ba, 38.72. Found: 38.62, 38.69.

The Preparation of Methyltartaric Acid.—The ethylene oxide ring of oxycitraconic acid shows a most remarkable stability. The substance fails to respond to the methods generally employed for opening a ring of this character.

The use of sulfuric acid as a hydrolytic agent was carefully studied. A wide variety of experiments had been executed in which both the concentration of the mineral acid and the temperatures of reaction were varied before it was found that methyltartaric acid could best be prepared in the following manner.

Two hundred g. of barium oxycitraconate was agitated with water and 58 g. of sulfuric acid was carefully added. The barium sulfate was filtered from the solution and the filtrate was concentrated in a vacuum until it weighed roughly 150 g. To it was added 16 g. of concd. sulfuric acid and the entire mixture was placed in a small bulb bearing a reflux condenser. The bulb was immersed in a boiling water-bath for six hours for the hydrolysis to reach completion. At the end of this time the mixture, which had assumed a light brown hue, was cooled and extracted twice with ether to remove any unchanged oxycitraconic acid. The sulfuric acid was then exactly removed by the addition of barium hydroxide. The solution was filtered, boiled with bone black a few times, and finally concentrated until its weight had reached 100 g. It was allowed to stand in an ice box for two days. At the end of this time the crystalline methyltartaric acid was filtered from the sirupy mother liquors and dried in the air; yield, about 65 g. The mother liquors containing some 15 g. of acid in solution were saved for further concentration.

Anal. Calcd. for $C_5H_8O_6$: C, 36.57; H, 4.91. Found: C, 36.42; H, 4.83.

In this manner methyltartaric acid was obtained without water of crystallization. The substance melts at 100° with decomposition. It is very soluble in water, alcohol, acetone and methyl alcohol, but is almost insoluble in ether, chloroform, benzene and petroleum ether. Like tartaric acid, in alkaline solution it does not precipitate copper sulfate solution. The acid does not decompose when boiled with water as does oxycitraconic or chlorocitramalic acid. Its flavor and its solubility resemble those of tartaric acid to a remarkable degree.

The Oxidation of Methyltartaric Acid with Hydrogen Peroxide.—Hydrogen peroxide should oxidize methyltartaric acid in the presence of ferrous sulfate in the following manner: $HOOC.CH(CH_3).CHOH.COOH + H_2O_2 = HOOC.C(CH_3)OH.C(OH)_2.COOH$ or $HOOC.C(CH_3)OH.CO.COOH + H_2O$. This new acid may be called hydroxy-methyl-keto-succinic acid. The method employed in the oxidation of the acid was as follows.

To a solution of methyltartaric acid containing equal portions of acid and water was added ferrous sulfate in the proportion 0.025 g. to 1 g. of acid. The solution was immersed in a freezing mixture and violently stirred with a mechanical turbine. A solution of 6% hydrogen peroxide containing the equivalent of one atom of oxygen per molecule of methyltartaric acid was added, drop by drop, to the mixture after it had reached a temperature of −18°. The addition of peroxide was maintained at such a rate that the lowest possible temperature could be held in the reaction mixture without the formation of an appreciable amount of ice.

The mixture, after the addition of peroxide and after standing for a half hour, contained no trace of the oxidizing agent. It had, in the cold, little reducing effect but, on standing or warming, the reducing effect was enormously increased. A small portion of the oxidized mixture evolved carbon dioxide most readily when warmed and the resultant solution had a powerful reducing effect on Fehling's solution in the cold. At 60° this loss of carbon dioxide is completed in a very short time. These observations indicate that the desired hydroxy-methyl-keto-succinic acid was present in appreciable quantities in the oxidized solution of methyltartaric acid and, like Fenton's dihydroxymaleic acid, this new acid is decomposed when warmed with water, involving the loss of carbon dioxide and the formation of a substance having a powerful reducing effect, probably

lactaldehyde. It was found, however, that this acid could not be isolated as a salt, for on account of its great instability it could not be fractionated from the salts of methyltartaric acid. The simplest manipulations, even at reduced temperatures (—25°) were accompanied by severe decomposition.

The Action of Phenylhydrazine on the Oxidation Product of Methyltartaric Acid

When the oxidation product of methyltartaric acid was warmed to 60° and after the evolution of carbon dioxide had ceased, the solution was cooled and treated with phenylhydrazine acetate. After 24 hours a copious precipitate had formed; this was filtered and washed. The crude material melted at 135–140°. When recrystallized first from 60% alcohol and finally from benzene a pale yellow osazone was obtained, melting at 145–146°. The compound proved to be the osazone of lactaldehyde and was identified by a mixed melting point with the same osazone prepared from methylglyoxal. From 10 g. of methyltartaric acid 3.9 g. of osazone was obtained, or a yield of 24.1%.

Attempts were made to isolate the hydrazone of hydroxy-methyl-keto-succinic acid. On account of the great instability of this new acid, the reaction with phenylhydrazine had to be carried out at —20°, a temperature obviously unfavorable for hydrazone formation. Although the experiments were carefully executed, and repeated under various conditions, no formation of hydrazone could be brought about. A small amount of lactaldehyde osazone was all that was secured.

A study of the effect of varying the amounts of oxidizing agent was made in an effort to increase the yield of hydroxy-methyl-keto-succinic acid and the results demonstrated that quantities in excess of one atom of oxygen per molecule of methyltartaric acid had little or no effect on increasing the yield, while quantities less than one atom decreased the yield proportionately.

The Action of Barium Hydroxide on the Oxidation Product of Methyltartaric Acid.—Attempts were made to isolate hydroxy-methyl-keto-succinic acid, $HOOC.CO.C(CH_3)OH.COOH$, as its barium salt.

The addition in excess of dil. barium hydroxide at 0° to an oxidized mixture of methyltartaric acid yielded an amorphous precipitate, throughout which were dispersed crystals. The filtrate of such a reaction contains only barium methyltartrate. This precipitate was dissolved in dil. sulfuric acid at 0°, the solution centrifuged, and the clear, supernatant liquid treated with phenylhydrazine acetate and sodium acetate. A yellow, osazone-like product was obtained, melting at 190°. This osazone was found to be almost completely soluble in dil. alkali; re-acidification yielded a purified product melting at 210°. The insoluble portion of the osazone proved to be lactaldehyde osazone and was present only in minute quantities. The product melting at 210° proved to be the osazone of diketo-butyric acid. It was identified as such after analysis by means of a mixed-melting-point determination with the osazone of diketo-butyric acid. The latter was produced by first hydrolyzing ethyl diketo-butyrate with barium hydroxide at 0°, acidifying with dil. sulfuric acid, centrifuging, and treating the supernatant liquid with phenylhydrazine acetate.

Anal. Calcd. for $C_{16}H_{16}O_2N_4$: N, 18.91. Found: 18.56, 18.74.

The formation of this osazone from the degradation of hydroxymethyl-

keto-succinic acid is readily explained by the fact that this acid is a β-ketonic acid and suffers, on treatment with dil. alkali, the loss of one molecule of carbon dioxide: $HOOC.CO.C(CH_3)OH.COOH = HOOC.CO.CHOHCH_3. + CO_2$.

Obviously no attempt has as yet been made at the isolation either of the complete or the partial degradation products of hydroxy-methyl-keto-succinic acid themselves. For the purpose of this particular research identification of the simplest and most readily isolated derivatives of these products has sufficed.

Summary

1. A method for the preparation of methyltartaric acid has been outlined.

2. A preliminary study of the behavior of methyltartaric acid toward hydrogen peroxide has been carried out.

3. A mechanism, based on the decomposition of the oxidation product of methyltartaric acid, for the decomposition of dihydroxymaleic acid has been suggested.

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[CONTRIBUTION FROM THE GEORGE WASHINGTON UNIVERSITY]

THE CONDENSATION OF THE ISOMERIC TOLYL-2-THIO-4-KETO-THIAZOLIDINES (RHODANIC ACIDS) WITH SUBSTITUTED VANILLINS

BY RAYMOND M. HANN

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The aldehyde condensation products of the rhodanic acid series are dyes, the majority of them being of slight value due to their fading by the action of light. It has been pointed out, however, that hydroxy-benzal-rhodanic acids when coupled with diazo compounds yield derivatives which dye silk or wool directly fast yellow or orange-yellow colors.[1]

The object of the present investigation was to prepare a series of halogen aldehyde condensation products of the isomeric tolyl-rhodanic acids in order to study the effect of the relative positions of the methyl group in the tolyl residue, as well as the halogen substitution effect in such a series of compounds upon their spectrophotometric behavior. Vanillin was selected as the parent aldehyde for two reasons: its mono-halogen substitution products are known (except chlorovanillin, which was prepared for this investigation), and it contains an hydroxy group in the *para* position to the aldehyde grouping, which should accentuate its dyeing

[1] Zipser, *Monatsh.*, **23**, 958 (1902).