[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Behavior of Some Halogen Substituted Enols. The Preparation of α-Chlorotetronic Acid

BY W. D. KUMLER

A number of organic compounds are known that contain "positive" chlorine or bromine atoms as exemplified by their ability to oxidize iodide to iodine. The analogous iodine compounds are rare probably because of their relative instability. The fact that the electrons are less tightly bound in iodine and that it is thus the most positive of the halogens, as indicated by the iodine going to the cathode when such compounds as iodine monobromide and iodine monochloride are electrolyzed in dichloroacetic acid,[1] suggests that iodoenols in water solution should be oxidizing agents.

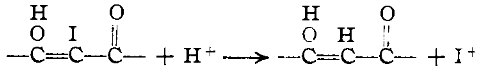
Wolff and Fertig[2] observed that α-iodotetronic acid oxidized iodide quantitatively to iodine. That ethyl α-iodoacetylacetone and *sym*-iodoacetylacetone likewise oxidize iodide quantitatively is shown by the following

	% iodine by titration	% iodine by Willard–Thompson Method
Ethyl α-iodoacetoacetate	50.3	50.0
sym-Iodoacetylacetone	55.3	55.7

The determination of the percentage of "positive" iodine by titration was carried out by dissolving the compound in 95% alcohol, adding an excess of aqueous potassium iodide, then adding dilute hydrochloric acid and titrating the iodine with thiosulfate using starch as an indicator.

The reaction is sensitive to hydrogen ion. The iodine comes out rapidly and completely only in solutions of high hydrogen ion concentration. This suggests that the reaction involved here is one of inverse substitution as has been suggested to be the case for bromodiethylmalonate and ethyl α-bromoacetoacetate[1] (p. 222).

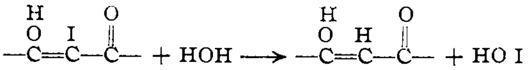
The reaction may be formulated thus



$$-\overset{\overset{\text{H}}{\text{O}}}{\text{C}}=\overset{\text{I}}{\text{C}}-\overset{\overset{\text{O}}{\|}}{\text{C}}- + H^+ \longrightarrow -\overset{\overset{\text{H}}{\text{O}}}{\text{C}}=\overset{\text{H}}{\text{C}}-\overset{\overset{\text{O}}{\|}}{\text{C}}- + I^+$$

$$I^+ + I^- \longrightarrow I_2$$

or



$$-\overset{\overset{\text{H}}{\text{O}}}{\text{C}}=\overset{\text{I}}{\text{C}}-\overset{\overset{\text{O}}{\|}}{\text{C}}- + HOH \longrightarrow -\overset{\overset{\text{H}}{\text{O}}}{\text{C}}=\overset{\text{H}}{\text{C}}-\overset{\overset{\text{O}}{\|}}{\text{C}}- + HO\,I$$

$$HOI + H^+ + I^- \longrightarrow I_2 + H_2O$$

When the titration is made in the same way but without adding any iodide more thiosulfate is used than corresponds to all the iodine present reacting as molecular iodine. This is probably due to iodine in a higher state of oxidation such as hypoiodous or iodic acid reacting with the thiosulfate.

Wolff and Fertig[2] proved that tetronic acid is formed when α-iodotetronic acid liberates iodine by taking advantage of the fact that tetronic acid forms an insoluble compound with acetone. That ethyl α-iodoacetoacetate is similarly converted to ethyl acetoacetate is indicated by the following experiment. Ethyl α-iodoacetoacetate was allowed to stand in the presence of water for several days. The compound turned dark brown due to the liberated iodine. The iodine was then put back in combination by treatment with hydrogen peroxide and the resulting substance after washing and drying had the same behavior and analysis as the original compound. This indicates that ethyl acetoacetate was formed when the iodine was liberated. Although ethyl α-iodoacetoacetate decomposes rapidly when exposed to moist air it was found possible to keep it unchanged for several months by storing it in a carbon dioxide atmosphere over anhydrous sodium sulfate. That it can oxidize ferrous to ferric ion is shown by the following experiment. Ethyl α-iodoacetoacetate was dissolved in alcohol and a freshly prepared solution of ferrous sulfate free from ferric ion added together with a little hydrochloric acid. The solution gave the characteristic red color of ferric thiocyanate when treated with potassium thiocyanate. The same test carried out with ethyl acetoacetate gave no ferric ion. α-Iodotetronic acid like ethyl α-iodoacetoacetate oxidizes ferrous to ferric ion. α-Bromotetronic acid in striking contrast to these iodo compounds does not oxidize ferrous to ferric ion. However when some potassium iodide was added to a solution containing α-bromotetronic acid, ferrous sulfate and potassium thiocyanate, the red color of ferric thiocyanate immediately appeared. This is direct evidence that α-iodotetronic acid is a considerably stronger oxidizing agent than α-

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[1] Waters and Lowry, "Physical Aspects of Organic Chemistry," D. Van Nostrand & Company, New York, N. Y., 1936, p. 169.

[2] Wolff and Fertig, *Ann.*, **312**, 144 (1900).

bromotetronic acid. Furthermore, it suggests that the first step in the mechanism of the oxidation of iodide by α-bromotetronic acid is the replacement of the bromine by iodine.

The percentage of enol was investigated in some of these compounds using the modified Kurt Meyer method. That in ethyl acetoacetate was run as a check, and a value of 7.4% was obtained, in agreement with the accepted value. In calculating the percentage of enol in the halogen substituted compounds a correction was made for the oxidation of the iodide by the compound itself.

Ethyl α-iodoacetoacetate was found to contain 20% enol. After standing for seventy-two hours in absolute alcohol it contained 49% enol. The fact that this compound reacts rapidly with bromine and has a rather high enol content is in contrast to ethyl α-bromoacetoacetate which according to Meyer and Kappelmeier[3] reacts very slowly with bromine and according to Rice[4] contains 4% enol.

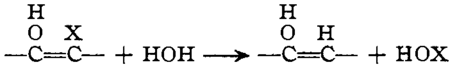
The tetronic acids are solids. Solids should be either pure keto or pure enol.[4] Tetronic acid was found to combine with 20–35% more bromine than corresponded to 100% enol. This indicates: first, the bromo derivative must combine rapidly with bromine; second, tetronic acid is either 100% enol or the equilibrium between the keto and enol forms is very fast. α-Bromotetronic acid was then investigated and was found to combine with bromine corresponding to 20–35% enol. The fact that this bromo derivative combines rapidly with bromine casts some doubt on the percentage of enol in compounds as determined by this method unless it has been proved definitely that bromine does not react rapidly with the bromo compounds formed. α-Iodotetronic acid combines with bromine corresponding to 50–70% enol.

α-Chlorotetronic Acid.—A number of attempts were made to esterify α-bromotetronic acid using dry hydrogen chloride and absolute alcohol but no ester was obtained. The analysis of the resulting substance indicated that chlorine had replaced the bromine in the compound. It was found possible to prepare a new compound α-chlorotetronic acid in a relatively pure state by this method. Two grams of α-bromotetronic acid was dissolved in 25 ml. of absolute alcohol and dry hydrogen chloride passed through the solution for twenty-four hours. The solution was evaporated at 35–40° *in vacuo* and the resulting solid recrystallized from ethyl acetate; white crystals, m. p. 205° with decomposition.

Anal. Calcd. for $C_4H_3O_3Cl$: equiv. wt., 134.4; Cl, 26.38. Found: equiv. wt., 136; Cl, 26.2, 26.6.

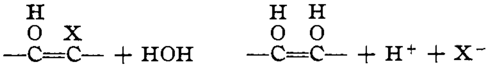
α-Chlorotetronic acid in contrast to the α-bromo and α-iodo compounds does not oxidize iodide quantitatively to iodine. A portion of the theoretical quantity of iodide is oxidized but the amount depends on the time the solution stands before titration. Thus after standing for five minutes 3% of the theoretical amount of iodide was oxidized. After standing for a week, 55% was oxidized. Apparently the chlorine in the compound is replaced slowly by iodine, giving iodotetronic acid which then oxidizes the iodide to iodine. This hypothesis is given support by the observation that bromine in α-bromotetronic acid is replaced easily by the other halogens. The replacement of bromine by chlorine has already been mentioned. In another experiment it was found possible to replace a large part of the bromine with iodine by warming α-bromotetronic acid with sodium iodide in absolute alcohol.

This change in oxidizing power in going from the iodine to the chlorine compound can be interpreted in the following way. Thus whether the replacement of the halogen goes by inverse substitution



$$-\overset{\overset{H}{O}}{C}=\overset{X}{C}- + HOH \longrightarrow -\overset{\overset{H}{O}}{C}=\overset{H}{C}- + HOX$$

in which case the compound will be an oxidizing agent in water solution, or whether it goes by regular substitution



$$-\overset{\overset{H}{O}}{C}=\overset{X}{C}- + HOH \qquad -\overset{\overset{H}{O}}{C}=\overset{\overset{H}{O}}{C}- + H^+ + X^-$$

depends on the result of the competition between the halogen and the carbon for the pair of electrons that form the carbon–halogen bond. In the case of iodine the electrons are held loosely by the iodine so when the bond breaks the organic radical retains the electrons, leaving positive halogen atoms that form hypoiodous acid with the water. Chlorine being smaller, binds the electrons more tightly and either the break does not occur or if it does the chlorine retains the electrons, instead of the organic radical, giving chloride ion which has no oxidizing properties.

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(3) Meyer and Kappelmeier, *Ber.*, **44**, 2718 (1911).

(4) Rice, "The Mechanism of Homogeneous Organic Reactions," The Chemical Catalog Company, 330 West 42d St., New York, N. Y., 1928, p. 80.

In the case of α-bromotetronic acid it appears that the bromine binds the electrons tightly enough to prevent inverse substitution, as indicated by the experiment with ferrous ions, but the carbon–bromine bond is sufficiently weak to permit rapid replacement of bromine with iodine.

It is interesting to note when a hydroxyl group[5] or an amino group[6,7] is attached to the α-carbon atom the compounds are good reducing agents. Thus we have the series

α-Iodotetronic acid—oxidizes iodide quantitatively
α-Bromotetronic acid—oxidizes iodide quantitatively. This is probably due to a rapid replacement of bromine by iodine
α-Chlorotetronic acid—oxidizes iodide only partially. This is probably due to a slow replacement of chlorine by iodine
Tetronic acid—does not oxidize iodide but reduces iodine to a slight extent forming α-iodotetronic acid
α-Hydroxytetronic acid—reduces iodine quantitatively
α-Aminotetronic acid—reduces iodine quantitatively

Summary

Ethyl α-iodoacetate and *sym*-iodoacetylacetone like α-iodotetronic acid oxidize iodide quantitatively to iodine, probably by inverse substitution. Ethyl α-iodoacetoacetate and α-iodotetronic acid oxidize ferrous to ferric ion, α-bromotetronic acid does not. Ethyl α-iodoacetoacetate contains 20% enol in the liquid state and 49% in absolute alcohol solution. α-Bromotetronic acid acts rapidly with bromine. The bromine titration method is not suitable for the accurate determination of the percentage of enol in the tetronic acids.

α-Chlorotetronic acid has been prepared. It does not oxidize iodide quantitatively to iodine. To account for the partial oxidation it is suggested that the iodide replaces chlorine to form some of the α-iodo compound which can oxidize iodide.

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[5] Micheel and Schulte, *Ann.*, **519**, 70 (1935).

[6] Wolff and Lüttringhaus, *ibid.*, **312**, 140 (1900).

[7] Micheel and Mittag, *Z. physiol. Chem.*, **247**, 34 (1937).

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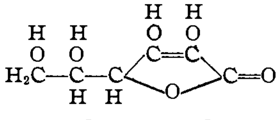
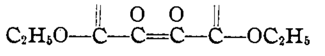
The Dissociation Constants of Some Enols Related to *l*-Ascorbic Acid. Tetronic Acid, α-Chlorotetronic Acid, α-Bromotetronic Acid, α-Iodotetronic Acid, α-Hydroxytetronic Acid and Ethyl α-Iodoacetoacetate

BY W. D. KUMLER

l-Ascorbic acid has a *pKa* = 4.85 in alcohol–water solution and diethyl dihydroxymaleate has a *pKa* = 7.88 in the same solution.[1] These results are anomalous for the structure assigned to these compounds has nearly the same grouping about the ionizable hydrogen.





$$C_2H_5O-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{O}}{C}=\overset{\overset{H}{O}}{C}-\overset{\overset{O}{\|}}{C}-OC_2H_5$$

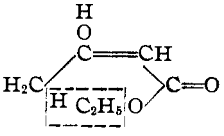
The work in this paper was undertaken to see whether or not other compounds containing the lactone ring found in *l*-ascorbic acid are strong acids and, if so, to investigate the cause of the high acid strength.

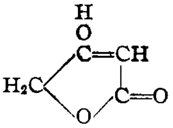
Five compounds containing this lactone ring were investigated. The hydrogen-ion concentrations of solutions of the partially neutralized acids were measured with a glass electrode and the dissociation constants were calculated. The results are given in Table I. The dissociation constant of ethyl α-iodoacetoacetate was measured. This and the dissociation constant for ethyl acetoacetate are included in the table.

TABLE I

	pKa	
α-Chlorotetronic acid	2.13 ± 0.013	
α-Bromotetronic acid	2.23 ± .005	
α-Iodotetronic acid	2.31 ± .005	
Tetronic acid	3.76 ± .003	
α-Hydroxytetronic acid	4.37 ± .02	
Ethyl α-iodoacetoacetate	7.0	
Ethyl acetoacetate	10.7	(Landolt–Börnstein)

If the formula for the ethyl acetoacetate molecule is written as follows, tetronic acid results when ethane is eliminated, and the oxygen of the ester group is attached to the methyl group.





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[1] Kumler and Daniels, THIS JOURNAL, **57**, 1929 (1935).