[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

1,2-DIKETONES FROM 1,3-DIBROMOKETONES. CONTRIBUTION III TO THE OXIDATION OF TETRONIC ACIDS[1]

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Two previous papers in this series have described the structural features (1) necessary for the formation of 1,2-diketones by acid oxidation of tetronic acids, and have advanced evidence (2) favoring a mechanisn for this oxidation which does not involve carbonium ions. This earlier work has clearly shown that the essential structural feature is the presence of one (and only one) enolizeable hydrogen atom in the tetronic acid molecule (Fig. 1, structure I). Further, circumstantial evidence has been advanced to show that the initial oxidation product is almost certainly to be represented by II. If the assumption is now made that the 3-hydroxytetronic acid (II) is capable of undergoing normal acid-catalyzed tetronic acid hydrolysis, *i.e.* hydrolysis of the lactone ring (1, 3), the result should be the α,γ-dihydroxy-β-keto-acid (III), a compound that would be expected to lose carbon dioxide easily, furnishing the ketodiol (IV). A dehydration of this ketodiol, (somewhat in the pinacol sense), might be expected to lead to the α-diketone (V).

A survey of the literature fails to afford clear-cut evidence on the dehydration step. Thus there is the fact that dihydroxyacetone is dehydrated by hot acids to form pyruvic aldehyde (4, 5), but it also appears possible to accomplish the same in basic solution [although a long time is required, (6)]. While it is true that α-diketones do not arise from the oxidation of tetronic acids unless acid is present, nevertheless the obviously close relationship between the dehydration of dihydroxyacetone and the scheme formulated in Fig. 1, warranted close investigation. We have been prevented from making a direct test of the scheme, however, due to the lack of synthetic methods for the preparation of the necessary ketodiols. Under the circumstances, then, we have had recourse to the corresponding 1,3-dibromoketones. While it must be admitted that this in itself constitutes a weakness in the general argument and relegates the evidence to a secondary status, nevertheless the results attendant upon the acid hydrolysis of several 1,3-dibromoketones accord so well with the earlier oxidation experiments that it is felt that the analogy is too close to be fortuitous.

There is in the literature only one example of the acid hydrolysis of 1,3-dibromoketones. Wolff (7) reported that the boiling in dilute acid of β, δ-dibromolevulinic acid furnished carbon dioxide, diacetyl, and γ-carboxy-α-ketovaleraldehyde. In the present investigation we have extended the acid hydrolysis of 1,3-dibromoketones to include examples in which bromine is attached to primary, secondary, and tertiary carbon atoms, *viz.;* 1,3-dibromopentanone-2 (VI), 1,3-dibromo-3-methylbutanone-2 (VIII), and 1,3-dibromo-4-methylpenta-

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[1] Most of this paper was presented before the Organic Division of the American Chemical Society, Boston Meeting, April 5, 1951.

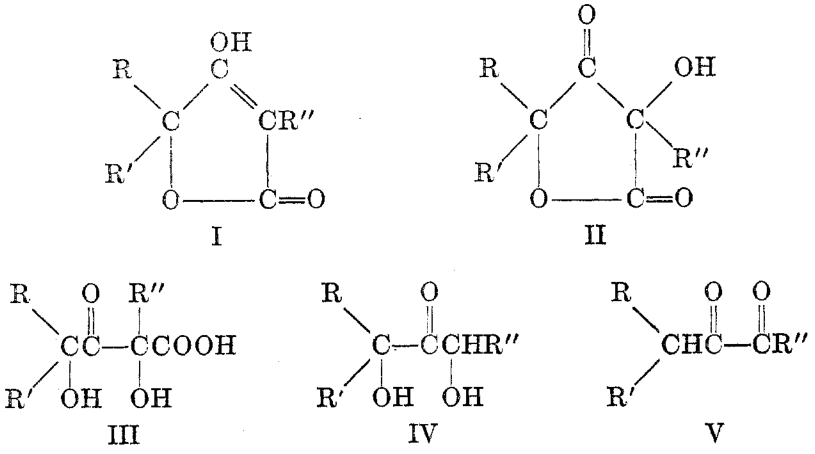


Fig. 1

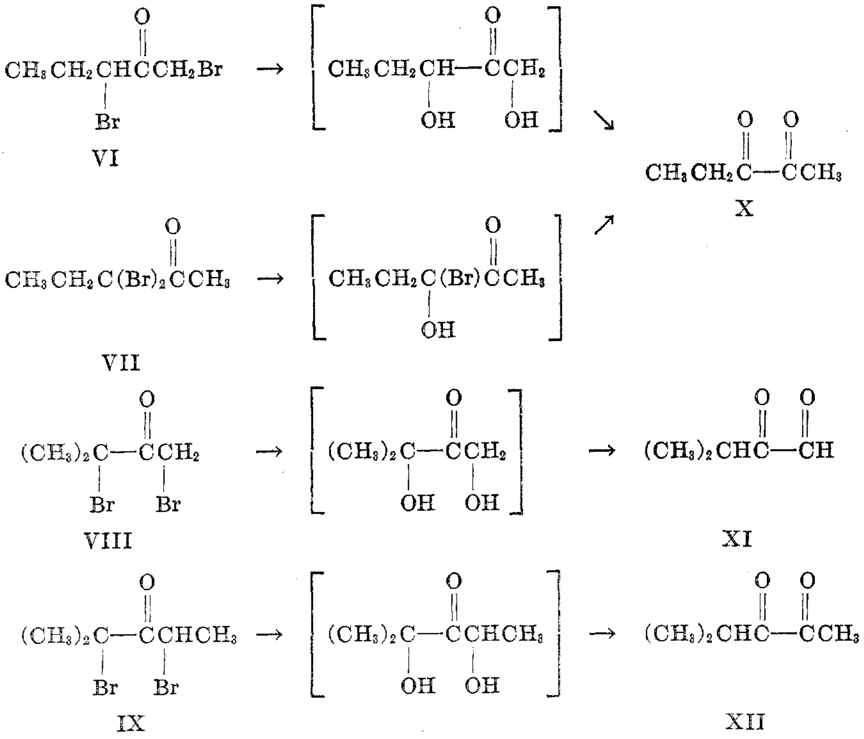
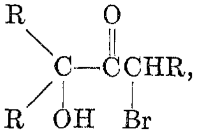


Fig. 2

none-3 (IX). In addition, 3,3-dibromopentanone-2 (VII) was hydrolyzed for comparison. Figure 2 shows these dibromides together with their hydrolysis products; included are possible ketodiol intermediates.

It may be noted here that the structure of the intermediate that actually furnishes the diketone is open to considerable doubt, since it is theoretically possible that the diketone is formed from a half-hydrolyzed dibromoketone, *i.e.* a bromoketol. For the branched chain examples, of the two isomeric bromoketols capable of formation the more likely would appear to be (in generalized form)  since the work of Richard (8) has shown that substitution reactions of monohaloketones are faster in those cases where the halogen atom is capable of being activated, in the allyl sense, by enolization of the ketone, and conversely, slower (or negligible) in those cases where such activation is structurally impossible. In the present instance, a dehydrobromination reaction, to furnish the diketone, might occur *via* the following scheme, Fig. 3.

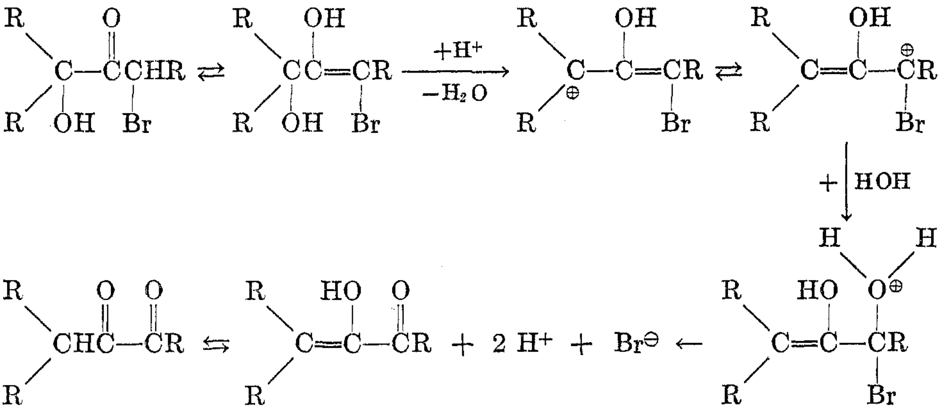


FIG. 3

It is apparent that the above transformation would be completely in harmony with what must obtain during the dehydration of the ketodiols (Fig. 2), if the latter are the actual intermediates. In either event, the green-yellow diketones formed slowly and in poor yield, due to simultaneous tar formation. In the case of VI and VII ethanol was added to the acidic mixture to increase the solubility of the haloketones. This resulted in alcoholic distillates of the diketones, and the latter had to be isolated through derivatives. The keto-aldehyde XI, and the diketone XII were formed in the absence of solubilizing agents and were isolated from the distillates and purified.

The specific interpretation of these hydrolyses, in terms of the six fundamental types of tetronic acid (Fig. 4) whose oxidations were earlier described (1) is as follows.

The first, 3-ethyltetronic acid (XIII), on oxidation followed by lactone ring hydrolysis with decarboxylation should furnish the ketodiol corresponding to the dibromide VI, Fig. 2. Similarly 3,5,5-trimethyltetronic acid (XIV), would produce the ketodiol corresponding to the dibromide IX; in the case of 5-methyltetronic acid (XV), however, which formed diacetyl, for reasons already discussed (1) oxidation at carbon 5 is preferred. This latter case then is analogous to the hydrolysis of 3,3-dibromopentanone-2 (VII). The diketone (acetylpropionyl) obtained from 3,5-dimethyltetronic acid (XVI), could arise from either oxidation at the 3- or the 5-carbon, since the same ketodiol would ultimately result. In the case of 3,3-dimethyltetronic acid (XVII), the formation of a ketodiol is prevented, although by oxidation similar to that of 5-methyltetronic acid (XV), some isobutyrylformaldehyde (XI, Fig. 2) might be expected. Lastly, although oxidation of 5,5-dimethyltetronic acid (XVIII) must attack the 3-carbon, because stabilizing resonance is possible for the hydroxylated tetronic acid (1), extensive degradation is to be expected, rather than formation of isobutyrylformaldehyde.

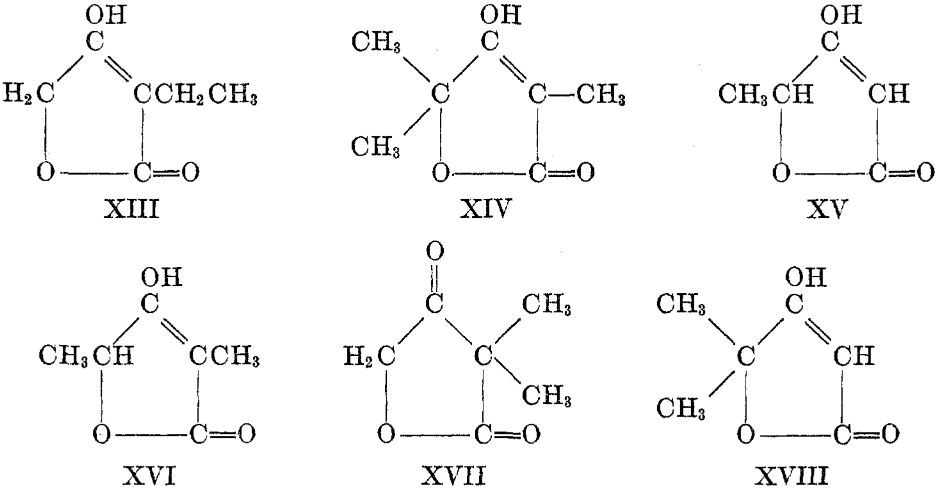


FIG. 4

There is thus very close correspondence between the formation of α-diketones from the hydrolysis of 1,3-dibromoketones and from the oxidation of appropriate tetronic acids, especially when the restrictions appertaining to the latter reaction are applied to the former. However, before it can be finally accepted that the formation of α-diketones is through the ketodiol mechanism described in this paper it would be desirable (a) to show that the dehydration of 2,4-dihydroxy-5,5-dimethylhexanone-3 [the ketodiol from 3-methyl-5-*tert*-butyltetronic acid (2)] proceeds without molecular rearrangement and in only one steric sense, *i.e.* to give 5,5-dimethyl-2,3-hexanedione but not 5,5-dimethyl-3,4-hexanedione. And (b) to demonstrate, either by isolation of ketodiols from the reaction mixtures or by determination of kinetic data on ketodiol dehydrations, the applicability of the possible mechanism discussed in this paper. Experiments toward these ends are in progress.

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EXPERIMENTAL

1,3-Dibromopentanone-2 and 3,3-dibromopentanone-2. The recent method of Catch, Hey, Jones, and Wilson (9) was used to brominate pure 2-pentanone, furnishing a mixture of 1-bromo- and 3-bromo-ketones. These were obtained pure by careful fractionation through a twelve-plate glass helix-packed column equipped with a total-condensation variable-take-off head. The 3-bromopentanone-2 was obtained in 62% yield, and had b.p. 67–70° at 40.0 mm., while 1-bromopentanone-2, of b.p. 80–84° at 40.0 mm. was obtained at 22% yield.

The introduction of the second bromine atom was carried out as was the first. From 1-bromopentanone-2 was obtained 1,3-dibromopentanone-2, b.p. 83–84.5° at 7.0 mm., yield, 86%, n_D^{20} 1.5177.

Anal. Calc'd for $C_5H_8Br_2O$: Br, 65.49. Found: Br, 65.52.

Similarly, bromination of 3-bromopentanone-2 yielded 1,3-dibromopentanone-2, along with the isomer. By an oversight, only one-half the stoichiometric amount of bromine was used, accounting for the low yield of products. The first fraction had b.p. 59–60° at 7.0 mm., n_D^{20} 1.5045, and was 3,3-dibromopentanone-2, yield 16%.

Anal. Calc'd for $C_5H_8Br_2O$: Br, 65.49. Found: Br, 65.27.

The second fraction had b.p. 80–81° at 7.0 mm., and was 1,3-dibromopentanone-2, n_D^{20} 1.5180, yield 18%.

Hydrolysis of 1,3-dibromopentanone-2 and 3,3-dibromopentanone-2. Five-gram samples of each dibromide were added to 30 ml. of 5 *M* sulfuric acid, and 10 ml. of ethanol was added to increase the solubility of the organic compounds in the aqueous layer. After refluxing for about 12 hours, the mixtures were distilled, yielding yellow alcoholic distillates, b.p. 78–80°. It proved impossible to separate the diketone from the alcohol (10), so derivatives were prepared directly. With excess phenylhydrazine our derivative (m.p. 160–161°) did not depress the m.p. of the phenylosazone of acetylpropionyl (1), and with excess hydroxylamine reagent our derivative (m.p. 169–170°) showed no depression of m.p. on admixture to the dioxime of acetylpropionyl (1).

Attempts to hydrolyze the dibromides by the use of acetic acid buffered with sodium acetate to about *p*H 7 were fruitless.

Bromomethyl bromoisopropyl ketone (VIII) and α-bromoethyl α-bromoisopropyl ketone (IX). These were prepared from the parent ketones by direct bromination according to the directions of Favorsky (11), except that both bromine atoms were introduced in one continuous operation.

Hydrolysis of bromomethyl α-bromoisopropyl ketone. Since the hydrolysis was much slower with the branched-chain dibromides, it was necessary to use weak acid in order to prevent extensive decomposition. Five-gram samples were gently boiled with a solution of 25 ml. of 5 *N* sulfuric acid and 75 ml. of water, in an apparatus equipped with a total condensation variable-take-off head. After several hours long crystals began to appear in the condenser. These were removed, filtered and washed. The m.p. was 95° either alone or admixed with authentic α-ketoisovaleraldehyde (isobutyrylformaldehyde) (1).

Hydrolysis of α-bromoethyl α-bromoisopropyl ketone. In the same apparatus as above, 5 g. of the dibromide was gently refluxed with the diluted acid. By controlling the application of heat, it was possible to distil over a few drops of a green-yellow oil after a refluxing period of 24 hours. After several such experiments, the oil was separated and dried. The b.p., determined by the inverted tube micro method was 116°. The literature (12) gives 116° for the b.p. of acetylisobutyryl, and its dioxime is reported to melt (1, 13) at 155°. Our product reacted with hydroxylamine to form white needles, m.p., after recrystallization from water-ethanol, 156.5°.

Anal.[2] Calc'd for $C_6H_{12}N_2O_2$: N, 19.43. Found: N, 19.61.

SUMMARY

Several 1,3-dibromoketones have been prepared and submitted to hydrolysis under acid conditions. The α-diketones thus formed may be considered to arise through intermediate formation of corresponding ketodiols (or bromoketols), which then undergo an elimination reaction similar to that obtaining in the dehydration of dihydroxyacetone. The appropriateness of this scheme to the formation of α-diketones by the acid oxidation of tetronic acids has been discussed.

BALTIMORE 18, MD.

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[2] Analysis by Mrs. A. Claggett of The Johns Hopkins Chemistry Department.