

Summary.

1. Dihydroxy-tartaric acid, considered as a diketone, has a structural resemblance to benzil.
2. This resemblance extends to the reactions of the two compounds.
3. The conversion of dihydroxy-tartaric acid and its salts into tartaric acid is an analog of the rearrangement of benzil to benzilic acid.
4. The composition and behavior of sodium dihydroxy-tartrate are discussed.
5. Data are given which will help in the development of the method proposed by Fenton for the direct quantitative estimation of sodium.

BERKELEY, CALIFORNIA.

[CONTRIBUTION NO. 6 FROM THE DEPARTMENT OF CHEMICAL RESEARCH, PARKE, DAVIS AND COMPANY.]

SPIRO-PYRIMIDINES. III. CONDENSATION OF CYCLOPROPANE-1,1-DICARBOXYLIC ESTER WITH UREAS.

By ARTHUR W. DOX AND LESTER YODER.

Received May 19, 1921.

The preparation of *spiro*-pyrimidines containing 4- and 6-membered hydrocarbon rings has been described in our previous papers.¹ The corresponding 3-membered ring with one of its carbon atoms identical with the 5-carbon atom of barbituric acid was cited as the simplest derivative of this type. Certain difficulties were encountered in preparing such derivatives, hence the discussion was reserved for a later paper. The condensation of cyclopropane-1,1-dicarboxylic ester with urea was readily effected, but the product was so entirely different in its properties from the corresponding cyclobutane and cyclohexane derivatives that it was thought advisable to repeat the work. It has now become evident that a very stable polymer is formed in this reaction, and although its constitution has not been definitely established, it seems advisable to publish the results thus far obtained, for the reason that further work along this line is not contemplated.

Preparation of Ethyl Cyclopropane-1,1-dicarboxylate.

This substance has been prepared by Perkin.²

In view of the tediousness of Perkin's process and the smallness of the yield, we undertook to apply the method by which we obtained good results in the preparation of cyclobutane-1,1-dicarboxylic ester. According to Perkin there is in this case, much less tendency toward the formation of the open chain tetracarboxylic ester.

¹ Dox and Yoder, *THIS JOURNAL*, **43**, 677-84, 1366-71 (1921).

² Perkin, *Ber.*, **17**, 54-9 (1884); *J. Chem. Soc.*, **47**, 808 (1885); *ibid.*, **51**, 849-53 (1887).

A mixture of 310 g. of ethylene bromide and 255 g. of ethyl malonate was placed in a flask provided with a reflux condenser and a mechanical stirrer. The flask was immersed in a bath of water maintained at about 80°. By means of a dropping funnel, a solution of 73 g. of sodium in 1100 cc. of absolute alcohol was slowly added during the course of 2½ hours. After the mixture had been heated and stirred for 5 hours the reaction product was neutral to litmus. Most of the alcohol was then distilled, while the solution was stirred continuously. A test portion now showed a slightly alkaline reaction, and hydrochloric acid was added to make the mixture exactly neutral. On the addition of water, the sodium bromide dissolved and a yellow oil separated. The latter was extracted with ether. The yield of crude oil was 237 g. On fractionation 148 g. or 60% of the oil distilled between 200° and 220°. This was fractionated twice and finally yielded 120 g. of a product which distilled between 214° and 216° (corr.) at 748 mm. pressure. Perkin reports a boiling point of 208–10° at 720 mm. Our yield of pure product was 40%, as compared with Perkin's yield of 27–9%.

Condensation with Urea.

To a solution of 3.7 g. of sodium in 65 cc. of absolute alcohol, 10 g. of ester and 5 g. of urea were added and the mixture was heated for 4 hours in an autoclave at 105°. The white insoluble product was collected on a filter, then dissolved in water and acidified with hydrochloric acid. A voluminous white amorphous precipitate immediately formed. It was insoluble in water, acids and organic solvents, but slowly soluble in caustic alkalis. The yield was 3.5 g. or 42%. On heating the substance it charred at a high temperature without melting. It is precipitated from its alkaline solutions by acetic acid, or by carbon dioxide. Repeated attempts to obtain it in crystalline form by slow neutralization of the alkaline solution or by slow dilution of its solution in conc. sulfuric acid were unsuccessful. The product was invariably amorphous.

Analysis. Subs., 0.2, 0.2: NH_3 , 26.16, 26.13 cc. of 0.1 *N*. Calc. for $\text{C}_6\text{H}_8\text{N}_2\text{O}_3$: N, 18.18. Found: 18.05, 18.03.

The insolubility and amorphous character of the above product as contrasted with the solubility, crystalline form and sharp melting points of the corresponding cyclobutane and cyclohexane derivatives justify the assumption that a polymerization has occurred. Experiments were conducted to determine whether such polymerization could be avoided by altering the conditions of the condensation. If the polymerization were due to the hydrochloric acid used in liberating the product from its sodium salt, an organic acid should obviate this difficulty. It was found, however, that treatment of the original sodium salt with acetic acid and even with carbon dioxide gave the same product as before. The high temperature of the autoclave or the excess of sodium ethylate did not account for polymerization, since the same product was obtained when the condensation was performed on a steam-bath under a reflux condenser, using 1 mole of sodium instead of 3. In every experiment performed the product obtained was amorphous, insoluble in water, acids and organic solvents, and infusible.

A cyclopropane ring might conceivably polymerize in a number of ways. The simplest possibility is the union of two molecules to form a cyclohexane ring. Such a product would yield on complete hydrolysis of the ureide groupings and loss of one carbon dioxide from each of the carbons carrying two carboxyls, hexahydro-phthalic or hexahydro-terephthalic acid. Again the cyclopropane-*spiro*-barbituric acid might rearrange into vinyl-barbituric acid and then polymerize into a cyclobutane ring with 2 barbituric acid groups attached. The acids which would result from hydrolysis of such a product have not been prepared. Still again, 3 molecules of vinyl-barbituric acid might polymerize with formation of a cyclohexane nucleus. In fact, a number of other possibilities still more remote might be cited.

Hydrolysis of the Polymer.

Long boiling of the polymer with conc. hydrochloric acid did not alter it. After 3 hours' heating in a sealed tube at 180° with conc. hydrochloric acid, the polymer was recovered quantitatively and the filtrate showed only a trace of ammonium chloride. It was found, however, that hydrolysis can be effected by boiling it with 10% sodium hydroxide for a long time. The substance goes into solution by the time the boiling point is reached, but the evolution of ammonia does not cease until the solution has been boiled for several hours. After complete hydrolysis, as shown by the absence of ammonia and the failure of a test portion, when acidified, to give a precipitate, the solution was acidified with hydrochloric acid and evaporated. Most of the sodium chloride was removed by crystallization and, finally, a sirupy acid was obtained. On heating this in an oil-bath to 200° a copious evolution of carbon dioxide occurred. The residue was then dissolved in water, decolorized with charcoal and crystallized twice. The white crystals, thus obtained, were readily soluble in water and in alcohol, difficultly soluble in ether and in chloroform, and had a strongly acid taste. The melting point was 152° (corr.); 0.1 g. required 11.97 cc. of 0.1 *N* sodium hydroxide for neutralization. The neutralization equivalent was 88. This corresponds to a dibasic acid of molecular weight 176, and is in close agreement with the various acids $C_8H_{12}O_4$ theoretically possible from polymerization of cyclopropane-carboxylic acid. Of the hexahydro-phthalic acids mentioned above, the only one that approximates this melting point is *cis*-hexahydro-terephthalic acid which melts at 161°. This, however, undergoes a rearrangement into the *trans* acid on heating with hydrochloric acid at 180°. Our acid remained unchanged after this treatment.

Mono-amide of Cyclopropane-1,1-dicarboxylic Acid.

From the mother liquor of the condensation product, after precipitation of the polymer by acid, 2 g. of a crystalline acid melting at 195° was obtained. It was readily

soluble in water and in alcohol. The nitrogen content and the neutralization equivalent correspond with the calculated values for the mono amide of cyclopropane-1,1-dicarboxylic acid.

Analyses. Subs., 0.2, 0.2: NH_3 , 16.1, 16.1 cc. of 0.1 *N*. Calc. for $\text{C}_5\text{H}_7\text{NO}_3$: N, 10.85. Found: 10.99, 10.99.

Subs., 0.1: NaOH, 15.72 cc. 0.1 *N*. Calc. neutral equiv. for $\text{C}_5\text{H}_7\text{NO}_3$: N, 129. Found: 127.

Di-amide of Cyclopropane-1,1-dicarboxylic Acid.

This was easily prepared by shaking the ester with aqueous ammonia. Five g. of ester and 20 cc. of conc. ammonium hydroxide were placed in a stoppered bottle and shaken 18 hours in a shaking machine. By that time the oily layer had completely disappeared and an abundance of white prismatic crystals had formed. The yield was 3.4 g. or 84%. The substance melts at 198°. It is moderately soluble in water and readily soluble in alcohol.

Analyses. Subs., 0.2, 0.2: NH_3 , 31.61, 31.21 cc. of 0.1 *N*. Calc. for $\text{C}_5\text{H}_9\text{N}_2\text{O}_2$: N, 21.80. Found: 21.84, 21.56.

Condensation of the Di-amide with Diphenyl Carbonate.

Einhorn and Ladisch³ prepared veronal by the condensation of diethylmalonyl amide with diphenyl carbonate at 200°. It was thought that the di-amide described above might condense in the same way, possibly without polymerization of the product. One g. of diamide and 2 g. of diphenyl carbonate were intimately mixed and heated in an oil-bath at 190–200°. A short test-tube was used and this was immersed up to the flange so that the phenol distilled as fast as it was formed. After 9 hours' heating the reaction mixture was extracted with dil. sodium hydroxide solution and filtered from the insoluble phenyl carbonate. When the filtrate was acidified, an amorphous white precipitate was obtained which showed all the properties of the polymer already described.

Condensation of the Ester with Guanidine.

A mixture consisting of 1.2 g. of sodium dissolved in 50 cc. of absolute alcohol, 10 g. of ester and 5 g. of guanidine carbonate was heated under a reflux condenser for 5½ hours. The white amorphous mass obtained was evaporated on a steam-bath to remove most of the alcohol and then taken up with water. An opalescent solution resulted which became more and more cloudy on standing. The addition of acetic acid caused the immediate precipitation of the free base. It was washed thoroughly with water, alcohol and ether, then dried at 100°. The yield was 3.5 g. or 43%. The substance showed the same properties as the corresponding urea derivative except that it was soluble in mineral acids as well as in alkalis.

Subs., 0.2, 0.2: NH_3 , 37.6, 37.6 cc. 0.1 *N*. Calc. for $\text{C}_6\text{H}_7\text{N}_3\text{O}_2$: N, 27.45. Found: 26.32, 26.32.

Condensation of the Ester with Thio-urea.

To a solution of 3.7 g. of sodium in 65 cc. of absolute alcohol, 10 g. of

³ Einhorn and Ladisch, *Ann.*, **359**, 184 (1908).

este and 5 g. of thio-urea were added and the mixture heated for 4 hours at 105°. The condensation product insoluble in the alcoholic solution was collected on a filter, then dissolved in water. On acidifying the solution with hydrochloric acid, a copious white amorphous precipitate formed at once. It was somewhat soluble in hot water and slightly more soluble in hot alcohol but could not be obtained from either solvent in crystalline form. The yield was 7 g. or 76%.

Subs., 0.2, 0.2: NH_3 , 22.76, 22.65 cc. 0.1 N. Calc. for $\text{C}_8\text{H}_6\text{O}_2\text{N}_2\text{S}$: N, 16.47. Found: N, 15.93, 15.85.

Subs., 0.2: BaSO_4 , 0.2808. Calc.: S, 18.80. Found: 19.28.

Summary.

1. Cyclopropane-1,1-dicarboxylic ester condenses with urea, guanidine and thio-urea to form stable, amorphous products. From comparison with the corresponding cyclobutane and cyclohexane derivatives it is apparent that these products are polymers.

2. Hydrolysis of the urea polymer, followed by elimination of carbon dioxide, gave a crystalline acid with melting point 152° and molecular weight 176 (by titration). Of the acids, $\text{C}_8\text{H}_{12}\text{O}_4$, theoretically possible from hydrolysis of a dimer only the hexahydrophthalic acids are known. It is probable that a cyclopropane-1.5-*spiro*-barbituric acid first formed undergoes rearrangement to vinyl-barbituric acid which then polymerizes. The product would then be a cyclobutane-dibarbituric acid, which on hydrolysis and loss of 2 molecules of carbon dioxide would yield cyclobutane-1,2- or -1,3-di-acetic acid, both of which could exist in *cis* and *trans* forms. It is probable that the polymer is not a *spiro* derivative but rather cyclobutane-dibarbituric acid.

DETROIT, MICHIGAN.

[CONTRIBUTION FROM THE BUREAU OF PLANT CHEMISTRY, U. S. DEPARTMENT OF AGRICULTURE.]

CHANGES IN THE COMPOSITION OF PAPRIKAS DURING THE GROWING PERIOD.

BY A. F. SIEVERS AND J. D. MCINTYRE.

Received June 9, 1921.

The change in chemical composition of plants during their growth and development has always been an inviting field of research for the chemist and plant physiologist. Especially is this true in connection with fruits, vegetables and drugs. Much work has been done in this direction, particularly when some definite chemical compound is of predominating influence in determining the quality of the product. As examples, one might mention the development of sugars in the orange, sugar-beet, sweet-corn and sweet potato: citric acid in the lemon; volatile