

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY, AND FIXED NITROGEN DIVISION OF THE BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

## THE SYNTHESSES OF 2-IMIDAZOLONE-4-CARBOXYLIC ACID AND 2-IMIDAZOLONE

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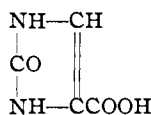
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Davidson and Baudisch<sup>1</sup> have utilized the von Pechmann reaction<sup>2</sup> for a novel synthesis of uracil by treating malic acid and urea with fuming sulfuric acid. More recently, Hilbert<sup>3</sup> in a similar manner prepared uracil-4-acetic acid from citric acid and urea. This method for the synthesis of cyclic ureides by condensing urea with a derivative of formylacetic acid, which is formed by the action of sulfuric acid on an  $\alpha$ -hydroxy- $\alpha,\beta$ -dicarboxylic acid, is practical only when the hydroxy acid is easily available. One other analog, tartaric acid, immediately suggests itself and the study of the product prepared from it and urea in sulfuric acid is the subject of this investigation.

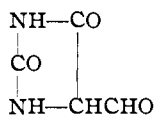
The initial product formed in a reaction between tartaric and sulfuric acids would be expected to be  $\alpha,\beta$ -dihydroxyacrylic acid (I) (formylglycolic acid)



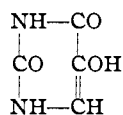
which upon subsequent reaction with sulfuric acid would yield glyoxal. The reaction of the degradation product of tartaric acid with urea can theoretically lead to a number of products. The condensation of urea with the  $\alpha$ - and  $\beta$ -hydroxy groups of (I) would be expected to yield 2-imidazolone-4-carboxylic acid (II) and the combination with either the  $\alpha$ - or  $\beta$ -hydroxy and the carboxyl group would be expected to produce 5-formylhydantoin (III) and isobarbituric acid (IV), respectively. A reaction between glyoxal and urea would yield acetylenediureide (V).



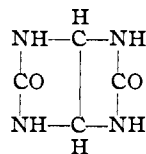
(II)



(III)



(IV)



(V)

Because of the presence of the additional  $\alpha$ -hydroxy group, it is difficult to predict which product will be formed. The cases, involving malic and citric acids are much simpler since each can yield only one cyclic nitrogen compound.

<sup>1</sup> Davidson and Baudisch, *THIS JOURNAL*, **48**, 2379 (1926).

<sup>2</sup> Von Pechmann, *Ber.*, **17**, 936 (1884); *Ann.*, **264**, 261 (1891).

<sup>3</sup> Hilbert, *THIS JOURNAL*, **54**, 2076 (1932).

The action of fuming sulfuric acid upon tartaric acid and urea actually leads to the formation of only one product which, considering the experimental conditions, is obtained in a satisfactory yield. It melts with decomposition at  $261^{\circ}$ , is insoluble in organic solvents, and slightly soluble in boiling water. The analytical results indicate that the empirical formula is  $C_4H_4O_5N_2$  which is that required by the isomers (II), (III), and (IV), and which definitely eliminates (V) from consideration. The possibility that the product is isobarbituric acid is excluded by the wide difference in the decomposition points and by the fact that the product neither responds to the Wheeler-Johnson color test<sup>4</sup> nor gives the characteristic blue color<sup>5</sup> with ferric chloride. Of the two remaining, 2-imidazolone-4-carboxylic acid (II) was shown to be more probable since the product is easily soluble in an aqueous solution of potassium carbonate.

The experimental evidence obtained by degradation and by conversion into derivatives definitely shows that the product is 2-imidazolone-4-carboxylic acid. It has a neutral equivalent of 121 (calcd. 128) and on appropriate treatment with sulfuric acid and alcohol forms an ester. Oxidation with chromic acid leads to the formation of parabanic acid, which is excellent evidence for the original presence of the imidazole ring.<sup>6</sup> Methylation with dimethyl sulfate in aqueous sodium hydroxide yields 1,3-dimethyl-2-imidazolone-4-carboxylic acid (decomp.  $229-230^{\circ}$ ), which, by a comparison of the properties, appears to be similar to that prepared by the hydrolysis of 7,8-dimethyldihydrouric acid (decomp.  $220^{\circ}$ )<sup>7</sup> and by the hydrolysis of 1,3-dimethyl-5-aminouracil-4-carboxylic acid (decomp.  $224-225^{\circ}$ ).<sup>8</sup> In order to obtain additional evidence that the methylated imidazolone carboxylic acid is the same as that reported by Biltz and Bülow, their work on the decarboxylation was repeated. The properties of the resulting 1,3-dimethyl-2-imidazolone are quite similar to those previously described.

2-Imidazolone-4-carboxylic acid reacts with acetic anhydride and yields a crystalline product which does not melt at  $300^{\circ}$ . As it is either sparingly soluble or insoluble in all ordinary solvents it is impossible to determine its molecular weight. The empirical formula is either  $C_6H_4O_5N_2$  or a multiple of this. Its striking behavior toward alkali indicates that it

<sup>4</sup> Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907).

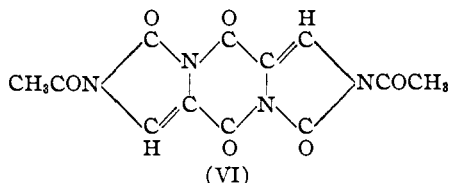
<sup>5</sup> Behrend and Roosen, *Ann.*, **251**, 235 (1889).

<sup>6</sup> The formation of parabanic acid by oxidation does not always necessarily indicate the original presence of an imidazole ring; see for example the oxidation of 1,4-dimethyluracil by Henkel, *Ann.*, **378**, 170 (1911), to 1-methylparabanic acid. A similar alteration in the ring is impossible in the present case since the presence of one of the carbon atoms in a carboxyl group does not allow a sufficient number to remain to form a pyrimidine ring.

<sup>7</sup> Biltz and Bülow, *Ann.*, **457**, 117 (1927).

<sup>8</sup> Beythien, *ibid.*, **389**, 214 (1912).

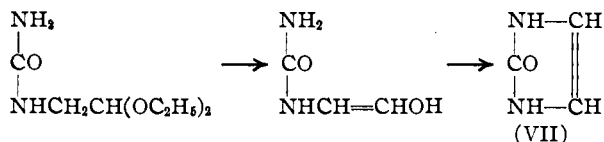
may be the diketopiperazine (VI). On treatment with potassium hydroxide the acetyl groups are removed and a crystalline canary yellow potassium salt forms, which analyzes well for  $C_8H_2N_4O_4K_2$ .



The condensation of urea with the hydroxyl groups of  $\alpha,\beta$ -dihydroxyacrylic acid, in preference to a reaction involving the carboxyl group, is very interesting and not without analogy. Certain rare rearrangements of pyrimidines to imidazolones seem to undergo a similar reaction. Beythien<sup>8,9</sup> for example, prepared 1,3-dimethyl-2-imidazolone-4-carboxylic acid from 1,3-dimethyl-5-aminouracil-4-carboxylic acid, and Johnson and Hadley<sup>10</sup> noted the transformation, on alkaline treatment, of 4-( $\alpha$ -hydroxyl ethyl)-uracil to 4,5-dimethyl-2-imidazolone. These pyrimidines are apparently hydrolyzed to form the open-chain urea derivatives in which the hydroxyl group combines with the amino radical to yield the imidazolone.

It is unfortunate that there is no method for the reduction of a lactam such as occurs in 2-imidazolone-4-carboxylic acid. All efforts toward this end resulted in failure. A successful means of reduction would have considerable significance as it would allow an easy method of entrance into the important imidazoline series of compounds.

**The Synthesis of 2-Imidazolone.**—The synthesis of 2-imidazolone has been reported twice in the literature. The properties of the product obtained, however, were quite different. Marckwald<sup>11</sup> by the hydrolysis of acetalylurea with dilute sulfuric acid isolated a product to which he assigned the structure of 2-imidazolone (VII).



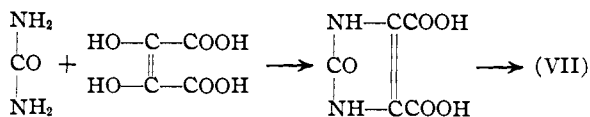
It was reported to be a semi-crystalline substance which did not melt at the boiling point of sulfuric acid. All attempts to convert this into some derivative were unsuccessful. Later Fenton and Wilks<sup>12</sup> by the condensation of dihydroxymaleic acid with urea obtained a crystalline product which decomposed at  $245^\circ$  and yielded a monoacetyl derivative.

<sup>8</sup> See also Bremar, *ibid.*, 378, 188 (1911).

<sup>10</sup> Johnson and Hadley, *THIS JOURNAL*, 39, 1715 (1917).

<sup>11</sup> Marckwald, *Ber.*, 25, 2357 (1892).

<sup>12</sup> Fenton and Wilks, *J. Chem. Soc.*, 95, 1329 (1909).



The analytical results and the molecular weight determination agreed well for 2-imidazolone. A direct comparison of this with Marckwald's compound definitely showed that they were different. Since Marckwald's substance was made by a more direct method, Fenton and Wilks apparently believed that he had obtained the true 2-imidazolone and accordingly named theirs "iso-imidazolone."

In order to throw further light on this question, 2-imidazolone-4-carboxylic acid was decarboxylated. This was effected by heating the acid at a temperature of 220° in a vacuum. The 2-imidazolone sublimed on the cooler parts of the vessel in the form of pyramidal crystals that decomposed at 250–251°. It had all the properties of the compound described by Fenton and Wilks, with the exception that it did not give a Weidel color reaction. The similarity of the chemical and optical properties and the fact that it also yielded an acetyl derivative melting at the same temperature as that of "iso-imidazolone" would seem to warrant the conclusion that these substances are identical and that Fenton and Wilks were the first to have obtained 2-imidazolone. The carbon and hydrogen values obtained by Fenton and Wilks for the acetyl derivative led them to believe that it was 1-acetyl-2-imidazolone. The product obtained in the present investigation, however, has been definitely shown to be 1,3-diacetyl-2-imidazolone.

I am indebted to Dr. David Davidson for a discussion concerning this work. The analytical results recorded were kindly carried out by Dr. Reid T. Milner and Mrs. Mildred S. Sherman.

### Experimental Part

**Preparation of 2-Imidazolone-4-carboxylic Acid.**—A series of experiments run under varying conditions was carried out and the following procedure was found to be the best. To a 2-liter three-necked flask fitted with a stirrer was added 400 cc. of 13% fuming sulfuric acid. After cooling this to 0°, 112 g. of finely powdered anhydrous tartaric acid was added at such a rate that the temperature did not rise above 10°—this required ten minutes. The ice-bath was removed and 100 g. of urea added. The temperature during this operation rose rapidly and was finally held with the aid of a burner at 80° for thirty minutes. A vigorous reaction ensued with the concomitant evolution of carbon monoxide and carbon dioxide; the reaction mixture rapidly turned black. After completion of the reaction the contents of the flask were cooled and poured on 1200 g. of ice. An amorphous chocolate colored precipitate immediately separated. This, having stood in the ice box overnight, was filtered; yield of crude dry product, 35 g. It was decolorized by boiling a water solution with large portions of bone black and finally recrystallizing from water from which it separated as colorless nodules; it melted with vigorous effervescence at 261°. 2-Imidazolone-4-carboxylic acid was slightly soluble in boiling water and insoluble in organic solvents.

*Anal.* Calcd. for  $C_4H_4O_3N_2$ : C, 37.50; H, 3.15; N, 21.88. Found: C, 37.95; H, 3.28; N, 21.98, 21.85.

The acid was dissolved in an excess of standardized sodium hydroxide and titrated back with standardized hydrochloric acid using phenolphthalein as the indicator.

*Neutral equivalent.* Subs., 0.1164, 0.0489: 14.06, 5.78 cc. of 0.0694 *N* NaOH. Calcd. for  $C_3H_3N_2O_3COOH$ : 128. Found: 119.3, 121.9.

On treating the acid with Tollens' reagent it formed a silver mirror. The same result was obtained by heating it with an ammoniacal solution of silver nitrate. A water solution of the acid yielded a dark brown color when treated with aqueous ferric chloride. It did not give a Weidel color reaction.

In order to obtain evidence concerning the structure of 2-imidazolone-4-carboxylic acid, its action toward various reagents was studied. The following did not yield satisfactory results. A water solution of the acid was treated with bromine. The water was removed and a pale yellow sirup resulted which did not crystallize on standing, and was not further investigated. Treatment of the imidazolone with phosphorus oxychloride led to complete decomposition. On evaporation to dryness with fuming hydrochloric acid a gummy residue resulted that was not amenable to the isolation of a homogeneous product.

Isobarbituric acid was shown neither to be an intermediate in the formation of the imidazolone nor to be susceptible to rearrangement. It was heated with both dilute and concentrated sulfuric acid, 12% fuming sulfuric acid, 48% hydrobromic and 20% sodium hydroxide and in every case was recovered unaltered.

**Oxidation of 2-Imidazolone-4-carboxylic Acid to Parabanic Acid.**—To a suspension of 1 g. of 2-imidazolone-4-carboxylic acid in 20 cc. of water was added 1 g. of sodium dichromate and 3 g. of concentrated sulfuric acid. A vigorous evolution of carbon dioxide took place. After this had slowed down the green reaction mixture was boiled for fifteen minutes, another gram of sodium dichromate added, and the heating continued on a steam-bath for an hour; the imidazolone gradually dissolved. After cooling, the solution was thoroughly extracted with 4 portions of 40 cc. of ether. The ether extract was washed with a small amount of water and dried with calcium chloride. The ether was removed by distillation and the parabanic acid remained as a colorless crystalline cake; yield, 0.28 g. After recrystallization from 2 cc. of water, from which it separated in the form of curved thin plates, it decomposed at  $247^\circ$  with effervescence. It was shown to be identical with an authentic specimen of parabanic acid.<sup>13</sup>

**Ethyl-2-imidazolone-4-carboxylate.**—The usual method of esterification, in which the acid is treated with alcohol in the presence of a small quantity of sulfuric acid, was unsuccessful in this case probably because of the insolubility of the imidazolone in alcohol.

The following procedure was found to give the best results. Seven grams of 2-imidazolone-4-carboxylic acid was dissolved in 17 cc. of concd. sulfuric acid by heating in an oil-bath to  $115^\circ$ . Upon adding 40 cc. of absolute ethyl alcohol, the dark brown solution was heated at  $100^\circ$  for three hours, allowed to stand overnight, and poured on 80 g. of ice. A pale yellow flocculent solid separated immediately. The mixture was cooled in an ice-salt bath and filtered. The ester was recrystallized several times from

<sup>13</sup> From a survey of the literature the simplest method for the preparation of parabanic acid appears to be that of Michael, *J. prakt. Chem.*, [2] 35, 457 (1887). This involves the condensation of urea with ethyl oxalate in the presence of sodium ethylate. A white precipitate immediately forms which was reported to be the sodium salt of parabanic acid (no analysis given). This reaction has been reinvestigated and definitely shown not to yield parabanic acid.

95% alcohol, from which it separated as colorless glistening plates, melting at 255°; yield, 50% of the theoretical. It was slightly soluble in boiling alcohol and insoluble in water.

*Anal.* Calcd. for  $C_8H_8O_2N_2$ : C, 45.84; H, 5.13; N, 17.95. Found: C, 46.14, 46.06; H, 5.17, 5.46; N, 18.13, 17.95.

Attempts to reduce the double bond in this compound by the Adams-Shriner method were unsuccessful.

**1,3-Dimethyl-2-imidazolone-4-carboxylic Acid.**—Five grams of 2-imidazolone-4-carboxylic acid was dissolved in a solution of 10 g. of sodium hydroxide in 30 cc. of water. This was cooled in an ice bath and 15 g. of dimethyl sulfate slowly added with stirring. A vigorous reaction took place with the evolution of heat. After this had practically ceased, the reaction mixture was made strongly alkaline with 20% sodium hydroxide and warmed on the steam-bath for one hour. It was filtered from a small amount of black flocculent material and then acidified with hydrochloric acid. On cooling, a mass of colorless needles separated which melted at 207–215°. It was impossible to raise the melting point by recrystallization. As the product was obviously still impure it was again subjected to methylation. This time, after decolorizing with bone black and recrystallizing from water, it separated as long colorless needles and melted sharply at 229–230° with effervescence; yield 4 g.

*Anal.* Calcd. for  $C_8H_{10}O_2N_2$ : C, 46.14; H, 5.17; N, 17.95. Found: C, 46.89; H, 5.05; N, 17.84, 17.95.

**Conversion of 1,3-Dimethyl-2-imidazolone-4-carboxylic Acid to 1,3-Dimethyl-2-imidazolone.**—One gram of 1,3-dimethyl-2-imidazolone-4-carboxylic acid was heated at its melting point until effervescence ceased. The colorless liquid on cooling and scratching solidified to a mass of dendritic crystals. The product was very hygroscopic, making it difficult to get either a good melting point or an analysis. It had all the properties of the substance reported by Biltz and Bülow, with the exception that it did not give the initial violet color reaction upon treatment with bromine. A water solution of the product obtained in this work immediately decolorized bromine water without undergoing any intermediate color change. It is possible that Biltz's product was slightly contaminated with an impurity.

**Treatment of 2-Imidazolone-4-carboxylic Acid with Acetic Anhydride.**—To 200 cc. of acetic anhydride was added 1.8 g. of the imidazolone and the mixture refluxed. After heating for one hour, a pale yellow solution resulted. On cooling and standing overnight, star-like clusters of colorless prisms separated; these were removed by filtration. The filtrate on concentration deposited a finely divided pale brown solid which proved to be identical with the above crystalline material. It was very slightly soluble in boiling acetic acid and acetic anhydride and insoluble in other organic solvents; it did not melt at a temperature of 300°. The product for analysis was boiled with acetic acid, filtered and well washed.

*Anal.* Calcd. for  $C_{12}H_8O_5N_4$ : C, 47.35; H, 2.65; N, 18.43. Found: C, 47.49, 47.49; H, 2.91, 2.72; N, 18.08, 18.24 (Kjeldahl).

The most striking property of this substance was that on treatment with a solution of potassium hydroxide or potassium carbonate, it was converted into a yellow potassium salt. Recrystallization from water, in which it was quite soluble, yielded yellow needle-like blades that charred at a temperature considerably above 300°.

*Anal.* Calcd. for  $C_8H_5N_4O_4K_2$ : C, 32.41; H, 0.68; N, 18.91; K, 26.40. Found: C, 32.46, 32.69; H, 1.31, 1.00;<sup>14</sup> N, 18.45, 18.52; K, 26.04.

<sup>14</sup> The percentage of hydrogen is so low that the values obtained are probably not very significant.

A water solution of the salt on acidification with hydrochloric acid precipitated a colorless solid which did not melt at 300°.

**2-Imidazolone.**—The application of the usual methods for the decarboxylation of an acid to 2-imidazolone-4-carboxylic acid was unsuccessful. Direct heating at atmospheric pressure was impractical owing to the fact, as later found out, that the acid melted with decomposition above the decomposition point of 2-imidazolone. The experiments in which the acid was heated in some medium such as diphenylmethane led to an amorphous brown product from which nothing crystalline could be isolated. It was finally found that heating the acid in a vacuum yielded a generous amount of 2-imidazolone. Under these conditions, the imidazolone, as soon as it was formed, sublimed to the cooler part of the flask and thus was removed from the heated zone.

One gram of finely powdered 2-imidazolone-4-carboxylic acid in a round-bottomed flask with a long wide neck was heated in an oil-bath at 220° for six hours at 2 mm. pressure. Glistening crystals were gradually deposited on the neck of the flask; yield, 0.45 g. It was recrystallized from 1 cc. of boiling water from which it separated as dendrites of pyramidal crystals. 2-Imidazolone colors at 225° and decomposes to a red liquid at 250–251° (corr.).

*Anal.* Calcd. for  $C_3H_4ON_2$ : C, 42.84; H, 4.80; N, 33.33. Found: C, 42.89, H, 5.08; N, 33.18.

It gives the dark red color reaction with aqueous ferric chloride previously described by Fenton and Wilks. It does not, however, give the Weidel color reaction. As this test is very sensitive and as it has never before been reported to be given by imidazolones, it would appear that the observation of the English investigators was probably due to the presence of a small amount of an impurity. The pink color reaction with hydrochloric acid and hydrogen peroxide, also described by Fenton and Wilks, is extremely faint, so faint that it can hardly be classified as being a significant property of 2-imidazolone.

Fenton and Wilks reported the results of a crystallographic examination of their crystals. A cursory examination of the crystals obtained by the decarboxylation of 2-imidazolone-4-carboxylic acid indicated that they were apparently uniaxial, optically negative and highly birefringent. They possibly have a lower symmetry than that of the tetragonal system, and appear to be identical with those described by Fenton and Wilks.

**1,3-Diacetyl-2-imidazolone.**—The acetyl derivative was made in the same manner as described by Fenton and Wilks. The easiest method of purification was that of sublimation. It occurs as long silky needles melting at 105–106°.

*Anal.* Calcd. for  $C_6H_6O_2N_2$ : C, 49.98; H, 4.80; N, 16.67. Found: C, 49.92, 49.71; H, 4.72, 4.74; N, 16.75, 16.61.

Fenton and Wilks reported a melting point of 106°. The percentages of carbon and hydrogen found by them were 48.07 and 5.00 (calcd. 47.62 and 4.76), respectively. Unfortunately the analysis for nitrogen, which would have been more significant, was not made. It seems reasonable to believe that Fenton and Wilks were dealing with the diacetyl derivative and that their analysis for carbon was somewhat low.

### Summary

1. Urea and tartaric acid in fuming sulfuric acid yield 2-imidazolone-4-carboxylic acid. Its structure was proved and a number of derivatives prepared.

2. The synthesis of 2-imidazolone was effected by the decarboxylation of 2-imidazolone-4-carboxylic acid. It is probably identical with the "iso-imidazolone" of Fenton and Wilks.