*Anal.* Calcd. for $C_{19}H_{27}NO_3{\cdot}HCl$ (XVIII): C, 64.48; H, 7.97; N, 3.96. Found: C, 64.58; H, 7.83; N, 3.65.

The dried ether layer was evaporated to dryness and the residue recrystallized from methanol to give colorless plates (m.p. 134–135°, yield 0.8 g.) which gave a positive Beilstein test for halogen; the test remained positive even after treatment of the compound with aqueous sodium hydroxide; $\lambda_{\max}^{\text{Nujol}}$ 3.04 (hydroxy), 6.24 (amido?), 7.59 (hydroxy), 8.98 (hydroxy), 13.44 and 13.80 $\mu$ (one of which is chloro). Treatment of XIX with boiling water gave XVIII.

*Anal.* Calcd. for $C_{19}H_{26}NO_2Cl$ (XIX): C, 67.94; H, 7.80; N, 4.17; Cl, 10.56. Found: C, 67.73; H, 7.47; N, 4.08; Cl, 10.26.

***meso-cis-cis*-Dihydroxydicyclohexylamine (*III*).**—Treatment of an aqueous solution of the amine hydrochloride XVIII with 10% sodium hydroxide yielded *dl-cis*-2-benzoyloxy-*cis*-2′-hydroxydicyclohexylamine (XX) which gave a negative Beilstein test for halogen; m.p. 56–59°; $\lambda_{\max}^{\text{Nujol}}$ 3.20 (hydroxy), 5.84 (ester carbonyl), 7.86 (ester) and 9.05 $\mu$ (ester).

*Anal.* Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.58; N, 4.41. Found: C, 71.67; H, 8.76; N, 4.18.

Compound XX was further hydrolyzed by a solution containing 1.2 equivalents of potassium hydroxide to give the *meso-cis-cis*-aminodiol III, m.p. 101°; see the procedure for the hydrolysis of XIII to VII.

*Anal.* Calcd. for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.86; N, 6.57. Found: C, 67.70; H, 10.86; N, 6.30.

Compound III showed a depression of m.p. on admixture with the *meso-trans-trans*-aminodiol I or the *dl-trans-cis*-aminodiol II.

**Acknowledgments.**—We wish to express our gratitude to the Microanalytical Laboratory of this Institute for the microanalyses, and to Mr. Ueda and Mr. Matsui of this Institute and to the Sankyo Co. for the infrared spectra.

KATAKASU, FUKUOKA, JAPAN

---

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

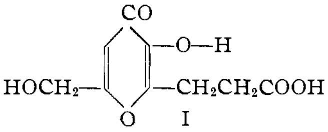
# Behavior of Kojic Acid toward Acrylonitrile, Halo Acids and Hydrogen Cyanide

BY CHARLES D. HURD AND SWIATOSLAW TROFIMENKO

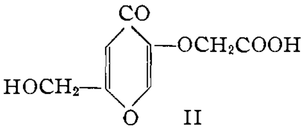
RECEIVED JANUARY 22, 1958

The published reactions of kojic acid with acrylonitrile or sodium 3-bromopropionate or potassium cyanide followed by acidification are open to question. The products cited were shown to be kojic acid. Kojyloxyacetic[1] acid was formed from sodium kojate and sodium bromoacetate. Infrared peaks for kojic acid in potassium bromide are presented.

In a recent article, Woods[2] stated that cyanoethylation of kojic acid in dioxane occurred on prolonged refluxing (19 hours) with acrylonitrile in the presence of a basic catalyst. The product was not isolated as such but was hydrolyzed by long boiling with dilute hydrochloric acid to yield an acid of m.p. 155°, regarded to be 6-(2-carboxyethyl)-kojic acid (I).



I



II

Prior to this work one of us (C.D.H.) also had studied the behavior of kojic acid toward acrylonitrile but since no such new compound was obtained, Woods' work was repeated. By following his directions as carefully as possible nothing was obtained except a black tarry product. From the latter some yellowish-orange sirup, but nothing crystalline, was obtained by extraction with isopropyl alcohol or with a 1:1 mixture of ethyl acetate and ethanol. Possibly some unused kojic acid was present, but we found none. Thus, in our hands decomposition did occur in these operations but no evidence for the simple crystalline product described by Woods could be obtained.

Woods later reported[3] formation of the same acid, m.p. 152°, by long refluxing of a mixture of kojic acid, alcohol and sodium 3-bromopropionate (actually, bromopropionic acid + $NaHCO_3$) and stated that the acids formed by the two methods gave identical acetyl and *p*-bromophenacyl derivatives.

We repeated this experiment and obtained complete agreement with the reported findings, but we interpreted the results quite differently. The white crystals obtained at the end of the operations melted at 152° and were considerably different in appearance from the original kojic acid, but its identity to kojic acid was attested to by its m.p. 152°, by no m.p. depression when mixed with authentic kojic acid and by the absence of carboxyl when tested with Davidson indicator.[4] Its infrared spectrum (Baird double beam spectrophotometer, employing a pellet of potassium bromide as the medium) was in complete agreement with one previously taken on an authentic sample of kojic acid. Both samples showed these peaks: two strong hydroxyl peaks, partly fused, at 3.08 and 3.16; weak peaks at 3.41, 3.51 and 5.88; the strong pyrone system at 6.04, 6.10 and 6.17 (the last two fused, yet sharp) and 6.29; also, weak peaks at 6.78, 6.92, and 7.16; medium at 7.40 and 7.78; strong at 8.12 (shoulder at 8.03), 8.42w, 8.72s, 9.28s, 10.10w, 10.59s, 11.55s, 11.70w, 12.85m, 13.00 (broad and fused), followed by a wide hump around 15.70 $\mu$. This agrees also with a published infrared spectrum[5] of kojic acid.

Since Woods stated that his two compounds (ref. 2 and 3) were identical and since we have established that the material of ref. 3 is kojic acid, then it follows that the acid of ref. 2 must also have

---

[1] The acyl radical of kojic acid, $C_6H_5O_3OH$, is $C_6H_5O_3$ or kojyl, analogous to picryl from picric acid.

[2] L. L. Woods, THIS JOURNAL, **74**, 3959 (1952).

[3] L. L. Woods, *ibid.*, **75**, 1510 (1953).

[4] D. Davidson, *J. Chem. Educ.*, **19**, 221, 582 (1942).

[5] L. P. Kuhn, *Anal. Chem.*, **22**, 276 (1950).

been kojic acid. On this point, however, we have no direct opinion, as stated above.

Unfortunately, Woods placed considerable reliance on analyses, but the C and H values reported were uncritical: calculated for kojic acid, C, 50.6; H, 4.24. Found for Woods 155° and 152° acids, respectively: C, 50.63, 50.78; H, 4.43, 4.82. Analysis of the acetyl derivative conforms to the diacetate of kojic acid (Calcd.: C, 53.09; H, 4.45. Found: C, 52.60; H, 4.69). The low m.p. of 85–87° suggests insufficient purification, and it is known[6] that several recrystallizations usually are required to bring the melting point of the diacetate to 103°. The C and H values for the *p*-bromophenacyl derivative (49.22, 3.39) also are good for bromophenacyl kojate (49.5, 3.27).

Another derivative, m.p. 164.5°, made with thionyl chloride is close in properties to the chloride of m.p. 166–167° made by Yabuta[7] from kojic acid and thionyl chloride. The analytical discrepancy for carbon (1% high) suggests impurities.

In view of this evident non-formation of I from sodium 3-bromopropionate it is of interest to record the synthesis of kojyloxyacetic acid (II) from kojic acid and sodium bromoacetate.

**Kojyloxyacetic Acid.**[8]—To a mixture of 4 g. of kojic acid and 4 g. of bromoacetic acid in 40 ml. of dry methanol was added a solution of 1.3 g. of sodium in 60 ml. of dry methanol. This solution was refluxed for 16 hr., occasionally filtering the product that separated to prevent excessive bumping. The sodium salt obtained was dissolved in 10 ml. of water and the free acid was precipitated by adding a slight excess of concd. hydrochloric acid. The dried product, m.p. 164–165°, weighed 5 g., an 89% yield. Two recrystallizations from acetone gave white crystals, m.p. 168–168.5°. Drying under diminished pressure gave no change. The compound gave no color with ferric chloride. It dissolved in aqueous sodium bicarbonate and reprecipitated on acidification. The observed neutral equivalent was 201.3 (calcd. 200.1).

*Anal.* (by J. Gibbs) Calcd. for $C_8H_8O_6$: C, 48.00; H, 4.00. Found: C, 47.76; H, 4.08.

The same product was formed but in lower yield (11%) if chloroacetic acid was used instead of bromoacetic acid.

**Acetate of II.**[8]—A solution of 2 g. of II in 9 ml. of pyridine that contained 2 ml. of acetic anhydride was allowed to stand for 24 hours at 20°. Then it was evaporated in an air stream at temperatures below 40°. The residue yielded 1.5 g. (62% yield) of white plates, m.p. 132–133°, on recrystallization from acetone.

*Anal.* (by M. Nielson) Calcd. for $C_{10}H_{10}O_7$: C, 49.60; H, 4.13. Found: C, 49.54; H, 4.25.

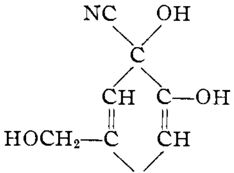
These attempts at acetylation of II were unsuccessful[8]: (1) acetic anhydride, 0.01 part of concd. sulfuric acid, 100° for 2 hours: result, black tar; (2) acetyl chloride, 2 hours of reflux: black tar; (3) acetic anhydride, 0.05 part of dry sodium acetate, 100° for 2 hours: result, brown solid that was insoluble in most solvents but soluble in hot nitromethane from which it separated on cooling as a gray, gelatinous precipitate that melted over a range up to 160°. Repeated crystallizations from nitromethane yielded no sharp melting product.

The apparent non-formation of I or an isomer from sodium 3-bromopropionate under conditions not unlike those used in forming II from sodium bromoacetate suggests that the 3-bromopropionate undergoes elimination instead of displacement, but we did not pursue the matter to see whether sodium acrylate or ethylene[9] was the compound formed.

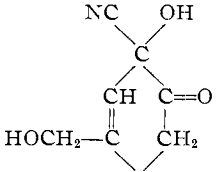
Conclusions from a third paper[10] also are brought into question and, indeed, a question about them was raised earlier by Beélik[11] in his review of the chemistry of kojic acid. In this paper, Woods treated kojic acid with potassium cyanide and acidified the resulting solid. An adduct of cyanohydrin structure was reported of m.p. 160°. Although nitrogen was evidently present in this material as judged by analysis, conditions for its preparation cannot be duplicated. Material obtained following the published directions melted in the range (about 153°) expected of kojic acid, did not depress the m.p. of kojic acid, contained no more than a trace of nitrogen, and showed the same infrared spectrum as kojic acid. There was no peak in the spectrum at 4.4 μ, indicative of the cyanide group. Here again, analysis of the listed derivatives is less helpful than one might desire since no analysis for nitrogen was made and since the values for C and H are in the range of analogous derivatives of kojic acid if allowance is made for impurities (such as carbanilide with the phenyl isocyanate derivative.)

These results were communicated to Dr. Woods who kindly sent us a sample of material regarded by him as the "cyanohydrin." Our tests showed it to be indistinguishable from kojic acid: m.p. 152.5–154.5°, mixed m.p. 151.5–153.5° with kojic acid of m.p. 152–154°. Nitrogen was absent by sodium fusion, and the infrared spectrum was the same as that of kojic acid. In a later private communication, Dr. Woods confirmed the essential absence of nitrogen in this material (less than 1%) and obtained an infrared spectrum independently that showed "no discernible difference from that of kojic acid."

A compound of the cyanohydrin structure III such as Woods proposed should no longer remain enolic but should change to the keto form IV;



III



IV

hence should not have given rise to the red color which was observed with ferric chloride. The fact that the "cyanohydrin" was prepared in the presence of hydrochloric acid casts additional doubt on the formation of any compound having a stable structure III or IV. Compound III is a pyran (not pyrone) and IV is essentially a dihydropyran, such types generally being very sensitive to acids[12] and, therefore, would have been destroyed. The accumulation of evidence points to kojic acid as the compound in question.

EVANSTON, ILLINOIS

---

[6] C. D. Hurd and R. J. Sims, THIS JOURNAL, **71**, 2442 (1949).

[7] T. Yabuta, *J. Chem. Soc.*, **125**, 578 (1924).

[8] Unpublished work of Rex J. Sims, Northwestern University.

[9] For a discussion of the decomposition of β-halogenated salts in solution at 60–100° into alkene, carbon dioxide and sodium halide, see Hurd, "The Pyrolysis of Carbon Compounds," Reinhold Publ. Corp., New York, N. Y., 1929, p. 489.

[10] L. L. Woods, THIS JOURNAL, **77**, 1702 (1955).

[11] A. Beélik, *Advances in Carbohydrate Chem.*, **11**, 174 (1956).

[12] R. C. Elderfield, "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 345, 349.