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Studies on Kojic Acid Derivatives

Part 4. Some Reactions of Kojic Acid

By

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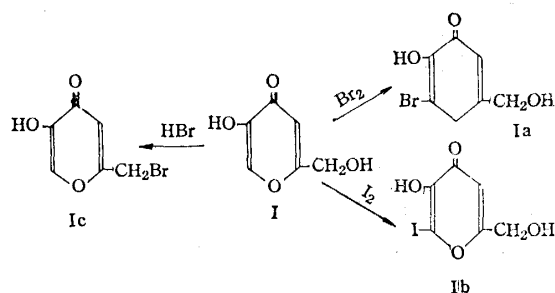
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A series of our works has been made on the derivatives of kojic acid (5-hydroxy-2-hydroxymethyl- γ -pyrone) and its homologue^{1,2,3}.

This paper is concerned primarily to the study of halogenation, esterification, nuclear substitution at position 6, replacement of oxygen atom of carbonyl group at position 4 with sulfur atom and oxidation of kojic acid.

Halogen derivatives of kojic acid

Since halogenation is often employed as an intermediate step for organic synthesis, halogen derivatives of kojic acid have been firstly studied in the present work. The preparation of 2-chloromethyl kojic acid, 2-iodo methyl kojic acid and 6-bromo kojic acid was studied by Yabuta^{4,5}. However, employing the method described by Yabuta, 6-bromo and 6-iodo kojic acid were not obtained in good yield. Therefore, we devised the new method and obtained both the derivatives in good yield as well as the new derivative, 2-bromomethyl kojic acid.

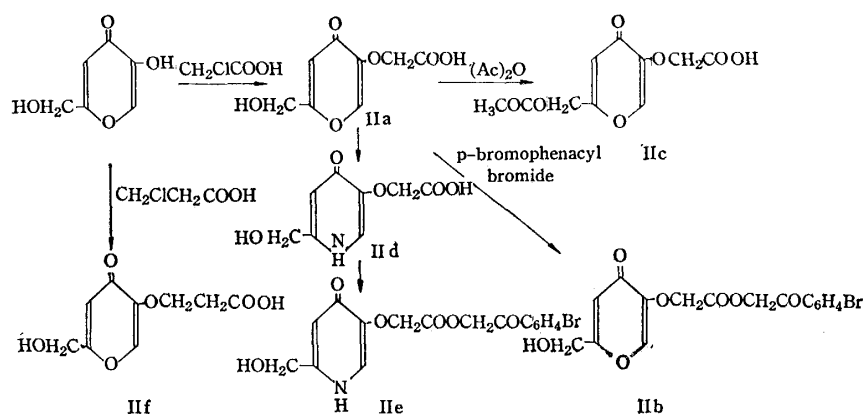


Synthesis of kojyloxyacetic acid

Recently, Hurd et al.⁶ reported on the preparation of kojyloxyacetic acid, in which they obtained it from kojic acid and monobromoacetic acid in dry methanol, which was refluxed for 16 hours., while they obtained the same product in lower yield when chloroacetic acid was used instead of bromoacetic acid. We found that kojyloxyacetic acid was easily obtained using monochloroacetic acid with potassium hydroxide as a catalyst. But melting point was not in good agreement with Hurd's report.

Phenacyl bromide derivative, acetyl derivative and pyridone of kojyloxyacetic acid were obtained by usual methods, but chloroderivative of kojyloxyacetic acid was unsuccessful.

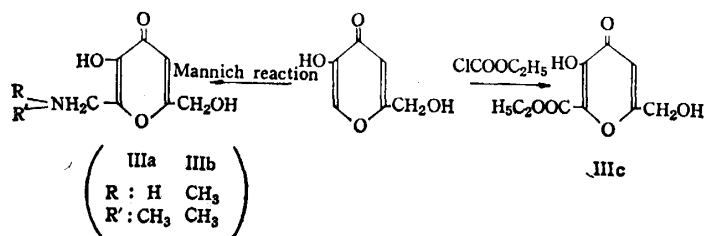
* A part of this paper already reported at the meeting of Agr. Chem. Soc. Japan, Kansai branch.



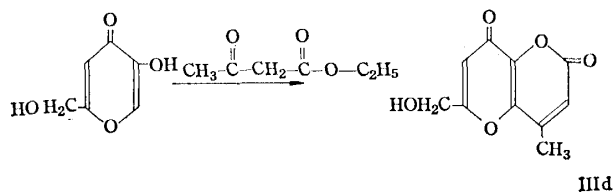
Kojyloxypropionic acid was obtained by the same method with that employed for the preparation of kojyloxyacetic acid.

Some nucleophilic reactions

Base catalyzed replacement reactions of kojic acid yield primarily 6-substituted kojic acid derivatives. Some of these derivatives had been reported in recent works^{7,8,9,10,11,12,13}). However, Mannich reaction with aliphatic amine had not been established. Therefore we attempted this reaction on kojic acid and obtained Mannich base of kojic acid (IIIa, IIIb) in good yield. The esterification of kojic acid with chloroethyl carbonate was failed but obtained an unexpected compound. Its probable structure was derived from the results of the ferric chloride test, infrared spectrum and elemental analysis, and is shown in IIIc.

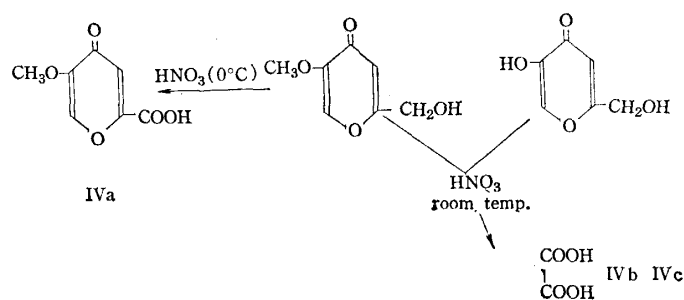


The reaction of phenol with ester of ketoacid such as acetoacetic acid ethylester yielding coumarin derivatives is known as Pechman reaction. We attempted the similar reaction on kojic acid with acetoacetic acid using conc. sulfuric acid as a catalyst and obtained an interesting material. A probable structure of the compound obtained was assumed as follows.

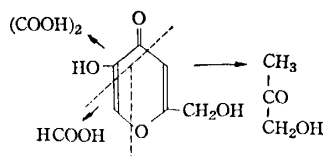


Nitric acid oxidation of kojic acid

Several workers^{14,15}) reported on oxidation of kojic acid to comenic acid with potassium permanganate or other oxidants previously. However, these were not carried out in good yield. In the present work employing a modification of the method described by Heyns and Vogelsang¹⁵), comenic acid was obtained with nitric acid at low temperature in good yield, while kojic acid was cleaved to oxalic acid at room temperature.



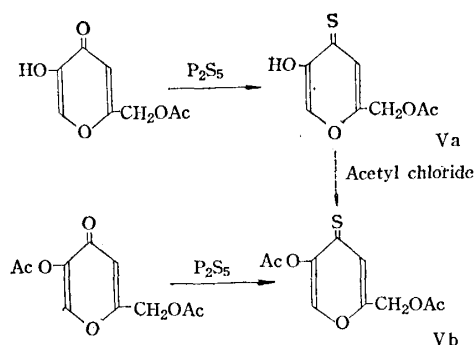
Arnstein et al.¹⁶⁾ reported on the alkaline cleavage of kojic acid and presented its mechanism as follows.



Our result may suggest that the mechanism of acid cleavage is same as that of alkaline cleavage. However, more detailed investigations are expected for this subject.

4-Thio- γ -pyrone derivatives from kojic acid

Syntheses of 4-thio kojic acid derivatives were carried out using the same technique for γ -pyrone^{17,18)}, the structures of which were assumed as follows.



Experimental

6-Bromo-5-hydroxy-2-hydroxymethyl- γ -pyrone, (6-Bromo-kojic acid), Ia. To a mixture of 14.2 g (0.1 mole) of kojic acid and 10 g of sodium acetate in 200 ml of acetic acid aqueous solution (40 ml of acetic acid and 160 ml of water) was added 8 g of bromine under stirring and cooling. After standing for over night in refrigerator, white crystal was filtered, and then washed with water. Recrystallized twice from water. Yield 10.0 g, m.p. 166-167°. Anal. Found: Br, 36.00. Calcd. for $C_6H_5O_4$: Br, 36.20%.

6-Iodo-5-hydroxy-2-hydroxymethyl- γ -pyrone (6-Iodo-kojic acid), Ib. To a solution of 14.2 g of kojic acid in 100 ml of 1 N sodium hydroxide aqueous solution was added 12.7 g of iodine under stirring and cooling. After completely dissolving iodine, the solution was kept for over night in refrigerator. White precipitate was obtained. Recrystallized twice from water. Yield 8.5 g, m.p. 182-183°.

5-Hydroxy-2-bromomethyl- γ -pyrone, Ic. A mixture of 25 ml of 48 per cent of hydrogen bromide aqueous solution, 30 ml of conc. sulfuric acid and 10 g of kojic acid was

heated under stirring for one hour on a water bath. The reaction mixture was neutralized with barium carbonate, and then separated from barium sulfate by filtration. Then the filtrate was evaporated under reduced pressure, crude crystal was obtained. Recrystallized from hot water. Yield 3.5 g, m.p. 148 - 152°. Anal. Found: Br, 33.8. Calcd. for $C_6H_5O_3$ Br: Br, 34.1%.

Kojyloxyacetic acid, IIa. A mixture of 14.2 g of kojic acid and 10 g of monochloroacetic acid in 80 ml of ethyl alcohol was added a solution of 11.2 g of potassium hydroxide in 20 ml of water. The solution was refluxed for one hour on a water bath. On chilling, the potassium salt of kojyloxyacetic acid was precipitated, and then was filtered. The salt obtained was dissolved in 30 ml of water and acidified with hydrochloric acid, white crystal being precipitated. Recrystallized from ethyl alcohol and ethylacetate. Yield 9.3 g, m.p. 172-173° (Hurd's value was 168°). The ferric chloride test was negative. Anal. Found: C, 47.84; H, 3.84. Calcd. for $C_8H_8O_6$: C, 48.00; H, 4.00%.

Phenyacyl derivative of kojyloxyacetic acid, IIb. One and half grams of the potassium salt of kojyloxyacetic acid was dissolved in 10 ml of water, and then 1 g of p-bromophenyacyl bromide in 30 ml of ethyl alcohol was added. The mixture was refluxed for 2 hours and then treated with a large amount of water. Pale yellowish crystal was obtained, and recrystallized twice from heptane. Yield 0.8 g, m.p. 177-178°. Anal. Found: C, 49.37; H, 3.09. Calcd. for $C_{16}H_{13}O_7Br$: C, 48.36; H, 3.27%.

Acetate of kojyloxyacetic acid, IIc. A solution of 2 g of kojyloxyacetic acid in 10 ml of pyridine which contained 3 ml of acetic anhydride was allowed to stand for over night at room temperature, then the solvent was evaporated under reduced pressure, and the residue was recrystallized twice from acetone. One gram of white plate crystal was obtained, m.p. 134-135°. Anal. Found: C, 49.49; H, 4.21. Calcd. for $C_{10}H_{10}O_7$: C, 49.60; H, 4.31%.

2-Hydroxy-5-oxoacetic acid- γ -pyridone, II d. One and half grams of kojyloxyacetic acid was dissolved in 20 ml of conc. aqueous ammonia and was allowed to stand for 24 hours at room temperature. The mixture was evaporated to dryness under reduced pressure. Yield 1.3 g. Sublimation of a portion of the sample gave white plate crystal, m.p. 140-141°. Anal. Found: N, 7.14. Calcd. for $C_8H_9O_5N$: N, 7.03%.

Phenyacyl derivative of 2-hydroxy-5-oxoacetic acid- γ -pyridone, IIe. One gram of the crude ammonium salt of II d was dissolved in 10 ml of water and mixed with 1 g of p-bromophenyacyl bromide in 30 ml of ethyl alcohol. The mixture was refluxed for one and half hours, then treated with a large amount of water. Soft crystal was precipitated, and recrystallized from heptane. Yield 0.9 g, m.p. 111°. Anal. Found: N, 3.48. Calcd. for $C_{16}H_{14}O_6NBr$: N, 3.53%.

Kojyloxypropionic acid, II f. A mixture consisting of 14.2 g of kojic acid, 7.5 g of β -chloropropionic acid, 1 g of potassium hydroxide and 100 ml of ethyl alcohol containing 20 ml of water was agitated for one hour at 70°. On chilling, the potassium salt of kojyloxypropionic acid was precipitated, filtered, then dissolved in 20 ml of water and acidified with hydrochloric acid, white crystal being precipitated. Recrystallized from ethyl alcohol. Yield 1.5 g, m.p. 168-169°. Anal. Found: C, 50.47; H, 4.79. Calcd. for $C_9H_{10}O_6$: C, 50.47; H, 4.71%.

2-Hydroxymethyl-5-hydroxy-6-monomethylaminomethyl- γ -pyrone, IIIa. Fourteen and one-tenths grams of kojic acid, 1 g of conc. hydrochloric acid, 3 g of paraformaldehyde and 3 g of methylamine was dissolved in 100 ml of absolute ethyl alcohol, and then refluxed for 2 hours. On chilling, white crystal was obtained, filtered and recrystallized from ethyl alcohol. Yield 2.8 g, m.p. 132-136°. Anal. Found: C, 57.43; H, 6.98. Calcd. for $C_8H_{11}O_4$: C, 56.14; H, 6.48%.

2-Hydroxymethyl-5-hydroxy-6-dimethylaminomethyl- γ -pyrone, IIIb. Fourteen and one-tenths grams of kojic acid, 1 g of conc. hydrochloric acid, 3 g of paraformaldehyde and 4.5 g of dimethylamine was treated as same procedure as above. White plate crystal was obtained from ethyl alcohol. Yield 4.2 g, m.p. 139-140°. Anal. Found: C, 58.86; H, 7.40; Calcd. for $C_9H_{13}O_4$: C, 58.37; H, 7.08%.

2-Hydroxymethyl-5-hydroxy-6-carboxyethyl- γ -pyrone, IIIc. To a mixture of 14.2 g of kojic acid and 11 g of chloroethyl carbonate in 80 ml of ethyl alcohol was added a solution of 10 g of potassium hydroxide in 20 ml of water. The solution was stirred for 90 minutes at 70-80° on a water bath. After standing for over night in refrigerator, a white crystal was obtained. Recrystallized from heptane. Yield 9.5 g, m.p. 123-124°. Anal. Found: C, 50.62; H, 4.64. Calcd. for $C_9H_{10}O_6$: C, 50.47; H, 4.71%.

Pechman reaction product, IIIId. To a mixture of 7.1 g of kojic acid and 7 g of acetoacetic ethylester was added 10 ml of conc. sulfuric acid. After standing for 5 days at room temperature, the solution was poured into a large amount of ice and water, a white precipitate was obtained. Twice recrystallized from dioxane. Yield 0.5 g, m.p. 156-157°. Anal. Found: C, 57.48; H, 3.86. Calcd. for $C_{10}H_8O_5$: C, 57.69; H, 3.87%.

5-Methoxy-2-carboxy- γ -pyrone (methyl comenic acid), IVa. A mixture of 5-methoxy kojic acid and 20 g of conc. nitric acid (d. 1.40) was allowed to stand for 3 days in refrigerator. White crystal was precipitated, then filtered and washed with water. Recrystallized from 30 per cent of ethyl alcohol. Yield 1.8 g, m.p. 261-262° (dec.). Anal. Found: C, 54.61; H, 5.13. Calcd. for $C_9H_{10}O_5$: C, 54.54; H, 5.09%. Infrared spectrum was agreed with that of the authentic sample.

Nitric acid cleavage, IVb. A mixture of 5 g of 5-methoxy kojic acid in 20 ml of conc. nitric acid (d. 1.40) was allowed to stand for over night at room temperature. Colorless crystalline product was obtained, then filtered, and washed with water. Recrystallized from ethyl alcohol. Yield 1.4 g, m.p. 101°. The Rf value of paper chromatogram was agreed with that of oxalic acid.

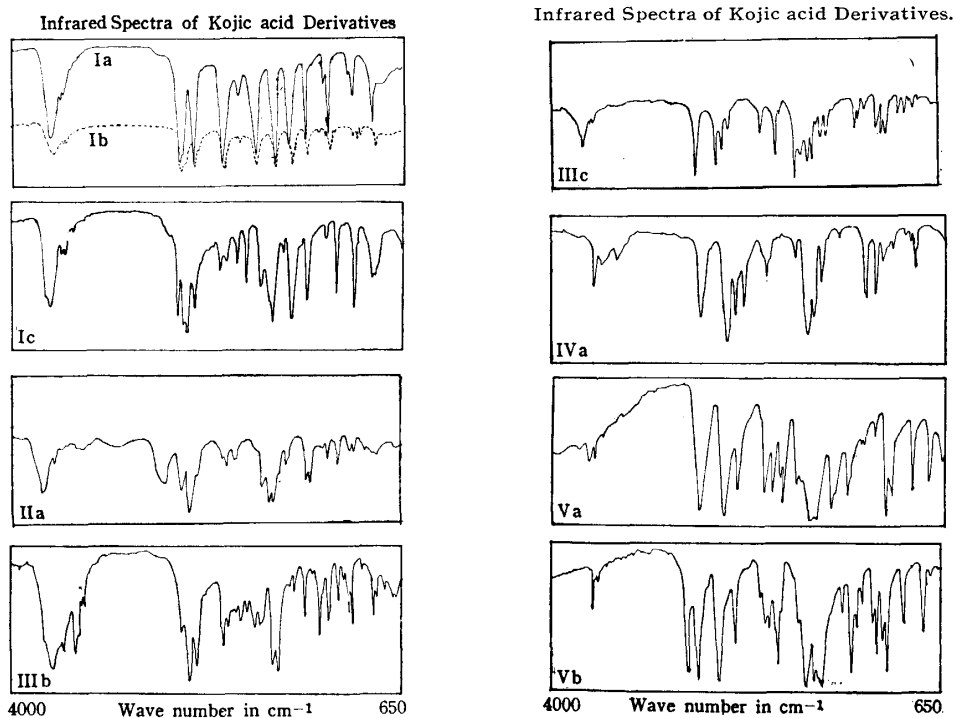
Nitric acid cleavage, IVc. Five grams of kojic acid was dissolved in 20 ml of conc. nitric acid. After standing for one hour, colorless crystalline product was obtained. Recrystallization from ethyl alcohol gave oxalic acid m.p. 101°.

5-Hydroxy-4-thio-2-acetoxymethyl- γ -pyrone, Va. To a solution of acetyl kojic acid (5-hydroxy-2-acetoxymethyl- γ -pyrone) in 500 ml of dry benzene was added 20 g of phosphorous pentasulfide. The mixture was refluxed for 4 hours and filtered in hot. After standing for over night in refrigerator, the filtrate gave a yellowish brown precipitate. Recrystallization from carbon tetrachloride was obtained a yellowish crystal. Yield 3.5 g, m.p. 114-115°. Anal. Found: C, 47.68; H, 4.16; S, 16.1. Calcd. for $C_8H_8O_4S$: C, 48.00; H, 4.02; S, 16.0%.

5-Acetoxy-4-thio-2-acetoxymethyl- γ -pyrone, Vb. The same procedure as described above was followed. A reddish brown crystal was obtained from diacetyl kojic acid (5-acetoxy-2-acetoxymethyl- γ -pyrone). Yield 3.8 g, m.p. 76-77°. Anal. Found: C, 49.56; H, 4.28; S, 13.4. Calcd. for $C_{10}H_{10}O_5S$: C, 49.60; H, 4.16; S, 13.2%.

Summary

New methods of preparation of halogen derivatives; 6-bromo, 6-iodo and 2-bromomethyl kojic acid was established. Kojyloxyacetic acid and its derivatives were also obtained. Mannich reaction of kojic acid with aliphatic amine was investigated, furthermore, it was



found that kojic acid may react with acetoacetic ethyl ester under the condition of Pechman ring close reaction using sulfuric acid as a catalyst. By oxidation with nitric acid, methyl comenic acid was obtained at 0° , while kojic acid was cleaved to oxalic acid. Some of thio-pyrone derivatives were also synthesized.

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