

REACTION OF KOJIC ACID WITH POTASSIUM IN DIOXANE

by

HARRY FREDERICK FREEMAN

B. S., Kansas State College
of Agriculture and Applied Science, 1936

A THESIS

submitted in partial fulfillment of the

requirements for the degree of

MASTER OF SCIENCE

KANSAS STATE COLLEGE
OF AGRICULTURE AND APPLIED SCIENCE

1937

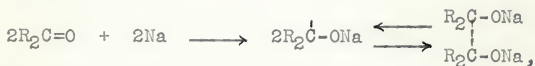
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INTRODUCTION

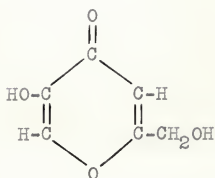
Metallic sodium and potassium react with aromatic ketones (1, 2, 3, 4, 5) and certain γ -pyrones (5, 6) in non-polar solvents to give deeply colored metal derivatives called ketyls. Schlenk (2, 3, 4) and co-workers studied the reaction of benzophenone with sodium in anhydrous ether and concluded that these sodium compounds are free radicals of the type, $R_2\dot{C}ONa$. Bachmann (5) later showed that the reaction between ketones and sodium proceeds in the following manner



the equilibrium being almost entirely in favor of the sodium pinacolate. The equilibrium mixture, when hydrolyzed in acetic acid, gave yields as high as 95 per cent pinacol. The ketyl radicals are, therefore, intermediates in the reduction of the ketone to the pinacol.

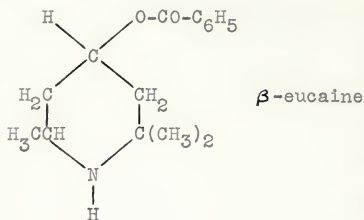
Kb̄jic acid, 2-hydroxymethyl-5-hydroxy- γ -pyrone, is a compound which has been prepared by fermenting a variety of organic compounds including polysaccharides, disaccharides, hexoses, pentoses, sugar alcohols, organic acids, etc. (7). Its importance lies in the fact that it may be prepared in

almost unlimited quantities from glucose and xylose recovered from farm wastes. At the present time neither kojic acid nor any of its derivatives are known to have useful properties but a glance at the structure of the kojic acid molecule



is sufficient to show the likelihood of it forming a great many derivatives, some of which might be of practical importance.

Armit and Nolan (8) saw in the reduction of kojic acid or its pyridone derivatives the possibility of forming synthetic drugs of the β -eucaïne type which might prove useful as local anesthetics.



In efforts made by Traeta-Mosca (9), Wijkman (10), Maurer (11), and Armit and Nolan (8) to reduce kojic acid by catalytic hydrogenation in the presence of colloidal platinum or palladium, the carbonyl group exhibited the same inertness that it has shown with numerous reagents which usually react characteristically with the ketone group. A study of their reduction products indicates the fixation of four hydrogen atoms at the double bonds of kojic acid, but the carbonyl group remained unaltered.

After their hydrogenation experiments had failed, Armit and Nolan (8) further made use of the Grignard reaction in an attempt to convert the carbonyl group of kojic acid or its pyridone derivatives into a tertiary alcohol. In this also they were unsuccessful.

The primary purpose of this investigation was to determine whether kojic acid, like certain other γ -pyrones, could be reduced to a pinacol by treatment with metallic potassium to form a ketyl and the subsequent hydrolysis of the ketyl with dilute acid.

EXPERIMENTAL

Apparatus

Considerable experimentation was necessary before the arrangement shown in Figure 1 was obtained. A 1-liter three-necked round-bottomed flask (A), with a stop-cock connection (E) sealed into the bottom, was fitted with an inlet tube, an outlet, provided with a reflux condenser, and a mercury-sealed stirrer (D). The stop-cock connection was necessary in overcoming the tendency of solid particles of reaction mixture to settle out when the suspension was forced out slowly through an outlet tube in the top. The inner parts of the mercury seal were made sufficiently long to prevent the entry of mercury to the reaction flask. Glass tubing connected the top of the condenser, the safety bottle (F), the mercury trap (C), and the hydrolysis flask (B), respectively, in series. The hydrolysis flask was a 1-liter three-necked round-bottomed flask fitted with an inlet tube for gas from trap (C), an inlet tube from stop-cock (E), an outlet tube passing through a mercury trap, and mercury-sealed stirrer. Pyrex glass was used throughout.

Key to Figure 1

- A. Reaction Flask
- B. Hydrolysis Flask
- C. Mercury Traps
- D. Mercury-sealed Stirrers
- E. Stop-cock
- F. Safety Bottle
- G. Dioxane Wash-bottle
- H. Benzophene-disodium Wash-bottle
- I. Concentrated Sulfuric Acid Wash-bottle

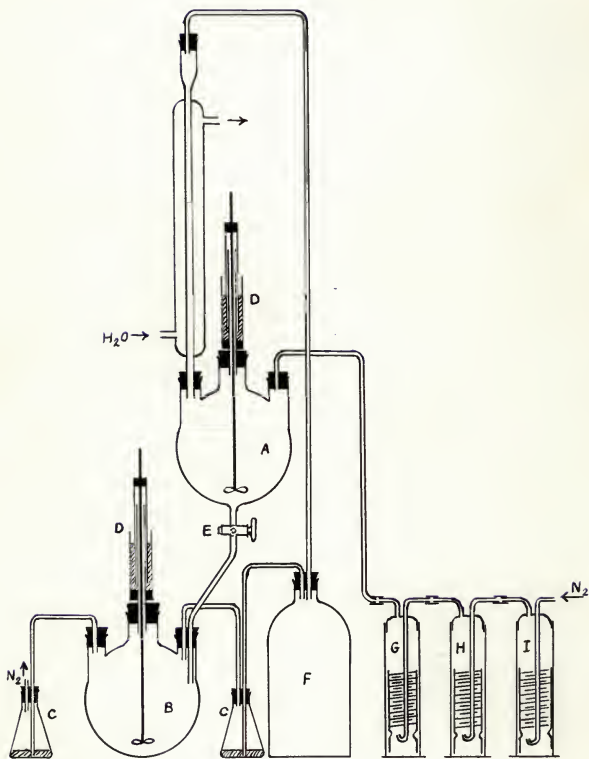


Figure 1

Purification of Nitrogen

Commercial nitrogen was purified by passing it through concentrated sulfuric acid (I) to remove water and through a solution of benzophene-disodium (H) which is capable of absorbing oxygen, water, and carbon dioxide. The benzophene-disodium reagent was prepared (5) by shaking 10 grams of benzophenone, dissolved in 100 cc. of ether and 100 cc. of toluene, for several days with 10 grams of 40 per cent sodium amalgam until the mixture was violet-red in color. The amalgam was made by adding a 4 gram piece of sodium metal to 6 grams of mercury in a large porcelain mortar and held in contact by means of a large pestle. Care was necessary in protecting the hands during the violent reaction. The mass was stirred until cool and used directly. The stream of nitrogen which had been washed with acid and benzophene-disodium was saturated with dioxane in wash-bottle (G) to maintain constant volume of solvent in the reaction flask.

Method of Procedure

In all experiments moisture and air were rigorously excluded. All operations were carried out in a stream of

purified nitrogen. Fourteen and two tenths grams (0.1 gram-mol) of k^uojic acid was suspended in 250 cc. of dry dioxane, previously distilled from over potassium, with 3.9 grams (0.1 gram-atom) of potassium ribbon and stirred at room temperature. The potassium immediately on addition developed a deep red film, with no visual evidence of hydrogen being liberated. Moreover, after seven to ten days there was no decrease in the very small amount of unreacted metal, indicating that only one equivalent of potassium was combining. The entire mixture was run slowly into 400 cc. of 10 per cent hydrochloric acid (freshly boiled and saturated with nitrogen) with vigorous stirring in order to avoid accumulation of the free alkali or ketyl, either of which would cause rapid decomposition of the pinacol (5). The acid solution became amber yellow in color. This was filtered and evaporated to half its original volume on a steam bath before drying to a residue in a current of air at room temperature. The dry brownish residue was extracted in a Soxhlet extractor first with ether and then with alcohol, leaving an inorganic residue of potassium chloride.

Experimental Results

In the first six experiments, kōjic acid was the only organic substance isolated. However, when the ether extracts, from which the kōjic acid had crystallized out, were allowed to evaporate, there appeared a small quantity of brownish material of only slightly crystalline nature which was not purified further. In the seventh experiment more attention was given to the purification of the ether soluble material. The period for the individual Soxhlet extractions was shortened from thirty minutes to about fifteen minutes in order to decrease the quantity of kōjic acid extracted by the ether and to avoid any possible affect of prolonged heating upon the ether soluble product. Two such ether extracts and one alcohol extract were made of the residue of experiment seven. The alcohol extract contained the bulk of the unused kōjic acid.

The crystalline material recovered from the ether extracts were snow-like in appearance with a melting point of 145-147°C. These crystals were placed in only enough ether to dissolve the major portion readily. Those not dissolved melted at 152.2-153.8°C. The crystals from the ether filtrate then melted roughly at 130-132°C.

Three more purifications of the ether fraction yielded a crystalline material melting in the range of 129.2-132.6°C. These crystals proved to be less soluble in water and more soluble in ether than k8jic acid. Like k8jic acid it gave a red coloration with ferric chloride, was neutralized by strong bases but, unlike k8jic acid, does not form an insoluble copper salt. All other fractions melted in the range of 150-154°C. which corresponded to the melting point range of k8jic acid. Time did not permit the study of the chemical properties to establish the structure of the compound.

Material Balance

Added		Recovered	
K8jic acid	14.2 g.	K8jic acid in ether	0.6 g.
Potassium	3.9 g.	K8jic acid in alcohol	11.7 g.
		New substance	<u>0.6 g.</u>
			12.9 g.
		Potassium in 6.7 g. KCl	3.5 g.

DISCUSSION OF RESULTS

A derivative has been formed from kojic acid by reduction that retains the phenolic hydroxyl group and acid character of the parent compound. Its formation does not involve the replacement of the hydrogen of the hydroxy- or hydroxymethyl-group since such metal derivatives would yield only kojic acid upon their hydrolysis. The only other probable point of attack by the potassium is at the ketone position. However, although kojic acid has been reduced by potassium metal, it remains to be determined whether the pinacol has been formed.

CONCLUSION

The production of a derivative having the original hydroxy-groups present appears to indicate that potassium reacts with the carbonyl group of kojic acid.

ACKNOWLEDGMENT

For his assistance and constructive criticism, the author owes to Dr. H. N. Barham, his major instructor, a great debt of gratitude, which cannot be adequately acknowledged.

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