Lactitol Dihydrate

By M. L. Wolfrom, Raymond M. Hann[1] and C. S. Hudson

Senderens,[2] who was the first to crystallize lactitol, reported it as a monohydrate of m.p. 78° and $[\alpha]_D$ +12.2° (water). In our experiences with lactitol a monohydrate has not been detected but instead an anhydrous form and a dihydrate have crystallized.

Lactitol was obtained crystalline[3] from dilute alcohol in the laboratories of The Ohio State University as an anhydrous form; m.p. 146°, $[\alpha]^{23}_D$ +14° (*c* 4, water). This form is now found to be metastable and in current preparations in both the Columbus and Bethesda laboratories a hydrated form is obtained; m.p. 72.5–74°, $[\alpha]^{20}_D$ +11.5° (*c* 4.5, water). This substance is a dihydrate.

Anal. Calcd. for $C_{12}H_{24}O_{11}\cdot 2H_2O$: C, 37.87; H, 7.42. Found: C, 37.87; H, 7.60.

Xylitol was first crystallized in the Columbus laboratory[4] as a hygroscopic, metastable form of m.p. 61°. Later preparations in that laboratory and in others now yield the stable dimorph of m.p. 93–94.5°.[5]

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[1] Deceased, April 30, 1949.

[2] J. B. Senderens, *Compt. rend.*, **170**, 47 (1920).

[3] M. L. Wolfrom, W. J. Burke, K. R. Brown and R. S. Rose, Jr., This Journal, **60**, 571 (1938); therein designated "lactositol."

[4] M. L. Wolfrom and E. J. Kohn, *ibid.*, **64**, 1739 (1942).

[5] J. F. Carson, S. W. Waisbrot and F. T. Jones, *ibid.*, **65**, 1777 (1943).

Department of Chemistry
The Ohio State University
Columbus 10, Ohio, and the
National Institutes of Health
Bethesda 14, Maryland

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2-Hydroxymethyl-5-hydroxy-6-benzoyl-4-pyrone[1]

By L. L. Woods

A theoretical consideration of the structure of 4-pyrones and an extension of the observations of Wheland[2] indicates that in the presence of acidic reagents polarization of the ring would activate positions 3 and 6. Since the separation of the formal charge between 1 and 3 is great, position 6 should be considerably more active than position 3. If such considerations are valid then acylation in position 6 should be easily effected and demonstrable.

However, the demonstration of the validity of this theory has not been easy due to the fact that kojic acid reacts with benzoyl chloride in the presence of fuming stannic chloride to form chiefly O-benzoylkojic acid.

Experiments have demonstrated that the benzoyl derivative of kojic acid formed by the influence of stannic chloride was not a C-benzoyl compound since it failed to give a chloro derivative with thionyl chloride, failed to participate in a Clemmensen reduction, and failed to be reduced by aluminum isopropoxide.

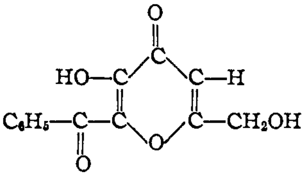
The reaction of kojic acid with benzoyl chloride in the presence of aluminum chloride gave the desired C-acylation. The probable structure 2-hydroxymethyl-5-hydroxy-6-benzoyl-4-pyrone (I) has been assigned to the product.

Experimental[3]

O-Benzoylkojic Acid.—A mixture consisting of 5 g. of kojic acid, 25 ml. of benzoyl chloride and 5 g. of fuming stannic chloride was heated in a Fisher Hi-Temp oil-bath for 4 hours at 74°.

The mixture was then treated with 50 ml. of water and shaken thoroughly; the excess benzoyl chloride was destroyed with about 150 ml. of cold 10% sodium hydroxide. The insoluble material was filtered off, washed repeatedly and air-dried. The crude yield was 12 g. A portion of the crude solid was recrystallized twice from absolute ethanol and analyzed. *Anal.* C, 65.66; H, 4.01. This composition does not conform to any of the calculated derivatives of benzoyl chloride with kojic acid.

Ten grams of the crude solid was placed in a mixture of 75 ml. of ethanol, 40 ml. of water and 5 ml. of concentrated hydrochloric acid, and heated at gentle reflux for 17 hours. The hot solution was decolorized with Norite, filtered and chilled in the refrigerator overnight; yield 6 g., yellow rosettes. The analytical sample was recrystallized from ethanol, m.p. 128–130°.



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Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.41; H, 4.06. Found: C, 63.70; H, 3.94.

The compound in an alcohol–water mixture developed a red color with ferric chloride.

2-Hydroxymethyl-5-hydroxy-6-benzoyl-4-pyrone (6-Benzoylkojic Acid).—To 200 ml. of carbon disulfide was added 14.2 g. of kojic acid and 40 g. of anhydrous aluminum chloride. The mixture was thoroughly agitated while 15 g. of benzoyl chloride was added from a separatory funnel. The stirring was discontinued in about 20 minutes and, after fully protecting the contents of the flask from atmospheric moisture, the reaction was allowed to proceed at room temperature for 24 hours.

At the end of the reaction period the carbon disulfide was decanted and the residual solid treated with a mixture of 100 ml. of concentrated hydrochloric acid and 100 g. of shaved ice. The solid particles were filtered off and dried. The yield was 9.8 g. after recrystallizing twice from absolute ethanol; m.p. 188°. The compound gave a red coloration with ferric chloride.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.41; H, 4.05. Found: C, 63.12; H, 4.30.

Clemmensen Reduction.—6-Benzoylkojic acid was subjected to Clemmensen reduction by allowing 4 g. of the ketone to react with amalgamated zinc and hydrochloric acid in a solvent mixture of 20 ml. of ethanol and 30 ml. of water.

The reflux time was 7 hours. The mixture was filtered into a crystallizing dish and allowed to stand several days. A rather large amount of soft yellow needles separated; after recrystallization from benzene, in which the (2-hydroxymethyl-5-hydroxy-4-pyrone-6)-phenylmethane was quite soluble, a yield of 1.4 g. was obtained; m.p. 78–80°.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.17. Found: C, 67.02; H, 5.31.

Reaction with Thionyl Chloride.—A small amount of the compound was allowed to react with a large excess of thionyl chloride in hexane. The hexane and excess thionyl chloride were decanted, and the residual chloro derivative was washed once with hexane. The compound, 2-chloromethyl-5-hydroxy-6-benzoyl-4-pyrone, was recrystallized from ethanol to produce golden yellow crystals; m.p. 185–187°.

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[1] The author is indebted to the Corn Products Company for the kojic acid used in these experiments and to the Research Corporation for a grant-in-aid on this project.

[2] G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., p. 135.

[3] All analyses are by Dr. Carl Tiedcke. All melting points were made on a Fisher–Johns melting point assembly.

Anal. Calcd. for $C_{13}H_9O_4Cl$: C, 58.98; H, 3.40. Found: C, 59.50; H, 3.70.

Acetylation.—The preparation of 2-acetoxymethyl-5-acetoxy-6-benzoyl-4-pyrone was accomplished by allowing 6-benzoylkojic acid to react with acetyl chloride in benzene. The benzene mixture was treated with water and the compound recrystallized from ethanol. White prisms were obtained which sublimed above 150° and melted at 182°.

Anal. Calcd. for $C_{18}H_{14}O_7$: C, 62.57; H, 4.09. Found: C, 62.66; H, 4.16.

Meerwein–Ponndorff–Verley Reduction.—Five grams of 6-benzoylkojic acid was refluxed with 7 g. of aluminum isopropoxide in absolute isopropyl alcohol for 8 hours, and all but 35 ml. of the isopropyl alcohol and acetone was distilled off. The residual material was acidified and 50 ml. of water added. Extraction with benzene gave 3.8 g. of a white solid which when boiled with 100 ml. of distilled water gave 1.3 g. of (2-hydroxymethyl-5-hydroxy-4-pyrone-6)-hydroxyphenylmethane as long white needles; m.p. 114–115°. This compound gave a very deep red coloration with iron salts.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.83. Found: C, 63.16; H, 4.59.

DEPARTMENT OF CHEMISTRY
TEXAS SOUTHERN UNIVERSITY
HOUSTON, TEXAS
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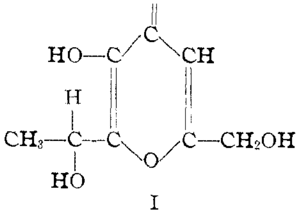
The Hydroxyethylation of Kojic Acid[1]

By L. L. WOODS

The reactions described are an attempt to determine the general applicability of the method of hydroxy alkylation of kojic acid reported previously[2] in which paraformaldehyde condensed with kojic acid in the presence of potassium bi carbonate.

It has been found that acetaldehyde participates in the hydroxy alkylation of the pyrone if certain slight modifications are made in the method mentioned. No reaction was obtained with chloral, but benzaldehyde reacted with the kojic acid under the same conditions which effected condensation in the case of acetaldehyde. However, all efforts to isolate a pure substance from the resulting tacky mixture were unsuccessful. When the reflux time was increased to four hours it was found that two molecules of kojic acid had combined with each molecule of benzaldehyde to produce, in good yield, bis-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-phenylmethane whose melting point is in agreement with the product obtained by Barham and Reed[3] using a different procedure.

The probable structure of the compound formed by hydroxy ethylation is given in (I) and the reason for assigning such a structure to the substance has been fully discussed elsewhere.[2]



I

Unfortunately the compounds so far produced by hydroxy alkylation have melting points very close to that for kojic acid. This similarity extends to the chloro derivatives obtained with thionyl chloride.

Experimental[4]

1-(2-Hydroxymethyl-5-hydroxy-4-pyrone-6)-1-hydroxyethane.—A mixture of 14.2 g. of kojic acid, 100 ml. of absolute ethanol and 1 g. of potassium bicarbonate was heated to gentle reflux and then 10 ml. of acetaldehyde was added in 2–3 ml. portions. Refluxing was continued for one-half hour after the addition of the last of the acetaldehyde.

The mixture was then cooled somewhat, a small amount of Norite added, and filtered.

The filtrate was placed in the freezer overnight. Upon filtering the cooled material 9.9 g. of yellow crystals was obtained. The analytical sample was recrystallized twice from ethanol; the substance softened at 149°, melted at 155° and gave a red coloration with ferric chloride.

Anal. Calcd. for $C_8H_{10}O_5$: C, 51.61; H, 5.37. Found: C, 51.42; H, 5.08.

The reaction of the above compound with thionyl chloride in ligroin produced a dark colored mass which when recrystallized from alcohol and then sublimed produced white needles, m.p. 166.5°.

Anal. Calcd. for $C_8H_8O_3Cl_2$: C, 43.04; H, 3.57. Found: C, 43.45; H, 3.80.

The acetyl derivative was prepared by allowing the compound to react 24 hours with acetyl chloride at room temperature in a small flask protected from moisture with a calcium chloride tube. The reaction mixture was treated with a large amount of water and then extracted with benzene. After the removal of the benzene the compound was dried in a vacuum desiccator over sulfuric acid; rosettes of white crystals were formed which sublimed above 108°, m.p. 136.5°.

Anal. Calcd. for $C_{14}H_{16}O_8$: C, 53.84; H, 5.12. Found: C, 53.49; H, 4.98.

Bis-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-phenylmethane.—A reaction mixture consisting of 14.2 g. of kojic acid, 10.8 g. of benzaldehyde, 1 g. of potassium bicarbonate and 50 ml. of absolute ethanol was refluxed for 4 hours. A viscous material was obtained from which 10.8 g. of solid was obtained by suction filtration after the mass had remained in the refrigerator for two days.

Recrystallization of the compound several times from ethanol produced flesh colored aggregates which decomposed above 245°.

Anal. Calcd. for $C_{19}H_{16}O_8$: C, 61.29; H, 4.30. Found: C, 61.25; H, 4.54.

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TEXAS SOUTHERN UNIVERSITY
HOUSTON 4, TEXAS
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[1] The author wishes to acknowledge the financial assistance given for this study by the Research Corporation with a grant-in-aid, and the Corn Products Company for the kojic acid used in these experiments.

[2] L. L. Woods, THIS JOURNAL, **72**, 4322 (1950).

[3] H. N. Barham and G. N. Reed, *ibid.*, **60**, 1541 (1938).

[4] All analyses were by Dr. Carl Tiedcke. All melting points were determined on a Fisher–Johns melting point assembly.

NEW COMPOUNDS

2,5-Disubstituted Oxazoles and Thiazoles

Certain 2-aza-1,4-diketones have been prepared and cyclized to give 2,5-disubstituted oxazoles or thiazoles.

4-Acetylbiphenyl and 2-acetylnaphthalene were brominated and the derived α-bromoketones were converted to the hexamethylenetetraminium salts[1] whose acid hydrolysis gave the corresponding α-aminoketones.[2] These were treated with benzoyl chloride, 2-furoyl chloride or myristoyl chloride to give the 2-aza-1,4-diketones. Oxazoles were

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[1] C. T. Bahner, M. D. Pickens, D. Pickens and W. K. Easley, THIS JOURNAL, **72**, 2266 (1950).

[2] C. Mannich and F. L. Hahn, *Ber.*, **44**, 1542 (1911).