tates are obtained by the action of titanium tetrachloride on the 2,3,4-tri-*O*-acetyl-1,6-anhydro-*β*-D-glycopyranoses as described by Zemplén and coworkers.[5] 2,3,4-Tri-*O*-acetyl-1,6-anhydro-*β*-D-glucopyranose (levoglucosan triacetate) is readily available and is thus easily converted in good yield to 1,2,3,4-tetra-*O*-acetyl-*β*-D-glucopyranose. A crystalline tetraacetate (m.p. 140–140.5°, $[\alpha]_D$ +37° in chloroform) was obtained in the D-galactose structure. The fact that it did not form a trityl derivative as does 1,2,3,4-tetra-*O*-acetyl-*β*-D-glucopyranose[2] and that it was recovered unchanged after solution in dilute aqueous alkali, offers strong presumptive evidence that an acetyl group had migrated to the sixth carbon atom. A migration from the fourth to the sixth carbon atom occurs readily in the D-glucopyranose structure in the presence of a trace of alkali or even in an aqueous solution in an alkaline glass container.[6] Table I lists the known tetraacetates of D-galactose.

TABLE I

TETRAACETATES OF D-GALACTOSE

Acetate position	Anomer	M.p., °C.	$[\alpha]^{25 \pm 5}_D$ (CHCl$_3$)	Reference
2,3,4,6	α	133	+144°	7
	β	127–128	+ 23	8
2,3,5,6	β	71–73	− 18	9
2,3,4,5	Aldehydrol	162	+ 10[a]	10, 11
1,3,4,6	β	128	+ 12[b]	12
?	β	140–140.5	+ 37, +36[b]	This work

[a] Initial rotation in pyridine; chloroform-insoluble. [b] Ethanol solution.

Experimental

1,2,3,4-Tetra-*O*-acetyl-*β*-D-glucopyranose.—2,3,4-Tri-*O*-acetyl-*α*-D-glucopyranosyl chloride[5] (40 g.) was dissolved in 100 ml. of acetic acid containing 35 g. of mercuric acetate and kept at room temperature for 1.5 hr. The solution was then diluted with 250 ml. of chloroform and washed with water, saturated aqueous sodium bicarbonate solution, and water again, dried with anhydrous sodium sulfate and evaporated below 40° under reduced pressure to a sirup. The sirup was dissolved in ether and was crystallized by the addition of petroleum ether; yield 26.5 g., m.p. 121–123° cor. Pure material was obtained on further crystallization from chloroform–ether–petroleum ether, m.p. 125–127° cor., $[\alpha]^{29}_D$ +10° (*c* 6, chloroform) in agreement with recorded[2] (128–129° cor., +12.1°) values for 1,2,3,4-tetra-*O*-acetyl-*β*-D-glucopyranose.

Tetra-*O*-acetyl-*β*-D-galactopyranose.—1,6-Anhydro-2,3,4-tri-*O*-acetyl-*β*-D-galactopyranose[13] (6 g.), which had been prepared by an adaptation of the method which Coleman, McCloskey and Kirby[14] had used for the corresponding D-glucose derivative, was dissolved in 100 ml. of U.S.P.[15] chloroform. To this solution was added 1 ml. of ethanol and a mixture of 10 ml. of titanium tetrachloride and 10 ml. of chloroform. A yellow precipitate was formed which redissolved upon heating the solution in an oil-bath at 100° for 45 min. After cooling, the solution was washed with ice and water, dried with sodium sulfate and evaporated under reduced pressure to a sirup. The sirup was dissolved in 20 ml. of acetic acid containing 2 g. of mercuric acetate and allowed to stand at room temperature for 1 hr. The solution was diluted with 75 ml. of chloroform and washed with water until free of acid. The chloroform solution was dried with anhydrous sodium sulfate and evaporated under reduced pressure at room temperature. The resulting sirup was dissolved in ether and brought to crystallization by the addition of petroleum ether; yield 1.0 g., m.p. 129–136°. The substance was purified by two recrystallizations from chloroform–ether; m.p. 140–140.5° cor., $[\alpha]^{30}_D$ +37.4° (*c* 3.2, chloroform), $[\alpha]^{30}_D$ +36° (*c* 1.9, ethanol); X-ray powder diffraction data: 10.78[16] m,[17] 8.41m, 7.06s, 6.45m, 5.97s, 5.37m, 5.06vs, 4.81m, 4.51w, 4.32m, 4.19m, 4.05w, 3.80w, 3.72s, 3.56w, 3.51s, 3.43w, 3.00vw, 2.94m, 2.85m.

Anal. Calcd. for $C_6H_8O_6(CH_3CO)_4$: C, 48.27; H, 5.79; CH_3CO, 11.48 ml. of 0.1 *N* NaOH per 100 mg. Found: C, 48.41; H, 6.10; CH_3CO, 11.60 ml.

The substance was recovered unchanged after treatment with pyridine and trityl chloride and also after solution in 0.001 *N* sodium hydroxide.

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(6) B. Helferich and W. Klein, *Ann.*, **455**, 173 (1927).

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(9) C. S. Hudson and J. M. Johnson, *ibid.*, **38**, 1223 (1916).

(10) F. Micheel and W. Spruck, *Ber.*, **67**, 1665 (1934).

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(13) F. Micheel, *Ber.*, **62**, 687 (1929).

(14) G. H. Coleman, C. H. McCloskey and R. Kirby, *Ind. Eng. Chem.*, **36**, 1040 (1944).

(15) United States Pharmacopoeia; contains ethanol.

(16) Interplanar spacing, Å., CuKα radiation.

(17) Relative intensity, estimated visually; vs, very strong; s, strong; m, medium; w, weak; vw, very weak.

DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY
COLUMBUS 10, OHIO

Kojic Acid in the Hoesch Reaction

BY L. L. WOODS[1]

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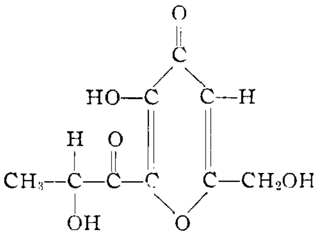
Continuing a study of kojic acid[2,3] we have condensed lactonitrile with it under the conditions of the Hoesch reaction. A compound $C_9H_{10}O_6$ was obtained. The reactions described below prove this product to be 2-hydroxymethyl-5-hydroxy-6-(*α*-hydroxy propionyl)-4-pyrone (I).

Prolonged heating of the substance with water fails to hydrolyze it, indicating that it is not a lactic acid ester.[4] Only the monochloro derivative is obtained when the reaction product with thionyl



I

chloride is recrystallized from water, which is to be expected from the proposed structure. The compound reacts with malonic acid to form a derived

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(2) L. L. Woods, THIS JOURNAL, **74**, 1105 (1952).

(3) L. L. Woods, *ibid.*, **75**, 3608 (1953).

(4) See A. A. Colon, K. H. Vogel and J. C. Warner, *ibid.*, **75**, 6074 (1953), for a discussion of neutral hydrolysis of lactic acid esters.

acrylic acid, as do other carbonyl-containing compounds but not kojic acid.[5]

The infrared spectrum of the substance indicates the presence of two carbonyls, one at 1668 cm.$^{-1}$ characteristic of the pyrone carbonyl, and the other at 1635 cm.$^{-1}$ in agreement with the literature[6] for a non-nuclear α-hydroxy carbonyl grouping.

Finally the substance was successfully converted to a pyridone.

The experimental facts outlined above all support the suggested structure.

Experimental[7]

2-Hydroxymethyl-5-hydroxy-6-(α-hydroxypropionyl)-4-pyrone (I).—A mixture consisting of 14.2 g. of kojic acid, 7 g. of zinc chloride, 7.1 g. of lactonitrile and 150 ml. of anhydrous ether was treated with hydrogen chloride for 17 hours. The gas was passed in rather rapidly at first and the mixture was externally cooled. After about two hours the cooling was discontinued and the rate of addition of hydrogen chloride was cut to a slow trickle for the rest of the reaction period. As the reaction proceeds the ketimine tends to cake with the unreacted kojic acid, this fact necessitated breaking up of the cake or thoroughly shaking the mixture every three or four hours.

Upon completion of the reaction the ether was decanted and discarded. The solid remaining was treated slowly with 50 ml. of distilled water. A vigorous reaction took place and the solid all dissolved. The resulting solution was placed in the freezer and allowed to stand overnight. Tan crystals were obtained which when filtered and air-dried weighed 11.3 g.

The ketimine was decomposed by refluxing it for four hours in 30 ml. of water containing 3 or 4 ml. of acetic acid. The solution was then evaporated to dryness over a steam-bath, and the resulting solid recrystallized twice from absolute ethanol, 9.8 g. of crystals was obtained. The sublimed compound, showed a melting point of 155°. The substance produced a wine-red coloration with dilute solutions of ferric chloride.

Anal. Calcd. for $C_9H_{10}O_6$: C, 50.47; H, 4.71. Found: C, 50.35; H, 4.49.

A sample was unchanged in composition, m.p. (155.5°), and mixed m.p. when refluxed in water for 44 hours.

Its infrared spectrum showed a characteristic absorption band for the hydroxyl group at 3210 cm.$^{-1}$. Two absorption bands for the carbonyl were located at 1668 and 1635 cm.$^{-1}$, indicating two carbonyls of different nature and conjugation. Two absorption bands characteristic of the pyrone ring structure were found at 1620 and 1590 cm.$^{-1}$.

Reaction with Malonic Acid.—One gram of compound I, 1 g. of malonic acid and 5 ml. of glacial acetic acid were mixed together, refluxed for 2 hours, evaporated to dryness over a steam-bath and the residue recrystallized twice from ethanol. Sublimation of the compound gave colorless crystals of β-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-γ-hydroxy-α,β-butenoic acid, m.p. 153–154°.

Anal. Calcd. for $C_{11}H_{12}O_7$: C, 51.56; H, 4.72. Found: C, 51.35; H, 4.49.

The remaining portion of the analytical sample was converted into the bis-*p*-bromophenacyl derivative using the general method reported previously.[8]

The compound was purified by recrystallizing twice from absolute ethanol. The substance sublimed at 273–276° and would not melt below 340°. Every effort to obtain a melting point failed since the compound either sublimed away or, in a sealed tube, sublimed in the exposed stem above the heating medium.

Anal. Calcd. for $C_{27}H_{22}Br_2O_9$: Br, 24.57. Found: Br, 24.20.

Reaction with Thionyl Chloride.—The reaction of I with an excess of thionyl chloride produced a compound which was quite soluble in hot water, from which it was recrystallized.

The resulting yellow needles were sublimed to a white compound; m.p. 161°. The white powder gave a red coloration with dilute solutions of ferric chloride, and the analysis indicated that only one hydroxyl had been displaced by chlorine. Since the 2-hydroxymethyl group is known to react with thionyl chloride and since this group had not been changed in any way during the formation of I it is presumed to be the group permanently affected during the reaction with thionyl chloride.

Anal. Calcd. for $C_9H_9O_5Cl$: C, 46.47; H, 3.90. Found: C, 45.99; H, 3.59.

Reaction with Ammonium Hydroxide.—Ten grams of compound I was placed in a pressure bottle along with 50 ml. of ammonium hydroxide and heated in an oil-bath at 105° for 3 hours. The resulting blue solution was evaporated to dryness and the black solid which remained was extracted with 100 ml. of boiling absolute ethanol. Chilling the filtrate in an ice–salt mixture produced 1.8 g. of a tan powder. Several recrystallizations from ethanol produced microscopic tan cubes of 2-hydroxymethyl-5-hydroxy-6-(α-hydroxypropionyl)-4-pyridone, m.p. 239–241°.

Anal. Calcd. for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57. Found: C, 50.98; H, 5.05; N, 6.42.

Oppenauer Oxidation.—A mixture of 3 g. of I, 5 g. of aluminum isopropoxide, 100 ml. of benzene and 100 ml. of acetone was distilled over a period of 2.5 hours. The residue in the flask was diluted with 150 ml. of water, acidified with hydrochloric acid, and extracted with ethyl acetate. Evaporation of the solvent gave 1.3 g. of long needles which when sublimed gave a light yellow powder, m.p. 153–154°.

Anal. Calcd. for $C_9H_8C_6$: C, 50.95; H, 3.80. Found: C, 51.10; H, 4.10.

The remainder of analytical samples I and the above oxidation product were resublimed twice. The melting point of I did not change but the melting point of the Oppenauer oxidation compound was found to be 158.5°. A mixed melt of the specially purified compounds was 151°, indicating the non-identity of the two substances.

TEXAS SOUTHERN UNIVERSITY
HOUSTON, TEXAS

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(5) See C. Weygand, "Organic Preparations," Interscience Publishing Co., New York, N. Y., 1945, p. 422, for a discussion of the reaction.

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, New York, N. Y., 1954, p. 124–125.

(7) All analyses were performed by Dr. Carl Tiedcke and all melting points were determined on a Fisher–Johns melting point assembly.

(8) L. L. Woods, THIS JOURNAL, **74**, 3959 (1952).