$(HOOC)_2C(C_2H_5)CH_2\overline{C=CHSC(C_6H_5)=N}$, **Ethyl-(2-phenyl-thiazole-4-methyl)-malonic acid (VI),** was obtained by saponification of the corresponding ester with alcoholic potassium hydroxide. The acid was recrystallized from dilute alcohol, m. p. 145°.

Anal. Calcd. for $C_{15}H_{15}O_4NS$: N, 4.59. Found: N, 4.31, 4.34.

$\overline{CONHCONHCO}C(C_2H_5)CH_2\overline{C=CHSC(C_6H_5)=N}$, **5-Ethyl-5-(2-phenyl-thiazole-4-methyl)-barbituric acid (VII),** was prepared by the condensation of the diethyl ester of VI with urea according to the method of Dox and Yoder.[5] The product was obtained by evaporation of the filtrate after acidification of the reaction mixture with hydrochloric acid. It crystallized from 1:3 benzene–alcohol in large colorless prisms of m. p. 210–211°.

Anal. Calcd. for $C_{16}H_{15}O_3N_3S$: N, 12.76. Found: N, 12.70, 12.61.

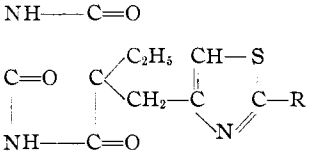
Several new thiazole compounds have also been prepared from IV. The properties of these compounds are shown in Table I.

TABLE I

2-Phenyl-4-( )-thiazole	B. p. or m.p., °C.	Formula	Nitrogen, % Calcd.	Found
Methoxymethyl-	B 116 at 1 mm.	$C_{11}H_{11}ONS$	6.82	6.89 6.71
Phenoxymethyl-	M 67–68	$C_{16}H_{13}ONS$	5.24	5.12
Thiophenoxymethyl-	M 42	$C_{16}H_{13}NS_2$	4.95	4.76 4.8

Summary

The thiazole barbituric acids represented by the formula shown below in which R = CH_3 and C_6H_5 have been prepared. These compounds are being tested pharmacologically.



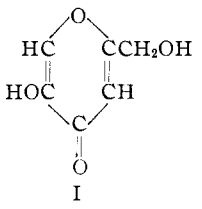
NEW HAVEN, CONN. RECEIVED NOVEMBER 8, 1933

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Synthesis of 5-β-d-Glucosidokojic Acid[1]

BY RAYMOND M. HANN

The production of kojic acid (2-hydroxymethyl-5-hydroxy-1,4-pyrone) I from carbohydrates by molds of the Aspergillus group[2] has made the compound readily available. This biological synthesis has been stimulated by the chemical synthesis of the diacetate of this acid from the hydrates of the tetraacetates of glucosone[3] and galactosone.[4] Evidently kojic acid can become the starting material for many syntheses.



I

Kojic acid should be capable of forming many types of glucosides through its possession of both phenolic and aliphatic hydroxyl groups. No glucoside of kojic acid has so far been found in nature.

In the present research a glucoside was prepared synthetically by condensation of the potassium salt of kojic acid with acetobromoglucose following the procedures of Michael and of Königs and Knorr. The operation yielded crystalline 5-(tetraacetyl-β-d-glucosido)-kojic acid (m. p. 201°, $[\alpha]_D^{20}$ −88.3° in $CHCl_3$), from which the crystalline free glucoside (m. p. 198°, $[\alpha]_D^{20}$ −107.3° in H_2O) was obtained by deacetylation with sodium methylate.

This synthetic substance is of the same type as the naturally occurring salicin, arbutin and coniferin, all being β-glucosides in which the sugar is combined with a phenolic hydroxyl group; it is therefore a glucoside of kojic acid which might be expected by analogy to exist in nature.

Experimental

5-β-Tetraacetyl-d-glucosidokojic Acid (2-Hydroxymethyl-5-β-tetraacetyl-d-glucosido-1,4-pyrone).—To a solution of 27.5 g. of glucose pentaacetate in 25 cc. of chloroform was added 75 cc. of glacial acetic acid saturated with dry hydrogen bromide gas and the solution allowed to stand for one hour.

The acid solution was transferred to a separatory funnel with 100 cc. of chloroform and 200 cc. of ice water. The chloroform solution was separated and the aqueous portion extracted successively with 100 cc. of ice water, 200 cc. of ice cold 2% sodium bicarbonate solution and then twice with 100 cc. of water. To this solution was now added a solution of 11 g. of kojic acid (10% excess) dissolved in 81.4 cc. of 0.865 *N* alcoholic potash. An oil which precipitated was carried into solution by addition of 50 cc. of 95% alcohol and the combined solutions refluxed for one-half hour, when potassium bromide precipitated. The solution was cooled, 1 liter of water added and the solution extracted five times with successive por-

(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) May, Moyer, Wells and Herrick, THIS JOURNAL, **53**, 774 (1931).

(3) Maurer, *Ber.*, **63**, 25 (1930).

(4) Maurer and Müller, *ibid.*, **63**, 2069 (1930).

tions of 100 cc. of chloroform. The chloroform extracts were combined, washed with dilute ice cold 3% sodium bicarbonate and then with ice water, the chloroform layer separated and dried over calcium chloride. Upon evaporation at gentle heat aided by an air current, a finely divided crystalline deposit was obtained. Filtered and washed with ether the yield was 18.0 g. (54%). The mother liquors yielded further material on concentration, the average yield being about 70%.

The compound could be recrystallized readily and practically quantitatively from 15 parts of boiling 95% alcohol; 6.3 g. recrystallized from 90 cc. of 95% alcohol gave a yield of 5.8 g. of material whose $[\alpha]_D^{20}$ value was $-88.3°$ (0.2109 g. in 25 cc. $CHCl_3$ rotated 1.49° to the left). A further single recrystallization gave $-88.4°$ (0.1485 g. in 25 cc. $CHCl_3$ rotated 1.05° to the left). It can also be recrystallized without decomposition from water at 80–90°, being soluble to the extent of about 0.4 g. in 100 cc.

The compound crystallizes in colorless brilliant needles 2 to 3 mm. long and melts at 201° (corr.) to a clear colorless oil.

An analysis for acetyl groups by the method of Kunz and Hudson showed the presence of four acetyl groups, 0.2378 g. substance consumed 20.30 cc. of 0.1 *N* sodium hydroxide; calcd. 20.14 cc.

Anal. Calcd. for $C_{20}H_{23}O_{13}$: C, 50.94; H, 4.92. Found: C, 50.83; H, 5.29.

5-β-*d*-Glucosidokojic Acid (2-Hydroxymethyl-5-β-*d*-glucosido-1,4-pyrone).—Attempts to deacetylate the tetraacetyl compound by ammonia in methyl alcohol solution were not successful. Incomplete deacetylation resulted even after allowing the deacetylation mixture to remain overnight, followed by gentle refluxing and resaturation of the resultant solution with ammonia and subsequent standing. However, sodium methylate brought about the desired result very smoothly.

Nine grams of the tetraacetylglucosidokojic acid was dissolved by warming in 300 cc. of chloroform and cooled to 10°. A solution of 75 cc. of 0.9 *N* sodium methylate and 25 cc. of anhydrous methyl alcohol was added and the mixed solutions allowed to stand in the ice-bath for one-half hour. A white gelatinous precipitate came down. The suspension was treated with the exact amount of dilute sulfuric acid to neutralize the original amount of sodium methylate and concentrated *in vacuo* at 60° to dryness. The dry residue was extracted with 75 cc. of 95% alcohol and the extract concentrated *in vacuo*. Colorless needles separated as the solution concentrated and the resulting yield of crude material was 2.8 g. The substance was recrystallized from 5 parts of 95% alcohol. The recrystallized glucoside gave $[\alpha]_D^{20}$ $-107.2°$ in water (0.1797 g. in 25 cc. H_2O rotated 1.54° to the left) and a further recrystallization gave $-107.4°$ (0.1470 g. in 25 cc. H_2O rotated 1.26° to the left); therefore the value $-107.3°$ is accepted as the true rotation. The compound melts at 197–198° (corr.) to a clear colorless oil.

Anal. Calcd. for $C_{12}H_{16}O_9$: C, 47.35; H, 5.30. Found: C, 47.42; H, 5.66.

The writer wishes to express appreciation for the assistance of Dr. F. H. Goldman in the analyses.

Summary

Kojic acid (2-hydroxymethyl-5-hydroxy-1,4-pyrone) has been condensed with acetobromoglucose to form 5-β-tetraacetyl-*d*-glucosidokojic acid. By deacetylation of this acetate with sodium methylate crystalline 5-β-*d*-glucosidokojic acid has been isolated and characterized.

WASHINGTON, D. C. RECEIVED DECEMBER 1, 1933

NOTES

Auto-Oxidation and Ionization Potentials of Molecules

BY NICHOLAS A. MILAS

Some years ago[1] the writer showed that the tendency to auto-oxidize of the hydrides, alkyl and aryl derivatives of the elements of the fifth group of the periodic table increases as the "effective nuclear charge" of these elements increases. This seems to be true also with similar derivatives of the elements of the sixth and seventh groups. Diethyl telluride, for example, is far more easily oxidized than diethyl ether. Similarly, ethyl iodide is more easily oxidized than ethyl chloride. If the auto-oxidation of these substances proceeds through a preliminary addition of molecular oxygen to the reactive unshared electrons present in each molecule, then there ought to exist a relationship between the tendency of these substances to auto-oxidize and the ionization potentials of the reactive electrons.

If one makes a simple calculation of the ionization potentials of the hydrides of these elements, on the assumption that the ratio of the first ionization potentials of any two elements in each group varies directly as the ionization potentials of their hydrides, one would find that the ionization potentials of the different hydrides are inversely proportional to their tendency toward auto-oxidation. The ionization potential of NH_3, for example, is 11.2 volts[2] while that of

(1) Milas, *J. Phys. Chem.*, **33**, 1204 (1929).

(2) Mackay, *Phys. Rev.*, **24**, 319 (1924); "Handbuch der Physik," **23**, Part I, 142 (1933).