[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

The Preparation of 2-Ketopolyhydroxy Acids

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It was observed by one of the authors[2] that when an aqueous solution of a methyl ester of a 2-ketohydroxy acid is heated in the presence of certain metallic elements, the esters are transformed into their corresponding ascorbic acid analogs. A marked difference was noted in the speeds with which the isomeric esters methyl 2-keto-D-gluconate and methyl 2-keto-L-gulonate, enolize and lactonize during this treatment.

In view of this, the present authors decided to study the rates of rearrangements of the four theoretically possible 2-ketohydroxy acids of the six-carbon series, namely, 2-keto-gluconic, -gulonic, -galactonic and -altronic acids. The latter two acids had not previously been prepared; 2-keto-D-gluconic acid was first obtained by Ohle,[3] from diacetone fructose, and 2-keto-L-gulonic acid was later prepared by Reichstein,[4] who used it as an intermediate in the synthesis of L-ascorbic acid. While the preparation of 2-keto-D-galactonic acid is described in the present paper, that of 2-keto-D-altronic acid is the subject of an ensuing communication.

In addition, it was thought advisable and of interest to explore the rearrangement mechanisms of seven-carbon 2-ketohydroxy acids. For purposes of structure the hitherto unknown 2-keto-D-glucoheptonic and 2-keto-D-galactoheptonic acids were prepared. These acids were expressly chosen because each has the hydroxy groups of carbon atoms 3 and 4 in *trans* position. If the rates of transformations into their ascorbic analogs are functions only of those groups which enter into the rearrangement, then their rates should be practically the same. If, however, the rate is influenced by the remaining part of the

COOH	COOH
CO	CO
HCOH	HCOH
HOCH	HOCH
HCOH	HOCH
HCOH	HCOH
CH_2OH	CH_2OH
(I)	(II)

molecule, then these acids should show a marked difference in rate of rearrangement, since the hydroxy groups on carbon atoms 4 and 5 of 2-keto-D-glucoheptonic acid (I) are in the *trans* position while on 5 and 6 they are in the *cis* position. But the structure of 2-keto-D-galactoheptonic acid (II) is the opposite of this; the hydroxy groups on carbon atoms 4 and 5 are in the *cis* position while on carbon atoms 5 and 6 they are in the *trans* position.

The present paper, which describes only the preparation of these acids (with the one exception above noted) will be followed by another containing the results of the rate studies.

Experimental

Calcium 2-Keto-D-gluconate.[5]—To 178 g. of D-glucono-γ-lactone dissolved by refluxing in one liter of methanol containing 5 cc. of 85% phosphoric acid, after cooling, 37 g. of sodium chlorate and 6 g. of vanadium pentoxide were added. The mixture was shaken for four days (20°) until dehydrogenation was complete as shown by the change from the yellow of the pentoxide to the green of the vanadium trioxide. The solid catalyst was then removed, and the solution was concentrated *in vacuo* to a sirup. After standing for two days at 3° the methyl 2-keto-D-gluconate (yield 60%) contaminated with sodium chloride, was collected, washed with methanol–acetone and recrystallized from dioxane: m. p. 175–176°; $[\alpha]^{20}D$ −76.8° (*c*, 2 in water) at equilibrium.[6]

The ester was hydrolyzed by dissolving 100 g. in one liter of 2 *N* sulfuric acid and storing at 30° for four days. The SO_4^{--} precipitated with barium carbonate, was filtered, the filtrate neutralized with calcium carbonate and evaporated to 250 cc. *in vacuo* at 40°. On standing overnight (20°) the calcium 2-keto-D-gluconate·$3H_2O$ crystallized. Two recrystallizations from water gave $[\alpha]^{20}D$ −70.8° (*c*, 2 in water).

Anal. Calcd. for $Ca(C_6H_9O_7)_2 \cdot 3H_2O$: Ca, 8.34; H_2O, 11.25. Found: Ca, 8.30; H_2O, 11.2.

The physical properties and composition of the salt have apparently not been previously reported. The degree of hydration was determined by heating the salt to constant weight at 90° for sixteen hours under 0.01 mm. pressure.

2-Keto-D-galactonic Acid.—To a solution containing 43.8 g. of potassium D-galactonate in 200 cc. of water, 8.2 g. of potassium chlorate, 0.5 g. of vanadium pentoxide and 3 cc. of phosphoric acid were added. After four days the solution was filtered, treated with calcium ferrocyanide and the vanadium ferrocyanide discarded. The filtrate was neutralized with calcium hydroxide to precipitate the PO_4^{---}, filtered, treated with 15 g. of calcium acetate, evaporated *in vacuo* to 60 cc., and the unreacted calcium D-galactonate allowed to crystallize (0°) during two days. Two further crops were recovered (a total of 40% of starting material), the excess Ca^{++} precipitated with oxalic acid, and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in 25 cc. of water, methanol slowly added, and after standing several days crude crystalline potassium 2-keto-D-galactonate was obtained (yield 30%), Two recrystallizations from water gave $[\alpha]^{20}D$ −6.7° (*c*, 1.2 in water).

Anal. Calcd. for $KC_6H_9O_7$: K, 16.84. Found: K, 16.78.

The free acid was liberated from the potassium salt by treatment with the exact amount of aqueous sulfuric acid and the potassium sulfate precipitated with dioxane. From the filtrate evaporated *in vacuo* to a sirup, and al-

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(2) Pasternack and Regna, U. S. Patents 2,165,151, 2,165,184, July 4, 1939.

(3) Ohle, *Ber.*, **58**, 2577 (1925).

(4) Reichstein, *Helv. Chim. Acta*, **16**, 561, 1019 (1933).

(5) *Cf.* Pasternack and Regna, U. S. Patent 2,207,991, July 16, 1940.

(6) Ohle, *Ber.*, **68**, 843 (1930).

lowed to stand overnight (0°) the crystalline 2-keto-D-galactonic acid was recovered, washed with aqueous dioxane and recrystallized from water: m. p. 170–171°; $[\alpha]^{20}D$ −6.0° (*c*, 2 in water), and on titration with alkali showed 99.9% purity.

Anal. Calcd. for $C_6H_{10}O_7$: C, 37.12; H, 5.19. Found: C, 37.02; H, 5.30.

Methyl 2-Keto-D-galactonate.—The acid (5 g.) was dissolved in 100 cc. of freshly distilled methanol containing 0.15% hydrogen chloride. The mixture was refluxed for two hours, and evaporated by repeated concentration *in vacuo* with methanol. Crystals of methyl 2-keto-D-galactonate were washed and recrystallized from alcohol-chloroform mixtures: m. p. 138–139° and $[\alpha]^{20}D$ −11.3° (*c*, 1.2 in water). D-Ascorbic acid m. p. 192° and $[\alpha]^{20}D$ −23° was made from this ester by the method of Maurer and Schiedt,[7] and this served to establish further the constitution of 2-keto-D-galactonic acid.

Sodium 2-Keto-D-glucoheptonate Monohydrate.—A hot solution of α-D-glucohepto-γ-lactone[8] (416 g.) was neutralized with 106 g. sodium carbonate, cooled, diluted to 4.2 liters and 73 g. of sodium chlorate, 40 cc. of 85% phosphoric acid and 20 g. of vanadium pentoxide were added. After stirring for two days, the reaction was complete; it was filtered, treated with enough calcium ferrocyanide to precipitate the V^{+++}, filtered again, the PO_4^{---} precipitated with calcium hydroxide, and the excess Ca^{++} removed with oxalic acid. The colorless solution containing only sodium salts was concentrated to 2 liters and an equal volume of methanol added dropwise with stirring during thirty-six hours. The crude crystalline sodium 2-keto-D-glucoheptonate (yield 38%) was recrystallized twice from 40% aqueous methanol: $[\alpha]^{20}D$ +45.5° (*c*, 2 in water).

Anal. Calcd. for $Na(C_7H_{11}O_8)\cdot H_2O$: Na, 8.70; C, 31.82; H, 4.96. Found: Na, 8.60; C, 31.87; H, 5.10.

The constitution of the 2-keto acid was established by preparing D-glucoascorbic acid from it. The free acid liberated from the sodium salt (26.4 g.) by sulfuric acid and precipitation with methanol was repeatedly evaporated *in vacuo* with methanol. The final residue was dissolved in 100 cc. of absolute methanol, treated with a measured quantity of diazomethane and concentrated *in vacuo* to 50 cc. The ester solution was stirred with 50 cc. of sodium methylate (containing 2.42 g. of sodium) at 45° under a current of nitrogen. When the suspension thinned out, it was treated with 10 cc. of 51.5% sulfuric acid, filtered, evaporated to dryness *in vacuo*, the residue dissolved in methanol, Norite was added and filtered. The filtrate was concentrated *in vacuo* to 25 cc. and allowed to stand several days at 0°. D-Glucoascorbic acid monohydrate recrystallized twice from methanol–acetone showed m. p. 140°, $[\alpha]^{20}D$ −22.0° (*c*, 1 in water) and iodine titration 99.7% which values agree with those obtained by Haworth, Hirst and Jones[9] who prepared D-glucoascorbic acid through the addition of hydrogen cyanide to glucosone.

Potassium 2-Keto-D-galactoheptonate.—A mixture of α- and β-D-galactoheptonic acids prepared by the addition of hydrogen cyanide to galactose, was neutralized with potassium carbonate. The dehydrogenation procedure described above for the isomeric acid was followed. However, the potassium 2-keto-D-galactoheptonate crystallized very readily on the addition of methanol to the aqueous solution of the potassium salts (yield about 65%). The crude potassium salt was recrystallized from water until a constant rotation was obtained; $[\alpha]^{20}D$ +67.5° (*c*, 2 in water).

Anal. Calcd. for $KC_7H_{11}O_8$: K, 14.91; C, 32.06; H, 4.23. Found: K, 14.90; C, 32.08; H, 4.37.

The constitution of 2-keto-D-galactoheptonic acid was established by preparing *d*-galactoascorbic acid from it by employing the procedure described above for 2-keto-D-glucoheptonic acid. Recrystallization from methanol–acetone yields the monohydrate. There is an evolution of gas at its m. p. 109° and a blackening at 190°, which observations are in agreement with those of Haworth,[10] *et al.*, who prepared D-galactoascorbic acid through the addition of hydrogen cyanide to galactosone.

Summary

1. A general method is described for the catalytic dehydrogenation of α-hydroxy groups of six- and seven-carbon membered polyhydroxy acids.

2. Of the six-membered polyhydroxy acids, the previously unknown 2-keto-D-galactonic acid is described, and the properties of calcium 2-keto-gluconate trihydrate are noted.

3. In the seven-membered polyhydroxy acids, 2-keto-D-glucoheptonic and 2-keto-D-galactoheptonic acids have been prepared and described, and from these keto acids, corresponding ascorbic acid analogs were made.

(7) Maurer and Schiedt, *Ber.*, **66**, 1054 (1933).

(8) Hudson, Hartley and Purves, THIS JOURNAL, **56**, 1248 (1934).

(9) Haworth, Hirst and Jones, *J. Chem. Soc.*, 549 (1937).

(10) Baird, Haworth, Herbert, Hirst, Smith and Stacey, *ibid.*, 62, (1934).

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A Method for the Preparation of Calcium D-Altronate[1]

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In the course of work being carried out in this Laboratory in connection with the rates of transformation of 2-ketopolyhydroxy acids[3] into their ascorbic acid analogs, 2-ketoaltronic acid was needed. For this purpose we were interested in catalytically dehydrogenating either allonic or altronic acid in attempts to prepare the last remaining unknown 2-ketoaldonic acid. Accordingly we have produced D-altronic acid in large quantities by the following series of reactions: pectin → sodium calcium D-galacturonate → calcium 5-keto-L-galactonate → calcium D-altronate and calcium L-galactonate. The steps in the procedure, indicated by the acids of the foregoing salts, are represented by the configurational formulas

(1) Presented before the Division of Organic Chemistry of the American Chemical Society, Pittsburgh meeting, September, 1943.

(2) This paper is constructed from a thesis presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, June, 1942. Present address: Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

(3) Regna and Caldwell, THIS JOURNAL, **65**, 246 (1943).