

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

Certain Derivatives of *l*- α -Rhamnohexonic Acid. An Improved Synthesis of *l*- α -Rhamnohexonic Lactone¹

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A convenient modification of the Kiliani synthesis of the higher carbon acids from reducing sugars was reported recently by Hudson, Hartley and Purves.² In the present paper the application of the method to the synthesis of α -rhamnohexonic lactone is described. The basic calcium salt of α -rhamnohexonic acid proved to be too soluble in water for convenient isolation, and this necessitated certain variations in the procedure. The cyanohydrin synthesis was carried out by the reaction of *l*-rhamnose with sodium cyanide and barium acetate in aqueous solution. After hydrolysis of the rhamnohexonic nitriles, the product was isolated as crystalline α -rhamnohexonic lactone (55%) which was separated readily from the sirupy lactone of the β -acid. This method is preferred to that of Fischer and Tafel,³ since it avoids the use of hydrocyanic acid and the step of separating barium α -rhamnohexonate, which is fairly soluble⁴ in water.

Our melting points and rotations of rhamnohexonic acid and certain of its derivatives are shown in Table I. The derivatives were recrystallized to constant rotation from 95% ethanol, and all rotations were measured with sodium light at concentrations (*c*) expressed as grams per 100 cc. of solution. The ethyl ester, the equilibrium rotations of the acid and its lactone, and the rotation of the phenylhydrazide are reported for the first time. The ethyl ester was obtained in the fractional crystallization of the crude lactone from ethanol, which evidently reacted with some of the lactone or admixed rhamnohexonic acid to yield the ester. As shown in Table I our melting point and rotation of the amide vary widely from the values given by Mikšić, who prepared it from the nitrile. We prepared the compound readily by the reaction of ammonia with the pure lactone or ethyl ester in absolute ethanol solution, which it seems would yield a pure product. The sign of rotation of the amide and phenylhydrazide agrees

with the amide⁵ and phenylhydrazide⁶ rules of rotation.

We have extended our investigation to α -rhamnohexose and several of its derivatives and the results will be communicated later.

TABLE I
RHAMNOHEXONIC ACID AND CERTAIN DERIVATIVES

Substance	M. p. (corr.) °C.	[α] _D ²⁰ in water		
		<i>c</i>	Initial	Constant
Rhamnohexonic acid ^a	171	1.9	+21.5	+74.0 ^b
Rhamnohexonic lactone	171-171.5	3.0	+87.3 ^c	+74.4
Ethyl rhamnohexonate	165-166 ^d	2.0	+12.9 ^e	+74.0 ^b
Rhamnohexonic amide ^f	177.5-178 ^d	3.2	-19.9	..
Rhamnohexonic phenylhydrazide ^g	205-206 ^d	1.0	- 5.2	..

^a Prepared by the method of Brackenbury and Upson [THIS JOURNAL, 55, 2512 (1933)] who reported m. p. 174-175° and [α]_D²⁵ +19.1° (10 min.). The [α]_D²⁰ +21.6° (8 min.) in water was found by freeing the acid from its sodium salt with an equivalent of hydrochloric acid. The acid prepared from the barium salt and sulfuric acid by Nef [Ann., 403, 273 (1914)] and Hedenburg's [THIS JOURNAL, 37, 363 (1915)] method showed [α]_D²⁰ +22.4° (10 min.) in water (*c*, 0.8), which at 20-25° sterilized with toluene changed to +19.3° (about 3 hrs.), +24.5° (21 hrs.), +35.0° (70 hrs.), +65.3° (33 days) and the constant +67.6° (as acid) or +74.0° (as lactone) after sixty-one days. The solubility of the acid in water at 18-19° is 7.38 g. in 100 cc. ^b Calcd. as lactone. ^c The [α]_D in aqueous solution (*c*, 0.8) sterilized with toluene decreased at 20-25° to +85.6° (47 hrs.), +78.5° (31 days) and the constant +74.4° (67 days). Fischer and Tafel [Ber., 21, 1657 (1888); cf. Will and Peters, *ibid.*, 21, 1815 (1888)] found m. p. 168°; Fischer and Piloty [*ibid.*, 23, 3102 (1890)] gave initial [α]_D²⁰ +83.8° in water, while van Ekenstein, Jorissen and Reicher [Z. physik. Chem., 21, 383 (1896)] reported +86° in water. ^d Decomposition. ^e In aqueous solution (*c*, 1.2) at 20-25° sterilized with toluene the [α]_D changed to +15.0° (48 hrs.), +50.8° (30 days) and the constant +59.7° (as ester) or +74.0° (as lactone) after seventy days. ^f Mikšić [Vestnik Kral. Čes. Spol. Nauk. Cl. II, 18 pp. (1926); Chem. Zentr., I, 2704 (1928)] found m. p. 194° and [α]_D²⁰ -47.3° in water. ^g Prepared from pure lactone by the method of Fischer and Passmore [Ber., 22, 2728 (1889)] who reported m. p. 210° (variable).

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

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

(3) Fischer and Tafel, Ber., 21, 2173 (1888).

(4) Fischer and Morrell, *ibid.*, 27, 382 (1894).

(5) Hudson, THIS JOURNAL, 40, 813 (1918).

(6) Hudson, *ibid.*, 39, 462 (1917); Levene, J. Biol. Chem., 23, 145 (1915); Levene and Meyer, *ibid.*, 31, 623 (1917).

Preparations

Rhamnohexonic Lactone.—To 400 g. of ice were added successively aqueous solutions of 100 g. of rhamnose hydrate (200 cc.), 105 g. of barium acetate monohydrate (150 cc.) and 32 g. of sodium cyanide (100 cc.). After keeping in ice for an hour and then in the refrigerator for seventy hours (negative Fehling's test), 122 g. of barium hydroxide octahydrate was added and the mixture boiled for six hours, adding water to maintain about half the original volume. The barium was balanced with sulfuric acid, 15 g. of carbon added, the mixture boiled for thirty minutes and the barium sulfate filtered off and washed with water. The calculated sulfuric acid (141.6 cc. of 4.61 *N*) was added to balance the sodium ions, and the combined solutions from three runs distilled to dryness under reduced pressure. The residue was mixed with 500 cc. of 95% ethanol, the distillation repeated and the organic products extracted from sodium sulfate by hot 95% ethanol followed by methanol. Concentration of the alcohol solution under reduced pressure gave several crops of colorless crystals and a sirup which yielded more crystals with acetone as solvent; air-dried; yield, about 200 g. consisting of α -rhamnohexonic acid, its lactone and ester. The sirup was doubtless a mixture of α - and β -rhamnohexonic acid and their derivatives. To convert the acid and ester into lactone, a solution of the crystals in 2 liters of water was evaporated to dryness on the steam-bath, the operation repeated with less water and the residue heated at 100° for several hours, washed with cold acetone and dried at 95–100° for three hours; yield of lactone, 175 g. (55%).

Ethyl Rhamnohexonate.—Recrystallization of crude lactone from absolute ethanol followed by fractionation from 95% ethanol yielded some ester (about 5% of the lactone).

Anal. Calcd. for $C_9H_{15}O_7$: C, 45.35; H, 7.62; OC_2H_5 , 18.91. Found: (micro) C, 45.46; H, 7.46; OC_2H_5 , 18.59.

Rhamnohexonic Amide.—A suspension of 5 g. of pure lactone in 100 cc. of absolute ethanol was saturated with dry ammonia. The lactone soon dissolved and after an hour the amide which crystallized (5.2 g.; m. p. 175°) was filtered off; evaporation of the filtrate made the yield quantitative. It is difficultly soluble in hot absolute ethanol or methanol and insoluble in ether.

Anal. Calcd. for $C_7H_{13}O_6N$: C, 40.17; H, 7.23; N, 6.70. Found: (micro) C, 40.48, 40.13; H, 6.86, 7.05; N (Kjeldahl), 6.69, 6.65.

The reaction of dry ammonia with 2 g. of pure ethyl ester in 250 cc. of hot absolute ethanol solution gave the theoretical yield of amide.

We are indebted to Dr. R. T. K. Cornwell for the analyses.

Summary

It is shown that crystalline *l*- α -rhamnohexonic lactone may be prepared in 55% yield by a convenient modification of the Kiliani synthesis, using *l*-rhamnose, sodium cyanide and barium acetate in aqueous solution. Ethyl rhamnohexonate is described and the equilibrium rotations of the acid, ester and lactone are shown to be $[\alpha]_D^{20} +74^\circ$ in water. Rhamnohexonic amide, prepared from both the ester and lactone, shows m. p. 177.5–178° (corr.) and $[\alpha]_D^{20} -19.9^\circ$ in water which vary widely from the values found by Mikšić, who prepared the compound from the nitrile. The sign of rotation of the amide and phenylhydrazide agrees with the amide and phenylhydrazide rules.

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[CONTRIBUTION FROM THE CHEMICAL AND BACTERIOLOGICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Preparation and Germicidal Properties of Some Derivatives of 4-*n*-Butylresorcinol

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Although the bactericidal properties of many derivatives of resorcinol have been studied, there is little information available concerning the compounds containing two or more unlike substituents. The present communication deals chiefly with some halogen and mercury derivatives of 4-*n*-butylresorcinol, a compound readily obtainable by a modification¹ of the synthesis originally employed by Johnson and Lane.²

Chlorination of *n*-butylresorcinol with sulfuryl chloride gives a compound identical with that

obtained by reduction of the ketone resulting from the condensation of 4-chlororesorcinol with *n*-butyric acid, thus establishing its structure as 6-chloro-4-*n*-butylresorcinol. Chlorination of *n*-butylresorcinol with sulfuryl chloride followed by reduction of the chloro ketone also gives this same compound.³

The structure of the chlororesorcinol obtained from resorcinol and sulfuryl chloride deserves some comment. It was first prepared by Reinhard,⁴

(1) Dohme, Cox and Miller, *THIS JOURNAL*, **43**, 1688 (1926).

(2) Johnson and Lane, *ibid.*, **43**, 348 (1921).

(3) Chloro-*n*-butylresorcinol has also been described very recently by Read, Reddish and Burlingame, *THIS JOURNAL*, **56**, 1377 (1934).

(4) Reinhard, *J. prakt. Chem.*, [II] **17**, 322 (1878).