[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Isolation of Aldonic Acid Lactones through their Hydrazides

BY ALVA THOMPSON[1] AND M. L. WOLFROM

The reluctance of lactones of the aldonic acids to crystallize from their reaction mixtures often poses a difficult problem in their preparation. The classic method for the isolation of these compounds from complex mixtures is through their alkaloidal salts. We find that the hydrazides of the aldonic acids, because they are readily prepared and easily crystallized, are very suitable derivatives for this purpose. A considerable number of aldonic acid hydrazides have been described by van Marle.[2] In this communication we wish to describe a convenient method for regenerating the lactones of the aldonic acids from their hydrazides.

For other purposes it became necessary for us to obtain a quantity of D-lyxono-γ-lactone. Nef[3] had made D-lyxono-γ-lactone by the oxidation of an alkaline solution of D-galactose with air. This general reaction of an aldose has been improved by Spengler and Pfannenstiel[4] by the substitution of oxygen for air and has been applied to various sugars by Hudson and co-workers[4a] and to D-galactose by Isbell.[5] Isolation of the D-lyxono-γ-lactone from the reaction mixture is difficult and uncertain. We find that the acid can be separated as the crystalline D-lyxonic acid hydrazide rather easily. The hydrazide group can then be readily removed by nitrous anhydride in dilute hydrochloric acid to produce the lactone. These procedures make D-lyxono-γ-lactone a readily available substance. The lactone can also serve as a source of D-lyxose[6] obtainable by the sodium amalgam reduction of the lactone. The generality of the procedure was established by the successful conversion to the lactone in good yield, of the hydrazides of D-galactonic acid and of D-gluco-D-*gulo*-heptonic acid. The latter compound is herein described for the first time.

The mechanism of the hydrazide decomposition is not entirely clear. Curtius found that treatment of benzoyl hydrazide with nitrous acid produced benzoyl azide[7] which he decomposed with sodium ethoxide to produce ethyl benzoate and sodium azide.[8] He also found that azides of certain α-hydroxy organic acids[9] decompose to form an aldehyde having one less carbon atom. In an unsuccessful attempt to apply the latter reaction in the sugar series by employing D-gluconic acid hydrazide and nitrous acid, Weerman[10] recorded the formation of di-D-gluconyl hydrazine but obtained D-gluconamide when he treated the hydrazide with ethyl nitrite in glacial acetic acid.

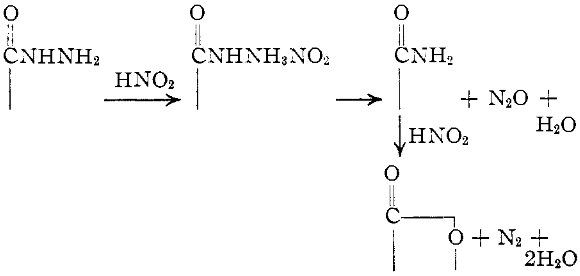
The reaction between hydrazine and nitrous acid is complex. Sommer and Pincas[11] have summarized the earlier investigations, have established the following reactions, and have shown that II and III are favored by acidity.

$$NH_2{-}NH_2 + HNO_2 \longrightarrow NH_3 + H_2O + H_2O \quad (I)$$

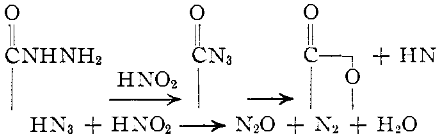
$$NH_2{-}NH_2 + HNO_2 \longrightarrow HN_3 + 2H_2O \quad (II)$$

$$HN_3 + HNO_2 \longrightarrow N_2 + N_2O + H_2O \quad (III)$$

By analogy with the reactions of nitrous acid upon hydrazine, one may postulate two mechanisms for the action of nitrous acid upon an organic acid hydrazide. The first postulated mechanism would be as follows.



This mechanism would explain the isolation by Weerman[10] of D-gluconamide from D-gluconic acid hydrazide. The second mechanism, which would probably be favored by acid conditions, was proposed, but not demonstrated, by Weerman.[10]



Which of the above two mechanisms is operative under our conditions, cannot be presently defined although the high acidity employed would probably favor the second mechanism.

Experimental

D-Lyxonic Acid Hydrazide.—Following the general procedure of Spengler and Pfannenstiel,[4] a stream of oxygen was passed through a porous tip into a solution of 250 g. of potassium hydroxide in 2.2 liters of water under violent mechanical agitation. The flask was placed in a water-bath and the temperature of the solution kept at 50° throughout the reaction. A solution of 260 g. of D-galac-

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[1] Research Foundation Associate of the Graduate School.

[2] T. W. J. van Marle, *Rec. trav. chim.*, **39**, 549 (1920).

[3] J. U. Nef, *Ann.*, **403**, 220, 244 (1914).

[4] O. Spengler and A. Pfannenstiel, *Z. Wirtschaftsgruppe Zucker-ind.*, **85**, T 546 (1935).

[4a] N. K. Richtmyer, R. M. Hann and C. S. Hudson, THIS JOURNAL, **61**, 340, 343 (1939); N. K. Richtmyer and C. S. Hudson, *ibid.*, **64**, 1609 (1942).

[5] H. S. Isbell, *J. Research Natl. Bur. Standards*, **29**, 227 (1942).

[6] E. Fischer and O. Bromberg, *Ber.*, **29**, 581 (1896).

[7] T. Curtius, *ibid.*, **23**, 3023 (1890).

[8] T. Curtius, *ibid.*, **24**, 3341 (1891).

[9] T. Curtius and C. Müller, *ibid.*, **34**, 2794 (1901).

[10] R. A. Weerman, *Rec. trav. chim.*, **37**, 52 (1918).

[11] F. Sommer and H. Pincas, *Ber.*, **49**, 259 (1916).

tose in 400 cc. of water was dropped slowly into the alkaline solution over a period of three hours. During the addition of the last half of the sugar solution, 150 g. of potassium hydroxide in 150 cc. of water was added in portions. The flow of oxygen was maintained for ninety minutes after the addition of the sugar. The solution was then made strongly acid with concentrated hydrochloric acid (600 cc., d. 1.18) and evaporated under reduced pressure until a heavy precipitate of potassium chloride began to form. One liter of absolute ethanol was added and the potassium chloride removed by filtration. The solution was concentrated again to a sirup. The precipitation of potassium chloride with ethanol was repeated with subsequent filtration and concentration until no more salt separated. The resulting sirup was dissolved in 300 cc. of hot water and treated with decolorizing carbon. The solution, when concentrated under reduced pressure, produced an almost water-white sirup. This sirup was dissolved in 500 cc. of ethanol and the solution was poured slowly with stirring into 100 cc. of hydrazine hydrate.[12] The hydrazide crystallized immediately and, after cooling to obtain maximum crystallization, was removed by filtration. Recrystallization was effected from water by the addition of ethanol; yield 110 g., m. p. 175–177°. After two recrystallizations from water, pure material was obtained; m. p. 186–187°, $[\alpha]^{24}\mathrm{D} -5.4°$ (c 1.8, water). van Marle[2] cites the following values for D-lyxonic acid hydrazide: m. p. 188°, $[\alpha]^{14}\mathrm{D} -3.6°$ (water).

D-Gluco-D-*gulo*-heptonic Acid Hydrazide.—D-Gluco-D-*gulo*-heptono-γ-lactone (15 g.) was dissolved in 20 cc. of hot water and 100 cc. of hot ethanol and the solution was poured slowly into 15 cc. of hydrazine hydrate dissolved in 25 cc. of ethanol. The hydrazide crystallized immediately; yield 14 g., m. p. 155–156°, $[\alpha]^{23}\mathrm{D} +6.6°$ (c 4.0, water). Two recrystallizations from water–ethanol did not alter these constants.

Anal. Calcd. for $C_7H_{16}O_7N_2$: C, 35.00; H, 6.71; N, 11.66. Found: C, 34.77; H, 6.45; N, 11.33.

D-Lyxono-γ-lactone.—D-Lyxonic acid hydrazide (100 g.) was dissolved in 250 cc. of water and 40 cc. of hydrochloric acid (d. 1.18). Into this solution, held at 15–20°, was bubbled oxides of nitrogen (essentially nitrous anhydride) generated by the action of concentrated sulfuric acid upon solid sodium nitrite. The reaction appeared to start very slowly but after two hours it had gained considerable momentum. At the peak of the reaction the evolution of gas from the solution was quite vigorous but could be controlled by the rate of flow of the nitrous anhydride. The reaction was complete when the vigorous evolution of gas from the solution had ceased. The solution was then made alkaline, while maintaining the temperature at 15–20°, by the addition of 50% potassium hydroxide solution, and was then concentrated under reduced pressure to a sirup. To this material was added 150 cc. of absolute ethanol and then concentrated hydrochloric acid (d. 1.18) until strongly acid. Under these conditions most of the potassium ion was precipitated as potassium chloride, leaving the D-lyxonic acid in ethanol solution. The latter was concentrated to a sirup, redissolved in ethanol and filtered from the remainder of the salt. Upon concentration under reduced pressure, a slightly colored sirup resulted. The color was removed by dissolving the sirup in 150 cc. of boiling water and treating with decolorizing carbon. The water-white solution was concentrated to a sirup. The remaining water was removed by repeatedly dissolving in absolute ethanol and concentrating under reduced pressure. The resulting thin sirup was nucleated and placed in the ice-box to crystallize; yield, including quantities obtained from the mother liquors, 66 g. (80.7%), m. p. 105°, $[\alpha]^{24}\mathrm{D} +77.0°$ (c 4.6, water). After recrystallization from absolute ethanol the pure material yielded the constants: m. p. 110–112°, $[\alpha]^{24}\mathrm{D} +82.5°$ (c 4.0, water). Isbell[5] reports for this compound the constants: m. p. 114°, $[\alpha]^{20}\mathrm{D} +82.7°$.

D-Gluco-D-*gulo*-heptono-γ-lactone and D-Galactono-γ-lactone.—D-Gluco-D-*gulo*-heptonic acid hydrazide and D-galactonic acid hydrazide[2] were treated with nitrous anhydride as described above. The constants for D-galactonic acid hydrazide were found to be: m. p. 176°, $[\alpha]^{23}\mathrm{D} +45.7°$ (c 1.2, water). van Marle[2] cites the constants: m. p. 178°, $[\alpha]^{13}\mathrm{D} +40.1°$ (water). The yield of D-galactono-γ-lactone was 82%; m. p. 132–134°, $[\alpha]^{23}\mathrm{D} -76.2°$ (c 4.1, water). After one recrystallization from water–ethanol, the constants were: m. p. 134–135°, $[\alpha]^{25}\mathrm{D} -77.5°$ (c 4.2, water), which are in good agreement with accepted values. The yield of D-gluco-D-*gulo*-heptono-γ-lactone was 65%; m. p. 145–147°, $[\alpha]^{23}\mathrm{D} -51°$ (c 4.5, water). After one recrystallization from water–ethanol, pure material was obtained; m. p. 149–151°, $[\alpha]^{23}\mathrm{D} -51.8°$ (c 4.3, water), which are in good agreement with the accepted values for this compound.

Acknowledgment.—We are pleased to acknowledge the advice in this work of Professor M. S. Newman of this department. One of us (A. T.) acknowledges a stipend from the funds of The Ohio State University Research Foundation administered by the Graduate School.

Summary

1. A method is given for the isolation of aldonic acid lactones through their hydrazides, from which the lactones are regenerated with nitrous anhydride. Application has been made to the D-lyxonic, D-galactonic and D-gluco-D-*gulo*-heptonic acid structures.

2. Details are reported for the ready conversion of D-galactose to D-lyxono-γ-lactone.

3. D-Gluco-D-*gulo*-heptonic acid hydrazide is reported.

COLUMBUS, OHIO

RECEIVED MAY 1, 1946

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[12] *Caution.* Hydrazine hydrate is very poisonous. All operations including filtrations, should be performed in the hood.