2-Deoxy Sugars. IX. 2,6-Dideoxy-D-*arabino*-hexose[1]

W. WERNER ZORBACH AND JOSEPH P. CIAUDELLI[2]

Department of Chemistry, Georgetown University, Washington, D. C.

Received September 24, 1964

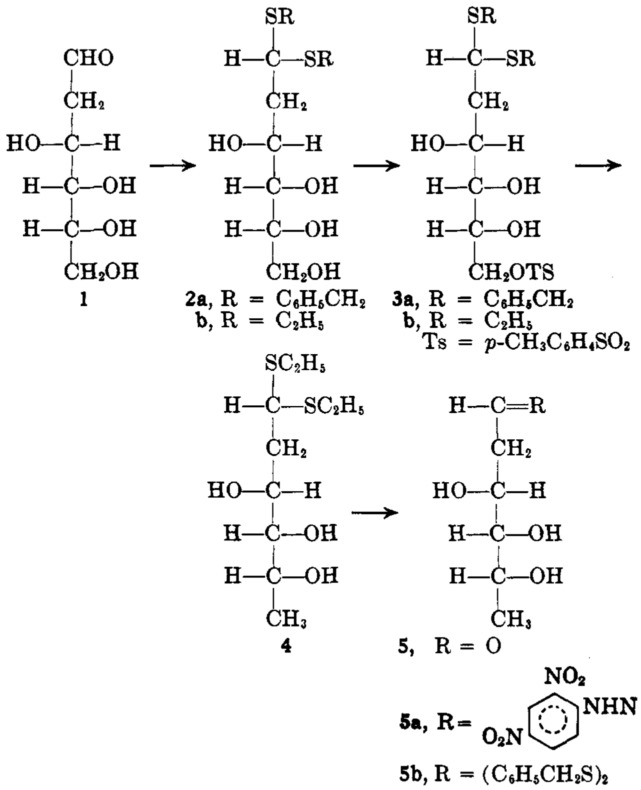
2,6-Dideoxy-D-*arabino*-hexose (**5**) recently has been isolated as the carbohydrate component of a cardenolide obtained from *Digitalis canariensis*. It was synthesized from 2-deoxy-D-glucose (2-deoxy-D-*arabino*-hexose, **1**) in four steps by converting **1** to its diethyl dithioacetal (**2b**) which was tosylated to give crystalline 2-deoxy-6-*O*-*p*-tolylsulfonyl-D-*arabino*-hexose diethyl dithioacetal (**3b**). Reduction of **3b** with lithium aluminum hydride gave crystalline 2,6-dideoxy-D-*arabino*-hexose diethyl dithioacetal (**4**) which was demercaptalated, affording crystalline 2,6-dideoxy-D-*arabino*-hexose (**5**). The sugar **5** was further characterized by its conversion to a crystalline 2,4-dinitrophenylhydrazone **5a** and a crystalline dibenzyl dithioacetal **5b**.

As a continuation of our studies designed to relate the effects of subtle changes in the carbohydrate component of a cardenolide on its cardiotonic activity, we undertook the preparation of 2,6-dideoxy-D-*arabino*-hexose (2,6-dideoxy-D-glucose, **5**), the C-3 epimer of the naturally occurring digitoxose (2,6-dideoxy-D-*ribo*-hexose). Digitoxose occurs as the carbohydrate component of evatromonoside [β-digitoxoside of digitoxigenin (3β,14β-dihydroxy-5β-card-20(22)-enolide)][3] and of helveticoside [β-digitoxoside of strophanthidin (3β,5β,14β-trihydroxy-19-oxocard-20(22)-enolide)].[4] The preparation of digitoxigenin and strophanthidin cardenolides containing 2,6-dideoxy-D-*arabino*-hexose (**5**) would therefore provide two additional pairs of cardenolides in which the sole difference in structure would be the reversal of configuration about C-3 of the carbohydrate component.[5]

During the course of our work on the synthesis of **5**, Meyer and co-workers reported[6] the natural occurrence of the sugar on its isolation as the carbohydrate component of a cardenolide containing xysmalogenin (3β,14β-dihydroxy-5(6),20(22)-cardadienolide from *Digitalis canariensis*, a species of foxglove which grows in the Canary Islands. The new sugar **5** was named "canarose." Its reported discovery provided an additional stimulus to our effort to synthesize it.

In 1944, Iselin and Reichstein reported[7] the synthesis of the enantiomeric form of **5**; this had been accomplished starting with the readily available L-rhamnose (6-deoxy-L-mannose) and proceeded *via* "6-deoxy-L-*arabino*-hexopyranos-1-ene." The principal obstacle in synthesizing the D-enantiomer **5** by this method is that there is no known, naturally occurring source for D-rhamnose (6-deoxy-D-mannose). Taking precedence from our previously published[8] synthesis of D-rhamnose, we investigated a procedure starting with 2-deoxy-D-*arabino*-hexose (2-deoxy-D-glucose, **1**)[9] and utilizing dithioacetal derivatives (see Chart I).

CHART I



Considering that, as a final step, demercaptalation usually can be accomplished most readily with a dibenzyl dithioacetal derivative, we converted 2-deoxy-D-glucose (**1**) to the known 2-deoxy-D-*arabino*-hexose dibenzyl dithioacetal (**2a**).[10] Tosylation of **2a** under the usual conditions gave a sirup, presumably **3a**. When treated with lithium aluminum hydride, the product underwent gross decomposition; consequently, this route was abandoned.

Substituting ethanethiol for toluenethiol we were able to convert **1** to its previously described[11] diethyl dithioacetal derivative **2b** and, when tosylated under the usual conditions, **2b** yielded crystalline 2-deoxy-6-*O*-*p*-tolylsulfonyl-D-*arabino*-hexose diethyl dithioacetal (**3b**), which was unstable at room temperature. Reduction of **3b** with lithium aluminum hydride gave crystal-

---

[1] This work was supported in part by U. S. Public Health Service Grants HE 05839 and AM 02764.

[2] Support by a U. S. Public Health Service Predoctoral Fellowship, No. GM-16083, is gratefully acknowledged. This work is taken from a dissertation submitted to the Graduate School of Georgetown University by J. P. Ciaudelli in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, Aug. 1964.

[3] R. Tschesche, S. Wirtz, and G. Snatzke, *Chem. Ber.*, **88**, 1619 (1955). See also F. Kaiser, E. Haack, and H. Spingler, *Ann. Chem.*, **603**, 75 (1957); W. W. Zorbach, N. Henderson, and S. Saeki, *J. Org. Chem.*, **29**, 2016 (1964).

[4] W. Nagata, Ch. Tamm, and T. Reichstein, *Helv. Chim. Acta*, **40**, 41 (1957).

[5] The 2-deoxy-β-D-*ribo*-hexopyranoside of digitoxigenin [W. W. Zorbach and W. Bühler, *Ann. Chem.*, **670**, 116 (1963)] and the corresponding 2-deoxy-β-D-*arabino*-hexopyranoside [W. W. Zorbach and G. Pietsch, *ibid.*, **655**, 26 (1962)] constitute the first known pair of cardenolides having this structural relationship.

[6] P. Studer, S. K. Pavanaram, G. R. Gavilanes, H. Linde, and K. Meyer, *Helv. Chim. Acta*, **46**, 23 (1963).

[7] B. Iselin and T. Reichstein, *ibid.*, **27**, 1146 (1944).

[8] W. W. Zorbach and C. O. Tio, *J. Org. Chem.*, **26**, 3543 (1961).

[9] The authors are grateful to Cancer Chemotherapy National Service Center for a gift of this sugar.

[10] W. G. Overend, M. Stacey, and J. Stanek, *J. Chem. Soc.*, 2841 (1949).

[11] H. R. Bolliger, *Helv. Chim. Acta*, **34**, 889 (1951).

line 2,6-dideoxy-D-*arabino*-hexose diethyl dithioacetal (**4b**) in 30% yield. Demercaptalation of **4b** afforded the desired hexose **5** as sirupy material which was homogeneous as disclosed by paper chromatograms and had an R_f value very close to that of digitoxose (2,6-dideoxy-D-*ribo*-hexose).

The 2,6-dideoxy-D-*arabino*-hexose (**5**) thus obtained could not be crystallized from solution, but, when set aside in a desiccator for 5 months, the entire sirupy mass of **5** gradually became crystalline. Equally difficult was the securing of a crystalline derivative of **5**. After repeated experiments with a wide variety of carbonyl reagents, we were able to obtain ultimately a crystalline 2,4-dinitrophenylhydrazone **5a** and a dibenzyl dithioacetal **5b**.

Experimental

All melting points were determined using a Kofler hot stage. Paper chromatography was carried out by spotting 50 μg. of the material on Whatman No. 1 paper and developing by an ascending technique employing 1-butanol–toluene (9:1) saturated with water. After developing, the paper was sprayed with a boric acid reagent as described[12] by Pöhm and Weiser. The spots were developed by heating the paper in an oven at 95° for 5 min.

2-Deoxy-6-*O*-*p*-tolylsulfonyl-D-*arabino*-hexose Diethyl Dithioacetal (3b).—A solution of 6.2 g. (0.033 mole) of *p*-toluenesulfonyl chloride in 30 ml. of dry pyridine was added dropwise over a period of 2 hr. to an ice-cold, stirred solution of 7.3 g. (0.027 mole) of 2-deoxy-D-glucose diethyl dithioacetal (**2b**)[11] in 30 ml. of dry pyridine. Without allowing the temperature to rise, stirring was continued for 30 min. and the mixture was allowed to stand for an additional 3 hr. After storing in a refrigerator for 3 days, the solution was added dropwise with stirring over a period of 90 min. to 1.5 l. of water maintained at 0°. The product was extracted with dichloromethane and washed with water; the extract was evaporated *in vacuo* at 35°, giving 8.5 g. (74%) of sirupy material. The latter was crystallized from benzene–cyclohexane followed by recrystallization from methanol–water, giving the tosyl ester **3b**[13] which melted at 81–85°.

Anal. Calcd. for $C_{17}H_{28}O_6S_3$: C, 48.09; H, 6.65; S, 22.65. Found: C, 48.35; H, 6.85; S, 23.05.

2,6-Dideoxy-D-*arabino*-hexose Diethyl Dithioacetal (4).—A mixture of 8.5 g. (0.02 mole) of sirupy **3b** and 4.0 g. of lithium aluminum hydride in 500 ml. of anhydrous ether was refluxed for 48 hr. The excess lithium aluminum hydride was destroyed by the careful addition of water and the mixture was then neutralized to pH 7.0 with 5 *N* hydrochloric acid. The mixture was filtered and the residue was washed with hot ethyl acetate. The combined filtrate and washings were evaporated *in vacuo* at 40° and the resulting residue was dissolved in methanol and treated with 5 g. of Rexyn 300 (H–OH) ion-exchange resin (Fisher Scientific Co.). After the residue was filtered and washed with methanol, the filtrate was evaporated *in vacuo* at 40° giving a solid residue which, after two recrystallizations from ether–pentane, yielded 1.56 g. (31%) of pure 2,6-dideoxy-D-*arabino*-hexose diethyl dithioacetal (**4**), m.p. 83–84°, $[\alpha]^{23}\mathrm{D}$ +11.8° (*c* 1.00, $CHCl_3$), +10.1° (*c* 1.00, CH_2Cl_2).

Anal. Calcd. for $C_{10}H_{22}O_3S_2$: C, 47.21; H, 8.72; S, 25.20. Found: C, 47.07; H, 8.73; S, 24.07.

2,6-Dideoxy-D-*arabino*-hexose ("Canarose," 5).—To a stirred, boiling solution of 25 ml. of acetone–water (2:1) were added 0.50 g. (1.96 mmoles) of the dithioacetal **4**, 2.14 g. of yellow mercuric oxide, and 2.67 g. of mercuric chloride. After refluxing for 3 hr., the mixture was cooled and filtered with the aid of Celite 545. To the filtrate was added 5 ml. of pyridine and the mixture was set aside in a refrigerator overnight. The pyridine–mercuric chloride complex was removed by filtration, and gaseous hydrogen sulfide was passed into the filtrate until precipitation of the mercuric sulfide was complete. After boiling to remove the excess hydrogen sulfide, the mixture was filtered with the aid of Darco G-60 The filtrate thus obtained was purified further by stirring with a small amount of Rexyn 300 (H–OH) ion-exchange resin and, after filtering, the clear solution was concentrated *in vacuo* at 40° to a clear sirup. Paper chromatography of the sirup revealed one spot, having R_f 0.49 (in the same system, digitoxose has R_f 0.50). The sirup was redissolved in absolute ethanol and was evaporated again *in vacuo* at 35°. The remaining solvent was removed at a pressure of 0.1 mm. The weight of the sirup thus obtained was 155 mg. (53%) and had $[\alpha]^{24}\mathrm{D}$ +53.5° (*c* 2.36, acetone) (Meyer and co-workers reported[6] $[\alpha]^{23}\mathrm{D}$ +57.7°).

The sirup was crystallized according to a method described[7] by Iselin and Reichstein for the L-enantiomeric form of **5**; after adding a few drops of acetone, the material was stored in a vacuum desiccator over phosphorus pentoxide for 2 weeks. Then, on alternate days for a period of 2 weeks the sirup was triturated with 2 drops of methyl ethyl ketone. Crystallization began about 1 month later and, after standing in the desiccator for an additional 3 months, the entire mass became crystalline. The crystals, which were extremely hygroscopic, melted at 76–89°. When recrystallized from acetone–ether, the melting point was raised to 86–98° (Meyer and co-workers reported[6] m.p. 100–103° and Iselin and Reichstein reported[7] m.p. 93–94° for 2,6-dideoxy-L-*arabino*-hexose). Our crystalline **5** had $[\alpha]^{23}\mathrm{D}$ +25.5° (*c* 2.61, water) after 80 min. and $[\alpha]^{24}\mathrm{D}$ +95.9° (*c* 1.21, acetone). Meyer and co-workers reported[6] $[\alpha]^{23}\mathrm{D}$ +19.6° (water) and $[\alpha]^{23}\mathrm{D}$ +110° (acetone). Iselin and Reichstein reported[7] for the L-enantiomer $[\alpha]^{14}\mathrm{D}$ −18.2° (water) and $[\alpha]^{17}\mathrm{D}$ −103.6° (acetone).

2,6-Dideoxy-D-*arabino*-hexose 2,4-Dinitrophenylhydrazone (5a).—To 200 mg. of 2,4-dinitrophenylhydrazine dissolved in 20 ml. of warm ethanol containing 0.4 ml. of acetic acid was added 166 mg. of sirupy **5** dissolved in 5 ml. of ethanol. The solution was refluxed for 90 min. and was then allowed to stand at room temperature. After evaporating the solution *in vacuo* at 35°, the sirupy residue was dissolved in 2 ml. of ethanol and was then treated with 4 ml. of ether. *n*-Pentane was added to incipient turbidity whereupon the derivative began to crystallize. The melting point of the crude product was 123–126.5° and, when recrystallized twice using the same combination of solvents, the pure 2,4-dinitrophenylhydrazone **5a** was obtained, having m.p. 132–132.5°.

Anal. Calcd. for $C_{12}H_{16}N_4O_7$: C, 43.90; H, 4.91; N, 17.07. Found: C, 44.05; H, 5.07; N, 17.05.

2,6-Dideoxy-D-*arabino*-hexose Dibenzyl Dithioacetal (5b).—To 313 mg. (2.1 mmoles) of sirupy **5** at 0° were added 0.4 ml. of toluenethiol and 1.0 ml. of concentrated hydrochloric acid with stirring. After stirring for 3 hr. at 0°, some crushed ice was added and the stirring was continued for an additional 30 min. The product was extracted with 20 ml. of chloroform and the extract was washed four times with water. After drying over magnesium sulfate, the solution was filtered and the filtrate was evaporated *in vacuo* at 35°. The resulting sirup was dissolved in 5 ml. of ethanol, treated with Darco G-60, and filtered. The ethanolic solution was concentrated to 2 ml. and was poured into 150 ml. of water heated to 95°, whereupon the dibenzyl dithioacetal **5b** was obtained as crystalline material, m.p. 88–91°.

Anal. Calcd. for $C_{20}H_{26}O_3S_2$: C, 63.46; H, 6.92; S, 16.94. Found: C, 63.52; H, 6.70; S, 16.64.

Acknowledgment.—For the elemental analyses, the authors are indebted to Miss Paula M. Parisius, Microanalytical Laboratory, Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, under the direction of Dr. W. C. Alford.

---

(12) M. Pöhm and R. Weiser, *Naturwissenschaften*, **24**, 582 (1956).

(13) Because of its instability at room temperature, the optical rotation of **3b** was not determined. Crystallization of **3b** appeared to be weather-dependent and on days of high humidity all attempts to secure crystalline material failed. Because of these properties, the subsequently described lithium aluminum hydride reduction was carried out without delay on the sirupy material obtained.