Carbohydrate Research, 193 (1989) 303–306
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Facile preparation of 6-deoxy-L-*arabino*-hexulose by isomerization of L-rhamnose in boiling pyridine

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(Received December 14th, 1988; accepted for publication, May 1st, 1989)

The advent of chiral h.p.l.c. columns has created a need for reference samples of aldoses and ketoses belonging to both the D and L series. For example, in the course of our work on the isomerization of monosaccharides[1], a sample of 6-deoxy-L-*arabino*-hexulose (6-deoxy-L-fructose) was needed. Customarily, to prepare such a sugar one would select a chemical method that was successfully used for the preparation of one isomer and apply it to an enantiomeric precursor. A review of the literature[2–9] revealed that several enzymatic methods and two chemical ones[2,6] are available for the preparation of 6-deoxy-D-*arabino*-hexulose. However, the chemical methods require starting materials that are not available in the L form, namely 2,3-*O*-isopropylidene-D-fructofuranose[2] and 6,6′-dichloro-6,6′-dideoxysucrose[5], so we were led to explore the epimerization of commercially available L-rhamnose.

It has been reported[10] that a solution of L-rhamnose undergoing isomerization at room temperature for five days in saturated calcium hydroxide affords only 6-deoxy-L-*arabino*-hexulose (25%, estimated by paper chromatography). On repeating the isomerization using h.p.l.c. to estimate the products, it was found that after one day the solution contained about 8% of 6-deoxy-L-*arabino*-hexulose and 3% of other 6-deoxy ketoses. The composition of the mixture had not changed significantly after five days.

Isomerization mediated by pyridine was examined next. As a tertiary amine, this base does not promote aldol reactions[11] and it can easily be removed by distillation. Also, isomerization of aldoses with boiling pyridine is much faster than that catalyzed by aqueous potassium or calcium hydroxide at room temperature. The lower temperatures in the latter cases are required to minimize fragmentation and the formation of saccharinic acids. These side-reactions consume large amounts of the ketoses formed during the isomerization of aldoses with aqueous alkali. Isomerization with pyridine has therefore been recommended for the production of ketoses from aldoses[12]. For example, Reichstein[13] obtained 6-deoxy-L-*lyxo*-

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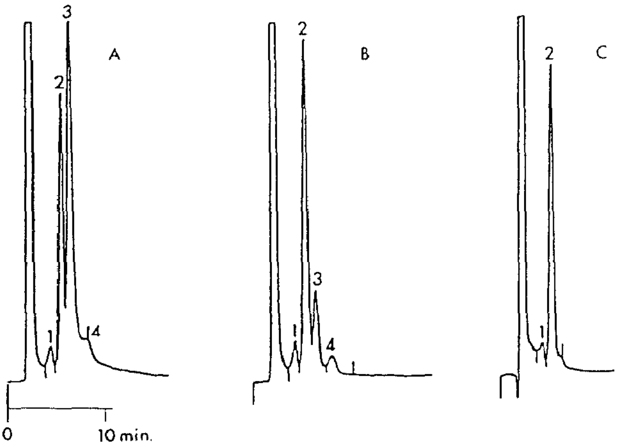

Fig. 1. High performance liquid chromatograms of the products from L-rhamnose refluxed 5 h in pyridine. (A) After removal of the pyridine; (B) after removal of unreacted L-rhamnose by filtration; (C) after oxidation of the filtrate with bromine–water and deionization. Peaks: 1, contaminant; 2, 6-deoxy-L-*arabino*-hexulose; 3, L-rhamnose; 4, L-quinovose.

hexulose (6-deoxy-L-tagatose) in 33–36% yield by isomerizing L-fucose in boiling pyridine.

To optimize the reaction time, L-rhamnose was refluxed in dry pyridine and the solution periodically analyzed by h.p.l.c. As expected, the concentration of the starting sugar gradually decreased, while that of 6-deoxy-L-*arabino*-hexulose increased. After 5 h the reaction mixture contained (see Fig. 1A): L-rhamnose (58%), L-quinovose (5%), 6-deoxy-L-fructose (34%), and a minor contaminant (3%), presumably the isomeric 6-deoxy-L-*ribo*-hexulose. After 24 h, the amounts of the last two products rose to 52% and 8%, respectively. Since these were difficult to separate, it was advantageous to terminate the reaction after 5 h. After evaporation of the pyridine, most of the unchanged rhamnose crystallized in a form pure enough to be recycled. The small amounts of L-rhamnose and L-quinovose remaining in solution (see Fig. 1B) were then removed by oxidation with bromine–water and absorption of the resulting aldonic acids on an ion-exchange resin. H.p.l.c. analysis of the deionized solution showed (see Fig. 1C) only two peaks, a major one corresponding to the desired product, 6-deoxy-L-*arabino*-hexulose (95–97%), and a minor one corresponding to the contaminant (3–5%). The overall yield of 6-deoxy-L-*arabino*-hexulose based on the L-rhamnose consumed was 60–65%.

The method described here is suitable for the preparation of 2–3 g batches of 95–97% pure 6-deoxy-L-*arabino*-hexulose, starting from about 5 g of L-rhamnose (in work on a larger scale the crystallization of the unreacted sugar becomes sluggish).

EXPERIMENTAL

Melting points were determined with a Kofler block and are corrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter, at $c = 1$, in water. Microanalyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, Michigan. High performance liquid chromatography was carried out with a Waters carbohydrate analysis column, a Rheodyne 7125 injector (20 μL loop), a Waters 501 pump, a Waters 410 differential refractometer, and a Hewlett–Packard 3392A integrator. Elution with 95:5 (v/v) acetonitrile–water achieved a satisfactory separation (L-quinovose, 7.9 min; L-rhamnose, 6.2 min; 6-deoxy-L-fructose, 5.2 min; contaminant, 4.1 min).

6-Deoxy-L-arabino-*hexulose*. — A solution of L-rhamnose monohydrate (4.5 g) in anhydrous pyridine (30 mL) was refluxed for 5 h. Pyridine was removed by concentration, then coevaporation (2×) with ethanol (complete removal is not necessary for crystallization of the unchanged rhamnose). The residue was triturated with acetone and seeded with crystals of L-rhamnose. After 1–2 h, more acetone (5 mL) was added and the mixture was left overnight at 0°. The crystals of L-rhamnose (2.6 g) formed were collected by filtration and washed with acetone (10 mL). The filtrate and the washings were concentrated, and a solution of the residue (1.9 g) in water (15 mL) was stirred with excess barium carbonate[14]. Bromine (about 0.5 mL) was added dropwise in the course of 1–2 h until a faint yellow color persisted. The solution was kept overnight in the dark, and then aerated to remove excess bromine, filtered, and passed successively through columns packed with Amberlite IRA-400 and Rexyn I-300 (mixed H^+–OH^-). After evaporation, the yield of colorless syrup composed of 95–97% pure 6-deoxy-L-fructose was 1.2 g (63% based on the L-rhamnose consumed).

6-Deoxy-D-arabino-*hexulose 2-nitrophenylhydrazone*. — A solution of 6-deoxy-L-fructose (100 mg) in water (1 mL) was treated with a solution of 2-nitrophenylhydrazine (100 mg) in hot ethanol (2 mL) and the mixture was refluxed for 10 minutes. After seeding, the 6-deoxy-L-fructose 2-nitrophenylhydrazone separated out as orange yellow crystals, m.p. 132–134°. Recrystallization from an absolute ethanol–ether mixture gave yellow needles, m.p. 135–137°, $[\alpha]_D^{20}$ −39° (lit.[2] for the D isomer, m.p. 136–137°; $[\alpha]_D^{20}$ +40°).

Anal. Calc. for $C_{12}H_{17}N_3O_6$: C, 48.16; H, 5.73; N, 14.04. Found: C, 48.19; H, 5.62; N, 14.19.

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