THE SYNTHESIS OF ω-DEOXY-ω-S-ETHYL-POLYOLS¹

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ABSTRACT

Treatment of an aldose diethyl thioacetal with a limited amount of aged Raney nickel catalyst resulted in the reductive cleavage of one thioethyl group. 1-Deoxy-1-S-ethyl derivatives of D-galactitol, L-rabitol, L-rhamnitol, and D-glucitol have thus been synthesized and their structures proved. 1-Deoxy-1-S-ethyl-L-galactitol has been prepared by the borohydride reduction of 6-deoxy-6-S-ethyl-D-galactose.

INTRODUCTION

Reductive desulphurization of aldose thioacetals (1, 2, 3, 4, 5, 6) and aldose thioacetal acetates (1, 7) using an excess of Raney nickel catalyst provides a simple method of preparing 1-deoxy sugar alcohols. In a review, Fletcher and Richtmyer (8) questioned the value of using as high catalyst ratios as have been reported in the literature. They tabulate examples of ratios from 9:1 to 15:1 (grams of Raney nickel catalyst to grams of thioacetal derivative). Generally, the yield of 1-deoxy-polyol or 1-deoxy-polyol acetate varied inversely with the catalyst ratio. The decrease in yield was probably due to adsorption of product on the catalyst. We found that when a catalyst with a low hydrogen content (e.g. W-2 catalyst) was used, and a low catalyst ratio was chosen (ca. 5:1), a mixture of three compounds resulted. When D-galactose diethyl thioacetal was thus treated, paper chromatographic examination of the product indicated the presence of a fast-moving compound, p-galactose diethyl thioacetal; a slow-moving compound, 1-deoxy-p-galactitol (L-fucitol); and a second sulphur-containing compound (II) which was between these two compounds on the chromatogram. A catalyst ratio was determined, by means of trial experiments in which compound II was the main product of the reaction. In this reaction one thioethyl group of the aldose diethyl thioacetal (I) was replaced by a hydrogen atom to give the monothioethyl derivative (II). Compound II on reductive desulphurization gave 1-deoxy-D-galactitol (L-fucitol) (III).



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The diethyl thioacetals of D-galactose, L-arabinose, D-glucose, and L-rhamnose were also partially desulphurized, and respectively yielded 1-deoxy-1-S-ethyl-(D-galactitol) (II), -(L-arabitol) (IV), -(D-glucitol) (V), and -(L-rhamnitol) (VI). Crystalline acetates of compounds II, IV, and V were also prepared. The yields were not appreciably reduced when large scale experiments were carried out. This result corresponded with the observations of Richtmyer and co-workers (2, 3, 4, 5, 6). Complete reductive desulphurization of compounds II, IV, V, and VI yielded the known ω -deoxy sugar alcohols, which are 1-deoxy-D-galactitol (L-fucitol), 1-deoxy-L-arabitol (L-lyxomethylitol), 1-deoxy-D-glucitol (L-gulomethylitol), and 1,6-dideoxy-L-mannitol respectively.

 ω -Deoxy- ω -S-alkyl polyols can also be synthesized by the reduction of the corresponding aldose (9). In this manner 6-deoxy-6-S-ethyl-D-galactose (6-deoxy-6-thioethyl-D-galactose) (10) was reduced with potassium borohydride to 1-deoxy-1-S-ethyl-L-galactitol (6-deoxy-6-S-ethyl-D-galactitol). This compound had about the same melting point and magnitude of optical rotation (but in the opposite direction) as the D-isomer. The D- and L-isomers had identical rates of movement on paper chromatograms. The racemate melted at about 10° C. lower than the isomers.

EXPERIMENTAL

Solutions were concentrated under reduced pressure (ca. 15 mm.) at a bath temperature of 50° C. or less. Melting points were uncorrected and optical rotations were determined in water unless otherwise stated. Paper chromatography was carried out by the descending method (11) on Whatman No. 1 filter paper using the following solvent systems (v: v): (a) ethyl acetate – acetic acid – water (9: 2: 2), (b) ethyl acetate – acetic acid – formic acid – water (18: 3: 1: 4), (c) *n*-butanol–ethanol–water (3: 1: 1), (d) *n*-butanol–pyridine– water (10: 3: 3). Non-reducing compounds were detected on paper chromatograms with a silver nitrate spray reagent (12). The rate of movement of the compound on paper chromatograms is quoted relative to that of the solvent front (R_f value) or relative to that of rhamnose (R_{Bh} value).

A standard method of preparing Raney nickel catalyst W-2 (13) was followed exactly. It was stored in ethanol at $0-5^{\circ}$ C. This catalyst will be referred to as catalyst (a) in these experiments. A catalyst of slightly lower hydrogen content was obtained from the Aldrich Chemical Company.* It was washed free from traces of alkali and was stored in ethanol at $0-5^{\circ}$ C. This catalyst will be referred to as catalyst (b). The activity of catalysts (a) and (b) did not change appreciably over a storage period of 4 months.

Preliminary Experiments

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Weighed samples (ca. 0.5 g.) of D-galactose diethyl thioacetal (14) were dissolved in 75% isopropanol (50 ml.). A range of catalyst ratios was chosen (ca. 3:1 to 8:1) and the appropriate volume of Raney nickel catalyst (a) was added to the flasks. The mixture was boiled under reflux for 2 hours and cooled. The solutions were filtered from the catalyst and examined by paper chromatography. The catalyst ratio that produced the maximum amount of component with a rate of movement between galactose diethyl thioacetal and fucitol was used in subsequent experiments. Catalyst ratios are expressed in liters of settled volume of nickel per mole of aldose thioacetal.

Preparation of 1-Deoxy-1-S-ethyl-D-galactitol

(i) D-Galactose diethyl thioacetal (3.73 g., 0.013 mole) and Raney nickel catalyst (a)

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(settled volume 30 ml. equivalent to 2.3 liters/mole) in 75% isopropanol (200 ml.) were shaken in a hydrogen atmosphere (pressure *ca.* 800 mm.) for 2 hours at 60° C. and then boiled under reflux on the water bath (100° C.) for an additional 3 hours. The filtered solution was concentrated to a crystalline mass, which was recrystallized from methanol and acetone (5:1) to give 1.24 g. (57.5%) of product melting at 151–153° C. (The catalyst was lost accidentally before it could be washed.) The rate of movement on a paper chromatogram ((*a*) $R_f 0.47$, $R_{Rh} 1.70$; (*b*) $R_f 0.52$, $R_{Rh} 1.29$) was intermediate between galactose diethyl thioacetal and fucitol, and the compound on treatment with silver nitrate spray reagent gave an intense spot which appeared immediately, whereas the spot due to fucitol appeared slowly. The product on recrystallization from methanol gave a chromatographically pure product that had m.p. 149–151° C. and $[\alpha]_D^{25°} - 9° \pm 2°$ (*c*, 0.95). Anal. Calc. for C₈H₁₈0₅S: C, 42.6; H, 8.1; S, 14.2. Found: C, 42.5; H, 8.1; S, 14.0.

(ii) Large scale experiment.—D-Galactosc diethyl thioacetal (11.0 g., 0.038 mole) and Raney nickel catalyst (a) (83.5 ml. settled volume equivalent to 2.2. liters/mole) in 75% isopropariol (1 liter) were boiled under reflux on the water bath (100° C.) for 3 hours. The solution was decanted from the catalyst, which was washed twice with ethanol and separated by centrifugation. The catalyst was digested with ethanol (3 times with 300 ml.) and then with water (2 times with 200 ml.), and the combined washings and decanted solution were filtered through a pad of Celite and evaporated to dryness. Recrystallization from methanol and acetone (5:1) gave 5.80 g. (67%) of product in three crops of crystals, m.p. 148–149° C. Duplicate readings gave $[\alpha]_{\rm D}^{21^\circ} - 8.2^\circ$ (c, 2.24); $[\alpha]_{\rm D}^{24^\circ} - 8.9^\circ$ (c, 2.33).

1-Deoxy-1-S-ethyl-D-galactitol Pentaacetate

1-Deoxy-1-S-ethyl-D-galactitol (88 mg.) in pyridine (1 ml.) was acetylated for 24 hours with acetic anhydride (1 ml.). The product crystallized when it was poured into a slurry of chipped ice and water, and it was collected by filtration. It was dissolved in hot methanol, and the solution was purified with a little charcoal and filtered through a pad of Celite. The filtrate was warmed and an equal volume of hot water was added. After cooling, the crystals in the form of flakes were collected by filtration and washed with cold water. Yield: 117 mg. (60%), m.p. 150.5–151.0° C. $[\alpha]_{2D}^{22}$ 8°±1° (c, 1.1, chloroform). Anal. Calc. for C₁₈H₂₄O₁₀S: C, 49.5; H, 6.5; S, 7.3. Found: C, 49.8; H, 6.7; S, 7.1.

Conversion of 1-Deoxy-1-S-ethyl-D-galactitol to L-Fucitol

1-Deoxy-1-S-ethyl-D-galactitol (120 mg.) was dissolved in 70% ethanol (10 ml.) containing Raney nickel W-2 catalyst (3 ml. settled volume) and the suspension was boiled under reflux on the water bath (100° C.) for 3 hours. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated to a crystalline mass. The product moved as a single spot on paper chromatograms developed in solvents (*a*), (*b*), (*c*), and (*d*) and had a rate of movement identical with that of L-fucitol prepared by the borohydride reduction of L-fucose. The following R_f and R_{Rh} values were obtained: $R_f 0.37$, $R_{Rh} 1.12$ (*a*); $R_f 0.39$, $R_{Rh} 1.07$ (*b*); $R_f 0.31$, $R_{Rh} 1.00$ (*c*); $R_f 0.30$, $R_{Rh} 0.93$ (*d*). Recrystallization from ethanol (3 ml.) gave 33.4 mg. (38%) of fine needles melting at 156.0–156.5° C. The mixed melting point with an authentic specimen was 156.0–156.5° C.

1-Deoxy-1-S-ethyl-L-arabitol

(i) L-Arabinose diethyl thioacetal (1.50 g., 0.008 mole) (15, 16) and freshly prepared Raney nickel catalyst (a) (settled volume 12 ml., 1.5 liters/mole) in 75% isopropanol (80 ml.) were boiled under reflux on the water bath (100° C.) for 3 hours. The cooled solution was decanted and the catalyst was washed with ethanol and separated by centrifugation. The catalyst was then digested with ethanol (2×100 ml.) and the combined

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washings and decanted solution were filtered through a pad of Celite and evaporated to dryness. The crystalline mass was examined by paper chromatography, which indicated the presence of two compounds. The main constituent had a rate of movement of R_f 0.61, R_{Rh} 1.79 (a) and the second component had a rate of movement of R_f 0.43, R_{Rh} 1.27 (a). The ratio of the two components was visually estimated to be 20:1. The crude product was dissolved in hot acetone (40 ml.), filtered, and chilled in the refrigerator. The crystals were collected by filtration and the mother liquors were concentrated to yield a second crop. Yield: 0.71 g. (68%), m.p. 118.5–119.5° C., $[\alpha]_{D}^{22^{\circ}} - 12^{\circ} \pm 1^{\circ}$ (c, 2.59). Anal. Calc. for $C_7H_{16}O_4S$: C, 42.8; H, 8.2; S, 16.3. Found: C, 43.1; H, 8.5; S, 16.1.

(ii) L-Arabinose diethyl thioacetal (19.0 g., 0.074 mole) and 75% isopropanol (3 liters) were stirred mechanically with aged Raney nickel catalyst of a low hydrogen content (settled volume 250 ml., 3.3 liters/mole) and boiled under reflux on the water bath (100° C.) for 3.5–4 hours. The cooled solution was decanted and the catalyst was treated in the manner described above. Examination of the product by paper chromatography revealed only a single spot (R_f 0.69, R_{Rh} 1.83 (a)). The product was recrystallized from acetone-ethanol (3:1) to give a total yield of 8.43 g. (58%) in four crops, m.p. 119–120° C., $[\alpha]_D^{26} - 12^\circ \pm 1^\circ$ (c, 1.75). Recrystallization from *iso*propanol gave fine needles, m.p. 118.5–119.5° C. When tested in high concentration, a trace of L-lyxomethylitol was revealed on the chromatogram and this impurity was removed by repeated recrystallizations from *iso*propanol, but the melting point remained unchanged (118.5–119.5° C.).

1-Deoxy-1-S-ethyl-L-arabitol Tetraacetate

The tetraacetate was prepared in the manner previously described for the acetylation of 1-deoxy-1-S-ethyl-D-galactitol. Recrystallization from ethanol and water (3:1) gave white plates (40%) melting at 58.0–58.5° C., $[\alpha]_{D}^{26^{\circ}} - 35^{\circ} \pm 1^{\circ}$ (c, 1.64, chloroform). Anal. Calc. for C₁₅H₂₄O₈S: C, 49.4; H, 6.6; S, 8.8. Found: C, 49.5; H, 6.5; S, 8.9.

1-Deoxy-L-arabitol (L-Lyxomethylitol)

1-Deoxy-L-arabitol (7) was prepared in 70% yield by the desulphurization of 1-deoxy-1-S-ethyl-L-arabitol in the same fashion as is described for the desulphurization of L-fucitol. The product (0.19 g.) was recrystallized from ethyl acetate (40 ml.), m.p. 128–129° C., $[\alpha]_{D}^{27^{\circ}} - 1.8^{\circ}$ (c. 1.70), (lit. m.p. 129–131° C., $[\alpha]_{D}^{30^{\circ}} - 1.46^{\circ}$ (water) (9)). 1-Deoxy-D-arabitol has a reported m.p. 129–131° C. and a $[\alpha]_{D}^{20^{\circ}} + 0.7^{\circ}$ (6).

1-Deoxy-1-S-ethyl-D-glucitol

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D-Glucose diethyl thioacetal (15) (5.0 g., 0.017 mole) in 75% isopropanol (600 ml.) was boiled under reflux with aged Raney nickel catalyst (b) (50 ml. settled volume, 2.9 liters/ mole) in exactly the same manner as is described for the preparation of 1-deoxy-1-Sethyl-D-galactitol in experiment (ii). The crude product, 1.94 g. (51%), contained a trace of 1-deoxy-D-glucitol (paper chromatography), and was recrystallized four times from isopropanol. The pure compound had a rate of movement on a paper chromatogram of $R_f 0.59$, $R_{Rh} 1.70$ (a); $R_f 0.61$, $R_{Rh} 1.53$ (b); $R_f 0.52$, $R_{Rh} 1.61$ (c); $R_f 0.53$, $R_{Rh} 1.48$ (d); a m.p. 107.5-108° C.; and $[\alpha]_D^{26^\circ} - 29^\circ \pm 1^\circ$ (c, 1.85). Anal. Calc. for $C_8H_{1s}O_5S$: C, 42.7; H, 8.1; S, 14.2. Found: C, 42.9; H, 8.2; S, 14.0.

When the experiment was repeated on a larger scale (D-glucose diethyl thioacetal, 23.6 g., Raney nickel catalyst (b), 215 ml. settled volume, and *iso*propanol, 3 liters) in the manner previously described for the preparation of 1-deoxy-1-S-ethyl-L-arabitol, part (ii), a yield of 9.87 g. (49%) of crude product was obtained. Repeated recrystallizations from *iso*propanol gave 6.9. g. (34%) of pure compound, m.p. 107.5–108° C., $[\alpha]_D^{24^\circ} - 30^\circ$ (c, 1.89).

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1-Deoxy-1-S-ethyl-D-glucitol Pentaacetate

The pentaacetate was prepared in the manner previously described and was crystallized from methanol and water (1:1) in a 59% yield, m.p. 82° C., $[\alpha]_{D}^{26^{\circ}} 5^{\circ} \pm 1^{\circ}$ (c, 1.1, chloroform). Anal. Calc. for C₁₈H₂₈O₁₀S: C, 49.5; H, 6.5; S, 7.4. Found: C, 49.7; H, 6.5; S, 7.4.

1-Deoxy-D-glucitol Pentaacetate

Reductive desulphurization of 1-deoxy-1-S-ethyl-D-glucitol in ethanol with an excess of Raney nickel catalyst (a) in the usual manner gave a non-crystalline product which appeared to be chromatographically pure (R_f 0.60, R_{Rh} 1.52 (a); R_f 0.28, R_{Rh} 0.95 (c); R_f 0.29, R_{Rh} 0.88 (d)). It was therefore acetylated and the pentaacetate was recrystallized from ethanol, m.p. 105.5–107° C., $[\alpha]_D^{26}$ 21°±1° (c, 1.26, methanol) (lit. m.p. 105–106° C., $[\alpha]_D^{21}$ 21° (methanol) (7, 17)).

1-Deoxy-1-S-ethyl-L-rhamnitol

L-Rhamnose diethyl thioacetal (15) (4.0 g., 0.015 mole) was dissolved in 75% isopropanol (600 ml.) and was boiled under reflux with Raney nickel catalyst (a) (33 ml. settled volume equivalent to 2.2 liters/mole) for 4 hours. The crude product (1.0 g. (32%)), m.p. 118–119.5° C., was isolated in the usual way. This compound was readily soluble in water, ethanol, and *iso*propanol but it could be recrystallized from a small volume of ethyl acetate. Repeated recrystallizations from ethyl acetate gave flat plates melting at 120.5–121° C. and with $[\alpha]_{D}^{26}$ –21.2° (c, 1.36). The rates of movement on paper chromatograms were R_f 0.76 (a) and R_f 0.73 (b). Anal. Calc. for C₈H₁₈O₄S: C, 45.7; H, 8.6; S, 15.2. Found: C, 46.1; H, 8.9; S, 15.1.

Reductive desulphurization of this compound in the usual way gave 1,6-dideoxy-Lmannitol. Recrystallization from a small volume of ethyl acetate gave clusters of crystals melting at 146–147° C. and with $[\alpha]_{\rm p}^{24^\circ} 23^\circ$ (*c*, 1.02) (lit. m.p. 145–146° C., $[\alpha]_{\rm p}^{20^\circ} 22.8^\circ$ (3)).

1-Deoxy-1-S-ethyl-L-galactitol

The preparation of 6-deoxy-6-S-ethyl-D-galactose described by Baker (10) was followed except that 1,2;3,4-di*iso*propylidene-6-O-methanesulphonyl-D-galactose (18) was used as the starting compound. 1,2;3,4-Di*iso*propylidene-6-deoxy-6-S-ethyl-D-galactose, $[\alpha]_{\rm D}^{29^{\circ}}$ 1.4765, $[\alpha]_{\rm D}^{26^{\circ}} - 85.8^{\circ}$ (c. 5.90, chloroform), was obtained in 92% yield after purification by high vacuum distillation. The reported constants are: $[\alpha]_{\rm D}^{24^{\circ}}$ 1.4795, $[\alpha]_{\rm D}^{22^{\circ}} - 85.7^{\circ}$ (chloroform) (10). Mild acid hydrolysis gave a reducing sirup that moved as a single spot on a paper chromatogram ($R_f 0.53$, $R_{Rh} 1.35$ (b)) (p-anisidine spray reagent).

A solution of this sirup (2.6 g. in 25 ml. of water) was added dropwise to a stirred solution of potassium borohydride (0.85 g. in 20 ml. of water). After 2 hours a test portion was neutralized with acetic acid and it gave a negative test with Fehling's solution. The solution was acidified with acetic acid, then percolated through a column of IR-120 (H form) ion exchange resin. The solution and washings were filtered and concentrated to dryness. After six codistillations with methanol, the residue was dissolved in a solution of methanolacetone (5:1)(15 ml.). Crystals (1.0 g. (39%)) were deposited when the solution was chilled to -20° C. A second recrystallization from methanol-acetone gave a chromatographically pure compound which had a rate of movement on a paper chromatogram identical with that of 1-deoxy-1-S-ethyl-D-galactitol in solvents (a), (b), and (c), m.p. $151-153^{\circ}$ C., $[\alpha]_{D}^{24}$ 8.6 (c, 4.18). The racemate melted at $141.5-142.0^{\circ}$ C. Anal. Calc. for $C_8H_{18}O_5S$: C, 42.6; H, 8.1; S, 14.2. Found: C, 42.8; H, 8.1; S, 13.9.

The pentaacetate was prepared in 57% yield in the usual way. Recrystallization from methanol-water (5:1) gave flakes melting at 151.0-151.5° C., $[\alpha]_{n}^{24^{\circ}} - 9^{\circ} \pm 1^{\circ}$ (c, 1.31

chloroform). Anal. Calc. for C₁₈H₂₄O₁₀S: C, 49.5; H, 6.5; S, 7.3. Found: C, 49.7, H, 6.7; S, 7.2.

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