Note

1,2,3,4,6-Penta-*O*-acetyl-5-thio-β-D-glucopyranose*

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Previously this laboratory prepared an analog[1] of normal α-D-glucopyranose in which sulfur replaced the ring oxygen. The sugar analog is showing such interesting biochemical properties, *e.g.* the inhibition of transport of D-glucose and amino acids[2,3], that a search for the β-D anomer has been made to extend information on the chemical characteristics of this sulfur sugar.

The α-D anomer of 6-thio-D-glucose has been prepared by way of the 1,2,3,4,6-penta-*O*-acetyl-5-thio-α-D-glucopyranose[4]. Acetylation of 5-thio-D-glucose in refluxing acetic anhydride and sodium acetate produced two components distinguishable by chromatography on silica gel. One, the acetate of the α-D anomer[1,4] crystallized as silky needles in 31% yield with a m.p. of 103° and a specific optical rotation of +213°. The other acetate, found to be the β-D anomer, crystallized as stout needles in 11% yield, and had a m.p. of 114° and a specific optical rotation of −11.9°. On the basis of the specific optical rotation it can be calculated that the original mixture of acetates consisted of 55% of the α and 45% of the β forms. No other isomers are indicated by chromatography. It is reported[5] that acetylation of α-D-glucopyranose with cold acetic anhydride and pyridine produced the acetate of only the α form. However,

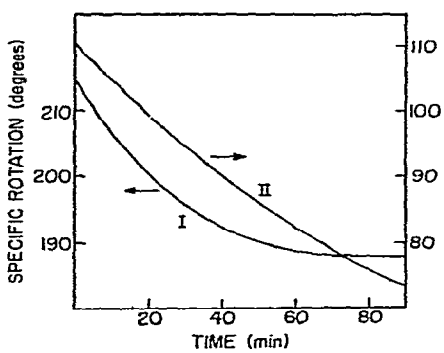

Fig. 1. Mutarotation rate of 5-thio-α-D-glucopyranose (I) and α-D-glucopyranose (II) in 50% aqueous ethanol at 25°.

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the same acetylation in the cold of 5-thio-α-D-glucopyranose produced a mixture of pentaacetates with 85% of α and 15% of the β forms present.

The β-D anomer acetate, on deacetylation in methanol with sodium methoxide at 25°, yielded as crystalline product only 5-thio-α-D-glucopyranose. The easy anomerization of the sugar is thus evident, and the mutarotation rate is indicated in Fig. 1. In 50% aqueous ethanol the specific optical rotation changed from +214° to the equilibrium value* of +188°, much more rapidly than does α-D-glucopyranose.

Anomerization is also evident by following the change in the n.m.r. (100 MHz) spectrum of the 5-thio-α-D-glucopyranose in deuterium oxide. In the anomeric region, a new signal at τ 5.18 (*J* 9.0 Hz) appeared in addition to the initial doublet at τ 4.96, after being kept for 1.5 h at 25°. The equilibrium mixture seems to contain α-D and β-D anomers in the ratio of 4:1, as indicated by the integral ratio. The gross features of the n.m.r. (60 MHz) spectra of both α-D and β-D forms of 5-thio-D-glucopyranose pentaacetate are not appreciately different from those of the α- and β-D-glucopyranose pentaacetate[5–8] and the anomeric protons appeared at τ 3.81 ($J_{1,2}$ 3.0 Hz) and τ 4.50 ($J_{1,2}$ 8.0 Hz) for the α-D and β-D forms, respectively. It is interesting to note that, in both forms of 5-thio-D-glucopyranose pentaacetates, the H-5 signals are distinguishable from those of H-6, possibly as a result of extra shielding of H-5 in the thio compounds.

EXPERIMENTAL

General methods. — Thin-layer chromatography was performed on Silica Gel G (E. Merck, Darmstadt, Germany) coated on 5.0 × 12.5-cm glass slides[9] and irrigated with 4:1 benzene–ethyl acetate (solvent A) or butyl acetate (solvent B). Components were located by spraying with 5% sulfuric acid in ethanol and heating. Melting points were determined with a Fisher–Johns apparatus and were corrected. Optical rotations were measured on a Perkin–Elmer Model 141 polarimeter. Nuclear magnetic resonance spectra were obtained in chloroform-*d* solution (tetramethylsilane as internal standard) or deuterium oxide (sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard) with a Varian A-60, or a Varian HA-100 spectrometer.

*1,2,3,4,6-Penta-*O*-acetyl-5-thio-α-D-glucopyranose and 1,2,3,4,6-penta-*O*-acetyl-5-thio-β-D-glucopyranose- — A. From column chromatography.* 5-Thio-D-glucopyranose[1] (0.605 g) was added to a boiling mixture of anhydrous sodium acetate (1.0 g) and acetic anhydride (15 ml) and heated at reflux for 3 min. The reaction mixture was poured into ice–water (100 g), stirred for 3 h, and extracted with chloroform (50 ml). The extract was washed with 5% sodium hydrogen carbonate and water, and then dried with sodium sulfate. Evaporation of the solvent under diminished pressure gave a syrup (1.164 g, 93%) which had $[\alpha]_D^{23}$ +112° (*c* 3.88, chloroform). On t.l.c., the syrup showed one spot (R_F 0.38) when irrigated with solvent A, but displayed two components (R_F 0.71 and 0.64) when solvent B was used as irrigant. The R_F value of

*The value previously reported[1] is $[\alpha]_D^{25}$ +188°.

the slower-moving component was identical to that of an authentic sample of 1,2,3,4,6-penta-*O*-acetyl-5-thio-α-D-glucopyranose. The syrup was applied to a silica gel (J. T. Baker Chemical Co., Phillipsburg, N. J.) column (700 g) and eluted with butyl acetate. Fractions containing the β-D anomer were collected and crystallized from ethanol to give 0.140 g (11%) of 1,2,3,4,6-penta-*O*-acetyl-5-thio-β-D-glucopyranose as stout needles; m.p. 114°; $[\alpha]_D^{23}$ −11.9° (*c* 1.3, chloroform); n.m.r. ($CDCl_3$, 60 MHz): τ 4.05 (d, 1, $J_{1,2}$ 8.0 Hz, H-1), 4.73 (m, 3, H-2, H-3, H-4), 5.73 (m, 2, H-6, H-6'), 6.50 (m, 1, H-5), 7.94, 7.99, 8.00 (15, Ac).

Anal. Calc. for $C_{16}H_{22}O_{10}S$: C, 47.28; H, 5.46; S, 7.87. Found: C, 47.17; H, 5.41; S, 8.02.

Further elution of the column gave 0.385 g (31%) of 1,2,3,4,6-penta-*O*-acetyl-5-thio-α-D-glucopyranose, crystallized from ethanol (silky needles); m.p. 103°; $[\alpha]_D^{23}$ +213° (*c* 1.56, chloroform); (lit.[1,2]: m.p. 103°, $[\alpha]_D^{20}$ +213°, $[\alpha]_D^{25}$ +212.5°); n.m.r. ($CDCl_3$, 60 MHz): τ 3.81 (d, 1, $J_{1,2}$ 3.0 Hz, H-1), 4.66 (m, 3, H-2, H-3, H-4), 5.76 (m, 2, H-6, H-6'), 6.40 (m, 1, H-5), 7.81, 7.92, 7.94, 7.97, 8.00 (15, Ac).

B. From fractional crystallization. In another run, the syrup containing the two anomers (1.140 g) was dissolved in ethanol (15 ml) and seeded with the α-D anomer at 0° to give 0.278 g (22%) of pure 1,2,3,4,6-penta-*O*-acetyl-5-thio-α-D-glucopyranose after recrystallization from ethanol. Another crop of crystals (0.404 g, 32%) was a mixture of α- and β-D anomers in the ratio of 3:2, as indicated by t.l.c. (irrigated with solvent B). The mother liquor seeded with 1,2,3,4,6-penta-*O*-acetyl-5-thio-β-D-glucopyranose gave 0.063 g (5%) of the pure β-D anomer.

C. Acetylation of 5-thio-α-D-glucopyranose with acetic anhydride and pyridine. — 5-Thio-α-D-glucopyranose (0.748 g) was added to a solution of acetic anhydride (10 ml) and pyridine (13 ml) at 0°. After 1 h, the temperature of the reaction mixture was raised to room temperature and kept at his level for 16 h. The mixture was poured into 200 ml of ice–water, and extracted with chloroform (50 ml). After successive washings with cold 2M hydrochloric acid, 5% sodium hydrogen carbonate solution, and water, the chloroform extract was dried with sodium sulfate and evaporated to a syrup (1.430 g, 92%), $[\alpha]_D^{23}$ +178° (*c* 4.77, chloroform). This syrup contained about 15% of the β-D anomer, as shown by t.l.c. (irrigated with solvent B). Crystallization of the syrup from ethanol gave 0.959 g (62%) of pure 5-thio-α-D-glucopyranose pentaacetate.

5-Thio-α-D-glucopyranose from penta-O-acetyl-5-thio-β-D-glucopyranose. — 5-Thio-β-D-glucopyranose pentaacetate (0.827 g) was suspended in methanol (10 ml), and the mixture stirred under nitrogen with a 0.1M sodium methoxide solution (5 ml). After being kept for 1.5 h at 25°, the resulting solution was neutralized with Amberlite IR-120 and filtered, and the filtrate evaporated to a pale-yellow syrup which, after crystallization from 2:1 chloroform–methanol, gave 5-thio-α-D-glucopyranose, m.p. 135°–136°; $[\alpha]_D^{23}$ +188° (*c* 1.97, methanol).

Mutarotation measurements. — A solution of 5-thio-α-D-glucopyranose was found to mutarotate in 50% aqueous ethanol to an equilibrium mixture with a specific rotation of +188° within 1.5 h. The half-life was 21 min. Under similar

conditions, normal α-D-glucopyranose mutarotated to a equilibrium value of +53° and the half-life was 82 min. Graphical plots of the data are shown in Fig. 1.

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