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Note

Synthesis of 2-amino-2-deoxy-3-thio-D-glucose

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The known effectiveness of β- and γ-aminothiol systems for protecting living tissue from damage by ionizing[1] radiation suggested that a carbohydrate molecule, especially one having the D-*gluco* configuration, containing these functional groups, might also have radiation-protective ability, and at the same time be more physiologically acceptable than noncarbohydrate analogs. As potential antiradiation drugs, several interesting carbohydrate structures containing these groups have been synthesized[2–8]. I have studied the reactivity of 2,3-epimino sugar derivatives for synthesis of amino sugars, and have investigated synthetic routes to 2-amino-2-deoxy-3-thio-D-glucose, which has not been synthesized until now.

Methyl 4,6-*O*-benzylidene-2,3-(*N*-benzylsulfonylepimino)-2,3-dideoxy-α-D-allopyranoside (**2**) (which has a removable *N*-protecting group), obtained from methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside[9] (**1**), reacted with α-toluenethiol under basic conditions to give methyl 2-*S*-benzyl-4,6-*O*-benzylidene-3-benzylsulfonamido-3-deoxy-2-thio-α-D-altropyranoside (**3**, 91%) and methyl 3-*S*-benzyl-4,6-*O*-benzylidene-2-benzylsulfonamido-2-deoxy-3-thio-α-D-glucopyranoside (**4**, 4%). The products were separated by chromatography on silica gel and their structures assigned from ^{1}H-n.m.r. spectral studies. The ^{1}H-n.m.r. spectrum of **3** showed a singlet for H-1 at δ 4.49. In compound **4**, the signal appeared as a doublet ($J_{1,2}$ 4 Hz) at δ 4.61, indicating an axial–equatorial (*cis*) arrangement[10] of H-1 and H-2. This result showed that the 4,6-*O*-benzylidene-*allo*-epimine was susceptible to *trans*-diaxial ring-opening according to the Fürst–Plattner rule[11].

In contrast, methyl 2,3-(*N*-benzylsulfonylepimino)-2,3-dideoxy-α-D-allopyranoside (**7**), derived from **2** by hydrolysis with cation-exchange resin reacted with α-toluenethiol under basic conditions to give methyl 3-*S*-benzyl-2-benzylsulfonamido-2-deoxy-3-thio-α-D-glucopyranoside (**8**, 86%) as the sole product. The ^{1}H-n.m.r. spectrum of **8** showed a doublet ($J_{1,2}$ 4 Hz) for H-1 at δ 4.55. The structure of **8** was confirmed as follows. Hydrolysis of **3** with Amberlite CG-120 (H$^+$) resin gave methyl 2-*S*-benzyl-3-benzylsulfonamido-3-deoxy-2-thio-α-D-al-

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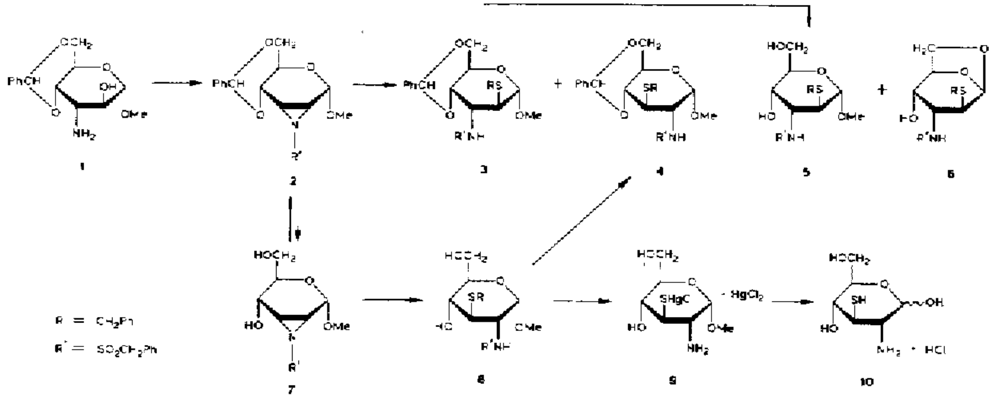

tropyranoside (**5**, 60.5%) and 1,6-anhydro-2-*S*-benzyl-3-benzylsulfonamido-3-deoxy-2-thio-β-D-altropyranose (**6**, 15.6%), which differed from **8**. The ^{1}H-n.m.r. spectrum of **6** showed signals characteristic of 1,6-anhydrohexopyranoses[12]. The ^{1}H-n.m.r. spectrum of **5** showed a singlet for H-1 at δ 4.55. Compounds **7** and **8** reacted with benzaldehyde to give **2** and **4**, respectively, which confirmed their structures. In contrast to the benzylidenated derivative **2**, the ring-opening reaction of **7** gave a product having the *gluco* configuration.

Reaction of **8** with sodium in liquid ammonia gave methyl 2-amino-2-deoxy-3-thio-α-D-glucoside, which was isolatd from the mixture as its mercuric chloride complex (**9**)[2]. Decomposition of the mercaptide salt (**9**) with hydrogen sulfide followed by treatment with dilute hydrochloric acid gave a good yield of 2-amino-2-deoxy-3-thio-D-glucose hydrochloride (**10**) as a hygroscopic, brownish solid, $[\alpha]_D$ +126.5→ +66.5° (*c* 0.5, methanol). The presence of the thiol group was indicated by a strong, positive nitroprusside test. The purity of the product was confirmed by t.l.c. and elemental analysis.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Specific rotations were measured with an automatic polarimeter DIP-SL (Jasco). I.r. spectra were recorded with a DS-701 type (Jasco) instrument, and ^{1}H-n.m.r. spectra with a JNM-MH 100 (Jeol) spectrometer. Column chromatography was performed on 100-mesh silicic acid (Mallinckrodt Chem. Co.) with the solvent system specified.

Methyl 4,6-O-benzylidene-2,3-(N-benzylsulfonylepimino)-2,3-dideoxy-α-D-allopyranoside (**2**). — To a solution of methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside[9] (**1**) in pyridine (30 mL) was added benzylsulfonyl chloride (7.5 g). The mixture was kept for 24 h at 0°, poured into ice–water, and extracted with chloroform. The extract was successively washed with water, 10% sulfuric acid, dried (sodium sulfate), and evaporated to give crystalline methyl 4,6-*O*-benzylidene-2-*O*-benzylsulfonyl-3-benzylsulfonamido-3-deoxy-α-D-altropyranoside

(10.3 g, 97%). A part of the product was recrystallized from ethanol to give colorless needles, m.p. 156–158°, $[\alpha]_D^{25}$ +131.7° (*c* 1, chloroform).

Anal. Calc. for $C_{28}H_{31}NO_9S_2$: C, 57.03; H, 5.29; N, 2.37. Found: C, 56.70; H, 5.19; N, 2.69.

A solution of the foregoing product (10.3 g) in 5M sodium hydroxide (200 mL) was heated in a boiling-water bath for 15 min, cooled to room temperature, and the resulting crystals were filtered off, washed with water and dried *in vacuo*. Recrystallization from acetone–ether gave **2** as colorless needles, m.p. 178–179°, $[\alpha]_D^{20}$ +133.6° (*c* 1, pyridine); ν_{max}^{Nujol} 1330 and 1140 cm^{-1} (SO_2), ^{1}H-n.m.r. ($CDCl_3$): δ 3.31 (q, 1 H, $J_{2,3}$ 8, $J_{3,4}$ 2 Hz, H-3), 3.42 (q, 1 H, $J_{1,2}$ 4, $J_{2,3}$ 8 Hz, H-2), 3.43 (s, 3 H, CH_3O), 4.45 (s, 2 H, SCH_2Ph), 5.59 (s, 1 H, *CH*Ph), and 7.20–7.60 (m, 10 H, aromatic).

Anal. Calc. for $C_{21}H_{23}NO_6S$: C, 60.42; H, 5.56; N, 3.35. Found: C, 60.30; H, 5.49; N, 3.25.

Reaction of **2** *with α-toluenethiol.* — Compound **2** (2.05 g) was added to a solution of α-toluenethiol in dry methanol (200 mL) containing metallic sodium (0.22 g). The mixture was boiled under reflux for 2 h, cooled to room temperature, acidified with acetic acid, and evaporated to give crystals that were extracted with ether after addition of water. The extract was evaporated to a syrup that was eluted from silica gel with chloroform. Eluted first was syrupy methyl 2-*S*-benzyl-4,6-*O*-benzylidene-3-benzylsulfonamido-3-deoxy-2-thio-α-D-altropyranoside (**3**, 2.37 g, 91%), $[\alpha]_D^{27}$ +178.3° (*c* 1, chloroform); ν_{max}^{neat} 3300 (NH), 1330 and 1145 cm^{-1} (SO_2), ^{1}H-n.m.r. ($CDCl_3$): δ 3.05 (d, 1 H, $J_{2,3}$ 2 Hz, H-2), 3.20 (s, 3 H, CH_3O), 3.85 (s, 2 H, SCH_2Ph), 4.19 (s, 2 H, SO_2CH_2Ph), 4.49 (s, 1 H, H-1), 5.47 (d, 1 H, *J* 8 Hz, NH, exchangeable with D_2O), 5.17 (s, 1 H, *CH*Ph), and 7.20–7.60 (m, 15 H, aromatic).

Anal. Calc. for $C_{28}H_{31}NO_6S_2$: C, 62.08; H, 5.77; N, 2.59. Found: C, 61.72; H, 5.94; N, 2.55.

Eluted second was crystalline methyl 3-*S*-benzyl-4,6-*O*-benzylidene-2-benzylsulfonamido-2-deoxy-3-thio-α-D-glucopyranoside (**4**, 0.11 g, 4%). Recrystallization from methanol gave colorless needles, m.p. 182–183°, $[\alpha]_D^{33}$ +50° (*c* 1, pyridine); ν_{max}^{KBr} 3260 (NH), 1330 and 1130 cm^{-1} (SO_2), ^{1}H-n.m.r. ($CDCl_3$): δ 2.96 (q, 1 H, $J_{2,3}$ 12 Hz, $J_{3,4}$ 9 Hz, H-3), 3.34 (s, 3 H, CH_3O), 3.92 (d, 1 H, J_{gem} 13 Hz, SCH_2Ph), 4.00 (d, 1 H, J_{gem} 13 Hz, SCH_2Ph), 4.41 (d, 1 H, *J* 10 Hz, NH, exchangeable with D_2O), 4.41 (s, 2 H, SO_2CH_2Ph), 4.61 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.49 (s, 1 H, *CH*Ph), and 7.20–7.60 (m, 15 H, aromatic).

Anal. Calc. for $C_{28}H_{31}NO_6S_2$: C, 62.08; H, 5.77; N, 2.59. Found: C, 62.16; H, 5.85; N, 2.62.

Hydrolysis of **3** *with Amberlite CG-120* (H^+) *resin.* — A mixture of **3** (1.04 g), resin (4.5 g), and 80% methanol (100 mL) was stirred for 30 h at 55°. The filtrate was then evaporated. The residue was eluted from silica gel with 1:1 chloroform–ethyl acetate to give solid 1,6-anhydro-2-*S*-benzyl-3-benzylsulfonamido-3-deoxy-2-thio-β-D-altropyranose (**6**, 126 mg, 15.6%), $[\alpha]_D^{21}$ −85.7° (*c* 1, chloroform); ν_{max}^{neat} 3460 (OH), 3260 (NH), 1330 and 1130 cm^{-1} (SO_2). ^{1}H-n.m.r. ($CDCl_3$): δ 2.11 (s, 1 H, OH, exchangeable with D_2O), 2.56 (d, 1 H, $J_{2,3}$ 14 Hz, H-2), 3.83 (s, 2 H, SCH_2Ph), 4.38 (s, SO_2CH_2Ph), 4.82 (d, 1 H, J 12 Hz, NH, exchangeable with D_2O), 5.30 (s, 1 H, H-1), and 7.10–7.60 (m, 10 H, aromatic).

Anal. Calc. for $C_{20}H_{23}NO_5S_2$: C, 56.99; H, 5.49; N, 3.32. Found: C, 56.66; H, 5.91; N, 3.27.

Eluted second was crystalline methyl 2-*S*-benzyl-3-benzylsulfonamido-3-deoxy-2-thio-α-D-altropyranoside (**5**, 524 mg, 60.2%). Recrystallization from ether–petroleum ether gave colorless needles; m.p. 97–98°, $[\alpha]_D^{26}$ +93.6° (*c* 1, chloroform); ν_{max}^{KBr} 3460, 3280 (OH), 3350 (NH), 1340 and 1150 cm^{-1} (SO_2). ^{1}H-n.m.r. ($CDCl_3$): δ 2.28 (t, 1 H, J 6 Hz, HO-6, exchangeable with D_2O), 2.83 (d, 1 H, J 6 Hz, HO-4, exchangeable with D_2O), 2.94 (d, 1 H, $J_{2,3}$ 2 Hz, H-2), 3.20 (s, 3 H, CH_3O), 3.76 (s, 2 H, SCH_2Ph), 4.16 (s, 2 H, SO_2CH_2Ph), 4.55 (s, 1 H, H-1), 5.70 (d, J 9 Hz, NH), and 7.20–7.60 (m, 10 H, aromatic).

Anal. Calc. for $C_{21}H_{27}NO_6S_2$: C, 55.61; H, 6.00; N, 3.08. Found: C, 55.17; H, 6.04; N, 2.99.

Hydrolysis of **2** *with Amberlite CG-120* (H^+) *resin.* — A mixture of **2** (4.99 g), resin (22.5 g), and 80% methanol (500 mL) was stirred for 15 h at 55°. The filtrate was then evaporated The residue was eluted from silica gel with ethyl acetate to give solid methyl 2,3-(*N*-benzylsulfonylepimino)-2,3-dideoxy-α-D-allopyranoside (**7**, 3.93 g, quantitative yield), $[\alpha]_D^{32}$ +96.6°(*c* 1, chloroform); ν_{max}^{neat} 3400 (OH), 1320 and 1150 cm^{-1} (SO_2), ^{1}H-n.m.r. ($CDCl_3$): δ 2.40 (broad, 1 H, HO-6, exchangeable with D_2O), 2.94 (d, 1 H, J 8 Hz, OH-4, exchangeable with D_2O), 3.44 (s, 3 H, CH_3O), 4.35 (d, J 14 Hz, SO_2CH_2Ph), 4.57 (d, 1 H, J 14 Hz, SO_2CH_2Ph), 4.93 (d, 1 H, J 4 Hz, H-1), and 7.20–7.60 (m, 5 H, aromatic).

Anal. Calc. for $C_{14}H_{19}NO_6S$: C, 51.05; H, 5.81; N, 4.25. Found: C, 50.66; H, 5.80; N, 4.01.

Reaction of **7** *with benzaldehyde.* — A mixture of **7** (201.4 mg), benzaldehyde (3 mL), and freshly powdered zinc chloride (1 g) was stirred for 24 h at room temperature, kept for 24 h at room temperature, and poured into ice–water. The resulting precipitate was filtered off, washed with hexane, and dried *in vacuo* to give crystals (m.p. 135–140°). Recrystallization from acetone gave **2** (187 mg, 73%) as colorless needles, m.p. 178°.

Reaction of **7** *with α-toluenethiol.* — Copound **7** (2 g) was added to a solution of α-toluenethiol (1.37 g) in dry methanol (200 mL) in which metallic sodium (0.25 g) had been dissolved. The mixture was boiled under reflux for 2 h, cooled to room temperature, acidified with acetic acid, and evaporated to a syrup that crystallized from water. The crystals were filtered off, washed with water, and dried *in vacuo* (crude yield 2.5 g, 92%). Recrystallization from chloroform gave methyl 3-*S*-benzyl-2-benzylsulfonamido-2-deoxy-3-thio-α-D-glucopyranoside (**8**, 2.3 g, 85%) as colorless needles, m.p. 158–159°, $[\alpha]_D^{30}$ +85.1° (*c* 1, pyridine); ν_{max}^{KBr} 3320 (OH), 3250 (NH), 1330 and 1180 cm^{-1} (SO_2). ^{1}H-n.m.r. ($CDCl_3$): δ 1.96 (broad, 1 H, HO-6, exchangeable with D_2O), 2.74 (q, 1 H, $J_{2,3}$ 12, $J_{3,4}$ 10 Hz, H-2), 2.80 (d, 1

H, J <1 Hz, HO-4, exchangeale with D_2O), 3.37 (s, 3 H, CH_3O), 3.85 (s, 2 H, SCH_2Ph), 4.40 (s, 2 H, SO_2CH_2Ph), 4.41 (d, 1 H, J 10 Hz, NH, exchangeable with D_2O), 4.55 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), and 7.20–7.60 (m, 10 H, aromatic).

Anal. Calc. for $C_{21}H_{27}NO_6S_2$: C, 55.61; H, 6.00; N, 3.08. Found: C, 55.30; H, 5.99; N, 2.95.

Reaction of **8** *with benzaldehyde.* — A mixture of **8** (200 mg), benzaldehyde (1.5 mg), and freshly powdered zinc chloride (1 g) was stirred for 48 h at room temperature. The product was purified by the procedure used for **5**. Recrystallization from methyl alcohol gave **4** (157.3 mg, 65%) as colorless needles, m.p. 182–183°.

*2-Amino-2-deoxy-3-thio-*D*-glucose hydrochloride* (**10**). — To a solution of **8** (1 g) in liquid ammonia (30 mL) was added metallic sodium (1.5 g). The mixture was stirred for 45 min under cooling by Dry Ice–acetone. After addition of chloroform until discharge of the blue color, liquid ammonia was distilled off. To a solution of the residue in a few mL of water, a saturated aqueous solution of mercuric chloride was added until no more precipitate was produced. The mercuric chloride complex of methyl 2-amino-3-chloromercurithio-2-deoxy-α-D-glucopyranoside (**9**) was filtered off, washed with water, and suspended in 50 mL of water. The stirred suspension was treated with a rapid stream of hydrogen sulfide for 30 min. The mixture was filtered through Celite. To the filtrate was added 0.2M hydrochloric acid (10 mL) and then the mixture was kept for 24 h at room temperature, made neutral with Amberlite IRA-400 resin, and evaporated. The resulting, partly crystalline syrup was dissolved in ethanol. The filtrate was evaporated to give **10** as a hygroscopic, brownish solid (377.4 mg, 73.9%), $[\alpha]_D^{17.5}$ +126.5→+66.6° (c 0.5, methanol).

Anal. Calc. for $C_6H_{13}NO_4S \cdot HCl$: C, 31.09; H, 6.09; N, 6.04. Found: C, 30.92; H, 6.15; N, 5.66.

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