Note

Acyclic-sugar nucleoside analogs. 6-Mercaptopurine nucleosides having acyclic D-galactose and D-glucose chains*†

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A program of this laboratory is concerned with (*a*) the synthesis of nucleoside analogs having the sugar residue in the acyclic form, and (*b*) reactions whereby the sugar chain might be cyclized. With this objective, various such acyclic-sugar nucleosides have been prepared, having adenine[2,3] or thymine[1] as the base, and with the sugar moiety derived from D-glucose or D-galactose.

With the possibility in mind that an attached, acylic sugar-chain might facilitate transport of heterocyclic bases *in vivo* to sites of biological action, and thereby modify the biological response, the synthesis was undertaken of various acyclic-sugar nucleoside analogs containing, as the base residue, structures having established carcinostatic activity. In this report, such incorporation is described for 6-mercaptopurine, a compound of demonstrated[4] antitumor potential, to afford 1-deoxy-1-*S*-ethyl-1-(6-mercaptopurin-9-yl)-1-thio-*aldehydo*-D-galactose aldehydrol (**5**) and its D-glucose analog (**9**).

2,3,4,5,6-Penta-*O*-acetyl-1-bromo-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-galactose aldehydrol[5] (**1**) was condensed with 6-chloro-9-(chloromercuri)purine[6] (**2**) to give, in high yield, 2,3,4,5,6-penta-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-galactose aldehydrol (**3**) as a syrup that was, presumably, a 1-epimeric mixture; a crystalline, single form of **3**, of undetermined stereochemistry at C-1, was isolated by column-chromatographic fractionation. Treatment of the levorotatory, crystalline nucleoside **3** with thiourea gave a 60% of the crystalline pentaacetate (**4**) of 1-deoxy-1-*S*-ethyl-1-(6-mercaptopurin-9-yl)-1-thio-*aldehydo*-D-galactose aldehydrol (**5**); *O*-deacetylation of **4** with methanolic ammonia gave the unprotected product **5**, also obtained crystalline.

Similarly, 2,3,4,5,6-penta-*O*-acetyl-1-bromo-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-glucose aldehydrol[7] (**6**) was converted in high yield into crystalline 2,3,4,5,6-penta-

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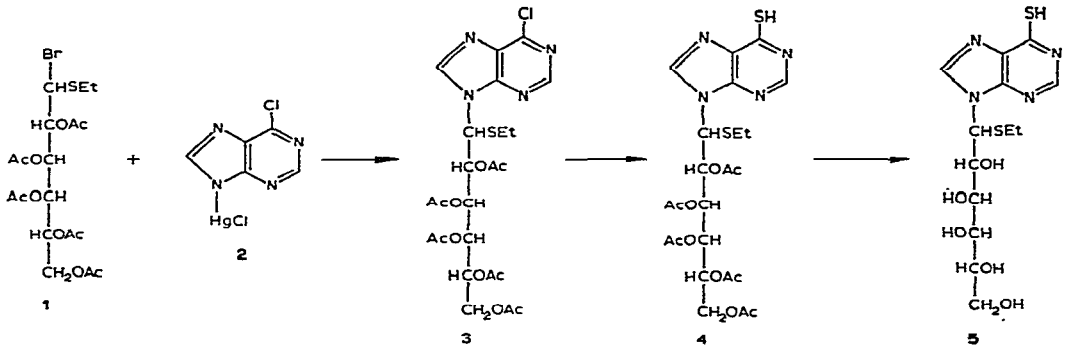
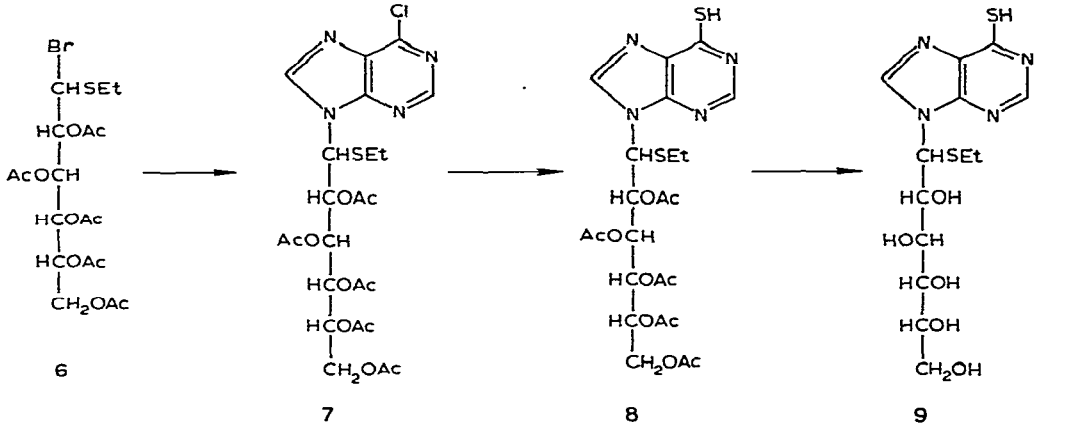


O-acetyl-1-deoxy-1-*S*-ethyl-1-(6-mercaptopurin-9-yl)-1-thio-*aldehydo*-D-glucose aldehydrol (**8**) by way of the syrupy 6-chloropurine analog (**7**); saponification of **8** gave crystalline 1-deoxy-1-*S*-ethyl-1-(6-mercaptopurin-9-yl)-1-thio-*aldehydo*-D-glucose aldehydrol (**9**) in excellent overall yield for the sequence.



Compound **9** showed confirmed antitumor activity against the L-1210 lymphoid leukemia test-system in mice, at a dose level of 500 mg/kg (body weight). In tests for bacterial inhibition, the D-*gluco* derivative **9** was found to inhibit the growth of *Escherichia coli* (K-12) by 50% at 4×10^{-5} M, whereas the D-*galacto* analog **5** was inactive at 10^{-3} M.

EXPERIMENTAL

General methods. — The procedures described in the accompanying paper[1] were also used in this work.

*2,3,4,5,6-Penta-*O*-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-*S*-ethyl-1-thio*-aldehydo-D-*galactose aldehydrol* (**3**). — To an azeotropically dried mixture of 6-chloro-9-(chloromercuri)purine[6] (**2**, 4 g), Celite (Johns–Manville Co., New York; 2 g),

cadmium carbonate (1 g), and toluene (250 ml) was added 2,3,4,5,6-penta-*O*-acetyl-1-bromo-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-galactose aldehydrol[5] (**1**, 5.1 g) and the mixture was boiled for 3 h under reflux, with stirring. The hot mixture was filtered, and the filter-cake was washed with chloroform (300 ml). The filtrate and washings were combined, successively washed with 30% aqueous potassium iodide (twice) and water (twice), dried (sodium sulfate), and evaporated to a syrup; yield 5.65 g (94%). The syrup was dissolved in a small volume of benzene, and placed on the top of a column (230 × 40 mm) of Microcel C (a product of Johns–Manville Co., New York). Elution with 20:1 benzene–methanol gave a fraction desorbed before a visible yellow band; evaporation of this fraction gave a product that crystallized from ethanol; yield 1.15 g, m.p. 135°. Recrystallization from ethanol, following decolorization with charcoal, gave needles, m.p. 136–137°, $[\alpha]_D^{21}$ −61.2° (*c* 1.1, chloroform); $\lambda_{max}^{CHCl_3}$ 267 nm (ε 8,400); λ_{max}^{KBr} 5.75 (C=O of acetate), 6.32, 6.42, 6.80 (purine ring), 7.35, 9.10, 9.30, 9.68, and 9.90 μm (C–O–C); X-ray powder diffraction data: 11.70 w, 9.31 m, 7.76 m, 6.86 vs (1), 5.96 m, 5.50 m, 4.96 vw, 4.48 s (2), 3.87 m, 3.47 s (3), 3.30 m, and 2.29 w.

Anal. Calc. for $C_{23}H_{29}ClN_4O_{10}S$: C, 46.89; H, 4.96; Cl, 6.02; N, 9.51; S, 5.44. Found: C, 47.37; H, 4.96; Cl, 6.00; N, 9.80; S, 5.62.

Further elution of the column gave a syrupy product, apparently a mixture of 1-epimers of **3**.

Omission of cadmium carbonate from the reaction mixture resulted in a decrease of the yield of crude, syrupy **3** to 70%.

*2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-*S*-ethyl-1-(6-mercaptopurin-9-yl)-1-thio*-aldehydo-D-*galactose aldehydrol* (**4**). — The crystalline chloro derivative **3** (1.8 g, 3.06 mmoles) was treated for 3 h under reflux with boiling abs. ethanol (15 ml) containing thiourea (0.26 g, 3.4 mmoles). The clear solution solidified on being cooled. Trituration with a small volume of ethanol gave crystals of **4**; yield 1.08 g (60%), m.p. 202–204°, $[\alpha]_D^{21}$ −112° (*c* 0.7, chloroform); λ_{max}^{EtOH} 316 nm (ε 20,500); λ_{max}^{KBr} 3.40 (C–H), 3.67 (SH), 5.70 (C=O of acetate), 6.27, 6.53, 6.80 (purine ring), 7.32, 9.03, 9.25, and 9.66 μm (C–O–C); X-ray powder diffraction data: 12.81 m, 10.34 vs (2), 8.51 m, 7.34 vs (1), 6.56 m, 5.57 m, 4.94 m, 4.68 s (3), 4.34 w, and 4.05 w.

Anal. Calc. for $C_{23}H_{30}N_4O_{10}S_2$: C, 47.07; H, 5.28; N, 9.55; S, 10.92. Found: C, 46.74; H, 5.39; N, 9.52; S, 10.48.

*1-Deoxy-1-*S*-ethyl-1-(6-mercaptopurin-9-yl)-1-thio*-aldehydo-D-*galactose aldehydrol* (**5**). — The pentaacetate **4** (1.0 g) was suspended in methanol (25 ml) almost saturated at 0° with ammonia. The mixture was kept overnight at 0–5°, and then the solvent was evaporated, to give a white solid. The solid was washed with ethanol, and dissolved in water, and, after treatment with charcoal, the solution was freeze-dried. Crystallization of the residue from aqueous ethanol during 5 days at 0–5° gave needles of **5**; yield 230 mg (36%) in 3 crops, m.p. 222–224°, $[\alpha]_D^{21}$ −114° (*c* 0.5, water), $\lambda_{max}^{H_2O}$ 324 nm (ε 25,200); λ_{max}^{KBr} 3.00 (OH), 3.45 (SH), 6.25, 6.55, 6.80 (purine ring), 9.05–9.2, and 9.60–9.72 μm (C–O–H); X-ray powder diffraction data: 10.92 s (2), 5.42 m (3), 4.82 vs (1), 4.04 w, and 3.68 m.

Anal. Calc. for $C_{13}H_{20}N_4O_5S_2$: C, 41.47; H, 5.36; N, 14.88; S, 17.04. Found: C, 41.21; H, 5.43; N, 14.61; S, 16.51.

2,3,4,5,6-Penta-O-acetyl-1-deoxy-1-S-ethyl-1-(6-mercaptopurin-9-yl)-1-thio-aldehydo-D-*glucose aldehydrol* (**8**). — To an azeotropically dried mixture of 6-chloro-9-(chloromercuri)purine[6] (**2**, 4.0 g), cadmium carbonate (3 g), Celite (1 g), and toluene (125 ml) was added 2,3,4,5,6-penta-*O*-acetyl-1-bromo-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-glucose aldehydrol[7] (**6**, 5.0 g), and the mixture was boiled for 4 h under reflux, with stirring. The hot mixture was filtered, and the crude chloro derivative **7** was isolated as for the D-galactose analog **3**; yield of **7** (as a glass) 6.5 g. Purification was effected by passage through a column (200 × 44 mm) of Microcel-C, with benzene as the eluant. The purified **7** emerged as a colorless band immediately before a yellow one; yield 5.0 g (83%). The syrupy **7** (1.9 g) was treated for 3 h under reflux with boiling abs. ethanol (40 ml) containing thiourea (0.7 g). On cooling, a crystalline mass resulted; this was broken up, collected on a filter, and washed with a small volume of abs. ethanol to give **8**; yield 1.4 g (74%). A solution of the product in chloroform was decolorized with charcoal; the material was then recrystallized from methanol, to give **8** having m.p. 223–224°, $[\alpha]_D^{21}$ −53° (*c* 1.2, chloroform); R_F 0.45 (one spot, t.l.c. on Silica Gel G with 10:1 benzene–methanol); $\lambda_{max}^{CHCl_3}$ 330 nm (ε 23,100); λ_{max}^{KBr} 5.70 (C=O of acetate), 6.24, 6.60, 6.85 (purine ring), 7.35 (CH_3), 9.40, and 9.75 μm (C–O–C); X-ray powder diffraction data: 13.81 w, 12.03 vw, 10.46 m (?), 9.35 s (2), 8.23 w, 7.20 vs (1), 3.93 w, and 3.54 w.

Anal. Calc. for $C_{23}H_{30}N_4O_{10}S_2$: C, 47.09; H, 5.28; N, 9.55; S, 10.92. Found: C, 47.00; H, 5.11; N, 9.64; S, 11.03.

1-Deoxy-1-S-ethyl-1-(6-mercaptopurin-9-yl)-1-thio-aldehydo-D-*glucose aldehydrol* (**9**). — Crude compound **8** (1.55 g) was suspended in abs. methanol (30 ml), and gaseous ammonia was passed into the suspension for 30 min at 0°. The mixture was kept overnight at 0° and then evaporated to give a white solid. A solution of this solid in boiling water was decolorized with charcoal and then freeze-dried, to give a white powder; yield 0.98 g (99%), m.p. 179–181°. Dissolution in warm ethanol by addition of a few drops of water, decolorization with charcoal, and cooling gave compound **9** as a mass of fine crystals, m.p. 189–190°, $[\alpha]_D^{20}$ −101° (*c* 0.7, water); R_F 0.48 (one spot, t.l.c. on Avicel[8] with water-saturated butyl alcohol), R_F 0.70 (one spot, t.l.c. on Avicel with 40:11:19 butyl alcohol–ethanol–water); $\lambda_{max}^{H_2O}$ 324 nm (ε 26,300); λ_{max}^{KBr} 3.00 (OH), 6.23, 6.52, 6.77 (purine ring), 7.50 (SEt), 9.10, 9.22, and 9.68 μm (C–OH); X-ray powder diffraction data: 7.90 vs (1), 5.52 m (2), 5.19 vs, 4.86 w, and 4.32 m (3).

Anal. Calc. for $C_{13}H_{20}N_4O_5S_2$: C, 41.47; H, 5.36; N, 14.88; S, 17.04. Found: C, 41.21; H, 5.66; N, 14.94; S, 16.70.

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