HALOGEN AND NUCLEOSIDE DERIVATIVES OF ACYCLIC 2-AMINO-2-DEOXY-D-GLUCOSE. III*†

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(Received June 14th, 1971)

ABSTRACT

3,4,5,6-Tetra-*O*-acetyl-2-deoxy-2-(trifluoroacetamido)-D-glucose diethyl dithioacetal was treated with bromine to give the 1-bromo-1-*S*-ethyl derivative, which was condensed with bis(trimethylsilyl)thymine to afford a pair of C-1 epimeric, acyclic-sugar nucleoside analogs. Deacylation of these two compounds with methanolic ammonia gave the 2-amino-1,1,2-trideoxy-1-(ethylthio)-1-thymin-1-yl-D-glucose aldehydrols, isolated as their hydrochlorides.

INTRODUCTION

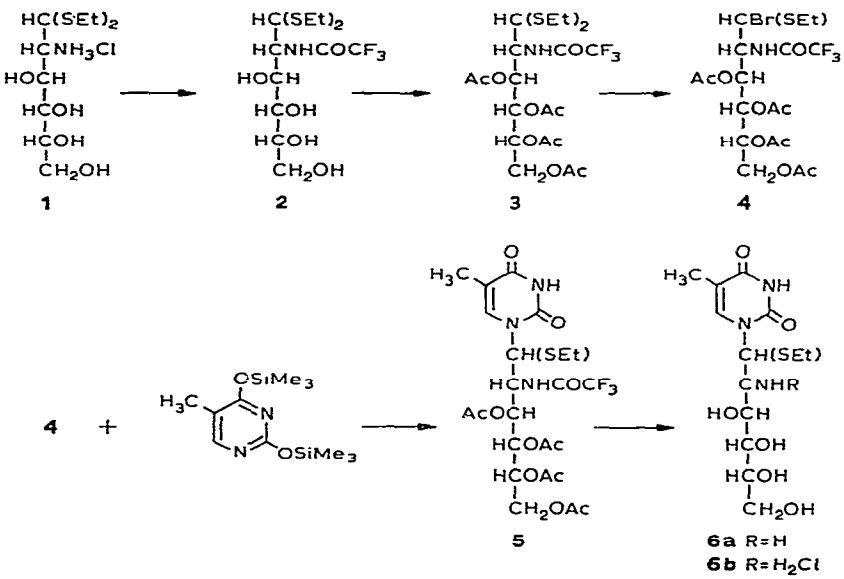
This laboratory has been interested in the synthesis of acyclic-sugar nucleoside analogs which may be considered as derived from the aldehydrol forms of various sugars[1–3]. In previous communications, there was reported the synthesis of adenine nucleoside analogs of acyclic 2-amino-2-deoxy-D-glucose having ethylthio[3], ethoxyl[1], and methoxyl[1] groups at C-1. 2,4-Dinitrophenyl was employed as the amino-protecting group for the synthesis of these compounds; however, attempted removal of this group from the final derivatives was unsuccessful. In all cases, only one of the C-1 epimeric forms possible was obtained. The present report describes the synthesis of both epimeric forms of a fully deblocked, acyclic 2-amino-2-deoxy-D-glucose nucleoside analog containing a thymine residue.

DISCUSSION

For this synthesis, trifluoroacetyl was chosen as the amino-protecting group as it is readily removable under mildly basic conditions. Previous experience with this amino-protecting group[4] has indicated that it is not a strongly participating group;

*This work was supported by Grants No. CA-03232-10 and CA-03232-11 from the Department of Health, Education, and Welfare, U. S. Public Health Service, National Institutes of Health, Bethesda, Md. (The Ohio State University Research Foundation Projects 759-I and 759-J).
†For the preceding paper in this series, see Ref. 1.
**Deceased, June 20th, 1969. Manuscript completed and submitted by D. Horton, Department of Chemistry, The Ohio State University, to whom enquiries should be directed.

this condition is desirable for this type of synthesis, because such strongly participating groups as acetamido[3] have been found to contribute to the instability of the acyclic 1-halo derivatives employed for condensation with a purine or pyrimidine derivative. The starting material for the synthesis was 2-amino-2-deoxy-D-glucose diethyl dithioacetal hydrochloride (**1**), which was prepared by the procedure of Kent[5] as modified by Hough and Taha[6]. Treatment of **1** with a molar equivalent of sodium methoxide in methanol followed by *S*-ethyl trifluorothioacetate yielded crystalline 2-deoxy-2-(trifluoroacetamido)-D-glucose diethyl dithioacetal (**2**) in 73% yield. Compound **2** was acetylated with acetic anhydride–pyridine to give crystalline 3,4,5,6-tetra-*O*-acetyl-2-deoxy-2-(trifluoroacetamido)-D-glucose diethyl dithioacetal (**3**) in 93% yield.



The method of Gauthier[7] was employed to convert **3** into the corresponding 1-bromo derivative. Treatment of a solution of **3** in ether with slightly more than a molar equivalent of bromine gave syrupy 3,4,5,6-tri-*O*-acetyl-1-bromo-1,1,2-trideoxy-1-(ethylthio)-2-(trifluoroacetamido)-D-glucose aldehydrol (**4**), which was immediately condensed with bis(trimethylsilyl)thymine[8,9] by the fusion technique[8,10] to give a mixture of 1-epimeric nucleoside analogs. Resolution of the crude product by preparative t.l.c. gave amorphous 3,4,5,6-tetra-*O*-acetyl-1,1,2-trideoxy-1-(ethylthio)-1-thymin-1-yl-2-(trifluoroacetamido)-D-glucose aldehydrol, (+) form of **5**, and the corresponding crystalline, 1-epimeric (−) form of **5**, in yields of 15 and 26%, respectively, from **3**. The designation of these two epimeric forms as (+) and (−) is made on the basis of the signs of their optical rotations. Each of the two epimeric forms of **5** was deacylated with methanolic ammonia at room temperature, to give the C-1 epimeric forms of 2-amino-1,1,2-trideoxy-1-(ethylthio)-1-thymin-1-yl-D-glucose alde-

hydrol (**6a**). In each case, the product was obtained in a hygroscopic, amorphous form which quickly became a gum by absorption of atmospheric moisture. Treatment of the two epimeric forms of **6a** with dilute hydrochloric acid in methanol gave 2-amino-1,1,2-trideoxy-1-(ethylthio)-1-thymin-1-yl-D-glucose aldehydrol hydrochloride, (+) form of **6b**, and the corresponding, 1-epimeric, (−) form of **6b**, in 79 and 76% yields, respectively, from the two epimeric forms of **5**. These hydrochlorides were both obtained in amorphous form, but were readily handled, non-hygroscopic solids.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover apparatus. Specific rotations were determined in a 2-dm, polarimeter tube. Infrared spectra were recorded with a Perkin–Elmer Infracord spectrometer. Ultraviolet spectra were recorded with a Bausch and Lomb Spectronic 505 spectrometer. Optical rotatory dispersion spectra were recorded with a Jasco ORD/UV5 spectrometer. X-Ray powder diffraction data give interplanar spacings (Å) for CuKα radiation. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The stronger lines are numbered (1, strongest); multiple numbers indicate approximately equal intensities. T.l.c. was performed with Desaga equipment by using Silica Gel G (E. Merck, Darmstadt, Germany) activated at 110°. Indication was by sulfuric acid, unless otherwise noted; proportions of developers are given by volume. Evaporations were performed under diminished pressure (water aspirator). Microanalyses were made by W. N. Rond.

2-Deoxy-2-(trifluoroacetamido)-D-glucose diethyl dithioacetal (**2**). — To a suspension of 2-amino-2-deoxy-D-glucose diethyl dithioacetal hydrochloride[6,7] (**1**, 3.0 g) in methanol (30 ml) was added an equivalent amount of sodium methoxide in methanol (0.22 g of sodium metal dissolved in 10 ml of methanol). The mixture was swirled until only a small residue (sodium chloride) remained. *S*-Ethyl trifluorothioacetate (2.0 g) was added, and the mixture was kept for 24 h at room temperature, and evaporated to a solid that was extracted repeatedly with hot isopropyl ether (total 400 ml). The extracts were combined, concentrated to 100 ml, and refrigerated overnight. The white solid that formed was recrystallized from isopropyl ether, to give a white, crystalline solid; yield 2.6 g (73%), m.p. 103–105°, $[\alpha]_D^{23}$ −30 ±1° (*c* 1.4, water); λ_{max}^{KBr} 3.0 (NH, OH), 5.85 (*N*-trifluoroacetyl carbonyl), 6.45 (NH), 8.5 (CF), 9.25, 9.52, 9.65, 9.85, 10.32, 19.7, 10.85, 11.2, 12.5, 12.92, 13.65, and 14.4 μm; X-ray powder diffraction data: 13.10 s (2), 9.66 s, 8.49 s, 6.11 vw, 5.79 vw, 5.25 s (1), 5.04 m, 4.78 m, 4.46 s, 4.22 w, 4.10 m, 4.00 vw, 3.83 s, 3.58 w, 3.41 w, 3.30 m, 3.18 m, 2.99 m, 2.83 m, 2.68 vw, 2.57 vw, 2.47 vw, 2.41 w, 2.31 vw, 2.19 w, and 2.06 vw.

Anal. Calc. for $C_{12}H_{22}F_3NO_5S_2$: C, 37.86; H, 5.81; N, 3.67; S, 16.81. Found: C, 38.06; H, 5.82; N, 3.78; S, 17.00.

This compound was homogeneous by t.l.c. with ethyl acetate or 3:2 chloroform–acetone as the developer.

3,4,5,6-Tetra-O-acetyl-2-deoxy-2-(trifluoroacetamido)-D-glucose diethyl dithioacetal (3). — Compound **2** (1.2 g) was dissolved in a precooled (0°) mixture of acetic anhydride (3.5 ml) and pyridine (8.0 ml), and the solution was kept for 24 h at room temperature, poured into ice and water (20 ml), and the mixture extracted with dichloromethane (100 ml). The extract was washed with water, dried (sodium sulfate), and evaporated to a clear syrup which was crystallized from ethanol–water; yield 1.6 g (93%), m.p. 66–67°, $[\alpha]_D^{22}$ +2 ±0.5° (*c* 4.5, chloroform); λ_{max}^{KBr} 3.05 (NH), 5.7–5.8 (*O*-acetyl and *N*-trifluoroacetyl carbonyl), 6.42 (NH), 8.15–8.35 (ester), 8.68 (CF), 6.98, 7.35, 8.5, 9.55, 9.77, 10.25, 10.65, 11.48, 11.65, 12.0, 12.6, 12.9, 13.3, 13.63, 13.85, and 14.25 μm; X-ray powder diffraction data: 8.85 vs (1), 7.83 vs (3), 7.12 m, 6.61 s, 6.24 m, 5.57 s, 5.29 vw, 4.93 s, 4.71 s, 4.24 vs (2), 4.05 m, 3.92 vs, 3.78 m, 3.50 vs, 3.31 s, 3.20 vw, 3.07 m, 2.83 w, 2.77 m, 2.65 m, 2.56 m, 2.48 m, 2.41 vw, 2.35 w, 2.30 w, 2.26 w, 2.19 m, 2.03 m, 1.99 w, 1.96 w, 1.87 w, and 1.66 w.

Anal. Calc. for $C_{20}H_{30}F_3NO_9S_2$: C, 43.71; H, 5.50; N, 2.55; S, 11.67. Found: C, 43.53; H, 5.58; N, 2.58; S, 11.88.

This compound was homogeneous by t.l.c. with 2:1 ether–hexane as the developer.

3,4,5,6-Tetra-O-acetyl-1,1,2-trideoxy-1-(ethylthio)-1-thymin-1-yl-2-(trifluoroacetamido)-D-glucose aldehydrol, (+) and (−) forms of **5**. — Compound **3** (1.4 g) was dissolved in anhydrous ether (20 ml), and bromine (0.5 g) was added. After the solution had been kept for 15 min at room temperature, cyclohexene was added until no excess of bromine remained (as shown by change in color of the solution from bright red-orange to pale yellow). The solvent was then evaporated at 20° to give a pale-yellow syrup. Bis(trimethylsilyl)thymine[8,9] (2.5 g) and chloroform (25 ml) were added, and the mixture was stirred until homogeneous. Evaporation of the solvent at 20° yielded a syrup which was heated under diminished pressure (water aspirator) for 15 min at 120–130°. After being cooled to room temperature, the mixture was added to 80% aqueous ethanol (50 ml), the mixture was heated for 15 min at 60°, the solvent was evaporated, and the residue was extracted with chloroform (120 ml). The extract was washed, dried (sodium sulfate), and evaporated to a brown syrup (1.28 g). T.l.c. with ether as the developer (2 developments) revealed three major components (R_F 0.95, 0.68, and 0.62). The crude product was resolved on 56 chromatoplates (200 × 200 × 1 mm), with ether as the developer (each plate being developed twice) and indication by u.v. light. The two slower-moving zones (R_F 0.68 and 0.62) were removed, and extracted with acetone. Evaporation of the extract of the faster of these two zones (R_F 0.68) gave a colorless glass. Attempted crystallization from ether–hexane gave 3,4,5,6-tetra-*O*-acetyl-1,1,2-trideoxy-1-(ethylthio)-1-thymin-1-yl-2-(trifluoroacetamido)-D-glucose aldehydrol, (+) form of **5**, as a white, amorphous* solid; yield 0.24 g (15%), m.p. 81–85° (softening above 75°), $[\alpha]_D^{22}$ +53 ±1° (*c* 1.2, chloroform); λ_{max}^{KBr} 3.1 (NH), 5.7–5.8 (*O*-acetyl and *N*-trifluoro-

*It was concluded that this compound was amorphous because it gave a blank, or foggy, X-ray powder diffraction pattern.

acetyl carbonyl), 5.9, 6.45, 6.9 (NH, thymine), 8.2 (ester), 8.6 (CF), 7.3, 8.5, 9.0, 9.1, 10.52, 11.4, 11.75, 12.15, 12.9, 13.5, and 13.8 μm; λ_{max}^{EtOH} 207 (ε 14,400) and 269 nm (ε 10,000).

Anal. Calc. for $C_{23}H_{31}F_3N_3O_{11}S$: C, 45.02; H, 4.93; N, 6.85; S, 5.23. Found: C, 45.02; H, 5.12; N, 6.57; S, 5.74.

This compound was homogeneous by t.l.c. with ether as the developer (2 developments).

Evaporation of the extract from the slower-moving zone (R_F 0.62) gave a colorless glass which was crystallized from ether–hexane to give 3,4,5,6-tetra-*O*-acetyl-1,1,2-trideoxy-1-(ethylthio)-1-thymin-1-yl-2-(trifluoroacetamido)-D-glucose aldehydrol, (−) form of **5**, as a colorless, crystalline solid; yield 0.42 g (26%), m.p. 163–165°, $[\alpha]_D^{21}$ −90 ±1° (*c* 1.2, chloroform); λ_{max}^{KBr} 3.1 (NH), 5.75 (*O*-acetyl and *N*-trifluoroacetyl carbonyl), 5.9, 6.46, 6.9 (NH, thymine), 8.1–8.3 (ester), 8.62 (CF), 8.5, 8.95, 9.22, 9.4, 9.52, 9.7, 10.26, 10.38, 10.55, 11.0, 11.4, 11.7, 11.9, 12.18, 12.25, 13.0, and 13.9 μm; λ_{max}^{EtOH} 208 (ε 13,800) and 269 nm (ε 10,100); X-ray powder diffraction data: 11.48 s, 9.99 w, 7.76 vs (1), 7.23 s, 5.91 vw, 5.05 m, 4.76 vs (2), 4.52 w, 4.23 s, 4.08 m, 3.88 s (3), 3.60 s, 3.47 w, 3.33 m, 3.16 vw, 3.01 s, 2.91 w, 2.79 m, 2.63 m, 2.46 vw, 2.41 m, 2.22 w, 2.10 w, and 1.98 w.

Anal. Calc. for $C_{23}H_{31}F_3N_3O_{11}S$: C, 45.02; H, 4.93; N, 6.85; S, 5.23. Found: C, 44.97; H, 4.96; N, 7.09; S, 5.44.

This compound was homogeneous by t.l.c. with ether as the developer (2 developments).

*2-Amino-1,1,2-trideoxy-1-(ethylthio)-1-thymin-1-yl-*D*-glucose aldehydrol hydrochloride, (+) form of* **6b**. — The (+) form of **5** (180 mg) was dissolved in methanol presaturated at 0° with ammonia (40 ml). After being kept for 6 days at room temperature, the solution was concentrated to ~5 ml, and ether (50 ml) was added. The resulting, flocculent precipitate was filtered off, to give **6a** as an amorphous solid that quickly absorbed moisture from the air to become a brown gum. Attempted crystallization of this compound was unsuccessful.

Crude **6a** was dissolved in methanol (25 ml), M hydrochloric acid (0.4 ml) was added, and the solution was concentrated to ~5 ml by evaporation at 20°; the excess of hydrogen chloride was removed by repeated addition and evaporation of methanol. The solution was evaporated to a syrup which was dissolved in methanol (5 ml); ether (30 ml) was added and the resulting precipitate was filtered off. Attempted crystallization from methanol–chloroform–ether gave a stable, white, amorphous* solid (**6b**); yield 89 mg (79%), m.p. 205–214° with softening above 130° and swelling above 150°; $[\alpha]_D^{22}$ +93 ±3° (*c* 0.5, water); λ_{max}^{KBr} 3.0–3.35 (OH, NH_2^+), 5.9, 6.7, 6.82 (thymine), 7.1, 7.3, 7.95, 8.2, 9.02, 9.3, 9.75, 10.25, 11.05, 11.3, and 12.9 μm; $\lambda_{max}^{H_2O}$ 208 (ε 8,920) and 270 nm (8,360).

Anal. Calc. for $C_{13}H_{24}ClN_3O_6S$: C, 40.46; H, 6.27; Cl, 9.19; N, 10.89; S, 8.31. Found: C, 40.22; H, 6.39; Cl, 9.43; N, 10.44; S, 8.20.

*2-Amino-1,1,2-trideoxy-1-(ethylthio)-1-thymin-1-yl-*D*-glucose aldehydrol hydrochloride, (−) form of* **6b**. — The (−) form of **5** (250 mg) was deacylated with methanolic

ammonia, and the amorphous product (**6a**) was immediately converted into the hydrochloride (**6b**) by the procedure described in the preceding experiment. Attempted crystallization of the product from methanol–chloroform–ether gave a stable, amorphous* solid; yield 120 mg (76%), m.p. 199–211° with softening above 122° and swelling above 136°, $[\alpha]_D^{22}$ −107 ±3° (*c* 0.7, water); λ_{max}^{KBr} 3.0–3.42 (OH, NH_3^+), 5.9, 6.68, 6.82 (thymine), 7. 3, 7.91, 8.22, 9.05, 9.3, 9.78, 10.25, 11.15, 12.5, and 13.25 μm; $\lambda_{max}^{H_2O}$ 208 (ε 8,700) and 270 nm (8,970).

Anal. Calc. for $C_{13}H_{24}ClN_3O_6S$: C, 40.46; H, 6.27; Cl, 9.19; N, 10.89; S, 8.31. Found: C, 40.37; H, 6.53; Cl, 9.46; N, 10.76; S, 8.05.

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