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Note

Acyclic-sugar nucleoside analogs derived from cytosine with the D-aldopentoses, and from uracil with D-lyxose and D-ribose*†

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The synthesis of various nucleoside analogs having the sugar chain acyclic has been documented in several current[2–4] and earlier[5,6] papers from this laboratory. The work reported here is an outgrowth of syntheses[6] of acyclic-sugar uracil nucleosides having D-galactose, D-glucose, D-arabinose, and D-xylose as the sugar component. This article is concerned with application of similar procedures for synthesis of cytosine analogs with the four D-aldopentoses, and of the corresponding uracil derivatives of two D-aldopentoses, namely D-lyxose and D-ribose, that were not included in the earlier report[6]. The general, synthetic approach has involved condensation of the bis(trimethylsilyl)ated pyrimidines under fusion with the unstable 1-monobromo derivatives obtained by treating acetylated D-aldopentose dithioacetals with bromine; the condensation products are subsequently deprotected. The reaction introduces a new center of asymmetry at C-1, and two 1-epimers are, in principle, possible. The present work establishes, in three separate examples in the cytosine series, the feasibility of direct separation of the 1-epimers; in two other instances, the 1-epimeric mixture was not resolved. These compounds form the basis of a systematic study, by chiroptical and n.m.r.-spectral methods, of questions of C-1 stereochemistry and sugar-chain conformation in this general class of compound[7].

RESULTS AND DISCUSSION

Tetra-*O*-acetyl-D-arabinose diethyl dithioacetal (**1a**) was treated with bromine to replace[8] one of the two ethylthio groups by bromine, and the resultant, unstable α-halo thioether was fused for 20 min at 140° with an equimolar amount of 2,4-bis-(trimethylsilyl)cytosine[9] (**2**). The product was decomposed with aqueous methanol to split off the labile trimethylsilyl groups and give the coupled product **3a** as a solid

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†Portions of this work have been reported in preliminary form; see ref. 1.

that melted over a broad range. It was purified by preparative, loose-layer chromatography[10], whereupon the product, a glass, underwent slow crystallization from dichloromethane–ether to give, in 16% yield, an epimerically pure product, (—)-**3a**, having $[\alpha]_D$ —33° (methanol). The mother liquors contained the other 1-epimer, (+)-**3a**, $[\alpha]_D$ +108° (methanol); it was obtained essentially pure, but amorphous, in 22% net yield. Epimeric homogeneity was established, especially on the basis of distinctive, ^{1}H-n.m.r. signals for H-5 and H-6 (pyrimidine component) that readily allowed the detection of the 1-epimers in admixture*.

O-Deacetylation of (+)- and (—)-**3a** with methanolic ammonia proceeded in high yield, to afford the corresponding, crystalline tetrols, (+)- and (—)-**4a**, having $[\alpha]_D$ +138° and —108°, respectively (in water).

Application of essentially the same procedure starting from tetra-*O*-acetyl-D-lyxose diethyl dithioacetal (**1b**) gave 49% of the coupled, acetylated, cytosine nucleoside analog **3b** as a 1:1 mixture (n.m.r.) of 1-epimers; although the amorphous product gave an acceptable, elemental analysis, no separation of the epimers could be achieved by column chromatography. Deacetylation of this product gave the analytically pure tetrol **4b**, likewise as a 1:1, 1-epimeric mixture.

In the D-ribose series, the dithioacetal precursor **1c** was coupled as before, to give 45% of the amorphous, coupled product **3c** that could be partially, but not completely, resolved by chromatography; a fraction estimated to contain the (+)- and (—)-forms in 3:2 ratio had $[\alpha]_D$ +15°, and a later fraction from the column ($[\alpha]_D$ —86°) was rich (~85%) in (—)-**3c**. The latter was *O*-deacetylated, and the product purified chromatographically to epimeric homogeneity, giving practically pure (—)-**4c**, $[\alpha]_D$ —122°.

The same coupling-reaction, setting out from tetra-*O*-acetyl-D-xylose diethyl dithioacetal (**1d**) gave the acetylated, mixed 1-epimers; these were readily and completely separable by crystallization[11]. The pure (+)-**3d**, $[\alpha]_D$ +92°, was obtained in 32% yield from chloroform, and (—)-**3d** ($[\alpha]_D$ —134°) was then crystallized in 19% yield from a solution of the material (from the mother liquors) in acetone. Deacetylation of each gave the corresponding tetrols (+)-**4d** and (—)-**4d** ($[\alpha]_D$ +160° and —150°, respectively, in water). Likewise, the corresponding diisobutyl dithioacetal (**1e**) could be converted by way of an intermediate 1-bromide into the acetylated cytosine nucleosides **3e**, which could be separated by crystallization into pure (—)-**3e** (yield 42%, $[\alpha]_D$ —123° in chloroform, obtained from ethyl acetate–ether), and (+)-**3e** ($[\alpha]_D$ +70° in chloroform, obtained in 24% yield after loose-layer chromatography, and crystallization from chloroform). The corresponding, deacetylated products, (+)-**4e** and (—)**4e** ($[\alpha]_D$ +91° and —103° in water) were readily obtained crystalline.

All of the preceding, cytosine derivatives, both acetylated and deprotected, displayed u.v. absorption (log ε ~4) near 275 nm, consistent with the assigned, N-1-

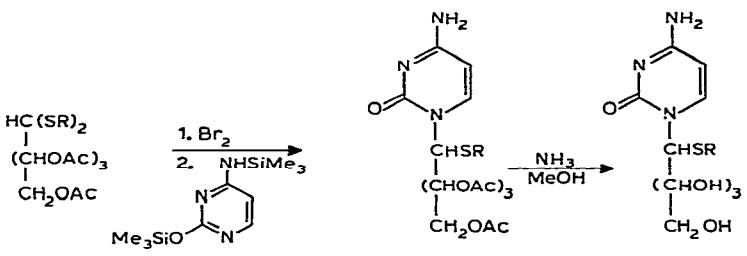
*Details of n.m.r.-spectral assignments from this and related work will be the subject of a separate, comparative report[7].

substituted structure that was also to be anticipated from mechanistic considerations and ample precedent in the literature.

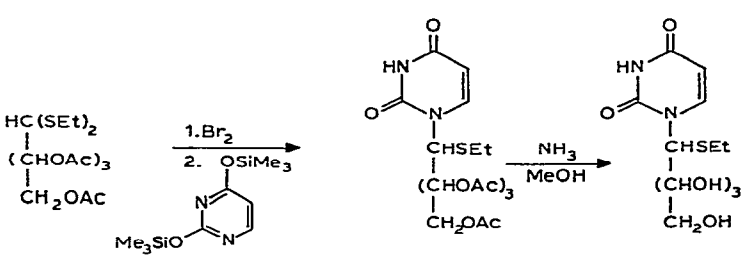
Starting out from tetra-*O*-acetyl-D-lyxose diethyl dithioacetal (**1b**), with initial bromination, followed by coupling *via* the fusion procedure with the bis(trimethylsilyl) derivative (**5**) of uracil, a syrupy, coupled product was isolated that could be crystallized to give 36% of pure (+)-**6b** ($[\alpha]_D$ +140°), but the corresponding (−)-**6b** could not be isolated. Deacetylation of (+)-**6b** gave the corresponding, crystalline tetrol (+)-**7b**, $[\alpha]_D$ +137° in water. The same sequence conducted in the D-ribose series gave (−)-**6c** as a pure, crystalline 1-epimer, $[\alpha]_D$ −61°, in 42% yield; the corresponding, deacetylated product (−)-**7c** was amorphous, but epimerically pure.

From the pairs of 1-epimers isolated in the foregoing work, it is noteworthy that one is strongly dextrorotatory at the sodium D line, whereas the other is strongly levorotatory. On the basis of the Generalized Heterocycle Rule[12,13], these products from the D sugars may be provisionally assigned[11] as the (1*R*) and (1*S*) epimers at C-1, but additional correlations need to be established for absolute verification of these assignments.

The compounds in this study did not significantly inhibit *Streptococcus faecalis* or *Escherichia coli* K-12; compound **4a** (1-epimeric mixture) displayed 32% inhibition of leukemia L-1210 cells at 100 μM.



a D-*arabino* R = Et
b D-*lyxo* R = Et
c D-*ribo* R = Et
d D-*xylo* R = Et
e D-*xylo* R = Me_2CHCH_2



b D-*lyxo*
c D-*ribo*

EXPERIMENTAL

General methods. — These were essentially as given in a preceding report[2]. T.l.c. was performed on Silica Gel G (E. Merck) activated at 100°, and R_F values refer to chromatographically homogeneous products. Loose-layer chromatography was performed on chromatoplates (200 × 200 × 2 mm) of Silica Gel 7734 (E. Merck) containing 1% of Lumilux Green 25 (a product of Riedel Dehaenag Seelze–Hannover, distributed by Brinkmann Instruments). The plates were prepared by techniques described by V. Černy and co-workers[10].

*2,3,4,5-Tetra-*O*-acetyl-1-(cytosin-1-yl)-1-*S*-ethyl-1-thio-*D*-arabinitol, (+) epimer* [(+)-**3a**] *and* (—) *epimer* [(—)-**3a**]. — Syrupy 2,3,4,5-tetra-*O*-acetyl-1-bromo-1-*S*-ethyl-1-thio-D-arabinitol[14] (9.2 g, 20 mmol; freshly prepared from compound **1a**) was mixed with 2,4-bis(trimethylsilyl)cytosine[9] (**2**; 6.72 g, 20 mmol) in a flask that was evacuated by means of a water aspirator. The flask was closed, the mixture was slowly heated to fusion, and the molten mixture was kept for 20 min at 140°, cooled under vacuum, and the dark residue triturated with 4:1 methanol–water (50 mL). The extract was evaporated to dryness, and the residue was extracted with hot chloroform (500 mL). The extract was filtered, and the filtrate was washed, dried (sodium sulfate), and evaporated. On trituration with ether, the residue yielded an amorphous solid, yield 5.5 g, m.p. 75–81°, that, by t.l.c., was ~95% homogeneous; R_F 0.26 (9:1 ethyl acetate–methanol); it contained a minor component having R_F 0.60 (9:1 ethyl acetate–methanol).

A sample (900 mg) of this crude material was subjected to preparative, loose-layer chromatography on 6 chromatoplates (200 × 200 × 2 mm). Each plate was developed twice with 19:1 chloroform–methanol. By using u.v. light as the indicator, the major band was collected. It was extracted with 19:1 chloroform–methanol (300 mL), and evaporation of the solvent gave a thick glass (650 mg) which, on slow crystallization from dichloromethane and ether, gave the pure, (—) epimer [(—)-**3a**]; yield 250 mg (16% overall), m.p. 129–130°, $[\alpha]_D^{24}$ —33° (*c* 1.0, methanol); R_F 0.44 (9:1 chloroform–methanol); λ_{max}^{MeOH} 278 nm (log ε 4.0); ν_{max}^{KBr} 4230 (NH_2), 3335 (NH), 1740 (OAc), 1670, 1640, 1525, 1490 (cytosine), and 1235–1205 cm^{-1} (ester); X-ray powder diffraction pattern: 9.38 s (2), 8.04 vs (1), 7.18 vw, 6.53 w, 5.85 s (3), 5.48 vw, 4.67 m, and 4.48 m; the compound gave a "soft", or hazy, X-ray powder diffraction pattern.

Anal. Calc. for $C_{19}H_{27}N_3O_9S$ (473.50): C, 48.19; H, 5.75; N, 8.87; S, 6.74. Found: C, 47.91; H, 6.04; N, 9.05; S, 6.87.

Evaporation of the mother liquor gave the (+) epimer [(+)-**3a**] as a chromatographically homogeneous (t.l.c.), amorphous product; yield 350 mg (22% overall), $[\alpha]_D^{21}$ +108° (*c* 0.5, chloroform); R_F 0.44 (9:1 chloroform–methanol); λ_{max}^{MeOH} 278 nm (log ε 3.95); ν_{max}^{film} 4230 (NH), 3330 (NH), 2985 (CH), 1750 (OAc), 1670, 1640, 1525, 1480 (cytosine), and 1240–1205 cm^{-1} (ester).

Anal. For $C_{19}H_{27}N_3O_9S$. Found: C, 47.75; H, 5.65; N, 9.04; S, 6.84.

*1-(Cytosin-1-yl)-1-*S*-ethyl-1-thio-*D*-arabinitol, (+) epimer* [(+)-**4a**] *and* (—)

epimer [(—)-**4a**]. — The dextrorotatory epimer **3a** (150 mg) was dissolved in methanol (40 mL) presaturated at 0° with ammonia. After 18 h at 25°, the solution was evaporated to a thin syrup. Methanol (5 mL) was added, and crystallization was induced by scratching the inside of the flask and evaporating off some of the methanol. The (+) epimer of **4a** crystallized from methanol; yield 80 mg (84%), m.p. 138–139°, $[\alpha]_D^{22}$ +138° (*c* 0.3, water); R_F 0.22 (1:1 chloroform–methanol); $\lambda_{max}^{H_2O}$ 275 nm (log ε 4.12); ν_{max}^{KBr} 3390–3330 (NH, OH), 2925 (CH), 1640, 1530, and 1480 cm^{-1} (cytosine); X-ray powder diffraction data: 12.80 m, 11.30 m, 9.56 m, 8.47 vw, 7.54 m, 6.94 vs (1), 6.37 m, 5.71 s (3), 5.21 s (3), 4.74 w, 4.64 m, 4.46 m, 4.16 s (2), 4.00 m, 3.91 m, 3.78 w, and 3.64 m.

Anal. Calc. for $C_{11}H_{19}N_3O_5S$ (305.35): C, 43.26; H, 6.27; N, 13.76; S, 10.49. Found: C, 42.87; H, 6.14; N, 13.72; S, 10.36.

The (—)-epimeric acetate **3a** (200 mg) was dissolved in methanol (40 mL) presaturated at 0° with ammonia. After 18 h at 25°, the solution was evaporated, giving a crystalline residue. The (—) epimer of **4a** was recrystallized from aqueous methanol; yield 110 mg (88%), m.p. 195–196° (softened at 155–156°), $[\alpha]_D^{21}$ —108° (*c* 0.35, water); R_F 0.22 (1:1 chloroform–methanol); $\lambda_{max}^{H_2O}$ 276 nm (log ε 3.96); ν_{max}^{KBr} 3330–3225 (NH, OH), 2925 (CH), 1640, 1530, and 1490 cm^{-1} (cytosine); X-ray powder diffraction data: 11.75 w, 9.71 m, 8.42 vw, 7.67 s (3), 7.12 vw, 6.64 vw, 5.86 w, 5.20 s, 4.83 s (2), 4.49 m, 4.26 w, 4.03 m, 3.80 vs (1), 3.60 w, 3.36 m, 3.27 m, and 3.11 m.

Anal. For $C_{11}H_{19}N_3O_5S$. Found: C, 43.26; H, 6.33; N, 13.51; S, 10.80.

*2,3,4,5-Tetra-*O*-acetyl-1-(cytosin-1-yl)-1-*S*-ethyl-1-thio-*D*-lyxitol, mixture of* (+) *and* (—) *epimers* (**3b**). — Syrupy 2,3,4,5-tetra-*O*-acetyl-1-bromo-1-*S*-ethyl-1-thio-D-lyxitol[14] (4.6 g, 10 mmol; freshly prepared from compound **1b**) was fused with 2,4-bis(trimethylsilyl)cytosine[9] (**2**; 3.35 g, 15 mmol) and then treated by the procedure used for the preparation of the D-arabinose analog **3a**, to yield a syrup (5.0 g). A portion (1.5 g) of this was purified by preparative, loose-layer chromatography on 10 chromatoplates (200 × 200 × 2 mm). Each plate was developed twice with 19:1 chloroform–methanol. The major band was collected, and the product extracted into 19:1 chloroform–methanol (300 mL). Evaporation of the extract gave the chromatographically homogeneous, amorphous, nucleoside derivative **3b**; yield 0.700 g (49% overall), $[\alpha]_D^{21}$ +31° (*c* 2.5, chloroform); R_F 0.35 (9:1 chloroform–methanol); λ_{max}^{MeOH} 278 nm (log ε 3.98); ν_{max}^{film} 3355 (NH), 3225 (NH_2), 2960 (CH), 1755 (OAc), 1650, 1575, 1500 (cytosine), 1375, and 1230–1215 cm^{-1} (ester).

Anal. For $C_{19}H_{27}N_3O_9S$. Found: C, 48.03; H, 5.81; N, 8.90; S, 7.03.

A sample (500 mg) of the foregoing compound was subjected to chromatography on a column (2 × 30 cm) of silica gel, with 24:1 chloroform–methanol as the eluant. The leading portion and the tailing portions of the peak eluted were collected separately. Evaporation of the solvent gave chromatographically homogeneous, amorphous products having $[\alpha]_D^{21}$ +30° (*c* 1.2, chloroform) and $[\alpha]_D^{21}$ +32°(*c* 0.8, chloroform), respectively, indicating no substantial epimeric resolution of the product.

*1-(Cytosin-1-yl)-1-*S*-ethyl-1-thio-*D*-lyxitol* (**4b**). — A sample (300 mg) of the

foregoing, acetylated derivative **3b** was deacetylated by the procedure described for the preparation of (+)-**4a**, and the resulting solution evaporated to give a thin syrup that was purified by preparative, loose-layer chromatography on 3 chromatoplates (200 × 200 × 2 mm). Each plate was first developed with ether, and then twice with 3:7 ethanol–ether (300 mL). Evaporation of the solvent gave chromatographically homogeneous, amorphous, compound **4b**; yield 100 mg (42%), $[\alpha]_D^{22}$ +38° (*c* 1.0, methanol); R_F 0.22 (1:1 ethyl acetate–methanol); $\lambda_{max}^{H_2O}$ 278 nm (log ε 4.05); ν_{max}^{film} 3310–3205 (NH, OH), 2925 (CH), 1640, 1610, 1530, and 1475 cm^{-1} (cytosine).

Anal. For $C_{11}H_{19}N_3O_5S$. Found: C, 43.01; H, 6.39; N, 13.51; S, 10.20.

*2,3,4,5-Tetra-*O*-acetyl-1-(cytosin-1-yl)-1-*S*-ethyl-1-thio-*D*-ribitol, mixture of* (+) *and* (—)*-epimers* (**3c**). — Syrupy 2,3,4,5-tetra-*O*-acetyl-1-bromo-1-*S*-ethyl-1-thio-D-ribitol[14] (4.6 g, 10 mmol; freshly prepared from compound **1c**) was fused with 2,4-bis(trimethylsilyl)cytosine[9] (**2**; 3.35 g, 15 mmol) and treated by the procedure used for compound **3a**, to yield a syrup (5.0 g); a portion (1.5 g) of this was purified by preparative, loose-layer chromatography on 10 chromatoplates (200 × 200 × 2 mm). Each plate was developed twice with 19:1 chloroform–methanol. The major band was collected, and extracted with 19:1 chloroform–methanol (300 mL). Evaporation of the extract gave chromatographically homogeneous, amorphous, product **3c**; yield 0.65 g (45% overall), $[\alpha]_D^{21}$ +8° (*c* 0.9, chloroform); R_F 0.42 (1:19 ethanol–ether).

The product was subjected to chromatography on a column (2 × 30 cm) of silica gel, with 24:1 chloroform–methanol as the eluant. The eluate was, as before, divided in two. Evaporation of one portion gave a chromatographically homogeneous, 3:2 mixture of the 1-epimeric, (+) and (—) forms of **3c**; yield 350 mg (24% overall), $[\alpha]_D^{21}$ +15° (*c* 0.5, chloroform); R_F 0.44 (9:1 chloroform–methanol; λ_{max}^{MeOH} 278 nm (log ε 3.98); ν_{max}^{film} 1750 (OAc), 1740 (cytosine), 1645, 1365, and 1220–1205 cm^{-1} (ester).

Anal. For $C_{19}H_{27}N_3O_9S$. Found: C, 48.24; H, 5.78; N, 8.97; S, 7.10.

Evaporation of the other portion of eluate gave a chromatographically homogeneous, amorphous product shown to be a 3:17 mixture of the (+) and (—) forms of **3c**; yield 200 mg (14%), $[\alpha]_D^{22}$ —86° (*c* 0.4, chloroform).

Data on the two fractions from the column showed that complete separation of the 1-epimers had still not been achieved.

*1-(Cytosin-1-yl)-1-*S*-ethyl-1-thio-*D*-ribitol* [(—)-**4c**]. — A sample of **3c** (fraction rich in levorotatory C-1-epimer; 160 mg) was deacetylated with methanolic ammonia by the procedure described for (+)-**4a**, and the resultant solution was evaporated to a thin syrup which was purified by preparative, loose-layer chromatography on 2 chromatoplates (200 × 200 × 2 mm). Each plate was developed 3 times with 4:1 chloroform–methanol. The band containing the major portion was collected, and extracted with 4:1 acetone–methanol (300 mL). Evaporation of the extract gave chromatographically homogeneous, amorphous, product (—)-**4c**; yield 70 mg (70%), $[\alpha]_D^{20.5}$ —122° (*c* 0.5, methanol); R_F 0.28 (1:1 ethyl acetate–methanol); $\lambda_{max}^{H_2O}$ 277 nm (log ε 4.02); ν_{max}^{film} 3335–3175 (NH, OH), 2925 (CH), 1640, 1610, 1530, and 1475 cm^{-1} (cytosine).

Anal. For $C_{11}H_{19}N_3O_5S$. Found: C, 42.95; H, 6.13; N, 13.66; S, 10.35.

*2,3,4,5-Tetra-*O*-acetyl-1-(cytosin-1-yl)-1-*S*-ethyl-1-thio-*D*-xylitol, (+) epimer* [(+)-**3d**] *and (—) epimer* [(—)-**3d**]. — Syrupy 2,3,4,5-tetra-*O*-acetyl-1-bromo-*S*-ethyl-1-thio-D-xylitol[14] (4.6 g, 10 mmol; freshly prepared from compound **1d**) was fused with 2,4-bis(trimethylsilyl)cytosine[9] (**2**; 3.36 g, 15 mmol) and treated by the procedure used for compound **3a**, to yield a thick glass (4.8 g) that, in t.l.c. with 9:1 chloroform–methanol, showed a major component having R_F 0.36 and a minor one with R_F 0.63. Trituration of this glass with ether yielded an amorphous solid (3.5 g) which was dissolved in chloroform, and ether was added to incipient turbidity. The (+) epimer **3d** separated slowly as a sharp-melting product; yield 1.5 g (32%), m.p. 111–112°, $[\alpha]_D^{22}$ +90° (*c* 0.35, chloroform). Recrystallization from acetone gave a yield of 1.1 g (23%) of (+)-**3d**; m.p. 125–126°, $[\alpha]_D^{22}$ +92° (*c* 0.30, chloroform); R_F 0.39 (9:1 chloroform–methanol); λ_{max}^{MeOH} 277 nm (log ε 4.05); ν_{max}^{KBr} 3335 (NH), 3095 (NH_2), 2970 (CH), 1745 (OAc), 1645–1400, 1480 (cytosine), 1365, and 1220–1205 cm^{-1} (ester). Although sharp-melting, the product gave a diffuse, X-ray powder diffraction pattern.

Anal. For $C_{19}H_{27}N_3O_9S$. Found: C, 47.96; H, 5.96; N, 8.82; S, 7.17.

The mother liquors from the isolation of (+)-**3d** were evaporated, to yield a thick glass (1.3 g) that was dissolved in acetone. On being kept, the (—) epimer of **3d** separated as a sharp-melting product; yield 900 mg (19%), m.p. 94–96°, $[\alpha]_D^{21}$ —134° (*c* 0.8, chloroform); R_F 0.39 (9:1 chloroform–methanol); λ_{max}^{MeOH} 277 nm (log ε 3.99); ν_{max}^{KBr} 3330 (NH), 3175 (NH_2), 2960 (CH), 1755 (OAc), 1650, 1550, 1480 (cytosine), 1370, and 1220–1205 cm^{-1} (ester). Although sharp-melting, the product gave a diffuse, X-ray powder diffraction pattern.

Anal. For $C_{19}H_{27}N_3O_9S$. Found: C, 48.03; H, 5.84; N, 9.01; S, 7.18.

*1-(Cytosin-1-yl)-1-*S*-ethyl-1-thio-*D*-xylitol, (+) epimer* [(+)-**4d**] *and (—) epimer* [(—)-**4d**]. — The dextrorotatory acetate (+)-**3d** (260 mg) was deacetylated with methanolic ammonia as described for the preparation of (+)-**4a**, and the resulting solution was concentrated until crystallization occurred. The resultant (+) epimer of **4d** was recrystallized from aqueous methanol; yield 160 mg (96%), m.p. 160–162°, $[\alpha]_D^{21}$ +160° (*c* 0.1, water); R_F 0.22 (1:1 ethyl acetate–methanol); $\lambda_{max}^{H_2O}$ 275 nm (log ε 4.05); ν_{max}^{KBr} 3450–3335 (NH, OH), 2925 (CH), 1655, 1615 and 1490 cm^{-1} (cytosine); X-ray powder diffraction data: 8.54 m, 7.03 m, 6.91 vw, 6.24 s (2), 5.75 s, 5.32 m, 5.24 vw, 4.61 vs (1,1), 4.47 w, 4.30 w, 3.90 vs (1,1), 3.99 m, 3.47 m, 3.04 w, 2.96 m, and 2.98 s.

Anal. For $C_{11}H_{19}N_3O_5S$. Found: C, 43.33; H, 6.28; N, 13.93; S, 10.80.

The levorotatory, epimeric acetate (—)-**3d** (600 mg) was deacetylated with methanolic ammonia as described for the preparation of (+)-**4a**, and the resulting solution was concentrated until crystallization occurred. The product, (—)-**4d**, was recrystallized from aqueous methanol; yield 350 mg (92%), m.p. 160–162°, $[\alpha]_D^{20}$ —150° (*c* 0.2, water); R_F 0.22 (1:1 ethyl acetate–methanol); $\lambda_{max}^{H_2O}$ 277 nm (log ε 4.0); ν_{max}^{KBr} 3390 (NH, OH), 3105 (CH), 1670, 1640, and 1505 cm^{-1} (cytosine); X-ray powder diffraction data (somewhat diffuse pattern): 11.04 s (2), 9.50 vw, 8.38 w,

7.53 m, 6.83 w, 6.37 s, 5.53 w, 5.06 s, 4.62 vs (1,1), 4.4 w, 4.09 w, 3.91 vw, and 3.73 vs (1,1).

Anal. For $C_{11}H_{19}N_3O_5S$. Found: C, 43.01; H, 6.68; N, 14.04; S, 10.63.

Tetra-O-acetyl-D-xylose diisobutyl dithioacetal (**1e**). — A solution of D-xylose diisobutyl dithioacetal[15] (4.68 g, 15 mmol) in pyridine (15 mL) and acetic anhydride (18 mL), prepared at 5°, was kept for 18 h at 25° and then poured into ice–water (300 mL) with continuous stirring. After 30 min at 25°, the product was extracted into chloroform (300 mL). The extract was washed, dried (sodium sulfate), and evaporated to a thick syrup. Traces of pyridine remaining in the syrup were removed by adding to, and evaporating from, the residue three, 50-mL portions of toluene, and then three, 50-mL portions of carbon tetrachloride. Further purification was effected on a column (30 × 3 cm) of silica gel, with 19:1 benzene–ethyl acetate as the eluant, to give chromatographically homogeneous (t.l.c.), syrupy **1e**; yield 4.6 g (64%), $[\alpha]_D^{21}$ +12° (*c* 1.4 chloroform); R_F 0.70 (1:1 benzene–ether); ν_{max}^{film} 2960 (CH), 1755 (OAc), 1470, 1370, and 1225–1200 cm^{-1} (ester).

Anal. Calc. for $C_{21}H_{36}O_8S_2$ (480.63): C, 52.47; H, 7.54; S, 13.34. Found: C, 52.49; H, 7.55; S, 13.09.

2,3,4,5-Tetra-O-acetyl-1-bromo-1-S-isobutyl-1-thio-D-xylitol. — Tetra-*O*-acetyl-D-xylose diisobutyl dithioacetal (**1e**; 4.5 g, 9.5 mmol) was dissolved in anhydrous ether (35 mL). The solution was cooled to 0–5°, and bromine (1.6 g, 10 mmol) was added. After 10 min at 5° and 5 min at 25°, the volatile constituents were evaporated off. The excess of bromine was removed by evaporating four, 30-mL portions of carbon tetrachloride from the residue, to afford a pale-yellow syrup; yield 4.4 g (100%). The product was unstable, and was used directly in the following experiment.

2,3,4,5-Tetra-O-acetyl-1-(cytosin-1-yl)-1-S-isobutyl-1-thio-D-xylitol, (+) epimer [(+)-**3e**] *and (−) epimer* [(−)-**3e**]. — The foregoing, syrupy bromide (4.4 g, 9.4 mmol) was fused with 2,4-bis(trimethylsilyl)cytosine[14] (**2**; 3.6 g, 15 mmol) and treated by the procedure described for the preparation of **3a**, to give a thick glass, yield 5.0 g, which, in t.l.c., with 9:1 ethyl acetate–methanol as the developer, showed a major component having R_F 0.44 and a minor one having R_F 0.97. The mixture was dissolved in ethyl acetate, and ether was added to incipient turbidity. The (−) epimer **3e** slowly separated as a sharp-melting solid. It was filtered off and washed three times with ether (30 mL); yield 1.5 g, m.p. 89–90°, $[\alpha]_D^{21}$ −121° (*c* 2.7, chloroform). The washings were mixed with the mother liquor, and evaporated to a thick glass which was dissolved in acetone, and ether was added to incipient turbidity. A second crop of a sharp-melting solid slowly separated, and was filtered off and washed with ether (30 mL); yield 700 mg, m.p. 89–90°, $[\alpha]_D^{21}$ −113° (*c* 1, chloroform). These two fractions were mixed, and recrystallized from chloroform–ether, to afford the (−) epimer (−)-**3e** as a sharp-melting solid; yield 2.0 g (42%), m.p. 89–91°, $[\alpha]_D^{21}$ −123° (*c* 1.5 chloroform); λ_{max}^{MeOH} 277 nm (log ε 4.02); R_F 0.31 (9:1 chloroform–methanol); ν_{max}^{KBr} 3450 (NH), 3175 (NH_2), 2985 (CH), 1760 (OAc), 1655, 1525, 1480 (cytosine), 1375, and 1230–1215 cm^{-1} (ester).

Anal. Calc. for $C_{21}H_{31}N_3O_9S$. (501.55): C, 50.28; H, 6.23; N, 8.37; S, 6.39. Found: C, 50.18; H, 6.39; N, 8.53; S, 6.38.

The mother liquors from the isolation of (—)-**3e** were evaporated to a thick glass (2.8 g), which, upon examination, showed the presence of the (+) epimer, (+)-**3e**. A sample (800 mg) was subjected to preparative, loose-layer chromatography on five plates (200 × 200 × 1.2 mm). Each plate was developed twice with 19:1 ethyl acetate–methanol. The band containing the nucleoside was isolated, and extracted with acetone (300 mL). Evaporation of the solvent gave a thick glass (400 mg) that was dissolved in chloroform. On slow evaporation, the (+) epimer (+)-**3e** separated out as a sharp-melting, white solid; yield 325 mg (24% overall), m.p. 112–114°, $[\alpha]_D^{21}$ +70° (*c* 0.3, chloroform); R_F 0.31 (9:1 chloroform–methanol); λ_{max}^{MeOH} 278 nm (log ε 3.92); ν_{max}^{KBr} 3425 (NH), 3175 (NH), 2940 (CH), 1760 (OAc), 1650, 1530, 1480 (cytosine), 1375, and 1230–1215 cm^{-1} (ester). Although (+)-**3e** and (—)-**3e** were sharp-melting, they gave diffuse, X-ray diffraction patterns.

Anal. For $C_{21}H_{31}N_3O_9S$. Found: C, 50.35; H, 6.40; N, 8.58; S, 6.26.

*1-(Cytosin-1-yl)-1-*S*-isobutyl-1-thio-*D*-xylitol, (+) epimer* [(+)-**4e**] *and* (—) *epimer* [(—)-**4e**]. — The dextrorotatory epimer (+)-**3e** (200 mg) was deacetylated with methanolic ammonia by the procedure described for (+)-**4a**, and the resulting solution was concentrated until crystallization occurred. The dextrorotatory epimer, (+)-**4e**, was filtered off, and washed twice with cold methanol (5 mL), and then with ether; yield 100 mg (76%), m.p. 210–212°, $[\alpha]_D^{22}$ +91° (*c* 0.6, water); R_F 0.21 (1:1 ethyl acetate–methanol); $\lambda_{max}^{H_2O}$ 274 nm (log ε 3.91); ν_{max}^{KBr} 3355 (OH), 3205 (NH_2), 2935 (CH), 1655, 1640, 1615, and 1490 cm^{-1} (cytosine); X-ray powder diffraction data: 9.40 s, 8.51 vw, 7.79 s, 7.40 vw, 6.59 s (2,2), 6.32 s (2,2), 6.01 m, 5.52 m, 5.36 vw, 4.68 vw (1,1), 4.35 vs (1,1), 4.23 w, and 3.99 w.

Anal. Calc. for $C_{13}H_{23}N_3O_5S$ (333.40)· C, 46.84; H, 6.96; N, 12.61; S, 9.62. Found: C, 46.57; H, 7.03; N, 12.79; S, 9.85.

The levorotatory epimer (—)-**3e** (1.5 g) was deacetylated with methanolic ammonia, and the product, **4e**, was isolated crystalline by the procedure just described; yield 700 mg (71%), m.p. 126–128°, $[\alpha]_D^{21}$ —103° (*c* 0.8, water); R_F 0.21 (1:1 ethyl acetate–methanol); $\lambda_{max}^{H_2O}$ 273 nm (log ε 3.94); ν_{max}^{KBr} 3330 (OH), 3205 (NH_2), 2940 (CH), 1640, 1605, 1490, and 1490 cm^{-1} (cytosine); X-ray powder diffraction data: 8.68 vs (1), 7.84 w, 7.02 s, 6.28 vs (2), 5.89 vw, 5.38 s, 4.97 m, 4.73 vw, 4.55 m, 4.32 m, 3.89 s (3), 3.75 vw, and 3.59 vw.

Anal. For $C_{13}H_{23}N_3O_5S$. Found: C, 46.74; H, 7.23; N, 12.81; S, 9.81.

*2,3,4,5-Tetra-*O*-acetyl-1-*S*-ethyl-1-thio-1-(uracil-1-yl)-*D*-lyxitol, (+) epimer* [(+)-**6b**]. — Syrupy 2,3,4,5-tetra-*O*-acetyl-1-bromo-1-*S*-ethyl-1-thio-D-lyxitol (2.0 g, 4.35 mmol; freshly prepared from compound **1b**) was fused with 2,4-bis(trimethylsilyloxy)pyrimidine[9] (**5**; 1.46 g, 6.5 mmol) and treated by the procedure used for compound **3a**, to yield a thick syrup that crystallized spontaneously. Recrystallization from ether gave pure compound (+)-**6b**; yield 500 mg (24%), m.p. 143–144°, $[\alpha]_D^{23}$ +140° (*c* 0.6, chloroform); R_F 0.39 (ether); λ_{max}^{MeOH} 266 nm (log ε 3.98); ν_{max}^{KBr} 3390 (NH), 1755 (OAc), 1695, and 1450 cm^{-1} (uracil); X-ray powder diffraction data:

10.88 w, 9.46 w, 8.66 vw, 7.76 vs (1), 7.18 vw, 6.56 s (2), 6.23 vw, 5.73 s (3), 5.53 m, 5.10 m, 5.10 m, 4.79 m, 4.32 s, 4.13 vw, 3.79 s, and 3.79 vw.

Anal. Calc. for $C_{19}H_{26}N_2O_{10}S$ (474.49): C, 48.15; H, 5.52; N, 5.90; S, 6.75. Found: C, 48.07; H, 5.24; N, 5.76; S, 6.98.

Concentration of the mother liquor gave a second fraction: yield 312 mg (16%), m.p. 136–138°, $[\alpha]_D^{20}$ +122° (*c* 1.3, chloroform). Recrystallization of the second crop gave pure (+)-**6b**, as identified by its X-ray powder diffraction pattern; yield 250 mg (36% overall).

1-S-*Ethyl-1-thio-1-(uracil-1-yl)*-D-*lyxitol, (+)-epimer* [(+)-**7b**]. — The foregoing, acetylated derivative (+)-**6b** (250 mg) was treated with methanolic ammonia as described for the preparation of (+)-**4a**. The resulting solution was evaporated to a thick syrup that crystallized spontaneously on being kept; yield 115 mg (90%), m.p. 134–136°, $[\alpha]_D^{20}$ +137° (*c* 0.3, water); R_F 0.34 (4:1 ethyl acetate–methanol); $\lambda_{max}^{H_2O}$ 266 nm (log ε 3.99); ν_{max}^{KBr} 3450–3330 (NH, OH), 2940 (CH), 1695, 1625, and 1470 cm^{-1} (uracil); X-ray powder diffraction data: 12.89 m, 8.15 w, 7.25 w, 6.15 vw (1,1), 5.73 vw (1,1), 5.23 w, 5.03 s (2,2), 4.8 s (2,2), 4.44 m, 3.91 m, 3.76 w, 3.63 w, 3.39 vw, 3.23 s, and 3.17 vw.

Anal. Calc. for $C_{11}H_{18}N_2O_6S$ (306.34): C, 43.12; H, 5.92; N, 9.14; S, 10.46. Found: C, 43.30; H, 6.08; N, 9.36; S, 10.57.

2,3,4,5-Tetra-O-acetyl-1-S-ethyl-1-thio-1-(uracil-1-yl)-D-*ribitol, (—) epimer* [(—)-**6c**]. — Syrupy 2,3,4,5-tetra-*O*-acetyl-1-bromo-1-*S*-ethyl-1-thio-D-ribitol (4.6 g, 10 mmol; freshly prepared from compound **1c**) was fused with 2,4-bis(trimethylsilyloxy)pyrimidine[9] (**6**; 3.36, 15 mmol) and treated by the procedure used for compound **3a**, to yield a thick syrup which was purified on a column (3 × 40 cm) of silica gel with 9:1 benzene–ethyl acetate as the eluant. Evaporation of the solvent gave a thick syrup which, upon trituration with ether, gave crystalline (—)-**6c**. It was recrystallized from ether; yield 1.98 g (42%), m.p. 102–103°, $[\alpha]_D^{21}$ —61° (*c* 1.2, chloroform); R_F 0.35 (ether); λ_{max}^{MeOH} 265 nm (log ε 4.01); ν_{max}^{KBr} 3450 (NH), 3030 (CH), 1755 (OAc), 1705, 1470 (uracil), 1370 and 1225–1205 cm^{-1} (ester); X-ray powder diffraction data: 11.50 m, 10.54 m, 7.1 vs (1,1), 6.21 vs (1,1), 5.82 w, 5.26 m, 4.62 m, 4.24 vw, 4.03 (2,2), and 3.83 (2,2).

Anal. For $C_{19}H_{26}N_2O_{10}S$. Found: C, 48.50; H, 5.77; N, 6.17; S, 6.99.

1-S-Ethyl-1-thio-(uracil-1-yl)-D-*ribitol, (—) epimer* [(—)-**7c**]. — The foregoing tetraacetate (—)-**6c** (1.0 g) was treated with methanolic ammonia as described for the preparation of (+)-**4a**, and the resulting solution was evaporated to a thick syrup which was purified by preparative, loose-layer chromatography on 10 chromatoplates (200 × 200 × 2 mm). Each plate was developed twice with 4:1 chloroform–methanol. The band containing the major product was collected, and extracted with 4:1 acetone–methanol (350 mL). Evaporation of the extract gave chromatographically homogeneous, amorphous, compound (—)-**7c**; yield 400 mg (~80%), $[\alpha]_D^{21}$ —91° (*c* 0.8, methanol); R_F 0.38 (4:1 ethyl acetate–methanol); $\lambda_{max}^{H_2O}$ 265 nm (log ε 4.05); ν_{max}^{film} 3450–3330 (NH, OH), 1680–1655, and 1460 cm^{-1} (uracil).

Anal. For $C_{11}H_{18}N_2O_6S$. Found: C, 43.32; H, 6.20; N, 9.37; S, 10.24.

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