Nucleosides. XLV. 1-α-L-*aldo*-Pentofuranosylpyrimidines[1]

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Methods are described for the synthesis of the 1-α-L-arabinofuranosyl derivatives of thymine, cytosine, and uracil. The uracil and thymine derivatives were converted *via* anhydronucleoside intermediates to nucleosides of the α-L-xylo and α-L-lyxo configurations. Two syntheses of 1-α-L-xylofuranosylcytosine (the C-4′ epimer of the biologically active 1-β-D-arabinofuranosylcytosine) from 2,2′-anhydro-1-(3′,5′-di-*O*-benzoyl-α-L-xylofuranosyl)uracil are described. Preliminary screening studies of these L nucleosides showed no significant activity against L1210 mouse leukemia or Burkitt's tumor cells in tissue culture. The cytosine nucleosides are not deaminated by human liver or mouse kidney homogenates, nor do they inhibit the deamination of 1-β-D-arabinofuranosylcytosine in these systems.

The sugar moieties of all nucleosides hitherto found in nature (*i.e.*, those derived from the nucleic acids or from nucleoside antibiotics) are of the D configuration.[2,3] This report deals with the synthesis of pyrimidine nucleoside analogs which differ from certain biologically important nucleosides *only* in the configuration of C-4′. Such C-4′ epimers are the hitherto unknown 1-α-L-*aldo*-pentofuranosylpyrimidines. Of special interest are the synthesis and biological study of the C-4′ epimer of the chemotherapeutically active 1-β-D-arabinofuranosylcytosine[4] and of the tRNA component, 1-β-D-ribofuranosylthymine.[5]

Direct access to α-L-thymine nucleosides (without the production of anomeric mixtures) was readily achieved by utilization of the mercuri procedure[6] (see Scheme I). Condensation of an anomeric mixture of tri-*O*-benzoyl-L-arabinofuranosyl bromides[7] (**1**) with dithyminyl mercury[6] in refluxing toluene afforded 50–70% yield of 1-(tri-*O*-benzoyl-α-L-arabinofuranosyl)-thymine (**2**) which was debenzoylated with NaOH in 50% ethanol to 1-α-L-arabinofuranosylthymine (**3a**). The L-*ara*-thymine nucleoside (**3a**) showed, as expected, ultraviolet absorption properties generally similar to those for 1-glycosylthymines[8] and, when treated with metaperiodate, **3a** consumed 1 mole/mole, *slowly* (40 hr), in accord with a *trans*-glycol system. The fact that the optical rotation of **3a** was of equal magnitude to but of opposite sign from the known enantiomorphic nucleoside, 1-α-D-arabinofuranosylthymine,[9] establishes the α-L configuration for **3a** and for all the nucleosides subsequently derived from it (**3a** → **9a**, **10a**). Mesylation of **3a** with methanesulfonyl chloride in pyridine afforded 1-(tri-*O*-mesyl-α-L-arabinofuranosyl)thymine (**4a**). Large-scale preparation of **4a** may be achieved from **1** in ~35% over-all yield without isolation of **2** and **3a**.

For the conversion of **4a** to the α-L-xylo and α-L-lyxo isomers (**9a** and **10a**), approaches previously employed in this laboratory[10,11] were adapted. Treatment of **4a** with 1 equiv of NaOH in 50% ethanol yielded the 2,2′-anhydro derivative **5a** which, after treatment with sodium benzoate in DMF, gave the 2,2′-anhydro 5′-benzoate (**6a**, X = O). Reaction of **6a** with sodium benzoate in DMF *and benzoic acid* gave, as major products, **7a** and **8a**.

A unified pathway for the conversion of anhydro nucleosides of type **6** ((X = O) to nucleosides of type **7** and **8** has been discussed.[11] Formation of anhydro nucleoside **7** probably proceeds *via* benzoate attack at C-2′ of the protonated nucleoside **6**, followed by the intramolecular displacement of the 3′-mesyloxy function with formation of a 2′,3′-orthoester ion. Attack by the 2-carbonyl on this orthoester would produce **7a**. Attack of benzoate ion on **7a** produced the α-L-lyxo nucleoside **8a**. Alkali treatment of **7a** and **8a** in dilute alcohol gave the unblocked crystalline nucleosides **9a** and **10a**, respectively. Nucleosides **9a** and **10a** differed in melting point and electrophoretic mobility from **3a** but showed ultraviolet absorption properties expected for 1-substituted glycosylthymines.[8] When **9a** was treated with metaperiodate, 1 equiv of oxidant was consumed. This consumption was very slow (170 hr) indicative of a *trans*-glycol system. These data establish the L-xylo configuration of **9a**. Nucleoside **10a** showed a rapid uptake of metaperiodate (within 3 min), similar to that reported for 1-α-D-ribofuranosylthymine,[6] consonant with a *cis*-glycol system. Nucleoside **10a** exhibited the same melting point as the enantiomorphic nucleoside 1-α-D-lyxofuranosylthymine[9] and gave identical nmr data. These data establish **10a** as 1-α-L-lyxofuranosylthymine. It should be noted that the L-lyxo (**10a**) and L-xylo (**9a**) nucleosides are the C-4′ epimers of 1-β-D-ribofuranosylthymine[6] and of "spongothymidine" (1-β-D-arabinofuranosylthymine).[12]

Easy access to the uracil nucleoside (**3b**) was accomplished by the deamination of **11** which was prepared by the procedure of Yamaoka, *et al.*[13,14] Condensa-

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748).

(2) J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959).

(3) J. J. Fox, K. A. Watanabe, and A. Bloch, *Progr. Nucleic Acid Res. Mol. Biol.*, **5**, 252 (1966).

(4) S. S. Cohen, *ibid.*, **5**, 2 (1966).

(5) P. R. Srinivasan and E. Borek, *ibid.*, **5**, 157 (1966).

(6) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).

(7) Tri-*O*-benzoyl-α,β-L-arabinofuranosyl bromide was prepared according to the method described for the enantiomorph; see H. G. Fletcher, Jr., *Methods Carbohydrate Chem.*, **2**, 228 (1963); R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **80**, 2007 (1958).

(8) J. J. Fox and D. Shugar, *Biochim. Biophys. Acta*, **9**, 369 (1952).

(9) T. Nishimura and B. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **7**, 803 (1965).

(10) J. F. Codington, R. Fecher, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 2794 (1960).

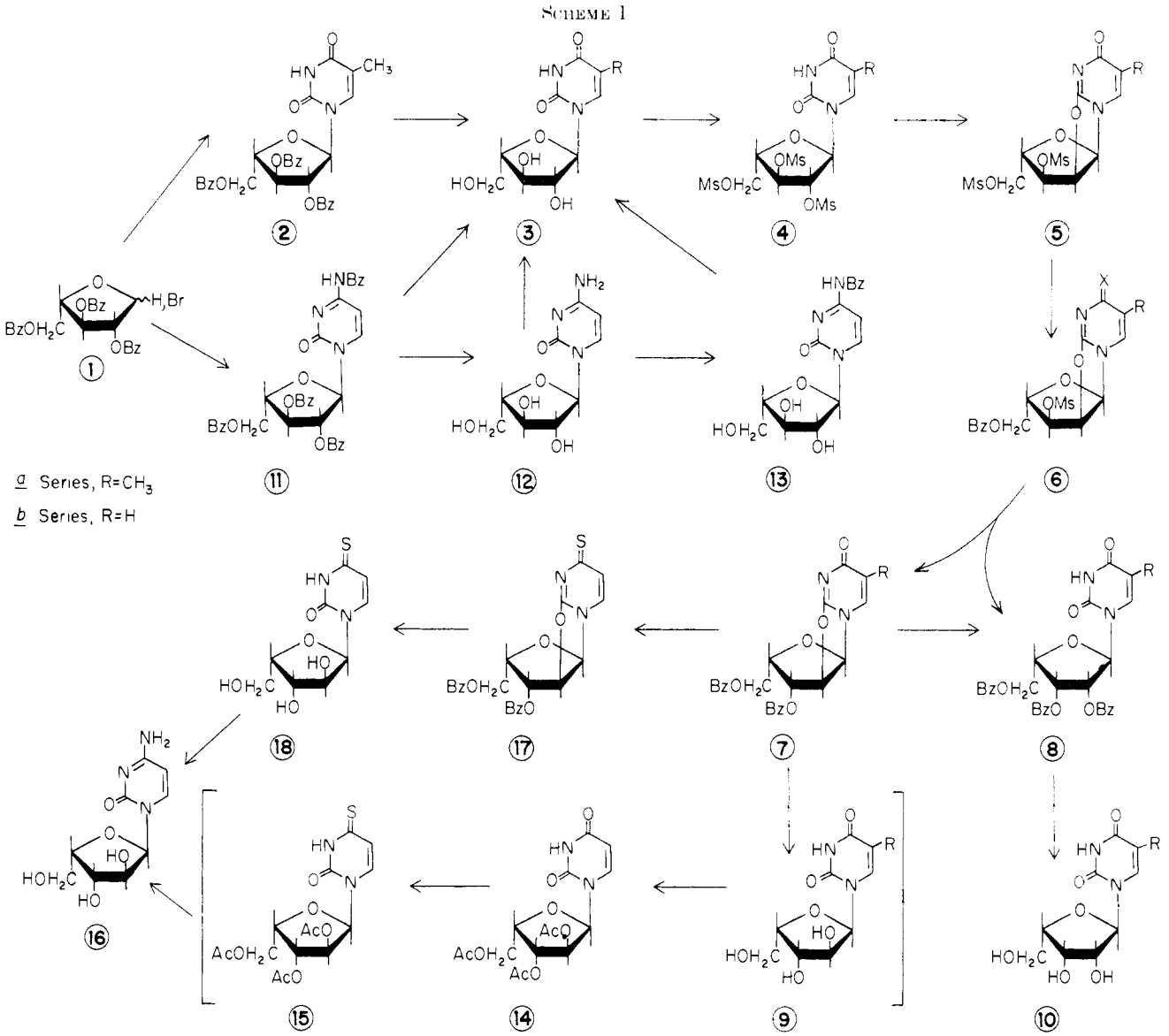
(11) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).

(12) J. J. Fox, N. Yung, and A. Bendich, *J. Am. Chem. Soc.*, **79**, 2775 (1957).

(13) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965).

(14) The direct synthesis of uracil nucleosides by this procedure is currently under investigation in this laboratory.

SCHEME I



tion of N^4-benzoylcytosine[15] with tri-*O*-benzoyl-α,β-L-arabinofuranosyl bromide (**1**) in nitromethane containing mercuric cyanide afforded a high yield (80–90%) of the tetrabenzoylated nucleoside (**11**). Treatment of **11** with alkali gave 1-α-L-arabinofuranosylcytosine (**12**) in quantitative yield. Conventional deamination of **12** with nitrous acid did yield **3**; however, the method was cumbersome and the yields were low. Selective N^4-benzoylation[16] of **12** gave **13** in good yield which was smoothly converted to **3b** by refluxing with hot aqueous acetic acid.[17] It was found more convenient to prepare **3b** by treatment of **11** with hot aqueous acetic acid and then with 1 *N* NaOH. The arabino nucleoside (**3b**) formed an amorphous tri-*O*-mesylate (**4b**) which was converted with alkali to the crystalline anhydro-L-ribo nucleoside (**5b**). Reaction of **5b** with sodium benzoate in DMF at 100° gave **6b** (X = O). Treatment of **6b** (X = O) with sodium benzoate in DMF with benzoic acid (as described above for the thymine nucleoside series) yielded a mixture of **7b** and **8b**, the latter of which was converted to 1-α-L-lyxofuranosyluracil (**10b**) by alkali. Nucleoside **10b** showed physical properties expected for the enantiomorph of the known 1-α-D-lyxofuranosyluracil.[9]

Nucleoside **7b** was converted to the crystalline 1-α-L-xylofuranosylcytosine (**16**) in 27% over-all yield in four steps (*via* **9b**, **14**, and **15**) without isolation of the intermediates. When treated with metaperiodate, nucleoside **16** consumed 1 equiv slowly (as did **12**) indicative of a *trans*-glycol system. Compound **16** differed from **12** in melting point, optical rotation, and paper-electrophoretic migration. All of the data permit the assignment of only the L-xylo configuration to **16**.

Earlier studies[18] had shown that certain anhydro nucleosides could be thiated to their 4-thiono derivatives, and when **6b** (X = O) was thiated with P_2S_5 in pyridine under mild anhydrous conditions, **6b** (X = S) was obtained. Similarly, thiation of the di-*O*-benzoate (**7b**) gave a 64% yield of **17**. Treatment

(15) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2384 (1956).

(16) K. A. Watanabe and J. J. Fox, *Angew. Chem. Intern. Ed. Engl.*, **5**, 579 (1966); B. A. Otter and J. J. Fox in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Interscience Publishers, Inc., New York, N. Y., in press.

(17) Brown, *et al.*,[15] had demonstrated that N^4-benzoylcytosine is converted to uracil and cytosine (ratio 33:1) by this procedure.

(18) N. Yung and J. J. Fox, *J. Org. Chem.*, **27**, 1447 (1962).

of **17** with dilute alkali afforded **18** which was converted to 1-α-L-lyxofuranosylcytosine (**16**) in ~45% over-all yield from **7b**. Nucleosides **10b** and **16** are the C-4′ epimers of uridine and 1-β-D-arabinofuranosylcytosine, respectively.

Screening Studies.[19,20]—In preliminary studies the 1-α-L derivatives of arabinosyl- and xylosylcytosine (**12** and **16**) were inactive against L1210 mouse leukemia at doses of 120 mg/kg given daily intraperitoneally, starting 24 hr after inoculation of leukemia and continued for 10 consecutive days. None of the 1-α-L nucleosides (**3a**, **9a**, **10a**, **12**, and **16**) were inhibitory to Burkitt's tumor cells in culture in doses as high as 30 mg/ml. The cytosine L-nucleosides **12** and **16** (unlike 1-β-D-arabinofuranosylcytosine) were not deaminated to their uracil analogs by human liver or mouse kidney homogenates, nor did they inhibit the deamination of 1-β-D-arabinofuranosylcytosine in these systems even with a substrate to inhibitor ratio of 10:1. These data attest to the importance of the configuration at C-4′ in the biological activity of 1-β-D-arabinofuranosylcytosine.

Experimental Section[21]

1-(Tri-*O*-benzoyl-α-L-arabinofuranosyl)thymine (2).—Powdered dithyminylmercury[6] (2.15 g, 4.76 mmoles) was added to 150 ml of dry toluene. The vigorously stirred suspension was dried by azeotropic distillation of about 50 ml of solvent. A solution of tri-*O*-benzoyl-α,β-L-arabinofuranosyl bromide[7] (5.0 g, 9.52 mmoles) in 30 ml of dry toluene was added and a further 30 ml of solvent removed by distillation. Refluxing was continued for 1 hr during which time most of the solid material dissolved. The warm solution was filtered from 0.5 g of insoluble material, and the filtrate was concentrated *in vacuo* to *ca.* 50 ml. The solution was treated with 500 ml of petroleum ether (bp 30–60°) and the resulting precipitate was collected and dissolved in $CHCl_3$. After filtration, the $CHCl_3$ solution was washed with freshly prepared 30% aqueous KI then H_2O and dried ($MgSO_4$). Removal of solvent *in vacuo* left a yellow, viscous syrup which contained **2** and several minor components. A solution of the syrup in C_6H_6–Et_2O (2:1) was placed on a column of silica gel (2.5 × 30 cm). The column was eluted with C_6H_6–Et_2O (2:1) until the minor components had been removed, then with EtOAc. The syrup, obtained by concentration of the EtOAc solution, was chromatographically pure but resisted all attempts at crystallization. When stored *in vacuo*, it changed to a colorless, amorphous solid (3.9 g, 72%): $\lambda_{max}^{dil\ EtOH}$ 235, 268 mμ; λ_{min} 210, 257 mμ.

Anal. Calcd for $C_{31}H_{26}N_2O_9$: C, 65.26; H, 4.95; N, 4.91. Found: C, 65.29; H, 4.75; N, 4.99.

1-α-L-Arabinofuranosylthymine (3a).—Amorphous **2** (1.0 g, 1.75 mmoles) was dissolved in 15 ml of warm, 50% aqueous EtOH containing 6.0 ml of 1 *N* NaOH. The solution was refluxed for 30 min, cooled, and neutralized with HOAc. The concentrated solution (*ca.* 7 ml) was treated with Dowex 50 (H^+) (*ca.* 1 g of moist resin). The precipitated benzoic acid was removed along with the resin, and the resin treatment was repeated. The last traces of benzoic acid were removed by extraction of the filtrate with $CHCl_3$. Concentration of the aqueous phase afforded 423 mg (90%) of an amorphous solid. The product, in 90% aqueous EtOH, crystallized after several months at 4°. Even with seed crystals, crystallization of **3a** (from several solvent systems) was difficult. Crystalline material melted indistinctly at 115–125° (eff) and showed $[\alpha]^{25}D$ −37° (*c* 0.7, H_2O). The enantiomorph, 1-α-D-arabinofuranosylthymine, was reported[9] as an amorphous solid with $[\alpha]D$ +40° (H_2O), $\lambda_{max}^{H_2O}$ 267 mμ, λ_{min} 235 mμ.

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 45.90; H, 5.50; N, 10.45.

1-(Tri-*O*-mesyl-α-L-arabinofuranosyl)thymine (4a). Method A.—$MeSO_2Cl$ (0.06 ml, 0.77 mmole) was added to a solution of 56.0 mg (0.22 mmole) of amorphous **3a** in 2 ml of dry pyridine. After 24 hr at room temperature, the dark solution was poured into 50 ml of ice–H_2O. Crystalline material slowly formed, and after *ca.* 30 min, the solid was collected and washed with H_2O. The solid was dissolved in hot 50% aqueous EtOH and the solution was treated with charcoal. The product (50 mg, 49%) crystallized from the cold filtrate as fine needles. Analytically pure material, mp 125–126°, was obtained after a further recrystallization; $\lambda_{max}^{dil\ EtOH}$ 266 mμ, λ_{min} 233 mμ.

Anal. Calcd for $C_{13}H_{20}N_2O_{12}S_3$: C, 31.70; H, 4.09; N, 5.69; S, 19.53. Found: C, 31.59; H, 4.29; N, 5.69; S, 19.29.

Method B.—Crude, syrupy **2** (obtained as above from 5.60 g of dithyminylmercury and 13.0 g of **1**) was dissolved in 150 ml of 50% aqueous EtOH containing 60 ml of 1 *N* NaOH; this was refluxed for 30 min and processed as described above for the preparation of **3a**. The resulting syrupy residue was dissolved in EtOH and dried by azeotropic distillation of the solvent. The syrup was dissolved in pyridine (100 ml) and the distillation was repeated. The dry syrup was dissolved in 100 ml of dry pyridine and the solution was cooled to 5°. $MeSO_2Cl$ (8.0 ml) was added dropwise, and the solution was kept at room temperature for 2 hr. The dark reaction mixture was poured into 700 ml of cold H_2O. After 2 hr at 4°, the crystalline material was collected and recrystallized from 50% aqueous EtOH (charcoal). The yield was 4.0 g (33%) of material (mp 123–125°) suitable for transformation to **5a**.

2,2′-Anhydro-1-(3′,5′-di-*O*-mesyl-α-L-ribofuranosyl)thymine (5a).—A hot solution of 1.0 g (2.03 mmoles) of **4a** in 100 ml of 50% aqueous EtOH was cooled quickly to avoid crystallization. When the temperature reached 40°, 2.08 ml of NaOH (1.0 *N*) was added slowly with stirring. Within 5 min of the addition, crystalline material formed. The mixture was kept at 5° for 1 hr then filtered. Recrystallization of the product (700 mg, 87%) from dilute EtOH afforded colorless needles: mp 246–247°; $\lambda_{max}^{dil\ EtOH}$ 227, 248 mμ; λ_{min} 214, 238 mμ.

Anal. Calcd for $C_{12}H_{16}N_2O_9S_2$: C, 36.38; H, 4.07; N, 7.07; S, 16.18. Found: C, 36.46; H, 3.96; N, 7.01; S, 15.90.

2,2′-Anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-α-L-ribofuranosyl)thymine (6a, X = O).—Compound **5a** (2.0 g, 5.04 mmoles) was added to a hot solution of 805 mg (5.6 mmoles) of sodium benzoate in 200 ml of dry DMF. A clear solution was obtained after *ca.* 30 min of heating on a steam bath. After 4 hr of heating, the solution was concentrated *in vacuo* (oil pump, bath 55°) to *ca.* 50 ml. The solution was poured into 400 ml of cold H_2O and, after 1 hr of cooling, the solid was collected and washed with H_2O. Recrystallization from EtOAc afforded 1.6 g (75%) of pure material: mp 234–235°; $\lambda_{max}^{dil\ EtOH}$ 232, shoulder 250–270 mμ; λ_{min} 212 mμ.

Anal. Calcd for $C_{18}H_{18}N_2O_8S$: C, 51.18; H, 4.29; N, 6.63; S, 7.58. Found: C, 51.09; H, 4.33; N, 6.47; S, 7.70.

2,2′-Anhydro-1-(3′,5′-di-*O*-benzoyl-α-L-xylofuranosyl)thymine (7a) and Tri-*O*-benzoyl-α-L-lyxofuranosylthymine (8a).—A solution of 2.0 g (4.73 mmoles) of **6a** (X = O) in 400 ml of dry DMF containing 2.72 g (18.82 mmoles) of sodium benzoate and 580 mg (4.73 mmoles) of benzoic acid was heated at *ca.* 150° for 4.5 hr. The dark reaction mixture was cooled and concentrated to dryness *in vacuo* (oil pump) at 50°. The solid residue was partitioned between 100 ml of H_2O and 100 ml of $CHCl_3$, and the organic layer was washed with H_2O and dried ($MgSO_4$). Removal of the solvent afforded a thin syrup from which the last traces of DMF were removed by codistillation with xylene. The residue was dissolved in 70 ml of hot EtOH and the solution cooled slowly to room temperature. Crystalline **7a** (1 g) was collected and washed with cold EtOH. Recrystallization from EtOH afforded 920 mg (43%) of pure material: mp 251–253°; $\lambda_{max}^{dil\ EtOH}$ 233, shoulder 250–270 mμ; λ_{min} 212 mμ.

Anal. Calcd for $C_{24}H_{20}N_2O_7$: C, 64.27; H, 4.50; N, 6.25. Found: C, 63.87; H, 4.41; N, 5.90.

The mother liquors and washings obtained from the preparation of **7a** were concentrated to dryness, and the residue was dissolved in the minimum of EtOAc–MeOH (20:1). The solution was placed on a column of silica gel (2.5 × 30 cm) and the column was eluted with the same solvent. Concentration of the 200–

(19) The authors are indebted to Drs. J. H. Burchenal, M. R. Dollinger, and R. W. Mackey of this institute for these preliminary data.

(20) See M. R. Dollinger, J. H. Burchenal, W. Kreis, and J. J. Fox, *Biochem. Pharmacol.*, **16**, 689 (1967), and references therein for a description of the experimental systems used in these screening studies.

(21) Microanalyses were performed by the Spang Microanalytical Laboratories, Ann Arbor, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points, determined on a Thomas–Hoover capillary melting point apparatus, are corrected.

350-ml portion of the eluate afforded 160 mg (7.5%) of pure **7a** mp and mmp 251–253°. Concentration of the 65–140-ml portion and recrystallization of the residue from EtOH afforded 270 mg (10%) of **8a**: mp 183–184°; $\lambda_{max}^{dil\ EtOH}$ 228, 265 mμ; λ_{min} 215, 255 mμ.

Anal. Calcd for $C_{31}H_{26}N_2O_8$: C, 65.26; H, 4.59; N, 4.91. Found: C, 65.35; H, 4.65; N, 4.69.

Treatment of 400 mg (0.9 mmole) of **7a** with sodium benzoate (520 mg, 3.6 mmoles) and benzoic acid (100 mg, 0.9 mmole) in 40 ml of DMF at 150° for 24 hr and work-up of the solution as described above afforded a syrup which contained starting material (**7a**) and **8a**. Fractional crystallization of the syrup from EtOH afforded 120 mg of **7a**. Column chromatography on silica gel, as described above, afforded 150 mg of **8a**, mp 183–184°, and a further 30 mg of starting material. The yield of **8a** was 45% (based on the amount of used starting material).

1-α-L-Xylofuranosylthymine (9a).—Compound **7a** (600 mg, 1.34 mmoles) was dissolved in 20 ml of hot 50% aqueous EtOH (300 ml) and 4.1 ml of 1 *N* NaOH was added to the clear solution. The solution was refluxed for 30 min and processed as described for the preparation of 1-α-L-arabinofuranosylthymine (**3a**). The syrup residue was dissolved in *ca.* 3 ml of EtOH and the solution was refrigerated. The crystalline product (242 mg, 70% in two crops) had mp 192–194°. A single recrystallization afforded material with mp 194–195°, $\lambda_{max}^{H_2O}$ 267 mμ, λ_{min} 236.

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.28; H, 5.60; N, 10.87.

1-α-L-Lyxofuranosylthymine (10a).—Compound **8a** (600 mg, 1.05 mmoles) was dissolved in 20 ml of warm, 50% aqueous EtOH containing 3.5 ml of 1 *N* NaOH. The solution was refluxed for 30 min and processed as described in the preparation of **3a**. The residue obtained was recrystallized twice from 5 ml of hot EtOH. The yield of pure material, mp 200–202°, was 200 mg (82%). The melting point and uv and nmr spectral data found for **10a** were in close agreement with values reported[9] for the enantiomorphic 1-α-D-lyxofuranosylthymine. Furthermore, the ir spectra of these compounds were identical.

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.32; H, 5.58; N, 10.79.

1-(Tri-*O*-benzoyl-α-L-arabinofuranosyl)-N^4-benzoylcytosine (11).—A mixture of 6.5 g of N^4-benzoylcytosine[15] and 4 g of $Hg(CN)_2$ was added to 3 l. of $MeNO_2$, and the suspension was dried azeotropically by distillation of 150 ml of solvent. Tri-*O*-benzoyl-α,β-L-arabinofuranosyl bromide (16 g) was added to the hot, stirred suspension, and the reaction mixture was refluxed. During the reflux period, 100 ml of solvent was distilled from the reaction mixture. After 2 hr of refluxing, another charge of $Hg(CN)_2$ (4 g) was added, and the mixture was dried azeotropically by distillation of some of the solvent. An additional 16 g of halogenose was added and refluxing was continued for a total of 4 hr. The *clear* reaction mixture was concentrated to dryness, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 30% freshly prepared aqueous KI and then with H_2O. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a syrup. In order to obtain seed crystals, a small amount of this syrup was dissolved in C_6H_6–Et_2O (1:1). The solution was absorbed on a silica gel column and washed with C_6H_6–Et_2O (1:1). The product was eluted from the column with EtOAc–MeOH (20:1) and the eluate evaporated to dryness. The syrup crystallized from hot EtOH. The syrup obtained by concentration of the $CHCl_3$ solution was dissolved in hot EtOH, and the solution was seeded with crystals of **11**. After slow cooling to ~40–50°, fine crystals of **11** were obtained (90% based on N^4-benzoylcytosine, mp 197–198°). Recrystallization from EtOH gave pure product: mp 198–199°; $\lambda_{max}^{dil\ EtOH}$ 232, 260, 302 mμ; λ_{min} 249, 290 mμ.

Anal. Calcd for $C_{37}H_{29}N_3O_9$: C, 67.37; H, 4.43; N, 6.37. Found: C, 67.43; H, 4.57; N, 6.40.

1-α-L-Arabinofuranosylcytosine (12).—Compound **11** (6.6 g) was added to a solution of 200 ml of EtOH and 100 ml of 1 *N* NaOH and the stirred mixture was heated for 1 hr at 75°. The solution was cooled to room temperature and added to a column of Dowex 50 (H^+) (100 g wet weight). The column was washed with 50% aqueous EtOH (500 ml), then with H_2O (400 ml) to remove benzoic acid. The unblocked nucleoside **12** was eluted from the column with 2.6 *N* NH_4OH (400 ml) and the eluate was concentrated to dryness *in vacuo*. The residue was dissolved in 50 ml of hot EtOH and cooled overnight in the refrigerator. The crystalline material (2.0 g plus an additional 0.4 g obtained from the mother liquor) was recrystallized from hot EtOH. The product, which was dried over P_2O_5 *in vacuo* at 80°, melted at 115–116° and showed $[\alpha]^{25}D$ +2 (*c* 3, H_2O), $\lambda_{max}^{0.1\ N\ HCl}$ 271 mμ, λ_{min} 249 mμ.

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.38; N, 17.28. Found: C, 44.42; H, 5.47; N, 17.30.

1-α-L-Arabinofuranosyl-N^4-benzoylcytosine (13).—A solution of 1.5 g of **12** in 150 ml of MeOH was treated with 1.5 g of benzoic anhydride and refluxed for 5 hr. Additional charges of 1.5 g of anhydride were added at 1-hr intervals during the reflux period according to the procedure described.[16] The hot reaction mixture was filtered from some insoluble material and the filtrate was concentrated *in vacuo* to a small volume which crystallized after treatment with Et_2O; yield 1.5 g (70%), mp 219–220°. Pure material, mp 228–229°, was obtained after recrystallization from hot MeOH: $\lambda_{max}^{(aq)}$ 258, 303 mμ; λ_{min} 230, 290 mμ.

Anal. Calcd for $C_{16}H_{15}N_3O_6$: C, 55.32; H, 4.93; N, 12.09. Found: C, 55.27; H, 4.90; N, 12.11.

1-α-L-Arabinofuranosyluracil (3b). Method A from 13.—Compound **13** (1 g) was refluxed for 3 hr in 100 ml of 85% aqueous AcOH. The reaction mixture was evaporated to dryness *in vacuo* at ~40°, and the residue was dissolved in H_2O and added to a column containing Dowex 50 (H^+). The column was eluted with H_2O until the eluate was free of uv-absorbing material. The eluate was concentrated to dryness *in vacuo*. The residue was dissolved in H_2O and washed with $CHCl_3$. The aqueous layer was evaporated to dryness *in vacuo*. The glassy residue was chromatographically pure (silica gel tlc in *n*-BuOH–H_2O, 86:14) but resisted all attempts at crystallization. The product, not analyzed, was converted directly to its tri-*O*-mesylate (**4b**).

Method *B* from 11.—The fully benzoylated nucleoside (**11**, 5 g) was refluxed for 3 hr in 85% aqueous AcOH and the reaction mixture evaporated to dryness *in vacuo* at 40°. The residue was added to a solution of 50 ml of EtOH and 25 ml of 1 *N* NaOH and the mixture was heated for 1 hr at 70°. The reaction mixture was worked up as in method A above. A chromatographically pure glass, 1.7 g (89%), was obtained: $\lambda_{max}^{(aq)}$ 262 mμ, λ_{min} 230 mμ. This product **3b** was used directly for the synthesis of **5b**.

2,2'-Anhydro-1-(3,5-di-*O*-mesyl-α-L-ribofuranosyl)uracil (5b).—The glassy residue **3b** was azeotropically dried by addition of toluene and distillation of solvent *in vacuo*. The residue (from 37 g of blocked nucleoside **11**) was then dissolved in 250 ml of dry pyridine, and the solution was cooled in an ice bath to 0–5°. The solution was treated dropwise with 33 g (twofold excess) of $MeSO_2Cl$, and the reaction mixture was allowed to remain overnight at room temperature, concentrated to a small volume, and poured into stirred ice–H_2O. The brown precipitate which formed was collected and washed several times with cold H_2O. The product (crude **4b**) was dried (P_2O_5) to yield 20 g of a dark residue. A portion of crude residue (5.4 g) was dissolved in hot anhydrous MeOH (700 ml) and the mixture was decanted from a small amount of a black syrup. The cooled decantate was treated dropwise at room temperature with almost 1 equiv of 1 *N* NaOH. A fine crystalline product (3.7 g) was filtered after 1 hr and an additional 0.4 g was obtained from the mother liquor (total yield 94%). After recrystallization from hot 80% aqueous EtOH, pure material was obtained with mp 250–251°: $\lambda_{max}^{dil\ EtOH}$ 225, 247 mμ; λ_{min} 234 mμ.

Anal. Calcd for $C_9H_{14}N_2O_9S_2$: C, 34.55; H, 3.69; N, 7.33; S, 16.77. Found: C, 34.70; H, 3.82; N, 7.26; S, 16.66.

2,2'-Anhydro-1-(3-*O*-mesyl-5-*O*-benzoyl-α-L-ribofuranosyl)uracil (6b, X = O).—Treatment of 2,2'-anhydro(3,5-di-*O*-mesyl-α-L-ribofuranosyl)uracil (**5b**) (3.0 g, 7.8 mmoles) with sodium benzoate (1.3 g, 9 mmoles) in dry DMF, as described above for the preparation of **6a**, afforded **6b** (94%), from hot EtOH, mp 233–234°, λ_{max}^{EtOH} 232 mμ; λ_{min} 208 mμ.

Anal. Calcd for $C_{17}H_{16}N_2O_8S$: C, 49.99; H, 3.95; N, 6.86; S, 7.85. Found: C, 50.07; H, 4.05; N, 6.81; S, 7.93.

2,2'-Anhydro-1-(3-*O*-mesyl-5-*O*-benzoyl-α-L-ribofuranosyl)-4-thiouracil (6b, X = S).—P_2S_5 (2.2 g, 0.01 mole) was added to 35 ml of dry pyridine, and the mixture was refluxed until solution occurred. Compound **6b** (X = O) (1.4 g, 3.7 mmoles) was added, and the solution was refluxed for 0.5 hr. The reaction mixture was concentrated *in vacuo* to a thin syrup which was then poured into stirred ice–H_2O. The brown solid material was filtered and washed well with cold H_2O. Recrystallization from hot 50% aqueous EtOH gave 1.0 g of **6b** (X = S) (69%). A further recrystallization from the same solvent (including treatment with charcoal) gave fine yellow crystals: mp 200–201°; $\lambda_{max}^{dil\ EtOH}$ 232, 328 mμ; λ_{min} 212, 258 mμ.

Anal. Calcd for $C_{17}H_{16}N_2O_7S_2$: C, 48.10; H, 3.80; N, 6.60; S, 15.11. Found: C, 48.18; H, 3.97; N, 6.62; S, 15.09.

2,2′-Anhydro-1-(3,5-di-*O*-benzoyl-α-L-xylofuranosyl)uracil (7b) and Tri-*O*-benzoyl-α-L-lyxofuranosyluracil (8b).—A solution of 2.0 g (4.9 mmoles) of **6b** (X = O) in 400 ml of dry DMF containing 3.0 g (20.8 mmoles) of sodium benzoate and 600 mg (4.9 mmoles) of benzoic acid was heated at 150° for 4.5 hr. The dark reaction mixture was processed as described previously for the preparation of **7a** and **8a**. Fractional crystallization of the residue from hot EtOH afforded 0.8 g (37%) of **7b** which, after a further recrystallization, had mp 131–132°, $\lambda_{max}^{dil\ EtOH}$ 231 mμ, λ_{min} 212 mμ.

Anal. Calcd for $C_{23}H_{18}N_2O_7$: C, 63.59; H, 4.17; N, 6.44. Found: C, 63.63; H, 4.02; N, 6.39.

Compound **8b** was isolated from the mother liquors as described above in the preparation of **8a**. Fractions of the column effluent (EtOAc–MeOH, 15:1) containing mostly **8b** were combined and concentrated to dryness *in vacuo*. Recrystallization of the residue from EtOH–Et_2O afforded pure **8b**: mp 146–148°; $\lambda_{max}^{dil\ EtOH}$ 230, 256 mμ; λ_{min} 211, 252 mμ.

Anal. Calcd for $C_{30}H_{24}N_2O_9$: C, 64.74; H, 4.34; N, 5.03. Found: C, 64.77; H, 4.46; N, 4.96.

1-α-L-Lyxofuranosyluracil (10b).—Compound **8b** (0.1 g) was suspended in a solution of EtOH (10 ml) and 1 *N* NaOH (5.4 ml), and the mixture was warmed at 70° for 1 hr. The clear solution was treated with Dowex 50 (H^+) and then filtered. The filtrate was evaporated to dryness *in vacuo*, and the residue was dissolved in a small amount of H_2O, then washed with $CHCl_3$ (three 20-ml portions). The H_2O layer was evaporated to dryness *in vacuo*, and the syrup residue was crystallized from EtOH. The yield of pure product, mp 202–203°, was 43 mg. For the enantiomorphic 1-α-D-lyxofuranosylthymine, Nishimura[9] reported mp 203–204.5°. The uv and nmr spectral data were in close agreement with the values reported for the enantiomorph and the infrared spectra were identical.

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.26; H, 4.95; N, 11.47. Found: C, 44.27; H, 4.89; N, 11.31.

2,2′-Anhydro-1-(3,5-di-*O*-benzoyl-α-L-xylofuranosyl)-4-thiouracil (17).—Compound **7b** (1.5 g, 3.3 mmoles) was added to a refluxing solution of P_2S_5 (2.2 g, 10 mmoles) in 35 ml of pyridine. After 30 min of refluxing, the dark brown solution was evaporated to dryness *in vacuo* to a dark syrup which crystallized when triturated in cold H_2O. Recrystallization of the crude product (1 g, 64%) from 50% aqueous EtOH afforded yellow needles of **17**: mp 236–237°; $\lambda_{max}^{dil\ EtOH}$ 231, 283, 329 mμ, shoulder 275 mμ; λ_{min} 258, 287 mμ.

Anal. Calcd for $C_{23}H_{18}N_2O_6S$: C, 61.32; H, 4.03; N, 6.22; S, 7.12. Found: C, 61.48; H, 4.05; N, 6.10; S, 7.15.

1-α-L-Xylofuranosylcytosine (16). Method A.—To a suspension of 800 mg (1.77 mmoles) of **17** in 100 ml of 50% aqueous EtOH was added 1 *N* NaOH (10 ml). The mixture was warmed at 70° for 5 min and then allowed to cool. After 1 hr, the clear yellow solution was treated with Dowex 50 (H^+) (13 g of moist resin). The resin was removed by filtration and the yellow filtrate was concentrated to dryness. A solution of the residue in H_2O was extracted with $CHCl_3$ (three 50-ml portions). Concentration of the aqueous layer afforded a yellow amorphous solid (**18**) ($\lambda_{max}^{dil\ EtOH}$ 332 mμ, λ_{min} 250 mμ) which was used directly for the synthesis of **17**. A sealed tube containing the above product (**18**) in 40 ml of ethanolic NH_3 was heated at 100° for 17 hr. The red-brown reaction mixture was evaporated to dryness *in vacuo* at 40°, and the residue was dissolved in 100 ml of H_2O. This solution was added to a column of Dowex 50 (H^+) (10 g of moist resin), and the column was eluted with 400 ml of H_2O. Compound **16** was eluted from the column by 400 ml of 2 *N* NH_4OH. The effluent was treated with charcoal and evaporated *in vacuo*. Crystallization of the product occurred in the concentrated solution. The solid (310 mg) was collected and recrystallized from dilute EtOH. The over-all yield from **17** was 68–70%. Pure **16** had mp 267–268° dec and $[\alpha]^{25}D$ +118° (*c* 0.1, H_2O); $\lambda_{max}^{H_2O}$ 273, shoulder 225 mμ; λ_{min} 246 mμ. The spectra at various pH values were closely similar to those previously reported for 1-β-D-ribofuranosylcytosine.[8]

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.43; H, 5.38; N, 17.27. Found: C, 44.56; H, 5.33; N, 17.32.

Method B.—Treatment of a solution of 2.0 g (**7b**) in 50% aqueous EtOH with NaOH and isolation of the product as described previously for the preparation of **9a** afforded 1.2 g of syrup which contained **9b**. The syrup was dissolved in 20 ml of pyridine and dried by azeotropic distillation of the solvent. The syrupy residue was dissolved in 10 ml of Ac_2O containing 1 ml of pyridine, and the solution was heated at 100° for 1 hr. Removal of the solvents *in vacuo* left a syrup containing the triacetate **14**. The syrup in 100 ml of pyridine was treated with 4.2 g of P_2S_5 and 0.09 ml of H_2O. The stirred mixture was refluxed for 6 hr and concentrated *in vacuo* to dryness. The residue was triturated with 50 ml of cold H_2O and the resulting brown solid was removed by filtration. The solid was dissolved in 300 ml of $CHCl_3$ and washed with H_2O. Concentration of the organic layer afforded semisolid material which contained thione **15**. Crude **15** in 80 ml of ethanolic NH_3 was heated in a sealed tube at 100° for 20 hr, and the brown reaction mixture was processed as described in method A above. The yield of pure **16**, mp and mmp 267–268°, was 300 mg (over-all yield from **7b**, 27%). The product had uv absorption characteristics identical with a sample prepared according to method A above.

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