25% aqueous sodium hydroxide. The precipitated acetamide was removed by filtration and the filtrate was extracted with ether (4 × 25 ml). The dried (KOH pellets) ether extract was evaporated to dryness and the residue was vacuum sublimed at 165° (0.1 mm). A yellow solid was isolated (0.124 g) which had a melting point of 190–199°. This was dissolved in 5.0 ml of water and made strongly basic with sodium hydroxide pellets until precipitation was complete. The yellow precipitate was removed by vacuum filtration, washed with small amounts of ice-cold water, dried, and vacuum sublimed, yield 0.102 g, mp 204–206°. The alkaline solution from the ether extraction was made more basic with sodium hydroxide pellets until precipitation was complete. The precipitate was removed by filtration, washed with ice-cold water, dried, and vacuum sublimed at 165° (0.1 mm), yield 0.197 g, mp 204–206°, total yield 0.299 g (38.7%). Anal. Calcd for $C_8H_7N_3$: C, 66.21; H, 4.83. Found: C, 66.19; H, 4.86. NMR (CF_3CO_2D) (external Me_4Si): 9.55 (d, 2-H), 9.18 (d, 7-H), 8.25 (m, 3-H), 8.22 (d, 4-H), 7.42 (d, 8-H), $J_{2,3}$ = 8.0, $J_{3,4}$ = 8.0, $J_{7,8}$ = 6.4 Hz.

8-Amino-1,6-naphthyridine. Crude 8-bromo-1,6-naphthyridine[22] (8.25 g) was combined with 150 ml of ammonium hydroxide (*d* 0.9) and 1.0 g of anhydrous copper(II) sulfate. The reaction mixture was heated in a reaction bomb for 39 hr at 180°. The contents of the bomb were cooled, made strongly basic with potassium hydroxide pellets, and continuously extracted with ether for 48 hr. The ether was dried over anhydrous calcium chloride and evaporated away on a steam bath. Yield of crude material was 2.27 g. The crude product was chromatographed on a silica gel column with methanol–benzene (20:80). From the column, 1.34 g of purified amine was isolated which was recrystallized from absolute ethanol, yield 0.95 g, mp 135–137°. Anal. Calcd for $C_8H_7N_3$: C, 66.21; H, 4.83; N, 28.97. Found: C, 66.50; H, 5.04; N, 28.70. NMR (CF_3CO_2D) (external Me_4Si): 9.50 (d, 2-H), 9.17 (d, 4-H), 8.98 (s, 5-H), 8.35 (s, 7-H), 8.18 (m, 3-H), $J_{2,3}$ = 5.2, $J_{3,4}$ = 8.8 Hz.

Registry No.—3-Bromo-1,6-naphthyridine, 17965-73-0; ammonium hydroxide, 1336-21-6; 5-chloro-1,6-naphthyridine, 23616-32-2; 8-bromo-1,6-naphthyridine, 17965-74-1.

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(1) To whom inquiries should be addressed.
(2) Submitted in partial fulfillment of the requirements for a Ph.D. at the University of Kentucky.
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Synthesis of Pyrimidine and Purine Nucleosides from L-Lyxopyranose and L-Arabinopyranose

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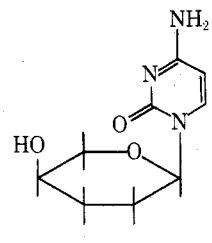
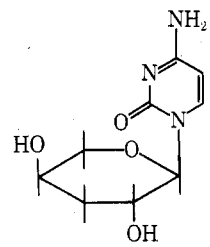
The syntheses of the following α-L-pentopyranosyl nucleosides are reported: 1-α-L-arabinopyranosyluracil (**5**), 1-α-L-lyxopyranosyluracil (**6**), 1-α-L-arabinopyranosylcytosine (**7**), 1-α-L-lyxopyranosylcytosine (**8**), 9-α-L-arabinopyranosyladenine (**13**), and 9-α-L-lyxopyranosyladenine (**16**). The uracil nucleoside **6** was converted to 2,2′-anhydro-1-α-L-xylopyranosyluracil (**9**), which was ring opened to give 1-α-L-xylopyranosyluracil (**10**). Deamination of **16** gave 9-α-L-lyxopyranosylhypoxanthine (**17**). Phosphorylation of the isopropylidene derivative of **16** followed by deblocking gave 9-(4-*O*-phosphoryl-α-L-lyxopyranosyl)adenine (**19**), which was deaminated to give 9-(4-*O*-phosphoryl-α-L-lyxopyranosyl)hypoxanthine (**20**).

Until recently, all known naturally occurring nucleosides have been of the D configuration.[1] Two cytosine nucleoside antibiotics, pentopyranine A and C, which are of the α-L configuration, have recently been isolated[2] from the fermentation broth of *Streptomyces griseochromogenes*. The syntheses of these nucleosides have been described by Fox and coworkers.[3] Several synthetic nucleosides derived from L sugars have previously been reported.[4] Baker and coworkers prepared a number of α-L-rhamnopyranosyl purines and pyrimidines.[5] In the present work α-L-lyxopyranosyl nucleosides (**2**) are viewed as being similar to natural ribonucleosides (**1**) in the configurations of the three hydroxyl groups of the carbohydrate moiety relative to the aglycon. Similarly, α-L-arabinopyranosyl nucleosides (**4**) may be considered as analogous to β-D-xylofuranosyl nucleosides (**3**) (Chart I). The structural relationship of these α-L-pentopyranosyl nucleosides to the nucleoside antibiotics pentopyranine A and C is also evident.



Pentopyranine A



Pentopyranine C

This report describes the synthesis of certain pyrimidine and purine α-L-pentopyranosyl nucleosides derived from

Chart I

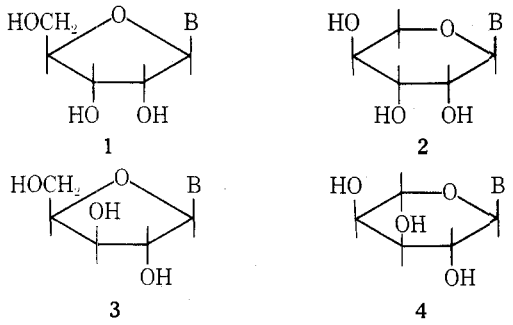
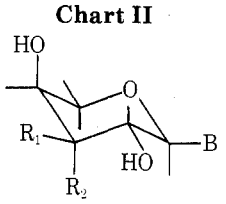


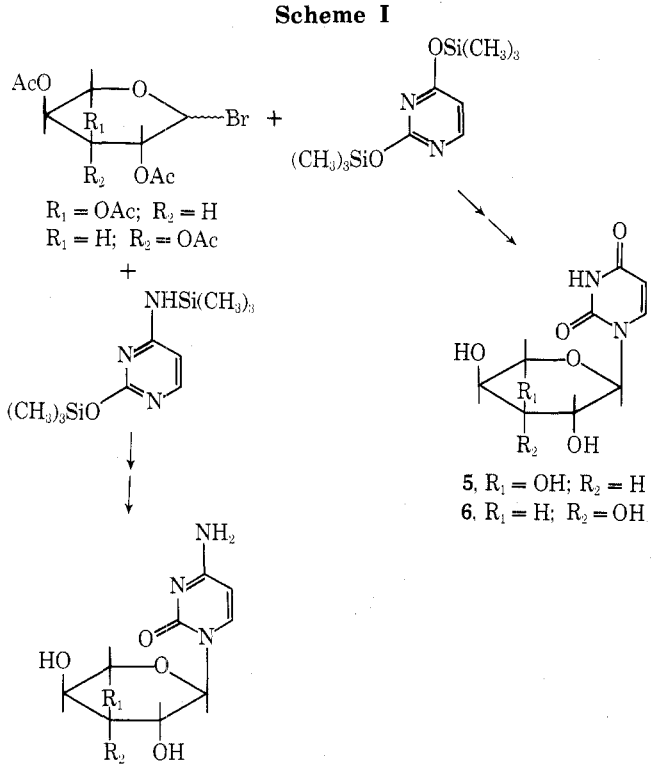
Chart II



5, $R_1 = OH$; $R_2 = H$
6, $R_1 = H$; $R_2 = OH$

L-lyxose and L-arabinose. The syntheses of the pyrimidine nucleosides were approached by glycosylation of the trimethylsilyl derivatives of uracil and cytosine with the appropriate blocked pyranosyl halides (Scheme I).

Scheme I



$R_1 = OAc$; $R_2 = H$
$R_1 = H$; $R_2 = OAc$

5, $R_1 = OH$; $R_2 = H$
6, $R_1 = H$; $R_2 = OH$

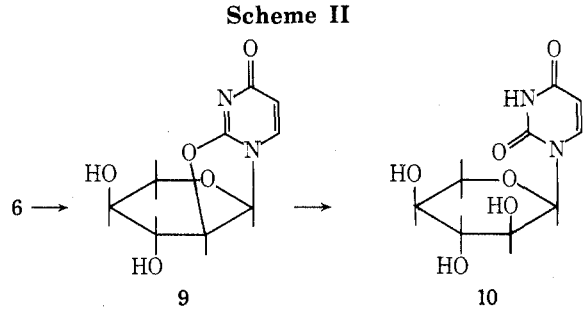
7, $R_1 = OH$; $R_2 = H$
8, $R_1 = H$; $R_2 = OH$

Treatment of the bis(trimethylsilyl) derivative of uracil with 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide in acetonitrile at room temperature afforded, after deacylation of the blocked intermediate, 1-α-L-arabinopyranosyluracil (**5**). The same procedure with 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl bromide provided the crystalline blocked nucleoside which was deacetylated to give 1-α-L-lyxopyranosyluracil (**6**). The ultraviolet spectra of both **5** and **6** are consistent with N-1 glycosylation of uracil. The coupling constants for the anomeric protons of **5** ($J_{1',2'}$ = 8.5 Hz) and **6** ($J_{1',2'}$ = 9.0 Hz) establish the α configuration for these nucleosides, since these values are consistent only with the trans-diaxial configuration for $H_{1'}$–$H_{2'}$ of the α anomer in the L series with the C1 conformation[6] (Chart II).

The syntheses of the cytosine L nucleosides were similar to those of the uracil nucleosides **5** and **6**. The treatment of the bis(trimethylsilyl) derivative of cytosine with the blocked arabinopyranosyl bromide afforded 1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)cytosine,[7] which was isolated as the crystalline hemihydrobromide salt in 82% yield. This blocked nucleoside was treated with sodium bicarbonate and then deacetylated to provide 1-α-L-arabinopyranosylcytosine (**7**). The same glycosylation procedure using 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl bromide again gave the blocked nucleoside as a crystalline hemihydrobromide salt. Deblocking of this intermediate gave 1-α-L-lyxopyranosylcytosine (**8**). The ultraviolet and NMR spectra of **7** and **8** are consistent with glycosylation at N-1 of cytosine and the α-anomeric configuration for these nucleosides.

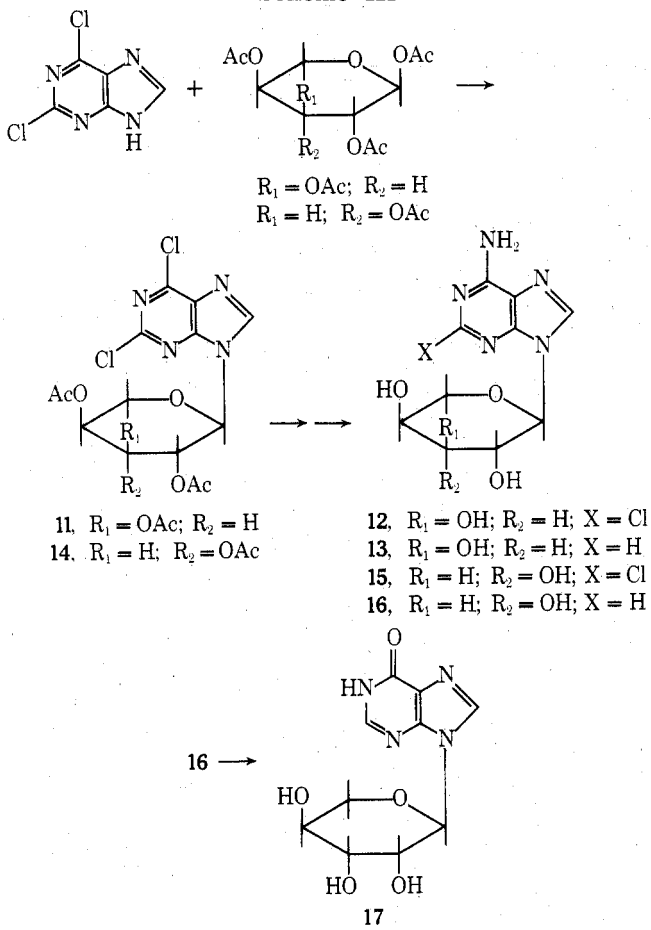
Cyclonucleoside formation of pyrimidine nucleosides is well known.[8] Certain 2,2′-anhydropyranosylpyrimidines have been obtained from the corresponding mesyl derivatives.[9] Treatment of nucleosides containing cis hydroxyl groups which are trans to the aglycon with diphenyl carbonate leads to 2,2′-anhydropyrimidine nucleosides.[10] This procedure with 1-(2-deoxy-β-D-ribopyranosyl)thymine has been reported to give the 2,3′-anhydronucleoside via the 3′,4′-cyclic carbonate.[11] Treatment of 1-α-L-lyxopyranosyluracil (**6**) with diphenyl carbonate and sodium bicarbonate in dimethylformamide afforded an anhydronucleoside **9** which exhibited an ultraviolet spectrum characteristic of a uracil cyclonucleoside. The structure of **9** was established as the 2,2′-anhydronucleoside and not the 2,3′-anhydro derivative as follows (Scheme II). Treatment of **9** with aqueous sodium hydroxide gave the uracil nucleoside **10**. Comparison of **10** with 1-α-L-arabinopyranosyluracil (**5**), which would result from opening of a 2,3′-anhydronucleoside, showed that these products are different. All properties of **10** are consistent with the 1-α-L-xylopyranosyluracil structure and the cyclonucleoside **9** is thus 2,2′-anhydro-1-α-L-xylopyranosyluracil.

Scheme II

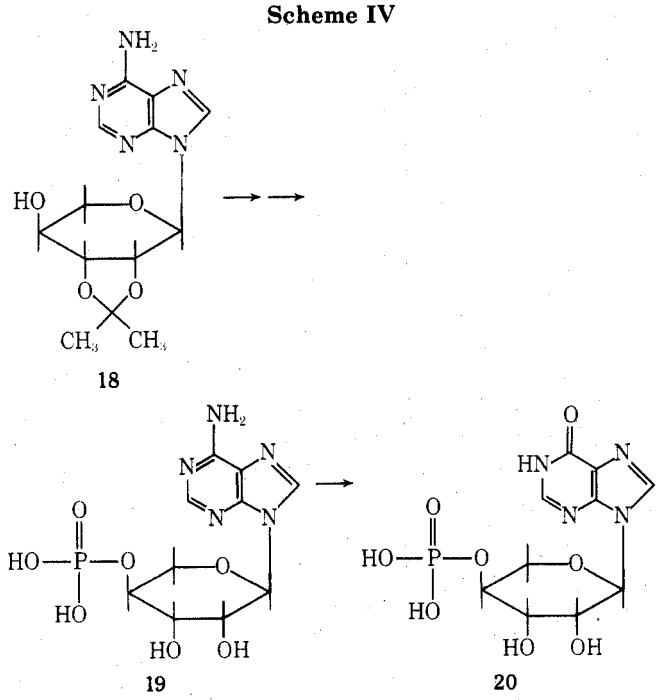


As an approach to the synthesis of purine nucleosides of L-arabinopyranose and L-lyxopyranose, the acid-catalyzed fusion procedure[12] with 2,6-dichloropurine and the tetra-*O*-acetyl sugars was employed (Scheme III). Fusion of 2,6-dichloropurine with 1,2,3,4-tetra-*O*-acetyl-α-L-arabinopyranose in the presence of an acid catalyst afforded crystalline 2,6-dichloro-9-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)purine (**11**). Treatment of **11** with methanolic ammonia gave 6-amino-2-chloro-9-α-L-arabinopyranosylpurine (**12**), which was dehalogenated to provide 9-α-L-arabinopyranosyladenine (**13**). Starting with 1,2,3,4-tetra-*O*-acetyl-α-L-lyxopyranose, the same sequence of reactions gave the blocked 2,6-dichloropurine nucleoside (**14**), the 6-amino-2-

Scheme III



Scheme IV



chloro derivative (**15**), and finally 9-α-L-lyxopyranosyladenine (**16**). A second route to **16** by glycosylation of N^6-benzoyladenine was investigated. Treatment of N^6-benzoyladenine with 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl bromide in the presence of mercuric cyanide[13] gave N^6-benzoyl-9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)adenine. Removal of blocking groups gave 9-α-L-lyxopyranosyladenine (**16**) identical with the product obtained via the acid-catalyzed fusion procedure. A second nucleoside derivative from the glycosylation of N^6-benzoyladenine appears to be the debenzoylated derivative, since deblocking of this product also gave **16**. Deamination of the adenine nucleoside **16** with nitrous acid gave 9-α-L-lyxopyranosylhypoxanthine (**17**). The ultraviolet and NMR spectra ($J_{1',2'}$ = 8.0–10.0 Hz) of these purine nucleosides establish these products as 9-α-L-pyranosylpurines.

The synthesis of nucleotide analogs of certain of the pyranosyl nucleosides obtained in this work was of interest. The procedure of Yoshikawa et al.[14] was used to phosphorylate the 4′-hydroxyl group of 9-(2,3-*O*-isopropylidene-α-L-lyxopyranosyl)adenine (**18**). Thus, treatment of **18** with phosphoryl chloride in triethyl phosphate followed by removal of the isopropylidene group and purification of the product by DEAE chromotography gave 9-(4-*O*-phosphoryl-α-L-lyxopyranosyl)adenine (**19**) (Scheme IV). An additional nucleotide analog was obtained by deamination of **19** with nitrous acid, which gave 9-(4-*O*-phosphoryl-α-L-lyxopyranosyl)hypoxanthine (**20**).

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were obtained on a Hitachi Perkin-Elmer R20A spectrometer using DSS or Me_4Si as internal standards. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Thin layer chromatography was performed on silica gel F254 (Woelm) and components were visualized with a uv lamp (254 mμ) or by spraying the plates with 10% sulfuric acid in methanol and heating at ca. 110°. Activated charcoal for chromatography was Type UU (Barneby-Cheney, Columbus, Ohio). Trimethylsilyl derivatives were prepared using the general procedure of Wittenburg.[15] The heterocyclic bases were heated under reflux in an excess of hexamethyldisilazane with a catalytic amount of ammonium sulfate under anhydrous conditions for an average of 24 hr. The excess of hexamethyldisilazane was removed by distillation under vacuum and the residue (oil or crystalline solid) was used directly without further purification.

Tetra-*O*-acetyl-α-L-lyxopyranose[16] and tetra-*O*-acetyl-α-L-arabinopyranose[17] were prepared by stirring a mixture of the sugar and acetic anhydride in the presence of a catalytic amount of 4-dimethylaminopyridine[18] at room temperature until the sugar was completely dissolved. The solution was evaporated to dryness under reduced pressure and the tetra-*O*-acetyl derivatives[19] were crystallized from ethanol. Tri-*O*-acetyl-β-L-arabinopyranosyl bromide[20] and tri-*O*-acetyl-α-L-lyxopyranosyl bromide[21] were prepared by bubbling hydrogen bromide into an ice-cold solution of the tetra-*O*-acetyl derivative in dry dichloromethane for 40–45 min. The solution was kept at 0° for 1 hr and at room temperature for 15 min. The solvent was removed under diminished pressure. In both cases the bromo acetyl sugar crystallized. 2,3,4-Tri-*O*-acetyl-α-L-lyxopyranosyl bromide is reported in the literature[21] as a syrup. In our hands the product crystallized (mp 110–112°).

1-α-L-Arabinopyranosyluracil (5). A solution of tri-*O*-acetyl-β-L-arabinopyranosyl bromide[20] (3.87 g, 11.1 mmol) and the bis(trimethylsilyl) derivative of uracil [prepared from 1.35 g (12.0 mmol) of uracil] in dry acetonitrile (100 ml) was kept at room temperature for 6 days. The solution was evaporated to dryness and the residue was chromatographed on a column of silica gel (250 g) packed in chloroform. Elution with 20:1 chloroform–acetone provided the tri-*O*-acetyl derivative of **5** (3.4 g, 83%) as a chromatographically pure foam. This product (2.7 g, 0.73 mmol) was treated with methanol (100 ml) containing sodium methoxide (from 100 mg of sodium) at room temperature overnight. The solution was neutralized with Dowex 50 (H^+) and filtered and the solvent was removed. The product was crystallized from ethanol containing a few drops of water to give **5** (0.90 g, 50%): mp 254–255°; $[\alpha]^{25}D$ +86.4° (*c* 1, water); uv λ_{max} (pH 1) 257 nm (ε 10,850); λ_{max} (pH 11) 257 nm (ε 8200); NMR (DMSO-d_6–D_2O) δ 7.67 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 5.73 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.28 (d, 1, $J_{1'2'}$ = 8.5 Hz, H-1′).

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.26; H, 4.95; N, 11.47. Found: C, 44.47; H, 5.02; N, 11.45.

1-α-L-Lyxopyranosyluracil (6). A solution of the bis(trimethylsilyl) derivative of uracil [from 2.46 g (22.0 mmol) of uracil] and tri-*O*-acetyl-α-L-lyxopyranosyl bromide[21] [from 6.36 g (20.0 mmol)

of the tetraacetate] in dry acetonitrile (150 ml) was kept at room temperature for 7 days. The solvent was removed and the residue was coevaporated successively with toluene and ethanol. The residue was dissolved in chloroform and the solution was washed with aqueous sodium bicarbonate and with water and dried over sodium sulfate. The solution was evaporated to dryness and the product was crystallized from ethyl acetate–cyclohexane to give 5.4 g (73%) of the tri-*O*-acetyl derivative of **6**: mp 208–209°; $[\alpha]^{25}D$ +73.8° (*c* 1, chloroform); uv λ_{max} (pH 1) 257 nm (ϵ 10,670); λ_{max} (pH 11) 256 nm (ϵ 7730); NMR ($CDCl_3$) δ 9.58 (br s, 1, NH), 7.37 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 6.05 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1'), 5.80 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.49 (t, 1, $J_{3,2}$ = $J_{3,4}$ = 3.5 Hz, H-3'), 5.25 (q, 1, $J_{1'2'}$ = 9.0, $J_{2'3'}$ = 3.5 Hz, H-2'), 2.22 and 2.0 (2 s, 3 each, CH_3).

Anal. Calcd for $C_{15}H_{18}N_2O_9$: C, 48.65; H, 4.90; N, 7.57. Found: C, 48.73; H, 4.95; N, 7.49.

The blocked nucleoside (1.11 g, 3.0 mmol) was treated with methanol (75 ml) containing sodium methoxide (from 200 mg of sodium) at room temperature for 2 hr. The solution was neutralized with Dowex 50 (H^+), filtered, and evaporated to dryness. The product was crystallized from aqueous ethanol to give 0.63 g (86%) of **6**: mp 256–257°; $[\alpha]^{25}D$ +10° (*c* 1, water); uv λ_{max} (pH 1) 258 nm (ϵ 10,660); λ_{max} (pH 11) 258 nm (ϵ 8060); NMR (DMSO-d_6–D_2O) δ 7.72 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 5.74 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.68 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.26; H, 4.95; N, 11.47. Found: C, 44.32; H, 4.91; N, 11.46.

1-α-L-Arabinopyranosylcytosine (7). A solution of the bis(trimethylsilyl) derivative of cytosine [from 2.44 g (22.0 mmol) of cytosine] and 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide (6.78 g, 20.0 mmol) in dry acetonitrile (100 ml) was kept at room temperature for 3 days. The solvent was removed and the residue was coevaporated successively with toluene and ethanol. Ethanol was added to the residue and the resulting product was collected by filtration and dried over phosphorus pentoxide to give 6.7 g (82%) of the tri-*O*-acetyl derivative of **7** as the hemihydrobromide salt. Recrystallization from ethanol gave pure material: mp 246–248°; $[\alpha]^{25}D$ +60° (*c* 1, ethanol); uv λ_{max} (pH 1) 273 nm (ϵ 12,900); λ_{max} (pH 11) 265 nm (ϵ 8670); NMR (DMSO-d_6–D_2O) δ 7.82 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 6.13 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.95 (d, 1, $J_{1',2'}$ = 8.0 Hz, H-1').

Anal. Calcd for $C_{15}H_{19}N_3O_8 \cdot 0.5HBr$: C, 43.96; H, 4.79; N, 10.25; Br, 9.74. Found: C, 44.01; H, 4.77; N, 10.22; Br, 9.65.

The above blocked nucleoside (6.0 g, 14.6 mmol) was suspended in chloroform and the mixture was shaken with aqueous sodium bicarbonate. The chloroform solution was washed with water, dried over sodium sulfate, and evaporated to dryness to give 4.35 g (80%) of 1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)cytosine as a homogenous foam. This product was treated with methanol saturated at 0° with ammonia and the solution was kept at 25° for 20 hr. The solvent was removed and the residue was coevaporated several times with methanol. The product was crystallized from ethanol to give 2.2 g (76%) of **7**: mp 266–267°; $[\alpha]^{25}D$ +99.9° (*c* 1, water ; uv λ_{max} (pH 1) 275 nm (ϵ 12,420); λ_{max} (pH 11) 267 nm (ϵ 8600); NMR (DMSO-d_6–D_2O) δ 7.63 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 5.84 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.41 (d, 1, $J_{1',2'}$ = 8.0 Hz, H-1').

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.51; H, 5.56; N, 17.32.

1-α-L-Lyxopyranosylcytosine (8). A solution of the bis(trimethylsilyl) derivative of cytosine [prepared from 2.44 g (22.0 mmol) of cytosine] and 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl bromide [from 6.36 g (20.0 mmol) of the tetra -*O*-acetyl derivative] in dry acetonitrile (100 ml) was kept at room temperature for 3 days. The solvent was removed and the residue was coevaporated with toluene. Addition of ethanol to the residue gave a solid product (7.0 g, 85%). Recrystallization from ethanol provided the pure tri-*O*-acetyl derivative of **8** as the hemihydrobromide salt, mp 263–264°.

Anal. Calcd for $C_{15}H_{19}N_3O_8 \cdot 0.5HBr$: C, 43.96; H, 4.79; N, 10.25; Br, 9.74. Found: C, 44.09; H, 4.59; N, 10.12; Br, 10.00.

Chloroform was added to the above blocked nucleoside (7.0 g, 17.0 mmol) and the mixture was shaken with aqueous sodium bicarbonate. The chloroform solution was washed with water, dried over sodium sulfate, and evaporated to dryness to give 4.5 g (71%) of the tri-*O*-acetyl derivative of **8** as an amorphous solid. This product (4.0 g) was treated with methanolic ammonia (100 ml) at room temperature for 24 hr. The solvent was removed and the residue was dissolved in methanol. Silica gel (20 g) was added to the solution and the mixture was evaporated to dryness. The silica gel mixture was applied to a column of silica gel (80 g) packed in chloroform. Elution with chloroform (150 ml), ethyl acetate (500 ml), 9:1 ethyl acetate–methanol (1 l.), and 7:3 ethyl acetate–methanol (2 l.) provided, after crystallization from ethyl acetate–methanol, 2.0 g (75%) of **8**: mp 246–247° dec; $[\alpha]^{25}D$ +21.4° (*c* 1, water); uv λ_{max} (pH 1) 275 nm (ϵ 11,950); λ_{max} (pH 11) 235 nm (ϵ 7550), 266 (8150); NMR (DMSO-d_6–D_2O) δ 7.67 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 5.88 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5), 5.78 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.37; H, 5.48; N, 17.11.

2,2'-Anhydro-1-α-L-xylopyranosyluracil (9). A mixture of 1-α-L-lyxopyranosyluracil (**6**, 1.0 g, 4.0 mmol), diphenyl carbonate (1.14 g, 5.3 mmol), and sodium bicarbonate (20 mg) in dimethylformamide (2.0 ml) was heated in an oil bath at 150° for 20 min. The mixture was poured into ether (120 ml) and the gummy solid was dried over phosphorus pentoxide. Then the solid was dissolved in methanol and silica gel (5 g) was added. The mixture was evaporated to dryness, slurried in a small volume of chloroform, and applied to a column of silica gel (40 g) packed in chloroform. Elution with 9:1 chloroform–methanol (500 ml) and 7:3 chloroform–methanol (500 ml) gave a chromatographically pure solid that was crystallized from ethanol to yield 0.54 g (60%) of **9**: mp 214–216°; $[\alpha]^{25}D$ −126.5° (*c* 1, water); uv λ_{max} (pH 1) 249 nm (ϵ 8500), 224 (8500); λ_{max} (pH 11) 249 nm (ϵ 8500), 229 (6800); NMR (DMSO-d_6–D_2O) δ 7.85 (d, 1, $J_{6,5}$ = 7.5 Hz, H-6), 5.98 (d, 1, $J_{5,6}$ = 7.5 Hz, H-5), 6.00 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1').

Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.90; H, 4.27; N, 12.39.

1-α-L-Xylopyranosyluracil (10). Compound **9** (0.23 g, 1.0 mmol) was treated with 0.2 *N* aqueous sodium hydroxide (10 ml) at room temperature for 3 hr. The reaction mixture was neutralized with Dowex 50 (H^+), filtered, and evaporated to dryness. The residue was coevaporated several times with ethanol and the product was crystallized from ethanol to give 0.15 g (62%) of **10**: mp 205–207°; $[\alpha]^{25}D$ +107.4° (*c* 1, water); uv λ_{max} (pH 1) 262 nm (ϵ 11,430); λ_{max} (pH 11) 262 nm (ϵ 8770); NMR (DMSO-d_6–D_2O) δ 7.81 (d, 1, $J_{6,5}$ = 8.0 Hz, H-6), 5.76 (d, 1, $J_{1',2'}$ = 5.0 Hz, H-1'), 5.64 (d, 1, $J_{5,6}$ = 8.0 Hz, H-5).

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.26; H, 4.95; N, 11.47. Found: C, 44.05; H, 5.13; N, 11.28.

2,6-Dichloro-9-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)-purine (11). 2,6-Dichloropurine (4.7 g, 25.0 mmol) and 1,2,3,4-tetra-*O*-acetyl-α-L-arabinopyranose (7.95 g, 25.0 mmol) were heated in an oil bath at 160°. When the mixture melted, bis(*p*-nitrophenyl) phosphate (100 mg) was added and the heating was continued for 10 min under vacuum. The residue was dissolved in chloroform and the solution was washed with aqueous sodium bicarbonate and with water, dried over sodium sulfate, and evaporated to dryness. The product was crystallized from ethanol to give 3.7 g of **11**, mp 151–153°. The filtrate was concentrated to dryness and the residue (7 g) was dissolved in a small amount of chloroform and applied to a silica gel column (150 g) packed in chloroform. Elution with chloroform provided 2.5 g more of nucleoside that was recrystallized from ethanol. Total yield of recrystallized product **11** was 5.6 g (50%): $[\alpha]^{25}D$ +52.3° (*c* 1, chloroform); uv λ_{max} (ethanol) 272 nm (ϵ 10,300); NMR (DMSO-d_6) λ 8.98 (s, 1, H-8), 6.17 (d, 1, $J_{1',2'}$ = 8.0 Hz, H-1').

Anal. Calcd for $C_{16}H_{16}Cl_2N_4O_7$: C, 42.99; H, 3.58; N, 12.53; Cl, 15.88. Found: C, 43.11; H, 3.62; N, 12.46; Cl, 15.80.

6-Amino-2-chloro-9-α-L-arabinopyranosylpurine (12). A mixture of compound **11** (3.0 g, 6.7 mmol) and methanol saturated with ammonia at −20° (100 ml) was kept in a bomb at room temperature for 2 days. The solution was concentrated to almost dryness and the residue was coevaporated several times with ethanol. The ethanolic solution was concentrated to a small volume and kept at −5° overnight. The solid product was collected by filtration and recrystallized from water to give 1.6 g (80%) of **12**: mp >300°; $[\alpha]^{25}D$ +62.2° (*c* 1, dimethylformamide); uv λ_{max} (pH 1) 263 nm (ϵ 15,780); λ_{max} (pH 11) 263 nm (ϵ 15,780); NMR (DMSO-d_6–D_2O) δ 8.35 (s, 1, H-8), 5.32 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_{10}H_{12}ClN_5O_4$: C, 39.81; H, 4.00; N, 23.21; Cl, 11.75. Found: C, 39.60; H, 4.14; N, 23.08; Cl, 11.64.

9-α-L-Arabinopyranosyladenine (13). A mixture of compound **12** (0.90 g, 3.0 mmol), 10% palladium on charcoal (0.68 g), and sodium acetate (0.30 g) in water (600 ml) was shaken in a Parr hydrogenator at 52 psi for 24 hr at room temperature. The catalyst was removed by filtration and the solvent was evaporated to a small volume. The solution was percolated through a column of activated charcoal. The column was washed with water until salt free and the product was eluted with ethanol–water–concentrated ammonium hydroxide (10:10:1). The product was crystallized from ethanol to give 0.65 g (81%) of **13**, mp 269–270° dec. Another crystalline

form of 13 with mp 235–236° dec was obtained when the product was crystallized from aqueous ethanol: $[\alpha]^{25}D$ +35.3° (c 1, water); uv λ_{max} (pH 1) 255 nm (ε 14,500); λ_{max} (pH 11) 258 nm (ε 14,800); NMR (DMSO-d_6–D_2O) δ 8.22 and 8.34 (2 s, 2, H-2 and H-8), 5.40 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.20; H, 5.41; N, 24.46.

2,6-Dichloro-9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)purine (14). 2,6-Dichloropurine (4.70 g, 25.0 mmol) and tetra-*O*-acetyl-α-L-lyxopyranose (7.95 g, 25.0 mmol) were fused in the presence of bis(*p*-nitrophenyl) phosphate (100 mg) in an oil bath at 160° for 15 min under reduced pressure. The residue was dissolved in chloroform and the solution was washed with aqueous sodium bicarbonate and with water. The organic solution was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was chromatographed on silica gel using chloroform as eluent. The appropriate fractions were collected and evaporated to dryness to give 5.6 g (50%) of chromatographically pure **14**. Recrystallization from ethanol gave an analytical sample: mp 177–179°; $[\alpha]^{25}D$ +72.4° (c 1, chloroform); uv λ_{max} (pH 1) 272 nm (ε 10,900); λ_{max} (pH 11) 272 nm (ε 13,370); NMR ($CDCl_3$) δ 8.30 (s, 1, H-8), 6.07 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_{16}H_{16}Cl_2N_4O_7$: C, 42.99; H, 3.58; N, 12.53; Cl, 15.88. Found: C, 43.03; H, 3.48; N, 12.49; Cl, 16.00.

6-Amino-2-chloro-9-α-L-lyxopyranosylpurine (15). Compound **14** (3.0 g, 6.7 mmol) was treated at room temperature for 4 days with methanol saturated with ammonia at −20°. The solution was concentrated to almost dryness and the residue was coevaporated several times with ethanol. The ethanolic solution was concentrated to a small volume and kept at −5° overnight. The product was collected by filtration to give 1.9 g (94%) of **14**. Recrystallization from water provided 1.6 g of analytical product: mp >300°; $[\alpha]^{25}D$ +26.4° (c 1, dimethylformamide); uv λ_{max} (pH 1) 263 nm (ε 15,500); λ_{max} (pH 11) 263 nm (ε 15,800); NMR (DMSO-d_6–D_2O) δ 8.37 (s, 1, H-8), 5.64 (d, 1, $J_{1',2'}$ = 9.0 Hz, H-1').

Anal. Calcd for $C_{10}H_{12}ClN_5O_4$: C, 39.81; H, 4.00; N, 23.21; Cl, 11.75. Found: C, 39.84; H, 4.13; N, 23.15; Cl, 11.92.

9-α-L-Lyxopyranosyladenine (16). Method 1. A mixture of **15** (0.80 g, 2.65 mmol), 10% palladium on charcoal (0.60 g), and sodium acetate (0.30 g) in water (600 ml) was shaken on a Parr hydrogenator at 53 psi for 24 hr. The catalyst was removed by filtration and the solution was evaporated to dryness. The residue was dissolved in a small volume of water and percolated through a column of activated charcoal. The column was washed with water until the eluate was salt free and the product was eluted with ethanol–water–concentrated ammonium hydroxide (10:10:1). Concentration of the appropriate fractions provided the product which was crystallized from ethanol to give 0.43 g (61%) of **16**: mp 179–181°, resolidification and final mp 249–250°; $[\alpha]^{25}D$ −19.3° (c 1, water); uv λ_{max} (pH 1) 256 nm (ε 14,900); λ_{max} (pH 11) 258 nm (ε 15,200); NMR (DMSO-d_6–D_2O) δ 8.40 and 8.26 (2 s, 2, H-2 and H-8), 5.77 (d, 1, $J_{1',2'}$ = 9.5 Hz, H-1').

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.30; H, 5.14; N, 24.50.

Method 2. A mixture of 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl bromide [from 9.54 g (30.0 mmol) of tetra-*O*-acetyl derivative], *mercuric cyanide* (9.0 g), and anhydrous calcium sulfate (15.0 g) in dry nitromethane (100 ml) was added to a solution of N^6-benzoyladenine (7.17 g, 30.0 mmol) in dry nitromethane (250 ml). The mixture was refluxed for 3 hr excluding moisture and stirred at room temperature overnight. The reaction mixture was filtered hot and the filtrate was evaporated to dryness. The residue was treated with chloroform, the mixture was filtered, and the solution was washed with 30% aqueous potassium iodide and with water. The organic layer was dried over sodium sulfate and evaporated to a syrup. The residue was dissolved in chloroform containing a small amount of methanol and applied to a silica gel column (600 g), packed in chloroform. Elution with 25:1 chloroform–methanol provided as the faster moving product 5.3 g (35%) of N^6-benzoyl-9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)adenine: mp 206–207° (from ethanol); $[\alpha]^{25}D$ +43.6° (c 1, chloroform); uv λ_{max} (ethanol) 277 nm (ε 21,560).

Anal. Calcd for $C_{23}H_{23}N_5O_8$: C, 55.53; H, 4.66; N, 14.08. Found: C, 55.48; H, 4.79; N, 13.85.

Subsequent fractions from the column gave 4.0 g of the above blocked nucleoside mixed with another compound which was not characterized. Treatment of this mixture with sodium methoxide as described below gave only the deblocked nucleoside **16**, which indicates that the contaminant is 9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)adenine.

The above blocked (N^6-benzoyl) nucleoside (4.97 g, 10.0 mmol) was refluxed with methanol (200 ml) containing sodium methoxide (from 200 mg of sodium) for 45 min. The solution was neutralized with Dowex 50 (H^+), filtered, and evaporated to dryness. The product was crystallized from ethanol to give 2.3 g (86%) of 9-α-L-lyxopyranosyladenine (**16**), identical with the product obtained by method 1.

9-α-L-Lyxopyranosylhypoxanthine (17). To an ice-cooled suspension of **16** (1.0 g, 3.74 mmol) in water (10 ml) and glacial acetic acid (1.5 ml) was added sodium nitrite (1.3 g, 20.0 mmol). The mixture was stirred at room temperature for 48 hr. The solution was evaporated to dryness and coevaporated with acetic acid (5 ml). The residue was dissolved in water and applied to a column containing 35 ml of Dowex 50 (H^+). The column was eluted with water and the fractions containing uv-absorbing material were evaporated. The product was crystallized from aqueous ethanol to give 0.70 g (70%) of **17**: mp 232–233°; $[\alpha]^{25}D$ −16.4° (c 1, water); uv λ_{max} (pH 1) 248 nm (ε 12,830); λ_{max} (pH 11) 252 nm (ε 14,070); NMR (DMSO-d_6–D_2O) δ 8.34 and 8.15 (2, s, 2, H-2 and H-8), 5.74 (d, 1, $J_{1',2'}$ = 10.0 Hz, H-1').

Anal. Calcd for $C_{10}H_{12}N_4O_5$: C, 44.77; H, 4.51; N, 20.88. Found: C, 44.42; H, 4.68; N, 20.67.

9-(2,3-*O*-Isopropylidene-α-L-lyxopyranosyl)adenine (18). A mixture of **16** (3.0 g, 11.2 mmol), 2,2-dimethoxypropane (75 ml), acetone (75 ml), and 70% perchloric acid (1.5 ml) was stirred at room temperature for 3 hr. The solution was neutralized with 2 *N* aqueous potassium hydroxide and filtered. The filtrate was evaporated to dryness and the product was purified by column chromatography on silica gel (125 g) with 40:1 chloroform–methanol as eluent. Evaporation of fractions containing the product gave 3.2 g (88%) of **18** as amorphous material: $[\alpha]^{25}D$ −61.6° (c 1, chloroform); NMR (DMSO-d_6–D_2O) δ 8.52 and 8.29 (2 s, 2, H-2 and H-8), 5.60 (d, 1, $J_{1',2'}$ = 8.0 Hz, H-1'), 1.55 and 1.36 (2, s, 3 each, CH_3).

Anal. Calcd for $C_{13}H_{17}N_5O_4 \cdot H_2O$: C, 48.00; H, 5.89; N, 21.53. Found: C, 47.99; H, 5.91; N, 21.64.

9-(4-*O*-Phosphoryl-α-L-lyxopyranosyl)adenine (19). A solution of phosphoryl chloride (4.6 g, 30.0 mmol) and triethyl phosphate (35 ml) was cooled to 0° and **18**[22] (2.62 g, 8.05 mmol) was added with stirring. The mixture was stirred at 0–5° for 18 hr and for 6 hr at room temperature. After cooling the mixture to 0°, ice water was added and the pH was adjusted to 3 with 2 *N* sodium hydroxide. The solution was extracted with chloroform to remove triethyl phosphate and the aqueous phase was desalted on a column of charcoal (80 ml). The column was washed with water until salt-free and the product was eluted with ethanol–water–concentrated ammonium hydroxide (1:1:1). Fractions containing the product were evaporated to dryness to give 2.5 g of crude material. TLC (silica gel, 7:3 acetonitrile–0.1 *N* aqueous ammonium chloride) indicated that this product was partially deisopropylidenated. Treatment of the product with 90% trifluoroacetic acid (30 ml) for 5 min at room temperature followed by evaporation of this mixture and several coevaporations of the residue with ethanol provided the crude deblocked phosphate mixed with the nucleoside **16**. This material was dissolved in water and the pH of the solution was adjusted to 8.5 with 1 *N* ammonium hydroxide. The solution was applied to a column of DEAE cellulose (HCO_3^-, 700 ml) and elution was with a gradient of water–0.3 *M* triethylamine bicarbonate (1000 ml each) followed by 0.3–0.4 *M* triethylamine bicarbonate (500 ml each). Fractions containing the nucleotide were evaporated to dryness and the residue was coevaporated several times with water. The product was dissolved in water and passed through a Dowex 50 (H^+) column (50 ml) using water to elute the nucleotide. The fractions containing the product were combined and evaporated to a small volume. Addition of ethanol gave crystalline **19** (1.58 g, 56%): mp 246–247° dec; uv λ_{max} (pH 1) 255 nm (ε 14,900); λ_{max} (pH 11) 258 nm (ε 15,200).

Anal. Calcd for $C_{10}H_{14}N_5O_7P$: C, 34.59; H, 4.06; N, 20.17. Found: C, 34.36; H, 4.08; N, 19.99.

9-(4-*O*-Phosphoryl-α-L-lyxopyranosyl)hypoxanthine (20). A suspension of **19** (0.35 g, 1.0 mmol) in acetic acid (10 ml) was cooled to 15° and a solution of sodium nitrite (0.10 g, 1.5 mmol) in water (0.5 ml) was added. The mixture was stirred in a stoppered flask for 48 hr at room temperature. The resulting solution was evaporated to dryness and the residue was dissolved in water. The solution was passed through a Dowex 50 (H^+) column (5 ml); the product was eluted with water. Fractions containing nucleotide were evaporated to dryness. The residue was dissolved in water and lyophilized to give **20** (0.22 g, 63%) as an amorphous product: uv λ_{max} (pH 1) 248 nm (ε 11,800); λ_{max} (pH 11) 252 nm (ε 12,700).

Anal. Calcd for $C_{10}H_{13}N_4O_8P \cdot 0.5H_2O$: C, 33.62; H, 3.95; N, 15.69. Found: C, 33.57; H, 3.86; N, 15.64.

Registry No.—**5**, 55555-55-0; **5** triacetate, 55530-09-1; **6**, 55555-56-1; **6** triacetate, 55530-10-4; **7**, 55530-11-5; **7** triacetate, 55530-12-6; **7** triacetate ½ HBr, 55530-13-7; **8**, 55530-14-8; **8** triacetate, 55530-15-9; **8** triacetate ½ HBr, 55530-16-0; **9**, 55530-17-1; **10**, 55555-57-2; **11**, 55530-18-2; **12**, 55530-19-3; **13**, 17434-53-6; **14**, 55530-20-6; **15**, 55530-21-7; **16**, 55555-58-3; **17**, 55530-22-8; **18**, 55530-23-9; **19**, 55530-24-0; **20**, 55530-25-1; tri-*O*-acetyl-β-L-arabinopyranosyl bromide, 14227-90-8; bis(trimethylsilyl)uracil, 10457-14-4; tri-*O*-acetyl-α-L-lyxopyranosyl bromide, 55555-59-4; bis(trimethylsilyl)cytosine, 18037-10-0; 1,2,3,4-tetra-*O*-acetyl-α-L-arabinopyranose, 17080-99-8; tetra-*O*-acetyl-α-L-lyxopyranose, 2595-11-1; N^6-benzoyladenine, 4005-49-6; N^6-benzoyl-9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)adenine, 55530-26-2; 2,2-dimethoxypropane, 77-76-9; phosphoryl chloride, 10025-87-3; 2,6-dichloropurine, 1839-23-2.

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Synthesis of 5-Vinyluridine and 5-Vinyl-2′-deoxyuridine as New Pyrimidine Nucleoside Analogs

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5-Formyluracil condensed smoothly with carbethoxymethylenetriphenylphosphorane to give *trans*- and *cis*-3-(5-uracilyl)acrylic acid ethyl ester (**3**). The analogous reaction, using methylenetriphenylphosphorane leading to 5-vinyluracil (**1**), failed. Alternatively, 5-chloromethyluracil was converted to the phosphonium salt **4** by reaction with triphenylphosphine. **4** readily condensed with paraformaldehyde in the presence of base to afford **1** in good yield. Condensation of the trimethylsilyl derivative of **1** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of stannic chloride gave, after deblocking, 5-vinyluridine (**7**). Similarly, condensation of the trimethylsilyl derivative **5** with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride, followed by transesterification with sodium methoxide, gave 5-vinyl-2′-deoxyuridine (**10**) and its α anomer **11**. The anomeric configuration was determined by NMR spectroscopy.

In view of the antiviral activity of 5-ethyl-2′-deoxyuridine,[1,2] which has been reported to be comparable to that of 5-iodo-2′-deoxyuridine[1,3] vs. Herpes Simplex and Vaccinia viruses, and that of other 5-alkylpyrimidine nucleosides,[4,5] it appeared worthwhile to synthesize 5-vinyluridine (**7**) and 5-vinyl-2′-deoxyuridine (**10**), whose 5 substituent has a van der Waals radius in-between that of the methyl and ethyl groups.

Although the necessary intermediate **1** had previously been prepared by dehydration[6] of 5-(1-hydroxyethyl)uracil, decarboxylation[7] of 3-(5-uracilyl)propenoic acid, and also by the base-catalyzed condensation[8] of 2-dimethoxymethyl-3-methoxybutyrate with urea, the yields were very low. Since a larger amount of **1** was needed for the synthesis of nucleosides, we sought to develop an improved procedure for the preparation of **1**.

Initially, we attempted the synthesis of **1** by condensation of methylenetriphenylphosphorane with 5-formyluracil (**2**), which was obtained by the oxidation of 5-hydroxymethyluracil.[9] However, this procedure failed to furnish **1** under a variety of experimental conditions. The failure of **2** to undergo Wittig reaction with methylenetriphenylphosphorane parallels the observation made by other workers,[10,11] when only trace amounts of 6-vinylpyrimidines were obtained by condensation of this relatively unstable ylide with 6-formylpyrimidines. Satisfactory results were