# Fluorinated Pyrimidine Nucleosides. 3.[1] Synthesis and Antitumor Activity of a Series of 5'-Deoxy-5-fluoropyrimidine Nucleosides

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A series of 5'-deoxy-5-fluoropyrimidine nucleosides has been prepared and evaluated against sarcoma 180 tumor in mice. 5'-Deoxy-5-fluorouridine (**5**) was prepared from 5-fluorouridine (**1**) by isopropylidination and iodination, followed by reduction and deprotection. The D-*lyxo* isomer **13** was prepared from **5** by treatment of the 2',3'-dimesyl intermediate **14** with water. The D-*arabino* isomer **7** was prepared via the 2,2'-anhydro intermediate **8**. Treatment of the 5'-iodo compound with sodium methoxide induced elimination in preference to anhydro formation to give the 4',5'-unsaturated compound **11**. Hydrogenation of **11** followed by deprotection gave the L-*lyxo* isomer **10**. 5'-Deoxy-5-fluorocytidine (**16**) was also synthesized via reduction of a 5'-iodo intermediate, **17**, and was converted into the D-*arabino* isomer **20** via the 2,2'-anhydro intermediate **19**. Reaction of **16** with methanesulfonyl chloride produced the 3'-*O*-mesyl-2,2'-anhydronucleoside **21**, which on treatment with sodium hydroxide yielded the *lyxo*-epoxide **22**. 5'-Deoxy-5-fluorouridine (**5**) was active against sarcoma 180 tumor over a wide dose range following intraperitoneal administration. The cytidine analogue **16** showed activity similar to that for **5**, and the anhydronucleoside **19** was also active in this system, but the antitumor effect was less than that seen with **5** or **16**. The other compounds in this series were all inactive against sarcoma 180 at the doses tested.

A large number of 5'-deoxynucleosides have been synthesized in recent years. Since several biologically active nucleosides require the presence of a 5'-hydroxyl group for activation, usually by phosphorylation, removal of this function provides a series of interesting compounds for biochemical and biological studies. 5'-Deoxy compounds are potentially interesting medicinal agents, since such materials cannot be phosphorylated and incorporated into nucleic acids and thus offer the possibility of reduced toxicity and increased specificity. Srivastava et al.[2] have synthesized a series of 5'-deoxyimidazole nucleosides for evaluation as potential antiviral or antibacterial agents; although no antiviral activity was detected, some antibacterial effects were observed. Falco and Fox[3] synthesized 5'-deoxy-*ara*-C from 5'-deoxyuridine for studies with the enzyme deoxycytidine deaminase; this compound was completely deaminated by both human liver and mouse kidney deaminases but was inactive against L1210 leukemia or Burkitts cell cultures. A series of 5'-modified thymidine derivatives, including 5'-deoxythymidine, has been examined as potential inhibitors of thymidine kinase.[4] Knappe and Schmitt[5] have shown that 5'-deoxyadenosine was produced from *S*-adenosylmethionine by an enzyme system involved in the activation of pyruvate formate-lyase. 5'-Deoxy-*ara*-A has also been synthesized from 5'-deoxyribose, although no antiviral testing data were reported.[6] As part of a continuing synthetic program designed to develop fluorinated pyrimidine nucleosides with improved antitumor activity, the present work describes the synthesis of a series of 5'-deoxy-5-fluorouridine and -cytidine nucleosides and their evaluation against sarcoma 180 tumor in mice.

**Chemistry.** Although 5'-deoxynucleosides can be readily prepared by introduction of a 5'-deoxy substituent into the appropriately protected sugar, followed by subsequent coupling with the base to produce the required nucleoside, the general strategy in this work was to employ preformed nucleosides as starting materials. This latter approach provides for greater flexibility, since the intermediates can also be employed for other modifications at the 5' atom.

**Fluorouracil Series.** 5-Fluorouridine (**1**)[7] (Scheme I) was used as the starting material for this series of compounds. After conversion of **1** into its isopropylidene derivative **2** by a standard procedure, treatment with methyltriphenoxyphosphonium iodide[8] in DMF gave the 5'-iodo compound **3** in good yield. Reduction of the 5'-iodo substituent was carried out catalytically using palladium on carbon as catalyst; under the conditions employed, complete reduction of the iodo substituent was usually achieved in less than 1.5 h, with no evidence for reduction of the pyrimidine double bond. The protected 5'-deoxynucleoside **4** could not be obtained in crystalline form, although an analytical sample was prepared by silica column chromatography. For practical purposes, crude **4** was deprotected using 90% trifluoroacetic acid, and 5'-deoxy-5-fluorouridine (**5**) was obtained as needles in an overall yield of 56% from **1**. An alternate procedure for **5** involved the direct iodination of **1** to give the unprotected 5'-iodo compound **6**, followed by catalytic reduction. The relatively poor yield (30%) of **6** obtained during the iodination reaction, however, did not make this route attractive for the preparation of larger amounts of the 5'-deoxy compound **5**. Since our initial report on the synthesis of **5**,[9] Hřebabecký and Beránek[10] have recently described an alternate synthesis via reduction of a 5'-chloro intermediate with tributyltin hydride; this procedure, however, also induced partial reduction of the 5-fluoro substituent.

Compound **5** was also converted into the *arabino* isomer **7**. Treatment with 2-acetoxyisobutyryl chloride[11] produced the 3'-*O*-acetyl-2,2'-anhydro compound **8** in good yield, and this material could be smoothly deacetylated without cleavage of the anhydro bond using sodium methoxide, to give the anhydro compound **9** in excellent yield. Cleavage of the anhydro bond was achieved by treatment of **9** with aqueous sodium hydroxide (0.01 N) for 2 h at room temperature, and the *arabino* isomer **7** was isolated without difficulty. Fox, Miller, and Cushley[12] have shown that arabinosyl nucleosides can undergo ring opening under alkaline conditions; the conditions employed for the synthesis of **7** are presumably sufficiently mild for this transformation not to occur.

The L-*lyxo* isomer **10** was synthesized from the protected 5'-iodo intermediate **3**. Treatment of **3** with sodium methoxide in methanol induced elimination in preference to anhydronucleoside formation, to give the 4',5'-unsaturated compound **11** in good yield. The presence of the 4',5'-unsaturated moiety was easily detected by NMR spectroscopy; the absence of a 4'-hydrogen, together with

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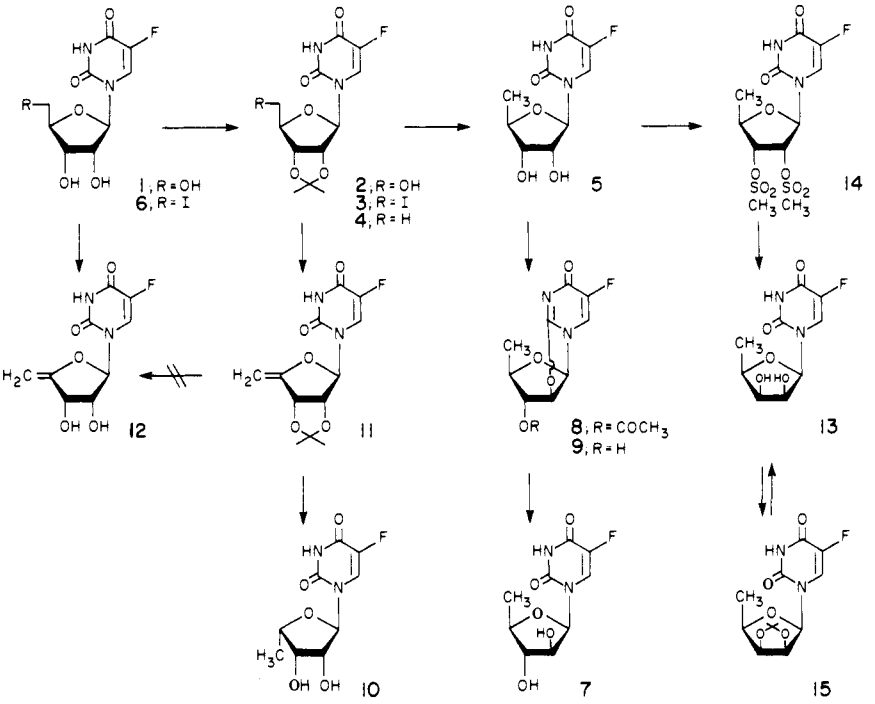
Scheme I

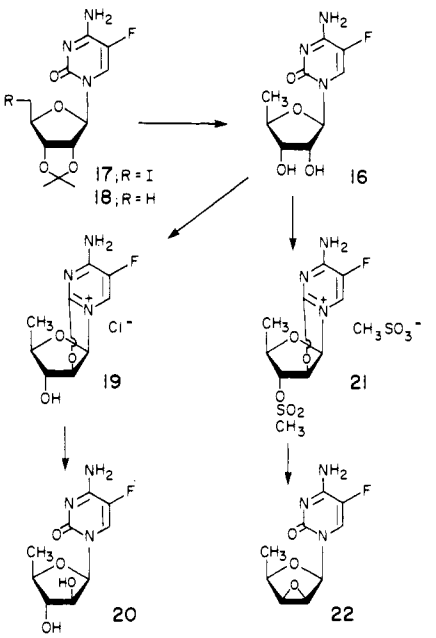



the presence of the two $C_{5'}$ protocols which were observed as doublets at $\delta$ 5.05 and 5.23, indicated the formation of a 4′,5′ double bond. The corresponding unfluorinated analogue of **11** has been synthesized by potassium *tert*-butoxide induced elimination of a 5′-iodo[13] or 5′-tosyl[14] intermediate. Reduction of the 4′,5′-unsaturated compound was achieved catalytically using 5% palladium on carbon as catalyst. The reduction appeared to be quite specific, since the L-*lyxo* isomer was almost exclusively formed; only a trace of the D-*ribo* isomer could be detected. Robins et al.[14] observed the same stereospecificity in the hydrogenation of the corresponding unfluorinated compound, in both cases the isopropylidene group presumably being the predominant directive influence in the production of the L-*lyxo* isomer. Removal of the isopropylidene group from the L-*lyxo* compound was accomplished under standard conditions to give 5′-deoxy-α-L-lyxofuranosyl-5-fluorouracil (**10**).

The unprotected 4′,5′-unsaturated compound **12** was also considered to be of interest for antitumor evaluation, and attempts were accordingly made to obtain this material by deprotection of the isopropylidene derivative **11** using aqueous trifluoroacetic acid. Under these conditions, the nucleoside was unstable, and 5-fluorouracil was found to be the only UV-absorbing product. The unprotected compound **12** was obtained by an alternate route via the 5′-iodo compound **6**. The latter could be obtained from 5-fluorouridine by direct iodination or more conveniently by deprotection of the isopropylidene derivative **3**. Treatment of **6** with sodium methoxide at 40 °C for 18 h induced elimination to give **12** which was isolated in 46% yield after silica column chromatography.

Attempts were made to convert 5′-deoxy-5-fluorouridine (**5**) into the D-*lyxo* isomer **13** as described by Fecher et al.[15] for 1-(β-D-lyxofuranosyl)uracil. Reaction with methanesulfonyl chloride gave the 2′,3′-dimesyl derivative **14**, which was treated with water under reflux for 6 h. Thin-layer chromatographic analysis indicated that two products were formed, one of which was identified as 5-fluorouracil, and the other was postulated as the *lyxo* isomer **13**. Since these two could not be readily separated by crystallization or by silica column chromatography, the reaction mixture was evaporated to dryness and treated directly with acetone and 2,2-dimethoxypropane. The methanesulfonic acid liberated during the hydrolysis served as the catalyst, and the 2′,3′-isopropylidene derivative **15** was produced in good yield. This latter could be purified either by solvent extraction or by column chromatography and **15** was obtained in crystalline form. The formation of this isopropylidene derivative also served to confirm the structure of this compound as a *lyxo* nucleoside, since it was clearly different from the *ribo* isomer **4**, and the *arabino* and *xylo* isomers would not be expected to form 2′,3′-isopropylidene derivatives for stereochemical reasons. Treatment of **15** with trifluoroacetic acid regenerated the unprotected *lyxo* isomer **13**.

Scheme II




**Fluorocytosine Series.** The synthesis of 5′-deoxy-5-fluorocytidine (**16**, Scheme II) closely parallels the route described for the corresponding fluorouridine analogue **5**.

A previous paper in this series reported the synthesis of 5′-deoxy-5-fluoro-5′-iodo-2′,3′-*O*-isopropylidenecytidine (**17**) from 5-fluorocytidine.[16] Hydrogenation of **17** in the presence of triethylamine gave the 5′-deoxy compound **18**, which could not be obtained crystalline, but which was characterized by isolation of a crystalline picrate. Removal of the isopropylidene group was carried out under standard conditions to give 5′-deoxy-5-fluorocytidine (**16**). Conversion of **16** into its 2,2′-anhydro derivative **19** was accomplished using 2-acetoxyisobutyryl chloride, followed by treatment of the intermediate 3′-*O*-acetyl derivative with methanolic hydrogen chloride. Cleavage of the 2,2′-anhydro bond was achieved much more readily than in the fluorouridine series; treatment with 1 equiv of aqueous lithium hydroxide at room temperature was sufficient for complete reaction as determined by TLC, and the arabinosyl isomer **20** was isolated in good yield.

Reaction of **16** with excess methanesulfonyl chloride produced a new, less polar, material as determined by TLC, presumably the 2′,3′-dimesyl compound. This material decomposed during the workup and extraction procedure, and a new, more polar, crystalline material was formed. The UV spectrum of this material revealed the presence of an anhydro species, rather than a normal fluorocytosine chromophore, indicating the formation of the 2,2′-anhydro-3′-*O*-mesyl nucleoside **21**. (The alternate 2,3′-anhydro-2′-*O*-mesyl structure has not definitely been ruled out, although considered to be less likely for steric reasons.) The presence of two methanesulfonyl groups was evident from the NMR spectrum, which revealed three proton singlets at $\delta$ 3.35 and 2.27. Treatment of the anhydro compound **21** with sodium hydroxide produced the 2′,3′-*lyxo*-epoxy compound **22**, the production of which can be rationalized by (a) cleavage of the 2,2′-anhydro bond and (b) attack of the 2′-hydroxyl on $C_{3'}$ with elimination of methanesulfonate ion. Thus, under alkaline conditions the attack by the 2′-hydroxyl to produce the epoxide is evidently facilitated in comparison with attack by the 2-oxygen atom of the pyrimidine ring, as has been observed by Codington et al. for the uridine series.[17]

**Antitumor Testing. Fluorouracil Nucleosides.** 5′-Deoxy-5-fluorouridine (**5**) was active against S180 tumor at doses of 200, 100, 50, and 25 mg/kg ip (Table I). When the stereochemical configuration of the 5′-deoxyribose moiety was inverted at either $C_{2'}$, $C_{4'}$, or at both $C_{2'}$ and $C_{3'}$ to give the corresponding D-*arabino*, L-*lyxo*, or D-*lyxo* isomers **7**, **10**, or **13**, respectively, no activity was detected. Protection of the 2′,3′-hydroxyl functions of **5** with an isopropylidene group to yield **4** resulted in a loss of activity. The 2,2′-anhydro derivative **9** and the 4′,5′-unsaturated compound **12** were found to be inactive, as was the unfluorinated analogue 5′-deoxyuridine. Thus, the structural requirements for retention of activity in this series seems to be relatively specific, since inversion or modification at $C_{2'}$, $C_{3'}$, or $C_{4'}$ all resulted in loss of activity.

A study of the comparative antitumor activity of 5′-deoxy-5-fluorouridine (**5**) and clinically used fluorinated pyrimidines, such as 5-fluorouracil, Ftorafur, and 2′-deoxy-5-fluorouridine, against several transplantable tumors in mice and rats has recently been reported.[18] The activity of 5′-deoxy-5-fluorouridine (**5**) was superior to that of the other test substances, and the greater activity of **5** was especially significant when the test substances were administered orally. Against sarcoma 180 tumor, for example, **5** was reported to be active over a dose range of 800 to 3.12 mg/kg. In addition, **5** was approximately fourfold less toxic than 2′-deoxy-5-fluorouridine based on leukopenia studies in mice and analysis of body-weight changes in experimental animals receiving doses of the substances which exerted an antitumor effect. Fluorinated pyrimidines, such as 5-fluorouracil and FUDR, are known to be activated by conversion into 2′-deoxy-5-fluorouridine 5′-phosphate (pFUDR), which then inhibits the enzyme thymidylate synthetase.[19] Since the presence of the 5′-deoxy substituent of **5** precludes the possibility of phosphorylation at the 5′ position, other mechanistic alternatives must be considered. Two general possibilities present themselves: (a) the compound is active per se, e.g., by inhibition of enzymes such as thymidine kinase, and (b) the compound is degraded to 5-fluorouracil by phosphorylases and then converted into pFUDR in the usual manner. Studies on the mechanism of action of **5**, as well as the reasons for the increase in activity when administered per os,[18] are currently in progress.[20]

Table I. Effect of Fluorinated Pyrimidine Nucleosides against Sarcoma 180 Tumor in Mice

| compd | dose, mg/kg, ip, × 8 | C/T index | act. |
|---|---|---|---|
| 4 | 200 | 1.08 | -- |
| 5 | 200 | 8.39 | +++ |
| | 100 | 8.45 | +++ |
| | 50 | 9.23 | +++ |
| | 25 | 3.11 | ++ |
| | 12.5 | 1.61 | -- |
| 7 | 100 | 1.13 | -- |
| 9 | 200 | 1.15 | -- |
| 10 | 100 | 1.70 | -- |
| 12 | 100 | 1.25 | -- |
| 13 | 100 | 0.90 | -- |
| 16 | 200 | 14.29 | +++ |
| | 100 | 7.14 | +++ |
| | 50 | 3.57 | ++ |
| | 25 | 2.78 | + |
| | 12.5 | 1.61 | -- |
| 19 | 200 | 2.24 | + |
| | 100 | 2.15 | + |
| | 40 | 3.10 | ++ |
| | 20 | 1.87 | -- |
| 20 | 100 | 0.85 | -- |
| 22 | 200 | 1.82 | -- |
| 5′-deoxyuridine | 200 | 1.10 | -- |
| 5′-deoxycytidine | 200 | 1.33 | -- |

**Fluorocytosine Series.** The most active compound in this series proved to be 5′-deoxy-5-fluorocytidine (**16**), which was active against S180 tumor at doses of 200, 100, 50, and 25 mg/kg ip. The 2,2′-anhydro compound **19** was active at 200, 100, and 40 mg/kg ip, whereas the corresponding arabinosyl compound **20** was inactive. This latter result is interesting in view of the fact that the 2,2′-anhydro bond is known to be labile in fluorocytosine nucleosides,[21] and cleavage of **19** to **20** is likely to occur in vivo. Chou et al.[22] have shown that administration of 2,2′-anhydro-1-($\beta$-D-arabinofuranosyl)-5-fluorocytosine to rats resulted in the recovery of the hydrolysis product *ara*-FC, demonstrating that at least partial cleavage of the anhydro bond occurs in vivo. The *lyxo*-epoxide **22** was inactive at 200 mg/kg ip, and the unfluorinated compound 5′-deoxycytidine, which was synthesized for comparison purposes, was inactive at the dose tested (200 mg/kg ip). Kreis et al.[23] have shown that the most active compound in this series, 5′-deoxy-5-fluorocytidine (**16**), is rapidly deaminated by mouse kidney cytidine deaminase, and, in fact, the presence of a 5-fluoro substituent was generally found to enhance the rate of deamination as compared with the corresponding unfluorinated analogue. Activation of **16**, therefore, is likely to occur via initial deamination to 5′-deoxy-5-fluorouridine (**5**); degradation of **16** to 5-fluorocytosine seems to be unlikely, since the latter is

known to be inactive as an antitumor agent.[24]

## Experimental Section

**General.** Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Proton magnetic resonance spectra were obtained using either a Varian XL-100 or HA-100 spectrometer and IR spectra with a Perkin-Elmer 621 or a Beckman IR-9 instrument. UV Spectra were obtained using a Cary Model 14 recording spectrometer.

**5'-Deoxy-5'-iodo-2',3'-*O*-isopropylidene-5-fluorouridine (3).** A solution of 2',3'-*O*-isopropylidene-5-fluorouridine[25] (46.4 g, 153.5 mmol) in DMF (250 mL, dry) was treated with methyltriphenoxyphosphonium iodide (86.7 g) and stored at room temperature for 50 min. Methanol (250 mL) was added, and after 30 min the solution was evaporated to an oil and partitioned between ethyl acetate (1 L) and aqueous sodium thiosulfate (5%, 1 L). The ethyl acetate layer was washed twice with water (1 L), dried overnight over sodium sulfate, and evaporated to dryness. The oil was crystallized from ethyl acetate (350 mL) to give **3**: yield 52.9 g (85%); mp 202–203.5 °C, lit.[16] mp 202–203.5 °C.

**5'-Deoxy-2',3'-*O*-isopropylidene-5-fluorouridine (4).** A solution of **3** (4.6 g) in methanol (140 mL) containing triethylamine (3 mL) was treated with hydrogen at atmospheric pressure in the presence of palladium on carbon (5%, 2.5 g) for 1.5 h at room temperature. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness and partitioned between ethyl acetate (250 mL) and water (250 mL). The water layer was extracted twice with ethyl acetate (250 mL), and the combined ethyl acetate layers were evaporated to dryness and applied to a silica column (300 g) which was eluted with chloroform/ethyl acetate (2:1). Fractions of 20 mL were collected, and tubes 50–100 were combined and evaporated to give **4** as a foam: yield 2.5 g (78%); UV ($CH_3OH$) $\lambda_{max}$ 204 nm ($\epsilon$ 10 900), 267 (8670); NMR ($Me_2SO$-$d_6$) $\delta$ 7.40 (d, 1, $J$ = 6 Hz, CHCF), 5.71 (d, 1, $J$ = 3 Hz, $C_{1'}$ H), 4.92 (dd, 1, $J$ = 3 and 7 Hz, $C_{2'}$ H), 4.54 (dd, 1, $J$ = 7 and 5 Hz, $C_{3'}$ H), 4.25 (m, 1, $C_{4'}$ H), 1.57 (s, 3, $CH_3$), 1.40 (d, 3, $J$ = 7 Hz, $CH_3$CH), 1.36 (s, 3, $CH_3$). Anal. ($C_{12}H_{15}FN_2O_5$) C, H, F, N.

**5'-Deoxy-5-fluorouridine (5).** A solution of 5'-deoxy-5'-iodo-2',3'-*O*-isopropylidene-5-fluorouridine (24 g) in methanol (800 mL) and triethylamine (15 mL) was treated with hydrogen at atmospheric pressure in the presence of palladium on carbon (12 g, 5%) for 90 min at room temperature. The reaction was agitated during this time using a "Vibromix" vibrator. The catalyst was removed by filtration through Celite and washed with methanol, the combined filtrate and washings were evaporated to dryness and triturated with ethyl acetate (200 mL) for 1 h, and the crystals were removed by filtration. The filtrate was evaporated to approximately half volume, stored overnight, and filtered again to remove a second batch of crystals. The filtrate was evaporated to dryness, pumped in vacuo, and the resulting 5'-deoxy-2',3'-*O*-isopropylidene-5-fluorouridine was treated with aqueous trifluoroacetic acid (90%, 200 mL) for 1 h. The product was evaporated to dryness, repeatedly coevaporated with ethanol to remove water and trifluoroacetic acid, triturated with ethyl acetate (70 mL), and recrystallized from ethyl acetate/methanol to give 5'-deoxy-5-fluorouridine: yield 11.35 g (79%); mp 189–190 °C, lit.[10] 186–188 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 11.7 (br s, 1, NH), 7.88 (d, 1, $J$ = 7 Hz, CHCF), 5.69 (dd, 1, $J$ = 2 and 5 Hz, $C_{1'}$ H), 5.3 (m, 2, OH), 4.10 (m, 1, $C_{2'}$ H), 3.83 (m, 1, $C_{4'}$ H), 3.71 (m, 1, $C_{3'}$ H), 1.29 (d, 3, $J$ = 6 Hz, $CH_3$CH); UV (MeOH) $\lambda_{max}$ 268–269 nm ($\epsilon$ 8550). Anal. ($C_9H_{11}FN_2O_5$) C, H, F, N.

**5'-Deoxy-5'-iodo-5-fluorouridine (6).** A solution of 5-fluorouridine (1; 2.62 g, 10 mmol) in DMF (50 mL) was treated with methyltriphenoxyphosphonium iodide (5.42 g, 12 mmol) for 1.75 h at room temperature. Methanol (10 mL) was added and after 30 min the solution was evaporated to an oil, dissolved in ethyl acetate (30 mL), and applied to a silica gel column (500 g, Merck). The column was eluted with ethyl acetate, and 20-mL fractions were collected. Fractions 61–130 were combined, evaporated to dryness, and dissolved in hot ethyl acetate (50 mL). Addition of hexane (10 mL) gave crystalline material. After storage at room temperature overnight, the crystals were collected, washed with hexane, and dried in vacuo. A second crop was obtained from the mother liquors: total yield 1.13 g (30%); mp 174.5–175.5 °C, lit.[16] mp 174.5–175.5 °C.

**2,2'-Anhydro-1-(3'-*O*-acetyl-5'-deoxy-β-D-arabinofuranosyl)-5-fluorouracil (8).** A suspension of **5** (4.92 g) in acetonitrile (100 mL) was stirred with 2-acetoxyisobutyryl chloride[11] (11.5 mL) for 18 h at room temperature. The crystals of **8** (3.18 g, 59%) were collected, and the filtrate was evaporated to dryness and triturated with ether (50 mL) to give a second crop of **8** (1.6 g, 30%). A sample was recrystallized for analytical purposes from methanol: mp 275–280 °C, indefinite, dec; NMR ($Me_2SO$-$d_6$) $\delta$ 8.33 (d, 1, $J$ = 4 Hz, CHCF), 6.33 (d, 1, $J$ = 6 Hz, $C_{1'}$ H), 5.51 (d, 1, $J$ = 6 Hz, $C_{2'}$ H), 5.15 (s, 1, $C_{3'}$ H), 4.44 (m, 1, $C_{4'}$ H), 2.07 (s, 3, $CH_3CO$), 1.19 (d, 3, $J$ = 6 Hz, $CH_3$CH); UV (MeOH) $\lambda_{max}$ 228 nm ($\epsilon$ 7200), 252 (8650). Anal. ($C_{11}H_{11}FN_2O_5$) C, H, F, N.

**2,2'-Anhydro-1-(5'-deoxy-β-D-arabinofuranosyl)-5-fluorouracil (9).** A suspension of **8** (4.35 g) in methanol (100 mL, dried over 3Å molecular sieves) was treated with methanolic sodium methoxide (0.5 M, 3.22 mL) with stirring for 100 min. An excess of CG 50 ($H^+$) resin was added with stirring, and the neutral solution was filtered through Celite, evaporated to dryness, and recrystallized from ethanol to give **9**: yield 3.22 g (88%); mp 225–228 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 8.32 (d, 1, $J$ = 4 Hz, CHCF), 6.27 (d, 1, $J$ = 4 Hz, $C_{1'}$ H), 5.85 (d, 1, $J$ = 3 Hz, OH), 5.27 (d, 1, $J$ = 4 Hz, $C_{2'}$ H), 4.20 (m, 3, $C_{3'}$ H, $C_{4'}$ H), 1.05 (d, 3, $J$ = 7 Hz, $CH_3$CH); UV (MeOH) $\lambda_{max}$ 227 nm ($\epsilon$ 7270), 252 (8600). Anal. ($C_9H_9FN_2O_4$) C, H, F, N.

**1-(5'-Deoxy-β-D-arabinofuranosyl)-5-fluorouracil (7).** A solution of **9** (2.2 g) in 0.01 N sodium hydroxide (1.7 L) was stored at room temperature for 2 h. IRC 50 ($H^+$) resin was added with stirring, and the neutral solution was filtered and evaporated to dryness. The residue was dissolved in methanol (30 mL), impregnated onto silica (35 g), and applied to the top of a silica column (250 g) which was eluted with chloroform/methanol (9:1). Fractions of 20 mL were collected, and tubes 61–100 were combined, evaporated to dryness, and crystallized from ethyl acetate to give **7**: yield 1.8 g (76%); mp 188–189 °C, lit.[10] mp 188–191 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 11.78 (br s, 1, NH), 7.60 (d, 1, $J$ = 7 Hz, CHCF), 5.94 (dd, 1, $J$ = 2 and 4 Hz, $C_{1'}$ H), 5.53 (d, 1, $J$ = 5 Hz, OH), 5.40 (d, 1, $J$ = 4 Hz, OH), 3.7–4.0 (m, 3, $C_{2'}$ H, $C_{3'}$ H, $C_{4'}$ H), 1.32 (d, 3, $J$ = 6 Hz, $CH_3$CH); UV (MeOH) $\lambda_{max}$ 204 nm ($\epsilon$ 10 600), 270 (9400). Anal. ($C_9H_{11}FN_2O_5$) C, H, F, N.

**1-(5'-Deoxy-2',3'-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)-5-fluorouracil (11).** A solution of **3** (8.26 g) and sodium (2.3 g) in dry methanol (500 mL) was heated at 40 °C for 24 h and then cooled and neutralized by stirring with an excess of IRC 50 ($H^+$) resin. The resin was removed by filtration, and the filtrate was impregnated onto silica (100 g) and applied to the top of a silica column (175 g) which was eluted with chloroform (4.5 L) followed by chloroform/ethyl acetate (2:1, 4 L). Fractions of 20 mL were collected, and tubes 76–290 were pooled, evaporated to dryness, and recrystallized from water to give **11**: yield 3.7 g (65%); mp 180–200 °C indefinite, dec; NMR ($Me_2SO$-$d_6$) $\delta$ 11.86 (s, 1, NH), 8.06 (d, 1, $J$ = 6 Hz, CHCF), 5.80 (s, 1, $C_{1'}$ H), 5.23 (d, 1, $J$ = 5 Hz, CH), 5.05 (d, 1, $J$ = 5 Hz, CH), 4.36 (d, 1, $J$ = 2 Hz, $C_{5'}$ H), 4.18 (d, 1, $J$ = 2 Hz, $C_{5'}$ H), 1.40 (s, 3, $CH_3$), 1.31 (s, 3, $CH_3$); UV (MeOH) $\lambda_{max}$ 267 nm ($\epsilon$ 8880). Anal. ($C_{12}H_{13}FN_2O_5$) C, H, N.

**1-(5'-Deoxy-α-L-lyxofuranosyl)-5-fluorouracil (10).** A solution of **11** (2.9 g) in methanol (150 mL) was treated with hydrogen at atmospheric pressure in the presence of 5% palladium on carbon (1.5 g) for 2 h at room temperature. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness and treated with 90% aqueous trifluoroacetic acid. After 1.5 h the solution was evaporated to dryness and coevaporated twice with ethanol (50 mL) to remove residual solvent. Recrystallization from ethanol gave **10**: yield 2.06 g (82%); mp 211–212 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 11.69 (s, 1, NH), 8.02 (d, 1, $J$ = 7 Hz, CHCF), 5.74 (dd, 1, $J$ = 2 and 8 Hz, $C_{1'}$ H), 5.17 (d, 1, $J$ = 6 Hz, OH), 4.87 (d, 1, $J$ = 4 Hz, OH), 4.5 (m, 2 × CH), 3.84 (br s, 1, CH), 1.15 (d, 3, $J$ = 7 Hz, $CH_3$); UV (MeOH) $\lambda_{max}$ 207 nm ($\epsilon$ 8650), 270 (8420). Anal. ($C_9H_{11}FN_2O_5$) C, H, F, N.

**1-(5'-Deoxy-β-D-*erythro*-pent-4-enofuranosyl)-5-fluorouracil (12).** Compound **6** (9.2 g) was treated with sodium (5.6 g) in dry methanol (500 mL) at 40 °C for 18 h. The reaction was cooled to room temperature and neutralized with IRC 50 ($H^+$) resin, and the resin was removed by filtration. The filtrate was

impregnated onto silica gel (150 g) and applied in chloroform to the top of a silica column (1 kg) packed in chloroform/methanol (9:1), and eluted with the same solvent. Fractions of 20 mL were collected, and tubes 180–500 were combined, evaporated to dryness, and recrystallized from ethanol to give **12**: yield 2.78 g (46%); mp 165–167 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 11.3 (br s, 1, NH), 7.87 (d, 1, $J$ = 7 Hz, CHCF), 5.93 (dd, 1, $J$ = 2 and 6 Hz, $C_{1'}$ H), 5.42 (d, 1, $J$ = 6 Hz, OH), 5.29 (d, 1, $J$ = 5 Hz, OH), 4.2–4.5 (m, 4, $C_{2'}$ H, $C_{3'}$ H, 2 × $C_{5'}$ H); UV (MeOH) $\lambda_{max}$ 205 nm ($\epsilon$ 17 600), 267 (8800). Anal. ($C_9H_9FN_2O_5$) C, H, N.

**5′-Deoxy-2′,3′-di-*O*-methanesulfonyl-5-fluorouridine (14).** A solution of **5** (1.0 g) in dry pyridine (10 mL) was treated with methanesulfonyl chloride (1 mL) for 18 h at 5 °C. Ethanol (10 mL) was added, and after 3 h at 0 °C the solution was evaporated to dryness and triturated with water (80 mL). The crystals were collected and dried in vacuo to give **14**: yield 1.58 g (96%); mp 142–143 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 11.83 (s, 1, NH), 7.95 (d, 1, $J$ = 7 Hz, CHCF), 5.83 (d, 1, $J$ = 4 Hz, $C_{1'}$ H), 5.47 (dd, 1, $J$ = 4 and 6 Hz, $C_{2'}$ H), 5.03 (t, 1, $J$ = 6 Hz, $C_{3'}$ H), 4.18 (m, 1, $C_{4'}$ H), 3.29 (s, 3, $CH_3SO_2$), 3.27 (s, 3, $CH_3SO_2$), 1.43 (d, 3, $J$ = 6 Hz, $CH_3$CH); UV (MeOH) $\lambda_{max}$ 264 nm ($\epsilon$ 8290). Anal. ($C_{11}H_{15}FN_2O_9S_2$) C, H, F, N, S.

**1-(5′-Deoxy-2′,3′-*O*-isopropylidene-$\beta$-D-lyxofuranosyl)-5-fluorouracil (15).** A suspension of **14** (1 g) in water (15 mL) was heated under reflux with stirring for 6.75 h, cooled, and evaporated to dryness. Ethanol (20 mL) was twice distilled over the residue which was then treated with acetone (30 mL) and 2,2′-dimethoxypropane (3 mL) for 3 h. The solution was neutralized with an excess of sodium bicarbonate and filtered, and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate (20 mL) with warming, and the solution was filtered to remove suspended solids. The filtrate was applied to a silica column (125 g) which was eluted with methylene chloride/ethyl acetate (3:1) and fractions of 20 mL were collected. Tubes 50–120 were combined and evaporated to dryness to give **15**, 410 mg (57%), as a white solid. A sample was recrystallized from ethyl acetate/hexane: mp 190.5–193 °C; NMR ($CDCl_3$) $\delta$ 9.38 (br s, 1, NH), 7.58 (d, 1, $J$ = 6 Hz, CHCF), 5.72 (dd, 1, $J$ = 1 and 3 Hz, $C_{1'}$ H), 4.78 (dd, 1, $J$ = 3 and 6 Hz, $C_{2'}$ H), 4.59 (dd, 1, $J$ = 3 and 6 Hz, $C_{3'}$ H), 3.87 (m, 1, $C_{4'}$ H), 1.47 (s, 3, $CH_3$), 1.40 (d, 3, $J$ = 6 Hz, $CH_3$CH), 1.30 (s, 3, $CH_3$); UV (MeOH) $\lambda_{max}$ 208 nm ($\epsilon$ 6750), 269 (8800). Anal. ($C_{12}H_{15}FN_2O_5$) C, H, F, N.

**1-(5′-Deoxy-$\beta$-D-lyxofuranosyl)-5-fluorouracil (13).** A solution of **15** (410 mg) in 90% aqueous trifluoroacetic acid (20 mL) was stored at room temperature for 1.5 h and then evaporated to dryness. Ethanol (20 mL) was twice distilled over the residue, which was then evacuated to remove the last traces of trifluoroacetic acid. The solid was recrystallized from ethanol/hexane to give **13**: yield 286 mg (81%); mp 195–197 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 11.69 (br s, 1, NH), 8.10 (d, 1, $J$ = 7 Hz, CHCF), 6.00 (dd, 1, $J$ = 2 and 7 Hz, $C_{1'}$ H), 5.4 (d, 2, $J$ = 3 Hz, 2 × OH), 4.39 (m, 1, $C_{2'}$ H), 3.8–4.0 (m, 2, $C_{3'}$ H, $C_{4'}$ H), 1.23 (d, 3, $J$ = 5 Hz, $CH_3$CH); UV ($H_2O$) $\lambda_{max}$ 203 nm ($\epsilon$ 10 600), 269–270 (8840). Anal. ($C_9H_{11}FN_2O_5$) C, H, N.

**5′-Deoxy-2′,3′-*O*-isopropylidene-5-fluorocytidine (18).** A solution of 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylidene-5-fluorocytidine (17;[16] 48 g, 116.5 mmol) in methanol (500 mL) and triethylamine (20 mL) was treated with hydrogen at atmospheric pressure in the presence of palladium on carbon (5%, 25 g) for 30 min at room temperature. During this time, the suspension was agitated using a "Vibromix" vibrator. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness and triturated with ethyl acetate (200 mL). After storage overnight, the crystals were removed by filtration, and the filtrate was evaporated to approximately 100 mL and again stored overnight. A second batch of crystals was removed by filtration, and the filtrate was evaporated to dryness, pumped in vacuo, to give 5′-deoxy-2′,3′-*O*-isopropylidene-5-fluorocytidine as a foam: yield 31 g (93%). This material was characterized by formation of a crystalline picrate salt: mp 168–170 °C; UV ($CH_3OH$) $\lambda_{max}$ 237–238 nm ($\epsilon$ 20 700), 282 (9400), 353–354 (15 300); NMR ($Me_2SO$-$d_6$) $\delta$ 9.0 (m, 3, $NH_3$), 8.58 (s, 2, picrate), 8.29 (d, 1, $J$ = 6 Hz, CHCF), 5.72 (d, 1, $J$ = 2 Hz, $C_{1'}$ H), 4.97 (dd, 1, $J$ = 2 and 7 Hz, $C_{2'}$ H), 4.54 (dd, 1, $J$ = 4 and 7 Hz, $C_{3'}$ H), 4.12 (m, 1, $C_{4'}$ H), 1.47 (s, 3, $CH_3$), 1.28 (s, 3, $CH_3$), 1.31 (d, 3, $CH_3$CH). Anal. ($C_{18}H_{19}FN_6O_{11}$) C, H, F, N.

**5′-Deoxy-5-fluorocytidine (16).** 5′-Deoxy-2′,3′-*O*-isopropylidene-5-fluorocytidine (**18**; 31 g) was treated with 90% trifluoroacetic acid (200 mL) for 40 min. The solution was evaporated to dryness, repeatedly evaporated with portions of ethanol to remove residual water and trifluoroacetic acid, and dissolved in ethyl acetate (400 mL). Triethylamine was added to alkalinity, and after a few minutes crystallization commenced. After storage overnight, the crystals were collected, washed with ethyl acetate, and dried in vacuo to give **16**: yield 14 g (49%). Additional material was obtained by chromatography of the mother liquors on a silica gel column (600 g), which was eluted with ethyl acetate (4 L) followed by ethyl acetate/methanol (5:1, 4 L). The appropriate fractions were evaporated to dryness and applied to a Dowex 50 column ($H^+$), 2.3 × 60 cm. After a preliminary water wash, the required material was recovered by elution with aqueous ammonia (1 N). The ammonia fractions were evaporated to dryness, and the residue was recrystallized from ethanol. In this way, an additional 6.7 g of 5′-deoxy-5-fluorocytidine was obtained: total yield 20.7 g (78%); mp 209–211 °C dec; NMR ($Me_2SO$-$d_6$) $\delta$ 7.60 (d, 1, $J$ = 7 Hz, CHCF), 7.5 (br s, 2, $NH_2$), 5.62 (dd, 1, $J$ = 2 and 3 Hz, $C_{1'}$ H), 5.17 (d, 1, $J$ = 4 Hz, OH), 4.84 (d, 1, $J$ = 5 Hz, OH), 3.6–4.0 (m, 3, $C_{2'}$ H, $C_{3'}$ H, $C_{4'}$ H), 1.31 (d, 3, $J$ = 6 Hz, $CH_3$CH); UV ($H_2O$) $\lambda_{max}$ 238 nm ($\epsilon$ 7900), 281 (7860). Anal. ($C_9H_{12}FN_3O_4$) C, H, F, N.

**2,2′-Anhydro-1-(5′-deoxy-$\beta$-D-arabinofuranosyl)-5-fluorocytosine Hydrochloride (19).** A mixture of 5′-deoxy-5-fluorocytidine (**16**; 5 g, 20.4 mmol) and 2-acetoxyisobutyryl chloride (11.6 mL) in acetonitrile (80 mL, dry) was stirred at room temperature for 3 h. The clear solution was evaporated to dryness and triturated with ether (150 mL), and the solid was collected, washed with ether, and treated with methanolic hydrogen chloride (100 mL, 0.35 N) for 3.5 days at room temperature. The solution was evaporated to dryness and recrystallized from methanol/ethyl acetate to give **19**: yield 4.3 g (80%); mp 252 °C dec; NMR ($D_2O$) $\delta$ 8.98 (d, 1, $J$ = 4 Hz, CHCF), 7.15 (d, 1, $J$ = 6 Hz, $C_{1'}$ H), 6.17 (d, 1, J = 6 Hz, $C_{2'}$ H), 5.1 (m, 2, $C_{3'}$ H, $C_{4'}$ H), 1.68 (d, 3, $J$ = 7 Hz, $CH_3$CH); UV ($H_2O$) $\lambda_{max}$ 214 nm ($\epsilon$ 8200), 230 (8900), 267 (11 580). Anal. ($C_9H_{10}FN_3O_3$·HCl) C, H, F, N.

**1-(5′-Deoxy-$\beta$-D-arabinofuranosyl)-5-fluorocytosine (20).** A solution of 2,2′-anhydro-1-(5′-deoxy-$\beta$-D-arabinofuranosyl)-5-fluorocytosine hydrochloride (**19**; 3.35 g, 12.7 mmol) in water (30 mL) was treated with aqueous lithium hydroxide (12.7 mL, 1 M) for 5 h at room temperature and then evaporated to half volume. The solution was heated to dissolve precipitated solids, and then stored at 5 °C overnight. The crystals were collected, washed briefly with 2-propanol, and dried in vacuo to give **20**: yield 1.1 g (35%). The liquors were evaporated to dryness, dissolved in methanol (20 mL), and applied to a silica gel column (400 g) which was eluted with ethyl acetate/methanol (5:1). The appropriate fractions were evaporated to dryness and recrystallized from ethanol/ethyl acetate to give additional **20**: yield 1.0 g (32%); mp 224–226 °C dec; NMR ($Me_2SO$-$d_6$) $\delta$ 7.54 (m, 3, CHCF, $NH_2$), 5.96 (dd, 1, $J$ = 2 and 5 Hz, $C_{1'}$ H), 5.42 (d, 1, $J$ = 5 Hz, OH), 5.36 (d, 1, $J$ = 4 Hz, OH), 3.65–4.0 (m, 3, $C_{2'}$ H, $C_{3'}$ H, $C_{4'}$ H), 1.32 (d, 3, $J$ = 6 Hz, $CH_3$CH); UV ($H_2O$) $\lambda_{max}$ 212 nm ($\epsilon$ 9400), 237 (7820), 282 (8270). Anal. ($C_9H_{12}FN_3O_4$) C, H, F, N.

**2,2′-Anhydro-1-(5′-deoxy-3′-*O*-methanesulfonyl-$\beta$-D-arabinofuranosyl)-5-fluorocytosine Methanesulfonate (21).** A solution of **16** (980 mg) in pyridine (20 mL) was treated with methanesulfonyl chloride (0.91 mL) and stored for 2 h at room temperature. The solution was cooled to 0 °C, treated with water (2 mL) for 30 min, and then evaporated to dryness and partitioned between chloroform and 5% aqueous sodium bicarbonate (20 mL each). The chloroform layer was washed with water (20 mL), evaporated to a foam, and triturated with ethyl acetate containing a few drops of methanol. The solid was recrystallized from ethyl acetate/methanol to give **21**: yield 549 mg (34%); mp 246–249 °C dec; NMR ($Me_2SO$-$d_6$) $\delta$ 9.72 (br s, 2, $NH_2$), 8.75 (d, 1, $J$ = 5 Hz, CHCF), 6.37 (d, 1, $J$ = 6 Hz, $C_{1'}$ H), 5.66 (dd, 1, $J$ = 1 and 6 Hz, $C_{2'}$ H), 5.19 (m, 1, $C_{3'}$ H), 4.55 (m, 1, $C_{4'}$ H), 3.35 (s, 3, $CH_3SO_2$), 2.27 (s, 3, $CH_3SO_3^-$), 1.15 (d, 3, $J$ = 6 Hz, $CH_3$CH); UV (MeOH) $\lambda_{max}$ 268 nm ($\epsilon$ 12 700), 232 (8950). Anal. ($C_{11}H_{16}FN_3O_8S_2$) C, H, N, S.

**1-(2′,3′-Anhydro-5′-deoxy-$\beta$-D-lyxofuranosyl)-5-fluorocytosine (22).** A solution of **16** (5 g) in dry pyridine (100 mL) was cooled to 0 °C, treated with methanesulfonyl chloride (4.55

mL), and stored at room temperature for 2.5 h. The solution was again cooled to 0 °C and water (10 mL) was added. After 1 h, the solution was evaporated to dryness and treated, with stirring, with 1 N sodium hydroxide (25 mL) for 18 h at room temperature. The product was evaporated to dryness, dissolved in methanol (100 mL), and impregnated onto silica gel (100 g). After evaporation to dryness, the silica was slurried in ethyl acetate/methanol (10:1) and applied to the top of a silica column (500 g) which had been packed in and was eluted with the same solvent. Tubes 130–210 were combined, evaporated to dryness, and recrystallized from ethyl acetate/methanol to give **22**: yield 1.4 g (30%). A second crop of less pure material, mp 237–238 °C dec (1.4 g, 30%), was obtained from the liquors: mp 237–239 °C dec; NMR ($Me_2SO$-$d_6$) $\delta$ 7.77 (br s, 2, $NH_2$), 7.55 (d, 1, $J$ = 7 Hz, CHCF), 6.00 (d, 1, $J$ = 2 Hz, $C_{1'}$ H), 4.17 (q, 1, $J$ = 6 Hz, $C_{4'}$ H), 3.98 (d, 1, $J$ = 2 Hz, $C_{2'}$ H), 3.87 (d, 1, $J$ = 2 Hz, $C_{3'}$ H), 1.31 (d, 3, $J$ = 6 Hz, $CH_3CH$); UV (MeOH) $\lambda_{max}$ 240 nm ($\epsilon$ 8780), 281 (7270). Anal. ($C_9H_{10}FN_3O_3$) C, H, N.

**Antitumor Testing.** $CD_1$ mice (Charles River, Wilmington, MA), weighing 18–20 g, were implanted subcutaneously in the right ventro-lateral area by trochar with approximately 20-mg fragments of sarcoma 180 tumor. Test substances were dissolved or suspended in $H_2O$ and 1.0 mL was administered intraperitoneally (ip) shortly after implantation and once daily thereafter for a total of eight treatments. Mice were sacrificed 8 days after implantation, tumors were excised and weighed, and the average weight of tumors in the drug-treated (T) mice was compared with the average weight of tumors in the $H_2O$-treated (C) mice. A C/T index of ≥2 indicated a significant antitumor effect.

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