Pyridine Nucleosides Related to 5-Fluorouracil (1)

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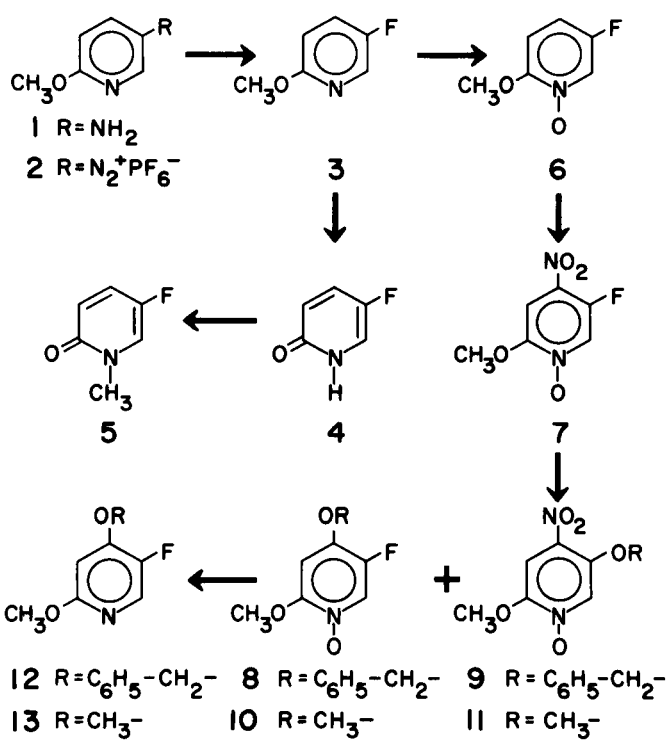
5-Fluoro-2-methoxypyridine (**3**) synthesized from 5-amino-2-methoxypyridine was converted to 4-benzyloxy-5-fluoro-2-methoxypyridine (**12**) and 2,4-dimethoxy-5-fluoropyridine (**13**) by a four step procedure employing the intermediate 5-fluoro-2-methoxy-4-nitropyridine *N*-oxide (**7**). Condensation of **3**, **12**, and **13** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide gave, after removal of the protecting groups, 4-deoxy-5-fluoro-3-deazauridine (**20**), 5-fluoro-3-deazauridine (**23**) and 5-fluoro-4-methoxy-3-deazauridine (**25**). Several alkylated and dealkylated derivatives of **3** and **12** were also prepared. Structure proof and anomeric configuration were determined from the uv, nmr, and CD data.

There has been recent interest in the synthesis and determination of the chemotherapeutic, and biochemical properties of pyridine nucleosides. 3-Deazauridine and 3-deazacytidine synthesized by Currie *et al.* (3) are both active as cytotoxic agents (4,5) *in vitro* and *in vivo*. Additional studies concerning their biochemistry (6-8) and their inhibition of RNA virus replication (9) have also been reported.

We have recently reported the synthesis and properties of 5-fluoro-3-deazauracil, and 3-deazathymine nucleosides (10). In an effort to do more detailed biochemical and pharmacological studies with these nucleosides we desired an alternate, more efficient method of synthesis of 5-fluoro-3-deazauracil and its nucleosides. In addition, we sought to prepare the following nucleoside derivatives of 5-fluorouracil as potential tumor-inhibitory agents; 4-deoxy-5-fluoro-3-deazauridine (**20**) and 5-fluoro-4-methoxy-3-deazauridine (**25**). This report describes the synthesis of these compounds by a method which represents a new entry into the 2,4-dialkoxypyridine ring system.

Commercially available 5-amino-2-methoxypyridine (**1**) was converted in 35% overall yield to 5-fluoro-2-methoxypyridine (**3**) *via* the diazonium hexafluorophosphate salt (**2**) using a modified (11) Schiemann reaction (Scheme 1). Oxidation of (**3**) with an excess of *m*-chloroperoxybenzoic acid gave 5-fluoro-2-methoxypyridine *N*-oxide (**6**). Nitration of (**6**) at 65° in sealed tubes with fuming HNO_3-H_2SO_4 gave a mixture of 5-fluoro-2-methoxy-4-nitropyridine *N*-oxide (**7**) and starting material, which were separated by fractional crystallization from water (12). The position of nitration in **7** was clearly shown to be C-4 by nmr and by reports that analogous compounds, 2-ethoxypyridine *N*-oxide (13) and 3-fluoropyridine *N*-oxide (14) are nitrated in the C-4 positions under similar conditions. The observation that $J_{3\text{-}F} > J_{6\text{-}F}$ in **7** and other fluorinated pyridines synthesized in this paper is corroborated by similar observations made by Lyle and Taft (15) for 5-fluorolutidines and Rowbotham *et al.* (16)

SCHEME I



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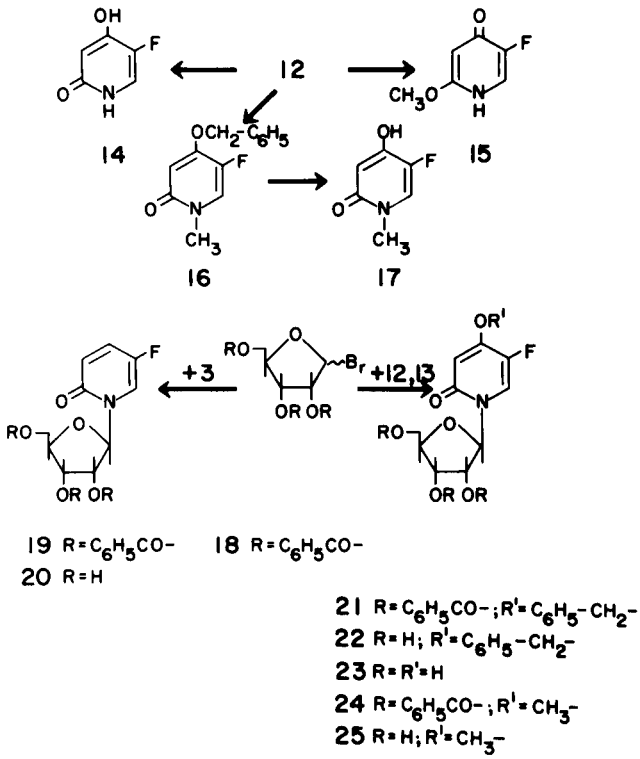

for methyl derivatives of 2-fluoropyridine. Den Hertog and Combé (17) have shown that the nitro group of 4-nitropyridine *N*-oxide is easily substituted by nucleophiles; this effect being due to the strong electron withdrawing ability of the *N*-oxide function. On the other hand, Talik and Talik (14) have shown that 3-fluoro-4-nitropyridine *N*-oxide reacts with nucleophiles to give only 3-substituted-4-nitropyridine *N*-oxides. Presumably, the nitro group activates the fluorine atom towards nucleophilic attack more than the *N*-oxide activates the nitro moiety. Reaction of **7** with a sodium alkoxide gave a mixture of 4-substituted (4-alkoxy-5-fluoro-2-methoxypyridine *N*-oxide) and 5-substituted (5-alkoxy-2-methoxy-4-nitropyridine *N*-oxide) products. Specifically, reaction of **7** with sodium benzyloxide gave 4-benzyloxy-5-fluoro-2-methoxypyridine *N*-oxide (**8**) and 5-benzyloxy-2-methoxy-4-nitropyridine *N*-oxide (**9**), and reaction of **7** with sodium methoxide gave 2,4-dimethoxy-5-fluoropyridine *N*-oxide (**10**) and 2,5-dimethoxy-4-nitropyridine *N*-oxide (**11**). The yields were in the range of 80-90%, and in both cases the 4-substituted products predominated. Each pair of products was easily separated by column chromatography on silica gel, and the structures determined by nmr and uv spectrometry and elemental analyses.

Reduction of the *N*-oxide function was accomplished by the phosphorus trichloride-chloroform method of Ochiai (18) giving 4-benzyloxy-5-fluoro-2-methoxypyridine (**12**) and 2,4-dimethoxy-5-fluoropyridine (**13**). Complete dealkylation of **12** with 25% hydrochloric acid gave 5-fluoro-4-hydroxy-2-pyridone (**14**) (Scheme 2). Both **13** and **14** were identical by uv, nmr, and mixture melting point to the same compounds synthesized by Nesnow *et al.* (10) using alternate procedures. The overall yield of **14** from starting material was 11% which represented a 28-fold increase when compared to the previously published route (10).

TABLE I

Uv Spectra of Selected Pyridines

Compound	0.1*N* HCl	Maximum Uv Absorption (nm) in Neutral Medium	1.0*N* NaOH
5-Fluoro-2-methoxypyridine (**3**)	280	280 (a)	
5-Fluoro-1-methyl-2-pyridone (**5**)	295	312 (a)	
5-Fluoro-1-(β-D-ribofuranosyl)-2-pyridone (**20**)	313	316 (a)	
2,4-Dimethoxy-5-fluoropyridine (**13**)	267	267 (b)	267
5-Fluoro-4-hydroxy-1-methyl-2-pyridone (**17**)	285	290 (b)	257; 275 (sh)
5-Fluoro-2-methoxy-4-pyridone (**15**) (d)	259	253 (c)	269
5-Fluoro-4-hydroxy-1-(β-D-ribofuranosyl)-2-pyridone (**23**)	288	290 (b)	257; 275 (sh)
5-Fluoro-4-methoxy-1-(β-D-ribofuranosyl)-2-pyridone (**25**)	288	293 (a)	291

(a) Spectra determined in methanol. (b) Spectra determined in 0.1*M* citrate buffer *p*H 3.2. (c) Spectra determined in water. (d) The previously reported uv data for this compound are incorrect (10).

Reference compounds needed for uv spectral analyses were synthesized in the following manner. 5-Fluoro-1-methyl-2-pyridone (**5**) was prepared by the action of potassium hydroxide and methyl iodide on **4**, which was obtained from the dealkylation of **3**. The alkylation reaction proceeded without formation of **3**, an observation in accord with the work of Chung and Tieckelmann (19) who described alkylation reactions of 5-substituted-2-pyridones. Debenzylation of **12** with hydrogen and Pd/C gave a 49% yield of **15**, while reaction of **12** with methyl iodide gave **16**, which was debenzylated by hydrogenolysis to give **17**.

Condensation of **3** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**18**) in acetonitrile gave the blocked nucleoside **19** in 46% yield. Deblocking of **19** with sodium methoxide gave 5-fluoro-1-(β-D-ribofuranosyl)-2-pyridone [4-deoxy-5-fluoro-3-deazauridine] (**20**). Reaction of **12** or **13** with **18** gave the blocked nucleosides **21** and **24**, which were deblocked as described above to give **22** and 5-fluoro-4-methoxy-1-(β-D-ribofuranosyl)-2-pyridone [5-fluoro-4-methoxy-3-deazauridine] (**25**). Compound **22** was debenzylated on Pd/C to yield 5-fluoro-4-hydroxy-1-(β-D-ribofuranosyl)-2-pyridone [5-fluoro-3-deazauridine] (**23**) which was identical by uv, nmr, and melting point to 5-fluoro-3-deazauridine prepared by an alternate route (10). The overall yield of **23** from **1** was 5%, which represents a 24-fold increase when compared with the previously published route (10).

Inspection of the uv data presented in Table I indicates that the site of glycosidic attachment of nucleosides **20**, **23**, and **25** is at N-1. Each of these nucleosides exhibits a positive Cotton effect as determined by CD, and the anomeric proton of each nucleoside exhibits a singlet in its nmr spectrum. This evidence suggests that all of the nucleosides are β-anomers (10).

Neither **20** nor **25** inhibited the growth of L-5178Y cells in culture at concentrations of 10^{-3} *M* or less when tested according to established assay procedures (20).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Uv spectra were recorded on a Gilford spectrophotometer model 2400S or a Beckman DB-G. Nmr spectra were obtained on a Perkin-Elmer R-12 using tetramethylsilane as internal reference. Circular dichroism spectra were obtained on a Cary spectropolarimeter Model 60. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Analytical tlc was performed on Eastman chromatoplates.

2-Methoxypyridine-5-diazonium Hexafluorophosphate (2).

5-Amino-2-methoxypyridine (**1**) [49.6 g., 0.4 mole] was dissolved in 72 ml. of concentrated hydrochloric acid and 320 ml. of water. The solution was cooled to -5° (salt-ice) whereupon 34.4 g. of sodium nitrite dissolved in a small amount of water was added in portions. Forty-five minutes after the last of the sodium nitrite was added, 80 ml. of HPF_6 was added at one time. After 20 minutes of stirring to insure complete reaction, the thick suspension was filtered, washed with 3 liters of ice-water, rinsed with 300 ml. of ether and dried *in vacuo* over phosphorus pentoxide and sodium hydroxide for 48 hours. This yielded 96 g. (86%) of **2** as a pink powder, m.p. 118-120°; ir 2270 cm^{-1}.

5-Fluoro-2-methoxypyridine (3).

2-Methoxypyridine-5-diazonium hexafluorophosphate (**2**) (96 g., 0.35 mole) was placed in a flask connected by rubber tubing to a 500 ml. 2-necked r.b. flask immersed in an oil bath. This flask was connected to a 2-liter 3-necked r.b. flask (immersed in an ice bath) with a short goose neck, and two condensers were connected to the other two necks. The diazonium salt was added in portions to the heated flask (bath temp. = 150°) over the course of 15 minutes. After cooling, the condensers, flasks, and connecting apparatus were washed with 3*N* sodium hydroxide and chloroform, and the aqueous layer was extracted exhaustively with chloroform. After the organic extracts were dried over sodium sulfate, filtered and evaporated, the red oil was distilled through a 5 cm Vigreaux column. This yielded 18 g. (41%) of **3** as a colorless liquid, b.p. 137-138°/760 mm Hg; uv λ max (methanol) 280 nm (ε, 2,820); nmr (deuteriochloroform): τ 1.97 (d, 1, $J_{4\text{-}6}$ = 3.0 Hz, H-6), 2.68 (d of d of d, 1, $J_{4\text{-}6}$ = 3.0 Hz, $J_{3\text{-}4}$ = 9.0 Hz, $J_{4\text{-}F}$ = 7.6 Hz, H-4), 3.31 (d of d, 1, $J_{3\text{-}4}$ = 9.0 Hz, $J_{3\text{-}F}$ = 3.7 Hz, H-3), 6.12 (s, 3, OCH_3).

Anal. Calcd. for C_6H_6FNO: C, 56.69; H, 4.72; N, 11.02; F, 14.96. Found: C, 56.73; H, 4.75; N, 10.94; F, 14.91.

5-Fluoro-2-pyridone (4).

5-Fluoro-2-methoxypyridine (**3**) (2.8 g., 22 mmoles) and 15 ml. of 25% hydrochloric acid were sealed in a glass tube and heated at 145° for 2 hours. After cooling, the tube was opened and the contents extracted with ether. The aqueous layer was neutralized with Dowex-1 (formate), filtered, washed with water and methanol, and evaporated to a colorless solid. Recrystallization from ethyl acetate gave 1.20 g. (49%) of **4** as colorless needles, m.p. 151-152°; uv λ max (*p*H 1.0) 290 nm (ε, 4,230), λ max (methanol) 307 nm (ε, 4,660), λ max (*p*H 14.0) 304 nm (ε, 5,660); nmr (deuterium oxide) τ 2.75 (m, 2, H-6, H-4), 3.75 (m, 1, H-3).

Anal. Calcd. for C_5H_4FNO: C, 53.09; H, 3.54; N, 12.39; F, 16.81. Found: C, 53.09; H, 3.60; N, 12.37; F, 16.83.

5-Fluoro-1-methyl-2-pyridone (5).

A mixture of **4** (565 mg., 5 mmoles), 45 ml. of dry methanol, 5 ml. of a 1.0 *N* potassium hydroxide/methanol solution and 2.5 ml. of methyl iodide were refluxed for 2 hours. The reaction mixture was evaporated to dryness and partitioned between 2*N* sodium hydroxide and chloroform. After extractions with chloroform (5 x 50 ml.) the organic layers were dried over anhydrous sodium sulfate, filtered, evaporated and the residue recrystallized from Skellysolve B to yield 335 mg. (53%) of **5** as colorless microplates, m.p. 56-57°; uv λ max (*p*H 1.0) 295 nm (ε, 5,470) λ max (methanol) 312 nm (ε, 5,090); nmr (deuteriochloroform): τ 2.60 (m, 2, H-4, H-6), 3.43 (m, 1, H-3), 6.49 (s, 3, NCH_3).

Anal. Calcd. for $C_6H_6FNO \cdot 0.5H_2O$: C, 52.94; H, 5.15; N, 10.29; F, 13.97. Found: C, 53.05; H, 5.11; N, 10.26; F, 13.96.

5-Fluoro-2-methoxypyridine *N*-Oxide (6).

m-Chloroperoxybenzoic acid (120 g., 0.7 mole) was added to **3** (26 g., 0.2 mole) in 200 ml. of dichloromethane and the solution was refluxed for 6 hours. After stirring for an additional 12 hours at room temperature, the reaction mixture was evaporated to

dryness. The residue was stirred for 6 hours with 1 liter of water and filtered. This process was repeated and the combined aqueous fractions were evaporated to 10% of the original volume. The slurry was filtered and the filtrate evaporated to dryness. Recrystallization from ethyl acetate-Skellysolve B gave 22 g. (77%) of **6** as colorless needles, m.p. 124-125°; uv λ max (methanol) 257 nm (ε, 7,570), 312 (5,290); nmr (DMSO-d_6): τ 1.72 (m, 1, H-6), 2.96 (m, 2, H-3, H-4), 5.90 (s, 3, OCH_3).

Anal. Calcd. for $C_6H_6FNO_2 \cdot 0.2H_2O$: C, 49.10; H, 4.36; N, 9.54; F, 12.96. Found: C, 49.10; H, 4.15; N, 9.66; F, 13.16.

5-Fluoro-2-methoxy-4-nitropyridine *N*-Oxide (**7**).

Into each of four glass tubes was added **6** (8 g., 0.056 mole) and 80 ml. of a 1:1 mixture of concentrated sulfuric acid and red fuming nitric acid. The tubes were sealed and heated at 65° for 8 hours. After cooling, the tubes were opened and neutralized with sodium bicarbonate. The reaction mixture was exhaustively extracted with chloroform and the organic layers dried over sodium sulfate. After filtration and evaporation, the mixture of starting material and product was separated by fractional crystallization from water; the product is slightly soluble in cold water. This yielded 15 g. (35%) of **7** as yellow needles, m.p. 181-182°; uv λ max (methanol) 260 nm (ε, 2,430), 357 (1,900); nmr (DMSO-d_6): τ 1.09 (d, 1, $J_{6\text{-}F}$ = 6.9 Hz, H-6), 2.14 (d, 1, $J_{3\text{-}F}$ = 8.4 Hz, H-3), 5.94 (s, 3, OCH_3).

Anal. Calcd. for $C_6H_5FN_2O_4$: C, 38.29; H, 2.66; N, 14.89; F, 10.11. Found: C, 38.11; H, 2.55; N, 14.81; F, 10.14.

4-Benzyloxy-5-fluoro-2-methoxypyridine *N*-Oxide (**8**) and 5-Benzyloxy-2-methoxy-4-nitropyridine *N*-Oxide (**9**).

Sodium (1.51 g., 66 g.-atoms) was reacted with 60 ml. of benzyl alcohol and the resulting solution dropped slowly into a stirred solution of **7** (11.28 g., 60 mmoles) in 180 ml. of benzyl alcohol. One hour after the last of the alkoxide solution was added, the reaction was quenched by pouring the reaction mixture into 1 l. of ice-water. The resulting mixture was extracted with chloroform (5 x 400 ml.) the organic layers washed several times with water, dried over sodium sulfate, filtered and evaporated to an oil. This mixture was chromatographed on a column of silica-gel using ethyl acetate as elution solvent. After all the benzyl alcohol had been eluted, the elution solvent was changed to ethyl acetate-methanol 95/5. The fractions containing **9** were pooled, evaporated and the residue recrystallized from Skellysolve B-chloroform to give 5.4 g. (33%) of **9** as yellow crystals, m.p. 197-198°; uv λ max (methanol) 265 nm (ε, 6,430), 308 (4,710), 369 (6,300); nmr (CF_3CO_2D): τ 1.59 (s, 1, H-6), 2.23 (s, 1, H-3), 2.62 (s, 5, phenyl), 4.69 (s, 2, benzyl), 5.75 (s, 3, OCH_3).

Anal. Calcd. for $C_{13}H_{12}N_2O_5 \cdot 0.6H_2O$: C, 54.39; H, 4.60; N, 9.76. Found: C, 54.[illegible]; H, 4.21; N, 9.54.

When the elution solvent was changed to methanol, compound **8** was eluted. The desired fractions were pooled, evaporated and the residue recrystallized from benzene to give 8.5 g. (57%) of **8** as colorless needles, m.p. 105-108°; uv λ max (methanol) 260 nm (ε, 14,000), 290 (3,850); nmr (DMSO-d_6): τ 1.54 (d, 1, $J_{6\text{-}F}$ = 6.8 Hz, H-6), 2.56 (s, 5, phenyl), 2.88 (d, 1, $J_{3\text{-}F}$ = 9.0 Hz, H-3), 4.71 (s, 2, benzyl), 6.03 (s, 3, OCH_3).

Anal. Calcd. for $C_{13}H_{12}FNO_3$: C, 62.65; H, 4.82; N, 5.62; F, 7.63. Found: C, 62.68; H, 4.77; N, 5.57; F, 7.63.

2,4-Dimethoxy-5-fluoropyridine *N*-Oxide (**10**) and 2,5-Dimethoxy-4-nitropyridine *N*-Oxide (**11**).

To a stirred slurry of **7** (3.76 g., 20 mmoles) in 70 ml. of methanol was slowly added a solution of sodium (485 mg., 21 g.-atoms) in 20 ml. of methanol. Sixty minutes after addition, the reaction mixture was filtered to yield 982 mg. (24%) of pure **11**. An analytical sample was prepared by recrystallization from methanol-chloroform to give yellow needles, m.p. 188.5-189.0°; uv λ max (methanol) 267 nm (ε, 5,470), 310 (5,340), 370 (7,320); nmr (deuteriochloroform): τ 1.50 (s, 1, H-6), 2.21 (s, 1, H-3), 5.93 (s, 3, OCH_3), 6.02 (s, 3, OCH_3).

Anal. Calcd. for $C_7H_8N_2O_5$: C, 42.01; H, 4.03; N, 14.00. Found: C, 41.97; H, 4.14; N, 13.95.

The filtrate from the reaction mixture contained mainly **10** with small amounts of **11** and was evaporated, placed on a silica gel column and washed with chloroform until all the **11** had eluted. The column was then washed with methanol and fractions containing **10** combined, evaporated to an oil and recrystallized from methanol-ether to yield 2.10 g. (60%) of **10** as colorless microcrystals, m.p. 154-156°; uv λ max (methanol) 257 nm (ε, 8,920), 300 sh (3,880); nmr (deuteriochloroform): τ 1.60 (d, 1, $J_{6\text{-}F}$ = 6.5 Hz, H-6), 2.95 (d, 1, $J_{3\text{-}F}$ = 8.0 Hz, H-3), 5.90 (s, 3, OCH_3), 5.95 (s, 3, OCH_3).

Anal. Calcd. for $C_7H_8FNO_3 \cdot 0.1 \cdot H_2O$: C, 48.05; H, 4.69; N, 8.00; F, 10.86. Found: C, 48.04; H, 4.40; N, 7.93; F, 10.77.

4-Benzyloxy-5-fluoro-2-methoxypyridine (**12**).

A solution of **8** (8.0 g., 32 mmoles), 54 ml. of freshly distilled phosphorus trichloride and 100 ml. of dry chloroform were stirred at 55° for 45 minutes. After evaporation *in vacuo*, the residue was treated with 100 ml. of 1*N* sodium hydroxide and the resulting suspension was extracted with chloroform (5 x 100 ml.). The organic layers were dried over sodium sulfate, filtered, evaporated and the crystalline residue recrystallized from ethanol to give 5.80 g. (78%) of **12** as colorless microcrystals, m.p. 58-58.5°; nmr (deuteriochloroform): τ 2.19 (d, 1, $J_{6\text{-}F}$ = 3.0 Hz, H-6), 2.70 (s, 5, phenyl), 3.77 (d, 1, $J_{3\text{-}F}$ = 6.0 Hz, H-3), 4.97 (s, 2, benzyl), 6.22 (s, 3, OCH_3).

Anal. Calcd. for $C_{13}H_{12}FNO_2$: C, 66.95; H, 5.15; N, 6.00; F, 8.15. Found: C, 66.83; H, 5.02; N, 5.98; F, 8.17.

2,4-Dimethoxy-5-fluoropyridine (**13**).

A solution of **10** (2.10 g., 12.1 mmoles) in 30 ml. dry chloroform was treated in a similar fashion as described above to yield 1.65 g. (83%) of pure **13** as a colorless solid, m.p. 60-61°; mixture melting point with an authentic sample 60-61°. The uv and nmr spectra of **13** were identical to those of 2,4-dimethoxy-5-fluoropyridine synthesized by an alternate route (10).

5-Fluoro-4-hydroxy-2-pyridone (**14**).

A mixture of 4-benzyloxy-5-fluoro-2-methoxypyridine (**12**) (2.33 g., 10 mmoles) and 10 ml. of 25% hydrochloric acid were sealed in a glass tube and heated for 6 hours at 145°. After cooling, the tube was opened, the contents extracted with chloroform (3 x 25 ml.), the aqueous layer evaporated to dryness and sublimed at 200°/1.00 mm Hg to yield 1.07 g. (83%) of **14** as a colorless powder, m.p. 263-264° dec.; mixture m.p. with an authentic sample 263-264° dec. The nmr and uv spectra of **14** were identical to 5-fluoro-4-hydroxy-2-pyridone synthesized by another route (10).

5-Fluoro-2-methoxy-4-pyridone (**15**).

A solution of **12** (570 mg., 2.45 mmoles) in 15 ml. of methanol was hydrogenated at 28 psi of hydrogen in the presence of 150 mg. of 5% Pd/C for 2 hours. The suspension was filtered through a bed of Celite, the filtrate evaporated to a solid and chromatographed on a silica gel column using ethyl acetate as elution solvent. The fractions containing the product were pooled, evaporated and the residue recrystallized from methanol to yield

172 mg. (49%) of **15** as colorless plates, m.p. 197-199°; uv λ max (*p*H 1.0) 259 nm (ε, 6,210), λ max (water) 253 nm (ε, 13,780), λ max (*p*H 14.0) 269 nm (ε, 3,890); nmr (DMSO-d_6): τ 2.21 (d, 1, $J_{6\text{-}F}$ = 3.3 Hz, H-6), 3.75 (d, 1, $J_{3\text{-}F}$ = 6.1 Hz, H-3), 6.21 (s, 3, OCH_3).

Anal. Calcd. for $C_6H_6FNO_2$: C, 50.34; H, 4.19; N, 9.79; F, 13.29. Found: C, 50.48; H, 4.26; N, 9.76; F, 13.39.

4-Benzyloxy-5-fluoro-1-methyl-2-pyridone (**16**).

A solution of **12** (233 mg., 1 mmole) and 10 ml. of methyl iodide was sealed in a glass tube and heated at 80° for 10 hours. Excess reactants were removed by evaporation *in vacuo* and the residue chromatographed on a silica gel column using Skellysolve-B and Skellysolve B-chloroform 9/1 as elution solvents. The fractions containing the product were pooled, evaporated, and the residue recrystallized from Skellysolve-B-chloroform to give 140 mg. (60%) of **16** as colorless microplates, m.p. 159-161°; nmr (deuteriochloroform): τ 2.60 (m, 5, phenyl), 2.84 (d, 1, $J_{6\text{-}F}$ = 6.5 Hz, H-6), 3.94 (d, 1, $J_{3\text{-}F}$ = 8.1 Hz, H-3), 4.95 (s, 2, benzyl), 6.59 (s, 3, NCH_3).

Anal. Calcd. for $C_{13}H_{12}FNO_2$: C, 66.95; H, 5.15; N, 6.00; F, 8.15. Found: C, 66.87; H, 5.18; N, 5.98; F, 8.09.

5-Fluoro-4-hydroxy-1-methyl-2-pyridone (**17**).

A suspension of **16** (100 mg., 0.43 mmole) and 15 mg. of 5% Pd/C in 20 ml. of methanol and 10 ml. of toluene was hydrogenated in a Parr apparatus at room temperature and 20 psi of hydrogen. After 3.5 hours, the reaction mixture was filtered through a bed of Celite, evaporated to dryness and sublimed at 200°/0.5 mm Hg to give 40 mg. (65%) of **17**, m.p. 222-224°; uv λ max (*p*H 1.0) 285 nm (ε, 2,030), λ max (*p*H 3.2) 290 nm (ε, 4,070), λ max (*p*H 7.2) 257 nm (ε, 7,230), 275 (sh) (4,730), λ max (*p*H 14.0) 257 nm (ε, 7,720), 275 (sh) (5,270); nmr (DMSO-d_6): τ 2.20 (d, 1, $J_{6\text{-}F}$ = 7.3 Hz, H-6), 4.32 (d, 1, $J_{3\text{-}F}$ = 8.6 Hz, H-3), 6.75 (s, 3, NCH_3).

Anal. Calcd. for $C_6H_6FNO_2$: C, 50.34; H, 4.19; N, 9.79; F, 13.28. Found: C, 50.40; H, 4.19; N, 9.76; F, 13.27.

5-Fluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyridone (**19**).

A mixture of **3** (635 mg., 5 mmoles), 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**18**) [prepared from 2.52 g. (5 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose] and 25 ml. of dry acetonitrile was sealed under nitrogen and stirred for 5 days at room temperature. Methanol was added to the reaction mixture and the precipitate filtered and washed with methanol to yield 1.27 g. (46%) of **19** as a colorless powder, m.p. 185.5-186.5°.

Anal. Calcd. for $C_{31}H_{24}FNO_8$: C, 66.78; H, 4.30; N, 2.51; F, 3.41. Found: C, 66.62; H, 4.06; N, 2.30; F, 3.74.

5-Fluoro-1-(β-D-ribofuranosyl)-2-pyridone (**20**).

A solution of **19** (1.11 g., 2 mmoles), sodium methoxide (378 mg., 7 mmoles) in 10 ml. of dry methanol and 25 ml. of dry THF was sealed and stirred for 14 hours at room temperature. The reaction mixture was evaporated to an oil, methanol was added and Dowex 50 (H^+) was then added until the *p*H = 3. The slurry was filtered, washed with methanol, evaporated to an oil, and partitioned between water and ether. After several ether extractions, the aqueous layer was evaporated and recrystallized from methanol-ether to give 233 mg. (48%) of **20** as microcrystals; m.p. 143-145°; uv λ max (methanol) 316 nm (ε, 5,450); nmr (DMSO-d_6): τ 1.69 (d of d, 1, $J_{6\text{-}F}$ = 5.4 Hz, $J_{4\text{-}6}$ = 3.2 Hz, H-6) 2.40 (d of d of d, 1, $J_{3\text{-}4}$ = 9.8 Hz, $J_{4\text{-}6}$ = 3.2 Hz, $J_{4\text{-}F}$ = 6.9 Hz, H-4), 3.55 (d of d, 1, $J_{3\text{-}4}$ = 9.8 Hz, $J_{3\text{-}F}$ = 5.3 Hz, H-3), 3.97 (s, 1, H-1'); [θ] 28° 316 nm + 12,482.

Anal. Calcd. for $C_{10}H_{12}FNO_5$: C, 48.97; H, 4.89; N, 5.71; F, 7.75. Found: C, 48.95; H, 4.96; N, 5.68; F, 7.76.

4-Benzyloxy-5-fluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyridone (**21**).

A mixture of **12** (2.33 g., 10 mmoles), (**18**) [prepared from 5.04 g. (10 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose], 50 ml. of dry acetonitrile and 1 g. of Linde molecular sieves 3A was sealed under nitrogen and stirred 5 days at room temperature. The reaction mixture was filtered, the filtrate evaporated to an oil and recrystallized from Skellysolve B-chloroform to give 5.12 g. (77%) of **21** as colorless fibers, m.p. 104° (sint), 114-116°.

Anal. Calcd. for $C_{38}H_{30}FNO_9 \cdot 0.25H_2O$: C, 68.31; H, 4.57; N, 2.10; F, 2.85. Found: C, 68.33; H, 4.75; N, 2.19; F, 2.89.

4-Benzyloxy-5-fluoro-1-(β-D-ribofuranosyl)-2-pyridone (**22**).

Sodium (530 mg., 25 g.-atoms) was reacted with 100 ml. of dry methanol, and **21** (5.10 g., 7.7 mmoles) was added to the resulting solution. After stirring at room temperature for 4 hours, the reaction mixture was neutralized with glacial acetic acid and then evaporated to a semi-solid. The residue was suspended in cold water, filtered, and washed thoroughly with ether. This yielded 2.01 g. (75%) of **22** as a colorless powder. Recrystallization from ethanol-water gave colorless crystals, m.p. 167-168.5°; nmr (DMSO-d_6): τ 1.75 (d, 1, $J_{6\text{-}F}$ = 8.2 Hz, H-6), 2.54 (s, 5, phenyl), 3.95 (m, 2, H-3, H-1'), 4.81 (s, 2, benzyl).

Anal. Calcd. for $C_{17}H_{18}FNO_6$: C, 58.12; H, 5.12; N, 3.99; F, 5.41. Found: C, 58.21; H, 5.16; N, 3.89; F, 5.49.

5-Fluoro-4-hydroxy-1-(β-D-ribofuranosyl)-2-pyridone (**23**).

A suspension of **22** (1.00 g., 2.85 mmoles) and 150 mg. of 5% Pd/C in 50 ml. of methanol was hydrogenated at 20 psi of hydrogen for 2½ hours in a Parr apparatus. The reaction mixture was filtered through a bed of Celite and the filtrate concentrated *in vacuo* to an oil, which crystallized on standing to give 570 mg. (75%) of **23** as colorless broad needles, m.p. 195-197° [lit. 197-198.5° (10)]. The uv and nmr of **23** were identical to those of 5-fluoro-3-deazauridine prepared in an alternate manner (10).

5-Fluoro-4-methoxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyridone (**24**).

Condensation of **13** (750 mg., 5 mmoles) with **18** [prepared from 2.76 g. (5.5 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose] in 50 ml. of dry acetonitrile at room temperature for 18 days gave, after evaporation and recrystallization from chloroform-Skellysolve B, 1.67 g. (57%) of **24** as colorless crystals, m.p. 217.5-218.0°.

Anal. Calcd. for $C_{32}H_{26}FNO_9$: C, 65.41; H, 4.43; N, 2.38; F, 3.24. Found: C, 65.41; H, 4.76; N, 2.48; F, 3.31.

5-Fluoro-4-methoxy-1-(β-D-ribofuranosyl)-2-pyridone (**25**).

To a solution of sodium (200 mg., 8.5 g.-atoms) in 30 ml. of dry methanol was added **24** (1.38 g., 2.36 mmoles) and the mixture stirred for 14 hours at room temperature. The *p*H was adjusted to 5 with glacial acetic acid, and the reaction mixture evaporated to an oil. This oil was partitioned between water and ether and extracted with ether (3 x 50 ml.). The aqueous layer was reduced in volume and placed on an Amberlite IRC-50 (H^+ form) column. Fractions were monitored at 280 nm and those containing the product were pooled, evaporated and recrystallized from ethyl acetate-methanol to yield 507 mg. (78%) of **25** as colorless microplates, m.p. 191-192.5°; uv λ max (*p*H 1.0) 288 nm (ε, 4,650), λ max (methanol) 293 nm (ε, 4,620), λ max (*p*H 14.0) 291 nm (ε, 4,750); nmr (DMSO-d_6): τ 1.82 (d, 1, $J_{6\text{-}F}$ =

8.3 Hz, H-6), 4.01 (s, 1, H-1[1]), 4.05 (d, 1, $J_{3\text{-}F}$ = 8.2 Hz, H-3), 6.18 (s, 3, OCH_3); [θ] 28° 293 nm + 11,772.

Anal. Calcd. for $C_{11}H_{14}FNO_6$: C, 48.00; H, 5.09; N, 5.09; F, 6.91. Found: C, 47.82; H, 5.28; N, 5.21; F, 6.82.

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