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Pyridine Nucleosides Related to 5-Fluorouracil and Thymine

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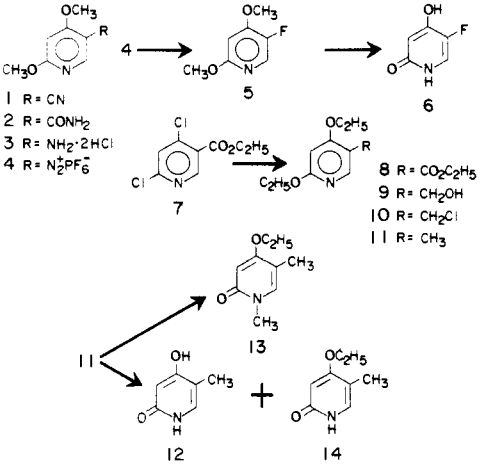
4-Hydroxy-5-fluoro-2-pyridone (5-fluoro-3-deazauracil, **6**) was synthesized from 2,4-dimethoxy-5-cyanopyridine (**1**) in a multistep procedure employing the intermediate, 2,4-dimethoxypyridine-5-diazonium hexafluorophosphate (**4**). Trimethylsilation of **6** and condensation with the appropriately protected halosugar gave (after deblocking) 5-fluoro-3-deazauridine (**28**) and 5-fluoro-2-deoxy-3-deazauridine (**19**) and its α anomer **23**. The ribonucleoside **28** was converted to 2-hydroxy-5-fluoro-1-(β-D-arabinofuranosyl)-4-pyridone ($O^2 \rightarrow 2'$)-cyclonucleoside (**29**), which was used in the determination of anomeric configuration. 4-Hydroxy-5-methyl-2-pyridone (3-deazathymine, **12**) was prepared from 2,4-dichloro-5-carbethoxypyridine (**7**) by a five-step procedure. Condensation of the trimethylsilyl derivative of **12** with the appropriately protected halosugar gave (after deblocking) 3-deazathymidine (**21**) and its α anomer **25**. Structure proof and anomeric configuration were determined from the uv, pK_a, nmr, and CD data. These compounds were not active as growth inhibitors of several cell lines in culture.

Because of a long standing interest in this laboratory in the synthesis of fluorinated pyrimidine nucleosides (see ref 1 for leading references) and the determination of their chemotherapeutic, pharmacological, and biochemical properties, it appeared worthwhile to expand our synthetic activities to include certain analogs in which there is an isosteric replacement of one of the nitrogen atoms in the pyrimidine ring. This paper reports our first effort along these lines: the synthesis of pyridine nucleoside analogs (3-deazapyrimidine nucleosides) of 5-fluorouracil and thymine.

There has recently been some interest in the synthesis and evaluation of the biological properties of 3-deazapyrimidine nucleosides. Currie and coworkers[2-6] have reported the preparation of 3-deazauridine, 3-deazacytidine, 3-deazaorotidine, and related nucleosides and have found marked cytotoxic activity of the uridine and cytidine analogs *in vitro* and *in vivo*. Other biochemical properties of 3-deazauridine and 3-deazacytidine have also been described, including their anti-RNA viral activity.[7]

The synthesis of 4-hydroxy-5-fluoro-2-pyridone (**6**), a necessary intermediate for the preparation of 5-fluoro-3-deazauracil nucleosides, was the crucial step in this synthetic sequence. After several preliminary unsuccessful attempts at ring closure of appropriately substituted acyclic precursors, it became obvious that substitution of fluorine on a preformed pyridine would be the method of choice. 2,4-Dimethoxy-5-cyanopyridine (**1**) was prepared from diethyl β-ketoglutarate according to the method of Taylor, *et al.*[8] This cyanopyridine **1** was then hydrolyzed by H_2O_2-NaOH to the amide **2** (Scheme I) which was converted *via* a Hoffmann hypochlorite rearrangement to the amine **3**. Introduction of the fluorine atom into the pyridine ring was accomplished with a Schiemann reaction, employing the diazonium hexafluorophosphate modification of Rutherford, *et al.*[9] 2,4-Dimethoxypyridine-5-diazonium hexafluorophosphate (**4**) was formed in 75% yield from the corresponding diazonium chloride and HPF_6. After thorough drying, **4** was decomposed at 250° to give 2,4-dimethoxy-5-fluoropyridine (**5**) in 31% yield.

Scheme I



The nmr of **5** revealed two aromatic doublets [τ 2.10 ($J_{6\text{-F}}$ = 2.9 Hz, H-6), 3.70 ($J_{3\text{-F}}$ = 5.8 Hz, H-3)] which supports the assigned structure. In addition, it indicates that no rearrangement had occurred, as any rearrangement would have produced a more complex spectrum.‡ The observation that $J_{3\text{-F}} > J_{6\text{-F}}$ was corroborated by similar observations made by Lyle and Taft[10] for 4-fluorolutidines and Rowbotham, *et al.*,[11] for methyl derivatives of 2-fluoropyridine.

Demethylation of **5** to give 4-hydroxy-5-fluoro-2-pyridone (**6**) was accomplished, albeit in low yield (11%), with 25% HCl at 145° for 4 hr.[12] Other attempts at demethylation including MeMgI,[13] BF_3-Ac_2O,[14] BBr_3-$CHCl_3$,[15] $Ph_2P^-Li^+$,[16] and NaI-HOAc[17] were unsuccessful. A marked change in the uv spectrum of **6** from pH 5 to 3 indicated an acidic proton with a pK_a of 4.6 ± 0.2. The nmr spectrum of **6** showed two doublets [τ 2.50 ($J_{6\text{-F}}$ = 6.2 Hz), 4.25 ($J_{3\text{-F}}$ = 8.0 Hz)], one of which disappeared (τ 4.25) upon addition of deuterium oxide. A similar effect was noted by Currie, *et al.*,[4] for 3-deazauridine, in which the H-3 proton under-

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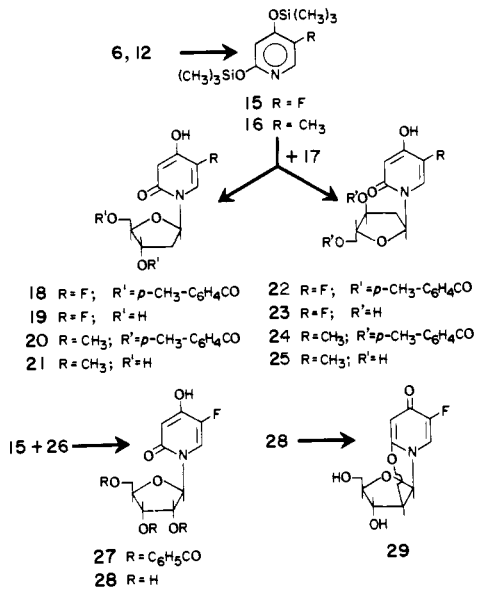
‡The nmr spectra of compounds 1, 2, and 3 showed no coupling between H-3 and H-6 while Currie, *et al.*,[6] reported $J_{3\text{-}5}$ = 2.5 Hz for 3-deazauridine.

went proton-deuterium exchange in the presence of D_2O, suggesting that the diketo form contributed to the tautomeric equilibrium.

The base **6** was smoothly converted to its trimethylsilyl derivative, 2,4-bis(trimethylsiloxy)-5-fluoropyridine (**15**), by hexamethyldisilazane with a catalytic amount of trimethylchlorosilane. Condensation of **15** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**26**) in acetonitrile (Scheme II) gave a 48% yield of 4-hydroxy-5-fluoro-1-(2,3,5-

Scheme II



tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyridone (**27**). Deblocking of **27** with methanolic sodium methoxide gave 4-hydroxy-5-fluoro-1-(β-D-ribofuranosyl)-2-pyridone (5-fluoro-3-deazauridine, **28**). The site of glycosyl attachment was determined from the uv and pK_a data. Table I summarizes the uv spectra of a series of related pyridines. The uv spectrum of **28** most closely resembles that of 1-methyl-4-hydroxy-5-fluoro-2-pyridone. The pK_a of **28** (4.5 ± 0.2) indicates a 4-OH proton, thus excluding ribosylation at O-4. These facts show N-1 to be the site of glycosidation.

Currie and coworkers[4] reported a value of 2.5 Hz for the coupling constant $J_{1'-2'}$ of the anomeric proton (τ 4.02) of 3-deazauridine. The anomeric proton of 5-fluoro-3-deazauridine (τ 4.08) appeared as a broadened singlet; this broadening presumably arose from further coupling to the fluorine nucleus. More compelling evidence for the β configuration of **28** came from the formation of the cyclonucleoside, 2-hydroxy-5-fluoro-1-(β-D-arabinofuranosyl)-4-pyridone ($O^2 \rightarrow 2'$)-cyclonucleoside (**29**), by the reaction of **28** with diphenyl carbonate.[18] Using the argument of Currie, *et al.*,[4] only the 1'-base 2'-OH trans arrangement of a β-ribonucleoside has the proper stereochemical configuration for formation of a cyclonucleoside in this reaction. The nmr and uv spectra of **29** are in accord with those of the cyclonucleoside obtained from 3-deazauridine with an additional coupling of fluorine to H-1' (J = 2.0 Hz) in the nmr and a bathochromic shift of 6 nm in the uv.

Fusion of **15** with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride (**17**)[19] at 125° gave (Scheme II) a 41% yield of blocked nucleosides with an anomeric ratio of α/β = 4:1.§ Separation of these anomers was accomplished by fractional crystallization, and each was deblocked with methanolic NaOMe to give 4-hydroxy-5-fluoro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-pyridone (**19**) (5-fluoro-2'-deoxy-3-deazauridine) and its α anomer **23**. The nmr of these nucleosides revealed the characteristic triplet and a pair of doublets for the β and α anomeric protons, respectively. In addition, CD showed a strong positive Cotton effect for **19** and a strong negative Cotton effect for **23** centered at 288 nm. The ribonucleoside **28**, previously shown to have a β configuration, also exhibited a strong positive Cotton effect. Thus, this evidence confirms the anomeric assignment.

3-Deazathymine (4-hydroxy-5-methyl-2-pyridone, **12**) was synthesized *via* the method outlined in Scheme I. 2,4-Dichloro-5-carbethoxypyridine (**7**)[20] on treatment with NaOEt gave 2,4-diethoxy-5-carbethoxypyridine (**8**). $LiAlH_4$ reduction of **8** by a procedure of Karrer and Mainoni[21] for a somewhat related compound gave 2,4-diethoxy-5-hydroxymethylpyridine (**9**). The hydroxymethyl compound **9** was converted into the chloromethyl derivative **10** by the thionyl chloride-DMF reagent developed by Ikehara and Uno.[22] The reduction of **10** to 2,4-diethoxy-5-methylpyridine (**11**) was accomplished with $LiAlH_4$.

Dealkylation of **11** with concentrated HCl at 140° for 24 hr afforded 3-deazathymine (**12**) in 63% yield. Shorter reaction times gave a mixture of **12** and 4-ethoxy-5-methyl-2-pyridone (**14**) which could be separated by sublimation. The nmr of **12** revealed no coupling between H-6 and H-3. In addition, H-6 and C-CH_3 appeared (as in almost all of these compounds) as very closely spaced multiplets that could not be resolved on our instrument; this effect was apparently due to the small coupling constant.

In the uv spectrum of **12**, ionization of the 4-OH proton caused the characteristic hypsochromic shift observed in many 2,4-dihydroxypyridines. When **11** was treated with iodomethane, 1,5-dimethyl-4-ethoxy-2-pyridone (**13**) was obtained, which was used as a model compound for comparison of uv data.

Condensation of 2,4-bis(trimethylsiloxy)-5-methylpyridine (**16**) (prepared from **12**) with **17** in refluxing CH_2Cl_2 gave a 1:1 mixture of α and β anomers (**20** and **24**) in 87% yield.

Table I. Uv Spectra of Selected Pyridines

Compound	Maximum uv absorption (nm) in 0.1 *N* HCl	Neutral medium	1.0 *N* NaOH
2,4-Dimethoxy-5-fluoropyridine (**5**)	267	267[a]	267
4-Hydroxy-5-fluoro-2-pyridone (**6**)	268	285[a]	254, 270 (sh)
1-Methyl-4-hydroxy-5-fluoro-2-pyridone[c]	285	290[a]	257, 275 (sh)
1-Methyl-4-methoxy-5-fluoro-2-pyridone[c]	287	287[a]	287
2-Methoxy-5-fluoro-4-pyridone[c]	265	257[a]	259
5-Fluoro-3-deazauridine (**28**)	288	290[a]	257, 275 (sh)
2,4-Diethoxy-5-methylpyridine (**11**)	267	267	267
4-Hydroxy-5-methyl-2-pyridone (**12**)	265	280[b]	256
4-Ethoxy-5-methyl-2-pyridone (**14**)	266	283[b]	283
4-Ethoxy-1,5-dimethyl-2-pyridone (**13**)	269	286[b]	286
3-Deazauridine[d]	278	282	255, 268 (sh)
3-Deazathymidine (**21**)	266	286[b]	258

[a] Spectra determined in 0.1 *N* citrate buffer, pH 3.2. [b] Spectra determined in aqueous alcohol. [c] Unpublished results. [d] See ref 4.

§ Condensation of these reactants in refluxing CH_2Cl_2 for 2 days gave the α anomer as the sole product in 45% yield.

These anomers could be separated for analytical purposes on Brinkman silica gel sheets with starch binder. Deblocking of the anomeric mixture with NaOMe and fractional crystallization from water yielded pure 3-deazathymidine (**21**) and its α anomer **25**. Comparison of the uv spectra of **21** with that of related pyridines (Table I) indicated N-1 to be the site of glycosidation. In the nmr, the anomeric carbon of **21** exhibited a triplet and of **25** a pair of doublets, demonstrating them to be β and α anomers, respectively. The CD spectra of these anomers revealed a positive Cotton effect for **21** and a negative one for **25** centered at 285 nm, thus confirming the anomeric assignments.

Biological Data. The following compounds were tested as growth inhibitors of the following tumor cell lines in culture, according to previously described assay procedures:[23] L-5178-Y–**6, 19, 21, 23, 25, 28, 29**; HeLa–**6, 19, 21, 23, 25, 28**; NS–**6, 28**; and BFY^+–**28**. No compound exhibited significant inhibitory activity at $10^{-4}M$. In view of the growth inhibitory activity of 3-deazauridine, 3-deazacytidine, and 5-fluorouracil nucleosides,[1] we were surprised to find the 5-fluoro-3-deazauracil nucleosides devoid of activity. The substitution of fluorine in place of hydrogen obviously has an effect on the pyridine π-electron system. One of these effects is the increased acidity of the 4-OH proton: 3-deazauridine, $pK_a = 6.5 \pm 0.2$; 5-fluoro-3-deazauridine (**28**), $pK_a = 4.5 \pm 0.2$. This effect could alter the binding of **28** to key enzymes needed for activation.

Experimental Section#

2,4-Dimethoxy-5-carboxamidopyridine (2). 2,4-Dimethoxy-5-cyanopyridine (**1**)[8] (32.8 g, 0.2 mol) was added to a mixture of 239 ml of 4 *N* NaOH and 675 ml of EtOH. To this slurry 239 ml of 30% H_2O_2 was added and the reaction mixture stirred for 3 hr at 70°. The straw-colored solution was cooled and the EtOH removed *in vacuo*. The remaining semisolid was poured into ice–water and the resulting precipitate was filtered, washed with H_2O, and dried. The crude product was recrystallized from ethyl acetate to yield 23.3 g (64%) of **2** as colorless needles: mp 157–158°; nmr ($CDCl_3$) τ 1.11 (s, 1, H-6), 3.77 (s, 1, H-3), 4.03 (s, 3, OCH_3), 4.07 (s, 3, OCH_3). *Anal.* ($C_8H_{10}N_2O_3$) C, H, N.

2,4-Dimethoxy-5-aminopyridine Dihydrochloride (3). To a solution of 2 (4.4 g, 0.024 mol) in 60 ml of H_2O was added 27 ml of freshly prepared 1 *N* NaOCl, and the mixture was stirred overnight at room temperature. The red solution was acidified with glacial AcOH and heated on a steam bath for 30 min. The cooled solution was basified with 3 *N* NaOH and extracted with $CHCl_3$ (6 × 50 ml) to give 4.0 g of a dark red oil that was used immediately in the next step. An analytical sample was prepared by taking up the oil in warm methanolic HCl, adding ether until turbidity, and cooling slowly. This yielded the dihydrochloride of the amine as slightly pink needles: mp 148–151°; nmr (DMSO-d_6) τ 1.91 (s, 1, H-6), 3.29 (s, 1, H-3), 6.03 (s 3, OCH_3), 6.10 (s, 3, OCH_3). *Anal.* ($C_7H_{10}N_2O_2 \cdot 2HCl$) C, H, N.

2,4-Dimethoxypyridine-5-diazonium Hexafluorophosphate (4). To 4.0 g of the crude oil obtained in the previous step was added 4 ml of concentrated HCl and 20 ml of water. This solution was stirred and cooled (salt–ice) to −5° and 2.1 g (0.03 mol) of $NaNO_2$ in 10 ml of H_2O was added dropwise. HPF_6 (7 ml) was poured into the orange-red mixture 30 min after the last of the $NaNO_2$ was added. The thick suspension was stirred for 5 min, filtered, washed with cold H_2O and ether, and air-dried. Further drying was completed *in vacuo* over P_2O_5 and NaOH to give 6.1 g (75%) of **4** as a light pink powder: mp 138–140°; ir 2220, 2260 cm^{-1}.

#Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Uv spectra were recorded on a Cary spectrophotometer Model 15 or a Beckman DB-G. Nmr spectra were recorded on a Varian A-60 or 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 Galbraith Laboratories Inc., Knoxville, Tenn., or Spang Microanalytical Laboratory, Ann Arbor, Mich. All analytical results were within 0.4% of the theoretical values. Analytical tlc was performed on Eastman chromatoplates.

2,4-Dimethoxy-5-fluoropyridine (5). The diazonium salt **4** (6.55 g, 0.021 mol) was placed in a 100-ml round-bottom flask connected by a short rubber tubing to a 500-ml three-necked round-bottom flask fitted with a stopper and condenser. Silicone oil was placed in the flask and heated with stirring to 250°, whereupon the salt was added in portions. The flask was cooled and the material in the condenser washed into the flask with 3 *N* NaOH and ether. An additional 50 ml of 3 *N* NaOH was added to the flask and the contents were steam distilled. The steam distillate was extracted with 5 × 100 ml of ether; the ethereal fractions were dried over anhydrous Na_2SO_4 and evaporated to 1.05 g (31%) of a colorless oil that solidified upon standing at 4°. Recrystallization of a sample from EtOH–H_2O yielded **5** as colorless needles: mp 59–60°; uv λ_{max}^{MeOH} 267 nm (ε 3100); nmr ($CDCl_3$) τ 2.10 (d, 1, $J_{6\text{-}F} = 2.9$ Hz, H-6), 3.70 (d, 1, $J_{3\text{-}F} = 5.8$ Hz, H-3), 6.10 (s, 6, OCH_3). *Anal.* ($C_7H_8NO_2F \cdot C_6H_3N_3O_7$; picrate mp 136–137°) C, H, N, F.

4-Hydroxy-5-fluoro-2-pyridone (6). A solution of 5 (1.57 g, 10 mmol) and 15 ml of 25% HCl was sealed in a glass tube and heated for 4.5 hr at 145°. After cooling the tube was opened; the contents were evaporated to 1/4 volume and extracted with ether (4 × 25 ml). The aqueous layer was evaporated to dryness and sublimed at 190° (2 mm) to yield 140 mg (11%) of **6** as a colorless powder: mp 268–269° dec; uv $\lambda_{max}^{pH\ 1.0}$ 268 nm (ε 4297), $\lambda_{max}^{pH\ 3.2}$ 285 nm (ε 3982), $\lambda_{max}^{pH\ 7.2}$ 254 nm (ε 6932), 270 (sh) (5387), $\lambda_{max}^{pH\ 14.0}$ 254 nm (ε 4663), 270 (sh) (3653); nmr (DMSO-d_6) τ 2.49 (d, 1, $J_{6\text{-}F} = 6.2$ Hz, H-6), 4.25 (d, 1, $J_{3\text{-}F} = 8.0$ Hz, H-3). *Anal.* ($C_5H_4NO_2F$) C, H, N, F.

4-Hydroxy-5-fluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyridone (27). 4-Hydroxy-5-fluoro-2-pyridone (**6**) (387 mg, 3 mmol) was refluxed for 2 hr with 10 ml of hexamethyldisilazane and 0.5 ml of trimethylchlorosilane. The excess reactants were removed *in vacuo* to yield **2,4-bis(trimethylsiloxy)-5-fluoropyridine (15)**, which was used immediately without further purification. 2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide (**26**) [prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose (1.512 g, 3 mmol)] and **15** were stirred at room temperature with 20 ml of dry CH_3CN and Linde Molecular Sieves 4A for 2 days sealed under dry N_2. The reaction mixture was filtered, the filtrate evaporated to an oil, and 10 ml of MeOH was added. After 10 min, a colorless solid appeared. Cooling of the mixture induced more crystallization, and filtration yielded 839 mg, 48%, of the blocked nucleoside. Recrystallization from MeOH–$CHCl_3$ gave colorless needles of **27**: mp 109–111°. *Anal.* ($C_{31}H_{24}NO_9F \cdot 0.25H_2O$) C, H, N, F.

4-Hydroxy-5-fluoro-1-(β-D-ribofuranosyl)-2-pyridone (28). To a solution of Na (110 mg, 4.8 g-atoms) in 100 ml of dry MeOH was added **27** (573 mg, 1.0 mmol), and the resulting solution was sealed and stirred for 4 hr at room temperature. The reaction mixture was neutralized with glacial HOAc–MeOH (1:1) and evaporated to a semisolid. This material was dissolved in H_2O and extracted with ether (5 × 25 ml) to remove methyl benzoate. The aqueous solution was reduced in volume and placed on an Amberlite IRC 50 (H^+ form, MeOH washed) column, and the effluent was monitored by uv. The fractions containing the product were pooled and evaporated to dryness to yield 260 mg (100%) of **28**. Recrystallization from MeOH afforded colorless prisms: mp 197–198.5°; uv $\lambda_{max}^{pH\ 1.0}$ 288 nm (ε 1975), $\lambda_{max}^{pH\ 3.2}$ 290 nm (ε 3321), $\lambda_{max}^{pH\ 7.2}$ 257 nm (ε 9431), 275 (sh) (5878), $\lambda_{max}^{pH\ 14.0}$ 257 nm (ε 9092), 275 (sh) (5400); nmr (DMSO-d_6) τ 1.85 (d, 1, $J_{6\text{-}F} = 8.3$ Hz, H-6), 4.08 (s, 1, H-1'), 4.25 (d, 1, $J_{3\text{-}F} = 8.1$ Hz, H-3); $[\theta]_{289}^{28°}$ nm +8947. *Anal.* ($C_{10}H_{12}NO_6F \cdot 0.75H_2O$) C, H, N, F.

2-Hydroxy-5-fluoro-1-(β-D-arabinofuranosyl)-4-pyridone ($O^2 \rightarrow 2'$)-Cyclonucleoside (29). A mixture of 28 (91 mg, 0.35 mmol), diphenyl carbonate (100 mg, 0.47 mmol), $NaHCO_3$ (3 mg), and 0.6 ml of DMF was heated at 150° for 30 min.[18] The warm dark reaction mixture was poured with vigorous stirring into 150 ml of ether and the brown precipitate was filtered. The solid was chromatographed on silica gel using ethyl acetate and ethyl acetate–MeOH (9:1) as eluents. The fractions containing the product were combined and evaporated, and the resulting solid was recrystallized from CH_3CN–MeOH to yeild 40 mg (47%) of colorless microcrystals of **29**: mp 222–225°; uv $\lambda_{max}^{pH\ 1.0}$ 258 nm (ε 10,580), 266 (sh) (10,520), 276 (sh) (7715), $\lambda_{max}^{pH\ 14.0}$ 258 nm (ε 17,376), 266 (sh) (15,059), 276 (sh) (6501); nmr (CH_3OD) τ 2.41 (d, 1, $J_{6\text{-}F} = 5.2$ Hz, H-6), 3.95 (d, 1, $J_{3\text{-}F} = 6.0$ Hz, H-3), 4.48 (d of d, 1, $J_{1',2'} = 5.9$ Hz, $J_{1',\text{-}F} = 2.0$ Hz, H-1'), 5.05 (d, 1, $J_{1',2'} = 5.9$ Hz, H-2'). *Anal.* ($C_{10}H_{10}NO_5F$) C, H, N, F.

4-Hydroxy-5-fluoro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-2-pyridone (18) and **4-Hydroxy-5-fluoro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)-2-pyridone (22).** 2,4-Bis(trimethylsiloxy)-5-fluoropyridine (**15**) (prepared from

1.07 g, 8.30 mmol of 6) was fused with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride (17)[19] (3.22 g, 8.30 mmol) *in vacuo* at 125° for 35 min. Tlc on silica plates in ethyl acetate–MeOH–H_2O–heptane, 10:6:5:3 (upper phase), resolved the anomeric mixture after three passes: R_{f_α} = 0.42; R_{f_β} = 0.38. MeOH–acetone (1:1) was added and the mixture stored at 4°. The first crop of material to crystallize [1.05 g (25%)] was pure α anomer **22.** Recrystallization from acetone afforded colorless needles, mp 205–205.5°. *Anal.* ($C_{26}H_{24}NO_7F$) C, H, N, F.

The second crop of material to crystallize [620 mg (16%)] contained a mixture of anomers in the ratio α/β = 0.5. This material was recrystallized from EtOH–acetone to yield 260 mg (7%) of colorless microcrystals of pure β anomer 18, mp 188–189°. *Anal.* ($C_{26}H_{24}NO_7F \cdot 0.25H_2O$) C, H, N, F.

4-Hydroxy-5-fluoro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-pyridone (19). A 212-mg (0.44 mmol) sample of 18 was deblocked by stirring for 14 hr with 34 mg (1.45 g-atoms) of Na dissolved in 20 ml of dry MeOH. After a work-up procedure similar to that of **28,** 97 mg (90%) of 19 was isolated and recrystallized from H_2O to yield colorless prisms: mp 182–184°; uv $\lambda_{max}^{pH\ 1.0}$ 289 nm (ε 2021), $\lambda_{max}^{pH\ 3.2}$ 290 nm (ε 3841), $\lambda_{max}^{pH\ 7.2}$ 257 nm (ε 7604), 277 (sh) (4578), $\lambda_{max}^{pH\ 14.0}$ 257 nm (ε 7550), 277 (sh) (4495); nmr (D_2O) τ 2.30 (d, 1, $J_{6\text{-}F}$ = 8.0 Hz, H-6), 3.70 (t, 1, $J_{1'\text{-}2',2''}$ = 6.0 Hz, H-1'); $[\theta]_{288\ nm}^{28°}$ +4135. *Anal.* ($C_{10}H_{12}NO_5F \cdot 0.125H_2O$) C, H, N, F.

4-Hydroxy-5-fluoro-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-2-pyridone (23). A 481-mg (1.0 mmol) sample of **22** was deblocked in a similar manner as described above employing 83 mg (3.6 g-atoms) of Na in 50 ml of dry MeOH. This yielded 230 mg (90%) of pure **23** which was recrystallized from H_2O: mp 139–140°; uv $\lambda_{max}^{pH\ 1.0}$ 289 nm (ε 1679), $\lambda_{max}^{pH\ 3.2}$ 290 nm (ε 4596), $\lambda_{max}^{pH\ 7.2}$ 257 nm (ε 9000), 277 (sh) (5372), $\lambda_{max}^{pH\ 14.0}$ 257 nm (ε 9289), 277 (sh) (5631); nmr (DMSO-d_6) τ 2.15 (d, 1, $J_{6\text{-}F}$ = 8.0 Hz, H-6), 3.72 (m, $J_{1'\text{-}2',2''}$ = 7.1 Hz, H-1'), 4.75 (d, 1, $J_{3\text{-}F}$ = 9.1 Hz, H-3); $[\theta]_{288\ nm}^{28°}$ −6176. *Anal.* ($C_{10}H_{12}NO_5F \cdot 0.75H_2O$) C, H, N, F.

2,4-Diethoxy-5-carbethoxypyridine (8). 2,4-Dichloro-5-carbethoxypyridine (7)[20] (30 g, 0.137 mol) was added to a solution of Na (6.5 g, 0.282 g-atom) in 150 ml of EtOH. After an initial exothermic reaction, the reaction mixture was stirred for 1 hr at room temperature. The reaction mixture was centrifuged and the supernatant reduced in volume. The resulting solution was poured into 1 l. of ice–water and filtered. The crude ester was recrystallized from Skellysolve B and then from aqueous EtOH to yield 25 g (75%) of 8, mp 68–69°. *Anal.* ($C_{12}H_{17}NO_4$) C, H, N.

2,4-Diethoxy-5-hydroxymethylpyridine (9). A solution of 8 (6.85 g, 29 mmol) in 130 ml of ether was added dropwise to a stirred suspension of $LiAlH_4$ (2.18 g, 57 mmol) in 50 ml of ether.[21] After 2.5 hr of stirring, 7 ml of H_2O was cautiously added to decompose the excess $LiAlH_4$. After filtration, the white residue was washed with ether and THF; the filtrate and washing were combined, dried over $MgSO_4$, filtered, and evaporated. The crude solid was recrystallized from Skellysolve B–benzene to yield 4.7 g (84%) of 9, mp 94–96°. *Anal.* ($C_{10}H_{15}NO_3$) C, H, N.

2,4-Diethoxy-5-chloromethylpyridine (10). Thionyl chloride (7.91 g, 66 mmol), 3.5 ml of DMF, and 212 ml of $CHCl_3$ were combined.[22] Ten minutes later, 9 (6.97 g, 35 mmol) was added and the mixture refluxed for 3 hr. After cooling, the reaction mixture was poured into 1 l. of ice–water, the product was extracted with $CHCl_3$ (4 × 250 ml), and the organic layers were dried over $MgSO_4$, filtered, and evaporated. Careful recrystallization of the crude oil from aqueous EtOH gave 5.54 g (72%) of 10, mp 45–46°. *Anal.* ($C_{10}H_{14}NO_2Cl$) C, H, N.

2,4-Diethoxy-5-methylpyridine (11). A solution of 10 (27.4 g, 0.127 mol) in 500 ml of dry THF was slowly added to a stirred slurry of $LiAlH_4$ (9.62 g, 0.254 mol) in 221 ml of dry THF. After complete addition, the mixture was refluxed for 2 hr and cooled. Water (52 ml) was carefully added, the reaction mixture was filtered, and the residue was washed with THF. The filtrate was evaporated to an oil which was recrystallized from EtOH to yield 17.5 g (74%) of 11: mp 27–28°; nmr ($CDCl_3$) τ 2.25 (m, 1, H-6), 3.90 (s, 1, H-3), 5.70 (q, 2, J = 7.0 Hz, OCH_2), 5.95 (q, 2, J = 7.0 Hz, OCH_2), 7.93 (s, 3, CH_3), 8.58 (t, 3, J = 7.0 Hz, OCH_2CH_3), 8.65 (t, 3, J = 7.0 Hz, OCH_2CH_3). *Anal.* ($C_{10}H_{15}NO_2 \cdot C_6H_3N_3O_7$; picrate mp 136°) C, H, N.

1,5-Dimethyl-4-ethoxy-2-pyridone (13). A mixture of 11 (500 mg, 2.75 mmol) and 8.3 ml of methyl iodide was refluxed for 22 hr. After evaporation, the residue was passed through a Dowex-1-X-2 column (formate form) using MeOH as eluent. Evaporation of the solvent and recrystallization from ethyl acetate gave 358 mg (77%) of 13: mp 135.5–136.5°; uv $\lambda_{max}^{pH\ 1.0}$ 269 nm (ε 4300), λ_{max}^{MeOH} 286 nm (ε 4300), $\lambda_{max}^{pH\ 14}$ 286 nm (ε 4038); nmr ($CDCl_3$) τ 3.04 (m, 1, H-6), 4.13 (s, 1, H-3), 6.03 (q, 2, J = 7.0 Hz, CH_2CH_3), 6.56 (s, 3, NCH_3), 8.05 (m, 3, 5-CH_3), 8.61 (t, 2, J = 7.0 Hz, CH_2CH_3). *Anal.* ($C_9H_{13}NO_2$) C, H, N.

4-Hydroxy-5-methyl-2-pyridone (12). Into each of four heavy-walled glass tubes was introduced 11 (2.00 g, 11 mmol) and 1.5 ml of concentrated HCl. The tubes were sealed and heated at 140° for 24 hr. After cooling, the tubes were opened and their contents combined and evaporated to a dark oil, which was dissolved in 100 ml of H_2O and neutralized with saturated $NaHCO_3$. The white solid precipitate was filtered, washed with water, and dried to give 3.46 g (63%) of crude **12.** Sublimation at 220° (0.5 mm) gave pure **12**: mp 315° dec; uv $\lambda_{max}^{pH\ 1.0}$ 265 nm (ε 3849), λ_{max}^{MeOH} 280 nm (ε 3684), $\lambda_{max}^{pH\ 14.0}$ 256 nm (ε 4234); nmr (DMSO-d_6) τ 2.92 (m, 1, H-6), 4.39 (s, 1, H-3), 8.16 (m, 3, CCH_3). *Anal.* ($C_6H_7NO_2$) C, H, N.

If shorter reaction times were employed, **4-ethoxy-5-methyl-2-pyridone (14)** could be isolated. Sublimation of the evaporated reaction mixture at 90–120° (0.5 mm) gave analytically pure 14: mp 180–182°; uv $\lambda_{max}^{pH\ 1.0}$ 266 nm (ε 4353), λ_{max}^{MeOH} 283 nm (ε 4040), $\lambda_{max}^{pH\ 14.0}$ 283 nm (ε 3305). *Anal.* ($C_8H_{11}NO_2$) C, H, N.

2,4-Bis(trimethylsiloxy)-5-methylpyridine (16). Hexamethyldisilazane (12 ml), dichlorodimethylsilane (0.3 ml), and **12** (2.59 g, 21 mmol) were refluxed in a dry apparatus immersed in an oil bath at 150°. After 2 hr of heating and stirring the flask was cooled and excess reagents were removed by evaporation at reduced pressure. Distillation of the residue gave 5.32 g (95%) of 16 as a colorless liquid, bp 95–105° (2 mm).

4-Hydroxy-5-methyl-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)-2-pyridone (24) and **4-Hydroxy-5-methyl-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-2-pyridone (20).** A solution of 16 (5 g, 18.5 mmol), 17[19] (5.53 g, 14.2 mmol), and 86 ml of CH_2Cl_2 was refluxed for 24 hr in an apparatus protected from moisture. The solvent was evaporated, MeOH was added, and the mixture was stirred until a colorless precipitate formed. After filtration, the filtrate was reduced in volume and refiltered. Both crops were combined to yield 5.92 g (87%) of an anomeric mixture of a crude blocked nucleosides. This mixture separated on Brinkman silica gel precoated sheets with starch binder using ethyl acetate as the solvent system (R_{f_α} = 0.1; R_{f_β} = 0.25). *Anal.* ($C_{27}H_{27}NO_7$) C, H, N.

4-Hydroxy-5-methyl-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-pyridone (21) and **4-Hydroxy-5-methyl-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-2-pyridone (25).** The anomeric mixture of blocked nucleosides **20** and **24** (6.43 g, 13.5 mmol) was added to a solution of Na (2.54 g, 47 g-atoms) in 270 ml of dry MeOH, and the resulting mixture was stirred at room temperature for 1 hr. The mixture was neutralized with Dowex-50 (H^+), filtered, and evaporated to an oil which was triturated with ether until all the methyl *p*-toluate was removed. This procedure yielded 2.91 g (87%) of crude, colorless deblocked nucleosides. Fractional crystallization from water separated the anomers; the β anomer was less soluble. This yielded 465 mg (14%) of **21**: mp 205–206°; uv $\lambda_{max}^{pH\ 1.0}$ 273 nm (ε 4300), λ_{max}^{MeOH} 286 nm (ε 4850), $\lambda_{max}^{pH\ 14.0}$ 258 nm (ε 9760); nmr (DMSO-d_6) τ 2.40 (m, 1, H-6), 3.64 (t, 1, $J_{1'\text{-}2'}$ = 7.8 Hz, H-1'), 4.36 (s, 1, H-3); $[\theta]_{285\ nm}^{28°}$ +5982. *Anal.* ($C_{11}H_{15}NO_5$) C, H, N.

The α anomer **25** was recrystallized from acetone, EtOH, and ether: mp 185–186°; uv $\lambda_{max}^{pH\ 1.0}$ 271 nm (ε 4200), λ_{max}^{MeOH} 285 nm (ε 4800), $\lambda_{max}^{pH\ 14.0}$ 258 nm (ε 8800); nmr (DMSO-d_6) τ 2.42 (m, 1, H-6), 3.75 (d of d, 1, $J_{1'\text{-}2',2''}$ = 3.5 and 7.3 Hz, H-1'), 4.39 (s, 1, H-3); $[\theta]_{285\ nm}^{28°}$ −8432. *Anal.* ($C_{11}H_{15}NO_5$) C, H, N.

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Antimalarials. 9. α-(2-Piperidyl)-4-quinolinemethanols Carrying 2-Aroxy and 2-(*p*-Chloroanilino) Groups†,[1]

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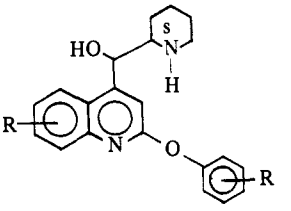
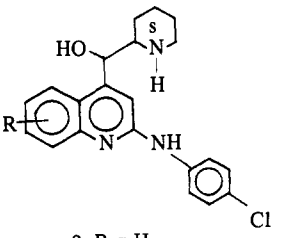
Twelve α-(2-piperidyl)-4-quinolinemethanols were synthesized from 2-chlorocinchoninic acids by additions of 2-PyLi, displacements of 2-Cl of the resulting 4-quinolyl 2-pyridyl ketones by aroxy or *p*-chloroanilino, and hydrogenations of the keto and pyridyl groups. Activities against *Plasmodium berghei* in mice were comparable with those of 2-aryl analogs. The 6,8-dichloro-2-(*p*-chlorophenoxy) compound was curative at 20 mg/kg but was phototoxic. 2-Chloro-α-diethylaminomethyl-4-quinolinemethanol, synthesized by a conventional route, was "inactive" against *P. berghei* but active against *Plasmodium gallinaceum* in birds

Syntheses of 12 α-(2-piperidyl)-4-quinolinemethanols (**1-12**) (and incidentally the 2-chlorodiethylamino alcohols **13** and **14**) were undertaken with the following expectations: that the 2-aroxy and 2-(*p*-chloroanilino) would prevent oxidative biotransformations to less active carbostyryls;[4] that these groups would lead to high activities against *Plasmodium berghei* in mice with firm binding of the molecules to the host tissues;[5] and that phototoxicity, formerly thought to be associated with conjugation of aryl and the 2-quinoline nuclei[6-8] in highly curative drugs such as **15**,[9] might be reduced by intervention between the aromatic nuclei of the heteroelement O or N which would destroy the direct conjugation although replacing it by forked conjugation.[10]

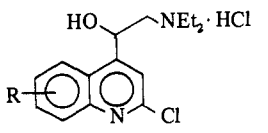
Chemistry. The α-(2-piperidyl)methanols **1-12** were synthesized from appropriate isatins through 2-hydroxy- and 2-chlorocinchoninic acids **16-20** (and ester **21**).[11-14] Rather than displacing the 2-Cl at this stage,[11] the reactions outlined in Scheme I were used, namely, additions of 2-PyLi,[15-19] then aroxy and anilino displacements of the active 2-Cl[20] of the 2-pyridyl ketones **22-26** (more difficult when an 8 substituent was present), and simultaneous Pt-H_2-AcOH[17] hydrogenations of the keto and pyridyl groups of **27-38**. Reduction of the *p*-methylthiophenoxy analog **40**, however, was incomplete and stopped at the α-(2-pyridyl)methanol stage **43**, presumably because of catalyst poisoning by sulfur of the substrate. The products **1-12** were isolated only in one of two possible racemic forms. Difficulties in and deviations from usual procedures are given in the Experimental Section.



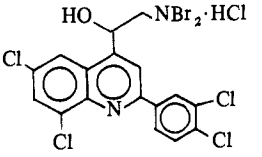
1, R = H; R' = 4-Me
2, R = 6-Me; R' = 4-Me
3, R = 6-Cl; R' = 4-Me
4, R = H; R' = 4-Cl
5, R = 6-Cl; R' = 4-Cl
6, R = 6,8-Me_2; R' = 4-Cl
7, R = 6,8-Cl_2; R' = 4-Cl
8, R = 6,8-Cl_2; R' = 3,4-Cl



9, R = H
10, R = 6-Me
11, R = 6-Cl
12, R = 6,8-Me_2



13, R = H
14, R = 6,8-Cl_2



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In preliminary experiments toward making α-diethylaminomethyl-4-quinolinemethanols carrying 2-hetero substituents which might then be displaced,[20] **13** and **14** were synthesized by the standard sequence, Scheme II.[9,21]

Biology. Results of tests against *P. berghei* in mice by the method of Rane[22] are given in Table I. In activities, the α-(2-piperidyl)-2-aroxy- and 2-(*p*-chloroanilino)-4-quino-

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