evaluation of the inhibitory properties of coenzyme–substrate adduct analogues of these PLP enzymes. The reaction mixture contained L-Ala (2–40 mM), PLP (150 μM), inhibitor (0–20 mM), enzyme solution (50 μL) in a final volume of 1 mL of buffer (0.1 M Tris-HCl, pH 8.9, for the enzyme of *P. aeruginosa*, 0.1 M phosphate, pH 8, for the enzyme of *S. faecalis*). Unlike the crude preparation of *P. aeruginosa*, the crude extract of *S. faecalis* required PLP for activity.

(C) D-Ala:D-Ala Ligase Assays. The formation of radioactive D-Ala-D-Ala from D-[U-^{14}C]Ala (specific activity, 43 mci/mmol, Radiochemical Center, Amersham, England) was evaluated by autoradiochromatography.[7] The assays were performed in a final volume of 50 μL containing 50 mM Tris-HCl, pH 7.8, 1 mM KCl, 5 mM ATP, 5 mM $MnCl_2$, 5–40 mM D-[^{14}C]Ala, 0–20 mM inhibitor, and enzyme solution in appropriate amount. The reaction was stopped after an incubation of 30 min at 37 °C by adding 20 μL of 0.1 M formate containing 10 mM of D-Ala-D-Ala as carrier. A 30-μL aliquot of the supernatant was chromatographied on Schleicher & Schull 2043 B paper in pyridine/acetic acid/H_2O (10:7:3) as the solvent phase; the amino acid (R_f 0.47) and the dipeptide (R_f 0.66) were located by autoradiography and counted with an Intertechnique SL 36 liquid scintillation spectrometer.

Primary Antimicrobial Screening of 4–6. Antimicrobial screening was carried out by an agar well diffusion method using both complete and minimal media. Penicillin G was used as a standard for bacteria and amphothericin B for fungi. Cultures employed for screening were *Escherichia coli* EK 12, UB 105, DC 2, MRE 600. The others were obtained either from the American Type Culture Collection, Rockeville, MD [*Candida albicans* (ATCC 26278), *Saccharomyces cerevisiae* (ATCC 7754)], from the Food and Drug Administration, Washington, DC (*Staphylococcus aureus* FDA 209P), or from the Pasteur Institut, Paris (*Candida albicans* 886, *Candida tropicalis* 204, *Torulopsis* 811).

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Registry No. GAR synthetase, 9032-01-3; GAR transformylase, 9032-02-4; AIR synthetase, 9023-53-4; 1, 98779-23-8; 2, 98779-24-9; 3, 98779-25-0; 4, 98779-26-1; 5, 98779-27-2; 6, 98855-93-7; L-Ala, 56-41-7; D-Ala, 338-69-2; 1,2,2,2-tetrachloro-*N*-(benzyloxycarbonyl)ethylamine, 98779-28-3; alanine racemase, 9024-06-0; D-Ala:D-Ala ligase, 9023-63-6.

Nucleosides. 136. Synthesis and Antiviral Effects of Several 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-alkyluracils. Some Structure–Activity Relationships

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In order to study structure–activity relationships between antiherpetic activity and the size of the C-5 alkyl substituents of 2′-fluoro-ara-U derivatives, six new nucleosides (**1c–h**) were synthesized. The 5-allyl analogue **1c** was prepared by a Pd(II)-catalyzed reaction of 5-(chloromercuri)-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil with allyl chloride. Partial hydrogenation of **1c** afforded the 5-*n*-propyl derivative **1d** (FPAU). Nucleosides **1e–h** were obtained by condensation of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinosyl bromide with the corresponding 5-substituted uracils. Preliminary in vitro data show that, as the alkyl side chain is increased by one carbon unit, the antiherpetic potency is decreased by approximately 1 log order. The cytotoxicity also diminishes as the size of the 5-substituent is increased. FPAU exerts good activity against HSV-1 and HSV-2. FiPAU still shows good therapeutic indices, whereas the higher alkyl analogues are essentially inactive.

In 1979, we reported[1] the syntheses and anti herpes virus activity of several 5-substituted (2-fluoro-2-deoxyarabinofuranosyl)cytosines and -uracils. Among these, 2′-fluoro-5-iodo-ara-C (FIAC) was found to be a potent inhibitor of the replication of herpes simplex virus (HSV) 1 and 2, varicella zoster virus (HZV), cytomegalovirus (CMV), and Epstein–Barr virus (EBV) in cell culture.[1-4] FIAC has demonstrated clinical efficacy against herpes virus infections in both phase 1[5] and phase 2[6] clinical trials in host compromised patients. Subsequently, the corresponding thymine analogue, 2′-fluoro-5-methyl-ara-U (FMAU) (**1a**), was found to be more potent than FIAC in mice infected with HSV-1[7] or with HSV-2[8] without toxicity at effective dose levels. FMAU was also found to be active in vitro and in vivo against P-815 and L-1210 cell lines resistant to arabinosylcytosine (ara-C).[9,10] A phase I clinical trial of FMAU in patients with advanced cancer showed that drug-induced central nervous system toxicity was dose-limiting. In view of the potent and selective antiviral activity of FMAU, future trials using low doses

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(1) Watanabe, K. A.; Reichman, U.; Hirota, K.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1979**, *22*, 21.
(2) Lopez, C.; Watanabe, K. A.; Fox, J. J. *Antimicrob. Agents Chemother.* **1980**, *17*, 21.
(3) Mar, E.; Patel, P. C.; Cheng, Y.; Fox, J. J.; Watanabe, K. A.; Huang, E. *J. Gen. Virol.* **1984**, *65*, 47.
(4) Lin, J.; Smith, M. C.; Cheng, Y.; Pagano, J. S. *Science*, **1983**, *221*, 578.
(5) Young, C. W.; Schneider, R.; Leyland-Jones, B.; Armstrong, D.; Tan, C. T. C.; Lopez, C.; Watanabe, K. A.; Fox, J. J.; Philips, F. S. *Cancer Res.* **1983**, *43*, 5006.
(6) Leyland-Jones, B.; Donnelly, H.; Myskowski, P.; Donner, A.; Groshen, S.; Lopez, C.; Armstrong, D.; Young, C. W.; Fox, J. J. *AFCR Publications Clin. Res.* **1983**, *31*, 369A.
(7) Fox, J. J.; Lopez, C.; Watanabe, K. A. "Medicinal Chemistry Advances"; de las Heras, F. G., Vega, S., Eds.; Pergamon Press: Oxford, 1981; p 21.
(8) Schinazi, R. F.; Peters, J.; Sokol, M. K.; Nahmias, A. J. *Antimicrob. Agents Chemother.* **1983**, *24*, 95.
(9) Burchenal, J. H.; Chou, T-C.; Lokys, L.; Smith, R. S.; Watanabe, K. A.; Su, T-L.; Fox, J. J. *Cancer Res.* **1982**, *42*, 2598.

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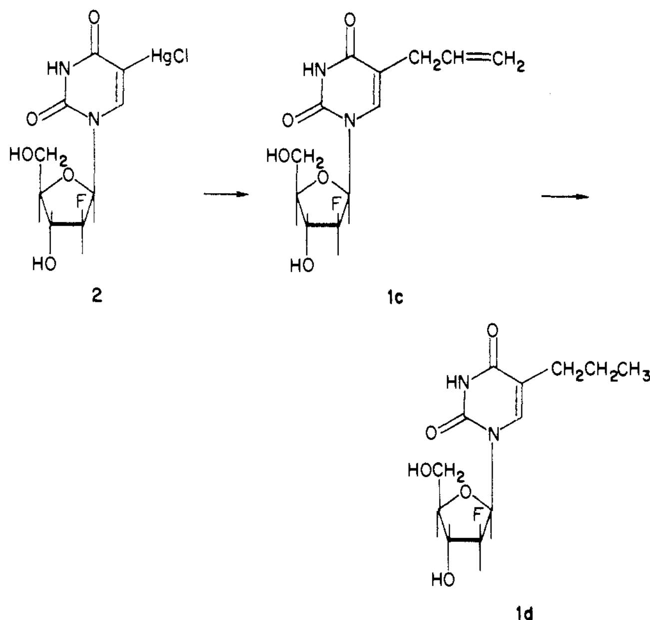
Scheme I



of this drug in immunosuppressed patients with herpes virus infections are under consideration.[11] Both FMAU and FIAC were reported to lack mutagenic activity in bacterial and mammalian cell mutagenesis assays.[12]

We have also synthesized analogues of FIAC and FMAU modified at C-2′ and have found that the 2′-fluoro substituent in the "up" (arabino) configuration confers better anti herpes virus activity than does a 2′-hydroxy, 2′-hydrogen, or other 2′-halogen substituent in these arabinofuranosyl nucleosides.[1,13]

With FMAU as a lead compound, we extended our synthetic efforts to the preparation of several 2′-fluoro-ara-U analogues with variation in size of the C-5 alkyl substituent. Of particular interest is 2′-fluoro-5-ethyl-ara-U (FEAU)[14,15] (**1b**), which, although about a log order less potent than FMAU against HSV-1 and HSV-2 in vitro, showed very low host cell toxicity, resulting in an extremely favorable therapeutic index (ID_{50}/ED_{90}). A comparative study of the antiviral effects of FEAU with FMAU and 5-ethyl-2′-deoxyuridine (EDU) in mice inoculated intracerebrally with HSV-2 showed that FEAU at doses of 100–200 mg/kg per day was highly effective in reducing the mortality in these mice.[16] At these dose levels, toxicity was not observed. In this preliminary study, FEAU was much more effective and less host-toxic than EDU[16] (the latter of which differs structurally from FEAU only by the absence of the 2′-fluoro substituent). EDU had been re-

(10) Chou, T-C.; Burchenal, J. H.; Schmid, F. A.; Braun, T. J.; Su, T-L.; Watanabe, K. A.; Fox, J. J.; Philips, F. S. *Cancer Res.* **1982**, *42*, 3957.
(11) Fanucchi, M. P.; Leyland-Jones, B.; Young, C. W.; Burchenal, J. H.; Watanabe, K. A.; Fox, J. J. *Cancer Treatment Rep.* **1985**, *69*, 55.
(12) Marquardt, H.; Westendorf, J.; Marquardt, H. *Carcinogenesis* **1982**, *3*, 593.
(13) Watanabe, K. A.; Su, T-L.; Klein, R. S.; Chu, C. K.; Matsuda, A.; Chun, M-W.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1983**, *26*, 152.
(14) Watanabe, K. A.; Su, T-L.; Reichman, U.; Greenberg, N.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1984**, *27*, 91.
(15) Perlman, M. E.; Watanabe, K. A.; Schinazi, R. F.; Fox, J. J. *J. Med. Chem.* **1985**, *28*, 741.
(16) Fox, J. J.; Watanabe, K. A.; Schinazi, R. F.; Lopez, C. "Pharmacological and Clinical Approaches to Herpes Viruses and Virus Chemotherapy"; Kono, R., et al., Eds.; Excerpta Medica: Amsterdam, 1985; pp 53–56.

Table I. ^1H NMR Parameters of 5-Carbon-Substituted 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)uracils[a]

	chemical shifts, δ									coupling constants, Hz						
compd	H-1′	H-2′	H-3′	H-4′	H-5′,5″	H-6	Me	CH_2	Ac	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{1',F}$	$J_{2',F}$	$J_{3',F}$	solvent
1b	6.13 dd	5.07 dt	4.27 dq	3.70–3.78 m		7.60	1.03 t	2.23 q		4.6	3.9	4.3	14.0	52.8	15.3	Me_2SO-d_6
1c	6.20 dd	5.06 dt	4.22 dq	3.78–3.81 m		7.58				4.6	3.3	4.4	15.0	53.0	21.0	Me_2SO-d_6
1d	6.13 dd	5.07 dt	4.24 dq	3.78–3.82 m		7.60	0.85 t	1.43 m 2.19 m		4.6	4.0	4.3	14.0	53.0	20.0	Me_2SO-d_6
1e	6.17 dd	5.11 dt	4.26 dt	3.72–3.82 m		7.57	1.07 d			4.9	4.6	5.4	12.2	53.0	20.8	Me_2SO-d_6
1f	6.13 dd	5.08 dt	4.24 dq	3.72–3.82 m		7.59	0.90 t	1.34 m, 2.21 t		4.6	3.8	5.2	14.0	53.4	20.0	Me_2SO-d_6
1g	6.14 dd	5.08 dt	4.24 dq	3.72–3.82 m		7.59	0.84 t	2.19 m		4.6	4.0	5.2	14.0	53.1	20.0	Me_2SO-d_6
1h	6.17 dd	5.12 dt	4.26 dt	3.60–3.83 m		7.57	0.78 t, 1.05 dd	1.50 m		4.0	4.0	4.0	12.3	53.1	20.8	Me_2SO-d_6
5b	6.25 dd	5.15 dd	5.40 dd	4.38 m	4.70 m	7.26	0.96 t	2.30 q	2.18	2.74	0.0	2.79	23.6	50.2	17.3	$CDCl_3$
α-5b	6.07 dd	5.41 dt	5.47 dt	4.76 m	4.56 m	7.54	1.41 t	2.39 q	2.10	1.21	1.25	1.23	14.3	49.7	17.1	$CDCl_3$
5e[b]	6.25 dd	5.16 dd	5.41 dd	4.71 m	4.65 m	7.28	0.98 dd		2.18	2.74	0.0	2.81	22.5	50.1	17.4	$CDCl_3$
α-5e[c,d]	6.07 dd	5.43 dt	5.49 dt	4.84 m	4.56 m	7.54	1.16 d		2.09	1.22	1.23	1.23	13.3	49.7	16.0	$CDCl_3$
5f	6.25 dd	5.15 dd	5.40 dd	4.34 m	4.66 m	7.27	0.80 t	1.26 m, 2.18 t	2.18	2.75	0.0	2.75	22.6	50.4	17.4	$CDCl_3$
α-5f	6.06 dd	5.41 dt	5.47 dt	4.77 m	4.56 d	7.53	0.92 m	1.49 m	2.09	1.21	1.23	1.22	14.6	50.1	17.7	$CDCl_3$
5g	6.26 dd	5.15 dd	5.40 dd	4.33 m	4.72 m	7.45	0.73 d, 0.76 d	1.97 m	2.18	2.74	0.0	2.74	22.6	50.4	17.4	$CDCl_3$
α-5g	6.04 dd	5.41 dt	5.47 dt	4.73 m	4.53 m	7.53	0.90 d	1.26 m	2.08	1.0	0.0	1.10	15.9	49.1	17.7	$CDCl_3$
5h	6.26 dd	5.15 dd	5.40 dd	4.33 m	4.72 m	7.43	0.72 dt, 0.96 dd	1.32 m	2.19	2.44	0.0	2.70	22.6	50.4	17.4	$CDCl_3$
α-5h	6.06 d	5.42 br d	5.48 br d	4.76 m	4.56 m	7.53	0.82 t, 1.14 d	1.49 m	2.10	0	0.5	0.5	16.1	50.0	17.6	$CDCl_3$

[a] Apparent signals are expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; br d, broad doublet; dd, double doublet; dt, double triplet; dq, double quartet; m, multiplet. Values given for coupling constants are first order. [b] Apparent octet for CH at δ 2.79. [c] The α-anomer of 5e. [d] Apparent quartet for CH at δ 3.00.

Table II. Antiviral and Cytotoxic Activities and Therapeutic Indices of 5-Carbon-Substituted (2-Deoxy-2-fluoro-β-D-arabinofuranosyl)uracils

no.	R	HSV-1 (F)[a] ED50, μM	HSV-1 (F)[a] ED90, μM	HSV-2 (G)[a] ED50, μM	HSV-2 (G)[a] ED90, μM	ID50[b]	therapeutic index: ID50/ED90 HSV-1	therapeutic index: ID50/ED90 HSV-2
1a	CH_3	0.018	0.047	0.023	0.09	2.75	59	31
1b	CH_2CH_3	0.024	0.26	0.24	0.96	1700	6538	1771
1c	$CH_2CH{=}CH_2$	3.3	21.3	6.0	29.7	1559	73	52
1d	$CH_2CH_2CH_3$	0.48	4.27	0.90	7.58	2352	551	310
1e	$CH(CH_3)_2$	1.0	8.7	13.0	72.3	>800	>92	>11
1f	$(CH_2)_3CH_3$	11.1	76.0	15.9	40.3	>800	>11	>20
1g	$CH_2CH_2(CH_3)_2$	28.7	92.7	113	422	>800		
1h	$CH(CH_3)CH_2CH_3$	15.6	305	>400	>400	>800		

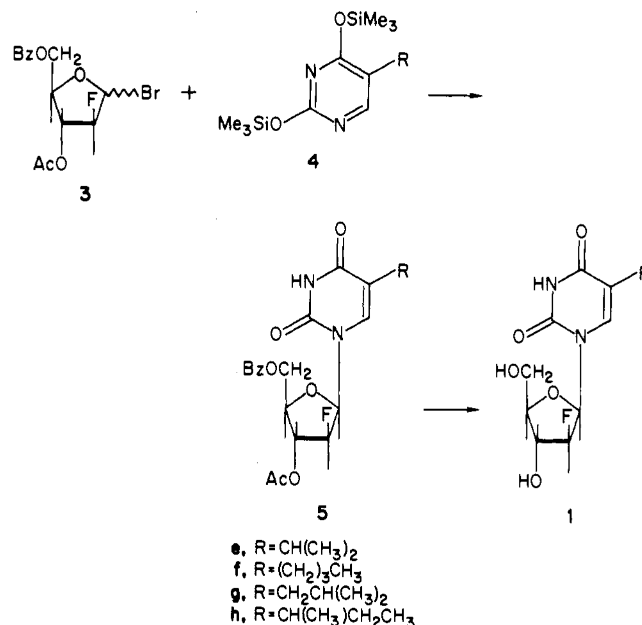
[a] Tested in Vero cells by a plaque-reduction assay. [b] Cytotoxic effect measured in rapidly dividing Vero cells.

ported to be active in cell culture against HSV-1[17] and HSV-2.[18] These data again attest to the enhanced antiviral activity conferred by the 2′-fluoro substituent in the arabino configuration in these 2′-deoxypyrimidine nucleosides.[1,2,7,19,20]

In order to study further structure–activity relationships between antiherpetic activity and the size of the C-5 alkyl substituent of 2′-fluoro-ara-U derivatives, we synthesized six new nucleosides (**1c–h**, Table II). The 5-allyl analogue **1c** (Scheme I) was prepared by a Pd(II)-catalyzed reaction[21] of 5-(chloromercuri)-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (**2**) with allyl chloride. Partial hydrogenation of **1c** afforded the 5-*n*-propyl derivative **1d** (FPAU). Nucleosides **1e–h** were obtained by condensation of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinosyl bromide[22] (**3**) with the corresponding 5-substituted uracils which were prepared from the corresponding 5-alkylbarbituric acids[23] by chlorination followed by reductive dehalogenation. Reaction of **3** with 5-substituted 2,4-bis[(trimethylsilyl)oxy]pyrimidines **4e–h** in methylene chloride afforded the protected nucleosides **5e-h**, which were saponified to give **1e-h**. The structures of these new compounds were determined by comparison of the UV and ^1H NMR spectral properties of these new nucleosides with those of FMAU and FEAU (Table I). The fact that the ultraviolet absorption spectra of **1c–h** between pH 7–13 were similar to those for FMAU and FEAU and thymidine establish N-1 as the site of glycosylation.[24] The close similarity of the ^1H NMR parameters of the sugar ring protons of the new nucleosides to those of FMAU and FEAU (Table I) confirmed the β configuration.

Preliminary in vitro data on the inhibitory activity of these new agents against replication of HSV-1 and HSV-2 in Vero cells by plaque reduction assay are given in Table II. All the compounds tested were more effective against HSV-1 than against HSV-2. It is interesting to note that, as the alkyl side chain is increased by one carbon unit, the antiherpetic potency decreases by approximately 1 log order. The cytotoxicity, however, also diminishes as the size of the 5-substituent is increased. The 5-isopropyl analogue **1e** (F-iso-PAU) still exerts good activity against HSV-1 and HSV-2, whereas the higher alkyl analogues were significantly less active. The branched-side-chain analogues are less effective than the corresponding straight-chain alkyl substituted nucleosides. Thus, FPAU is somewhat more active than the 5-isopropyl congener **1e**, and although the 5-*n*-butyl nucleoside **1f** shows weak but measurable activity against HSV-1, the corresponding isobutyl or *sec*-butyl analogues **1g** and **1h** were essentially inactive.

Scheme II



Among the new compounds tested, FEAU (**1b**) and FPAU (**1d**) showed the greatest antiviral acitivty against both HSV-1 and HSV-2 and were not toxic to Vero cells up to 1000 μM. These compounds are currently being evaluated in animal models for herpetic infections.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. TLC was performed on Uniplates purchased from Analtech Co. and column chromatography on silica gel G60 (70–230 mesh, ASTM, Merck). Elemental analyses were performed by MHW Laboratories and Galbraith Laboratories, Inc. ^1H NMR spectra (Table I) were recorded on a JEOL PFT-100 spectrometer using Me_4Si as the internal standard for organic solvents and DSS for deuterium oxide.

5-Alkyl-6-chlorouracils.[25] A mixture of 5-alkylbarbituric acid[23] (0.01 mol), 87% H_3PO_4 (7 mL), and $POCl_3$ (45 mL) was heated at 90–100 °C for 2 h. After cooling of the mixture in an

(17) De Clercq, E.; Shugar, D. *Biochem. Pharmacol.* **1975**, *24*, 1073.
(18) Teh, C-Z.; Sacks, S. L. *Antimicrob. Agents Chemother.* **1983**, *23*, 637.
(19) Fox, J. J.; Lopez, C.; Watanabe, K. A. "Antiviral Chemotherapy: Design of Inhibitors of Viral Functions"; Gauri, K. K., Ed.; Academic Press: New York, 1981; p 219.
(20) Fox, J. J.; Watanabe, K. A.; Lopez, C.; Philips, F. S.; Leyland-Jones, B. "Herpesvirus: Clinical, Pharmacological and Basic Aspects"; Shiota, H., Cheng, Y-C., Prussoff, W. H., Eds.; Excepta Medica: Amsterdam, 1982; pp 135–147.
(21) Ruth, J. L.; Bergstrom, D. E. *J. Org. Chem.* **1978**, *43*, 2870.
(22) Reichman, U.; Watanabe, K. A.; Fox, J. J. *Carbohydr. Res.* **1975**, *42*, 233.
(23) Volwiler, E. H. *J. Am. Chem. Soc.* **1925**, *47*, 2236.
(24) Fox, J. J.; Shugar, D. *Biochim. Biophys. Acta* **1952**, *9*, 369.

(25) We express our gratitude to Miss Nina Paul of the State University of New York at Purchase, who prepared some of these starting materials.

ice bath, crushed ice (200 g) was added carefully with stirring to decompose unreacted $POCl_3$. The mixture was stored in a refrigerator overnight and the crystalline precipitate was collected by filtration, washed well with water, and air-dried to give the 5-alkyl-6-chlorouracils: 6-chloro-5-isopropyluracil, mp 243–244 °C (51%), 5-butyl-6-chlorouracil, mp 195–196 °C (lit.[26] mp 197–198 °C) (53%), 6-chloro-5-isobutyluracil, mp 292–293 °C (47%), 6-chloro-5-*sec*-butyluracil, mp 166–167 °C (39%).

5-Alkyluracils.[25] A mixture of 5-alkyl-6-chlorouracil (46 mmol) and 10% Pd/C (500 mg) in 2 N NaOH (200 mL) was shaken in a hydrogen atmosphere for 3 h with the initial pressure of 40 psi. The catalyst was removed by filtration and the filtrate was acidified with concentrated HCl to pH ~2. The precipitate was collected, washed, and air-dried to give the following 5-alkyluracils: 5-isopropyluracil, mp 286–287 °C (lit.[27] mp 283–284 °C) (80%); 5-butyluracil, mp 288–290 °C (lit.[28] mp 291–293 °C) (83%); 5-isobutyluracil, mp 295–296 °C (lit.[27] mp 296–298 °C) (81%); 5-*sec*-butyluracil, mp 256–257 °C (lit.[29] mp 280–284 °C) (81%).

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-allyluracil (1c). To a solution of $Hg(OAc)_2$ (2.3 g, 7.2 mmol) in water (10 mL) was added a solution of 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil[1] (1.80 g, 7.0 mmol) in water (10 mL) and the mixture was heated at 60 °C with stirring for 4.5 h. The thick suspension that formed was treated with 0.16 M NaCl (20 mL) and the colorless crystals that precipitated were collected, washed successively with 0.16 M NaCl, cold water, EtOH, and Et_2O, and dried over P_2O_5 in vacuo to give 1.26 g (36%) of 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-(chloromercuri)uracil (**2**).

To a mixture of **2** (1.26 g, 2.6 mmol) and allyl chloride (2 mL, 24 mmol) in MeOH (10 mL) was added 0.1 M Li_2PdCl_4 in MeOH (5.7 mL). The mixture was stirred overnight at room temperature and then treated with H_2S. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was then chromatographed on a silica gel column (30 × 2 cm) using $CHCl_3$–MeOH (10:1, v/v) as the eluent. The UV-absorbing fractions were concentrated, and the residue crystallized from MeCN to give 385 mg (24%) of **1c**, mp 120–121 °C.

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-propyluracil (1d). A solution of **1c** (86 mg, 0.3 mmol) in MeOH (50 mL) was shaken in hydrogen (30 psi) in the presence of 10% Pd/C (15 mg) for 2 h. The catalyst was removed by filtration and the filtrate concentrated in vacuo to dryness to give 84 mg of **1d** as a syrup.

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-isopropyluracil (1e). A solution of 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranose[22] (**3**; 2.0 g, 5.9 mmol) in dry CH_2Cl_2 (40 mL) was chilled in an ice bath and HBr was bubbled in for 20 min. The mixture was kept at 4 °C overnight and then the solvent was removed in vacuo. Traces of HOAc were removed by several coevaporations with toluene, and then the residue was redissolved in CH_2Cl_2 (50 mL).

The above solution was added to 2,4-bis[(trimethylsilyl)oxy]-5-isopropylpyrimidine (**4e**). The latter compound was freshly prepared by refluxing 5-isopropyluracil (0.89 g, 5.8 mmol) in $(Me_3Si)_2NH$ (10 mL) in the presence of about 5 mg of $(NH_4)_2SO_4$ until a clear solution was obtained and then the excess $(Me_3Si)_2NH$ was removed by evaporation in vacuo. The mixture was stirred at room temperature for 4 days. The reaction mixture was diluted with MeOH (5 mL) and the suspension was filtered through a Celite pad and the Celite was thoroughly washed with CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo, and the residue was chromatographed on a silica gel column (30 × 2 cm) using $CHCl_3$ as the eluent. The UV-absorbing fractions were concentrated in vacuo to give crude 1-(3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-isoporpyluracil (**5a**; 1.24 g, 49%) as a syrup. This crude **5e** was contaminated with ~20% of the α-anomer.

The crude **5e** (1.24 g) was dissolved in NH_3/MeOH (100 mL, saturated at 0 °C) and the solution was kept overnight at room temperature. After removal of the solvent in vacuo, the residue was chromatographed on a silica gel column (25 × 3 cm) using $CHCl_3$–MeOH (20:1, v/v) as the eluent. The major UV-absorbing fractions were concentrated in vacuo, the residue was dissolved in a mimimal amount of CH_2Cl_2, and the solution was applied to a preparative TLC plate (20 × 20 cm, silica gel, 250 μm thick, purchased from Analtech). After four developments in *n*-C_6H_{14}–EtOAc (3:7), the major UV-absorbing band was scraped and extracted with EtOAc. The pure β-anomer **1e** was obtained as a syrup (364 mg, 49%).

Compounds **1f–h** were prepared in a similar manner. In these cases, the α- and β-anomers of the protected nucleosides were separated on a silica gel column (the α-anomer was always the minor product and eluted first from the column), and the pure β-anomers **5f–h** were saponified to afford **1f–h**. Compound **1f** was crystallized from $CHCl_3$–EtOH, mp 119–120 °C, but **1g** and **1h** resisted crystallization.

Biological Evaluation

Compounds reported in this paper were screened for activity against HSV-1 (Strain F) and HSV-2 (Strain G) by using the methodologies previously described. Cytotoxicity assays were carried out in rapidly dividing Vero cells as previously described.[30]

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Registry No. **1c**, 99097-05-9; **1d**, 99097-06-0; **1e**, 99097-08-2; **1f**, 99097-12-8; **1g**, 99097-13-9; **1h**, 99097-14-0; **2**, 99097-04-8; **3**, 56632-81-6; **4e**, 51223-63-3; **4f**, 40110-78-9; **4g**, 77421-92-2; **4h**, 99097-15-1; **5e**, 99097-07-1; **5f**, 99097-09-3; **5g**, 99097-10-6; **5h**, 99097-11-7; 5-isopropylbarbituric acid, 7391-69-7; 5-butylbarbituric acid, 1953-33-9; 5-isobutylbarbituric acid, 42846-91-3; 5-*sec*-butylbarbituric acid, 14077-79-3; 6-chloro-5-isopropyluracil, 96796-80-4; 5-butyl-6-chlorouracil, 18493-80-6; 6-chloro-5-isobutyluracil, 99097-02-6; 6-chloro-5-*sec*-butyluracil, 99097-03-7; 5-isopropyluracil, 17432-95-0; 5-butyluracil, 5442-52-4; 5-isobutyluracil, 41300-21-4; 5-*sec*-butyluracil, 61568-02-3; 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil, 69123-94-0; allyl chloride, 107-05-1; 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranose, 84025-00-3.

(26) Gauri, K. K.; Pastenheimer, H. German Patent 1 250 829; *Chem. Abstr.* **1968**, *68*, 105226k.
(27) Mulvey, D. M.; Babson, R. D.; Zawoiski, S.; Ryder, M. A. *J. Heterocycl. Chem.* **1973**, *10*, 79.
(28) Burckhatter, J. H.; Scarborough, H. C. *J. Am. Pharm. Assoc.* **1955**, *44*, 545.
(29) Melnik, S. Y.; Bakhmedova, A. A.; Yartzeva, I. V.; Preobrazhenskaya, M. N.; Zagulyaeva, O. A.; Mamaer, V. P.; Chekunova, E. V.; Bektemirev, T. A.; Andzhaparidze, O. G. *Bioorg. Khim.* **1982**, *8*, 1102.
(30) Schinazi, R. F.; Peters, J.; Williams, C. C.; Chance, D.; Nahmias, A. J. *Antimicrob. Agents Chemother.* **1982**, *22*, 499.