tology of this Division. Antimalarial activity against *Plasmodium falciparum* was determined by the semiautomated system described by Desjardins et al.[23] Two strains of the parasite were utilized, i.e., the multidrug-resistant Vietnam Smith strain[24] and the chloroquine-susceptible, pyrimethamine-resistant Camp strain.[25] Compounds were initially dissolved in a 50:50 (v/v) mixture of $Me_2SO$ and EtOH to a concentration of 1 mg/mL. Subsequent dilutions were made with culture medium. [G-$^3$H]Hypoxanthine was diluted in culture medium to a concentration of 10 $\mu$Ci/mL. Twenty-five microliters of this solution was added to each well of a 96-well microtiter plate. Incorporation of radioactivity by the parasites served as an index of parasite viability and antimalarial activity. Each drug was serially diluted 2-fold for a total of seven concentrations over a 64-fold range. Four wells of each microtiter plate contained chloroquine and mefloquine as controls. Plates were incubated at 37 °C for 24 h under an atmosphere of 5% $O_2$–5% $CO_2$–90% $N_2$. At this time, each well was treated with the [G-$^3$H]hypoxanthine, and incubation continued for an additional 18 h. The contents of each well were then collected on paper, and the paper was washed and subsequently dried at 80 °C for 1 h. Dried filter disks were individually counted in minivials containing a xylene-based scintillation fluid. Radioactivity was assayed in a Searle Delta 300 scintillation spectrometer to a counting error of 1%. The data were analyzed by a nonlinear regression analysis to obtain the 50% inhibitory dose ($ID_{50}$), the drug concentration corresponding to a 50% inhibition of the uptake of radiolabeled hypoxanthine by the parasites.

**Registry No.** 1, 87587-01-7; **2**, 87587-02-8; **3**, 87587-03-9; **4**, 87587-04-0; **5**, 87587-05-1; **6**, 87587-06-2; **7**, 87587-07-3; **8**, 87587-08-4; **9**, 87587-09-5; **10**, 87587-10-8; 11, 87587-11-9; **12**, 87587-12-0; **13**, 87587-13-1; **14**, 87587-14-2; **15**, 87587-22-2; **16**, 87587-15-3; **17**, 87587-16-4; **18**, 87587-17-5; **19**, 87587-18-6; **20**, 87587-19-7; **21**, 87587-20-0; II, 87587-00-6; IV, 87587-21-1; dimethylamine, 124-40-3; pyrrolidine, 123-75-1; piperidine, 110-89-4; hexahydroazepine, 111-49-9; 2-methylpiperidine, 109-05-7; 3-methylpiperidine, 626-56-2; 4-methylpiperidine, 626-58-4; thiomorpholine, 123-90-0; 1-piperazinecarboxaldehyde, 7755-92-2; ethyl 1-piperazinecarboxylate, 120-43-4; 1-(2-pyridinyl)piperazine, 34803-66-2; 1-phenylpiperazine, 92-54-6; 2,6-dimethylmorpholine, 141-91-3; 3-azabicyclo[3.2.2]nonane, 283-24-9; methyl hydrazinecarbodithioate, 5397-03-5; 2-acetyl-1-pyridinone, 2457-50-3; 2-acetylpyridine, 112-62-9.

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# Nucleosides. 129. Synthesis of Antiviral Nucleosides: 5-Alkenyl-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracils

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Synthesis of 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracils containing a vinyl (**4a**), 2-halovinyl (**4b–d**), or ethyl substituent at C-5 was achieved. These nucleosides were found to be about a log order less active than 2′-fluoro-5-iodo-*ara*-C (FIAC) against HSV-1, but they are much less cytotoxic against normal human lymphocytes than FIAC. Nucleosides **4a** and **4e** showed good activity against HSV-1 ($ED_{50}$ = 0.16 and 0.24 $\mu$M, respectively) and HSV-2 ($ED_{50}$ = 0.69 and 0.65 $\mu$M) with very little cytotoxicity ($ID_{50}$ > 100 $\mu$M).

The discovery[1,2] of the potent and selective anti herpes virus activity of 5-iodo-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (2′-fluoro-5-iodo-*ara*-C or FIAC)[1] and its clinical efficacy in phase 1 studies[3] of immunosuppressed patients with advanced cancer experiencing acute herpes virus infections led us to synthesize analogues of FIAC and test their antiviral activity. Among the analogues tested, 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-thymine (2′-fluoro-5-methyl-*ara*-U or FMAU)[4] was found to be about equal to FIAC in potency against herpes simplex virus type 1 (HSV-1) in vitro, yet it is far superior to it in vivo.[5,6] Not only is FMAU antiherpetic, but it is also antileukemic in mice at high dose levels.[7]

Our previous structure–activity relationship studies[1,4] showed the importance of substituents at C-5 and C-2′ of arabinosylpyrimidine nucleosides in determining anti herpes virus and cytotoxic activities. Thus, the fluoro substituent in the 2′-"up" arabino configuration, in general, brings about more potent and selective inhibitory activity against replication of herpes viruses than a hydrogen,[1] hydroxyl,[1] or other halogeno[4] substituent.

Recent reports on the potent antiherpetic activity of 5(*E*)-(halovinyl)-2′-deoxyuridines[8] and -*ara*-U[9] prompted us to prepare several 2-fluoroarabinosyl analogues containing 5(*E*)-(halovinyl)uracil for studies of their antiviral activity. These compounds were tested against both

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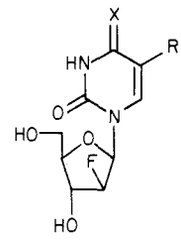
Table I. Antiherpetic Activity of 2'-Fluoro-5-alkenylarabinosyluracils[a]



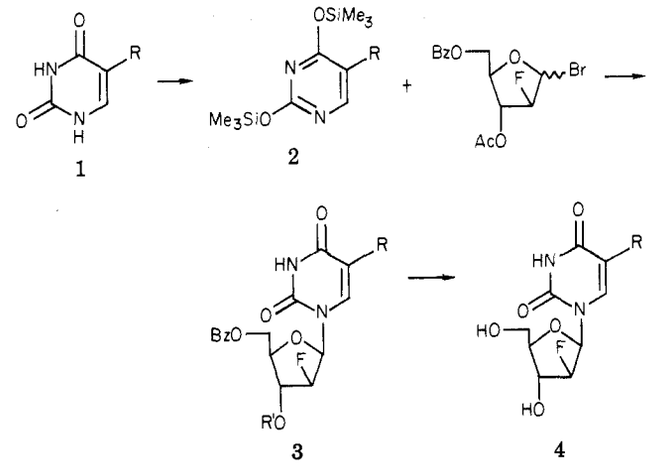
| compd | X | R | $ED_{50}$,[b] μM HSV-1 | $ED_{50}$,[b] μM HSV-2 | $ID_{50}$,[c] μM | formula[d] |
|---|---|---|---|---|---|---|
| 4a | O | $CH=CH_2$ | 0.16 | 0.69 | >100 | $C_{11}H_{13}FN_2O_3$ |
| 4b | O | CH=CHCl | 0.54 | 6.9 | >100 | $C_{11}H_{12}ClFN_2O_3$ |
| 4c | O | CH=CHBr | 0.4 | 13.9 | >100 | $C_{11}H_{12}BrFN_2O_3$ |
| 4d | O | CH=CHI | 1.1 | 17.3 | >100 | $C_{11}H_{12}FIN_2O_3$ |
| 4e | O | $CH_2CH_3$ | 0.24 | 0.65 | >100 | $C_{11}H_{15}FN_2O_3$ |
| FIAC | NH | I | 0.024 | 0.014 | 8.6 | (ref 1) |
| BrVdU[e] | | | 0.07 | 12.95 | | (ref 8) |

[a] All of these compounds were evaluated in parallel in three experiments. The data represent the mean from three separate but similar experiments. [b] Concentrations required for 50% reduction of plaque formation. [c] Concentrations necessary for 50% inhibition of growth of normal human lymphocytes. [d] Chemical formulas are given for new compounds that were analyzed for all the elements except oxygen, and analytical results were within ±0.4% of the theoretical values. References are cited in parentheses for analyses of the known compounds. [e] We thank Dr. E. DeClercq for the gift of BrVdU.

HSV-1 and HSV-2 in order to determine whether they demonstrate selectivity for HSV-1 over HSV-2 as has been seen with the closely related compounds of De Clercq et al.[8] Although our earlier studies showed that certain compounds containing the 2-chloroarabinosyl moiety had greater activity with HSV-2 than with HSV-1,[4] more recent studies with several strains of HSV-2 showed that these compounds did not discriminate between HSV-1 and HSV-2 strains.

The (halovinyl)uracils (1) were prepared according to the methods of Jones et al.[10] by condensation of 5-formyluracil with malonic acid, followed by halosuccinimide treatment. 5-Vinyluracil (**1a**) was prepared from 5-acetyluracil according to the published procedure,[11] and 5-ethyluracil (**1e**) was obtained from **1a** by palladium-catalyzed hydrogenation. These 5-substituted uracils (1) were converted into the corresponding trimethylsilyl derivatives (2) (Scheme I) and then condensed with 3-*O*-acetyl-5-*O*-benzoyl-2-fluoro-D-arabinofuranosyl bromide[12] in methylene chloride without catalyst. The protected 5-halovinyl nucleosides (**3b–d**) were obtained in crystalline form after chromatographic purification. During isolation of the protected nucleosides **3**, we often observed partial deacylation of the less stable 3'-*O*-acetyl group as noted previously.[1] Both fully and partially protected nucleosides **3** afforded the corresponding same nucleotides **4** upon saponification. The overall pattern of the $^1H$ NMR spectra of **4** was very similar to that of FIAC[4] (see Table II, a double doublet for the H-1' signal is indicative of the β-nucleoside) but quite different than that of α-FIAC,[4] which exhibited a doublet for the H-1' signal. The following considerations may account for the predominant formation of the β-nucleosides **4**: The $^1H$ NMR spectrum[12] of the 2-fluoroarabinosyl bromide showed it to be the α-anomer. The presence of the electron-withdrawing fluoro substituent at C-2 should make the dissociation of bromide ion from the sugar more difficult. Consequently, condensation

Scheme I



a series R = $CH=CH_2$
b series R = CH=CHCl
c series R = CH=CHBr
d series R = CH=CHI
e series R = $CH_2CH_3$

reaction of the sugar bromide with silylated bases **1** would proceed in large measure by the $S_N2$ mechanism, resulting in the predominant formation of the β-nucleosides. The 5-vinyluracil derivative (**3a**) was obtained as an unstable syrup, which polymerized on standing at room temperature. The protected 5-ethyluracil nucleoside (**3e**) was also obtained as a syrup. Saponification of **3** with $NH_3$/MeOH afforded the corresponding free nucleosides (**4**) in crystalline form.

Preliminary results of in vitro antivirial assays are listed in Table I. Clearly, FIAC exhibited the most potent activity in vitro against HSV-1 and HSV-2. All the newly synthesized nucleosides **4** showed activity about 1 log unit less than that of FIAC. The 5-vinyl (**4a**) and 5-ethyl (**5e**) analogues were found to exhibit good activity against HSV-1 and HSV-2 without any cytotoxicity at 100 μM concentration. The 5-ethyl analogue (**4e**), a stable nucleoside, has a better therapeutic index than FIAC and may be a potentially useful antiherpetic drug. All the new nucleosides (**4a–e**) were found to show no inhibitory ac-

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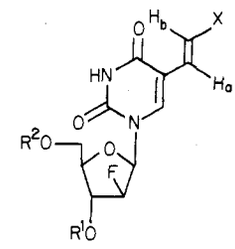
Table II. $^1$H NMR Parameters of 5(*E*)-(2-Halovinyl)-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracils[a]



| | | | | chemical shifts, δ | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| compd | X | $R^2$ | $R^1$ | H-1′ | H-2′ | H-3′ | H-4′ | H-5′, H-5″ | H-6 | $H_a$ | $H_b$ |
| 3a | H | Bz | Ac | 6.26 (dd) | 5.17 (dd) | 5.40 (dq) | 4.38 (m) | 4.74 (d) | 7.44 (s) | 5.81 (dd) | 5.12 (dd) |
| 3b | Cl | Bz | H | 6.22 (dd) | 5.10 (dq) | 4.42 (dm) | 4.23 (t) | 4.63 (d) | 7.61 (s) | 6.48 (d) | 7.18 (d) |
| 3c | Br | Bz | Ac | 6.25 (dd) | 5.16 (dd) | 5.40 (dd) | 4.37 (m) | 4.76 (t) | 7.49 (s) | 6.39 (d) | 7.32 (d) |
| 3c | Br | Bz | H | 6.23 (dd) | 5.11 (dq) | 4.38 (dm) | 4.21 (t) | 4.62 (d) | 7.61 (s) | 6.77 (d) | 7.27 (d) |
| 3d | I | Bz | H | 6.13 (dd) | 5.10 (dt) | 4.43 (dm) | 4.21 (t) | 4.62 (d) | 7.62 (s) | 7.03 (d) | 7.26 (d) |
| 4a | H | H | H | 6.15 (dd) | 5.11 (dt) | 4.26 (dq)[b] | 3.85-3.66 (m) | | 8.00 (s) | 5.92 (dd) | 5.16 (dd) |
| 4b | Cl | H | H | 6.12 (dd) | 5.07 (dt) | 4.26 (dq)[b] | 3.83 (m) | 3.67 (m) | 7.98 (s) | 6.62 (d) | 7.71 (d) |
| 4c | Br | H | H | 6.12 (dd) | 5.08 (dt) | 4.24 (dq)[b] | 3.80 (m) | 3.67 (m) | 8.01 (s) | 6.88 (d) | 7.29 (d) |
| 4d | I | H | H | 6.11 (dd) | 5.08 (dt) | 4.20 (dq)[b] | 3.80 (m) | 3.64 (m) | 8.00 (s) | 7.19 (d) | 7.22 (d) |

| | | | | coupling constants, Hz | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| compd | X | $R^2$ | $R^1$ | $J_{1',2'}$ | $J_{1',F}$ | $J_{2',3'}$ | $J_{2',F}$ | $J_{3',4'}$ | $J_{3',F}$ | $J_{H_a,H_b}$ | solvent |
| 3a | H | Bz | Ac | 2.7 | 23.0 | 0 | 50.7 | 2.4 | 17.0 | 18.0[c] | $CDCl_3$ |
| 3b | Cl | Bz | H | 4.1 | 17.2 | 2.0 | 52.1 | 2.0 | 19.3 | 13.5 | $Me_2SO$-$d_6$ |
| 3c | Br | Bz | Ac | 2.8 | 21.8 | 0 | 50.0 | 2.2 | 17.0 | 12.9 | $CDCl_3$ |
| 3c | Br | Bz | H | 4.3 | 16.7 | 2.0 | 52.0 | 2.2 | 17.0 | 13.7 | $Me_2SO$-$d_6$ |
| 3d | I | Bz | H | 4.0 | 17.3 | 4.0 | 53.1 | 2.0 | 17.0 | 14.5 | $Me_2SO$-$d_6$ |
| 4a | H | H | H | 4.6 | 13.0 | 4.0 | 53.0 | 4.0 | 20.5 | 18.0[d] | $Me_2SO$-$d_6$ |
| 4b | Cl | H | H | 4.3 | 14.5 | 4.0 | 52.8 | 4.0 | 20.0 | 13.4 | $Me_2SO$-$d_6$ |
| 4c | Br | H | H | 4.3 | 14.3 | 4.1 | 53.0 | 4.1 | 20.0 | 13.4 | $Me_2SO$-$d_6$ |
| 4d | I | H | H | 4.3 | 14.5 | 4.1 | 53.0 | 4.1 | 20.0 | 14.6 | $Me_2SO$-$d_6$ |

[a] Signals are expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; dt, double triplet; dq, double quartet; dm, double multiplet. Values given for coupling constants are first order. [b] Changed into a double triplet upon addition of $D_2O$. [c] $J_{H_a,H_b}$ = 11.0 Hz, $J_{H_b,H}$ = 2.1 Hz. [d] $J_{H_a,H}$ = 11.0 Hz, $J_{H_b,H}$ = 2.1 Hz.

tivity against mouse leukemia cell lines P815 and L5178Y in culture.[13]

It is noteworthy that the introduction of a 2′-fluoro substituent in the up (arabino) configuration in BVDU (to give compound **4a**) did not confer selective activity against HSV-2, nor did this 2′-fluoro substitution improve the efficacy against HSV-1.

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. TLC was performed on Uniplates purchased from Anatech Co., and column chromatography was perfomred on silica gel G60 (70–230 mesh, ASTM, Merck). Elemental analyses were performed by Galbraith Laboratories, Inc., or Spang Microanalytical Laboratory. $^1$H NMR spectra (Table II) were recorded on a JEOL PFT-100 spectrometer, and $Me_4Si$ was the interal standard for organic solvents and DSS for deuterium oxide; chemical shifts are reported in parts per million (δ).

**5(*E*)-(2-Bromovinyl)-1-(3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (3c, $R^1$ = Ac).** A solution of 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranose[12] (2.0 g, 5.86 mmol) in dry $CH_2Cl_2$ (20 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 below 35 °C. Traces of AcOH were removed by several coevaporations with $C_6H_6$, and the residue was dissolved in $CH_2Cl_2$.

The above solution was added to 2,4-bis(trimethylsilyl)-5-(*E*)-(2-bromovinyl)uracil (**2c**) [freshly prepared by refluxing 5-(*E*)-(2-bromovinyl)uracil (**1c**; 1.2 g, 5.53 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 excess $(Me_3Si)_2NH$ was removed by evaporation in vacuo], and the mixture was stirred at room temperature for 4 days. MeOH (2 mL) was added to the reaction mixture, and then the solvent was removed in vacuo. The residue was triturated several times with $Me_2CO$, and insoluble materials were removed by filtration. The combined filtrates were evaporated, and the residual syrup was placed on a silica gel column (25 × 2.5 cm) and eluted with $CHCl_3$–MeOH (30:1, v/v). Two major nucleoside fractions were obtained. Each fraction was concentrated to dryness in vacuo, and the residue was crystallized by trituration with EtOH. From the first fraction, 200 mg (8%) of **3c** (R′ = Ac) was obtained, mp 143–147 °C. The 3-O-deacetylated product (**3c**, R′ = H) was obtained from the second fraction, 650 mg (26%), mp 202–203 °C dec. The $^1$H NMR data for **3c** are given in Table II.

In a similar manner, the 5-ethyl derivative (**3e**, $R^1$ = Ac) was prepared (syrup, 41% yield): $^1$H NMR ($CDCl_3$) δ 0.95 (3 H, t, $CH_2CH_3$), 2.18 (3 H, s, OAc), 2.24 (2 H, q, $CH_2$Me), 4.33 (1 H, m, H-4′), 4.76 (2 H, m, H-5′, H-5″), 5.15 (1 H, dd, H-2′, $J_{1',2'}$ = 2.7 Hz, $J_{2',F}$ = 50.2 Hz, $J_{2',3'}$ = 0 Hz), 5.40 (1 H, dd, H-3′, $J_{3',4'}$ = 2.8 Hz, $J_{3',F}$ = 17.3 Hz), 6.25 (1 H, dd, H-1′, $J_{1',2'}$ = 2.7 Hz, $J_{1',F}$ = 23.6 Hz), 7.26 (1 H, s, H-6), 7.44–8.11 (5 H, m, Bz), 8.65 (1H, br s, NH). The major product isolated from a reaction mixture of condensation of silylated 5(*E*)-(2-chlorovinyl)- or 5(*E*)-(2-iodovinyl)uracil (**2b** or **2d**) was the 3′-O-deacetylated derivative **3b** (R′ = H, mp 202–207 °C, 37%) or **3d** (R′ = H, mp 201–202 °C, 15%). The $^1$H NMR data of **3b** and **3d** are listed in Table II.

**1-(3-*O*-Acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-vinyluracil (3a, $R^1$ = Ac).** To a mixture of 5-vinyluracil (**1a**; 1.38 g, 10 mmol) and $Me_3SiCl$ (2.48 g, 20 mmol) in dry $C_6H_6$ (60 mL) was slowly added a solution of $Et_3N$ (2.02 g, 20 mmol) in $C_6H_6$ (20 mL) over a period of 30 min, and the mixture was stirred overnight at room temperature. The insoluble $Et_3NHCl$ was removed by filtration and washed with $C_6H_6$, and the combined filtrate and washings were concentrated in vacuo to obtain 2,4-bis(trimethylsilyl)-5-vinyluracil (**2a**) as an oil, which was dissolved in $CH_2Cl_2$ (80 mL) and added to a solution of the

(13) Burchenal, J. H., personal communication.

bromo sugar [prepared from 3.40 g (10 mmol) of 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinose] in $CH_2Cl_2$ (50 mL). The mixture was stirred for 7 days at room temperature, and then saturated $NaHCO_3$ solution (30 mL) was added. The mixture was filtered through a Celite pad, and the Celite was washed with $CH_2Cl_2$. The combined organic solutions were washed with $NaHCO_3$ solution and water, dried ($Na_2SO_4$), and evaporated in vacuo. The residue was chromatographed over a silica gel column using $n$-$C_3H_{14}$–EtOAc (3:2) as the eluent. The β-anomer (**3a**, $R^1$ = Ac) was obtained as the major product (1.82 g, 43%) as a syrup. This product slowly decomposed upon long standing at room temperature. The $^1H$ NMR data are given in Table II.

**5(*E*)-(2-Bromovinyl)-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (4c).** Compound **3c** ($R^1$ = H; 450 mg) was dissolved in saturated $NH_3$/MeOH (50 mL). After 24 h, the solvent was removed in vacuo, and the residue was triturated several times with $Et_2O$ and $CH_2Cl_2$. The solid residue (contaminated with a minute amount of impurities) was chromatographed over a silica gel column using $CHCl_3$–MeOH (20:1, v/v) as the eluent. The major nucleoside fraction was concentrated to dryness, and the residue was triturated with $Et_2O$ to crystallize the product **4c** (315 mg, 91%), mp 189–190 °C dec. The same compound **4c** was also obtained in a similar manner from **3c** (R′ = Ac).

In a similar manner, **4b**, mp 225–225.5 °C, and **4d**, mp 178–179 °C dec, were obtained from the corresponding protected nucleosides. For the $^1H$ NMR data of **4b–d**, see Table II. The 5-ethyluracil analogue (**4e**), mp 163–164 °C, was also prepared similarly from **3e**: $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.03 (3 H, t, $CH_2CH_3$), 2.22 (2 H, q, $CH_2Me$), 3.70–3.78 (3 H, m, H-5′, H-5″), 4.23 (1 H, dq, H-3′, $J_{2',3'} = J_{3',4'} = 4.3$ Hz, $J_{3',F} = 18$ Hz), 5.07 (1 H, ddd, H-2′, $J_{1',2'} = J_{2',3'} = 4.3$ Hz, $J_{2',F} = 53.0$ Hz), 6.13 (1 H, dd, H-1′, $J_{1',2'} = 4.3$, $J_{1',F} = 14.0$ Hz), 7.57 (1 H, s, H-6), 11.43 (1 H, br s, NH).

**1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-vinyluracil (4a).** Compound **3a** (1.8 g) was dissolved in $NH_3$/MeOH (150 mL), and the solution was left standing for 24 h at room temperature. After concentration of the mixture in vacuo, the residue was crystallized from EtOH to give pure 4a: yield 650 mg (58%); mp 170 °C (sinter), 235–270 °C (dec). The $^1H$ NMR spectral data of **4a** are given in Table II.

**Antiviral Activity.** Antiviral activity was determined by the plaque-reduction assay.[2] Vero cell monolayers were infected with approximately 20–30 plaque-forming units (pfu) of HSV-1 (strain 2931) or HSV-2 (strain G) per well and incubated for 2 h. Maintenance media containing various concentrations of drugs were used to overlay the monolayers. When the plates were fully developed (2 days), the number of plaques were counted, and a linear regression was developed in order to calculate concentration of the drug required to reduce plaque formation by 50% ($ED_{50}$).

**Cytotoxicity.** Cytotoxicity was determined by the method reported previously[2,14] using normal, PHA-stimulated human lymphoblasts. The concentration of drug causing a 50% inhibition of replication ($ID_{50}$) was determined.

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**Registry No.** **1a**, 37107-81-6; **2a**, 55520-62-2; **2b**, 87782-42-1; **2c**, 73446-72-7; **2d**, 73446-76-1; **2e**, 31167-05-2; **3a** (R′ = Ac), 87782-45-4; **3b** (R′ = H), 87782-43-2; **3c** (R′ = H), 87782-40-9; **3c** (R′ = Ac), 87782-46-5; **3d** (R′ = H), 87782-44-3; **3e** (R′ = Ac), 87782-41-0; **4a**, 87782-49-8; **4b**, 87782-48-7; **4c**, 79637-79-9; **4d**, 87782-47-6; **4e**, 83546-42-3; 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranose, 84025-00-3; 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide, 56632-81-6.

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# Synthesis and Evaluation of Radioiodinated (*E*)-18-Iodo-17-octadecenoic Acid as a Model Iodoalkenyl Fatty Acid for Myocardial Imaging

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$^{125}I$-labeled (*E*)-18-iodo-17-octadecenoic acid (**13**) has been prepared and evaluated in rats to determine the myocardial uptake and retention and degree of in vivo deiodination of this model iodivinyl-substituted fatty acid, which contains no structural perturbation to inhibit metabolism. This new agent was prepared by NaI–chloramine-T treatment of (17-carbomethoxyheptadec-1-en-1-yl)boronic acid (**11**) prepared by catecholborane treatment of methyl 17-octadecynoate (**10**), followed by basic hydrolysis to the free acid (**13**). The pivotal substrate, 17-octadecynoic acid (**9**), was prepared by two new routes. The $^{125}I$-labeled acid **13** showed high myocardial uptake (1 h, 1.90–2.28% dose/g) with 45% washout after 2 h but lower heart/blood ratios in comparison to analogues containing the tellurium heteroatom. Deiodination was low for the first 2 h after injection (2 h, 61% dose/g). Excellent myocardial images were obtained in a dog with the $^{123}I$-labeled agent.

The use of radioiodinated fatty acids for the evaluation of coronary artery disease is well established.[1] A variety of structurally modified long-chain fatty acids labeled with radioiodide are extracted by the myocardial tissue like normal plasma fatty acids, and the uptake and subsequent metabolism can be used to measure regional fatty acid metabolism. Iodine-123 is the most attractive single-photon radionuclide for labeling fatty acids because of the ease of iodine chemistry and the attractive properties of this isotope. These properties include an attractive 13-h half-life, which makes radiosynthesis, purification, and distribution of these agents feasible. In addition, the abundant 159-keV γ photon is in the optimal region for detection with Anger cameras, and single photon emission tomography with this radioisotope is feasible. We have recently described the stablization of radioiodide as a vinyl iodide on tellurium fatty acids,[2] and more recently, the

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