vacuo over P_2O_5. The yield was 0.120 g (22%), and the diastereomeric mixture of 11 so formed had mp 101–103 °C. TLC (Merck; $CHCl_3$–MeOH–H_2O, 65:25:3) showed one UV-absorbing spot, which was also positive using a phosphate spray reagent.[50] IR (KBr, disk) showed 1753, 1700 (C=O), 1255 (P=O), 1168 (P=N), and 1045, 1020 cm^{-1} (P–O–C) as identifiable bands.

1-β-D-**Arabinofuranosylcytosine 5′-Monophosphate–L-1,2-Dipalmitin Sodium Salt (5).** A solution of 11 (0.165 g, 0.00015 mol) in $CHCl_3$–MeOH–H_2O (2:3:1; 50 mL) was heated at 60 °C for 2 h. Monitoring by TLC (Merck, MeOH–$CHCl_3$, 3:7) indicated complete reaction, and the solution was evaporated to dryness. The residue was dissolved in $CHCl_3$–MeOH–H_2O (4:6:1; 100 mL) and applied to a column of DEAE-Sephadex (acetate form; 15 × 4 cm) packed in the same solvent.[53] Elution was initially with $CHCl_3$–MeOH–H_2O (4:1:1; 500 mL) and then with a linear gradient (700 mL in each reservoir) of 0–0.1 N ammonium acetate made up in $CHCl_3$–MeOH–H_2O (4:6:1). Fractions containing the required product were pooled and evaporated to small volume. Acetone (50 mL) was added, and the white precipitate of the NH_4^+ salt so obtained was filtered off andd then converted to the Na^+ salt by dissolution in $CHCl_3$–MeOH–H_2O (4:6:1) and passage down a Cellex-CM (Na^+ form) column 31 × 2.5 cm), packed, and developed in the same solvent. The fractions containing the required product were pooled and concentrated, and **5** was obtained as a white precipitate upon addition of acetone–H_2O (9:1). This material was filtered off, washed with acetone, and dried over P_2O_5 in vacuo for 20 h: yield 0.122 g (89%); mp 212–214 °C dec.

(53) The DEAE-Sephadex (acetate form) was prepared as described in ref 51, with the exception that the final equilibration and packing was carried out in $CHCl_3$–MeOH–H_2O (4:6:1).

Acknowledgment. The authors thank Drs. N. G. Anderson, N. L. Anderson, and J. S. Edwards for their continuing interest and helpful discussions. We thank M. McCroskey for some preliminary experiments and C. F. Ainsworth for obtaining the spectroscopic data. This work was supported in part by Grant CA26168, awarded by the National Cancer Institute, Department of Health, Education, and Welfare, and the U.S. Department of Energy under Contract W-31-109-ENG-38.

Synthesis and Antiviral Properties of Some 2′-Deoxy-5-(fluoroalkenyl)uridines

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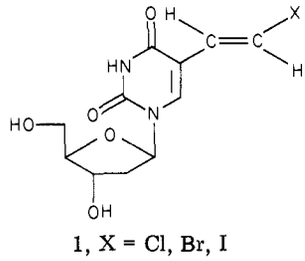
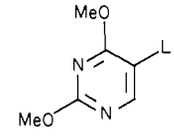
The following 5-substituted 2,4-dimethoxypyrimidines were synthesized: 5-(2,2,2-trichloro-1-hydroxyethyl), 5-(2,2,2-trichloro-1-fluoroethyl), 5-(2,2-dichloro-1-fluorovinyl) (**5**), and 5-(perfluoropropen-1-yl) (a mixture of *E* and *Z* isomers, **6** and **7**). Demethylation of **5** gave 5-(2,2-dichloro-1-fluorovinyl)uracil, and demethylation of the mixture of **6** and **7** gave some pure (*E*)-5-(perfluoropropen-1-yl)uracil. Compound **5** was converted into its 2′-deoxyribonucleoside (**12**) and its α-anomer by standard procedures. 2′-Deoxy-3,5-dilithio-3′,5′-*O*-bis(trimethylsilyl)uridine was reacted with the appropriate fluoroalkene to give the following 5-substituted 2′-deoxyuridines in low yield (6–24%): 5-(2-chloro-1,2-difluorovinyl) (a mixture of *E* and *Z* isomers, **15** and **16**, which were separated on a small scale), 5-(perfluoropropen-1-yl), 5-(perfluorocyclohexen-1-yl), and 5-(perfluorocyclopenten-1-yl). In these reactions, 2′-deoxy-5-(trimethylsilyl)uridine and 2′-deoxyuridine were also formed. The 5-substituted 2′-deoxyuridines were tested for activity against herpes simplex virus type 1. Compound **12** and the mixture of **15** and **16** had an ID_{50} of 20–26 μg/mL in Vero cells. The activity of the mixture resided in one isomer, which by analogy with the corresponding (*Z*)- and (*E*)-5-(2-bromovinyl)-2′-deoxyuridines was concluded to be the *Z* isomer (**16**).

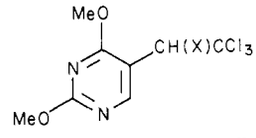
(*E*)-5-(2-Halogenovinyl)-2′-deoxyuridines (**1**) have been



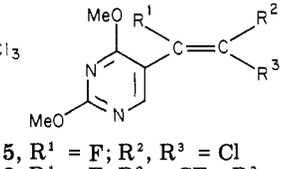
1, X = Cl, Br, I



2



3, X = OH
4, X = F



5, R^1 = F; R^2, R^3 = Cl
6, R^1 = F; R^2 = CF_3; R^3 = F
7, R^1 = F; R^2 = F; R^3 = CF_3

shown to be active against certain herpes viruses;[1] the bromo derivative is the most active, showing highly selective action against herpes simplex virus type 1 and against varicella zoster virus.[2] The compound has been extensively studied in vitro and in vivo and has shown promising results.[3] Similar compounds that also show high activity against herpes viruses are the (*E*)-5-(propen-1-yl)- and (*E*)-5-(3,3,3-trifluoropropen-1-yl) derivatives.[4] On the other hand, (*Z*)-5-(2-bromovinyl)-2′-deoxyuridine has only a very low activity, thus showing the critical nature of the configuration around the ethylenic double bond.[5] Obviously it is of interest to synthesize similar compounds and investigate their antiviral properties. In the present study, attention has turned to ob-

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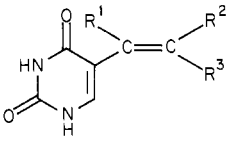
taining a series of 5-(fluoroalkenyl)-2′-deoxyuridines.

The first approach was to synthesize 5-(fluoroalkenyl)uracils, which could then be converted by known procedures into the required 2′-deoxyribonucleosides. Initial attempts to carry out these syntheses on 5-formyluracil by Wittig-type reactions, as has been used to synthesize 5-(2,2-dibromovinyl)uracil,[6] were not successful. The syntheses were carried out, therefore, on 5-lithio-2,4-dimethoxypyrimidine (**2**), which is obtained by the action of butyllithium on 5-bromo-2,4-dimethoxypyrimidine. Reaction of **2** with trichloroacetaldehyde gave 5-(2,2,2-trichloro-1-hydroxyethyl)-2,4-dimethoxypyrimidine (**3**), which upon treatment with (diethylamino)sulfur trifluoride gave 5-(2,2,2-trichloro-1-fluoroethyl)-2,4-dimethoxypyrimidine (**4**). Dehydrochlorination of the latter with sodium methoxide gave 5-(2,2-dichloro-1-fluorovinyl)-2,4-dimethoxypyrimidine (**5**). This route to **5** is long, and the overall yield from 5-bromo-2,4-dimethoxypyrimidine is only 18%. An alternative route was to react **2** with 1,1-dichlorodifluoroethene. It is known that in this type of reaction the CF_2 group is the more reactive, and fluoride ion is displaced.[7-9] The product was obtained in one step in 55% yield, and it was identical with the compound obtained by the longer route. When this compound is synthesized by the shorter route, it is necessary to make sure that compound **2** is not contaminated by traces of unreacted 5-bromo-2,4-dimethoxypyrimidine because it is extremely difficult to separate this from the required product.

In a similar way, **2** was reacted with perfluoropropene to give a mixture of (*E*)- and (*Z*)-5-(perfluoropropen-1-yl)-2,4-dimethoxypyrimidine (**6** and **7**). ^{19}F NMR spectroscopy showed two sets of peaks in the integral ratio of 5.6:1 attributable to a mixture of *E* and *Z* isomers. The major set showed peaks (reference: CCl_3F) at 165.5 (dqt), 135.7 (dqt), and 67.8 ppm (dd), while the minor set had peaks at 150.7 (overlapping dqt), 112.2 112.2 (overlapping dqt), and 67.8 ppm (dd). The structural assignment about the double bond is based on the F, F coupling constants. It has been shown[10] that in *cis*- and *trans*-phenylperfluoropropenes there is a large difference between the CF_3 and F couplings depending on their stereochemical relationships. If the CF_3 and F are cis, $J_{CF_3,F}$ = 23 Hz; if they are trans, $J_{CF_3,F}$ = 13 Hz. Similarly cis and trans F–F couplings are 9 and 131 Hz, respectively.

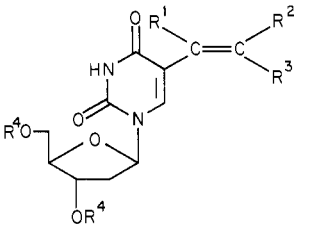
In our case, the major isomer has $J_{CF_3,F_{vic}}$ = 21.7 Hz and $J_{F,F}$ = 141 Hz, clearly indicating it to be the *E* isomer. The minor isomer has small F–F coupling, which cannot be measured due to overlap and a CF_3–F coupling of 11.2 Hz, indicating the *Z* isomer. The isomers could be separated by multiple development TLC and by analytical GLC or HPLC.

Removal of the methyl groups from **5** was accomplished by the use of sodium iodide in acetic acid[11] to give 5-(2,2-dichloro-1-fluorovinyl)uracil (**8**) in 61% yield. When the mixture of **6** and **7** was treated in the same way, the corresponding 5-substituted uracils were obtained. A pure sample of (*E*)-5-(perfluoropropen-1-yl)uracil (**9**) was obtained by fractional crystallization. In order to obtain the

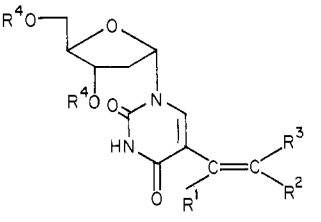


8, R^1 = F; R^2, R^3 = Cl
9, R^1 = F; R^2 = CF_3; R^3 = F

2′-deoxyribonucleoside, **8** was converted into its bis(trimethylsilyl) derivative, which was condensed with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranoyl chloride to give a mixture of β and α anomers (**10** and **11**). The

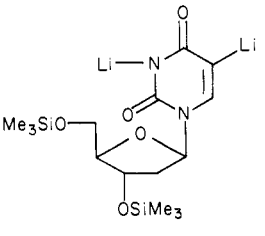


10, R^1 = F; R^2, R^3 = Cl; R^4 = *p*-toluoyl
12, R^1 = F; R^2, R^3 = Cl; R^4 = H
15, R^1 = F; R^2 = F; R^3 = Cl; R^4 = H
16, R^1 = F; R^2 = Cl; R^3 = F; R^4 = H



11, R^1 = F; R^2, R^3 = Cl; R^4 = *p*-toluoyl
13, R^1 = F; R^2, R^3 = Cl; R^4 = H

configuration at C_1 was established by ^1H NMR spectroscopy; the β anomer (**10**) gave the characteristic pseudotriplet at δ 6.38, whereas the α anomer (**11**) gave a double doublet at δ 6.32. Treatment of **10** and **11** with methanolic ammonia gave 5-(2,2-dichloro-1-fluorovinyl)-2′-deoxyuridine (**12**) and its α anomer (**13**), respectively. This route to **12** was very long, and the overall yield was low (~2%). In order to obtain sufficient amounts of 2′-deoxyribonucleosides for biological investigations, a shorter route, starting from the commercially available 2′-deoxy-5-iodouridine, was used. Treatment of this with hexamethyldisilazane and trimethylsilyl chloride gave the bis(trimethylsilyl) derivative, which upon treatment with butyllithium gave the dilithio compound (**14**), which was then



14

reacted with a series of fluoroalkenes. Reaction with chlorotrifluoroethene gave a mixture of (*E*)- and (*Z*)-5-(2-chloro-1,2-difluorovinyl)-2′-deoxyuridine (**15** and **16**) in low yield (6%). The structures of the components of this mixture were assigned on the basis of mass spectrometry and ^1H and ^{19}F NMR spectroscopy. It was possible on the basis of F–F coupling constants to assign peaks due to each isomer by virtue of the very large differences between cis F–F and trans F–F couplings (~10 and ~130 Hz, re-

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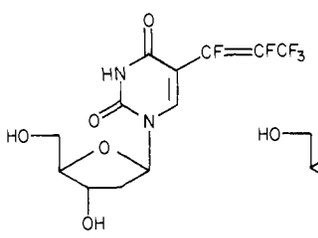
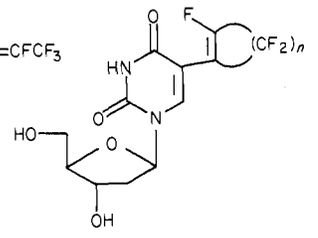
spectively). We find 6.5 and 133 Hz for the two compounds. The isomers were separated on a small scale by HPLC, but the structure of each was not directly established. In addition to these required compounds, there were also produced, 2'-deoxy-5-(trimethylsilyl)uridine (7%) and 2'-deoxyuridine (61%). The former, which has been prepared before but only partly characterized,[12] was probably produced by reaction with unremoved silylating agent, and the latter was produced from the reaction of water on unreacted lithio compound (14).

A similar reaction was attempted in which the fluoroalkene used was bromotrifluoroethene. However, no 5'-(fluorovinyl)-2'-deoxyuridine was obtained: the products were 2'-deoxy-5-(trimethylsilyl)uridine, 5-bromo-2'-deoxyuridine, and 2'-deoxyuridine. It appears that in this case metal–bromide exchange occurs in preference to addition to the fluoroalkene, followed by elimination of fluoride ion. Analogous examples are to be found in the literature.[9,13,14]

The lithio compound, 14, was reacted also with perfluoropropene to give 2'-deoxy-5-(perfluoropropen-1-yl)-uridine (17) as a mixture of *E* and *Z* isomers. These were



17



18, $n = 4$
19, $n = 3$

not separated, but from their NMR spectra it was deduced that about 90% of the mixture was the *E* isomer when the same arguments given above for 6 were used. Perfluorocyclohexene and perfluorocyclopentene reacted with 14 to give 5-(perfluorocyclohexene-1-yl) and 5-(perfluorocyclopenten-1-yl) derivatives (18 and 19), respectively. The structures of these compounds were deduced from their NMR spectra. The best yield (24%) in these reactions was with perfluoropropene. In all of these reactions, 2'-deoxy-5-(trimethylsilyl)uridine and 2'-deoxyuridine were also produced.

Compounds 12, 13, and 17–19 and the mixture of 15 and 16 were tested for antiviral activity against various strains of herpes simplex virus, type 1. Compound 12 (ID_{50} = 26 μg/mL) and the mixture of 15 and 16 (ID_{50} = 20–24 μg/mL) showed significant activity, whereas the other compounds were inactive at concentrations up to 100 μg/mL. When 15 and 16 were tested separately, it was found that the activity resided in only one isomer. Although not enough material was isolated to identify unequivocally which isomer was active, analogy with the corresponding 5-(2-bromovinyl) derivatives[5] strongly suggests that it is the *Z* isomer (16). The activities of these compounds should be compared with the ID_{50} of established antiviral compounds that were evaluated in the same system, namely, arabinosyladenine (21 μg/mL), 2'-deoxy-5-iodouridine (4.4 μg/mL), acycloguanosine (0.8 μg/mL), and (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (0.07 μg/mL). The active fluorine-containing compounds synthesized in the present work have about the same activity as arabinosyladenine, therefore, but considerably lower than the activities of the other compounds cited.

The absence of activity in the 5-(perfluoropropen-1-yl) derivative (17) was rather surprising in view of the appreciable and identical activities of the 5-(propen-1-yl) and 5-(3,3,3-trifluoropropen-1-yl) derivatives.[4] This indicates that the anti-HSV-1 activity is lowered when the vinylic hydrogens are replaced by fluorine. This effect is seen also in 16, which is about 300 times less active than (*E*)-5-(2-bromovinyl)-2'-deoxyuridine. [Note: (*E*)-5-(2-chlorovinyl)-2'-deoxyuridine has been found to be about half as active against HSV-1 as the corresponding bromo compound.[2]]

Experimental Section

Chromatography. TLC was carried out with silica gel, MN-Kieselgel G/UV_{254}, and column chromatography was carried out with Kieselgel 60, 70–230 mesh, ASTM type 7734. Both were supplied by E. Merck AG, Darmstadt, West Germany. Analytical HPLC was performed on Spherisorb 5 μ ODS silica, and preparative HPLC with 50 μ ODS silica.

Spectroscopy. NMR spectra were recorded on either a Perkin-Elmer R12 (60 MHz) or a Varian XL-100 (100 MHz); FT spectra were recorded on a Brucker (80 MHz) spectrometer. Tetramethylsilane was used as internal standard for ^1H NMR spectra, and trichlorofluoromethane was used for ^{19}F spectra. Me_2SO-d_6 was used as the solvent unless otherwise stated. UV absorption spectra were measured in aqueous ethanol (unless otherwise stated) under acidic, neutral, and alkaline conditions. Only the latter two are quoted because those taken for acidic solutions differed little from those taken at neutrality. Mass spectrometry was carried out in the electron-impact (EI) (70 eV) or chemical-ionization (CI) (NH_3) mode. All reactions were carried out under scrupulously anhydrous conditions unless otherwise indicated.

5-(2,2,2-Trichloro-1-hydroxyethyl)-2,4-dimethoxypyrimidine (3). A solution of butyllithium (2.85 mL, 1.6 M, 4.56 mmol) in hexane was added dropwise over 5 min to a stirred suspension of 5-bromo-2,4-dimethoxypyrimidine (1.00 g, 4.56 mmol)[15] in ether (15 mL) at −70 °C under nitrogen, and then a solution of trichloroacetaldehyde (0.74 g, 5.02 mmol) in ether (10 mL) was added. The reaction mixture was stirred at −70 °C for 1 h, allowed to warm slowly to room temperature, and then quenched with water (20 mL). The aqueous layer was separated and extracted with ether (2 × 25 mL), the extracts were combined with the ethereal layer and then dried over $MgSO_4$, and the solvent was removed by evaporation. The residue (2.71 g) was applied to a silica column (270 g) that was eluted with chloroform. Faster running components were eluted first, followed by the required material. This was crystallized from light petroleum (60–80 °C) to give **5-(2,2,2-trichloro-1-hydroxyethyl)-2,4-dimethoxypyrimidine** (683 mg, 52% yield) as colorless plates: mp 132–133 °C; UV (ethanol) λ_{max} 262.5 nm (ε 7370), λ_{min} 242.5 nm (ε 3300); NMR δ 3.92 (3 H, s, CH_3), 3.96 (3 H, s, CH_3), 5.37 (1 H, d, H-1', $J_{H\text{-}1',OH\text{-}1'}$ = 6 Hz, coupling collapses on addition of D_2O), 7.34 (1 H, d, OH-1', $J_{OH\text{-}1',H\text{-}1'}$ = 6 Hz, removed on addition of D_2O), 8.52 (1 H, s, H-6); mass spectrum (EI), *m/e* 287 (M^+, 0.6%), 215 (2.8), 169 ($M^+ - CCl_3$, 100), 85 (9.5), 42 (19). Anal. ($C_8H_9Cl_3N_2O_3$) C, H, Cl, N.

5-(2,2,2-Trichloro-1-fluoroethyl)-2,4-dimethoxypyrimidine (4). A solution of compound 3 (5.20 g, 18.1 mmol) in dichloromethane (50 mL) was added dropwise over 30 min to a stirred solution of (diethylamino)sulfur trifluoride (3.22 g, 20 mmol) in dichloromethane (20 mL) at −70 °C under nitrogen. The reaction mixture was then stirred for a further 30 min at −70 °C, allowed to warm to room temperature, and then boiled under reflux for 30 min. It was allowed to cool and then poured into ice–water (100 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 50 mL). The extracts were combined with the organic layer and dried over $MgSO_4$, and the solvent was

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evaporated off. The residue (5.94 g) was applied to a column of silica (150 g) and fractionated with chloroform as the eluant. The crude product was recrystallized from aqeous methanol to give **5-(2,2,2-trichloro-1-fluoroethyl)-2,4-dimethoxypyrimidine** (2.80 g, 53% yield): mp 54 °C; UV (ethanol) λ_{max} 262 nm (ϵ 6290), λ_{min} 243.5 nm (ϵ 3460); ^{1}H NMR δ 3.98 (3 H, s, CH_3), 4.01 (3 H, s, CH_3), 6.26 (1 H, d, H-1', $J_{H\text{-}1',F\text{-}1'}$ = 42.0 Hz), 8.58 (1 H, s, H-6); ^{19}F NMR ϕ 167.75 (1 F, d, F-1', $J_{F\text{-}1',H\text{-}1'}$ = 42.0 Hz); mass spectrum (EI), m/e 288 (M^+ - Cl, 2.5), 171 (M^+ - CCl_3, 100), 141 (2.0), 73 (8), 42 (21). Anal. ($C_8H_8Cl_3FN_2O_2$) C, H, Cl, F, N.

5-(2,2-Dichloro-1-fluorovinyl)-2,4-dimethoxypyrimidine (5). Method A. Sodium (794 mg, 34.5 mmol) was dissolved in methanol (50 mL) and to the solution there was added, with stirring, over 15 min a solution of compound 4 (2.00 g, 6.91 mmol) in methanol (20 mL). Precipitation of sodium chloride occurred during the addition. The reaction mixture was stirred at room temperature for 24 h and boiled under reflux for 4 h, and the solvent was removed by evaporation. The residue (1.80 g) was applied to a column of silica gel (100 g), and the product was eluted with chloroform to give **5-(2,2-dichloro-1-fluorovinyl)-2,4-dimethoxypyrimidine** (1.13 g, 65% yield) as a colorless oil: UV (ethanol) λ_{max} 226 nm (ϵ 10100), 243 (ϵ 10200), λ_{min} 233 nm (ϵ 9800); ^{1}H NMR δ 4.01 (3 H, s, CH_3), 4.05 (3 H, s, CH_3), 8.57 (1 H, d, H-6, $J_{H\text{-}6,F\text{-}1'}$ = 1.7 Hz); ^{19}F NMR ϕ 92.35 (1 F, d, F-1', $J_{F\text{-}1',H\text{-}6}$ = 1.7 Hz); mass spectrum (CI) (NH_3), m/e 253 (MH^+, 100%). Anal. ($C_8H_7Cl_2FN_2O_2$) C, H, Cl, F, N.

Method B. A solution of butyllithium (12.5 mL, 1.6 M, 20 mmol) in hexane was added dropwise over 20 min to a stirred suspension of 5-bromo-2,4-dimethoxypyrimidine (2.19 g, 10 mmol) in ether (50 mL) at -70 °C under nitrogen. To this suspension there was added 1,1-dichlorodifluoroethene (cooled to -70 °C) (6.65 g, 50 mmol). The reaction mixture (which changed color from yellow to purple) was stirred at -70 °C for 1.5 h and then packed in solid CO_2 for 4 days. The reaction was monitored by TLC in chloroform so as to ensure that no 5-bromo-2,4-dimethoxypyrimidine remained. The reaction mixture was then allowed to warm slowly to room temperature and poured into water (50 mL). The aqueous layer was separated and extracted with ether (2 × 50 mL). The extracts were combined with the ethereal layer and dried over $MgSO_4$, and the solvent was removed by evaporation. The residue was distilled under reduced pressure (<120 °C, 0.05 mmHg) to give an oil, which was shown by TLC to contain two components. This distillate (2.05 g) was applied to a column of silica (150 g) and eluted with chloroform. The first product eluted was distilled under reduced pressure with a Kugelrohr distillation apparatus at 73–93 °C to give **5-(2,2-dichloro-1-fluorovinyl)-2,4-dimethoxypyrimidine** (1.39 g, 55% yield) as a colorless oil. The physical properties of this product were identical with those of the compound prepared by method A.

The second product that was eluted was isolated in a similar manner and shown to be 2,4-dimethoxypyrimidine (0.55 g, 39% yield).

***(E)*- and *(Z)*-5-(Perfluoropropen-1-yl)-2,4-dimethoxypyrimidine (6 and 7).** A solution of butyllithium (11.4 mL, 1.6 M, 18.2 mmol) in hexane was added dropwise over 10 min to a stirred suspension of 5-bromo-2,4-dimethoxypyrimidine (2.00 g, 9.12 mmol) in ether at -70 °C under nitrogen. To this was added liquid perfluoropropene (cooled to -40 °C, 4.3 mL, 6.84 g, 45.6 mmol). The reaction mixture, which changed from yellow to crimson, was stirred at -70 °C for 1 h and then packed in solid CO_2 and kept for 4 days. The reaction mixture was then allowed to warm slowly to room temperature and poured into water (50 mL). The material in the organic layer (3.59 g) was isolated in the usual way and fractionated on a column of silica (350 g) with chloroform as the eluant to give **5-(perfluoropropen-1-yl)-2,4-dimethoxypyrimidine** (1.03 g, 42% yield) (as a mixture of *E* and *Z* isomers) as a colorless oil: bp 213 °C (741 mmHg); UV (ethanol) λ_{max} 263.5 nm (ϵ 10400), 238 (11400), λ_{min} 255 nm (ϵ 10200); ^{1}H NMR ($CDCl_3$) δ 4.07 (s, CH_3, *E* and *Z* isomers), 8.27 (br d, H-6, *Z* isomer), 8.37 (br d, H-6, *E* isomer); ^{19}F NMR ϕ ($CDCl_3$) 67.8 (m, F-3', *E* and *Z* isomers), 112.2 (m, F-1', *Z* isomer), 135.7 (dqt, F-1', *E* isomer), 150.7 (m, F-2', *Z* isomer), 165.6 (dqt, F-2', *E* isomer); coupling constants for *E* isomer, $J_{F\text{-}1',F\text{-}2'}$ = 141 Hz; $J_{F\text{-}1',F\text{-}3'}$ = 21.7 Hz; $J_{F\text{-}2',F\text{-}3'}$ = 10.8 Hz; coupling constants for *Z* isomer not discernible; *E*/*Z* ratio = 5.6:1; mass spectrum (EI), m/e 270 (M^+, 100%), 269 (M^+ - H, 34), 255 (M^+ - CH_3, 13), 240 (M^+ - $2CH_3$, 63), 201 (M^+ - CF_3, 12), 171 (M^+ - CF_3 - $2CH_3$, 14), 69 (CF_3^+, 15), 44 (19). Anal. ($C_9H_7F_5N_2O_2$) C, H, F, N.

The presence of the two isomers was also demonstrated by multiple-development TLC in benzene, analytical GLC with Sigum on a Celite column at 140 °C, and analytical HPLC with hexane–chloroform (19:1) as eluant.

5-(2,2-Dichloro-1-fluorovinyl)uracil (8). Sodium iodide (3.64 g, 24.3 mmol) was added to a solution of compound **5** (2.05 g, 8.10 mmol) in glacial acetic acid (40 mL) and the mixture heated at 100 °C for 5 h. The solvent was removed by evaporation under reduced pressure, and benzene (20 mL) was added to the dark red residue. The solid that formed was filtered off, washed with benzene (3 × 10 mL), and then dissolved in boiling water. The solution was decolorized by the addition of a small amount of sodium thiosulfate and then cooled to 0 °C to precipitate the crude product. Recrystallization from methanol gave **5-(2,2-dichloro-1-fluorovinyl)uracil** (1.12 g, 61% yield) as small white needles: mp 226–228 °C; UV λ_{max} 220 nm (ϵ 10600), 271 (8560), λ_{min} 249 nm (ϵ 5570) (neutral); UV λ_{max} 250 nm (ϵ 10300), 291 (11300), λ_{min} 270 nm (ϵ 7860) (alkaline); ^{1}H NMR δ 8.01 (1 H, d, H-6, $J_{H\text{-}6,F\text{-}1'}$ = 2.6 Hz), 11.00–12.00 (2 H, br d, NH); ^{19}F NMR ϕ 90.96 (d, F-1', $J_{F\text{-}1',H\text{-}6}$ = 2.6 Hz); mass spectrum (EI), m/e 224 (M^+, 5%), 189 (M^+ - Cl, 100), 154 (M^+ - 2Cl, 17), 146 (30), 91 (18). Anal. ($C_6H_3Cl_2FN_2O_2$) C, H, Cl, F, N.

***(E)*-5-(Perfluoropropen-1-yl)uracil (9).** Sodium iodide (832 mg, 5.55 mmol) was added to a solution of 5-(perfluoropropen-1-yl)-2,4-dimethoxypyrimidine (*E*/*Z* ratio 5.6:1) (500 mg, 1.85 mmol) in glacial acetic acid (10 mL), and the mixture was heated at 100 °C for 5 h. The solvent was removed by evaporation, benzene (10 mL) was added to the dark red residue, and the solid that was formed was filtered off and washed with benzene (3 × 5 mL). This solid was dissolved in boiling water (10 mL), and the solution was decolorized by the addition of a small amount of sodium thiosulfate. While the solution was cooling to 0 °C, a precipitate was obtained. This was filtered off and crystallized from methanol to give **(*E*)-5-(perfluoropropen-1-yl)uracil** (140 mg, 31% yield): mp 241–244 dec; UV λ_{max} 222 nm (ϵ 9660), 271.5 (9440), λ_{min} 244 nm (ϵ 3900) (neutral); UV λ_{max} 253.5 nm (ϵ 10000), 294 (12100), λ_{min} 270.5 nm (ϵ 6030) (alkaline); ^{1}H NMR δ 8.09 (1 H, d, H-6, $J_{H\text{-}6,F\text{-}1'}$ = 2.0 Hz), 11.56 (2 H, br d, NH); ^{19}F NMR ϕ 66.37 (3 F, dd, F-3'), 131.63 (1 F, dqt, F-1'), 166.21 (1 F, dqt, F-2'); $J_{F\text{-}1',F\text{-}2'}$ = 141.0 Hz, $J_{F\text{-}1',F\text{-}3'}$ = 22.3 Hz, $J_{F\text{-}2',F\text{-}3'}$ = 12.6 Hz, $J_{F\text{-}1',H\text{-}6}$ = 2.0 Hz; mass spectrum (EI), m/e 242 (M^+, 100%), 223 (M^+ - F, 11), 199 (M^+ - CONH, 5), 173 (M^+ - CF_3, 41), 172 (M^+ - CF_3 - H, 25), 171 (M^+ - CF_3 - 2H, 26), 130 (M^+ - CF_3 - CONH, 26), 122 (15), 75 (16), 69 (CF_3^+, 9). Anal. ($C_7H_3F_5N_2O_2$) C, H, F, N. The filtrate and washings were concentrated and cooled to 0 °C to give a second crop of crystals that was shown by ^{19}F NMR to be a mixture of the *E* and *Z* isomers of 5-(perfluoropropen-1-yl)uracil (160 mg, 36% yield): ^{19}F NMR ϕ 66.00 (dd, F-3', *E* isomer), 66.37 (dd, F-3', *E* isomer). Coupling constants for *E* isomer as indicated for the pure compound; coupling constants for *Z* isomer, $J_{F\text{-}1',F\text{-}3'}$ = 13.0 Hz, $J_{F\text{-}2',F\text{-}3'}$ = 8.5 Hz.

5-(2,2-Dichloro-1-fluorovinyl)-2'-deoxy-3',5'-di-*O*-*p*-toluoyluridine (10) and Its α Anomer (11). Compound 8 (1.18 g, 5.24 mmol) was suspended in hexamethyldisilazane (HMDS) (15 mL) and chlorotrimethylsilane (0.1 mL), and the suspension was boiled under reflux for 18 h. The excess of HMDS was evaporated off in vacuo, and the residual oily trimethylsilyl derivative was dissolved in dry dichloromethane (50 mL). This was added to a solution of 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose (1.63 g, 4.19 mmol) in dry dichloromethane (50 mL), the reaction mixture was cooled to 0 °C and tin(IV) chloride (0.1 mL) was added. The mixture was stirred at 0 °C for 8 h and then at room temperature for 24 h and then poured onto ice–water (100 mL). The emulsion that formed was centrifuged, and the aqueous layer was separated and extracted with dichloromethane (2 × 50 mL). The extracts were combined with the organic layer and dried over magnesium sulfate, and the solvent was removed by evaporation under reduced pressure. The residue (2.34 g) was fractionated on a column of silica (200 g). Elution with benzene removed sugar degradation products; then benzene–ethyl acetate (7:3) removed firstly a fraction containing mainly the required blocked nucleoside and secondly a fraction containing mainly its α anomer. The first fraction was crystallized from methanol to give **5-(2,2-dichloro-1-fluorovinyl)-2'-**

deoxy-3′,5′-*O*-*p*-toluoyluridine (720 mg, 30% yield): mp 171–172 °C; UV λ_{max} 241 nm (ϵ 39500), 274 (11600), λ_{min} 267 nm (ϵ 11100) (neutral); UV λ_{max} 235 nm (ϵ 41300), 274 (9140), λ_{min} 264.5 nm (ϵ 8340) (alkaline); ^{1}H NMR δ ($CDCl_3$) 2.43 (6 H, s, CH_3), 2.12–2.96 (2 H, m, H-2′), 4.58 (1 H, m, H-4′), 4.70 (2 H, m, H-5′), 5.61 (1 H, m, H-3′), 6.38 (1 H, t H-1′), 7.14–7.34 (4 H, m, aromatic H), 7.80–8.02 (5 H, m, aromatic H and H-6), 9.32 (1 H, br d, NH); ^{19}F NMR ϕ ($CDCl_3$) 96.22 (d, F-1″, $J_{F\text{-}1'',H\text{-}6}$ = 2.0 Hz); mass spectrum (CI) (NH_3), *m/e* 594 (MNH_4^+, 24%). Anal. ($C_{27}H_{23}Cl_2FN_2O_7$) C, H, Cl, F, N.

The second fraction was crystallized from methanol to give **5-(2,2-dichloro-1-fluorovinyl)-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)uracil** (680 mg, 28% yield): mp 137–138 °C; UV λ_{max} 241 nm (ϵ 37500), 275 (11400), λ_{min} 265 nm (ϵ 10600) (neutral); UV λ_{max} 238.5 nm (ϵ 39500), 272.5 (10400), λ_{min} 265 nm (ϵ 9900) (alkaline); ^{1}H NMR δ ($CDCl_3$) 2.43 (6 H, s, CH_3), 2.56–3.31 (2 H, m, H-2′), 4.54 (2 H, m, H-5′), 4.91 (1 H, m, H-4′), 5.62 (1 H, m, H-3′), 6.32 (1 H, m, H-1′), 7.14–7.34 (4 H, aromatic H), 7.68–8.00 (5 H, m, aromatic H and H-6); ^{19}F NMR ϕ ($CDCl_3$) 94.31 (d, F-1′, $J_{F\text{-}1',H\text{-}6}$ = 1.9 Hz). Anal. ($C_{27}H_{23}Cl_2FN_2O_7$) C, H, Cl, F, N.

5-(2,2-Dichloro-1-fluorovinyl)-2′-deoxyuridine (12) and Its α Anomer (13). Compound **10** (436 mg, 0.75 mmol) was dissolved in methanol (30 mL) that had previously been saturated at 0 °C with ammonia, and the solution was kept at room temperature for 80 h. The solvent was evaporated off, and the residue was dissolved in water (20 mL). The solution was extracted with dichloromethane (5 × 20 mL), and the aqueous layer was lyophilized to give **5-(2,2-dichloro-1-fluorovinyl)-2′-deoxyuridine** (60 mg, 24% yield): UV λ_{max} 227 nm (ϵ 8800), 275.5 nm (10700), λ_{min} 249.5 (ϵ 6020) (neutral); UV λ_{max} 233.5 nm (ϵ 9330), 274.5 (7150), λ_{min} 256 nm (ϵ 5620) (alkaline); ^{1}H NMR δ 2.16 (2 H, m, H-2′), 3.60 (2 H, br d, H-5′), 3.84 (1 H, m, H-4′), 4.26 (1 H, br d, H-3′), 5.16 (2 H, m, OH-5′ and OH-3′), 6.12 (1 H, m, H-1′), 8.51 (1 H, d, H-6, $J_{H\text{-}6,F\text{-}1''}$ = 2.56 Hz), 11.60 (1 H, br d, NH); mass spectrum (EI), *m/e* 224 (base$^+$ + H, 25%), 189 (base$^+$ + H − Cl, 100), 154 (base$^+$ + H − 2Cl, 18), 146 (30), 117 (sugar$^+$, 63).

Compound **11** (180 mg, 0.31 mmol) was treated with methanolic ammonia in a similar way to give **5-(2,2-dichloro-1-fluorovinyl)-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)uracil** (50 mg, 47% yield): UV λ_{max} 224.5 nm (ϵ 10800), 277.5 (10400), λ_{min} 251.5 nm (ϵ 5510) (neutral); UV λ_{max} 275 nm (ϵ 8370), λ_{min} 258.5 nm (ϵ 6680) (alkaline); ^{1}H NMR δ 1.84–2.70 (2 H, m, H-2′), 3.58 (2 H, m, H-5′), 4.23 (2 H, m, H-3′ and H-4′), 4.81 (1 H, m, OH-5′), 5.24 (1 H, m, OH-3′), 6.06 (1 H, m, H-1′), 8.28 (1 H, d, H-6, $J_{H\text{-}6,F\text{-}1''}$ = 2.40 Hz), 11.52 (1 H, br d, NH); ^{19}F NMR ϕ 91.52 (d, F-1″, $J_{F\text{-}1'',H\text{-}6}$ = 2.40 Hz); mass spectrum (EI), *m/e* 224 (base$^+$ + H, 29%), 189 (base$^+$ + H − Cl, 100), 154 (base$^+$ + H − 2Cl, 16), 146 (26), 117 (sugar$^+$, 90), 99 (35), 73 (52), 45 (46).

(*E*)- and (*Z*)-5-(2-Chloro-1,2-difluorovinyl)-2′-deoxyuridine (15 and 16). 2′-Deoxy-5-iodouridine (3.54 g, 10 mmol) was converted into its trimethylsilyl derivative by dissolving it in dry pyridine (50 mL) and adding hexamethyldisilazane (13.9 mL, 66 mmol) and chlorotrimethylsilane (7.0 mL, 55 mmol) and allowing the reaction to proceed with stirring for 15 h at room temperature. Filtration of the resulting suspension and evaporation of the filtrate under reduced pressure gave the required trimethylsilyl derivative as a yellow oil. This was dissolved in ether, and to it was added a solution of butyllithium (18.8 mL, 1.6 M, 30 mmol) in hexane dropwise over 15 min at −70 °C. To the resulting yellow suspension there was added liquid chlorotrifluoroethene (5.8 g, 50 mmol); the reaction mixture, which turned red, was stirred at −70 °C for 1 h, then packed in solid CO_2, left for 4 days, and allowed to warm to room temperature, and then water (50 mL) was added. The aqueous layer was separated, neutralized with sulfuric acid (TLC showed the presence of three nucleoside derivatives), and evaporated to dryness. The residue was extracted with methanol, the insoluble material (lithium sulfate) was filtered off, and the filtrate was evaporated to dryness. The residue (3.05 g) was applied to a column of silica (300 g). Elution with chloroform–ethanol (9:1) removed traces of fast running material, and then elution with chloroform–ethanol (6:1) gave 2′-deoxy-5-(trimethylsilyl)uridine (200 mg, 7% yield): UV (ethanol) λ_{max} 267 nm (ϵ 8490), 205 (9550), λ_{min} 236 nm (ϵ 3440) (neutral); UV λ_{max} 263.5 nm (ϵ 6640), 222 (11000), λ_{min} 242.4 nm (ϵ 5230) (alkaline); ^{1}H NMR δ 0.16 [9 H, s, $Si(CH_3)_3$], 2.12 (2 H, m, H-2′), 3.56 (2 H, m, H-5′), 3.80 (1 H, m, H-4′), 4.24 (1 H, m, H-3′), 4.96 (1 H, m, OH-5′), 5.18 (1 H, m, OH-3′), 6.20 (1 H, m, H-1′), 7.72 (1 H, s, H-6), 11.08 (1 H, s, NH); mass spectrum (EI), *m/e* 300 (M^+, 3%), 184 (base$^+$ + H, 12), 169 (base$^+$ + H − CH_3, 100), 117 (sugar$^+$, 51), 99 (24), 73 (38). Anal. ($C_{12}H_{20}N_2O_5Si$) C, H, N.

Further elution of the column with the same solvent gave **5-(2-chloro-1,2-difluorovinyl)-2′-deoxyuridine** (202 mg, 6% yield) as a mixture of *E* and *Z* isomers: UV λ_{max} 216 nm (ϵ 9310), 275 (8810), λ_{min} 246 nm (ϵ 3780) (neutral); UV λ_{max} 230.5 nm (ϵ 9360), 273 (6950), λ_{min} 252 nm (ϵ 5030) (alkaline); ^{1}H NMR δ 2.15 (2 H, m, H-2′), 3.58 (2 H, m, H-5′), 3.80 (1 H, m, H-4′), 4.22 (1 H, m, H-3′), 5.05 (1 H, m, OH-5′), 5.17–6.09 (1 H, m, OH-3′), 8.39–8.49 (1 H, m, H-6), 11.70 (1 H, br d, NH); ^{19}F NMR ϕ 102.66 (d, F-2″, *E* isomer), 117.38 (d, F-2″, *Z* isomer), 122.13 (dd, F-1″, *E* isomer), 135.94 (dd, F-1″, *Z* isomer); $J_{F\text{-}1'',F\text{-}2''}$ = 6.5 Hz, $J_{H\text{-}6,F\text{-}1''}$ = 2.3 Hz. *E*/*Z* ratio = 1.4:1; mass spectrum (EI), *m/e* 324 (M^+, 1%), 99 (37), 73 (54), 45 (52). This product was separated into two components by HPLC on Spherisorb 50 μ ODS by elution with water–methanol (9:1). These components had identical mass spectra with the unfractionated material and were presumably the *E* and *Z* isomers, but they were not positively identified.

A third component was eluted from the column and identified as 2′-deoxyuridine (1.40 g, 61% yield), mp 160–161 °C.

A similar experiment to that described above was carried out, but bromotrifluoroethene was used instead of chlorotrifluoroethene. The products were 2′-deoxy-5-(trimethylsilyl)uridine (15% yield), 2′-deoxyuridine (38% yield), and 5-bromo-2′-deoxyuridine (19% yield) (identified by NMR and mass spectrometry).

2′-Deoxy-5-(perfluoroalkenyl)uridines. Similar reactions were carried out to those described for **15** and **16** but with the alkenes perfluoropropene, perfluorocyclohexene, and perfluorocyclopentene to give the following products. **(*E*/*Z*)-2′-Deoxy-5-(perfluoropropen-1-yl)uridine (17)**: 24% yield; UV λ_{max} 219 nm (ϵ 10600), 274 (ϵ 11900), λ_{min} 244.5 (ϵ 4450) (neutral); UV λ_{max} 227 nm (ϵ 14500), 273 (ϵ 8940), λ_{min} 253.5 nm (ϵ 6480) (alkaline); ^{1}H NMR δ 2.19 (2 H, m, H-2′), 3.59 (2 H, m, H-5′), 3.82 (1 H, m, H-4′), 4.23 (1 H, m, H-3′), 5.09 (1 H, m, OH-5′), 5.24 (1 H, m, OH-3′), 6.09 (1 H, m, H-1′), 8.59 (1 H, d, H-6, *E* isomer, $J_{H\text{-}6,F\text{-}1''}$ = 1.0 Hz), 11.82 (1 H, br d, NH); ^{19}F NMR ϕ 66.06 (dd, F-3″, *Z* isomer), 66.47 (dd, F-3″, *E* isomer), 132.71 (dqt, F-1″, *E* isomer), 165.91 (dqt, F-2″, *E* isomer); coupling constants for *E* isomer, $J_{F\text{-}1'',F\text{-}2''}$ = 12 Hz, $J_{F\text{-}1'',H\text{-}6}$ = 1.0 Hz; coupling constants for *Z* isomer not discernible; *E*/*Z* ratio = 8.1; mass spectrum (CI), *m/e* 376 (MNH_4^+, 100%), 358 (M^+, 9.41); mass spectrum (EI), *m/e* 243 (base$^+$ + 2H, 3), 242 (base$^+$ + H, 14), 117 (sugar$^+$, 100), 99 (21), 73 (31), 45 (29), 43 (18). Anal. ($C_{12}H_{11}F_5N_2O_5$) C, H, N. **2′-Deoxy-5-(perfluorocyclohexen-1-yl)uridine (18)** 9% yield; UV λ_{max} 205 nm (ϵ 8650), 275 (10500), λ_{min} 228.5 nm (ϵ 2780) (neutral); UV λ_{max} 227 nm (ϵ 7560), 275 (6710), λ_{sh} 258.0 nm (ϵ 6140), λ_{min} 238 nm (ϵ 5560) (alkaline); ^{1}H NMR δ 2.22 (2 H, m, H-2′), 3.60 (2 H, m, H-5′), 3.84 (1 H, m, H-4′), 4.26 (1 H, m, H-3′), 5.04 (1 H, m, OH-5′), 5.26 (1 H, d, OH-3′), 6.16 (1 H, m, H-1′), 8.40 (1 H, s, H-6), 11.90 (1 H, br d, NH); ^{19}F NMR ϕ 108.76 (2 F, br d, F-6″), 117.90 (3 F, br d, F-2″ and F-3″), 133.14 (4 F, br d, F-4″ and F-5″); mass spectrum (CI), *m/e* 488 (MNH_4^+, 45%), 470 (M^+, 3.5); mass spectrum (EI), *m/e* 355 (base$^+$ + 2H, 3), 354 (base$^+$ + H, 8.5), 117 (sugar$^+$, 100), 99 (17), 72 (26), 45 (21), 44 (11). **2′-Deoxy-5-(perfluorocyclopenten-1-yl)uridine (19)**: 7% yield; UV λ_{max} 262.5 nm (ϵ 10300), λ_{min} 232.5 nm (ϵ 5410) (neutral); UV λ_{max} 228.5 nm (ϵ 11100), 258.5 (6480), λ_{min} 246.5 nm (ϵ 6040) (alkaline); ^{1}H NMR δ 2.20 (2 H, m, H-2′), 4.06 (1 H, m, H-4′), 4.32 (1 H, m, H-3′), 4.74 (2 H, br d, H-5′), 5.36–5.68 (2 H, m, OH-5′ and OH-3′), 6.20 (1 H, m, H-1′), 7.60 (1 H, m, H-6), 11.32 (1 H, br d, NH); ^{19}F NMR ϕ 113.50 (2 F, m, F-5″), 115.19 (2 F, m, F-3″), 128.75 (2 F, m, F-4″), 159.88 (1 F, br d, F-2″); mass spectrum (EI), *m/e* 420 (M^+, 2.2%), 309 (100), 291 (7), 265 (25), 263 (9.5), 237 (6), 191 (10), 113 (30), 69 (32), 45 (43).

In all of these reactions, 2′-deoxy-5-(trimethylsilyl)uridine (5–10% yield) and 2′-deoxyuridine (~50% yield) were also produced.

Biological Activity. The antiviral activity of the 2′-deoxy-5-(fluoroalkenyl)uridines (**12**, **13**, and **15–19**), synthesized as described above, was determined by measuring the inhibition of virus-induced plaque formation in confluent monolayers of Vero (African green monkey kidney) cells infected with a number of strains of herpes simples virus type 1. The only compounds to

show activity when tested at concentrations up to 100 μg/mL were 5-(2,2-dichloro-1-fluorovinyl)-2′-deoxyuridine (12), which showed an ID_{50} of 26 μg/mL against the HFEM strain of the virus, and (*E*/*Z*)-5-(2-chloro-1,2-difluorovinyl)-2′-deoxyuridine (15 and 16), which showed an ID_{50} of 20–24 μg/mL against KOS, SC16, and HFEM strains. At none of the concentrations tested did either of these compounds cause destruction of the cell monolayer. Separation of the *E* and *Z* isomers (15 and 16) was accomplished on a small scale. One isomer showed an ID_{50} of 24 μg/mL against the HFEM strain of the virus, whereas the other isomer showed no activity even at 100 μg/mL. Simultaneously, standard compounds were assayed against the HFEM strain to give the following values for ID_{50}: arabinosyladenine, 21 μg/mL; acycloguanosine, 0.80 μg/mL; 2′-deoxy-5-iodouridine, 4.4 μg/mL; and (*E*)-5-(2-bromovinyl)-2′-deoxyuridine, 0.07 μg/mL.

The mixed isomers 15 and 16 were tested for inhibition of the multiplication of rapidly dividing Vero cells and MRC-5 (human diploid fibroblast) cells. With Vero cells an 18% reduction in cell growth was observed at 100 μg/mL, and with MRC-5 cells there was no observable effect upon cell proliferation at concentrations up to 200 μg/mL.

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Synthesis and Antiviral Activity of Certain Carbamoylpyrrolopyrimidine and Pyrazolopyrimidine Nucleosides

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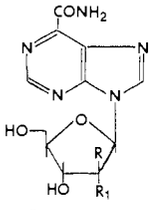
Following our recent discovery that 9-β-D-ribofuranosylpurine-6-carboxamide (1) exhibits potent antiviral activity, we were prompted to synthesize certain pyrrolopyrimidine and pyrazolopyrimidine nucleosides containing a carbamoyl function (**7a,b** and **13**). The key precursor, 7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-4-carbonitrile (**8a**), required for the synthesis of **7a** was prepared from the corresponding 4-chloro analogue (**4a**). Reaction of **4a** with methanethiol, followed by oxidation, gave the 4-methylsulfonyl derivative (**6a**), which with NaCN in DMF gave **8a**. Alkaline hydrolysis of **8a** provided **7a**. Similarly, **7b** was prepared from 4-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*] pyrimidine (**4b**) via the carbonitrile intermediate **8b**. Starting with thioformycin B or 7-chloro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine (**10**) and following the similar sequence of reactions, we obtained compound **13**. The in vitro antiviral studies of these carbamoyl and certain related nucleosides indicated **7a** to be a potent antiviral agent against vaccinia virus, whereas **13** was moderately active. 4-Chloro-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine was found to be one of the most active compounds against RVF, PICH, YF, and SF viruses in culture.

The introduction of a carbamoyl function at the 6-position of certain purine nucleosides resulted in compounds with significant antiviral efficacy.[1] 9-β-D-Ribofuranosylpurine-6-carboxamide (**1**) was found to be a po-



1: R = H, R_1 = OH

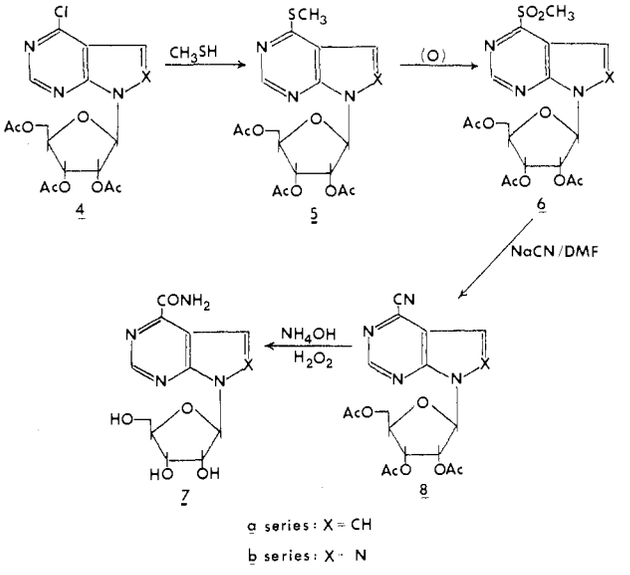
2: R = OH, R_1 = H

3: R = R_1 = H

tent, broad-spectrum antiviral agent.[1] Compound **1** inhibited the growth of Rift Valley fever (RVF) virus and Pichinde (PICH) virus to the extent of 90% at 250 μg/mL, and inhibition was nearly complete at 500 μg/mL. In an attempt to gain further insight into the nature of this antiviral potency, we recently reported[2] on the synthesis and biological activity of β-D-arabinosyl (**2**) and 2′-deoxy-β-D-ribosyl (**3**) analogues of **1**. This report describes the synthesis and antiviral activity of certain analogues of **1** modified at the aglycon portion.

Chemistry. Because of the natural occurrence of the 7-deazapurine ring system, e.g., in tubercidin, toyocamycin, sangivamycin, nucleoside Q and Q*, and their unusual biological properties, there has been a great deal of interest

Scheme I



a series: X = CH

b series: X = N

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