37 °C and was terminated by the addition of 0.5 mL of 0.5 M borate buffer, pH 10. The ^{14}C-labeled product was extracted into 6 mL of toluene–isoamyl alcohol (97:3). One milliliter of the organic layer was added to 10 mL of liquid scintillation cocktail, counted in a Nuclear-Chicago scintillation counter for 10 min, and quantitated in terms of the nanomoles of *N*-(methylphenyl)ethanolamine produced. Percent inhibition was determined by comparison of the quantity of *N*-(methylphenyl)-ethanolamine formed in the presence of various concentrations of test compound with controls. Concentrations causing 50% inhibition of PNMT (IC_{50}) were derived graphically from at least four such measurments, at least one of which produced less than 50% inhibition.

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Synthesis and Antiviral Properties of (*Z*)-5-(2-Bromovinyl)-2′-deoxyuridine

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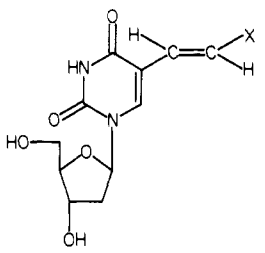
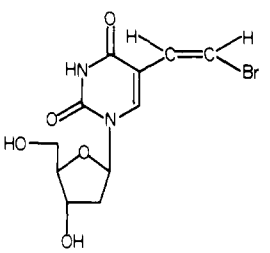
(*Z*)-5-(2-Bromovinyl)uracil was obtained by photoisomerization of the *E* isomer. Similarly, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine gave the required *Z* isomer. (*Z*)-5-(2-Bromovinyl)-2′-deoxyuridine is much less active against herpes simplex virus type 1 (HSV-1) and somewhat less active against herpes simplex virus type 2 than is the *E* isomer. Both isomers show similar activity against vaccinia virus. Therefore, the highly potent and selective activity of (*E*)-5-(2-bromovinyl)-2′-deoxyuridine against HSV-1 is due to its *E* configuration.

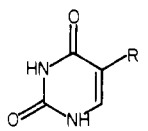
(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine (1) is a potent and



1, X = Br
3, X = CO_2H



2



4, R = C≡CBr
5, R = (*Z*)-CH=CHBr
6, R = CH=CH_2
7, R = C≡CH
8, R = (*E*)-CH=CHBr

selective inhibitory agent for herpes simplex virus type 1 (HSV-1).[1] The corresponding chloro and iodo compounds are only slightly less active, and (*E*)-5-(propen-1-yl)-2′-deoxyuridine and (*E*)-5-[3,3,3-(trifluoromethyl)propen-1-yl]-2′-deoxyuridine also show high activity.[2] These compounds have attached to the ethylenic double bond, a bulky group which is oriented trans with respect to the nucleoside residue. There have been no reports of the synthesis or antiviral activity of compounds in which these groups are in the cis orientation and so it seemed important to synthesize (*Z*)-5-(2-bromovinyl)-2′-deoxyuridine (2) and to determine its antiviral activity.

Compound 1 has been obtained from (*E*)-5-(2-carboxyvinyl)-2′-deoxyuridine (3) by treatment with *N*-bromosuccinimide in aqueous potassium acetate.[3] Originally, we found none of the corresponding *Z* isomer; a surprising result in view of the fact that in similar systems either the *Z* isomer is formed exclusively (i.e., in relatively nonpolar solvents) or a mixture of *Z* and *E* isomers is produced.[4-7] Upon completion of the present work it became apparent that in our system, however, about 8% of the *Z* isomer is formed.

To synthesize the required *Z* isomer (2), the first approach was to hydrogenate selectively 5-(bromoethynyl)-uracil (4) by the use of a quinoline-poisoned Lindlar palladium catalyst to obtain (*Z*)-5-(2-bromovinyl)uracil (5), which could then be converted into 2 by standard procedures. However, the major product was 5-vinyluracil (6). Since traces of 5-ethynyluracil (7) were detected as an intermediate in the reaction, it appeared that hydrogenolysis of the C–Br bond preceded the hydrogenation of the triple bond. Attempts to alter this situation by changing the solvent and the catalyst were unsuccessful.

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Table I. Antiviral Activity of Some 5-Substituted 2'-Deoxyuridines

virus[a]	min inhibitory concn, μg/mL[b]		
	Z isomer (2)[c]	E isomer (1)	IdUrd[d]
HSV-1 (KOS)	4	0.02	0.2
HSV-1 (McIntyre)	1	0.01	0.2
HSV-1 (F)	2	0.02	0.2
HSV-2 (Lyons)	4	0.4	0.2
HSV-2 (G)	2	0.7	0.4
HSV-2 (196)	4	0.4	0.4
vaccinia	4	4	0.1
vesicular stomatis	>200	>200	>200

[a] All cultures were assayed in primary rabbit kidney cell cultures. [b] Required to reduce virus-induced cytopathogenicity by 50%. [c] Contains 0.5% of the E isomer. [d] 2'-Deoxy-5-iodouridine.

The conditions for the bromination of (E)-5-(2-carboxyvinyl)-2'-deoxyuridine (3) were varied in order to obtain more of the Z isomer (2). When the reaction was carried out with bromine in acetone, the Z/E ratio of the products was 1:2, but, because only 30% of the starting material reacted, the yield of the Z isomer was low and the product was not isolated. It was also shown that a small amount (~8%) of the Z isomer was produced by the procedure previously reported.[3] The detection of this was due to the use of more sensitive techniques (e.g., reversed phase high-performance LC).

The most successful attempt to obtain the required compound was to photoisomerize the E isomer. When carried out on (E)-5-(2-bromovinyl)uracil (8), this process gave an additional component which was isolated and identified as (Z)-5-(2-bromovinyl)uracil (5). Definitive proof was provided by the ^{1}H NMR spectrum, which showed the coupling constant for the vinylic protons to be 7 Hz compared to 13 Hz for the E isomer. Application of this reaction to (E)-5-(2-bromovinyl)-2'-deoxyuridine gave the required Z isomer (2), the structure of which was also established by NMR spectroscopy. Under optimum conditions, the ratio of E/Z isomers in the mixture of products was 1:1. However, the irradiation caused considerable decomposition of the material, and so the yield of pure (Z)-5-(2-bromovinyl)-2'-deoxyuridine (2) was 27%. The final isolation and purification was carried out by HPLC.

The Z isomer was tested for activity against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) and against vaccinia and vesicular stomatis viruses in primary rabbit kidney cell cultures by the techniques previously reported.[1] The E isomer and 2'-deoxy-5-iodouridine (IdUrd) were included as reference materials.

The results (see Table I) show that the sample of the Z isomer was about 100 times less active against HSV-1 and about 10 times less active against HSV-2 than was the E isomer. HPLC analysis of this sample of the Z isomer showed that it contained about 0.5% of the E isomer, and this accounts for almost all of the activity against HSV-1. Both isomers were equally active against vaccinia virus and inactive against vesicular stomatis virus. It can be concluded, therefore, that (Z)-5-(2-bromovinyl)-2'-deoxyuridine has little, if any, activity against HSV-1; hence, the selectivity of the E isomer as an anti-HSV-1 agent depends upon its E configuration. Recent results show that the Z isomer has a much lower affinity than has the E isomer for HSV-1-induced thymidine kinase (Cheng et al., to be published) and this may account in part for these observations.

Experimental Section

Photoisomerizations were carried out in the absence of oxygen using a Hanovia 500-W medium-pressure UV lamp.

Action of Hydrogen on 5-(Bromoethynyl)uracil in the Presence of a Poisoned Lindlar Catalyst. 5-(Bromoethynyl)uracil (67 mg, 0.3 mmol), Lindlar catalyst (10 mg),[9] and quinoline (0.01 mL) in dry methanol were shaken at room temperature with hydrogen at atmospheric pressure. The reaction was monitored by TLC. After 7 h, two components were present, one identical (UV, TLC) with starting material and the other with 5-ethynyluracil. After 60 h, only one component was present. This was isolated (35 mg, 85% yield) and shown to be identical with 5-vinyluracil by comparison with an authentic specimen.[10]

(Z)-5-(2-Bromovinyl)uracil (5). (E)-5-(2-Bromovinyl)uracil (130 mg, 0.6 mmol) and benzophenone (26 mg) were dissolved in dry methanol (130 mL), and the solution was irradiated at 40–50 °C for 30 min [TLC of the reaction mixture in $CHCl_3$/MeOH (19:1) showed the presence of starting material (R_F 0.33) and a faster component (R_F 0.38)]. The reaction mixture was evaporated to dryness, and the residue (~70 mg) was separated by chromatography in $CHCl_3$/MeOH (19:1) on a plate of Whatman PLK 5F silica. After eight developments, the components were eluted with methanol. The slower component was the starting material (21 mg): UV (MeOH) λ_{max} 250 nm, 291; λ_{min} 270 nm; NMR [$(CD_3)_2SO$] δ 6.75 (1 H, d, vinylic H, J = 13 Hz), 7.12 (1 H, d, vinylic H, J = 13 Hz), 7.72 (1 H, d, H-6). The faster component was 5 (20 mg): UV (MeOH) λ_{max} 242 nm (ε 9513), 293 (7203); λ_{min} 268 nm (ε 4741); NMR [$(CD_3)_2SO$] δ 6.38 (1 H, d, vinylic H, J = 7 Hz), 6.90 (1 H, d, vinylic H, J = 7Hz), 8.20 (1 H, s, H-6).

(Z)-5-(2-Bromovinyl)-2'-deoxyuridine (2). (E)-5-(2-Bromovinyl)-2'-deoxyuridine (260 mg, 0.78 mmol) and benzophenone (52 mg) were dissolved in dry methanol (175 mL) and irradiated at 40–50 °C for 30 min. The solution was evaporated to dryness and fractionated by preparative HPLC on ODS silica, 40–63 μm (100 × 2.5 cm column), using a gradient of MeOH/H_2O (1:4, 1.5 L) to MeOH/H_2O (4:1, 1.5 L) and collecting 30-mL fractions. Evaporation to dryness of fractions 41–46 gave 2 (70 mg, 27% yield): UV (EtOH) λ_{max} 234 nm (ε 11 904), 295 (8040); λ_{min} 264 nm (ε 3608); NMR (CD_3OD) δ 2.27 (2 H, t, H-2'), 3.63 (2 H, m, H-5'), 3.85 (1 H, m, H-4'), 4.30 (1 H, m, H-3'), 6.25 (1 H, t, H-1'), 6.45 (1 H, d, vinylic H, J = 8 Hz), 6.88 (1 H, d, vinylic H, J = 8 Hz), 8.57 (1 H, s, H-6). Anal. ($C_{11}H_{13}BrN_2O_5 \cdot 0.5H_2O$) C, H, N.

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