structure was refined further with anisotropic heavy atoms (C, N, and O) and isotropic hydrogen atoms to convergence at R = 0.043. At this point, analysis of the agreement between calculated and observed structure factors suggested the presence of secondary extinction ($F_c > F_o$), which affected the strongest low-order reflections: the (20-4), (200), and (202) reflections (with $\sin\theta/\lambda \leq 0.131$ Å^{-1}). Correction for secondary extinction and a final cycle of refinement produced the residuals R = 0.036 and weighted R = 0.047 by using the 1952 observed reflections. The final difference map showed no significant peaks.

Computer programs used were from the CRYSNET package.[27] The full-matrix least-squares program was UCLALS4,[28] modified by H. L. Carrell.[29] Other programs for the structural solution and plotting (VIEW and DOCK) were developed at the Institute for Cancer Research.[30] The atomic scattering factors used for oxygen, nitrogen, and carbon atoms[31] and for hydrogen atoms are listed in the literature.[32] Final positional and thermal parameters are listed in Table I. Lists of calculated and observed structure factors are available (see paragraph at end of paper regarding supplementary material).

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Registry No. Metyrapone, 54-36-4; cytochrome P-450, 9035-51-2.

Supplementary Material Available: Lists of calculated and observed structure factor amplitudes (9 pages). Ordering information is given on any current masthead page.

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Structural Requirements of Olefinic 5-Substituted Deoxyuridines for Antiherpes Activity†

John Goodchild,*,‡ Roderick A. Porter,‡ Robert H. Raper,§ Iain S. Sim,§ Roger M. Upton,‡ Julie Viney,‡ and Harry J. Wadsworth‡

Departments of Chemistry and Biology, Searle Research and Development, Division of G.D. Searle and Co. Ltd., High Wycombe, Buckinghamshire, United Kingdom. *Received January 31, 1983*

A number of structurally related 5-substituted pyrimidine 2′-deoxyribonucleosides were synthesized and tested for antiviral activity against herpes simplex virus type 1 (HSV-1) in cell culture. A minimum inhibitory concentration was determined for each compound, and from a comparison of these values a number of conclusions were drawn with regard to those molecular features that enhance or reduce antiviral activity. Optimum inhibition of HSV-1 in cell culture occurred when the 5-substituent was unsaturated and conjugated with the pyrimidine ring, was not longer than four carbon atoms in length, had *E* stereochemistry, and included a hydrophobic, electronegative function but did not contain a branching point. Such features are contained in (*E*)-5-(2-bromovinyl)-2′-deoxyuridine, which was the most active of the compounds described.

Attempts to identify chemical antiviral agents that allow the effective and safe control of virus diseases of man have been largely unsuccessful. However, a number of nucleoside analogues are known that inhibit herpes simplex virus (HSV) replication.[1,2] The extent to which these inhibit virus growth without causing cellular toxicity reflects their degree of selectivity in reacting with virus-specific functions rather than interfering with cellular metabolism. There is evidence that the mechanism of action of these nucleoside analogues involves virus-coded enzymes important in DNA replication, and the exploitation of differences between virus-specific enzymes and the corresponding host cell enzymes provides a promising strategy in the search for more effective and less toxic antiherpes drugs.

The mechanism of action of the known antiviral nucleosides is, in many cases, not clearly defined. It has been proposed that some may interact with the virus-coded DNA polymerase[3-5] either as substrates or inhibitors, while others inhibit thymidylate synthetase.[6] However, such

† This work was first presented at the North American Medicinal Chemistry Symposium, June 1982.
‡ Department of Chemistry.
§ Department of Biology.

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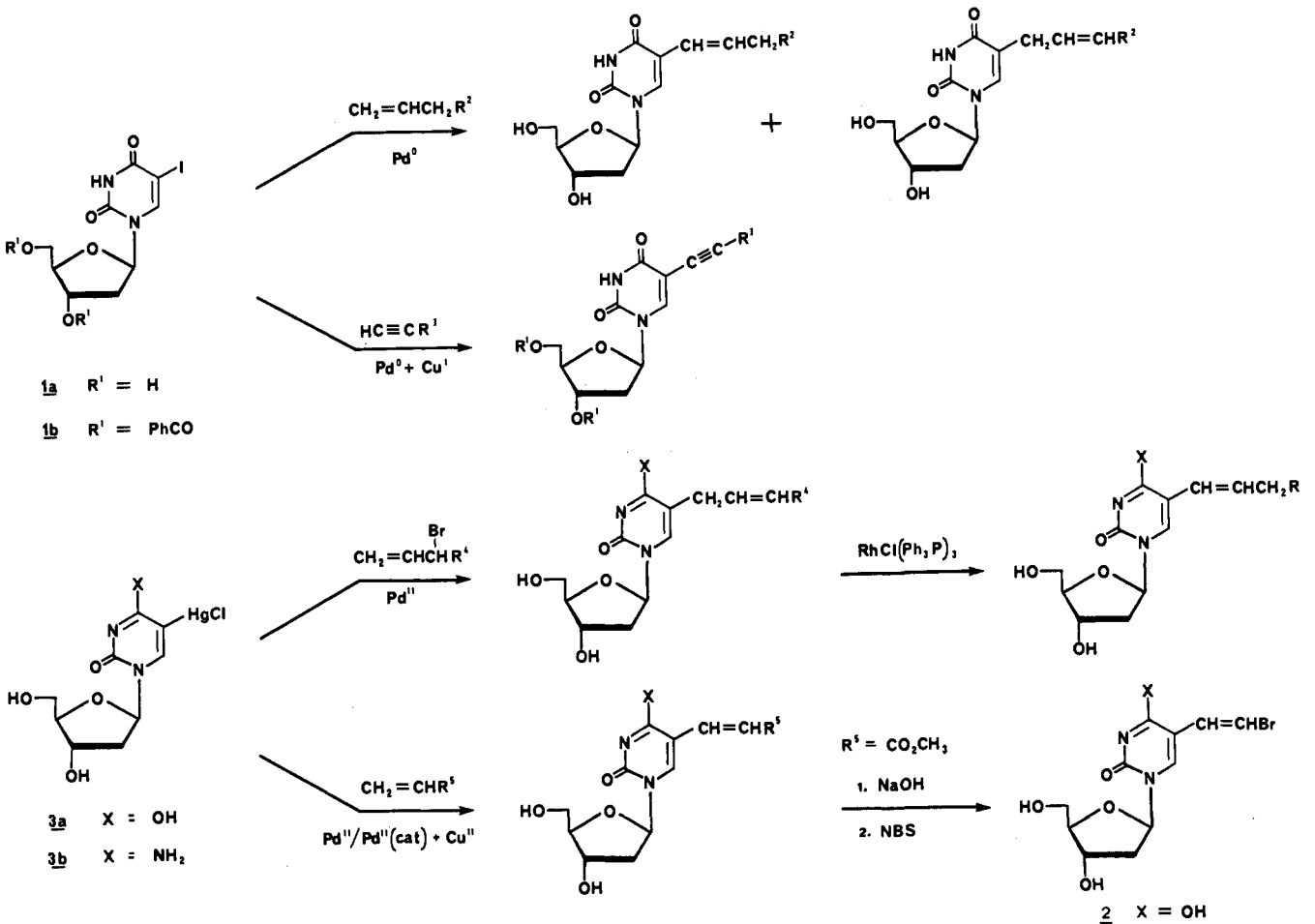
Scheme I



interactions require that the compounds first be phosphorylated. This is best accomplished intracellularly, since nucleotides are inefficiently taken up by cells and, therefore, have little potential for therapeutic use.[7,8] Certain herpes viruses, such as HSV and Varicella-Zoster virus (VZV), code for a unique thymidine kinase[9,10] that increases the ability of infected cells to phosphorylate thymidine compared with uninfected cells. Consequently, analogues of thymidine are potentially more active as antimetabolites in such virus-infected cells than in uninfected cells and those compounds that interact specifically with herpes virus induced, but not host cell, thymidine kinase would be expected to exhibit a high degree of selectivity of drug action.

The thymidine kinase of HSV type 1 (HSV-1) is particularly tolerant of pyrimidines substituted at the 5-position of the base, and many such compounds show antiherpes activity. 5-Iodo-2′-deoxyuridine (IDU, **1a**) inhibits HSV-1 replication and is used in certain clinical situations, but it has the disadvantage of being phosphorylated in uninfected cells, is toxic, and may be mutagenic and teratogenic (for review, see ref 11). (*E*)-5-(2-Bromovinyl)-2′-deoxyuridine (BVDU, **2**) is a better inhibitor of HSV-1 than is IDU,[12,13] and, with a high affinity for HSV thymidine kinase and a low affinity for the corresponding cell enzyme,[14] it is more selective in its action. Many of the substituents introduced at the 5-position of deoxyuridine that result in antiherpes activity are either unsaturated or electronegative or both. This paper reports the antiherpes activity of a series of pyrimidine 2′-deoxynucleosides with unsaturated substituents at the 5-position (Table I). Certain features in these substituents are identified as promoting antiviral activity.

Chemistry. One of the most useful methods for the introduction of unsaturated substituents into the 5-position of pyrimidines is by a modification of the Heck reaction.[15] This involves the palladium-catalyzed addition of alkenes or alkynes to either 5-halogenated (e.g., **1**) or 5-mercuri (e.g., **3**) derivatives, the former generally requiring harsher reaction conditions. In agreement with the results of Bergstrom et al.,[16] we have found this reaction to be most effective with alkenes having an electron-withdrawing substituent or a leaving group in an allylic position. Although the latter case produces 2-alkenyl substituents (Scheme I), isomerization to the conjugated product is

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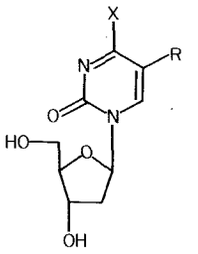
Table I. Physical Characteristics and Antiviral Activity of 5-Substituted Deoxypyrimidine Nucleosides



no.	X	R	mp, °C	recrystn solvent	UV λ_{max}, nm	NMR J,[a] Hz	formula	anal.	MIC, μg/mL
2	OH	(*E*)-CH=CHBr[b]	141–143	H_2O	296	17	$C_{11}H_{13}BrN_2O_5$	C, H, N, Br	0.005
4	OH	(*Z*)-CH=CHBr[c]			230, 291[d]	8	$C_{11}H_{13}BrN_2O_5$		0.1
5	OH	CH=CBr_2[e]	184.5–185	CH_3CN	295		$C_{11}H_{12}Br_2N_2O_5$	C, H, N, Br	0.1
6	OH	(*E*)-CH=CHSCH$_3$	219–220	MeOH	271, 322	16	$C_{12}H_{16}N_2O_5S$	C, H, N, S	0.5
7	OH	(*E*)-CH=CHCN	>310	MeOH	275 (sh), 301	18	$C_{12}H_{13}N_3O_5$	C, H, N	>25
8	OH	(*E*)-CH=CHCO$_2$CH$_3$	168–170	H_2O	304	16	$C_{13}H_{16}N_2O_7$	C, H, N	10
9	OH	$CH_2CH=CH_2$[f]	124.5–126	CH_3CN	269		$C_{12}H_{16}N_2O_5$	C, H, N	100
10	OH	(*E*)-CH=CHCH$_3$[f]	191–192	CH_3CN	292	16	$C_{12}H_{16}N_2O_5$	C, H, N	0.5
11	OH	(*Z*)-CH=CHCH$_3$	171.5–173.5	H_2O/MeOH	286	11	$C_{12}H_{16}N_2O_5$	C, H, N	100
12	OH	C≡CCH$_3$	181–182	H_2O	228, 293		$C_{12}H_{14}N_2O_5$	C, H, N	1
13	SH	(*E*)-CH=CHCH$_3$	117–118	CH_3CN/H_2O	277, 351	16	$C_{12}H_{16}N_2O_4S$	C, H, N	100
14	NH_2	(*E*)-CH=CHCH$_3$[f]	197–201	CH_3CN/CH_3OH	295	15	$C_{12}H_{17}N_3O_4$	H, N; C[g]	50
15	NH_2	(*Z*)-CH=CHCH$_3$	161.5–162.5	CH_3CN/MeOH	290	11	$C_{12}H_{17}N_3O_4$	H, N; C[h]	>100
16	OH	$CH_2C(Cl)=CH_2$	79–81	CH_3CN	270		$C_{12}H_{15}ClN_2O_5$	C, H, N, Cl	50
17	OH	(*E*)-C(CH$_3$)=CHBr	130–131 dec	H_2O	235, 285		$C_{12}H_{15}BrN_2O_5$	C, H, N, Br	0.1
18	OH	(*E*)- + (*Z*)-CH=C(Br)CH$_3$	194–196	H_2O	233, 293		$C_{12}H_{15}BrN_2O_5$	C, H, N, Br	1
19	OH	(*E*)-C(CH$_3$)=CHCl	148–149	H_2O	234, 285		$C_{12}H_{15}ClN_2O_5$	C, H, N, Cl	>100
20	OH	(*E*)-C(CH$_3$)=CHCO$_2$CH$_3$	178–179	H_2O	260 (sh), 296		$C_{14}H_{18}N_2O_7$	C, H, N	>100
21	OH	(*E*)-CH=C(CH$_3$)CO$_2$CH$_3$	181–182	H_2O	263, 302		$C_{14}H_{18}N_2O_7$	C, H, N[i]	>100
22	OH	(*E*)- + (*Z*)-CH_2CH=CHCH$_3$[j]	149–150	CH_3CN	270	ND[p]	$C_{13}H_{18}N_2O_5$	C, H, N	10
23	OH	(*E*)-CH=CHCH$_2$CH$_3$	189–190.5	H_2O	295	16	$C_{13}H_{18}N_2O_5$	C, H, N	0.5
24	OH	$CH_2CH_2CH_2CH_3$[k]	121	CH_3CN	270		$C_{13}H_{20}N_2O_5$	H, N; C[l]	10
25	OH	C≡CCH_2CH_3[m]	180–181	H_2O	230, 293		$C_{13}H_{16}N_2O_5$	H, N; C[n]	10
26	OH	CH=C(CH$_3$)$_2$	208–209	CH_3CN	233, 290		$C_{13}H_{18}N_2O_5$	C, H, N	>50
27	OH	(*E*)-C(CH$_3$)=CHCH$_3$	160–164	H_2O	279		$C_{13}H_{18}N_2O_5$	C, H, N	50
28	OH	(*Z*)-C(CH$_3$)=CHCH$_3$	152–155	H_2O	273		$C_{13}H_{18}N_2O_5$	C, H, N	>100
29	OH	(*E*)-CH=CHCH$_2$CH$_2$CH$_3$	129–130	H_2O	241, 296	16	$C_{14}H_{20}N_2O_5$	C, H, N	>100
30	OH	(*E*)-CH=CHCH$_2$CH$_2$CH$_2$CH$_3$[o]	138–140	H_2O/MeOH	241, 297	16	$C_{15}H_{22}N_2O_5$	C, H, N	>100
31	OH	(*E*)-CH=CHC(CH$_3$)$_3$	150–152	H_2O	239, 294	16	$C_{15}H_{22}N_2O_5$	C, H, N	>10
32	OH	(*E*,*E*)-CH=CHCH=CHCO$_2$CH$_3$	188 dec	MeOH	330	15, 15	$C_{15}H_{18}N_2O_7$	C, H, N	>100

[a] Coupling constants for vinyl protons in R. [b] See ref 18. [c] This material was a gift from Prof. A. S. Jones; see ref 19. [d] Values reported in the literature[19] are 234, 295 nm. [e] Perman, J.; Sharma, R. A.; Bobek, M. *Tetrahedron Lett.* 1976, 2427–2430. [f] See ref 17. [g] C: calcd, 53.92; found, 53.42. [h] C: calcd, 53.92; found, 53.39. [i] Anal. correct for $^1/_2$ H_2O. [j] See ref 16. [k] Szabolcs, A.; Sagi, J.; Otvos, L. *J. Carbohydr., Nucleosides, Nucleotides* 1975, 2, 197–211. [l] C: calcd, 54.92; found, 54.39. [m] Robins, M. J.; Barr, P. J. *Tetrahedron Lett.* 1981, 22, 421–424. [n] C: calcd, 55.71; found, 55.19. [o] Vincent, P.; Beaucourt, J. P.; Pichat, L. *Tetrahedron Lett.* 1982, 23, 63–64. [p] ND = not done.

Table II. Synthesis of 5-Substituted Deoxypyrimidine Nucleosides

product	starting materials[a]	method (equivalents of catalyst[a])	reaction time, h	yield, %
7	3a + CH_2=CHCN (7.0)	A (1.0)	12	16[b]
8	3a + CH_2=$CHCO_2CH_3$ (5.0)	A (0.25) + $CuCl_2$ (1.0)	3	60[b]
9	3a + CH_2=$CHCH_2Cl$ (9.5)	A (0.5)	0.5	71[c]
10	9	D (0.14)	16	29[b]
12	1b + CH≡CCH_3 (excess)	C (0.25) + CuI (0.1)	7	60[c]
14, 15	3b + CH_2=$CHCH_2Cl$ (8.4)	A (0.44) + $CuCl_2$ (1.1) and D (0.1)	3, 16	23[b], 40[b]
16	3a + CH_2=$C(Cl)CH_2Cl$ (9.0)	A (1.0)	24	21[c]
20	3a + CH_3CH=$CHCO_2CH_3$ (9.0)	A (1.0) + $CuCl_2$ (1.0)	96	21[b]
21	3a + CH_2=$C(CH_3)CO_2CH_3$ (4.5)	A (1.0)	16	63[c]
22	3a + CH_2=$CHCH(Cl)CH_3$ (9.0)	A (0.25)	0.5	58[c]
23	22	D (0.1)	16	12[b]
25	1b + CH≡CCH_2CH_3 (excess)	C (0.25) + CuI (0.05)	9	28[c]
26	3a + CH_2=$C(CH_3)CH_2Cl$ (9.5)	A (0.3) and D (0.15)	4, 16	30,[d] 61[c,e]
27, 28	3a + CH_3CH=$CHCH_2Cl$ (8.7)	A (0.2) and D (0.1)	0.5, 16	51,[d] 18[c,e]; 42[c,d]
29	3a + CH_2=$CHCH(OTs)CH_2CH_3$ (5.3)	A (0.25) and D (0.1)	2.5, 18	80,[d] 36[c,e]
29	1a + CH_2=$CHCH_2CH_2CH_3$ (5.0)	B (0.1)	12	25[c]
30	1a + CH_2=$CH(CH_2)_3CH_3$ (16)	B (0.1)	2	15[c]
31	1a + CH_2=$CHC(CH_3)_3$ (12)	B (0.08)	48	16[d]
32	2 + CH_2=$CHCO_2CH_3$ (3.7)	*f* (0.05)	2.5	55[c]

[a] Figures in parentheses are equivalents of reagent and catalyst to 1 equiv of nucleoside. [b] Yield after recrystallization. [c] Yield after chromatography. [d] Yield for first stage of the preparation. [e] Yield for second stage of the preparation. [f] For method see text.

readily carried out with Wilkinson's catalyst.[17] Most of the compounds under study were prepared by such palladium-catalyzed reactions, which are summarized in Table II. 5-(4-Carbomethoxybuta-1,3-dienyl)-2′-deoxyuridine (**32**) was synthesized by the analogous reaction of the vinyl bromide (**2**) and methyl acrylate. Those compounds with vinyl halide substituents, i.e., BVDU (**2**) and the methyl derivatives (**17–19**), were prepared from the corresponding acrylate esters by hydrolysis–halogenation procedures.[18] A Wittig reaction on 5-formyl-2′-deoxyuridine gave the (*E*)-5-[2-(methylthio)vinyl]-2′-deoxyuridine (**6**).

The stereochemical assignments of the compounds in Table I have been made, where appropriate, from ^{1}H NMR and UV data. The disubstituted alkenes **2**, **6–8**, **10**, **14**, **23**, and **29–32** have coupling constants for the olefinic protons of J = 16–18 Hz and have been assigned the *E* stereochemistry. Several isomeric compounds, **4**, **11**, and **15**, with J = 8–11 Hz are of the *Z* configuration. In order to ascertain the geometry of the trisubstituted alkenes, nuclear Overhauser enhancements (NOE) of the various side-chain protons were determined during irradiation of the base proton H-6. The occurrence of positive NOE effects on the vinyl protons of **17**, **19**, **20**, and **27** and on the methyl group of **21** indicated that these were *E* isomers, while a positive NOE effect on the terminal methyl group of **28** indicated that this was the *Z* isomer.

Further structural information for the 5-(substituted-alkenyl)pyrimidine nucleosides has been gained from λ_{max} values. A substituent in conjugation with the pyrimidine ring results in a bathochromic shift of >20 nm relative to either the parent nucleoside or its 5-alkyl derivatives [compare 5-(1-butenyl)-2′-deoxyuridine (**23**), λ_{max} 295 nm, with 5-(2-butenyl)-2′-deoxyuridine (**22**), λ_{max} 270 nm, and 5-butyl-2′-deoxyuridine (**24**), λ_{max} 270 nm]. In addition, the λ_{max} of *E* isomers are approximately 5 nm greater than those of the *Z* isomers (compare **2** and **4**, **10** and **11**, **14** and **15**, and **27** and **28**, Table I). These observations are viewed in terms of steric interactions in the *Z* isomers between either the 2-bromo or 2-methyl groups and the pyrimidine ring atoms which prevent the side chain adopting a conformation coplanar with the ring. The consequent reduction in the extent of conjugation is reflected in the reduced λ_{max} values.

Results and Discussion

The compounds were tested for antiviral activity against HSV-1 in a microplaque reduction assay. The antiviral activities of **2**, **4**, **9**, and **10** have already been reported,[12,19–21] and **2** is the most effective inhibitor of HSV-1 replication in cell culture so far described. The minimum inhibitory concentration (MIC) for each compound is shown in Table I. For comparison, **1a** has an MIC of 0.5 μg/mL against HSV-1 in the test system employed here. An analysis of the results of the antiviral evaluations indicated that certain features were required in the substituent of 5-modified deoxyuridines for optimum antiherpes activity, whereas other features were undesirable. Those features enhancing or reducing antiviral activity are as follows.

(1) Conjugation. There was a considerable increase in antiviral activity against HSV-1 when the double bond in the side chain of **9** or **22** was brought into conjugation with the pyrimidine ring, as in **10** and **23**, respectively. The saturated butyl derivative **24** had similar anti-HSV-1 activity to the nonconjugated alkene **22**. A similar effect is also seen with the saturated propyl (not shown here), which is less active than the conjugated alkene **10**.[6] The propyne (**12**) showed no additional advantage over the propene (**10**) against HSV-1, with a minimal difference in MICs, but the butyne (**25**) was significantly less active than the butene (**23**).

(2) Chain Length. In a homologous series of side chains from propene to hexene, it was observed that extending the side chain longer than four carbons caused a

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sharp cutoff in antiviral activity. In vitro, the propene (**10**) and butene (**23**) were equally effective against HSV-1, while the pentene (**29**) and hexene (**30**) were without antiviral activity at the maximum concentration tested. Extension of the side chain in **8** by another vinyl group to give **32** also resulted in a loss of antiviral activity.

(3) *E*/*Z* Isomerization. In all four cases where both *E* and *Z* isomers of a compound were tested, the *E* isomer was more active against HSV-1 than the *Z* isomer. This was true for both antiviral deoxyuridines (compare **2** with **4**, **10** with **11**, and **27** with **28**) and deoxycytidines (compare **14** and **15**) and was particularly marked in the case of **10** and **11**.

(4) Substitution of Br in Compound 2. Replacement of the bromine in **2** with either nitrile (**7**) or methyl (**10**), both of which have a smaller molar refraction (an estimate of steric bulk) than bromine, failed to afford a more inhibitory compound. If, in this instance, size is not a constraint on antiviral activity, then other properties of bromine, not shared with nitrile or methyl, may also be important in conferring antiviral properties on the substituted nucleoside. In particular, the hydrophobicity and inductive effects of bromine may be important. The reduced antiviral activity of **7** compared with **2** may be due to the hydrophilic nature of nitriles, and it is worthy of note that the use of the less hydrophobic halogen chlorine gave a less active antiviral compound than **2**.[22] The superior activity of **2** compared with **10** cannot be readily explained in terms of hydrophobic properties, methyl and bromine being very similar in this respect, but may be attributable to the inductive property of bromine not found with methyl. While the greater size of thiomethyl (**6**) and methoxycarbonyl (**8**) may be of prime importance in limiting their antiviral activity compared with **2**, the superior activity of **6** compared to **8** may be because of the hydrophobic nature of the former.

(5) Branching. The antiviral activity of **10** was substantially reduced when either of the olefinic carbon atoms in the side chain were methylated (see **26** and **27**) or when the terminal carbon was a branching point (**31**). Methylation of either olefinic carbon in **8** produced a similar effect (see **20** and **21**). The introduction into **2** of vinyl methyl groups was not advantageous in that **17** was less active than **2** and, similarly, **19** was less active than the equivalent (*E*)-5-(2-chlorovinyl)-2′-deoxyuridine.[22] A mixture of *E* and *Z* isomers of the 2-methylated derivative **18** was less active than either isomer (**2** and **4**) of the parent compound. The introduction of a second bromine atom (**5**) resulted in a compound that was less active than the monohalogenated *E* isomer **2** but more active than **18**, whose bromo and methyl groups should have very similar steric requirements to the two bromine atoms. The antiviral activity of **5** might, therefore, reflect the opposing effects of the electronic properties (beneficial) of the second bromine atom and its steric requirements (deleterious).

(6) Replacement of O at C-4 in Compound 10. 5-Substituted deoxycytidine derivatives have not been investigated as antiherpes compounds to the same extent as deoxyuridines. Although some have been found to be as inhibitory toward HSV-1 as their deoxyuridine equivalents, this is not always the case.[23] Here we found that 5-propenyl-2′-deoxycytidine (**14**) was less active than the corresponding compound (**10**) in the deoxyuridine series. The 4-thiouracil derivative (**13**) was less active than either the uracil or cytosine analogues.

Experimental Section

Melting points were determined on an Electrothermal apparatus and are not corrected. Ultraviolet spectra were recorded in methanol with a Pye-Unicam SP1800 spectrophotometer. All compounds were characterized by NMR on a Varian FT80A instrument and by chemical-ionization mass spectrometry on a Finnigan 4000 instrument and have elemental analysis correct to within ±0.4% unless stated otherwise. Nuclear Overhauser experiments were carried out on a Bruker WM250 instrument. Compounds were prepared according to general methods (A–D) or specific methods described.

Method A. (*E*)-5-(2-Carbomethoxy-2-methylvinyl)-2′-deoxyuridine (21). Methyl methacrylate (1 mL, 9.35 mmol), **3a**[24] (1 g, 2.15 mmol), and a 0.1 M methanolic solution of Li_2PdCl_4 (22 mL, 2.2 mmol) [together with copper(II) chloride where indicated in Table II] were stirred together at room temperature for 16 h. Hydrogen sulfide was passed through the solution for 1–2 min, followed by nitrogen (to remove excess H_2S), and the precipitated metal sulfides were removed by filtration through Celite. The filtrate was basified with methanolic ammonia and filtered, and then the filtrate was concentrated under vacuum. The product was chromatographed on silica in $CHCl_3$/EtOH to give **21** (0.70 g, 63%), which crystallized from water, mp 181–182 °C. Anal. ($C_{14}H_{18}N_2O_7 \cdot {}^1/_2H_2O$) C, H, N.

Method B. (*E*)-5-(3,3-Dimethyl-1-butenyl)-2′-deoxyuridine (31). Compound **1a** (500 mg, 1.41 mmol), palladium(II) acetate (25 mg, 0.11 mmol), triethylamine (0.7 mL, 5 mmol), 3,3-dimethyl-1-butene (2 mL, 16.83 mmol), and CH_3CN (10 mL) were heated at 100 °C in a steel pressure reactor for 48 h. The palladium residues were removed by centrifugation, and the supernatant was evaporated under vacuum and purified on a column of ODS reverse-phase silica by using a gradient of 10–20% methanol in water. This gave 70 mg (16%) of **31**, which was crystallized from water to give an analytically pure sample, mp 150–152 °C. Anal. ($C_{15}H_{22}N_2O_5$) C, H, N.

Method C. 5-(1-Propynyl)-2′-deoxyuridine (12). Propyne gas was slowly bubbled through a vigorously stirred mixture of 3′,5′-di-*O*-benzoyl-5-iodo-2′-deoxyuridine (prepared from **1a** and 2.0 equiv of benzoyl chloride by conventional means;[25] 500 mg, 1 mmol), $Pd(PPh_3)_4$ (100 mg, 0.25 mmol), and CuI (60 mg, 0.10 mmol) in Et_3N (200 mL) at 25 °C for 7 h. The solvent was evaporated under vacuum, and the residue was refluxed with NaOMe (540 mg, 10 mmol) in MeOH for 30 min. The solution was neutralized with Dowex 50W-X8 (H^+) ion-exchange resin, and the product was chromatographed on ODS reverse-phase silica (0–30% methanol in water gradient) to give 160 mg (60%) of **12**. Crystallization from water gave an analytically pure sample, mp 181–182 °C. Anal. ($C_{12}H_{14}N_2O_5$) C, H, N.

Method D. Preparation of (*E*)-5-(1-Propenyl)-2′-deoxyuridine (10) by Isomerization of Compound 9. Compound **9**[17] (1.3 g, 4.86 mmol) and $RhCl(PPh_3)_3$ (prepared by the method of Bennett and Longstaff;[26] 278 mg, 0.7 mmol) were refluxed in EtOH (50 mL) for 16 h. The solvent was evaporated under vacuum, and the residue was crystallized from CH_3CN to give 364 mg (29%) of **10**: mp 191–192 °C. Anal. ($C_{12}H_{16}N_2O_5$) C, H, N.

(*E*)-5-(2-Bromo-1-methylvinyl)-2′-deoxyuridine (17). An aqueous solution of sodium hydroxide (0.1 M) was added dropwise to a solution of **20** (0.61 g, 1.87 mmol) in water (30 mL) until no starting material remained by TLC. The solution was neutralized with AcOH and then heated to 70 °C. *N*-Bromosuccinimide (0.33 g, 1.85 mmol) was added in portions over 30 min to the hot stirred solution. The reaction mixture was cooled and evaporated to dryness, and the product was chromatographed on silica in

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$CHCl_3$/EtOH (6:1). Recrystallization from water gave 91 mg (15%) of **17** as pale yellow plates, mp 130–131 °C dec. Anal. ($C_{12}H_{15}BrN_2O_5$) C, H, N, Br.

Compound **18** was prepared by the above procedure from compound **21** (500 mg, 1.5 mmol): yield of **18** after recrystallization from water 65 mg (13%); mp 194–196 °C. Anal. ($C_{12}H_{15}BrN_2O_5$) C, H, N, Br.

Compound **19** was prepared by a similar method from **20** (2.0 g, 6.1 mmol) and *N*-chlorosuccinimide (1.06 g, 8 mmol): yield of **19** after recrystallization from water 307 mg (16%); mp 148–149 °C. Anal. ($C_{12}H_{15}ClN_2O_5$) C, H, N, Cl.

5-(2,2-Dibromovinyl)-2′-deoxyuridine (5). A solution of bromine in DMF was added dropwise to a solution of **2** (156 mg, 0.48 mmol) in DMF (2 mL) at 5 °C until TLC showed that no starting material remained. The solution was then heated at 100 °C for 25 min, the solvent was removed under vacuum, and the product was purified on silica in $CHCl_3$/EtOH to give **5**: yield 83 mg (42%). Recrystallization from CH_3CN gave an analytically pure sample, mp 184.5–185 °C. Anal. ($C_{11}H_{12}Br_2N_2O_5$) C, H, N, Br.

(*E*)-5-[2-(Methylthio)vinyl]-2′-deoxyuridine (6). A solution of [(methylthio)methyl]triphenylphosphonium chloride[27] (1.23 g, 3.44 mmol) in dry MeOH (4 mL) under nitrogen was treated with a freshly prepared 0.8 M methanolic solution of NaOMe (4.7 mL, 3.44 mmol) at 20 °C to give a white precipitate. To this was added a solution of 3′,5′-di-*O*-acetyl-5-formyl-2′-deoxyuridine[28] (508 mg, 1.72 mmol) in MeOH (5 mL), and the reaction was stirred for 15 h. After neutralization with Dowex 50W-X8 (H^+) ion-exchange resin, the solution was concentrated under vacuum when the product separated as crystals. Recrystallization from MeOH gave **6**: yield 311 mg (60%); mp 219–220 °C. Anal. ($C_{12}H_{16}N_2O_5S$) C, H, N, S.

(*Z*)-5-Propenyl-2′-deoxyuridine (11). The *E* isomer (**10**; 1 g, 3.73 mmol) and benzophenone (1 g) in MeOH (100 mL) were irradiated with a 6-W mercury UV lamp (quartz filter) for 24 h. The solvent was evaporated under vacuum, and the residue was chromatographed on ODS reverse-phase silica using an aqueous methanol (10–30% methanol) gradient. The *Z* isomer, which eluted before the starting material, was recrystallized from aqueous methanol: yield 110 mg (11%); mp 171–173.5 °C. Anal. ($C_{12}H_{16}N_2O_5$) C, H, N.

Preparation of (*E*)-5-(1-Propenyl)-4-thio-2′-deoxyuridine (13). 3′,5′-Di-*O*-benzoyl-5-(1-propenyl)-2′-deoxyuridine (prepared from **10** and 2.0 equiv of benzoyl chloride by conventional means;[25] 6 0 g, 12.6 mmol) was refluxed with phosphorus pentasulfide (20 g) in pyridine (350 mL) with vigorous mechanical stirring for 4 h. The solvent was evaporated under vacuum, and the residual oil was poured into water (1 L) and then extracted with $CHCl_3$ (3 × 100 mL). 4-Thio-3′,5′-di-*O*-benzoyl-5-(1-propenyl)-2′-deoxyuridine was obtained as a pale yellow solid from the organic extract and was recrystallized from EtOH to give 3.9 g (63%), mp 88–90 °C. The protected nucleoside (500 mg, 1 mmol) was stirred in 1 M methanolic NaOMe (5 mL) at room temperature for 12 h. The solution was neutralized by passing through a column of Dowex 50W-X8 (H^+) ion-exchange resin, and solvent was removed under vacuum. The product was chromatographed on silica in $CHCl_3$/EtOH to give 180 mg (64%) of **13**. Recrystallization from CH_3CN/Et_2O gave an analytically pure sample, mp 117–118 °C. Anal. ($C_{12}H_{16}N_2O_4S$) C, H, N, S.

5-Butyl-2′-deoxyuridine (24). A methanolic solution of **22** (1.52 g, 5.4 mmol) was stirred with 10% Pd on charcoal (200 mg) in an atmosphere of hydrogen until 1 equiv of gas was absorbed (10 min). The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness. The residue was recrystallized from CH_3CN to give **24**, 1.02 g (67%), mp 121 °C. Anal. ($C_{13}H_{20}N_2O_5$) H, N; C: calcd, 54.92; found, 54.39.

3-(Toluenesulfonyloxy)pent-1-ene. 1-Penten-3-ol (8.6 g, 0.1 mmol) was treated with tosyl chloride (22.3 g, 0.12 mmol) in pyridine (200 mL) at 20 °C for 18 h. The reaction products were poured into water, and the tosylate was extracted with ether. The organic phase was washed with dilute HCl and water and then dried. Evaporation of the solvent under vacuum below room temperature gave the tosylate, 4.8 g (20%), as a mobile yellow liquid: NMR ($CDCl_3$) δ 1.0 (3 H, t, J = 7 Hz, CH_3), 1.85 (2 H, m, CH_2), 2.47 (3 H, s, CH_3-Ar), 4.20 (1 H, m, CHOTs), 5.2 (2 H, m, CH_2=), 5.8 (1 H, m, =CH), 7.35 (2 H, d, J = 10 Hz, Ar), 7.87 (2 H, d, J = 10 Hz, Ar). The tosylate was not purified further but used directly for the preparation of **29** by method A. Yields from this latter reaction were variable, possibly as a result of instability of the tosylate.

(*E,E*)-5-(4-Carbomethoxy-1,3-butadienyl)-2′-deoxyuridine (32). Palladium(II) acetate (160 mg, 0.7 mmol), triphenylphosphine (380 mg, 1.45 mmol), and triethylamine (2.5 mL) were heated in refluxing dioxane (15 mL) for 20 min to give a black solution. A suspension of **2** (5 g, 15 mmol) in dioxane (20 mL) was added, followed by methyl acrylate (5 mL, 55.5 mmol), and the reaction mixture was vigorously stirred and heated under reflux for a further 8 h. The palladium residues were filtered from the hot reaction mixture, and the filtrate was evaporated to dryness under vacuum and washed with CH_2Cl_2 (2 × 50 mL). Chromatography on silica in CH_2Cl_2/EtOH gave 3.2 g (55%) of **32**, which was recrystallized from MeOH to give pale yellow needles, mp 188 °C dec. Anal. ($C_{15}H_{18}N_2O_7$) C, H, N.

Antiviral Assays. The antiviral activity of the compounds was assessed by a microplaque reduction method using the S3 strain of HSV-1.[29] Virus infectivity end-point titrations were performed by inoculation of serial 0.5 log dilutions of virus on monolayers of baby hamster kidney cells[10] in flat-bottomed microtiter plates (Flow Laboratories, Irvine, Scotland). Test compounds were included at the required concentration in the overlay [Eagles minimal essential medium, Dulbecco's modification, containing 10% donor calf serum (Flow Laboratories) (growth medium) and 0.5% carboxymethylcellulose (Sigma Chemical Co)]. The minimum inhibitory concentration (MIC) of each compound was determined to be the least concentration that gave a reduction in virus infectivity end point of not less than 1 log compared with the non-drug-treated control.

Registry No. **1a**, 54-42-2; **1b**, 4833-07-2; **2**, 69304-47-8; **3a**, 65505-76-2; **3b**, 65523-09-3; **4**, 77530-02-0; **5**, 61135-36-2; **6**, 86163-16-8; **7**, 80173-35-9; **8**, 86163-17-9; **9**, 73-39-2; **10**, 66270-29-9; **11**, 68972-52-1; **12**, 84558-94-1; **13**, 86176-91-2; **14**, 66270-34-6; **15**, 66270-35-7; **16**, 86163-18-0; **17**, 86163-19-1; (*E*)-**18**, 86163-20-4; (*Z*)-**18**, 86163-34-0; **19**, 86163-21-5; **20**, 86163-22-6; **21**, 86163-23-7; (*E*)-**22**, 76334-43-5; (*Z*)-**22**, 76334-44-6; **23**, 85328-78-5; **24**, 57741-91-0; **25**, 77875-96-8; **26**, 86163-24-8; **27**, 86163-25-9; **28**, 86163-26-0; **29**, 86163-27-1; **30**, 81710-43-2; **31**, 86163-28-2; **32**, 86163-29-3; methyl methacrylate, 80-62-6; 3,3-dimethyl-1-butene, 558-37-2; propyne, 74-99-7; 3′,5′-di-*O*-acetyl-5-formyl-2′-deoxyuridine, 86163-30-6; (*E*)-3′,5′-di-*O*-benzoyl-5-(1-propenyl)-2′-deoxyuridine, 86163-31-7; (*E*)-4-thio-3′,5′-di-*O*-benzoyl-5-(1-propenyl)-2′-deoxyuridine, 86163-32-8; 1-penten-3-ol, 616-25-1; 3-(tosyloxy)pent-1-ene, 86163-33-9.

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