Synthesis and Properties of 5-(1,2-Dihaloethyl)-2′-deoxyuridines and Related Analogues

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The regiospecific reaction of 5-vinyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**2**) with HOX (X = Cl, Br, I) yielded the corresponding 5-(1-hydroxy-2-haloethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridines **3a-c**. Alternatively, reaction of **2** with iodine monochloride in aqueous acetonitrile also afforded 5-(1-hydroxy-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3c**). Treatment of 5-(1-hydroxy-2-chloroethyl)- (**3a**) and 5-(1-hydroxy-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3b**) with DAST (Et_2NSF_3) in methylene chloride at -40° gave the respective 5-(1-fluoro-2-chloroethyl)- (**6a**, 74%) and 5-(1-fluoro-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6b**, 65%). In contrast, 5-(1-fluoro-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6c**) could not be isolated due to its facile reaction with methanol, ethanol or water to yield the corresponding 5-(1-methoxy-2-iodoethyl)- (**6c**), 5-(1-ethoxy-2-iodoethyl)- (**6d**) and 5-(1-hydroxy-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3c**). Treatment of 5-(1-hydroxy-2-chloroethyl)- (**3a**) and 5-(1-hydroxy-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3b**) with thionyl chloride yielded the respective 5-(1,2-dichloroethyl)- (**6f**, 85%) and 5-(1-chloro-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6g**, 50%), whereas a similar reaction employing the 5-(1-hydroxy-2-iodoethyl)- compound **3c** afforded 5-(1-methoxy-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6c**), possibly *via* the unstable 5-(1-chloro-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine intermediate **6h**. The 5-(1-bromo-2-chloroethyl)- (**6i**) and 5-(1,2-dibromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6j**) could not be isolated due to their facile conversion to the corresponding 5-(1-ethoxy-2-chloroethyl)- (**6k**) and 5-(1-ethoxy-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6l**). Reaction of 5-(1-hydroxy-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3b**) with methanolic ammonia, to remove the 3′,5′-di-*O*-acetyl groups, gave 2,3-dihydro-3-hydroxy-5-(2′-deoxy-β-D-ribofuranosyl)-furano[2,3-*d*]pyrimidine-6(5*H*)-one (**8**). In contrast, a similar reaction of 5-(1-fluoro-2-chloroethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6a**) yielded (*E*)-5-(2-chlorovinyl)-2′-deoxyuridine (**1b**, 23%) and 5-(2′-deoxy-β-D-ribofuranosyl)furano[2,3-*d*]pyrimidin-6(5*H*)-one (**9**, 13%). The mechanisms of the substitution and elimination reactions observed for these 5-(1,2-dihaloethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridines are described.

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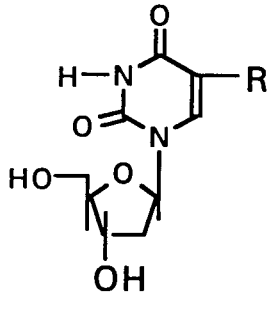
Introduction.

Many 5-substituted-2′-deoxyuridines such as (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU, **1a**), (*E*)-5-(2-chlorovinyl)-2′-deoxyuridine (CVDU, **1b**), 5-vinyl-2′-deoxyuridine (VDU, **1c**), 5-ethyl-2′-deoxyuridine (EDU, **1d**) and 5-(2-chloroethyl-2′-deoxyuridine (CEDU, **1e**), that exhibit potent and selective antiviral activity against herpes simplex virus type 1 (HSV-1), have been discovered [1-3]. In contrast, 5-(2-hydroxyethyl)-2′-deoxyuridine (HEDU, **1f**) is an inactive antiviral agent [2]. The 5-substituted-2′- deoxyuridines **1a-d** undergo enzymatic cleavage of the C-N glycosidic bond by thymidine phosphorylase to the inactive 5-substituted-uracil derivatives [4-5]. In addition, EDU (**1d**) undergoes extensive metabolism to the inactive 5-(1-hydroxyethyl)uracil metabolite [6].

It was therefore of interest to synthesize 5-(1,2-dihaloethyl)-2′-deoxyuridines which can be considered to be hybrids of **1a-b** and **1d-e**. It was postulated that 5-(1,2-dihaloethyl)-2′-deoxyuridines, which possess a 1-halogeno substituent in the 1,2-dihaloethyl moiety may, in contrast to EDU (**1d**), be resistant to metabolic hydroxylation at the C-1 position of the 5-substituent, due to obstructive halogenation. Furthermore, it is conceivable that 5-(1,2-dihaloethyl)-2′-deoxyuridines may serve as prodrugs due to elimination of hydrogen chloride or hydrogen bromide under physiological conditions to yield



1a, R = (E)-CH=CHBr
1b, R = (E)-CH=CHCl
1c, R = $CH=CH_2$
1d, R = CH_2CH_3
1e, R = CH_2CH_2Cl
1f, R = CH_2CH_2OH
1g, R = $CH(OSO_2Me)CH_3$
1h, R = $CH(OMe)CH_2I$
1i, R = $CH(OEt)CH_2I$
1j, R = $CH(OMe)CH_2Cl$
1k, R = $CH(OMe)CH_2Br$

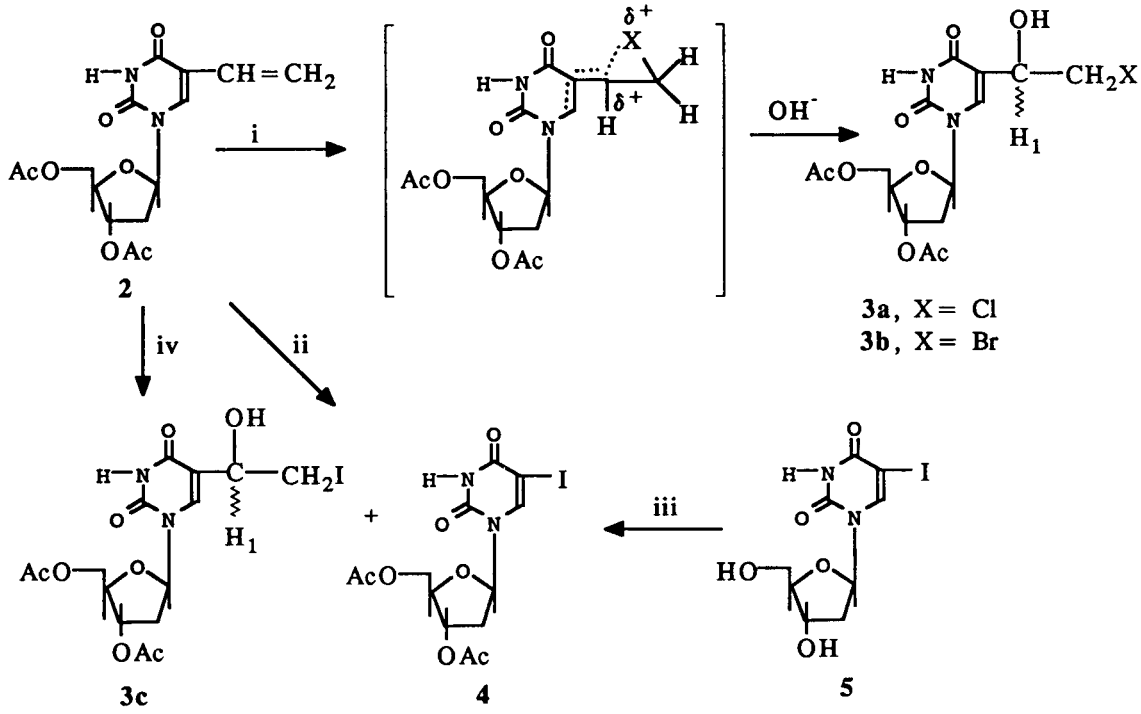
BVDU (**1a**) or CVDU (**1b**). There is precedent for the latter postulate since 5-(1-mesyloxyethyl)-2′-deoxyuridine (**1g**) was spontaneously converted to VDU (**1c**) during its attempted synthesis [7]. We now describe the synthesis and chemical properties of 5-(1,2-dihaloethyl)-2′-deoxyuridines **6a,b,f,g**.

Chemistry.

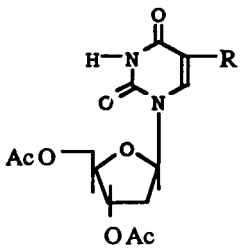
Reaction of 5-vinyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**2**) with *N*-chlorosuccinimide or *N*-bromosuccinimide in aqueous dioxane afforded the respective 5-(1-hydroxy-2-chloroethyl)- (**3a**, 52%) and 5-(1-hydroxy-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3b**, 60%) (see Scheme I), 5-(1-Hydroxy-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3c**) could not be synthesized in this way due to the instability of *N*-iodosuccinimide in aqueous dioxane. However, reaction of 5-vinyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**2**) with iodine and iodic acid, using the procedure of Cornforth *et al.* [8] yielded **3c** in 43% yield and 5-iodo-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**4**, 26% yield) which was identical (^{1}H nmr) to an authentic sample prepared by acetylation of 5-iodo-2′-deoxyuridine (**5**). Alternatively, reaction of **2** with iodine monochloride in aqueous acetonitrile also afforded 5-(1-hydroxy-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3c**, 54%) which presumably arises *via* a 5-(1-chloro-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine intermediate. The ^{13}C nmr spectra (J modulated spin echo) for 5-(1-hydroxy-2-haloethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridines **3a-c** provided conclusive evidence for the regiospecific addition of HOX across the C-5 vinyl substituent of **2**. Thus, the chloro substituent of 5-(1-hydroxy-2-chloroethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3a**) is attached to a methylene carbon that exhibited a resonance at δ 48.17, whereas the hydroxyl substituent is attached to a methine chiral carbon which exhibited dual resonances at δ 68.03 and 67.68. Compounds **3a-c** are each mixtures of two diastereomers, that could not be separated by silica gel column or tlc chromatography, which differ in configuration (*R* and *S*) at the C-1 position of the 5-(1-hydroxy-2-haloethyl) substituent. This regiospecific addition is consistent with the results of Dalton *et al.* [9] in which unsymmetrical olefins capable of halonium ion formation were found to favor an unsymmetrical bridged intermediate of the type illustrated in Scheme I even in solvents having a high dipole moment.

Treatment of the 5-(1-hydroxy-2-chloroethyl)- (**3a**) and 5-(1-hydroxy-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3b**) with DAST (Et_2NSF_3) at -40° in anhydrous dichloromethane afforded the respective 5-(1-fluoro-2-chloroethyl)- (**6a**, 74%) and 5-(1-fluoro-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6b**, 65%). Although a similar reaction of 5-(1-hydroxy-2-iodoethyl)-3′,5′-di-*O*-

Scheme Ia



[a]Reagents: i, N-chlorosuccinimide (**3a**), N-bromosuccinimide (**3b**), dioxane-water (3:7, v/v), glacial acetic acid, 25°; ii, I_2, KIO_3, water, MeCN, 5N H_2SO_4; iii, Ac_2O, pyridine; iv, ICl, MeCN, water, 50° (**3c**).



6a, R = $CH(F)CH_2Cl$ **6g**, R = $CH(Cl)CH_2Br$

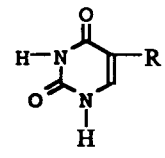
6b, R = $CH(F)CH_2Br$ **6h**, R = $CH(Cl)CH_2I$

6c, R = $CH(OMe)CH_2I$ **6i**, R = $CH(Br)CH_2Cl$

6d, R = $CH(OEt)CH_2I$ **6j**, R = $CH(Br)CH_2Br$

6e, R = $CH(F)CH_2I$ **6k**, R = $CH(OEt)CH_2Cl$

6f, R = $CH(Cl)CH_2Cl$ **6l**, R = $CH(OEt)CH_2Br$



7a, R = $CH=CH_2$

7b, R = (E)-CH=CHI

7c, R = $CH(Cl)CH_2I$

7d, R = $CH(Br)CH_2Br$

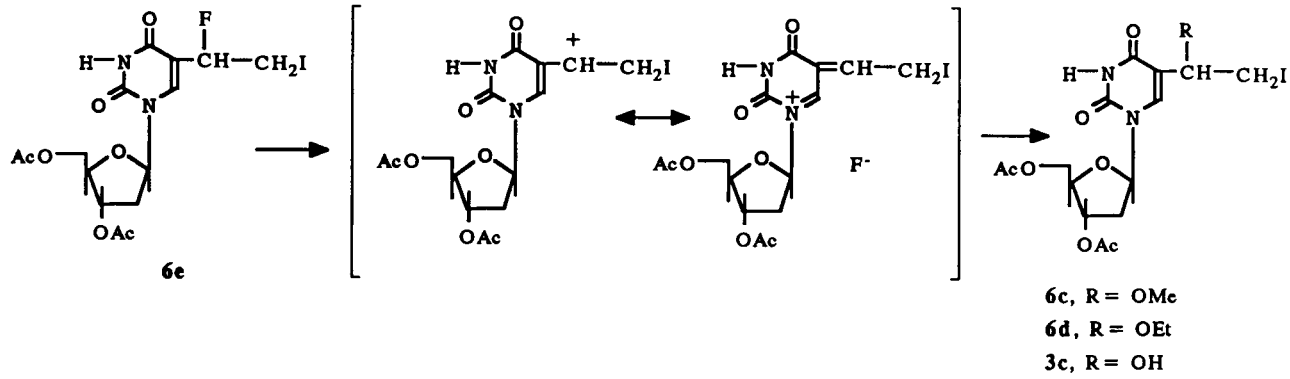
7e, R = (E)-CH=CHBr

acetyl-2'-deoxyuridine (**3c**) proceded almost instantaneously showing one major product by analytical tlc, a second more polar compound was present after the reaction mixture was quenched with methanol and washed with aqueous sodium bicarbonate and water. Separation of this reaction mixture by silica gel column chromatography using chloroform:methanol (19:1, v/v) as eluent afforded a mixture of 5-(1-methoxy-2-iodoethyl)- (**6c**) and 5-(1-ethoxy-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6d**) in a ratio of 1:2 which could not be separated by preparative tlc. Each compound **6c** and **6d** is a mixture of two diastereoisomers. Thus, the ^1H nmr spectrum of **6c** and **6d** exhibited four closely spaced singlets at δ 7.70, 7.72, 7.75 and 7.76 for the H-6 proton. The ^{13}C nmr spectrum showed resonances at δ 10.77 and 12.65 (CH_2I of **6c**), 11.08 and 13.10 (CH_2I of **6d**), 15.14 and 15.28 (OCH_2CH_3 of **6d**), 56.96 (OCH_3 of **6c**), 63.85 and 64.20 (OCH_2CH_3 of **6d**), 73.64, 73.70, 74.49, 74.63 ($CHOCH_3$ and $CHOCH_2CH_3$ of **6c** and **6d**). These spectral assignments are consistent with those for authentic samples of **6c** and **6d** prepared by acetylation of **1h** and **1i**, respectively. The more polar compound which arose after the methanol reaction quench and water washing was identical (mp, ^1H nmr) to the starting material **3c**.

A plausible mechanism for the formation of **6c**, **6d** and **3c** involves the decomposition of 5-(1-fluoro-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6e**), which is formed at -40°, to a carbonium ion intermediate at 25° which undergoes reaction with methanol, ethanol or water to yield the respective products that were isolated (see Scheme II). The intermediacy of related carbonium ions have been previously proposed [7,10]. The 5-(1-methoxy-2-iodoethyl)-(**6c**) and 5-(1-ethoxy-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6d**) products are likely formed during silica gel column chromatography (chloroform:methanol eluent; chloroform contains 0.75% ethanol as a preservative). If **6c** was formed during the methanol quench, one would not have expected the formation of **6d**. 5-(1-Hydroxy-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**3c**) is presumed to arise during the isolation procedure from the aqueous sodium bicarbonate and/or water wash procedures.

5-(1,2-Dichloroethyl)- (**6f**, 85%) and 5-(1-chloro-2-bromoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6g**, 50%) were prepared by the reaction of **3a** and **3b** with thionyl chloride in dry chloroform at 25°, respectively. In contrast, a similar reaction of the 5-(1-hydroxy-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**3c**) did not yield the

Scheme II



6e

6c, R = OMe

6d, R = OEt

3c, R = OH

desired 5-(1-chloro-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6h**) since 5-(1-methoxy-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6c**, 51%) was the only product isolated after preparative tlc purification (dichloromethane:methanol, 96:4, v/v). It is possible that **6c** is formed *via* a carbonium ion intermediate as illustrated in Scheme II. These results suggest that 5-(1-fluoro-2-iodoethyl) (**6e**) and 5-(1-chloro-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6h**) are highly unstable.

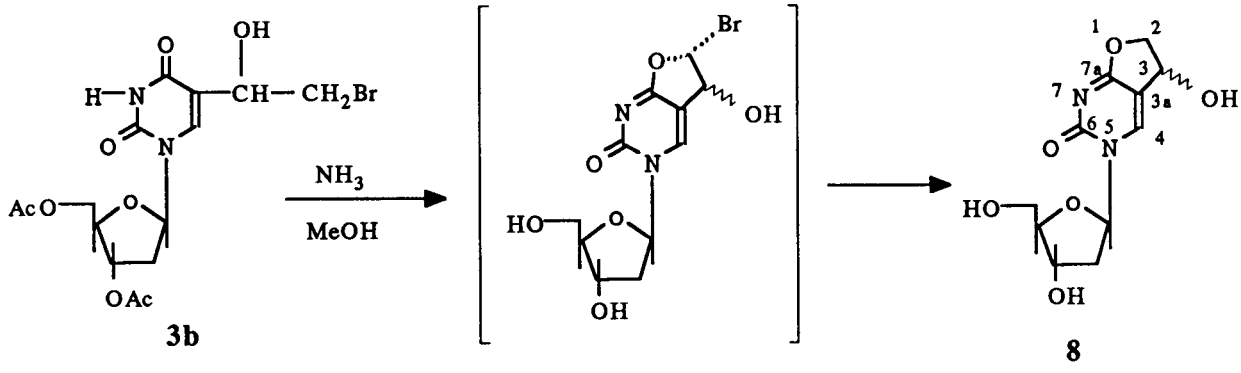
A further attempt to prepare the 5-(1-chloro-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6h**) by reaction of 5-vinyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**2**) with iodine monochloride in aqueous acetonitrile was also unsuccessful since 5-(1-hydroxy-2-iodoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3c**, 54%) was the only isolabile product. In a related, reaction, Walker *et al.* [11, 12] observed that the reaction of 5-vinyluracil with iodine monochloride in dimethylformamide at 100° yielded (*E*)-5-(2-iodovinyl)uracil (**7b**) which was postulated to arise from the unstable 5-(1-chloro-2-iodoethyl)uracil (**7c**).

The reaction of the 5-(1-hydroxy-2-chloroethyl)- (**3a**) and 5-(1-hydroxy-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3b**) with thionyl bromide, unlike the reactions with thionyl chloride, did not afford the expected 5-(1-bromo-2-chloroethyl)- (**6i**) and 5-(1,2-dibromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6j**). In these reactions, 5-(1-ethoxy-2-chloroethyl)- (**6k**, 16%) and 5-(1-ethoxy-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6l**, 31%) were the only isolabile products obtained after preparative silica gel tlc or column chromatography (chloroform:ethyl acetate). An attempt to prepare 5-(1,2-dibromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6j**) by reaction of 5-vinyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**2**) with bromine in dry benzene at 25° was also unsuccessful since the only isolabile products were the 5-(1-hydroxy-2-bromoethyl)-(**3b**, 60%) and 5-(1-ethoxy-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6l**, 30%). These results suggest that the 5-(1-bromo-2-chloroethyl)- (**6i**) and 5-(1,2-dibromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6j** are highly unstable non-isolabile products. In a related reaction, Bleackly *et al.* [13] have reported that the reaction of 5-vinyluracil (**7a**) with bromine in DMF at 25° afforded an unstable product, which is likely 5-(1,2-dibromoethyl)uracil (**7d**), that decomposed during isolation. When the reaction was carried out at 100°, (*E*)-5-(2-bromovinyl)uracil (**7e**) was isolated.

Treatment of 5-(1-hydroxy-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3b**) with a saturated solution of ammonia in methanol, to remove the 3′,5′-di-*O*-acetyl groups, yielded 2,3-dihydro-3-hydroxy-5-(2′-deoxy-β-D-ribofuranosyl)furano[2,3-*d*]pyrimidin-6(5*H*)-one (**8**, 49%) as illustrated in Scheme III. This base catalyzed intramolecular cyclization reaction of **3b** to **8** is analogous to the reported conversion of 5-[2-[(methylsulfonyl)oxy]ethyl]-uracil to 2,3-dihydrofurano[2,3-*d*]pyrimidin-6(5*H*)-one using potassium *t*-butoxide in DMSO [14].

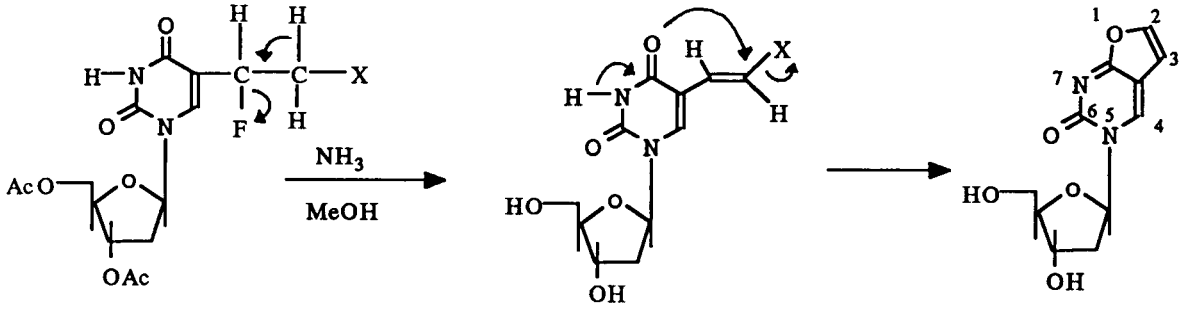
Treatment of 5-(1-fluoro-2-chloroethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6a**) with sodium methoxide in methanol at 25°, to remove the 3′,5′-di-*O*-acetyl protecting groups, afforded 5-(1-methoxy-2-chloroethyl)-2′-deoxyuridine (**1j**) due to displacement of the fluoro substituent by methoxide anion. In an attempt to circumvent this displacement reaction, treatment of the 5-(1-fluoro-2-chloroethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6a**) with a saturated solution of ammonia in methanol at 25° yielded (*E*)-5-(2-chlorovinyl)-2′-deoxyuridine (**1b**, 23%) and the fluorescent 5-(1′-deoxy-β-D-ribofuranosyl)furano[2,3-*d*]pyrimidin-6-(5*H*)-one (**9**, 13%). A similar reaction employing 5-(1-fluoro-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**6b**) gave (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (**1a**, 7.5%) and the bicyclic product **9** (50%). The most plausible mechanism for the formation of **1a** and **1b** is an E_2 elimination reaction as illustrated in Scheme IV, since an E_1 elimination reaction would have also been expected to afford the respective 5-(1-methoxy-2-chloroethyl)- (**1j**) or 5-(1-methoxy-2-bromoethyl)-2′-deoxyuridine (**1k**), resulting from reaction of the carbonium ion intermediate produced by an E_1 mechanism (see Scheme II). This observation is also in agreement with the fact that E_2 elimination reac-

Scheme III



3b **8**

Scheme IV



6a, X = Cl
6b, X = Br

1a, X = Br
1b, X = Cl

9

tions are favored relative to nucleophilic S_N2 displacement reactions in the presence of an external base [15]. The bicyclic compound **9** is likely formed by the nucleophilic displacement of bromide (**1a**) or chloride (**1b**) by the negatively charged oxygen at C-4 of the pyrimidine ring.

EXPERIMENTAL

Melting points were determined with a Buchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^1H nmr, ^{13}C nmr) were recorded on a Bruker AM-300 spectrometer using tetramethylsilane as internal standard (^1H nmr). The ^{13}C nmr spectra were determined using the J modulated spin echo technique where methyl and methine carbon resonances appear as positive peaks and methylene and quaternary carbon resonances appear as negative peaks. Mass spectra were recorded on a Hewlett-Packard 5995A (EI) spectrometer. Thin layer chromatography was performed using Whatman MK6F silica gel microslides (250 μM thickness). Silica gel column chromatography was carried out using Merck 7734 silica gel (100-200 μ particle size). 5-Vinyl-3',5'-di-*O*-acetyl-2'-deoxyuridine (**2**) [16], 5-(1-methoxy-2-iodoethyl)-2'-deoxyuridine (**1h**) [17] and 5-(1-ethoxy-2-iodoethyl)-2'-deoxyuridine (**1i**) [18] were prepared according to the literature procedures.

5-(1-Hydroxy-2-chloroethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**3a**).

N-Chlorosuccinimide (0.2 g, 1.5 mmoles) was added slowly with stirring to a solution of **2** (0.5 g, 1.47 mmoles) in dioxane-water (3:7, v/v, 10 ml) and glacial acetic acid (60 μl) during a period of 5 minutes. The reaction was allowed to proceed at 25° for 24 hours. An additional aliquot of *N*-chlorosuccinimide (0.1 g, 0.75 mmole) and glacial acetic acid (50 μl) was added and the reaction was allowed to proceed for 10 hours at 25°. Removal of the solvent *in vacuo* and purification of the product by elution from a silica gel column using chloroform-methanol (97:3, v/v) as eluent afforded **3a** (0.3 g, 52%), mp 200-205° dec; ^1H nmr (chloroform-d_1): (mixture of two diastereomers in a ratio of 1:1) δ 2.20 (m, 7H, H-2', MeCO), 2.52 (m, 1H, H-2'), 3.25 and 3.38 (two d, $J_{CH,OH}$ = 6 Hz, 1H total, CHO*H*CH_2Cl, exchanges with deuterium oxide), 3.72 (m, 1H, C*H*Cl), 3.96 (m, 1H, C*H'*Cl), 4.28-4.50 (complex m, 3H, H-4',H-5'), 4.84 (m, 1H, C*H*OHCH_2Cl), 5.25 (m, 1H, H-3'), 6.38 (d, J = 6 Hz of d, J = 5.0 Hz, 1H, H-1'), 7.72 (s, 1H, H-6), 9.08 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C nmr (chloroform-d_1): δ 20.74 (*C*H_3CO), 20.78 (*C*H_3CO), 37.60 and 37.71 (C-2'), 48.17 (CHOH*C*H_2Cl), 63.83 (C-5'), 67.68 and 68.03 (*C*HOHCH_2Cl), 74.31 (C-3'), 82.46 and 82.55 (C-1'), 85.18 and 85.39 (C-4'), 113.35 and 113.59 (C-5), 137.11 and 137.20 (C-6), 149.98 and 150.06 (C-2), 162.45 and 162.48 (C-4), 170.37 (CH_3*C*O), 170.76 (CH_3*C*O).

Anal. Calcd. for $C_{15}H_{19}ClN_2O_8 \cdot 1H_2O$: C, 44.07; H, 5.17; N, 6.85. Found: C, 44.16; H, 5.43; N, 7.05.

5-(1-Hydroxy-2-bromoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**3b**).

N-Bromosuccinimide (36 mg, 0.2 mmole) was added slowly with stirring to a solution of **2** (68 mg, 0.2 mmole) in dioxane-water (3:7, v/v, 4 ml) and glacial acetic acid (15 μl) during a period of 5 minutes. The reaction was allowed to proceed at 25° for 2 hours with stirring and the solvent was removed *in vacuo*. Purification of the product by elution from a silica gel column using chloroform-methanol (98:2, v/v) as eluent afforded **3b** (50 mg, 60%), mp 168-170° dec; ^1H nmr (chloroform-d_1): (mixture of two diastereomers in a ratio of 1:1) δ 2.20 (m, 7H, H-2', MeCO), 2.53 (m, 1H, H-2'), 3.16 and 3.24 (two d, $J_{CH,OH}$ = 6 Hz, 1H total, CHO*H*CH_2Br, exchanges with deuterium oxide), 3.62 (m, 1H, C*H*Br), 3.88 (m, 1H, C*H'*Br), 4.25-4.46 (complex m, 3H, H-4', H-5'), 4.85 (m, 1H, C*H*OH), 5.26 (m, 1H, H-3'), 6.40 (m, 1H, H-1'), 7.72 (s, 1H, H-6), 8.95 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C nmr (chloroform-d_1): δ 20.85 (*C*H_3CO), 37.72, 37.86 and 37.97 (C-2', CHOH*C*H_2Br), 63.85 (C-5'), 67.56 and 67.92 (*C*HOHCH_2Br), 74.30 and 74.36 (C-3'), 82.57 and 82.69 (C-1'), 85.23 and 85.41 (C-4'), 113.66 and 113.93 (C-5), 136.79 and 137.08 (C-6), 149.75 and 149.84 (C-2), 162.07 (C-4), 170.36 (CH_3*C*O), 170.69 (CH_3*C*O).

Anal. Calcd. for $C_{15}H_{19}BrN_2O_8 \cdot \frac{3}{4}H_2O$: C, 40.14; H, 4.60; N, 6.24. Found: C, 40.04; H, 4.24; N, 6.10.

5-(1-Hydroxy-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**3c**) and 5-Iodo-3',5'-di-*O*-acetyl-2'-deoxyuridine (**4**).

A solution of **2** (0.325 g, 0.96 mmole), iodine (0.127 g, 1.0 mmole) and potassium iodate (40 mg, 0.186 mmole) in water (3 ml), acetonitrile (3 ml) and sulfuric acid (100 μl of 5 *N*) was stirred at 55° for 2 hours. Removal of the solvent *in vacuo* and elution of the residue from a silica gel column using chloroform-methanol (95:5, v/v) as eluent yielded **3c** and **4**.

Compound **3c** had mp 100-105° dec, (0.2 g, 43%); 1H nmr (chloroform-d_1): (mixture of two diastereomers in a ratio of 1:1) δ 2.18 (m, 7H, H-2', C*H*$_3$CO), 2.51 (m, 1H, H-2'), 3.0 and 3.10 (two d, $J_{CH,OH}$ = 6 Hz, 1H total, CHO*H*CH$_2$I, exchanges with deuterium oxide), 3.51 (m, 1H, C*H*I), 3.72 (m, 1H, C*H*'I), 4.26-4.47 (complex m, 3H, H-4',H-5'), 4.62 (m, 1H, C*H*OH), 5.24 (m, 1H, H-3'), 6.38 (m, 1H, H-1'), 7.66 and 7.68 (two s, 1H total, H-6), 8.68 (s, 1H, NH, exchanges with deuterium oxide): ^{13}C nmr (chloroform-d_1): δ 14.0 and 14.45 (*C*H$_2$I), 20.90 (*C*H$_3$CO), 21.04 (*C*H$_3$CO), 37.68 and 37.87 (C-2'), 63.88 (C-5'), 67.35 and 68.10 (*C*HOH), 74.32 (C-3'), 82.57 and 82.66 (C-1'), 85.05 and 85.34 (C-4'), 114.38 (C-5), 136.82 (C-6), 170.36 (CH$_3$*C*O).

Anal. Calcd. for $C_{15}H_{19}IN_2O_8 \cdot 1H_2O$: C, 36.01; H, 4.22; N, 5.60. Found: C, 35.79; H, 3.71; N, 5.65 [21].

Compound **4** had mp 157-159° (lit [19] mp 157-159°), 0.11 g, 26%); 1H nmr (chloroform-d_1): δ 2.16 (m, 7H, H-2', C*H*$_3$CO), 2.54 (m, 1H, H-2'), 4.36 (complex m, 3H, H-4', H-5'), 5.22 (m, 1H, H-3'), 6.30 (dd, J = 6 Hz, J = 5 Hz, 1H, H-1'), 7.98 (s, 1H, H-6), 8.63 (s, 1H, NH, exchanges with deuterium oxide): ^{13}C nmr (chloroform-d_1): δ 20.75 (*C*H$_3$CO), 20.98 (*C*H$_3$CO), 38.12 (C-2'), 63.70 (C-5'), 68.94 (C-5), 74.0 (C-3'), 83.56 (C-1'), 85.44 (C-4'), 143.73 (C-6), 149.99 (C-2), 159.87 (C-4), 170.09 (CH$_3$*C*O) and 170.27 (CH$_3$*C*O).

Anal. Calcd. for $C_{13}H_{15}IN_2O_7 \cdot \frac{3}{4}H_2O$: C, 34.56; H, 3.67; N, 6.20. Found: C, 34.26; H, 3.10; N, 5.87 [21].

5-Iodo-3',5'-di-*O*-acetyl-2'-deoxyuridine (**4**).

A solution of **5** (50 mg, 0.14 mmole) in dry pyridine (5 ml) and acetic anhydride (0.11 ml, 1.26 mmole) was allowed to stir at 25° for 20 hours. Removal of the solvent *in vacuo*, and co-evaporation of the residue with benzene and ethanol to remove all the pyridine, followed by silica gel column purification with chloroform-methanol (95:5, v/v) as eluent afforded **4**, (60 mg, 97%), mp 157-159°. The 1H nmr and ^{13}C nmr spectra for **4** were identical to the spectral data described in the previous synthesis above.

Reaction of 5-Vinyl-3',5'-di-*O*-acetyl-2'-deoxyuridine (**2**) with Iodine Monochloride.

A solution of **2** (35 mg, 0.1 mmole) and iodine monochloride (32 mg, 0.2 mmole) in acetonitrile (5 ml) and water (100 μl) was stirred at 50° for 30 minutes. After warming to 25°, the solvent was removed *in vacuo* and the product was purified by elution from a silica gel column using chloroform-methanol (95:5, v/v) as eluent to yield **3c** (26 mg, 54%) as a white solid that was a mixture of two diastereomers in a ratio of 1:1 as indicated by 1H nmr. The mp and 1H nmr spectrum of **3c** was identical to that described earlier.

5-(1-Fluoro-2-chloroethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6a**).

Diethylaminosulfur trifluoride (20 μl, 0.15 mmole) was added to a suspension of **3a** (39 mg, 0.1 mmole) in dry dichloromethane (5 ml) at -40°. The cooling bath was removed and the reaction mixture was allowed to stir at 25° for 25 minutes. The reaction mixture was cooled to -10°, quenched by addition of methanol (2 ml), and the solvent was removed *in vacuo*. The residue was extracted with dichloromethane, the extract was washed consecutively with saturated aqueous sodium bicarbonate (3 ml) and cold water (10 ml). The dichloromethane fraction was dried sodium sulfate), filtered and the solvent was removed *in vacuo* to give a viscous oil which was purified by preparative tlc using chloroform-methanol (95:5, v/v) as development solvent. Extraction of the ultraviolet visible band with chloroform-methanol (94:6, v/v) afforded **6a** as a white foam, (29 mg, 74%), mp 156-160° dec; 1H nmr (chloroform-d_1): (mixture of two diastereomers in a ratio of 1:1) δ 2.12 (m, 7H, H-2', C*H*$_3$CO), 2.47 (m, 1H, H-2'), 3.76 (m, 1H, C*H*Cl), 4.0 (m, 1H, C*H*'Cl), 4.30 (complex m, 3H, H-4', H-5'), 5.20 (m, 1H, H-3'), 5.70 (m, $J_{CH,F}$ = 44.6 Hz, 1H, C*H*FCH$_2$Cl), 6.33 (m, 1H, H-1'), 7.65 and 7.70 (two s, 1H total, H-6), 9.4 (br s, 1H, NH, exchanges with deuterium oxide); ^{13}C nmr (chloroform-d_1): δ 20.51 (*C*H$_3$CO), 20.81 (*C*H$_3$CO), 38.07 (C-2'), 44.87, 45.00, 45.20, 45.31 (CHF*C*H$_2$Cl, couples to F in each diastereomer), 63.87 (C-5'), 74.35 (C-3'), 82.67 and 82.77 (C-1'), 85.20, 84.45, 85.58, 85.61 and 87.98 (C-4', *C*HFCH$_2$Cl, couples to fluorine), 110.32, 110.49, 110.59 and 110.77 (C-5, couples to fluorine), 137.28, 137.36, 137.44 and 137.51 (C-6, couples to fluorine), 149.73 and 149.81 (C-2), 161.10 (C-4), 170.29 (CH$_3$*C*O), 170.38 (CH$_3$*C*O).

Anal. Calcd. for $C_{15}H_{18}ClFN_2O_7 \cdot \frac{1}{2}H_2O$: C, 44.84; H, 4.76; N, 6.97. Found: C, 44.49; H, 4.53; N, 6.88.

5-(1-Fluoro-2-bromoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6b**).

Diethylaminosulfur trifluoride (120 μl, 0.906 mmole) was added to a suspension of **3b** (0.252 g, 0.579 mmole) in dry dichloromethane (8 ml) at -40° with stirring. The reaction mixture was warmed to 25°, stirred for 30 minutes, cooled to -10° and quenched with methanol (2 ml). The product was isolated, using the procedure described for **6a**, and purified by silica gel column chromatography using chloroform-methanol (95:5, v/v) as eluent to yield **6b**, (165 mg, 65%), mp 132-135° dec; 1H nmr (chloroform-d_1): (mixture of two diastereomers in a ratio of 1:1) δ 2.20 (m, 7H, H-2', C*H*$_3$CO), 2.54 (m, 1H, H-2'), 3.70 (m, 1H, C*H*Br), 3.90 (m, 1H, C*H*'Br), 4.36 (complex m, 3H, H-4', H-5'), 5.28 (m, 1H, H-3'), 5.72 (m, $J_{CH,F}$ = 44.4 Hz, 1H, C*H*FCH$_2$Br), 6.40 (m, 1H, H-1'), 7.70 and 7.75 (two s, 1H total, H-6), 9.02 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C nmr (chloroform-d_1): δ 20.51 (*C*H$_3$CO), 20.71 (*C*H$_3$CO), 33.05, 33.39, 33.71 and 34.04 (CHF*C*H$_2$Br, couples to fluorine in each diastereomer), 37.87 (C-2'), 63.80 (C-5'), 74.26 (C-3'), 82.46 and 82.57 (C-1'), 84.96, 85.25, 87.25, 87.33 (C-4' and *C*HFCH$_2$Br, couples to fluorine), 111.05 and 111.32 (C-5), 137.08 and 137.26 (C-6, couples to fluorine), 149.87 and 149.93 (C-2), 161.28 and 161.31 (C-4), 170.24 (CH$_3$*C*O), 170.35 (CH$_3$*C*O).

Anal. Calcd. for $C_{15}H_{18}BrFN_2O_7 \cdot \frac{1}{2}H_2O$: C, 40.37; H, 4.28; N, 6.27. Found: C, 40.68; H, 4.22; N, 6.18.

Reaction of 5-(1-Hydroxy-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**3c**) with Diethylaminosulfur Trifluoride.

Diethylaminosulfur trifluoride (60 μl, 0.37 mmoles) was added to a suspension of **3c** (0.16 g, 0.33 mmole) in dry dichloromethane (5 ml) at -40° with stirring. The cooling bath was removed and the reaction mixture was stirred at 25° for 20 minutes at which time tlc indicated the reaction was completed. The reaction mixture was cooled to -10°, methanol (2 ml) was added and the solvent was removed *in vacuo*. Extraction of the residue obtained with chloroform, washing the chloroform extract with saturated aqueous sodium bicarbonate (3 ml), cold water (10 ml), drying the chloroform extract (sodium sulfate), filtration and removal of the solvent *in vacuo* yielded a viscous oil which now exhibited an additional spot on tlc. This material was purified by silica gel column chromatography using chloroform-methanol (95:5, v/v) as eluent. The first fraction eluted (0.045 g) was found to be a mix-

ture of 5-(1-methoxy-2-iodoethyl)- (**6c**) and 5-(1-ethoxy-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6d**) in a ratio of 1:2 based on the ^{1}H nmr spectral data; ^{1}H nmr (chloroform-d_1): (**6c** and **6d** are each a mixture of two diastereomers) δ 1.22 (two overlapping t, J = 7 Hz, 3H total, OCH_2CH_3 of **6d**), 2.1-2.3 (m, 14H total, H-2', CH_3CO), 2.48 (m, 2H total, H-2'), 3.31-3.74 (complex m, 9H total, CHI, CH'I, OCH_2CH_3 of **6d**, OMe of **6c**), 4.10-4.46 (complex m, 8H total, H-4', H-5', CHOMe and CHOEt), 5.27 (m, 2H total, H-3'), 6.32-6.52 (m, 2H total, H-1'), 7.66, 7.70, 7.72 and 7.75 (four s, 2H total, H-6), 9.16 and 9.19 (two s, 2H total, NH, exchanges with deuterium oxide); ^{13}C nmr (chloroform-d_1): δ 10.77 and 12.65 (CH_2I of **6c**), 11.08 and 13.10 (CH_2I of **6d**), 15.14 and 15.28 (OCH_2CH_3 of **6d**), 20.86, 20.98 and 21.25 (CH_3CO), 37.49, 37.67 and 37.80 (C-2'), 56.96 (OCH_3 of **6c**), 63.85 and 64.20 (OCH_2CH_3 of **6d**), 65.25 and 65.33 (C-5'), 71.99 and 72.17 (C-3'), 73.64, 73.70, 74.49 and 74.63 (CHOMe and CHOEt), 82.27 and 82.43 (C-1'), 84.49, 84.69, 85.09 and 85.19 (C-4'), 113.69 and 114.42 (C-5), 136.90, 137.01 and 137.20 (C-6), 149.83 and 149.91 (C-2), 161.70 (C-4), 170.33, 170.42 and 170.57 (CH_3CO). These ^{1}H nmr and ^{13}C nmr spectral data are similar to those of authentic samples of **6c** and **6d** described in the subsequent two experiments listed below. Further elution afforded **3c** (19 mg, 12%) which was identical (^{1}H nmr, mp and mass spectrum) to the starting material (**3c**).

5-(1-Methoxy-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6c**).

A solution of **1h** (41 mg, 0.1 mmole) in dry pyridine (6 ml) and acetic anhydride (0.11 ml, 1.26 mmole) was stirred for 12 hours at 25°. The reaction mixture was evaporated to dryness *in vacuo* and the residue was co-evaporated with benzene and ethanol to remove all the pyridine. The product was purified by silica gel column chromatography using chloroform-methanol (98:2, v/v) as eluent to yield **6c**, (40 mg, 80%), mp 128-132° dec; ^{1}H nmr (chloroform-d_1): (mixture of two dastereomers in a ratio of 1:1) δ 2.15 (m, 7H, H-2', CH_3CO), 2.40 (m, 1H, H-2'), 3.28 and 3.30 (two s, 3H total, OMe), 3.38 (m, 1H, CHI), 3.62 (m, 1H, CH'I), 4.06 (m, 1H, $CHOCH_3$), 4.24 (m, 3H, H-4', H-5'), 5.20 (m, 1H, H-3'), 6.36 (m, 1H, H-1'), 7.48 and 7.52 (two s, 1H total, H-6), 9.80 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C nmr (chloroform-d_1): δ 10.79 and 12.65 (CH_2I), 20.81 (CH_3CO), 21.02 (CH_3CO), 37.64 (C-2'), 56.93 (OCH_3), 64.05 and 64.14 (C-5'), 73.63 (C-3'), 74.48 and 74.62 ($CHOCH_3$), 82.37 (C-1'), 84.48 and 85.08 (C-4'), 113.69 and 113.78 (C-5), 136.99 and 137.20 (C-6), 149.99 and 150.10 (C-2), 161.89 (C-4), 170.33 (CH_3CO), 170.62 (CH_3CO).

Anal. Calcd. for $C_{16}H_{21}IN_2O_8 \cdot 1H_2O$: C, 37.35; H, 4.47; N, 5.44. Found: C, 37.49; H, 4.07; N, 5.28.

5-(1-Ethoxy-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6d**).

Acetic anhydride (30 μl, 0.34 mmoles) was added to a solution of **1i** (12 mg, 0.028 mmole) in dry pyridine (3 ml) at 0° and the reaction was allowed to proceed for 12 hours at 25° with stirring. Removal of the solvent *in vacuo* and elution of the product from a silica gel column using chloroform as eluent yielded **6d**, (8 mg, 54%) as a viscous oil; ^{1}H nmr (chloroform-d_1): δ 1.20 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.20 (m, 7H, H-2', CH_3CO), 2.48 (m, 1H, H-2'), 3.36-3.70 (complex m, 4H, CH_2I, OCH_2CH_3), 4.20-4.45 (m, 4H, H-4', H-5', CHOEt), 5.27 (m, 1H, H-3'), 6.44 (m, 1H, H-1'), 7.64 (s, 1H, H-6), 8.22 (s, 1H, NH, exchanges with deuterium oxide): ^{13}C nmr (chloroform-d_1): δ 11.10 and 13.14 (CH_2I), 15.14 and 15.26 (OCH_2CH_3), 20.88 (CH_3CO), 21.28 (CH_3CO), 37.47 and 37.78 (C-2'), 63.85 and 64.21 (OCH_2CH_3), 65.31 (C-5'), 71.96 and 72.11 (C-3'), 74.24 and 74.63 (CHOEt), 82.23 and 82.41 (C-1'), 84.64 (C-4'), 114.37 (C-5), 136.88 (C-6), 149.76 (C-2), 161.52 (C-4), 170.34 (CH_3CO).

Anal. Calcd. for $C_{17}H_{23}IN_2O_8$: C, 40.01; H, 4.54; N, 5.49. Found: C, 40.08; H, 4.10; N, 5.50.

5-(1,2-Dichloroethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6f**).

Thionyl chloride (0.1 ml, 1.23 mmoles) was added to a solution of **3a** (25 mg, 0.067 mmole) in dry chloroform (5 ml) at 0° with stirring and the reaction was allowed to proceed for 30 hours at 25°. Removal of the solvent *in vacuo*, purification of the product by preparative tlc using ethyl acetate-hexane (1:4, v/v) as development solvent and extraction of the ultraviolet visible spot with ethyl acetate afforded **6f** as a foam, (22 mg, 85%), mp 145-150° dec; ^{1}H nmr (chloroform-d_1): (mixture of two diastereomers in a ratio of 1:1) δ 2.1 (m, 7H, H-2', CH_3CO), 2.50 (m, 1H, H-2'), 3.90 (m, 1H, CHH'Cl), 4.08 (m, 1H, CHH'Cl), 4.22-4.44 (complex m, 3H, H-4', H-5'), 5.12 (m, 1H, $CHClCH_2Cl$), 5.21 (m, 1H, H-3'), 6.24 (m, 1H, H-1'), 7.75 (s, 1H, H-6), 9.26 (s, 1H, NH, exchanges with deuterium oxide): ^{13}C nmr (chloroform-d_1): δ 20.85 (CH_3CO), 38.21 (C-2'), 46.83 and 47.07 (CH_2Cl), 54.71 and 54.86 ($CHClCH_2Cl$), 63.79 (C-5'), 74.29 (C-3'), 82.84 and 82.93 (C-1'), 85.68 and 85.92 (C-4'), 111.53 and 111.77 (C-5), 139.15 and 139.24 (C-6), 149.46 and 149.51 (C-2), 160.94 (C-4), 170.33 (CH_3CO), 170.45 (CH_3CO).

Anal. Calcd. for $C_{15}H_{18}Cl_2N_2O_7 \cdot \frac{1}{4}H_2O$: C, 43.54; H, 4.44; N, 6.77. Found: C, 43.53; H, 4.63; N, 6.30.

5-(1-Chloro-2-bromoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6g**).

Thionyl chloride (0.1 ml, 1.23 mmoles) was added to a solution of **3b** (38 mg, 0.09 mmole) in dry chloroform (5 ml) at 0° with stirring and the reaction was allowed to proceed at 25° for 24 hours. Removal of the solvent *in vacuo*, purification of the product by preparative tlc using chloroform-ethyl acetate (9:1, v/v) as development solvent and extraction of the ultraviolet visible spot yielded **6g**, (20 mg, 50%), mp 53-58° (sublimes); ^{1}H nmr (chloroform-d_1): (mixture to two diastereomers in a ratio of 1:1) δ 2.17 (m, 7H, H-2', CH_3CO), 2.60 (m, 1H, H-2'), 3.88 (m, 1H, CHBr), 4.10 (m, 1H, CH'Br), 4.25-4.50 (complex m, 3H, H-4', H-5'), 5.15 (m, 1H, $CHClCH_2Cl$), 5.23 (m, 1H, H-3'), 6.32 (m, 1H, H-1'), 7.76 and 7.78 (two s, 1H total, H-6), 9.48 (br s, 1H, NH, exchanges with deuterium oxide); ^{13}C nmr (chloroform-d_1): δ 20.83 (CH_3CO), 20.92 (CH_3CO), 34.88 and 35.51 (CH_2Br), 38.18 (C-2'), 54.35 and 54.44 (CHCl), 63.75 (C-5'), 74.18 and 74.26 (C-3'), 82.80 and 82.92 (C-1'), 85.65 and 85.86 (C-4'), 112.03 and 112.22 (C-5), 138.91 and 139.02 (C-6), 149.39 and 149.45 (C-2), 160.78 (C-4), 170.30 (CH_3CO), 170.42 (CH_3CO).

Anal. Calcd. for $C_{15}H_{18}BrClN_2O_7 \cdot \frac{1}{4}H_2O$: C, 39.32; H, 4.06; N, 6.11. Found: C, 39.17; H, 4.16; N, 6.01.

Reaction of 5-(1-Hydroxy-2-iodoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine with Thionyl Chloride.

Thionyl chloride (0.1 ml, 1.23 mmoles) was added to a solution of **3c** (15 mg, 0.031 mmole) in dry chloroform (10 ml) at 0° with stirring and the reaction was allowed to proceed at 25° for 3 days. Removal of the solvent *in vacuo*, purification of the product by preparative tlc using dichloromethane-methanol (96:4, v/v) as development solvent and extraction of the utraviolet visible spot with dichloroform-methanol (19:1, v/v) afforded **6c**, (8 mg, 51%) which was identical [mp, ^{1}H nmr, m/z 496 (M^+)] to the authentic sample of **6c** described previously.

Reaction of 5-(1-Hydroxy-2-chloroethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**3a**) with Thionyl Bromide.

Thionyl bromide (50 μl, 0.65 mmole) was added to a solution of **3a** (35 mg, 0.093 mmole) in dry chloroform (10 ml) at 0° with stirring and then the reaction was allowed to proceed at 25° for 2 hours. Removal of the solvent *in vacuo*, purification of the product by preparative tlc using chloroform-ethyl acetate (4:1, v/v) as development solvent and extraction of the ultraviolet visible spot with ethyl acetate afforded **6k** as a viscous oil, (6 mg, 16%); ^{1}H nmr (chloroform-d_1): δ 1.12 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.12 (m, 7H, H-2', CH_3CO), 2.42 (m, 1H, H-2'), 3.4-4.68 (complex m, 3H, CHCl, OCH_2CH_3), 3.82 (m, 1H, CH'Cl), 4.18-4.42 (m, 3H, H-4', H-5'), 4.62 (m, 1H, CHOEt), 5.20 (m, 1H, H-3'), 6.37 (m, 1H, H-1'), 7.64 (s, 1H, H-6), 8.42 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C nmr (chloroform-d_1): δ 15.14 (OCH_2CH_3), 20.87 (CH_3CO), 37.91 (C-2'), 46.62 (CH_2Cl), 64.27 (OCH_2CH_3), 65.66 (C-5'), 73.38 (C-3'), 74.78 (CHOEt), 82.57 (C-1'), 84.92 (C-4'), 112.34 (C-5), 137.47 (C-6), 149.72 (C-2), 161.64 (C-4), 170.33 (CH_3CO), 170.59 (CH_3CO).

Anal. Calcd. for $C_{17}H_{23}ClN_2O_8 \cdot 5/4H_2O$: C, 46.26; H, 5.81; N, 6.34. Found: C, 46.61; H, 5.41; N, 6.68.

Reaction of 5-(1-Hydroxy-2-bromoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**3b**) with Thionyl Bromide.

Thionyl bromide (50 μ, 0.65 mmole) was added to a solution of **3b** (30 mg, 0.69 mmole) in dry chloroform (10 ml) at 0° with stirring. The reaction was allowed to proceed at 25° for 1 hour, the solvent was removed *in vacuo* and the residue was purified by elution from a silica gel column using chloroform-ethyl acetate (4:1, v/v) as eluent to yield 5-(1-ethoxy-2-bromoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6l**, 10 mg, 31% as a viscous oil); ^{1}H nmr (chloroform-d_1): (mixture of two diastereomers in a ratio of 1:1) δ 1.2 (two overlapping t, J = 7 Hz, 3H total, OCH_2CH_3), 2.18 (m, 7H, H-2', CH_3CO), 2.50 (m, 1H, H-2'), 3.4-3.65 (m, 3H, CHBr, OCH_2CH_3), 3.78 (m, 1H, CH'Br), 4.25-4.42 (m, 3H, H-4', H-5'), 4.62 (m, 1H, CHOEt), 5.27 (m, 1H, H-3'), 6.40 (m, 1H, H-1'), 7.62 and 7.70 (two s, 1H total, H-6), 9.0 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C nmr (chloroform-d_1): δ 15.12 and 15.28 (OCH_2CH_3), 20.85 and 20.99 (CH_3CO), 35.09 and 36.35 (CH_2Br), 37.52 and 37.85 (C-2'), 63.79 and 64.24 (OCH_2CH_3), 65.49 and 65.55 (C-5'), 72.60 and 72.69 (C-3'), 74.23 and 74.72 (CHOEt), 82.29 and 82.51 (C-1'), 84.82 and 85.25 (C-4'), 113.06 and 113.36 (C-5), 137.31 and 137.60 (C-6), 149.88 (C-2), 161.81 (C-4) and 170.60 (CH_3CO).

Anal. Calcd. for $C_{17}H_{23}BrN_2O_8 \cdot 1/4H_2O$: C, 43.64; H, 5.06; N, 5.99. Found: C, 43.91; H, 5.54; N, 6.54 [21].

Reaction of 5-Vinyl-3',5'-di-*O*-acetyl-2'-deoxyuridine (**2**) with Bromine.

A solution of bromine in dry benzene was added to a suspension of **2** (90 mg, 0.264 mmole) in dry benzene (5 ml) at 0° with stirring until the pale yellow color persisted. The reaction was allowed to proceed at 25° for 30 minutes, the solvent was removed *in vacuo* and the residue was dissolved in chloroform. This chloroform solution was washed with water, dried (sodium sulfate) and the solvent was removed. The residue obtained was purified by silica gel column chromatography using chloroform-methanol (97:3, v/v) as eluent. The first product eluted (37 mg, 30%) was identical (^{1}H nmr, ^{13}C nmr) to that of 5-(1-ethoxy-2-bromoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (**6l**). Further elution afforded 5-(1-hydroxy-2-bromoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine (70 mg, 60%) which was identical (mp, ^{1}H nmr) to that of **3b**.

2,3-Dihydro-3-hydroxy-5-(2'-deoxy-β-D-ribofuranosyl)furano-[2,3-*d*]pyrimidin-6(5*H*)-one (**8**).

A solution of **3b** (65 mg, 0.15 mmole) in a saturated solution of ammonia in methanol (5 ml) was stirred at 25° for 4 hours. Removal of the solvent *in vacuo* yielded a residue which was purified by silica gel column chromatography using chloroform-methanol (85:15, v/v) as eluent to yield **8** (20 mg, 49%) as a viscous oil; ^{1}H nmr (DMSO-d_6): (mixture of two diastereomers in a ratio of 1:1) δ 2.0 and 2.28 (two m, 1H each, H-2'), 3.65 (m, 2H, H-5'), 3.88 (m, 1H, H-4'), 4.23 (m, 1H, H-3'), 4.35 (d, J_{gem} = 10.2 Hz of d, J_{vic} = 2.71 Hz, 1H, furanyl CHCH*H'*), 4.70 (d, J_{gem} = 10.2 Hz of d, J_{vic} = 5.75 Hz, 1H, furanyl CHC*H*H'), 5.14 (m, 2H, furanyl C*H*OH, O*H*, hydroxyl exchanges with deuterium oxide), 5.29 (d, $J_{CH,OH}$ = 4.5 Hz, 1H, OH, exchanges with deuterium oxide), 5.76 and 5.80 (two d, $J_{CH,OH}$ = 4.5 Hz, 1H total, OH, exchanges with deuterium oxide), 6.14 (two overlapping d, J = 6 Hz of d, J = 6 Hz, 1H total, H-1'), 8.40 and 8.42 (two s, 1H total, H-6); ^{13}C nmr (methanol-d_4): δ 42.51 and 42.55 (C-2'), 62.52 (C-5'), 67.78 and 67.84 (C-3), 71.81 (C-3'), 82.50 (C-2), 88.96 and 89.07 (C-1'), 89.54 (C-4'), 110.07 (C-3a), 142.84 (C-4), 158.87 (C-6), 179.02 (C-7a).

Anal. Calcd. for $C_{11}H_{13}N_2O_6 \cdot 1/2H_2O$: C, 47.48; H, 5.06; N, 10.07. Found: C, 47.32; H, 4.93; N, 9.93.

Reaction of 5-(1-Fluoro-2-chloroethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine with Sodium Methoxide.

Sodium methoxide (11 mg, 0.2 mmole) was added to a solution of **6a** (28 mg, 0.071 mmole) in methanol (3 ml) with stirring and the reaction was allowed to proceed for 2 hours at 25°. The reaction mixture was neutralized to *p*H 7 using acidic resin Dowex 50X-8-200, the solvent was removed *in vacuo* and the residue obtained was purified by preparative tlc using chloroform-methanol (4:1, v/v) as development solvent. Extraction of the ultraviolet visible spot using chloroform-methanol (88:12, v/v) afforded 5-(1-methoxy-2-chloroethyl)-2'-deoxyuridine (**1j**, 13 mg, 57%); mp 155-158° dec which was identical (lit [20] mp 157° dec, ^{1}H nmr) to an authentic sample.

Reaction of 5-(1-Fluoro-2-bromoethyl)-3',5'-di-*O*-acetyl-2'-deoxyuridine with Methanolic Ammonia.

A solution of **6b** (35 mg, 0.08 mmole) in a saturated solution of ammonia in methanol (4 ml) was stirred at 25° for 2 hours. Removal of the solvent *in vacuo* and purification of the residue obtained by elution from a silica gel column using chloroform-methanol (88:12, v/v) as eluent yielded (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (**1a**, 2 mg, 7.5%), mp 125-128° dec (lit [11] mp 123-125° dec) which was identical (^{1}H nmr) to an authentic sample of **1a**. Further elution with the same solvent afforded 5-(2'-deoxy-β-D-ribofuranosyl)furano[2,3-*d*]pyrimidine-6(5H)-one (**9**, 10 mg, 50%) as a viscous oil); ^{1}H nmr (DMSO-d_6): δ 2.08 and 2.40 (two m, 1H, each, H-2'), 3.62 (m, 2H, H-5'), 3.92 (m, 1H, H-4'), 4.22 (m, 1H, H-3'), 5.15 (t, $J_{CH,OH}$ = 4.5 Hz, 1H, C-5' OH, exchanges with deuterium oxide), 5.30 (d, $J_{CH,OH}$ = 4.5 Hz, 1H, C-3' OH, exchanges with deuterium oxide), 6.16 (dd, J = 6 Hz, J = 6 Hz, 1H, H-1'), 6.80 (d, J = 2.5 Hz, 1H, OC*H* = CH), 7.74 (d, J = 2.5 Hz, 1H, OCH = C*H*), 8.86 (s, 1H, H-6); ^{13}C nmr (methanol-d_4): δ 42.89 (C-2'), 62.29 (C-5'), 71.37 (C-3'), 89.78 and 90.04 (C-1' and C-4'), 106.18 and 107.63 (C-3, C-3a), 140.56 (C-4), 146.40 (C-2),

156.80 (C-6), 173.16 (C-7a).

Anal. Calcd. for $C_{11}H_{12}N_2O_5 \cdot \frac{1}{2}H_2O$: C, 50.57; H, 5.01; N, 10.72. Found: C, 50.85; H, 4.82; N, 10.27.

Reaction of 5-(1-Fluoro-2-chloroethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine with Methanolic Ammonia.

Compound **6a** (30 mg, 0.076 mmole) was treated with a saturated solution of ammonia in methanol (4 ml) with a reaction time of 6 hours at 25° and the products were isolated and separated as described in the previous experiment. The first product eluted from the column was (E)-5-(2-chlorovinyl)-2′-deoxyuridine (**1b**, 5 mg, 23%), mp 153-156° dec; ^{1}H nmr (DMSO-d_6): δ 2.12 (m, 2H, H-2′), 3.58 (m, 2H, H-5′), 3.78 (m, 1H, H-4′), 4.23 (m, 1H, H-3′), 5.10 and 5.25 (two br s, 1H each, 3′-OH, 5′-OH, exchange with deuterium oxide), 6.12 (dd, J = 6 Hz, J = 6 Hz, 1H, H-1′), 6.57 (d, $J_{CH=CH}$ = 13 Hz, 1H, C*H* = CHCl), 7.14 (d, $J_{CH=CH}$ = 13 Hz, 1H, CH = C*H*Cl), 8.04 (s, 1H, H-6), 11.57 (br s, 1H, NH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{11}H_{13}ClN_2O_5 \cdot \frac{1}{2}H_2O$: C, 44.37; H, 4.73; N, 9.41. Found: C, 44.43; H, 4.55; N, 9.42. Further elution afforded **9** (2.5 mg, 13%) which was identical (^{1}H nmr) to the same product obtained in the previous experiment.

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[21] These were the best microanalytical values that we were able to obtain.