Synthesis and Biological Evaluation of 5-(1-Alkoxy-2-haloethyl)-2′-deoxyuridines and Related Uracil Analogues

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A new class of 5-[1-alkoxy-2-iodo(or 2,2-diiodo)ethyl] derivatives of 2′-deoxyuridine and uracil were synthesized by a regiospecific reaction of the C-5 vinyl substituent with iodine monochloride and an alcohol. These compounds were either weak or inactive antiviral and inactive cytotoxic agents.

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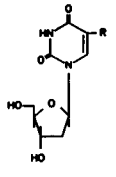
Introduction.

(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine (**1a**, BVDU) [1], (*E*)-5-(2-iodovinyl)-2′-deoxyuridine (**1b**, IVDU) [2] and 5-(2-chloroethyl)-2′-deoxyuridine (**1c**, CEDU) [3] are the most potent and selective antiviral agents against herpes simplex virus type 1 (HSV-1), from the many 5-substituted pyrimidine nucleosides that have been investigated [4]. In earlier studies, we reported that the 5-(1-methoxy-2-bromoethyl)- (**1d**, ID_{50} = 0.1-1 μg/ml) [5] and 5-(1-methoxy-2-iodoethyl)- (**1e**, ID_{50} = 0.1 μg/ml) [6] derivatives of 2′-deoxyuridine exhibited appreciable *in vitro* anti-HSV-1 activity, relative to acyclovir (ID_{50} = 0.01 μg/ml) or IVDU (ID_{50} < 0.1 μg/ml). Inactivation of CEDU is thought to result from hydroxylation of the C-5 substituent, in a manner similar to that reported for 5-ethyl-2′-deoxyuridine (**1f**, EDU) [7]. It was therefore of interest to develop further



1a: R= (E)-CH=CH-Br
1b: R= (E)-CH=CH-I
1c: R= CH_2CH_2Cl
1d: R= $CH(OMe)CH_2Br$
1e: R= $CH(OMe)CH_2I$
1f: CH_2CH_3

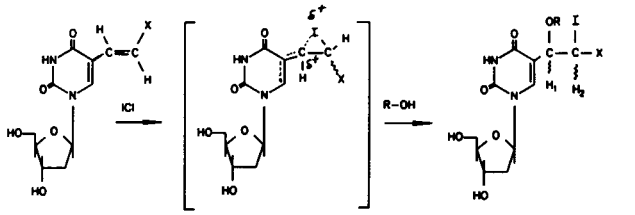
structure-activity correlations for the novel class of 5-(1-alkoxy-2-haloethyl)-2′-deoxyuridine compounds recently discovered which, unlike CEDU and EDU [7], are not expected to undergo inactivation due to hydroxylation of the C-5 substituent. However, like BVDU and EDU [8], these compounds could undergo selective phosphorylation by HSV-1 virus-encoded thymidine kinase to exhibit selective antiviral activity. We now report the synthesis, antiviral and cytotoxic activities of some novel 5-(1-alkoxy-2-iodoethyl) and 5-(1-ethoxy-2,2-diiodoethyl) derivatives of 2′-deoxyuridine **3a-d** and uracil **5a-d**.

Chemistry.

The target 5-(1-ethoxy-2,2-diiodoethyl) **3a** and 5-(1-alkoxy-2-iodoethyl) **3b-d** derivatives of 2′-deoxyuridine were synthesized, by reaction of the respective (*E*)-5-(2-iodovinyl) **2a** and 5-vinyl-2′-deoxyuridine (**2b**) with iodine monochloride and an alcohol such as ethanol, 2-fluoroethanol or 2,2,2-trifluoroethanol, in 33-90% yields as illustrated in Scheme 1. The products **3a-d** exist as mixtures of two diastereomers in a ratio of 1:1, which differ in configuration (*R* or *S*) at the 1- and/or 2-positions of the 5-[1-alkoxy-2-iodo (or 2,2-diiodo)ethyl] substituent that could not be separated by thin layer or column chromatography. The ^{13}C nmr (J modulated spin echo) spectra provided conclusive evidence for the regiospecific addition of ROI across the C-5 vinyl substituents of **2a-b**. For example, the iodine substituent of **3c** is attached to a methylene carbon that exhibited resonances at δ 10.33 and 11.01, whereas the 2-fluoroethoxy substituent is attached to a methine carbon which displayed resonances at δ 74.08 and 74.57. 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 1, even in solvents having a high dipole moment.

Similar reactions of 5-vinyluracil (**4**) with iodine monochloride in the presence of ethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol or 2,2,2-trichloroethanol afforded the respective 5-(1-ethoxy-2-iodoethyl) **5a**, 5-[1-(2-fluoroethoxy)-2-iodoethyl] **5b**, 5-[1-(2,2,2-trifluoroethoxy)-2-iodoethyl] **5c**

Scheme 1

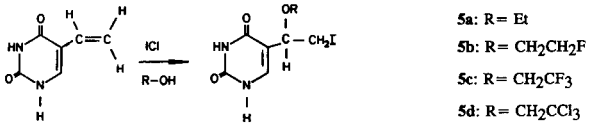


2a: X= I
2b: X= H

3a: R= Et; X= I
3b: R= Et; X= H
3c: R= CH_2CH_2F; X= H
3d: R= CH_2CF_3; X= H

and 5-[1-(2,2,2-trichloroethoxy)-2-iodoethyl] **5d** derivatives of uracil in 22-54% yields as illustrated in Scheme 2. In contrast to the 5-substituted-2′-deoxyuridines **3a-d**, compounds **5a-d** possess a single chiral atom and therefore can not exist as mixtures of diastereomers.

Scheme 2



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Biological Results.

The antiviral activities for the 5-(1-ethoxy-2,2-diiodoethyl)- **3a**, 5-(1-alkoxy-2-iodoethyl)-2′-deoxyuridines **3b-d**, and 5-(1-alkoxy-2-iodoethyl)uracils **5a-d** were determined by measuring their ability to inhibit the virus-induced cytopathic effect in Vero cells infected with herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). The 5-(1-ethoxy-2-iodoethyl **3b**, 5-[1-(2-fluoroethoxy)-2-iodoethyl)] **3c** and 5-(1-(2,2,2-trifluoroethoxy)-2-iodoethyl] **3d** analogues of 2′-deoxyuridine and 5-[1-(2,2,2-trifluoroethoxy)-2-iodoethyl]uracil (**5c**) exhibited MIC_{50} values of 25, 25, 25 and 20 μg/ml, respectively, relative to the reference drug BVDU (**1a**, MIC_{50} = 0.2 μg/ml). These test results indicate that a 5-[1-ethoxy-2,2-diiodoethyl] substituent **3a** is detrimental to antiviral activity since 5-(1-methoxy-2-iodoethyl)-2′-deoxyuridine (**1e**) [6] exhibited antiviral activity approaching the potency of IVDU (**1b**). Although compounds **3b** (R = C_2H_5), **3c** (R = CH_2CH_2F), **3d** (R = CH_2CF_3) and **5c** (R = CH_2CF_3) exhibit weak HSV-1 antiviral activity, these R substituents are less effective than a R = Me substituent [5,6]. Compounds **3a-d** and **5a-d** were inactive in the HSV-2 antiviral screen (MIC_{50} > 100 μg/ml), relative to BVDU (**1a**, MIC_{50} = 25 μg/ml). No cytotoxicity toward uninfected Vero cells was observed at test compound concentrations of 100 μg/ml.

Compounds **3a-d** and **5a-d** were also inactive anticancer agents in the *in vitro* KB cytotoxic screen at test compound concentrations of 10 μg/ml, relative to the reference drug 5-fluorouridine (ED_{50} = 0.5 μg/ml).

The antiviral and cytotoxicity test results suggest that these 5-(1-alkoxy-2-iodoethyl)- and 5-(1-alkoxy-2,2-diiodoethyl)-2′-deoxyuridines **3a-d** may not undergo phosphorylation by HSV-encoded deoxythymidine kinase which is a prerequisite for antiviral or cytotoxic activity, respectively.

EXPERIMENTAL

Melting points were determined with a Buchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H nmr, ^{13}C nmr) were determined for solutions in DMSO-d_6 or methanol-d_4 with TMS as internal standard (^{1}H nmr) with a Bruker AM-300 spectrometer. 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. Electron impact (EI) mass spectra were measured on a Hewlett Packard 5995A spectrometer. Silica gel column chromatography was carried out using Merck 7734 silica gel (100-200 μ particle size). Thin-layer chromatography (tlc) was performed with Whatman MK6F silica gel microslides (25 μ thickness). (*E*)-5-(2-Iodovinyl)-2′-deoxyuridine (**2a**) [10], 5-vinyl-2′-deoxyuridine (**2b**) [11] and 5-vinyluracil (**4**) [12] were prepared by using the literature procedures.

5-(1-Ethoxy-2,2-diiodoethyl)-2′-deoxyuridine (**3a**).

A solution of iodine monochloride (64.8 mg, 0.4 mmole) in ethanol (1 ml) was added to a solution of **2a** (125 mg, 0.33 mmole) in ethanol (3 ml) and the mixture was allowed to react for one hour with stirring at 50°. Removal of the solvent *in vacuo* gave a pale brown oil which was purified by preparative tlc using chloroform-methanol (9:1, v/v) as development solvent. Extraction of the ultraviolet visualized band with chloroform-methanol (88:12, v/v) afforded **3a** as a viscous oil which solidified upon trituration with hexane (80 mg, 44%), mp 136-140° dec; ^{1}H nmr (DMSO-d_6): (mixture of two diastereomers in a ratio of 1:1) δ 1.14 (t, J = 7 Hz, 3H, Me), 2.0 and 2.12 (two m, 1H each, H-2′), 3.42 and 3.46 (two q, J = 7 Hz, 2H total, OCH_2CH_3), 3.52 (m, 2H, H-5′), 3.80 (m, 1H, H-4′), 4.06 and 4.10 (two d, J = 3.4 Hz, 1H total, $CHCHI_2$), 4.22 (m, 1H, H-3′), 4.50 (br s, 2H, 3′-OH, 5′-OH, exchanges with deuterium oxide), 5.28 and 5.32 (two d, J = 3.4 Hz, 1H total, $CHCHI_2$), 6.14 and 6.18 (two t, J = 6 Hz, 1H total, H-1′), 7.82 and 7.87 (two s, 1H total, H-6), 11.53 and 11.55 (two s, 1H total, NH, exchanges with deuterium oxide); ^{13}C nmr (DMSO-d_6): δ −15.75 and −16.51 (CHI_2), 14.90 and 14.99 (CH_3), 61.34 and 61.57 (C-5′), 65.26 (OCH_2CH_3), 70.38 and 70.66 (C-3′), 79.26 and 79.54 (C-1′), 84.18 and 84.67 ($CHCHI_2$), 87.42 and 87.56 (C-4′), 111.14 and 111.35 (C-5), 138.66 (C-6), 149.78 (C-2), 162.18 (C-4).

Anal. Calcd. for $C_{13}H_{18}I_2N_2O_6$: C, 28.27; H, 3.28; N, 5.07. Found: C, 28.53; H, 3.59; N, 4.84.

5-(1-Ethoxy-2-iodoethyl)-2′-deoxyuridine (**3b**).

A solution of **2b** (50.8 mg, 0.2 mmole) and iodine monochloride (32.4 mg, 0.2 mmole) in ethanol (5 ml) was stirred at 25° for 10 minutes at which time tlc indicated the reaction was complete. Removal of the solvent *in vacuo* gave a residue which was purified by silica gel column chromatography. Elution with chloroform-ethanol (90:10, v/v) afforded **3b** (40 mg, 47%), mp 106-110° dec; ^{1}H nmr (methanol-d_4): (mixture of two diastereomers in a ratio of 1:1) δ 1.1 (two overlapping t, 3H, Me), 2.25 (m, 2H, H-2′), 3.32 (m, 1H, CHH′I), 3.52 (m, 3H, CH_2CH_3 and CHH′I), 3.76 (m, 2H, H-5′), 3.94 (m, 1H, H-4′), 4.28 (m, 1H, CHCHH′I), 4.40 (m, 1H, H-3′), 6.30 (two overlapping d, 1H total, H-1′), 7.96 and 8.04 (2 s, 1H total, H-6); ^{13}C nmr (methanol-d_4): δ 10.69 and 9.43 (CH_2I), 15.51 (Me), 41.54 and 41.42 (C-2′), 62.94 (C-5′), 66.37 and 66.16 (OCH_2CH_3), 72.40 and 72.30 (C-3′), 75.86 and 74.93 ($CHCH_2I$), 86.77 and 86.62 (C-1′), 89.04 and 88.96 (C-4′), 114.20 (C-5), 139.79 (C-6), 151.91 (C-2), 164.54 (C-4).

Anal. Calcd. for $C_{13}H_{19}IN_2O_6 \cdot 1H_2O$: C, 35.14; H, 4.76; N, 6.30. Found: C, 34.91; H, 4.46; N, 6.44.

5-[1-(2-Fluoroethoxy)-2-iodoethyl]-2′-deoxyuridine (**3c**).

A solution of iodine monochloride (81 mg, 0.5 mmole) in 2-fluoroethanol (1 ml) was added to a solution of **2b** (125 mg, 0.49 mmole) in 2-fluoroethanol (2 ml) and the reaction was allowed to proceed at 50° for one hour with stirring. Removal of the solvent *in vacuo* and elution of the product from a silica gel column using chloroform-methanol (97:3, v/v) as eluent yielded **3c** (125 mg, 57%) as a white foam, mp 94-96° dec; ^{1}H nmr (DMSO-d_6): (mixture of two diastereomers in a ratio of 1:1) δ 2.1 (m, 2H, H-2'), 3.28 (m, 1H, CH*H*'I), 3.38 (m, 1H, C*H*H'I), 3.5 (m, 2H, H-5'), 3.70 (br s, 2H, 3'-OH, 5'-OH, exchanges with deuterium oxide), 3.65 (m, 2H, OCH_2), 3.78 (m, 1H, H-4'), 4.20 (m, 1H, H-3'), 4.30 (m, 1H, C*H*CH_2I), 4.52 (d, J = 48 of d, J = 7 of d, J = 7 Hz, 2H, CH_2F), 6.16 and 6.18 (two t, J = 6 Hz, 1H total, H-1'), 7.80 and 7.82 (two s, 1H total, H-6), 10.48 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C nmr (DMSO-d_6): δ 10.33 and 11.01 (*C*H$_2$I), 40.34 (C-2', overlapped by solvent resonances), 61.34 and 61.42 (C-5'), 68.29, 68.43, 68.55 and 68.67 (O*C*H$_2$CH$_2$F, coupling to fluorine in each diastereomer), 70.52 (C-3'), 74.08 and 74.57 (*C*HCH$_2$I), 81.89 and 84.11 (*C*H$_2$F, couples to fluorine), 84.51 and 84.64 (C-1'), 87.53 and 87.62 (C-4'), 111.95 (C-5), 137.96 and 138.14 (C-6), 150.11 (C-2), 162.37 (C-4).

Anal. Calcd. for $C_{13}H_{18}FIN_2O_6$: C, 35.14; H, 4.08; N, 6.30. Found: C, 35.13; H, 4.36. N, 5.93.

5-[1-(2,2,2-Trifluoroethoxy)-2-iodoethyl]-2'-deoxyuridine (**3d**).

A solution of **2b** (150 mg, 0.59 mmole) in acetonitrile (20 ml), 2,2,2-trifluoroethanol (6 ml) and water (1 drop) was warmed to 50° and this temperature was maintained for 15 minutes. A solution of iodine monochloride (27.2 mg, 0.6 mmole) in acetonitrile (2 ml) was added to the clear solution previously prepared and the reaction was allowed to proceed at 50° for 15 minutes with stirring. Removal of the solvent *in vacuo* and purification of the product by elution from a silica gel column using dichloromethane-methanol (98:2, v/v) as eluent yielded **3d** (95 mg, 33%), mp 120-125° dec; ^{1}H nmr: (mixture of two diastereomers in a ratio of 1:1) δ 2.12 (m, 2H, H-2'), 3.36 (m, 1H, CH*H*'I), 3.45 (m, 1H, *H*H'I), 3.55 (m, 2H, H-5'), 3.78 (m, 1H, H-4'), 4.08 (q, J = 9.6 Hz, 2H, CH_2CF$_3$), 4.24 (m, 1H, H-3'), 4.48 (m, 1H, C*H*CHH'I), 6.14 and 6.19 (two t, J = 6 Hz, 1H total, H-1'), 6.68 and 7.28 (two br s, 1H each, exchanges with deuterium oxide), 7.84 and 7.86 (two s, 1H, total, H-6), 11.50 and 11.54 (two s, 1H total, NH, exchanges with deuterium oxide); ^{13}C nmr (DMSO-d_6): δ 7.45 and 8.39 (*C*H$_2$I), 41.48 and 41.57 (C-2'), 62.23 and 62.81 (C-5'), 66.94, 67.39, 67.84 and 68.29 (*C*H$_2$CF$_3$, couples to fluorine in each diastereomer, J_{CCF} = 34 Hz), 72.18 and 72.24 (C-3'), 77.04 and 77.78 (*C*HCH$_2$I), 86.65 and 86.81 (C-1'), 88.95 and 89.07 (C-4'), 112.76 (C-5), 119.85, 123.54, 127.23 and 130.92 (*C*F$_3$, $J_{C,F}$ = 277 Hz), 140.32 and 140.38 (C-6), 151.20 (C-2), 163.02 (C-4).

Anal. Calcd. for $C_{13}H_{16}F_3IN_2O_6 \cdot 2H_2O$: C, 30.24; H, 3.89; N, 5.42. Found: C, 30.31; H, 3.79; N, 5.17.

5-(1-Ethoxy-2-iodoethyl)uracil (**5a**).

A solution of **4** (33.1 mg, 0.24 mmole) and iodine monochloride (40 mg, 0.246 mmole) in ethanol (3 ml) was maintained at 50° for one hour with stirring. The solution was allowed to cool to 25°, the solvent was removed *in vacuo*, and the product was purified by elution from a silica gel column using chloroform-methanol (19:1, v/v) as eluent to yield **5a**, (40 mg, 54%) after recrystallization from ethanol, mp 136-140° dec; ^{1}H nmr (DMSO-d_6) δ 1.1 (t, J = 7 Hz, 3H, Me), 3.3 (d, J_{gem} = 10.8 of d, J_{vic} = 6.0 Hz, 1H, C*H*H'I), 3.38 (q, J = 7 Hz, 2H, CH_2CH$_3$), 3.52 (d, J_{gem} = 10.8 Hz of d, J_{vic} = 4.2 Hz, 1H, CH*H*'I), 4.13 (d, J_{vic} = 6.0 of d, J_{vic} = 4.2 Hz, 1H, C*H*CHH'I), 7.28 (d, $J_{NH,6}$ = 6 Hz, 1H, H-6, collapses to a singlet after exchange with deuterium oxide), 10.98 (d, $J_{NH,6}$ = 6 Hz, 1H, N^1-H, exchanges with deuterium oxide), 11.22 (s, 1H, N^3-H, exchanges with deuterium oxide); ^{13}C nmr (DMSO-d_6): δ 11.97 (*C*H$_2$I), 15.39 (Me), 64.56 (O*C*H$_2$CH$_3$), 73.43 (*C*HCH$_2$I), 111.44 (C-5), 139.38 (C-6), 151.07 (C-2), 163.61 (C-4); ms: (EI) m/z 310 (M$^+$).

Anal. Calcd. for $C_8H_{11}IN_2O_3$: C, 30.98; H, 3.57; N, 9.03. Found: C, 30.86; H, 3.51; N, 8.87.

5-[1-(2-Fluoroethoxy)-2-iodoethyl]uracil (**5b**).

A solution of iodine monochloride (80 mg, 0.49 mmole) in acetonitrile (2 ml) was added to a solution of **4** (99.4 mg, 0.72 mmole) in acetonitrile (5 ml) and 2-fluoroethanol (2 ml). The reaction was allowed to proceed at 50° for 15 minutes, the solvent was removed *in vacuo*, and the product was purified by elution from a silica gel column using dichloromethane-methanol (97:3, v/v) as eluent to afford **5b** as a white solid after recrystallization from methanol (90 mg, 37%), mp 145-148° dec; ^{1}H nmr (DMSO-d_6): δ 3.38 (d, J_{gem} = 10.2 of d, J_{vic} = 6.0 Hz, 1H, C*H*H'I), 3.56 (d, J_{gem} = 10.2 of d, J_{vic} = 3.9 Hz, 1H, CH*H*'I), 3.65 (m, 2H, OCH_2CH$_2$F), 4.28 (d, J_{gem} = 6.0 of d, J_{vic} = 3.9 Hz, 1H, C*H*CHH'I), 4.52 (d, J = 52.8 of d, J = 6.5 of d, J = 6.5 Hz, 1H, CH_2F), 7.30 (d, $J_{NH,6}$ = 6.2 Hz, 1H, H-6, collapses to a singlet after exchange with deuterium oxide), 11.0 (d, $J_{NH,6}$ = 6.2 Hz, 1H, N^1-H, exchanges with deuterium oxide), 11.22 (s, 1H, N^3-H, exchanges with deuterium oxide); ^{13}C nmr (DMSO-d_6): δ 11.14 (*C*H$_2$I) 68.18 and 68.43 (O*C*H$_2$CH$_2$F, J_{CCF} = 18 Hz), 73.94 (*C*HCH$_2$I), 81.87 and 84.06 (*C*H$_2$F, J_{CF} = 164 Hz), 110.60 (C-5), 139.30 (C-6), 150.87 (C-2), 163.25 (C-4); ms: (EI) m/z 328 (M$^+$).

Anal. Calcd. for $C_8H_{10}FIN_2O_3$: C, 29.28; H, 3.07; N, 8.54. Found: C, 29.51; H, 2.79; N, 8.38.

5-[(1-(2,2,2-Trifluoroethoxy)-2-iodoethyl]uracil (**5c**).

A solution of iodine monochloride (64.8 mg, 0.4 mmole) in dry acetonitrile (1 ml) was added to a solution of **4** (70 mg, 0.5 mmole) in acetonitrile (6 ml), 2,2,2-trifluoroethanol (3 ml) and water (1 drop). The reaction was allowed to proceed at 50° for 15 minutes with stirring, the solvent was removed *in vacuo*, and the product was eluted from a silica gel column using dichloromethane-methanol (49:1, v/v) as eluent to afford **5c** (70 mg, 38%) after recrystallization from methanol, mp 140-145° dec; ^{1}H nmr (DMSO-d_6): δ 3.48 (d, J_{gem} = 10.5 of d, J_{vic} = 6.4 Hz, 1H, C*H*H'I), 3.60 (d, J_{gem} = 10.5 of d, J_{vic} = 4.4 Hz, 1H, CH*H*'I), 4.1 (q, $J_{CH,CF}$ = 8.9 Hz, 2H, CH_2CF$_3$), 4.46 (d, J_{vic} = 6.4 of d, J_{vic} = 4.4 Hz, 1H, C*H*CHH'I), 7.36 (d, $J_{NH,6}$ = 7 Hz, 1H, H-6, collapses to a singlet after deuterium oxide exchange), 11.06 (d, $J_{NH,6}$ = 7 Hz, 1H, N^1-H, exchanges with deuterium oxide), 11.28 (s, 1H, N^3-H); ^{13}C nmr (DMSO-d_6): δ 9.25 (*C*H$_2$I), 64.75, 65.17, 65.61 and 66.06 (*C*H$_2$CF$_3$), J_{CCF} coupling), 75.41 (*C*HCH$_2$I), 109.37 (C-5), 118.64, 122.32, 126.00 and 129.68 (*C*F$_3$), 139.92 (C-6), 150.83 (C-2), 162.99 (C-4).

Anal. Calcd. for $C_8H_8F_3IN_2O_3 \cdot 1H_2O$: C, 25.14; H, 2.63; N, 7.33. Found: C, 25.42; H, 2.76; N, 7.19.

5-[(1-(2,2,2-Trichloroethoxy)-2-iodoethyl]uracil (**5d**).

A solution of iodine monochloride (64.8 mg, 0.4 mmole) in dry acetonitrile (1 ml) was added to a solution of **4** (60 mg, 0.44 mmole) in acetonitrile (6 ml) and 2,2,2-trichloroethanol (3 ml). The reaction was allowed to proceed at 50° for 15 minutes with

stirring, the solvent was removed *in vacuo*, and the product was eluted from a silica gel column using dichloromethane-methanol (49:1, v/v) as eluent to afford **5d** (40 mg, 22%) mp 165-170° dec; ^{1}H nmr (DMSO-d_6): δ 3.56 (d, J_{gem} = 11 of d, J_{vic} = 6 Hz, 1H, C*H*H'I), 3.70 (d, J_{gem} = 11 of d, J_{vic} = 4.2 Hz, 1H, CH*H'*I), 4.25 (s, 2H, CH_2CCl_3), 4.62 (d, J_{vic} = 6 of d, J_{vic} = 4.2 Hz, 1H, C*H*CHH'I), 7.43 (d, $J_{NH,6}$ = 6 Hz, 1H, H-6, collapses to a singlet after deuterium oxide exchange), 11.10 (d, $J_{NH,6}$ = 6 Hz, 1H, N^1-H, exchanges with deuterium oxide), 11.30 (s, 1H, N^3-H, exchanges with deuterium oxide); ms: (EI) m/z 412 (M^+).

Anal. Calcd. for $C_8H_8Cl_3IN_2O_3$: C, 23.23; H, 1.95; N, 6.77. Found: C, 23.58; H, 1.96; N, 6.78.

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