

Rakesh Kumar, Leonard I. Wiebe and E. E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta,
Edmonton, Alberta, Canada T6G 2N8

Mark L. Tempest

SynPhar Laboratories Inc., 4290-91A Street,
Edmonton, Alberta, Canada T6E 5V2

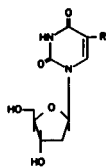
Received June 21, 1990

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.

J. Heterocyclic Chem., **28**, 237 (1991).

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**, ID₅₀ = 0.1-1 μg/ml) [5] and 5-(1-methoxy-2-iodoethyl)- (**1e**, ID₅₀ = 0.1 μg/ml) [6] derivatives of 2'-deoxyuridine exhibited appreciable *in vitro* anti-HSV-1 activity, relative to acyclovir (ID₅₀ = 0.01 μg/ml) or IVDU (ID₅₀ < 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 = CH₂CH₂Cl
1d: R = CH(OMe)CH₂Br
1e: R = CH(OMe)CH₂I
1f: R = CH₂CH₃

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**.

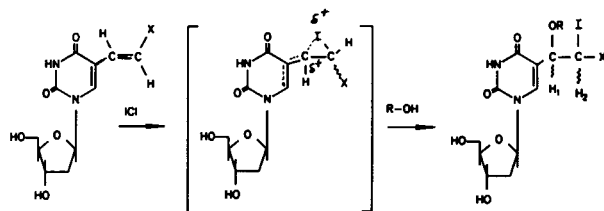
Chemistry.

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 ¹³C 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 re-

Scheme 1



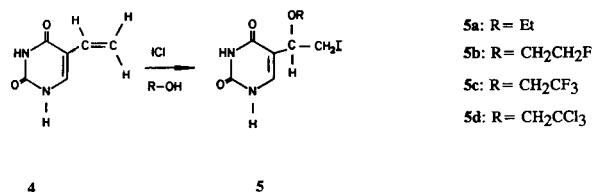
- 2a:** X = I
2b: X = H

- 3a:** R = Et; X = I
3b: R = Et; X = H
3c: R = CH₂CH₂F; X = H
3d: R = CH₂CF₃; X = H

spective 5-(1-ethoxy-2-iodoethyl) **5a**, 5-[1-(2-fluoroethoxy)-2-iodoethyl] **5b**, 5-[1-(2,2,2-trifluoroethoxy)-2-iodoethyl] **5c**

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



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 MIC₅₀ values of 25, 25, 25 and 20 µg/ml, respectively, relative to the reference drug BVDU (**1a**, MIC₅₀ = 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 = C₂H₅), **3c** (R = CH₂CH₂F), **3d** (R = CH₂CF₃) and **5c** (R = CH₂CF₃) 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 (MIC₅₀ > 100 µg/ml), relative to BVDU (**1a**, MIC₅₀ = 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 (ED₅₀ = 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 (¹H

nmr, ¹³C nmr) were determined for solutions in DMSO-d₆ or methanol-d₄ with TMS as internal standard (¹H nmr) with a Bruker AM-300 spectrometer. The ¹³C nmr spectra were determined using the J modulated spin echo technique where methylene 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; ¹H nmr (DMSO-d₆): (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, OCH₂CH₃), 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, CHCH₂), 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, CHCH₂), 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); ¹³C nmr (DMSO-d₆): δ - 15.75 and - 16.51 (CH₂), 14.90 and 14.99 (CH₃), 61.34 and 61.57 (C-5'), 65.26 (OCH₂CH₃), 70.38 and 70.66 (C-3'), 79.26 and 79.54 (C-1'), 84.18 and 84.67 (CHCH₂), 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 C₁₃H₁₈I₂N₂O₆: 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; ¹H nmr (methanol-d₄): (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, CH₂CH₃ 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); ¹³C nmr (methanol-d₄): δ 10.69 and 9.43 (CH₂I), 15.51 (Me), 41.54 and 41.42 (C-2'), 62.94 (C-5'), 66.37 and 66.16 (OCH₂CH₃), 72.40 and 72.30 (C-3'), 75.86 and 74.93 (CHCH₂I), 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 C₁₃H₁₉I₂N₂O₆·1H₂O: 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; ¹H nmr (DMSO-d₆): (mixture of two diastereomers in a ratio of 1:1) δ 2.1 (m, 2H, H-2'), 3.28 (m, 1H, CHH'), 3.38 (m, 1H, CHH'), 3.5 (m, 2H, H-5'), 3.70 (br s, 2H, 3'-OH, 5'-OH, exchanges with deuterium oxide), 3.65 (m, 2H, OCH₂), 3.78 (m, 1H, H-4'), 4.20 (m, 1H, H-3'), 4.30 (m, 1H, CHCH₂I), 4.52 (d, J = 48 of d, J = 7 of d, J = 7 Hz, 2H, CH₂F), 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); ¹³C nmr (DMSO-d₆): δ 10.33 and 11.01 (CH₂I), 40.34 (C-2', overlapped by solvent resonances), 61.34 and 61.42 (C-5'), 68.29, 68.43, 68.55 and 68.67 (OCH₂CH₂F, coupling to fluorine in each diastereomer), 70.52 (C-3'), 74.08 and 74.57 (CHCH₂I), 81.89 and 84.11 (CH₂F, 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 C₁₃H₁₈FIN₂O₆: 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; ¹H nmr: (mixture of two diastereomers in a ratio of 1:1) δ 2.12 (m, 2H, H-2'), 3.36 (m, 1H, CHH'), 3.45 (m, 1H, HH'), 3.55 (m, 2H, H-5'), 3.78 (m, 1H, H-4'), 4.08 (q, J = 9.6 Hz, 2H, CH₂CF₃), 4.24 (m, 1H, H-3'), 4.48 (m, 1H, CHCHH'), 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); ¹³C nmr (DMSO-d₆): δ 7.45 and 8.39 (CH₂I), 41.48 and 41.57 (C-2'), 62.23 and 62.81 (C-5'), 66.94, 67.39, 67.84 and 68.29 (CH₂CF₃, couples to fluorine in each diastereomer, J_{CCF} = 34 Hz), 72.18 and 72.24 (C-3'), 77.04 and 77.78 (CHCH₂I), 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 (CF₃, J_{CF} = 277 Hz), 140.32 and 140.38 (C-6), 151.20 (C-2), 163.02 (C-4).

Anal. Calcd. for C₁₃H₁₆F₃IN₂O₅·2H₂O: 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; ¹H nmr (DMSO-d₆) δ 1.1 (t, J = 7 Hz, 3H, Me), 3.3 (d, J_{gem} = 10.8 of d, J_{vic} = 6.0 Hz, 1H, CHH'), 3.38 (q, J = 7 Hz, 2H, CH₂CH₃), 3.52 (d, J_{gem} = 10.8 Hz

of d, J_{vic} = 4.2 Hz, 1H, CHH'), 4.13 (d, J_{vic} = 6.0 of d, J_{vic} = 4.2 Hz, 1H, CHCHH'), 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, N¹-H, exchanges with deuterium oxide), 11.22 (s, 1H, N³-H, exchanges with deuterium oxide); ¹³C nmr (DMSO-d₆): δ 11.97 (CH₂I), 15.39 (Me), 64.56 (OCH₂CH₃), 73.43 (CHCH₂I), 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 C₈H₁₁IN₂O₃: 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; ¹H nmr (DMSO-d₆): δ 3.38 (d, J_{gem} = 10.2 of d, J_{vic} = 6.0 Hz, 1H, CHH'), 3.56 (d, J_{gem} = 10.2 of d, J_{vic} = 3.9 Hz, 1H, CHH'), 3.65 (m, 2H, OCH₂CH₂F), 4.28 (d, J_{gem} = 6.0 of d, J_{vic} = 3.9 Hz, 1H, CHCHH'), 4.52 (d, J = 52.8 of d, J = 6.5 of d, J = 6.5 Hz, 1H, CH₂F), 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, N¹-H, exchanges with deuterium oxide), 11.22 (s, 1H, N³-H, exchanges with deuterium oxide); ¹³C nmr (DMSO-d₆): δ 11.14 (CH₂I) 68.18 and 68.43 (OCH₂CH₂F, J_{CCF} = 18 Hz), 73.94 (CHCH₂I), 81.87 and 84.06 (CH₂F, 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 C₈H₁₀FIN₂O₃: 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; ¹H nmr (DMSO-d₆): δ 3.48 (d, J_{gem} = 10.5 of d, J_{vic} = 6.4 Hz, 1H, CHH'), 3.60 (d, J_{gem} = 10.5 of d, J_{vic} = 4.4 Hz, 1H, CHH'), 4.1 (q, J_{CH,CF} = 8.9 Hz, 2H, CH₂CF₃), 4.46 (d, J_{vic} = 6.4 of d, J_{vic} = 4.4 Hz, 1H, CHCHH'), 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, N¹-H, exchanges with deuterium oxide), 11.28 (s, 1H, N³-H); ¹³C nmr (DMSO-d₆): δ 9.25 (CH₂I), 64.75, 65.17, 65.61 and 66.06 (CH₂CF₃), J_{CCF} coupling), 75.41 (CHCH₂I), 109.37 (C-5), 118.64, 122.32, 126.00 and 129.68 (CF₃), 139.92 (C-6), 150.83 (C-2), 162.99 (C-4).

Anal. Calcd. for C₈H₈F₃IN₂O₃·H₂O: 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; ¹H nmr (DMSO-*d*₆): δ 3.56 (d, *J*_{gem} = 11 of d, *J*_{vic} = 6 Hz, 1H, CHH'I), 3.70 (d, *J*_{gem} = 11 of d, *J*_{vic} = 4.2 Hz, 1H, CHH'I), 4.25 (s, 2H, CH₂CCl₃), 4.62 (d, *J*_{vic} = 6 of d, *J*_{vic} = 4.2 Hz, 1H, CHCHH'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, N¹-H, exchanges with deuterium oxide), 11.30 (s, 1H, N³-H, exchanges with deuterium oxide); ms: (EI) *m/z* 412 (M⁺).

Anal. Calcd. for C₈H₈Cl₂IN₂O₃: C, 23.23; H, 1.95; N, 6.77. Found: C, 23.58; H, 1.96; N, 6.78.

Acknowledgments.

We are grateful to the Medical Research Council of Canada (Grant No. MA-5965) for financial support of this work, and to the Alberta Heritage Foundation for Medical Research for a fellowship to one of us (R.K.).

REFERENCES AND NOTES

[1] E. De Clercq, J. Descamps, P. De Somer, P. Barr, A. S. Jones and R. T. Walker, *Proc. Natl. Acad. Sci. U. S. A.*, **76**, 2947 (1979).

[2] M. E. Perlman, K. A. Watanabe, R. F. Schinazi and J. J. Fox, *J. Med. Chem.*, **28**, 741 (1985).

[3] H. Griengl, M. Bodenteich, W. Hayden, E. Wanek, W. Streicher, P. Stutz, H. Bachmayer, I. Ghazzouli and B. Rosenwirth, *J. Med. Chem.*, **28**, 1679 (1985).

[4] E. De Clercq, in *Approaches to Antiviral Agents*, M. R. Harnden ed, MacMillan, London, 1985, p 57.

[5] R. Kumar, L. I. Wiebe, T. W. Hall, E. E. Knaus, D. R. Tovell, D. L. Tyrrell, T. M. Allen and R. Fathi-Afshar, *J. Med. Chem.*, **32**, 941 (1989).

[6] R. Kumar, L. Xu, E. E. Knaus, L. I. Wiebe, D. R. Tovell, D. L. Tyrrell and T. M. Allen, *J. Med. Chem.*, **33**, 717 (1990).

[7] E. Szinai, M. Bihari, K. Ujszaszy, Z. Veras, A. Szaboles, S. Holly, E. Gacs-Baitz and L. Otvos, in *Bio-organic Heterocycles*, H. C. Van der Plas, L. Otvos and M. Simonyi, eds, Elsevier Press, Amsterdam, 1985, p 335.

[8] E. De Clercq and R. Bernaerts, *J. Biol. Chem.*, **262**, 14905 (1987).

[9] D. R. Dalton, V. P. Dutta and D. C. Jones, *J. Am. Chem. Soc.*, **90**, 5498 (1968).

[10] A. S. Jones, G. Verhelst and R. T. Walker, *Tetrahedron Letters*, 4415 (1979).

[11] S. G. Rahim, M. J. H. Duggan, R. T. Walker, A. S. Jones, R. L. Dyer, J. Balzarini and E. De Clercq, *Nucleic Acids Res.*, **10**, 5285 (1982).

[12] R. Kumar, L. I. Wiebe, E. E. Knaus, T. M. Allen, R. Fathi-Afshar, D. R. Tovell and D. L. Tyrrell, *Drug Design Delivery*, **4**, 227 (1989).