Synthesis of 1-Alkoxy-5-alkyluracils

Dae-Kee Kim*, Ganghyeok Kim, Jinsoo Lim and Key H. Kim

Life Science Research Center, Sunkyong Industries, 600, Jungja-Dong,
Changan-Ku, Suwon-Si, Kyungki-Do 440-745, Korea

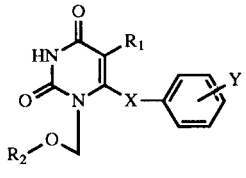
Received April 27, 1995

1-Alkoxy-5-alkyluracils **2a-f** have been prepared by the reaction of 2-alkyl-3-methoxyacryloyl isocyanates **8a-b** with alkoxyamines **9a-c** followed by cyclization of the resulting *N*-alkoxy-*N'*-(2-alkyl-3-methoxyacryloyl)ureas **10a-f**. The isocyanates **8a-b** were prepared from ethyl 2-alkylacrylates **3a-b** in 5 steps.

J. Heterocyclic Chem., **32**, 1625 (1995).

Acquired immunodeficiency syndrome (AIDS) [1], caused by human immunodeficiency virus (HIV), is one of the world's most serious health problems, with current protocols being inadequate for either prevention or successful long-term treatment. The nucleoside derivative 3'-azido-3'-deoxythymidine (AZT), a potent reverse transcriptase (RT) inhibitor of HIV, is known to prolong survival in AIDS patients [2], yet its long-term treatment is often associated with serious side effects such as bone marrow suppression [3]. Furthermore, prolonged AZT treatment often leads to the emergence of AZT-resistant HIV-1 strains [4]. It seems, therefore, still imperative to find novel chemotherapeutic agents that have potent antiviral activity and low toxicity.

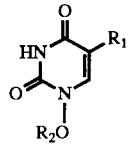
The acyclic 6-substituted uridine derivative 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) **1a** is a potent and HIV-1-specific RT inhibitor [5]. Several of HEPT derivatives such as 1-(benzyloxymethyl)-6-[(3,5-dimethylphenyl)thio]-5-ethyluracil **1b** [6], 5-ethyl-1-(ethoxymethyl)-6-(phenylselenenyl)-uracil **1c** [7], and 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil **1d** [8] inhibit HIV-1 replication in the nanomolar concentration range. As a part of our program to develop metabolically stable HEPT analogues, 6-substituted-1-alkoxy-5-alkyluracils, we required to synthesize 1-alkoxy-5-alkyluracils **2a-f** as the key intermediates.



1

a: R_1 = Me, R_2 = CH_2CH_2OH, X = S, Y = H
b: R_1 = Et, R_2 = CH_2Ph, X = S, Y = 3,5-Me_2
c: R_1 = Et, R_2 = Et, X = Se, Y = H
d: R_1 = *i*-Pr, R_2 = Et, X = CH_2, Y = H

Scheme 1 illustrates the synthetic approach used in the preparation of 1-alkoxy-5-alkyluracils **2a-f**. Ethyl 2-alkylacrylates **3a-b** were prepared by reaction of alkyl malonic acid monoester with formaldehyde and diethylamine according to a published method [9]. Bromination of **3a-b** with bromine in ethanol at room temperature gave the dibromo compounds **4a-b**. Reaction of **4a-b** with sodium methoxide in methanol at reflux temperature yielded a mixture of methyl 2-alkyl-3-methoxyacrylates **5a-b** and the corresponding methyl 2-alkyl-3,3-dimethoxypropionates, which were completely converted to the **5a-b** when heated at 180° in the presence of sodium bisulfate. Dörnyei *et al.* [10] previously reported that methylation of the sodium salt of methyl 2-formyl-3-methylbutyrate with dimethyl sulfate in benzene afforded a mixture of **5b** and its *Z*-isomer (58:42) in 68% yield. It is noteworthy that the *E*-isomers **5a-b** were obtained from **4a-b** as the sole products in this reaction in excellent yields. Hydrolysis of **5a-b** with 2*N* sodium hydroxide at reflux temperature gave 2-alkyl-3-methoxyacrylic acids **6a-b**. The compounds **6a-b** were reacted with oxalyl chloride in the presence of one drop of *N,N*-dimethylformamide in benzene at room temperature to give 2-alkyl-3-methoxyacryloyl chlorides **7a-b**. Employing the method of Shaw and Warrener [11], the compounds **7a-b** were treated with silver cyanate in benzene at reflux temperature to generate isocyanates **8a-b** *in situ*, which were subsequently reacted with alkoxyamines **9a-c** at room temperature to yield *N*-alkoxy-*N'*-(2-alkyl-3-methoxyacryloyl)ureas **10a-f**.

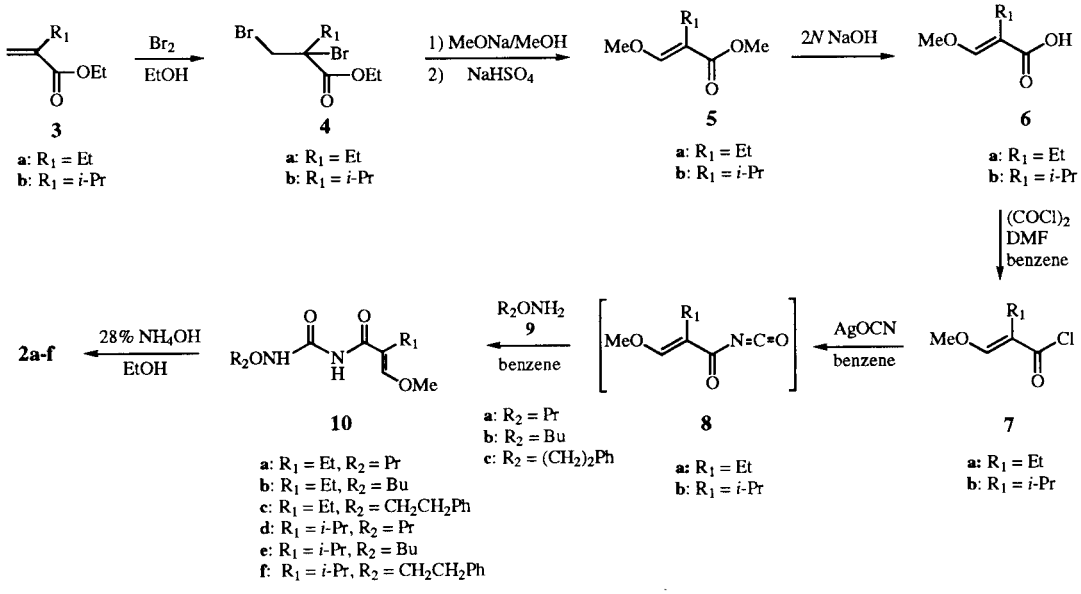


2

a: R_1 = Et, R_2 = Pr
b: R_1 = Et, R_2 = Bu
c: R_1 = Et, R_2 = CH_2CH_2Ph
d: R_1 = *i*-Pr, R_2 = Pr
e: R_1 = *i*-Pr, R_2 = Bu
f: R_1 = *i*-Pr, R_2 = CH_2CH_2Ph

Cyclization of ureas **10a-f** in 28% aqueous ammonium hydroxide solution and ethanol afforded 1-alkoxy-5-alkyluracils **2a-f** in excellent yields.

Scheme 1



EXPERIMENTAL

Melting points were determined on either an Electrothermal F500MA digital or a Mettler FP62 melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. The ^{1}H nmr and ^{13}C nmr spectra were run in deuteriochloroform on a Varian Unity 300 spectrometer. The chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane for ^{1}H nmr, and deuteriochloroform served as the internal standard at δ 77.0 for ^{13}C nmr. The tlc analysis was performed on Merck silica gel 60F-254 glass plates. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

General Procedure for the Bromination of Ethyl 2-Alkylacrylates **3a-b**.

To a stirred solution of ethyl 2-alkylacrylate, **3a-b**, (0.5 mole) in ethanol (500 ml) was added bromine (0.6 mole) dropwise at 0°. The mixture was stirred at room temperature for 16 hours, and to it, a saturated sodium thiosulfate solution (25 ml) was added to remove the remaining bromine. The resulting colorless reaction mixture was concentrated under reduced pressure and diluted with diethyl ether (200 ml). The ethereal solution was passed through a pad of Celite, and the filtrate was washed with brine (100 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness. The oily residue was purified by distillation *in vacuo*.

Ethyl 2-Bromo-2-(bromomethyl)butanoate (**4a**).

This compound was obtained from **3a** in 81% yield as a colorless oil, bp 69-70° (0.7 mm Hg); ir (neat): 1740 (C=O) cm^{-1}; ^{1}H nmr: δ 1.07 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.33 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.25 (m, 2H, CH_2CH_3), 3.77 (d, J = 10.2 Hz, 1H, CHBr), 4.16 (d, J = 10.2 Hz, 1H, CHBr), 4.29 (qd, J = 7.2, 3.3 Hz, 2H, OCH_2CH_3); ^{13}C nmr: δ 8.9, 13.9, 29.5, 34.7, 62.5, 73.7, 168.6.

Anal. Calcd. for $C_7H_{12}Br_2O_2$: C, 29.20; H, 4.20. Found: C, 29.32; N, 4.18.

Ethyl 2-Bromo-2-(bromomethyl)-3-methylbutanoate (**4b**).

This compound was obtained from **3b** [12] in 64% yield as a colorless oil, bp 128-130° (5 mm Hg); ir (neat): 1741 (C=O) cm^{-1}; ^{1}H nmr: δ 1.04 (d, J = 6.6 Hz, 3H, $CHCH_3$), 1.12 (d, J = 6.6 Hz, 3H, $CHCH_3$), 1.33 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.37 (septet, J = 6.6 Hz, 1H, CH), 3.90 (d, J = 10.2 Hz, 1H, CHBr), 4.05 (d, J = 10.2 Hz, 1H, CHBr), 4.29 (qd, J = 7.2, 2.0 Hz, 2H, OCH_2CH_3); ^{13}C nmr: δ 14.0, 17.6, 20.6, 34.0, 37.7, 62.6, 72.5, 168.3.

Anal. Calcd. for $C_8H_{14}Br_2O_2$: C, 31.82; H, 4.67. Found: C, 31.65; H, 4.82.

General Procedure for the Preparation of Methyl 2-Alkyl-3-methoxyacrylates **5a-b**.

To a stirred solution of ethyl 2-alkyl-2,3-dibromopropanoate, **4a-b**, (0.5 mole) in methanol (500 ml) was added 30% sodium methoxide solution in methanol (w/w) (1.0 mole) dropwise at 0° under a nitrogen atmosphere, and the mixture was heated at reflux for 16 hours. After cooling, the reaction mixture was concentrated under reduced pressure, diluted with water (300 ml), and extracted with diethyl ether (2 x 300 ml). The ethereal solution was washed with brine (200 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness. The colorless oily residue was treated with sodium bisulfate (2 g), heated at 180° until evolution of methanol was complete (about 1 hour), and then distilled *in vacuo*.

Methyl 2-Ethyl-3-methoxyacrylate (**5a**).

This compound was obtained from **4a** in 96% yield as a colorless oil, bp 58-65° (1 mm Hg); ir (neat): 1707 (C=O), 1639 (C=C) cm^{-1}; ^{1}H nmr: δ 0.99 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.24 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.70 (s, 3H, CO_2CH_3), 3.80 (s, 3H, OCH_3), 7.24 (s, 1H, vinylic); ^{13}C nmr: δ 13.4, 17.3, 51.0, 61.1, 112.7, 158.2, 168.8.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C,

58.45; H, 8.35.

Methyl 2-Isopropyl-3-methoxyacrylate (**5b**).

This compound was obtained from **4b** in 90% yield as a colorless oil, bp 40-54° (0.25 mm Hg); ir (neat): 1707 (C=O), 1639 (C=C) cm^{-1}; ^1H nmr: δ 1.14 (d, J = 7.1 Hz, 6H, $CH(CH_3)_2$), 2.96 (septet, J = 7.1 Hz, 1H, $CH(CH_3)_2$), 3.68 (s, 3H, CO_2CH_3), 3.78 (s, 3H, OCH_3), 7.19 (s, 1H, vinylic); ^{13}C nmr: δ 20.6, 24.9, 50.9, 61.2, 116.2, 158.4, 168.6.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.80; H, 8.65.

General Procedure for the Hydrolysis of Methyl 2-Alkyl-3-methoxyacrylates **5a-b**.

A stirred suspension of methyl 2-alkyl-3-methoxyacrylate, **5a-b**, (0.2 mole) in 2*N* sodium hydroxide (0.3 mole) was heated at reflux for 3 hours. After cooling, the reaction mixture was washed with diethyl ether (50 ml), acidified to *p*H 4 with 3*N* hydrochloric acid. The resulting white suspension was extracted with diethyl ether (3 x 100 ml). The ethereal solution was washed with brine (100 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness to give a white solid, which was crystallized from water.

2-Ethyl-3-methoxyacrylic Acid (**6a**).

This compound was obtained from **5a** in 82% yield as white crystals, mp 89.6-90.2°; ir (potassium bromide): 3447 (OH), 1668 (C=O) cm^{-1}; ^1H nmr: δ 1.00 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.24 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.84 (s, 3H, OCH_3), 7.37 (s, 1H, vinylic); ^{13}C nmr: δ 13.3, 16.9, 61.4, 112.0, 160.3, 174.5.

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.72; H, 7.53.

2-Isopropyl-3-methoxyacrylic Acid (**6b**).

This compound was obtained from **5b** in 81% yield as white crystals, mp 58.1-59.1°; ir (potassium bromide): 3447 (OH), 1668 (C=O), 1642 (C=C) cm^{-1}; ^1H nmr: δ 1.15 (d, J = 7.1 Hz, 6H, $CH(CH_3)_2$), 2.94 (septet, J = 7.1 Hz, 1H, $CH(CH_3)_2$), 3.82 (s, 3H, OCH_3), 7.34 (s, 1H, vinylic); ^{13}C nmr: δ 20.5, 24.7, 61.5, 115.4, 160.4, 174.2.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.38; H, 8.31.

General Procedure for the Preparation of 2-Alkyl-3-methoxyacryloyl Chlorides **7a-b**.

To a stirred solution of 2-alkyl-3-methoxyacrylic acid, **6a-b**, (20.0 mmoles) and one drop of *N,N*-dimethylformamide in anhydrous benzene (15 ml) was added oxalyl chloride (24.0 mmoles) dropwise at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 hours and evaporated to dryness. The oily residue was purified by distillation *in vacuo*.

2-Ethyl-3-methoxyacryloyl Chloride (**7a**).

This compound was obtained from **6a** in 82% yield as a colorless oil, bp 58° (1.2 mm Hg); ir (neat): 1740 (C=O), 1635 (C=C) cm^{-1}; ^1H nmr: δ 0.99 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.28 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.99 (s, 3H, OCH_3), 7.69 (s, 1H, vinylic); ^{13}C nmr: δ 12.6, 18.6, 62.5, 118.4, 165.4, 167.5.

Anal. Calcd. for $C_6H_9ClO_2$: C, 48.50; H, 6.10. Found: C, 48.18; H, 6.45.

2-Isopropyl-3-methoxyacryloyl Chloride (**7b**).

This compound was obtained from **6b** in 82% yield as a colorless oil, bp 65° (0.8 mm Hg); ir (neat): 1743 (C=O), 1622 (C=C) cm^{-1}; ^1H nmr: δ 1.13 (d, J = 7.1 Hz, 6H, $CH(CH_3)_2$), 2.99 (septet, J = 7.1 Hz, 1H, $CH(CH_3)_2$), 3.98 (s, 3H, OCH_3), 7.69 (s, 1H, vinylic); ^{13}C nmr: δ 19.9, 26.3, 62.7, 121.8, 164.0, 168.2.

Anal. Calcd. for $C_7H_{11}ClO_2$: C, 51.70; H, 6.82. Found: C, 51.35; H, 7.20.

General Procedure for the Preparation of *N*-Alkoxy-*N'*-(2-alkyl-3-methoxyacryloyl)ureas **10a-f**.

A mixture of 2-alkyl-3-methoxyacryloyl chloride, **7a-b**, (10.0 mmoles) and silver cyanate (1.80 g, 12.0 mmoles) in anhydrous benzene (20 ml) was heated at reflux for 30 minutes under a nitrogen atmosphere in the dark to generate isocyanate, **8a-b**, *in situ* and cooled to 0°. To this mixture was added alkoxyamine **9a-c** (11.0 mmoles) in anhydrous benzene (10 ml) dropwise. After stirring at room temperature for 1 hour, the mixture was filtered through a pad of Celite, and the filtrate was again filtered using a millipore filter (0.22 μm). The filtrate was evaporated to dryness, and the residue was purified by flash column chromatography on silica gel or crystallization from a suitable solvent to give **10a-f** as white crystals.

N-(2-Ethyl-3-methoxyacryloyl)-*N'*-propoxyurea (**10a**).

This compound was obtained from **7a** and **9a** [13] in 85% yield after crystallization from ethanol, mp 103.6-104.2°; ir (potassium bromide): 3294 and 3219 (NH), 1695 and 1656 (C=O) cm^{-1}; ^1H nmr: δ 0.96 (t, J = 7.5 Hz, 3H, $OCH_2CH_2CH_3$), 1.01 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.69 (qt, J = 7.5, 6.8 Hz, 2H, OCH_2CH_2), 3.88 (s, 3H, OCH_3), 3.90 (t, J = 6.8 Hz, 2H, OCH_2), 7.39 (s, 1H, vinylic), 8.73 (br s, 1H, NH), 10.90 (br s, 1H, NH); ^{13}C nmr: δ 10.2, 13.3, 17.0, 21.3, 61.5, 78.5, 113.9, 154.7, 158.5, 168.5.

Anal. Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.02; H, 7.56; N, 12.30.

N-Butoxy-*N'*-(2-ethyl-3-methoxyacryloyl)urea (**10b**).

This compound was obtained from **7a** and **9b** [13] in 89% yield after column chromatography with a mixture of methanol and dichloromethane (1:99, v/v) as eluent, mp 95.9-96.9° (ethanol); ir (potassium bromide): 3414, 3295 and 3219 (NH), 1696 and 1654 (C=O) cm^{-1}; ^1H nmr: δ 0.94 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.01 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.41 (m, 2H, $OCH_2CH_2CH_2$), 1.65 (m, 2H, $OCH_2CH_2CH_2$), 2.28 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.88 (s, 3H, OCH_3), 3.94 (t, J = 6.8 Hz, 2H, OCH_2), 7.38 (s, 1H, vinylic), 8.69 (br s, 1H, NH), 10.89 (br s, 1H, NH); ^{13}C nmr: δ 13.3, 13.8, 17.0, 19.0, 30.0, 61.5, 76.8, 113.9, 154.7, 158.5, 168.5.

Anal. Calcd. for $C_{11}H_{20}N_2O_4$: C, 54.08; H, 8.25; N, 11.47. Found: C, 54.35; H, 8.40; N, 11.25.

N-(2-Ethyl-3-methoxyacryloyl)-*N'*-(2-phenylethoxy)urea (**10c**).

This compound was obtained from **7a** and **9c** [14] in 91% yield after crystallization from ethanol, mp 131.4–132.5°; ir (potassium bromide): 3300 and 3226 (NH), 1697 and 1657 (C=O) cm^{-1}; ^1H nmr: δ 1.01 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.27 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.00 (t, J = 7.2 Hz, 2H, CH_2Ar), 3.85 (s, 3H, OCH_3), 4.17 (t, J = 7.2 Hz, 2H, OCH_2), 7.19-7.32 (m, 5H, Ar H), 7.34 (s, 1H, vinylic), 8.31 (br s, 1H, NH), 10.89 (br s, 1H, NH); ^{13}C nmr: δ 13.3, 17.0, 34.5, 61.6, 77.3, 113.7, 126.5, 128.5, 128.8, 137.6, 154.7, 158.6, 168.4.

Anal. Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.42; H, 6.88; N, 9.42.

N-(2-Isopropyl-3-methoxyacryloyl)-*N'*-propoxyurea (**10d**).

This compound was obtained from **7b** and **9a** in 93% yield after column chromatography with a mixture of methanol and dichloromethane (1:99, v/v) as eluent, mp 61.9-63.0° (ethyl acetate-hexane); ir (potassium bromide): 3312 and 3219 (NH), 1699 and 1654 (C=O) cm^{-1}; ^1H nmr: δ 0.96 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_3$), 1.17 (d, J = 7.2 Hz, 6H, $CH(CH_3)_2$), 1.69 (qt, J = 7.4, 6.8 Hz, 2H, OCH_2CH_2), 2.86 (septet, J = 7.2 Hz, 1H, $CH(CH_3)_2$), 3.85 (s, 3H, OCH_3), 3.89 (t, J = 6.8 Hz, 2H, OCH_2), 7.12 (s, 1H, vinylic), 8.41 (br s, 1H, NH), 10.79 (br s, 1H, NH); ^{13}C nmr: δ 10.2, 20.5, 21.2, 25.5, 61.5, 78.4, 118.2, 155.0, 157.5, 169.2.

Anal. Calcd. for $C_{11}H_{20}N_2O_4$: C, 54.08; H, 8.25; N, 11.47. Found: C, 54.25; H, 8.45; N, 11.40.

N-Butoxy-*N'*-(2-isopropyl-3-methoxyacryloyl)urea (**10e**).

This compound was obtained from **7b** and **9b** in 93% yield after column chromatography with a mixture of methanol and dichloromethane (1:99, v/v) as eluent, mp 43.5-44.5° (water); ir (potassium bromide): 3253 (NH), 1701 and 1661 (C=O) cm^{-1}; ^1H nmr: δ 0.93 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.16 (d, J = 7.1 Hz, 6H, $CH(CH_3)_2$), 1.40 (m, 2H, $OCH_2CH_2CH_2$), 1.64 (m, 2H, OCH_2CH_2), 2.88 (septet, J = 7.1 Hz, 1H, $CH(CH_3)_2$), 3.85 (s, 3H, OCH_3), 3.93 (t, J = 6.8 Hz, 2H, OCH_2), 7.18 (s, 1H, vinylic), 8.84 (br s, 1H, NH), 10.84 (br s, 1H, NH); ^{13}C nmr: δ 13.8, 19.0, 20.6, 25.5, 30.0, 61.5, 76.7, 118.3, 154.8, 157.4, 169.1.

Anal. Calcd. for $C_{12}H_{22}N_2O_4$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.53; H, 8.53; N, 10.68.

N-(2-Isopropyl-3-methoxyacryloyl)-*N'*-(2-phenylethoxy)urea (**10f**).

This compound was obtained from **7b** and **9c** in 98% yield after column chromatography with a mixture of methanol and dichloromethane (1:99, v/v), mp 81.1-82.4° (ethanol); ir (potassium bromide): 3297 and 3224 (NH), 1697 and 1654 (C=O) cm^{-1}; ^1H nmr: δ 1.17 (d, J = 7.1 Hz, 6H, $CH(CH_3)_2$), 2.84 (septet, J = 7.1 Hz, 1H, $CH(CH_3)_2$), 3.00 (t, J = 7.2 Hz, 2H, CH_2Ar), 3.82 (s, 3H, OCH_3), 4.17 (t, J = 7.2 Hz, 2H, OCH_2), 7.09 (s, 1H, vinylic), 7.22-7.30 (m, 5H, Ar H), 8.18 (br s, 1H, NH), 10.80 (s, 1H, NH); ^{13}C nmr: δ 20.6, 25.5, 34.5, 61.6, 77.3, 118.2, 126.5, 128.5, 128.8, 137.6, 154.9, 157.5, 169.0.

Anal. Calcd. for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.82; H, 7.35; N, 8.92.

General Procedure for the Preparation of 1-Alkoxy-5-alkyluracils **2a-f**.

A stirred suspension of *N*-alkoxy-*N'*-(2-alkyl-3-methoxyacryloyl)urea, **10a-f**, (5.0 mmoles) in 28% ammonium hydroxide solution in water (w/w) (50 ml) and ethanol (5 ml) was heated at reflux for 4 hours. After cooling, the reaction mixture was evaporated to dryness, and the residue was purified by flash column chromatography on silica gel to give **2a-f**.

5-Ethyl-1-propoxyuracil (**2a**).

This compound was obtained from **10a** in 99% yield after column chromatography with a mixture of methanol and chloroform (3:97, v/v) as eluent, mp 78.6-79.0° (ethyl acetate-hexane); ir (potassium bromide): 1693 and 1616 (C=O) cm^{-1}; ^1H nmr: δ 1.03 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_3$), 1.14 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.75 (qt, J = 7.4, 6.6 Hz, 2H, OCH_2CH_2), 2.35 (q, J = 7.4 Hz, 2H, CH_2CH_3), 4.13 (t, J = 6.6 Hz, 2H, OCH_2), 7.19 (s, 1H, H-6), 8.88 (s, 1H, NH); ^{13}C nmr: δ 10.1, 12.6, 19.9, 21.2, 79.2, 115.2, 138.2, 147.9, 162.9.

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.38; H, 7.40; N, 14.08.

5-Ethyl-1-butoxyuracil (**2b**).

This compound was obtained from **10b** in 99% yield after column chromatography with a mixture of ethyl acetate and hexane (1:2, v/v) as eluent, mp 84.6-85.2° (diethyl ether); ir (potassium bromide): 1712 and 1668 (C=O) cm^{-1}; ^1H nmr: δ 0.98 (t, J = 7.5 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.14 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.47 (m, 2H, $OCH_2CH_2CH_2$), 1.70 (m, 2H, OCH_2CH_2), 2.36 (q, J = 7.5 Hz, 2H, CH_2CH_3), 4.17 (t, J = 6.6 Hz, 2H, OCH_2), 7.18 (s, 1H, H-6), 8.75 (s, 1H, NH); ^{13}C nmr: δ 12.6, 13.7, 18.9, 19.9, 29.8, 77.4, 115.2, 138.2, 147.9, 162.9.

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.62; H, 7.76; N, 13.02.

5-Ethyl-1-(2-phenylethoxy)uracil (**2c**).

This compound was obtained from **10c** in 94% yield after column chromatography with a mixture of methanol and chloroform (3:97, v/v) as eluent, mp 80.3-80.6° (ethyl acetate-hexane); ir (potassium bromide): 1742 and 1654 (C=O) cm^{-1}; ^1H nmr: δ 1.07 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.29 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.05 (t, J = 6.9 Hz, 2H, CH_2Ar), 4.42 (t, J = 6.9 Hz, 2H, OCH_2), 6.94 (s, 1H, H-6), 7.24-7.36 (m, 5H, Ar H), 8.35 (br s, 1H, NH); ^{13}C nmr: δ 12.4, 19.8, 34.4, 78.0, 115.1, 126.9, 128.7, 128.8, 136.9, 138.1, 147.8, 162.5.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.45; H, 6.35; N, 10.72.

5-Isopropyl-1-propoxyuracil (**2d**).

This compound was obtained from **10d** in 92% yield after column chromatography with a mixture of methanol and dichloromethane (5:95, v/v) as eluent, mp 94.2-94.4° (ethyl acetate-hexane); ir (potassium bromide): 1738 and 1661 (C=O) cm^{-1}; ^1H nmr: δ 1.03 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_3$), 1.16 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.75 (qt, J = 7.4, 6.9 Hz, 2H, OCH_2CH_2), 2.89 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.13 (t, J = 6.9 Hz, 2H, OCH_2), 7.14 (s, 1H, H-6), 8.85 (br s, 1H, NH); ^{13}C nmr: δ 10.1, 21.2, 21.4, 25.8, 79.2, 119.7, 137.4, 147.8, 162.6.

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.65; H, 7.70; N, 13.12.

1-Butoxy-5-isopropyluracil (**2e**).

This compound was obtained from **10e** in 81% yield after column chromatography with a mixture of ethyl acetate-hexane (1:2, v/v) as eluent, mp 53.0-53.6° (diethyl ether-pentane); ir (potassium bromide): 1736 and 1654 (C=O) cm^{-1}; ^1H nmr: δ 0.98 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.16 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.48 (m, 2H, $OCH_2CH_2CH_2$), 1.73 (m, 2H, OCH_2CH_2), 2.89 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.17 (t, J = 6.6 Hz, 2H, OCH_2), 7.13 (s, 1H, H-6), 8.70 (br s, 1H, NH); ^{13}C nmr: δ 13.7, 18.9, 21.4, 25.8, 29.8, 77.5, 119.7, 137.4, 147.8, 162.6.

Anal. Calcd. for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.45; H, 7.92; N, 12.40.

5-Isopropyl-1-(2-phenylethoxy)uracil (**2f**).

This compound was obtained from **10f** in 86% yield after column chromatography with a mixture of methanol and chloroform (3:97, v/v) as eluent, mp 64.3-65.3° (ethyl acetate-hexane); ir (potassium bromide): 1737 and 1652 (C=O) cm^{-1}; ^1H nmr: δ 1.08 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.83 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.05 (t, J = 6.8 Hz, 2H, CH_2Ar), 4.43 (t, J = 6.8 Hz, 2H, OCH_2), 6.89 (s, 1H, H-6), 7.22-7.36 (m, 5H, Ar H), 9.48 (s, 1H, NH); ^{13}C nmr: δ 21.3, 25.6, 34.3, 77.9, 119.6, 126.8, 128.6, 128.8, 136.9, 137.3, 148.0, 162.7.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$; C, 65.68; H, 6.61; N, 10.21. Found: C, 65.70; H, 6.48; N, 10.18.

REFERENCES AND NOTES

* To whom correspondence should be addressed.

[1] F. Barré-Sinoussi, J. C. Chermann, F. Rey, M. T. Nugeyre, S. Chamaret, J. Gruest, C. Dauguet, C. Axler-Blin, F. Vézinet-Brun, C. Rouzioux, W. Rozenbaum and L. Montagnier, *Science*, **220**, 868 (1983).

[2] M. A. Fischl, D. D. Richman, M. H. Grieco, M. S. Gottlieb, P. A. Volberding, O. L. Laskin, J. M. Leedom, J. E. Groopman, D. Mildvan, R. T. Schooley, G. G. Jackson, D. T. Durack and D. King, *N. Engl. J. Med.*, **317**, 185 (1987).

[3] D. D. Richman, M. A. Fischl, M. H. Grieco, M. S. Gottlieb, P. A. Volberding, O. L. Laskin, J. M. Leedom, J. E. Groopman, D. Mildvan, M. S. Hirsch, G. G. Jackson, D. T. Durack and S. Nusinoff-Lehrman, *N. Engl. J. Med.*, **317**, 192 (1987).

[4] B. A. Larder, G. Darby and D. V. Richman, *Science*, **243**, 1731 (1989).

[5] T. Miyasaka, H. Tanaka, M. Baba, H. Hayakawa, R. T. Walker, J. Balzarini and E. De Clercq, *J. Med. Chem.*, **32**, 2507 (1989).

[6] H. Tanaka, H. Takashima, M. Ubasawa, K. Sekiya, I. Nitta, M. Baba, S. Shigeta, R. T. Walker, E. De Clercq and T. Miyasaka, *J. Med. Chem.*, **35**, 4713 (1992).

[7] N. M. Goudgaon, A. McMillan and R. F. Schinazi, *Antiviral Chem. Chemother.*, **3**, 263 (1992).

[8] M. Baba, S. Shigeta, S. Yuasa, H. Takashima, K. Sekiya, M. Ubasawa, H. Tanaka, T. Miyasaka, R. T. Walker and E. De Clercq, *Antimicrob. Agents Chemother.*, **38**, 688 (1994).

[9] Y. Iwakura, M. Sato and Y. Matsuo, *Nippon Kagaku Zasshi*, **80**, 502 (1959).

[10] G. Dörnyei, M. Bárczai-Beke, B. Majoros, P. Sohár and Cs. Szántay, *Acta Chim. Acad. Sci. Hung.*, **90**, 275 (1976).

[11] G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 157 (1958).

[12] K. Hayashi, K.-i. Nunami, K. Sakai, Y. Ozaki, J. Kato, K. Kinashi and N. Yoneda, *Chem. Pharm. Bull.*, **33**, 2011 (1985).

[13] W. Theilacker and K. Ebke, *Angew. Chem.*, **68**, 303 (1956).

[14] B. J. Mavunkel, W. J. Rzeszotarski, P. V. Kaplita and D. L. DeHaven-Hudkins, *Eur. J. Med. Chem.*, **29**, 659 (1994).