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A Facile Synthetic Method for Pyrimidine Acyclonucleoside Derivatives

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A facile synthetic method for pyrimidine acyclonucleosides is described. Bis(trimethylsilyl) ethers of uracils (**1**—**3**) react with 2-substituted 1,3-dioxolanes (**4**) in the presence of a Lewis acid to form 1-[α-(2-hydroxyethoxy)alkyl]uracil derivatives. Treatment of these reaction mixtures with methanol containing sodium hydrogen carbonate or aqueous sodium hydroxide gives pyrimidine acyclonucleosides (**5a**—**g**).

Keywords——pyrimidine acyclonucleoside; 2-alkyl-1,3-dioxolane; uracil; 5-methyluracil; 5-fluorouracil; bis(trimethylsilyl)uracil

Acyclonucleosides have as a structural feature a 2-hydroxyethoxymethyl N_1-substituent instead of the ribosyl or 2-deoxyribosyl group in the natural nucleosides. Many acyclonucleosides of the purine and pyrimidine series have been synthesized and tested for biological activities. It is known that in the purine series, acycloadenosine[1] acts as an inhibitor of adenosine deaminase, and acycloguanosine[2] shows specific and potent properties against herpes-simplex virus. Niedzwicki *et al.*[3] reported that some pyrimidine acyclonucleosides show competitive inhibition of uridine phosphorylase.[4]

Our interest in both the structure and biological activities of pyrimidine acyclonucleosides stimulated us to explore new methods for their preparation. This paper deals with a new and facile synthesis of uracil acyclonucleosides involving the reaction of bis (trimethylsilyl) uracils with 1,3-dioxolanes as the key step.

1-(2-Hydroxyethoxy)methyluracils can be readily obtained in the usual way by the reaction of bases with (2-benzoyloxyethoxy)methyl or (2-benzyloxyethoxy)methyl chloride prepared from ethylene glycol or ethylene chlorohydrin *via* several steps involving chloromethylation[5] with formaldehyde and hydrogen chloride.[6] However, this route can not be applied to the preparation of 1-substituted 2-hydroxyethoxymethyl derivatives because of difficulties in obtaining the required chlorides. The search for superior starting materials led us to the use of 2-substituted 1,3-dioxolanes instead of the above reagents, and several uracil acyclonucleosides were successfully obtained.

Treatment of uracil, 5-methyluracil, and 5-fluorouracil (5-FU) with excess trimethylchlorosilane (TMCS) or/and hexamethyldisilazane (HMDS) afforded the corresponding bis (trimethylsilyl)uracils (**1**—**3**), as an oil in each case. 2-Substituted 1,3-dioxolanes, other than commercially available ones,[7] were prepared by dehydration reaction between aldehydes and ethylene glycol in the presence of acid catalysts according to Meskens' procedure.[8]

Compounds **1**—**3** and 1,3-dioxolanes (**4**) thus obtained were treated with a Lewis acid (anhydrous stannic chloride or zinc chloride) in an inert solvent under similar conditions to

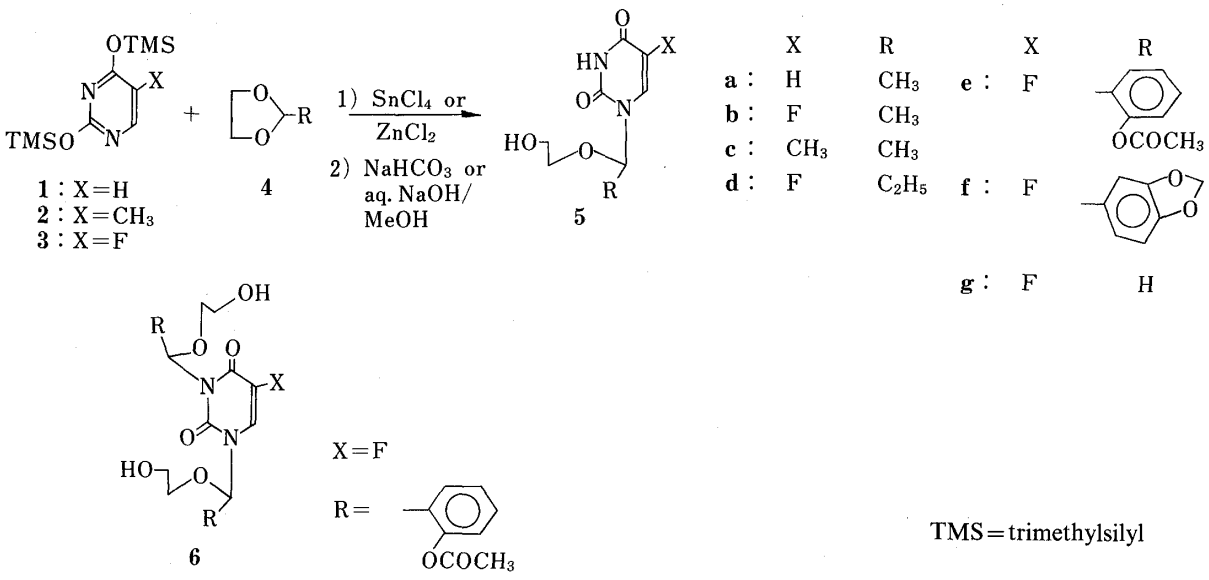

Chart 1

those of the modified Hilbert–Johnson method.[9] Next, the reaction mixture was treated with methanol containing sodium hydrogen carbonate or aqueous sodium hydroxide to give N_1-substituted pyrimidine (uracil) acyclonucleosides (**5**) in fairly good yields (30—70%). The products **5** were purified by chromatography and recrystallization, and their structures were confirmed by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy, particularly on the basis of the α-methine or α-methylene proton signals arising from N_1–C bond formation (see the experimental section). Acetylation of **5b**, **5f**, and **5g** with acetic anhydride and pyridine gave the corresponding *O*-acetyloxyethoxy derivatives.

In addition to products **5**, a trace of minor product was detected as a less polar component on thin layer chromatography (TLC) in each case. Attempts to isolate these minor products in pure form by column chromatography were unsuccessful, except in one case, only a trace of untractable oil being obtained. When the mother liquor from recrystallization of **5e** was chromatographed on silica gel, a crystalline compound was obtained. The elemental analyses and the ^{1}H-NMR spectra were consistent with the structure 1,3-bis[α-(2-hydroxyethoxy)-2-acetoxybenzyl]-5-fluorouracil (**6**). This result suggests that the reaction may also occur at the N_3-position of uracils, and it might be possible to obtain N_1,N_3-bis-substituted derivatives as major products under appropriate conditions.[10]

The above-mentioned reaction sequence is a promising synthetic method for a variety of acyclonucleosides. Pyrimidine acyclonucleosides thus obtained and their derivatives are now being tested for antitumor activity against several experimental tumor cells and for other biological activities[11] in our laboratories.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Hitachi R-24B spectrometer, using tetramethylsilane as an internal standard, and the following abbreviations are used: s, singlet; br s, broad singlet; d, doublet; m, multiplet; q, quartet. Column chromatography was carried out using Wakogel C-200 (Wako) and TLC was carried out using Kieselgel 60 F254 (Merck). Concentration of solutions was carried out under reduced pressure below 40 °C (bath temp.).

1-[1-(2-Hydroxyethoxy)ethyl]uracil (5a)——Uracil (5.0 g) was refluxed in excess HMDS (40 ml) for 5 h, and the resultant solution was evaporated off to give bis (trimethylsilyl)uracil (**1**) as an oil. To a solution of **1** and 2-methyl-1,3-dioxolane (1.0 ml) in dry CH_2Cl_2 (50 ml), a solution of anhyd. $SnCl_4$ (0.5 ml) in dry CH_2Cl_2 (15 ml) was added dropwise over 15 min. The mixture was stirred at room temperature for 1 h, and then poured into 50% aq. MeOH

(100 ml) containing $NaHCO_3$ (24 g) with vigorous stirring. The precipitate was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography on porous polymer HP-20 (Nihon Rensui Co. Ltd.) with H_2O–MeOH to give 5.0 g (65%) of **5a**, mp 118—120 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.50, 5.58 (each 1H, d, J=9 Hz, H-6, 5), 5.7 (1H, q, J=5 Hz, C<u>H</u>$<^{O}_{N}$), 3.43 (4H, br s, –C<u>H</u>$_2$C<u>H</u>$_2$O–), 1.39 (3H, d, J=5 Hz, C<u>H</u>$_3$CH$<^{O}_{N}$). *Anal.* Calcd for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99. Found: C, 48.12; H, 6.01; N, 13.65.

1-[1-(2-Hydroxyethoxy)ethyl]-5-fluorouracil (5b)——Reaction of bis(trimethylsilyl)-5-fluorouracil (**3**) [prepared from 5-FU (5.0 g)] with 2-methyl-1,3-dioxolane (1.0 ml) and anhyd. $SnCl_4$ (0.3 ml) under the conditions described above, followed by similar processing gave 2.8 g (33%) of **5b**, mp 118—120 °C. ^{1}H-NMR (CD_3OD) δ: 7.78 (1H, d, J=6 Hz, H-6), 6.0—5.6 (1H, q, J=6 Hz, CH_3C<u>H</u>$<^{O}_{N}$), 3.8—3.4 (4H, m, –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 1.44 (3H, d, J=6 Hz, C<u>H</u>$_3$CH$<^{O}_{N}$). *Anal.* Calcd for $C_8H_{11}FN_2O_4$: C, 44.04; H, 5.08; N, 12.84. Found: C, 43.94; H, 5.05; N, 12.80.

Acetylation of **5b** with Ac_2O and pyridine afforded 1-[1-(2-acetyloxyethoxy)ethyl]-5-fluorouracil, mp 121—122 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 7.44 (1H, d, J=6 Hz, H-6), 6.10—5.70 (1H, q, J=6 Hz, C<u>H</u>$<^{O}_{N}$), 4.45—4.10 (2H, m, AcOC<u>H</u>$_2$CH$_2$O–), 3.58—3.85 (2H, m, AcOCH$_2$C<u>H</u>$_2$O–), 2.07 (3H, s, C<u>H</u>$_3$CO), 1.49 (3H, d, J=6 Hz, C<u>H</u>$_3$CH$<^{O}_{N}$).

1-[1-(2-Hydroxyethoxy)ethyl]-5-methyluracil (5c)——TMCS (4 ml) was added to a suspension of 5-methyluracil (5.0 g) in HMDS (20 ml), and the mixture was refluxed for 5 h. The resulting precipitate of NH_4Cl was removed by filtration and the filtrate was concentrated to give bis(trimethylsilyl)-5-methyluracil (**2**) as an oil. Treatment of compound **2** and 2-methyl-1,3-dioxolane (1.5 ml) and anhyd. $SnCl_4$ (0.5 ml) under the conditions described above, followed by similar processing, afforded **5c** (4.6 g, 54%), mp 149—150 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.48 (1H, br s, H-6), 5.94—5.55 (1H, q, J=6 Hz, CH_3C<u>H</u>$<^{O}_{N}$), 3.75—3.25 (4H, m, –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 1.80 (3H, br s, 5-C<u>H</u>$_3$), 1.39 (3H, d, J=6 Hz, C<u>H</u>$_3$CH$<^{O}_{N}$). *Anal.* Calcd for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.15; H, 6.34; N, 12.99.

1-[1-(2-Hydroxyethoxy)propyl]-5-fluorouracil (5d)——Compound **3**[prepared from 5-FU (10 g)] and 2-ethyl-1,3-dioxolane (15 ml) were dissolved in dry $CHCl_3$ (20 ml). Then, anhyd. $SnCl_4$ (3 ml) in dry $CHCl_3$ (10 ml) was added dropwise under cooling in an ice bath during 1 h. After being stirred at room temperature for 2 h, the reaction mixture was poured into MeOH (100 ml) containing $NaHCO_3$ (30 g). The resulting precipitate was filtered and the filtrate was concentrated. The residue was purified by column chromatography on Amberlite XAD-4 (Rohm & Haas Co., Ltd.). Elution with aq. MeOH afforded **5d** (6.7 g, 75%), mp 111—112 °C (C_6H_6). ^{1}H-NMR (DMSO-d_6) δ: 7.75 (1H, d, J=6 Hz, H-6), 5.75—5.45 (1H, t, CH_3CH_2C<u>H</u>$<^{O}_{N}$), 3.85—3.40 (4H, m, –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 1.75 (2H, m, CH_3C<u>H</u>$_2$CH$<^{O}_{N}$), 0.95 (3H, t, C<u>H</u>$_3$CH$_2$CH$<^{O}_{N}$). *Anal.* Calcd for $C_9H_{13}FN_2O_4$: C, 46.55; H, 5.64; N, 12.06. Found: C, 46.45; H, 5.54; N, 12.01.

1-[α-(2-Hydroxyethoxy)-2-acetyloxybenzyl]-5-fluorouracil (5e)——Compound **3** [prepared from 5-FU (5.0 g)] and 2-(2-acetyloxyphenyl)-1,3-dioxolane (13.1 g) were dissolved in dry DMF (25 ml). Then, anhyd. $ZnCl_2$ (1.0 g) was added and the mixture was stirred at 120 °C for 2 h. After cooling, the reaction mixture was poured into cold H_2O and the resulting oil was extracted with AcOEt. The organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated. The residue was dissolved in MeOH (20 ml) and AcOH (0.5 ml), and the mixture was warmed at 40 °C for 1 h, then concentrated. The residue was treated with C_6H_6 to give crude crystals of **5e**. Recrystallization from C_6H_6 afforded pure **5e** (6.16 g, 47%), mp 158—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 11.60 (1H, s, N<u>H</u>), 7.84 (1H, m, H-3 of phenyl group), 7.28 (4H, m, H-6 and phenyl group), 6.83 (1H, d, J=2 Hz, C<u>H</u>$<^{O}_{N}$), 4.60 (1H, s, CH$_2$O<u>H</u>), 3.69 (4H, m, –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 2.26 (3H, s, COC<u>H</u>$_3$). *Anal.* Calcd for $C_{15}H_{15}FN_2O_6$: C, 53.26; H, 4.47; N, 8.28. Found: C, 53.30; H, 4.49; N, 8.28.

The mother liquor from recrystallization of **5e** was concentrated and the residue was chromatographed on silica gel with 5% (v/v) acetone in $CHCl_3$ to give 1,3-bis[α-(2-hydroxyethoxy)-2-acetoxybenzyl]-5-flurouracil (**6**) (0.4 g), mp 135—136 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.10—7.50 (2H, m, phenyl group), 7.50—6.88 (6H, m, phenyl group), 6.78 (2H, d, J=3 Hz, C<u>H</u>$<^{O}_{N}$), 4.00—2.90 (8H, m, –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 2.33, 2.04 (each 3H, s, COC<u>H</u>$_3$). *Anal.* Calcd for $C_{26}H_{27}FN_2O_{10}$: C, 57.14; H, 4.98; N, 5.12. Found: C, 57.21; H, 5.06; N, 5.22.

1-[α-(2-Hydroxyethoxy)-3,4-methylenedioxybenzyl]-5-fluorouracil (5f)——Compound **3** [prepared from 5-FU (0.5 g)] and 2-(3,4-methylenedioxyphenyl)-1,3-dioxolane (9.1 g) [prepared from piperonal and ethylene glycol] were dissolved in dry CH_2Cl_2 (25 ml). Then, a solution of anhyd. $SnCl_4$ (0.5 ml) in dry CH_2Cl_2 (5 ml) was added dropwise during 1 h and the mixture was stirred at room temperature for 3 h. MeOH (5 ml) was added dropwise to the reaction

mixture under ice cooling at 0—5 °C, then 10% NaOH was added dropwise to adjust the pH to 8. The resulting precipitate was filtered off and the filtrate was concentrated. The residue was dissolved in $CHCl_3$ and the organic layer was washed, dried, and concentrated. The residue was dissolved in a small amount of $CHCl_3$ and stored overnight in a refrigerator. The crude crystals of **5f** were collected and recrystallized from acetone–diisopropyl ether to give pure **5f** (6.3 g, 51%), mp 125—129 °C. ^{1}H-NMR ($CDCl_3+CD_3OD$, 50% (v/v)) δ: 7.37 (1H, d, J=6 Hz, H-6), 7.0—6.80 (3H, m, phenyl group), 6.83 (1H, d, J=2 Hz, C<u>H</u>$<^{O}_{N}$), 6.98 (2H, s, C<u>H</u>$_2<^{O}_{N}$), 4.10—3.70 (4H, br s, –OC<u>H</u>$_2$C<u>H</u>$_2$O–).

Acetylation of **5f** with Ac_2O and pyridine gave the *O*-acetyloxyethoxy compound: 1-[α-(2-acetyloxyethoxy)-3,4-methylenedioxybenzyl]-5-fluorouracil, colorless crystals, mp 134.5—135 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 9.90 (1H, br s, N<u>H</u>), 7.20 (1H, d, J=6 Hz, H-6), 6.80 (3H, s, phenyl group), 6.70 (1H, d, J=2 Hz, C<u>H</u>$<^{O}_{N}$), 5.91 (2H, s, C<u>H</u>$_2<^{O}_{N}$), 4.20—4.55 (2H, m, AcOC<u>H</u>$_2$CH$_2$O–), 4.00—3.75 (2H, m, AcOCH$_2$C<u>H</u>$_2$O–), 2.02 (3H, s, C<u>H</u>$_3$CO). *Anal.* Calcd for $C_{16}H_{15}FN_2O_7$: C, 52.46; H, 4.10; N, 7.65. Found: C, 52.49; H, 4.15; N, 7.55.

1-[(2-Hydroxyethoxy)methyl]-5-fluorouracil (5g)[12]——Reaction of compound **3** [prepared from 5-FU (5.0 g)] with 1,3-dioxolane (5 ml) and anhyd. $SnCl_4$ (3 ml) under the same conditions as in the case of **5a** afforded **5g** (5.5 g, 57%), mp 153.5—155 °C (MeOH). ^{1}H-NMR (DMSO-d_6) δ: 7.98 (1H, d, J=6 Hz, H-6), 4.98 (2H, s, C<u>H</u>$_2<^{O}_{N}$), 3.47 (4H, br s, –OC<u>H</u>$_2$C<u>H</u>$_2$O–).

Acetylation of **5g** with Ac_2O and pyridine gave the *O*-acetyloxyethoxy compound, mp 145—146.5 °C (MeOH). ^{1}H-NMR ($CDCl_3$+DMSO-d_6, 4:1) δ: 7.77 (1H, d, J=6 Hz, H-6), 5.11 (2H, s, C<u>H</u>$_2<^{O}_{N}$), 4.30—4.04 (2H, m, AcOC<u>H</u>$_2$CH$_2$O–), 3.92—3.64 (2H, m, AcOCH$_2$C<u>H</u>$_2$O–), 2.02 (3H, s, C<u>H</u>$_3$CO).

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References and Notes

1) H. J. Schaeffer, S. Gurwara, R. Vince, and S. Bittner, *J. Med. Chem.*, **14**, 367 (1971).
2) B. R. Jones, D. J. Coster, P. N. Fison, G. M. Thompson, L. M. Cobo, and M. G. Falcon, *Lancet*, **1979**, 243; J. A. Fyfe, P. M. Keller, P. A. Furman, R. L. Miller, and G. B. Elion, *J. Biol. Chem.*, **253**, 8721 (1978).
3) J. G. Niedzwicki, M. H. el Kouni, S. H. Chu, and S. Cha, *Biochem. Pharmacol.*, **30**, 2097 (1981).
4) J. L. Kelly, M. P. Krochmal, and H. J. Schaeffer, *J. Med. Chem.*, **24**, 472 (1981); J. L. Kelly, J. E. Kelsey, W. R. Hall, M. P. Krochmal, and H. J. Schaeffer, *ibid.*, **24**, 753 (1981).
5) R. C. Fuson and C. H. McKeever, "Organic Reactions," Vol. 1, John Wiley and Sons, Inc., New York, p. 63.
6) H. M. Abrams, L. Ho, and S. H. Chu, *J. Heterocyclic Chem.*, **18**, 947 (1981).
7) 1,3-Dioxolane and 2-methyl-1,3-dioxolane were obtained from Tokyo Kasei Co., Ltd.
8) F. J. A. Meskens, *Synthesis*, **1981**, 501.
9) J. J. Fox and I. Wempen, *Adv. Carbohydr. Chem.*, **14**, 283 (1959).
10) Further investigations are in progress in this laboratory.
11) A part of this work was presented at the 103rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1983. The details will be reported shortly.
12) M. Ya. Karpeiskii, S. M. Mikhailov, A. S. Tsieminya, A. A. Ziderman, I. M. Kravchenko, M. Yu. Lidak, and R. A. Zhuk, *Khim. Geterotsikl. Soedin*, **1980**, 1541 [*Chem. Abstr.*, **94**, 175027*g* (1981)].