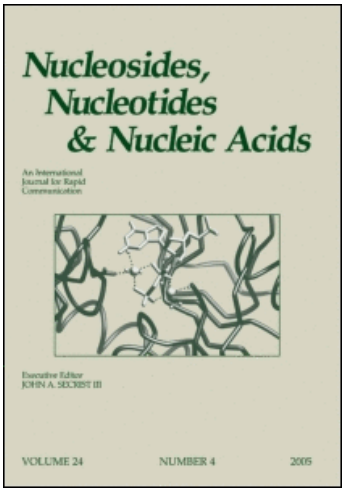


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Nucleosides and Nucleotides. 106. Synthesis and Biological Activity of 1-(2-Deoxy-2-hydroxyimino- or Methoxyimino-β-D-erythro-pentofuranosyl)-thymine and -Cytosine[§,1]

To cite this Article (1992) 'Nucleosides and Nucleotides. 106. Synthesis and Biological Activity of 1-(2-Deoxy-2-hydroxyimino- or Methoxyimino-β-D-erythro-pentofuranosyl)-thymine and -Cytosine[§,1]', Nucleosides, Nucleotides and Nucleic Acids, 11: 2, 237 — 246
To link to this Article: DOI: 10.1080/07328319208021699
URL: http://dx.doi.org/10.1080/07328319208021699

NUCLEOSIDES & NUCLEOTIDES, 11(2-4), 237-246 (1992)

NUCLEOSIDES AND NUCLEOTIDES. 106. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1-(2-DEOXY-2-HYDROXYIMINO- OR METHOXYIMINO-β-D-*ERYTHRO*-PENTOFURANOSYL)-THYMINE AND -CYTOSINE§, 1

Akira MATSUDA,* Yuki NAKAJIMA, and Tohru UEDA

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan

Takuma SASAKI

Cancer Research Institute, Kanazawa University, Takara-machi, Kanazawa 920, Japan

Abstract: Reaction of 1-(3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-*erythro*-2-pentofuran-2-ulosyl)uracil (**8**) with hydroxylamine hydrochloride in pyridine at room temperature for 24 h or at 80°C for 3 h gives the 2'-deoxy-2'-hydroxyiminouridine derivative **9** in good yield. Similarly, oximation of **8** with methoxyamine has been done to obtain 2'-deoxy-2'-methoxyimino derivatives **11** in a high yield. Compound **9** was converted into 1-(2-deoxy-2-hydroxyimino-β-D-*erythro*-pentofuranosyl)cytosine (**3**). Cytotoxicity *in vitro* of these nucleosides against murine leukemia L1210 cells was also examined.

A new type of antineoplastic nucleoside, 2'-deoxy-2'-methylidenecytidine (DMDC) has been synthesized and its activity evaluated.[2,3] DMDC showed, unlike the activity of 1-β-D-arabinofuranosylcytosine (ara-C), highly potent cytotoxicity against not only mouse leukemia cell lines but also human leukemia, lymphoma, adenocarcinoma, and carcinoma cells *in vitro*.[2] DMDC also had therapeutic activity against some human tumor xenografts.[3] Moreover, a thymine derivative of DMDC (DMDT) has antiviral activity toward human cytomegalovirus.[4] In the course of studying structure-activity relationships of these 2'-deoxy-2'-methylidene nucleosides, we have found that the allylic alcohol

§This paper is dedicated to the memory of the late Professor Tohru Ueda, the former editor of this journal.

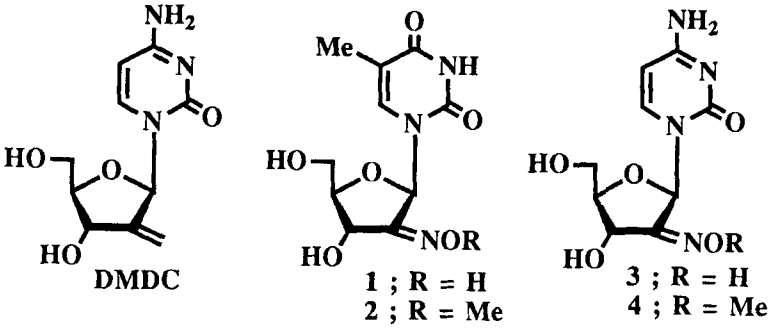
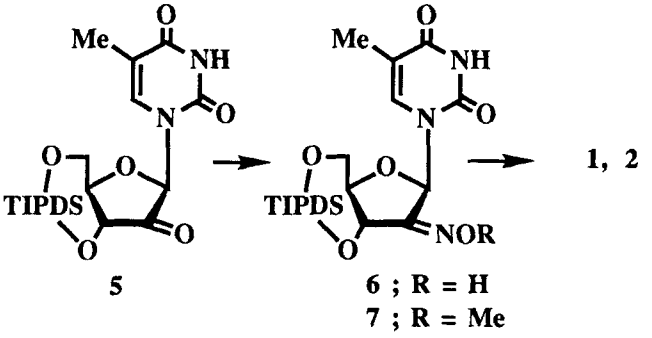


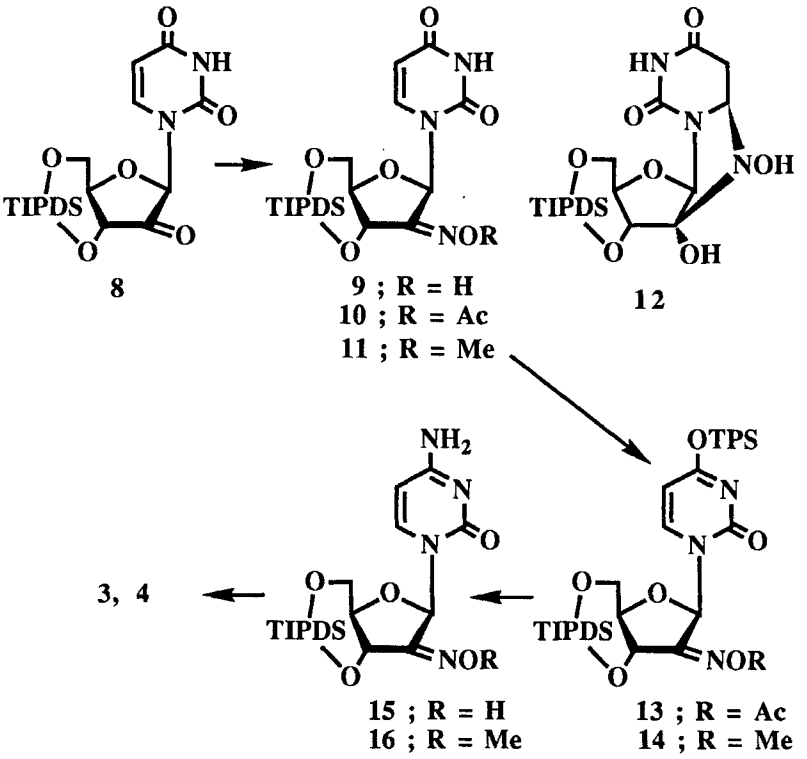
Chart 1



Scheme 1

system together with the 3'-secondary alcohol in the sugar moiety is essential for the activity.[5] If the 2'-methylidene group can be replaced by imino derivatives such as an oxime, the structural feature of the resulting oxime derivatives is similar to DMDC and DMDT and they would show the activity. This report describes the syntheses and preliminary evaluation of a series of 2'-oxime derivatives of pyrimidine nucleosides **1-4**.

Synthesis of the target oxime and the methoxyme is straightforward. When 1-(3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-*erythro*-2-pentulofuran-2-ulosyl)-5-methyluracil (**5**) was treated with hydroxylamine hydrochloride (2.5 molar equiv.) in anhydrous pyridine at room temperature for 24 h, the desired 1-(2-deoxy-2-hydroxylimino-3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-*erythro*-2-pentofuranosyl)-5-methyluracil (**6**) was obtained in 94% yield as a foam. Mass spectrum of **6** showed a molecular ion peak at *m/z* 513. In its ^{1}H NMR spectrum in $CDCl_3$, a dissociable proton signal at δ 8.55 ppm was assigned as a hydroxyl proton of the 2'-hydroxyimino group. At δ 6.24 ppm, a 1'-proton appeared as a doublet coupled with the 3'-proton ($J_{1',3'}$ = 1.8 Hz) through a W shape long-



Scheme 2

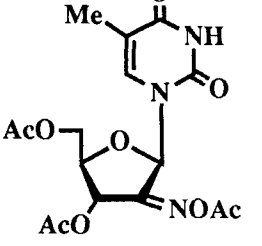
range coupling. From the evidence of the overall ^{1}H NMR spectrum of **6**, only one isomer, whose configuration could not be identified in this stage, was obtained. Deblocking of **6** with tetrabutylammonium fluoride (TBAF) in THF gave a crystalline 1-(2-deoxy-2-hydroxyimino-β-D-*erythro*-pentofuranosyl)-5-methyluracil (**1**) in 95% yield. The ^{1}H NMR spectrum of **1** in DMSO-d_6 showed several two sets of peaks, which indicate this nucleoside **1** contains *anti* and *syn* isomers on the oxime. The anomeric protons of each isomer showed singlets at δ 6.50 and 6.33 ppm in a ratio of 1 : 1.5. .Each peak was identified by its nuclear Overhouser effect (NOE). When one of signals at δ 6.33 ppm was irradiated, the NOE were observed 20% at δ 7.35 (H-6) and 5.4% at δ 11.32 ppm (NO<u>H</u> and N^3<u>H</u>), respectively. On the other hand, irradiation at δ 6.50 ppm (H-1') indicated that the NOE was observed 5.1% at δ 7.42 ppm (H-6) and no NOE was found at the signal assigned as =NO<u>H</u> (11.50 ppm). Thus, the protons corresponding to N^{3}H, =NOH, H-6, H-1', and 5'-OH of the *anti* isomer are present in a higher field than those of the *syn* form except 3'-OH, H-4', and H-5'a,b.

In a similar way, the reaction of **5** with methoxylamine hydrochloride in pyridine gave the desired **7** in 75% yield. Deprotection of **7** with TBAF afforded **2** as crystals. The isomer ratio was also measured as described above (see experimental section).

Cytidine derivatives **3** and **4** could not be obtained from the reaction of 1-(3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-*erythro*-2-pentulofuran-2-ulosyl)-cytosine or its *N*-benzoylcytosine derivatives under similar conditions. In these cases, isolable products were the cytosine base and the starting material (data not shown). We synthesized **3** and **4** from uridine derivative **8** instead. Recently, Tronchet and coworkers have reported that when a mixture of 2'- and 3'-ketouridine derivatives were treated with hydroxylamine hydrochloride in pyridine they gave a mixture of the corresponding oximes.[6] More recently, they found that compound **8** with hydroxylamine hydrochloride in a mixture of ethanol and pyridine gave a mixture of a desired oxime **9** and a cyclonucleoside **12**, whose structure was identified by X-ray crystallographic studies after further derivatizations.[7] However, when we tried the similar reaction in *anhydrous* pyridine the only isolable nucleosidic product was **9** as a mixture of geometric isomers in 83% yield. Although differences in the reaction conditions include using ethanol as a solvent, the formation of the cyclonucleoside **12** would be related to water contents in the reagent and/or the solvent. Although hydroxylamine reacts with the uracil base moiety to form adducts[8] or isoxazoles,[9] we have not found such products after careful TLC and ^{1}H-NMR spectral analyses.

The oxime **9** was first converted into its acetate **10** with acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine (DMAP), followed by activation of 4-position of the uracil moiety with triisopropylbenzenesulfonyl (TPS) chloride. The resulting 4-*O*-TPS derivative **13** was further treated with methanolic ammonia at room temperature. The desired cytosine derivative **15** was obtained in 41% yield from **9** as crystals after purification with silica gel column chromatography. Treatment of **15** with TBAF in THF afforded 1-(2-deoxy-2-hydroxyimino-β-D-*erythro*-pentofuranosyl)cytosine (**3**) in 77% yield as crystals. Similarly a methoxime derivative **4** was also synthesized from **8**.

We next examined cytotoxicity of these nucleosides against mouse leukemia L1210 and human oral epidermoid carcinoma KB cells *in vitro*. Compounds **1-4** did not show any cytotoxicity against both cells up to 100 μg/mL. The ineffectiveness of these nucleosides might be related to insusceptibility to nucleoside kinases because of the bulky hydroxyl or methoxy groups at the imino group. Tri-*O*-acetate of **1** (see experimental), however, had cytotoxicity against both cell lines with IC_{50} values of 85 μg/mL and 40 μg/mL, respectively, probably due to acting as an



alkylating agent. Antiviral activity of **1-4** against HIV-1 and HSV-1 and 2 were examined but none of these had significant activity.

Experimental Section.

Melting points were measured on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a JEOL JNM-FX 100 (100 MHz) or JEOL JNM-GX 270 (270 MHz) spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. UV absorption spectra were recorded with a Shimadzu UV-240 spectrophotometer. Mass spectra (MS) were measured on a JEOL JMX-DX303 spectrometer. TLC was done on Merck Kieselgel F254 precoated plates. The silica gel used for column chromatography was YMC gel 60A (70-230 mesh).

1-(2-Deoxy-2-hydroxyimino-3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-*erythro*-pentofuranosyl)-5-methyluracil (6). A mixture of **5** (997 mg, 2 mmol) and hydroxylamine hydrochloride (347 mg, 5 mmol) in anhydrous pyridine (10 mL) was stirred for 24 h at room temperature. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc (100 mL) and H_2O (3 x 50 mL). The separated organic phase was dried (Na_2SO_4) and concentrated to dryness. The residue was purified on a silica gel column (3.4 x 6 cm) with 2% EtOH in $CHCl_3$. The main UV-absorbing fractions were combined and concentrated to give **6** (969 mg, 94% as a white foam). EI-MS *m/z* 514 (M^++1), 470 (M^+-isoPr). ^{1}H NMR ($CDCl_3$): 8.70 (br s, 1H, N^3H), 8.55 (br s, 1H, NOH), 6.91 (d, 1H, H-6, $J_{6,Me}$ = 1.5 Hz), 6.24 (d, 1H, H-1', $J_{1',3'}$ = 1.8 Hz), 5.20 (dd, 1H, H-3', $J_{3',1'}$ = 1.8 Hz, $J_{3',4'}$ = 8.2 Hz), 4.12 (dd, 1H, H-5'a, $J_{5'a,4'}$ = 4.4 Hz, $J_{5'a,b}$ = 12.6 Hz), 4.05 (dd, 1H, H-5'b, $J_{5'b,4'}$ = 3.3 Hz, $J_{5'a,b}$ = 12.6 Hz), 3.83 (ddd, 1H, H-4', $J_{4',3'}$ = 8.2 Hz, $J_{4',5'a}$ = 4.4 Hz, $J_{4',5'b}$ = 3.3 Hz), 1.88 (d, 3H, 5-Me, $J_{Me,6}$ = 1.5 Hz), 1.04-1.14 (m, 28H, isoPr).

1-(2-Deoxy-2-hydroxyimino-β-D-*erythro*-pentofuranosyl)-5-methyluracil (1). A THF solution of TBAF (1 M, 4 mL, 4 mmol) was added to a mixture of **6** (1.03 g, 2 mmol) in THF (10 mL) for 1 h at 0°C. The reaction mixture was neutralized with AcOH and the whole was mixed with silica gel. The resulting suspension was concentrated to dryness in vacuo and the residue was placed on top of the silica gel column (2.3 x 12.5 cm), which was eluted with 10% EtOH in $CHCl_3$. The main UV-absorbing fractions were combined and concentrated to dryness. The solid was crystallized from EtOH/Et_2O to afford **1** (516 mg, 95%): mp 211-212°C. EI-MS *m/z* 271 (M^+). ^{1}H NMR (DMSO-d_6): 11.50 and 11.32 (each br s, 1H, NOH), 11.41 and 11.31 (each br s, 1H, N^3H), 7.42 and 7.35 (each s, 1H, H-6), 6.50 and 6.33 (each s, 1H, H-1'), 5.75 and 5.68

(each d, 1H, 3'-OH), 5.01 and 4.89 (each t, 1H, 5'-OH), 4.68 and 4.62 (each dd, 1H, H-3'; syn; $J_{3',3'OH}$ = 6.6 Hz, $J_{3',4'}$ = 5.1 Hz; anti; $J_{3',3'OH}$ = 7.1 Hz, $J_{3',4'}$ = 6.1 Hz), 3.71-3.52 (m, 3H, H-4', 5'a, b), 1.75 (s, 3H, 5-Me). *Anal* Calcd for $C_{10}H_{13}N_3O_6$: C, 44.28; H, 4.83; N, 15.49. Found: C, 44.11; H, 4.89; N, 15.37.

1-(2-Deoxy-2-methoxyimino-3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-*erythro*-pentofuranosyl)-5-methyluracil (7). Methoxyamine hydrochloride (205 mg, 2.5 mmol) was added to a solution of **5** (499 mg, 1 mmol) in anhydrous pyridine (5 mL). The reaction mixture was heated at 80°C for 4 h with stirring. A work-up similar to that described in **6** was done and the crude product was purified on a silica gel column (2.7 x 10 cm), which was eluted with 1% EtOH in $CHCl_3$ to afford **7** (396 mg, 75% as a white foam). EI-MS *m/z* 528 (M^++1), 484 (M^+-isoPr). ^1H NMR ($CDCl_3$): 8.18 and 8.08 (each br s, 1H, N^3H), 6.85 (d, 1H, H-6, $J_{6,Me}$ = 1.5 Hz), 6.38 and 6.20 (d, 1H, H-1', $J_{1',3'}$ = 2.0 Hz), 5.15 and 5.09 (dd, 1H, H-3', $J_{3',1'}$ = 2.0 Hz, $J_{3',4'}$ = 8.3 Hz), 4.08-4.00 (m, 3H, H-4', 5'a, b), 3.89 (s, 3H, =NOMe), 1.89 (d, 3H, 5-Me, $J_{Me,6}$ = 1.5 Hz), 1.13-1.05 (m, 28H, isoPr).

1-(2-Deoxy-2-methoxyimino-β-D-*erythro*-pentofuranosyl)-5-methyluracil (2). Compound **7** (538 mg, 1.02 mmol) was deprotected with TBAF in THF similarly to **1**. After purification with silica gel column chromatography, **2** was crystallized from EtOH/Et_2O (112 mg, 39%): mp 145-146.5°C. EI-MS *m/z* 285 (M^+). ^1H NMR (DMSO-d_6): 11.44 and 11.36 (each br s, 1H, N^3H), 7.44 and 7.39 (each d, 1H, H-6, $J_{6,Me}$ = 1.1 Hz), 6.48 and 6.29 (each d, 1H, H-1'; syn; $J_{1',3'}$ = 1.7 Hz; anti; $J_{1',3'}$ = 2.2 Hz), 5.90 and 5.79 (each d, 1H, 3'-OH), 4.99 and 4.91 (each t, 1H, 5'-OH), 4.66 and 4.65 (each ddd, 1H, H-3'; syn; $J_{3',1'}$ = 1.7 Hz, $J_{3',3'OH}$ = 7.2 Hz, $J_{3',4'}$ = 3.8 Hz; anti; $J_{3',1'}$ = 2.2 Hz, $J_{3',3'OH}$ = 6.6 Hz, $J_{3',4'}$ = 3.8 Hz), 3.85-3.53 (m, 3H, H-4', 5'a, b), 3.81 and 3.77 (each s, 3H, NOMe), 1.76 and 1.72 (each s, 3H, 5-Me, $J_{Me,6}$ = 1.1 Hz). *Anal* Calcd for $C_{11}H_{15}N_3O_6$: C, 46.32; H, 5.30; N, 14.73. Found: C, 46.20; H, 5.32; N, 14.61.

1-(2-Deoxy-2-hydroxyimino-3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-*erythro*-pentofuranosyl)uracil (9). A mixture of **8** (1.94 g, 4 mmol) and hydroxylamine hydrochloride (695 mg, 10 mmol) in anhydrous pyridine (15 mL) was heated at 80°C for 3 h with stirring. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was taken in EtOAc (100 mL) and washed with H_2O (3 x 50 mL). The separated organic phase was dried (Na_2SO_4) and concentrated to dryness. The residue was purified on a silica gel column (2.2 x 9.5 cm) with hexane/EtOAc (3 : 1 - 2 : 1). The main UV-absorbing fractions were combined and concentrated to give a solid, which was crystallized from hexane/EtOAc to afford **9** (1.66 g, 83%): mp 201-203°C. EI-MS *m/z* 456 (M^+-isoPr). ^1H NMR ($CDCl_3$): 9.04 and 8.66

(each br s, 1H, NOH), 8.37 and 8.19 (each br s, 1H, N^3H), 7.09 and 7.10 (each d, 1H, H-6, $J_{6,5}$ = 8.1 Hz), 6.41 and 6.17 (each d, 1H, H-1'), 5.70 and 5.71 (each d, 1H, H-5, $J_{6,5}$ = 8.1 Hz), 4.02-4.14 (m, 2H, H-5'a, b), 3.83-3.89 (m, 1H, H-4'), 1.04-1.13 (m, 28H, isoPr). *Anal* Calcd for $C_{21}H_{37}N_3O_7Si_2$: C, 50.48; H, 7.46; N, 8.41. Found: C, 50.32; H, 7.63; N, 8.43.

1-(2-Deoxy-2-methoxyimino-3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-*erythro*-pentofuranosyl)uracil (11). A mixture of **8** (1.94 g, 4 mmol) and methoxyamine hydrochloride (820 mg, 10 mmol) in anhydrous pyridine (15 mL) was heated at 80°C for 4 h with stirring. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was taken in EtOAc (100 mL) and washed with H_2O (3 x 50 mL). The separated organic phase was dried (Na_2SO_4) and concentrated to dryness. The residue was purified on a silica gel column (3 x 16 cm) with 1% EtOH in $CHCl_3$. The main UV-absorbing fractions were combined and concentrated to give **11** (1.67 g, 81% as a white foam). EI-MS *m/z* 513 (M^+). ^1H NMR ($CDCl_3$): 8.35 and 8.18 (each br s, 1H, N^3H), 7.05 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz), 6.40 and 6.10 (each d, 1H, H-1', $J_{1',3'}$ = 1.7 Hz), 5.70 and 5.69 (each d, 1H, H-5, $J_{6,5}$ = 8.1 Hz), 4.95 and 5.16 (each dd, 1H, H-3', $J_{3',1'}$ = 1.7 Hz, $J_{3',4'}$ = 8.1 Hz), 4.09-3.98 (m, 3H, H-4', 5'a, b), 3.89 (s, 3H, NOMe), 1.02-1.13 (m, 28H, isoPr).

1-(2-Deoxy-2-hydroxyimino-3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-*erythro*-pentofuranosyl)cytosine (15). Acetic anhydride (0.28 mL, 3 mmol) was added to a mixture of **9** (999 mg, 2 mmol) and DMAP (10 mg) in anhydrous pyridine (15 mL). The reaction mixture was stirred for 2.5 h at room temperature, then ice-water was added to the mixture. The mixture was diluted with EtOAc (200 mL) and the whole was washed with H_2O (100 mL), aq. sat. $NaHCO_3$ (100 mL), then H_2O (100 mL). The separated organic phase was dried (Na_2SO_4) and concentrated to dryness to leave an oily residue **10**. Triethylamine (0.84 mL, 6 mmol) was added to a mixture of **10**, triisopropylbenzenesulfonyl chloride (1.82 g, 6 mmol), and DMAP (50 mg) in CH_3CN (20 mL) at 0°C under argon. The reaction mixture was stirred for 2 h at room temperature, then the solvent was removed *in vacuo*. The residue was treated with NH_3/MeOH (saturated at 0°C, 30 mL) for 13 h at room temperature. After concentration of the mixture, the resulting solid was purified on a silica gel column (3 x 12), which was eluted with 10% EtOH in $CHCl_3$ to afford **15** (409 mg, 41%, crystallized from EtOAc): mp 167-170°C. EI-MS *m/z* 498 (M^+). ^1H NMR ($CDCl_3$): 11.31 (s, 1H, NOH), 7.55 (d, 1H, H-6, $J_{6,5}$ = 7.1 Hz), 7.25 (br s, 1H, 4-NH_2), 7.15 (br s, 1H, 4-NH_2), 6.09 (s, 1H, H-1'), 5.65 (d, 1H, H-5, $J_{5,6}$ = 7.1 Hz), 5.25 (d, 1H, H-3', $J_{3',4'}$ = 7.1 Hz), 4.00 (dd, 1H, H-5'a, $J_{5'a,4'}$ = 7.1 Hz, $J_{5'a,b}$ = 11.5 Hz), 3.90 (dd, 1H, H-5'b, $J_{5'b,4'}$ = 3.3 Hz, $J_{5'a,b}$ = 11.5 Hz), 3.77 (ddd, 1H, H-4', $J_{4',5'a}$ = 7.1 Hz, $J_{4',5'b}$ = 3.3 Hz, $J_{4',3'}$ = 7.1 Hz), 1.11-0.97 (m,

28H, isoPr). *Anal* Calcd for $C_{21}H_{38}N_4O_6Si_2 \cdot 1/3\ H_2O$: C, 49.97; H, 7.72; N, 11.10. Found: C, 49.70; H, 7.70; N, 11.36.

1-(2-Deoxy-2-hydroxyimino-β-D-*erythro*-pentofuranosyl)cytosine (3). A THF solution of TBAF (1 M, 1 mL, 1 mmol) was added to a mixture of **15** (200 mg, 0.4 mmol) in THF (5 mL) for 1 h at 0°C. The reaction mixture was neutralized with AcOH and the solvent was removed *in vacuo*. The residue was crystallized from MeOH to afford **3** (79 mg, 77%): mp 212-213°C. FAB-MS *m/z* 257 (M^++1). ^1H NMR (DMSO-d_6): 11.12 (br s, 1H, NO<u>H</u>), 7.42 (d, 1H, H-6, $J_{6,5}$ = 7.7 Hz), 7.21 and 7.19 (each br s, 2H, 4-NH_2), 6.26 (d, 1H, H-1', $J_{1',3'}$ = 1.1 Hz), 5.68 (d, 1H, H-5, $J_{5,6}$ = 7.7 Hz), 5.65 (d, 1H, 3'-OH, $J_{OH,\ 3'}$ = 7.1 Hz), 4.82 (t, 1H, 5'-OH), 4.63 (ddd, 1H, H-3', $J_{3',3'OH}$ = 7.1 Hz, $J_{3',4'}$ = 6.0 Hz, $J_{3',1'}$ = 1.1 Hz), 3.71-3.64 (m, 2H, H-5'a, b), 3.59-3.50 (m, 1H, H-4'). *Anal* Calcd for $C_9H_{12}N_4O_5 \cdot 1/4\ H_2O$: C, 42.05; H, 4.96; N, 21.20. Found: C, 42.03; H, 5.07; N, 21.04.

1-(2-Deoxy-2-methoxyimino-3,5-*O*-tetraisopropyldisiloxan-1,3-diyl-β-D-*erythro*-pentofuranosyl)cytosine (16). Triethylamine (0.84 mL, 6 mmol) was added to a mixture of **11** (1.03 g, 2 mmol), triisopropylbenzenesulfonyl chloride (1.82 g, 6 mmol), and DMAP (50 mg) in CH_3CN (20 mL) at 0°C under argon. The reaction mixture was stirred for 2.5 h at room temperature, then the solvent was removed *in vacuo*. The residue was treated with NH_3/MeOH (saturated at 0°C, 30 mL) for 19 h at room temperature. After concentration of the mixture, the resulting solid was purified on a silica gel column (3 x 13), which was eluted with 2-10% EtOH in $CHCl_3$ to afford **16** (710 mg, 69% as a pale yellow foam). EI-MS *m/z* 512 (M^+). ^1H NMR ($CDCl_3$): 7.05 (d, 1H, H-6, $J_{6,5}$ = 7.3 Hz), 6.48 and 6.21 (each s, 1H, H-1'), 5.86 and 5.79 (each d, 1H, H-5, $J_{5,6}$ = 7.3 Hz), 5.59 (br s, 2H, 4-NH_2), 5.18 and 5.01 (m, 1H, H-3'), 4.16-3.91 (m, 3H, H-4', 5'a,b), 3.84 and 3.80 (each s, 3H, NOMe), 1.22-1.02 (m, 28H, isoPr).

1-(2-Deoxy-2-methoxyimino-β-D-*erythro*-pentofuranosyl)cytosine (4). A THF solution of TBAF (1 M, 1.5 mL, 1.5 mmol) was added to a mixture of **16** (350 mg, 0.7 mmol) in THF (5 mL) for 1 h at 0°C. The reaction mixture was neutralized with AcOH and the solvent was removed *in vacuo*. The residue was purified on a silica gel column (2.1 x 11 cm) with 20% MeOH in $CHCl_3$ to afford **4** (97 mg, 53% as a white foam). FAB-MS *m/z* 271 (M^++1). ^1H NMR (DMSO-d_6): 7.47 (d, 1H, H-6, $J_{6,5}$ = 7.1 Hz), 7.32 and 7.27 (each br s, 2H, 4-NH_2), 6.51 and 6.20 (each s, 1H, H-1'), 5.83 and 5.74 (each d, 1H, 3'-OH, $J_{3'OH,\ 3'}$ = 6.9 Hz), 5.73 (m, 1H, H-3'), 4.93 and 4.83 (each t, 1H, 5'-OH), 4.69 and 4.66 (each d, 1H, H-5, $J_{5,6}$ = 7.1 Hz), 3.78 and 3.73 (each s, 3H, NOMe), 4.37-3.52 (m, 3H, H-4', 5'a, b). *Anal* Calcd for $C_{10}H_{14}N_4O_5 \cdot 1/2$ MeOH: C, 44.06; H, 5.63; N, 19.57. Found: C, 43.87; H, 5.55; N, 19.29.

1-(3,5-Di-*O*-acetyl-2-*O*-acetoxyimino-2-deoxy-β-D-*erythro*-pentofuranosyl)-5-methyluracil. Acetic anhydride (72 mL, 0.76 mmol) was added to a solution of **1** (51.4 mg, 0.19 mmol) and DMAP (5 mg) in CH_3CN (2 mL) was stirred for 2.5 h at room temperature. The reaction mixture was diluted with EtOAc (50 mL) and the whole was washed with H_2O (3 x 10 mL). The separated organic phase was dried (Na_2SO_4) and concentrated to dryness. The product was purified on a silica gel column (2.3 x 13 cm), eluted with 4% EtOH in $CHCl_3$ to give the title compound (58 mg, 77%, crystallized from EtOH/Et_2O): mp 204-207°C. EI-MS *m/z* 397 (M^+). ^1H NMR ($CDCl_3$): 8.47 (br s, 1H, N^3H), 7.01 and 6.87 (each d, 1H, H-6, $J_{6,Me}$ = 1.1 Hz), 6.31 and 6.22 (each d, 1H, H-1', $J_{1',3'}$ = 1.5 Hz), 5.92 (dd, 1H, H-3', $J_{3',1'}$ = 1.5 Hz, $J_{3',4'}$ = 6.6 Hz), 4.52 (dd, 1H, H-5'a, $J_{5'a,4'}$ = 2.9 Hz, $J_{5'a,b}$ = 12.7 Hz), 4.36 (dd, 1H, H-5'b, $J_{5'b,4'}$ = 4.0 Hz, $J_{5'a,b}$ = 12.7 Hz), 4.31 (ddd, 1H, H-4', $J_{4',3'}$ = 6.6 Hz, $J_{4',5'a}$ = 2.9 Hz, $J_{4',5'b}$ = 4.0 Hz), 2.17 (s, 3H, Ac), 2.11 (s, 6H, Ac), 1.95 (d, 3H, 5-Me). *Anal* Calcd for $C_{16}H_{19}N_3O_9 \cdot 1/3\ H_2O$: C, 47.65; H, 4.91; N, 10.42. Found: C, 47.73; H, 4.82; N, 10.17.

Acknowledgments.

This investigation was supported in part by Grants-in-Aid for Cancer Research, Special Project Research on Cancer-Bioscience, and Scientific Research on Priority Areas from the Ministry of Education, Science, and Culture of Japan.

REFERENCES

(1) Part 105: Ono, A.; Ohdoi, C.; Matsuda, A.; Ueda, T. *Nucleosides Nucleotides,* in press.

(2) a) Takenuki, K.; Matsuda, A.; Ueda, T.; Sasaki, T.; Fujii, A.; Yamagami, K. *J. Med. Chem.*, **1988**, *31*, 1063. b) Matsuda, A.; Takenuki, K.; Tanaka, M.; Sasaki, T.; Ueda, T. *J. Med. Chem.*, **1991**, *34*, 812.

(3) Yamagami, K.; Fujii, A.; Arita, M.; Okumoto, T.; Sakata, S.; Matsuda, A.; Ueda, T.; Sasaki, T. *Cancer Res.*, **1991**, *51*, 2319.

(4) Machida, H.; Matsuda, A. unpublished data.

(5) Matsuda, A.; Okajima, H.; Masuda, A.; Kakefuda, A.; Yoshimura, Y.; Ueda, T. *Nucleosides Nucleosides*, in press.

(6) Tronchet, J. M.; Benhamza, R.; Dolatshahi, N.; Geoffroy, M.; Turler, H. *Nucleosides Nucleotides*, **1988**, *7*, 249.

(7) Tronchet, J. M.; Benhamza, R.; Bernardinelli, G.; Geoffroy, M. *Tetrahedron Lett.*, **1990**, *31*, 531.

(8) a) Baron, F.; Brown, D. M. *J. Chem. Soc.*, **1955**, 2858. b) Brown, D. J.; Paddon-Row, M. N. *J. Chem. Soc. (c)*, **1967**, 1928. c) Lingens, F.; Schneider-Bernlohr, H. *Ann.*, **1965**, *686*, 134. d) Witzel, H. *Ann.*, **1959**, *620*, 126.

(9) Kochetkov, N. K.; Budowsky, E. I.; Shibaeva, R. P. *Biochim. Biophys. Acta*, **1966**, *68*, 493.

Received 9/9/91
Accepted 10/31/91