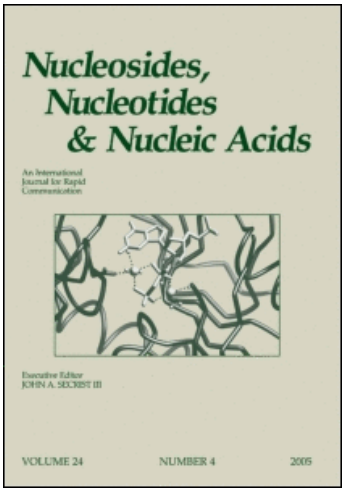

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Synthesis of Some Analogues Of 1-[(2-Hydroxyethoxy)-methyl]-6-(phenylthio) Thymine (HEPT) which have Different types of Acyclic Structures

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SYNTHESIS OF SOME ANALOGUES OF 1-[(2-HYDROXYETHOXY)-METHYL]-6-(PHENYLTHIO)THYMINE (HEPT) WHICH HAVE DIFFERENT TYPES OF ACYCLIC STRUCTURES

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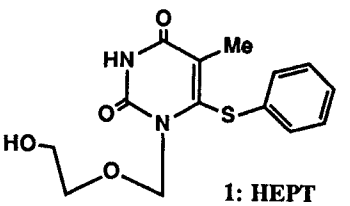
Abstract: Analogues of a recently developed specific anti-HIV-1 agent HEPT, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine, having different types of acyclic moieties were synthesized based on lithiation chemistry. Anti-HIV-1 activity of these analogues is also described.

Recently, as an application of our continuing studies on lithiation chemistry of nucleosides,[1)] 6-iodo- and 6-phenylthio derivatives of 1-[(2-hydroxyethoxy)methyl]uracils were synthesized.[2)] Among these compounds, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (**1**: HEPT), was found to be active against HIV-1 (human immunodeficiency virus type 1).



1: HEPT

HEPT is a unique lead for anti-HIV agents in that

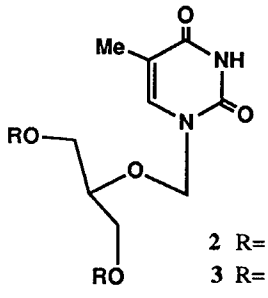
This paper is dedicated to the memory of Professor Tohru Ueda.

its activity is highly specific to HIV-1: other viruses such as SIV_{MAC} (simian immunodeficiency virus), SRV (simian AIDS-related virus), MSV (murine Moloney sarcoma virus), and even HIV-2 are totally non-susceptible to this compound.[3,4] Another salient feature regarding HEPT is that its triphosphate does not inhibit HIV-1 reverse transcriptase at concentrations much higher than the EC_{50} of HEPT.[2]

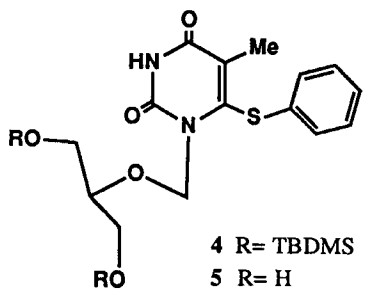
We have already reported on the synthesis of base-modified HEPT analogues.[5,6] Although deoxy analogues of HEPT have recently been synthesized and some of them were found to show an improved activity,[7,8] modification at the acyclic portion of HEPT remained to be undertaken. In this article, based on the lithiation strategy, we describe the synthesis of HEPT analogues that differ in the structure of the acyclic moiety and show their anti-HIV-1 activity.

Synthesis

First, the HEPT analogue having the acyclic side chain of DHPG,[9] 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine, was synthesized. The two hydroxyl groups of 1-[(1,3-dihydroxy-2-propoxy)-methyl]thymine (**2**), prepared according to the published method,[10] were protected with *tert*-butyldimethylsilyl (TBDMS) group in a conventional way (TBDMSCl/imidazole/DMF) to give **3** in 81% yield. The C-6 lithiation of **3** was carried out with 3 equiv of LTMP (lithium 2,2,6,6-tetramethylpiperidide) in THF at −70 °C for 1 h. Subsequent



2 R= H
3 R= TBDMS

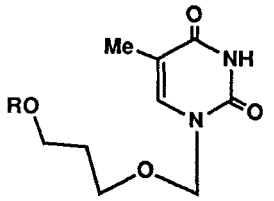


4 R= TBDMS
5 R= H

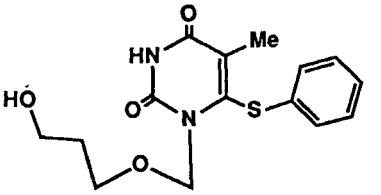
electrophilic reaction of $(PhS)_2$ (2 equiv) with the C-6 lithiated species of **3** for 2 h at −70 °C afforded the 6-phenylthio derivative **4** in 25% yield after silica gel column chromatography. Deprotection of the TBDMS groups was effected by heating **4** at 60 °C for 5 h in a

mixture of THF/AcOH/H_2O. The desired **5** was isolated in 77% yield simply by crystallization of the reaction mixture.

Synthesis of "5'"-homologue of HEPT was next carried out. Compound **6**, 1-[(3-benzyloxypropoxy)methyl]thymine, was prepared in 79% yield by condensation of trimethylsilylated thymine with (3-benzyloxypropoxy)methyl chloride in the presence of *p*-toluenesulfonic acid. When **6** was treated with LTMP and then reacted with $(PhS)_2$ in a similar manner to the case of **3**, the corresponding 6-phenylthio derivative was obtained in 21% yield. However, an attempted deprotection of this product by hydrogenolysis in the presence of $Pd(OH)_2/C$ in MeOH resulted in complete recovery of the starting material. Debenzylation with BBr_3 in CH_2Cl_2 also failed, giving an intractable mixture of products.



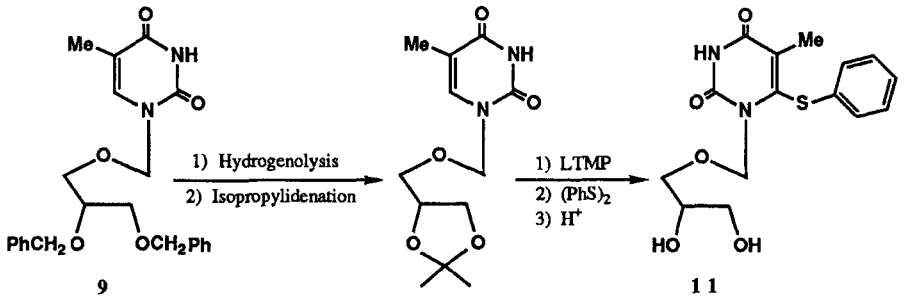
6 R= $CH_2C_6H_5$
7 R= TBDMS



8

We, therefore, turned to the use of the TBDMS group for protection of the hydroxyl function. Compound **7** was obtained in 63% yield upon hydrogenolysis of **6** followed by silylation. Introduction of a phenylthio group to the C-6 position of **7** was carried out by using LTMP and $(PhS)_2$ in a similar manner to the case of **3**. Without isolating the resulting product, the reaction mixture was treated with THF/AcOH/H_2O to give the desired **8** in 29% yield from **7**.

Another type of analogue having the (2,3-dihydroxypropoxy)-methyl group as an acyclic portion was also synthesized starting from **9**. Compound **9** was prepared in a similar manner to that described for the preparation of **6**. Due to the anticipated difficulty in deprotecting the benzyl groups in the final step, **9** was subjected to hydrogenolysis and then the resulting vicinal diol was reprotected with isopropylidene group to give **10** (94%) as shown in Chart 1. The desired **11** was obtained in 25% yield by the LTMP lithiation which



9 10 11

Chart 1

was followed by treatment with $(PhS)_2$ and deprotection with MeOH/aqueous HCl.

Finally, it may deserve a short comment that, although the yields of 6-substituted derivatives resulting from the present lithiation reactions were not high enough, the remainder was the respective starting material.[11]

Anti-HIV-1 activity

The anti-HIV-1 activity of HEPT analogues synthesized in this study was examined by using the HTLV-III_B strain based on the inhibition of the virus-induced cytopathic effect in MT-4 cells as previously described.[12]

As shown in Table 1, no significant activity was observed in **5**, **8**, and **11**. In our recent study on the synthesis of deoxy analogues of HEPT,[7] compounds having an ethoxymethyl or benzyloxymethyl acyclic portion, which is less polar than that of HEPT, exhibited an improved activity. It was also observed that introduction of a bulky "5'"-substituent tends to decrease the anti-HIV-1 activity. The present result combined with these previous observations suggests that, for anti-HIV-1 activity, a certain size of hydrophobic surrounding is necessary as the acyclic portion of HEPT analogues.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. ^1H NMR spectra were recorded at 250 MHz on a AC-250 Bruker NMR spectrometer using tetramethylsilane as an internal standard. UV spectra were recorded with a Shimadzu UV-260 spectrophotometer. Mass spectra were

Table 1. Anti-HIV-1 activity of **5**, **8**, and **11** in MT-4 cells.

Compd.	EC_{50} (μM)[a]	CC_{50} (μM)[b]	SI[c]
HEPT	7.0	740	106
5	>140	140	<1
8	120	170	1.4
11	>250	>250	~1
DDA[d]	6.3	890	141

a) Effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1.
b) Cytotoxic concentration of compound required to reduce the viability of mock-infected MT-4 cells by 50%.
c) Selectivity index: ratio of CC_{50}/ED_{50}.
d) 2',3'-Didehydro-2',3'-dideoxyadenosine.

taken on a Hitachi M-80A spectrometer. Column chromatography was carried out on Merck Silica gel 60 H. TLC was performed on silica gel (precoated silica gel plate 60 F254, Merck). Elemental analyses were performed on a Perkin-Elmer 240-C elemental analyzer.

1-[[1,3-Bis(*tert*-butyldimethylsilyloxy)-2-propoxy]-methyl]thymine (3) A mixture of **2** (806 mg, 3.5 mmol), TBDMSCl (2.1 g, 14 mmol), and imidazole (950 mg, 14 mmol) in DMF (5 mL) was stirred for 16 h at room temperature. The reaction mixture was evaporated and the residue was partitioned between H_2O and $CHCl_3$. Column chromatography ($CHCl_3$) of the organic layer gave **3** (1.3 g, 81%), which was crystallized from hexane (mp 100–101 °C). *Anal.* Calcd for $C_{21}H_{42}N_2O_5Si_2$: C, 54.98; H, 9.23; N, 6.11. Found: C, 55.04; H, 9.38; N, 6.28. UV absorption in MeOH: λ_{max} 265 nm (ε 9000). ^1H NMR ($CDCl_3$) δ: 0.03 (12H, s, SiMe), 0.88 (18H, s, SiBu-*t*), 1.93 (3H, s, 5-Me), 3.51–3.74 (5H, m, OCH_2CHCH_2O), 5.26 (2H, s, NCH_2O), 7.20 (1H, s, H-6). MS *m/z*: 443 (M^+–Me) and 401 (M^+–Bu-*t*).

1-[[1,3-Bis(*tert*-butyldimethylsilyloxy)-2-propoxy]-methyl]-6-(phenylthio)thymine (4) To a solution of LTMP (3.0 mmol) in THF (10 mL), **3** (450 mg, 0.98 mmol) in THF (5 mL) was added under nitrogen atmosphere, at a rate such that the temperature did not exceed −70 °C. After the mixture was stirred for 1 h,

$(PhS)_2$ (310 mg, 2.0 mmol) in THF (2 mL) was added and the temperature was maintained at −70 °C for 2 h. The reaction mixture was quenched by adding AcOH (0.2 mL), diluted with EtOAc, washed with H_2O, and evaporated. Column chromatography (toluene) of the resulting residue gave **4** (138 mg, 25%), the structure of which was confirmed by ^1H NMR spectrometry. ^1H NMR ($CDCl_3$) δ: 0.01 (12H, s, SiMe), 0.85 (18H, SiBu-*t*), 2.00 (3H, s, 5-Me), 3.49–3.58 (5H, m, OCH_2CHCH_2O), 5.68 (2H, s, NCH_2O), 7.10–7.36 (5H, m, Ph).

1-[(1,3-Dihydroxy-2-propoxy)methyl]-6-(phenylthio)thymine (5) Compound **4** (138 mg) was treated with a mixture of THF (2 mL), AcOH (2 mL), and H_2O (1 mL) at 60 °C for 5 h. Evaporation of the mixture followed by crystallization from EtOAc gave **5** (64 mg, 77%), which was analytically pure (mp 161–162 °C). *Anal.* Calcd for $C_{15}H_{18}N_2O_5S \cdot 1/2H_2O$: C, 51,86; H, 5.51; N, 8.06. Found: C, 51.96; H, 5.27; N, 8.18. UV absorption in MeOH: λ_{max} 244 nm (ε 9800) and 273 nm (ε 7900). ^1H NMR (DMSO-d_6, after addition of D_2O) δ: 1.76 (3H, s, 5-Me), 3.19–3.56 (5H, m, OCH_2CHCH_2O), 5.46 (2H, s, NCH_2O), 7.27–7.35 (5H, m, Ph). MS *m/z*: 338 (M^+).

1-[(3-Benzyloxypropoxy)methyl]thymine (6) A mixture of thymine (2.7 g, 22 mmol) and bis(trimethylsilyl)acetamide (10.8 mL, 44 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 5 h. After evaporation of the solvent, (3-benzyloxypropoxy)methyl chloride (4.3 g, 20 mmol), *p*-toluenesulfonic acid monohydrate (0.38 g, 2.0 mmol), and CH_3CN (20 mL) were added to the residue. The resulting mixture was refluxed for 3 d, evaporated, and partitioned between H_2O and EtOAc. Column chromatography ($CHCl_3$) of the organic layer gave **6** (4.8 g, 79%), which was crystallized from EtOAc–hexane (mp 63–65 °C). *Anal.* Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.15; H, 6.67; N, 9.06. UV absorption in MeOH: λ_{max} 264 nm (ε 8600). ^1H NMR ($CDCl_3$) δ: 1.91 (3H, s, 5-Me), 1.97 (2H, m, $OCH_2CH_2CH_2O$), 3.53 and 3.65 (2H each, t, *J*= 7.0 Hz, $OCH_2CH_2CH_2O$), 4.48 (2H, s, CH_2Ph), 5.11 (2H, s, NCH_2O), 7.10 (1H, s, H-6), 7.32 (5H, s, Ph). MS *m/z*: 304 (M^+).

1-[3-(*tert*-Butyldimethylsilyloxypropoxy)methyl]thymine (7) Hydrogenolysis of **6** (910 mg, 3.0 mmol) was carried out in MeOH (5 mL) in the presence of a catalytic amount of $Pd(OH)_2/C$ for 23 h at room temperature. After removal of the

catalyst by filtration, the solvent was evaporated. To the resulting residue, DMF (5 mL), TBDMSCl (680 mg, 4.5 mmol), and imidazole (310 mg, 4.5 mmol) were added. The reaction mixture was stirred overnight at room temperature, evaporated, and partitioned between H_2O and EtOAc. Column chromatography ($CHCl_3$) of the organic layer gave **7** (620 mg, 63%), which was crystallized from 2-propanol (mp 131–132 °C). *Anal.* Cald for $C_{15}H_{28}N_2O_4Si$: C, 54.85; H, 8.59; N, 8.53. Found: C, 54.78; H, 8.76; N, 8.49. UV absorption in MeOH: λ_{max} 264 nm (ε 8700). ^1H NMR ($CDCl_3$) δ: 0.03 (6H, s, SiMe), 0.88 (9H, s, SiBu-*t*), 1.74 (2H, m, $OCH_2CH_2CH_2O$), 1.91 (3H, s, 5-Me), 3.60–3.63 (4H, m, $OCH_2CH_2CH_2O$), 5.10 (2H, s, NCH_2O), 7.11 (1H, s, H-6). MS *m/z*: 271 (M^+–Bu-*t*).

1-[(3-Hydroxypropoxy)methyl]-6-(phenylthio)thymine (8) LTMP lithiation of **7** was carried out by the procedure described for that of **3**. The following amounts of reagents and **7** (330 mg, 1.0 mmol) in THF (5 mL) were used: LTMP (3.0 mmol) in THF (10 mL), $(PhS)_2$ (310 mg, 2.0 mmol) in THF (2 mL). The reaction mixture was quenched by adding AcOH (0.2 mL), diluted with EtOAc, washed with H_2O, and evaporated. The resulting residue was treated with a mixture of THF (5 mL), AcOH (5 mL), and H_2O (2.5 mL) for 5 d at room temperature. Evaporation of the solvent followed by column chromatography ($CHCl_3$) gave **8** (93 mg, 29% from **7**), which was crystallized from EtOAc (mp 92–93 °C). *Anal.* Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.62; N, 8.69. Found: C, 56.25; H, 5.64; N, 8.75. UV absorption in MeOH: λ_{max} 244 nm (ε 9900) and 274 nm (ε 8000). ^1H NMR ($CDCl_3$) δ: 1.75 (2H, m, $OCH_2CH_2CH_2O$), 2.04 (3H, s, 5-Me), 3.67 and 3.70 (2H each, t, J= 6.4 Hz, $OCH_2CH_2CH_2O$), 5.55 (2H, s, NCH_2O), 7.12–7.50 (5H, m, Ph), 9.30 (1H, br, NH). MS *m/z*: 322 (M^+).

1-[(2,3-Dibenzyloxypropoxy)methyl]thymine (9) This compound was obtained as an oil in 82% yield by the procedure described for the preparation of **6**. The following amounts of reagents were used: thymine (630 mg, 5.0 mmol), bis(trimethylsilyl)-acetamide (2.6 mL, 10.5 mmol), *p*-toluenesulfonic acid monohydrate (95 mg), and (2,3-dibenzyloxypropoxy)methyl chloride (1.6 g, 5.0 mmol). UV absorption in MeOH: λ_{max} 264 nm. ^1H NMR ($CDCl_3$) δ: 1.88 (3H, s, 5-Me), 3.43–3.82 (5H, m, OCH_2CHCH_2O), 4.52 (2H, s, CH_2Ph), 4.61 and 4.68 (1H each, d, J_{gem}= 12.0 Hz, CH_2Ph), 5.12 (2H, s, NCH_2O),

7.07 (1H, s, H-6), 7.22–7.42 (10H, m, Ph), 8.36 (1H, br, NH). MS *m/z*: 410 (M^+).

1-[[(2,3-Dihydroxy-2,3-*O*-isopropylidene)propoxy]-methyl]thymine (10) Hydrogenolysis of **9** (820 mg) was carried out by the procedure described for that of **6**. To the residue obtained after work-up, 2,2-dimethoxypropane (3 mL) and a catalytic amount of *p*-toluenesulfonic acid monohydrate were added. The mixture was stirred for 40 h at room temperature and passed through a silica gel column. This gave **10** (510 mg, 94%), which was crystallized from diisopropyl ether (mp 75–76 °C). *Anal.* Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.57; H, 6.97; N, 10.42. UV absorption in MeOH: λ_{max} 264 nm (ε 8700). ^1H NMR ($CDCl_3$) δ: 1.36 and 1.42 (3H each, s, isop. Me), 1.94 (3H, s, 5-Me), 3.56–3.72 and 3.98–4.34 (5H, m, OCH_2CHCH_2O), 5.19 (2H, s, NCH_2O), 7.15 (1H, s, H-6), 8.57 (1H, br, NH). MS *m/z*: 270 (M^+).

1-[(2,3-Dihydroxypropoxy)methyl]-6-(phenylthio)-thymine (11) LTMP lithiation of **10** was carried out by the procedure described for that of **3**. The following amounts of reagents and **10** (510 mg, 1.9 mmol) in THF (5 mL) were used: LTMP (6.0 mmol) in THF (19 mL) and $(PhS)_2$ (620 mg, 4.0 mmol) in THF (5 mL). After being quenched with AcOH (0.4 mL), the reaction mixture was evaporated. To the resulting residue, MeOH (5 mL) was added and the solution was acidified to approximately pH 1 with 1 *M* aqueous HCl . The mixture was stirred for 16 h at room temperature, evaporated, and chromatographed on a silica gel column (10% MeOH in toluene). This gave **11** (160 mg, 25% from **10**), which was crystallized from EtOAc–hexane (mp 83–84 °C). *Anal.* Calcd for $C_{15}H_{18}N_2O_5S$: C, 53.24; H, 5.36; N, 8.27. Found: C, 52.91; H, 5.37; N, 8.14. UV absorption in MeOH: λ_{max} 244 nm (ε 9900) and 274 nm (ε 8000). ^1H NMR ($CDCl_3$) δ: 2.07 (3H, s, 5-Me), 2.58 and 2.97 (1H each, br, OH), 3.44–3.86 (5H, m, OCH_2CHCH_2O), 5.58 (2H, s, NCH_2O), 7.08–7.40 (5H, m, Ph), 9.51 (1H, br, NH). MS *m/z*: 338 (M^+).

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