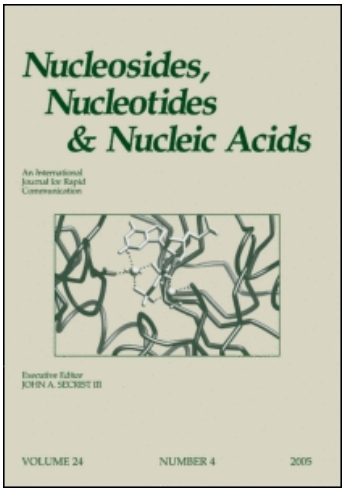

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DESIGN AND SYNTHESIS OF REGIOISOMERIC ANALOGUES OF A SPECIFIC ANTI-HIV-1 AGENT 1-[(2-HYDROXYETHOXY)METHYL]-6-(PHENYLTHIO)THYMINE (HEPT)

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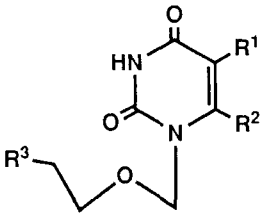
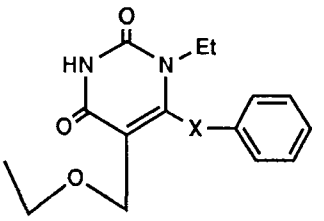
Abstract Regioisomeric analogues of the anti-HIV-1 lead 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (**1**: HEPT) have been synthesized. These compounds, having an ethoxymethyl side chain at C-5 and an ethyl group at the N-1 position of the uracil ring, also possess activity against HIV-1.

In 1989, we reported that 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (**1**: HEPT) exhibited an inhibitory activity against replication of Human Immunodeficiency Virus type 1 (HIV-1) in vitro.[1,2] Although HEPT is structurally an acyclonucleoside, its activity is highly specific to HIV-1 and required no phosphorylation of the hydroxyl group, which contrasts with the known anti-HIV nucleosides such as 3'-azido-3'-deoxythymidine (AZT) or 2',3'-didehydro-2',3'-dideoxyinosine (DDI). Several heterocyclic compounds were reported later to show a similar specificity to HIV-1.[3-7] These compounds, including HEPT, manifest their activity by directly inhibiting the reverse transcriptase of HIV-1.

This paper is dedicated to the memory of Professor Roland K. Robins.



1 R^1= Me, R^2= SPh, R^3= OH
2 R^1= Me, R^2= CH_2Ph, R^3= OH
3 R^1= Et, R^2= SPh, R^3= OH
4 R^1= Et, R^2= SPh, R^3= H



5 X = S
6 X = CH_2

As a result of extensive synthetic studies carried out so far,[8] the structure-activity relationships of HEPT analogues are fairly well defined. Some of these can be seen in the structures of compounds **2**-**4**: 1) replacement of the sulfur atom of the 6-phenylthio group with a methylene,[8a] 2) replacement of the 5-methyl group with a bulkier alkyl group such as an ethyl group,[8d] and 3) removal of the hydroxyl group in the acyclic structure.[8c] Also, the presence of N^3-H proved indispensable for the anti-HIV-1 activity.[8b] Based on these results, we wondered whether the regioisomeric analogues **5** and **6** might have a similar antiviral property. In this paper, synthesis of these analogues and their anti-HIV-1 activity are described.

Selective N-1 alkylation of 5-(ethoxymethyl)uracil (**7**)[9] was carried out by treatment with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) followed by EtI in refluxing 1,2-dichloroethane.[10] Column chromatographic purification of the reaction mixture gave two products. The less polar product appeared to be the required N^1-ethyl derivative **8** (55% yield). The ^{1}H NMR spectrum of the more polar product showed the presence of two ethyl groups, two protons attributable to H-6 (δ: 7.65 and 7.78 ppm), and two D_2O exchangeable protons. Together with its FAB-MS spectrum that showed a protonated positive molecular ion $[M+H]^+$ at *m/z* 323, the structure of this product was deduced to be **9** (11% yield).

Lithiation chemistry was used for the C-6 functionalization of **8**.[11] As reported earlier in the case of LDA lithiation of ribofuranosylthymine,[12] the presence of an electron-donating alkyl group at the C-5 position decreases the C-6 lithiation level. Accordingly, when **8** was treated with LDA (2.5 equiv) in THF at below −70 °C and then reacted with $(PhS)_2$, **5** was not formed even in a trace amount. The use of a more basic lithiating agent lithium 2,2,6,6-tetramethylpiperidide (LTMP), on the other hand, furnished **5** in 53% yield along

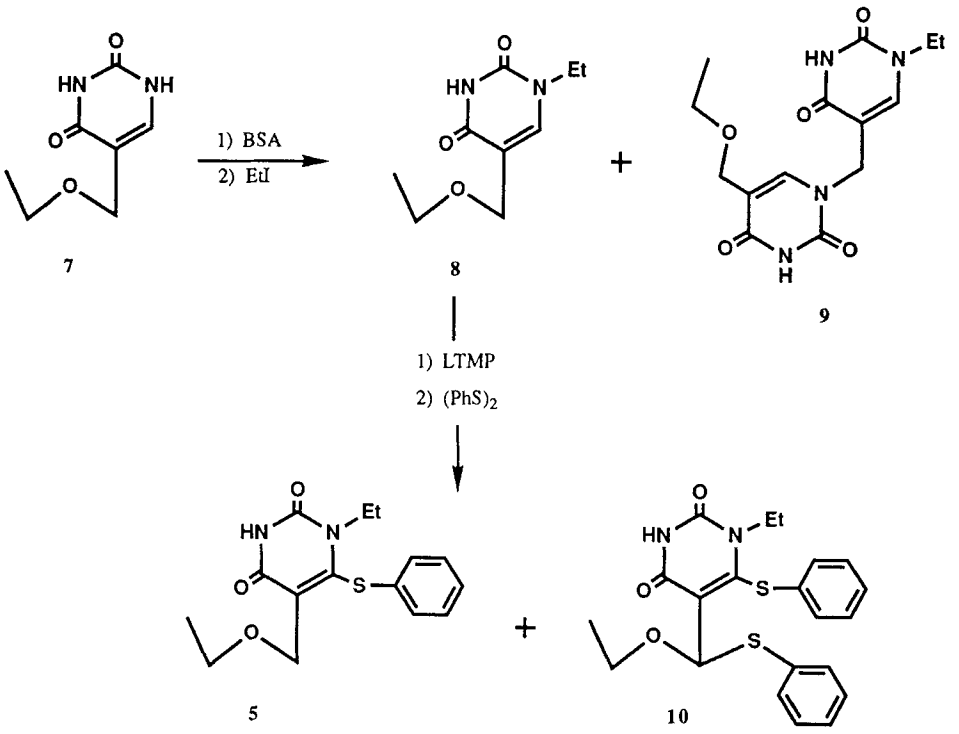
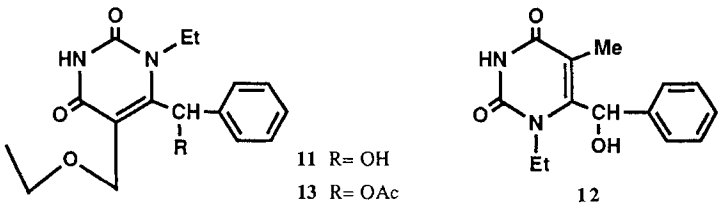


FIG. 1

with **10** (30%). The formation of **10** is a likely consequence of benzylic metallation of **5** that can be stabilized by the sulfur atom of the 6-phenylthio group.[14]

For the synthesis of the 6-benzyl derivative (**6**), **8** was lithiated with LTMP in a similar manner and then reacted with benzyl bromide. However, this reaction turned out to result in complete recovery of the starting material. After careful examination of the reaction mixture, formation of *trans*-stilbene was confirmed. This suggests that the benzyl bromide underwent α-elimination with the C-6 lithiated species of **8** to form a carbene.[15]



As an alternative way to synthesize **6**, the 6-phenylhydroxymethyl derivative (**11**) was first prepared in 81% yield based on the LTMP lithiation of **8** and successive reaction with benzaldehyde. When **11** was subjected to hydrogenolysis in the presence of 10% Pd-C in EtOH, the reaction occurred with extreme sluggishness and gave **12** as the main product.[16] This unfavorable situation can be changed simply by acetylating **11**. Thus, the hydrogenolysis of **13** under similar conditions gave the desired **6** as the sole product in 97% yield.

Finally, the anti-HIV-1 (HTLV-III_B strain) activity of **5** and **6** was measured in MT-4 cells by the MTT method.[17] As we had anticipated, both **5** and **6** appeared to protect MT-4 cells against the cytopathic effect of HIV-1 with an EC_{50} 1.4 μM and 16 μM, respectively. However, when the EC_{50} value of **5** is compared with the reported value of the corresponding regioisomer **4** (EC_{50} 0.022 μM),[18] **5** is apparently much less active. As has been observed earlier in the case of 5-substituted 6-phenylthiouridines,[19] the presence of a C-5 substituent forces the 6-phenylthio group to alter its conformation due to steric hindrance. This conformational change is considered to be an important factor for HEPT analogues to exert their anti-HIV-1 activity: uracil counterpart of HEPT, in which the 6-phenylthio group lies perpendicular to the uracil ring, proved to be inactive.[1] The observed discrepancy in the EC_{50} values of **4** and **5** can be, therefore, attributable to the difference in bond lengths of C5-C6 in **4** and N1-C6 in **5**: the closer disposition of the two substituents (ethyl and phenylthio groups), the higher the activity. In the case of HEPT (**1**), bond lengths have been measured to be 1.35 Å for C5-C6 and 1.40 Å for N1-C6.[20] These results confirm that it is the overall shape and charge distribution within the HEPT series of molecules which are responsible for their antiviral activity.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured at 23 °C (internal standard, Me_4Si) either with a JEOL JNM-FX 100 or with a JEOL JNM-GX 400 spectrometer. Mass spectra (MS) were taken either on a JEOL JMS-D 300 in electron impact mode or on a JEOL SX-102A spectrometer in fast atom bombardment (FAB) mode (*m*-nitrobenzyl alcohol as a matrix). Ultraviolet spectra (UV) were recorded on a JASCO Ubest-55 spectrophotometer. Commercially available hexane solution of BuLi was titrated before use with diphenylacetic acid in THF. THF was distilled from benzophenone ketyl. Column chromatography was carried out on silica gel (Wakogel® C-200). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck).

5-Ethoxymethyl-1-ethyluracil (8) A mixture of 5-ethoxymethyluracil (**7**, 1.64 g, 9.63 mmol) and *N,O*-bis(trimethylsilyl)acetamide (15 mL, 61 mmol) in 1,2-dichloroethane (30 mL) was stirred at room temperature for 0.5 h. To the resulting solution, EtI (8.0 mL, 100 mmol) was added and the whole was refluxed for 5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$. Extraction with $CHCl_3$ followed by silica gel column chromatography (1-2% EtOH in $CHCl_3$) gave **8** (1.05 g, 55%), which was crystallized from EtOH (mp 121-121.5 °C). *Anal.* Calcd for $C_9H_{14}N_2O_3$: C, 54.50; H, 7.12; N, 14.10. Found: C, 54.37; H, 6.96; N, 14.08. UV absorption in MeOH: λ_{max} 259 nm (ε 11500). ^1H NMR 100 MHz ($CDCl_3$) δ: 1.25 and 1.32 (6H, each as t, NCH_2CH_3 and OCH_2CH_3), 3.61 and 3.81 (4H, each as q, NCH_2Me and OCH_2Me), 4.26 (2H, d, *J*= 1.0 Hz, CH_2OEt), 7.27 (1H, d, H-6). FAB-MS *m/z*: 199 (M^++H).

Compound **9** (167 mg, 11%) was also isolated by elution with 4% EtOH in $CHCl_3$. Crystallization from EtOH gave an analytically pure sample (mp 215-216 °C). *Anal.* Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63; N, 17.38. Found: C, 51.89; H, 5.62; N, 17.15. UV absorption in MeOH: λ_{max} 273 nm (ε 22400). ^1H NMR 100 MHz (DMSO-d_6) δ: 1.10 and 1.15 (6H, each as t, NCH_2CH_3 and OCH_2CH_3), 3,43 and 3.70 (4H, each as q, OCH_2Me and NCH_2Me), 5.05 and 4.45 (4H, each as s, CH_2OEt and NCH_2), 7.65 and 7.78 (2H, each as s, H-6), 11.29 and 11.41 (2H, each as s, NH). FAB-MS *m/z*: 323 (M^++H), 277 (M^+–OEt).

5-Ethoxymethyl-1-ethyl-6-(phenylthio)uracil (5) In a three-necked flask equipped with a gas-inlet adaptor, thermometer, and rubber septum, a THF (10 mL) solution of lithium 2,2,6,6-tetramethylpiperidide (5.0 mmol) was prepared from butyllithium and 2,2,6,6-tetramethylpiperidine below –70 °C. To this, **8** (396 mg, 2.0 mmol) in THF (5 mL) was added, under positive pressure of dry argon, at a rate such that the temperature did not exceed –70 °C. After the mixture was stirred for 1 h, diphenyl disulfide (1.09 g, 5.0 mmol) in THF (5 mL) was added, while maintaining the temperature below –70 °C. The reaction mixture was stirred for 2.5 h and quenched with AcOH (0.3 mL). The whole was evaporated and partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), evaporated, and chromatographed on a silica gel column. Elution with $CHCl_3$ gave **5** (325 mg, 53%) and **10** (248 mg, 30%).

Compound **5** was crystallized from EtOH (mp 157-158 °C). *Anal.* Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 59.04; H, 5.97; N, 9.28. UV absorption in MeOH: λ_{max} 240 nm (ε 10600) and 266 nm (ε 10200). ^1H NMR 100 MHz ($CDCl_3$) δ: 1.05 (3H, t, *J*= 7.0 Hz, OCH_2CH_3), 1.17 (3H, t, *J*= 6.8 Hz, NCH_2CH_3), 3.56 (2H, q, OCH_2CH_3), 4.04 (2H, q, NCH_2CH_3), 4.54 (2H, s, CH_2OEt), 7.31 (5H, s, Ph). MS *m/z*: 306 (M^+).

Compound **10** was obtained as a foam. *Anal.* Calcd for $C_{21}H_{22}N_2O_3S_2$: C, 60.85; H, 5.35; N, 6.76. Found: C, 60.50; H, 5.31; N, 6.62. UV absorption in MeOH: λ_{max} 275 nm (ε 9000). ^1H NMR 100 MHz ($CDCl_3$) δ: 1.03 and 1.10 (6H, each as t, NCH_2CH_3 and OCH_2CH_3), 3.13-4.12 (4H, m, NCH_2CH_3 and OCH_2CH_3), 6.33 (1H, s, OCHSPh), 7.22-7.54 (10H, m, Ph), 9.04 (1H, br, NH). MS *m/z*: 414 (M^+).

5-Ethoxymethyl-1-ethyl-6-(phenylhydroxymethyl)uracil (11) This compound was synthesized by the procedure described for the preparation of **5**. The following amounts of reagents and **8** (666 mg, 3.4 mmol) in THF (15 mL) were used: LTMP (8.4 mmol) in THF (9 mL) and freshly distilled benzaldehyde (0.75 mL, 7.4 mmol). The reaction was continued for 1 h at below

-70 °C. Quenching with AcOH followed by silica gel column chromatography (1% MeOH in $CHCl_3$) of the reaction mixture gave **11** (831 mg, 81%). Crystallization from EtOH gave an analytically pure sample (mp 205-206.5 °C). *Anal.* Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 62.86; H, 6.62; N, 9.23. UV absorption in MeOH: λ_{max} 276 nm (ε 10600). ^{1}H NMR 100 MHz ($CDCl_3$) δ: 1.03 and 1.19 (6H, each as t, NCH_2CH_3 and OCH_2CH_3), 3.50 and 3.93 (4H, each as q, NCH_2CH_3 and OCH_2CH_3), 4.10 and 4.44 (2H, each as d, J_{gem}= 11.5 Hz, CH_2OEt), 4.69 (1H, br, OH), 6.16 (1H, d, *J*= 5.9 Hz, CH(OH)Ph), 7.38 (5H, s, Ph), 8.95 (1H, br, NH). FAB-MS *m/z*: 305 (M^++H).

6-Benzyl-5-ethoxymethyl-1-ethyluracil (6) Compound **11** (504 mg) was acetylated with Ac_2O (0.5 mL) in pyridine (5 mL) at room temperature overnight. After quenching with H_2O, the reaction mixture was evaporated to dryness to give **13** as a syrup, which was used in the next reaction without any purification. A solution of **13** in EtOH (20 mL) was subjected to hydrogenolysis (1 atm of H_2) in the presence of 10% Pd-C (50 mg) at room temperature for 24 h. The catalyst was removed by filtration. Evaporation of the filtrate followed by short column chromatograpy (1% EtOH in $CHCl_3$) gave **6** (495 mg, 97% from **11**) as a foam. Crystallization from EtOH-ether gave an analytically pure sample (mp 142-143 °C). *Anal.* Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.81; H, 6.91; N, 9.64. UV absorption in MeOH: λ_{max} 274 nm (ε 11100). ^{1}H NMR 400 MHz ($CDCl_3$) δ: 1.12 and 1.16 (6H, each as t, NCH_2CH_3 and OCH_2CH_3), 3.53 and 3.75 (4H, each as q, NCH_2CH_3 and OCH_2CH_3), 4.12 and 4.35 (4H, each as s, CH_2OEt and CH_2Ph), 7.11-7.16 (2H, m, Ph), 7.28-7.37 (3H, m, Ph), 9.44 (1H, br, NH). FAB-MS *m/z*: 289 (M^++H), 243 (M^+- OEt). MS *m/z*: 288 (M^+), 259 (M^+-Et), 245 (M^+-OEt+H).

Anti-HIV-1 activity of compounds 5 and 6 MT-4 cells ($1x10^4$ cells/well) were infected with HIV-1 (HTLV-III_B strain) at a mutiplicity of infection of 0.02 and incubated in the presence of various concentrations of compound **5** or **6**. After 4 days incubation at 37 °C, the number of viable cells was recorded by the MTT method. The results obtained are as follows:

Compound **5**; EC_{50} 1.4 μM, CC_{50} 203 μM (Selectivity Index 145)

Compound **6**; EC_{50} 16 μM, CC_{50} 303 μM (Selectivity Index 19).

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