Synthesis of Cyclic and Acyclic Nucleoside Analogues Having a Thiophene or Dihydrothiophene Ring Fused to the *d* Side of an Uracil

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Synthesis of cyclic and acyclic nucleosides was achieved by alkylation of various new aglycones following the Vorbrüggen and Niedballa's procedure [6]. The analytical results allowed us to conclude that the alkylation occured on N1 site and led to the β anomeric form for the cyclic nucleosides.

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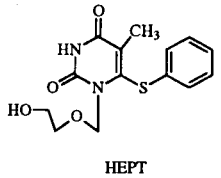
Since the discovery of its prime role in the HIV replication, the Reverse Transcriptase has been considered as an attractive target in the search for agents to combat the spread of the Acquired Immmunodeficiency Syndrome (AIDS) [1]. Thus, a lot of potential antiviral agents have been screened in order to explore their ability to inhibit this pivotal enzyme. Among the numerous compounds showing such activity, nucleoside analogues are an essential chemical family. Thus, azidothymidine (AZT) (Scheme I) and other 2',3'-dideoxynucleosides are very potent Reverse Transcriptase inhibitors [2], but their toxicity prompted researchers to find new anti-HIV agents.

As a result acyclic nucleosides such as 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) or 1-(benzyloxymethyl)-5-ethyl-6-(phenylthio)uracil (EBPU) have been reported [3] (Scheme I). Unlike AZT, their biological mechanism which appears to be non competitive is the result of an interaction at an allosteric site of the Reverse Transcriptase [4].

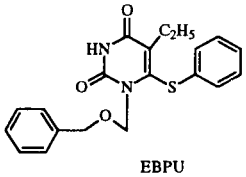
Although the non competitive inhibitors encompass a large variety of chemical structures, they share a number of common features such as the presence of an hydrophobic region and their overall steric bulk [5].

In this article we describe the synthesis of HEPT and EBPU related acyclic nucleosides and ribofuranosyl nucleosides. These latter compounds will be precursors of modified nucleosides. We have also obtained analogues of Ganciclovir or 1-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG) which is used for the treatment against cytomegalovirus, an opportunist virus of AIDS (Scheme I).

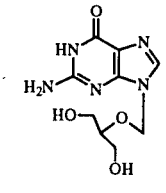
Scheme I



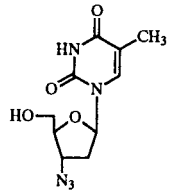
HEPT



EBPU



DHPG



AZT

The aglycons of our compounds present a lipophilic region constituted by an heterocycle (thiophene or dihydrothiophene) fused on the *d* side of an uracil ring. For the heterocycles **5**, **7** and **9**, a phenyl ring increases the lipophilicity of the thiophene ring. Their N1 position was alkylated by acyclic ethers and ribofuranose.

Chemistry.

Our general strategy for the synthesis of nucleoside analogues was based on the alkylation of silylated aglycones following Vorbrüggen and Niedballa's procedure [6]. The synthesis of each aglycone required a functionalized thiophene or dihydrothiophene ring.

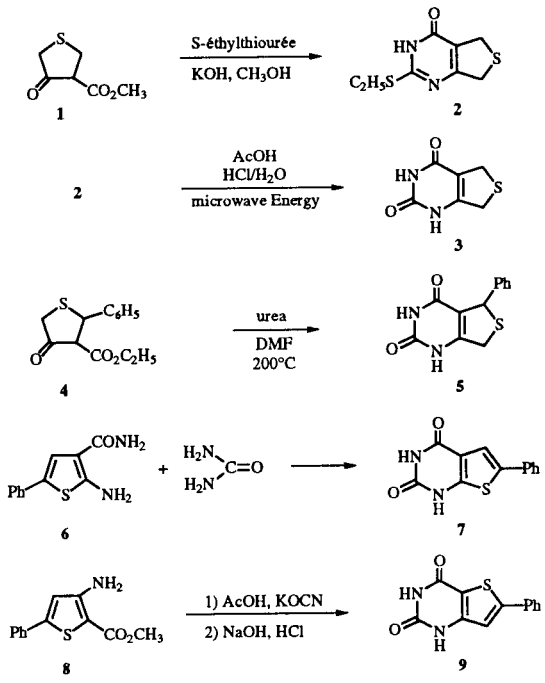
Methyl 4-oxothiolane-3-carboxylate **2** was prepared according to the literature [7] and its cyclization was carried out with *S*-ethylthiourea [8] to yield an *S*-ethylated intermediate **3**. Acidic hydrolysis of compound **3** was improved by the use of micro-wave energy instead of classical refluxing (50 hours) with the result that the hydrolysis yield reached 65% after 20 minutes. The overall yield starting from the compound **2** approached 50%.

The preparation of heterocycle **5** required methyl 4-oxo-2-phenylthiolane-3-carboxylate **4** described by Surey and co-workers [9]. This dihydrothiophene derivative was then refluxed with urea in *N,N*-dimethylformamide in order to form the uracil ring (Scheme II).

According to a Gewald's procedure [10] we could synthesize a thiophene ring. Compound **6** upon reaction with urea at fusion temperature yielded the desired heterocycle **7** (Scheme II). Excess urea could be removed by the use of water and column chromatography.

The synthesis of the heterocycle **9** started from methyl 3-amino-5-phenylthiophene-2-carboxylate **8** described by Hartman and co-workers [11]. The corresponding urea derivative resulted from its reaction with potassium cyanate in acetic acid medium. This intermediate was then

Scheme II



treated in aqueous alkaline medium to yield compound **9**.

The second phase of our work consisted in the alkylation of the various heterocycles. We have carried out this essential step by the use of Vorbrüggen and Niedballa's procedure [6] for the following reasons:

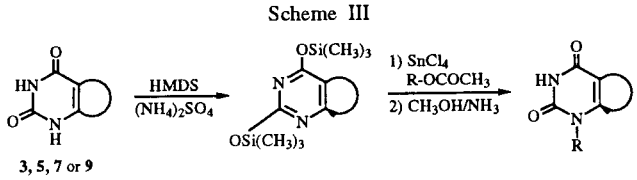
(a) The overall yield is quite acceptable.

(b) The satisfactory regioselectivity usually leads to the desired N1 alkylated compounds.

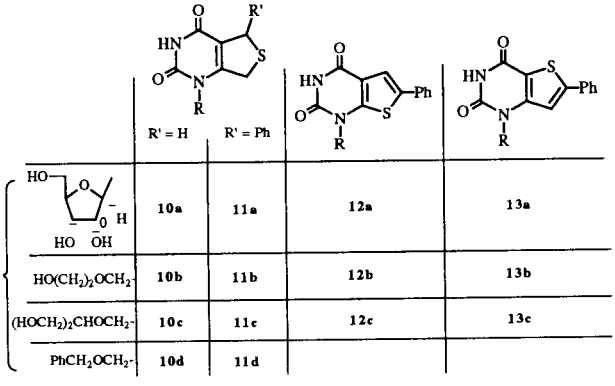
(c) The mechanism of glycosylation [6] explains that only β anomers are obtained in the case of D-ribonucleosides.

This method started with a bis(trimethylsilylation) of the various heterocycles leading to their reactive form.

Scheme III



3, 5, 7 or 9



R =	R' = H	R' = Ph		
	10a	**11a**	**12a**	**13a**
$HO(CH_2)_2OCH_2$-	**10b**	**11b**	**12b**	**13b**
$(HOCH_2)_2CHOCH_2$-	**10c**	**11c**	**12c**	**13c**
$PhCH_2OCH_2$-	**10d**	**11d**		

This reaction was accomplished with hexamethyldisilazane (HMDS) in the presence of a catalytic amount of ammonium sulphate (Scheme III). This activated form was subjected to reaction with 2-acetoxyethyl acetoxymethyl ether, 2-(acetoxymethoxy-1,3-propanediyl) dibenzoate or benzyloxymethyl acetate. These reactions were carried out in dry 1,2-dichloroethane with tin(IV) chloride as a catalyst. The same procedure was used with 1-acetate-2,3,5-tri-*O*-benzoyl-D-ribofuranose giving the protected ribofuranosyl nucleosides, followed by deblocking using ammonia. Chromatographic purification yielded the free nucleoside analogues.

All final compounds were characterized by ^{1}H-nmr, ^{13}C-nmr, and ir spectra. According to Fox and Shugar's method [12], in the uv spectra, the lack of a bathochromic effect of an *N*-alkylated uracil derivative in alkaline medium indicates N1-alkylation. This was observed for all final compounds. The use of ^{13}C-nmr provided the confirmation [13], thus a deshielding of carbon C4a in the nucleoside analogues provides a comparison with the corresponding heterocycle. This provided a second argument for a N1 alkylation. With respect to the anomeric configuration of ribonucleosides, we made use of the Imbach's rule [14] to confirm the β configuration.

EXPERIMENTAL

Melting points were taken on a Köfler block and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus and only noteworthy absorptions in cm^{-1} are listed. The uv spectra were recorded on a SECOMAM.S 1000 G spectrometer and only noteworthy absorptions (nanometers) are listed. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Jeol FX 200 in DMSO-d_6 solution using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS.

5H,7H-2-Ethylthiodihydrothieno[3,4-*d*]pyrimidin-4-one **2**.

Methyl 4-oxothiolane-3-carboxylate **1** (16 g, 0.1 mole) was added dropwise at room temperature to a stirred aqueous solution of sodium carbonate (21.2 g, 0.2 mole) and *S*-ethylthiourea hydrobromide (26.9 g, 0.15 mole). The mixture was stirred for 12 hours. The precipitate of **2** was collected, washed with water and diethyl ether successively to yield 17.8 g (83%) of a white solid, mp 220°; ir (potassium bromide): 1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 1.25 (t, J_{H-H} = 7.3 Hz, 3H, CH_3), 3.02 (q, J_{H-H} = 7.3 Hz, 2H, CH_2S), 3.83 (s, 2H, CH_2), 3.98 (s, 2H, CH_2), 10.88 (s, 1H, NH).

5H,7H-Dihydrothieno[3,4-*d*]pyrimidine-2,4-dione **3**.

A solution of **2** (17.1 g, 0.08 mole), acetic acid (150 ml), concentrated hydrochloric acid (30 ml) and water (100 ml) was refluxed in a microwave oven for 20 minutes. The reaction mixture was then cooled and the precipitate which appeared was collected, washed with water and diethyl ether successively to yield 8.9 g (65%) of **4** as a white solid, mp > 260°; ir (potassium bromide): 3140-3100 (NH), 1680 and 1630 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.76 (t, J_{H-H} = 2.9 Hz, 2H, H5), 3.98 (t, J_{H-H} = 2.9 Hz, 2H, H7), 11.09 (s, 1H, NH), 11.29 (s, 1H, NH); ^{13}C-nmr

(DMSO-d_6): δ 31.6 (C5), 34.8 (C7), 108.4 (C4a), 151.7 (C7a), 151.9 (C2), 160.7 (C4).

Anal. Calcd. for $C_6H_6N_2O_2S$ (170.19): C, 42.35; H, 3.55; N, 16.46. Found: C, 42.19; H, 3.51; N, 16.23.

5*H*,7*H*-5-Phenyldihydrothieno[3,4-*d*]pyrimidine-2,4 dione **5**.

A mixture of ethyl 2-phenyl-4-oxothiolane-3-carboxylate **4** (7.5 g, 0.03 mole) and urea (3.6 g, 0.06 mole) in *N,N*-dimethylformamide (50 ml) was refluxed for 3 hours. The reaction mixture was cooled and poured into water (200 ml). The precipitate was collected, washed with water and diethyl ether successively and purified by column chromatography to yield a white solid (4.5 g, 61%), mp >260°; ir (potassium bromide): 3200-3140 (NH), 1700 and 1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.98 (d, J_{H-H} = 16.1 Hz, 1H, H7), 4.29 (dd, J_{H-H} = 16.1 Hz and 3.9 Hz, 1H, H7), 5.39 (d, J_{H-H} = 3.9 Hz, 1H, H5), 7.27 (s, 5H, phenyl protons), 11.05 (s, 1H, NH), 11.40 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 34.8 (C7), 51.7 (C5), 111.6 (C4a), 126.9, 127.1, 128.1 and 143.4 (Ph), 151.6 (C2), 153.0 (C7a), 160.3 (C4).

Anal. Calcd. for $C_{12}H_{10}N_2O_2S$ (246.28): C, 58.52; H, 4.09; N, 11.37. Found: C, 58.50; H, 4.12; N, 11.21.

6-Phenylthieno[2,3-*d*]pyrimidine-2,4-dione **7**.

A mixture of 2-amino-5-phenylthiophene-3-carboxamide **6** (6.4 g, 0.04 mole) was heated with urea (10 g, 0.16 mole) at fusion temperature (180°) for 30 minutes. After cooling, water (100 ml) was added. The suspension was stirred for 30 minutes at room temperature and filtered. The precipitate was purified by a column chromatography to give a white solid, 3.65 g (75%), mp >260°; ir (potassium bromide): 3200 (NH), 3060 (NH), 1700 (CO); ^{1}H-nmr (DMSO-d_6): δ 7.35 (s, 1H, H5), 7.56 (m, 2H, phenyl protons), 7.63 (m, 3H, phenyl protons), 11.32 (s, 1H, NH), 11.75 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 116.0 (C4a), 117.1 (C5), 124.9, 127.7, 129.0 and 132.5 (Ph), 133.1 (C6), 150.4 (C7a), 151.6 (C2), 159.0 (C4).

Anal. Calcd. for $C_{12}H_8N_2O_2S$ (244.27): C, 59.00; H, 3.30; N, 11.46. Found: C, 59.03; H, 3.42; N, 11.38.

6-Phenylthieno[3,2-*d*]pyrimidine-2,4-dione **9**.

2-Methyl 3-amino-5-phenylthiophene-2-carboxylate **8** (6.0 g, 0.026 mole) was dissolved in an aqueous solution of acetic acid (15%). After cooling, potassium cyanate (12 g, 0.15 mole) in water (40 ml) was added dropwise at room temperature and the mixture stirred for 12 hours. The precipitate was collected, washed with water then poured into a hot 10% sodium hydroxide solution. The resulting solution was stirred for 2 hours. Acidification with a 15% aqueous acetic acid solution yielded a white precipitate which was collected and purified by a column chromatography, 4.25 g (67%) mp >260°; ir (potassium bromide): 3100 (NH), 1680 (CO); ^{1}H-nmr (DMSO-d_6): δ 7.23 (s, 1H, H7), 7.48 (m, 2H, phenyl protons), 7.75 (m, 3H, phenyl protons), 11.28 (s, 1H, NH), 11.67 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 112.7 (C4a), 112.8 (C7), 125.9, 129.2, 129.7 and 132.0 (Ph), 146.8 (C6), 151.3 (C7a), 151.4 (C2), 158.7 (C4).

Anal. Calcd. for $C_{12}H_8N_2O_2S$ (244.27): C, 59.00; H, 3.30; N, 11.46. Found: C, 58.92; H, 3.52; N, 11.28.

5*H*,7*H*-1-(β-D-ribofuranosyl)dihydrothieno[3,4-*d*]pyrimidine-2,4-dione **10a**.

A suspension of 5*H*,7*H*-dihydrothieno[3,4-*d*]pyrimidine-2,4-dione **3** (1.70 g, 0.01 mole) and ammonium sulphate (15 mg, 1.1 x 10^{-4} mole) in hexamethyldisilazane (40 ml) was stirred and refluxed for 4 hours. Hexamethyldisilazane in excess was evaporated under reduced pressure to give the bis(trimethylsilyl) compound. A solution of 1-acetate-2,3,5-tri-*O*-benzoyl-D-ribofuranose (5.06 g, 0.01 mole) in dry 1,2-dichloroethane (60 ml) and tin(IV)chloride was added to the residue of silylated compound and stirred at room temperature for 18 hours. After addition of pyridine (4 ml) the mixture was filtered to remove inorganic materials. The filtrate was diluted with chloroform (100 ml). The organic layer was washed with a saturated solution of sodium hydrogenocarbonate (150 ml) followed by a 1*N* solution of hydrochloric acid (150 ml), then brine (100 ml) and water successively, dried over magnesium sulphate and concentrated to dryness under reduced pressure. The protected form of **10a** was dissolved in methanol saturated with ammoniac and stirred for two days at room temperature. Then the solution was concentrated to dryness and the residue was purified by a column chromatography to give the deprotected nucleoside **10a** as a white solid, 1.38 g (46%) mp 203°; ir (potassium bromide): 3520-3300 (OH), 3160 (NH), 1700 (CO), 1640 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.65 (m, 2H, H5'), 3.72 (m, 1H, H4') 3.82 (s, 2H, H5), 4.03 (m, 1H, H3'), 4.30 (d, J_{H-H} = 3.9 Hz, 2H, H7), 4.44 (m, 1H, H2'), 4.77 (m, 2H, OH), 5.24 (s, 1H, OH), 5.45 (d, J_{H-H} = 4.4 Hz, 1H, H1'), 11.49 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 31.7 (C5), 35.7 (C7), 61.3 (C5'), 69.2 (C3'), 70.9 (C2'), 84.8 (C4'), 92.1 (C1'), 112.0 (C4a), 150.7 (C7a), 151.8 (C2), 159.7 (C4); uv (*p*H 7): λ max 262.3 nm; (*p*H 1): λ max 263.1 nm; (*p*H 14): λ max 263.8 nm.

Anal. Calcd. for $C_{11}H_{14}N_2O_6S$ (302.29): C, 43.71; H, 4.67; N, 9.27. Found: C, 43.85; H, 4.46; N, 9.02.

5*H*,7*H*-1-[(2-Hydroxyethoxy)methyl]dihydrothieno[3,4-*d*]-pyrimidine-2,4-dione **10b**.

Compound **10b** was prepared from heterocycle **3** (1.70 g, 0.01 mole) and 2-acetoxyethyl acetoxymethyl ether (1.76 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 1.45 g (59%), mp 198°; ir (potassium bromide): 3440 (OH), 3140 (NH), 1675 (CO), 1630 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.49 (m, 4H, O-CH_2-CH_2-O), 3.84 (s, 2H, H5), 4.32 (s, 2H, H7), 4.68 (s, 1H, OH), 5.19 (s, 2H, O-CH_2-N), 11.48 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 32.1 (C5), 35.0 (C7), 59.8 (CH_2), 70.3 (CH_2), 73.6 (O-CH_2-N), 111.1 (C4a), 151.7 (C2), 152.6 (C7a), 159.9 (C4a); uv (*p*H 7): λ max 262.6 nm; (*p*H 1): λ max 263.1 nm; (*p*H 14): λ max 263.8 nm.

Anal. Calcd. for $C_9H_{12}N_2O_4S$ (244.27): C, 44.25; H, 4.95; N, 11.46. Found: C, 44.31; H, 4.68; N, 11.48.

5*H*,7*H*-1-[2-Hydroxy-1-(hydroxymethyl)-ethoxymethyl]-dihydrothieno[3,4-*d*]pyrimidine-2,4-dione **10c**.

Compound **10c** was prepared from heterocycle **3** (1.70 g, 0.01 mole) and 2-(acetomethoxy-1,3-propanediyl) dibenzoate (3.72 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 1.40 g (51%), mp 178°; ir (potassium bromide): 3400 (OH), 3140 (NH), 1705 (CO), 1665 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.34 (m, 1H, CH), 3.46 (m, 4H, CH_2), 3.83 (s, 2H, H7), 4.36 (s, 2H, H5), 4.66 (s, 2H, OH), 5.27 (s, 2H, O-CH_2-N), 11.42 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 32.3 (C7), 35.2 (C5), 60.73 (CH_2), 73.5 (CH), 80.4 (O-CH_2-N), 111.1 (C4a), 151.8 (C2), 153.3 (C7a), 160.2 (C4); uv (*p*H 7): λ max 261.8; (*p*H 1) λ max 263.2; (*p*H 14): λ max 264.3.

Anal. Calcd. for $C_{10}H_{14}N_2O_5S$ (274.28): C, 43.79; H, 5.14; N, 10.2. Found: C, 43.56; H, 4.86; N, 9.94.

5*H*,7*H*-1-(Benzyloxymethyl)dihydrothieno[3,4-*d*]pyrimidine-2,4-dione **10d**.

Compound **10d** was prepared from heterocycle **3** (1.70 g, 0.01 mole) and benzyloxymethyl acetate (1.80 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 1.50 g (52%), mp 205°; ir (potassium bromide): 3150 (NH), 1700 (CO), 1640 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.82 (t, J_{H-H} = 3.4 Hz, 2H, H5), 4.29 (t, J_{H-H} = 3.4 Hz, 2H, H7), 4.57 (s, 2H, CH_2), 5.27 (s, 2H, O-CH_2-N), 7.35 (s, 5H, phenyl protons), 11.47 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 32.1 (C5), 35.1 (C7), 70.2 (CH_2), 73.3 (O-CH_2-N), 111.3 (C4a), 127.4, 127.5, 128.1 and 137.3 (Ph), 151.7 (C2), 152.3 (C7a), 159.9 (C4); uv (*p*H 7): λ max 261.9; (*p*H 1): λ max 262.8; (*p*H 14): λ max 263.6.

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$ (290.33): C, 57.92; H, 4.86; N, 9.66. Found: C, 57.70; H, 4.82; N, 9.68.

5*H*,7*H*-1-(β-D-ribofuranosyl)-5-phenyldihydrothieno[3,4-*d*]-pyrimidine-2,4-dione **11a**.

The ribonucleoside **11a** was prepared from heterocycle **5** (2.46 g, 0.01 mole) and 1-acetate-2,3,5-tri-*O*-benzoyl-D-ribofuranose (5.06 g, 0.01 mole) by the same procedure as for **12a** to yield a white solid as a diastereoisomeric mixture, 2.60 g (69%), mp 212°; ir (potassium bromide): 3300-3500 (OH), 3160 (NH), 1700 and 1640 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.66 (m, 2H, H5'), 3.75 (m, 1H, H4'), 4.08 (m, 1H, H3'), 4.30 (d, J_{H-H} = 15.7 Hz, 1H, H7), 4.43 (m, 1H, H2'), 4.51 (dd, J_{H-H} = 15.7 Hz and J_{H-H} = 3.9 Hz, 1H, H7), 4.63 (s, 1H, OH), 4.79 (s, 1H, OH), 5.06 (s, 1H, OH), 5.44 (d, J_{H-H} = 3.9 Hz, 1H, H5), 5.54 (d, J_{H-H} = 3.9 Hz, 1H, H1'), 7.28 (m, 5H, phenyl protons), 11.45 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 35.3 and 35.4 (C7), 51.1 (C5), 61.2 and 61.3 (C5'), 69.1 and 69.3 (C3'), 70.9 (C2'), 84.7 and 84.8 (C4'), 92.2 and 92.7 (C1'), 114.7 and 115.0 (C4a), 127.0, 127.1, 127.2, 128.4, 143.2 and 143.3 (Ph), 150.7 and 150.8 (C2), 153.0 and 153.2 (C7a), 159.1 (C4); uv (*p*H 7): λ max 262.9 nm; (*p*H 1): λ max 263.1 nm; (*p*H 14): λ max 263.9 nm.

Anal. Calcd. for $C_{17}H_{18}N_2O_6S$ (378.40): C, 53.96; H, 4.79; N, 7.40. Found: C, 54.01; H, 4.83; N, 7.28.

5*H*,7*H*-1-[(2-Hydroxyethoxy)methyl]-5-phenyldihydrothieno-[3,4-*d*]pyrimidine-2,4-dione **11b**.

Compound **11b** was prepared from heterocycle **5** (2.46 g, 0.01 mole) and 2-acetoxyethyl acetoxymethyl ether (1.76 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 1.34 g (42%), mp 157°; ir (potassium bromide): 3400 (OH), 3160 (NH), 1710 and 1685 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.54 (m, 4H, CH_2), 4.34 (d, J_{H-H} = 16.6 Hz, 1H, H7), 4.63 (dd, J_{H-H} = 16.6 Hz, J_{H-H} = 4.4 Hz, 1H, H7), 4.77 (s, 1H, OH), 5.28 (s, 2H, O-CH_2-N), 5.45 (d, J_{H-H} = 4.4 Hz, 1H, H5), 7.29 (m, 5H, phenyl protons), 11.40 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 34.6 (C7), 51.7 (C5), 59.9 (CH_2), 70.5 (CH_2), 73.6 (O-CH_2-N), 113.9 (C4a), 126.8, 126.9, 128.1 and 143.3 (Ph), 151.8 (C2), 153.6 (C7a), 159.2 (C4); uv (*p*H 7): λ max 269.0 nm; (*p*H 1): λ max 269.0 nm; (*p*H 14): λ max 269.5 nm.

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$ (320.36): C, 56.24; H, 5.03; N, 8.74. Found: C, 56.50; H, 4.73; N, 8.51.

5*H*,7*H*-1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-5-phenyldihydrothieno[3,4-*d*]pyrimidine-2,4-dione **11c**.

Compound **11c** was prepared from heterocycle **5** (2.46 g, 0.01 mole) and 2-(acetoxymethoxy-1,3-propanediyl) dibenzoate (3.72 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 1.90 g (55%), mp 188°; ir (potassium bromide): 3380-3440 (OH), 3160 (NH), 1710 and 1665 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.45 (m, 5H, CH_2-CH-CH_2), 4.38 (d, J_{H-H} = 16.6 Hz, 1H, H7), 4.68 (dd, J_{H-H} = 16.6 Hz, J_{H-H} = 3.9 Hz, 1H, H7), 4.78 (m, 2H, OH), 5.34 (s, 2H, O-CH_2-N), 5.43 (d, J_{H-H} = 3.9 Hz, 1H, H5), 7.26 (m, 5H, phenyl protons), 11.34 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 34.4 (C7), 51.8 (C5), 60.8 (CH_2), 61.0 (CH_2), 72.9 (CH), 80.3 (O-CH_2-N), 113.7 (C4a), 126.9, 127.0, 128.1 and 143.3 (Ph), 152.0 (C2), 154.2 (C7a), 159.4 (C4); uv (*p*H 7): λ max 263.3 nm; (*p*H 1): λ max 263.5 nm; (*p*H 14): λ max 264.7 nm.

Anal. Calcd. for $C_{16}H_{18}N_2O_5S$ (350.38): C, 54.85; H, 5.18; N, 7.99. Found: C, 54.58; H, 5.12; N, 8.21.

5*H*,7*H*-1-(Benzyloxymethyl)-5-phenyldihydrothieno[3,4-*d*]-pyrimidine-2,4-dione **11d**.

Compound **11d** was prepared from heterocycle **5** (2.46 g, 0.01 mole) and benzyloxymethyl acetate (1.80 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 2.60 g (71%), mp 209°; ir (potassium bromide): 3170 (NH), 1700 and 1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 4.32 (d, J_{H-H} = 15.9 Hz, 1H, H7) 4.53 (dd, J_{H-H} = 15.9 Hz, J_{H-H} = 3.9 Hz, 1H, H7), 4.64 (s, 2H, CH_2), 5.35 (s, 2H, O-CH_2-N), 5.43 (d, J_{H-H} = 3.9 Hz, 1H, H5), 7.26 (s, 5H, phenyl protons), 7.35 (s, 5H, phenyl protons), 11.42 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 34.6 (C7), 51.6 (C5), 70.5 (CH_2), 73.5 (O-CH_2-N), 114.0 (C4a), 128.0, 126.9, 127.4, 127.5, 128.1, 137.5 and 143.2 (Ph), 151.7 (C2), 153.3 (C7a), 159.1 (C4); uv (*p*H 7): λ max 263.5 nm; (*p*H 1): λ max 263.3 nm; (*p*H 14): λ max 263.8 nm.

Anal. Calcd. for $C_{20}H_{18}N_2O_3S$ (366.43): C, 65.56; H, 4.95; N, 7.64. Found: C, 65,29; H, 4.86; N, 7.44.

1-(β-D-ribofuranosyl)-6-phenylthieno[2,3-*d*]pyrimidine-2,4-dione **12a**.

Ribonucleoside **12a** was prepared from heterocycle **7** (2.44 g, 0.01 mole) and 1-acetate-2,3,5-tri-*O*-benzoyl-D-ribofuranose (5.06 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 2.10 g (56%), mp 242°; ir (potassium bromide): 3420 (NH), 3260 (NH), 1690 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.72 (m, 2H, H5'), 3.87 (d, J_{H-H} = 4.4 Hz, 1H, H4'), 4.08 (m, 1H, H3'), 4.49 (m, 1H, H2'), 4.96 (s, 1H, OH), 5.19 (s, 1H, OH), 5.44 (s, 1H, OH), 6.02 (d, J_{H-H} = 6.3 Hz, 1H, H1'), 7.40 (m, 3H, H5, phenyl protons), 7.68 (m, 3H, phenyl protons), 11.77 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 61.4 (C5'), 69.4 and 69.7 (C2', C3'), 85.5 (C4'), 90.1 (C1'), 117.3 (C4a), 118.0 (C5), 125.1, 128.0, 129.6 and 132.3 (Ph), 132.4 (C7a), 135.2 (C6), 149.7 (C2), 157.9 (C4); uv (*p*H 7): λ max 292.2 nm; (*p*H 1): λ max 293.4 nm; (*p*H 14): λ max 293.8 nm.

Anal. Calcd. for $C_{17}H_{16}N_2O_6S$ (376.39): C, 54.24; H, 4.28; N, 7.44. Found: C, 53.97; H, 4.33; N, 7.51.

1-[(2-Hydroxy ethoxy)methyl]-6-phenylthieno[2,3-*d*]pyrimidine-2,4-dione **12b**.

Compound **12b** was prepared from heterocycle **7** (2.44 g, 0.01 mole) and 2-acetoxyethyl acetoxymethyl ether (1.76 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 1.6 g (63%), mp 164°; ir (potassium bromide): 3300 (OH), 1690 and 1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.50 (m, 4H, CH_2), 3.55 (s, 1H, OH), 5.39 (s, 2H, O-CH_2-N), 7.44 (m, 3H, H5, phenyl protons), 7.67 (m, 3H, phenyl protons), 11.61 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 59.6 (CH_2), 70.5 (CH_2), 75.8 (O-CH_2-N), 117.0 (C4a), 117.6 (C5), 125.2, 127.8, 130.1 and 132.0 (Ph), 134.7 (C6), 150.0 (C7a), 151.5 (C2), 158.0 (C4); uv (*p*H 7): λ max 298.6 nm; (*p*H 1): λ max 298.7 nm; (*p*H 14): λ max 299.3 nm.

Anal. Calcd. for $C_{15}H_{14}N_2O_4S$ (318.35): C, 56.59; H, 4.43; N, 8.79. Found: C, 56.63; H, 4.52; N, 8.50.

1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-6-phenylthieno[2,3-*d*]pyrimidine-2,4-dione **12c**.

Compound **12c** was prepared from heterocycle **7** (2.44 g, 0.01 mole) and 2-(acetoxymethoxy-1,3-propanediyl) dibenzoate (3.72 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 1.63 g (47%), mp 220°; ir (potassium bromide): 3400-3250 (OH), 3180 (NH), 1680 and 1620 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.45 (m, 5H, CH_2-CH-CH_2), 4.68 (m, 2H, OH), 5.46 (s, 2H, O-CH_2-N), 7.41 (s, 1H, H5), 7.55 (m, 2H, phenyl protons), 7.93 (m, 3H, phenyl protons), 11.40 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 60.61 (CH_2), 75.4 (CH), 80.8 (O-CH_2-N), 117.0 (C4a), 117.1 (C5), 125.0, 127.0, 132.0, and 132.4 (Ph), 134.3 (C6), 150.3 (C7a), 151.6 (C2), 158.3 (C4); uv (*p*H 7): λ max 297.1 nm; (*p*H 1): λ max 297.3 nm; (*p*H 14): λ max 298.8 nm.

Anal. Calcd. for $C_{16}H_{16}N_2O_5S$ (348.38): C, 55.16; H, 4.62; N, 8.04. Found: C, 55.22; H, 4.51; N, 8.24.

1-(β-D-ribofuranosyl)-6-phenylthieno[3,2-*d*]pyrimidine-2,4-dione **13a**.

Ribonucleoside **13a** was prepared from heterocycle **9** (2.44 g, 0.01 mole) and 2,3,5-tri-*O*-benzoyl-D-ribofuranose-1-acetate (5.06 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 1.84 g (49%), mp 242°; ir (potassium bromide): 3380-3260 (OH), 3170 (NH), 1690 and 1650 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.70 (m, 2H, H5'), 3.90 (m, 1H, H4'), 4.10 (m, 1H, H3'), 4.50 (m, 1H, H2'), 4.72 (m, 1H, OH), 4.80 (s, 1H, OH), 5.22 (s, 1H, OH), 5.61 (s, 1H, H1'), 7.22 (s, 1H, H7), 7.74 (m, 5H, phenyl protons), 10.92 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 60.7 (C5'), 68.4 (C3'), 69.8 (C2'), 85.3 (C4'), 88.1 (C1'), 112.6 (C7), 115.8 (C4a), 125.7, 125.9, 129.3, 132.5 (Ph), 145.0 (C6), 150.8 (C7a), 151.1 (C2), 157.6 (C4); uv (*p*H 7): λ max 296.1 nm; (*p*H 1): λ max 296.7 nm; (*p*H 14): λ max 297.5 nm.

Anal. Calcd. for $C_{17}H_{16}N_2O_6S$ (376.39): C, 54.24; H, 4.28; N, 7.44. Found: C, 54.31; H, 4.40; N, 7.38.

1-[(2-hydroethoxy)methyl]-6-phenylthieno[3,2-*d*]pyrimidine-2,4-dione **13b**.

Compound **13b** was prepared from heterocycle **9** (2.44 g, 0.01 mole) and 2-acetoxyethyl acetoxymethyl ether (1.76 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 1.40 g (56%), mp 220°; ir (potassium bromide): 3370 (OH), 3180 (NH), 1680 and 1660 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.52 (m, 4H, CH_2), 4.52 (s, 1H, OH), 5.46 (s, 2H, O-CH_2-N), 7.27 (s, 1H, H7), 7.67 (m, 2H, phenyl protons), 7.79 (m, 3H, phenyl protons), 11.50 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 59.9 (CH_2), 69.9 (CH_2), 73.7 (O-CH_2-N), 112.3 (C7), 113.7 (C4a), 125.7, 125.9, 129.1 and 132.4 (Ph), 146.8 (C6), 149.2 (C7a), 153.6 (C2), 160.7 (C4); uv (*p*H 7): λ max 292.7 nm; (*p*H 1): λ max 293.1 nm; (*p*H 14): λ max 294.1 nm.

Anal. Calcd. for $C_{15}H_{14}N_2O_4S$ (318.35): C, 56.59; H, 4.43; N, 8.79. Found: C, 56.48; H, 4.33; N, 8.85.

1-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]-6-phenylthieno[3,2-*d*]pyrimidine-2,4-dione **13c**.

Compound **13c** was prepared from heterocycle **9** (2.44 g, 0.01 mole) and 2-(acetoxymethoxy-1,3-propanediyl) dibenzoate (3.72 g, 0.01 mole) by the same procedure as for **10a** to yield a white solid, 2.25 g (65%), mp 222°; ir (potassium bromide): 3340 (OH), 3160 (NH), 1660 and 1630 (CO); ^{1}H-nmr (DMSO-d_6): δ 3.40 (m, 1H, CH), 3.65 (m, 4H, CH_2), 4.68 (s, 2H, OH), 5.54 (s, 2H, O-CH_2-N), 7.41 (s, 1H, H7), 7.69 (m, 2H, phenyl protons), 7.93 (m, 3H, phenyl protons), 11.56 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 60.9 (CH_2), 73.3 (CH), 80.1 (O-CH_2-N), 111.2 (C7), 114.3 (C4a), 125.7, 125.9, 129.7 and 132.1 (Ph), 147.2 (C6), 151.0 (C7a), 151.2 (C2), 157.9 (C4); uv (*p*H 7): λ max 294.2 nm; (*p*H 1): λ max 294.3 nm; (*p*H 14): λ max 295.9 nm.

Anal. Calcd. for $C_{16}H_{16}N_2O_5S$ (348.38): C, 55.16; H, 4.62; N, 8.04. Found: C, 55.34; H, 4.68; N, 8.18.

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REFERENCES AND NOTES

[1] H. Mitsuya, R. Yarchoan and S. Broder, *Science*, **249**, 1533 (1990).

[2] H. Mitsuya, K. J. Weingold, P. A. Furman, M. H. Saint Clair, S. N. Lehrman, R. C. Gallo, D. P. Bolognesi, D. W. Barry and S. Broder, *Proc. Natl. Acad. Sci.*, (USA), **82**, 7096 (1985).

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

[4] R. G. Nanni, J. Ding, A. Jacobo-Molina, S. H. Hughes and E. Arnold, *Perspectives Drug Discovery Design*, **1**, 129 (1993).

[5] S. D. Young, *Perspectives Drug Discovery Design*, **1**, 181 (1993).

[6a] U. Niedballa and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, **9**, 461 (1970); [b] U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3654 (1974); [c] U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **41**, 2084 (1976).

[7] L. C. Cheney and J. R. Piening, *J. Am. Chem. Soc.*, **67**, 729 (1945).

[8] *Org. Synth.*, Coll. Vol. **3**, 440 (1955).

[9] A. R. Surrey, H. F. Hammer and C. M. Suter, *J. Am. Chem. Soc.*, **66**, 1933 (1944).

[10] K. Gewald, E. Schinke and H. Bottcher, *Chem. Ber.*, **94**, 99 (1966).

[11] H. Hartmann and J. Liebscher, *Synthesis*, 275 (1984).

[12a] J. J. Fox and S. Shugar, *Biochim. Biophys. Acta*, **9**, 369 (1952); [b] J. J. Fox and S. Shugar, *Biochim. Biophys. Acta*, **9**, 199 (1952).

[13a] R. J. Pugmire, D. M. Grant, L. B. Townsend and R. K. Robins, *J. Am. Chem. Soc.*, **95**, 2791 (1973); [b] P. Dea, G. Revankar, R. Tolman, R. K. Robins and M. P. Schweitzer, *J. Org. Chem.*, **39**, 3226 (1974); [c] R. D. Elliot and J. A. Montgomery, *J. Med. Chem.*, **21**, 112 (1978).

[14a] J. L. Imbach, J. L. Barascut, B. L. Kam, B. Rayner, C. Tamby and C. Tapiero, *J. Heterocyclic Chem.*, **10**, 1069 (1973); [b] Y. Mizuno, M. Ikeharakyoichi, A. Watanabe and S. Suzak, *J. Org. Chem.*, **28**, 331 (1963); [c] J. L. Imbach and B. L. Kam, *J. Carbohydr. Nucleosides Nucleotides*, **1**, 271 (1974); [d] J. L. Imbach, J. L. Barascut B. L. Kam and C. Tapiero, *Tetrahedron Letters*, **129** (1974); [e] A. G. M. Barett, D. H. R. Barton, R. Bielski and S. W. Mc Combie, *J. Chem. Soc., Perkins Trans., 1*, 2378 (1979).