SYNTHESIS AND ANTIVIRAL EVALUATION OF FUROPYRIMIDINE DIONES CYCLIC AND ACYCLIC, NUCLEOSIDE ANALOGUES

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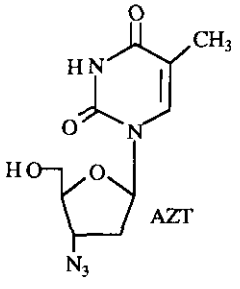
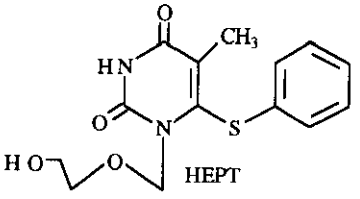
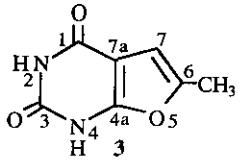
Abstract - Following Vorbrüggen and Niedballa's method,[1] we have carried out the synthesis of new cyclic and acyclic nucleoside analogues, whose aglycone was the furopyrimidinedione (**3**). Among the various compounds that we obtained was the β-D-ribonucleoside (**8**) which gave us access to the β-D-arabinonucleoside (**11**) whose synthesis by Vorbrüggen and Niedballa's method[1] had remained unsuccessful. All the new compounds were tested against human immunodeficiency virus 1 (HIV-1). None of these compounds showed significant activity.

Nucleoside analogues constitute a prime class of potential anti Human Immunodeficiency Virus (HIV) agents. Most of them are reverse transcriptase inhibitors and two categories can be distinguished: competitive inhibitors such as azidothymidine (AZT) and other dideoxynucleosides;[2] and noncompetitive inhibitors of which HEPT was the leading compound[3](Scheme 1).

In this paper, we wish to describe the synthesis and antiviral evaluation of cyclic and acyclic nucleoside analogues. Their aglycone was a furopyrimidine [compound (**3**), Scheme 1] whose preparation is based on pyrrolopyrimidine synthesis.[4] In this aglycone, a furan ring was fused on the *d* side of an uracil. This characteristic aimed at forming a lipophilic region which seems to have a prime part in the antiviral activity of 1-(2-hydroxyethoxy)methyl-6-phenylthiothymine (HEPT) analogues.[5]



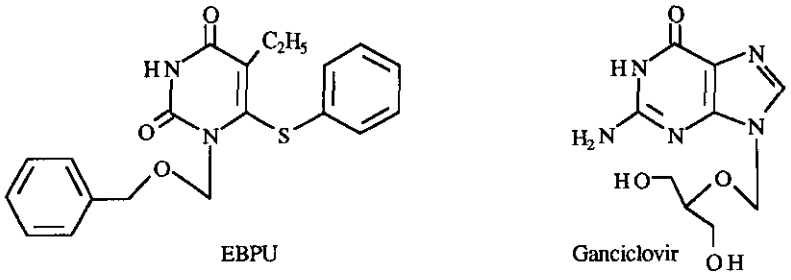




Scheme 1

The sugar moiety may be cyclic or acyclic: as regards acyclonucleosides, the side chain was that of HEPT, 5-ethyl-1-benzyloxymethyl-6-phenylthiouracil (EBPU, a very potent HEPT analogue), and Ganciclovir, an anticytomegalovirus agent (Scheme 2). Regarding cyclic nuleosides, we could obtain ribonucleoside, xylonucleoside and arabinonucleoside.

As part of the antiviral program of the Agence Nationale de Recherche sur le Sida (ANRS), our compounds underwent a cell culture evaluation against HIV-1 virus.

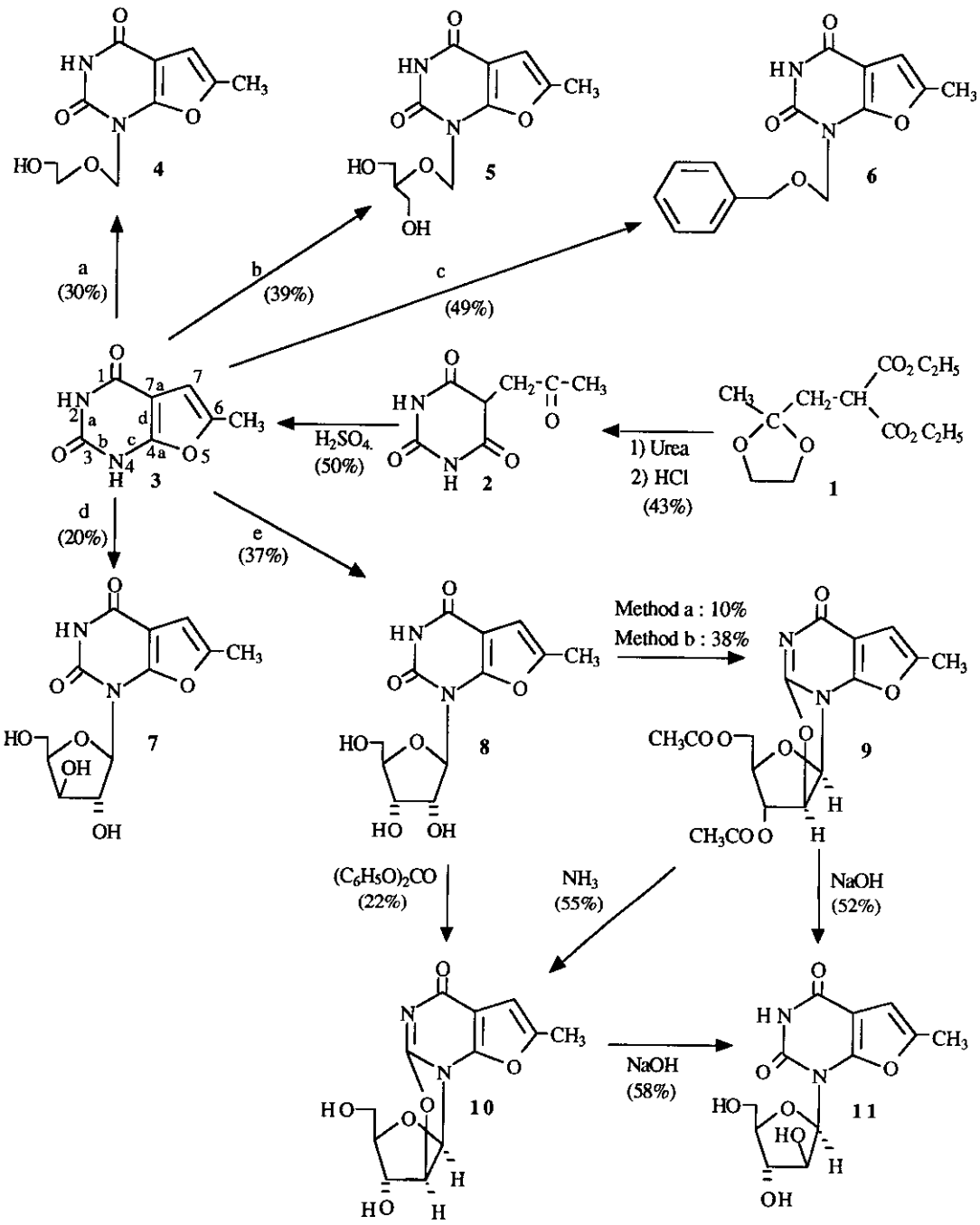


Scheme 2

Most of the syntheses were achieved by the use of Vorbrüggen and Niedballa's procedure.[1] The main reasons for this choice were a quite acceptable yield, a good stereoselectivity for the synthesis of ribonucleoside with the obtainment of the β form, and lastly, a good regioselectivity that enabled us to obtain N4 alkylated compounds. This method started with the bis(trimethylsilylation) of the heterocycle (**3**) leading to its reactive form. This silylated compound was then subjected to reaction with the various acyclic or cyclic sugar moiety: 2-acetoxyethyl acetoxymethyl ether, 2-acetoxymethoxy-1,3-propanediyldibenzoate or benzyloxymethyl acetate, leading to the protected derivatives.

These reactions were carried out in dry 1,2-dichloroethane with tin(IV) chloride as a catalyst. The same procedure was first used for the cyclic sugars: D-xylofuranose-1-acetate-2,3,5-tribenzoate and D-ribofuranose-1-acetate-2,3,5-tribenzoate. For the latter, the yield remained very low (20%) and we attempted a second procedure:[6] the silylated derivative of heterocycle (**3**), dissolved in dry acetonitrile, was added to a mixture of D-ribofuranose-1-acetate-2,3,5-tribenzoate, sodium iodide, molecular sieves and chlorotrimethylsilane instead, using tin(IV) chloride. The benzoylated ribosyl iodide is suggested to be the active sugar species in this reaction.[7] The yield was clearly improved and reached 50%.

Irrespective of the technique used, the last step consisted of the deblocking of the various sugar moieties using ammonia. Chromatographic purification then yielded the free nucleoside analogues.



a- 1) HMDS, $CH_3CO_2(CH_2)_2OCH_2OCOCH_3$, $SnCl_4$, 2) NH_3.
b- 1) HMDS, $(C_6H_5CO_2CH_2)_2CHOCH_2OCOCH_3$, $SnCl_4$, 2) NH_3.
c- HMDS, $C_6H_5CH_2OCH_2OCOCH_3$, $SnCl_4$.
d- 1) HMDS, D-xylofuranose1-acetate-2,3,5-tribenzoate, $SnCl_4$, 2) NH_3.
e- 1) HMDS, NaI, $(CH_3)_3SiCl$, D-ribofuranose-1-acetate-2,3,5-tribenzoate, $SnCl_4$, 2) NH_3.

Scheme 3

Unlike the previous nucleoside analogues, the arabino nucleoside (**11**) resulted from a functionalization. Its synthesis, following Vorbrüggen and Niedballa's glycosidation[1] had led to a poor yield and to a mixture of both anomeric forms; this result could be explained by the mechanism of condensation[1] which involved the participation of the 2-ester group of the protected sugar moiety.

For this reason, we undertook a different strategy using the β-D-ribonucleoside (**8**) as a starting material: at first we used diphenyl carbonate according to a known method[8] which gave access to the desired cyclonucleoside (**10**) with a poor yield (22%). A second procedure was then carried out using acetoxyisobutyryl chloride in acidic medium.[9] This method provided the acetylated cyclonucleoside (**9**) whose alkaline hydrolysis enabled us to obtain the desired β-arabinoside (**11**). This epimerisation strategy offered an acceptable overall yield (20%) and unlike Vorbrüggen and Niedballa's glycosylation,[1] spared us the problem of anomeric separation.

An attempt to obtain 2',3'-dideoxynucleoside and 2'-deoxynucleoside induced us again to make use of the β-D-ribonucleoside (**8**) as a starting material. The latter was subjected to reaction with acetyl bromide[10] in order to isolate the 4-[(3',5'-di-O-acetyl-2'-bromo)-β-D-ribofuranosyl]-6-methylfuro[2,3-*d*]pyrimidine-1,3-dione (**12**). Its reduction using tri-*n*-butyltin hydride[11] might then furnish the 2'-deoxynucleoside whereas the 2',3'-dideoxynucleoside could be obtained by means of an elimination using a Zn/Cu couple[12] in acidic medium. Unfortunately, the reaction of acetyl bromide with the ribonucleoside (**8**) led to the cyclonucleoside (**9**) which was an intermediate in the formation of the desired compound (**12**).[10]

All final compounds were fully characterized using the following analytical techniques: ^{1}H-nmr, ^{13}C-nmr and ir spectra. According to Fox and Shugar's method[13] in uv spectra, the lack of bathochromic effect of an *N*-alkyklated uracil derivative in alkaline medium indicates a *N*1-alkylation. This was obtained for the compounds (**4**, **5**, **6**,**7** and **8**) that resulted from Vorbrüggen and Niedballa's glycosydation,[1] confirming its good selectivity. The utilization of ^{13}C-nmr gave a confirmation of this result: thus a deshielding of the C4a carbon in nucleoside analogues, in comparison to the corresponding heterocycle, provides a second argument for a *N*4 alkylation[14] corresponding to the *N*1 site of an uracil.
With respect to the anomeric configuration of the ribonucleoside (**8**), we made use of the Imbach and co-workers rule.[15] This procedure couldn't be applied to the xylonucleoside (**7**) but the mechanism of glycosylation, the chemical shift and the coupling constant of the anomeric proton, similar to the one of the β-D-ribonucléoside (**8**), are all in favour of the β-anomer. This is in accord with Imbach 's work,[16] stating that the preparation of α-anomers require a different strategy.

All compounds were tested and compared to AZT both for their toxicity and their ability to inhibit the cytopathic effect induced by HIV-1 infection. The CEM cl 13, a subclone enriched in CD4 receptors, was

treated with each compound dilution (0 to 30 μg/ml) or PBS alone and incubated for 1 h at 37°C. Cells were then infected with the virus suspension (LAV-Bru strain of HIV-1) and cultured for at least 7 days. Mock infected cultures were carried out at the same time to determine the cytotoxicity of the compounds. Cell viability was then evaluated by the MTT method. Unfortunately, none of our compounds showed any significant activity under the conditions of this antiviral test.

EXPERIMENTAL

General Methods. Melting points were taken on Köfler bank and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus. Nmr spectra were recorded on a Jeol FX 200 in DMSO-d6 solution using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS.

5-(2-Oxopropyl)perhydropyrimidine-2,4,6-trione (**2**)

Sodium (11.4 g, 0.49 mol) was subjected to reaction with ethanol (200 ml). Urea (9.9 g, 0.165 mol) and diethyl (2-methyl-1,3-dioxolan-2-yl)methylmalonate (43 g, 0.165 mol) were added to the sodium ethoxide solution. The mixture was heated at 80°C with a mechanical stirrer for 3 h, diluted with water (100 ml) and acidified to pH 1 with a concentrated aqueous hydrochloride solution. The resulting solution was stirred at room temperature for 1 h and the resulting precipitate was collected and crystallized from ethanol to yield **2** (13 g, 43%) : mp > 260°C. Ir (KBr) : 3250 and 3100 cm^{-1} (NH), 1700 (CO); ^{1}H-nmr 1.85 (s, 3H, CH_3), 2.95 (d, 2H, $J_{H5\text{-}CH2}$ = 4.5 Hz, CH_2), 3.35 (t, 1H, $J_{CH2\text{-}H5}$ = 4.5 Hz, CH). Anal. Calcd for $C_7H_8N_2O_4$: C,45.65; H, 4.37; N, 15.21. Found: C, 45.49; H, 4.51; N, 15.33.

6-Methylfuro[2,3-*d*]pyrimidine-1,3-dione (**3**)

5-(2-Oxopropyl)perhydropyrimidine-2,4,6-trione (**2**) (13 g, 0.07 mol) was dissolved in concentrated sulfuric acid (100 ml) and the solution was stirred for 48 h. Water (100 ml) was added and the resulting precipitate was collected and washed with water (2x50 ml) to yield a white solid which was crystallized from chloroform/ethanol. (5.8 g, 50%) : mp > 260°C. Ir (KBr) : 3150 (NH), 1700 (CO); ^{1}H-nmr 2.26 (s, 3H, CH_3), 6.35 (s, 1H, H7), 10.90 (s, 1H, NH); ^{13}C-nmr 12.7 (CH_3), 96.2 (C7a), 101.6 (C7), 147.6 (C6), 149.9 (C4a), 152.2 (C3), 158.7 (C1). Anal. Calcd for $C_7H_6N_2O_3$: C, 50.60; H, 3.64; N, 16.86. Found: C, 50.35; H, 3.88; N, 17.01.

4-[(2-Hydroxyethoxy)methyl]-6-methylfuro[2,3-*d*]pyrimidine-1,3-dione (**4**)

A mixture of **3** (1.66 g, 0.01 mol) and ammonium sulfate (10 mg, 0,075 mmol) in hexamethyldisilazane (HMDS) (30.4 g, 0,18 mol) was stirred and refluxed for 3 h. HMDS in excess was evaporated under reduced pressure. A solution of 2-acetoxyethyl acetoxymethyl ether (1.76 g, 0.01 mol) in dry 1,2-dichloroethane (50 ml) and tin(IV) chloride (2.22 g, 0.0085 mol) were added to the residue of the silylated heterocycle. Then, the mixture was stirred at room temperature for 18 h. The unreacted $SnCl_4$ was eliminated by addition of pyridine (3 ml), the inorganic materials were removed, and the filtrate was diluted with chloroform (50 ml). The resulting organic layer was washed with a saturated solution of sodium hydrogen carbonate (100 ml) then with brine (100 ml), dried over $MgSO_4$, filtered and concentrated to dryness. The residue of protected nucleoside was dissolved in methanol, then the solution was saturated

with ammonia. The solvent was evaporated under reduced pressure and the deprotected compound (**4**) obtained by silica gel chromatography (CH_2Cl_2 : CH_3OH 90/10) (**4**). (0.73 g, 30%) : mp 188℃. Ir (KBr) 3450 (OH), 3200 (NH), 1680 (CO) ; ^{1}H-nmr 2.32 (s, 3H, CH_3), 3.50 (m, 2H, CH_2), 3.58 (m, 2H, CH_2), 4.68 (s, 1H, OH), 5.33 (s, 2H, O-CH_2-N), 6.46 (s, 1H, H5), 11.30 (s, 1H, NH) ; ^{13}C-nmr 12.9 (CH_3), 59.8 (CH_2), 71.3 (CH_2), 71.8 (CH_2), 97.6 (C7a), 102.3 (C7), 149.0 (C7a), 149.6 (C6), 155.0 (C3), 157.9 (C1); uv λ max (nm) 274.6 (pH 7) 274.6 (pH 1) 273.0 (pH 14). Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found : C, 49.80; H, 4.98; N, 11.52.

4-[(1,3-Dihydroxy-2-propoxy)methyl]-6-methylfuro[2,3-*d*]pyrimidine-1,3-dione (**5**)

The compound (**5**) was prepared from the heterocycle (**3**) (1.66 g) and 2-acetoxymethoxypropanediyl-1,3-dibenzoate (3.72 g) by the same procedure as **4** to yield, after silica gel chromatography (CH_2Cl_2: CH_3OH 85/15), (1.05 g, 39%) mp 171℃. Ir (KBr) 3400 (OH), 1680 (CO); ^{1}H-nmr 2.30 (CH_3), 3.40 (m, 4H, CH_2), 3.50 (m, 1H, CH), 4.61 (m, 2H, OH), 5.39 (s, 2H, OCH_2N), 6.44 (s, 1H, H7), 11.74 (s, 1H, NH) ; ^{13}C-nmr 12.9 (CH_3), 60.8 (CH_2), 71.4 (CH), 81.6 (O-CH_2-N), 97.4 (C7a), 102.2 (C7), 148.8-149.6 (C6-C4a), 155.2 (C3), 158,0 (C1); uv λmax (nm) 274.6 (pH 7) 274.8 (pH 1) 274.3 (pH 14). Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.93; H, 5.28; N, 10.14.

4-Benzyloxymethyl-6-methylfuro[2,3-*d*]pyrimidine-1,3-dione (**6**)

The compound (**6**) was prepared from the heterocycle (**3**) (1.66 g) and benzyloxymethyl acetate (1.80 g) by the same procedure as **4** to yield, after silica gel chromatography (CH_2Cl_2: CH_3OH 95/5), a white solid. (1.32 g, 49%): mp 138℃. Ir (KBr): 3150 (NH), 1710 (CO); ^{1}H-nmr 2.31 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 5.38 (s, 2H, O-CH_2-N), 6.44 (s, 1H, H7), 7.30 (m, 5H, Ph), 11.27 (s, 1H, NH); ^{13}C-nmr 12.9 (CH_3), 70.7-72.7 (CH_2), 97.7 (C7a), 102.3 (C7), 127.4-128.1-137.4 (Ph), 149.0-149.6 (C4a-C6), 154.9 (C3), 157.9 (C1); uv λmax (nm) 274.6 (pH 7) 274.8 (pH 1) 274.3 (pH 14). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93. Found C, 62.81; H, 4.82.

4-D-Xylofuranosyl-6-methylfuro[2,3-*d*]pyrimidine-1,3-dione (**7**)

The compound (**7**) was prepared from the heterocycle (**3**) (1.66 g, 0.01 mol) and D-xylofuranose-1-acetate-2,3,5-tribenzoate (5.04 g, 0.01 mol) by the same procedure as **4** to yield, after silica gel chromatography (CH_2Cl_2 : CH_3OH 80/20) a white solid. (0.58 g, 20%): mp 215℃; ir (KBr) 3400 (OH), 1680 (CO); ^{1}H-nmr 2.31 (s, 3H, CH_3), 3.67 (m, 2H, H5'), 4.00 (m, 2H, osidic protons), 4.42 (s, 1H, OH), 4.58 (m, 1H, osidic protons), 5.23 (s, 1H, OH), 5.65 (s, 1H, OH), 5.75 (d, 1H, H1', J = 5.9 Hz), 6.47 (s, 1H, H7), 11.36 (s, 1H, NH); ^{13}C-nmr 12.8 (CH_3), 60.2 (C5'), 75.4-76.3 (C3'-C2'), 80.7 (C4'), 87.7 (C1'), 98.7 (C7a), 101.9 (C7), 149.2-149.4 (C4a-C6), 154.1 (C3), 157.6 (C1); uv λ max (nm) 270 (pH 7) 270 (pH 1) 270 (pH 14). Anal. Calcd for $C_{12}H_{14}N_2O_7$:C, 48.33; H, 4.73; N, 9.39. Found C, 48.12; H, 4.53; N, 9.27.

4-(β-D-Ribofuranosyl)-6-methylfuro[2,3-*d*]pyrimidine-1,3-dione (**8**)

A mixture of NaI (3.95 g, 0.026 mol) and trimethylsilyl chloride (2.82 g, 0.026 mol) was stirred with

molecular sieves 4 Å (0.40 g) in dry acetonitrile (30 ml) for 5 min. A solution of D-ribofuranose-1-acetate-2,3,5-tribenzoate (5.04 g, 0.01 mol) in dry acetonitrile (60 ml) was added. The mixture was stirred for 30 min. Then, a solution of the silylated heterocycle (**3**) (3.10 g,0.01 mol), obtained by the same procedure as for the preparation of compound (**4**), in dry acetonitrile (30 ml) was added. This mixture was stirred at room temperature for 3 h, then filtered and concentrated under reduce pressure. The residue was dissolved in dichloromethane (100 ml) and washed with aqueous saturated solutions of sodium hydrogen carbonate (100 ml), sodium thiosulfate (100 ml) then with water (100 ml). The solution was dried over $MgSO_4$, filtered and concentrated to dryness. The protected nucleoside was dissolved in methanol and the solution was saturated with ammonia. The solvent was eliminated under reduced pressure and the crude product was purified by silica gel chromatography (CH_2Cl_2 : CH_3OH 85/15 to yield a white solid. (1.1 g, 37%): mp 245°C; ir (KBr) 3350 (OH), 1700 (CO);^{1}H-nmr 2.31 (d, $J_{CH_3\text{-}H}$ = 1.1 Hz, CH_3), 3.50 (m, 1H, H5'a), 3.60 (m, 1H, H5'b), 3.80 (q, J = 4.5 Hz, 1H, H4'), 4.10 (q, J = 5.3 Hz, 1H, H3'), 4.59 (q, J = 5.6 Hz, 1H, H2'), 5.85 (t, J = 5.8 Hz, 1H, OH5'), 5.38 (d, J = 5.4 Hz, 1H, OH3'), 5.95 (d, $J_{H1'\text{-}H2'}$ = 5.4 Hz, 1H, H1'), 6.46 (d, J = 1.1 Hz, 1H, H7), 11.36 (s, 1H, NH);^{13}C-nmr 12.7 (CH3), 61.5 (C5'), 69.8-70.3 (C2'-C3'), 84.8 (C4'), 87.8 (C1'), 98.5 (C7a), 101.8 (C7), 149.1 (C4a-C6), 154.1 (C3), 157.6 (C1); uv λmax (nm) 275.2 (pH 7) 275.6 (pH 1) 275.6 (pH 14). Anal. Calcd for $C_{12}H_{14}N_2O_7$: C, 48.33; H, 5.05; N, 9.39. Found: C, 48.42; H, 4.86; N, 9.47.

3,2'-Anhydro-4-[(5,5'-di-*O*-acetyl)β-d-arabinofuranosyl]-6-methylfuro[2,3-*d*]pyrimidine-1,3-dione (**9**)

Method a:

The ribonucleoside (**8**) (1 g, 0.00335 mol) was dissolved in a mixture of dry dichloromethane (20 ml) and dry acetonitrile (50 ml). The mixture was heated to 50°C and acetyl bromide (2.38 g, 0.019 mol) diluted in dry acetonitrile (10 ml), was added dropwise. The heating (50°C) was maintained for 10 min, and the resulting solution was concentrated under reduced pressure. The residue was dissolved in dichloromethane and the solution was washed with water (100 ml). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica gel chromatography (CH_2Cl_2: CH_3OH 98/2) to yield a white solid. (0.12 g, 10%).

Method b:

A mixture of ribonucleoside (**8**) (0.77 g, 0.0025 mol) and acetoxyisobutyryl chloride (1.25 g, 0.0076 mol) in acetic acid (15 ml) was refluxed for 2 h. The acetic acid was then evaporated under reduced pressure. The residue was dissolved in dichloromethane (100 ml), washed with water (50 ml), and then with a saturated solution of sodium hydrogen carbonate (50 ml). The organic layer was dried over sodium sulfate and concentrated to dryness. The residue was purified by silica gel chromatography (CH_2Cl_2 : CH_3OH 98/2) to yield a white solid. (0.35 g, 38%). mp 174°C; ir (KBr) 1730 and 1680 (CO); ^{1}H-nmr ($CDCl_3$) 1.93 (s, 3H, CH_3-CO), 2.18 (s, 3H, CH_3), 2.36 (s, 3H, CH_3CO), 4.00 (dd, $J_{H5'a\text{-}H5'b}$ = 12.2 Hz, $J_{H5'a\text{-}H4'}$ = 4.0 Hz, 1H, H5'a), 4.30 (dd, $J_{H5'b\text{-}H5'a}$ = 12.2 Hz, $J_{H5'bH4'}$ = 4.0 Hz, 1H, H5'b), 4.51 (m, 1H, H4'), 5.39 (m, 1H, osidic proton), 5.42 (m, 1H, osidic proton), 6.42 (s, 1H, H7), 6.65 (d, $J_{H1'H2'}$ = 5.8 Hz, 1H, H1'); ^{13}C-nmr ($CDCl_3$) 13.7 (CH_3), 20.3 ($\underline{C}H_3CO$), 20.61 ($\underline{C}H_3CO$), 63.3 (C5'), 77.4 (C3'), 84.6-86.7 (C2'-C4'), 87.7 (C1'), 101.7-103.2 (C7-C7a), 151.1 (C6), 154.3 (C4a), 155.7 (C1), 164.6 (C3), 169.5-170.2 (CH_3-$\underline{C}O$). Anal. Calcd for $C_{16}H_{16}N_2O_8$: C, 52.75; H, 4.42; N, 7.68. Found : C, 52.82; H, 4.60; N, 7.52.

3',2'-Anhydro-4-(β-D-arabinofuranosyl)-6-methylfuro[2,3-*d*]pyrimidine-1,3-dione (**10**)

From compound (**9**): The compound (**9**) (0.5 g, 0.0014 mol) was dissolved in methanol (50 ml). The solution was then saturated with ammonia and stirred at room temperature for 24 h. The methanol was evaporated to dryness and the residue triturated with diethyl ether to yield a white solid (0.21 g, 55%).

From compound (**8**) A mixture of ribonucleoside (**8**) (0.5 g, 0.0016 mol), diphenyl carbonate (0.46 g, 0.0021 mol), and sodium hydrogen carbonate (0.1 g, 1.2 mmol) in *N*,*N*-dimethylformamide (20 ml) was heated to 120°C for 30 min. The solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (CH_2Cl_2 : CH_3OH 90/10) to yield a white solid. (0.10 g, 22%). mp 196°C; ir (KBr) 3300 (OH), 1630 (CO); ^{1}H-nmr 2.37 (s, 3H, CH_3), 3.28 (m, 1H, H5'a), 3.35 (m, 1H, H5'b), 4.14 (m, 1H, H4'), 4.43 (m, 1H, H3'), 4.98 (m, 1H, OH), 5.85 (d, $J_{H2'\text{-}H1'}$ = 5.8 Hz, 1H, H2'), 5.96 (s, 1H, OH), 6.50 (s, 1H, H7), 6.65 (d, $J_{H1'H2'}$ = 5.8 Hz, 1H, H1') ; ^{13}C-nmr 13.0 (CH_3), 60.6 (C5'), 74.5 (C3'), 88.3-89.1-89.7 (C1', C2', C4'), 102.2 (C7a), 102.7 (C7), 149.8 (C6), 150.3 (C4a), 156.6 (C1), 166.0 (C3). Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.31; N, 9.99. Found: C, 51.69; H, 4.53; N, 9.84.

4-(β-D-Arabinofuranosyl)-6-methylfuro[2,3-*d*]pyrimidine-1,3-dione (**11**)

From compound (**9**) The compound (**9**) (0.4 g, 0.0011 mol) was stirred in a mixture of water (20 ml) and ethanol (10 ml). A 1N aqueous solution of sodium hydroxide (10 ml) was added and the mixture was stirred at room temperature for 30 min. The resulting solution was then acidified to pH 4 by a 2N aqueous solution of acetic acid. The solution was concentrated to dryness and the solid residue was triturated with acetone (20 ml). The suspension was filtered to remove the sodium salts and the filtrate concentrated to dryness then purified by silica gel chromatography (CH_2Cl_2 : CH_3OH 90/10) to yield a white solid (0.17 g, 52%).

From compound (**10**) The compound (**10**) (0.3 g, 0.001 mol) was stirred in a 1N aqueous solution of sodium hydroxide (30 ml) at room temperature for 1 h. The solution was acidified to pH 4 by a 2N aqueous solution of acetic acid, concentrated to dryness and the solid residue was triturated with acetone (20 ml). The suspension was filtered and the filtrate concentrated to dryness then purified by silica gel chromatography (CH_2Cl_2 : CH_3OH 90/10) to yield a white solid (0.27 g, 58%). mp 212°C; ir (KBr) 3350 (OH), 1740 and 1690 (CO); ^{1}H-nmr 2.17 (s, 3H, CH_3), 3.52 (m, 2H, H5'), 3.95 (m, 2H, osidic protons), 4.10 (m, 3H, osidic protons), 5.50 (m, 1H, OH), 6.43 (d, 1H, $J_{H1'H2'}$ = 7.3 Hz), 6.52 (s, 1H, H7); ^{13}C-nmr 13.2 (CH_3), 61.5 (C5'), 77.6-79.1-80.9-81.6 (C1'-C2'-C3'-C4'), 93.5 (C7a), 101.2 (C7), 143.8 (C6), 158.5 (C3), 161.1 (C1). Anal. Calcd for $C_{12}H_{14}N_2O_7$: C, 48.33; H, 5.05; N, 9.39. Found: C, 48.20; H, 5.08; N, 9.12.

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