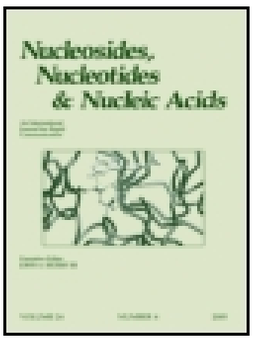

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SYNTHESIS OF 1-(β-D-RIBOFURANOSYL)THIENO[3,2-*d*] PYRIMIDINE-2,4-DIONE AND 4-SUBSTITUTED DERIVATIVES.

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Abstract: Regiospecific ribosylation of the bis(trimethylsilyl) derivative of thieno[3,2-*d*]pyrimidine-2,4-dione in the presence of a Lewis acid followed by debenzoylation has afforded 1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione, a uridine analogue. The site of ribosylation and anomeric configuration of this N-nucleoside were established by NMR and UV. Thiation of the β-anomer was followed by treatment with methanolic ammonia to afford 4-amino-1-(β-D-ribofuranosyl)thieno [3,2-*d*]pyrimidin-2-one, a cytidine analogue.

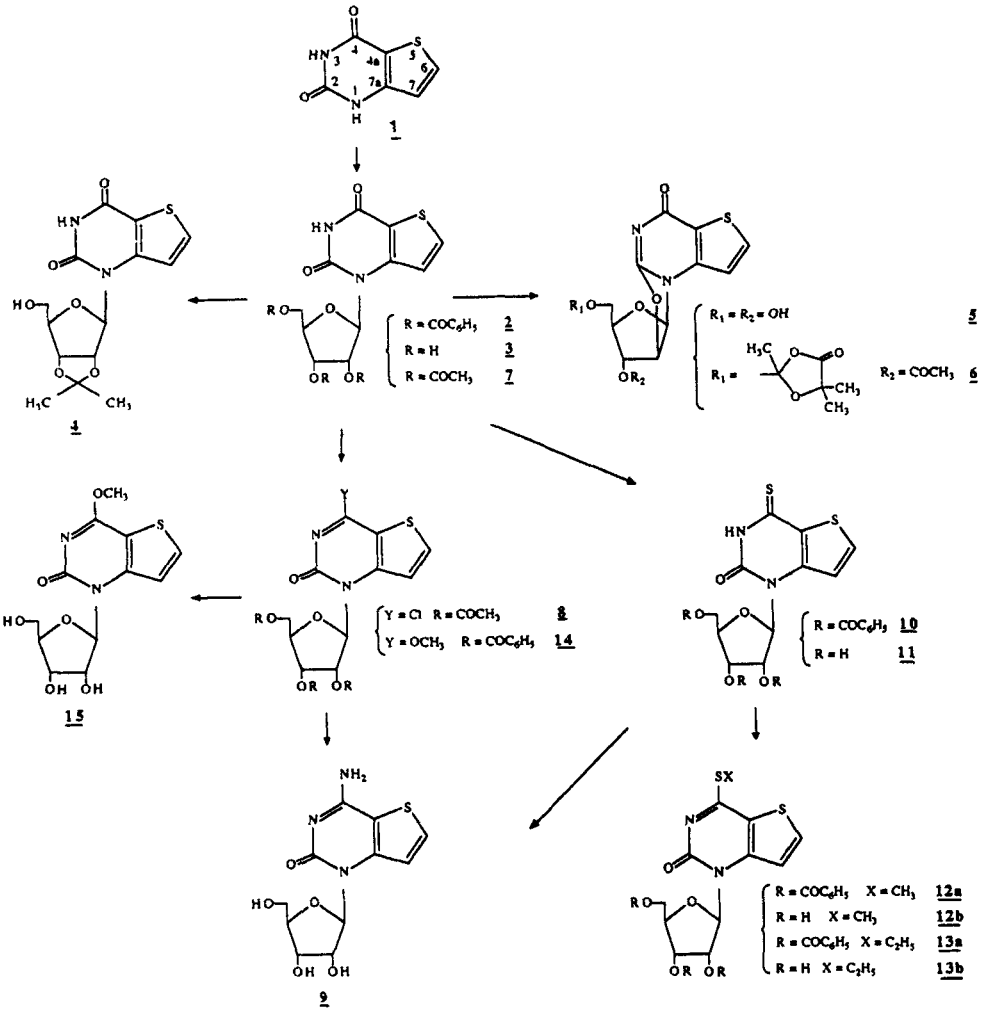
Traditional research in the antiviral area has concentrated in recent years on nucleoside analogues for new therapies against viral infections. This prompted us to investigate the synthesis of bicyclic heterocyclic nucleosides which possess a pyrimidine ring fused to thiophen. This heterocycle: the thieno[3,2-*d*]pyrimidine-2,4-dione could be regarded as thieno-uracil. In the present paper we furher describe synthetic procedures to obtain N_1-β-D-ribofuranosyl thieno [3,2-*d*]pyrimidine-2,4-dione and several structurally similar pyrimidine-type nucleosides such as thieno-uridine and -cytidine.

CHEMISTRY

A key intermediate for the synthesis of the uridine analogue was thieno[3,2-*d*]pyrimidine-2,4-dione 1. This heterocycle was prepared in 40% yield by fusing a mixture of 3-amino-2-carbomethoxythiophen with urea or in 80% yield by cyclization with potassium cyanate [1]. The silylation of 1 was accomplished with hexamethyldisilazane (HMDS) and a catalytic amount of ammonium sulfate [2]. The procedure developed by NIEDBALLA & VORBRÜGGEN [3] was then adapted and the bis(trimethylsil) derivative was condensed with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in the presence of stannic chloride in 1,2-dichloroethane to furnish a single blocked nucleoside 2 (98%). Debenzoylation of 2 with methanolic ammonia led to 1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione 3 that was isolated in crystalline form (60%) [4]. The possibility in which the sugar could be attached to the 3-nitrogen (N-3) seemed highly unlikely because of the presence of an absorption maxima at 296 ± 3 nm (both pH 1 and 11) in the

ultraviolet spectra of 3 [5]. These facts indicated an heterocyclic substitution at N-1 position on the uracil ring.

The anomeric configurational assigment was determined using the Imbach's rule [6]. This method involved the preparation of the 2',3'-isopropylidene derivative 4, and even only one anomer was available during the synthesis, the rule was applicable. The ^1H NMR spectrum of 4 exhibited a difference in chemical shift values ($\Delta\delta$) between the methyl groups for the 2',3'-isopropylidene moiety of 0.22 ppm which was indicative of the β-configuration. In addition, this argument has been substantiated by ^{13}C RMN data since it has been observed that the chemical methyl group signals occured at 25.0-27.0 ppm ($\Delta\delta$ = 2 ppm) [7].



In order to make an unequivocal anomeric assignment, we then initiated a straightforward route for the synthesis of the 2,2'-anhydrocyclonucleoside. Treatment of 3 with diphenyl carbonate and

sodium bicarbonate in DMF gave the expected 2,2'-anhydro-1-(β-D-arabinofuranosyl)thieno [3,2-*d*]pyrimidin-4-one 5 [8]. The structure of 5 was apparent from its NMR spectra. Its ^{1}H NMR spectrum showed the anomeric proton H-1' at 6.68 ppm as a doublet [$J_{1',2'}$= 5.86 Hz] while the H-1' of 3 appeared at 6.09 ppm as a narrow doublet ($J_{1',2'}$= 6.84 Hz). This showed that the 2'-substituent was oriented to *cis* to the glycosyl linkage. Moreover the ^{13}C NMR spectrum of 5 exhibited a strong deshielding for the carbon C-2 (Δδ = 14.1 ppm) and C-2' (Δδ = 19.3 ppm) when compared to 3, indicating the 2,2'-anhydro bridged structure.

In support of this assigment, we then investigated an alternate route involving the 2-acetoxyisobutyryl chloride as reagent [9]. Thus treatment of 3 with 2-acetoxyisobutyryl chloride in acetonitrile at room temperature afforded crystalline 2,2'-anhydro-3'-O-acetyl-5'-dioxolanone cyclonucleoside 6 isolated by preparative TLC. Its IR spectrum exhibited an intense peak at 1800 cm^{-1} and its NMR spectrum a non equivalent dimethyl group, and a 3 proton singlet at 1.79 ppm characteristic of a dioxolanone group. Selective removal of the dioxolanone group was achieved by brief treament with methanolic hydrogen chloride. Subsequent deacetylation of the resulting crude intermediate with methanolic sodium methoxide yielded the expected 2,2'-anhydro cyclonucleoside 5. This established that 3 was the β-anomer, since the anhydronucleoside derivative 5 can only be formed by a β-nucleoside.

In an effort to prepare the cytidine analogue, it was necessary to functionalize the 4-position of the aglycon so that nucleophilic substitution by ammonia could be used. The 4-amino-1-(β–D-ribofuranosyl)thieno[3,2-d]pyrimidin-2-one 9 was obtained from the uracil derivative 3 after chlorination in phosphorus oxychloride-pyridine and subsequent treatment with methanolic ammonia in an overall yield of 78%. We then initiated an alternate route involving the direct displacement of a thio group by ammonia [10]. The 2',3',5'-tri-O-benzoyl protected nucleoside 2 on treatment with Lawesson's reagent [11] in refluxing toluene gave a good yield (62%) of 4-thioxo-2',3',5'-tri-O-benzoyl nucleoside 10 after silica gel column chromatography. Its structure imparted in its ^{13}C NMR spectrum a strong deshielding of the carbon C-4 at 182.7 ppm when compared to nucleoside 2 at 157.7 ppm [12].

However, treatment of 10 with methanolic ammonia at room temperature afforded 1-(β-D-ribofuranosyl)-4-thioxo thieno[3,2-d]pyrimidin-2-one 11. This prompted us to carry out the same reaction in an autoclave at 100°C which not only removed the protecting benzoyl groups but also displaced the thio group to give the expected cytidine analogue 9 [13].

Intermediate 10 was then converted into 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-S-methyl thieno[3,2-*d*]pyrimidin-2-one 12a by treatment with methyl iodide in the presence of potassim carbonate [14]. A removal of the protecting groups from 12a (methanolic ammonia) afforded the free 4-S-methyl nucleoside 12b. Extension of the above alkylation reaction with ethyl bromide yielded 4-S-alkylated intermediate 13a, which on treatment with methanolic ammonia gave crystalline 13b.

Finally, we adapted the attractive procedure developed by Matsuda [15] for 4-O-alkylation under mild conditions. Although 4-methoxy-1(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidin-2-one 15 was obtained from the uracil derivative 3 by nucleophilic substitution with 1-methylimidazole and phosphorus oxychloride and subsequent treatment with methanolic ammonia in an overall yield of 11 %.

The free nucleosides 3, 5 , 9, 11 on one side and the blocked nucleosides 7 , 12a , 14 (with increased lipophilicity) on the other side were tested for their protective activity against the

cytopathic effect (CPE) induced by the human HIV-1 (LAV strain, 100-200 $CCID_{50}$) in CEM cl 13 cell cultures (5.10^4 cells/ml) in the concentration range of 0-30 µg/ml [16]. However, no compounds exhibited any significant inibitory activity against HIV-1.

EXPERIMENTAL SECTION

Melting points (mp) were determined with a KOFLER apparatus and are uncorrected. Infrared (IR) spectra were obtained on a PHILIPS SP-3 Pye Unicam spectrophotometer with samples in KBr disk. Ultraviolet (UV) spectra were recorded on a SECONAM S-1000G spectrometer. Mass spectra (MS) were recorded with a JEOL D-300 instrument using the ionisation by electronic impact technique or with a JEOL JMS SX-102 instrument by using the fast-atom bombardment (FAB) technique. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX 200 or a JEOL EX-90 spectrometer, and chemical shifts were expressed in δ ppm relative to tetramethylsilane (TMS) as an internal standard. Thin layer chromatography (TLC) was performed on silica gel 60F-254 plates purchased from E. MERCK and Co.with UV light for visualization and column chromatography was performed on silica gel (grade 60). Column chromatography was performed on a silica gel 60 (230-400 mesh, ASTM, Merck).

Thieno[3,2-*d*]pyrimidine-2,4-dione (1) [1] (white crystalline solid- 80%) mp > 260C; IR (KBr) cm^{-1} : 3480-3380 (NH), 1670 (CO), 1570, 1540, 1450, 780; ^1H NMR (DMSO-d_6) : δ 6.90 (d, 1H, H-7, J =5.37 Hz), 8.05 (d, 1H, H-6), 11.20 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 111.0 (C-4a), 117.0 (C-7), 135.8 (C-6), 146.3 (C-7a), 151.4 (C-2), 158.9 (C-4).

1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (2). A mixture of 1 (1.68 g; 10mmol), hexamethyldisilazane (HMDS, 40 ml) in the presence of a catalytic amount of ammonium sulfate (30 mg) was heated at reflux with exclusion of moisture for 5 h. The excess HMDS was removed by vacuum distillation and 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (5.06 g; 0.01 mol) which had been dissolved in 1,2-dichloroethane (40 ml) was added to the residue. The reaction mixture was then added with stannic chloride (4 ml) and stirred at room temperature for 18 h. In order to avoid the heavy emulsion which is generally formed during the extraction of the reaction mixture with sodium hydrogencabonate, pyridine (3 ml) was added to complex the excess of stannic chloride. The reaction mixture was stirred for 1 h, and the precipitate which had formed was collected by filtration . The precipitate was washed with $CHCl_3$ (2X80 ml), and the combined filtrates were then washed successively with aqueous $NaHCO_3$ solution (100 ml) and H_2O (2X100 ml). The organic layer was dried over $MgSO_4$, the drying agent was removed by filtration, and the organic layer evaporated *in vacuo* to give 2 (beige crystalline solid- 98%-TLC, CH_2Cl_2, Rf=0.55) mp : 174°C; IR (KBr) cm^{-1} : 3130 (NH), 1720-1630 (CO), 1460, 1260, 1110, 680; ^1H NMR (DMSO-d_6) : δ 3.38 (m, 2H, OCH_2), 6.10 (s, 1H, H-1'), 6.99 (d, 1H, H-7, J =5.37 Hz), 8.09 (d, 1H, H-6), 7.76 (m, 15H, COC_6H_5), 11.82 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 63.2 (C-5'), 70.0 (C-3'), 72.7 (C-2'), 78.1 (C-4'), 90.0 (C-1'), 113.5 (C-4a), 117.8 (C-7), 128.4-129.1-133.2-133.6 (C_6H_5), 135.6 (C-6), 145.5 (C-7a), 150.4 (C-2), 157.7 (C-4), 164.5-164.6-165.3 (3 CO); Anal. Cald. For $C_{32}H_{24}N_2O_9S$ (612.6) : C, 62.74 ; H, 3.95 ; N, 4.57 ; S, 5.23. Found : C, 62.46 ; H, 3.99 ; N, 4.38 ; S, 4.92.

1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (3). A solution of 2 (6 g; 9.79 mmol) in methanolic ammonia (200 ml) was stirred at room temperature for 3 days. The solvent was removed *in vacuo* and the residue was co-evaporated several times with methanol to give a yellow oil which was crystallized from methanol after 3 days (68 %) mp : 250°C; $[\alpha]_D^{20}$ = - 6° (DMF); IR (KBr) cm^{-1} : 3400-3300 (OH), 3140 (NH), 1700-1640 (CO), 1495, 1300, 1115, 1045; ^1H NMR (DMSO-d_6) : δ 3.64 (m, 2H, CH_2OH), 3.83 (m, 1H, H-3'), 4.10 (m, 1H, H-2'), 4.31 (m, 1H, H-4'), 5.07 (1H, OH), 5.13 (1H, OH), 5.28 (1H, OH), 6.09 (d, 1H, H-1', J = 6.84 Hz), 7.69 (d, 1H, H-7, J =5.37 Hz), 8.09 (d, 1H, H-6), 11.63 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 60.9 (C-5'), 68.7 (C-3'), 69.6 (C-2'), 84.0 (C-4'), 88.4 (C-1'), 114.0 (C-4a), 119.4 (C-7), 134.9 (C-6), 144.5 (C7a), 151.1 (C-2), 157.7 (C-4); UV λ_{max} (log ε) : 294 (3.99) (pH 1, HCl), 294 (4.03) (pH 7, H_2O), 299 (3.80) (pH 14, NaOH); Anal. Cald. For $C_{11}H_{12}N_2O_6S$ (300.3) : C, 44.00 ; H, 4.03 ; N, 9.83 ; S, 10.68. Found : C, 43.72 ; H, 4.13 ; N, 9.54 ; S, 10.40.

1-(2,3-di-O-isopropylidene-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (4) 2,2-dimethoxypropane (1.01 g; 9.69 mmol) and *p*-toluenesulfonic acid monohydrate (200 mg) were added successively to a suspension of 3 (500 mg; 1.68 mmol) in dry acetone (40 ml). The reaction mixture was heated under reflux for 2 h, then cooled to room temperature and stirred for an additional 30 min. $NaHCO_3$ (1 g) was then added and the stirring continued for further 3 h. The inorganic materials were collected by filtration and washed with acetone (2X20 ml). The combined filtrates were evaporated to dryness *in vacuo* to give 4 (white crystalline solid- 94 %) mp : 130°C; IR (KBr) cm^{-1} : 3520-3320 (OH), 3200 (NH), 1710-1670 (CO), 1480, 1370, 1210, 1100, 770; ^1H NMR (DMSO-d_6) : δ 1.29 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.60 (m, 2H, CH_2OH), 3.99-4.87-5.13 (m, osidic H), 6.14 (d, 1H, H-1', J = 2.68 Hz), 7.49 (d, 1H, H-7, J =5.37 Hz), 8.13 (d, 1H, H-6); ^{13}C NMR (DMSO-d_6) : δ 25.0-27.0 (CH_3), 61.0 (C-5'), 80.2 (C-3'), 82.1 (C-2'), 86.4 (C-4'), 90.5 (C-1'), 113.6 (C-4a), 118.3 (C-7), 129.2 (CCH_3), 135.6 (C-6), 145.1 (C-7a), 150.5 (C-2), 157.8 (C-4); Anal. Cald. For $C_{14}H_{16}N_2O_6S$ (340.3) : C, 49.41 ; H, 4.74 ; N, 8.23 ; S, 9.42. Found : C, 49.30 ; H, 5.04 ; N, 8.27 ; S, 9.52.

2,2'-anhydro-1-(β-D-arabinofuranosyl)thieno[3,2-*d*]pyrimidin-4-one (5). *Method 1:* diphenyl carbonate (0.46 g; 2.15 mmol) and $NaHCO_3$ (10 mg) were added successively to a solution of 3 (500 mg; 1.67 mmol) in DMF (10 ml). The reaction mixture was heated under reflux for 1 h, and evaporated to dryness *in vacuo*. The resulting oil was triturated in diethyl oxide to give crystals which were purified by column chromatography using as eluent a gradient of 0 to 60 % CH_3OH in CH_2Cl_2 to afford 5 (white crystalline solid- 81 %- TLC, CH_2Cl_2:CH_3OH 85:15, Rf = 0.33). *Method 2:* A solution of 6 (500 mg; 1 mmol) in methanolic hydrogen chloride (70 ml) was stirred at room temperature for 90 min and evaporated *in vacuo*. The resulting oil was dissolved in 0.5N methanolic sodium methoxide (50 ml), and the reaction mixture stirred at room temperature for 90 min. The solution was neutralized by rapid addition of Dowex 50W-X8 (H^+) resin and filtered. The filtrate was evaporated to dryness *in vacuo*, and the crude product was purified by preparative TLC (chloroform-methanol 8:2) to afford 5 (26%). mp : 236°C; $[\alpha]_D^{20}$ = - 172° (DMF); IR (KBr) cm^{-1} : 3280-3380 (OH), 1620-1600 (CO), 1520, 1495, 1075, 1000, 780; ^1H NMR (DMSO-d_6) : δ 3.25 (m, 2H, CH_2OH), 4.12 (m, 1H, H-4'), 4.45 (m, 1H, H-3'), 4.93 (1H, OH-5'), 5.30 (d, 1H, H-2',J =5.86 Hz), 5.94 (1H, OH-3'), 6.69 (d, 1H, H-1'), 7.37 (d, 1H, H-7, J =5.37 Hz), 8.15 (d, 1H, H-6); ^{13}C NMR (DMSO-d_6) : δ 60.7 (C-5'), 74.6 (C-3'), 88.9 (C-2'), 89.3 (C-4'), 89.4 (C-1'), 116.2 (C-4a), 118.8 (C-7), 134.8 (C-6), 140.7 (C-7a), 159.8 (C-4), 165.2 (C-2); Anal. Cald. For $C_{11}H_{10}N_2O_5S$ (282.3) : C, 46.81 ; H, 3.57 ; N, 9.92 ; S, 11.86. Found : C, 46.63 ; H, 3.37 ; N, 9.74 ; S, 11.62.

2,2'-anhydro-1-[3-O-acetyl-5-O-(2,5,5-trimethyl-dioxolan-4-one-2-yl)-β-D-arabinofuranosyl]thieno[3,2-*d*]pyrimidin-4-one (6). 2-acetoxyisobutyryl chloride (2.4 ml) was added to a suspension of 3 (1 g; 3.33 mmol) in anhydrous acetonitrile (20 ml), and the reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated *in vacuo*, and the residue triturated with diethyl oxide. The crude product was purified by preparative TLC (chloroform-methanol 8:2) to afford 6 (white crystalline solid- 34%) mp : 120°C; IR (KBr) cm^{-1} : 3600-3300 (NH), 1730-1700-1675 (CO), 1500, 1480, 1200, 1150; ^1H NMR (DMSO-d_6) : δ 1.34 (m, 9H, dioxolanone-CH_3), 1.79 (s, 3H, dioxolanone-CH_3), 2.12 (s, 3H, $COCH_3$), 3.53 (m, 2H, CH_2-5'), 4.57-5.35 (m, H-3' and H-4'), 5.61 (d, 1H, H-2', J =5.86Hz), 6.74 (d, 1H, H-1'), 7.35 (d, 1H, H-7, J =5.37 Hz), 8.17 (d, 1H, H-6); ^{13}C NMR (DMSO-d_6) : δ 20.7 ($COCH_3$), 23.7-24.5 (CH_3), 62.0 (C-5'), 77.2 (C-3'), 84.6 (C-2'), 86.2 (C-4'), 89.8 (C-1'), 116.2 (C-4a), 119.5 (C-7), 135.1 (C-6), 140.5 (C-7a), 159.4 (C-4), 169.6 (C-2); Anal. Cald. For $C_{19}H_{20}N_2O_9S$ (452.4) : C, 50.44 ; H, 4.46 N, 6.19 ; S, 7.09. Found : C, 50.39 ; H, 4.38 ; N, 6.08 ; S, 6.99.

1-(2,3,5-triO-acetyl-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (7) Acetic anhydride (3,15 ml; 33.3 mmol) was added to a solution of 3 (1 g; 3.33 mmol) in pyridine (30 ml) at 0°C. The reaction mixture was stored at 4°C for 24 h, and the solvent was evaporated *in vacuo*. The residue was co-evaporated several times with ethanol to give a yellow oil that crystallized at 4°C 3 days later. The crude product was washed successively with ethanol (20 ml) and diethyl oxide (20 ml) to afford 7 (99 %). mp : 98°C; IR (KBr) cm^{-1} : 3240 (NH), 1750-1710 (CO), 1490, 1380, 1240, 1050; ^1H NMR (DMSO-d_6) : δ 2.05 (s, 9H,

$COCH_3$), 4.23 (m, 2H, CH_2OH), 4.34 (t, 1H, H-4', J =6.84 Hz), 5.47 (t, 1H, H-3'), 5.60 (m, 1H, H-2'), 6.15 (d, 1H, H-1', J =3.23 Hz), 7.49 (d, 1H, H-7, J =5.37 Hz), 8.18 (d, 1H, H-6), 11.74 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 20.1-20.4 (CH_3), 62.7 (C-5'), 69.1 (C-3'), 71.4 (C-2'), 78.2 (C-4'), 89.5 C-1'), 113.6 (C-4a), 127.8 (C-7), 135.8 (C-6), 145.2 (C-7a), 150.4 (C-2), 157.7 (C-4), 169.4-169.6-169.9 (3 CO); MS m/z=426; Anal. Cald. For $C_{17}H_{18}N_2O_9S$ (426.4) : C, 47.89 ; H, 4.25 ; N, 6.57 ; S, 7.52. Found : C, 48.10 ; H, 4.43 ; N, 6.47 ; S, 7.22.

4-amino-1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidin-2-one (9). *Method 1:* Pyridine (1 ml) was added slowly to phosphorus oxychloride (10 ml) at 0°C in order to obtain a complex. A solution of 7 (1 g; 2.34 mmol) in anhydrous acetonitrile (10 ml) was then added dropwise to the resulting complex at 0°C. The solution was refluxed for 30 min and concentrated to dryness *in vacuo* . The resulting oil was dissolved in a mixture of aqueous ammonia (20 ml) and dioxane (20 ml). The solution was stirred at room temperature for 14 h, and evaporated to dryness *in vacuo*. The resulting oil was dissolved in methanolic ammonia (50 ml). This solution was stirred at room temperature for 14 h, and concentrated *in vacuo* to give a crude product which was purified by column chromatography using as eluent a gradient of 0 to 60 % CH_3OH in CH_2Cl_2 to yield 9 (beige solid- 79%). *Method 2:* A solution of 10 (1 g; 1.59 mmol) in saturated methanolic ammonia (150 ml) was heated in an autoclave at 100°C for 18 h. The reaction mixture was allowed to stand at room temperature and then evaporated *in vacuo*. The resulting oil was triturated with CH_2Cl_2 (30 ml). The crystalline residue was collected by filtration, and purified by column chromatography using as eluent a gradient of 0 to 60 % CH_3OH in CH_2Cl_2 to yield 9 (beige solid- 74%- TLC, CH_2Cl_2:CH_3OH 7:3, Rf = 0.47) mp : 220°C; $[\alpha]_D^{20}$ = - 4° (DMF); IR (KBr) cm^{-1} : 3540 (NH), 3420-3040 (OH), 1640-1600 (CO), 1570, 1530, 1110, 1050; ^1H NMR (DMSO-d_6) : δ 3.63 (m, 2H, CH_2OH), 3.80-4.10-4.37 (m, osidic H), 5.04 (1H, OH), 6.12 (d, 1H, H-1', J = 6.83 Hz), 7.50 (d, 1H, H-7, J =5.37 Hz), 7.66 (s, 2H, NH_2, disapppeared after addition of D_2O), 7.96 (d, 1H, H-6); ^{13}C NMR (DMSO-d_6) : δ 61.2 (C-5'), 69.1 (C-3'), 70.0 (C-2'), 84.7 (C-4'), 89.8 (C-1'), 106.1 (C-4a), 118.1 (C-7), 132.9 (C-6), 148.0 (C-7a), 155.8 (C-2), 158.9 (C-4); UV λ_{max} (log ε) : 315 (3.33) (pH 1, HCl), 305 (3.36) (pH 7, H_2O), 302 (3.47) (pH 14, NaOH); Anal. Cald. For $C_{11}H_{13}N_3O_5S$ (299.3) : C, 44.14 ; H, 4.38 ; N, 14.04. Found : C, 44.24 ; H, 4.47 ; N, 13.90.

1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-thioxo thieno[3,2-*d*]pyrimidin-2-one (10). Lawesson's reagent (495 mg; 1.22 mmol) was added portionwise to a solution of 2 (1.5 g; 2.45 mmol) in anhydrous toluene (50 ml). The reaction mixture was heated under reflux for 24 h, and then concentrated *in vacuo*. The resulting oil was co-evaporated several times with toluene to give a residue that crystallized from diethyl oxide. The solid was collected by filtration and purified by column chromatography using as eluent a gradient of 0 to 60 % methanol in dichloromethane to yield 950 mg (62 %) of 10 as a yellow solid. (TLC, CH_2Cl_2:CH_3OH 8:2, Rf = 0.95) mp : 263°C; IR (KBr) cm^{-1} : 3280 (NH), 1750-1710 (CO), 1560, 1500, 1290, 1150; ^1H NMR (DMSO-d_6) : δ 4.71 (m, 2H, $CH_2OCOC_6H_5$), 6.11 (m, 1H, H-1'), 7.43-7;65-7.90-7.98 (m, aromatic H), 8.15 (d, 1H, H-6, J =5.37 Hz), 13.08 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 63.2 (C-5'), 70.0 (C-3'), 72.8 (C-2'), 78.3 (C-4'), 90.5 (C-1'), 117.8 (C-7), 125.5 (C-4a), 128.4-129.1-133.2-133.6 (aromatic C), 139.6 (C-6), 141.0 (C-7a), 147.9 (C-2), 164.5-164.6-165.3 (3 CO), 182.7 (C-4); Anal. Cald. For $C_{32}H_{24}N_2O_8S_2$ (628.7) : C, 61.14 ; H, 3.85 ; N, 4.46 ; S, 10.20. Found : C, 61.11 ; H, 3.66 ; N, 4.39 ; S, 10.44.

1-(β-D-ribofuranosyl)-4-thioxo thieno[3,2-*d*]pyrimidin-2-one (11). A solution of 10 (520 mg; 0.8 mmol) in methanolic ammonia was stirred at room temperature for 14 h. The solvent was evaporated to dryness *in vacuo* . The resulting oil crystallized from methanol 3 days later to afford 11 (yellow crystalline solid- 40%- TLC, CH_2Cl_2:CH_3OH 9:1, Rf = 0.30) mp : 240°C; $[\alpha]_D^{20}$ = + 30° (DMF); IR (KBr) cm^{-1} : 3500-3100 (OH), 1710-1670 (CO), 1540, 1480, 1090, 1020; ^1H NMR (DMSO-d_6) : δ 3.64 (m, 2H, CH_2OH), 3.84-4.09-4.32 (m, osidic H), 5.06-5.29 (1H, OH), 6.09 (d, 1H, H-1', J =6.84 Hz), 7.72 (d, 1H, H-7, J =5.37 Hz), 8.12 (d, 1H, H-6), 12.88 (1H, NH); ^{13}C NMR (DMSO-d_6) : δ 60.8 (C-5'), 68.8 (C-3'), 69.8 (C-2'), 85.3 (C-4'), 88.9 (C-1'), 119.3 (C-7), 125.9 (C-4a), 138.5 (C-6), 140.0 (C-7a), 146.7 (C-2), 182.4 (C-4); Anal. Cald. For $C_{11}H_{12}N_2O_5S_2$ (316.3) : C, 41.76 ; H, 3.82 ; N, 8.86 ; S, 20.27. Found : C, 41.79 ; H, 3.66 ; N, 8.80 ; S, 20.28.

1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-S-methyl thieno[3,2-*d*]pyrimidin-2-one (12a). Methyl iodide (0.1 ml; 1.6 mmol; 2 Eq) and potassium carbonate (1 g) were added successively to a solution of 10 (500 mg; 0.80 mmol) in dry tetrahydrofuran (40 ml). The reaction mixture was stirred at room temperature for 14 h. The inorganic materials were removed by filtration and washed with tetrahydrofuran (2X10 ml). The combined filtrates were concentrated *in vacuo* . The resulting oil was crystallized from a mixture of diethyl oxide/petroleum ether (10 ml/10 ml) to afford 12a (white solid- 49%- TLC, CH_2Cl_2:CH_3OH 98:2, Rf = 0.41). mp: 155°C, IR (KBr) cm^{-1} : 1760-1710 (CO), 1670, 1270, 1120, 720; ^1H NMR (DMSO-d_6) : δ 2.66 (s, 3H, SCH_3), 4.77 (m, 2H, $CH_2OCOC_6H_5$), 6.12 (s, 1H, H-1'), 7.41-7.63-7.978 (m, aromatic H), 8.17 (d, 1H, H-6,*J* =5.37 Hz); ^{13}C NMR (DMSO-d_6) : δ 12.0 (SCH_3), 63.6 (C-5'), 70.7 (C-3'), 73.0 (C-2'), 78.7 (C-4'), 91.3 (C-1'), 117.3 (C-7), 128.5-129.1-133.3-133.6 (aromatic C), 136.3 (C-6), 148.0 (C-7a), 152.5 (C-2), 164.6-164.7-165.3 (3 CO), 170.5 (C-4); Anal. Cald. For $C_{33}H_{26}N_2O_8S_2$ (642.7) : C, 61.67 ; H, 4.08 ; N, 4.36 ; S, 9.98. Found : C, 61.52 ; H, 3.94 ; N, 4.28 ; S, 9.87.

4-S-methyl-1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidin-2-one (12b). A solution of 12a (200 mg; 0.31 mmol) in methanolic ammonia (20 ml) was stirred at room temperature for 5 h, then concentrated in *vacuo*. The crude product (100 mg) was purified by column chromatography using as eluent a gradient of 0 to 60 % CH_3OH in CH_2Cl_2 to yield 12b (pale yellow solid- 29%- TLC, CH_2Cl_2:CH_3OH 9:1, Rf = 0.29) mp : 110 °C, IR (KBr) cm^{-1} : 3460-3260 (OH), 1620 (CO), 1490, 1260, 1090, 770; ^1H NMR (DMSO-d_6) : δ 2.62 (s, 3H, SCH_3), 3.65 (m, 2H, CH_2OH), 3.86-4.14-4.34 (m, osidic H), 5.08-5.20 (m, OH), 6.22 (d, 1H, H-1', *J* =6.84 Hz), 7.77 (d, 1H, H-7, *J* =4.89Hz), 8.15 (d, 1H, H-6); ^{13}C NMR (DMSO-d_6) : δ 11.9 (SCH_3), 61.0 (C-5'), 69.0 (C-3'), 70.4 (C-2'), 85.3 (C-4'), 89.8 (C-1'), 118.5 (C-7), 135.4 (C-6), 146.9 (C-7a), 152.5 (C-2), 170.5 (C-4); Anal. Cald. For $C_{12}H_{14}N_2O_5S_2$ (330.4) : C, 43.63 ; H, 4.27 ; N, 8.48 ; S, 19.41. Found : C, 43.59 ; H, 4.24 ; N, 8.39 ; S, 19.37.

1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-S-ethyl thieno[3,2-*d*]pyrimidin-2-one (13a). (White crystalline solid- 62 %) mp : 90°C, IR (KBr) cm^{-1} : 1730-1660 (CO), 1560, 1270, 1120, 700; ^1H NMR (DMSO-d_6) : δ 1.37 (t, 3H, SCH_2CH_3), 4.74 (m, 2H, SCH_2CH_3), 6.13 (s, 1H, H-1'), 7.46-7.65-7.92 (m, aromatic H), 8.17 (d, 1H, H-6, *J* =5.37 Hz); ^{13}C NMR (DMSO-d_6) : δ 14.2 (SCH_2CH_3), 23.6 (SCH_2CH_3), 63.6 (C-5'), 70.7 (C-3'), 73.0 (C-2'), 78.7 (C-4'), 91.4 (C-1'), 117.3 (C-7), 128.4-129.1-133.3-133.5 (aromatic C), 136.4 (C-6), 148.1 (C-7a), 152.5 (C-2), 164.6-164.7-165.3 (CO), 170.1 (C-4); Anal. Cald. For $C_{34}H_{28}N_2O_8S_2$ (656.7) : C, 62.18 ; H, 4.30 ; N, 4.27 ; S, 9.76. Found : C, 62.07 ; H, 4.24 N, 4.19 ; S, 9.71.

4-S-ethyl-1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidin-2-one (13b). (Beige crystalline solid- 32 %) ^1H NMR (DMSO-d_6) : δ 1.34 (s, 3H, SCH_2CH_3), 3.64 (m, 2H, CH_2OH), 4.00 (m, 2H, SCH_2CH_3), 3.85-4.13-4.34 (m, osidic H), 5.17 (m, OH), 6.22 (d, 1H, H-1', *J* =5.86 Hz), 7.77 (d, 1H, H-7, *J* =5.86Hz), 8.15 (d, 1H, H-6); ^{13}C NMR (DMSO-d_6) : δ 14.2 (SCH_2CH_3), 23.6 (SCH_2CH_3), 63.6 (C-5'), 70.7 (C-3'), 73.0 (C-2'), 78.7 (C-4'), 91.4 (C-1'), 117.3 (C-7), 136.4 (C-6), 148.1 (C-7a), 152.5 (C-2), 170.1 (C-4); Anal. Cald. For $C_{13}H_{16}N_2O_5S_2$ (344.4) : C, 45.34 ; H, 4.68 ; N, 8.13 ; S, 18.62. Found : C, 45.27 ; H, 4.61 ; N, 8.02 ; S, 18.48.

1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-methoxy thieno[3,2-*d*]pyrimidin-2-one (14) 1-methylimidazole (0.5 ml) was added slowly to phosphorus oxychloride (0.15 ml) at 0°C. A solution of 2 (1 g; 1.63 mmol) in anhydrous acetonitrile (5 ml) was then added dropwise to the yellow resulting complex at 0°C, then stirred at room temperature for 2 h 30 min. Methanol (50 ml) and triethylamine (2.2 ml; 15.5 mmol) were added successively to the reaction mixture. The stirring was carried on for 14 h, and the solvents were evaporated to dryness *in vacuo*. The resulting syrup (3.2 g) was purified by column chromatography using as eluent a gradient of 0 to 80 % CH_3OH in CH_2Cl_2 to afford 14 (white solid- 31 %- TLC, CH_2Cl_2:CH_3OH 9:1, Rf=0.94). mp : 139°C; IR (KBr) cm^{-1} : 1730-1670 (CO), 1580, 1280, 1110, 710; ^1H NMR (DMSO-d_6) : δ 4.04 (s, 3H, OCH_3), 4.79 (m, 2H, $CH_2OCOC_6H_5$), 6.12 (s, 1H, H-1'), 7.45-7.65-7.97 (m, aromatic H), 8.17 (d, 1H, H-6,*J* =5.37 Hz); ^{13}C NMR (DMSO-d_6) : δ 54.5 (OCH_3), 63.6

(C-5'), 70.7 (C-3'), 73.0 (C-2'), 78.6 (C-4'), 91.0 (C-1'), 117.3 (C-7), 128.5-129.1-133.3-133.6-136.4 (aromatic C), 136.5 (C-6), 154.9 (C-7a), 150.9 (C-2), 165.0 (C-4), 164.6-164.7-165.3 (3 CO); Anal. Cald. For $C_{33}H_{26}N_2O_9S$ (626.6) : C, 63.25 ; H, 4.18 ; N, 4.47 ; S, 5.12. Found : C, 63.21 ; H, 4.14 ; N, 4.43 ; S, 5.10.

4-methoxy-1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidin-2-one (15). A solution of 14 (220 mg; 0.35 mmol) in methanolic ammonia (20 ml) was stirred at room temperature for 14 h and concentrated to dryness *in vacuo*. The crude product (100 mg) was purified by column chromatography using as eluent a gradient of 0 to 60 % CH_3OH in CH_2Cl_2 to give 15 (white solid- 36 %- TLC, CH_2Cl_2:CH_3OH 8:2, Rf=0.85). mp : 140°C; IR (KBr) cm^{-1} : 3400-3200 (OH), 1620 (CO), 1590, 1550, 1500, 1065; ^1H NMR (DMSO-d_6) : δ 3.65 (m, 2H, CH_2OH), 4.00 (s, 3H, OCH_3), 3.86-4.11-4.34 (m, osidic H), 5.20-5.08 (OH), 6.22 (d, 1H, H-1', J =6.84 Hz), 7.74 (d, 1H, H-7,J =5.37 Hz), 8.16 (d, 1H, H-6); Anal. Cald. For $C_{12}H_{14}N_2O_6S$ (314.3) : C, 45.86 ; H, 4.49 ; N, 8.91 ; S, 10.20. Found : C, 45.64 ; H, 4.28 ; N, 8.68 ; S, 10.04.

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