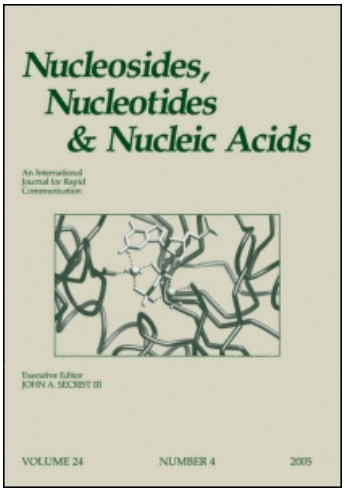

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Synthesis of 7-(β-D-Glucopyranosyl)-6-Thiotheophylline and 7-(α-D-Arabinopyranosyl)-6-Thiotheopwlline. Conformational Study of the Peracetyl Derivatives.

Rodrigo Rico-Gómez[a]; Ezequiel P. de Inestrosa-Villatoro[a]; Juan Manuel López-Romero[a]; Francisco Nájera[a]; Rafael López-Corpas[a]
[a] Departamento de Quimica Orgánica, Universidad de Málaga, Málaga, Spain

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SYNTHESIS OF 7-(β-D-GLUCOPYRANOSYL)-6-THIOTHEOPHYLLINE AND 7-(α-D-ARABINOPYRANOSYL)-6-THIOTHEOPHYLLINE. CONFORMATIONAL STUDY OF THE PERACETYL DERIVATIVES.

Rodrigo Rico-Gómez*, Ezequiel P. de Inestrosa-Villatoro, Juan Manuel López-Romero, Francisco Nájera and Rafael López-Corpas.

Departamento de Química Orgánica, Universidad de Málaga, 29071 Málaga, Spain.

Abstract: The synthesis of two 7-glycosyl-6-thiotheophylline nucleosides where the sugar moieties are β-D-glucose (**1b**) and α-D-arabinose (**2b**) is reported. The *syn-anti* equilibrium of the peracetyl derivatives was studied by the line-shape and the ^{1}H-NMR nOe methods, and molecular mechanics analysis.

Introduction

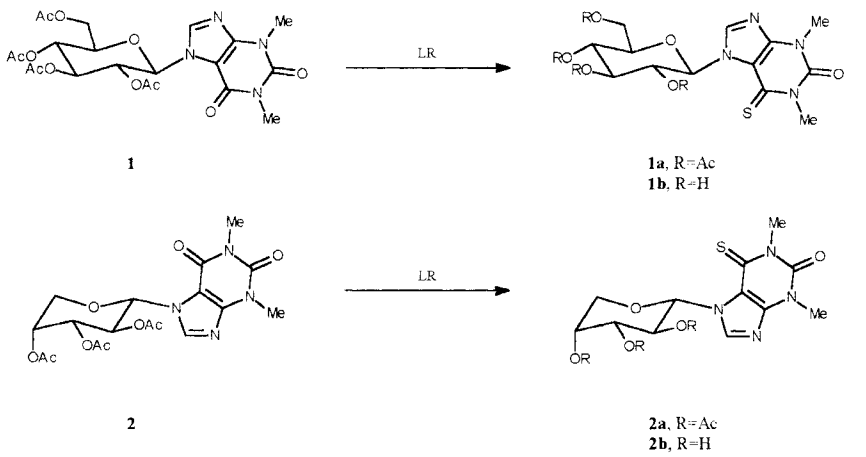
Xanthine and thioxanthine are compounds of great interest on account of their biological activity. Thiopyrimidine and thiopurine nucleosides occur as components of transfer ribonucleic acids.[1] 6-Thiopurines and 6-thiopurine nucleosides have shown significant antitumor activity.[2] A number of alkylxanthines, such as theophylline and derivatives, have become interesting as adenosine receptors antagonist.[3] 1,3-Dialkyl-7-ribosylxanthines have been found to be a partial agonist at A3 adenosine receptor.[4] Contrary to alkylxanthine bases, their nucleosides are less studied both from the chemical and biological viewpoints.

We have found that Lawesson's reagent[5] replaces the 6-oxo group of 7-glycosyl-8-methyl-theophylline effectively with a thioxo group, even when is not enolizable. We have exploited this finding by preparing 8-methyl-6-thiotheophylline nucleosides.[6] In the present paper we report the synthesis of 7-glycosyl-6-thiotheophylline nucleosides where the sugar moieties are respectively β-D-glucopyranose and α-D-arabinopyranose, together with some interesting conformational aspects of their peracetyl derivatives.

Results and Discussion

Treatment of 7-(2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosyl)theophylline (**1**) with the Lawesson's reagent (LR) in boiling toluene yielded 7-(2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosyl)-6-thiotheophylline (**1a**). The UV spectrum showed a maximun at 344 nm, which was consistent with the 6-thioxo group.[7] The EI mass spectrum showed the molecular-ion peak at *m/z* 526. The ^{13}C-NMR spectrum showed the 21 signals corresponding to the 21 carbon atoms present in the molecule; the signal corresponding to C-6 at 176.8 ppm confirmed the replacement of the oxygen atom by one sulphur atom at that position.[8] The ^{1}H-NMR spectrum was a first-order spectrum, H-1' appeared at 7.38 ppm, 1.28 ppm lower than H-1' of **1** because of the anistropic effect of the thioxo group.[9]

Treatment of **1a** with sodium methoxide in methanol yielded 7-(β-D-glucopyranosyl)-6-thiotheophylline (**1b**). The structure of **1b** was confirmed by the spectral data.



1 **1a**, R=Ac; **1b**, R=H

2 **2a**, R=Ac; **2b**, R=H

Similarly, from 7-(2, 3, 4-tri-O-acetyl-α-D-arabinopyranosyl)theophylline (**2**), 7-(2, 3, 4-tri-O-acetyl-α-D-arabinopyranosyl)-6-thiotheophylline (**2a**) was obtained. The spectral data: UV (λ_{max} 344 nm), the EI mass (*m/z* 454), and the ^{13}C-NMR (C-6, signal at 176.8 ppm) confirmed the proposed structure. The ^{1}H-NMR is consistent with a *1C* conformation for the arabinopyranose ring and α configuration in C-1' (H-1', 7.42 ppm, $J_{1',2'}$, and $J_{2',3'}$, 9.7 Hz implies *anti*-periplanar layout).

Deacetylation of **2a** with sodium methoxide in methanol gave 7-(α-D-arabinopyranosyl)-6-thiotheophylline (**2b**). The spectral data confirmed the structure.

The starting nucleosides, 7-(2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosyl)-theophylline (**1**) and 7-(2, 3, 4-tri-O-acetyl-α-D-arabinopyranosyl)theophylline (**2**), were

synthesized from either 6-amino-1,3-dimethyl-5-N-D-glucosylideneiminouracil or 6-amino-1,3-dimethyl-5-N-D-arabinosylideneiminouracil by treatment with diethoxymethyl acetate (DEMA), followed by acetylation with acetic anhydride in pyridine.[10]

The ^{1}H-NMR for both peracetyl derivatives **1a** and **2a** showed a first order spectra with sharp and well-defined signals. However, for compounds **1** and **2** the ^{1}H-NMR signals corresponding to H-1' and H-2' were broadened. This was attributed to a high molecular crowding that hinders rotation about the glycoside bond. Examination of the molecular model showed two conformers seeming to have the minimal steric hindrances, *syn* and *anti*. Considering the dihedral angle χ H(1')-C(1')-N(7)-C(8), we defined the *syn*-conformer as that with $\chi = 0^o$, where H-1' and C-8 are in a *syn*-coplanar layout, and the *anti*-conformer that with $\chi = 180^o$, with H-1' and C-8 in a *anti*-periplanar arrangement (Figure 1).

Variable temperature ^{1}H-NMR experiments confirmed the occurrence of the two postulated rotamers for compounds **1** and **2**. For compound **1**, the ^{1}H-NMR recorded at 203 K showed all the signals sharps. The signal corresponding to H-8 split in two singlets at 7.95 ppm, integral 0.80 H (*anti*-conformer) and 7.72 ppm, integral 0.20 H (*syn*-conformer), H-1' at 6.36 ppm as a doublet (J 9.6 Hz), and H-2' at 5.55 ppm as a pseudo-triplet (J 9.6-9.6 Hz). When the spectrum was recorded at 333 K the signals also became narrow, showing the signals of H-8 (singlet), H-1' (doublet) and H-2' (pseudotriplet), at 7.79, 6.09 and 5.55 ppm, respectively.

For compound **2**, ^{1}H-NMR spectra were recorded at temperatures between the 198 K - rt interval. The spectrum at 198 K showed the protons of the *anti*-conformer at 7.98 ppm (s, H-8, integral 0.79 H), 6.13 ppm (d, J 9.6 Hz, H-1') and 5.63 ppm (t, J 9.6 Hz, H-2'), and those of the *syn*-conformer at 7.75 ppm (s, H-8, integral 0.21 H) and 6.56 (t, J 9.5 Hz, H-2').

Kinetics parameters for the two equilibria were calculated by line-shape analysis and the Eyring equation.[6b,11] Since the signal corresponding to H-8, was a singlet not involved in any coupling, it was good enough for calculating accurate values (Table 1). The ΔG^* of the equilibrium obtained by this method are 11.7 kcal mol^{-1} for compound **1** and 11.8 kcal mol^{-1} for compound **2**. These values define a rotational energy barrier that accounts for a *syn-anti* equilibrium at room temperature. From the integral of ^{1}H-NMR in the low temperature spectra, a ratio *anti-syn* of 80%:20% for **1** and 79%:21% for **2** were obtained.

The replacement of the oxygen atom at C-6 by a sulphur atom in both nucleosides **1** and **2**, increase the rotational energy barrier with the *anti* rotamer looking the more stable conformation. The rotation about the glycoside bond is now completely restricted by the considerable larger volume of the sulphur atom, and consequently the

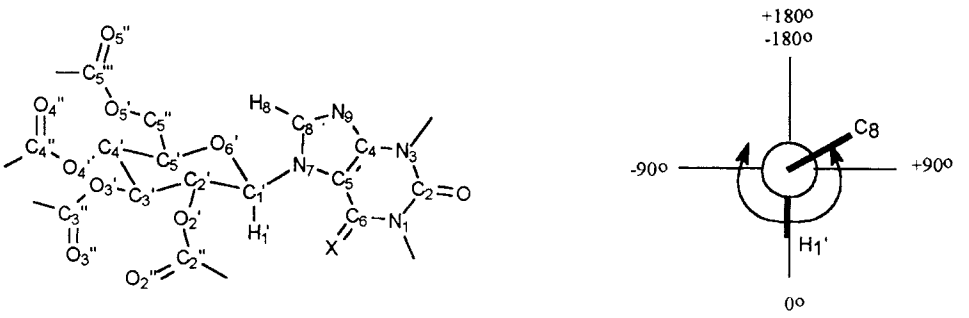


FIGURE 1. Angle definition.

TABLE 1. Line-shape analysis: corrected line width ($\delta\nu$), rate constants (Kv), and activation parameters for **1** and **2**.

Compound	T	$\delta\nu$	Kv	ΔH*	ΔS*	ΔG*
	K	Hz	s^{-1}	Kcal/mol	cal/mol K	Kcal/mol
1	203	1.08	3.393			
	213	2.34	7.351			
	223	5.59	17.562			
	233	10.09	31.699			
	242	*Coalescence*	*Temperature*	10.0	-7.0	11.7
	243	9.37	288.032			
2	217	2.75	8.639			
	227	7.63	23.970			
	233	10.37	32.578			
	235	14.65	46.024			
	239	*Coalescence*	*Temperature*	10.8	-4.1	11.8
	253	8.58	314.540			

^{1}H-NMR spectra of compounds **1a** and **2a** showed all the signals sharp. The down-field chemical shift of H-1' for both compounds indicates the proximity of the thioxo group, and therefore an *anti* conformation.

In order to confirm these results ^{1}H nOe difference experiments have been carried out.[12] For compound **1a** upon irradiation of H-8 a 10% of nOe was observed at H-2'. No nOe was observed at the others protons of the sugar moiety. Similarly, for compound **2a** a 9% of nOe was observed at H-2', with no additional nOe being observed.

In case of compound **1** at rt, upon irradiation of H-8, nOe was observed at H-1' (2%) and at H-2' (6%). When the same experiment was carried out at 215 K upon irradiation of H-8 (δ 7.92 ppm), 6% nOe was observed at H-2'. For compound **2** nOe at H-1' (2%) and H-2' (6%) was also observed. Upon irradiation of H-8 (δ 7.98 ppm) a 6% of nOe was observed at H-2'. These values clearly demonstrate a conformation in the *anti* range for **1a** and **2a** and a *syn-anti* equilibrium for **1** and **2**. Considering an inverse relationship between the nOe and the interproton distances (Table 2), the obtained results from the nOe difference experiments give a ratio of the *anti* conformer between 3 and 4 times more than the *syn* conformer, which is in good accord with those obtained from the ^{1}H-NMR integral.

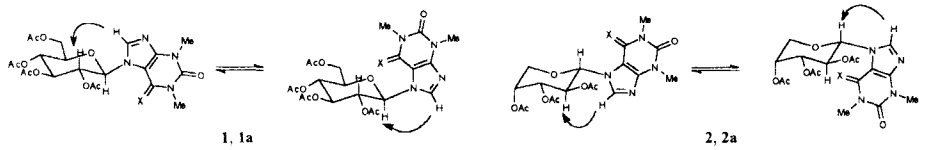
Empirical force-field molecular mechanics calculations are used to calculate the geometries and energies for different types of molecules.[6b,13] We used the ChemX program with an MME-type force-field to calculate the geometries and the minimum energy conformations of the peracetyl derivatives **1**, **1a**, **2**, and **2a**. The results represent the gas-phase properties only, but are very similar to the experimental data obtained in chloroform solution (Table 3). In any case, minimization was also done by using different relative permittivity values[14] (5.6 for chloroform, and 11.2), even though the results thus obtained did not substantially improve the prior calculations.

The procedure used to search for minima was based on the rotation of the sugar moiety with respect to the base about the glycoside bond, because the sugar-base interaction was assumed to be prominent and to contribute the most to the overall energy. Previously, relative position of the acetates and sugar were optimized in order to minimize the interactions between them.

Molecular mechanics analysis of the four compounds **1**, **1a**, **2**, and **2a**, provided the geometries and energies shown in Tables 3 and 4. In the case of compound **1** two minima were found, at χ 156.1° (*anti*-conformer), and χ -11.7° (*syn*-conformer), with an equilibrium rotational energy barrier of 14.8 kcal mol^{-1} between them (calculated from the plot of *E versus* χ). The population distribution for each minimum, calculated from the Boltzmann equation, was 78% for the *anti*-conformer and 22% for the *syn*-conformer. In the same way, compound **1a** showed the *anti*-conformer at χ -127.4°, and the *syn*-conformer at χ -12.3°, but with a population distribution of 100%:0% for the *anti*-conformer and a rotational barrier of 34.4 kcal mol^{-1}, due to the larger volume of the sulphur atom. The calculated values for the arabinosyl derivatives, **2** and **2a**, were very similar to those obtained for **1** and **1a** : the *anti*-conformers were found at χ -147.8° and -142.4°, and the *syn*-conformers at χ 12.3° and 16.4°, respectively; the population distribution for compound (**2**) (*anti*) 82%:18% (*syn*), and for compound **2a** (*anti*) 100%:0% (*syn*), with rotational energy barriers of 15.0 and 38.5 kcal mol^{-1}, respectively.

TABLE 2. Computed proton-proton distances (Å), nOe (%), and torsion angles (°) for compounds **1**, **1a**, **2** and **2a**.

Compound	Protons	Å	nOe	χ
1/*anti*	H-8, H-2'	2.86	6	156.1
1/*syn*	H-8, H-1'	2.53	2	-11.7
1a/*anti*	H-8, H-2'	2.15	10	-127.4
2/*anti*	H-8, H-2'	3.06	6	-147.8
2/*syn*	H-8, H-1'	2.50	2	12.3
2a/*anti*	H-8, H-2'	3.11	9	-142.4



1, **1a** **2**, **2a**

TABLE 3. Results obtained by line-shape, and ^{1}H NMR (exp.), and molecular mechanics analysis (calc.) for **1**, **1a**, **2** and **2a**.

Compound	Conformer	$Pop_{calc.}$ %	$Pop_{exp.}$ %	$\Delta G^*_{calc.}$ Kcal/mol	$\Delta G^*_{exp.}$ Kcal/mol
1	*anti*	78	80	14.8	11.7
	syn	22	20		
1a	*anti*	100	100	34.3	---
	syn	0	0		
2	*anti*	82	79	15.0	11.8
	syn	18	21		
2a	*anti*	100	100	38.5	---
	syn	0	0		

The molecular mechanics results are reasonably consistent with those obtained in the NMR experiments. Therefore, the combined use of molecular mechanics analysis and NMR techniques constitutes a useful method for studying *syn-anti* equilibria and molecular geometries in high molecular crowding nucleosides.

Experimental

Melting points were determined on a Gallenkamp instrument and are uncorrected. Optical rotations were measured by using a Perkin-Elmer Model 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. UV spectra were recorded on a Hewlett-Packard 8452A

TABLE 4. Principal geometrical features of the minimum-energy conformers of compounds **1**, **1a**, **2** and **2a**.

Conf.	E	Gly*	Acetates*								
	Kcal/mol	χ	a	b	c	d	e	f	g	h	i
1/*anti*	41.853	156.1	56.4	-33.3	-28.1	-23.9	32.7	-11.6	-67.6	174.2	-0.9
1/*syn*	42.471	-11.7	56.8	-31.9	-28.1	-26.4	32.7	-11.1	-67.7	173.5	-0.6
1a/*anti*	44.577	-127.4	57.0	-27.7	-26.1	-28.5	28.9	-5.6	-65.6	174.0	0.5
1a/*syn*	51.693	-12.3	54.9	-29.5	-28.0	-25.8	31.7	-9.5	-66.7	175.5	-1.2
2/*anti*	28.103	-147.8	-33.0	-109.0	41.4	104.1	-35.6	54.3			
2/*syn*	28.780	12.3	-5.3	59.3	34.1	103.8	-40.0	54.8			
2a/*anti*	31.210	-142.4	24.0	2.6	-67.0	48.5	-48.2	32.6			
2a/*syn*	37.712	16.4	36.3	-32.8	-52.9	58.7	-49.0	49.7			

*Angles in °, χ =H1'-C1'-N7-C8, a=H2'-C2'-O2'-C2", b=C2'-O2'-C2"-O2", c=H3'-C3'-O3'-C3", d=C3'-O3'-C3"-O3", e=H4'-C4'-O4'-C4", f=C4'-O4'-C4"-O4", g=H5'-C5'-C5"-O5', h=C5'-C5"-O5'-C5"', i=C5"-O5'-C5"'-O5".

spectrophotometer, and IR spectra were recorded on a Perkin-Elmer 883 spectrophotometer. Mass spectrometry was carried out on a HP-MS 5988A instrument using the direct injection and electron-impact (EI) modes. The NMR spectra were obtained on Bruker WP-200 SY instrument at 200 MHz for ^{1}H and 50 MHz for ^{13}C. Variable temperature NMR spectra were obtained in a sealed nmr tube using a 0.2 M sample. ^{1}H Chemical shifts (δ_H) are given in ppm, relative to either residual $CHCl_3$ (δ_H 7.24) in deuteriochloroform, or residual HOD (δ_H 4.80) in dideuterium oxide. ^{13}C Chemical shifts (δ_C) are given in ppm, relative to either $CDCl_3$ (δ_C 77.0) in deuteriochloroform, or CD_3COCD_3 (δ_C 29.8) in dideuterium oxide. For the nOe measurements, the solutions (ca. 0.1M) were degassed by bubbling N_2 through, followed by ultrasound sonication. nOe measurements (irr. of H-8) were run on these nucleosides in $CDCl_3$. All compounds were measured under identical spectral and processing conditions by applying the NOEDIFF pulse sequence of the Bruker software package (release version 1989) applying its recommendations for steady-state nOe measurements. An irradiation time of 1.0 s with an irradiation power of 40-50 dB below 0.2 W yielded a saturation of < 95%. The analysis of spectral data was performed by subtraction of two FIDS followed by exponential multiplication and fourier transformation of the differential FIDS. All nOe values were obtained by repeated integration of the peaks of the difference spectra. Molecular mechanics calculations were carried out by running the Chem-X software (copyright 1992, Chemical Design Ltd, Oxford, UK) on a Silicon Graphics model 4D/420VGX computer. TLC analyses were performed on silica gel 60 F 254 plates and column chromatography was carried out on silica gel 60 (70-230 mesh).

7-(2 ,3 ,4, 6-tetra-O-acetyl-β-D-glucopyranosyl)theophylline (**1**).- 0.50 g of 7-β-D-glucopyranosyltheophylline[10] were dissolved in a solution of acetic anhydride (6 ml) and pyridine (2 ml). The reaction mixture was kept at rt for 24 h. After this period, the solvents were removed at low pressure; then water (8 ml) was added to the residue, followed by evaporation to dryness. The same procedure was carried out twice with methanol in order to obtain a solid foam. Recristallization from ethanol gave title compound **1** in 78% yield, m.p. 145-7 °C (lit.,[15] m.p. 146-8 °C); $[\alpha]_D^{24}$ -17° (c 1, $CHCl_3$) (lit.,[15] $[\alpha]_D$ -17°); δ_H ($CDCl_3$) 7.85 (s, 1 H, H-8), 6.10 (br d, 1 H, H-1'), 5.61 (br pt, 1 H, H-2'), 5.35 (pt, *J* 9.6-9.6 Hz, 1 H, H-3'), 5.20 (pt, *J* 9.6-9.6 Hz, 1 H, H-4'), 4.15 (dq, 2 H, H-6', 6''), 3.95 (m, 1 H, H-5'), 3.50 and 3.35 (two s, 3 H each, N-C$\underline{H}_3$) and 2.00-1.85 (four s, 3 H each, 4 C$\underline{H}_3$ acetates); δ_C ($CDCl_3$) 154.6 (C-6), 151.3 (C-2), 148.9 (C-4), 139.7 (C-8), 106.5 (C-5), 82.1 (C-1'), 74.8 (C-5'), 72.9 (C-3'), 70.1 (C-2'), 67.6 (C-4'), 61.4 (C-6'), 29.8 and 28.0 (N-$\underline{C}H_3$).

7-(2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosyl)-6-thiotheophylline (**1a**).- A mixture of compound **1** (0.25 g, 0.5 mmol), LR (0.2 g, 0.5 mmol), and dry distilled toluene (20 ml) was refluxed until complete disappearance of the starting material. The reaction was monitored by tlc. Additional LR (0.5 mmol) was required at 48 h. Toluene was removed under reduced pressure, and the residue was separated by silica gel column chromatography, using first ethyl ether:acetone (LR and its by-products were separated) and then chloroform as eluents. The isolated product was recrystallized from methanol as yellow crystals, yield 69%, m.p. 132-4 °C; $[\alpha]_D^{20}$ -47° (c, 0.56 $CHCl_3$); (Found C, 47.85; H, 5.02; N, 10.49. $C_{21}H_{26}N_4O_{10}S$ requires C, 47.90; H, 4.97; N, 10.64%); EI *m/z*: 526 (10%, M^+), 407 (21), 331 (21), 197 (84), 196 (6), 169 (100), 127 (24), 109 (67); ν_{max} (KBr)/cm^{-1} 1750, 1700, 1650, 1200; λ_{max} ($CHCl_3$)/nm 344 (ε 14200); δ_H ($CDCl_3$) 8.10 (s, 1 H, H-8), 7.38 (d, *J* 9.7 Hz, 1 H, H-1'), 5.58 (t, *J* 9.7 Hz, 1 H, H-2'), 5.42 (t, *J* 9.7 Hz, 1 H, H-3'), 5.20 (t, *J* 9.7 Hz, 1 H, H-4'), 4.25 (dd, *J* 12.6-4.7 Hz, 1 H, H-6'), 4.16 (dd, *J* 12.6-1.0 Hz, 1 H, H-6''), 4.11 (o, *J* 9.7-4.7-1 Hz, 1 H, H-5'), 3.85 and 3.65 (two s, 3 H each, N-C$\underline{H}_3$) and 2.07-1.95 (four s, 3 H each, C$\underline{H}_3$ acetates); δ_C ($CDCl_3$) 176.8 (C-6), 170.4, 169.7 and 169.3 (C=O acetates), 149.8 and 145.3 (C-2 and C-4), 141.5 and 116.7 (C-8 and C-5), 80.4 (C-1'), 74.3 (C-5'), 73.6, 69.6, 68.0 (C-2', C-3', C-4'), 61.5 (C-6'), 34.2 and 30.4 (N-$\underline{C}H_3$), and 20.1, 20.0, 19.9 ($\underline{C}H_3$ acetates).

7-(β-D-glucopyranosyl)-6-thiotheophylline (**1b**).- 0.1 g (0.2 mmol) of **1a** were solved in 10 ml of methanol, then 3 ml of sodium methoxide in methanol (0.16 M) were added. The reaction was stirred at rt for 12 h. After this time, the precipitate appeared **1b** was filtered

and recrystallized from methanol (90 % yield). M.p. 252-4 °C; (Found C, 43.48; H, 5.03; N, 15.57. $C_{13}H_{18}N_4O_6S$ requires C, 43.57; H, 5.06; N,15.63%); EI *m/z* 358 (1%, M^+), 196 (6-thioth-H^+, 100); ν_{max} (KBr)/cm^{-1} 3500-3200 (OH asoc.), 1650, 1600; λ_{max} ($CHCl_3$)/nm 360 (e 18000); δ_H (D_2O) 8.21 (s, 1 H, H-8), 6.90 (d, *J* 9.6 Hz, 1 H, H-1'), 3.75 (t, *J* 9.6 Hz, 1 H, H-2'), 3.60-3.25 (m, 5 H, sugar), 3.51 and 3.32 (two s, 3 H each, N-C$\underline{H}_3$); δ_C (D_2O) 177.0 (C-6), 152.0 (C-2), 146.0 (C-4), 144.5 (C-8), 118.5 (C-5), 83.0 (C-1'), 79.0, 77.5, 72.5, and 70.0 (C-5', C-2', C-3', and C-4'), 61.5 (C-6') and 35.0 and 31.5 (N-$\underline{C}H_3$).

7-(2, 3, 4-tri-O-acetyl-α-D-arabinopyranosyl)theophylline (**2**).- Compound **2** was obtained from 7-α-D-arabinopyranosyltheophylline[10] (0.50 g) by treatment with acetic anhydride (6 ml) in pyridine (2 ml), following the same procedure as for **1**. Yield 84%. δ_H ($CDCl_3$) 7.93 (1 H, s, H-8), 6.07 (1 H, bd, *J* 9.0 Hz, H-1'), 5.71 (1 H, bt, *J* 9.0 Hz, H-2'), 5.48 (1 H, m, H-4'), 5.21 (1 H, dd, *J* 9.0-3.0 Hz, H-3'), 4.12 (1 H, dd, *J* 9.0-1.5 Hz, H-5_{ax}), 3.92 (1 H, dd, *J* 9.0-0.5 Hz, H-5_{eq}), 3.62 and 3.43 (6 H, 2 s, 2 N-C$\underline{H}_3$), 2.21, 2.02 and 1.92 (9 H, 3 s, 3 COC$\underline{H}_3$); δ_C ($CDCl_3$) 154.8 (C-6), 151.4 and 148.8 (C-2 and C-4), 140.0 (C-8), 106.4 (C-5), 82.9 (C-1'), 70.9 (C-3'), 68.2, 67.8 (C-2', C-4'), 67.2 (C-5'), 29.9 and 28.0 (N-$\underline{C}H_3$).

7-(2, 3, 4-tri-O-acetyl-α-D-arabinopyranosyl)-6-thiotheophylline (**2a**).- 0.25 g (0.5 mmol) of **2** were treated with 0.2 g (0.5 mmol) of LR in 20 ml refluxing, dry and distilled toluene. The reaction was monitored by tlc. Additional LR (0.5 mmol) was required at 24 h. Toluene was removed under reduced pressure. The residual product was separated and purified by silica gel column chromatography. Eluents, first ethyl ether:acetone (LR and its by-products were separated) and then chloroform. The product was recrystallized from methanol as yellow crystals (60%). M.p. 158-60 °C; $[\alpha]_D^{24}$ -45.5 (c, 0.4 $CHCl_3$); (Found C, 47.48; H, 4.79; N, 12.14. $C_{18}H_{22}N_4O_8S$ requires C, 47.57; H, 4.88; N, 12.33%); EI *m/z* 454 (10%, M^+), 407 (21), 331 (21), 197 (100), 196 (75), 139 (24), 97 (67); ν_{max} (KBr)/cm^{-1} 1750, 1700, 1650, 1200; λ_{max} ($CHCl_3$)/nm 344 (ε 15500); δ_H ($CDCl_3$) 8.10 (s, 1 H, H-8), 7.42 (d, *J* 9.7 Hz, 1 H, H-1'), 5.72 (pt, *J* 9.7 Hz, 1 H, H-2'), 5.45 (m, 1 H, H-4'), 5.31 (dd, *J* 9.7-4.3 Hz, 1 H, H-3'), 4.12 (dd, *J* 12.6-2.0 Hz, 1 H, H-5'), 4.02 (dd, *J* 12.6-1.0 Hz, 1 H, H-5''), 3.85 and 3.65 (two s, 3 H each, N-C$\underline{H}_3$) and 2.24, 2.07, 1.95 (three s, 3 H each, C$\underline{H}_3$ acetates); δ_C ($CDCl_3$) 176.8 (C-6), 170.0, 169.6 and 169.5 (C=O acetates), 149.9 and 145.3 (C-2 and C-4), 142.3 (C-8), 116.7 (C-5), 81.4 (C-1'), 71.5 (C-3'), 68.3, 68.2 (C-2', C-4'), 66.9 (C-5'), 34.2 and 30.4 (N-$\underline{C}H_3$), and 20.8, 20.4 ($\underline{C}H_3$ acetates).

7-(α-D-arabinopyranosyl)-6-thiotheophylline (**2b**).- 0.12 g (0.26 mmol) of **2a** were solved in 7 ml of methanol, and 3 ml of a solution of sodium methoxide in methanol (0.16 M) were added. The solution was stirred at rt for 24 h, and the precipitate that appeared was filtered. Recrystallization from methanol gave pure **2b** in 70% yield. M.p. 256-8 °C; $[\alpha]_D^{24}$ -28.5 (c, 0.3 water); (Found C, 43.78; H, 5.05; N, 16.91. $C_{12}H_{16}N_4O_5S$ requires C, 43.90; H, 4.91; N,17.06%); EI *m/z* 328 (5, M^+), 197 (100, 6-thioTh-H^+), 196 (35, thio-Th^+); ν_{max} (KBr)/cm^{-1} 3600-3250 (OH), 1630, 1600; λ_{max} ($CHCl_3$)/nm 344 (ε 18300); δ_H (D_2O) 8.31 (s, 1 H, H-8), 6.83 (d, *J* 9.6 Hz, 1 H, H-1'), 4.09 (pt, *J* 9.6 Hz, 1 H, H-2'), 3.90 (m, 1 H, H-4'), 3.81 (s, 2 H, H-5' and H-5'') and 3.70 (dd, *J* 9.6-3.0 Hz, H-3'), 3.56 and 3.40 (two s, 3 H each, N-C$\underline{H}_3$); δ_C (D_2O) 177.3 (C-6), 152.0 (C-2), 146.0 (C-4), 144.8 (C-8), 118.6 (C-5), 84.2 (C-1'), 74.0, 70.3, 70.7 (C-2', C-3', and C-4'), 69.8 (C-5') and 35.0 and 31.5 (N-$\underline{C}H_3$).

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