Synthesis of 8-Methyl-6-thio-7-(β-D-xylopyranosyl)theophylline. Conformational Study of its Peracetyl Derivatives. Molecular Mechanics Calculations and Minimum-Energy Geometries of 8-Methyl-7-(2',3',4'-tri-*O*-acetyl-β-D-xylopyranosyl)theophylline and 8-Methyl-6-thio-7-(2',3',4'-tri-*O*-acetyl-β-D-xylopyranosyl)theophylline

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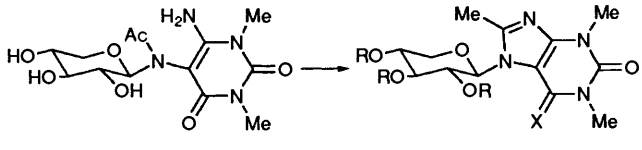
The synthesis of a thioxanthine nucleoside, 8-methyl-6-thio-7-(β-D-xylopyranosyl)theophylline, is reported. The triacetyl derivatives, **3** and **4**, exhibit major molecular crowding and restricted rotation about the glycoside bond. The stability of the rotamers and the *syn–anti* equilibrium were studied by molecular mechanics. The results obtained were quite consistent with those provided by the line-shape method.

Xanthine and thioxanthine are compounds of great interest on account of their biological activity. Our group has lately been concerned with the preparation of theophylline and thiotheophylline nucleosides. In previous work[1] we synthesized 7-glycosyl-8-methyltheophylline derivatives from 4-amino-5-[(glycosyl)acetylamino]uracils following the original procedure developed by Todd for preparing purine nucleosides by cyclization of an imidazole ring with an 5-amino-4-[(glycosyl)-aminopyrimidine. We found that Lawesson's reagent[2a] replaces the 6-oxo group in caffeine effectively with a thioxo group even though the alkaloid possesses no enolizable group. We exploited this finding by preparing 8-methyl-6-thiotheophylline nucleosides, using glucose and galactose as sugar moieties under moderate reaction conditions.[2]

In this work, application of the previous procedure was extended to the synthesis of 8-methyl-7-(β-D-xylopyranosyl)-6-thiotheophylline, some interesting conformational aspects of which were studied by using a molecular mechanics program.

Results and Discussion

In previous work[3] we synthesized 8-methyl-7-(β-D-xylopyranosyl)theophylline **2** from 6-amino-1,3-dimethyl-5-[N-(β-D-xylopyranosyl)acetamido]uracil **1** by treatment with sodium methoxide. Acetylation of compound **2** with acetic anhydride and pyridine yielded 8-methyl-7-(2',3',4'-tri-*O*-acetyl-β-D-xylopyranosyl)theophylline, **3**, the spectral data of which are described below.



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2 R = H, X = O
3 R = Ac, X = O
4 R = Ac, X = S
5 R = H, X = S

The EI mass spectrum of compound **3** exhibited the molecular-ion peak at *m/z* 452 (4%, M^+) and those for two ions corresponding to the cleavage of the glycoside bond, at *m/z* 194 (39%, base moiety) and *m/z* 259 (26%, triacetylxylose moiety). Cleavage of the glycoside bond of this nucleoside gave 8-methyltheophylline ion, with *m/z* 194, which is consistent with protonation of the base moiety. Two different groups of ions were observed that arose from fragmentation of triacetylxylose, *m/z* 199 (23%, 259 – AcOH), 157 (58%, 199 – CH_2CO), 139 (67%, 259 – 2 AcOH) and 97 (100%, 139 – CH_2CO) and the purine moiety, *m/z* 137 (4%, 194 – MeNCO) and 109 (10%, 137 – CO). This sequence is similar to that reported for caffeine,[4] which is an isomer of 8-methyltheophylline. The acetyl-group ion at *m/z* 43 accounts for only a negligible proportion of the ion current.

The ^{13}C NMR spectrum showed 19 signals corresponding to 19 carbon atoms present in the molecule, *viz.* δ_C 169.7, 169.6 and 169.0 for the acetate carbonyls; 154.6 (C-6), 152.1 (C-8), 151.5 (C-2), 148.5 (C-4) and 106.8 (C-5) ppm for the purine base; 83.1 (C-1'), 72.7 (C-2'), 70.3 (C-3'), 68.6 (C-4', which defines the pyranosyl ring), and 65.7 (C-5') ppm for the five carbons in the sugar moiety; 29.7 and 28.1 ppm the NMe groups; 20.5, 20.5 and 20.1 ppm for the methyl groups in the acetates; and 15.2 ppm for the methyl group at C-8.

The ^1H NMR spectrum (Fig. 1b) shows the following signals: δ_H 1.83, 2.03 and 2.05, three singlet signals of three-protons intensity, corresponding to the three acetyl groups; 2.63 ppm, broad singlet, three-protons intensity, for the methyl group at C-8; 3.40 and 3.54 ppm, singlets, three-protons intensity, corresponding to the N-methyl groups at N-1 and N-3 in the purine ring. As shown in Fig. 1b, these are the only well defined signals in addition to a pseudo-triplet at 3.6 ppm (5'-H_{ax}), a double doublet at 4.3 ppm (5'-H_{eq}), a pseudo-triplet at 5.4 ppm, and a broad signal at 5.2 ppm. Integration between 6.5 and 5.5 ppm gave poor results.

The absence of signals for protons 1'-H and 2'-H, and the broadened signals in the ^1H NMR spectrum for compound **3** obtained in $CDCl_3$ at room temperature, may be due to the occurrence of various conformers.

Treatment of compound **3** with Lawesson's reagent (LR) in refluxing toluene afforded 8-methyl-6-thio-7-(2',3',4'-tri-*O*-acetyl-β-D-xylopyranosyl) theophylline, **4**, the spectral data for which are described below.

The EI mass spectrum for compound **4** was similar to that for analogue **3**, and included the following ions: *m/z* 468 (12%, M^+); 210 (35%), corresponding to 8-methyl-6-thiotheophylline, as expected for oxygen–sulfur replacement; and the same sequence for the sugar moiety from the ion at *m/z* 259 (12%), and the base peak at *m/z* 97 (100%), as noted earlier for compound **3**.

The UV spectrum exhibited a maximum at 342 nm that is consistent with the proposed structure.

The ^{13}C NMR spectrum showed the 19 following signals: one signal δ_C 175.7 (C-6), which confirms replacement of one oxygen atom by one sulfur atom at that position; three signals at δ_C

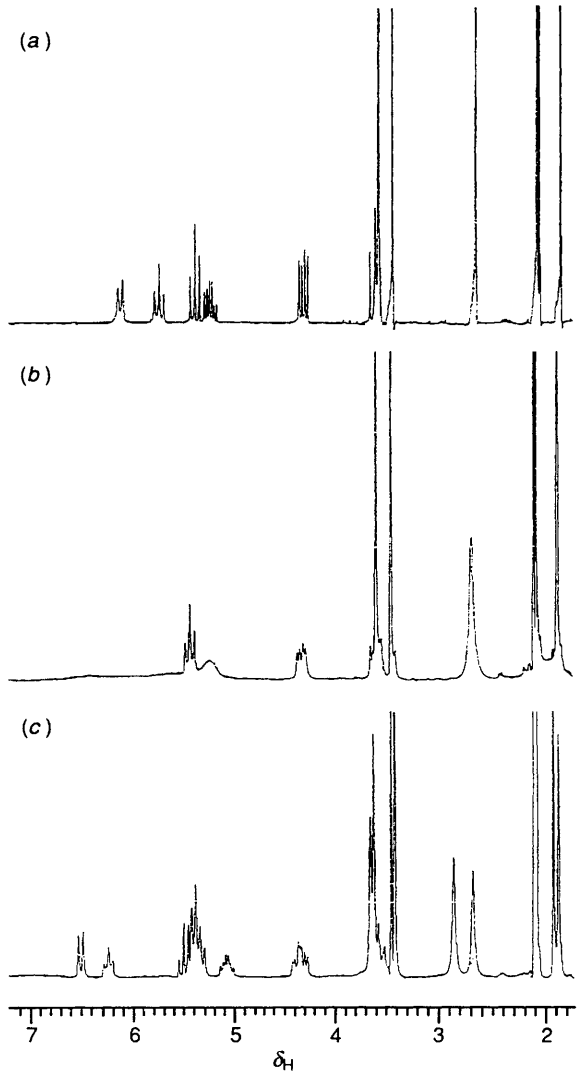


Fig. 1 ^{1}H NMR ($CDCl_3$) spectra of compound **3**, (a) 333 K, (b) 296 K and (c) 243 K

Table 1 ^{13}C Chemical shifts (δ_C/ppm) for compounds **3** and **4**

Compound	C-2	C-4	C-5	C-6	C-8
3	151.5	148.5	106.8	154.6	152.1
4	149.9	144.7	117.3	175.7	155.8

169.8, 169.6 and 169.6 corresponding to the carbonyls in the three acetate groups; four signals at 155.8 (C-8), 149.9 (C-2), 144.7 (C-4) and 117.3 (C-5) ppm for the purine ring; five signals at 81.0 (C-1'), 72.7 (C-2'), 69.8 (C-3'), 69.0 (C-4') and 65.6 (C-5') ppm from the xylopyranosyl moiety; two signals at 34.2 and 30.3 ppm corresponding to N-methyl groups; three signals at 20.8, 20.5 and 20.2 ppm for the methyl groups in the acetates; and one signal at 16.8 ppm for the methyl group at C-8 in the purine ring. It should be noted that the signal at 175.7 ppm, corresponding to the thiocarbonyl group at C-6 in the purine ring, is shifted by 21 ppm downfield[5] relative to that for compound **2**. The signal for the C-5 atom is also markedly affected (shifted 10 ppm downfield). The chemical shifts for the other carbons were also affected, though less significantly (Table 1).

The ^{1}H NMR spectrum (Fig. 2) showed the following signals: δ_H 8.11, a multiplet (eight signals) integrating to one proton. A

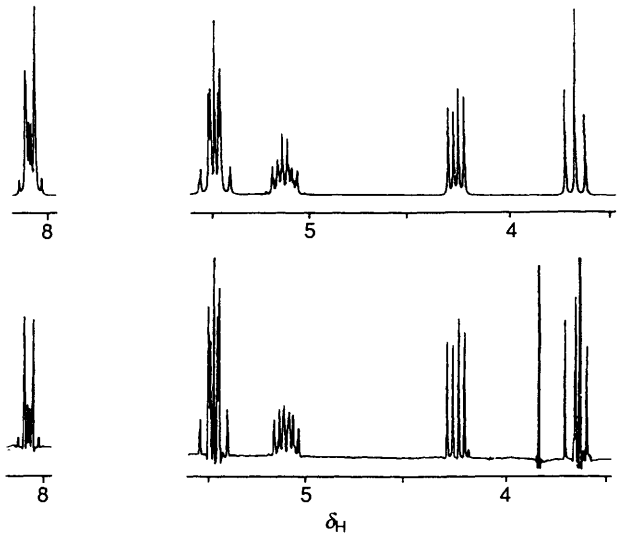


Fig. 2 ^{1}H NMR spectrum of compound **4**. Simulated (top), and experimental (bottom).

multiplet (nine signals) appeared between 5.39 and 5.53 ppm, integrating for two protons. Based on the reported chemical shifts for thionucleosides,[2,6] the proton at 8.11 ppm must be 1'-H, and the multiplet between 5.39 and 5.53 ppm must be due to protons 2'-H and 3'-H. However, the 1'-H signal must be a doublet, consistent with one *trans*-diaxial coupling, and 2'-H and 3'-H signals must be two pseudo-triplets corresponding to two *trans*-diaxial couplings. A pseudo-sextet appeared at 5.07 ppm that integrates to one proton and was assigned to 4'-H, consistent with coupling to 3'-H (J 10.3 Hz), 5'-H_{ax} (J 10.3 Hz) and 5'-H_{eq} (J 5.7 Hz). A double doublet at 4.20 ppm, integrating to one proton, was also observed, and was assigned to 5'-H_{eq} coupled with 5'-H_{ax} (J 10.3 Hz) and 4'-H (J 5.7 Hz). A pseudo-triplet at 3.60 ppm, integrating to one proton, was assigned to 5'-H_{ax} coupled with 5'-H_{eq} and 4'-H (J 10.3 Hz). Finally, six three-proton singlets appeared at δ_H 3.78, 3.57, 2.04, 2.02, 1.78 and 2.73 ppm, corresponding to two NMe, three acetyl groups, and one methyl group at C-8, respectively.

On the assumption of first-order coupling, the predicted spectrum was consistent with its experimental counterpart except for the 1'-H, 2'-H and 3'-H signals. Although the chemical shifts were predictable, the multiplicity was not. For 2'-H and 3'-H, this can be ascribed to the relationship between the resonance frequency and the coupling constant: the frequency range over which 2'-H and 3'-H appeared was 28 Hz wide, and ~20 Hz for a pseudo-triplet, so the ratio was not large enough for a first-order approximation. This accounts for the anomalous multiplicity of the signals.

The anomalous multiplicity of the anomeric proton signal, which should be a doublet, can be ascribed to 'virtual coupling' between 1'-H and 3'-H. Virtual coupling occurs when a three-proton system exists[7] where each proton is attached to a vicinal carbon atom and two of these protons are strongly coupled and have similar chemical shifts. These prerequisites are met by this system.

The simulated spectrum provided by PANIC (BRUKER), Fig. 2, confirmed the assumed virtual coupling between 1'-H and 3'-H and the three-proton multiplicity.

Deprotection of triacetate **4** was accomplished by treatment with sodium methoxide in methanol at room temperature, and gave the thiopurine nucleoside 8-methyl-6-thio-7-(β-D-xylopyranosyl)theophylline, **5**, the structure of which was confirmed by the spectral data given below.

The EI mass spectrum included two major ions, *viz.* one at

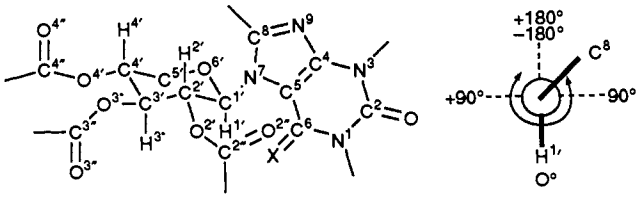


Fig. 3 Angle definition for compounds **3** and **4**

m/z 342 (9%, M^+) and the other one at *m/z* 210 (100%, 8-methyl-6-thiotheophylline). Other ions were seen in the spectrum, but their intensities were much lower. The observed fragmentation was consistent with those reported for 7-glycosylpurines, where cleavage of the C(1')–N(7) bond is easier than in 9-glycosylpurines.

The IR spectrum showed the absorption band for the OH group stretching (3350 cm^{-1}), which confirmed deacetylation. No absorption from the acetate C=O was observed.

The UV spectrum exhibited two maxima: one at 221 nm and the other at 342 nm, consistent with the proposed structure.

The ^{13}C NMR spectrum showed 13 signals corresponding to the 13 carbons in the molecule: δ_C 175.0 (C-6), 156.6 (C-8), 150.7 (C-2), 144.4 (C-4) and 118.4 (C-5) ppm for the five carbons in the purine ring; 83.3 (C-1'), 77.0 (C-2'), 71.6 (C-3'), 69.3 (C-4') and 68.5 (C-5') ppm for the xylopyranosyl moiety; and 33.8 (N-3), 30.7 (N-1) and 16.2 (C-8) ppm for three methyl groups.

The ^1H NMR spectrum (D_2O) showed the following signals: δ_H 7.55, a doublet (1 H, *J* 9.5 Hz) for the anomeric proton; between 4 and 3 ppm, multiplets for the potons in the pyranosyl ring; 3.49 and 3.33 ppm, two singlets for three protons corresponding to the two NMe groups, and 2.48 ppm, a three-proton singlet for the methyl group at C-8.

Line-shape Analysis.—Two primary aspects were considered in dealing with the conformation of the nucleosides in solution, *viz.* one related to the dihedral angles of the sugar, and the other associated with the relative orientation of the base and sugar about the glucoside bond. These were analysed some years ago, and have been the subject of much theoretical and experimental work.[8]

Examination of the molecular model for compound **3** revealed high molecular crowding and impeded rotation about the C(1')–N(7) bond. Two conformers seem to be subject to less marked steric interactions about the dihedral angle τ [H(1')–C(1')–N(7)–C(8)] *viz.* the *syn* and *anti* conformer.

We defined the *syn* conformer as that with a dihedral angle $\tau = 0°$ with 1'-H and C-8 in a *syn*-coplanar arrangement and the *anti* conformer that at $\tau = 180°$, with 1'-H and C-8 in an *anti*-periplanar layout. Consequently, the *syn* region was $\tau = 0 \pm 90°$ and *anti* region $\tau = 180° \pm 90°$ (Fig. 3).

In order to confirm the existence of the two postulated rotamers for compound **3**, a ^1H NMR spectrum was recorded at low temperature, where no 1'-H or 2'-H signal was observed and the methyl group at C-8 appeared as a broad singlet. The spectrum recorded at 243 K (Fig. 1c) showed a doublet at δ 6.48, *J* 9.1 Hz, integral 0.5 H; 6.21 ppm, a triplet, integral 0.5 H; 5.6–5.2 ppm, a multiplet, integral 2.5 H; 5.03 ppm, a multiplet, integral 0.5 H; 4.31 ppm, a multiplet, integral 1 H; 2.83 ppm, a singlet, integral 1.5 H; and 2.65 ppm, a singlet, integral 1.5 H. The doublet at 6.48 ppm must be due to the anomeric proton of the *anti* conformer, and the triplet at 6.21 ppm to 2'-H in the *syn* conformer through deshielding of the anisotropic effect of the 6-carbonyl group. The multiplet between 5.6 and 5.2 ppm corresponds to 3'-H for both conformers (the chemical shift of which is not appreciably affected), 2'-H for the *anti* conformer, 4'-H and 1'-H for the *syn* conformer. The multiplet at 5.03 ppm corresponds to 4'-H for the *anti* conformer. The broad singlet in the room-temp. spectrum at 2.63 ppm corresponding to the methyl group on C-8 was clearly split into two narrow signals at 2.83 and 2.65 ppm. Three other signals were split, that for the methyl group in the acetate at C-2', and those for both methyl groups at N-1 and N-3.

The signals in the spectrum recorded at 333 K (Fig. 1a) were narrower. Their chemical shifts were as follows: δ 6.12 ppm, a doublet, *J* 9.2 Hz, 1'-H; 5.73 ppm, a pseudo-triplet, *J* 9.2 Hz, 2'-H; 5.37 ppm, a pseudo-triplet, *J* 9.2 Hz, 3'-H; 5.22 ppm, a sextet, 4'-H; 4.28 ppm, a double doublet, *J* 11.3 and 5.5 Hz, 5'-H_{eq}; 3.50 ppm, a pseudo-triplet, *J* 11.3 Hz, 5'-H_{ax}; 3.53 and 3.40 ppm, two singlets, two NMe; 2.61 ppm, a singlet, 8-Me; and 2.03, 2.01 and 1.80 ppm, three singlets, three acetates.

These spectra confirmed the occurrence of a *syn–anti* equilibrium at room temperature. From the spectrum recorded at 243 K, a 47% proportion of the *syn* conformer and 53% for the *anti* conformer was obtained. Also, an increase in temperature by 40 °C over ambient enabled free rotation around the glycoside bond to occur.

In order to study the above mentioned equilibrium, ^1H NMR spectra were recorded at various temperatures from 228 to 333 K with $CDCl_3$ as solvent. Kinetic parameters were obtained by line-shape analysis.[9] Since the signal for the methyl group at C-8 was a singlet not involved in any coupling, it was good enough for calculating accurate values.

The rate constants K_v were calculated by taking ν_{AB} to be the difference in chemical shift (Hz) between the methyl protons at C-8 in both *anti* and *syn* rotamers, at temperatures where the difference was constant (ν_{AB} was obtained from the values at 248 and 256 K; ν_{AB} = 31.89 Hz), and $\delta\nu$ as the corrected linewidth, also in Hz. The coalescence temperature (T_c) was calculated from a plot of ν_{AB} *versus* *T*, and found to be 283 K (at temperatures near coalescence). The activation parameters ΔH^*, ΔS^* and ΔG^* were calculated from the Eyring equation[10] for the absolute reaction-rate theory using least-squares linear regression analysis (r^2 = 0.997). The transmission coefficient used was unity. The results obtained are shown in Table 2.

The ΔG^*-value, 13.9 kcal/mol,† defines a rotational energy barrier that accounts for a *syn–anti* equilibrium at room temperature. Such an equilibrium was, for compound **4**, not observed: only one rotamer was found to exist at room temperature. Long-range selective proton decoupling (LSPD) is reported as an efficient method for determining *syn* and *anti* conformers of nucleosides.[11] Thus, an LSPD experiment was carried out on compound **4**. The coupling constant between 1'-H and C-8 was 5.9 Hz, consistent with reported data for the *anti* conformation.[11]

Molecular Mechanics Calculations.—Empirical force-field molecular mechanics calculations procedures are frequently used to calculate the energies and geometries for hydrocarbons and other types of molecules containing various heteroatoms. In combination with NMR techniques, they make excellent methods for elucidating the stereochemistry of compounds including, their conformations at equilibrium.[12] We used the Chem-X program with an MME-type force-field similar to Allinger's MM2.

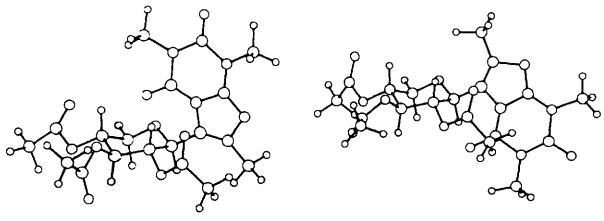
The procedure used to search for minima for both compounds **3** and **4** was based on the rotation of the sugar moiety with respect to the base about the glycoside bond because the sugar–base interaction was assumed to be prominent and to contribute the most to the overall energy. This was followed by a fine minimization at each point. Before each minimum was processed, the relative positions of the acetates and sugar were

† 1 cal = 4.184 J.

Table 2 Line-shape analysis: corrected linewidth, rate constants, and activation parameters for compound **3**

Temp. (T/K)	$\delta\nu$/Hz	K_v/s^{-1}	ΔH^*/kcal mol^{-1}	ΔS^*/cal mol^{-1} K^{-1}	ΔG^*/kcal mol^{-1}
228	2.20	6.912			
248	1.98	6.236			
256	3.36	10.556			
268	13.27	41.705			
273	17.40	54.664			
283	Coalescence	temperature (T_c)	11.3	−9.3	13.9
296	7.33	217.934			
313	2.14	746.475			
333	0.30	5324.853			

Table 3 Principal geometrical features of the minimum-energy conformers of compound **3**



syn-conformer *anti*-conformer

Conformer	E_{MME}/ kcal mol^{-1}	E_{rel}/ kcal mol^{-1}	Pop. (%)	Gly. bond[a] τ	Acetates[a] a	b	c	d	e	f
anti	35.741	0.334	3.729	152.8	−27.6	−9.3	−29.4	−25.6	46.4	−13.1
	35.720	0.313	3.859	152.4	−36.3	14.6	−29.1	−25.6	45.6	−12.6
	35.802	0.395	3.367	155.2	41.9	−27.9	−43.0	8.9	53.3	−20.0
	35.720	0.312	3.864	161.1	37.4	0.3	−40.7	11.6	45.9	−15.7
	35.806	0.399	3.343	160.6	37.2	−11.5	−45.0	20.1	44.6	−3.1
	35.976	0.569	2.512	152.2	−30.3	5.3	−27.6	−24.7	49.6	−18.8
	35.700	0.292	3.997	154.2	−38.1	19.1	−28.2	−22.2	46.6	−19.4
	35.974	0.567	2.521	151.6	−22.3	−20.2	−35.6	−8.1	50.6	−28.5
	35.758	0.351	3.622	152.2	33.0	5.2	−28.0	−22.9	46.2	−15.9
	35.676	*0.269*	*4.158*	*154.2*	*−35.0*	*10.5*	*−24.6*	*−21.3*	*44.8*	*−21.6*
	35.913	0.506	2.794	151.3	−29.3	13.5	−26.7	−20.1	48.8	−20.5
	35.783	0.376	3.473	150.9	46.3	−10.8	−25.0	−27.9	45.5	−12.2
	35.942	0.535	2.662	151.9	−18.7	−4.6	−27.8	−26.0	46.5	−13.2
	35.760	0.353	3.612	152.0	−34.6	3.0	−27.3	−22.8	46.7	−17.2
	35.789	0.382	3.440	147.9	51.7	−21.7	−30.5	−18.0	49.7	−16.7
syn	35.793	0.386	3.415	−24.6	−26.5	−9.6	−28.2	−25.1	46.5	−15.5
	35.631	0.223	4.486	−22.8	−34.7	11.1	−30.0	−24.2	46.8	−15.7
	35.981	0.574	2.491	−18.3	−28.5	19.4	−41.5	−6.6	52.1	−30.2
	35.806	0.399	3.342	−18.3	−36.8	13.0	−29.8	−17.0	44.6	−30.8
	35.630	0.223	4.492	−21.2	−37.3	17.9	−31.3	−17.6	50.4	−22.9
	35.767	0.360	3.569	−25.9	34.1	−0.3	−30.2	−20.2	48.5	−20.2
	35.620	0.213	4.567	−19.9	−34.0	0.2	−29.6	−18.0	48.5	−28.5
	35.795	0.388	3.406	−22.6	−38.2	14.8	−32.3	−22.5	49.5	−16.3
	35.407	*0.000*	*6.525*	*−15.8*	*−33.6*	*13.5*	*−39.8*	−0.4	*44.9*	*−37.2*
	35.943	0.535	2.659	−27.4	47.4	−15.0	−26.5	−25.8	46.6	−15.3
	35.619	0.212	4.573	−23.5	−33.6	0.4	−30.1	−23.1	48.3	−16.9
	35.862	0.455	3.044	−23.0	−36.5	15.8	−31.0	−21.9	49.9	−17.5
	35.984	0.577	2.479	−29.7	53.2	−25.2	−30.8	−14.5	50.6	−21.3

[a] Angles in °: τ = H(1′)–C(1′)–N(7)–C(8), a = H(2′)–C(2′)–O(2′)–C(2″), b = C(2′)–O(2′)–C(2″)–O(2″), c = H(3′)–C(3′)–O(3′)–C(3″), d = C(3′)–O(3′)–C(3″)–O(3″), e = H(4′)–C(4′)–O(4′)–C(4″), f = C(4′)–O(4′)–C(4″)–O(4″).

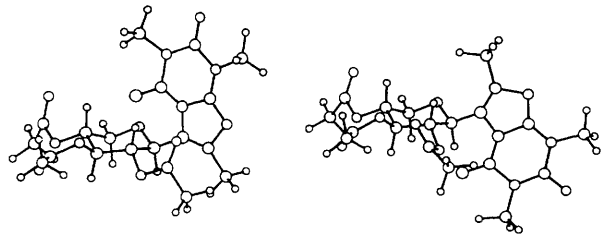
studied by conformational searching in each of the four minimum-energy conformations so as to minimize interactions between acetates, as well as those between the C-2 acetate and the base.

Minimization to convergence provided the geometries and energy differences shown in Tables 3 and 4.

Compound **3** exhibited two minima, at τ −15.8° (*syn* conformer), and τ 154.2° (*anti* conformer). The energy difference between the two minima was 269 cal/mol. The population distribution for each minimum, calculated from the Boltzmann equation, was 49% for the *syn* conformer and 51% for the *anti* conformer. The equilibrium rotational energy barrier obtained from the plot of E *versus* τ was 13.5 kcal mol^{-1} (Fig. 4).

Compound **4** exhibited two minima: τ −18.6° for the *syn* conformer and 149.4° for the *anti* conformer. However, the population difference between the two minima as per the Boltzmann equation is very much larger than for compound **3**; this implies the occurrence of the *anti* conformer only (96%) at room temperature. Moreover, the associated rotational barrier is very high (~31.0 kcal mol^{-1}, Fig. 4) because each rotation includes some positions where the sulfur atom or the methyl group at C-8 interacts strongly with the acetate group at C-2.

Table 4 Principal geometrical features of the minimum-energy conformers of compound **4**



syn-conformer *anti*-conformer

Conformers	E_{MME}/ kcal mol^{-1}	E_{rel}/ kcal mol^{-1}	Pop. (%)	Gly. bond[a] τ	Acetates[a] a	b	c	d	e	f
anti	38.062	0.406	4.566	151.0	−36.0	10.2	−26.9	−21.4	46.8	−21.2
	38.142	0.485	3.997	149.0	−36.1	5.2	−29.1	−19.2	50.0	−22.3
	38.102	0.445	4.276	146.1	−36.3	13.7	−34.3	−16.5	47.1	−27.6
	37.657	*0.000*	*9.019*	*149.4*	*43.0*	*−3.4*	*−32.2*	*−14.8*	*49.7*	*−21.0*
	38.014	0.357	4.955	150.0	38.4	−9.1	−40.0	3.9	46.5	−24.9
	38.055	0.398	4.624	150.6	−33.1	1.6	−30.0	−19.1	48.1	−21.4
	38.026	0.370	4.853	147.7	36.1	10.7	−30.9	−15.9	45.9	−28.0
	38.096	0.440	4.313	147.9	35.0	6.7	−37.0	−9.8	46.6	−28.8
	37.782	0.125	7.313	149.6	48.8	−16.7	−34.6	−9.5	51.3	−25.5
	38.182	0.525	3.737	153.9	41.8	−18.2	−46.2	15.7	48.0	−8.6
	38.193	0.537	3.667	152.4	41.4	−7.5	−44.3	21.3	46.8	−17.8
	37.952	0.295	5.500	146.8	41.3	−9.5	−47.3	9.3	45.5	−25.1
	37.858	0.202	6.430	152.0	36.7	−3.2	−45.5	18.3	45.3	−10.0
	38.176	0.519	3.774	151.6	41.6	1.1	−48.7	29.6	50.7	−15.7
	37.869	0.212	6.321	151.1	−34.7	13.5	−31.6	−17.1	51.7	−26.9
	38.185	0.529	3.717	151.7	−27.6	−2.9	−32.7	−8.2	52.7	−29.3
	37.905	0.248	5.950	149.7	−32.8	14.2	−32.9	−17.5	52.3	−25.4
	38.100	0.443	4.289	152.0	−30.9	−2.8	−32.6	−7.6	51.5	−30.1
	38.083	0.427	4.409	148.0	25.7	3.4	−43.1	5.0	47.7	−22.9
syn	*38.100*	*0.443*	*4.290*	*−18.6*	*−36.3*	*8.4*	*−35.8*	*−12.9*	*51.3*	*−32.4*

[a] Angles in °: τ = H(1′)–C(1′)–N(7)–C(8), a = H(2′)–C(2′)–O(2′)–C(2″), b = C(2′)–O(2′)–C(2″)–O(2″), c = H(3′)–C(3′)–O(3′)–C(3″), d = C(3′)–O(3′)–C(3″)–O(3″), e = H(4′)–C(4′)–O(4′)–C(4″), f = C(4′)–O(4′)–C(4″)–O(4″).

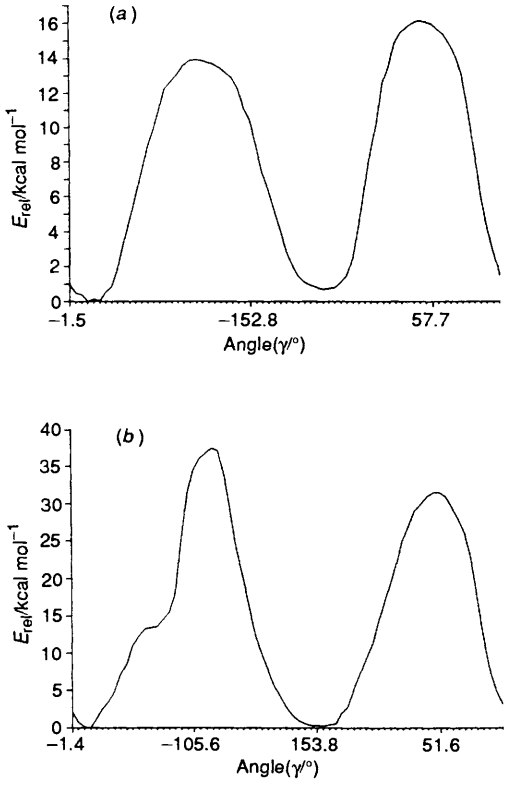


Fig. 4 τ angle (°) *versus* E_{rel} (kcal mol^{-1}). (a) Compound **3** and (b) **4**.

These results are also consistent with the experimental data.

All these results represent the gas-phase properties only, but are very similar to the experimental data obtained in chloroform solution (Table 5). In any case, minimization was also done by using different relative permittivity values[13] (5.6 for chloroform, and 11.2), even though the results thus obtained did not substantially improve on the prior calculations.

In conclusion, 8-methyl-6-thio-7-(β-D-xylopyranosyl)theophylline was prepared in satisfactory yield by using Lawesson's reagent under moderate reaction conditions and starting from a theophylline nucleoside, readily accessible *via* Todd's approach.

The triacetyl derivative of 8-methyl-7-(β-D-xylopyranosyl)-theophylline, compound **3**, exhibits a high molecular crowding that hinders rotation about the glycoside bond; the *syn* and *anti* rotamers are in equilibrium at ~50% each. This equilibrium results in broadened signals in the ^{1}H NMR spectrum obtained at room temperature. On cooling, both rotamers can readily be distinguished; also, heating at 333 K enables free rotation to take place.

If the oxygen atom at C-6 is replaced by the bulkier sulfur (compound **4**) then the rotational barrier is increased and the *anti* rotamer becomes significantly more stable. The signals in the ^{1}H NMR spectrum are quite sharp, and are illustrative of the occurrence of uncommon virtual coupling.

Molecular mechanics analyses provided two minima for both compounds **3** and **4**, corresponding to *syn* and *anti* conformers. The energy difference between the minima calculated from the Boltzmann equation resulted in a population distribution of ~50% *syn* and *anti* conformers for compound **3**, but 96% *anti* conformer for compound **4**. These results are quite consistent

Table 5 Results obtained by line-shape, and molecular mechanics analysis for compounds **3** and **4** in chloroform

Compound	Conformer	$Pop._{calc}$ (%)	$Pop._{exp}$ (%)	ΔG^*_{calc}/kcal mol^{-1}	ΔG^*_{exp}/kcal mol^{-1}
3	*syn*	49	47	13.5	13.9
	anti	51	53		
4	*syn*	4	0	31.0	
	anti	96	100		

with those obtained in the NMR experiments (Table 5), so the joint use of NMR spectra and molecular mechanics analysis makes this a useful method for studying *syn–anti* equilibria and molecular geometries.

Experimental

M.p.s 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 spectrophotometer, and IR spectra were recorded on Beckman Model Aculab IV and Perkin-Elmer 883 spectrophotometers. 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 mol dm^{-3} sample. LSPD was done by irradiation on 8-Me. ^{1}H Chemical shifts (δ_H) are given relative to either residual $CHCl_3$ (δ 7.27) in deuteriochloroform or residual HOD (δ_H 4.8) in dideuterium oxide. In multiplicities, p means pseudo. *J* Values are in Hz. ^{13}C Chemical shifts (δ_C) are given relative to either $CDCl_3$ (δ_C 77.0) in deuteriochloroform or CD_3COCD_3 (δ_C 29.8) in dideuterium oxide. 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).

8-Methyl-7-(β-D-xylopyranosyl)theophylline **2**.—6-Amino-1,3-dimethyl-5-(*N*-xylopyranosylacetamido)uracil or 6-acetamido-1,3-dimethyl-5-(*N*-xylopyranosylacetamido)uracil (1 mmol) was treated with (1.2 mmol) sodium methoxide in refluxing methanol (30 cm^3) for 6 h. The reaction mixture was neutralized with Amberlite IR 120 resin. The solution was concentrated at low pressure to give, after recrystallization from ethanol, the *title compound* **2** (85%), m.p. 230 °C; $[\alpha]_D^{23}$ −24.3 (*c* 1, water) (Found: C, 47.65; H, 5.4; N, 16.9. $C_{13}H_{18}N_4O_6$ requires C, 47.65; H, 5.52; N, 17.17%); EI *m/z* 326 (M^+) and 194 (100%).

8-Methyl-7-(2',3',4'-tri-O-acetyl)β-D-xylopyranosyl)theophylline **3**.—8-Methyl-7-(β-D-xylopyranosyl)theophylline **2** (200 mg, 0.44 mmol) was dissolved in a freshly prepared solution of acetic anhydride (3 cm^3) and pyridine (1 cm^3). The reaction mixture was kept at room temperature for 24 h. The solvents were removed at low pressure; then water (5 cm^3) 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. Recrystallization from ethanol gave *title compound* **3** (215 mg, 78%), m.p. 187–188 °C; $[\alpha]_D^{23}$ −12.4 (*c* 1, $CHCl_3$) (Found: C, 50.2; H, 5.45; N, 12.2. $C_{19}H_{24}N_4O_9$ requires C, 50.44; H, 5.30; N, 12.38%); EI *m/z* 452 (4%, M^+), 259 (26, xylopyranosyl triacetate) 199 (23, 259 − AcOH), 194 (39, 8-methyltheophylline), 157 (58, 199 − CH_2CO), 139 (67, 259 − 2 × AcOH), 137 (4, 194 − MeNCO), 109 (10, 194 − MeNCO − CO) and 97 (100, 139 − CH_2CO); ν_{max}(KBr)/cm^{-1} 1760, 1740, 1700, 1660 and 760; δ_H($CDCl_3$) 5.4 (br pt, 3'-H), 5.2 (br m, 4'-H), 4.3 (dd, 5'-H_{eq}), 3.6 (pt, 5'-H_{ax}) 3.54 and 3.40 (2 × 3 H, 2 s, 2 × NMe), 2.63 (3 H, br s, 8-Me) and 1.83, 2.03 and 2.05 (3 × 3 H, 3 s, 3 × Ac); δ_C($CDCl_3$) 169.7, 169.6 and 169.0 (3 × *C*OMe). 154.6 (C-6), 152.1 (C-8), 151.5 (C-2), 148.5 (C-4), 106.8 (C-5), 83.1 (C-1'), 72.7 (C-2'), 70.3 (C-3'), 68.6 (C-4'), 65.7 (C-5'), 29.7 and 28.1 (2 × NMe), 20.5, 20.5, 20.1 (3 × CO*Me*) and 15.2 (8-Me).

8-Methyl-6-thio-7-(2',3',4'-tri-O-acetyl)β-D-xylopyranosyl)-theophylline **4**.—A mixture of compound **3** (0.226 g, 0.5 mmol), Lawesson's reagent (LR) (0.33 g, 0.8 mmol), and dry distilled toluene (20 cm^3) was refluxed until complete disappearance of the starting material (TLC). Additional LR (0.8 mmol) was required at 48 h. The toluene was removed under reduced pressure, and the residue was separated by silica gel column chromatography using (8 : 2) chloroform–acetone as eluent. The isolated product, *compound* **4**, was recrystallized from methanol as yellow crystals (41%), m.p. 165–166 °C; $[\alpha]_D^{20}$ +13.3 (*c* 1, $CHCl_3$) (Found C, 48.5; H, 5.1; N, 11.6. $C_{19}H_{24}N_4O_8S$ requires C, 48.71; H, 5.16; N, 11.95%); EI *m/z* 468 (12%, M^+), 409 (2, M^+ − AcOH), 349 (22, M^+ − 119), 289 (17%, M^+ − 119 − 60), 259 (12, xylopyranosyl triacetate), 210 (35, 1,3,8-trimethylthioxanthine) and 97 (100, 139 − CH_2CO); ν_{max}(KBr)/cm^{-1} 2950, 1750, 1690, 1550, 1225, 1040 and 750; λ_{max}($CHCl_3$)/nm 342 (ε 22 200) and 206 (15 000); δ_H($CDCl_3$) 8.11 (1 H, m, 1'-H), 5.53–5.39 (2 H, m, 2'- and 3'-H), 5.07 (1 H, psex, *J* 10.3, 10.3 and 5.7, 4'-H), 4.20 (1 H, dd, *J* 10.3 and 5.7, 5'-H_{eq}), 3.78 (3 H, s, NMe), 3.60 (1 H, pt, *J* 10.3 and 10.3, 5'-H_{ax}), 3.57 (3 H, s, NMe), 2.73 (3 H, s, 8-Me) and 2.04, 2.02 and 1.78 (3 × 3 H, 3 s, 3 × Ac); δ_C($CDCl_3$) 175.7 (C-6), 169.8, 169.6 and 169.6 (3 × *C*OMe), 155.8 (C-8), 149.9 (C-2), 144.7, (C-4), 117.3 (C-5), 81.0 (C-1'), 72.7 (C-2'), 69.8 (C-3'), 69.0 (C-4'), 65.6 (C-5'), 34.2 and 30.3 (2 × NMe), 20.8, 20.5 and 20.2 (3 × CO*Me*) and 16.8 (8-Me).

8-Methyl-6-thio-7-(β-D-xylopyranosyl)theophylline **5**.—Compound **4** (250 mg, 0.51 mmol) was dissolved in methanol (15 cm^3) and was treated with a solution of sodium methoxide in methanol (4 cm^3) [sodium (0.3 g) in methanol (30 cm^3)]. The mixture was kept at room temperature for 12 h before being neutralized with Amberlite IR-120 resin. After filtration, the solvent was removed under reduced pressure. Recrystallization from methanol gave *title compound* **5** in quantitative yield, m.p. 198 °C $[\alpha]_D^{20}$ +14.7 (*c* 1, MeOH) (Found C, 43.4; H, 5.1; N, 16.0. $C_{13}H_{18}N_4O_5S$ requires C, 45.60; H, 5.29; N, 16.36%); EI *m/z* 342 (9%, M^+) and 210 (100, 1,3,8-trimethylthioxanthine); ν_{max}(KBr)/cm^{-1} 3350, 1695, 1600, 1090 and 750; λ_{max}(MeOH)/cm^{-1} 342 (ε 23 000) and 221 (16 000); δ_H(D_2O) 7.55 (1 H, d, *J* 9.5, H-1'), 4.0–3.0 (5 H, m, 2'-, 3'-, 4'-H and 5'-H_2), 3.49 and 3.33 (2 × 3 H, 2 × s, 2 × NMe) and 2.48 (3 H, s, 8-Me); δ_C(D_2O, ref. CD_3COCD_3) 175.0 (C-6), 156.6 (C-8), 150.7 (C-2), 144.4 (C-4), 118.4 (C-5), 83.3 (C-1'), 77.0 (C-2'), 71.6 (C-3'), 69.3 (C-4'), 68.5 (C-5'), 33.8 (3-Me), 30.7 (1-Me) and 16.2 (8-Me).

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