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Study of the Prototropic Tautomerism of 8-Azatheophylline by ^{13}C and ^{15}N NMR Spectroscopy

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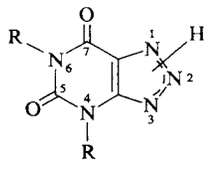
Comparison of the ^{13}C and ^{15}N NMR spectra of 8-azatheophylline with those of its three methylated derivatives and other model compounds from the literature showed that 8-azatheophylline exists to the extent of 80% in the N-2 tautomeric form in DMSO solution.

KEY WORDS ^{13}C NMR ^{15}N NMR Prototropism 4,6-Dimethyl-5,7-dioxo-1,2,3-triazolo[4,5-*d*]pyrimidine

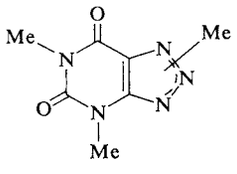
INTRODUCTION

In 1965, Nübel and Pfleiderer[1] reported the synthesis of all the methylated derivatives of 1,2,3-triazolo[4,5-*d*]pyrimidine (8-azaxanthine) (**1**), and established their structures by unequivocal synthesis and UV spectroscopy. They also considered the tautomeric problem of the 4,6-dimethyl derivative **2** (8-azatheophylline) and concluded that the H atom is probably attached to N-1. This was established on the basis of UV evidence and by recognition of possible hydrogen bonding between NH and the 7-oxo function.

Several workers have utilized this standard work[1] to substantiate the structure of products obtained by alkylation of 8-azatheophylline (**2**).[2,3] For instance, Senga *et al.*[3] reported that methylation of the **2** anion, prepared by cyclization of 6-azido-1,3-dimethyluracil in DMF, furnished **3**. However, the melting point did not correspond to that mentioned in the literature.[1] In re-investigating this work, we synthesized the three methylated products **3–5** for NMR analysis (see Experimental), which enabled us to solve the tautomeric problem of **2** as shown below.



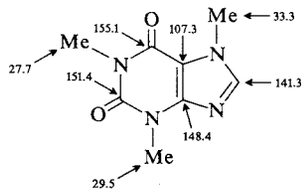
1 R = H
2 R = Me



3 1-Me
4 2-Me
5 3-Me

RESULTS AND DISCUSSION

The ^1H, ^{13}C and ^{15}N NMR data of **2–5** are summarized in Tables 1–3, respectively. The ^{13}C NMR absorptions were assigned by consideration of the multiplicity in the proton-coupled spectra and by comparison with caffeine (**6**) as a model compound.



6 ($CDCl_3$)

The assignment of the nitrogen resonances in the ^{15}N NMR spectra was based on the following arguments: (i) pyrrole-type nitrogen atoms absorb at higher field than pyridine-type nitrogen atoms (see **7** and **8** for model compounds);[4] (ii) the non-detectable nitrogen atoms in the DEPT pulse sequence are evidently N-3 of **3** and

Table 1. ^1H NMR spectral data for 2–5 at 50 °C in DMSO-d_6 solution

Compound	1-Me	2-Me	3-Me	4-Me	6-Me
2	—	—	—	3.44	3.25
3	4.26	—	—	3.48	3.23
4	—	4.26	—	3.39	3.23
5	—	—	4.29	3.67	3.23

Table 2. ^{13}C NMR spectral data for 2–5 at 50 °C in DMSO-d_6 solution[a]

	Ring C atoms				Methyl C atoms		
Compound	C-3a	C-5	C-7	C-7a	1,2,3-Me	4-Me	6-Me
2	148.6	150.9	155.9	123.4	—	30.7	28.0
3	149.8	150.5	153.2	113.0	36.8	29.8	27.8
4	149.4	150.7	155.6	124.5	42.9	30.6	27.9
5	141.1	150.6	155.1	124.7	36.6	31.0	28.2

[a] When the spectra were recorded at 25 °C, similar δ values were obtained with a maximum deviation of 0.1 ppm. The spectrum of **2** was also recorded in DMF, giving similar δ values with a maximum deviation of only 0.2 ppm.

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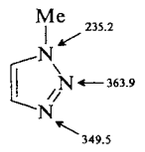
Table 3. ^{15}N NMR spectral data for 2–5 at 25 °C[a]

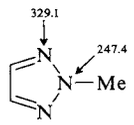
Compound	Solvent	N-1	N-2	N-3	N-4	N-6
2	DMSO-d_6	325 (br)	not observed	290	103.9	152.3
	DMF-d_7	324.5[b]	268.5[b]	290.5[b]	Solvent	152.3
3	$CDCl_3$	230.2	370.5	313.7[b]	105	151.7
4	$CDCl_3$	333.2	246.1	295.9	102.4	151.7
5	DMSO-d_6	346.9[b]	362.2	216.3	105.1	149.1

[a] δ values from liquid ammonia quoted, using nitromethane as external reference.
[b] Not observed with the DEPT pulse sequence.

N-1 of **5** (see Table 3); (iii) since N-3 of **3** (δ 313.7) absorbs at higher field than N-1 of **5** (δ 346.9), the same situation is expected for the corresponding atoms of **4**, i.e. N-3 at δ 295.9 and N-1 at δ 333.2.

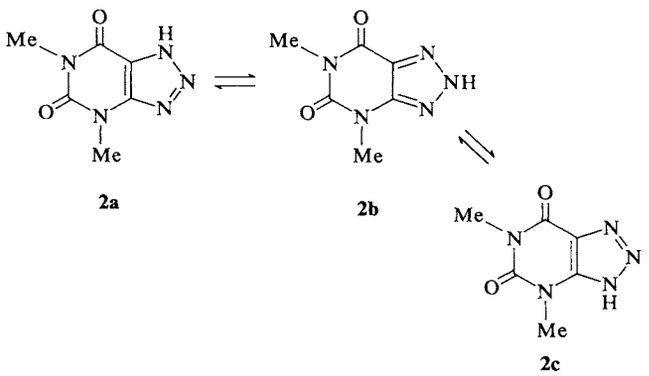


7 ($CDCl_3$)



8 ($CDCl_3$)

We used the ^{13}C NMR data of **3–5** to determine the tautomeric distribution in 8-azatheophylline (**2**). The proton-decoupled spectrum of **2** in DMSO solution shows only six signals, indicating a fast tautomeric exchange between **2a**, **2b** and **2c** on the NMR time scale.



2a **2b** **2c**

From a comparison of the chemical shifts (C-3a and C-7a) of **2** with those of the methylated model compounds **3–5**, we can conclude that **2b** is the predominant tautomer. The observed chemical shifts of **2** are weighted mean values of the shifts for the individual tautomers:

$$\delta(\text{obs}) = X_a\delta_a + X_b\delta_b + X_c\delta_c \quad (1)$$

where δ_{a-c} are the chemical shifts of the tautomers **2a–c** and X_{a-c} are the molar fractions of **2a–c**:

$$X_a + X_b + X_c = 1 \quad (2)$$

The C-3a and C-7a carbon resonances of the tautomers **2a–c** are estimated from the corresponding shifts in **3–5** without considering any correction factor for the methyl substituent. Indeed, indole and indazole also exhibit C-3a and C-7a absorptions similar to their N-1 methyl derivatives.[5] Application of Eqn (1) to the C-3a and C-7a resonances leads to the values $X_a = 0.10$, $X_b = 0.80$ and $X_c = 0.10$. Hence **2b** is present to the extent of 80% in the tautomeric equilibrium. This predominance of the N-2 isomer has been observed in general for 1,2,3-triazoles in polar solvents,[4,6] except for benzotriazole, which would give an unfavourable *ortho*-quinonoid arrangement.[4]

In the ^{15}N NMR spectrum (in deuteriated DMF solution), **2** exhibits one set of nitrogen resonances, resulting from a tautomeric equilibration of **2a–c**. However, in contrast with the ^{13}C NMR spectrum, the N-1, N-2 and N-3 absorptions are broadened, with line widths ($w_{1/2}$) of 25, 40 and 12 Hz, respectively (see Fig. 1). This is due, of course, to the large differences in chemical shifts of the tautomeric nitrogen atoms ($\Delta\delta = 116$ ppm for N-1, 124 ppm for N-2 and 97 ppm for N-3, calculated from the model compounds **3–5**), and leaves no doubt about the assignment of the N-1,2,3 nitrogen atoms of **2**.

The averaged chemical shifts of the N-1, N-2 and N-3 atoms, calculated from Eqn (1) using the obtained molar fractions X_{a-c} and the corresponding shift values of **3–5**

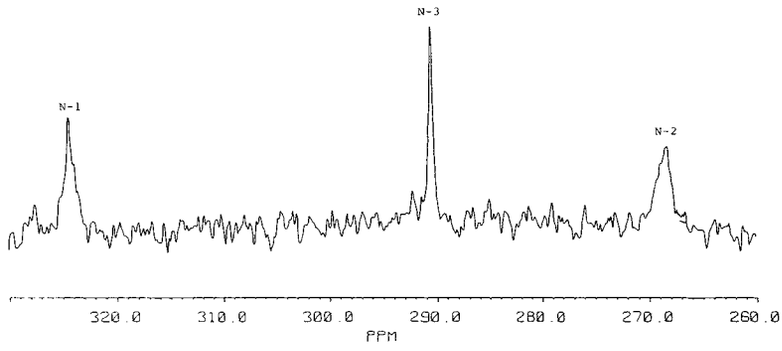


Figure 1. Partial ^{15}N NMR spectrum of **2** in DMF-d_7 solution.

which serve as model compounds for **2a–c**, are N-1 = 324.3, N-2 = 270.2 and N-3 = 289.7 ppm. The results are in excellent agreement with the values found experimentally (see Table 3).

A comment on the methyl substituent effect is in order. We have deliberately not corrected for the influence of the methyl group ($\delta_{NH} - \delta_{NMe}$) on the α and β nitrogen absorptions, although values of +5 and −8 ppm, respectively, have been reported.[7] Indeed, if these corrections are taken into account, the chemical shifts of **2b** would be δ 325 (N-1), 251 (N-2) and 288 (N-3). Thus, the N-1 and N-3 resonances would be very close to those determined experimentally (see Table 3) (suggesting the absence of **2a** and **2c**), whereas N-2 deviates strongly. Hence, the β-correction term, as reported for unsubstituted azoles, is probably unreliable for 4,5-disubstituted derivatives. In view of the observed incoherence, we prefer to rely on the uncorrected nitrogen shifts of the methylated model compounds.

EXPERIMENTAL

Synthesis of 2–5

When 6-azido-1,3-dimethyluracil was refluxed with methyl iodide in DMF containing potassium carbonate, the NMR spectrum of the reaction mixture indicated the presence of **3** and **4** in a ratio of 2:3. This mixture was treated with methyl tosylate at 125 °C for 1 h in order to transform **3** into the N-3 methylated salt[1] and to isolate **4** as white crystals (m.p. 197 °C). Alternatively, when **2** (m.p. 260 °C), prepared by the method of Senga *et al.*[3] was reacted with diazomethane, **3** and **4** were formed in a 3:2 ratio. Fractional crystallization from DMSO solution furnished pure **3** (8-azacaffeine) (m.p. 224 °C). Finally, **5** (m.p. 222 °C) was prepared by nitrosation of 5-amino-6-aminomethyl-1,3-dimethyluracil.[8]

Spectra

The ^1H and ^{13}C NMR spectra were recorded on a Bruker WM (FT) spectrometer at 250 and 62.9 MHz, respectively, using a 5 mm dual probe. The chemical shifts are reported in ppm relative to TMS as an internal reference. All these spectra were recorded in DMSO-d_6 solution at 50 °C to prevent crystallization of **3** and **4**.

Natural abundance ^{15}N NMR spectra were recorded on a Bruker WM-250 spectrometer, operating at 25.35 MHz, and equipped with a selective ^{15}N 10 mm probe. The chemical shifts were determined with respect to external nitromethane contained in a 4 mm capillary held centrally in the sample tube. This reference was given a δ value of 380.2 ppm, thus converting the N chemical shifts to the liquid ammonia shielding scale. The spectra of the products were recorded in their best solvents: $CDCl_3$ for **3** and **4**, DMSO-d_6 for **2** and **5** and DMF-d_7 for **2**, all as saturated solutions. Shift deviations of up to 2.5 ppm may be expected for the methylated triazoles when chloroform is substituted for dimethyl sulphoxide.[4]

The DEPT pulse sequence, based on polarization transfer through long-range coupling [^2J(NH) and ^3J(NH)], was used to detect the nitrogen two or three bonds away from non-exchanging protons. For **4**, the five nitrogens were detected by the DEPT pulse technique and a proton-coupled spectrum was obtained [^2J(N-2, CH_3) = 2.5 Hz, ^3J(N-1, CH_3) ≈ ^3J(N-3, CH_3) ≈ 1.5 Hz, ^2J(N-4, CH_3) = ^2J(N-6, CH_3) ≈ 1 Hz]. To allow the detection of all the nitrogens of **2**, **3** and **5**, $Cr(Acac)_3$ was added as a relaxation reagent, and the spectra were recorded by the inverse gated heteronuclear decoupling technique. The shift deviation caused by this reagent ranges from 0.3 to 0.7 ppm.

Typial acquisition parameters for the DEPT pulse sequence are spectral width 8 kHz, pulse angle 45°, delay time 0.1 s and number of scans 1000, and for the inverse gated heteronuclear decoupling, spectral width 8 kHz, pulse angle 70°, relaxation delay 5 s and number of scans 10 000–50 000.

Acknowledgements

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