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Thioanalogues of *N*-1-methylanabasine and nicotine – Synthesis and structure

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ABSTRACT

The synthesis, spectral characteristics and structures of *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-thione (**1**) (thioanalogue of *N*-1-methylanabasine) and *N*-1-methyl-(5-pyridin-3-yl)pyrrolidine-2-thione (**2**) (thioanalogue of nicotine) are reported. Both compounds were obtained using Lawesson's reagent. The structures of compounds **1** and **2** are confirmed by NMR, IR, UV and mass spectroscopy, as well as, by X-ray diffraction analysis. Pyridine ring of compound **1** adopts a pseudo-axial orientation in solution, as well as in a solid state. A substantial lengthening of the C=S bond in the crystals of **1** is interpreted as a sign of an enhanced electron delocalization within the thiolactam group due to the presence of several C—H groups in the nearest vicinity of the sulfur atom. In the crystals of **2**, which differ from **1** in that the relatively puckered piperidine-2-thione moiety is replaced by the flat pyrrolidine-2-thione ring, no short CH···S(=C) contacts are observed. Instead, the packing is governed by stacking interactions between pyridine rings. The pyrrolidine and pyridine rings in **2** are nearly perpendicular to each other and the pyrrolidine moiety adopts a flattened half-chair conformation.

1. Introduction

The tobacco alkaloids nicotine, nornicotine and anabasine show a wide spectrum of biological activity and are used as precursors for drug design and pesticide preparation [1–3]. They exert negative effect on the cardio-vascular system and alimentary system, cause sleep disturbance and addiction [4–6]. Despite these known negative effects they are considered promising for therapy of some neurodegenerative diseases such as Alzheimer's, Parkinson's [4–6], Tourette's syndrome [7], attention deficit hyperactivity disorder (ADHD) [8] and schizophrenia [9–12]. These effects presumably are a result of interaction with nicotinic acetylocholine receptors (nAChR) [13,14], which are found on skeletal muscles at the neuromuscular junction, in the peripheral nervous system, and at numerous sites in the central nervous system [15]. Examination of the impact of derivatization on the therapeutic properties of important biologically active molecules has remained an active area of investigation [16–18]. Derivatives of anabasine are compounds showing antitumor, antiviral, antibacterial and other activities [19,20]. Some metal complexes of these compounds can modulate the biological activity of the organic ligand [21]. Recent studies have demonstrated that thiolactam analogues of bioactive compounds show important therapeutic activity, for example replacement of the lactam with thiolactam pharmacophore in thiocytisine resulted in a change in affinity at nAChR [22]. In view of the above, thioanalogues of *N*-1-methylanabasine and nicotine have been synthesised. In the present study, we report the synthesis, spectral analysis and X-ray studies of *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-thione (**1**) and *N*-1-methyl-5-(pyridin-3-yl)pyrrolidine-2-thione (**2**) (Fig. 1). Although nicotine is a very important alkaloid available commercially in large quantities, its thioanalogue has not been thoroughly characterized. The thiolactam of nicotine was first prepared by direct sulfurization of cotinine (**3**) with P_4S_{10} [23]. Despite good yield of this synthesis (77%) only UV–Vis spectra and melting point were recorded. This fact has prompted us to examine the structure of thioanalogue of nicotine with the application of the high resolution and 2D NMR, CD and X-ray diffraction analysis. Furthermore, we have now attempted a microwave-accelerated solvent-free synthesis of **2** using Lawesson's reagent.

2. Experimental

2.1. General techniques

The IR spectra were recorded using FT-IR Bruker IFS 113V spectrometer (KBr pellets and $CDCl_3$ solution). Electron-impact mass spectra were taken on an AMD 402 spectrometer at standard parameters. The UV–Vis and CD spectra were recorded by means of JASCO V-550 spectrophotometer at 200–600 nm of measurement range.

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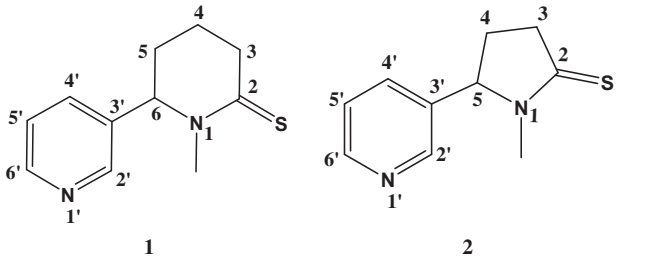


Fig. 1. Atom numbering in *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-thione (**1**) and *N*-1-methyl-5-(pyridin-3-yl)pyrrolidine-2-thione (**2**).

Elemental analysis was carried out by means of a Perkin–Elmer 24000 CHN automatic device. Melting points were determined on Melt-Temp II apparatus (Laboratory Devices Inc.) Optical rotations were measured on a Perkin–Elmer 243 b Polarimeter. Microanalyses were performed on a Euro Ea-2000 (Euro-Vector) apparatus.

The NMR spectra were recorded using a Varian Gemini 300 MHz spectrometer. All spectra were locked to deuterium resonance of $CDCl_3$.

The ^{1}H NMR measurements in $CDCl_3$ we re-carried out at the operating frequency 300.069 MHz for **1** and 600.312 MHz for **2**; flip angle, pw = 8.8°; spectral width, sw = 9000 Hz; acquisition time, at = 4.0 s; relaxation delay, d1 = 0.5 s; T = 293.0 K and using TMS as the internal standard and 10 mm tubes. No window function or zero filling was used. Digital resolution was 0.2 Hz per point. The error of chemical shift value was 0.01 ppm.

The ^{13}C NMR spectra were recorded at the operating frequency 75.460 MHz; flip angle, pw = 9.3°; spectral width, sw = 22573 Hz; acquisition time, at = 1.5 s; relaxation delay, d1 = 0 s; T = 293.0 K and using TMS as the internal standard and 10 mm tubes. Line broadening parameters were 0.5 or 1 Hz. The error of chemical shift value was 0.01 ppm.

The ^{1}H and ^{13}C NMR signals were assigned using one- or two-dimensional ^{1}H–^{1}H COSY and ^{1}H–^{13}C HETCOR spectra.

2.2. Synthesis

2.2.1. Cotinine (*3*) and N-1-Methyl-6-(pyridin-3-yl)piperidine-2-one (*4*)

Cotinine was synthesised from commercial (*S*)-(−)-nicotine according to the procedure described by Wenkert and Angell [24]. *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-one was prepared from *N*-1-methylanabasine by the application of the same method.

2.2.2. Microwave-accelerated solvent-free synthesis of N-1-methyl-6-(pyridin-3-yl)piperidine-2-thione (*1*) and N-1-methyl-5-(pyridin-3-yl)pyrrolidine-2-thione (*2*)

A mixture of *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-one (**4**) (83 mg; 0.44 mM) and Lawesson's reagent (141 mg; 0.35 mM) was taken in a glass tube and mixed thoroughly. The glass tube was placed in an aluminia bath inside the microwave oven (800 W) and irradiated for 3.5 min. On completion of the reaction, followed by TLC examination the coloured crude material was dissolved in chloroform, adsorbed on neutral aluminia (3.32 g) [alkaloid–Al_2O_3 mass ratio 1:40] and purified by aluminia column chromatography using ethyl ether as initial eluent and chloroform, which afforded the pure compound **1** as pale yellow oil (78 mg). Analogous procedure was carried out with cotinine (**3**) (528 mg; 3 mM) and Lawesson's reagent (967 mg; 2.4 mM) to obtain 540 mg of **2**.

Transparent crystals of **1** (58 mg, yield 80%) and **2** (414 mg, yield 90%) were obtained by dissolving the oils in 5 ml of boiling *n*-hexane. The melting points were 78–80 °C and 91–92 °C (lit. 90 °C [19]) for **1** and **2**, respectively.

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.08; H, 6.80; N, 13.59; S, 15.53. Found: C, 64.12; H, 6.82; N, 13.60; S, 15.58.

Anal. Calcd. for $C_{10}H_{12}N_2S$: C, 62.50; H, 6.25; N, 14.58; S, 16.66. Found: C, 62.33; H, 6.32; N, 14.63; S, 16.57. $[\alpha]_D^{20} = -23.5°$ (0.03, CH_3OH).

2.3. X-ray crystal structure determination

Single crystals were obtained by slow evaporation of saturated *n*-hexane solution. Transparent crystals of thiolactams of *N*-1-methylanabasine and nicotine were selected for the X-ray investigations.

Intensity data were recorded at ambient temperature on KUMA-CCD four circle diffractometer, equipped with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) using experimental parameters provided in Table 1 [25]. The empirical absorption correction was performed using the procedure supplied by CrystAlis RED software [26]. The structure was solved by direct methods applying the SHELXS-97 [27] program, followed by full-matrix least-squares refinements on F^2, applying the SHELXL-97 [28] system of programs. Non-hydrogen atoms were treated anisotropically. The positions of the hydrogen atoms were calculated and refined using a riding model with isotropic temperature factors 20% higher than the isotropic equivalent for the atom to which the H-atom was bonded. The correctness of the absolute configuration was checked on the basis of a refined Flack parameter: x = 0.08 (12) for **1** and x = 0.2 (2) for **2** [29]. The CIF files have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 270145 and 271381 for thiolactams of *N*-1-methylanabasine and nicotine, respectively).

3. Results and discussion

The title compounds **1** and **2** were prepared by the route illustrated in Scheme 1.

The synthesis of the nicotine thiolactam was carried out in two steps, whereas the preparation of the analogous thiolactam from *N*-1-methylanabasine involved three steps, as anabasine was firstly converted by Eschweiler–Clark's reaction into its *N*-methyl derivative [30]. The corresponding lactams of *N*-1-methylanabasine and cotinine were obtained following the oxidation of these tertiary amines with $Hg(CH_3COO)_2$ [24]. The last step involved microwave-accelerated solvent-free sulfurization of lactams with Lawesson's reagent.

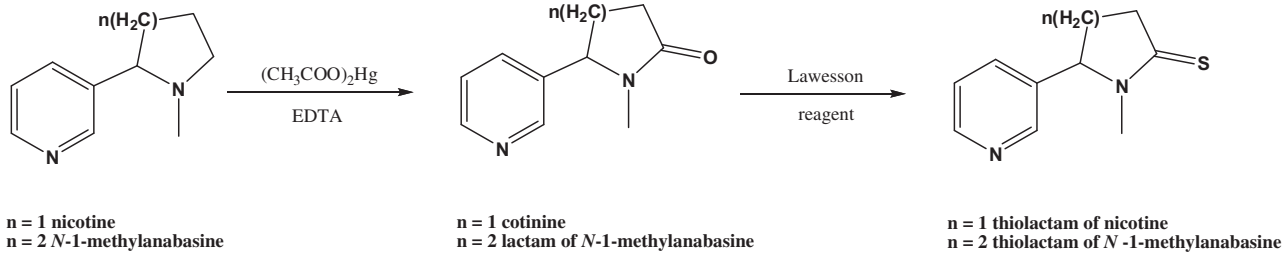
The common features of the mass spectral fragmentation of the molecular ions of nicotine and *N*-1-methylanabasine thiolactams are the presence of three signals: M^+, M+1 and M+2, a typical pattern of compounds containing sulfur atoms (see Table 2).

Even-electron fragment ions $[M-33]^+$ generated by loss of SH**.** radical at m/z 173 (36%) for **1** and at m/z 159 (8%) for **2**, additionally corroborate these structures. It was observed that the relative intensity of this ion increases with thiolactam's molecular mass. In the mass spectra of **1** and **2** the even-electron fragment ion NCS^+ at m/z 58 is observed. Moreover, there are fragment ions typical of cleavages of pyridine, piperidine and pyrrolidine rings.

In the electronic absorption spectrum recorded in acetonitrile (Fig. 2, top), *N*-1-methyl-6-(pyridin-3-yl)pyrrolidine-2-thione (**2**) displays two intense transitions in the UV-region at 207 and 270 nm and a small absorption ($\varepsilon \sim 50$) at 341 nm. The maximum at 270 nm corresponds to the π–π^* transition in pyridine and thiolactam chromophores while the maximum at 207 nm should be interpreted as the forbidden n_δ–π^* transition in thiolactam

Table 1
Selected crystal data, data collection and refinement parameters for thioanalogues of *N*-1-methyl-anabasine and nicotine.

Compound	**1**	**2**
Chemical formula	$C_{11}H_{14}N_2S$	$C_{10}H_{12}N_2S$
Chemical formula weight	206.3	192.28
Crystal size (mm)	0.40 × 0.40 × 0.08	0.40 × 0.15 × 0.05
Colour, habit	Colourless, plate	Colourless, plate
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a (Å)	6.9181 (6)	7.2250 (14)
b (Å)	6.1224 (5)	10.878 (2)
c (Å)	13.2770 (10)	12.766 (3)
V (Å^3)	545.19 (8)	1003.3 (3)
Z	2	4
D_x (mg m^{-3})	1.257	1.273
No. of reflections for cell parameters	3643	1180
Absorption coefficient (mm^{-1})	0.259	0.277
Diffractometer	Kuma KM-4CCD κ-geometry	Kuma KM-4CCD κ-geometry
Monochromator	Graphite	Graphite
Data collection method	ω Scans	ω Scans
No. of measured reflections	4871	6024
No. of independent reflections	2206	1783
No. of observed reflections	1647	1124
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0727	0.0802
θ_{max} (°)	27.03	25.06
Range of h, k, l	$-5 \rightarrow h \rightarrow 8$ $-7 \rightarrow k \rightarrow 7$ $-16 \rightarrow l \rightarrow 16$	$-8 \rightarrow h \rightarrow 5$ $-12 \rightarrow k \rightarrow 12$ $-15 \rightarrow l \rightarrow 15$
Absorption correction	Empirical	Empirical
T_{min}, T_{max}	0.91161, 0.97662	0.94727, 0.98579
Refinement on	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$	0.0503	0.0598
$wR(F^2)$	0.1399	0.1324
S	0.977	0.997
No. of reflections used in refinement	2206	1783
No. of parameters used	129	119
H-atom treatment	Riding model	Riding model
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0925P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0517P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$
Flack parameter	0.08 (12)	0.2 (2)
$\Delta\rho_{max}$ (e Å^{-3})	0.281	0.168
$\Delta\rho_{min}$ (e Å^{-3})	−0.339	−0.177



n = 1 nicotine
n = 2 *N*-1-methylanabasine

n = 1 cotinine
n = 2 lactam of *N*-1-methylanabasine

n = 1 thiolactam of nicotine
n = 2 thiolactam of *N* -1-methylanabasine

Scheme 1. Synthesis of thionalogues of *N*-1-methylanabasine and nicotine.

Table 2
Molecular ion signals in mass spectra of compounds **1** and **2.**

Molecular ion signals	**1** *m*/*z* (%)	**2** *m*/*z* (%)
M^+	206 (100)	192 (100)
M+1	207 (15)	193 (13)
M+2	208 (5)	194 (5)

chromophore. At variance, a single UV absorption maximum of much lower intensity at 273 nm is displayed by thiolactam **1**.

In the circular dichroism spectrum (Fig. 2, bottom), **2** shows a weak negative Cotton effect in the long-wavelength range (about 341 nm) that was assigned to the n–π^* transition of the thiolactam group. However, this effect is not observed for the six-membered thiolactam derivative of **1**. This can be accounted for by the substantial conformational flexibility of the thiolactam group in solution, which is expected to be higher for the six-membered lactam ring of **1** than for the five-membered ring of **2**. It is well known that this negative Cotton effect is highly intense for conformationally rigid bicyclic thiolactams [31] but may be diminished in the more flexible systems such as the investigated thiolactames **1** and **2**.

Both compounds **1** and **2** display subsequent Cotton effects at 270 nm and 257 nm. The longer-wavelength negative Cotton effect should be assigned to the π–π^* transition in the thiolactam chromophore. The occurrence of the exciton coupling in these two chromophores cannot be excluded. The subsequent positive Cotton effect is noted at 223 nm for compound **2** and at 209 nm for compound **1**. The nature of these transitions should probably be related to the σ_{C-S}–π^* transition in the thiolactam chromophore. The corresponding transitions and molar extinction coefficients are presented in Table 3.

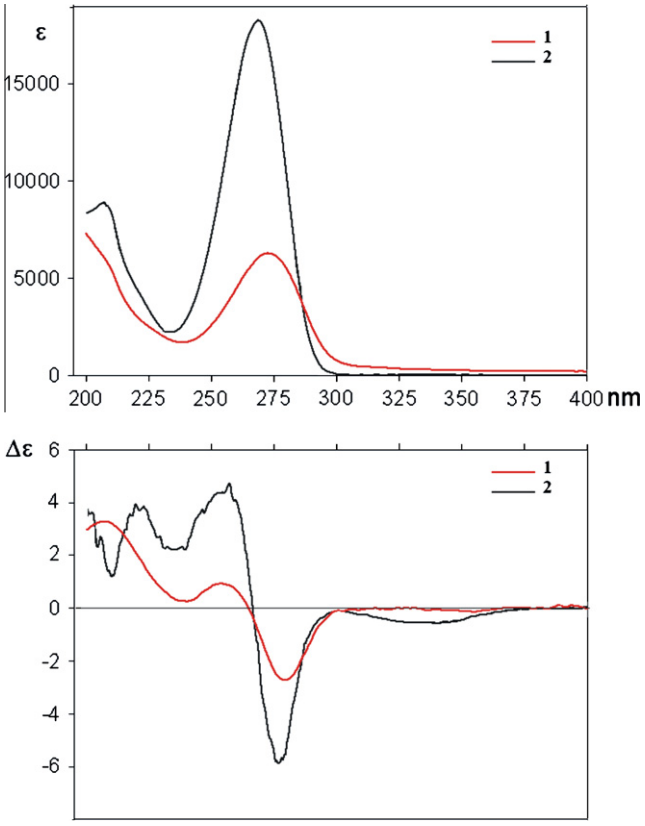


Fig. 2. UV (top) and CD (bottom) spectra of *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-thione (**1**) (red line) and *N*-1-methyl-5-pyridin-3-yl-pyrrolidine-2-thione (**2**) (black line) in acetonitrile. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
UV and CD spectral data of *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-thione (**1**) and *N*-1-methyl-5-pyridin-3-yl-pyrrolidine-2-thione (**2**) in acetonitrile.

Compound	**1**	**2**
ε UV (nm)	6300 (273)	50 (341) 18200 (270) 8900 (207)
$\Delta\varepsilon$ CD (nm)	−2.7 (279) 0.9 (254) 3.3 (209)	−0.6 (341) −5.9 (277) 4.7 (257) 3.8 (223)

In the IR spectra of **1** and **2** there is no absorption band in the region of 1687 cm^{-1} and 1636 cm^{-1} ($\nu_{C=O}$). Instead, a very intense single absorption band is observed at 1518 cm^{-1} and 1506 cm^{-1} ($\nu_{-N-C=S}$), respectively. In the region of 1122–1072 cm^{-1} for **1** and 1160–1100 cm^{-1} for **2** we can observe the three intensive absorption bands connected with the thiocarbonyl group ($\nu_{C=S}$) (see Fig. 3a and b).

Moreover, in the spectrum of **1** in $CDCl_3$ there is an absorption band at ca. 2226 cm^{-1} connected with the stretching vibrations $\nu_{C-D\cdots N1}$ of $CDCl_3$ molecules bonded to a piperydyl ring.

Further information on the structure of **1** and **2** was derived from their NMR spectra. The assignment of the ^1H NMR signals to particular protons was made by two-dimensional methods, mainly ^1H–^1H, ^1H–^{13}C COSY and ^1H–^1H NOESY. The corresponding data have been accumulated in Tables 4–6.

The ^{13}C NMR spectra of **1** and **2** were analysed by comparing with those of the corresponding lactams, i.e. *N*-1-methylanabasine (**4**) and cotinine (**3**). Such a procedure allowed calculations of the substituent effects by subtracting the chemical shifts of individual carbon atoms of compounds **4** and **3** from the values of the chemical shifts of the corresponding carbon atoms of **1** and **2**, respectively. ^{13}C chemical shifts of thiolactams and their oxygen analogues are shown in Table 4, whereas ^1H NMR data of **1** and **2**, are given in Tables 5 and 6, respectively.

In the ^{13}C NMR spectra of **1** and **2** the chemical shifts of the carbon atoms are similar to those assigned for their oxygen analogues in pyridine moiety. As expected, the differences in the chemical shifts of the carbon atoms appear for the atoms in piperidine moiety of **1** and **4** and in pyrrolidine ring in **2** and **3**.

The ^{13}C NMR spectrum of **1** reveals a high, lowfield effect on thiocarbonyl atom C2 (+30.67 ppm). As expected, a large β-effect of the substituent is observed on C3 (+9.41 ppm) at α position to the C=S group. The β-effect on the methyl group is similar to that on C3. The ^{13}C chemical shifts of C2, C3, C4, and C5 of **2** (Table 4) approximate the analogous δ_C values for cotinine. The observed lowfield effects in pyrrolidine ring are a consequence of a substitution of the oxygen atom by the sulfur atom. Consequently, the largest substituent effect is on the thiocarbonyl atom C2 (+27.24 ppm). We also observe a large positive β-effect on carbon atoms C3, C5 and —CH_3 at the α position to the thiolactam N—C=S group: +13.27, +7.55 and +5.78 ppm, respectively. The β-effect on C3, adjacent to the thiocarbonyl group, is slightly larger than that on C5 and on the methyl group.

The ^1H NMR spectra of **1** and **2** in $CDCl_3$ are similar to those of **4** and **3**, respectively. The differences observed are a logical consequence of substitution of an oxygen lactam atom by a sulfur atom in piperidine moiety of **1** and in pyrrolidine ring in **2**.

In the ^1H NMR spectra of **1** and **2** the values of chemical shifts in pirydyl moiety are similar. The greatest ^1H deshielding effect is on *N*-methyl protons being at the α position to the thiolactam nitrogen atom (δ_H = 3.33 ppm for **1** and δ_H = 3.08 ppm for **2**) and at the α position to the thiocarbonyl group. Over 20 coupling constants were successfully determined directly from the ^1H NMR spectra of **1** and **2**. Both axial and equatorial protons of C3 carbon atom have a large *geminal* coupling constant (J > 18 Hz). Such a high value of coupling constant was also found in other thiolactams of alkaloids, for example in thioderivatives of lupanine and sparteine [32,33]. For compound **1** the signal of H6 proton (doublet of doublets) at δ_H = 4.81 ppm had a relatively small coupling constant 5.8 Hz and has been assigned as equatorial. Hence, the pyridine moiety in **1** adopts an axial position, in contrast to the orientation observed in anabasine hydrochloride [34,35] and in *N*-1-methylanabasine, where the H6 proton is axial. For **2** the signal of H5 proton (doublet of doublets) that occurred at δ_H = 4.94 ppm had a coupling constant of 8.5 Hz and has been assigned as axial. An analysis of ^1H–^1H COSY and ^1H–^1H NOESY spectra of **2** allowed finding an ^1H–^1H correlation. Apart from the correlation between the *vicinal* and *geminal* protons of pyrrolidine ring seen in ^1H–^1H COSY spectrum, correlations H4—H2′, H4—H4′, $H5_{ax}$—H2′, $H5_{ax}$—H4′ were detected. Correlations between methyl protons and H4′ and H2′ were also observed.

Presented results confirm that the introduction of thiolactam group induces structural changes within the piperidyl or pyrrolidine rings of *N*-1-methylanabasine and nicotine, respectively. On the basis of NMR data we cannot determine the ratio of *sofa*/*half-chair* conformers of the piperidyl ring of **1** in solution [36]. At variance, the pyrrolidine ring of **2** adopts a well defined *half-chair* conformation but the free rotation around the C^*—$C(sp^2)$ bond leads to an existence of several possible conformers of this thiolactam in solution.

3.1. X-ray results

The structure of **1** present in the crystal lattice is illustrated in Fig. 4 and torsion angles describing its molecular conformation

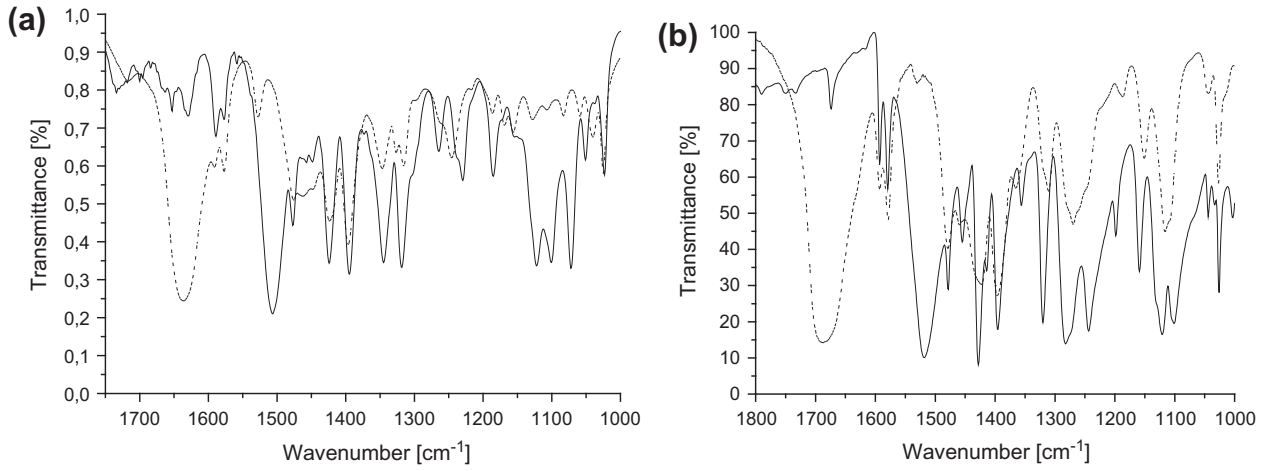


Fig. 3. (a) IR spectra of *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-one (**4**) (dots) and *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-thione (**1**) (solid). (b) IR spectra of cotinine (**3**) (dots) and *N*-1-methyl-5-(pyridin-3-yl)pyrrolidine-2-thione (**2**) (solid).

Table 4
^{13}C NMR shifts of carbon atoms of lactams and thiolactams of nicotine and *N*-1-methylanabasine in $CDCl_3$. Atom numbering is shown in Fig. 1. Numbers given in italics represents the substituent effect. (−) Designates an upfield shift, (+) designates a downfield shift. Substituent effects were calculated by subtracting the chemical shifts of the individual carbon atoms of lactams from the values of the chemical shifts of the corresponding carbon atoms in the corresponding thiolactams.

Carbon atoms	**4** δ_C (ppm)	**1** δ_C (ppm)	**3** δ_C (ppm)	**2** δ_C (ppm)
2′	148.29	148.07	148.25	148.34
		−0.22		*+0.09*
3′	136.90	135.88	136.36	135.04
		−1.02		*−1.32*
4′	133.87	133.75	133.54	133.68
		−0.12		*+0.14*
5′	123.63	123.69	123.85	124.10
		+0.06		*+0.25*
6′	149.08	149.41	149.34	150.12
		+0.33		*+0.78*
2	170.85	201.52	175.12	202.36
		+30.67		*+27.24*
3	32.10	41.51	29.96	43.23
		+9.41		*+13.27*
4	17.37	16.70	28.26	29.58
		−0.67		*+1.32*
5	32.05	31.76	62.12	69.67
		−0.29		*+7.55*
6	61.42	64.18		
		+2.76		
CH_3	33.91	43.34	28.26	34.04
		+9.43		*+5.78*

are listed in Table 7. The absolute configuration at the chiral centre C7 has been determined as (*S*) (for details see Section 2.3). Somewhat unexpectedly, the pyridine substituent, attached at C7, was found in a pseudo-axial orientation. Such orientation of the pyridine substituent has also been reported for the crystals of thiourea derivatives of anabasine [37,38], where it has been ascribed to the presence of bulky substituents at the thiourea nitrogen. Moreover, the axial orientation of a methyl substituent has been observed in (1′R,6S)-1-(2′-hydroxy-1′-phenyl–ethyl)-6-methyl-piperidin-2-thione [39]. However, in protonated anabasine [35] the pyridine ring is equatorial. The above observations indicate that the axial orientation of the pyridine ring in **1** results from the presence of the *N*-methyl-thiolactam group. Such orientation allows to avoid unfavorable steric interactions with *N*-methyl substituent and is free from 1,3-diaxial interactions that would exist in the normal piperidine ring, as the carbon atom in the piperidine two-position in **1** is sp^2 hybridized. The angle between the thiolactam group defined by S1, C9 and N8, and the plane of the pyridine substituent amounts to 97.2 (3)°, while the angle between the line joining the pyridine and piperidine-2-thione rings, and the normal to the average piperidine plane is 20.4 (4)°. The thiolactam system is nearly planar, as indicated by the value of the torsion angle C13—N8—C9—S1 being only 2.4 (4)° and the piperidyl ring adopts the C11,C12 *half-chair* conformation. In order to compare the geometry of the *N*-methyl-thiolactam system, we have performed a search of the Cambridge Crystallographic data Base [40] (CSD, version 5.31 plus 3 three updates) looking for the

Table 5
^{1}H NMR chemical shifts of *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-thione (**1**) in $CDCl_3$.

Carbon atoms	DEPT	δ_H (ppm)	Splitting pattern[a]	Coupling constants, *J* (Hz)	Correlations ^{1}H–^{1}H COSY
2′	CH	8.48	dd	2.3; ∼ 0.4	7.42
4′	CH	7.42	dt	7.9; 1.7; ∼0.6	8.48; 7.35
5′	CH	7.35	ddd	7.9; 4.7; ∼0.9	8.60; 7.42
6′	CH	8.60	dd	4.7; 1.7	7.35; 7.42
3	CH_2	3.25[b]	dt	18.9; 5.1; 5.1	3.09; 1.67
		3.09[b]	dt	18.9; 7.8; 7.8	3.25; 1.67
4	CH_2	1.67[b]	m		3.25; 3.09; 2.35; 1.96
5	CH_2	2.35[b]	m		4.81; 1.96; 1.67;
		1.96[b]	dddd	13.8; 9.0; 4.8; 1.3	4.81; 2.35; 1.67
6	CH	4.81_{eq}	dd	5.8; 4.4	2.35; 1.96
CH_3	CH_3	3.33	s		

[a] As seen in the spectrum, m, multiplet; s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; dt, doublet of triplets; dddd, doublet of doublet of doublet of doublets.
[b] δ_H values extracted from ^{13}C–^{1}H and ^{1}H–^{1}H COSY spectra.

Table 6
^{1}H NMR chemical shifts of *N*-1-methyl-5-(pyridin-3-yl)pyrrolidine-2-thione (**2**) in $CDCl_3$.

Carbon atoms	DEPT	δ_H (ppm)	Splitting pattern[a]	Coupling constants, *J* (Hz)	Correlations ^{1}H–^{1}H COSY	Correlations ^{1}H–^{1}H NOESY
2′	CH	8.52	dd	2.4; 0.9	7.50; 7.38	4.94; 3.08; 2.00
4′	CH	7.50	ddd	8.0; 2.2; 1.8	7.38; 8.52	4.94; 3.08; 2.00
5′	CH	7.38	ddd	7.9; 4.9; 0.8	8.64; 7.50; 8.52	8.64
6′	CH	8.64	dd	4.7; 1.6	7.38	7.50; 7.38
3	CH_2	3.26[b]	dddd (q)	18.1; 9.3; 6.6; 1.0 (3 × 1.0)	2.00; 3.14	4.94; 3.14; 2.62; 2.00
		3.14[b]	ddd (q)	18.1; 9.3; 6.4 (3 × 1.1)	2.62; 3.26	4.94; 3.26; 2.62; 2.00
4	CH_2	2.62[b]	dddd	13.2; 9.3; 8.7; 6.3	4.94; 2.00; 3.14	4.94; 3.26; 3.14; 2.00
		2.00[b]	dddd	13.1; 9.3; 6.5; 5.6	4.94; 2.62; 3.26	8.52; 7.50; 4.94; 3.26; 3.14; 2.62
5	CH	4.94_{ax}	dd	8.5; 5.3	2.62; 2.00	8.52; 7.50; 3.26; 3.14; 3.08; 2.62; 2.00
CH_3	CH_3	3.08[b]	s			8.52; 7.50; 4.94

[a] As seen in the spectrum, m, multiplet; s, singlet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; ddd (q), doublet of doublet of doublet of quartets; dddd (q), doublet of doublet of doublet of doublet of quartets.
[b] δ_H values extracted from ^{13}C–^{1}H and ^{1}H–^{1}H COSY spectra.

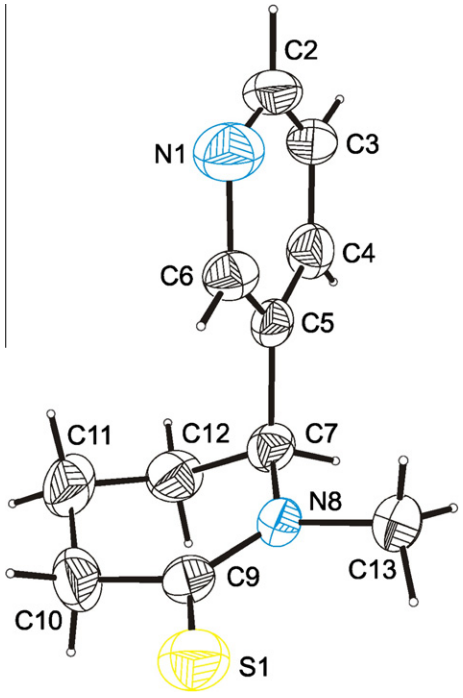


Fig. 4. Molecular structure of **1** in the crystal. Atomic displacement parameters are drawn at 40% probability level. H-atoms are represented as spheres of the arbitrary size.

Table 7
Torsion angles (°) for *N*-1-methyl-6-(pyridin-3-yl)piperidine-2-thione (**1**).

C(6)—N(1)—C(2)—C(3)	1.9 (5)
N(1)—C(2)—C(3)—C(4)	−0.2 (5)
C(2)—C(3)—C(4)—C(5)	−0.7 (5)
C(3)—C(4)—C(5)—C(6)	−0.2 (4)
C(3)—C(4)—C(5)—C(7)	177.9 (3)
C(2)—N(1)—C(6)—C(5)	−2.7 (5)
C(4)—C(5)—C(6)—N(1)	1.9 (4)
C(7)—C(5)—C(6)—N(1)	−176.2 (2)
C(4)—C(5)—C(7)—N(8)	153.2 (2)
C(4)—C(5)—C(7)—C(12)	−80.8 (4)
C(6)—C(5)—C(7)—C(12)	97.2 (3)
C(6)—C(5)—C(7)—N(8)	−28.8 (3)
C(5)—C(7)—N(8)—C(9)	101.7 (3)
C(12)—C(7)—N(8)—C(9)	−24.3 (4)
C(12)—C(7)—N(8)—C(13)	162.4 (3)
C(5)—C(7)—N(8)—C(13)	−71.6 (3)
C(13)—N(8)—C(9)—C(10)	−176.4 (2)
C(7)—N(8)—C(9)—C(10)	10.7 (4)
C(13)—N(8)—C(9)—S(1)	2.4 (4)
C(7)—N(8)—C(9)—S(1)	−170.56 (2)
N(8)—C(9)—C(10)—C(11)	−21.7 (4)
S(1)—C(9)—C(10)—C(11)	159.5 (3)
C(9)—C(10)—C(11)—C(12)	46.1 (4)
C(10)—C(11)—C(12)—C(7)	−59.5 (4)
N(8)—C(7)—C(12)—C(11)	48.4 (3)
C(5)—C(7)—C(12)—C(11)	−76.5 (4)

Table 8
Environment around the sulfur atom and parameters describing C—H···π interactions in the crystal of **1.**

	D···A (Å)	H···A (Å)	D—H···A (°)	Symmetry operations on A
C7—H7···S1	3.815 (3)	2.93	153	*x*, 1 + *y*, *z*
C10—H102···S1	3.928 (4)	3.11	144	−2 − *x*, 0.5 + *y*, −2 − *z*
C11—H111···S1	3.868 (4)	3.13	135	−1 + *x*, *y*, *z*
C12—H121···S1	3.973 (3)	3.17	143	−2 − *x*, 0.5 + *y*, −2 − *z*
C13—H132···S1	3.852 (4)	3.08	139	*x*, 1 + *y*, *z*
C13—H133···C_g[a]	3.452	2.98	112	1 + *x*, *y*, *z*

[a] Centroid of the pyridine ring.

C(sp^3)—N(CH_3)—C(=S)—C(sp^3) fragments containing sulfur atoms bonded exclusively to one carbon atom. Compared with the mean value of 28 C=S bonds deposited in the CSD, which amounts to 1.673 (3) Å, the value of 1.6891 (3) Å that we observe in **1** is considerably longer. The significant lengthening of the C=S bond might indicate more severe than in other crystal structures delocalization of electrons within the thiolactam group, in line with the aforementioned planarity of this group, although the expected simultaneous shortening of the C—N bond is not so well pronounced, the corresponding values being 1.329 (2) vs 1.320 (4) Å.

Studies of the crystal environment around S1 reveal several C—H groups at distances close to the sum of the van der Waals radii of S and H (1.80 and 1.1 Å, Table 8). Such an environment may induce an increase in the delocalization of the C=S bond and its consequent lengthening (vide infra). Multiple weak interactions of sulfur atoms with surrounding aliphatic groups have been recently reported to significantly stabilize an iron–sulfur protein molecule [41]. The crystal structure is additionally stabilized by the C13—H133 (*N*-methylpiperidine)···π (pyridine) intermolecular interactions (Table 8). Several C—H···S=C hydrogen bonds join molecules into layers parallel to (0 0 1) (Fig. 5) with interacting pyridine and methyl groups within these layers.

Nicotine, the parent compound of **2**, has not been studied in the solid state, as nicotine is a colourless oily liquid, boiling at atmospheric pressure at 246 °C. The thioanalogue of nicotine is a crystalline compound, not yet investigated by X-ray diffraction methods. Therefore we have decided to perform such investiga-

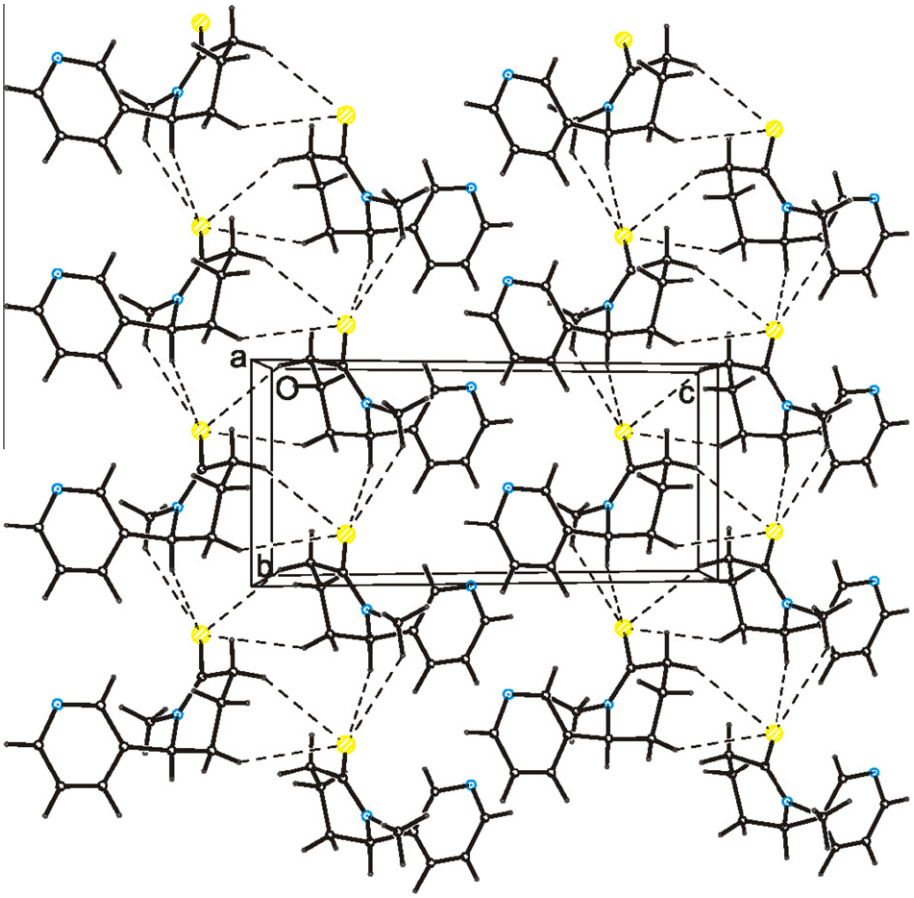


Fig. 5. Packing diagram of **1** showing crystal environment near thiocarbonyl group and C—H···S interactions.

tions to supplement structural characteristics of this important class of compounds. Fig. 6 shows the molecular structure, present in the crystal lattice while Fig. 7 displays a packing diagram. Torsion angles are given in Table 9.

The pyridine ring is essentially planar with a mean deviation from the six-atom plane being only 0.009 Å, while the pyrrolidine ring is slightly puckered approaching C7, C11 half-chair form. The mean deviation from the five-atom plane is 0.046 Å, while C7 and C11 deviate from the plane defined by N8, C9 and C10 by 0.10 (1) and −0.07 (1) Å, respectively. This is contrasted with the situation observed in nicotine monomethyl iodide and nicotine monohydrogen iodide [42] in which the pyrrolidine rings are appreciably folded. In the investigated thioanalogue (**2**), the pyridine and pyrrolidine rings are nearly perpendicular to each other, the interplanar angle being 84.1 (2)°, while the C2—C3—C7—N8 torsion angle is

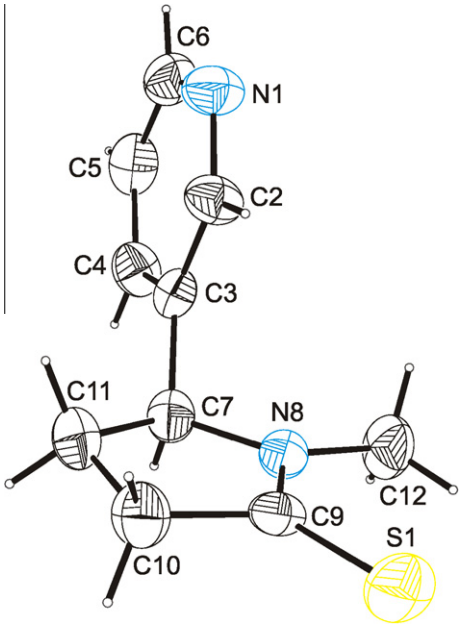


Fig. 6. Molecular structure of the thioanalogue of nicotine and atom numbering scheme. Thermal ellipsoids are drawn at 40% probability level. H-atoms are represented as spheres of the arbitrary size.

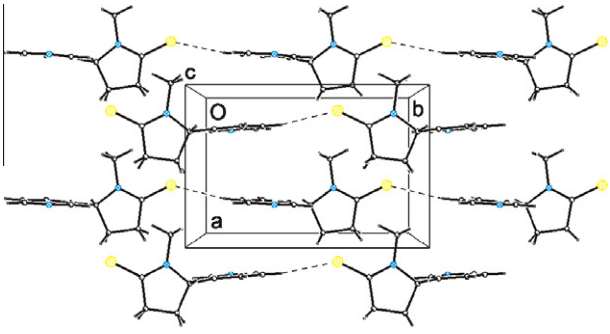


Fig. 7. Packing diagram as viewed along the *c*-direction showing stacking interactions between pyridine rings and C—H(pyridine)···S=C hydrogen bonds.

Table 9
Torsion angles (°) for *N*-1-methyl-5-pyridin-3-yl-pyrrolidine-2-thione (**2**).

C(6)—N(1)—C(2)—C(3)	1.2 (7)
N(1)—C(2)—C(3)—C(4)	0.9 (7)
N(1)—C(2)—C(3)—C(7)	−175.7 (4)
C(2)—C(3)—C(4)—C(5)	−2.1 (7)
C(7)—C(3)—C(4)—C(5)	174.6 (4)
C(3)—C(4)—C(5)—C(6)	1.3 (7)
C(2)—N(1)—C(6)—C(5)	−2.1 (7)
C(4)—C(5)—C(6)—N(1)	0.9 (8)
C(2)—C(3)—C(7)—N(8)	−49.0 (5)
C(4)—C(3)—C(7)—N(8)	134.5 (4)
C(2)—C(3)—C(7)—C(11)	67.1 (6)
C(4)—C(3)—C(7)—C(11)	−109.3 (5)
C(3)—C(7)—N(8)—C(9)	131.9 (4)
C(11)—C(7)—N(8)—C(9)	9.6 (5)
C(3)—C(7)—N(8)—C(12)	−58.5 (5)
C(11)—C(7)—N(8)—C(12)	179.2 (4)
C(12)—N(8)—C(9)—C(10)	−173.5 (4)
C(7)—N(8)—C(9)—C(10)	−4.4 (5)
C(12)—N(8)—C(9)—S(1)	4.9 (7)
C(7)—N(8)—C(9)—S(1)	173.9 (3)
N(8)—C(9)—C(10)—C(11)	−2.9 (6)
S(1)—C(9)—C(10)—C(11)	178.7 (4)
C(9)—C(10)—C(11)—C(7)	8.5 (6)
N(8)—C(7)—C(11)—C(10)	−10.5 (5)
C(3)—C(7)—C(11)—C(10)	−132.1 (4)

−49.0 (5)°. The intramolecular separation of the two nitrogen atoms N1 and N8 measures 4.293 (5) Å. Inspection of the CSD (version 5.31 plus 3 three updates) [40] reveals that among 30 compounds containing pyridin-3-yl-pyrrolidine moieties the mutual disposition of pyrrolidine and pyridine rings varies from 52° to 90°, with the mean value of 77 (1)° while the separation of the two nitrogen atoms is in the range 4.161–4.963 Å with the mean value of 4.497 (35) Å. It follows from this comparison that incorporation of the thiolactam group and connected with it flattening of the pyrrolidine ring promotes nearly perpendicular arrangement of the rings and brings the two nitrogen atoms at a distance closer than the average value. The geometry of the *N*-methyl-thiolactam system is comparable with that obtained from the CSD (vide supra). The corresponding values of the C═S and N—C (═S) bonds are: 1.673 (3) Å (the average of 28 observations) vs. 1.666 (3) Å (observed in the investigated crystal structure) and 1.329 (2) vs. 1.312 (4) Å, respectively.

In the crystal structure we observe an off-face-to-face (OFF) stacking interactions between pyridine rings arranged in stacks along the *a*-axis (Fig. 7). The centre to centre distance in the stack is 3.93 (4) Å while the distance from one plane to the centroid of the other plane is only 3.50 (4) Å. The interplanar angle between the two interacting rings is 8.63 (4)°, and the angle between the axis of the stack and the lattice *a*-direction is 23.7 (5)°. The interacting rings are mutually antiparallel, as indicated by the value of the angle between N1,C4 vectors in the interacting rings which amounts to 174.4 (5)°. Worth to note is that the stacking interactions have not been observed in **1**, which differs from **2** in that the relatively flat pyrrolidine-2-thione ring is replaced by the puckered piperidine-2-thione moiety.

4. Conclusions

Reported are the synthesis and structure of new thionalogues of *N*-methylanabasine and *N*-methylnicotine obtained by the solvent-free microwave-accelerated conversion of lactam to the corresponding thioanalogue. The advantages of microwave-expedited transformation in our case are not only shorter reaction times and the ease of manipulation but also good yield of a desired product. Introduction of the *N*-methyl-thiolactam group to the piperidine ring of anabasine changes its conformation to a *half-chair* in which the pyridine ring adopts a pseudo-axial disposition to avoid steric interactions with the *N*-methyl substituent. Hence, the rotation about the bond joining the pyridine and piperidine-2-thione rings may be sterically restricted. Comparison of molecular geometries in the solid state reveals that several C—H bonds present in the nearest vicinity of the sulfur atom can enhance the electron delocalization within the thiolactam group. Introduction of the thiocarbonyl group to the pyrrolidine ring induces a change of the pyrrolidine ring conformation from folded to nearly planar and results in an almost perpendicular orientation of this moiety with respect to the pyridine ring. This in turn creates conditions favourable for intermolecular stacking interactions.

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