Chemistry of Natural Compounds, Vol. 45, No. 2, 2009

SYNTHESIS OF THIOUREA DERIVATIVES OF THE ALKALOID ANABASINE AND CRYSTAL STRUCTURE OF *N*-(ANABASINO-1-THIOCARBONYL)FURAN-2-CARBOXAMIDE

I. V. Kulakov,[1*] O. A. Nurkenov,[1] D. M. Turdybekov,[2] B. T. Ibragimov,[3] S. A. Talipov,[3] Z. M. Zhambekov,[1] A. A. Ainabaev,[1] and K. M. Turdybekov[2]

UDC 547.94;548.737

A series of new N-acylsubstituted thioureas, the compositions and structures of which were determined by IR and PMR spectroscopy and mass spectrometry, were synthesized from the alkaloid anabasine. The crystal structure of one of the products, N-(anabasino-1-thiocarbonyl)furan-2-carboxamide, was confirmed by x-ray structure analysis. It was also shown that this compound exhibited moderate antibacterial activity.

Key words: alkaloid anabasine, thiourea derivatives, isothiocyanates, PMR spectroscopy, x-ray structure analysis, antibacterial activity.

Anabasine was discovered in 1929 by Orekhov A. P. from *Anabasis aphilla* and acts as a respiratory and cardiac stimulant. It is used in practical medicine as anabasine hydrochloride as an anti-smoking agent [1, 2]. It was also broadly used previously as an insecticide for pests of such industrial cultures as cotton, fruit trees, and vegetables and gourds [3, 4].

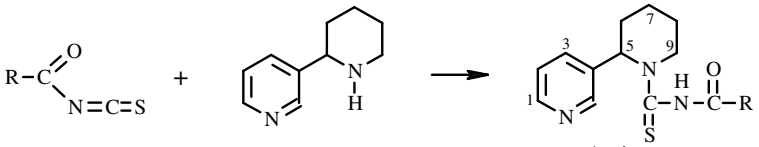
Introducing a sulfur atom into physiologically active compounds not only decreases their overall toxicity due to the facile oxidizability of its derivatives *in vivo* but also produces other types of bioactivity. Also, it is known that most thiourea derivatives possess valuable pharmacological properties and are used as antituberculosis, antitumor, antimicrobial, anti-ulcer, and other therapeutic agents [5-7].

We have previously synthesized thiourea derivatives of the alkaloids cytisine, 1-ephedrine, and d-pseudoephedrine with unsaturated and aromatic acyl derivatives.

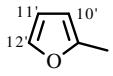
In continuation of that work we synthesized acyl-substituted thiourea derivatives based on anabasine by a convenient preparative isothiocyanate method. Isothiocyanates are very reactive compounds and react with amines under rather mild conditions.

The starting isothiocyanates were synthesized by a convenient preparative *in situ* method (without isolation) by heating the corresponding acid chlorides (benzoylchloride, *p*-methylbenzoylchloride, *p*-bromobenzoylchloride, 2-furancarboxylic acid chloride) with KSCN in acetone. Further reaction of the resulting isothiocyanate lutions with anabasine under mild conditions formed **1**-**4**.

The products were white (or slightly yellowish) crystalline compounds that were soluble in polar organic solvents.



1 - 4

R = C_6H_5- (**1**); 4-$CH_3C_6H_4$- (**2**); 4-BrC_6H_4 (**3**);  (**4**)

1) Institute of Organic Synthesis and Carbon Chemistry of the Republic of Kazakhstan, Kazakhstan, 100008, Karaganda, ul. Alikhanova, 1, fax (87212) 41-38-66, e-mail: kulakov_iv@mail.ru; 2) Scientific-Production Center Fitokhimiya, Kazakhstan, 100009, Karaganda, ul. Gazalieva, 4; 3) Institute of Bioorganic Chemistry, Uzbekistan, 100125, Tashkent, ul. Mirzo-Ulugbeka, 83. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 183-185, March-April, 2009. Original article submitted October 16, 2008.

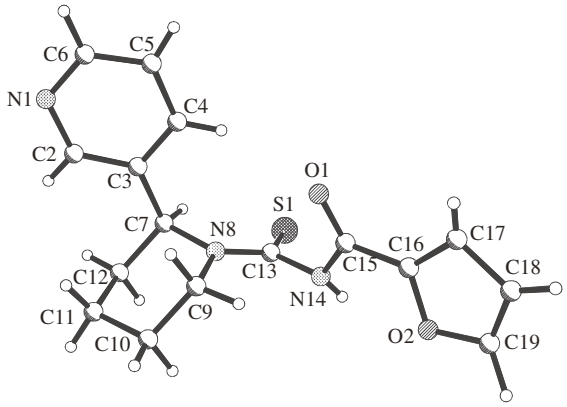


Fig. 1. Molecular structure of **4**.

The compositions, structures, and purities of synthesized **1**-**4** were confirmed by elemental analyses, IR and PMR spectroscopy, and mass spectrometry.

IR spectra of **1**-**4** contained absorption bands at 1545-1535 cm^{-1} that were characteristic of a C=S group and at 1687-1689 cm^{-1}, of a C(O)NH amide.

PMR spectra of **1**-**4** exhibited characteristic resonances for the alkaloid part. For example, proton resonances of the anabasine pyridine ring in the spectrum of **1** appeared at weak field; the H_1 and H_3 doublets at 8.71 and 8.00 ppm; the H_4 singlet, 8.50; and the H_2 doublet of doublets, at 7.47. The six methylene protons H_6, H_7, and H_8 resonated as a complicated multiplet at 1.37-2.05 ppm; methylene protons H_9 and methine proton H_5 of the piperidine ring, at 2.60 (multiplet) and 3.04 ppm (triplet), respectively. Aromatic benzene protons H_{10}, H_{11}, and H_{12} resonated as a doublet and two triplets at 7.93, 7.52, and 7.78 ppm, respectively. The N–H amide proton appeared as a singlet at 10.93 ppm.

The molecular structure of **4** was established from an x-ray structure analysis. Figure 1 shows a general view of **4**.

The bond lengths and angles were almost usual. The piperidine ring adopted an ideal chair conformation (ΔC^8s = 1Å), like in anabasine *O*,*O*-diethylthiophosphate, anabasine *O*,*O*-diisopropylthiophosphate [9], and anabasino(2-vinyloxyethylamino)methanethione [10]. The pyridine ring was planar within ±0.007 Å and was oriented axially (torsion angle C3C7C8C9 = 72.8°) relative to the piperidine ring, in contrast with anabasine *O*,*O*-diethylthiophosphate and anabasine *O*,*O*-diisopropylthiophosphate, where it was oriented equatorially. We previously observed this same orientation of the pyridine ring in anabasino(2-vinyloxyethylamino)methanethione, where quantum chemistry methods showed that this was due to non-bonding repulsion between the S atom and the pyridine ring. The bulky substituent on N8 was oriented equatorially. Atoms C13, N14, O1, and C15 were coplanar within ±0.027 Å. The furan ring was planar within ±0.004 Å.

Pharmacologically active groups such as 4-bromophenyl, which is found in many antiviral preparations, and a 2-furancarboxylic acid derivative, which is found in many antibacterial preparations based on nitrofuran, could enhance or cause the appearance of new types of bioactivity, including antibacterial, when introduced into thiourea derivatives of alkaloids.

Bioscreening of the compounds for antibacterial and antifungal activity showed the **3** and **4** were moderately active toward gram-positive strains (*Staphylococcus aureus*, *Bacillus subtilis*) and a gram-negative strain (*Eschericia coli*).

Thus, reaction of anabasine with benzoyl- and carboxyisothiocyanates produced new *N*-(anabasinothiocarbonyl) carbamides. The compositions and structures of the synthesized thiourea derivatives were confirmed by elemental analysis, IR and PMR spectroscopy, and mass spectrometry.

EXPERIMENTAL

IR spectra in KBr disks were recorded on an Avatar-320 spectrometer; PMR spectra in DMSO-d_6, on a Bruker DRX 500 spectrometer at 500 MHz relative to TMS (internal standard); mass spectra, in a Finnigan MAT.INCOS 50 instrument by direct sample introduction at ionization energy 70 eV. TLC was performed on Sorbfil plates using isopropanol:benzene:ammonia (10:5:2) with detection by iodine vapor.

X-ray Structure Analysis. Cell constants and intensities of 2572 independent reflections were measured on an Xcalibur diffractometer using CuKα-radiation, graphite monochromator, θ/2θ-scanning, 2θ ≤ 128.8°. Crystals were orthorhombic, a = 7.63120(10), b = 7.63120(10), c = 27.8819(5) Å, V = 1623.71(4) Å^3, d_{calc} = 1.290 g/cm^3, Z = 4 ($C_{16}H_{17}N_3O_2S$), space group $P4_1$. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for nonhydrogen atoms. H atoms were located in a difference synthesis. A total of 2308 reflections with $I > 2\sigma(I)$ was used in the calculations. The final agremeent factors were R = 0.036 and $_wR2$ = 0.094. The structure was solved and refined using the SHELXS-97 and SHELXL-97 programs. All geometric parameters of **4** were deposited in the Cambridge Crystallographic Data Centre (number CCDC 704556).

***N*-(Anabasino-1-thiocarbonyl)benzamide (1).** A solution of benzoylchloride (1.4 g, 0.01 mol) in acetone (10 mL) was stirred on a magnetic stirrer, treated with KSCN (0.97 g, 0.01 mol), and stirred and refluxed for 2 h. The KCl was filtered onto a paper filter. The solution was added to a solution of anabasine (1.62 g, 0.01 mol) in acetone (10 mL). The mixture was stirred for 3 h at 30-40°C. Solvent was distilled. The solid was crystallized with cooling from 2-propanol. The product was recrystallized from 2-propanol to afford a crystalline compound (1.82 g, 56.2%), mp 186-187°C, $C_{18}H_{19}N_3OS$. PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.37-2.05 (6H, m, H-6, H-7, H-8), 2.60 (2H, m, H-9), 3.04 (1H, t, $J_{5,6}$ = 13.0, H-5), 7.47 (1H, dd, $J_{2,1}$ = 4.6, $J_{2,3}$ = 4.78, H-2), 7.52-7.93 (5H, m, H-Ar), 8.00 (1H, d, $J_{3,2}$ = 4.78, H-3), 8.50 (1H, d, $J_{1,2}$ = 4.6, H-1), 8.71 (1H, s, H-4), 10.93 (1H, s, N–H).

***p*-Methyl-*N*-(anabasino-1-thiocarbonyl)benzamide (2)** was synthesized analogously to **1** from 4-methylbenzoic acid chloride (1.54 g, 0.01 mol), KSCN (0.97 g, 0.01 mol), and anabasine (1.62 g, 0.01 mol) to afford a crystalline compound (1.86 g, 55.0%), mp 77-78°C, $C_{19}H_{21}N_3OS$. PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.37-2.00 (6H, m, H-6, H-7, H-8), 2.30 (3H, s, C$\underline{H}_3$-Ar), 2.62 (2H, m, H-9), 3.00 (1H, t, $J_{5,6}$ = 13.0, H-5), 7.45 (1H, dd, $J_{2,1}$ = 4.5, $J_{2,3}$ = 4.75, H-2), 7.35, 7.91 (4H, dd, $J_{10',11'}$ = 8.18, $J_{11',10'}$ = 8.15, H-Ar), 8.00 (1H, d, $J_{3,2}$ = 4.6, H-3), 8.48 (1H, d, $J_{1,2}$ = 4.5, H-1), 8.65 (1H, s, H-4), 10.64 (1H, s, N–H).

***p*-Bromo-*N*-(anabasino-1-thiocarbonyl)benzamide (3)** was synthesized from 4-bromobenzoic acid chloride (2.20 g, 0.01 mol), KSCN (0.97 g, 0.01 mol), and anabasine (1.62 g, 0.01 mol) to afford a crystalline compound (2.46 g, 61.0%), mp 82-85°C, $C_{18}H_{18}BrN_3OS$. PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.35-2.10 (6H, m, H-6, H-7, H-8), 2.64 (2H, m, H-9), 3.01 (1H, t, $J_{5,6}$ = 13.0, H-5), 7.42 (1H, dd, $J_{2,1}$ = 4.5, $J_{2,3}$ = 4.75, H-2), 7.76, 7.92 (4H, dd, $J_{10',11'} = J_{11',10'}$ = 8.57, H-Ar), 7.53 (1H, d, $J_{3,2}$ = 4.6, H-3), 8.50 (1H, d, $J_{1,2}$ = 4.5, H-1), 8.70 (1H, s, H-4), 10.78 (1H, s, N–H).

***N*-(Anabasino-1-thiocarbonyl)furan-2-carboxamide (4)** was synthesized from 2-furancarboxylic acid chloride (1.30 g, 0.01 mol), KSCN (0.97, 0.01 mol), and anabasine (1.62 g, 0.01 mol) to afford a crystalline compound (1.41 g, 45%), mp 173-174°C, $C_{16}H_{17}N_3O_2S$. Mass spectrum (EI, 70 eV, *m/z*, *I*rel, %): 315 (30) $[M]^+$, 282 (50), 204 (76), 161 (100), 95 (93). PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.32-2.00 (6H, m, H-6, H-7, H-8), 2.60 (2H, m, H-9), 3.03 (1H, t, $J_{5,6}$ = 13.0, H-5), 7.44 (1H, dd, $J_{2,1}$ = 4.5, $J_{2,3}$ = 4.7, H-2), 6.71 (1H, dd, $J_{11',12'}$ = 1.72, $J_{11',10'}$ = 1.53, H′-11), 7.51 (1H, d, $J_{3,2}$ = 4.6, H-3), 7.88 (1H, br.s, H′-10), 7.98 (1H, d, $J_{12',11'}$ = 1.72, H′-12), 8.51 (1H, d, $J_{1,2}$ = 4.5, H-1), 8.68 (1H, s, H-4), 10.79 (1H, s, N–H).

REFERENCES

1. A. P. Orekhov, *Chemistry of Alkaloids* [in Russian], Khimiya, Moscow (1955).
2. A. S. Sadykov, *Chemistry of Alkaloids Anabasis Aphilla* [in Russian], Tashkent (1950).
3. S. S. Sakhobiddinov, *Wild Medicinal Plants of Central Asia* [in Russian], Tashkent (1948).
4. L. K. Klyshev, *Biology of Anabasis aphilla* [in Russian], Alma-Ata (1961).
5. V. V. Mozolis and S. P. Iokubaitite, *Usp. Khim.*, **7**, 1310 (1973).
6. H. Hasegawa et al., U.S. Pat. No. 5,190,961, "Thiourea derivatives and antimicrobial agent and anti-ulcer agent containing the same," March 2, 1993; *Ref. Zh. Khim.*, 15059P (1995).
7. M. D. Mashkovskii, *Drugs of the 20th Century* [in Russian], Novaya Volna, Moscow (1998).

8. A. A. Ainabaev, I. V. Kulakov, O. A. Nurkenov, and A. M. Gazaliev, in: Proceedings of the All-Russia Scientific Conference “Modern Problems of Organic Chemistry,” Dedicated to the 100th Brithday of Academician N. N. Vorozhtsov, Founder and First Director of the Sci. Inst. Org. Chem., Sib. Br., Russ. Acad. Sci., Novosibirsk (2007), p. 129.
9. A. M. Gazaliev, M. Zh. Zhurinov, S. A. Dyusembaev, K. M. Turdybekov, S. V. Lindeman, and Yu. V. Struchkov, *Khim. Prir. Soedin.*, 500 (1990).
10. M. K. Ibraev, D. M. Turdybekov, A. T. Takibaeva, O. A. Nurkenov, K. M. Turdybekov, A. M. Gazaliev, and S. M. Adekenov, *Zh. Obshch. Khim.*, **76**, 672 (2006).