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Synthesis and Spatial Structure of 1-(Cytisin-1-ylmethyl)benzimidazole-2-thione

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Abstract—New derivatives of cytisine and anabasine alkaloids containing benzothiazole and benzimidazole fragments were discussed. Physicochemical characteristics of the new compounds were determined. The structure of 1-(cytisin-1-yl-methyl)benzimidazole-2-thione was studied by X-ray diffraction analysis.

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Benzimidazole derivatives attract attention by their high biological activity, they are used to produce a variety of drugs [1–3] and as tuberculocidal, antimicrobial, antineoplastic, anti-inflammatory, antiulcer agent [4]. Depending on the substitution in the scaffold they can be assigned to different classes of drugs. The presence of small substituents in the positions 2 and 5 of the benzimidazole moiety is typical for anthelmintic drugs. On the contrary, benzimidazole derivatives with bulky substituents in the 2 position are used for treating gastric ulcer and duodenal ulcer. The presence of bulky substituents at the atoms N^1 and C^2 is characteristic of H1-antihistamines [5]. Benzimidazole system is also present in a number of natural substances [4].

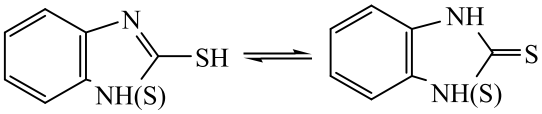
This defines the high importance of further development of research in the field of chemistry of benzimidazole and its derivatives. It is promising to look for new pharmacologically active compounds, particularly promising is the polyfunctional targeted synthesis of benzimidazole derivatives which exhibit selective activity. An important area in benzimidazole chemistry is chemical modification with various functions, leading to a variety of compounds with a broad spectrum of biological activities.

It is known that the compound having at least one reactive hydrogen atom react with formaldehyde and amines to form a Mannich base. Recently, the range of compounds entering into the Mannich reaction is greatly expanded.

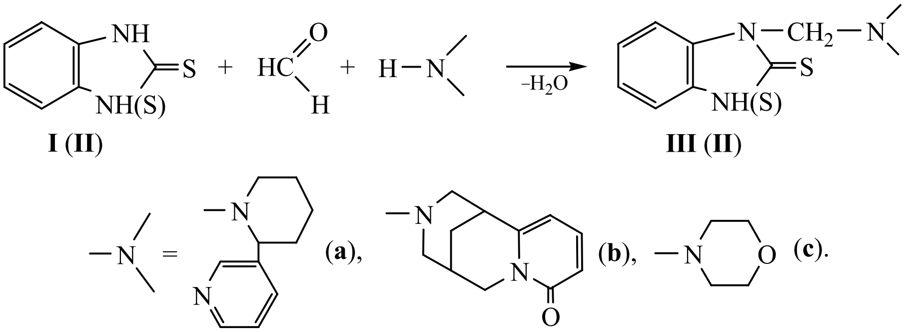
Synthesis of new Mannich compounds based on 2-mercaptobenzimidasole (**I**) and 2-mercaptobenzothiazole (**II**), the study of their structure, physicochemical properties, reactivity, and mechanisms of formation are the object of this work.

Cytisine, anabasine, and morpholine were used as the amines. Anabasine and cytisine are alkaloids, natural nitrogen-containing organic compounds of the basic nature with strong physiological and pharmacological action. Anabasine is used as insecticide, as well as for the treatment of head lice and ringworm in animals [6]. Cytisine acts as an exciter of the respiratory and cardiac function, as well as exhibits insecticidal, anti-smoking and other activities [4]. Morpholine derivatives also are part of the drugs and are used as narcotic analgesics, i.e., belong to the neurotrophic substances of central action, the main feature of which is the selective control of pain sensitivity without loss of consciousness [1]. In this regard, the use of biogenic amines in modifying benzimidazole and benzothiazole would make possible not only to expand the spectrum of biological activity, but also the new synthetic possibility of compounds obtained.

It is known that 2-mercaptobenzimidazole **I** and 2-mercaptobenzothiazole **II** can react both in the thiol and thione forms.



According to the UV spectral data, in solutions the compounds are mainly in the thione form irrespective of the nature of the solvent; and only the alkalis shift the equilibrium toward the thiol form. The reaction giving the Mannich bases can be represented as follows.



The reaction of the starting compound with formaldehyde and amine was performed in an alcohol solution at cooling. The synthesized Mannich bases containing cytisine or anabasine fragment are crystalline or oily substances, respectively. These compounds are insoluble in water and readily soluble in most organic solvents. They are unstable at high temperatures and easily decompose by the action of aqueous alkaline and acid solutions: a 10% hydrochloric acid even at room temperature decomposes them into the original substances. The decomposition occurs significantly faster and more completely when heated. Diluted aqueous solutions of sodium hydroxide and ammonia act similarly.

The resulting compounds **III**, **IV** may be of interest for a comprehensive study of their biological activity. Physicochemical constants, elemental analysis data of the Mannich bases of 2-mercaptobenzimidazole and 2-mercaptobenzothiazole are shown in Table 1.

The structures of compounds **III**, **IV** was confirmed by the IR and ^{1}H NMR spectroscopy and X-ray diffraction data. Thus, continuing the study of stereochemistry of cytisine derivatives we carried out the XRD analysis of 1-(cytisin-1-ylmethyl)benzimidazol-2-thione **IIIb**. General view of its molecule is shown in the figure.

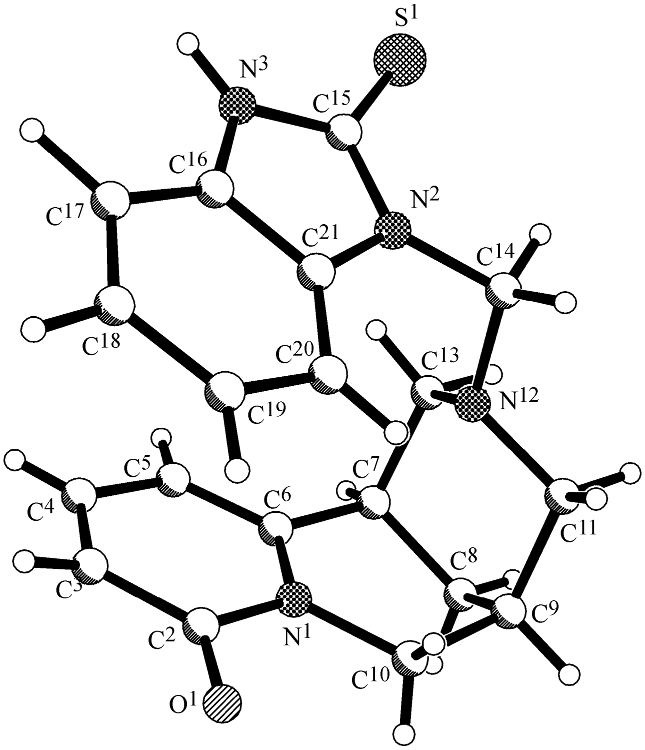
The bond lengths and angles in cytisine scaffold are close to the standard values [7]. The exception is the bond angles at the atom N^{12}: here the plane trigonal coordination is observed (sum of bond angles is 341°). In the previously investigated *N*-methylcytisine [8] and *N*-cyanomethylcytisine [9] the coordination of the N^{12} atom is pyramidal (sum of the bond angles equals 335.7° and 334.0°, respectively). The difference in the coordination of the nitrogen atom in the above-mentioned molecules is due to the mesomeric effect.

The dihydropyridine ring is planar to within 0.005 Å. The carbonyl atom O^1 is almost in this plane (deviation

Table 1. Physicochemical constants, elemental analysis of compounds **III**, **IV**

Comp. no.	Yield, %	mp, °C	R_f	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
Ia	77.71	155–156	0.68^a	66.67	6.18	17.30	$C_{18}H_{20}N_4S$	66.63	6.21	17.27
Ib	84.79	296–297	0.88^b	64.67	5.78	15.93	$C_{19}H_{20}N_4OS$	64.75	5.72	15.90
Ic	86.78	211–212	0.93^b	57.68	6.07	16.87	$C_{12}H_{15}N_3OS$	57.81	6.06	16.85
IIa	68.66	57–58	0.85^a	63.34	5.65	12.36	$C_{18}H_{19}N_3S_2$	63.31	5.61	12.30
IIb	89.94	140–141	0.75^a	61.79	5.22	11.38	$C_{19}H_{19}N_3OS_2$	61.76	5.18	11.37
IIc	68.29	144–145	0.80^a	54.02	5.26	10.58	$C_{12}H_{14}N_2OS_2$	54.11	5.30	10.52

[a] Acetone–benzene, 1:1. [b] Isopropanol–ammonia–water, 7:2:1.



Crystal structure of 1-(cytisine-1-ylmethyl)benzimidazol-2-thione **IIIb** molecule.

is 0.06 Å). The tetrahydropyridine ring is in a *semi-chair* conformation (ΔC_s^8 10.5°). The bridging atom C^8 deviates from the mean plane of the remaining ring atoms by 0.76 Å. The piperidine ring adopts an almost perfect *chair* conformation (ΔC_s^9 0.73°).

Atoms of benzimidazole fragment are coplanar within ±0.006 Å, the sulfur atom lies in the plane of the remaining atoms. We believe that the flattening of the substituent is due to the coupling of the electron clouds of free electron pair of the nitrogen atom and of the double bond of the sulfur atom in imidazolethione. The bulky substituent is equatorially oriented relative to the piperidine ring (torsion angle $C^7C^{13}N^{12}C^{14}$ is –165.4°), while the average plane through the benzimidazole-2-thione is virtually parallel to the mean plane of cytisine (interplanar distance is 4.26 Å). The molecules in the crystal are bound by a strong intermolecular hydrogen bond N^3–H(*x*, *y*, *z*)···O^1(1 – *x*, 0.5 + *y*, 2 – *z*) (N^3–H···O^1 1.87 Å, <N^3–HO^1 = 162.79°), which stabilizes the molecule and builds endless spiral along the axis *b*. Main characteristics of the crystal lattice parameters are shown in Tables 2, 3.

EXPERIMENTAL

The melting points were determined on a Boetius instrument. The reaction progress and purity of the products were monitored by thin layer chromatography using Silufol UV-254 plates.

XRD analysis. The unit cell parameters and the intensities of the 1827 independent reflections were measured on a Bruker P4 automatic diffractometer at room temperature (MoK_α-irradiation, graphite monochromator, θ/2θ-scanning, $2\theta \leq 52°$). The transparent crystals are monoclinic (0.8×0.4×0.15), $C_{19}H_{20}N_4OS$; cell parameters: *a* 8.2961(7), *b* 12.4753(9), *c* 8.9381(7) Å, β 106.362(7)°, *V* 887.60(12) Å^3, d_{calc} 1.319 g cm^{-3}, *Z* 2, space group *P*21. The structure was solved by the direct method and refined by full-matrix least-square method in anisotropic approximation for non-hydrogen atoms. The positions of H atoms were geometrically calculated and refined in the *rider* model. In the calculations 1735 reflections with $I > 2\sigma(I)$ were used. The final divergence factors are *R* 0.0314 and wR_2 0.0846. The structure was solved by the program SIR-2002 [10] and refined by the program SHELXL-97 [11]. The geometrical parameters of compound **Ib** were deposited in the Cambridge Structural Database (CCDC 773770).

1-(Anabasin-1-ylmethyl)benzimidazole-2-thione (IIIa). To a solution of 0.5 g (0.003 mol) of 2-mercaptobenzimidazole **I** in 50 ml of alcohol was added with stirring 0.25 g (0.003 mol) of formalin solution. Then to the mixture was added 0.52 ml (0.003 mol) of anabasine dissolved in alcohol. After evaporation of the solvent, the thick orange oil was triturated with diethyl ether. The product is a white amorphous substance, mp 155–156°C (ethyl alcohol, water). Yield 77.71%, R_f 0.68.

1-(Cytisin-1-ylmethyl)benzimidazole-2-thione (IIIb) was synthesized similarly from 0.5 g (0.003 mol) of 2-mercaptobenzimidazole **I**, 0.25 g (0.003 mol) of formalin, and 0.63 g (0.003 mol) of cytisine. Upon standing the reaction mixture for 4 h the precipitate forms. Yield 1 g (84.8%), colorless crystals, mp 296–297°C (alcohol), R_f 0.88.

1-(Morpholin-4-ylmethyl)benzimidazole-2-thione (IIIc) was synthesized similarly from 0.5 g (0.003 mol) of 2-mercaptobenzimidazole **I**, 0.25 g (0.0033 mol) of formalin, and 0.29 g (0.0033 mol) of morpholine. Upon standing the reaction mixture for 4 h the precipitate forms, which was recrystallized from alcohol.

Table 2. Bond lengths (*d*, Å) and bond angles (ω, deg) in the molecule of **IIIb**

Bond, angle	*d*, ω	Bond	ω	Bond, angle	*d*, ω	Bond	ω
$S^1{-}C^{15}$	1.673(3)	$C^{14}N^{12}C^{13}$	113.64(18)	$C^7{-}C^8$	1.525(4)	$C^8C^9C^{11}$	111.0(2)
$N^1{-}C^6$	1.368(3)	$C^{14}N^{12}C^{11}$	115.47(18)	$C^7{-}C^{13}$	1.531(3)	$N^1C^{10}C^9$	114.9(2)
$N^1{-}C^2$	1.398(3)	$C^{13}N^{12}C^{11}$	112.10(18)	$C^8{-}C^9$	1.521(4)	$N^{12}C^{11}C^9$	109.37(18)
$N^1{-}C^{10}$	1.482(3)	$O^1C^2N^1$	118.2(3)	$C^9{-}C^{10}$	1.515(4)	$N^{12}C^{13}C^7$	108.57(18)
$N^2{-}C^{15}$	1.363(3)	$O^1C^2C^3$	125.6(3)	$C^9{-}C^{11}$	1.524(3)	$N^{12}C^{14}N^2$	109.05(15)
$N^2{-}C^{21}$	1.395(3)	$N^1C^2C^3$	116.2(3)	$C^{16}{-}C^{21}$	1.385(3)	$N^3C^{15}N^2$	106.4(2)
$N^2{-}C^{14}$	1.463(3)	$C^4C^3C^2$	121.6(3)	$C^{16}{-}C^{17}$	1.395(4)	$N^3C^{15}S^1$	126.68(19)
$N^3{-}C^{15}$	1.355(3)	$C^3C^4C^5$	120.7(3)	$C^{17}{-}C^{18}$	1.371(6)	$N^2C^{15}S^1$	126.95(17)
$N^3{-}C^{16}$	1.379(4)	$C^6C^5C^4$	119.2(3)	$C^{18}{-}C^{19}$	1.392(5)	$N^3C^{16}C^{21}$	107.2(2)
$N^{12}{-}C^{14}$	1.442(3)	$C^5C^6N^1$	120.1(2)	$C^{19}{-}C^{20}$	1.378(4)	$N^3C^{16}C^{17}$	131.9(3)
$N^{12}{-}C^{13}$	1.457(3)	$C^5C^6C^7$	120.9(2)	$C^{20}{-}C^{21}$	1.387(4)	$C^{21}C^{16}C^{17}$	120.9(3)
$N^{12}{-}C^{11}$	1.459(3)	$N^1C^6C^7$	118.8(2)	$C^6N^1C^2$	122.2(2)	$C^{18}C^{17}C^{16}$	117.0(3)
$O^1{-}C^2$	1.248(4)	$C^6C^7C^8$	111.8(2)	$C^6N^1C^{10}$	123.0(2)	$C^{17}C^{18}C^{19}$	121.7(3)
$C^2{-}C^3$	1.410(4)	$C^6C^7C^{13}$	107.42(18)	$C^2N^1C^{10}$	114.8(2)	$C^{20}C^{19}C^{18}$	121.9(3)
$C^3{-}C^4$	1.339(5)	$C^8C^7C^{13}$	109.3(2)	$C^{15}N^2C^{21}$	110.16(18)	$C^{19}C^{20}C^{21}$	116.3(3)
$C^4{-}C^5$	1.404(5)	$C^9C^8C^7$	106.83(18)	$C^{15}N^2C^{14}$	126.07(19)	$C^{16}C^{21}C^{20}$	122.2(2)
$C^5{-}C^6$	1.360(4)	$C^{10}C^9C^8$	108.6(2)	$C^{21}N^2C^{14}$	123.7(2)	$C^{16}C^{21}N^2$	105.9(2)
$C^6{-}C^7$	1.512(3)	$C^{10}C^9C^{11}$	112.69(19)	$C^{15}N^3C^{16}$	110.3(2)	$C^{20}C^{21}N^2$	131.8(2)

Table 3. Torsion angles in the molecule of **IIIb**

Angle	τ, deg	Angle	τ, deg	Angle	τ, deg	Angle	τ, deg
$C^6N^1C^2O^1$	177.2(2)	$C^5C^6C^7C^{13}$	83.4(3)	$C^8C^7C^{13}N^{12}$	–61.8(2)	$C^{17}C^{18}C^{19}C^{20}$	–1.3(6)
$C^{10}N^1C^2O^1$	–2.2(3)	$N^1C^6C^7C^{13}$	–91.3(3)	$C^{13}N^{12}C^{14}N^2$	79.0(2)	$C^{18}C^{19}C^{20}C^{21}$	0.5(5)
$C^6N^1C^2C^3$	–3.1(3)	$C^6C^7C^8C^9$	–58.6(3)	$C^{11}N^{12}C^{14}N^2$	–149.40(19)	$N^3C^{16}C^{21}C^{20}$	178.3(2)
$C^{10}N^1C^2C^3$	177.6(2)	$C^{13}C^7C^8C^9$	60.2(2)	$C^{15}N^2C^{14}N^{12}$	–111.5(2)	$C^{17}C^{16}C^{21}C^{20}$	–1.1(4)
$O^1C^2C^3C^4$	–177.5(3)	$C^7C^8C^9C^{10}$	65.8(2)	$C^{21}N^2C^{14}N^{12}$	66.7(3)	$N^3C^{16}C^{21}N^2$	0.4(3)
$N^1C^2C^3C^4$	2.8(5)	$C^7C^8C^9C^{11}$	–58.6(2)	$C^{16}N^3C^{15}N^2$	0.1(3)	$C^{17}C^{16}C^{21}N^2$	–179.0(2)
$C^2C^3C^4C^5$	–0.3(6)	$C^6N^1C^{10}C^9$	12.9(3)	$C^{16}N^3C^{15}S^1$	–178.64(17)	$C^{19}C^{20}C^{21}C^{16}$	0.7(4)
$C^3C^4C^5C^6$	–2.0(5)	$C^2N^1C^{10}C^9$	–167.8(2)	$C^{21}N^2C^{15}N^3$	0.1(2)	$C^{19}C^{20}C^{21}N^2$	178.0(3)
$C^4C^5C^6N^1$	1.8(4)	$C^8C^9C^{10}N^1$	–43.4(3)	$C^{14}N^2C^{15}N^3$	178.48(19)	$C^{15}N^2C^{21}C^{16}$	–0.4(2)
$C^4C^5C^6C^7$	–172.9(3)	$C^{11}C^9C^{10}N^1$	80.0(3)	$C^{21}N^2C^{15}S^1$	178.91(16)	$C^{14}N^2C^{21}C^{16}$	–178.74(18)
$C^2N^1C^6C^5$	0.9(3)	$C^{14}N^{12}C^{11}C^9$	168.49(19)	$C^{14}N^2C^{15}S^1$	–2.8(3)	$C^{15}N^2C^{21}C^{20}$	–178.0(2)
$C^{10}N^1C^6C^5$	–179.9(2)	$C^{13}N^{12}C^{11}C^9$	–59.2(2)	$C^{15}N^3C^{16}C^{21}$	–0.4(3)	$C^{14}N^2C^{21}C^{20}$	3.6(4)
$C^2N^1C^6C^7$	175.67(19)	$C^{10}C^9C^{11}N^{12}$	–64.1(3)	$C^{15}N^3C^{16}C^{17}$	179.0(3)		
$C^{10}N^1C^6C^7$	–5.1(3)	$C^{14}N^{12}C^{13}C^7$	–165.40(18)	$N^3C^{16}C^{17}C^{18}$	–179.0(3)		
$C^5C^6C^7C^8$	–156.7(2)	$C^{11}N^{12}C^{13}C^7$	61.4(2)	$C^{21}C^{16}C^{17}C^{18}$	0.3(4)		
$N^1C^6C^7C^8$	28.6(3)	$C^6C^7C^{13}N^{12}$	59.6(2)	$C^{16}C^{17}C^{18}C^{19}$	0.9(6)		

Yield 0.82 g (84.8%), colorless amorphous solid, mp 211–212°C, R_f 0.93.

1-(Anabasin-1-ylmethyl)benzothiazole-2-thione (IVa) was obtained analogously from 0.97 g (0.006 mol) of anabasine, 0.45 g of 40% formalin solution and 1 g (0.006 mol) of 2-mercaptobenzothiazole **II**. After evaporation of the solvent, a thick brown oily substance was obtained, which crystallizes after boiling in hexane. Yield 68.66%, mp 57–58°C, R_f 0.85.

1-(Cytisin-1-ylmethyl)benzothiazole-2-thione (IVb) was synthesized analogously from 1 g (0.006 mol) of 2-mercaptobenzothiazole **II**, 0.45 g (0.006 mol) of formalin solution, and 1.14 g (0.006 mol) of cytisine. After evaporation of the solvent, the resulting oil was triturated with ether and recrystallized from a mixture of ethanol and ether (1:1) to give 2 g (89.94%) of pale yellow powder, mp 140–141°C, R_f 0.75.

1-(Morpholin-1-ylmethyl)benzothiazole-2-thione (IVc) was synthesized analogously from 1 g (0.006 mol) of 2-mercaptobenzothiazole **II**, 0.45 g (0.006 mol) of formalin solution, and 0.52 ml (0.006 mol) of morpholine. After recrystallization from alcohol 1.1 g (89.94%) of light yellow crystalline substance was obtained, mp 144–145°C, R_f 0.80.

REFERENCES

1. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Medicine, 2000, vol. 1, 2.
2. Lagorce, J.F., Fatimi, J., Lakhdar, M., Chabernaud, M.L., Buxeraud, J., and Raby, C., *Arzneimit*., 1995, vol. 45, p. 1207.
3. Garaliene, V., Labanauskas, L., Brukstus, A., and Dauksas, V., *Arzneimit*., 1998, vol. 48, p. 1137.
4. Pozharskii, A.F., Garnovskii, A.D., and Simonov, A.M., *Usp. Khim*., 1966, vol. 35, no. 2, p. 261.
5. Velik, J., Baliharova, V., Fink-Gremmels, J., Bull, S., Lamka, J., and Skalova, L., *Res. Vet. Sci*., 2004, vol. 76, p. 95.
6. Orekhov, A.P., *Khimiya alkaloidov* (Alkaloid Chemistry), Moscow: Akad. Nauk SSSR.
7. Allen, F.H., Kennard, O., Watson, D.G., Brammer, L., Orpen, A.G., and Taylor, R., *J. Chem. Soc., Perkin Trans. 2*, 1987, no. 3, p. 1356.
8. Freer, A.A., Robins, D.J., and Sheldrake, G.N., *Acta Cryst. (C)*, 1987, vol. 43, p. 1119.
9. Nurkenov, O.A., Gazaliev, A.M., Shalbaeva, A.B., Turdybekov, K.M., Zhurinov, M.J., Aubakirova, A., *Zh. Obshch. Khim*., 1999, vol. 69, no. 4, p. 675.
10. Burla, M.C., Camalli, M., Carrozzini, B., Cascarano, G.L., Giacovazzo, C., Polidori, G., and Spagna, R., *J. Appl. Cryst*., 2003, vol. 36, no. 4, p. 1103.
11. Sheldrick, G.M., *SHELXL-97. Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, 1997.