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ALKYLATION AND AMINOMETHYLATION OF 1,3-DIHYDRO-2*H*-BENZIMIDAZOLE-2-THIONE

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Alkylation of 1,3-dihydro-2H-benzimidazole-2-thione (2-mercaptobenzimidazole) with bromoethane and chloroacetic acid derivatives occurrs at the sulfur atom, leading to the corresponding 2-sulfanylbenzimidazole derivatives. Aminomethylation of 1,3-dihydro-2H-benzimidazole-2-thione with piperidine and 4-methylpiperidine gives reaction products at both nitrogen atoms, while reaction with morpholine gives derivative at only one nitrogen atom, which is in an equilibrium with the starting compound and bis-adduct in DMSO solution.

Keywords: 1,3-dihydro-2*H*-benzimidazole-2-thione, 2-mercaptobenzimidazole, 2-sulfanylbenzimidazole, alkylation, aminomethylation.

Benzimidazole derivatives attract a continuing interest of researchers due to diverse biological activity and wide application in medicine [1-7]. Various biological effects of these compounds are explained by their bioisosteric nature with respect to natural nucleotides, enabling easy interaction with biological polymers in living cells. This is especially true for compounds of 2-mercaptobenzimidazole series, which show antimicrobial [8-10], anthelmintic [11], antihistamine [12], antiulcer [13], neurotropic [14], and anticonvulsant [15] activity. 2-[(2-Pyridylmethyl)sulfinyl]benzimidazoles, such as omeprazole, lansoprazole, and pantoprazole, can suppress hydrochloric acid secretion in stomach [16], which is the main factor in pathogenesis of stomach and duodenal ulcers, reflux esophagitis, and damage from non-steroidal anti-inflammatory drugs [17]. The anxiolytic medication aphobazolum [18], the active ingredient of which is 5-ethoxy-2-(2-morpholinoethyl)-sulfanylbenzimidazole, also offers positive results in the therapy of gallstone disease [19] and in early diagnosis of cancers [20]. Besides, 2-mercaptobenzimidazole derivatives are widely used for detection and removal of copper [21], mercury [22-24], and lead traces [25] from sewage waters, as well as for anticorrosive protection of metals [26-29].

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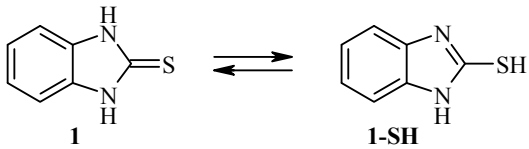
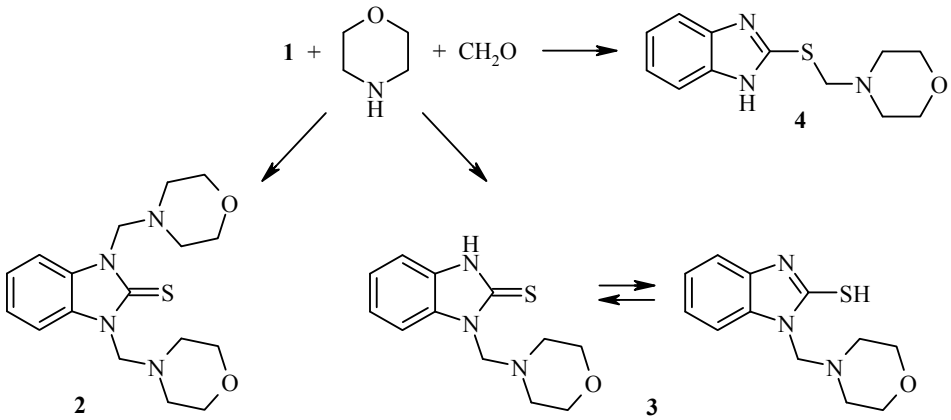
The search for new drugs containing the fragment of 2-mercaptobenzimidazole motivates the need for detailed understanding of such simple but synthetically important transformations as alkylation and aminomethylation of 2-mercaptobenzimidazole derivatives (1,3-dihydro-2*H*-benzimidazole-2-thione (**1**), more accurate). However, the structures of alkylation and acylation products obtained from compound **1** were not always reliably proved, and occasionally there are major contradictions in the published data.



1 **1-SH**

For example, already in 1957 it was shown that aminomethylation of compound **1** in methanol with a wide range of secondary amines led to the exclusive formation of bis-adducts at both nitrogen atoms in all cases even when equimolar amounts of reagents were used [30], and this conclusion was confirmed by elemental analysis data. The most stable bis-adduct was formed with morpholine **2**, that could even be recrystallized from ethanol. However, a recent report [31] indicated that aminomethylation of benzimidazole-2-thione **1** in ethanol with 1 equiv. of morpholine, cytisine, or anabasine gave products from reaction at only one of nitrogen atoms, in particular, compound **3**. These conclusions were also based on elemental analysis (!), as well as X-ray crystallography of monoadduct between benzimidazolethione **1** and anabasine. It is interesting that the melting points reported in these articles for two supposedly different products obtained by aminomethylation of compound **1** with morpholine were very close (mp 213-214°C [30], mp 211-212°C [31]).



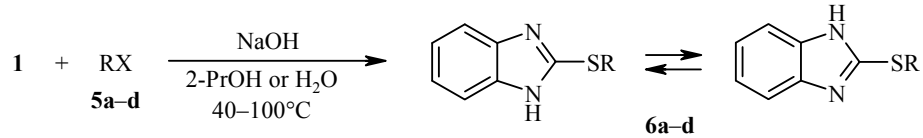
2 **3** **4**

Meanwhile, the author of an earlier publication [32] reported the formation of monoadduct **3** (mp 205°C) in 80% yield upon reaction of equimolar amounts of reagents in ethyl acetate, while doubling the amount of morpholine and formaldehyde gave the bis-adduct **2** (mp 135°C). It should be noted that the ^{1}H NMR spectra given in article [32] for both of the obtained products were practically identical (with differences only in relative intensity of signals), but the shape of signal at 5.1 ppm (doublet of doublets!), which was assigned by the author to protons of NCH_2N group, was in clear disagreement with the proposed structures **2** and **3**. Finally, the authors of article [15] claimed that reaction with morpholine and a whole series of other secondary amines in methanol gave monoaminomethylation products at the sulfur atom (structure **4**)! Remarkably, the melting point of condensation product with morpholine (130-132°C [15]) in this case was much lower than in articles [30-32], but its ^{1}H NMR spectrum was in poor agreement with the proposed structure. In conclusion, we should note that, according to the literature data, aminomethylation of 5-substituted benzimidazole-2-thiones with secondary amines usually proceeds simultaneously at both nitrogen atoms [33-36], while reactions with aromatic amines produced both bis- [35] and monoadducts [37].

In our opinion, these inconsistencies could be caused by at least three factors. First of all, there is a possible tautomerism in starting compounds (involving migration of acidic proton between three heteroatoms) as well as in some aminomethylation products. Secondly, compound **1** can react with electrophiles both at the sulfur atom as well as at one or two of the nitrogen atoms. Thirdly, the aminomethylation products are not very stable and can decompose to starting materials, especially in the presence of acids or bases. In order to clear the reasons for the observed inconsistencies, we have performed alkylation and aminomethylation of compound **1** with the reagents reported in previous publications as well as we have studied the structure of compound **1** and its aminomethylation products with modern instrumental methods.

First of all, we should note that the obtained ^{1}H and ^{13}C NMR spectra for DMSO-d_6 solution of the starting compound **1** corresponded to the structure of 1,3-dihydro-2*H*-benzimidazole-2-thione (**1**), but not 2-mercaptobenzimidazole (1*H*-benzimidazole-2-thiol) (**1-SH**). For example, the ^{1}H NMR spectrum of this compound contained a symmetric AA'BB' system multiplet of aromatic protons at 7.06-7.15 ppm, while two equivalent NH protons gave one broadened signal at 12.5 ppm; the ^{13}C NMR spectrum contained only 4 signals at 109.3 (C-4,7), 122.1 (C-5,6), 132.2 (C-3a,7a), and 168.1 ppm (C=S). Such a spectral pattern could also be possible, in principle, for the structure **1-SH**, provided that proton exchange between both nitrogen atoms was fast on the NMR timescale. However, the position of the C-2 signal in ^{13}C NMR spectrum was not in agreement with thiol structure. As will be shown below, the ^{13}C NMR spectra of compounds of type **6**, containing an alkylated sulfur atom and aromatic benzimidazole fragment, exhibit the signal of the C-2 atom around 150 ppm, while the same signal was observed above 170 ppm for the products of bisaminoalkylation at both nitrogen atoms, which are definitely known to have the symmetrical thione structure **8**. The IR spectrum of compound **1**, recorded in KBr pellet, featured strong bands for NH stretching vibrations at 3170 cm^{-1} and only a very weak absorption band at 2570 cm^{-1}, which could be assigned to the stretching vibrations of S–H belonging to thiol form, but this band disappeared when recording the spectrum in Nujol [38]. Thus, even if fast thione-thiol tautomerism is present, its equilibrium would be practically completely shifted to the thione form both in DMSO solution and in solid phase. This conclusion is in good agreement with the structural data of monocyclic imidazole-2-thione derivatives, which also exist mainly or exclusively in the thione form [39], and with the results of quantum-chemical calculations for the tautomeric equilibrium **1** $\rightleftarrows$ **1-SH** [40].

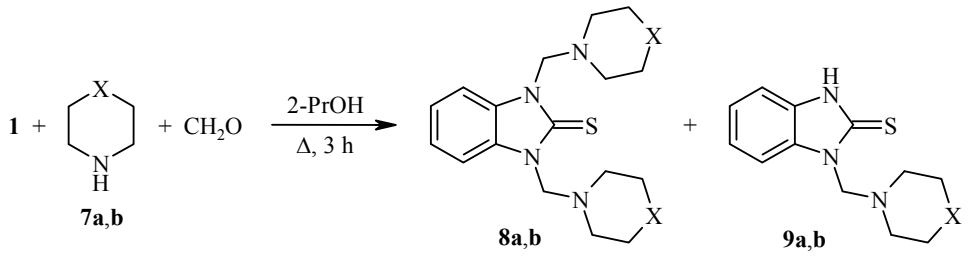
In order to determine the spectral characteristics of "fixed" **1-SH** thiol form of 2-mercaptobenzimidazole derivatives, we alkylated benzimidazole-2-thione **1** in the presence of NaOH with ethyl bromide, sodium chloroacetate, ethyl chloroacetate, and chloroacetamide. These reactions proceeded as described in the literature [41-45] exclusively or mainly at the sulfur atom and gave 2-(ethylsulfanyl)-1*H*-benzimidazole (**6a**) or derivatives of [(1*H*-benzimidazol-2-yl)sulfanyl]acetic acid **6b-d**.



a R = Et, **b** R = CH_2COOH, **c** R = CH_2COOEt, **d** R = CH_2CONH_2; **5 a** X = Br, **b–d** X = Cl

The possible migration of proton between the two nitrogen atoms in compounds **6a-d** was quite fast on the NMR timescale and led to a noticeable simplification of their spectra. This process occurred the fastest in the case of [(1*H*-benzimidazol-2-yl)sulfanyl]acetic acid (**6b**), and its ^{1}H NMR spectrum contained two accurate symmetrical multiplets of aromatic AA'XX' proton system at 7.07-7.13 (H-5,6) and 7.38-7.44 ppm (H-4,7), while the proton signals of NH and OH groups and water molecules were at the baseline. However, the ^{13}C NMR signals of the closest atoms to the tautomeric fragment (C-3a,7a and C-4,7) were already significantly broadened for this compound. The ^{1}H NMR spectra of the other alkylation products **6a**,**c**,**d** contained a downfield multiplet for the aromatic protons H-4,7 (spectrum of the amide **6d**) that was noticeably broadened or lacked fine structure at all (compounds **6a**,**c**), and, correspondingly, the ^{13}C NMR spectra of these compounds had broad signals of C-4,7 atoms and, in particular, C-3a,7a atoms, which nearly merged with baseline in the

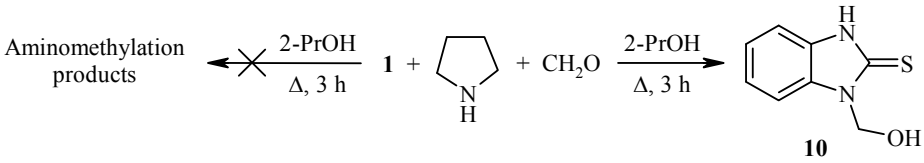
case of 2-(ethylsulfanyl)-1*H*-benzimidazole (**6a**). Finally, we should note that the NMR spectra for the product obtained in reaction of benzimidazole-2-thione **1** with ethyl chloroacetate (**5c**) contained weak signals of minor component (approximately 8%), which probably originated from double alkylation at both the sulfur atom and a nitrogen atom.



7a,**b** **8a**,**b** **9a**,**b**

7–9 a X = CH_2, **b** X = CHMe

We obtained the most interesting results when studying the aminomethylation of benzimidazole-2-thione **1** in isopropanol. In agreement with the literature [30], the interaction with even 1 equiv. of piperidine (**7a**) or 4-methylpiperidine (**7b**) produced the bis-adducts **8a**,**b** substituted at both nitrogen atoms. The symmetrical structure of these compounds still possesing the thione fragment unequivocally follows from NMR spectra. For example, the ^{1}H NMR spectra of compounds **8a**,**b** showed two well resolved aromatic multiplets of AA'XX' system at 7.20 and 7.45 ppm – slightly downfield compared to the products of alkylation at sulfur atom. The ^{13}C NMR spectra contained a characteristic signal at 171 ppm for the C-2 atom of thione group. At the same time, ^{1}H NMR spectra indicated the presence of monoaminomethylation products **9a**,**b** as minor components (10-16%) in the both of the isolated mixtures.



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However, performing the reaction under the same conditions with pyrrolidine yielded only the monohydroxymethyl derivative **10** instead of aminomethylation product. This compound was probably an intermediate in the previous cases as well, but in this case the reaction for some reason did not proceed further. Beside that, the spectrum of the obtained product contained weak signals, which could be assigned to the bis(hydroxymethyl) derivative. Interestingly, only the bis(hydroxymethyl) derivative of benzimidazole-2-thione **1** and its various transformations have been described previously [30].

The main difficulties arose with the compositional and structural characterization of products obtained by aminomethylation of benzimidazole-2-thione **1** with morpholine, while the literature precedents were quite contradictory. The product isolated in this study had the same melting range (215-216°C) as previously reported [30, 31], while the ^{1}H NMR (Fig. 1*a,b*) and ^{13}C NMR spectra for DMSO solution contained doubled sets of closely located signals, therefore the product represented a mixture of related compounds. The ^{1}H NMR spectrum featured two narrow multiplets of morpholine ring at 2.63 ppm (NCH_2) and 3.52 ppm (OCH_2) (the signals of mono- and bis-adducts **2** and **3** exactly matched in this case), very similar singlets of the NCH_2N fragment in mono- (5.02 ppm) and bis-adduct (5.11 ppm), multiplets of three aromatic protons of the monoadduct **3** at 7.14-7.20 ppm (H-4,5,6) and its fourth proton H-7 at 7.42-7.48 ppm, two characteristic multiplets of AA'XX' system in bis-adduct **2** (7.23-7.29 and 7.49-7.55 ppm), as well as the symmetrical multiplet of AA'BB' system of aromatic protons in the starting benzimidazole-2-thione **1** at 7.06-7.14 ppm. It was shown by 1D TOCSY experiment that these three aromatic systems are independent (Fig. 1*c*,*d*,*e*).

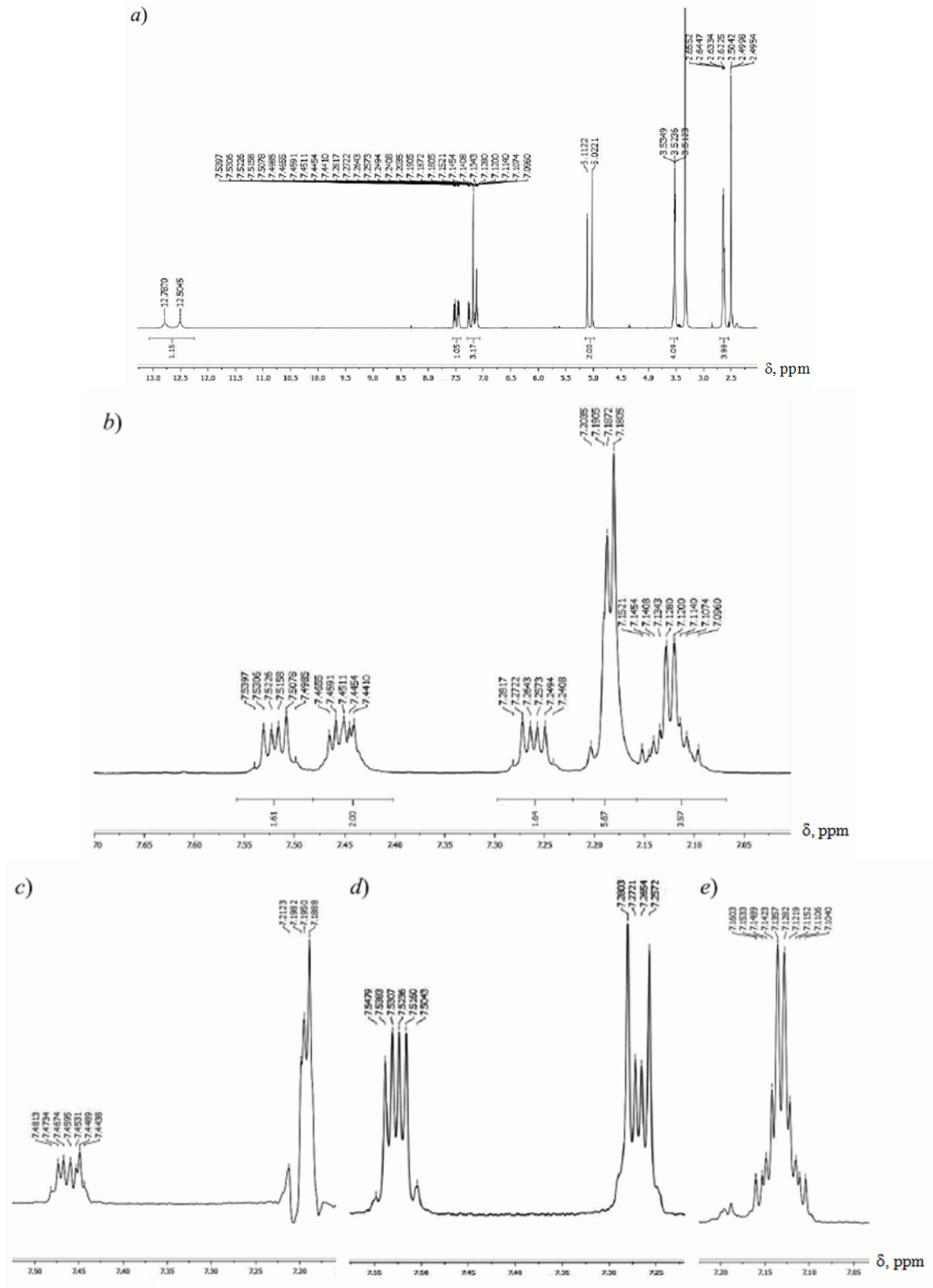

Fig. 1. The ^{1}H NMR spectrum (DMSO-d_6) of aminomethylation product obtained from benzimidazole-2-thione **1** and morpholine (*a*) and expansion of its aromatic part (*b*) on the deposits of compounds **3** (*c*), **2** (*d*), and **1** (*e*), showing by 1D TOCSY spectra.

The 2D NOESY spectrum of this product contained a cross peak of NCH_2N protons at 5.11 ppm with the aromatic proton multiplet of bis-adduct at downfield region, confirming its assignment specifically to bis-adduct. The signal of NCH_2N protons at 5.02 ppm correlated with the downfield multiplet of one aromatic proton of monoadduct at 7.45 ppm, allowing to assign the latter to the H-7 proton. There were broad singlets in the downfield region for the NH protons of starting benzimidazole-2-thione **1** (12.50 ppm) and monoadduct **3** (12.80 ppm). The assignment of ^{13}C NMR signals of the NCH_2N group and C-4–C-7 atoms was achieved for both products by using ^{1}H–^{13}C HSQC spectrum, the signals of C=S group were identified from ^{1}H–^{13}C HMBC spectrum, which showed their correlation with the corresponding signals of the NCH_2N group protons.

The NH proton signal in the ^{1}H NMR spectrum of monoadduct **3** (at 12.80 ppm) was coupled to the ^{15}N signal at 159 ppm, according to the ^{1}H–^{15}N HSQC experiment. The ^{1}H–^{15}N HMBC experiment showed the signal of the N-1 atom at 159.5 ppm, which correlated with the signals of H-7 (through 3 bonds) and NCH_2N protons (through 2 bonds). Besides that, correlation of morpholine nitrogen atom (around 50 ppm) was observed with protons of the adjacent CH_2NCH_2 methylene groups of the heterocycle (through 2 bonds) and OCH_2 groups (through 3 bonds). However, we should note that its correlation with signals of the adjacent NCH_2N methylene fragment through 2 bonds was not observed, probably due to the low value of spin-spin coupling constant.

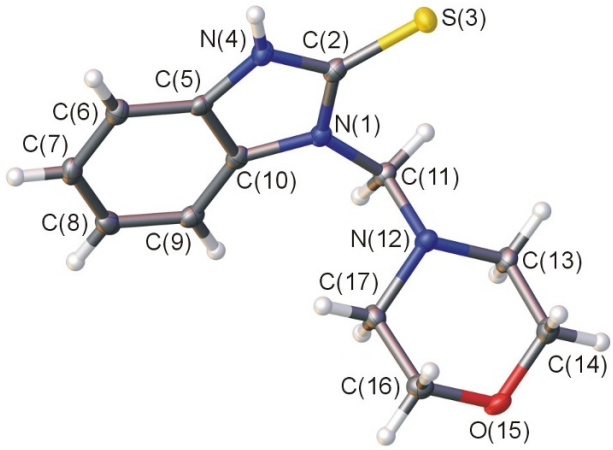

Fig. 2. The crystal structure of compound **3** according to X-ray structural analysis.

Thus, we established that the major component in the obtained mixture was the monoaminomethylation product **3**, which formed equilibrium in solution phase with the bis-adduct **2** and the starting compound **1** (Fig. 1). We successfully obtained pure monoadduct **3** by recrystallization and characterized its structure by X-ray structural analysis (Fig. 2). However, upon dissolving in DMSO, according to NMR spectroscopy data, this compound quite readily formed an equilibrium mixture with its disproportionation products: bis-adduct **2** and the starting benzimidazole-2-thione **1**. The equilibrium ratio of **3** : (**2**+**1**) was approximately 2.4 : 1 at 26°C, with only slight and reversible changes (to 2.9:1) upon increasing the temperature to 120°C. It should be mentioned here that the ^{1}H NMR spectra of the mono- and bis-adduct had clear differences in the aromatic region (Fig. 1), but were nearly identical in the upfield region, while the set of signals for the **2**+**1** mixture was very similar in the number of signals and intensity ratios to the set of signals observed for the monoadduct **3**. In addition, nearly all the corresponding ^{13}C NMR signals of product **3** and **2**+**1** mixture were also very similar.

Finally, in contrast to the previously published data [30], we found that the bis-adduct **2** could not be obtained even by aminomethylation of benzimidazole-2-thione **1** with 2 equiv. of morpholine and formaldehyde. That experiment produced a precipitate with melting point and ^{1}H NMR spectrum identical to those of product obtained by using equimolar amounts of reactants.

According to X-ray structural analysis, the length of C=S bond in compound **3** was 1.682(2) Å, the length of C(2)–N(1) bond was 1.374(3) Å, C(2)–N(4) bond was 1.352(3) Å, while the unconjugated bonds N(1)–C(11) (1.447 (3) Å) and N(12)–C(11) (1.460 (3) Å) were noticeably longer. These values clearly illustrate the effect of *n*-π-conjugation on the C=S and C–N bond orders and are in good agreement with the literature data. For example, the length of C=S bond in thioacetone is equal to 1.636 Å [46], in thiobenzamide – 1.665 Å [46], in dimethylamide of thioacetic acid – 1.674 Å [46], while in thiourea the length of this bond is already 1.720 Å, at the same time as the length of C–N bonds in thiourea is only 1.340 Å [47]. Apparently, the conjugation of C=S bond with the lone electron pairs of adjacent nitrogen atoms causes its gradual lengthening (for comparison, the single C–S bond in methyl mercaptan has the length of 1.830 Å [46]), while the C–N bonds are noticeably shortened at the same time. Thus, compound **3** exists in thione form in crystalline state as well, as additionally confirmed by the absence of IR absorption bands in the 2600-2550 cm^{-1} range, but its >N–C(=S)–N< fragment is structurally very similar to a molecule of thiourea.

In conclusion, the compound commonly known as 2-mercaptobenzimidazole exists in thione form both in DMSO solution and in solid phase, and is actually 1,3-dihydro-2*H*-benzimidazole-2-thione. Its alkylation occurs at sulfur atom, leading to 2-sulfanylbenzimidazole derivatives, while aminomethylation occurs at nitrogen atoms. Depending on the nature of amine, these reactions may produce bis-adducts at both nitrogen atoms, as well as monoadducts, but the reaction with pyrrolidine unexpectedly stops at the stage of monohydroxymethyl adduct. The aminomethylation of benzimidazole-2-thione with piperidine and 4-methylpiperidine gives predominantly bis-adducts, while the major product in reaction with morpholine is the derivative at only one nitrogen atom, which undergoes facile and reversible disproportionation in DMSO solution, forming a mixture of bis-adduct and the starting compound.

EXPERIMENTAL

IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance III 400 instrument (400 and 100 MHz, respectively) in DMSO-d_6, with the residual solvent proton (2.50 ppm for ^{1}H nuclei) and carbon atom of solvent (39.5 ppm for ^{13}C nuclei) signals as internal standards. The ^{13}C NMR signals were assigned by additional DEPT and ^{1}H–^{13}C HSQC experiments. The ^{15}N chemical shift values were determined by ^{1}H–^{15}N HSQC and ^{1}H–^{15}N HMBC experiments, and are reported on "ammonia scale" (relative to the signal of liquid ammonia). The mixing time in 2D NOESY experiments was 700 ms, in 1D TOCSY experiments – 40-70 ms. High-resolution mass spectra were recorded on a Bruker microTOF instrument, using electrospray ionization. Melting points were determined on a Stuart SMP30 apparatus. The purity of the isolated compounds was controlled by TLC on Sorbfil UV-254 plates (Imid Ltd., Russia). 1,3-Dihydro-2*H*-benzimidazole-2-thione (**1**) (98% assay) was purchased from Lancaster, commercially available reagents and solvents were used.

1,3-Dihydro-2*H*-benzimidazole-2-thione (1). IR spectrum, ν, cm^{-1}: 3158 (s), 3112 (s), 2984, 2879, 2762, 2571 (w), 1625 (w), 1513, 1467, 1357, 1179, 744, 709, 659, 600. ^{1}H NMR spectrum, δ, ppm: 7.06-7.15 (4H, m, H Ar); 12.50 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 109.3 (C-4,7); 122.1 (C-5,6); 132.2 (C-3a,7a); 168.1 (C=S).

Aminomethylation of 1,3-Dihydro-2*H*-benzimidazole-2-thione (1) with Morpholine. Benzimidazole-2-thione **1** (1.50 g, 10 mmol) and morpholine (0.87 ml, 0.87 g, 10 mmol) were dissolved in 2-PrOH (30 ml); 37% aqueous formaldehyde (0.90 ml, 12 mmol) was added, and the mixture was refluxed for 3 h (precipitate formed almost immediately). The precipitate was filtered off, dried, and recrystallized from EtOH. The major component of the obtained mixture was compound **3**, which partially disproportionated in solution to bis-adduct **2** and the starting compound **1**. Yield 1.70 g (68%).

1,3-Bis(morpholin-4-ylmethyl)-1,3-dihydro-2*H*-benzimidazole-2-thione (2). The NMR spectral parameters of this compound were determined for its mixtures with the monoadduct **3** and the starting

benzimidazole-2-thione **1**. ^{1}H NMR spectrum, δ, ppm: 2.63 (8H, m, $2CH_2NCH_2$); 3.52 (8H, m, $2CH_2OCH_2$); 5.11 (4H, s, $2NCH_2N$); 7.23-7.29 (2H, AA'XX' system, H-5,6); 7.49-7.55 (2H, AA'XX' system, H-4,7). ^{13}C NMR spectrum, δ, ppm: 51.0 (CH_2NCH_2); 65.4 (NCH_2N); 66.0 (CH_2OCH_2); 110.7 (C-4,7); 122.9 (C-5,6); 132.1 (C-3a,7a); 171.4 (C-2).

1-(Morpholin-4-ylmethyl)-1,3-dihydro-2*H*-benzimidazole-2-thione (3). Colorless crystals, mp 215-216°C. IR spectrum, ν, cm^{-1}: 3463 (br.), 3146, 3096, 3055, 2989, 2949, 2933, 2869, 2830, 2804, 2748, 2709, 1516, 1470, 1438, 1110, 1000, 739. ^{1}H NMR spectrum of the obtained compound is presented in Figure 1. ^{1}H NMR spectrum, δ, ppm: 2.63 (4H, m, CH_2NCH_2); 3.52 (4H, m, CH_2OCH_2); 5.02 (2H, s, NCH_2N); 7.14-7.20 (3H, m, H-4,5,6); 7.42-7.48 (1H, m, H-7); 12.80 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 51.0 (CH_2NCH_2); 64.5 (NCH_2N); 66.0 (CH_2OCH_2); 109.5 and 110.7 (C-4,7); 122.2 and 123.0 (C-5,6); 130.6 and 133.1 (C-3a,7a); 169.7 (C-2). Found, *m*/*z*: 250.1009 $[M+H]^+$. $C_{12}H_{16}N_3OS$. Calculated, *m*/*z*: 250.1009.

Reaction of benzimidazole-2-thione 1 with 2 equiv. of morpholine was performed analogously to the aminomethylation procedure described above, using one half the amount of benzimidazole-2-thione **1** (0.75 g, 5 mmol). Yield 0.75 g (60%), white crystals, mp 215-216°C. The ^{1}H NMR spectrum of the obtained compound was identical to the spectrum of product obtained by reaction with 1 equiv. of morpholine.

2-(Ethylsulfanyl)-1*H*-benzimidazole (6a). Sodium hydroxide (1.2 g, 30 mmol) was dissolved in 2-PrOH (30 ml); benzimidazole-2-thione **1** (4.5 g, 30 mmol) was added, followed by treatment of the stirred and cooled mixture with bromoethane (2.3 ml, 3.3 g, 30 mmol). The reaction mixture was then heated for 1 h at 40°C (precipitate formed almost immediately). The suspension was cooled, the precipitate was filtered off, washed with H_2O, and dried. Yield 5.0 g (94%), colorless crystals, mp 175-177°C (mp 168-170°C [41], mp 170°C [42]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 3.26 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 7.06-7.10 (2H, m, H-5,6); 7.40 (2H, br. s, H-4,7); 12.43 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 15.2 (CH_3); 25.5 (CH_2); 113.7 (br. s, C-4,7); 121.2 (C-5,6); 139.0 (br. s, C-3a,7a); 150.0 (C-2). Found, *m*/*z*: 179.0636 $[M+H]^+$. $C_9H_{11}N_2S$. Calculated, *m*/*z*: 179.0639.

(1*H*-Benzimidazol-2-ylsulfanyl)acetic Acid (6b). Sodium hydroxide (1.2 g, 30 mmol) was dissolved in H_2O (30 ml); benzimidazole-2-thione **1** (4.5 g, 30 mmol) was added followed by sodium chloroacetate (3.5 g, 30 mmol). The mixture was refluxed for 3 h, cooled, and acidified with dilute HCl to weakly acidic pH. The obtained precipitate was filtered off, dried, and recrystallized from MeOH. Yield 5.05 g (81%), colorless crystals, mp 214-216°C (mp 214°C [42], mp 212-213°C [43]). ^{1}H NMR spectrum, δ, ppm: 4.11 (2H, s, CH_2); 7.07-7.13 (2H, m, H-5,6); 7.38-7.44 (2H, m, H-4,7). ^{13}C NMR spectrum, δ, ppm: 33.6 (CH_2); 113.8 (br. s, C-4,7); 121.4 (C-5,6); 139.5 (br. s, C-3a,7a); 149.6 (C-2); 169.8 (C=O). Found, *m*/*z*: 209.0378 $[M+H]^+$. $C_9H_9N_2O_2S$. Calculated, *m*/*z*: 209.0379.

Ethyl (1*H*-Benzimidazol-2-ylsulfanyl)acetate (6c). Sodium hydroxide (1.6 g, 40 mmol) was dissolved in 2-PrOH (40 ml); benzimidazole-2-thione **1** (6.0 g, 40 mmol) was added followed by ethyl chloroacetate (4.3 ml, 4.9 g, 40 mmol). The reaction mixture was refluxed for 5 h, cooled, and poured into water. The precipitate formed was filtered off, washed with water, dried, and recrystallized from CCl_4. Yield 7.2 g (76%), colorless crystals, mp 94-96°C (mp 92-93°C [43], mp 105°C [46]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.13 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 4.18 (2H, s, SCH_2); 7.08-7.13 (2H, m, H-5,6); 7.41 (2H, br. s, H-4,7); 12.55 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 13.9 (CH_3); 33.3 (SCH_2); 61.1 (OCH_2); 110.3 (br. s) and 117.3 (br. s, C-4,7); 121.4 (br. s, C-5,6); 136.6 (br. s) and 143.4 (br. s, C-3a,7a); 149.1 (C-2); 168.5 (C=O). The spectra contained also some signals due to an impurity, possibly a double alkylation product at the nitrogen atom. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.55 (2H, s); 7.28-7.36 (with a broad signal of the main product in the background, ~2H, m); 7.57 (1H, d, *J* = 7.8); 7.87 (1H, d, *J* = 7.3). ^{13}C NMR spectrum, δ, ppm: 111.8; 118.5; 123.4; 125.4. Found, *m*/*z*: 237.0694. $C_{11}H_{13}N_2O_2S$ $[M+H]^+$. Calculated, *m*/*z*: 237.0692.

Amide of (1*H*-Benzimidazol-2-ylsulfanyl)acetic Acid (6d). Sodium hydroxide (1.60 g, 40 mmol) was dissolved in 2-PrOH (70 ml), benzimidazole-2-thione **1** (6.00 g, 40 mmol) was added followed by portionwise addition of chloroacetamide (3.75 g, 40 mmol). The reaction mixture was refluxed for 3 h, cooled, the precipitate was filtered off, washed with water, and dried. Yield 6.75 g (81%), colorless crystals, mp 206-208°C

(mp 206-207°C [47]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.99 (2H, s, CH_2); 7.08-7.13 (2H, m, H-5,6); 7.21 (1H, br. s) and 7.72 (1H, br. s, $CONH_2$); 7.38-7.44 (2H, m, H-4,7); 11.50-13.50 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 35.1 (CH_2); 113.8 (br. s, C-4,7); 121.4 (C-5,6); 139.4 (br. s, C-3a,7a); 150.0 (C-2); 169.3 (C=O). Found, *m*/*z*: 208.0542 $[M+H]^+$. $C_9H_{10}N_3OS$. Calculated, *m*/*z*: 208.0539.

1,3-Bis(piperidin-1-ylmethyl)-1,3-dihydro-2*H*-benzimidazole-2-thione (8a). Benzimidazole-2-thione **1** (1.50 g, 10 mmol) and piperidine (**7a**) (1.0 ml, 0.86 g, 10 mmol) were dissolved in 2-PrOH (30 ml); 37% aqueous formaldehyde solution (0.9 ml, 12 mmol) was added, and the mixture was refluxed for 3 h. The reaction mixture was left overnight in a refrigerator. The precipitate that formed was filtered off, dried, and recrystallized from aqueous EtOH. Yield 0.31 g (18%), colorless crystals, mp 115-117°C (mp 124-125°C [13]). ^{1}H NMR spectrum, δ, ppm: 1.30-1.42 (4H, m, 4,4'-CH_2 piperidine); 1.42-1.55 (8H, m, 3,3',5,5'-CH_2 piperidine); 2.55-2.70 (8H, m, 2,2',6,6'-CH_2 piperidine); 5.05 (4H, s, $2NCH_2N$); 7.18-7.25 (2H, AA'XX' system, H-5,6); 7.42-7.49 (2H, AA'XX' system, H-4,7); impurity signals (15-16%) are also present, possibly the monoaminomethylation product **9a**: 2.30-2.40 (4H, m, 2,6-CH_2 piperidine); 4.97 (2H, s, NCH_2N); 7.12-7.18 (3H, m, H Ar); 7.38-7.42 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.6 (C-4 of piperidine); 25.3 (C-3,5 of piperidine); 51.7 (C-2,6 of piperidine); 66.0 (NCH_2N); 110.7 (C-4,7); 122.7 (C-5,6); 132.2 (C-3a,7a); 171.2 (C-2). Found, *m*/*z*: 345.2113 $[M+H]^+$. $C_{19}H_{29}N_4S$. Calculated, *m*/*z*: 345.2107.

1,3-Bis[(4-methylpiperidin-1-yl)methyl]-1,3-dihydro-2*H*-benzimidazole-2-thione (8b) was obtained analogously to compound **8a** from 4-methylpiperidine (**7b**) (1.2 ml, 1.00 g, 10 mmol). Yield 0.65 g (35%), colorless crystals, mp 118-119°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.86 (6H, d, J = 7.5, $2CH_3$); 1.00-1.13 (4H, m, 3,3',5,5'-CH_{ax} piperidine); 1.20-1.35 (2H, m, 4,4'-CH_2 piperidine); 1.50-1.60 (4H, dm, $J_{gem} \approx 11.5$, 3,3',5,5'-CH_{eq} piperidine); 2.15-2.26 (4H, m, 2,2',6,6'-CH_{ax} piperidine); 3.00-3.08 (4H, dm, $J_{gem} \approx 11.3$, 2,2',6,6'-CH_{eq} piperidyl); 5.06 (4H, s, $2NCH_2N$); 7.17-7.24 (2H, AA'XX' system, H-5,6); 7.41-7.48 (2H, AA'XX' system, H-4,7); impurity signals (~10%) were also present, possibly the monoaminomethylation product **9b**: 4.98 (2H, s, NCH_2N); 7.13-7.17 (3H, m, H Ar); 7.37-7.41 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.7 (CH_3); 29.9 (C-4 piperidine); 33.7 (C-3,5 piperidine); 51.1 (C-2,6 piperidine); 65.7 (NCH_2N); 110.6 (C-4,7); 122.6 (C-5,6); 132.2 (C-3a,7a); 171.2 (C-2). Found, *m*/*z*: 395.2240 $[M+Na]^+$. $C_{21}H_{32}N_4NaS$. Calculated, *m*/*z*: 395.2240.

1-(Hydroxymethyl)-1,3-dihydro-2*H*-benzimidazole-2-thione (10). Benzimidazole-2-thione **1** (1.5 g, 10 mmol) and pyrrolidine (0.8 ml, 0.7 g, 10 mmol) were dissolved in 2-PrOH (30 ml); 37% aqueous formaldehyde solution (0.9 ml, 12 mmol) was added, and the mixture was refluxed for 3 h. The reaction mixture was cooled and the solvent was evaporated. The residue crystallized upon treatment with petroleum ether, the product was filtered off, dried, and recrystallized from EtOAc. Yield 0.55 g (31%), white crystals, mp > 270°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.62 (2H, d, J = 7.0, CH_2); 6.55 (1H, t, J = 7.3, OH); 7.14-7.18 (3H, m, H Ar); 7.39-7.44 (1H, m, H Ar); 12.70 (1H, br. s, NH); weak impurity signals were present, possibly due to bis(hydroxymethyl) derivative and the starting benzimidazolethione **1**: 5.69 (4H, d, J = 7.3, CH_2); 6.63 (2H, t, J = 7.4, OH); 7.23-7.28 (2H, m, H Ar); 7.46-7.51 (2H, m, H Ar); 12.50 (1H, br. s, NH compounds **1**). ^{13}C NMR spectrum, δ, ppm: 66.3 (CH_2); 109.6 and 110.1 (C-4,7); 122.2 and 123.0 (C-5,6), 130.7 and 132.0 (C-3a,7a), 168.4 (C=S). Found, *m*/*z*: 203.0253 $[M+Na]^+$. $C_8H_8N_2NaOS$. Calculated, *m*/*z*: 203.0250.

X-ray structural analysis of compound 3 was performed on an Agilent Technologies Supernova Atlas monocrystal diffractometer with monochromatic CuKα radiation (λ 1.54184 Å) at 100 K. The crystallographic data and structure refinement parameters are given in Table 1.

The structure of compound **3** was solved directly and refined by least squares method in anisotropic approximation with the SHELXS software [48], which is part of the OLEX2 software suite [49]. Correction for absorption was introduced empirically by using the CrysAlisPro software suite [50], with spherical harmonics, performed by the scaling algorithm SCALE3 ABSPACK. The hydrogen atom positions were calculated by algorithms built into the SHELXS software: for CH_3 groups $U_{iso}(H) = 1.5U_{eq}(C)$, C–H bond length 0.96 Å; for CH_2 groups $U_{iso}(H) = 1.2U_{eq}(C)$, C–H bond length 0.97 Å; for CH groups $U_{iso}(H) = 1.2U_{eq}(C)$, C–H bond length 0.93 Å; for NH_2 groups $U_{iso}(H) = 1.2U_{eq}(N)$, N–H bond length 0.86 Å. Complete structural data set for compound **3** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1013456).

TABLE 1. Crystallographic Data and Structure Refinement Parameters for Compound **3**

Parameter	Compound **3**
Molecular formula	$C_{12}H_{15}N_3OS$
M	249.33
Temperature, K	100(2)
Syngony	Monoclinic
Space group	$P2_1$
a, Å	8.5892(7)
b, Å	7.3899(3)
c, Å	10.0730(8)
α, deg	90.00
β, deg	115.222(10)
γ, deg	90.00
V, Å^3	578.41(7)
Z	2
ρ, g/cm^3	1.432
μ, mm^{-1}	2.379
F(000)	264.0
Crystal dimensions, mm	0.15 × 0.12 × 0.08
Measurement range 2θ, deg.	9.7–145
Range of values *h, k, l*	$-10 \le h \le 10,\ -6 \le k \le 9,\ -12 \le l \le 12$
Total number of reflections	3481
Independent reflections	1477
R_{int}	0.0499
R_1 ($\|F_o\| \ge 4\sigma_F$)	0.0330
wR_2 ($\|F_o\| \ge 4\sigma_F$)	0.0774
R_1 (all data)	0.0378
wR_2 (all data)	0.0803
S	1.029
Maximum/minimum residual electron density, *e*·Å^{-3}	0.29/-0.22

$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$;
$w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = (F_o^2 + 2F_c^2)/3$; $s = \{\Sigma[w(F_o^2 - F_c^2)]/(n-p)\}^{1/2}$,
where *n* – number of reflections, *p* – number of refinement parameters.

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