Regioselectivity of *N*-substitution in bis-alkylation of 1,2,4-triazolo[1,5-*a*]benzimidazole-2-thione

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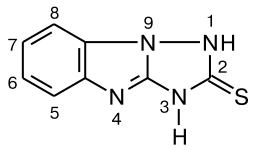
Cyclization of the corresponding *N*-substituted 1,2-diaminobenzimidazoles with carbon disulfide in refluxing DMF leads to 3-methyl- and 3-benzyl-1,2,4-triazolo[1,5-*a*]benzimidazole-2-thiones. Based on the results of their *S*-alkylation, quantum chemical calculations by the density functional theory method, and 1D and 2D NMR spectroscopic studies, it was concluded that the bis-alkylation of *N*-unsubstituted 1,2,4-triazolo[1,5-*a*]benzimidazole-2-thione in the presence of a base proceeds with the formation of *N*(4)-derivatives of 2-alkylthio-1,2,4-triazolo[1,5-*a*]benzimidazole, rather than *N*(3)-derivatives as was believed earlier.

Key words: 1,2-diaminobenzimidazole, 1-amino-2-alkylaminobenzimidazoles, 1,2,4-triazolo[1,5-*a*]benzimidazole-2-thiones, alkylation, quantum chemical calculations, density functional theory method, 1D and 2D NMR spectroscopy, NOESY.

Recently, it was reported[1] that 1,2,4-triazolo[1,5-*a*]-benzimidazole-2-thione (**1**), obtained from 1,2-diaminobenzimidazole and carbon disulfide, upon treatment with 1 equiv. of alkyl halides in acetone in the presence of potash was converted to *S*-alkylthio derivatives **2**, whose subsequent alkylation or reaction of the initial thione **1** with 2 equiv. of alkyl halides under the same conditions led to 2-alkylthio-3-alkyltriazolobenzimidazoles (**3**). These compounds displayed antibacterial, antituberculosis, and fungicide activities comparable with those for the clinically used agents. However, the authors of the work[1] did not show evidence to the fact that the *N*-alkylation in this case occurred at position 3 of the tricyclic system.



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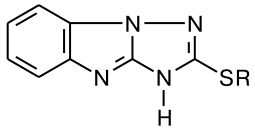

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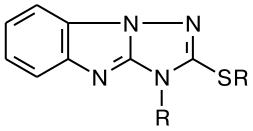
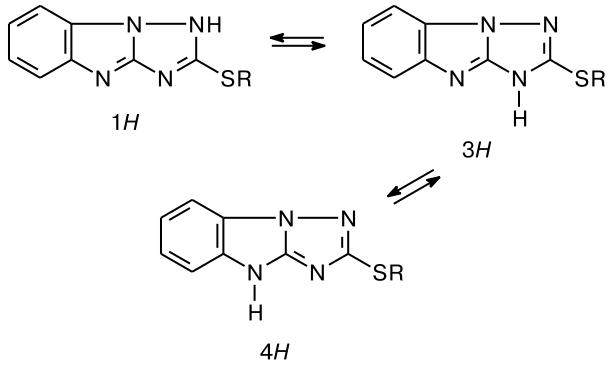


3

Meanwhile, the 2-alkylthio derivative **2** formed in the first step of the reaction can theoretically exist in three tautomeric forms (1*H*, 3*H*, and 4*H* (Scheme 1)) and the regioselectivity of their *N*-alkylation should depend on both the position of the tautomeric equilibrium and the nucleophilicity of each of the tautomers.

Scheme 1



Earlier, the studies of the tautomerism of unsubstituted 1,2,4-triazolo[1,5-*a*]benzimidazole and its 2-methyl- and 2-phenyl derivatives showed that in all these cases predominate the 4*H*-forms, whose contents in the equilibrium mixtures exceeded the content of 3*H*-tautomer by 2—3 orders of magnitude. No signs of existence of the 1*H*-form were detected. As a result, alkylation of the indicated azoles in alkaline medium, which favors formation of the substrate N-anions, basically leads to *N*(4)-alkyl derivatives, rather than to *N*(3) derivatives.[2]

Taking the given data into account, it seemed reasonable to perform additional studies in order to more pre-

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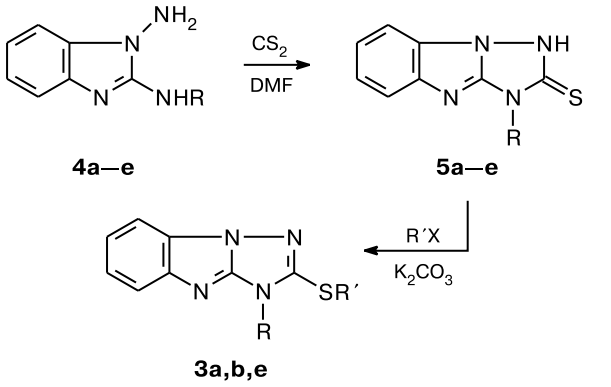
cisely determine the structure of the products of bis-alkylation of thione **1**. To accomplish this goal, it was necessary to synthesize *N*-substituted 1,2,4-triazolo[1,5-*a*]-benzimidazole-2-thiones with a certain position of the N-substituent. We showed that 1-amino-2-R-aminobenzimidazoles (**4a**—**e**), which are very reluctant to cyclize with acid anhydrides to form the corresponding 3-R-triazolo[1,5-*a*]benzimidazoles,[3] upon reflux with carbon disulfide in DMF smoothly were converted to the *N*(3)-substituted thiones **5a**—**e** (Scheme 2, Table 1). In this case, the electrophile most likely initially attacks the *N*-amino group as the most nucleophilic center of the molecule.

In the ^{1}H NMR spectra of compounds **5**, the signals for the protons H(5) and H(8), under the influence of anisotropic effect of the atoms N(4) and N(9), are shifted downfield by ~0.3 ppm as compared to the protons H(6) and H(7) and resonate either as two multiplets (**5a**—**c**), or as a combined multiplet (**5d**), or as two well resolved doublets (**5e**). The structure of thiones **5** was confirmed by the mass spectrometric data obtained for compound **5a**.

The methylation of thione **5a** with iodomethane in acetone in the presence of potash gives rise to the authentic 3-methyl-2-(methylthio)triazolobenzimidazole (**3a**), which in its physicochemical characteristics differs from the product described in the work[1] (let us designate it as **6a**) and formed by bismethylation of thione **1**. Compound **3b**, which we synthesized by reflux of thione **5b** with benzyl chloride in DMF with potash, was not identi-

Scheme 2



3: R = R´ = Me (**a**), R = R´ = Bn (**b**), R = $CH_2CH_2NEt_2$, R´ = 3,4-Cl_2Bn (**e**)

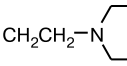
4, 5: R = Me (**a**), Bn (**b**), CH_2CH_2OH (**c**),  (**d**), $CH_2CH_2NEt_2$ (**e**)

Table 1. Yields and physicochemical characteristics of *N*(3)-substituted 1,2,4-triazolo[1,5-*a*]benzimidazole-2-thiones **5**

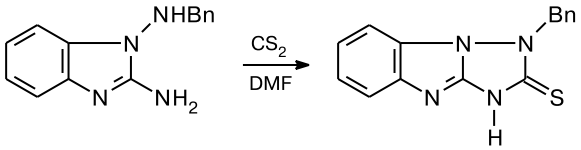
Compound	Yield (%)	M.p./°C (from DMF)	Found / Calculated (%)				Molecular formula	^{1}H NMR (DMSO-d_6, δ, *J*/Hz)
			C	H	N	S		
5a*	93	247—248	52.75 52.92	4.03 3.95	27.20 27.20	15.82 15.70	$C_9H_8N_4S$	3.56 (s, 3 H, Me); 7.33—7.40 (m, 2 H, H(6), H(7)); 7.63—7.68 (m, 1 H, H(5) or H(8)); 7.70—7.75 (m, 1 H, H(8) or H(5)); 13.20 (br.s, 1 H, NH)
5b	84	248—249	64.47 64.26	4.12 4.31	19.85 19.98	11.67 11.44	$C_{15}H_{12}N_4S$	5.42 (s, 2 H, CH_2); 7.23—7.42 (m, 5 H, H(3´), H(4´), H(5´), Ph, H(6), H(7)); 7.46 (d, 2 H, H(2´), H(6´), Ph, *J* = 7.3); 7.60—7.68 (m, 1 H, H(5) or H(8)); 7.72—7.80 (m, 1 H, H(8) or H(5)); 13.80 (br.s, 1 H, NH)
5c	72	224—225	51.43 51.27	4.17 4.30	23.70 23.91	13.52 13.69	$C_{10}H_{10}N_4OS$	3.76 (t, 2 H, $C\underline{H}_2OH$, *J* = 5.0); 4.21 (t, 2 H, NCH_2, *J* = 5.0); 5.11 (s, 1 H, OH); 7.33—7.42 (m, 2 H, H(6), H(7)); 7.59—7.67 (m, 1 H, H(5) or H(8)); 7.70—7.78 (m, 1 H, H(8) or H(5)); 13.56 (br.s, 1 H, NH)
5d	85	229—230	55.27 55.43	5.80 5.65	23.25 23.08	10.37 10.57	$C_{14}H_{17}N_5OS$	3.35—4.30 (m, 10 H, 8 H (morpholino), $C\underline{H}_2$ (morpholino)); 4.61 (t, 2 H, NCH_2, *J* = 5.0); 7.38—7.49 (m, 2 H, H(6), H(7)); 7.72—7.85 (m, 2 H, H(5), H(8)); 9.60 (br.s, 1 H, NH)
5e	83	210—212	58.32 58.10	6.38 6.62	24.45 24.20	11.23 11.08	$C_{14}H_{19}N_5S$	1.23 (t, 6 H, 2 Me, *J* =7.1); 3.24 (q, 4 H, 2 $C\underline{H}_2$Me); 3.60 (degen.t, 2 H, $C\underline{H}_2NEt_2$); 4.44 (t, 2 H, NCH_2, *J* = 5.5); 6.96—7.10 (m, 2 H, H(6), H(7)); 7.42 (d, 1 H, H(5) or H(8), *J* = 7.3); 7.49 (d, 1 H, H(8) or H(5), *J* = 7.4); 9.61 (br.s, 1 H, NH)

* MS, *m*/*z* (I_{rel} (%)): 204 $[M]^+$ (83.3), 146 (45.8), 118 (98.3), 104 (60.8), 90 (75.0), 77 (100), 64 (53.3), 59 (40.0), 51 (48.3), 39 (45.8).

cal to compound **6b**, obtained by bisbenzylation of thione **1** under analogous conditions, either (the comparative characteristics of compounds **3a**,**b** and **6a**,**b** are given below). To sum up, it turned out that thione **1** in the presence of a base gave no alkylation at position 3 and, hence, either *N*(1)- or *N*(4)-substituted 2-alkylthiotriazolobenzimidazoles were the reaction products.

For the preparation of authentic 1-methyl(benzyl)-triazolobenzimidazole-2-thiones **7**, the corresponding *N*(1)-substituted 1,2-diaminobenzimidazoles are required as the starting compounds, from which only 2-amino-1-benzylaminobenzimidazole (**8**) is easily available. The latter can be obtained by the reduction of 2-amino-1-benzylidenaminobenzimidazole[2]. The cyclization of diamine **8** with carbon disulfide to thione **7** (Scheme 3) proceeds considerably slower as compared to 1,2-diaminobenzimidazole and amines **4**, upon prolonged (25 h) reflux of the reagents in DMF, in the not higher than 55—60% yield. Apparently, this reaction is hindered not only by steric shielding of the *N*-amino group, but also by the insufficiently high nucleophilicity of the *C*-amino group. Note that no cyclization of amine **8** to the corresponding 1-substituted triazolobenzimidazoles was observed upon the action of acid anhydrides or formamide.[2] The structure of thione **7** was confirmed by ^{1}H NMR spectroscopic and mass spectrometric data.

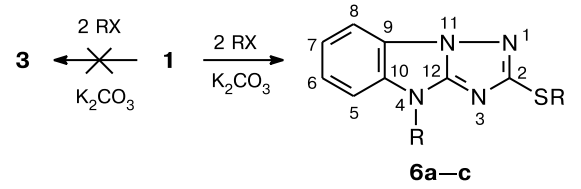
Scheme 3



8 **7**

The *S*-benzylation of thione **7** with benzyl chloride under the conditions of smooth dibenzylation of thione **1** leads to a complicated, difficult to separate mixture of products, which does not contain compound **6b** (Scheme 4). Most likely, this is attributable to the instability of the 1*H*-tautomeric form of triazolobenzimidazole system found earlier,[2] which, in our opinion, results from the presence of the fragment N(9)$^{sp^3}$—N(1)$^{sp^3}$ with two unshared pairs of electrons almost parallel oriented inclined to the strong repulsive interaction. This leads to a reduction in the aromaticity of the triazole ring in the 1*H*-form, considerable elongation of the N—N bond, which, in the end, makes it thermodynamically unfavorable. For example, quantum chemical calculations (B3LYP/6-31G**) show that in the 1*H*-form of 2-mercapto-1,2,4-triazolo[1,5-*a*]-benzimidazole, the N—N bond (1.397 Å) is ~0.02—0.03 Å longer than that in two other tautomeric forms of the indicated compound. In this case, the energy of the 1*H*-form is higher by 18.3 and 9.9 kcal mol^{-1} than that for the most stable 4*H*-form and the intermediate in stability 3*H*-form, respectively.*

Scheme 4



6a—c

6: R = Me (**a**), Bn (**b**), 4-FC$_6$H$_4$OCH$_2$CH$_2$ (**c**)

Quantum chemical studies of the model methylation reaction of the N-anion of 2-(methylthio)triazolobenzimidazole with methyl chloride showed that the N(4) atom is the most nucleophilic site in the indicated anion. Among three isomeric transition states (TS) of this reaction, the transition state **TS1** leading to the methylation of position 4 possesses the minimal energy (Fig. 1).** The transition states for the *N*(1)- and *N*(3)-methylation **TS2** and **TS3** have higher energies by 6.3 and 3.1 kcal mol^{-1}, respectively, with respect to the **TS1**.

Along with the given experimental data, this indicates that thione **1**, like other 1,2,4-triazolo[1,5-*a*]benzimidazoles studied earlier, undergoes *N*-alkylation in the presence of bases at position 4 with the formation of compounds **6**.

In comparison with 3-substituted 2-methylthio- and 2-benzylthiotriazolobenzimidazoles **3a**,**b**, their 4-alkyl-(benzyl)-substituted isomers **6a**,**b** possess higher chromatographic mobility (R_f 0.6 and 0.7, respectively). The 3-methyl derivative **3a** has a melting point 20 °C lower than that in the case of compound **6a**. The dibenzyl-substituted isomers **3b** and **6b** have very close melting points, but, likewise compounds **3a** and **6a**, different IR spectra. It is characteristic that in the ^{1}H NMR spectra of disubstituted **3a**,**b**, like in the spectra of the starting thiones **5a**,**b**, the signals for the two protons H(5) and H(8) are found downfield shifted from the multiplet of other aromatic protons, whereas in the 4-isomers **6a**,**b** because of the absence of the sp^2-hybridized nitrogen atom neighboring to the atom H(5), only signal for the proton H(8) is downfield shifted.

Additional evidence for the *N*(4)-substitution in the thione **1** upon its bis-alkylation was obtained during studies of compound **6a** by heteronuclear 2D ^{13}C—H and ^{15}N—H NMR spectroscopy, as well as by NOESY.

* The total energies of the indicated tautomeric 4*H*-, 3*H*-, and 1*H*-form (without allowance for the vibration energy) were found to be –925.652766, –925.639314, and –925.623539 au, respectively.

** The total energies of transition states **TS1**, **TS2**, and **TS3** are equal to –1425.195930, –1425.201742, and –1425.207095 au, respectively.

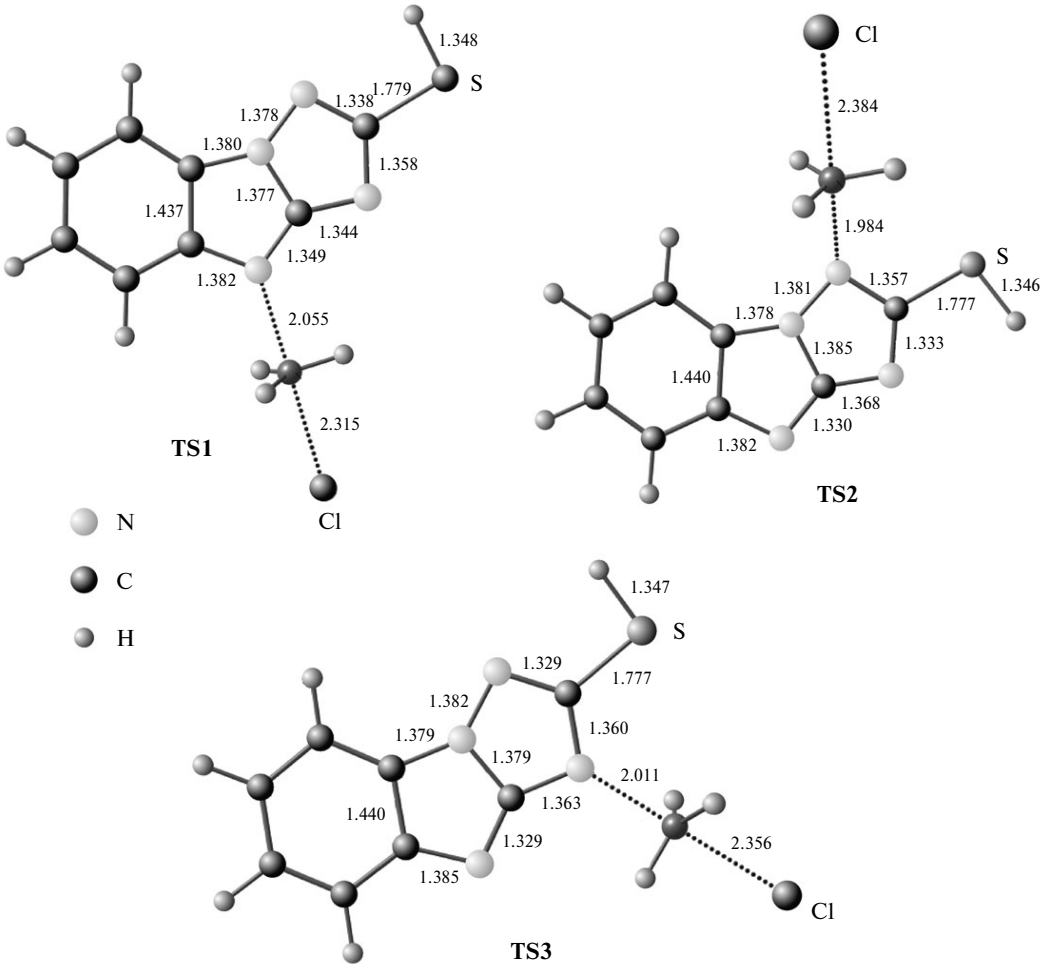


Fig. 1. The structures of the transition states **TS1**—**TS3** for the methylation of 2-methylthio-1,2,4-triazolo[1,5-*a*]benzimidazole N-anion with methyl chloride. Here and in Fig. 2, the bond distances are given in Å.

The ^{13}C NMR spectra of dimethyl derivative **6a** with proton decoupling ($CDCl_3$) exhibited all the expected signals from ten carbon nuclei, which were assigned based on the analysis of the heteronuclear 2D $^{13}C—^{1}H$ NMR HSQC- and HMBC spectra.

The $^{13}C—^{1}H$ HSQC spectrum of this compound contains the expected cross-peaks in the region for aliphatic signals attributable to the carbon-proton interaction in two methyl groups and the fragments C(5)—H, C(6)—H, C(7)—H, and C(8)—H.

Attachment of the *N*-methyl group in the dimethyl derivative **6a** to the N(4) nitrogen atom, rather than to an alternative N(1) position, was confirmed by the $^{13}C—^{1}H$ HMBC spectrum and 2D $^{15}N—^{1}H$ spectrum. The $^{13}C—^{1}H$ HMBC spectrum, besides other cross-peaks, has two characteristic cross-peaks C(10)/N—Me and C(12)/N—Me, but has no cross-peak for the protons C(2)/N—Me. In the 2D $^{15}N—^{1}H$ spectrum, besides very strong cross-peak for the fragment N—Me at δ 94.90, 3.74, a much weaker double cross-peak at δ 94.86, 3.74 were also found, which was assigned to the interaction of the nitrogen atom of this fragment with the protons H(5) and H(6). The cross-peak from the nitrogen atom of the *N*-methyl group and the protons of the *S*-methyl group is absent. In addition, this spectrum has weak cross-peaks of the nitrogen N(3) interacting with the protons of the *N*- and *S*-methyl groups (at δ 143.60, 3.74 and 143.60, 2.66, respectively), as well as a cross-peak attributable to the interaction of the $^{15}N(1)$ nucleus with the proton of the *S*-methyl group at δ 254.40, 2.66.

In accordance with the structure of **6a**, the NOESY spectrum of the dimethyl derivative exhibited a cross-peak for the pair of proton groups NMe and H(5), but had no cross-peak for the protons of two methyl groups, whose presence should have been expected for the *N*(1)-isomer.

Unfortunately, attempted synthesis of *N*(4)-methyl-substituted triazolobenzimidazole-2-thione (**9**), from which an authentic compound **6a** could have particularly been obtained, was unsuccessful. 1-Amino-2-imino-3-methylbenzimidazoline (**10**)[4] taken for this synthesis as

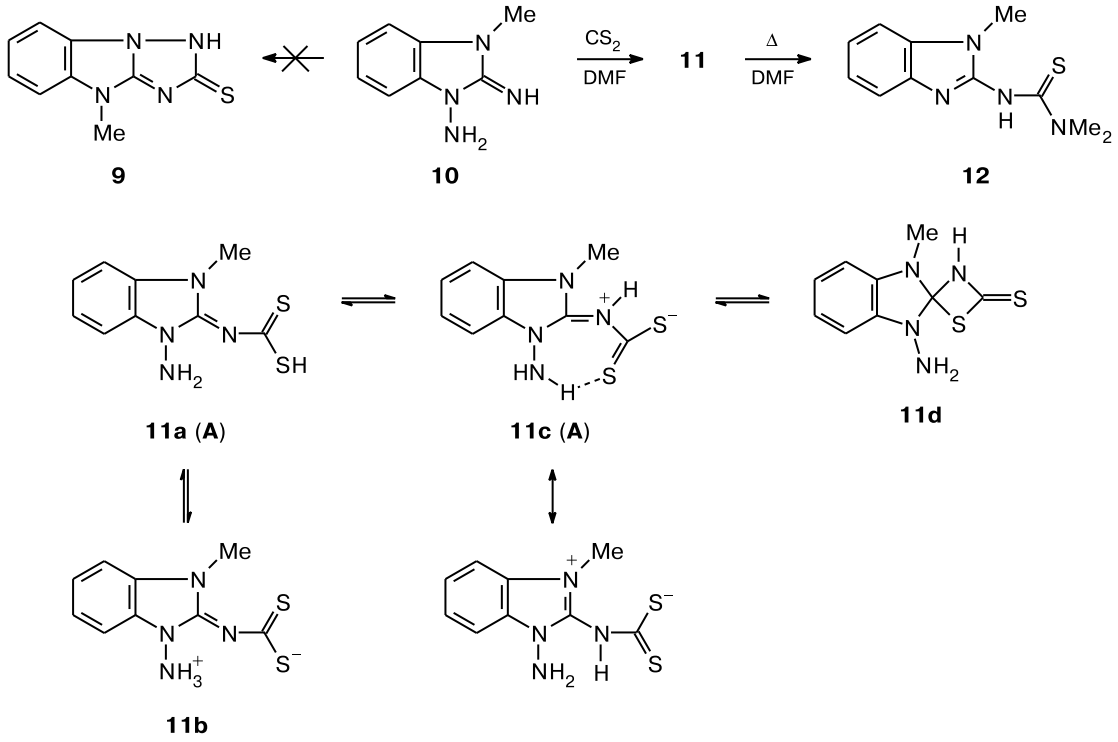
a starting compound, which readily cyclized with acid anhydrides and formamide to the corresponding 4-methyl-1,2,4-triazolo[1,5-*a*]benzimidazoles,[2] in the reaction with carbon disulfide in DMF at 20—25 °C formed poorly soluble yellow product **11** which, according to the elemental analysis data, was the product of addition of imine **10** to CS_2. Upon subsequent reflux of the reaction mixture, this compound, undergoing no cyclization at the *N*-amino group, unexpectedly reacted with dimethylamine present in the reaction mixture. The process was accompanied by *N*-deamination and led to 1-methyl-2-(3,3-dimethylthioureido)benzimidazole (**12**), which was confirmed by the ^{1}H NMR spectroscopic and mass spectrometric data.

Attempted thermal cyclization of compound **11** in the absence of a solvent was not successful, either: at 140 °C it rapidly decomposed with the formation of hardly identifiable resin-like residue.

It is obvious that compounds of the type **11** are always intermediately formed in the reactions of amines with carbon disulfide, but, as a rule, they are unstable and, therefore, seldom isolable. In the series of benzimidazole, for example, only one analogous compound was described, which was formed from 2-amino-1-(β-aminoethyl)benzimidazole and carbon disulfide at the aliphatic amino group.[5] In our case, the stability of the adduct **11** is apparently due to the very high nucleophilicity of the imine group of the guanidine fragment in the starting molecule, which not only facilitated its formation, but also made difficult a reverse decomposition to the starting compounds.

For compound **11**, there are four prototropic tautomers theoretically possible: dithiocarbamoic acid **11a**, two zwitterionic forms with localization of the labile proton on the amino or the imine group (**11b**,**c**), and a spirocyclic form with thiazetidine ring (**11d**) (Scheme 5). The zwitterionic form **11b** can be ruled out from consideration based on the ^{1}H NMR spectrum of compound **11**, which has no a three-proton signal for the $^+NH_3$ group, but does have two broad singlets: a two-proton one at δ 5.34 and a one-proton at δ 6.06. The firsts from them, undoubtedly, belongs to the *N*-amino group, whereas the second belongs to either the SH group of the form **11a** or the 2-imine group of any of the forms **11c**,**d**. The choice between the forms **11a**,**c**,**d** was made in favor of the form **11c** based on the mass spectrometric and IR spectroscopic data, as well as on the results of quantum chemical calculations. In the mass spectrum of compound **11**, a peak of the molecular ion is absent, but two very strong peaks with *m*/*z* 162 (100%) and 76 (93%) are observed, which respectively correspond to the ions $[M - CS_2]^+$ and $[M - M_{10}]^+$, where M_{10} is the molecular weight of imine **10**. This indicates that compound **11** is very easily cleaved at the C—N bond with the extrusion of carbon disulfide, which should be characteristic of the zwitterionic tautomer **11c**. The IR spectrum of compound **11** has an absorption band at 3208 cm^{-1} (NH^+),

Scheme 5



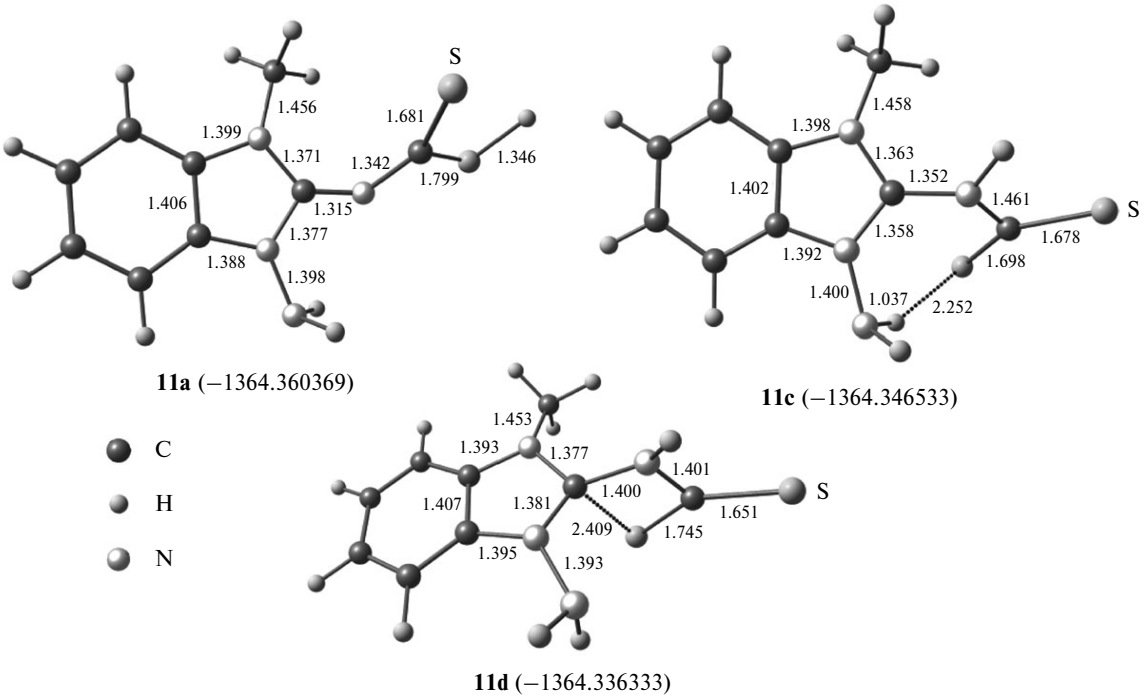


Fig. 2. The prototropic forms of *N*-(1-amino-3-methyl-1,3-dihydrobenzimidazol-2-ylidene)dithiocarbamoic acids **11a**,**c**,**d** and their energies (in parentheses, at. units) according to the data of the B3LYP/6-31G** quantum chemical calculations.

but has no absorption band for the S—H bond in the indicative region ~2400 cm^{-1}.

The quantum chemical calculations performed (B3LYP/6-31G**) show that under the gas-phase conditions, the moderately polar (μ_{calc} = 4.9 D) form **11a** is the most stable (Fig. 2). The relative energies of other forms (in kcal mol^{-1}) and their calculated dipole moments (in D, given in parentheses) are as follows: 7.9 (12.3) for the conformer **11c** (**A**) with the H-bond HN—H...S=C<, 13.1 (14.0) for the less stable conformer **11c** (**B**), which does not have such a bond, and 14.4 (10.1) for the tautomer **11d** with a thiazetidine ring (see Scheme 5). However, the tautomer **11c** should predominate in solutions in the form of its most stable conformer **A** (**11c** (**A**)). The zwitterionic structure with the benzimidazolium cationic center and a considerable spatial separation of charges is one of its important resonance forms. This is the factor which explains a high dipole moment of the tautomer **11c** and the fact that it becomes predominant in polar media, being stabilized by solvation stronger than a competing tautomeric form **11a**.

This suggestions were confirmed by the PCM calculations with the optimization of geometry,* according to which in DMSO, which is close to DMF in the polarity, the zwitterionic tautomer-conformer form **11c** (**A**) and the acid form **11a** almost did not differ in energies (the energy difference was only ~0.5 kcal mol^{-1}). However, the PCM method essentially underestimates solvation energy of ions and highly polar molecules, and in the reality, the most polar form **11c** had proved to be the most stable in solutions. It turned out that the thiazetidine form **11d**, when nonpolar solvents were changed to polar ones was no longer in the minimum on the PES and underwent the thiazetidine ring opening at its least strong C—S bond, leading to the formation of zwitterionic form **11c**.

Considerable localization of the positive charge on the benzimidazolium fragment in the form **11c**, apparently, decreases the nucleophilicity of the *N*-amino group to a such extent, that deactivates it to further cyclization.

In conclusion, the investigation performed in this work showed that bis-alkylation of 1,2,4-triazolo[1,5-*a*]benzimidazole-2-thione (**1**) in the presence of a base led not to *N*(3)-alkyl-2-(alkylthio)triazolobenzimidazoles **3**, as it was mistakenly believed earlier, but to their *N*(4)-substituted isomers **6**.

Experimental

IR spectra were recorded on a Varian Excalibur 3100 FT-IR spectrometer in the solid phase, ^{1}H NMR spectra were recorded on a Varian Unity-300 spectrometer (300 MHz) in the mode of internal stabilization of the ^{2}H polar-resonance line of the deuterated solvent, ^{13}C NMR spectra and 2D NMR spectra were recorded on a Bruker Avance 600 spectrometer (600 MHz).

* The calculations were performed with allowance for the electrostatic effect, repulsive and dispersion interactions with the solvent, as well as the cavitation energy.

Chemical shifts for the ^{15}N nuclei are given relative to ammonia. Mass spectra were recorded on a Finnigan MAT INCOS50 instrument with direct injection of the samples into the source of ions (70 eV). The reaction progress and individuality of compounds were monitored by TLC on Al_2O_3 plates of III degree of activity, $CHCl_3$ was an eluent, iodine vapors were used for visualization.

Quantum chemical calculations were performed using the Firefly program[6] partially based on the code of the Gamess program.[7] The energy values were obtained without allowance for the energies of the ground-state vibrational levels (ZPE). Identification of the energy minima and the transition states of the molecular systems under study was performed with the calculation of their force constant matrices.

Preparation and properties of 1,2,4-triazolo[1,5-*a*]benzimidazole-2-thione (**1**)[1], 1-amino-2-R-aminobenzimidazoles (**4a—e**),[3] 2-amino-1-(benzylamino)benzimidazole (**8**),[2] and 1-amino-2-imine-3-methylbenzimidazoline (**10**)[4] have been described earlier.

3-Substituted 1,2,4-triazolo[1,5-*a*]benzimidazole-2-thiones (5). Carbon disulfide (1.5 mL) was added to a solution of the corresponding 1-amino-2-(R-amino)benzimidazole **4** (5 mmol) in DMF (5 mL) and the mixture was refluxed for 5—8 h. A colorless precipitate was formed in the refluxing solution, which after cooling was filtered off and washed with acetone. Physicochemical constants and yields of the obtained thiones **5** are given in Table 1.

3-Methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]benzimidazole (3a). A mixture of thione **5a** (0.41 g, 2 mmol) and iodomethane (1.3 mL, 2 mmol) in acetone (10 mL) was stirred at 25 °C in the presence of potash (0.28 g, 2 mmol) for 4 h. A precipitate was filtered off and washed with acetone (5 mL). The mother liquor was concentrated to dryness. The residue was subjected to chromatography on a column with Al_2O_3 (15×50 mm), using chloroform as an eluent and collecting the fraction with R_f 0.6. The yield was 0.35 g (80%), m.p. 139—140 °C (ethyl acetate). Found (%): C, 55.27; H, 4.68; N, 25.84; S, 14.52. $C_{10}H_{10}N_4S$. Calculated (%): C, 55.03; H, 4.62; N, 25.67; S, 14.69. ^1H NMR ($CDCl_3$), δ: 2.73 (s, 3 H, SMe); 3.67 (s, 3 H, NMe); 7.18—7.27 (m, 2 H, H(6), H(7)); 7.67—7.71 (m, 2 H, H(5), H(8)).

4-Methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]benzimidazole (6a) was synthesized according to the procedure described earlier,[1] stirring thione **1** (0.38 g, 2 mmol) with iodomethane (2.6 mL, 4 mmol) in acetone (10 mL) in the presence of potash (0.56 g, 4 mmol). The yield was 73%. M.p. 159—160 °C (ethyl acetate) (*cf.* Ref. 1: m.p. 150—152 °C, R_f 0.7). Found (%): C, 55.16; H, 4.53; N, 25.47; S, 14.73. $C_{10}H_{10}N_4S$. Calculated (%): C, 55.03; H, 4.62; N, 25.67; S, 14.69. IR, ν/cm^{-1}: 1625 m, 1599 s, 1495 s, 1475 s. ^1H NMR ($CDCl_3$), δ: 2.67 (s, 3 H, SMe); 3.79 (s, 3 H, NMe); 7.21—7.35 (m, 3 H, H(5)—H(7)); 7.71—7.74 (m, 1 H, H(8)). ^{13}C NMR ($CDCl_3$), δ: 14.49 (SMe); 29.52 (NMe); 109.99 (C(5)); 110.36 (C(8)); 121.48 (C(7)); 123.25 (C(6)); 124.01 (C(9)); 134.36 (C(10)); 154.41 (C(12)), 165.25 (C(2)). 2D ^{13}C—^1H HMBC ($CDCl_3$), δ: 165.31, 2.66 (C(2)/SMe); 134.42, 3.74 (C(10)/NMe); 154.47, 3.74 (C(12)/NMe); 110.47, 7.22 (C(8)/H(7)); 124.06, 7.22 (C(9)—H(7)); 121.65, 7.26 (C(5)/H(6)); 123.35, 7.65 (C(6)/H(8)); 134.37, 6.65 (C(10)/H(8)). NOESY ($CDCl_3$), δ: 3.74, 7.25 (NMe—H(5)); 7.22, 7.65 (H(7)—H(8)).

3-Benzyl-2-benzylthio-1,2,4-triazolo[1,5-*a*]benzimidazole (3b). A solution of 3-benzyl-substituted **5b** (0.28 g, 1 mmol) and benzyl chloride (0.12 mL, 1 mmol) in DMF (2 mL) was refluxed for 1 h in the presence of potash (0.14 g, 1 mmol), then cooled, diluted with water (5 mL), and the thus formed precipitate was filtered off. The residue was subjected to chromatography on a column with Al_2O_3 (15×50 mm), using chloroform as an eluent and collecting the fraction with R_f 0.6. The yield was 0.28 g (75%), m.p. 129—131 °C (ethyl acetate). Found (%): C, 71.40; H, 4.72; N, 15.28; S, 8.54. $C_{22}H_{18}N_4S$. Calculated (%): C, 71.33; H, 4.90; N, 15.12; S, 8.65. IR, ν/cm^{-1}: 1638 s, 1587 m, 1557 s, 1485 m, 1441 s. ^1H NMR ($CDCl_3$), δ: 4.36 (s, 2 H, SCH_2); 5.11 (s, 2 H, NCH_2); 7.16—7.38 (m, 12 H, 2 Ph, H(6), H(7)); 7.72 (d, 1 H, H(5), J = 8.5 Hz); 7.75 (d, 1 H, H(8), J = 8.7 Hz).

4-Benzyl-2-benzylthio-1,2,4-triazolo[1,5-*a*]benzimidazole (6b). A solution of thione **1** (0.19 g, 1 mmol) and benzyl chloride (0.25 mL, 2 mmol) in DMF (2 mL) was refluxed for 3 h with potash (0.28 g, 2 mmol). After cooling, the mixture was diluted with water (5 mL), a precipitate formed was filtered off, and the residue was subjected to chromatography on a column with Al_2O_3 (15×50 mm), using chloroform as an eluent and collecting the fraction with R_f 0.7. The yield was 0.3 g (80%), m.p. 132—133 °C (ethyl acetate). Found (%): C, 71.27; H, 4.93; N, 15.00; S, 8.71. $C_{22}H_{18}N_4S$. Calculated (%): C, 71.33; H, 4.90; N, 15.12; S, 8.65. IR, ν/cm^{-1}: 1619 m, 1582 v.s, 1491 s, 1450 s (C=N, C=C). ^1H NMR ($CDCl_3$), δ: 4.46 (s, 2 H, SCH_2); 5.38 (s, 2 H, NCH_2); 7.17—7.39 (m, 11 H, H(5), H(6), H(7), Ph, H(3′), H(4′), H(5′)); 7.44 (d, 2 H, H(2′), H(6′), J = 8.2 Hz); 7.75—7.76 (m, 1 H, H(8)).

2-(3,4-Dichlorobenzyl)thio-3-(2-diethylaminoethyl)-1,2,4-triazolo[1,5-*a*]benzimidazole hydrochloride (3e). A solution of thione **5e** (0.58 g, 2 mmol) and 3,4-dichlorobenzyl bromide (0.48 g, 2 mmol) in DMF (4 mL) was refluxed for 45 min in the presence of potash (0.28 g, 2 mmol). After cooling, the mixture was diluted with water (20 mL) and the thus formed dense oil was extracted with chloroform (15 mL). The extract was concentrated to the minimum volume and subjected to chromatography on a column with Al_2O_3 (20×60 mm), using chloroform as an eluent and collecting the fraction with R_f 0.45. Chloroform was evaporated to dryness, the residue was dissolved in acetone (5 mL) and treated with the saturated solution of HCl in isopropyl alcohol to pH 1. The crystals formed were filtered off and washed with acetone. The yield was 0.65 g (67%), m.p. 199—200 °C (Pr^iOH). The compound is readily soluble in water. Found (%): C, 52.18; H, 5.12; N, 14.62; S, 6.47. $C_{21}H_{23}Cl_2N_5S \cdot HCl$. Calculated (%): C, 52.02; H, 4.95; N, 14.45; S, 6.60. ^1H NMR (DMSO-d_6), δ: 1.24 (t, 6 H, 2 $CH_2\underline{Me}$, J = 7.2 Hz); 3.25 (q, 4 H, 2 $C\underline{H}_2Me$, J = 7.2 Hz); 3.64 (t, 2 H, $C\underline{H}_2NEt_2$); 4.54 (s, 2 H, SCH_2); 4.61 (t, 2 H, CH_2N_{cycl}, J = 6.7 Hz); 7.33—7.40 (m, 2 H, H(6), H(7)); 7.49 (dd, 1 H, H (6′), Ar, J = 8.4 Hz, J = 2.1 Hz); 7.62 (d, 1 H, H(2′), Ar, J = 8.4 Hz); 7.72 (d, 1 H, H(5), J = 7.6 Hz); 7.79 (d, 1 H, H (5′), Ar, J = 1.8 Hz); 7.86 (d, 1 H, H(8), J = 7.3 Hz); 10.98 (s, 1 H, NH).

4-[2-(4-Fluorophenoxyethyl)]-2-[2-(4-fluorophenoxyethyl)]-thio-1,2,4-triazolo[1,5-*a*]benzimidazole (6c) was obtained similarly to compound **6b** from thione **1** (0.38 g, 2 mmol) and 2-(4-fluorophenoxy)ethyl bromide (0.88 g, 4 mmol) in DMF (4 mL). The yield was 0.68 g (73%). M.p. 109—110 °C (heptane). Found (%): C, 61.62; H, 4.50; N, 12.27; S, 6.93. $C_{24}H_{20}F_2N_4O_2S$. Calculated (%): C, 61.79; H, 4.32; N, 12.01; S, 6.87. ^1H NMR ($CDCl_3$), δ: 3.53 (t, 2 H, SCH_2, J = 6.9 Hz); 4.30 (t, 2 H, $SCH_2C\underline{H}_2O$, J = 6.9 Hz); 4.35 (t, 2 H, $NCH_2C\underline{H}_2O$, J = 5.3 Hz); 4.53 (t, 2 H, NCH_2, J = 5.3 Hz); 6.66—6.73 (m, 2 H, H(2′), H(6′), Ar); 6.84—6.97 (m, 6 H, other protons of the Ar groups); 7.26—7.38

(m, 2 H, H(6), H(7)); 7.53 (d, 1 H, H(5) or H(8), J = 7.3 Hz); 7.72 (d, 1 H, H(8) or H(5), J = 7.3 Hz); 10.96 (s, 1 H, NH).

1-Benzyl-1,2,4-triazolo[1,5-*a*]benzimidazole-2-thione (7). A solution of 2-amino-1-(benzylamino)benzimidazole (**8**) (0.48 g, 2 mmol) in DMF (5 mL) was refluxed for 25 h with carbon disulfide (2 mL). A precipitate formed on cooling was filtered off and washed with acetone. The yield was 0.4 g (72%), m.p. 238—239 °C (BuOH). Found (%): C, 64.00; H, 4.02; N, 19.67; S, 11.77. $C_{15}H_{12}N_4S$. Calculated (%): C, 64.26; H, 4.31; N, 19.98; S, 11.44. IR, ν/cm^{-1}: 3200—2500 (NH); 1606 s, 1590 s, 1486 m (C=N, C=C). ^{1}H NMR (DMSO-d_6), δ: 5.91 (s, 2 H, CH_2); 7.19 (t, 1 H, H(4´), Ph, J = 7.7 Hz); 7.23—7.36 (m, 4 H, H(6), H(7), H(3´), H(5´), Ph); 7.40 (d, 2 H, H(2´), H(6´), Ph, J = 7.9 Hz); 7.44—7.53 (m, 2 H, H(5), H(8)); 13.17 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 280 [M]$^+$ (55.8), 222 (20.0), 148 (10.0), 91 (100), 65 (10,0).

***N*-(1-Amino-3-methyl-1,3-dihydrobenzimidazol-2-ylidene)dithiocarbamoic acid (11).** A solution of 1-amino-2-imino-3-methylbenzimidazoline (**10**) (0.32 g, 2 mmol) in DMF (3 mL) was mixed with carbon disulfide (1.5 mL). After 3—5 min, a lemon-yellow precipitate began to form, which was filtered off after 0.5 h, washed with DMF (2 mL) and diethyl ether, dried in a vacuum desiccator. The yield was 0.45 g (94%), m.p. 140—142 °C (with decomp.). The compound was not recrystallized because of thermal instability. Found (%): C, 45.51; H, 4.33; N, 23.37; S, 26.75. $C_9H_{10}N_4S_2$. Calculated (%): C, 45.38; H, 4.20; N, 23.52; S, 26.90. IR, ν/cm^{-1}: 3208, 3119, 2360, 1671, 1538. MS, m/z (I_{rel} (%)): 162 [M_{10}]$^+$ (100), 147 (65.0), 119 (51.6), 92 (28.3), 76 (93.3) [M$^+$ CS_2^+], 65 (23.3), 51 (25.8), 44 (54.2).

2-(3,3-Dimethylthioureido)-1-methylbenzimidazole (12). A solution of 1-amino-3-methylbenzimidazolin-2-imine (**10**) (0.49 g, 3 mmol) and carbon disulfide (2 mL) in DMF (4 mL) was refluxed for 20 min until the yellow precipitate of the salt **11** was completely dissolved, then the mixture was refluxed for another 3 h, the latter was accompanied by the formation of a colorless precipitate, which after cooling was filtered off and washed with diethyl ether. The yield was 0.34 g (48%), m.p. 194—195 °C (BuOH). Found (%): C, 56.57; H, 5.83; N, 24.11; S, 13.52. $C_{11}H_{14}N_4S$. Calculated (%): C, 56.38; H, 6.02; N, 23.91; S, 13.68. IR, ν/cm^{-1}: 1627 s, 1594 v.s, 1492 s (C=S, C=N, C=C). ^{1}H NMR ($CDCl_3$), δ: 3.36 (s, 3 H, NMe); 3.44 (s, 3 H, NMe); 3.54 (s, 3 H, NMe—benzimidazole); 7.10—7.29 (m, 4 H, H of benzimidazole); 13.71 (s, 1 H, NH). MS, m/z (I_{rel} (%)): 234 [M]$^+$ (71.7), 201 (26.7), 190 (100), 158 (60.0), 145 (20.0), 132 (69.2), 88 (69.2), 77 (31.7), 42 (45.8).

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