Synthesis of 1(11)*H*-2,3,4,5-tetrahydro[1,3]diazepino[1,2-*a*]benzimidazole starting from benzimidazole-2-sulfonic acid. Intramolecular cyclization of 2-(δ-chlorobutylamino)benzimidazole

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The intramolecular cyclization of 2-(δ-chlorobutylamino)benzimidazole (**3c**) follows the unusual pathway involving the predominant attack on the exocyclic amino group rather than on the much more nucleophilic endocyclic nitrogen atom. This reaction affords 2-pyrrolidinobenzimidazole and 1(11)*H*-2,3,4,5-tetrahydro[1,3]diazepino[1,2-*a*]benzimidazole as the major product and the by-product, respectively. The cyclization can be directed exclusively toward the annulation of the diazepine ring only after the acetylation of the amino group of compound **3c**. According to the quantum chemical calculations, the unusual regioselectivity of the cyclization of chloramine **3c** is associated primarily with a substantially less steric strain and the higher entropy of pyrrolidine transition states compared to diazepine transition states.

Key words: 2-(δ-chlorobutylamino)benzimidazole, 1(11)*H*-2,3,4,5-tetrahydro[1,3]diazepino[1,2-*a*]benzimidazole, 2-pyrrolidinobenzimidazole, quantum chemical calculations, 2-(δ-chlorobutylamino)imidazole, transition states, activation energies, steric effects.

Many derivatives of fused heterocycles containing the guanidine fragment in the ring, including 1(9)*H*-2,3-dihydroimidazo- (**1a**) and 1(10)*H*-1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazoles (**1b**) studied by us, efficiently decrease the blood sugar level and inhibit thrombosis.[1—7] A comparison of the properties of bicyclic guanidines containing the hydrogenated imidazole, pyrimidine, and diazepine rings showed that the imidazo[1,2-*a*][1,3]diazepine derivative exhibits the highest hypoglycemic activity.[3]

This prompted us to undertake the present study in order to develop a preparative procedure for the synthesis of the seven-membered analog of compounds **1a,b**, *viz.*, 1(11)*H*-2,3,4,5-tetrahydro[1,3]diazepino[1,2-*a*]benzimidazole (**1c**). Earlier, compound **1c** has been synthesized by the thermal rearrangement of difficultly accessible 1-cyano-2-phenyltetrahydropyridazine.[8] The synthesis of the 9-nitro derivative of this compound in moderate yield by the cyclization of 2-(3-nitrophenylimino)-2,3,4,5,6,7-hexahydro-1*H*-1,3-diazepine was documented.[9]

In our opinion, the more promising procedure for the synthesis of diazepine **1c**, by analogy with the formation of tricyclic compounds **1a,b**,[10,11] (Scheme 1) could involve the replacement of the sulfo group in benzimidazole-2-sulfonic acid with 4-aminobutan-1-ol followed by the transformation of amino alcohol **2c** into chlorobutylamine **3c** and its thermal cyclization. In the case of chloroethyl(propyl)-substituted compounds **3a,b**, the intramolecular S_N2-like *N*-alkylation as the last step of this procedure proceeds exclusively at the most nucleophilic endocyclic nitrogen atom in 2-aminobenzimidazoles.[12,13]

Results and Discussion

Our investigations showed that amino alcohol **2c** and chloro derivative **3c** are formed in high yields without any complications. However, the subsequent cyclization of compound **3c** occurs predominantly at the exocyclic amino group to form 2-pyrrolidinobenzimidazole (**4**) (in 70—80% yield), whereas the cyclization at the endocyclic nitrogen atom giving rise to diazepine **1c** (15—25% yield) is the minor process. This is rather unexpected from the theoretical point of view because five-membered hydrogenated rings are more strained per ring unit than seven-membered rings[14] and the side amino group in compound **3c** is much less nucleophilic than the endocyclic nitrogen atom. The regioselectivity of the reaction is virtually independent of the nature of the solvent (refluxing in H_2O, EtOH, MeCN, toluene, xylene, or DMF) and remains the same in the reaction performed in a melt at 130—135 °C; however, exclusively pyrrolidine **4** is formed

† Deceased.

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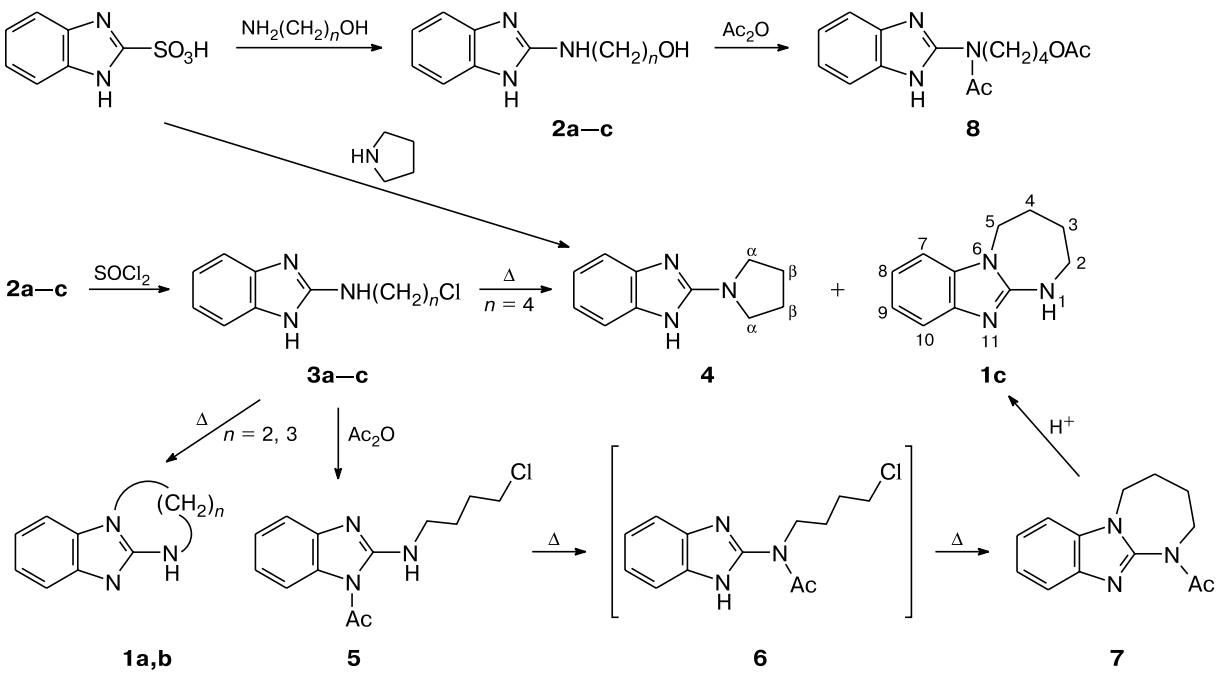
Scheme 1



1—3: n = 2 (**a**), 3 (**b**), 4 (**c**)

in the presence of NaOH due, apparently, to the involvement of the N-anion of the substrate in the reaction.

Isomers **4** and **1c** were identified by comparing their ^{1}H NMR spectra. In pyrrolidine **4**, the tetramethylene fragment is symmetrical and is characterized by two four-proton multiplets of the β- and α-pyrrolidine protons at δ 1.90—1.96 and 3.40—3.46, respectively, whereas the unsymmetrical tetramethylene group in compound **1c** is characterized by three multiplets, *viz.*, one four-proton multiplet (C(3)H_2 and C(4)H_2) and two two-proton multiplets (C(2)H_2 and C(5)H_2) at δ 1.93—1.99, 3.21—3.28, and 3.96—4.04, respectively. The validity of the structural assignments was additionally confirmed by the independent synthesis of compound **4** from benzimidazole-2-sulfonic acid and pyrrolidine.

To protect the secondary amino group from the undesired alkylation and to direct the cyclization toward the predominant diazepine ring closure, compound **3c** was acylated with Ac_2O at 20—25 °C. Under these conditions, the acetylation appeared to proceed at the imidazole ring to form 1-acetyl-substituted derivative **5**, which is rather stable at room temperature. The structure of compound **5** was unambiguously confirmed by the ^{1}H NMR spectrum, which shows a strong spin-spin coupling between the protons of the exocyclic NH group and the adjacent methylene fragment (J = 6.4 Hz). Earlier,[15—19] it has been demonstrated that primary 2-aminobenzimidazoles and their 1-alkyl-substituted derivatives are acylated at low temperature at the imidazole ring to form 1-acyl-2-aminobenzimidazoles and 3-acyl-1-alkyl-2-aminobenzimidazolium salts, respectively, which rather readily undergo thermal acylotropic isomerization to thermodynamically more stable 2-acylaminobenzimidazoles by the inter- or intramolecular mechanism. Hence, heating in Ac_2O, most likely, leads to the rearrangement of compound **5** into its isomer **6**. The latter was not isolated because of the rapid cyclization to 1-acetyldiazepine **7** (94% yield). The immediate heating of a solution of **3c** in Ac_2O to boiling results in the formation of pyrrolidine **4** as a by-product. Compound **7** is smoothly transformed into diazepine **1c** by acid hydrolysis.

The formation of 2-[*N*-(4-acetoxybutyl)-*N*-acetyl]amine **8** by refluxing amino alcohol **2c** in Ac_2O is circumstantial evidence for the migration of the acetyl group in compound **5**. The IR spectrum of amine **8** shows absorption bands of the NCOMe, OCOMe, and NH groups at 1645, 1705, and 3340 cm^{-1}, respectively. The ^{1}H NMR spectrum contains, along with other signals, singlets for the protons of these groups at δ 2.05, 2.45, and 11.5 and two triplets of the methylene groups (δ 4.15 and 4.23), which is indicative of the absence of a considerable spin-spin coupling between the protons of the NH fragment and the methylene group.

An alternative mechanism of the formation of 1-acetyldiazepine **7** involving the cyclization of 1-acetyl derivative **5** directly to 11-acetyl-substituted diazepine **1c** followed by the isomerization to the final product is unlikely because of the expected considerable decrease in

the nucleophilicity of the endocyclic nitrogen atom in compound **5** under the influence of the electron-withdrawing acetyl group.

Therefore, the regioselectivity of thermal cyclization can be efficiently influenced by introducing the acetyl protection of the amino group in chlorobutylamine **3c**, which allows the synthesis of tricyclic compound **1c** in high yield.

It should also be noted that earlier,[20] with the aim of studying pharmacologically active 11-acylmethyl-2,3,4,5-tetrahydro[1,3]diazepino[1,2-*a*]benzimidazoles, we have synthesized 1-acetyl derivative **7** according to an analogous scheme but by the one-pot reaction starting from potassium benzimidazole-2-sulfonate and an equimolar amount of 4-aminobutanol without isolation of intermediates **2c**, **3c**, and **5**. However, this reaction is accompanied by considerable resinification, and the total yield of compound **7** is at most 48%.

To reveal the factors responsible for the observed regioselectivity of the thermal cyclization of chlorobutylamine **3c**, we performed the quantum chemical study of this reaction and the analogous transformation of the simpler model compound, 2-(δ-chlorobutylamino)imidazole (**9**), by the density functional theory method (B3LYP/6-31G**). In addition, to gain a better understanding of the results, we studied the ring and non-ring *N*-methylation of 2-methylaminoimidazole (**10a**) and 2-methylaminobenzimidazole (**10b**) with methyl chloride and the analogous reactions of their tautomeric imino forms (the transitions states for these four processes are denoted as **TS1**, **TS2** and **TS3**, **TS4**, respectively). These reactions were chosen because they are similar in the mechanism to the cyclization of compounds **3c** and **9** and taking into account that they are sterically uncomplicated bimolecular transformations proceeding with the involvement of structurally similar substrates. The transition states **TS1—TS8** were located for all mono- and bimolecular transformations under consideration. These transition states are highly polar with μ_{calc} of about 10—16 D. The characteristics of the reagents and the transition states, including their total energies, the activation energies in the absence of solvation ($\Delta E^{\neq} = E^{tot}_{TS} - E^{tot}_{reag}$), the Gibbs free energies ($\Delta G^{\neq}$) in EtOH, and the imaginary vibrational frequencies are given in Table 1.

The intramolecular cyclization of 2-(δ-chlorobutyl)amines **3c** and **9** to diazepines **1c** and **11** and pyrrolidines **4** and **12**, respectively, like the methylation of amines **10a,b**, can follow four pathways involving the analogous but monomolecular trigonal-bipyramidal transition states **TS5—TS8** corresponding to the formation of each cyclic product from amino and imino forms of compounds **3c** and **9** (Scheme 2). However, the transition states can exist as different conformers because of the conformational diversity of the reagents containing the chlorobutyl fragment.

The cyclization of the amino forms for each chlorobutylamino derivative involves the same set of transition states, including, in particular, two diazepine conformer states **TS5**, in which the seven-membered ring adopts a distorted boat or chair conformation. These transition states ensure the preliminary formation of two corresponding conformers of diazepine **1c**. In addition, four pyrrolidine-type transition states (**TS6**) containing the pyrrolidine ring in the envelope conformation with the β-carbon atom of the δ-chlorobutyl group at the flap are formed. These states differ by the N(1)—C(2)—N_{Pyr}—C_{δ} dihedral angle characterizing the degree of twist of the pyrrolidinyl group with respect to the imidazole ring and the mutual arrangement of the diazolyl group and the β-carbon atom (see Scheme 2). The latter can be either on the same side (*Z*-**TS**) or different sides (*E*-**TS**) of the plane passing through the other atoms of the pyrrolidine ring (see Table 1). The structures of selected transition states for the cyclization of amino forms of substrates **3c** and **9** are presented in Fig. 1.

In the case of the cyclization to diazepine, the boat-like transition states **TS5** have the lowest energy; the total energy of these state is 0.5—0.7 kcal mol^{-1} lower than the energy of their chair-like analogs. In the case of the cyclization to pyrrolidine, the *E* conformations of the transition states **TS6** with the N(1)—C(2)—N_{Pyr}—C_{δ} dihedral angles of 43 (**3c**) and 34° (**9**) serve this function; these states are ~1 kcal mol^{-1} more favorable than the highest-energy transition states *Z*-**TS6** (see Table 1).

In the first approximation, the regioselectivity of cyclization of unsolvated chlorobutylamines **3c** and **9** is determined by the difference between the total energies of the pyrrolidine and diazepine transition states

$$\Delta E^{tot}_{TS5,TS6} = E^{tot}_{TS6} - E^{tot}_{TS5} = \Delta\Delta E^{\neq}_{TS5,TS6},$$

which is −4.0 and −6.2 kcal mol^{-1}, respectively (calculated at the B3LYP/6-31G** level). This indicates that the pathway giving rise to diazepine is somewhat more favorable with respect to this parameter. However, this parameter is 4.0—4.5 kcal mol^{-1} lower in magnitude than the analogous (and also negative) difference $\Delta\Delta E^{\neq}_{TS1,TS2}$ characterizing the selectivity of the sterically uncomplicated *N*-methylation of the amino forms of 2-methylaminodiazoles **10a,b** with methyl chloride. The higher-level calculations (MP2/6-311G**) give an even smaller energy difference $\Delta E^{tot}_{TS5,TS6}$ for chlorobutylamine **9** (−1.7 kcal mol^{-1}; see Table 1). In spite of a certain difference in the values, both methods show that the cyclization of chlorobutylamines **3c** and **9** is characterized by the substantially smaller difference between the activation energies $\Delta E^{\neq}$ of the electrophilic attack on the ring and on the exocyclic atoms compared to the bimolecular *N*-alkylation.

It should be emphasized that the transformation of amines **3c** and **9** into diazepines is more hindered than the

Table 1. Results of calculations at the B3LYP/6-31G** level of theory for the reagents and transition states of the cyclization and *N*-methylation involving compounds **3c**, **9**, and **10a,b** and their tautomeric imino forms

TS and reagents[a]	Conformer TS[b]	$-E^{tot}$/Hartree	$\Delta E^{\neq}$ ($\Delta G^{\neq}_{352}$ (EtOH)) /kcal mol^{-1}	μ_{calc} /D	C—N[c] / Å	C—Cl / Å	Angle N—C—Cl[c] /deg	ν_i /cm^{-1}
MeCl	—	499.978024	—	2.1	—	1.80	—	—
MeCl[d]	—	500.031228	—	2.1	—	1.78	—	—
3c	—	1051.430735	—	5.5	—	1.83	133.7	—
9	—	897.911874	—	5.6	—	1.83	136.5	—
13a	—	897.935190	—	11.6	1.47	—	—	—
14a	—	897.904347	—	7.7	1.53	—	—	—
15a	—	897.897962	—	5.7	—	1.83	148.3	—
15b	—	1051.423227	—	4.4	—	1.83	149.5	—
TS1 (Im)	—	820.525263	25.9	14.7	1.88	2.42	178	471.8
TS1 (Bzm)	—	974.042178	27.2	14.4	1.89	2.43	176	480.3
TS2 (Im)	—	820.512229	34.1	9.6	1.83	2.49	172	411.8
TS2 (Bzm)	—	974.024694	38.1	11.1	1.79	2.54	175	376.4
TS3 (Im)[d]	—	820.522736	48.2	16.1	1.74	2.57	178	405.9
TS3 (Bzm)[d]	—	974.040969	55.7	16.1	1.73	2.57	178	407.2
TS4 (Im)	—	820.517462	22.3	13.7	1.93	2.38	178	479.5
TS4 (Bzm)	—	974.038365	24.5	13.5	1.91	2.40	178	482.3
TS5 (DI)	Distorted boat	897.862380	31.1 (13.6)	14.6	1.95	2.51	166	437.3
	Distorted boat[e]	896.457916	—	14.1	1.91	2.39	169	—
	Distorted chair	897.861921	31.3 (14.5)	14.1	1.95	2.49	163	442.9
TS5 (DB)	Distorted boat	1051.379015	32.5 (15.8)	14.5	1.94	2.52	166	442.1
	Distorted chair	1051.377883	33.2 (17.2)	13.8	1.94	2.51	163	448.9
TS6 (PI)	*E* (34)	897.855964	35.1 (12.9)	10.0	1.83	2.59	166	329.3
	E (33)[e]	896.455201	—	8.5	1.88	2.40	169	—
	E (132)	897.855436	35.4 (14.2)	11.7	1.80	2.63	168	308.7
	Z (41)	897.855537	35.4 (15.3)	10.3	1.85	2.61	164	344.5
	Z (52)[e]	896.455236	—	9.9	1.88	2.44	169	—
	Z (139)	897.853410	36.7 (13.6)	11.8	1.81	2.64	169	340.9
TS6 (PB)	*E* (43)	1051.369050	38.7 (18.8)	10.9	1.79	2.64	165	296.4
	E (129)	1051.368599	40.0 (17.8)	12.0	1.78	2.66	168	278.6
	Z (46)	1051.368650	40.1 (18.8)	10.8	1.82	2.64	163	323.5
	Z (126)	1051.366817	41.0 (20.8)	12.4	1.80	2.67	168	315.7
TS7 (DI)	—	897.824880	45.9 (23.8)	13.0	1.81	2.69	161	366.4
TS7 (DB)	—	1051.346346	48.2 (25.8)	13.0	1.80	2.70	162	403.6
TS8 (PI)	—	897.861102	23.1 (8.2)	13.3	1.98	2.45	169	479.5
TS8 (PB)	—	1051.383258	25.1 (10.6)	13.0	1.96	2.46	170	424.1

[a] The corresponding heterosystems are given in parentheses after the notations of TS: Im and Bzm are imidazole and benzimidazole, respectively; DI and DB are diazepinoimidazole and diazepinobenzimidazole, respectively; PI and PB are pyrrolidylimidazole and pyrrolidylbenzimidazole, respectively. The transition states **TS1** and **TS2** correspond to the attack of 2-methylaminoazoles **10a,b** on the exocyclic and endocyclic nitrogen atoms, respectively; the transition states **TS3** and **TS4** correspond to the analogous attack of the corresponding imino tautomers.

[b] For the pyrrolidine transition state, the N(1)—C(2)—N_{Pyr}—C_{δ} dihedral angle is given in parentheses.

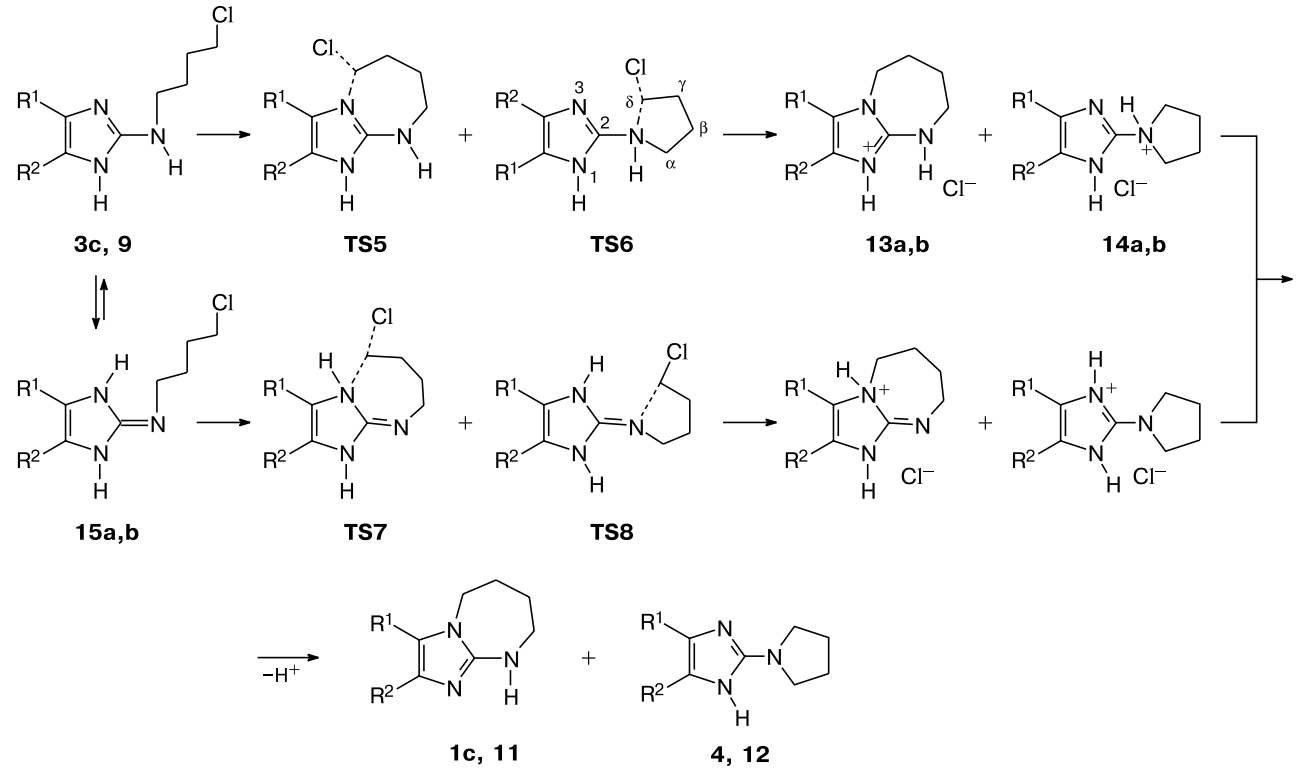
[c] For the nitrogen atom involved in the reaction.

[d] The calculation at the BHHLYP/6-31G(d,p) level.

[e] The calculation at the MP2/6-311G** level.

N-methylation of methylamino-substituted derivatives **10a,b** with methyl chloride at the heterocyclic ring, which has the same direction of the electrophilic attack taking into account that $\Delta\Delta E^{\neq}_{\mathbf{TS1},\mathbf{TS5}}$ is larger than 5 kcal mol^{-1}. Unlike this reaction, the cyclization of chlorobutylamines to pyrrolidines proceeds almost as easily as the methylation of compounds **10a,b** at the exocyclic amino group ($\Delta\Delta E^{\neq}_{\mathbf{TS2},\mathbf{TS6}} \leq 1.0$ kcal mol^{-1}) (see Table 1). These data indicate that the diazepine transition states are higher in energy than the pyrrolidine transition states. This can be attributed to their higher steric strain, the lower entropy due to higher rigidity of these systems, and, apparently, less efficient solvation. The higher strain of **TS5** is evident from the following structural features: first, the deviation

Scheme 2



9, 11, 12, 13a—15a: $R^1 = R^2 = H$;
1c, 3c, 4, 13b—15b: $R^1R^2 = —CH=CH—CH=CH—$

of the electrophilic attack from the most favorable direction along the axis of the lone electron pair of the nitrogen atom subjected to the attack, which is more pronounced in chair-like transition states; second, an elongation of the C—N bond in the reaction center by 0.07 Å compared to the unstrained transition states **TS1**, which is, evidently, a consequence of the steric hindrance to the optimal proximity between the reaction centers; and finally,

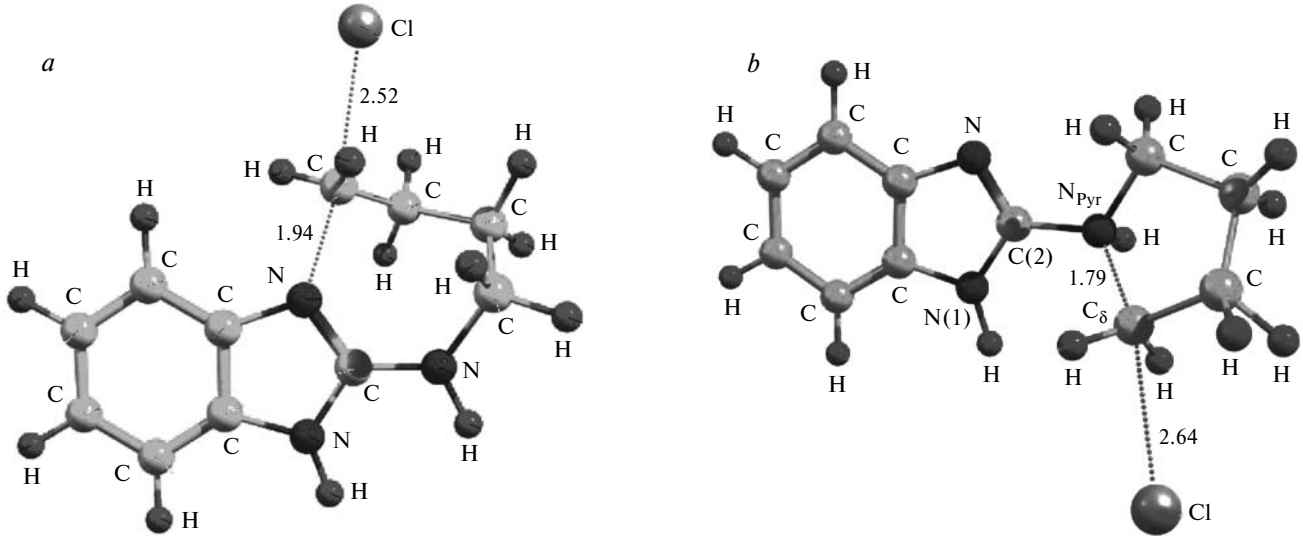


Fig. 1. Diazepine transition state **TS5** (distorted boat) (*a*) and the pyrrolidine transition state *E*-**TS6** (the N(1)—C(2)—N_{Pyr}—C_δ dihedral angle is 43°) (*b*) for the cyclization of chlorobutylaminobenzimidazole **3c** (calculations at the B3LYP/6-31G** level). The C—N and C—Cl bond lengths in the reaction centers are given (in Å).

the substantially larger total deviation of the bond angles of the tetramethylene bridge from the optimal tetrahedral angles compared to that in the pyrrolidine transition states (see Table 1).

The difference between the entropies of the transition states **TS5** and **TS6** with the minimum energy for each chlorobutylamine is ~3 kal mol^{-1} K^{-1}, which is responsible for an additional increase (by more than 1 kcal mol^{-1}) in the free activation energy of the cyclization to diazepine compared to the cyclization to pyrrolidine at the reaction temperature.

All together these factors lead to the fact that the pyrrolidine transition states **TS6** for the imidazole are formed in solution with somewhat lower free activation energies $\Delta G^{\neq}$ than the corresponding diazepine transition states,★ as was demonstrated by the calculations at the B3LYP/6-31G** level of theory in terms of the PCM solvation model (EtOH) (see Table 1). For the benzimidazole transition states, the inverse ratio of the Gibbs free energies of the transition states was estimated by this method, but the energy difference is small (1.6 kcal mol^{-1}).

It should be noted that the contribution of the minor imino forms of substrates **15a,b** to both types of the cyclization of compounds **3c** and **9** can be ignored. In particular, the formation of diazepines **1c** and **11** from imines is virtually impossible due to the very high activation energies ($\Delta E^{\neq}_{\mathbf{TS7}}$ > 45 kcal mol^{-1}). The fact that the cyclization of imines to pyrrolidines is non-competitive is attributed to the fact that the corresponding total expenditure of energy by this reaction channel, including $\Delta E^{\neq}_{\mathbf{TS8}}$ and the energy of tautomerization of the amino forms, $E^{\mathrm{tot}}{}_{\mathrm{imino}} - E^{\mathrm{tot}}{}_{\mathrm{amino}}$ is substantially higher than the activation energies $\Delta E^{\neq}_{\mathbf{TS6}}$ for the direct cyclization of amino forms **3c** and **9** (see Table 1).

An analysis of the results of quantum chemical calculations shows that the activation energies for all imidazole substrates are, on the whole, lower than those for their benzimidazole analogs, which is, evidently, a consequence of the higher nucleophilicity of the imidazole heterosystem.

Therefore, the thermal cyclization of 2-(δ-chlorobutylamino)benzimidazole **3c**, unlike the cyclization of shorter-chain-length 2-(ω-chloroalkylamino)benzimidazoles, is characterized by the predominant attack on the low-nucleophilic nitrogen atom and, consequently, the qualitatively different regioselectivity. The above-considered data suggest that this is also typical of imidazole analogs of compounds **3c**.

★ It should be noted that the cyclization to pyrrolidine is more favorable even in spite of substantially higher stability of diazepinobenzimidazolium cations **13** compared to cations **14** (for the imidazole pair of cations **13a** and **14a**, ΔE^{tot} is higher than 19 kcal mol^{-1} (see Table 1)).

Experimental

The progress of the reactions and the individuality of the reaction products were monitored by TLC on alumina plates (Brockmann activity III) using $CHCl_3$ as the eluent; spots were visualized by exposure to iodine vapor in a wet box. The ^{1}H NMR spectra were recorded on a Varian XL-300 instrument. The IR spectra were measured on a Specord-75 IR spectrometer in Nujol mulls.

The quantum chemical calculations were carried out with the use of the PC GAMESS 6.4 version[21] of the GAMESS (US) quantum-chemical program package[22] and by the DFT method (B3LYP/6-31G**).

The first- and second-order stationary points were identified by calculations of their force matrices and the frequencies corresponding to normal vibrational modes. In addition, the calculations by the intrinsic reaction coordinate (IRC) method were carried out for the transition states. Since this method requires a large volume of calculations, most of calculations were performed at the RHF/6-31G level (sometimes, at the B3LYP/6-31G** level). Of a large set of conformations of the starting compounds **3c** and **9** with similar energies, one most stable conformation was chosen for each type of cyclization. Then the geometry of these structures was optimized by the DFT method with the 6-31G** basis set. The total energies were used in the calculations of $\Delta E^{\neq}$. The calculations were carried out with the zero-point energy (ZPE) correction. In the calculations at the B3LYP/6-31G(d,p) level, the scaling coefficient of 0.961 was used.[23]

2-(4-Hydroxybutylamino)benzimidazole (2c). A mixture of benzimidazole-2-sulfonic acid (4 g, 20 mmol) and 4-aminobutanol (4.6 mL, 50 mmol) was heated with stirring to 150—155 °C and kept at this temperature for 1.5 h. After completion of the reaction, the melt was cooled to ~90 °C and treated with water (25 mL). After 2—3 h, the precipitate was filtered off and washed with ice water (3×10 mL). The yield was 3.48 g (85%), slightly yellowish flakes, m.p. 161—162 °C (from MeCN). Found (%): C, 64.29; H, 7.2; N, 20.56. $C_{11}H_{15}N_3O$. Calculated (%): C, 64.37; H, 7.37; N, 20.47. IR, ν/cm^{-1}: 1620 (C=N); 3000—3200 (NH, OH); 3400 (NH). ^{1}H NMR ($CDCl_3$), δ: 1.48—1.72 (m, 4 H, β-CH_2, γ-CH_2); 3.30 (q, 2 H, NCH_2, J = 5.3 Hz); 3.45 (t, 2 H, OCH_2, J = 6.0 Hz); 6.26 (t, 1 H, NH, J = 5.3 Hz); 6.73—6.87 (m, 2 H, H(5), H(6)); 7.00—7.11 (m, 2 H, H(4), H(7)); 11.40 (br.s, 1 H, NH).

2-(4-Chlorobutylamino)benzimidazole (3c). Freshly distilled $SOCl_2$ (1.08 mL, 15 mmol) was slowly added to a suspension of amino alcohol **2c** (2.05 g, 10 mmol) in dry $CHCl_3$ (30 mL) at a temperature no higher than 35 °C. The reaction solution was refluxed for 1 h and concentrated. The residue was treated with acetone. Hydrochloride **3c** was filtered off and washed with acetone until the washing liquid became colorless and then with petroleum ether. The yield of hydrochloride **3c** was 2.4 g (93%), m.p. 140—141 °C (from MeCN). Found (%): C, 50.69; H, 5.74; Cl, 27.18; N, 16.35. $C_{11}H_{15}Cl_2N_3$. Calculated (%): C, 50.78; H, 5.81; Cl, 27.26; N, 16.15. IR, ν/cm^{-1}: 1660 (C=N$^+$H); 3000—3200 (NH). ^{1}H NMR (DMSO-d_6), δ: 1.73—1.94 (m, 4 H, C(2)H_2, C(3)H_2); 3.50 (q, 2 H, NCH_2, J = 6.3); 3.66 (t, 2 H, CH_2Cl, J = 6.1 Hz); 7.08—7.18 (m, 2 H, H(5), H(6)); 7.32—7.43 (m, 2 H, H(4), H(7)); 9.23 (t, 1 H, 2-N<u>H</u>CH_2, J = 6.3 Hz); 12.97 (br.s, 2 H, 2 NH).

The resulting hydrochloride (1.3 g, 5 mmol) was dissolved in water (10 mL) at room temperature. The solution was carefully made alkaline with concentrated NH_4OH to pH 8—9. The oil that formed rapidly crystallized to give colorless crystals. After 0.5 h, the crystals were filtered off, washed with water, and dried in air. The yield was 1.1 g (98%), m.p. 115—116 °C. Found (%): C, 58.95; H, 6.30; Cl, 15.70; N, 18.96. $C_{11}H_{14}ClN_3$. Calculated (%): C, 59.06; H, 6.31; Cl, 15.85; N, 18.78. IR, ν/cm^{-1}: 1630 (C=N); 2500—2750 (NH); 3400 (NH).

Thermal cyclization of 2-(4-chlorobutylamino)benzimidazole (3c). A melt of chlorobutylamine **3c** (0.5 g, 2.2 mmol) was kept at 130—135 °C for 10 min. After cooling, the melt was treated with concentrated NH_4OH (2 mL). The precipitate consisting of 2-pyrrolidinobenzimidazole **4** (R_f 0.35) and diazepinobenzimidazole **1c** (R_f 0.35) (TLC data) was filtered off and washed with water. The yield was 0.39 g (95%). According to the ^{1}H NMR spectra, compounds **4** and **1c** were obtained in a ratio of ~3 : 1. The ^{1}H NMR spectra of individual compounds **4** and **1c** are given below. The selectivity of cyclization in the reactions performed in solutions is virtually the same.

2-Pyrrolidinobenzimidazole (4). ***A.*** A suspension of hydrochloride **3c** (0.26 g, 1 mmol) was refluxed in a 5% NaOH solution (4 mL) for 2 h. After cooling, the precipitate was filtered off and washed with water. The yield was 0.17 g (91%), m.p. 334—335 °C (from EtOH, with decomp.). Found (%): C, 70.45; H, 7.22; N, 22.56. $C_{11}H_{13}N_3$. Calculated (%): C, 70.56; H, 7.00; N, 22.24. IR, ν/cm^{-1}: 1633 (C=N); 3000—3100 (NH). ^{1}H NMR (DMSO-d_6), δ: 1.90—1.96 (m, 4 H, $(CH_2)_2$); 3.40—3.46 (m, 4 H, $N(CH_2)_2$); 6.83—6.89 (m, 2 H, H(5), H(6)); 7.11—7.14 (m, 2 H, H(4), H(7)); 11.08 (br.s, 1 H, NH).

B. A mixture of benzimidazole-2-sulfonic acid (2.0 g, 10 mmol) and pyrrolidine (2.5 mL, 30 mmol) was heated in a sealed tube at 140—150 °C for 1.5 h. After cooling, the reaction mixture was treated with water (20 mL). The precipitate was filtered off, washed with water, and recrystallized from ethanol containing activated carbon. The yield was 1.27 g (68%), m.p. 334—335 °C (with decomp.). A mixture of compound **4** and the sample prepared according to the procedure ***A*** showed no melting point depression.

1-Acetyl-2-(4-chlorobutylamino)benzimidazole (5). A solution of chloramine **3c** (0.22 g, 1 mmol) in Ac_2O (4 mL) was kept at 20—25 °C for ~24 h. The progress of the reaction was monitored by TLC (R_f(**3c**) 0.15, R_f(**5**) 0.95). Then Ac_2O was concentrated to dryness at 30—35 °C *in vacuo*. The residue was treated with diethyl ether, filtered off, and dried in air. The yield was 0.25 g (94%), m.p. 62 °C. Found (%): C, 58.68; H, 6.10; Cl, 13.22; N, 15.96. $C_{13}H_{16}ClN_3O$. Calculated (%): C, 58.75; H, 6.07; Cl, 13.34; N, 15.81. IR, ν/cm^{-1}: 1640 (C=N); 1700 (C=O); 3370 (NH). ^{1}H NMR (DMSO-d_6), δ: 1.67—1.81 (m, 4 H, $C(2)H_2$, $C(3)H_2$); 2.74 (s, 3 H, Me); 3.46 (q, 2 H, NCH_2, J = 6.3 Hz); 3.67 (t, 2 H, CH_2Cl, J = 6.3 Hz); 6.99 (t, 1 H, H(5) or H(6), J = 7.7 Hz); 7.15 (t, 1 H, H(6) or H(5), J = 7.6 Hz); 7.24 (d, 1 H, H(7), J = 7.8 Hz); 7.53 (d, 1 H, H(4), J = 8.0 Hz); 7.89 (t, 1 H, NH, J = 6.3 Hz).

1-Acetyl-2,3,4,5-tetrahydro[1,3]diazepino[1,2-*a*]benzimidazole (7). ***A.*** A solution of chlorobutylamine **3c** (2.23 g, 10 mmol) in acetic anhydride (20 mL) was kept at 20—25 °C until the complete acetylation of the amino group was achieved (see the synthesis of compound **5**). Then the reaction mixture was refluxed for 2 h, cooled, and poured into water (50 mL). Excess Ac_2O was quenched, and the reaction mixture was carefully made alkaline with concentrated NH_4OH. The precipitate of compound **7** was filtered off and washed with water. The yield was 2.1 g (92%), m.p. 154—155 °C (from C_6H_6). Found (%): C, 68.04; H, 6.72; N, 18.43. $C_{13}H_{15}N_3O$. Calculated (%): C, 68.10; H, 6.59; N, 18.33. IR, ν/cm^{-1}: 1618, 1602 (C=C); 1668 (C=N); 1675 (C=O). ^{1}H NMR (DMSO-d_6), δ: 1.90—1.98 (m, 4 H, $C(3)H_2$, $C(4)H_2$); 2.20 (s, 3 H, COMe); 3.72—3.88 (m, 2 H, $C(5)H_2$); 4.10—4.18 (m, 2 H, $C(2)H_2$); 7.27—7.35 (m, 3 H, H(7)—H(9)); 7.73 (dd, 1 H, H(10), J_1 = 6.3 Hz, J_2 = 2.0 Hz).

B. Compound **5** (0.27 g, 1 mmol) was heated at 80 °C for 10 min. The melt was cooled and treated with a 22% ammonia solution. The precipitate was filtered off and washed with water. The yield was 0.22 g (96%). The compound is identical to that synthesized according to the method ***A.***

1(11)*H*-2,3,4,5-Tetrahydro[1,3]diazepino[1,2-*a*]benzimidazole (1c). Compound **7** (2.29 g, 10 mmol) was refluxed in concentrated HCl (20 mL) for 1 h. Then the reaction solution was cooled and made alkaline with concentrated NH_4OH to pH 9—10. After 2 h, the precipitate that formed was filtered off and washed with water. The yield was 1.73 g (93%), colorless needle-like crystals, m.p. 199—200 °C (from C_6H_6) (*cf.* lit. data[11]: m.p. 192 °C). Found (%): C, 70.63; H, 7.05; N, 22.56. $C_{11}H_{13}N_3$. Calculated (%): C, 70.56; H, 7.00; N, 22.44. IR, ν/cm^{-1}: 1585, 1600, 1629 (C=C, C=N); 3218 (NH). ^{1}H NMR (DMSO-d_6), δ: 1.93—1.99 (m, 4 H, $C(3)H_2$, $C(4)H_2$); 3.21—3.28 (m, 2 H, $C(2)H_2$); 3.96—4.04 (m, 2 H, $C(5)H_2$); 5.47 (br.s, 1 H, NH); 7.06—7.17 (m, 3 H, H(7)—H(9)); 7.44 (d, 1 H, H(10), J = 8.4 Hz).

2-[*N*-(4-Acetoxybutyl)-*N*-acetylamino]benzimidazole (8). A solution of amino alcohol **2c** (0.4 g, ~2 mmol) in Ac_2O (3 mL) was refluxed for 1.5 h, cooled, and poured into water (20 mL). Acetic anhydride was quenched, and the reaction mixture was carefully made alkaline with concentrated NH_4OH. The reaction product was extracted with $CHCl_3$ (3×7 mL), and the extract was passed through a layer of Al_2O_3 ($CHCl_3$ as the eluent). The yield was 0.53 g (91%), m.p. 101—102 °C (from light petroleum ether). Found (%): C, 62.35; H, 6.78; N, 14.75. $C_{15}H_{19}N_3O_3$. Calculated (%): C, 62.27; H, 6.62; N, 14.52. IR, ν/cm^{-1}: 1645 (NCOMe); 1705 (OCOMe); 3340 (NH). ^{1}H NMR ($CDCl_3$), δ: 1.75—1.96 (m, 4 H, $C(2)H_2$, $C(3)H_2$); 2.05 (s, 3 H, NCOMe); 2.45 (s, 3 H, OCOMe); 4.15 (t, 2 H, NCH_2 or OCH_2, J = 6.5 Hz); 4.23 (t, 2 H, OCH_2 or NCH_2, J = 7.8 Hz); 7.15—7.28 (m, 2 H, H(5), H(6)); 7.38 (d, 1 H, H(4), J = 8.0 Hz); 7.65 (d, 1 H, H(7), J = 7.8 Hz); 11.50 (s, 1 H, NH).

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