Tautomerism of 1,2,4-triazino[2,3-*a*]benzimidazol-5(4)*H*-3-ones

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Studies by X-ray diffraction and quantum chemical methods demonstrated that 1,2,4-triazino[2,3-*a*]benzimidazol-5(4)*H*-3-ones exist in the condensed state primarily in the 5*H*-tautomeric form, whereas these compounds exist, most likely, predominantly as 4*H* tautomers in the gas phase. The low-barrier tautomerism of 1,2,4-triazino[2,3-*a*]benzimidazol-5(4)*H*-3-ones occurs through the intermediate formation of hydrogen-bonded cyclic dimers followed by the concerted two-proton transfer. *N*-Alkylation of both the electroneutral and *N*-anionic forms of 2-methyl-1,2,4-triazino[2,3-*a*]benzimidazol-5(4)*H*-3-one affords predominantly *N*(4)-alkyl derivatives.

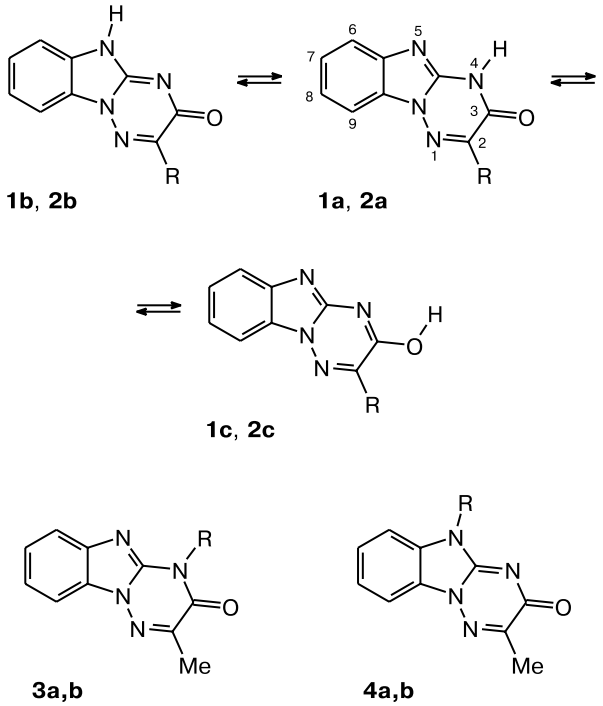
Key words: 1,2,4-triazino[2,3-*a*]benzimidazol-5(4)*H*-3-ones, X-ray diffraction study, quantum chemical calculations, dipole moments, tautomerism, *N*-alkylation, hydrogen-bonded dimers, polymorphism.

Evidently, 1,2,4-triazino[2,3-*a*]benzimidazol-5(4)*H*-3-ones **1** and **2** (see Refs 1—4), which are close structural analogs of biologically active 1,2,4-triazino[4,3-*a*]benzimidazol-4(10)*H*-ones,[5—8] can exist as three tautomeric forms, in which the proton is localized at the N(4), N(5), and oxygen atom, respectively (Scheme 1).

In the study,[9] the results of mass spectrometry, IR spectroscopy, and photoionization spectroscopy were analyzed, and 2-methyl-1,2,4-triazino[2,3-*a*]benzimidazol-5(4)*H*-3-one (**1**) (see Ref. 1) was concluded to exist in 4*H*-tautomeric form **1a** both in the gas phase and the condensed medium.

In continuation of our investigation of triazino[2,3-*a*]benzimidazolones,[10,11] in the present study we report the results of investigation of tautomerism in compound **1** by quantum chemical methods and X-ray diffraction. Based on these results, we revised the conclusion[9] about the nature of the tautomeric form existing as the major structure both in the solid phase and solution and estimated the character of the influence of intermolecular interactions on the position of the tautomeric equilibrium. We also performed quantum chemical calculations for an as yet uncharacterized parent compound of this series (compound **2**). Procedures for the synthesis of model *N*-substituted structures with the known positions of *N* substituents (**3** and **4**), which were required for investigation of the tautomerism, based on cyclization of 1-amino-2-R-aminobenzimidazoles and 1,2-diamino-3-R-benzimidazolium salts have been developed earlier.[9—11]

Scheme 1



Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 475—483, March, 2006.

Results and Discussion

Quantum chemical calculations by the MP2/6-31G* method (see Table 1) demonstrated that all tautomeric forms of triazinones **1** and **2** are virtually planar, which is favorable for the efficient conjugation in their π-electron systems. In the gas phase, 4*H* tautomers **1a** and **2a** are the most stable structures, which is consistent with the conclusion drawn in the study.[9] The total energies (E_{tot}) of 5*H* and OH tautomers **1b,c** and **2b,c** are higher than those of **1a** and **2a** by approximately 3—6 kcal mol^{-1}. The calculations demonstrated also that the 5*H*-tautomeric form is much more polar than the two other forms. The calculated dipole moments (μ_{calc}) for 5*H* tautomers **1b** and **2b** in the gas phase (5.9—6.9 D) are larger than those of 4*H* tautomers **1a** and **2a** by more than 4 D (see Table 1). In polar media, the dipole moments increase to ~9 D. The high polarity of the 5*H* form is also evidenced by a substantially lower chromatographic mobility of *N*(5)-substituted triazinobenzimidazolones **4a,b** compared to their *N*(4)-substituted analogs **3a,b**.

In the condensed medium, where the electrostatic and polarization interactions of heterocyclic molecules with each other and with the solvent molecules play a great role, the relative energies of three tautomers are substantially different (see Table 1). According to calculations, the energy of electrostatic interactions of highly polar 5*H* tautomers **1b** and **2b** with the solvent (E_{es}) in an aqueous solution is higher than that of the corresponding hydrated 4*H* forms by approximately 6 kcal mol^{-1}, whereas the free energy (G_{tot}) of the former tautomers is, on the whole, lower. In addition, the OH tautomers in solution are substantially destabilized with respect to the 5*H* forms (E_{tot}(OH) − E_{tot}(5*H*) ≈ 12 kcal mol^{-1} in H_2O and

Table 1. Results of calculations of the energy characteristics, dipole moments, and charges of the monomeric, dimeric, and anionic forms of 1,2,4-triazino[2,3-*a*]benzimidazol-4(5)*H*-3-ones **1** and **2** and transition states of the two-proton transfer and *N*-alkylation

Structure[a]	μ_{calc} /D	$-E_{tot}$[b] /au	ΔE_{4H}[c]	$-\Delta E_{stab}$[d]	$-G_{tot}$ /au	$-E_{es}$	ΔG_{4H}	Mulliken charges		
			kcal mol^{-1}			kcal mol^{-1}		N(1) (N(1′))	N(4) (N(4′))	N(5) (N(5′))
		(gas phase)			(aqueous solution)					
1a	1.54	677.9103	0	—	675.7945	11.4	0	−0.21	−0.80	−0.52
1b	6.42	677.9026	4.8	—	675.7978	17.5	−1.5	−0.26	−0.71	−0.95
1c	2.89	677.8999	6.5	—	675.7779	13.0	10.5	−0.23	−0.51	−0.51
2a	1.66	638.7598	0	—	636.7839	11.5	0	−0.14	−0.80	−0.51
2b	6.86	638.7521	5.1	—	636.7870	18.1	−1.9	−0.16	−0.53	−0.81
2c	2.13	638.7506	6.0	—	636.7683	12.4	9.8	−0.18	−0.50	−0.50
1d	7.83	677.5405	—	—	—	—	—	−0.27	−0.56	−0.57
2d	7.84	638.3639	—	—	—	—	—	−0.21	−0.56	−0.57
7b	0.08	1351.0697	0	19.5	1350.9948	17.4	0	−0.07	−1.09	−1.10
8b	0.04	1351.0738	−2.6	26.9	1351.0020	19.1	−4.5	−0.13	−0.80	−1.11
9b	6.73	1351.0611	5.4	16.6	1350.9960	25.7	−0.8	−0.15 (−0.13)	−0.75 (−1.08)	−1.11 (−0.75)
10b	0.00	1351.0220	29.9	20.2	1350.9502	19.8	28.0	−0.15	−0.77	—
TS1	5.3	1273.0259 (9.7, 7.6)	—	—	—	—	—	—	—	—
7a	—	1273.0380	—	—	—	—	—	—	—	—
8a	—	1273.0415	—	—	—	—	—	—	—	—
TS2	14.5	1179.0019 (3.5)	0	—	—	—	—	−0.26	−0.92	0.71
TS3	13.7	1178.9989 (5.3)	1.8	—	—	—	—	−0.27	−0.76	−0.89
1d[e]	—	679.0333	—	—	—	—	—	—	—	—
MeCl	—	499.9741	—	—	—	—	—	—	—	—

[a] The structures were calculated by the following methods: **1a—c** and **2a—c**, by MP2/6-31G*; **1d** and **2d**, by MP2/6-31++G*; **TS2**, **TS3**, **1d**, and MeCl, by DFT (B3LYP/6-31G**); dimeric structures, by RHF/6-31G; for aqueous solutions, by RHF/6-31G* and RHF/6-31G (for dimers) (t = 298 °C).

[b] For the transition states, the energy barriers $\Delta E^{\neq}$/kcal mol^{-1} for either the forward reaction or the forward and reverse reactions (in the case of **TS1**) are given in parentheses.

[c] The energy of the tautomer, dimer, or TS relative to the energy of the corresponding 4*H* form or relative to TS corresponding to the attack on position 4.

[d] The stabilization energy of the dimer relative to two molecules of the monomer.

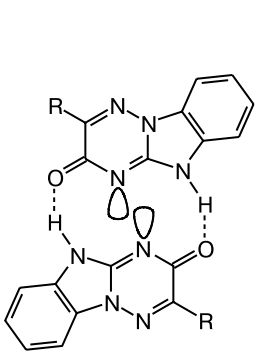
[e] The calculation by the DFT method (B3LYP/6-31G**).

~17 kcal mol^{-1} in DMSO) compared to those in the gas phase (see Table 1). Consequently, the OH tautomers, most likely, do not play a noticeable role in the reactions of triazinobenzimidazolones **1** and **2** in the condensed phase.

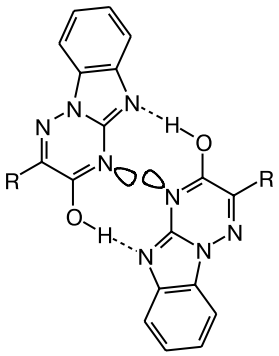
The ratio of the tautomeric forms of compounds **1** and **2** in solution and the crystalline state can also depend on the formation of hydrogen bonds and hydrogen-bonded dimers. Among dimeric structures **5—10** potentially possible for triazinones **1** and **2**, structures **5** and **6**, which are strongly destabilized by repulsion between the lone electron pairs of the N(4) and N(4′) atoms directed toward each other, can be excluded from consideration. Calculations for the other dimers, which were performed by the restricted Hartree—Fock (RHF) method for compound **1**, demonstrated that, in the gas phase, all these dimers are characterized by rather high stabilization energies with respect to the monomers (ΔE_{stab}) due to the presence of two hydrogen bonds, the resistance of these dimers to dissociation decreasing in the series **8b** > **10b** > **7b** > **9b** (see Table 1). The absolute stability determined by the total energy E_{tot} of the dimer of 5*H* form **8b** is also higher than that of the other dimers of triazinone **1**. In particular, the energy of this dimer in the gas phase is approximately 2.6 kcal mol^{-1} lower than that of dimer **7b** composed of the 4*H* tautomers. In an aqueous solution, this energy difference increases to ~4.5 kcal mol^{-1} (see Table 1). Consequently, structure **8** most likely corresponds to the global minimum on the potential energy hypersurface describing different dimeric states of compounds **1** and **2**.

Therefore, the 5*H*-tautomeric form is stabilized not only due to its high polarity but also due to dimerization, resulting in the probable existence of this form as the major structure in the condensed medium.

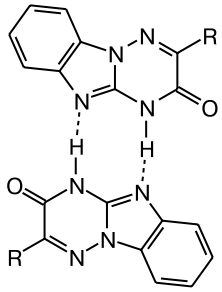
To confirm this conclusion by experimental data, we analyzed the IR spectra of compound **1** and its fixed model forms **3** and **4**. The spectra of *N*(4)-substituted triazinobenzimidazoles **3** show three intense absorption bands at 1600 (C=C), 1620 (C=N), and 1680 cm^{-1} (C=O). The spectra of *N*(5)-substituted isomers also show three analogous bands, but their intensity sharply decreases in the series of the C=C, C=N, and C=O bonds, and the weak absorption band of the CO group is shifted to 1630—1640 cm^{-1}. In the spectrum of triazinone **1**, the intensity of this band is also low and the band is shifted to longer wavelengths (1618 cm^{-1}) due, apparently, to the influence of hydrogen bonding. On the whole, the IR spectrum of triazinone **1** containing the free NH group is more similar to the spectra of 5-substituted isomers of **4**. It should be noted that the low intensity of the CO band in the spectrum of the 5*H* tautomer of compound **1** was predicted also by quantum chemical calculations of the vibrational spectrum of this tautomer (RHF/6-31G*).



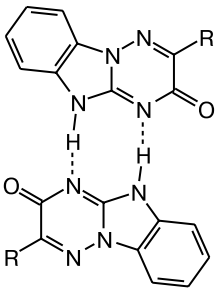
5a,b



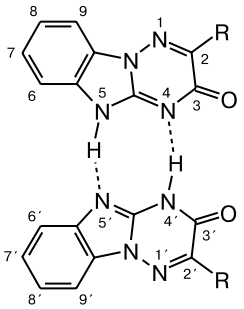
6a,b



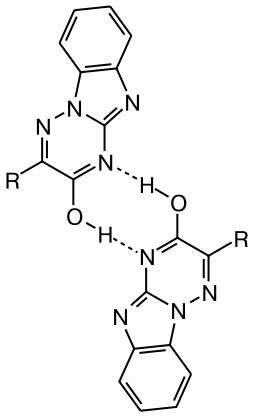
7a,b



8a,b



9a,b



10a,b

R = H (**a**), Me (**b**)

The crystal structure of 2-methyl-1,2,4-triazino[2,3-*a*]benzimidazol-3-one (**1**) was unambiguously established by X-ray diffraction. It appeared that this compound exists as two polymorphs, *viz.*, prismatic (α form) and needle-like (β form), which are formed as a mechanical mixture of crystals by crystallization from standard solvents (DMF, DMSO, or ethanol) and are composed of 5*H* tautomers **1b** (Table 2). Therefore, crystallization of triazinone **1** leads to concomitant polymorphism regardless of the polarity of the solvent. Taking into account also the fact that the polymorphs are characterized by

Table 2. Principal crystallographic data and parameters in two polymorphs of compound **1**

Parameter	α form	β form
Molecular formula	$C_{10}H_8N_4O$	
Molecular weight	200.20	
T/K	120	
Crystal shape	Prismatic	Needle-like
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$
Z (Z')	2 (1)	4 (1)
a/Å	7.1315(10)	3.8876(5)
b/Å	7.9578(11)	10.2206(13)
c/Å	8.2600(11)	22.263(3)
α/deg	95.690(3)	
β/deg	93.629(3)	91.494(3)
γ/deg	108.762(2)	
V/Å^3	439.41(10)	884.3(2)
d_{calc}/g cm^{-3}	1.513	1.504
μ/cm^{-1}	1.05	1.04
F(000)	208	416
$2\theta_{max}$/deg	60	60
Number of measured reflections	2479	4996
R_{int}	0.0209	0.0662
Number of independent reflections	3621	2022
Number of reflections with $I > 2\sigma(I)$	2479	1050
Number of parameters in refinement	168	168
R_1	0.0584	0.0595
wR_2	0.1308	0.1249
GOOF	1.060	0.968
Residual electron density /e A^{-3} (d_{min}/d_{max})	0.464/−0.367	0.288/−0.246

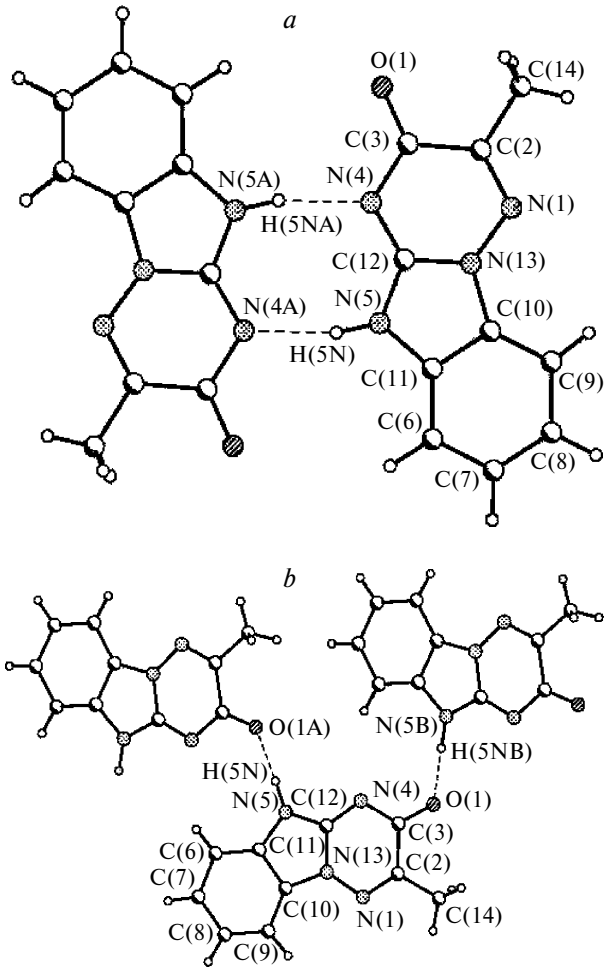


Fig. 1. Hydrogen-bonded associates in the α- (*a*) and β-polymorphs (*b*) of compound **1**.

similar crystal densities (see Table 2), the crystal packing energy of the α form is likely to be similar to that of the β form.[12]

Two polymorphs of structure **1b** radically differ in the character of the surpamolecular organization. For example, the molecules in the α form are linked to each other by strong N(5)—H(5N)...N(4A) bonds (N(5)...N(4), 2.805(2) Å; H(5N)...N(4A), 1.91 Å; N(5)—H(5N)—N(4A), 167°) to form centrosymmetric dimers of type **8b** (Fig. 1, *a*). For comparison, the corresponding H(5N)...N(4A) distance in dimer **8b** calculated by the RHF/6-31G method is 1.872 Å. The molecules in the β form are linked to each other by the strong N(5)—H(5N)...O(1A) bonds (N(5)...O(1A), 2.739(4) Å; H(5N)...O(1A), 1.77 Å; N(5)—H(5N)—O(1A), 171°) to form chains along the crystallographic axis *b* (see Fig. 1, *b*). Interestingly, the absolutely identical C(7)—H(7)...O(1A) contacts are present in both polymorphs (H...O, 2.29 Å; the angle at the hydrogen atom is 167 and 159° in the α and β forms, respectively).

To compare the stability of the above-described hydrogen-bonded associates found in two polymorphs, we performed quantum chemical calculations (B3LYP/6-311G**) for the corresponding dimer and trimer. The H-bond energy was estimated by performing the topological analysis of the electron density function (ρ(r))[13] using the semiquantitative dependence of the H-bond energy on the potential energy density at its critical point (CP) (3, −1).[14] The calculated hydrogen bond parameters agree rather well with those observed in the crystal. However, the N(5)...N(4A) distance in the isolated dimer is slightly longer (2.842 Å), whereas the N(5)...O(1A) distance is, on the contrary, shorter (2.705 Å). According to the above-described dependence,[14a] the N—H...N and N—H...O bond energies are 10.3 and 13.7 kcal mol^{-1}, respectively. This fact, taking into account the above-mentioned strengthening and weakening of the H bonds in the dimer and trimer compared to those in the crystal, suggests that the H-bond energies in both polymorphs are similar.

In addition to the above-mentioned strong and weak H bonds, molecules **1** are involved in stacking interactions in both modifications. Actually, the molecules in the α and β forms are located in stacks parallel to each other at almost equal distances (3.33 and 3.34 Å, respectively). The character of the mutual superposition of the π systems in the stacks are, in principle, different (Fig. 2). In the α form, the molecules are arranged in a head-to-tail fashion. The dipole moments of the adjacent molecules are antiparallel, so that the shortest C...C distance is observed for the C(10) atom of the benzimidazole ring (3.322(2) Å). The other C...N contacts (N(1)...C(7A), 3.417(2) Å; N(13)...C(9), 3.372(2) Å) are somewhat longer. To the contrary, the molecules in the β form are arranged in the head-to-head fashion (the dipole moments are parallel), the surface area of the superposition being virtually the same; the shortest N(4)...N(13A) distance is 3.370(4) Å, whereas the C...C (C(12)...C(10A), 3.383(4) Å; C(10)...C(9A), 3.432(4) Å; C(6)...C(7A), 3.433(4) Å) and C...N (N(5)...C(11A), 3.417(4) Å; C(3)...N(1A), 3.419(4) Å) contacts are somewhat longer. It can be seen that the total number of shortened contacts between the adjacent molecules in the stacks in the α form is one less than that in the β form.

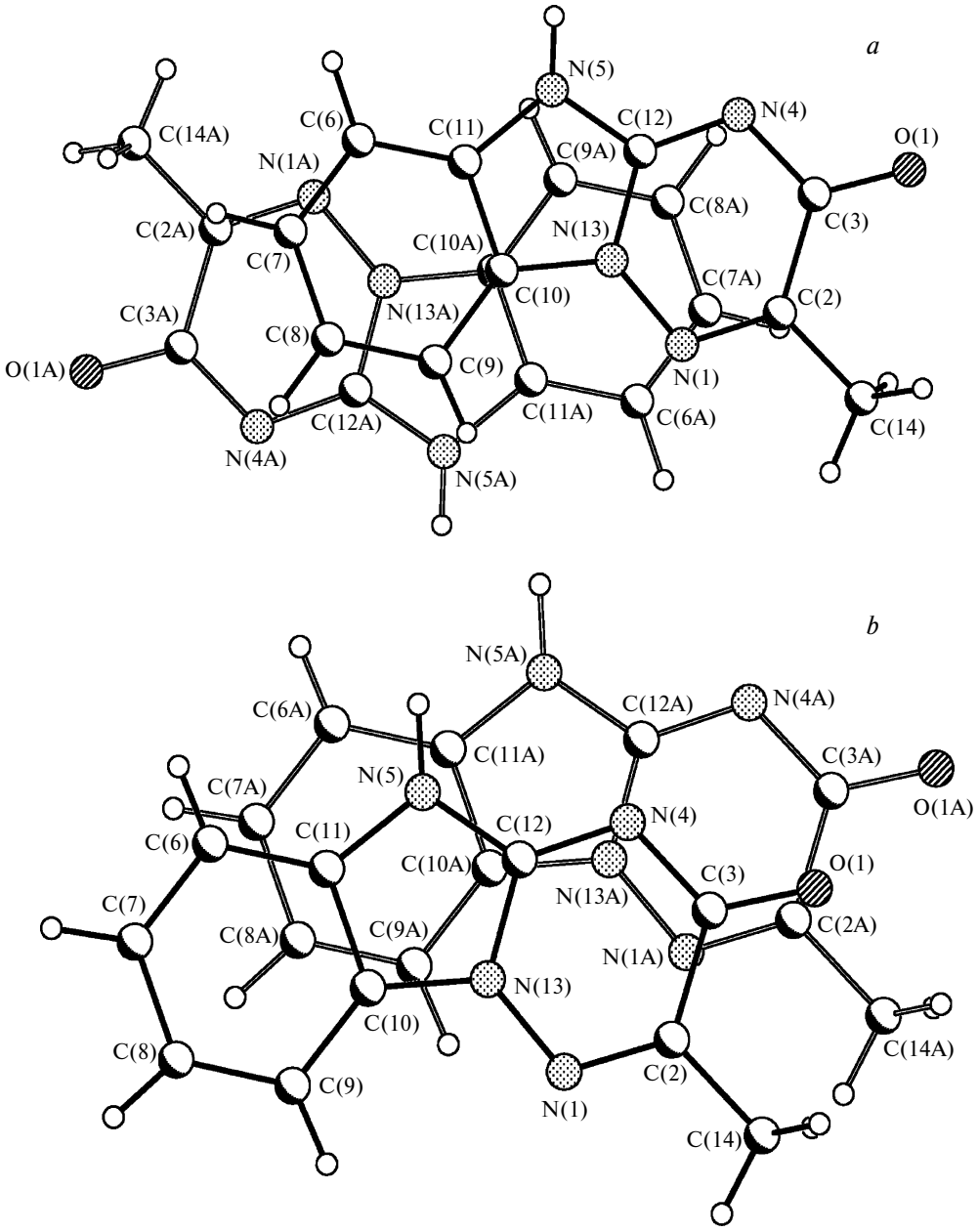


Fig. 2. Character of superposition of the molecules in the stacks in the α- (*a*) and β-polymorphs (*b*) of compound **1**.

A comparison of the molecular geometry in the α and β forms demonstrated that the largest differences in the lengths are observed for the bonds formed by the atoms involved in the stacking interactions. In particular, the C(9)—C(10) bond in the β form is shorter and the C(12)—N(3) bond is longer compared to the analogous bonds in the α form (Table 3). To the contrary, variations in the types of the H bonds in the crystals have virtually no effect on the character of the bond length distribution in the ring.

Table 3. Selected bond lengths (*d*) and bond angles (ω) in the polymorphs of compound **1**

Parameter	Value	
	d/Å	
Bond	α form	β form
O(1)—C(3)	1.233(2)	1.240(3)
N(1)—N(13)	1.3626(19)	1.362(3)
N(1)—C(2)	1.295(2)	1.296(3)
N(4)—C(12)	1.313(2)	1.318(3)
N(5)—C(11)	1.397(2)	1.404(3)
N(5)—C(12)	1.345(2)	1.350(3)
C(2)—C(3)	1.494(2)	1.502(3)
C(2)—C(14)	1.480(2)	1.494(3)
C(3)—N(4)	1.372(2)	1.365(3)
C(6)—C(7)	1.388(2)	1.396(3)
C(6)—C(11)	1.379(2)	1.377(3)
C(7)—C(8)	1.394(3)	1.398(4)
C(8)—C(9)	1.392(2)	1.381(3)
C(9)—C(10)	1.383(2)	1.393(3)
C(10)—C(11)	1.398(2)	1.409(3)
C(10)—N(13)	1.393(2)	1.392(3)
C(12)—N(13)	1.361(2)	1.381(3)
Angle	ω/deg	
C(2)—N(1)—N(13)	114.50(13)	114.7(19)
N(1)—C(2)—C(14)	118.39(14)	118.4(2)
N(1)—C(2)—C(3)	123.28(14)	123.0(2)
C(14)—C(2)—C(3)	118.32(14)	118.5(2)
O(1)—C(3)—N(4)	121.51(15)	122.6(2)
O(1)—C(3)—C(2)	120.11(15)	118.4(2)
N(4)—C(3)—C(2)	118.37(14)	118.9(2)
C(12)—N(4)—C(3)	115.70(14)	115.8(2)
C(12)—N(5)—C(11)	108.25(14)	108.9(2)
C(11)—C(6)—C(7)	117.00(16)	117.1(2)
C(6)—C(7)—C(8)	121.37(16)	121.2(2)
C(9)—C(8)—C(7)	122.04(16)	122.1(2)
C(10)—C(9)—C(8)	115.84(16)	116.6(2)
C(9)—C(10)—N(13)	132.22(15)	132.7(2)
C(9)—C(10)—C(11)	122.44(15)	121.4(2)
N(13)—C(10)—C(11)	105.30(13)	105.8(19)
C(6)—C(11)—N(5)	130.64(16)	130.9(2)
C(6)—C(11)—C(10)	121.30(15)	121.5(2)
N(4)—C(12)—N(5)	126.94(15)	128.0(2)
N(4)—C(12)—N(13)	124.41(15)	123.9(2)
N(5)—C(12)—N(13)	108.65(14)	108.1(2)
C(12)—N(13)—N(1)	123.70(13)	123.64(19)
C(12)—N(13)—C(10)	109.71(13)	109.66(19)
N(1)—N(13)—C(10)	126.59(13)	126.70(19)

To estimate the energy of stacking interactions in the two polymorphs, we performed the topological analysis of ρ(r)[13] using the results of B3LYP/6-311G** calculations for two adjacent molecules in the stack without the geometry optimization based on the same correlation as in the case of H bonds.[14] The number of interactions between the aromatic rings in the dimers, *i.e.*, the number of CP (3, −1), in the α form differs from that in the β form (5 and 6, respectively; according to the results of the topological analysis of ρ(r)). However, the potential energy density at the CP (3, −1) in the β form (from −0.0033 to −0.0025 au) is slightly lower in magnitude than that in the α form (from −0.0033 to −0.0030 au). As a result, in spite of the different number of interactions, the total energy of stacking interactions is virtually the same in both modifications (4.98 and 4.95 kcal mol^{-1}). For comparison, the energy of stacking interactions in 3-amino-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (the distance in the dimer is 3.33 Å), which was estimated from the results of high-resolution X-ray diffraction study,[15] is 3.2 kcal mol^{-1}.

Therefore, there is virtually no difference in the energy of intermolecular interactions in both polymorphs of triazinone **1**, which is, apparently, responsible for the existence of concomitant polymorphism. The principally different character of the supramolecular organization of the molecules in the crystals of two polymorphs suggests that, regardless of intermolecular contacts in the solid state, 5*H* tautomer **1b** is the most stable structure, as opposed to the gas phase.

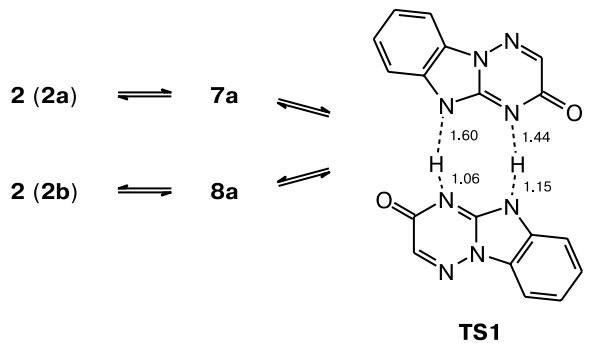
We failed to use ^{1}H NMR spectroscopy for studying the tautomeric equilibrium of compound **1** in solutions because the spectra of 4- and 5-substituted fixed structures **3** and **4** do not show rather characteristic differences in the chemical shifts and multiplicities of the signals. In addition, under standard conditions, the spectrum of *N*-unsubstituted triazinone **1** shows neither an impurity of the minor tautomer nor broadened signals, which could be indicative of the occurrence of dynamic processes due to tautomerism.

The data from electronic spectroscopy appeared to be more informative. Although the UV spectra of both fixed forms **3b** and **4b** ($2.5 \cdot 10^{-5}$ mol L^{-1}, MeCN) substantially differ from the spectrum of triazinone **1** in the positions and intensities of long-wavelength absorption bands, the relatively short-wavelength region of the spectrum (230—260 nm), which is less subjected to the perturbing effect of intermolecular interactions, of NH-unsubstituted compound **1** is similar to that of *N*(5)-benzyl derivative (λ_{max}/nm (logε): **1**, 237 (4.47) and 260 (shoulder against the longer-wavelength band); **4b**, 239 (4.43) and 260 (3.94)). On the contrary, this region of the spectrum of *N*(4)-benzyl isomer **3b** (λ_{max}/nm (logε): 253 (4.33) and

246 sh) substantially differs from that of triazinone **1**. This is evidence that the 5*H* form is the major structure in solution.

Tautomerization of triazinobenzimidazolones **1** and **2** cannot be provided by the proton migration within one molecule of the tautomer, because these processes are associated with very high activation barriers.[16—18] The reaction pathway involving the formation and tautomerization of hydrogen-bonded associates (in particular, of dimers) according to the two-proton transfer mechanism (see, for example, Refs 19—22) is more favorable. For the parent compound of the series, *viz.*, for compound **2**, the transition state (TS) of the two-proton transfer, which was revealed by the RHF/6-31G method, is presented in Scheme 2 by structure **TS1**. For this transition state, the internuclear N—H distances (Å) in the reaction unit of TS are given in the scheme.

Scheme 2



TS1

Although being composed of the identical monomers, dimeric TS of type **TS1**, unlike dimers **7** and **8**, are unsymmetrical and polar structures (μ_{calc} = 5.3 D) due to a substantial shift of both protons of the NH groups to one of the monomeric fragments. The fact that **TS1** corresponds to the two-proton transfer was confirmed by investigation of the reaction coordinate in both directions. The calculated energy barriers $\Delta E^{\neq}$ for the direct and reverse two-proton transfer in **TS1** are low (7.6 and 9.7 kcal mol^{-1}, respectively).

Based on the general characteristic features of *N*-alkylation of nitrogen-containing tautomeric systems[23] and our data on the character of the tautomeric equilibrium in the simplest 1,2,4-triazino[2,3-*a*]benzimidazol-5(4)*H*-3-ones **1** and **2**, it can be predicted that alkylation of such compounds under neutral conditions will afford *N*(4)-substituted isomers as the major products. These isomers correspond to the attack of the pyridine nitrogen atom. By contrast, the reaction in an alkaline medium giving rise to the *N*-anionic forms of the substrates should afford *N*(5)-substituted isomers because the nitrogen atom to which the proton is bound is, generally, the most active atom.[23] Yet another potential site for the electrophilic attack, *viz.*, the *N*(1) atom, is obviously noncompetitive due to the low negative charge on this atom (see Table 1).

Experimental studies demonstrated that the reactivity of compound **1** toward alkylating agents in a neutral medium is rather low and, at room temperature, compound **1** does not react even with reactive phenacyl bromide. Alkylation in refluxing acetonitrile does not virtually occur as well. However, prolonged heating with such reagents as dimethyl sulfate, benzyl chloride, phenacyl bromide, or β-phenoxyethyl bromide in nitromethane or DMF afforded the expected 4-substituted triazinones **3a—d** in good yields. *N*(5)-Substituted isomers **4** were prepared in small amounts, which is, apparently, indicative of the presence of minor 4*H* tautomer **1b** in the reacting system.

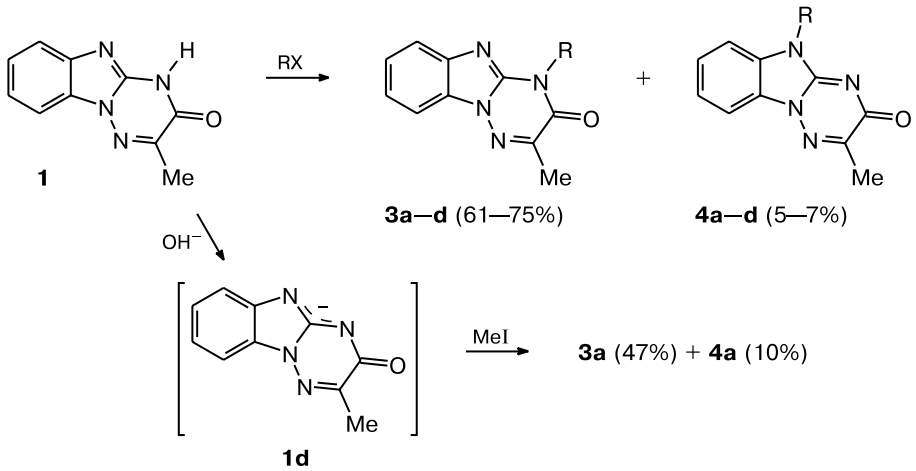
The physicochemical characteristics of 4-methyl and 4-benzyl derivatives **3a,b** produced by alkylation are identical to those prepared by cyclization of the corresponding 2-alkylamino-1-aminobenzimidazoles.[10] The properties of compounds **3c,d** differ from those of the corresponding *N*(5)-substituted isomers **4**, which confirms the structures of compounds **3c,d** as *N*(4)-substituted derivatives of triazinone **1**. 5-Phenacyltriazinone **4c** was synthesized from the 1,2-diamino-3-phenacylbenzimidazolium salt and ethyl pyruvate.[11] In the cited study, 2-methyl-5-(2-phenoxyethyl)-1,2,4-triazino[2,3-*a*]benzimidazol-3-one isomeric with **3d** was also described. It should be noted that the above-considered procedure for the synthesis of 4-substituted 1,2,4-triazino[2,3-*a*]benzimidazol-3-ones is of considerable preparative value because, unlike the known procedure,[10] it does not require the synthesis of difficultly accessible 2-alkylamino-1-aminobenzimidazoles.

We studied alkylation of triazinone **1** in the presence of bases (KOH or NaH) using the reaction of this compound with iodomethane in DMSO as an example. Under these conditions, the process occurs already at room temperature. However, contrary to the expectations, this reaction also afforded 4-methyltriazinone **4a** as the major product (the ratio of the 4-substituted isomer to the 5-substituted isomer in the reaction mixture was ~4 : 1; ^{1}H NMR spectroscopic data) (Scheme 3).*

This untypical behavior of *N*-anion **1d** can be attributed to the decisive influence of the difference in the hybridization of the orbitals of the lone electron pairs on the N(4) and N(5) atoms, the negative charges on these atoms being very similar (see Table 1). According to the results of the NBO analysis, the hybridization of the orbitals of these two atoms are $sp^{2.71}$ and $sp^{2.32}$, respectively, the more pronounced p character of the orbital of the N(4) atom creating a substantially higher electrostatic potential in the vicinity of this atom, resulting in its higher nucleophilicity. The high reactivity of position 4 in

* Similar results were obtained in the reaction performed in the presence of bases in acetone and methanol.[9]

Scheme 3



RX = Me_2SO_4, $PhCH_2Cl$, $PhCOCH_2Br$, $PhO(CH_2)_2Br$. **3, 4:** R = Me (**a**), $PhCH_2$ (**b**), $PhCOCH_2$ (**c**), $PhO(CH_2)_2$ (**d**)

N-anion **1d** is not associated with the influence of the orbital factor, because AOs of both competitive nitrogen atoms make approximately equal contributions to HOMOs. The results of quantum chemical calculations for the transition state of methylation of *N*-anion **1d** with chloromethane by density functional theory (DFT/B3LYP) are consistent with the experimental data. The calculations demonstrated that the energy of nonsolvated **TS2** for the attack on position 4 is approximately 1.8 kcal mol^{-1} lower than that of isomeric **TS3** corresponding to the attack on position 5 (see Table 1). The energy barriers $\Delta E^{\neq}$ for two reaction pathways are low (3.5 and 5.3 kcal mol^{-1}, respectively), which is indicative of the high reactivity of the *N*-anion in the absence of solvation and counterions.

In the general case, the disagreement between the position of the attachment of the proton and the major direction of the attack by the alkylating agent is apparently a consequence of the fact that the most basic position differs from the most nucleophilic position in the *N*-anion.

Experimental

The ^1H NMR spectra were recorded on a Varian XL-300 spectrometer (300 MHz). The IR spectra were measured on a Specord IR-75 instrument in Nujol mulls. Electronic spectra were recorded on a Specord MK-40 spectrometer. Quantum chemical calculations were carried out in the Cartesian coordinates using the PC GAMESS* version of the quantum chemical GAMESS program package (US).[24] The geometry of the calculated structures was initially optimized using the 3-21G basis set. The transition states **TS1—TS3** were identified from the presence of the imaginary vibrational mode and with the use of the intrinsic reaction coordinate (IRC) method. All calculations of the energy characteristics were carried out with the zero-point energy correction.

The solvation parameters of the tautomeric forms were calculated in terms of the PCM model using the Hartree—Fock method with the 6-31G* basis set for monomers and the 6-31G basis set for dimers using the preliminary geometry optimization in the absence of the solvent. In calculations of G_{tot} for solutions, the dispersion component was ignored. The NBO analysis of *N*-anion **1d** was performed by the RHF/3-21G//MP2/6-31G* method using the GAUSSIAN 98 program. The topological analysis of the function ρ(r) was performed using the MORPHY 98 program[25] with the use of the wave function obtained in calculations by the B3LYP method.

X-ray diffraction data for compound **1** were collected on a SMART CCD diffractometer. The structures were solved by direct methods and refined against F^2_{hkl} by the least-squares method with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms were located in difference Fourier maps and refined isotropically. All calculations were carried out using the SHELXTL PLUS program package. The principal crystallographic data and parameters of the structure refinement are given in Table 2.

The purity of the reaction products was checked by TLC on Al_2O_3 plates (Brockmann activity III) using chloroform as the eluent; the spots in the chromatograms were visualized with UV light.

4-Benzyl-2-methyl-1,2,4-triazino[2,3-*a*]benzimidazol-3-one (3b). ***A.*** A solution of 1-amino-2-benzylaminobenzimidazole[10] (0.71 g, 3 mmol) and ethyl pyruvate (0.33 mL, 3 mmol) in acetic acid (5 mL) was refluxed for 0.5 h. The precipitate that formed was filtered off and washed with water. The yield was 0.75 g (86%). Colorless crystals, m.p. 234—235 °C (from BuOH). Found (%): C, 70.05; H, 5.04; N, 19.47. $C_{17}H_{14}N_4O$. Calculated (%): C, 70.33; H, 4.86; N, 19.30. IR, ν/cm^{-1}: 1600 (C=C), 1623 (C=N), 1682 (C=O). ^1H NMR (DMSO-d_6), δ: 2.38 (s, 3 H, Me); 5.32 (s, 2 H, CH_2); 7.22—7.38 (m, 5 H, H(7), H(8), *m*,*p*-H_{Ph}); 7.46 (d, 2 H, *o*-H_{Ph}, J = 6.9 Hz); 7.60—7.66 (m, 1 H, H(6) or H(9)); 7.70—7.78 (m, 1 H, H(9) or H(6)).

* A. A. Granovsky, http://www.classic.chem.msu.su/gran/gamess/index.html.

B. A mixture of 2-methyl-1,2,4-triazino[2,3-*a*]benzimidazol-5(4)*H*-3-one (**1**) (0.60 g, 3 mmol) and benzyl chloride (0.35 mL, 3 mmol) in anhydrous DMF (5 mL) was refluxed for 8 h, the starting compound being completely dissolved after 5 h. The solution was cooled. The precipitate that formed was filtered off, washed with diethyl ether, and treated with hot chloroform (15 mL). After separation of the starting triazinobenzimidazole **1** that remained undissolved (0.12 g), the mother liquor was chromatographed on an alumina column (2×15 cm) using $CHCl_3$ as the eluent, and the fraction with R_f 0.85 was collected. The yield was 0.53 g (61%). The physicochemical characteristics of the sample of compound **3b** prepared according to the method *A* are identical to those of the sample prepared by the method *B*.

5-Benzyl derivative **4b** with m.p. 242—243 °C (from BuOH) was isolated from the second fraction (R_f 0.3) in a yield of 0.06 g (7%). A mixture of compound **4b** and the authentic sample of **4b** (see Ref. 11) showed no melting point depression.

2-Methyl-5-phenacyl-1,2,4-triazino[2,3-*a*]benzimidazol-3-one (4c). A suspension of 1,2-diamino-3-phenacylbenzimidazolium bromide[26] (1.74 g, 5 mmol) and ethyl pyruvate (0.60 mL, 5 mmol) in glacial acetic acid (30 mL) was refluxed for 1.5 h until the precipitate was completely dissolved. Then the mixture was refluxed for 0.5 h. The solvent was distilled off *in vacuo* using a water-jet pump, the residue was treated with water, and the precipitate that formed was filtered off. The yield was 1.27 g (80%), colorless crystals, m.p. 278—279 °C (from DMF), R_f 0.35. Found (%): C, 67.78; H, 4.21; N, 17.75. $C_{18}H_{14}N_4O_2$. Calculated (%): C, 67.92; H, 4.43; N,17.60. IR, ν/cm^{-1}: 1580 (C=C), 1610 (C=N), 1635 (CO), 1705 ($CH_2\underline{CO}$). ^{1}H NMR (DMSO-d_6), δ: 2.48 (s, 3 H, Me); 5.94 (s, 2 H, CH_2); 7.38—7.40 (m, 2 H, H(7), H(8)); 7.63 (t, 2 H, *m*-H_{Ph}, J = 7.5 Hz); 7.68—7.73 (m, 1 H, H(6)); 7.75—7.81 (m, 1 H, *p*-H_{Ph}); 7.83—7.87 (m, 1 H, H(9)); 8.11—8.16 (m, 2 H, *o*-H_{Ph}).

2-Methyl-4-phenacyl-1,2,4-triazino[2,3-*a*]benzimidazol-3-one (3c) was prepared by alkylation of triazinobenzimidazole **1** with phenacyl bromide analogously to compound **3b**. The yield was 68%. Colorless crystals, m.p. 255—256 °C (from BuOH), R_f 0.8. Found (%): C, 68.08; H, 4.87; N, 17.53. $C_{18}H_{14}N_4O_2$. Calculated (%): C, 67.92; H, 4.43; N, 17.60. IR, ν/cm^{-1}: 1597 (C=C), 1623 (C=N), 1680 (C=O), 1720 ($CH_2\underline{CO}$). ^{1}H NMR (DMSO-d_6—CCl_4), δ: 2.46 (s, 3 H, Me); 5.73 (s, 2 H, CH_2); 7.25—7.33 (m, 2 H, H(7), H(8)); 7.46—7.53 (m, 1 H, H(6)); 7.58 (t, 2 H, *m*-H_{Ph}, J = 7.5 Hz); 7.66—7.76 (m, 2 H, H(9), *p*-H_{Ph}); 8.15 (d, 2 H, *o*-H_{Ph}, J = 7.7 Hz). The yield of isomeric 5-phenacyl derivative **4c** was 6%.

2-Methyl-4-(2-phenoxyethyl)-1,2,4-triazino[2,3-*a*]benzimidazol-3-one (3d) was synthesized from triazinobenzimidazole **1** and β-phenoxyethyl bromide analogously to compounds **3b,c** in 65% yield. Colorless crystals, m.p. 201—202 °C (from BuOH). Found (%): C, 67.32 ; H, 5.24; N, 17.73. $C_{18}H_{16}N_4O_2$. Calculated (%): C, 67.49; H, 5.03; N, 17.49. IR, ν/cm^{-1}: 1595 (C=C), 1620 (C=N), 1678 (C=O). ^{1}H NMR ($CDCl_3$), δ: 2.50 (s, 3 H, Me); 4.37 and 4.62 (both t, 2 H each, CH_2, J = 4.9 Hz); 6.73—6.80 (m, 2 H, *o*-H_{Ph}); 6.92 (tt, 1 H, *p*-H_{Ph}, J_1 = 7.3 Hz, J_2 = 1.1 Hz); 7.18—7.25 (m, 2 H, *m*-H_{Ph}); 7.40 (td, 1 H, H(7) or H(8), J_1 = 7.6 Hz, J_2 = 1.3 Hz); 7.46 (td, 1 H, H(8) or H(7), J_1 = 7.7 Hz, J_2 = 1.4 Hz); 7.69—7.73 (m, 1 H, H(6)); 7.73—7.77 (m, 1 H, H(9)). The yield of the corresponding 5-phenoxyethyl derivative was 5%, m.p. 189—190 °C (from MeCN). The compound was identical to the authentic sample described earlier.[11]

Methylation of 2-methyl-1,2,4-triazino[2,3-*a*]benzimidazol-5(4)*H*-3-one (1). ***A.*** A solution of compound **1** (1.88 g, 0.01 mol) and dimethyl sulfate (1.0 mL, 0.01 mol) in nitromethane (10 mL) was refluxed for 6 h. After completion of the reaction, the nitromethane was distilled off to one-half of the initial volume. The precipitate that formed upon cooling was filtered off and washed with an aqueous sodium bicarbonate solution to neutral pH. The resulting mixture of isomers was separated by chromatography on an alumina column using $CHCl_3$ as the eluent. 4-Methyl isomer **3a** (R_f 0.9) was eluted from the column first in a yield of 1.5 g (75%). Colorless crystals with m.p. 232—234 °C (from EtOH). 5-Methyl isomer **4a** (R_f 0.3) with m.p. 268 °C (from EtOH) was isolated in a yield of 0.05 g (5%). Mixtures of the compounds and authentic samples of methyl derivatives **3a** (see Ref. 10) and **4a** (see Ref. 9) showed no melting point depression.

B. Methylation of the *N*-anion. Iodomethane (0.25 mL, 4 mmol) was added to a solution of triazinobenzimidazole **1** (0.60 g, 3 mmol) and powdered KOH (0.28 g, 4 mmol) in anhydrous DMSO (5 mL). The reaction mixture was kept at 20 °C for 24 h. The precipitate (0.41 g) that formed after dilution with water (15 mL) was filtered off. The reaction product was a mixture of *N*(4)- and *N*(5)-methyl derivatives of triazinobenzimidazoles **3a** and **4a** in a ratio of 4 : 1 (^{1}H NMR spectroscopic data in $CDCl_3$). 2,4-Dimethyl derivative **3a** was isolated in a yield of 0.3 g (47%) from the first fraction, and 5-methyl isomer **4a** was isolated from the second fraction in a yield of 0.07 g (10%) by chromatography of this mixture on an alumina column (2×15 cm, $CHCl_3$ as the eluent).

This study was financially supported by the Russian Foundation for Basic Research and the Administration of the Rostov Region (Project Nos 04-03-96804 and 06-03-32557) and the Council on Grants of the President of the Russian Federation (Program for State Support of Young Scientists, Grant MK-1054.2005.3).

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Received November 16, 2005;
in revised form February 17, 2006