Synthesis of first nonannulated 1,2,3,4-tetrazine 1,3-dioxides

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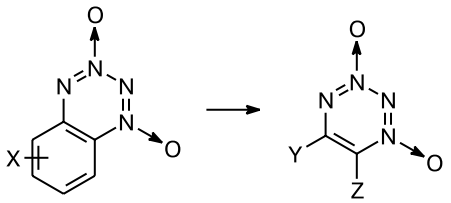
Thermolysis of *o*-diazidobenzotetrazine 1,3-dioxides was accompanied by cleavage of the C—C bond of the benzene ring to give nonannulated 1,2,3,4-tetrazine 1,3-dioxides. The structures of these first representatives of nonfused 1,2,3,4-tetrazines were confirmed by ^{13}C and ^{14}N NMR spectroscopy.

Key words: azides, 1,2,3,4-tetrazines, benzo-1,2,3,4-tetrazines, *N*-oxides, ^{13}C NMR spectroscopy.

1,2,3,4-Tetrazines represent one of the main monocyclic heteroaromatic systems.[1] However, relevant data are fragmentary. Fully unsaturated 1,2,3,4-tetrazines have been found hitherto only as annulated structures. Two *N*-oxide O atoms in positions 1 and 3 of the tetrazine ring substantially stabilize the system. 1,2,3,4-Tetrazine 1,3-dioxides annulated with the benzene,[2] pyridine,[3] and furazan rings[2] are known to be comparatively stable. Fused 1,2,3,4-tetrazines that contain no *N*-oxide O atoms (*e.g.*, 2-phenyl-2*H*-[1,2,3]triazolo[4,5-*e*][1,2,3,4]tetrazine[4]) or only one O atom of this kind (*e.g.*, benzotetrazine 1-oxides[2]), are much less stable.

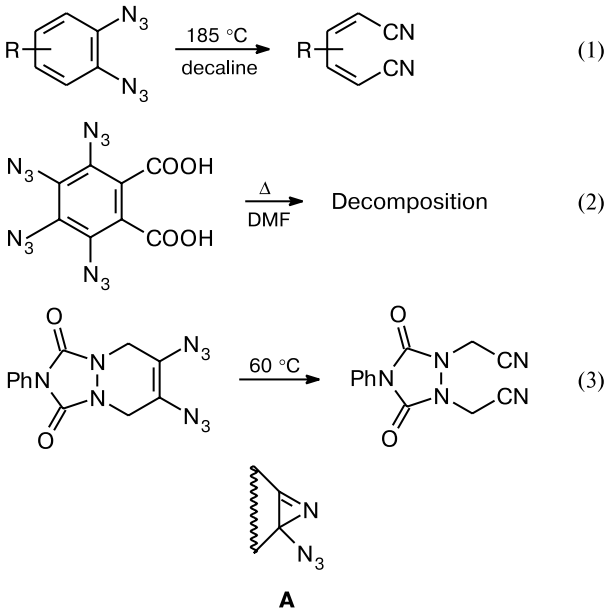
The goal of the present work was to obtain nonannulated 1,2,3,4-tetrazine 1,3-dioxides (TDO). Two different approaches to the synthesis of such compounds are possible *a priori*. The first approach involves the direct synthesis of TDO from linear compounds. According to the second one, the TDO ring is initially formed on an aromatic (*e.g.*, benzene) ring, which is then made to undergo opening. It is the latter version of the synthesis that we discuss below. Since we have already developed methods for the synthesis of benzotetrazine 1,3-dioxides (BTDO), the problem was to discover ways of opening the C—C bond of the benzene ring as shown in Scheme 1.

Scheme 1



A known method for opening of the C—C bond involves thermolysis of 1,2-diazidobenzenes and 1,2-diazidonaphthalene to *cis*,*cis*-1,4-dicyanobuta-1,3-dienes[5] (Scheme 2, reaction 1). The drastic conditions of the thermolysis (boiling decalin, 185 °C) allow one to suggest that the reaction proceeds through the formation of intermediate nitrene.[5] Data on the thermolysis of other types of polyazidobenzenes are very scarce. It is known that, *e.g.*, tetraazidophthalic acid (m.p. 113 °C) on heating in DMF releases four nitrogen molecules; however, the resulting organic products have not been identified[6] (Scheme 2, reaction 2).

Scheme 2



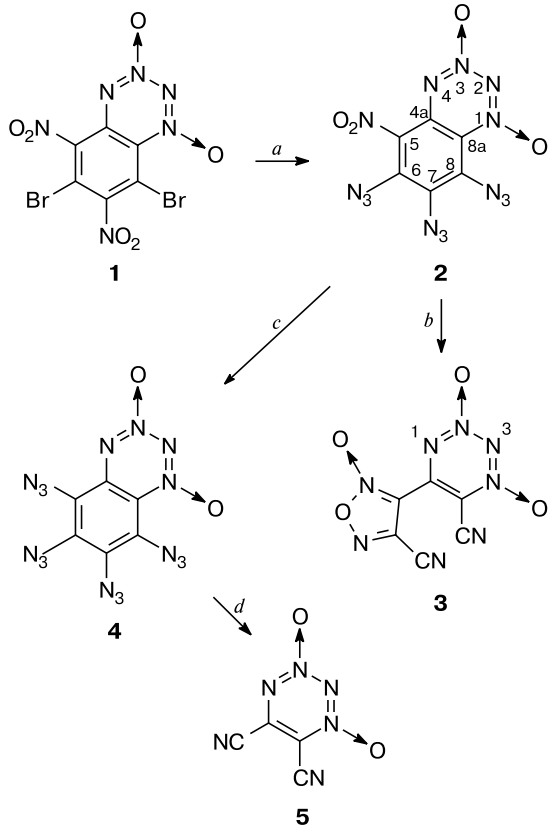
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1589—1594, September, 2006.

Note that vicinal cyclic diazidoethylenes undergo opening under substantially milder conditions[7] (Scheme 2, reaction 3). Supposedly, their decomposition proceeds through intermediate azirines of the type **A** rather than nitrene.

Results and Discussion

Synthesis of the starting reagents. Azidobenzotetrazine 1,3-dioxides were prepared by replacement of the nitro groups and the Br atoms in BTDO **1** (Scheme 3).

Scheme 3



Reagents, conditions, and yields: *a*, NaN_3, acetone/H_2O, 20 °C, 5 min (88%); *b*, toluene, 100 °C, 8 min (35%); *c*, NaN_3, DMF, 20 °C, 1.5 h (45%); *d*, toluene, 80 °C, 1.5 h (50%).

Treatment of this compound with NaN_3 (3 equiv.) in aqueous acetone gave triazido-BTDO **2**. The reaction of the latter with one more equivalent of NaN_3 in DMF afforded tetraazido-BTDO **4**. When heated, these compounds decomposed very vigorously, which precluded elemental analyses. Their structures were unambiguously confirmed by ^{13}C, ^{14}N, and ^{15}N NMR spectra.

The ^{13}C NMR spectrum of either compound shows six signals with the expected chemical shifts. To assign the signals, we used the additive scheme (see Experimental).

The ^{14}N NMR spectrum of BTDO **2** in acetone-d_6 confirmed the presence of the nitro group (a narrow signal at δ –23), three azido groups (a signal at δ –150 with the corresponding integral intensity), and the TDO ring (a narrow signal at δ –44, whose integral intensity corresponds to two N atoms).

Note that for all the known benzotetrazine 1,3-dioxides,[2] the ^{14}N NMR spectra in solvents with low viscosity ($CDCl_3$ or acetone-d_6) show two comparatively narrow signals for the N atoms of the TDO ring at δ(N(1)) –40 to –43 ($\Delta\nu_{1/2}$ = 35—40 Hz) and δ(N(3)) –45 to –49 ($\Delta\nu_{1/2}$ = 45—70 Hz), the signals usually being spaced at 2 to 8 ppm. Only in more viscous solvents (DMSO-d_6) do the signals for the N(1) and N(3) atoms coalesce because of their considerable broadening. With compound **2**, we observed for the first time a coincidence of these signals and had to record a ^{15}N NMR spectrum containing signals for all N atoms in the expected ranges in order to unambiguously confirm its structure (Table 1).

The structure of BTDO **4** was also confirmed by its ^{14}N NMR spectrum (DMSO-d_6) showing a broad signal for the N(1) and N(3) atoms at δ –45 and a broad signal for four azido groups.

Thermolysis of BTDO 2 and 4. Heating of BTDO **2** in toluene at 100 °C for 8 min resulted in closure of a furoxane ring and opening of the benzene ring along the C(7)—C(8) bond to give TDO **3** in 35% yield (Scheme 3). This compound is colorless (in contrast to the red starting BTDO **2**) and melts with decomposition at 165—167 °C. Its solutions in benzene or acetone are pale yellowish green, probably because of complex formation with the solvent.

Table 1. ^{14}N and ^{15}N NMR spectra

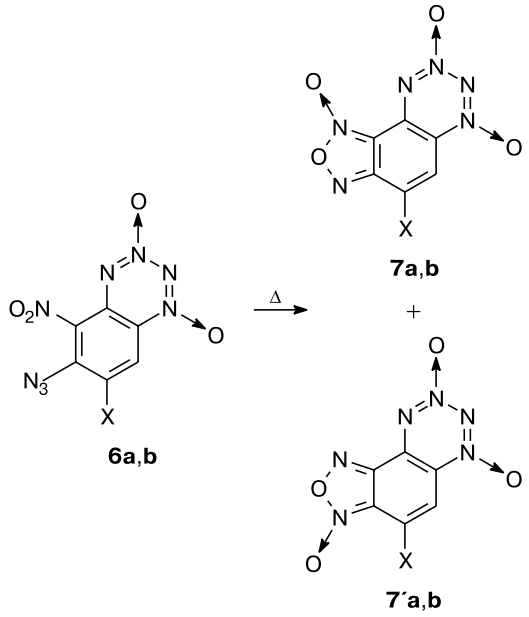
Compound	NMR spectrum	Solvent	δ ($\Delta\nu_{1/2}$/Hz)[a]	
			N(1) and N(3)	Other signals[b]
2	^{14}N	Acetone-d_6	–44 (70)	–23 (70, NO_2), –150 (100, N_3)
	^{15}N	Acetone-d_6	–44.9, –48	–23.4 (NO_2), –26.2 (N(2)),–97.3 (N(4)), –140.8, –143.3, –147.6, –148.1, –150.3, –152.4, –286.2, –292.4, –292.9 [c]
4	^{14}N	DMSO-d_6	–45 (200)	–146 (280, N_3)

[a] With $MeNO_2$ as a standard; the high-field signals are negative.
[b] In the ^{14}N NMR spectra, the narrowest signal for the azido group is given only.
[c] Nine signals for three azido groups.

Heating of BTDO **4** in toluene at 80 °C for 1.5 h gave TDO **5** in 50% yield. This compound is also colorless but is less stable than TDO **3**. At 110 °C, its crystals begin to "gutter" and a gas evolves. Melting is completed at 130 °C with vigorous gas evolution.

Discussion of a plausible thermolysis mechanism. Earlier, we have considered transformations of 6-azido-5-nitro-BTDO **6a** and **6b** into the corresponding furoxanes[8] (Scheme 4).

Scheme 4



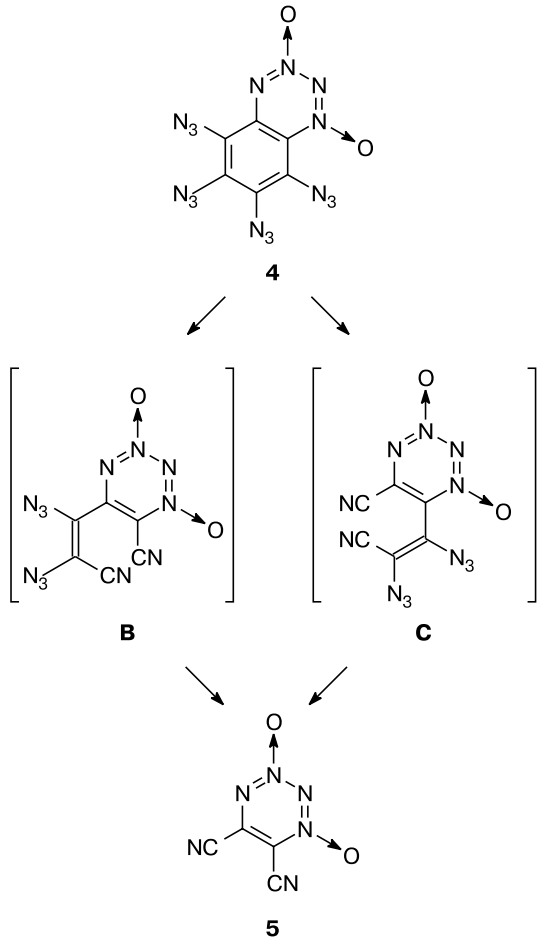
X = H (**a**), Br (**b**)

The cyclization of BTDO **6a** occurs at 90 °C in 30 min, while that of sterically hindered BTDO **6b** takes 30 min at 120 °C. These conditions are comparable with the cyclization conditions for BTDO **2**. Therefore, one could believe that the thermolytic cleavage of the C(7)—C(8) bond is preceded by closure of a furoxane ring. At the same time, the reverse reaction sequence is also possible: the opening of the benzene ring along the C(7)—C(8) bond is followed by the formation of a furoxane ring. Indeed, the benzene ring of BTDO **4** undergoes opening under close conditions, although the formation of furoxane at the first step is impossible in this compound.

Most likely, the transformation of BTDO **4** into TDO **5** is a two-step process (Scheme 5). First, cleavage of a C—C bond of the benzene ring gives rise to intermediates **B** or **C** and then the resulting diazidoethylene fragment decomposes. The decomposition of the aforementioned similar fragments is possible under relatively mild conditions, probably through an azirine intermediate of the type **A** (see Ref. 7 and Scheme 2).

Note that the cleavage of the C—C bond of the benzene ring in BTDO **4** at the first step requires a lower temperature than an analogous process in *o*-diazidobenzenes[5] (see Scheme 2, reaction 1) and hence involves no nitrene intermediates. The initial formation of an azirine intermediate of the type **A** also seems to be unlikely.

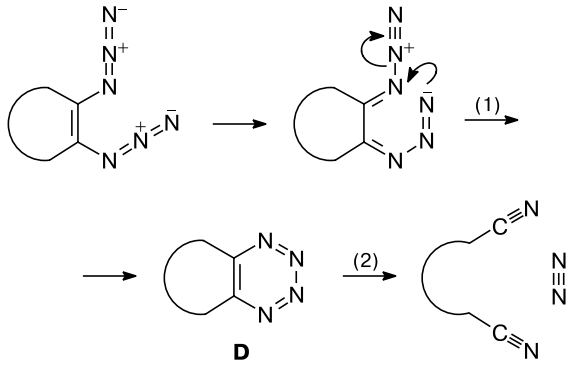
Scheme 5



A possible reaction pathway could involve the formation of intermediate tetrazine **D** followed by its decomposition into dinitrile and molecular nitrogen (Scheme 6).

Direct literature analogs for the first step of this process are lacking. Nevertheless, one can assume that the tetrazine 1,3-dioxide ring in BTDO **4**, on the other hand, polarizes the azido groups, thus facilitating the cyclization and, on the other hand, enhances the thermodynamic stability of the tetrazine ring, thus favoring ring closure. However, high-level quantum-mechanical calculations are required to estimate the possibility of this reaction mechanism.

Scheme 6



Known[9–12] literature analogs for the second step suggest that it is real enough. Some reactions involving cleavage of the ring C—C bond and the formation of dinitrile are explained by degradation of an hypothetic intermediate tetrazine ring.[9–12]

Confirmation of TDO structures. The structures of TDO **3** and **5** were confirmed by elemental analysis and spectroscopic data. The mass spectra (EI, 70 eV) of these compounds contain molecular ion peaks. The mass spectrum of TDO **5** shows a fragmentation characteristic of the 1,2,3,4-tetrazine 1,3-dioxide ring[2] (elimination of two N_2O molecules).

Previously,[2] we have easily identified the TDO ring in benzoannulated compounds by using ^{14}N NMR spectroscopy. The spectra exhibit two comparatively narrow signals for the N(1) and N(3) atoms. The chemical shifts for benzotetrazine 1,3-dioxide (**8**) as the simplest representative of this series are given in Table 2 as an example. The spectrum of TDO **5** shows only one signal in the expected range. However, its integral intensity corresponds to two N atoms (this was determined by integration of signals for a sample containing a specified amount of $MeNO_2$). An analogous coincidence of the signals for the N(1) and N(3) atoms have already been noted for BTDO **2** (see Table 1). In the spectrum of TDO **3**, two signals with an integral intensity ratio of 1 : 1 are still distinguishable, though being spaced at only 2 ppm.

The ^{13}C NMR spectrum of compound **5** (Table 3) consists of four signals, two of which (δ 105.40 and 107.80) are in the range characteristic of a nitrile group. The broadened signal at δ 114.7 was assigned to the C(2) atom bound to the *N*-oxide nitrogen atom. Earlier, an analogous broadening of the signal for the respective C atom, which results from a $^{13}C—^{14}N$ spin-spin coupling, had always been observed by us in the spectra of benzotetrazine 1,3-dioxides.[2] The remaining signal at δ 141.9 is due to the C(3) atom.

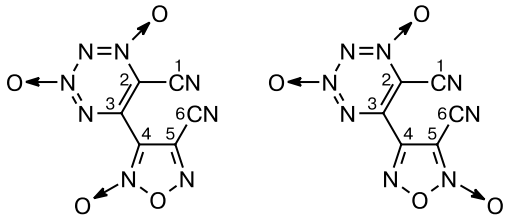
Table 2. ^{14}N NMR spectra of benzotetrazine 1,3-dioxide (**8**) and TDO **3** and **5**

Compound	Solvent	δ ($\Delta\nu_{1/2}$/Hz)	
		N(1)	N(3)
3	Acetone-d_6	–38 (30)	–40 (45)
5	CD_2Cl_2	–42 (25)	
8[2]	Acetone-d_6	–41 (20)	–48 (30)

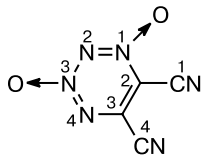
Table 3. DFT-calculated[a] (δ_{calc}) and experimental[b] (δ_{exp}) ^{13}C NMR spectra

Compound	Atom	δ_{calc}	δ_{exp}	Δ^c
3	C(3)	159.5	150.8	8.7
	C(5)	137.1	133.8	3.3
	C(2)	116.1	112.9 br.s	3.2
	C(4)	111.3	109.6[d]	1.7
	C(1)	111.1	107.2	4.0
	C(6)	110.5	106.8	3.5
3′	C(3)	158.6	150.8	7.8
	C(4)	153.1	133.8	19.3
	C(2)	113.9	112.9 br.s	1.0
	C(1)	110.2	109.6d	0.6
	C(6)	107.4	107.2	0.2
	C(5)	97.0	106.8	–9.8
5	C(3)	149.2	141.9	7.3
	C(2)	119.0	114.7 br.s	4.3
	C(4)	112.5	107.80	4.7
	C(1)	109.9	105.40	4.5

[a] The calculations were performed with the Priroda-04 program system.
[b] In acetone-d_6 for TDO **3** and in CD_2Cl_2 for TDO **5**.
[c] $\Delta = \delta_{calc} - \delta_{exp}$.
[d] The signal is slightly broadened.



3 **3′**



5

The structures of tetrazine 1,3-dioxides were confirmed by DFT-calculations of the ^{13}C chemical shifts with the Priroda-04 program system[13] (see Table 3).

For TDO **5**, the calculated and experimental data are in satisfactory agreement. The largest discrepancy was noted for the C(3) atom (Δ = 7.3 ppm).

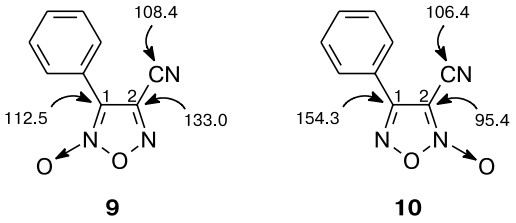


Fig. 1. ^{13}C NMR spectra of compounds **9** and **10** ($CDCl_3$, δ).

The ^{13}C NMR spectrum of TDO **3** shows a set of six signals, which could be due to isomers **3** or **3´** differing in the position of the *N*-oxide O atom.

Cyano(phenyl)furoxanes **9** and **10** are structurally close to TDO **3** and **3´** (see Ref. 14). At elevated temperatures (toluene, 110 °C), compounds **9** and **10** exist as an equilibrium mixture of both isomers in the ratio 64 : 36, which was confirmed by their ^{13}C NMR spectra. A comparison of the chemical shifts of the C(1) and C(2) atoms in furoxanes **9** and **10** showed that the *N*-oxide O atom strongly shields the nearest C atom (this phenomenon is well known[15]). Isomers **9** and **10** can be distinguished by the difference $\delta_{C(1)} - \delta_{C(2)}$ (Fig. 1), which is ~20 and ~59 ppm, respectively.

In the spectrum of TDO **3**, the signal at δ 112.9 is broadened and, accordingly, relates to the C(2) atom. The lowest-field signal at δ 150.8 should be assigned to the C(3) atom by analogy with the corresponding signal for TDO **5**. The chemical shifts of two high-field signals (δ 106.8 and 107.2) allow them to be assigned to two cyano groups (*cf.* the data for compounds **9** and **10**). The remaining two signals at δ 109.6 and 133.8 are due to the C(4) and C(5) atoms of the furoxane ring, the lower-field signal relating to the atom that is closer to the *N*-oxide O atom. The difference between the signals is ~24 ppm, which corresponds to isomer **3** rather than **3´**.

The calculated chemical shifts of the C atoms fit better the experimental ones in structure **3** (see Table 3). As with TDO **5**, the signal for the C(3) atom is predicted worst (Δ = 8.7 ppm). In structure **3´**, the experimental and calculated data for the C(4) and C(5) atoms are largely discrepant.

Thus, we obtained first representatives of nonannulated 1,2,3,4-tetrazine 1,3-dioxides and accomplished signal assignment in their ^{13}C NMR spectra.

Experimental

^1H, ^{13}C, ^{14}N, and ^{15}N NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13, 75.5, 21.5, and 30.4 MHz, respectively). Chemical shifts were measured relative to Me_4Si (^1H and ^{13}C) or $MeNO_2$ (^{14}N and ^{15}N; the external standard; high-field signals are negative). IR spectra were recorded on a UR-20 instrument. Mass spectra were recorded on a Varian MAT-311A instrument (EI, 70 eV). The course of the reactions was monitored by TLC on Silufol UV-254 plates. Compounds were purified by column chromatography on Silica 32-63 silica gel (Fisher Scientific).

Caution! The products obtained are sensitive to impact and friction and should be handled with as with explosives.

6,7,8-Triazido-5-nitro-1,2,3,4-benzotetrazine 1,3-dioxide (2). A solution of NaN_3 (332 mg, 5.1 mmol) in a mixture of acetone (14 mL) and water (14 mL) was added at 20 °C to a stirred solution of BTDO **1** (700 mg, 1.7 mmol) in acetone (14 mL). After 5 min, the solution was concentrated *in vacuo* and diluted with water (20 mL). The product was extracted with CH_2Cl_2 (3×80 mL) and the extract was dried with $MgSO_4$ and concentrated *in vacuo*. The resulting oil was crystallized by adding benzene (5 mL). The red crystals were filtered off and dried. The yield of BTDO **2** was 500 mg (88%), m.p. 97—102 °C (decomp.). IR (KBr), ν/cm^{-1}: 1289 m, 1402 m, 1448 m, 1497 m, 1533 m, 1575 m, 1630 s, 2150 s (N_3). ^{13}C NMR (acetone-d_6), δ: 121.7 (br.s C(8a)); 129.3; 130.2 (C(8) and C(7)); 130.0 (br.s C(5)) ($^{13}C\{^{14}N\}$ selective decoupling was used); 135.8; 136.9 (C(6) and C(4a)). MS, *m/z*: 248 $[M - 3\ N_2]^+$.

5-Cyano-6-(4-cyano-2-oxido-1,2,5-oxadiazol-3-yl)-1,2,3,4-tetrazine 2,4-dioxide (3). A solution of BTDO **2** (500 mg) in toluene (20 mL) was heated on a boiling water bath for 8 min. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with benzene—1% CF_3CO_2H as an eluent, washed with a small amount of Et_2O, and dried. The yield of compound **3** was 130 mg (35%), colorless crystals, m.p. 165—167 °C (decomp.). Found (%): C, 28.84; N, 45.32. $C_6N_8O_4$. Calculated (%): C, 29.04; N, 45.16. IR (KBr), ν/cm^{-1}: 1003 m, 1060 w, 1124 s, 1155 w, 1287 m, 1404 s, 1450 s, 1497 s, 1532 s, 1585 s, 1627 s, 2247 w. MS, *m/z*: 248 $[M]^+$.

5,6,7,8-Tetraazido-1,2,3,4-benzotetrazine 1,3-dioxide (4). Finely divided NaN_3 (88 mg, 1.35 mmol) was added in portions for 30 min to a stirred solution of BTDO **2** in dry DMF (40 mL). The reaction mixture was stirred for an additional 1 h at 20 °C and poured into water. The product was extracted with EtOAc (4×50 mL) and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue was passed through a short column with silica gel (with CH_2Cl_2 as an eluent). The eluate was concentrated *in vacuo* to a reddish brown oil. The yield of compound **4** was 200 mg (45%). IR (film between NaCl windows), ν/cm^{-1}: 1240 m, 1293 m, 1385 s, 1417 s, 1467 s, 1501 s, 1555 m, 2140 s. ^{13}C NMR (DMSO-d_6), δ: 120.4, 121.4 (C(8) and C(5)), 121.5 br.s (C(8a)), 128.4 (C(7)), 132.4, 137.4 (C(4a) and C(6)).

5,6-Dicyano-1,2,3,4-tetrazine 1,3-dioxide (5). A solution of BTDO **4** in toluene was heated at 80 °C for 1.5 h and then concentrated *in vacuo*. The residue was extracted with benzene and chromatographed on a short column with silica gel (with benzene—1% CF_3CO_2H as an eluent). The eluate was concentrated *in vacuo*. The yield of compound **5** was 50 mg (50%), colorless crystals, m.p. 110—130 °C (decomp.). Found (%): C, 29.49; N, 50.97. $C_4N_6O_2$. Calculated (%):C, 29.28; N, 51.22. IR (KBr), ν/cm^{-1}: 1163 s, 1195 w, 1308 m, 1388 s, 1430 s, 1485 s, 1525 s, 1547 s, 1658 s, 2247 m, 2265 w. MS, *m/z*: 164 [M] (25), 90 $[M - NO - N_2O]$ (3), 76 $[M - 2\ N_2O]$ (65), 44 $[N_2O]$ (100).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 04-03-32432).

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Received July 5, 2006;
in revised form July 28, 2006