Nitration and bromination of benzo-1,2,3,4-tetrazine 1,3-dioxides

O. Yu. Smirnov, A. M. Churakov, Yu. A. Strelenko, S. L. Ioffe, and V. A. Tartakovsky*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: churakov@ioc.ac.ru

Benzo-1,2,3,4-tetrazine 1,3-dioxide (BTDO) and its derivatives were nitrated with HNO_3/H_2SO_4 or HNO_3/oleum and brominated with dibromoisocyanuric acid in CF_3CO_2H/H_2SO_4 (5 : 1) or H_2SO_4. The reactivity of positions in the benzene ring of this heterocyclic system as regards electrophilic substitution was found to change in the following order: 5 ≈ 7 > 8 > 6. Mono- and dinitro-BTDOs and mono- and polybromo-BTDOs were synthesized. Their structures were confirmed by ^1H, ^{13}C, and ^{14}N NMR spectra.

Key words: benzo-1,2,3,4-tetrazines, *N*-oxides, nitration, bromination, dibromoisocyanuric acid.

This work is part of the systematic investigation of benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs).[1] Some compounds of this class have been synthesized earlier[2,3] by cyclization of 2-(*tert*-butyl-*NNO*-azoxy)anilines[4,5] in the presence of nitrating reagents. However, BTDOs obtained by this method can contain only a certain set of substituents in the benzene ring since the number of accessible starting anilines is limited; in addition, some limitations are imposed by cyclization conditions. At the same time, the application of electrophilic and nucleophilic substitution to the BTDO series will significantly broaden the range of compounds of this class.

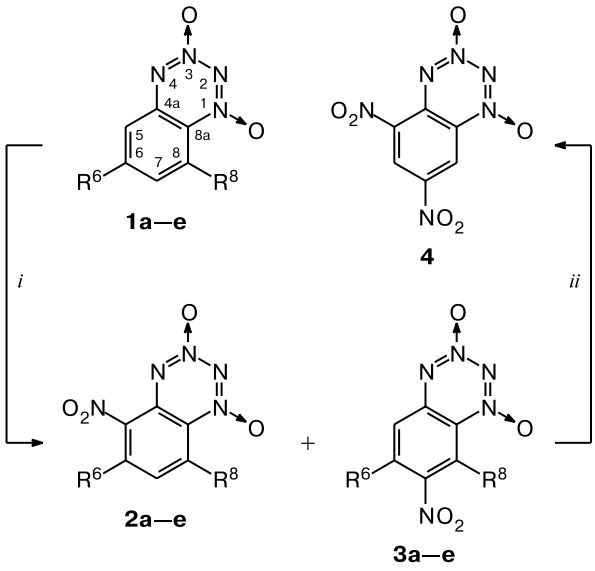
In the present work, nitration and bromination of BTDO derivatives were studied with the aim of finding out, first, whether the tetrazine-1,3-dioxide (TDO) ring can withstand drastic reaction conditions and, second, what is the direction of electrophilic substitution in these compounds.

Nitration of BTDO. Benzotetrazine 1,3-dioxide (**1a**) is easily nitrated with a mixture of sulfuric and nitric acids to give 5-NO_2- (**2a**) and 7-NO_2-isomers (**3a**) in a ratio of 1 : 2. Heating BTDO **1a** with an HNO_3/oleum mixture affords 5,7-dinitro derivative **4** with retained TDO ring.

Table 1. Ratio of isomers **2** and **3** obtained in the nitration of BTDOs **1a—e**

Starting compound	Ratio of isomers (%)
1a	**2a** : **3a** (33 : 67)
1b	**2b** : **3b** (90 : 10)
1c	**2c** : **3c** (99 : 1)
1d	**2d** : **3d** (100 : 0)
1e	**2e** : **3e** (19 : 81)

Scheme 1



a: $R^6 = R^8 = H$; **b:** $R^6 = Br$, $R^8 = H$; **c:** $R^6 = OMe$, $R^8 = H$; **d:** $R^6 = NMe_2$, $R^8 = H$; **e:** $R^6 = H$, $R^8 = Br$

i. HNO_3, H_2SO_4, 20 °C; *ii*. HNO_3, oleum, 90 °C.

Nitration of 6-substituted BTDOs also yields 5- or 7-nitro derivatives, the former being dominant (Table 1). Nitration of 6-Br-BTDO **1b** yields 5- and 7-NO_2-isomers **2b** and **3b** in a ratio of 9 : 1. The nitration is even more selective for 6-MeO- (**1c**) and 6-Me_2N-BTDO (**1d**). In the latter case, the formation of 7-NO_2-isomer **3d** was not detected at all (TLC).

At the same time, 8-Br-BTDO **1e** is predominantly nitrated at position 7 (see Table 1). Note that the nitra-

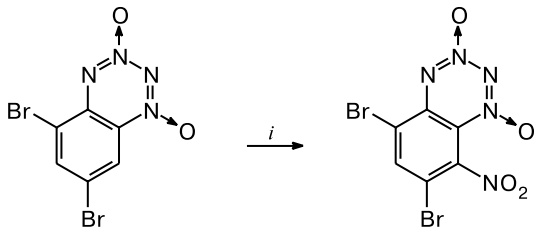
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 1694—1700, October, 2002.

1066-5285/02/5110-1841 $27.00

tion rate of this compound is somewhat higher than those of nonsubstituted BTDO **1a** and 6-Br-BTDO **1b**. This effect needs further investigation.

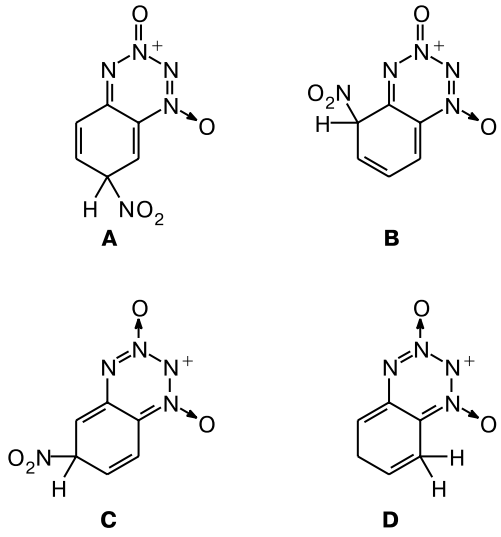
Nitration of BTDO **5** bearing bromine atoms at positions 5 and 7 exclusively gives 8-NO_2-BTDO **6** (Scheme 2).

Scheme 2



i. HNO_3, oleum, 80 °C.

Thus, the nitration rate at different positions of the BTDO ring changes in the following order: $5 \approx 7 \gg 8 > 6$. Obviously, this is due to the fact that σ-complexes **A** and **B** are more stable than σ-complexes **C** and **D**, in which the positive charge is delocalized less efficiently. Complexes **A** and **B** differ only slightly in stability, and the ratio between the nitration rates at positions 5 and 7 depends on the electronic and steric effects of 6- and 8-substituents.



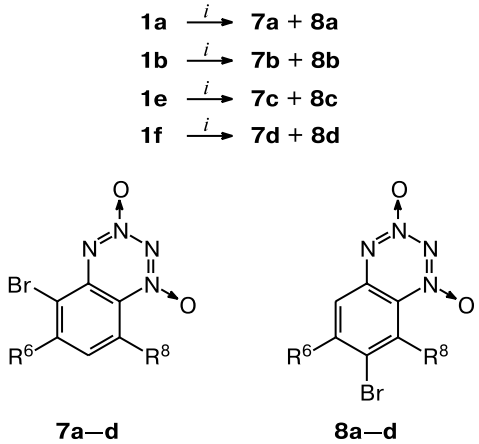
Bromination of BTDO. To simultaneously introduce more than one bromine atom into a deactivated aromatic compound, dibromoisocyanuric acid (DBI) in H_2SO_4 or oleum is commonly employed.[6] We found that BTDO **1a** is monobrominated with DBI in CF_3COOH containing H_2SO_4 (15—20%) to give a mixture of 5-Br- (**7a**) and 7-Br-BTDO (**8a**) in a nearly equal ratio (Table 2). Bromination of 6-Br-BTDO **1b** proceeds analogously, yielding a mixture of isomers **7b** and **8b**. 8-Bromo-BTDO **1e** is mainly brominated at position 5, probably because of steric shielding of position 7. Bromination of 6,8-dibromo-BTDO **1f** exclusively affords 5,6,8-tribromo-BTDO **7d**.

Table 2. Ratio of isomers **7** and **8** obtained in the bromination of BTDOs **1a,b,e,f**

Starting compound	Ratio of isomers (%)
1a	**7a** : **8a** (47 : 53)
1b	**7b** : **8b** (50 : 50)
1e	**7c** : **8c** (87 : 13)
1f	**7d** : **8d** (100 : 0)

Note that 8-bromo- and 6,8-dibromo-BTDOs **1e** and **1f** are brominated significantly more rapidly than 6-bromo-BTDO **1b** and unsubstituted BTDO **1a**. Apparently, the reasons for this acceleration are the same as in the nitration of 8-Br-BTDO **1e**.

Scheme 3



$R^6 = R^8 = H$ (**a**); $R^6 = Br$, $R^8 = H$ (**b**); $R^6 = H$, $R^8 = Br$ (**c**); $R^6 = R^8 = Br$ (**d**).

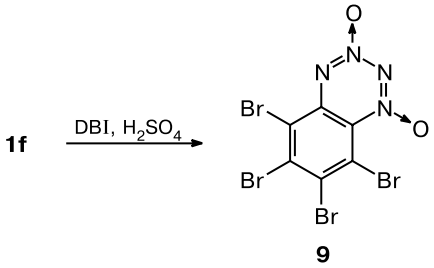
i. DBI, CF_3CO_2H/H_2SO_4.

Under more drastic conditions[6] (DBI/H_2SO_4), several bromine atoms can be introduced into the BTDO benzene ring in one step. Thus tetrabromo derivative **9** was obtained from 6,8-dibromo-BTDO **1f**.

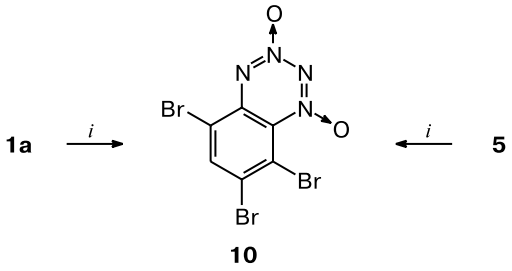
Bromination of BTDO **1a** under these conditions afforded derivative **10** containing bromine atoms in positions 5, 7, and 8. Compound **10** was also obtained from 5,7-dibromo-BTDO **5** (Scheme 5).

To a first approximation, the benzene ring in BTDOs is brominated at the same positions as those involved in

Scheme 4

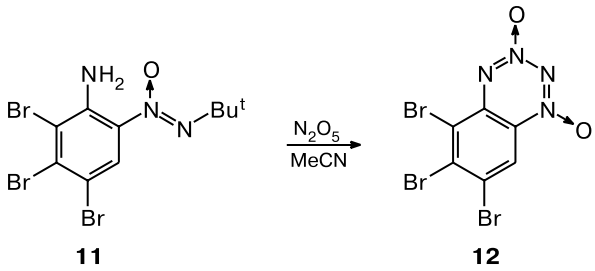


Scheme 5

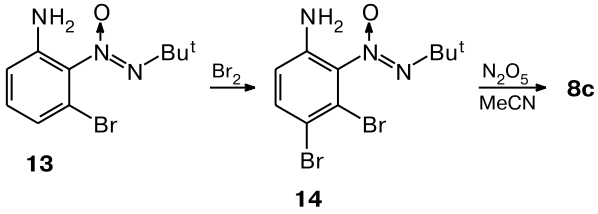


i. DBI, H_2SO_4.

Scheme 6



Scheme 7



nitration, though bromination is usually less selective when there is a choice between positions 5 and 7.

The aforementioned reactions of nitration and bromination of BTDO are not equivalent in preparative aspect. They are convenient for the synthesis of compounds **2c,d**, **4**, **6**, **7d**, **9**, and **10**, which are obtained as individual products. In the other cases, isomers should be separated by chromatography. Note that 5-Br- (**7a**) and 7-Br-BTDO (**8a**) are difficult to separate because they have close R_f values. 5,8-Dibromo-BTDO **7c** is admixed with an unidentified impurity hardly separable by chromatography and thus cannot be purified easily.

The structures of the nitration and bromination products were determined by chemical and spectroscopic methods. In some cases, isomers with a given arrangement of substituents were synthesized by closing the TDO ring. For instance, 5,6,7-tribromo-BTDO **12** was obtained by cyclization of azoxyaniline **11** (Scheme 6). The arrangement of bromine atoms in derivative **10**, which is isomeric to compound **12**, was thus unambiguously confirmed.

The structure of compound **8c** was proved by an independent synthesis from dibromide **14** (Scheme 7).

Among spectroscopic methods, NMR spectroscopy was used most widely to identify the products obtained (Tables 3, 4). Some isomers (*e.g.*, **2a/3a**—**2d/3d** and **7a/8a**) were easily distinguished since their ^{1}H NMR spectra differ in signal multiplicity. However, ^{13}C NMR spectroscopy, which makes it possible to unambiguously locate substituents in the BTDO ring, proved to be most informative. As a rule, signals for the carbon atoms were assigned by direct methods using special techniques. A comparatively low coupling constant $^3J(^1H,^{13}C)$ for the H(8) and H(5) protons was taken into account when assigning signals for the C(4a) and C(8a) atoms.[3]

Relatively good coincidence of the ^{13}C chemical shifts calculated according to the additive scheme[7] (see Table 4) with experimental data indicates that this scheme can be applied to the BTDO series. The chemical shifts for unsubstituted BTDO **1a** (Table 4) were used to calculate δ values for mono- and disubstituted BTDOs; the best results for trisubstituted derivatives were calculated from chemical shifts of the corresponding disubstituted compounds.

Compound **7d** was identified as 5,6,8-tribromo-BTDO (^{13}C NMR data). In the spectrum of this compound, $^3J_{HC}$ = 8.3 Hz for the C(5) atom, which is *meta* to the proton, while the *ortho*-C(6) and C(8) atoms have $^2J_{HC}$ = 4.2 and 3.6 Hz, respectively. An alternative isomer (6,7,8-tribromo-BTDO), in which the C(8) atom is *para* to the proton, would have a much lower coupling constant ^4J. In addition, the chemical shifts for the carbon atoms in BTDO **7d** are close to the calculated values, substantially differing from those for the alternative isomer.

The presence of the TDO ring in BTDO was confirmed by ^{14}N NMR data. The spectra show two comparatively narrow signals at δ –40 to –49 for the N(1) and N(3) atoms.[3] The IR spectra contain absorption bands at 1470—1520 and 1400—1440 cm^{-1} assigned to the synphase and antiphase stretching vibrations of two azo groups in the tetrazine ring (*cf.* Ref. 8).

Table 3. ^{1}H and ^{14}N NMR spectra of BTDO

Compound	Solvent	^{1}H NMR, δ (*J*/Hz)	^{14}N NMR, δ ($\Delta\nu_{1/2}$/Hz)
2b	Acetone-d_6	8.28 (d, 1 H, H(7), ^{3}J = 9.1); 8.53 (d, 1 H, H(8))	−20 (55) (NO_2); −42 (45), −47 (55) (N(1), N(3))
2c	DMSO-d_6	4.21 (s, 3 H, Me); 7.90 (d, 1 H, H(7), ^{3}J = 9.7); 8.56 (d, 1 H, H(8))	−20 (280) (NO_2); −43 (350) (N(1), N(3))
2d	DMSO-d_6	3.19 (s, 6 H, 2 Me); 7.60 (d, 1 H, H(7), ^{3}J = 9.8); 8.11 (d, 1 H, H(8))	−20 (350) (NO_2); −48 (350) (N(1), N(3))
2e	Acetone-d_6	8.34 (d, 1 H, ^{3}J = 8.6), 8.50 (d, 1 H), H(6) and H(7)	—[a]
3b	Acetone-d_6	8.55 (s, 1 H, H(5)); 9.00 (s, 1 H, H(8))	−16 (70) (NO_2); −40 (45), −45 (55) (N(1), N(3))
3c	DMSO-d_6	7.58 (s, 1 H), 8.93 (s, 1 H), H(5) and H(8)	—[a]
3e	Acetone-d_6	8.16 (d, 1 H, H(5), ^{3}J = 9.0); 8.47 (d, 1 H, H(6))	−11 (70) (NO_2); −40 (30), −46 (45) (N(1), N(3))
6	DMSO-d_6	9.10 (s, 1 H, H(6))	−20 (350) (NO_2); −49 (300) (N(1), N(3))
7b	Acetone-d_6	8.18 (d, 1 H, H(7), ^{3}J = 9.1); 8.32 (d, 1 H, H(8))	−41 (40), −46 (50) (N(1), N(3))
7c	Acetone-d_6	8.02 (d, 1 H, ^{3}J = 8.4), 8.25 (d, 1 H), H(6) and H(7)	−40 (30),−48 (55) (N(1), N(3))
7d	Acetone-d_6	8.46 (s, 1 H, H(7))	−41 (50), −46 (60) (N(1), N(3))
8c	DMSO-d_6	7.88 (d, 1 H, H(5), ^{3}J = 9.0); 8.41 (d, 1 H, H(6))	−44 (170) (N(1), N(3))
9	Acetone-d_6	—	−43 (50), −47 (90) (N(1), N(3))
10	DMSO-d_6	8.85 (s, 1 H, H(6))	−44 (350)
13	Acetone-d_6	8.77 (s, 1 H, H(8))	−42 (70), −47 (85) (N(1), N(3))

[a] No data.

Table 4. Experimental (δ) and calculated (δ_{calc}) ^{13}C NMR spectra of BTDO

Compound	Solvent	δ (δ_{calc}), *J*/Hz					
		C(4a)	C(5)	C(6)	C(7)	C(8)	C(8a)
1a[a]	Acetone-d_6	144.7	125.2	139.2	132.3	119.9	129.0
1a[a]	DMSO-d_6	143.3	124.2	138.4	131.8	118.9	128.0
2b	DMSO-d_6	137.0 (140.1) $^{3}J_{C(4a),H(8)}$ = = 5.9, $^{4}J_{C(4a),H(7)}$ = = 1.3	141.9 br.s (145.8) $^{3}J_{C(5),H(7)}$ = = 7.9, $^{4}J_{C(5),H(8)}$ = = 1.8	123.57 (125.7) $^{3}J_{C(6),H(8)}$ = = 12.3, $^{2}J_{C(6),H(7)}$ = = 1.9	134.49 (134.2)	122.06 (126.5)	128.09 (128.6) $^{3}J_{C(8a),H(7)}$ = = 11.0, $^{2}J_{C(8a),H(8)}$ = = 3.0
2c[b]	DMSO-d_6	137.9 (139.2) $^{3}J_{C(4a),H(8)}$ = = 6.2	128.7 br.s (128.3) $^{3}J_{C(5),H(7)}$ = = 7.3	157.2 (165.2) $^{3}J_{C(6),H(8)}$ = = 10.8	118.3 (116.7)	123.5 (125.6)	122.9 br.s (121.9) $^{3}J_{C(8a),H(7)}$ = = 10.9
2d[c]	DMSO-d_6	141.20 (138.9) $^{3}J_{C(4a),H(8)}$ = = 5.6	122.8 br.s (127.9) $^{3}J_{C(5),H(7)}$ = = 7.2	148.40 (156.1) $^{3}J_{C(6),H(8)}$ = = 9.9	121.2[d] (117.6)	122.7[d] (126.4)	119.54 (117.6) $^{3}J_{C(8a),H(7)}$ = = 9.1
2e	Acetone-d_6	140.4 (140.1)	142.3 br.s (141.5)	132.4[d] (135.7)	136.9[d] (140.0)	118.8 (118.3)	128.9 br.s (129.7)
3b	DMSO-d_6	144.3 (148.0) $^{3}J_{C(4a),H(8)}$ = = 5.9, $^{2}J_{C(4a),H(5)}$ = = 2.1	130.1 (129.5)	122.7 (125.7) $^{3}J_{C(6),H(8)}$ = = 8.5, $^{2}J_{C(6),H(5)}$ = = 3.8	149.5 (150.7) $^{3}J_{C(7),H(5)}$ = = 9.5, $^{2}J_{C(7),H(8)}$ = = 4.7	116.4 (117.4)	127.4 br.s (126.9) $^{3}J_{C(8a),H(5)}$ = = 7.4, $^{2}J_{C(8a),H(8)}$ = = 4.0
3e	Acetone-d_6	148.0 (148.0) $^{3}J_{C(4a),H(6)}$ = = 10.6	127.0 (125.2)	132.1 (133.9)	153.6 br.s (150.7)	107.3 (109.2) $^{3}J_{C(8),H(6)}$ = = 7.5	—[e]

(*to be continued*)

Table 4 (*continued*)

Compound	Solvent	δ (δ_{calc}), *J*/Hz					
		C(4a)	C(5)	C(6)	C(7)	C(8)	C(8a)
6	DMSO-d_6	142.4 (144.3) $^3J_{C(4a),H(6)}$ = = 8.6	120.6 (126.9) ^2J = 4.6	144.1 (146.3)	117.3 (119.8) ^2J = 3.3	138.8 br.s (141.5) ^3J = 9.3	121.9 br.s (125.8)
7b	DMSO-d_6	143.1 (147.1)	120.2 (120.0)	136.0 (135.3)	134.9 (136.5)	118.9 (119.3)	128.5 br.s (129.2)
7c	DMSO-d_6	144.2 (149.1)	117.0 (118.0)	140.5[d] (140.7)	137.2[d] (139.4)	112.0 (111.0)	—[e]
7d	Acetone-d_6	—[e]	121.3 (120.1) ^3J = 8.3	136.0 (134.3) ^2J = 4.2	140.2 (141.1)	113.4 (112.8) ^2J = 3.6	—[e]
8c	DMSO-d_6	145.3 (144.8) $^3J_{C(4a),H(6)}$ = = 10.4	124.7 (126.2)	141.2 (140.7)	129.2 (131.2) $^3J_{C(7),H(5)}$ = = 9.6	115.5 (115.4) $^3J_{C(8),H(6)}$ = = 8.2, $^4J_{C(8),H(5)}$ = = 1.8	130.5 (129.2) $^3J_{C(8a),H(5)}$ = = 7.8
9[f]	Acetone-d_6	145.3 (145.3)	122.5 (120.4)	140.2 (139.1)	134.6 (133.2)	117.1 (117.1)	—[e]
10	DMSO-d_6	143.3 (144.7) $^3J_{C(4a),H(6)}$ = = 8.5	117.3 (118.7) ^2J = 4.7	143.2 (146.7)	130.1 (127.8)	115.2 (115.8) ^3J = 8.0	—[e]
13	DMSO-d_6	141.9 (144.7) $^3J_{C(4a),H(8)}$ = = 5.9	122.0 (123.0) ^2J = 4.3	139.2 (138.5) ^3J = 9.4	127.3 (127.8) ^2J = 3.6	121.6 (122.0)	128.6 (129.5) ^2J = 3.6

[a] See Refs. 2 and 3.
[b] δ = 58.9 (OMe).
[c] δ = 41.7 (NMe_2).
[d] Assignments of the signals may be interchanged.
[e] No data.
[f] For BTDO **9**, signals were assigned using an additive scheme.

Experimental

^1H, ^{13}C, and ^{14}N NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13, 75.5, and 21.5 MHz, respectively). The chemical shifts were measured relative to Me_4Si (^1H and ^{13}C) or $MeNO_2$ (^{14}N, external standard). Signals in ^1H and ^{13}C NMR spectra were assigned using two-dimensional ^1H—^{13}C NMR spectroscopy and ^{13}C NMR spectroscopy with selective proton decoupling. IR spectra were recorded on a UR-20 instrument. Mass spectra were obtained with a Varian MAT-311A instrument (EI, 70 eV). Preparative thin-layer and column chromatography was carried out on Silpearl silica gel. The course of the reactions was monitored by TLC (Silufol UV-254). All BTDOs, except for amino derivatives, are bright yellow; 6-amino derivatives are red (the UV spectra of BTDOs were described in Ref. 9). When exposed to the ammonia vapor, a spot of 5-nitro-BTDO **2a** reversibly turned red, while 7-nitro-BTDO **3a** turned violet; a spot of 5,7-dinitro-BTDO **4** irreversibly turned red.

BTDOs **1a,b,f**, **2a**, **3a**, **4**, **5**, **8a,b**,[3] and **1e** [10] were obtained by closing the tetrazine ring. BTDOs **1c,d** were prepared by nucleophilic substitution for bromine in BTDO **1b**.[10] Azoxyanilines **11** [5] and **13** [10] were synthesized according to the known procedures.

Nitration was performed with conc. HNO_3 (d = 1.5 g cm^{-3}) and H_2SO_4 (d = 1.8 g cm^{-3}). Nitration products were isolated according to *procedure A*: the reaction mixture was poured into finely crushed ice, and the precipitate that formed was filtered off, washed with water to a neutral reaction, and dried *in vacuo*. In some cases, *additional procedure B* was used: organic material was extracted from the acidic filtrate with ethyl acetate, and the extract was washed with a dilute solution of $NaHCO_3$ and dried with $MgSO_4$. The solvent was removed *in vacuo* to give additional amounts of products.

Nitration of benzo-1,2,3,4-tetrazine 1,3-dioxide (1a). Nitric acid (570 mg, 9 mmol) in 0.5 mL of H_2SO_4 was added at 20 °C to a stirred solution of BTDO **1a** (500 mg, 3.05 mmol) in 1.5 mL of H_2SO_4. After 2 h, the corresponding work-up (procedures *A* and *B*) of the reaction mixture gave a solid mixture

(582 mg), which was separated by chromatography (eluent was CH_2Cl_2—EtOAc, 5 : 1) into 5-nitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (**2a**) (190 mg, 30%, m.p. 193—195 °C) and 7-nitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (**3a**) (390 mg, 61%, m.p. 166—168 °C). The products were identical* with authentic samples obtained previously[3] by the TDO ring closure.

Nitration of 6-bromobenzo-1,2,3,4-tetrazine 1,3-dioxide (1b). A solid mixture (530 mg) was obtained analogously from BTDO **1b** (486 mg, 2 mmol) in 10 mL of H_2SO_4 and HNO_3 (760 mg, 12 mmol) in 0.5 mL of H_2SO_4. Chromatography of the mixture (eluent was benzene—Et_2O, 5 : 1) gave compounds **2b** (468 mg, 81%) and **3b** (52 mg, 9%).

6-Bromo-5-nitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (2b), m.p. 245—246 °C. Found (%): C, 25.24; H, 0.75; Br, 28.01; N, 24.15. $C_6H_2BrN_5O_4$. Calculated (%): C, 25.02; H, 0.70; Br, 27.74; N, 24.32. IR (KBr), ν/cm^{-1}: 1442, 1518 (N(O)NN(O)N); 1352, 1552 (NO_2). MS, *m/z* (integral intensity ratio): 287, 289 $[M]^+$ (1 : 1).

6-Bromo-7-nitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (3b), m.p. 230—235 °C (decomp.). Found (%): C, 24.16; H, 0.73; Br, 27.92; N, 24.17. $C_6H_2BrN_5O_4$. Calculated (%): C, 25.02; H, 0.70; Br, 27.74; N, 24.32. IR (KBr), ν/cm^{-1}: 1424, 1504 (N(O)NN(O)N); 1352, 1548 (NO_2). MS, *m/z* (integral intensity ratio): 287, 289 $[M]^+$ (1 : 1).

Nitration of 6-methoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (1c). Nitric acid (28 mg, 0.44 mmol) in 0.5 mL of H_2SO_4 was added at −5 °C to a stirred solution of BTDO **1c** (65 mg, 0.34 mmol) in 2 mL of H_2SO_4. The reaction mixture was kept at 20 °C for 30 min and then treated according to procedures *A* and *B* to give a solid mixture (57 mg), which was separated by chromatography (eluent was benzene—Et_2O, 6 : 1) into compounds **2c** (50 mg, 62%) and **3c** (0.7 mg, 1%).

6-Methoxy-5-nitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (2c), m.p. 254—256 °C. Found (%): C, 35.21; H, 2.07; N, 29.15. $C_7H_5N_5O_5$. Calculated (%): C, 35.16; H, 2.11; N, 29.28. IR (KBr), ν/cm^{-1}: 1436, 1520 (N(O)NN(O)N); 1373, 1550 (NO_2). MS, *m/z*: 239 $[M]^+$.

6-Methoxy-7-nitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (3c), m.p. 245—247 °C. MS, *m/z*: 239 $[M]^+$.

6-Dimethylamino-5-nitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (2d). A solution of HNO_3 (28 mg, 0.44 mmol) in 1 mL of CF_3COOH was added at 20 °C to a stirred solution of 6-dimethylamino-BTDO **1d** (60 mg, 0.31 mmol) in 2 mL of CF_3COOH. After 5 min, the reaction mixture was treated according to procedure *A* to give BTDO **2d** (60 mg, 77%) as orange crystals, m.p. 238—239 °C. Found (%): C, 38.05; H, 3.22; N, 33.18. $C_8H_8N_6O_4$. Calculated (%): C, 38.10; H, 3.20; N, 33.32. IR (KBr), ν/cm^{-1}: 1428, 1496 (N(O)NN(O)N); 1333, 1555 (NO_2). MS, *m/z*: 252 $[M]^+$.

Nitration of 8-bromobenzo-1,2,3,4-tetrazine 1,3-dioxide (1e). Nitric acid (80 mg, 1.27 mmol) in 1 mL of H_2SO_4 was added at 20 °C to a stirred solution of BTDO **1e** (90 mg, 0.37 mmol) in 1 mL of H_2SO_4. After 15 min, the reaction mixture was treated according to procedure *A* to give a solid mixture (83 mg), which was separated by chromatography (eluent was ethyl acetate—hexane, 1 : 5) into compounds **2e** (16 mg, 15%) and **3e** (67 mg, 56%).

8-Bromo-5-nitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (2e), m.p. 157—158 °C. Found (%): C, 24.90; H, 0.73; Br, 27.52; N, 24.14. $C_6H_2BrN_5O_4$. Calculated (%): C, 25.02; H, 0.70; Br, 27.74; N, 24.32. IR (KBr), ν/cm^{-1}: 1425, 1520 (N(O)NN(O)N); 1330, 1535 (NO_2). MS, *m/z* (integral intensity ratio): 287, 289 $[M]^+$ (1 : 1).

8-Bromo-7-nitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (3e), m.p. 204—205 °C. Found (%): C, 24.91; H, 0.68; Br, 27.53; N, 24.05. $C_6H_2BrN_5O_4$. Calculated (%): C, 25.02; H, 0.70; Br, 27.74; N, 24.32. IR (KBr), ν/cm^{-1}: 1420, 1508 (N(O)NN(O)N); 1352, 1548 (NO_2). MS, *m/z* (integral intensity ratio): 287, 289 $[M]^+$ (1 : 1).

5,7-Dinitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (4). Nitric acid (1.66 g, 26 mmol) was added at 0 °C to a stirred solution of BTDO **1a** (700 mg, 4.3 mmol) in 10 mL of H_2SO_4. The reaction mixture was kept at ~20 °C for 1.5 h and cooled. After addition of 20% oleum (3 mL) at 0 °C, heating was continued at 90 °C for 1.5 h. The reaction mixture was cooled to ~20 °C and treated according to procedures *A* and *B* to give BTDO **4** (600 mg, 55%), m.p. 209—211 °C. This compound was identical with an authentic sample[3] obtained by closing the DTO ring.

5,7-Dibromo-8-nitrobenzo-1,2,3,4-tetrazine 1,3-dioxide (6). A solution of HNO_3 (2.56 g, 40 mmol) in a mixture of 5 mL of H_2SO_4 and 0.8 mL of 20% oleum was added at 20 °C to a stirred solution of 5,7-dibromobenzo-1,2,3,4-tetrazine 1,3-dioxide (**5**) (800 mg, 2.5 mmol) in 15 mL of H_2SO_4. The reaction mixture was heated at 80 °C for 30 min and then cooled to ~20 °C. Work-up according to procedure *A* gave BTDO **6** (520 mg). An additional amount (70 mg) of the product was extracted from the filtrate with CH_2Cl_2. The total yield of BTDO **6** was 590 mg (64%), m.p. 252—254 °C. Found (%): C, 19.79; H, 0.27; Br, 43.28; N, 18.81. $C_6HBr_2N_5O_4$. Calculated (%): C, 19.64; H, 0.27; Br, 43.55; N, 19.09. IR (KBr), ν/cm^{-1}: 1415, 1508 (N(O)NN(O)N); 1340, 1557 (NO_2). MS, *m/z* (integral intensity ratio): 365, 367, 369 $[M]^+$ (1 : 2 : 1).

Bromination of benzo-1,2,3,4-tetrazine 1,3-dioxides with dibromoisocyanuric acid (general procedure). Dibromoisocyanuric acid (144 mg, 0.5 mmol) was added at 20 °C to a stirred solution of a BTDO (**1a,b,e,f**) (0.5 mmol) in a mixture of 15 mL of CF_3COOH and 3 mL of H_2SO_4. Stirring was continued for 2 (**1a**) and 2.5 h (**1b**) or for 20 min (**1e,f**). Then the reaction mixture was poured into water with ice, and the products were extracted with CH_2Cl_2. The extract was washed with a dilute solution of Na_2CO_3 and water and dried with $CaCl_2$. The solvent was removed *in vacuo*, and the residue was separated by chromatography (eluent was benzene—light petroleum, 1 : 1).

Bromination of benzo-1,2,3,4-tetrazine 1,3-dioxide (1a) (82 mg) gave a mixture (100 mg), which was separated into compounds **7a** (53 mg, 44%) and **8a** (45 mg, 37%).

5-Bromobenzo-1,2,3,4-tetrazine 1,3-dioxide (7a), m.p. 203—208 °C (decomp.). Found (%): C, 29.43; H, 1.23; Br, 32.62; N, 22.84. $C_6H_3BrN_4O_2$. Calculated (%): C, 29.65; H, 1.24; Br, 32.88; N, 23.05. MS, *m/z* (integral intensity ratio): 242, 244 $[M]^+$ (1 : 1).

7-Bromobenzo-1,2,3,4-tetrazine 1,3-dioxide (8a), m.p. 220—221 °C. Found (%): C, 29.48; H, 1.24; Br, 32.70; N, 22.79. $C_6H_3BrN_4O_2$. Calculated (%): C, 29.65; H, 1.24; Br, 32.88; N, 23.05. IR (KBr), ν/cm^{-1}: 1415, 1508 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 242, 244 $[M]^+$ (1 : 1).

* Hereafter, the products were identified from melting points, ^{1}H NMR spectra, and TLC data.

Bromination of 6-bromobenzo-1,2,3,4-tetrazine-1,3-dioxide (1b) (122 mg) gave a mixture (130 mg), which was separated into compounds **7b** (62 mg, 39%) and **8b** (62 mg, 39%).

5,6-Dibromobenzo-1,2,3,4-tetrazine 1,3-dioxide (7b), m.p. 237—239 °C. Found (%): C, 22.25; H, 0.64; N, Br, 49.47; 17.24. $C_6H_2Br_2N_4O_2$. Calculated (%): C, 22.39; H, 0.63; Br, 49.64; N, 17.40. MS, *m/z* (integral intensity ratio): 320, 322, 324 $[M]^+$ (1 : 2 : 1).

6,7-Dibromobenzo-1,2,3,4-tetrazine 1,3-dioxide (8b), m.p. 252—254 °C. Found (%): C, 22.21; H, 0.64; Br, 49.39; N, 17.15. $C_6H_2Br_2N_4O_2$. Calculated (%): C, 22.39; H, 0.63; Br, 49.64; N, 17.40. IR (KBr), ν/cm^{-1}: 1430, 1495 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 320, 322, 324 $[M]^+$ (1 : 2 : 1).

Bromination of 8-bromobenzo-1,2,3,4-tetrazine 1,3-dioxide (1e) (122 mg) gave a mixture (120 mg), which was separated into compounds **7c** (102 mg, 63%) and **8c** (16 mg, 10%).

5,8-Dibromobenzo-1,2,3,4-tetrazine 1,3-dioxide (7c), m.p. 240—247 °C (decomp.). Found (%): C, 22.20; H, 0.62; Br, 49.17; N, 17.27. $C_6H_2Br_2N_4O_2$. Calculated (%): C, 22.39; H, 0.63; Br, 49.64; N, 17.40. MS, *m/z* (integral intensity ratio): 320, 322, 324 $[M]^+$ (1 : 2 : 1).

7,8-Dibromobenzo-1,2,3,4-tetrazine 1,3-dioxide (8c), m.p. 200—204 °C (decomp.). Found (%): C, 22.25; H, 0.62; Br, 49.80; N, 17.13. $C_6H_2Br_2N_4O_2$. Calculated (%): C, 22.39; H, 0.63; Br, 49.64; N, 17.40. IR (KBr), ν/cm^{-1}: 1401, 1505 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 320, 322, 324 $[M]^+$ (1 : 2 : 1).

5,6,8-Tribromobenzo-1,2,3,4-tetrazine 1,3-dioxide (7d) was obtained from 6,8-dibromo-BTDO **1f** (161 mg). The yield of BTDO **7d** was 160 mg (80%), m.p. 230—232 °C (decomp.). Found (%): C, 18.18; H, 0.25; Br, 59.65; N, 13.68. $C_6HBr_3N_4O_2$. Calculated (%): C, 17.98; H, 0.25; Br, 59.81; N, 13.98. IR (KBr), ν/cm^{-1}: 1420, 1490 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 398, 400, 402, 404 $[M]^+$ (1 : 3 : 3 : 1).

5,6,7,8-Tetrabromobenzo-1,2,3,4-tetrazine 1,3-dioxide (9). Dibromoisocyanuric acid (178 g, 0.62 mmol) was added at 20 °C to a stirred solution of 6,8-dibromo-BTDO **1f** (100 mg, 0.31 mmol) in 10 mL of H_2SO_4. After 15 min, the reaction mixture was poured into water with ice, and the product was extracted with CH_2Cl_2. The extract was washed with a dilute solution of $NaHCO_3$ and water and dried with $CaCl_2$. Solvent evaporation gave compound **9** (145 mg, 96%), m.p. 235—238 °C. Found (%): C, 14.83; Br, 66.80; N, 11.41. $C_6Br_4N_4O_2$. Calculated (%): C, 15.02; Br, 66.63; N, 11.68. IR (KBr), ν/cm^{-1}: 1420, 1488 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 476, 478, 480, 482, 484 $[M]^+$ (1 : 4 : 6 : 4 : 1).

5,7,8-Tribromobenzo-1,2,3,4-tetrazine 1,3-dioxide (10). ***A*. Synthesis from BTDO 1a.** Dibromoisocyanuric acid (85 mg, 0.3 mmol) was added at 20 °C to a stirred solution of BTDO **1a** (16 mg, 0.1 mmol) in 1 mL of H_2SO_4. After 20 min, the reaction mixture was treated as described above to give BTDO **10** (36 mg, 90%), m.p. 216—219 °C (decomp.). Found (%): C, 18.13; H, 0.24; Br, 59.77; N, 14.05. $C_6HBr_3N_4O_2$. Calculated (%): C, 17.98; H, 0.25; Br, 59.81; N, 13.98. IR (KBr), ν/cm^{-1}: 1410, 1492 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 398, 400, 402, 404 $[M]^+$ (1 : 3 : 3 : 1).

***B*. Synthesis from BTDO 5.** Dibromoisocyanuric acid (28 mg, 0.1 mmol) was added at 20 °C to a stirred solution of 5,7-dibromo-BTDO **5** (32 mg, 0.1 mmol) in 2 mL of H_2SO_4. After 10 min, the reaction mixture was treated as described above to give BTDO **10** (36 mg, 95%), m.p. 216—219 °C (decomp.). The product was identical with that obtained according to procedure *A*.

Synthesis of BTDOs 8d and 12 by closing the TDO ring (general procedure). The synthesis was performed by analogy with a known procedure.[3] A solution of a corresponding aniline (1.5 mmol) in 5 mL of anhydrous MeCN was added dropwise at −15 °C over 10 min to a stirred suspension of N_2O_5 (650 mg, 6 mmol) in 20 mL of MeCN. After the addition was completed, stirring was continued for an additional 10 min, the reaction mixture being warmed to 0 °C. Then the mixture was cooled to −30 °C; the resulting precipitate of a virtually pure product was filtered off, washed with a small amount of MeOH, and dried. The filtrate was poured into water with ice, and the product was extracted with CH_2Cl_2. The extract was washed with dilute aqueous $NaHCO_3$ and concentrated *in vacuo*. The residue was purified by chromatography with benzene as the eluent to give an additional amount of the product.

7,8-Dibromobenzo-1,2,3,4-tetrazine 1,3-dioxide (8c) was obtained from aniline **14** according to the general procedure. The yield of compound **8c** was 202 mg (42%), m.p. 200—204 °C (decomp.). Found (%): C, 22.34; H, 0.62; Br, 49.78; N, 17.15. $C_6H_2Br_2N_4O_2$. Calculated (%): C, 22.39; H, 0.63; Br, 49.64; N, 17.40. IR (KBr), ν/cm^{-1}: 1401, 1505 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 320, 322, 324 $[M]^+$ (1 : 2 : 1).

5,6,7-Tribromobenzo-1,2,3,4-tetrazine 1,3-dioxide (12) was obtained from aniline **11** (645 mg) according to the general procedure. The yield of compound **12** was 162 mg (27%), m.p. 204—207 °C (decomp.). Found (%): C, 18.18; H, 0.24; Br, 59.92; N, 13.69. $C_6HBr_3N_4O_2$. Calculated (%): C, 17.98; H, 0.25; Br, 59.81; N, 13.98. IR (KBr), ν/cm^{-1}: 1410, 1489 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 398, 400, 402, 404 $[M]^+$ (1 : 3 : 3 : 1).

3,4-Dibromo-2-(*tert*-butyl-*NNO*-azoxy)aniline (14). A solution of bromine (1.6 g, 10 mmol) in 10 mL of AcOH was added at 20 °C to a stirred solution of 3-bromo-2-(*tert*-butyl-*NNO*-azoxy)aniline[10] (**13**) (2.72 g, 10 mmol) and AcONa (1 g, 12.2 mmol) in 25 mL of glacial AcOH. After 20 min, the reaction mixture was poured into water, and the product was extracted with CH_2Cl_2 (2×50 mL). The extract was washed with water and a dilute solution of Na_2CO_3 dried with $MgSO_4$; the solvent was removed *in vacuo*. Recrystallization from CH_2Cl_2 gave aniline **14** (2.02 g, 57%), m.p. 137—138 °C. Found (%): C, 34.38; H, 3.70; Br, 45.24; N, 11.71. $C_{10}H_{13}Br_2N_3O$. Calculated (%): C, 34.21; H, 3.73; Br, 45.52; N, 11.97. ^1H NMR (acetone-d_6), δ: 1.48 (s, 9 H, 3 Me); 5.10 (br.s, 2 H, NH_2); 6.92 (d, 1 H, H(5), ^3J = 8.8 Hz); 7.46 (d, 1 H, H(6)). ^{13}C NMR (acetone-d_6), δ (calculated chemical shifts are given in brackets): 25.77 (Me); 60.70 ($\underline{C}Me_3$); 111.37 [115.0] (C(4)); 118.45 [118.3] (C(6)); 118.82 [118.3] (C(3)); 134.10 [133.3] (C(5)); 138.2 [138.3] (br.s, C(2)); 142.12 [140.5] (C(1)). IR (KBr), ν/cm^{-1}: 1485 (N(O)=N); 3320, 3405 (NH_2). MS, *m/z* (integral intensity ratio): 349, 351, 353 $[M]^+$ (1 : 2 : 1).

This work was financially supported in part by the Federal Target Program "Integratsiya nauki i vysshego obrazovaniya" (Project No. IO 667).

References

1. O. Yu. Smirnov, Ph.D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow, 1995, 120 pp.
2. A. M. Churakov, S. L. Ioffe, and V. A. Tartakovsky, *Mendeleev Commun.*, 1991, 101.
3. A. M. Churakov, O. Yu. Smirnov, S. L. Ioffe, Yu. A. Strelenko, and V. A. Tartakovsky, *Eur. J. Org. Chem.*, 2002, 2342.
4. A. M. Churakov, O. Yu. Smirnov, S. L. Ioffe, Yu. A. Strelenko, and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1620 [*Russ. Chem. Bull.*, 1994, **43**, 1532 (Engl. Transl.)].
5. D. L. Lipilin, A. M. Churakov, Yu. A. Strelenko, and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 295 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 311].
6. W. Gottardi, *Monatsh. Chem.*, 1969, **100**, 42.
7. D. E. Ewing, *Org. Magn. Reson.*, 1979, **12**, 499.
8. K. I. Rezchikova, A. M. Churakov, V. A. Shlyapochnikov, and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 2187 [*Russ. Chem. Bull.*, 1995, **44**, 2093 (Engl. Transl.)].
9. K. I. Rezchikova, A. M. Churakov, K. Ya. Burshtein, V. A. Shlyapochnikov, and V. A. Tartakovsky, *Mendeleev Commun.*, 1997, 174.
10. O. Yu. Smirnov, A. M. Churakov, A. Yu. Tyurin, Yu. A. Strelenko, S. L. Ioffe, and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1701 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 1849].

Received February 4, 2002;
in revised form May 17, 2002