Nucleophilic substitution in benzo-1,2,3,4-tetrazine 1,3-dioxides

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Nucleophilic substitution in nitro- and bromobenzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs) was studied. In most cases, the bromo and nitro groups are replaced by methylamino, dimethylamino, azido, and methoxy groups without opening of the tetrazine ring. It was illustrated with the reactions of dibromo-BTDOs with sodium methoxide that the reactivity of positions 5 to 8 in their benzene ring as regards nucleophilic substitution changes in the following order: 6 > 8 > 7 > 5. The structures of the BTDOs obtained were confirmed by ^{1}H, ^{13}C, and ^{14}N NMR data.

Key words: benzo-1,2,3,4-tetrazines, *N*-oxides, nucleophilic substitution.

This work was done within the scope of the systematic investigation of benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs).[1,2] Here we studied nucleophilic substitution in halogen and nitro derivatives of this new heterocyclic system. The primary question to be answered was: whether can such reactions occur without opening of the 1,2,3,4-tetrazine 1,3-dioxide (TDO) ring. In addition, it was interesting to compare substitution rates for halogen atoms and nitro groups in different positions of the BTDO benzene ring.

Accessible 6-, 7-, and 8-bromo-BTDOs **1a—c** and 7- and 5-nitro-BTDOs **2a,b** were chosen as objects of investigation. Methanolic KOH (Table 1, reaction 1), sodium azide in DMF (reaction 2), dimethylamine in DMF (reaction 3), and methylamine in DMSO (reaction 4) were used as nucleophilic reagents. Reactions were

Table 1. Synthesis of BTDOs **3a—c**, **4a—c**, **5a—c**, and **6a—c** from BTDOs **1a—c** and **2a** (20 °C)

Reaction	Starting BTDO	X	C^a /mol L^{-1}	Solvent	Reagent	τ^b /h	Product	Y	Yield (%)
1	**1a**	7-Br	0.018	MeOH	MeOH/KOH	1[c]	**3a**	7-MeO	45
1	**1b**	6-Br	0.018	MeOH	MeOH/KOH	3	**3b**	6-MeO	83
1	**1c**	8-Br	0.018	MeOH	MeOH/KOH	0.5[c]	**3c**	8-MeO	27
1	**2a**	7-NO_2	0.04	MeOH	MeOH/KOH	1	**3a**	7-MeO	76
2	**1a**	7-Br	0.15	DMF/H_2O	NaN_3	48	**4a**	7-N_3	53
2	**1b**	6-Br	0.15	DMF/H_2O	NaN_3	0.3	**4b**	6-N_3	88
2	**1c**	8-Br	0.15	DMF/H_2O	NaN_3	0.7	**4c**	8-N_3	90
2	**2a**	7-NO_2	0.15	DMF/H_2O	NaN_3	1	**4a**	7-N_3	75
3	**1a**	7-Br	0.25	DMF	Me_2NH	24	**5a**	7-Me_2N	45
3	**1b**	6-Br	0.5	DMF/H_2O	Me_2NH	0.15	**5b**	6-Me_2N	94
3	**1c**	8-Br	0.5	DMF/H_2O	Me_2NH	6	**5c**	8-Me_2N	75
3	**2a**	7-NO_2	0.17	DMF/H_2O	Me_2NH	8	**5a**	7-Me_2N	76
4	**1a**	7-Br	0.25	DMSO	$MeNH_2$	9	**6a**	7-MeNH	89
4	**1b**	6-Br	0.25	DMSO	$MeNH_2$	0.1	**6b**	6-MeNH	92
4	**1c**	8-Br	0.25	DMSO	$MeNH_2$	1.5	**6c**	8-MeNH	89
4	**2a**	7-NO_2	0.25	DMSO	$MeNH_2$	2[d]	**6a**	7-MeNH	0

[a] Concentration of the starting BTDO.
[b] Reaction time.
[c] At 65 °C.
[d] The time required for complete consumption of the starting BTDO **2a**.

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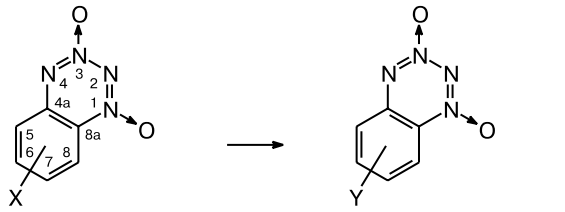
conducted until the starting BTDOs were completely consumed (TLC). Reaction times and other conditions are specified in Table 1.

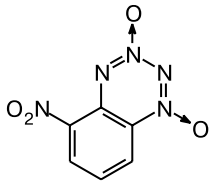
It was found that bromo-BTDOs **1a—c** react with the above nucleophiles to give products **3a—c**, **4a—c**, **5a—c**, and **6a—c** in 27—94% yields (Scheme 1).

Scheme 1



1a—c, 2a **3a—c, 4a—c, 5a—c, 6a—c**

The nitro group in BTDO is not always replaced smoothly. The reactions of 7-nitro-BTDO **2a** with such nucleophiles as MeO^-, N_3^-, and $HNMe_2$ afford the same products **3a**, **4a**, and **5a** as in the reactions with bromo-BTDOs, yet proceeding somewhat more rapidly (see Table 1, reactions 1—3). However, an analogous reaction with $MeNH_2$ yields a mixture containing no expected product **6a**. Neither do the expected products form in the reactions of 5-nitro-BTDO **2b** with any of the above nucleophiles. Apparently, the TDO ring undergoes opening in this reaction.



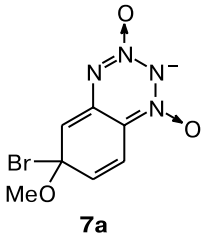
2b

As can be seen in Table 1, the reactions of monobromo-BTDOs with the nucleophiles studied proceed at rates decreasing in the order: 6-Br > 8-Br > 7-Br (the rates were estimated from the time required for complete consumption of the starting BTDO).

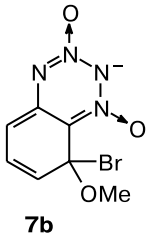
Probably, nucleophilic substitution follows the addition—elimination (AE) mechanism. In this case, the variation in substitution rates with ring positions is due to different thermodynamic stabilities of intermediate anionic σ-complexes **7**.

Better delocalization of the negative charge over the TDO ring in complexes **7a,b** makes them more stable than complexes **7c,d**. For this reason, positions 6 and 8 are preferable for substitution, though the 5- and 7-Br atoms can also be replaced rather easily. Thus, nucleophilic substitution in BTDO is possible for any position of the benzene ring.

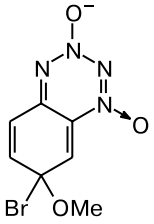
Relative substitution rates for 6,8-dibromo-, 6,7-dibromo-, and 5,7-dibromo-BTDOs **8a—c** were determined in their reactions with methanolic KOH. These reactions were stopped when trace amounts of dimethoxy-BTDO



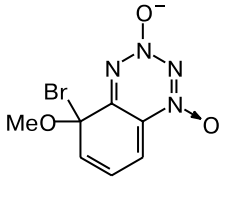
7a



7b



7c



7d

11 were detected in the reaction mixture. A ratio between monosubstituted products **9** and **10**, determined from integrated signal intensities in the ^1H NMR spectra (Scheme 2, Table 2), was taken to be a ratio between the substitution rates at different ring positions.

As regards the ease of nucleophilic substitution, the positions in the benzene ring are arranged as follows: 6 > 8 > 7 > 5 (Table 2). This order correlates with the activity order for monosubstituted BTDOs and is the opposite of the order found for electrophilic substitution in BTDOs.[2]

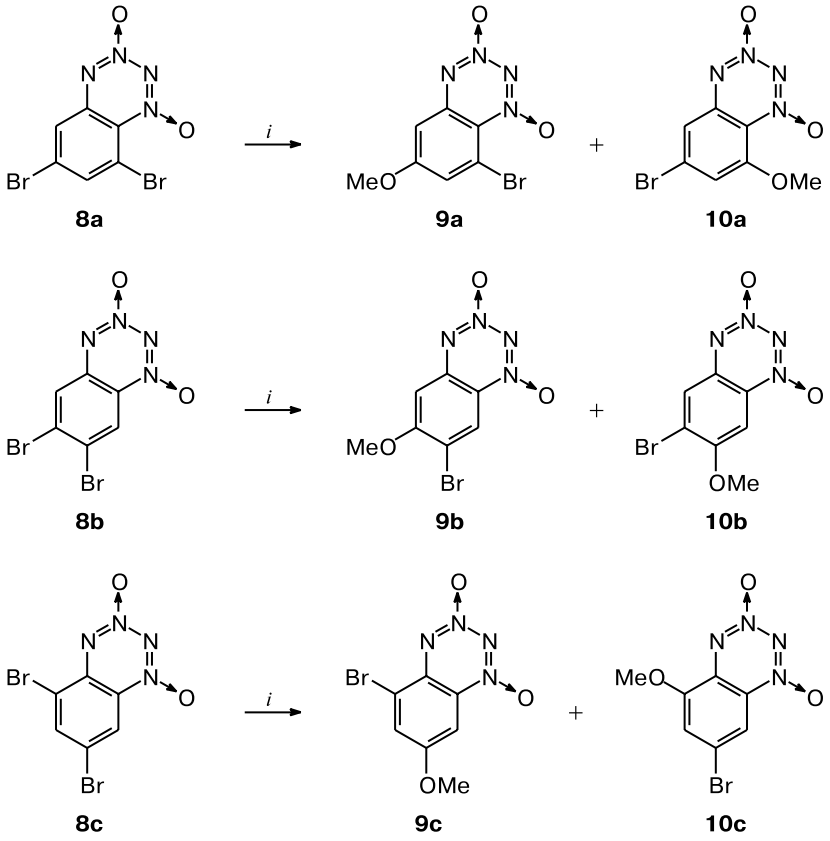
With excess KOH or for a longer reaction time, BTDO **8** gave dimethoxy derivatives **11**. Compounds **11a** and **11b** are stable; they were isolated in good yields.

The structures of BTDOs **3—6** and **9—11** were determined from IR and ^1H, ^{13}C, and ^{14}N NMR data (Tables 3 and 4) and mass spectra. The spectra of BTDO were analyzed in detail previously.[2] Experimental chemical shifts in the ^{13}C NMR spectra of BTDO coincide well with those calculated according to an additive scheme. The chemical shifts for monosubstituted BTDOs were calculated from the δ values for unsubstituted BTDO, while analogous calculation for disubstituted BTDOs **9—11** was based on the chemical shifts of the corresponding methoxy-BTDOs (for details, see Ref. 2).

Table 2. Synthesis of BTDOs **9** and **10** from BTDO **8**

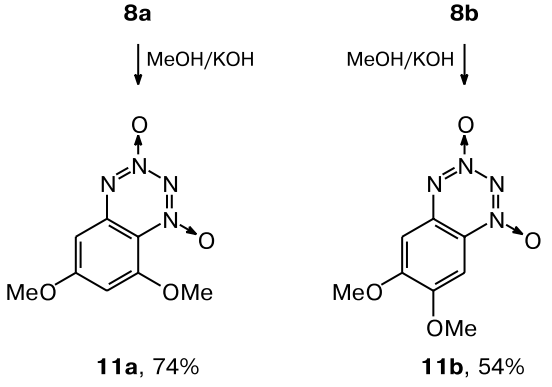
Starting BTDO	Ratio of products (%)
8a	**9a** : **10a** (62 : 38)
8b	**9b** : **10b** (98 : 2)
8c	**9c** : **10c** (90 : 10)

Scheme 2

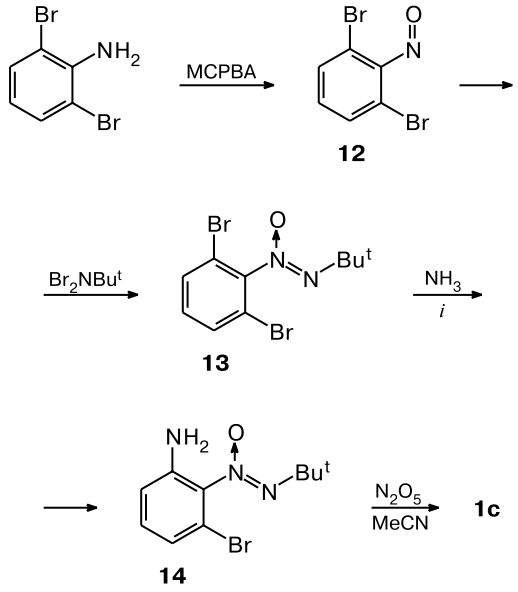


i. MeOH/KOH.

Scheme 3



Scheme 4



i. 210 °C, 300 atm.

8-Bromo-BTDO **1c** was synthesized according to the known method[3] by treating azoxyaniline **14** with a solution of nitric anhydride in MeCN (Scheme 4).

Compound **14** was synthesized according to the method described earlier.[4] 2,6-Dibromoaniline was oxidized into nitroso compound **12**, which was treated with *N*,*N*-dibromo-*tert*-butylamine to give compound **13**. The

Table 3. ^{1}H and ^{14}N NMR spectra of BTDOs **3a—c**, **4a—c**, **5a—c**, **6a—c**, **9a—c**, **10a—c**, and **11a,b**

Compound	Solvent[a]	^{1}H NMR, δ (*J*/Hz)[a]	^{14}N NMR, δ ($\Delta\nu_{1/2}$/Hz)
3a	Acetone-d_6	4.10 (s, 3 H, Me); 7.66 (d, 1 H, H(8), ^{4}J = 2.7); 7.78 (dd, 1 H, H(6), ^{3}J = 9.3); 7.87 (d, 1 H, H(5))	−45 (40), −51 (55) (N(1), N(3))
3b	Acetone-d_6	4.12 (s, 3 H, Me); 7.26 (d, 1 H, H(5), *J* = 2.4); 7.44 (dd, 1 H, H(7)); 8.25 (d, 1 H, H(8), *J* = 9.5)	−43 (65), −45 (55) (N(1), N(3))
3c	DMSO-d_6	4.01 (s, 3 H, Me); 7.36 (d, 1 H, H(7), *J* = 10.1); 7.40 (d, 1 H, H(5), *J* = 10.1); 8.00 (t, 1 H, H(6))	−41 (110), −49 (130) (N(1), N(3)
4a	Acetone-d_6	7.86 (dd, 1 H, H(6)); 7.93 (d, 1 H, H(8), ^{4}J = 2.6); 7.95 (d, 1 H, H(5), ^{3}J = 8.9)	−43 (55), −50 (95) (N(1), N(3)); −143 (110) (N_3)[b]
4b	Acetone-d_6	7.53 (d, 1 H, H(5), *J* = 2.3); 7.55 (dd, 1 H, H(7)); 8.34 (d, 1 H, H(8), *J* = 8.9)	−42 (45), −46 (45) (N(1), N(3)); −144 (60) (N_3)[b]
4c	Acetone-d_6	7.63, 7.69 (both dd, 1 H each, H(5), H(7), ^{3}J = 8.1, ^{4}J = 1.1); 8.04 (t, 1 H, H(6))	−39 (60), −46 (75) (N(1), N(3)); −142 (120) (N_3)[b]
5a	Acetone-d_6	3.26 (s, 6 H, 2 Me); 7.12 (d, 1 H, H(8), ^{4}J = 2.7); 7.72 (d, 1 H, H(5), ^{3}J = 9.4); 7.81 (dd, 1 H, H(6))	−49 (45), −55 (60) (N(1), N(3))
5b	DMSO-d_6	3.21 (s, 6 H, 2 Me); 6.69 (d, 1 H, H(5), *J* = 2.6); 7.41 (dd, 1 H, H(7)); 8.02 (d, 1 H, H(8), *J* = 9.4)	−45 (220) (N(1), N(3))
5c	DMSO-d_6	2.97 (s, 6 H, 2 Me); 7.07, 7.11 (both d, 1 H each, H(5), H(7), ^{3}J = 10); 7.80 (t, 1 H, H(6))	−43 (220) (N(1), N(3))
6a	DMSO-d_6	2.88 (s, 3 H, Me); 6.85 (s, 1 H, H(8)); 7.53, 7.65 (both d, 1 H each, H(5), H(6), ^{3}J = 9.4); 7.50 (br.s, 1 H, NH)[c]	−51 (95), −56 (130) (N(1), N(3))[c]
6b	DMSO-d_6	2.90 (d, 3 H, Me, ^{3}J = 4.4); 6.50 (d, 1 H, H(5), ^{4}J = 2.3); 7.14 (dd, 1 H, H(7)); 7.92 (d, 1 H, H(8), ^{3}J = 9.5); 7.96 (br.s, 1 H, NH)[c]	−44 (50), −49 (80) (N(1), N(3))[c]
6c	Acetone-d_6	3.11 (d, 3 H, Me, ^{3}J =7.7); 6.85 (d, 2 H, H(5), H(7), ^{3}J = 12.3); 7.84 (t, 1 H, H(6), ^{3}J = 12.3); 8.85 (br.s, 1 H, NH)	−37 (50), −47 (50) (N(1), N(3))
9a	DMSO-d_6	4.01 (s, 3 H, Me); 7.35 (d, 1 H, H(5), ^{4}J = 2.5); 7.75 (d, 1 H, H(7))	−44 (70), −46.5 (90) (N(1), N(3))[c]
9b	DMSO-d_6	4.12 (s, 3 H, Me); 7.48 (s, 1 H, H(5)); 8.52 (s, 1 H, H(8))	−46 (350) (N(1), N(3))
9c	DMSO-d_6	4.01 (s, 3 H, Me); 7.66 (d, 1 H, H(8), ^{4}J = 2.6); 8.22 (d, 1 H, H(6))	−44 (100), −52 (180) (N(1), N(3))[c]
10a	DMSO-d_6	4.05 (s, 3 H Me); 7.53 (d, 1 H, H(7), ^{4}J = 1.8); 7.73 (d, 1 H, H(5))	−41 (70), −46 (90) (N(1), N(3))[c]
10b	DMSO-d_6	4.11 (s, 3 H Me); 7.70 (s, 1 H, H(8)); 8.38 (s, 1 H, H(5))	−48 (200) (N(1), N(3))[c]
10c	DMSO-d_6	4.07 (s, 3 H, Me); 7.81 (d, 1 H, H(8), ^{4}J = 1.7); 8.03 (d, 1 H, H(6))	−44 (90), −51 (130) (N(1), N(3))[c]
11a	DMSO-d_6	3.97 (s, 3 H, MeOC(8)); 3.99 (s, 3 H, MeOC(6)); 6.84 (d, 1 H, H(5)); 6.86 (d, 1 H, H(7))	−43 (70), −45 (70) (N(1), N(3))[c]
11b	Acetone-d_6	4.12, 4.16 (both s, 3 H each, Me); 7.25, 7.60 (both s, 1 H each, H(5), H(8))	−48 (60) (N(1), N(3))

[a] The spectra were recorded at 298 K, unless otherwise specified.
[b] Chemical shift for the central nitrogen atom of the azido group (*cf.* Ref. 5).
[c] The NMR spectrum was recorded at 343 K.

reaction of the latter with ammonia in an autoclave yielded aniline **14**.

Experimental

IR spectra were recorded on a UR-20 instrument. Mass spectra were obtained with a Varian MAT-311A instrument (EI, 70 eV). ^{1}H, ^{13}C, ^{14}N, and ^{15}N NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13, 75.5, 21.5, and 30.42 MHz, respectively); the chemical shifts were measured with reference to Me_4Si (^{1}H and ^{13}C) and $MeNO_2$ (^{14}N and ^{15}N, external standard). The procedures used while recording the NMR spectra were described previously.[2] The course of the reaction was monitored by TLC (Silufol UV-254). Compounds **1a,b** and **8a—c** were synthesized by closing the tetrazine ring;[3] compounds **2a,b** were prepared by nitration of BTDO.[2] Reaction products were purified using preparative TLC on Silpearl silica gel. Melting points were determined on a Kofler hot stage. All BTDOs, except for amino derivatives, are bright yellow; 6-amino-BTDOs are red, while 7-amino-BTDOs are violet.*

Synthesis of methoxybenzo-1,2,3,4-tetrazine 1,3-dioxides 3a—c from BTDOs 1a—c and 2a (general procedure). A solution of KOH (112 mg, 2 mmol) in 5 mL of MeOH was added to a

* UV spectra of BTDO were described in Ref. 6.

Table 4. ^{13}C NMR spectra of BTDOs **3a—c**, **4a—c**, **5a—c**, **6a—c**, **9a—c**, **10a,c**, and **11a**

Compound[a]	δ_{exp} (δ_{calc}), J/Hz						
	C(4a)	C(5)	C(6)	C(7)	C(8)	C(8a) br.s	Me
3a[b]	140.9 (136.8)	126.8 (126.3)	131.4 (124.8)	162.9 (163.8)	98.5 (105.5)	129.8 (130.1)	57.4
3b	146.7 (144.4)	102.8 (109.8)	166.8 (169.9)	123.7 (117.4)	121.0 (120.0)	123.2 (120.1)	57.3
3c	145.5 (144.4) $^3J_{C(4a),H(6)} = 9.9$	114.9 (116.3)	138.6 (139.5)	112.2 (117.4)	152.5 (150.4) $^3J_{C(8),H(6)} = 9.4$	120.4 (113.6)	57.2
4a[b]	142.4 (140.4) $^3J_{C(4a),H(6)} = 9.7$ $^3J_{C(4a),H(8)} = 5.0$	127.2 (126.9)	131.8 (130.1) $^3J_{C(6),H(5)} = 6.1$	144.9 (144.3) $^3J_{C(7),H(5)} = 11.0$	107.9 (110.8)	129.5 (130.7)	—
4b	145.1 (145.0) $^3J_{C(4a),H(8)} = 5.3$	111.6 (115.1) $^3J_{C(5),H(7)} = 4.6$	150.2 (150.4) $^3J_{C(6),H(8)} = 10.8$	124.3 (122.7) $^3J_{C(7),H(5)} = 5.8$	121.2 (120.6)	125.3 (123.7)	—
4c	145.4 (146.5) $^3J_{C(4a),H(6)} = 10.5$	120.0[c] (120.9)	137.7 (140.9)	122.4[c] (123.2)	133.8 (131.9) $^3J_{C(8),H(6)} = 9.6$	121.6 (119.9)	—
5a[d]	136.2 (131.3)	124.7 (124.7)	126.3 (122.6) $^3J_{C(6),H(8)} = 6.1$	151.3 (154.4)	92.7 (103.5) $^3J_{C(8),H(6)} = 4.0$	128.2 (128.5)	39.5
5b	—[e]	97.55 (108.4)	—[e]	120.0[c] (116.0)	120.3[c] (119.4)	—[e]	40.2
5c	137.4 (143.8)	115.3[c] (112.2)	137.6 (138.9)	110.9[c] (112.2)	145.6 (141.5)	112.2 (116.0)	43.3
6a[d]	137.4 (133.7)	128.9[c] (125.0)	124.7[c] (122.2)	152.1 (153.2)	89.9 (102.7)	128.8 (128.8)	29.2
6b[d,f]	147.1 (144.1)	95.0 br.s (108.0)	157.1 (159.8)	123.5 br.s (115.6)	120.2 br.s (119.7)	119.8 (116.4)	29.4
6c	144.7 (144.1) $^3J_{C(4a),H(6)} = 10.2$	106.7[c] (112.6)	139.2 (139.2)	109.1[c] (115.6)	143.5 (140.3) $^3J_{C(8),H(6)} = 9.2$	116.9 (111.8)	29.9
9a	148.5 (148.7)	103.4 (101.5)	164.9 (168.8) $^3J_{C(6)OMe} = 9.0$ $^2J_{C(6),H(7)} = 3.8$	128.1 (126.8)	113.8 (114.8)	122.4 (126.3)	57.3
9b	145.6 (145.5) $^3J_{C(4a),H(8)} = 5.8$	103.2 (104.8)	162.7 (169.9) $^3J_{C(6),H(8)} = 8.9$	117.9 (117.5) $^3J_{C(7),H(5)} = 8.9$	123.07 (124.1)	123.12 (125.0) $^3J_{C(8a),H(5)} = 7.3$	58.4
9c	137.9 (144.0) $^3J_{C(4a),H(6)} = 8.3$ $^3J_{C(4a),H(8)} = 5.0$	118.5 (120.6)	132.6 (134.5)	161.0 (164.9)	98.1 (97.3)	130.2 (131.8)	57.2
10a	146.2 (147.5)	117.2 (118.0) $^3J_{C(5),H(7)} = 5.2$	132.6 (132.4)	115.2 (115.3)	152.9 (151.3)	120.1 (122.4) $^3J_{C(8a),H(7)} = 8.5$ $^3J_{C(8a),H(5)} = 6.3$	58.0
10c	135.2 (128.1) $^3J_{C(4a),H(6)} = 7.5$ $^3J_{C(4a),H(8)} = 5.0$	152.3 (157.0) $^2J_{C(5),H(8)} = 4.3$ $^2J_{C(5),H(6)} = 5.2$	120.4 (126.9)	125.0 (125.6)	111.8 (113.1) $^3J_{C(8),H(6)} = 5.4$	129.2 (129.9)	57.7
11a	148.1 (146.7)	102.4 (100.5)	166.8 (169.6)	95.5 (97.8)	154.0 (153.7)	116.5 (112.5)	56.9[g] 57.3[h]

[a] The spectra were recorded in DMSO-d_6 at 298 K, unless otherwise specified.
[b] In acetone-d_6.
[c] Assignments of the signals may be interchanged.
[d] The spectrum was recorded at 343 K.
[e] No signals appeared because of poor solubility of the compound.
[f] At 298 K, all signals are broadened, except those for the C(6) atom and the HNMe group; two signals for the latter appear at δ 29.3 and 29.4 in an intensity ratio of 1 : 8.
[g] MeOC(6).
[h] MeOC(8).

stirred solution of a BTDO (**1a—c**) (243 mg, 1 mmol) in 50 mL of MeOH or BTDO **2a** (209 mg, 1 mmol) in 20 mL of MeOH (the reaction conditions are specified in Table 1). After the reaction was completed (TLC), the reaction mixture was neutralized with aqueous HCl. After 90% of the solvent was removed *in vacuo*, the product was filtered off, washed with water, and dried *in vacuo*.

7-Methoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (3a). *A*. Synthesis from 7-bromo-BTDO 1a. The yield of compound **3a** was 87 mg (45%), m.p. 163—165 °C (from CH_2Cl_2). Found (%): C, 43.25; H, 3.14; N, 28.75. $C_7H_6N_4O_3$. Calculated (%): C, 43.31; H, 3.11; N, 28.86. IR (KBr), ν/cm^{-1}: 1404, 1486 (N(O)NN(O)N). MS, *m/z*: 194 $[M]^+$.

***B*. Synthesis from 7-nitro-BTDO 2a.** The yield of compound **3a** was 145 mg (75%). The product is identical with that obtained from BTDO **1a**.*

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

6-Methoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (3b) was obtained from BTDO **1b**. The yield of compound **3b** was 161 mg (83%), m.p. 210—211 °C (from CH_2Cl_2). Found (%): C, 43.20; H, 3.08; N, 28.61. $C_7H_6N_4O_3$. Calculated (%): C, 43.31; H, 3.11; N, 28.86. IR (KBr), ν/cm^{-1}: 1424, 1496 (N(O)NN(O)N). MS, *m/z*: 194 $[M]^+$.

8-Methoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (3c) was obtained from BTDO **1c**. The yield of compound **3c** was 53 mg (27%), m.p. 193—195 °C (from CH_2Cl_2). Found (%): C, 43.23; H, 3.15; N, 28.58. $C_7H_6N_4O_3$. Calculated (%): C, 43.31; H, 3.11; N, 28.86. IR (KBr), ν/cm^{-1}: 1405, 1510 (N(O)NN(O)N). MS, *m/z*: 194 $[M]^+$.

Synthesis of azidobenzo-1,2,3,4-tetrazine 1,3-dioxides 4a—c from BTDOs 1a—c and 2a (general procedure). A solution of NaN_3 (130 mg, 2 mmol) in 3 mL of DMF and 0.25 mL of water was added to a stirred solution of BTDO **1** or **2** (1 mmol) in 4 mL of DMF (the reaction conditions are specified in Table 1). After the reaction was completed, the reaction mixture was poured into water, and the product was filtered off, washed with water, and dried *in vacuo*.

7-Azidobenzo-1,2,3,4-tetrazine 1,3-dioxide (4a). ***A*. Synthesis from 7-bromo-BTDO 1a.** The yield of compound **4a** was 108 mg (53%), m.p. 140—146 °C (decomp.) (from CH_2Cl_2). Found (%): C, 35.01; H, 1.44; N, 47.64. $C_6H_3N_7O_2$. Calculated (%): C, 35.13; H, 1.47; N, 47.80. IR (KBr), ν/cm^{-1}: 1400, 1485 (N(O)NN(O)N); 2132 (N_3). MS, *m/z*: 205 $[M]^+$.

***B*. Synthesis from 7-nitro-BTDO 2a.** The yield of compound **4a** was 154 mg (75%). The product is identical with that obtained from BTDO **1a**.

6-Azidobenzo-1,2,3,4-tetrazine 1,3-dioxide (4b) was obtained from BTDO **1b**. The yield of compound **4b** was 180 mg (88%), m.p. 156—158 °C (decomp.) (from CH_2Cl_2). Found (%): C, 34.93; H, 1.51; N, 47.59. $C_6H_3N_7O_2$. Calculated (%): C, 35.13; H, 1.47; N, 47.80. IR (KBr), ν/cm^{-1}: 1428, 1500 (N(O)NN(O)N); 2122 (N_3). MS, *m/z*: 205 $[M]^+$.

8-Azidobenzo-1,2,3,4-tetrazine 1,3-dioxide (4c) was obtained from BTDO **1c**. The yield of compound **4c** was 185 mg (90%), decomp. 110—120 °C (without melting). Found (%): C, 35.10; H, 1.44; N, 47.88. $C_6H_3N_7O_2$. Calculated (%): C, 35.13; H, 1.47; N, 47.80. IR (KBr), ν/cm^{-1}: 1403, 1520 (N(O)NN(O)N); 2129 (N_3). MS, *m/z*: 205 $[M]^+$.

Synthesis of dimethylaminobenzo-1,2,3,4-tetrazine 1,3-dioxides 5a—c from BTDOs 1b,c and 2a (general procedure). A 30% aqueous solution of Me_2NH (0.6 mL, 4 mmol) was added to a stirred solution of BTDO (1 mmol) in DMF (the reaction conditions are specified in Table 1). After the reaction was completed, the reaction mixture was poured into water, and the precipitate that formed was filtered off, washed with water, EtOH (4 mL), and Et_2O (4 mL), and dried *in vacuo*.

Synthesis of 7-dimethylaminobenzo-1,2,3,4-tetrazine 1,3-dioxide (5a) from 7-nitro-BTDO 2a. The yield of compound **5a** was 157 mg (76%), violet crystals, m.p. 247—253 °C (decomp.) (from MeCN). Found (%): C, 46.49; H, 4.35; N, 33.51. $C_8H_9N_5O_2$. Calculated (%): C, 46.38; H, 4.38; N, 33.80. IR (KBr), ν/cm^{-1}: 1408, 1474 (N(O)NN(O)N). MS, *m/z*: 207 $[M]^+$.

6-Dimethylaminobenzo-1,2,3,4-tetrazine 1,3-dioxide (5b) was obtained from BTDO **1b**. The yield of compound **5b** was 195 mg (94%), red crystals, m.p. 274—276 °C (decomp.) (from MeCN). Found (%): C, 46.51; H, 4.35; N, 33.62. $C_8H_9N_5O_2$. Calculated (%): C, 46.38; H, 4.38; N, 33.80. IR (KBr), ν/cm^{-1}: 1404, 1468 (N(O)NN(O)N). MS, *m/z*: 207 $[M]^+$.

8-Dimethylaminobenzo-1,2,3,4-tetrazine 1,3-dioxide (5c) was obtained from BTDO **1c**. The yield of compound **5c** was 155 mg (75%), violet crystals, m.p. 212—214 °C (decomp.) (from MeCN). Found (%): C, 46.45; H, 4.40; N, 33.82. $C_8H_9N_5O_2$. Calculated (%): C, 46.38; H, 4.38; N, 33.80. IR (KBr), ν/cm^{-1}: 1412, 1512 (N(O)NN(O)N). MS, *m/z*: 207 $[M]^+$.

Synthesis of compound 5a from 7-bromo-BTDO 1a. A saturated solution of Me_2NH (2 mL) in DMF was added to a stirred solution of BTDO **1a** (243 mg, 1 mmol) in 2 mL of DMF (the reaction conditions are specified in Table 1). The reaction mixture was treated as described above. The yield of compound **5a** was 93 mg (45%). The product is identical with that obtained from BTDO **2a**.

Synthesis of methylamino-BTDOs 6a—c from compounds 1a—c (general procedure). A solution of BTDO **1** (243 mg, 1 mmol) was added to a stirred saturated solution of $MeNH_2$ (0.322 mg, 10.4 mmol) in 4 mL of DMSO (the reaction conditions are specified in Table 1). After the reaction was completed, the reaction mixture was poured into water, and the product was filtered off, washed with water, EtOH (4 mL), and Et_2O (4 mL), and dried *in vacuo*.

7-Methylaminobenzo-1,2,3,4-tetrazine 1,3-dioxide (6a). The yield of compound **6a** was 172 mg (89%), violet crystals (from MeCN), decomp. 240 °C (without melting). Found (%): C, 43.70; H, 3.70; N, 35.98. $C_7H_7N_5O_2$. Calculated (%): C, 43.53; H, 3.65; N, 36.26. IR (KBr), ν/cm^{-1}: 1450 (N(O)NN(O)N). MS, *m/z*: 193 $[M]^+$.

6-Methylaminobenzo-1,2,3,4-tetrazine 1,3-dioxide (6b). The yield of compound **6b** was 178 mg (92%), red crystals (from MeCN), decomp. 240 °C (without melting). Found (%): C, 43.69; H, 3.68; N, 36.02. $C_7H_7N_5O_2$. Calculated (%): C, 43.53; H, 3.65; N, 36.26. IR (KBr), ν/cm^{-1}: 1432, 1490 (N(O)NN(O)N). MS, *m/z*: 193 $[M]^+$.

8-Methylaminobenzo-1,2,3,4-tetrazine 1,3-dioxide (6c). The yield of compound **6c** was 173 mg (89%), violet crystals, m.p. 240—246 °C (decomp.) (from MeCN). Found (%): C, 43.59; H, 3.59; N, 35.92. $C_7H_7N_5O_2$. Calculated (%): C, 43.53; H, 3.65; N, 36.26. IR (KBr), ν/cm^{-1}: 1435, 1507 (N(O)NN(O)N). MS, *m/z*: 193 $[M]^+$.

Synthesis of bromomethoxy-BTDOs 9a—c and 10a—c from compounds 8a—c (general procedure). A solution of KOH (70 mg, 1.24 mmol) in 5 mL of MeOH was added at 20 °C to a stirred solution of BTDO **8** (200 mg, 0.62 mmol) in a minimum amount of MeOH. The reaction was stopped when trace amounts of disubstituted products were detected (TLC, benzene—Et_2O, 5 : 1). The reaction mixture was neutralized with aqueous HCl, and the solvent was removed *in vacuo*. The ratio between isomers **9** and **10** was determined from integrated signals in the ^1H NMR spectra (see Table 2). The products were separated by preparative TLC (benzene—Et_2O, 5 : 1).

8-Bromo-6-methoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (9a) and 6-bromo-8-methoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (10a). The reaction of a solution of BTDO **8a** (200 mg) in 65 mL of MeOH was carried out for 2.3 h. The unreacted **8a** (60 mg, 70% conversion) was recovered; the yields of compounds **9a** and **10a** were 59 mg (50%, from the consumed **8a**) and 37 mg (31%, from the consumed **8a**), respectively.

Compound 9a, m.p. 209—210 °C (from CH_2Cl_2). Found (%): C, 30.57; H, 1.83; Br, 29.40; N, 20.30. $C_7H_5BrN_4O_3$. Calculated (%): C, 30.79; H, 1.85; Br, 29.26; N, 20.52. IR (KBr), ν/cm^{-1}: 1410, 1490 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 272, 274 $[M]^+$ (1 : 1).

Compound 10a, m.p. 213—215 °C (decomp.) (from CH_2Cl_2). Found (%): C, 30.65; H, 1.84; Br, 29.15; N, 20.23. $C_7H_5BrN_4O_3$. Calculated (%): C, 30.79; H, 1.85; Br, 29.26; N, 20.52. IR (KBr), ν/cm^{-1}: 1400, 1505 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 272, 274 $[M]^+$ (1 : 1).

7-Bromo-6-methoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (9b) and 6-bromo-7-methoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (10b). The reaction of a solution of BTDO **8b** (200 mg) in 200 mL of MeOH was carried out for 2.3 h. The unreacted **8b** (75 mg, 62% conversion) was recovered; the yields of compounds **9b** and **10b** were 96 mg (91%, from the consumed **8b**) and 2 mg (2%, from the consumed **8b**), respectively.

Compound 9b, m.p. 214—216 °C (from CH_2Cl_2). Found (%): C, 30.57; H, 1.86; Br, 29.36; N, 20.34. $C_7H_5BrN_4O_3$. Calculated (%): C, 30.79; H, 1.85; Br, 29.26; N, 20.52. IR (KBr), ν/cm^{-1}: 1420, 1505 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 272, 274 $[M]^+$ (1 : 1).

Compound 10b, m.p. 240—243 °C (decomp.) (from CH_2Cl_2). MS, *m/z* (integral intensity ratio): 272, 274 $[M]^+$ (1 : 1).

5-Bromo-7-methoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (9c) and 7-bromo-5-methoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (10c). The reaction of a solution of BTDO **8c** (200 mg) in 75 mL of MeOH was carried out for 2.3 h. The unreacted **8c** (110 mg, 45% conversion) was recovered; the yields of compounds **9c** and **10c** were 56 mg (73%, from the consumed **8c**) and 7 mg (9%, from the consumed **8c**), respectively.

Compound 9c, m.p. 203—204 °C (from CH_2Cl_2). Found (%): C, 30.75; H, 1.88; Br, 29.1; N, 20.4. $C_7H_5BrN_4O_3$. Calculated (%): C, 30.79; H, 1.85; Br, 29.26; N, 20.52. IR (KBr), ν/cm^{-1}: 1440, 1512 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 272, 274 $[M]^+$ (1 : 1).

Compound 10c, m.p. 184—185 °C (from CH_2Cl_2). IR (KBr), ν/cm^{-1}: 1404, 1485 (N(O)NN(O)N). MS, *m/z* (integral intensity ratio): 272, 274 $[M]^+$ (1 : 1).

6,8-Dimethoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (11a). A solution of KOH (224 mg, 4 mmol) in 5 mL of MeOH was added to a stirred solution of BTDO **8a** (322 mg, 1 mmol) in 50 mL of MeOH. After 6 h, the reaction mixture was neutralized with aqueous HCl. The solvent was evaporated, and chromatography (benzene—Et_2O, 5 : 1) gave compound **11a** (164 mg, 74%), m.p. 209—210 °C (from CH_2Cl_2). Found (%): C, 42.79; H, 3.68; N, 24.69. $C_8H_8N_4O_4$. Calculated (%): C, 42.86; H, 3.60; N, 24.99. IR (KBr), ν/cm^{-1}: 1424, 1484 (N(O)NN(O)N). MS, *m/z*: 224 $[M]^+$.

6,7-Dimethoxybenzo-1,2,3,4-tetrazine 1,3-dioxide (11b). Compound **8b** (322 mg, 1 mmol) was added to a stirred solution of KOH (224 mg, 4 mmol) in 50 mL of MeOH. After 16 h, the reaction mixture was neutralized with aqueous HC1. The solvent was evaporated, and chromatography (benzene—Et_2O, 5 : 1) gave compound **11b** (120 mg, 54%), m.p. 255—256 °C (from CH_2Cl_2). Found (%): C, 42.76; H, 3.65; N, 24.8. $C_8H_8N_4O_4$. Calculated (%): C, 42.86; H, 3.60; N, 24.99. IR (KBr), ν/cm^{-1}: 1428, 1516 (N(O)NN(O)N). ^{13}C NMR (DMSO-d_6), δ: 57.1, 57.5 (both Me); 97.1, 102.3 (both CH). MS, *m/z*: 224 $[M]^+$.

2,6-Dibromonitrosobenzene (12). A solution of 55% *m*-chloroperbenzoic acid (3.76 g, 12 mmol) in 30 mL of CH_2Cl_2 was added at 20 °C to a solution of 2,6-dibromoaniline (2.51 g, 10 mmol) in 40 mL of CH_2Cl_2. After 4 h, the precipitate of *m*-chlorobenzoic acid that formed was filtered off. The resulting solution was washed with aqueous Na_2CO_3 to remove the residual amount of the acid, dried over $MgSO_4$, and concentrated to give nitroso compound **12** (2.52 g, 95%). After recrystallization from $CHCl_3$, m.p. 134—135 °C (Ref. 7: m.p. 135—136 °C). MS, *m/z* (integral intensity ratio): 263, 265, 267 $[M]^+$ (1 : 2 : 1).

2,6-Dibromo(*tert*-butyl-*NNO*-azoxy)benzene (13). A solution of *N*,*N*-dibromo-*tert*-butylamine (12 g, 0.052 mol) in 50 mL of CH_2Cl_2 was added at 20 °C to a stirred suspension of nitroso compound **12** (13.25 g, 0.05 mol) in 300 mL of CH_2Cl_2. The reaction mixture was stirred until the nitroso compound was dissolved completely and then kept for 12 h. The solvent was evaporated *in vacuo*, and the residue was washed with aqueous sodium sulfite to remove an excess of *N*,*N*-dibromo-*tert*-butylamine. Recrystallization from hexane gave product **13** (14.1 g, 84%), m.p. 107—107.5 °C. Found (%): C, 35.80; H, 3.55; Br, 47.48; N, 8.19. $C_{10}H_{12}Br_2N_2O$. Calculated (%): C, 35.74; H, 3.60; Br, 47.56; N, 8.34. ^{1}H NMR ($CDCl_3$), δ: 1.51 (s, 9 H, 3 CH_3); 7.05 (t, 1 H, H(4), J = 8.0 Hz); 7.47 (d, 2 H, H(3), H(5)). ^{13}C NMR ($CDCl_3$), δ: 25.4 (Me); 60.4 (CMe_3); 116.0 (C(2)); 130.4 (C(4)); 132.4 (C(3)); 147.6 (C(1)). MS, *m/z* (integral intensity ratio): 334, 336, 338 $[M]^+$ (1 : 2 : 1).

3-Bromo-2-(*tert*-butyl-*NNO*-azoxy)aniline (14). A solution of compound **13** (1.68 g, 5 mmol) in 50 mL of toluene was placed in a 150-mL steel autoclave precooled with liquid nitrogen. Liquid NH_3 (75 mL) was added, and the reaction mixture was heated at 210 °C and a pressure of 300 atm for 24 h. The solvent was removed *in vacuo*, and the residue was separated by column chromatography on silica gel (eluent was hexane—ethyl acetate, 19 : 1). The unreacted **13** (0.7 g, 58% conversion) was recovered. Aniline **14** was obtained as an oil; the yield was 0.67 g (85%, from the consumed **13**). Found (%): C, 44.29; H, 5.13; Br, 29.47; N, 15.24. $C_{10}H_{14}BrN_3O$. Calculated (%): C, 44.13; H, 5.19; Br, 29.36; N, 15.44. IR (film between NaCl plates), ν/cm^{-1}: 1480 (N(O)=N); 3340, 3460 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 1.45 (s, 9 H, 3 CH_3); 4.60 (br.s, 2 H, NH_2); 6.65 (dd, 1 H, H(6), J = 7.8 Hz, J = 1.1 Hz); 6.81 (dd, 1 H, H(4), J = 7.8 Hz, J = 1.1 Hz); 6.84 (d, 1 H, H(5), J = 7.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 25.5 (Me); 59.9 (CMe_3); 115.2 (C(3)); 116.3 (C(6)); 121.2 (C(4)); 130.2 (C(5)); 136.3 (br.s, C(2)); 141.7 (C(1)). MS, *m/z* (integral intensity ratio): 271, 273 $[M]^+$ (1 : 1).

8-Bromobenzo-1,2,3,4-tetrazine 1,3-dioxide (1c). A solution of aniline **14** (544 mg, 2 mmol) in 4 mL of dry MeCN was added dropwise over 10 min to a stirred suspension of N_2O_5 (870 mg, 8 mmol) in 8 mL of dry MeCN while maintaining the temperature at a level of −20 °C. Stirring was continued at this temperature for an additional 5 min. The precipitate that formed was filtered off, washed with 5 mL of cold MeOH, and dried *in vacuo* to give BTDO **1c** (209 mg, 43%), m.p. 208—209 °C (CH_2Cl_2). Found (%): C, 29.58; H, 1.23; Br, 33.02, N, 22.81. $C_6H_3BrN_4O_2$. Calculated (%): C, 29.65; H, 1.24; Br, 32.88; N, 23.05. IR (KBr), ν/cm^{-1}: 1404, 1515 (N(O)NN(O)N). ^{1}H NMR (acetone-d_6), δ: 7.90, 8.13 (both dd, 1 H each, H(5), H(7), ^3J = 8.3 Hz, ^4J = 1.4 Hz); 7.97 (t, H(6)). ^{13}C NMR (DMSO-d_6), δ: 112.3; 124.2 (CH); 127.2 (br.s); 137.4 (CH); 137.6 (CH); 146.0. ^{14}N NMR (acetone-d_6), δ: −42 ($\Delta\nu_{1/2}$ = 25 Hz), −49 ($\Delta\nu_{1/2}$ = 120 Hz) (N(1) and N(3)). MS, *m/z* (integral intensity ratio): 242, 244 $[M]^+$ (1 : 1).

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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. O. Yu. Smirnov, A. M. Churakov, Yu. A. Strelenko, S. L. Ioffe, and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1694 [*Russ. Chem. Bull., Int. Ed.*, 2002, 1841] and the references cited therein.
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. F. R. Benson, *The High Nitrogen Compounds*, Wiley, New York, 1984, p. 328.
6. K. I. Rezchikova, A. M. Churakov, K. Ya. Burshtein, V. A. Shlyapochnikov, and V. A. Tartakovsky, *Mendeleev Commun.*, 1997, 174.
7. R. R. Holmes and R. P. Bayer, *J. Am. Chem. Soc.*, 1960, **82**, 3454.

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