Annulated benzotetrazine 1,3-dioxides
1. [1,2,5]Oxadiazolo[3,4-*f*][1,2,3,4]benzotetrazine 2,4,7- and 2,4,9-trioxides

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Thermolysis of 6-azido-5-nitro-7-R-benzotetrazine 1,3-dioxides (R = H and Br) gave benzotetrazine 1,3-dioxides annulated with the furoxan ring at the C(5)—C(6) bond. According to the NMR data, these compounds at 297 K are equilibrium mixtures of two isomers with different positions of the *N*-oxide oxygen atom in the furoxan ring. Full assignment of signals in the ^{13}C NMR spectra of the compounds obtained was accomplished.

Key words: benzotetrazines, *N*-oxides, 1,2,5-oxadiazoles, ^{13}C NMR spectroscopy.

Recently,[1—3] it has been found that benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDO) belong to a novel class of donors of a nitrogen oxide. BTDO containing electron-withdrawing substituents, in particular, the nitro groups in position 5 or 7, exhibit a high biological activity. BTDO annulated with electron-withdrawing heterocycles could also be highly active. The goal of the present study was to obtain first representatives of such compounds, namely, benzotetrazine 1,3-dioxides annulated with the furoxane ring.

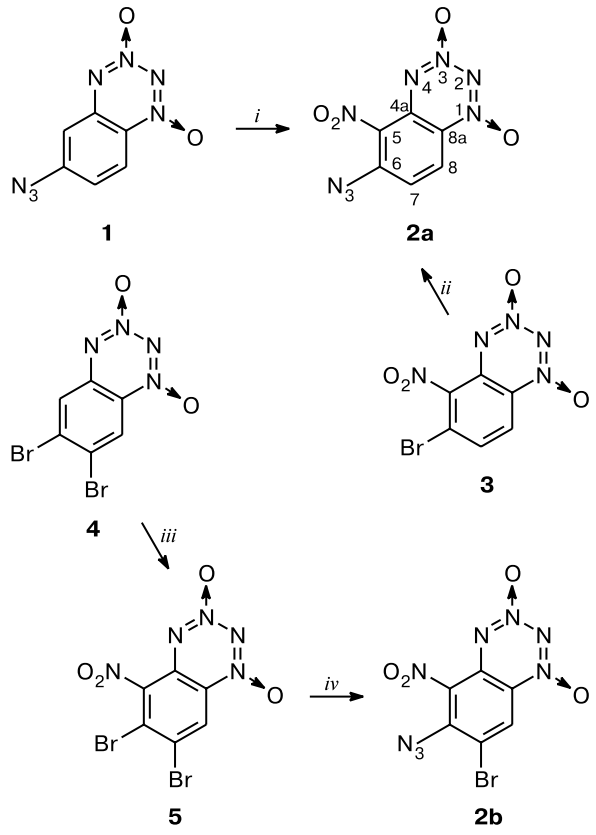
Results and Discussion

To obtain furoxan-annulated benzotetrazine 1,3-dioxides, we employed a conventional approach, *viz.*, an intramolecular interaction between the azido and nitro groups *ortho* to each other.[4]

Synthesis of the starting compounds. *ortho*-Azidonitro-BTDO were prepared by electrophilic and/or nucleophilic substitution reactions; their mechanisms had been discussed in detail previously.[5,6] Nitration of 6-azido-BTDO **1** with an equivalent of HNO_3 in H_2SO_4 gave 6-azido-5-nitro-BTDO **2a** (Scheme 1). As expected,[5] the nitration occurred virtually exclusively at position 5. The structure of BTDO **2a** was unambiguously confirmed by ^1H, ^{13}C, ^{14}N, and ^{15}N NMR spectra with complete assignment of signals (see Experimental).

Compound **2a** can also be prepared by treating 6-bromo-5-nitro-BTDO **3** with sodium azide, which results in replacement of the bromine atom by the azido group (see Scheme 1).

Scheme 1



Reagents, reaction conditions, and yields: *i*. HNO_3/H_2SO_4, 0→20 °C (82%); *ii*. NaN_3, DMF, 20 °C, 10 min (85%); *iii*. HNO_3/oleum, 20 °C, 24 h (84%); *iv*. NaN_3, DMF, 20 °C, 5 min (67%).

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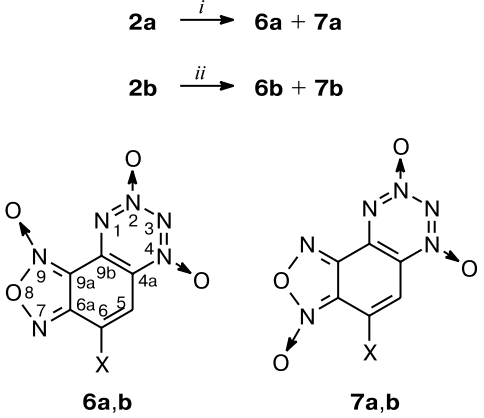
Compound **2b** was prepared by nitration of BTDO **4** followed by treatment of product **5** with sodium azide. As expected,[6] the replacement involved exclusively position 6.

Synthesis of furoxane-annulated BTDO. Heating of compound **2a** without a solvent or in AcOH at ~100 °C resulted in closure of a furoxan ring (Scheme 2).

Scheme 2



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

Reagents, reaction conditions, and yields: *i*. Heating in AcOH, 90 °C, 30 min (83%); *ii*. Heating without a solvent, 120—125 °C, 30 min (66%).

^{1}H and ^{13}C NMR spectra recorded at 297 K show that the product exists as a 1 : 1 mixture of two isomers **6a** and **7a** (Table 1). On heating to 373 K in DMSO-d_6, the signals from the isomers in the ^{1}H NMR spectra coalesce. The original spectral pattern was recovered upon cooling the heated sample to 297 K, which confirms the presence of an equilibrium mixture of isomers **6a** and **7a** in the ratio 1 : 1.

As expected, cyclization of compound **2b** occurred under slightly more drastic conditions (heating without a solvent at 120—125 °C).

The resulting product was also an equilibrium mixture of two isomers; however, isomer **6b** was dominant (**6b** : **7b** = 9 : 1). At 373 K in DMSO-d_6, signals in the ^{1}H NMR spectra broadened without coalescence. Yet coalescence at this temperature was observed in the specimen added by benzene (25 mol.% of the mixture of isomers **6b**/**7b**). On cooling to 273 K, the ratio of the signals returned to the initial value.

Note that although benzofuroxans usually exist as a thermodynamically more stable isomer, both isomers have been detected in solutions of structurally similar naphtho[1,2-*c*]furoxan and quinolino[7,8-*c*]furoxan. Interestingly, the dominant isomer in naphtho[1,2-*c*]furoxan contains the inward-directed *N*-oxide oxygen atom (66%), while that in quinolino[7,8-*c*]furoxan has the outward-directed *N*-oxide oxygen atom (58%).[7]

Table 1. ^{1}H and ^{14}N NMR spectra of compounds **6a**,**b** and **7a**,**b**

Compound	Solvent	^{1}H NMR (δ, *J*/Hz)[a]		^{14}N NMR (δ, $\Delta\nu_{1/2}$/Hz)[b]
		H(5)	H(6)	–N(O)=N–N(O)=N–
6a	DMSO-d_6	8.02 (s)	8.02 (s)	—
	Acetone-d_6	8.12 (d, *J* = 10.0)	8.00 (d)	–42.5 (50), –48 (50)
7a	DMSO-d_6	7.86 (d, *J* = 9.8)	7.77 (d)	—
	Acetone-d_6	7.98 (d, *J* = 9.8)	7.77 (d)	–42.5 (50), –45.5 (50)
6b	DMSO-d_6	8.55 (s)	—	—
	Acetone-d_6	8.44 (s)	—	–42 (70), –48 (70)
7b	DMSO-d_6	8.25 (s)	—	—
	Acetone-d_6	8.21 (s)	—	—[c]

[a] Recorded at 297 K. The integral intensity ratio of the signals for **6a** : **7a** = 1 : 1 and for **6b** : **7b** = 9 : 1. For isomers **6a**/**7a** in DMSO-d_6 at 373 °C, a broadened signal appears at δ 7.93. For isomers **6b**/**7b** in DMSO-d_6 + 25 mol.% benzene at 373 °C, a broadened signal appears at δ 8.32.

[b] The signals for the N(1) and N(3) atoms of the tetrazine 1,3-dioxide fragment.

[c] The signals were not observed because of their low intensities.

To assign signals in the NMR spectra of equilibrium mixtures of compounds **6** and **7**, ^{13}C signals were accumulated without proton decoupling and with selective proton decoupling, as well as ^{1}H—^{1}H (HH COSY) correlation and selective polarization transfer from protons (SPT) (see Tables 1, 2).

The ^{14}N NMR spectra of bromides **6b**/**7b** show two narrow signals at δ –42 and –48 characteristic of the N(1) and N(3) atoms of the tetrazine 1,3-dioxide ring.[3] Obviously, the signals relate to the dominant isomer **6b**. The ^{14}N NMR spectra of compounds **6a**/**7a** contain signals at δ –42.5 (its integral intensity corresponds to two N atoms), –45.5, and –48. Taking into account that the presence of the bromine atom in position 7 of benzotetrazine 1,3-dioxide does not shift the signal for N(3), yet only slightly shifting upfield the signal for N(1) (for benzotetrazine 1,3-dioxide, δ(^{14}N) = –48.0 (N(3)), –40 (N(1)); for 7-bromobenzotetrazine 1,3-dioxide, δ(^{14}N) = –48.0 (N(3)), –43 (N(1))),[8] the signals at δ –42.5 and –48 can be assigned to isomer **6a**. Then, the remaining signals at δ –42.5 and –45.5 relate to isomer **7a**. Note that in substituted benzotetrazine 1,3-dioxides, a signal for N(3) is usually somewhat broader than a signal for N(1),[9] while in furoxane-annulated benzotetrazine 1,3-dioxides **6a**/**7a** and **6b**/**7b**, the corresponding signals are nearly equal in width.

Table 2. ^{13}C NMR spectra of compounds **6a**,**b** and **7a**,**b** (273 K)

Compound	Solvent	δ (*J*/Hz)					
		C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
6a	DMSO-d_6	127.0 (^3J = 10.0, ^2J = 2.0)	122.1 (^1J = 178.1)	121.1 (^1J = 180.6)	152.0 (^3J = 13.3)	105.5 (^3J = 5.0)	141.7 (^3J = 4.0)
7a	DMSO-d_6	129.7 (^3J = 10.1)	117.9 (^1J = 179.6)	116.7 (^1J = 183.0)	114.1 (^3J = 11.9, ^2J = 1.3)	146.0 (^3J = 4.4)	142.0 (^3J = 4.7)
6b	Acetone-d_6	127.7 (br.s)	124.9 (^1J = 179.6)	114.5 (^2J = 6.0)	152.3 (^3J = 9.5)	107.0	142.4 (^3J = 5.3)
7b	Acetone-d_6	—	120.8	110.5	–*	–*	–*

* The signal was not observed because of its low intensity.

Experimental

^1H, ^{13}C, ^{15}N, and ^{14}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, upfield shifts 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 (Silufol UV-254). Column chromatography was carried out on Silica 32-63 (Fisher Scientific™).

All the benzotetrazine 1,3-dioxides obtained were colored yellow.

6-Azido-5-nitrobenzotetrazine 1,3-dioxide (2a). Procedure *A*. Synthesis of compound 2a from 6-azido-BTDO 1. Concentrated HNO_3 (d = 1.5 g cm^{-3}; 90 mg, 1.41 mmol) was added at –10 °C to a stirred suspension of BTDO **1** (210 mg, 1 mmol) in conc. H_2SO_4 (d = 1.84 g cm^{-3}; 3.5 mL). The reaction mixture was allowed to warm to ~20 °C, kept for 10 min, and poured onto finely crushed ice. The precipitate that formed was filtered off, successively washed with water (to pH 7), MeOH, and Et_2O, and dried in air to give BTDO **2a** (205 mg, 82%), m.p. 97 °C. Found (%): C, 28.97; H, 0.79; N, 44.56. $C_6H_2N_8O_4$. Calculated (%): C, 28.81; H, 0.81; N, 44.80. IR (KBr), ν/cm^{-1}: 1442, 1517 (N_4O_2)*; 1379, 1553 (NO_2); 2135 (N_3). ^1H NMR (acetone-d_6), δ: 8.06 (d, 1 H, H(7), ^3J = 9.4 Hz); 8.57 (d, 1 H, H(8)). ^{13}C NMR (acetone-d_6), δ: 123.0 (C(8)); 124.0 (C(7)); 125.7 (C(8a), ^3J = 11.0 Hz); 131.4 (C(5), ^3J = 10.0 Hz); 139.0 (C(4a), ^3J = 5.9 Hz); 143.5 (C(6), J = 10.8 Hz). ^{14}N NMR (acetone-d_6), δ: –21 (1 N, NO_2, $\Delta\nu_{1/2}$ = 80 Hz); –41 (1 N, N(1), $\Delta\nu_{1/2}$ = 5.0 Hz); –44 (1 N, N(3), $\Delta\nu_{1/2}$ = 60 Hz); –146 (1 N, azido group, $\Delta\nu_{1/2}$ = 90 Hz). ^{15}N NMR (natural content of the ^{15}N isotope; DMSO-d_6), δ: –21.5 (NO_2); –25.5 (N(2)); –42.9 (N(1)); –46.4 (N(3)); –95.4 (N(4)); –138.7 (N(2) of the azido group); –147.1 (N(3) of the azido group); –277.9 (N(1) of the azido group). MS, m/z: 250 $[M]^+$.

Procedure *B*. Synthesis of compound 2a from 6-bromo-5-nitro-BTDO 3. Sodium azide (70 mg, 1.1 mmol) was added at 20 °C to a stirred solution of BTDO **3** (280 mg, 1.0 mmol) in DMF (15 mL). After 10 min, the reaction mixture was poured into water and the product was extracted with EtOAc. The organic layer was dried with $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with C_6H_6—EtOAc (5 : 1) as the eluent to give BTDO **2a** (210 mg, 85%), m.p. 97 °C. The product was identical with that obtained according to procedure *A*.

6-Azido-7-bromo-5-nitrobenzotetrazine 1,3-dioxide (2b). Sodium azide (15 mg, 0.23 mmol) was added at 20 °C to a stirred solution of 5-NO_2-6,7-Br_2-BTDO **5** (83 mg, 0.23 mmol) in dry DMF (2 mL). After 5 min, the reaction mixture was poured into water (20 mL) and the product was extracted with EtOAc (3×20 mL). The organic layer was dried with $MgSO_4$ and the solvent was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with benzene as the eluent to give BTDO **2b** (50 mg, 67%), m.p. 129—131 °C (decomp.). Found (%): C, 21.96; H, 0.38; Br, 24.48; N, 33.87. $C_6HBrN_8O_4$. Calculated (%): C, 21.90; H, 0.31; Br, 24.28; N, 34.06. IR (KBr), ν/cm^{-1}: 1422, 1509 (N_4O_2); 1372, 1554 (NO_2); 2141 (N_3). ^1H NMR (acetone-d_6), δ: 8.86 (s, 1 H, H(8)). ^{13}C NMR (acetone-d_6), δ: 120.8 (C(7), ^2J = 4.8 Hz); 126.2 (C(8a)); 126.6 (C(8)); 138.2 (C(4a), ^3J = 6.0 Hz); 139.9 (C(6), ^3J = 9.0 Hz). ^{14}N NMR (acetone-d_6), δ: –23 (1 N, NO_2, $\Delta\nu_{1/2}$ = 70 Hz), –43 (2 N, N(1) and N(3), $\Delta\nu_{1/2}$ = 80 Hz), –150 (1 N, N_3, $\Delta\nu_{1/2}$ = 70 Hz). MS, m/z: 300, 302 (1 : 1) $[M - N_2]^+$.

6,7-Dibromo-5-nitrobenzotetrazine 1,3-dioxide (5). 20% Oleum (0.2 mL) and conc. HNO_3 (d = 1.5 g cm^{-3}; 0.09 mL) were added at 0 °C to a stirred solution of 6,7-Br_2-BTDO **4** (100 mg, 0.31 mmol) in conc. H_2SO_4 (d = 1.84 g cm^{-3}; 2 mL). The solution was kept at 20 °C for 24 h and poured onto finely crushed ice. The precipitate that formed was filtered off, successively washed with water (to pH 7), MeOH, and Et_2O, and dried in air to give BTDO **5** (95 mg, 84%), m.p. >230 °C (decomp.). Found (%): C, 19.80; H, 0.28; Br, 43.81; N, 18.87. $C_6HBr_2N_5O_4$. Calculated (%): C, 19.64; H, 0.27; Br, 43.55; N, 19.09. IR (KBr), ν/cm^{-1}: 1430, 1511 (N_4O_2); 1343, 1555 (NO_2). ^1H NMR (acetone-d_6), δ: 8.95 (s, 1 H, H(8)). ^{13}C NMR (acetone-d_6), δ: 125.4 (C(8)); 128.0 (C(7), ^2J = 4.6 Hz); 128.4 (C(6), ^3J = 9.6 Hz); 128.9 (br.s, C(8a)); 137.0 (C(4a), ^3J = 6.0 Hz); 144.6 (br.s, C(5)). ^{14}N NMR (acetone-d_6), δ: –19 (NO_2, $\Delta\nu_{1/2}$ = 35 Hz); –42 (N(1), $\Delta\nu_{1/2}$ = 35 Hz); –47 (N(3), $\Delta\nu_{1/2}$ = 50 Hz). MS, m/z: 365, 367, 369 (1 : 2 : 1) $[M]^+$.

* Assignment of the bands in the IR spectra of BTDO has been discussed earlier.[9]

Furoxan-annulated benzotetrazine 1,3-dioxides: [1,2,5]oxadiazolo[3,4-*f*][1,2,3,4]benzotetrazine 2,4,9-trioxide (6a) and [1,2,5]oxadiazolo[3,4-*f*][1,2,3,4]benzotetrazine 2,4,7-trioxide (7a).* A solution of 5-NO_2-6-N_3-BTDO **2a** (210 mg, 0.84 mmol) in acetic acid (10 mL) was heated on a water bath at 90 °C for 30 min. The reaction mixture was cooled and poured into water with ice. The product was filtered off, successively washed with small portions of water, MeOH, and Et_2O, and dried *in vacuo* to give a mixture of isomers **6a**/**7a** (150 mg, 80%), m.p. 204 °C. Found (%): C, 32.21; H, 0.90; N, 37.64. $C_6H_2N_6O_4$. Calculated (%): C, 32.44; H, 0.91; N, 37.84. IR (KBr), ν/cm^{-1}: 1410, 1492 (N_4O_2). ^{14}N NMR (acetone-d_6), δ: −42.5 (2 N, $\Delta\nu_{1/2}$ = 50 Hz); −45.5 (1 N, $\Delta\nu_{1/2}$ = 50 Hz); −48 (1 N, $\Delta\nu_{1/2}$ = 50 Hz). MS, *m*/*z*: 222 $[M]^+$.

Furoxan-annulated 7-bromobenzotetrazine 1,3-dioxides: 6-bromo[1,2,5]oxadiazolo[3,4-*f*][1,2,3,4]benzotetrazine 2,4,9-trioxide (6b) and 6-bromo[1,2,5]oxadiazolo[3,4-*f*][1,2,3,4]benzotetrazine 2,4,7-trioxide (7b).** 6-Azido-7-bromo-5-nitro-BTDO **2b** (50 mg) was heated without a solvent at 120—125 °C for 30 min. The product was purified on a thin layer of silica gel with CH_2Cl_2 as the eluent. The yield of a mixture of isomers **6b**/**7b** was 30 mg (66%), m.p. 95—105 °C (from $CHCl_3$). Found (%): C, 30.15; H, 0.33; Br, 26.69; N, 27.63. $C_6HBrN_6O_4$. Calculated (%): C, 29.94; H, 0.33; Br, 26.54; N, 27.92. IR (KBr), ν/cm^{-1}: 1405, 1488 (N_4O_2). MS, *m*/*z*: 300, 302 (1 : 1) $[M]^+$.

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* Compounds **6a,b** and **7a,b** are named according to the IUPAC nomenclature.

References

1. M. O. Ratnikov, D. L. Lipilin, A. M. Churakov, Yu. A. Strelenko, and V. A. Tartakovsky, *Org. Lett.*, 2002, 3227.
2. N. V. Pyatakova, Yu. V. Khropov, A. M. Churakov, N. I. Tarasova, V. A. Serezhenkov, A. F. Vanin, V. A. Tartakovsky, and I. S. Severina, *Biokhimiya*, 2002, **67**, 396 [*Biochemistry (Moscow),* 2002, **67**, 329].
3. A. M. Churakov and V. A. Tartakovsky, *Chem. Rev.*, 2004, **104**, 2601.
4. L. I. Khmel´nitskii, S. S. Novikov, and T. I. Godovikova, *Khimiya furoksanov. Stroenie i sintez* [*Chemistry of Furoxanes. Structures and Synthesis*], 2nd ed., Nauka, Moscow, 1996, 383 pp. (in Russian).
5. 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, **51**, 1841].
6. 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].
7. L. I. Khmel´nitskii, S. S. Novikov, and T. I. Godovikova, *Khimiya furoksanov. Reaktsii i primenenie* [*Chemistry of Furoxanes. Reactions and Application*], Nauka, Moscow, 1996, p. 48 (in Russian).
8. A. M. Churakov, O. Yu. Smirnov, S. L. Ioffe, Yu. A. Strelenko, and V. A. Tartakovsky, *Eur. J. Org. Chem.*, 2002, 2342.
9. K. I. Rezchikova, A. M. Churakov, V. A. Shlyapochnikov, and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 2187 [*Russ. Chem. Bull.*, *Int. Ed.*, 1995, **44**, 2093].

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