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REACTION OF 4,6-DICHLORO-5-NITROBENZOFUROXAN WITH AROMATIC AMINES AND NITROGEN-CONTAINING HETEROCYCLES

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4,6-Dichloro-5-nitrobenzofuroxan reacts with aromatic and heterocyclic amines via the chlorine atom at the position 4 of the aromatic ring to give monosubstitution products. In a similar reaction with piperazine, both amino groups undergo arylation to give a compound containing two benzofuroxan fragments.

Keywords: benzofuroxan, amination, aromatic ring, arylation, monosubstitution.

In recent decades the biological activity of benzofuroxans has been actively studied. Compounds having antibacterial, antifungal, antiparasitic, cytotoxic, and herbicidal activity have been found [1, 2]. It should be noted that if unsubstituted benzofuroxan shows modest biological activity, then the presence of functional groups (nitro, methoxy etc.) in its molecule leads to a sharply increased efficacy of the derivatives obtained [3]. We have previously examined the reaction of 4,6-dichloro-5,7-dinitrobenzofuroxan with aromatic amines, where both chlorine atoms react to give double substitution products [4, 5]. A study of the acaricidal and bactericidal properties of the compounds obtained has revealed the dependence of their activity on the structure of the substituting aromatic amine [6].

4,6-Dichloro-5-nitrobenzofuroxan derivatives (**1**), including compounds with fungicidal properties [3], are undoubtedly of interest in terms of biological activity. We have previously shown that the reaction of 4,6-dichloro-5-nitrobenzofuroxan (**1**) with aliphatic amines (methylamine, dimethylamine, and 2,2-dimethoxyethylmethylamine) is accompanied by the substitution of the chlorine atom at the position 4 of the aromatic ring [7].

In this study, we report the reaction of furoxan **1** with aromatic and heterocyclic amines with the aim of preparing novel types of aminated benzofuroxans and studying their properties. The amines selected were *o*-aminophenol, *o*-phenylenediamine, *o*-toluidine, *m*-nitroaniline, and benzylamine. The ratio of starting reagents and the nature of the solvent were varied. In spite of using an excess of the amine, only the chlorine atom at the position 4 of the benzene ring reacted, and the monosubstituted products **2-5** were obtained.

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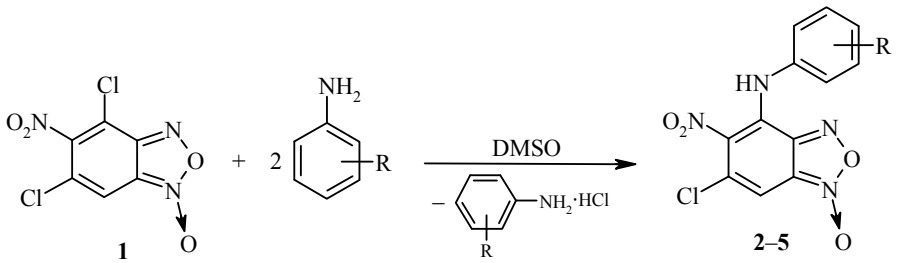
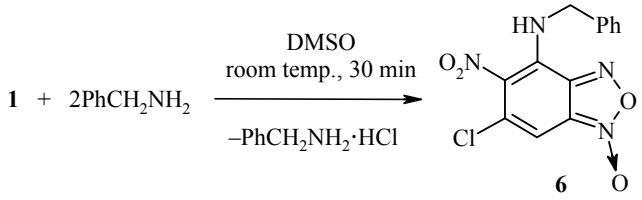
Their structure was demonstrated using IR and ^{1}H NMR spectroscopy, and also by X-ray structural analysis (Figs. 1 and 2). Reaction of furoxan **1** with benzylamine gave compound **6**. The highest yield of the target compounds in the reported reactions was achieved with using DMSO as solvent.



2 R = 2-NH_2, **3** R = 2-Me, **4** R = 2-OH, **5** R = 3-NO_2



The ease of furoxan **1** interaction with aromatic amines depends on the nature of the substituents in the aromatic ring. The methyl-, amino-, and hydroxy derivatives readily form the products **2-4** at room temperature, while interaction of furoxan **1** with *m*-nitroaniline requires prolonged heating. *Ortho*- and *para*-nitroanilines, and also 2,4-dichloro- and 2,5-dichloroanilines do not react with furoxan **1**. In the reaction of furoxan **1** with *o*-phenylenediamine only one amino group undergoes arylation, apparently for steric reasons.

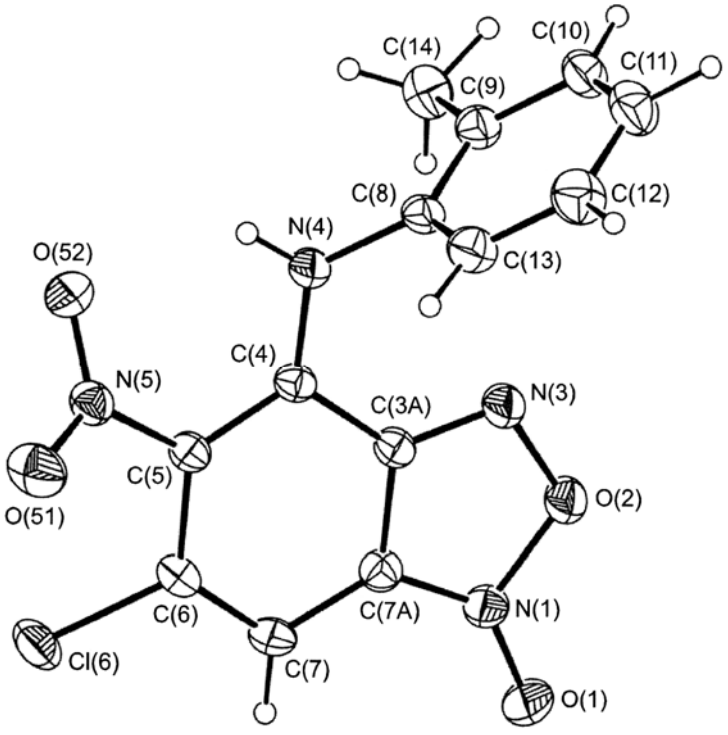


Fig. 1. Molecular structure of compound **3** with atoms represented by thermal vibration ellipsoids of 50% probability.

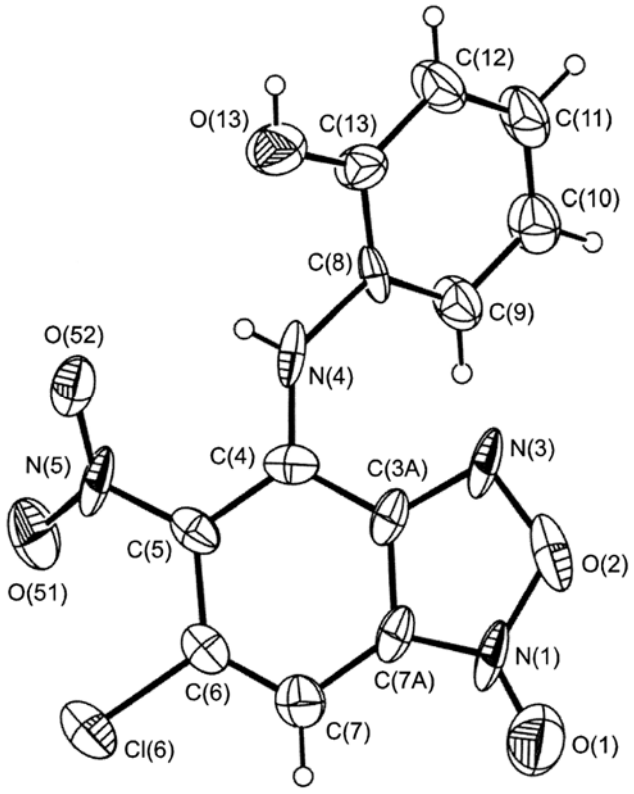
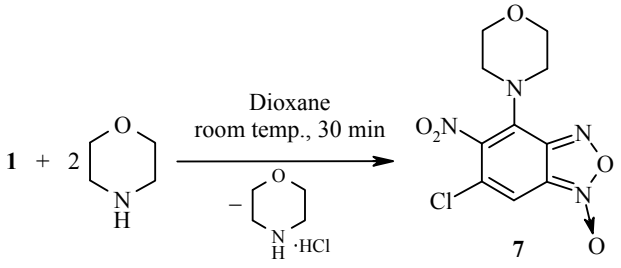
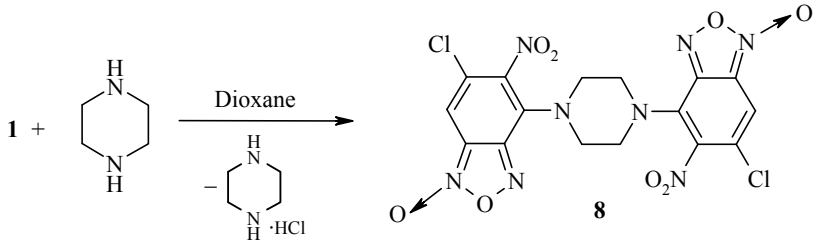


Fig. 2. Molecular structure of compound **4** with atoms represented by thermal vibration ellipsoids of 50% probability.

In the same way as with aromatic amines, morpholine reacts with furoxan **1** by substituting one chlorine atom at the position 4 of the aromatic ring. The structure of compound **7** was established by X-ray structural analysis (Fig. 3).



Unlike with *o*-phenylenediamine, in the reaction of equimolar amounts of furoxan **1** and piperazine both amino groups of the latter take part, leading to the compound **8** with structure confirmed by X-ray structural analysis data (Fig. 4).



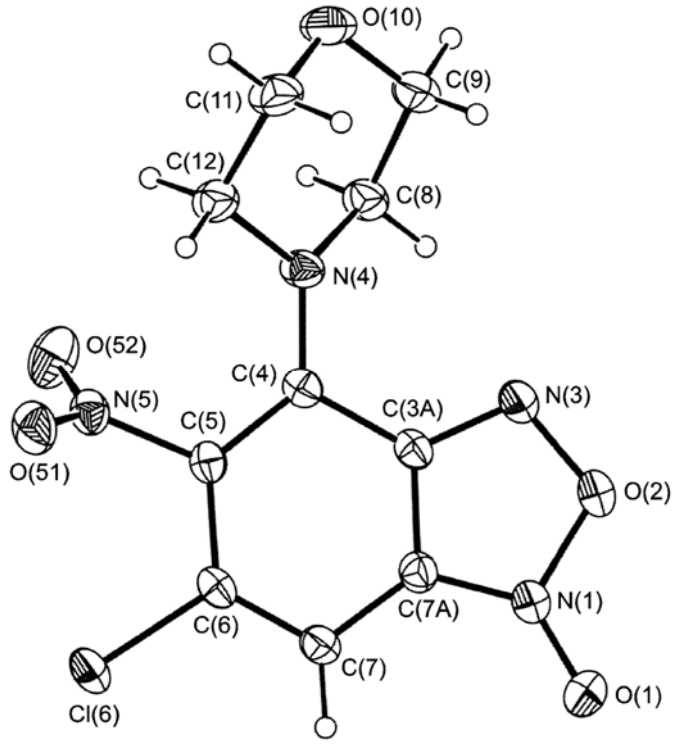


Fig. 3. Molecular structure of compound **7** with atoms represented by thermal vibration ellipsoids of 50% probability.

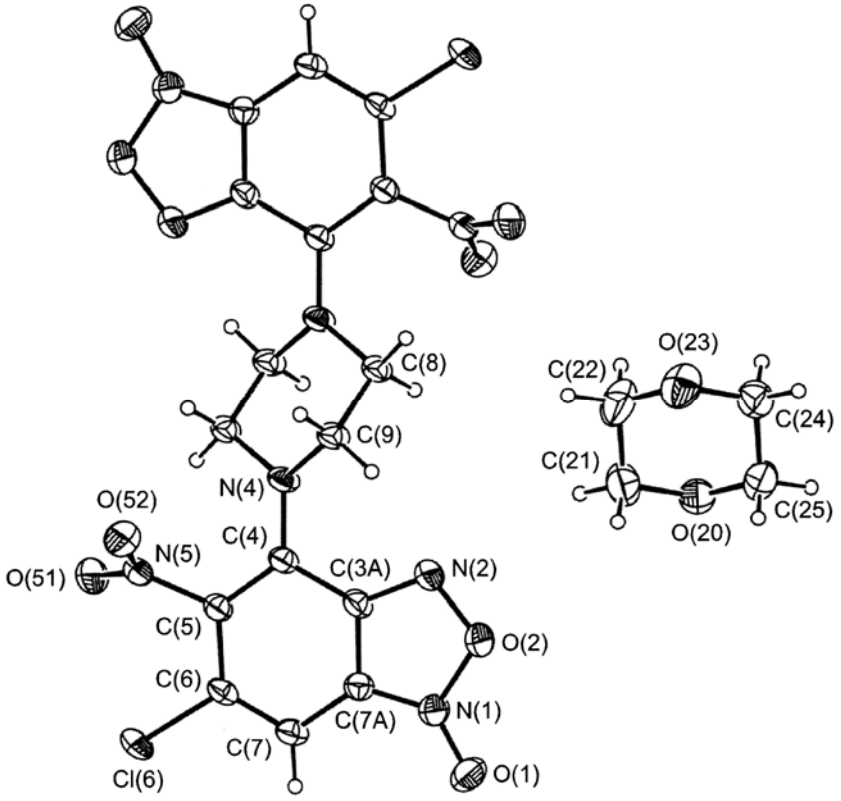


Fig. 4. Molecular structure of the compound **8** with atoms represented by thermal vibration ellipsoids of 50% probability.

TABLE 1. Crystallographic Parameters and Refinement Details for the Structures of Compounds **3**, **4**, **7**, and **8**

Parameter	**3**	**4**	**7**	**8**
Color, habit	Red, prismatic	Red, prismatic	Red, prismatic	Red, prismatic
Empirical formula	$C_{13}H_9ClN_4O_4$	$C_{12}H_7ClN_4O_5$	$C_{10}H_9ClN_4O_5$	$C_{16}H_{10}Cl_2N_8O_8$
M	320.69	322.67	300.66	689.43
Symmetry	Triclinic	Monoclinic	Monoclinic	Triclinic (partial molecular position)
Space group	*P*-1	*C*2/*c*	$P2_1/c$	*P*-1
Unit cell parameters				
a, Å	5.2531(5)	29.815(5)	4.9584(8)	8.5434(8)
b, Å	11.374(1)	4.578(5)	28.360(5)	8.6446(8)
c, Å	12.625(1)	21.469(5)	8.868(2)	11.778(1)
α, deg.	113.293(1)	—	—	73.417(1)
β, deg.	100.156(1)	112.327(5)	103.379(2)	75.234(1)
γ, deg.	95.593(1)	—	—	64.229(1)
V, Å^3	670.2(1)	2711(3)	1213.2(3)	742.08(12)
Z	2	8	4	1
d_{calc}, g/cm^3	1.589	1.581	1.646	1.543
Absorption coefficient, μMo, cm^{-1}	3.11	3.13	3.43	2.96
F(000)	328	1312	616	356
θ interval, deg.	1.98-26.00	2.89-26.00	2.47-27.00	2.67-26.00
R(int)	0.0150	0.2278	0.0198	0.0174
Range of index measurements	$-6 \le h \le 6$, $-14 \le k \le 14$, $-15 \le l \le 15$	$-36 \le h \le 32$, $-5 \le k \le 5$, $-26 \le l \le 22$	$-6 \le h \le 6$, $-36 \le k \le 36$, $-11 \le l \le 10$	$-10 \le h \le 10$, $-10 \le k \le 10$, $-14 \le l \le 14$
Total reflections	6771	6162	9782	9415
Independent reflections	2605	2553	2643	2913
Reflections with $I > 2\sigma(I)$	2116	721	2284	2465
Final p factor values				
R	0.0337	0.1367	0.0346	0.0332
R_w	0.0890	0.2143	0.0874	0.0906
R_{all}	0.0953	0.3405	0.0407	0.0402
$R_{w\,all}$	0.0953	0.2812	0.0919	0.0962
Refinement parameter	1.049	0.986	1.040	1.052
Number of refinement parameters	235	198	217	208

According to X-ray analysis, the asymmetric part of the unit cell in the crystals of compounds **3**, **4**, and **7** contains one independent molecule of the compound, while the molecule of compound **8** occupies a particular position, where the center of symmetry of the crystal coincides with the center of piperazine ring. In addition to a molecule of this compound, the unit cell of crystal **8** contains a solvent molecule of dioxane (Fig. 4). In the molecules of compounds **8** and **7**, the piperazine and morpholine rings assume a "chair" type conformation.

It should be noted that the possibility of a true intermolecular hydrogen bonding is only realized in the molecule of compound **4**, where a classical O–H···O type hydrogen bond leads to the formation of chains along the 0y axis.

The crystals of compounds **3**, **7**, **8** show shortened C–H···O type contacts, which means that the benzofuroxan **3** forms dimers, compound **8** forms associates with two molecules of solvent for each molecule of the title compound, and compound **7** forms chains along the 0z axis.

EXPERIMENTAL

IR spectra were recorded on a Bruker Vector 22 Fourier spectrometer. Crystalline materials were studied in vaseline oil. ^{1}H NMR spectra were recorded on a Bruker Avance-600 instrument (600 MHz) using acetone-d_6 (compounds **2**, **5**) or $CDCl_3$ (compounds **3**, **4**, **6-8**) with the residual solvent signals as internal standards (7.26 ppm for $CDCl_3$ and 2.05 ppm for acetone-d_6). Elemental analysis was carried out on a Carlo-Erba EA 1108 instrument. Melting points for the compounds prepared were determined using a Boetius hot stage apparatus. The starting 4,6-dichloro-5-nitrobenzofuroxan (**1**) was prepared by method [7].

4-(2-Aminophenylamino)-6-chloro-5-nitro-2,1,3-benzoxadiazole 1-Oxide (2). A solution of *o*-phenylenediamine (0.108 g, 1.0 mmol) in DMSO (5 ml) was added dropwise with stirring at room temperature to a solution of the 4,6-dichloro-5-nitrobenzofuroxan (**1**) (0.125 g, 0.5 mmol) in DMSO (5 ml). The reaction mixture was maintained for 30 min, poured into water, and the precipitate formed was filtered off, washed with water, and dried *in vacuo* (40ºC, 0.06 mm Hg) to constant weight. It was recrystallized from hexane. Yield 0.110 g (70%); mp 195-196ºC. IR spectrum, ν, cm^{-1}: 1360 (NO_2 sym.), 1562 (NO_2 asym.), 1625 (furoxan), 3092 (ArH), 3224, 3227 (NH_2), 3417 (NH). ^{1}H NMR spectrum, δ, ppm: 3.57 (2H, br. s, NH_2); 6.60-6.63 (2H, m, H Ar); 6.69-6.71 (2H, m, H Ar); 7.38 (1H, s, H-7); 8.21 (1H, s, NH). Found, %: C 44.91; H 2.45; Cl 11.20; N 21.75. $C_{12}H_8ClN_5O_4$. Calculated, %: C 44.81; H 2.51; Cl 11.02; N 21.77.

6-Chloro-4-(2-methylphenylamino)-5-nitro-2,1,3-benzoxadiazole 1-oxide (3) was prepared similarly to compound **2** from 4,6-dichloro-5-nitrobenzofuroxan (**1**) (0.125 g, 0.5 mmol) and *o*-methylaniline (0.107 g, 1.0 mmol). Yield 0.110 g (70%); mp 118-119ºC. IR spectrum, ν, cm^{-1}: 1359 (NO_2 sym.), 1561 (NO_2 asym.), 1612 (furoxan), 3096 (ArH), 3306 (NH). ^{1}H NMR spectrum, δ, ppm: 2.10 (3H, s, CH_3); 6.71-6.73 (2H, m, H Ar); 7.05 (1H, s, H-7); 7.21-7.24 (2H, m, H Ar); 8.26 (1H, s, NH). Found, %: C 49.01; H 2.78; Cl 11.19; N 17.32. $C_{13}H_9ClN_4O_4$. Calculated, %: C 48.69; H 2.83; Cl 11.06; N 17.47.

6-Chloro-4-(2-hydroxyphenylamino)-5-nitro-2,1,3-benzoxadiazole 1-oxide (4) was prepared similarly to compound **2** from 4,6-dichloro-5-nitrobenzofuroxan (**1**) (0.125 g, 0.5 mmol) and *o*-aminophenol (0.109 g, 1.0 mmol). Yield 0.130 g (79%); mp 140-141ºC. IR spectrum, ν, cm^{-1}: 1362 (NO_2 sym.), 1563 (NO_2 asym.), 1625 (furoxan), 3096 (ArH), 3400 (NH), 3427 (OH). ^{1}H NMR spectrum, δ, ppm: 5.32 (1H, s, OH); 6.89 (1H, s, H-7); 6.93 (3H, m, H Ar); 7.22-7.23 (1H, m, H Ar); 8.43 (1H, s, NH). Found, %: C 44.69; H 1.95; Cl 11.03; N 17.18. $C_{12}H_7ClN_4O_5$. Calculated, %: C 44.67; H 2.19; Cl 10.99; N 17.36.

6-Chloro-5-nitro-4-(3-nitrophenylamino)-2,1,3-benzoxadiazole 1-Oxide (5). A solution of *m*-nitroaniline (0.138 g, 1.0 mmol) in DMSO (5 ml) was added dropwise with stirring at room temperature to a solution of the 4,6-dichloro-5-nitrobenzofuroxan (**1**) (0.125 g, 0.5 mmol) in DMSO (5 ml). The reaction mixture was maintained at 70ºC for 8 h, poured into water, and the precipitate formed was filtered off, washed with water, and dried *in vacuo* (40ºC, 0.06 mm Hg) to constant weight. Yield 0.208 g (73%); mp 159-160ºC. IR spectrum, ν, cm^{-1}: 1331 (NO_2 sym.), 1360 (NO_2 sym.), 1536 (NO_2 asym.), 1564 (NO_2 asym.), 1620 (furoxan), 3087 (ArH), 3312 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.39 (1H, s, H-7); 7.66 (1H, t, *J* = 8.1, H Ar); 7.80 (1H, d, *J* = 7.7, H Ar); 8.08 (1H, d, *J* = 8.1, H Ar); 8.22 (1H, s, H Ar); 9.26 (1H, s, NH). Found, %: C 40.88; H 1.76; Cl 10.13; N 19.87. $C_{12}H_6ClN_5O_6$. Calculated, %: C 40.99; H 1.72; Cl 10.08, N 19.92.

4-Benzylamino-6-chloro-5-nitro-2,1,3-benzoxadiazole 1-oxide (6) was prepared similarly to compound **2** from 4,6-dichloro-5-nitrobenzofuroxan (**1**) (0.125 g, 0.5 mmol) and benzylamine (0.107 g, 1.0 mmol). Yield 0.129 g (82%); mp 149-150°C. IR spectrum, ν, cm^{-1}: 1362 (NO_2 sym.), 1562 (NO_2 asym.), 1622 (furoxan), 3090 (ArH), 3310 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.26 (2H, d, *J* = 8.8, CH_2Ph); 6.71 (1H, s, H-7); 7.34-7.36 (5H, m, H Ph); 8.29 (1H, s, NH). Found, %: C 49.08; H 2.99; Cl 11.24; N 17.25. $C_{13}H_9ClN_4O_4$. Calculated, %: C 48.69; H 2.83; Cl 11.06; N 17.47.

6-Chloro-4-morpholino-5-nitro-2,1,3-benzoxadiazole 1-oxide (7) was prepared similarly to compound **2** from 4,6-dichloro-5-nitrobenzofuroxan (**1**) (0.125 g, 0.5 mmol) and morpholine (0.087 g, 1.0 mmol). Yield 0.140 g (93%); mp 169-170ºC. IR spectrum, ν, cm^{-1}: 1365 (NO_2 sym.), 1565 (NO_2 asym.), 1621

(furoxan), 3086 (ArH). ^{1}H NMR spectrum, δ, ppm: 2.83–2.84 (4H, m, CH_2NCH_2); 3.61-3.62 (4H, m, CH_2OCH_2); 7.01 (1H, s, H-7). Found, %: C 39.69; H 3.22; Cl 11.87; N 18.48. $C_{10}H_9ClN_4O_5$. Calculated, %: C 39.95; H 3.02; Cl 11.79; N 18.63.

***N*,*N*'-Bis[6-chloro-5-nitro-2,1,3-benzoxadiazol-1-oxide-4-yl]piperazine (8)** was prepared similarly to compound **2** from 4,6-dichloro-5-nitrobenzofuroxan (**1**) (0.125 g, 0.5 mmol) and piperazine (0.043 g, 0.5 mmol). Yield 0.090 g (70%); mp 164-165ºC. IR spectrum, ν, cm^{-1}: 1360 (NO_2 sym.), 1563 (NO_2 asym.), 1622 (furoxan), 3099 (ArH). ^{1}H NMR spectrum, δ, ppm: 3.12 (8H, s, $4CH_2$); 6.89 (2H, s, H-7,7'). Found, %: C 37.51; H 2.14; Cl 14.02; N 21.70. $C_{16}H_{10}Cl_2N_8O_8$. Calculated, %: C 37.45; H 1.96; Cl 13.82; N 21.83.

X-ray structural analysis of compounds 3, 4, 7, and 8 was carried out on a Bruker Smart APEX II CCD automatic diffractometer (graphite monochromator; λMoKα = 0.71073 Å, ω-scanning; temperature 293 K). Semiempirical calculation of the absorption was carried out using the SADABS program [8]. The structures were solved by the direct method with the SIR program [9] and refined in the isotropic and then in the anisotropic approximation with the SHELXL97 program [10]. In structures **3** and **7**, the coordinates of the hydrogen atoms were revealed in Fourier difference synthesis and refined isotropically. In structures **4** and **8** the hydrogen atoms were placed in geometrically calculated positions and included in the refinement using the "rider" model. All of the calculations were performed using the WinGX and APEX2 programs [11]. All of the figures and analysis of the intermolecular interactions were carried out with the help of the PLATON program [12]. The atomic coordinates and geometric parameters for the structure of compounds **3**, **4**, **7**, **8** were placed in the Cambridge Crystallographic Data Center with the reference numbers CCDC 822929, 822931, 822930, and 822928, respectively. The crystallographic parameters and structure refinement details for compounds **3**, **4**, **7**, **8** are given in Table 1.

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