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Dedicated to the 100th Anniversary of Corresponding Member of the Russian Academy of Sciences A.A. Petrov

Synthesis, Structure, and Antibacterial Activity of Aminobenzofuroxan and Aminobenzofurazan

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Abstract—The amination of 4,6-dichloro-5,7-dinitrobenzofuroxan and 4,6-dichloro-5,7-dinitrobenzofurazan with dibenzylamine followed the aromatic nucleophilic substitution pattern (S_NAr) and gave products of replacement of both chlorine atoms in the six-membered ring with elimination of hydrogen chloride. Regardless of the reactant ratio, 4,6-dichloro-5,7-dinitrobenzofuroxan was converted into 4,6-bis(dibenzylamino)-5,7-dinitrobenzofuroxan, whereas 4,6-dichloro-5,7-dinitrobenzofurazan under analogous conditions gave rise to unusual bisammonium derivative which lost proton from the amino group on C^4 and benzyl group from the amino group on C^6; as a result, the corresponding diamine with secondary and tertiary nitrogen atoms was obtained. The structure of the isolated compounds was determined by IR and NMR spectroscopy, elemental analysis, and X-ray analysis; their thermal stability was studied by simultaneous thermogravimetry and differential scanning calorimetry.

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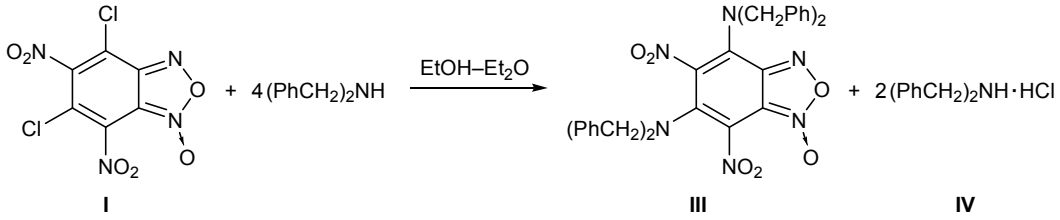
Benzofuroxans and benzofurazans exhibit a broad spectrum of biological activity [1–11] and are nitrogen oxide donors [1–5]. They may be regarded as prodrugs whose biological activity develops through a series of intermediates inside cells [6–11]. In recent years, much effort was made by researchers in various fields to find biologically active compounds among benzofurazan and benzofuroxan derivatives, taking into account their structural similarity to nucleic acid bases such as adenine, guanine, 6-methylaminopurine, 6-dimethylaminopurine, and others. With a view to discover new pharmacologically active compounds with a broad spectrum of biological activity in the series of purine base analogs we examined reactions of dichlorodinitro-substituted benzofuroxan and benzofurazan with dibenzylamine. There are no published data on nucleophilic substitution in the benzofuroxan or benzofurazan ring with dibenzylamine, though we believe that introduction of pharmacophoric benzylamino groups into benzofurazan and benzofuroxan molecules may be promising from the viewpoint of obtaining new pharmaceuticals. We previously reported on reactions of triphenylphosphine with various chloronitrobenzofuroxans and chloronitrobenzofurazans; these reactions involved both chloro and nitro substituents and led to phosphorylation products which showed high and diverse pharmacological activity [12–20].

The present article describes the results of our study on the reactions of 4,6-dichloro-5,7-dinitrobenzofuroxan (**I**) and 4,6-dichloro-5,7-dinitrobenzofurazan (**II**) with dibenzylamine in ethanol–diethyl ether (3 : 1). Furoxan **I** reacted with 4 equiv of dibenzylamine at

Scheme 1.



I III IV

room temperature to give red crystalline compound **III** and dibenzylammonium chloride (**IV**) (Scheme 1).

The IR spectrum of bis(dibenzylamino)benzofuroxan **III** contained absorption bands typical of benzofuroxan ring at 1624 (C=N), 1523 (NO_2), and 980 cm^{-1} (N–O); no NH stretching vibration band was present at about 3300 cm^{-1}. The purity and high thermal stability of diamine **III** (up to 159.7°C) were proved by simultaneous thermogravimetry and differential scanning calorimetry (TGA/DSC; Fig. 1). Melting of a sample of **III** (8.372 mg) under argon was accompanied by decomposition in the temperature range from 174.1 to 188.0°C with strong heat evolution (903.2 J/g). The weight loss at 300°C was 65.25%.

The X-ray diffraction data for compound **III** confirmed replacement of both chlorine atoms in the benzene ring by dibenzylamino groups (Fig. 2). The benzofuroxan fragment in molecule **III** was characterized by essentially distorted geometry; deviations of atoms from the mean-square plane were 0.267(5) (C^4), –0.372(5) (C^5), and 0.238(5) Å (C^7); the five-membered ring $N^1O^2N^3C^{3a}C^{7a}$ together with the adjacent C^4 and C^7 atoms is planar within 0.040(5) Å, and the C^5 and C^6 atoms deviate from that plane toward one side but by different distances, –0.959(5) and –0.662(5) Å, respectively. Thus the benzene ring is distorted to form a flattened unsymmetrical *boat*. The benzene ring taken separately is also nonplanar, the C^4 and C^5 atoms deviate from the mean-square plane by 0.234(5) and –0.214(5) Å, respectively, and the nitrogen atoms of the substituents (nitro and dibenzylamino groups) deviate from that plane by 0.790(4) (N^8), –1.218(5) (N^5), 0.059(4) (N^{23}), and 1.094(5) Å (N^7), i.e., the nitrogen atoms in the nitro group decline to a stronger extent than the amino nitrogen atoms. Despite steric hindrances, all nitrogen atoms in the substituents are trigonal, and their bond planes almost coincide with

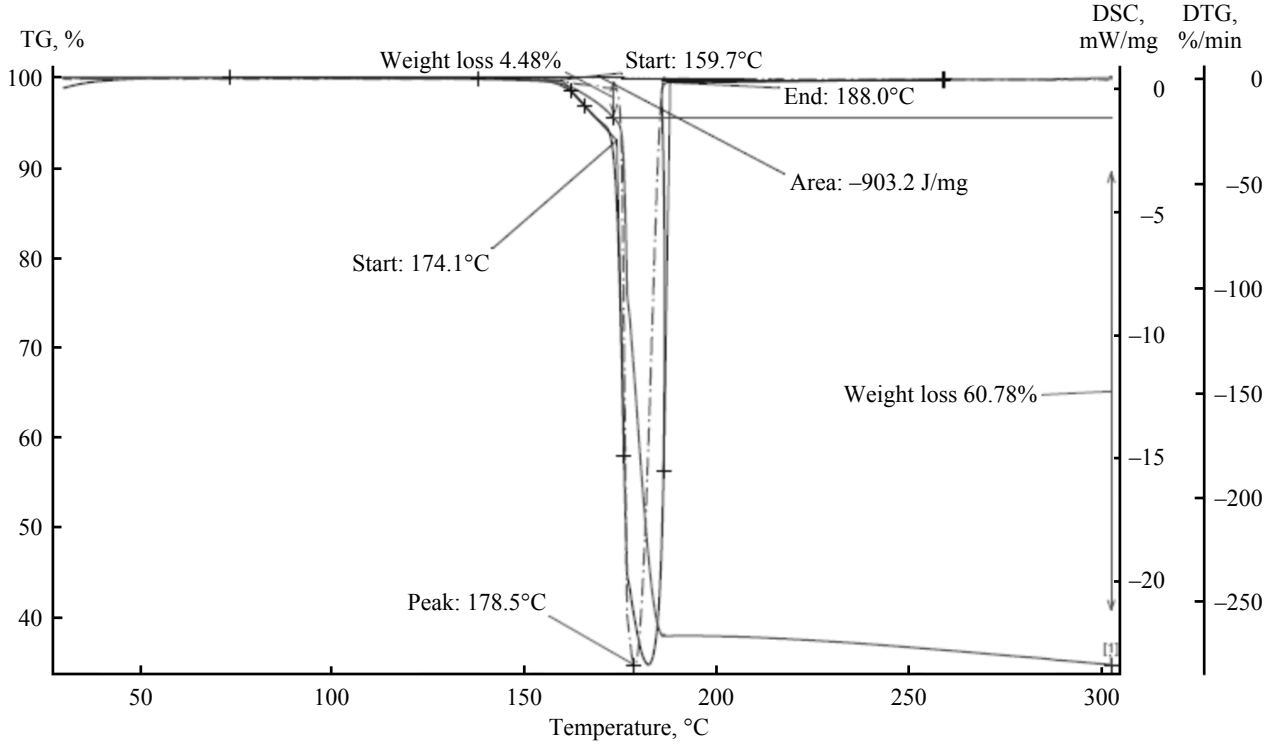


Fig. 1. Simultaneous TG/DSC curves for compound **III**.

the planes formed by the bonds at the corresponding carbon atoms in the benzene ring: the torsion angles are as follows: $C^9N^8C^4C^{3a}$ –0.6(7), $C^{24}N^{23}C^6C^5$ –27.0(6), $C^4C^5N^5O^{51}$ –4.8(7), $C^6C^7N^7O^{72}$ 10.5(7)°. The dibenzylamino group on C^6 is turned through a slightly larger angle since it is located between two nitro groups. Presumably, the large deviation of the nitro group on C^5 is also determined by steric factor, i.e., extrusion by two bulky substituents. However, the C^5–N^5 and C^7–N^7 bond lengths are equal within the experimental error and are 1.424(5) and 1.437(6) Å, respectively. By contrast, the C^4–N^8 and C^6–N^{24} bond lengths are appreciably different [1.312(5) and 1.338(5) Å, respectively], and the longer bond is that with the nitrogen atom whose bond plane is considerably turned with respect to the benzene ring. Probably, conjugation between the substituents and π-system of the benzene ring or multiple bonds dominates over bond twisting, i.e., conjugation with the amino and nitro groups is retained despite distorted planarity of the benzene ring. The bonds in the benzene ring (Table 1) are appreciably longer than standard $C{=}C_{arom}$ bond (1.395 Å). The benzyl fragments are characterized by usual geometric parameters.

The use of 4 equiv of dibenzylamine in the reaction with benzofuroxan **I** is necessary to bind two hydrogen chloride molecules released as a result of replacement of two chlorine atoms. Dibenzylamine hydrochloride (**IV**) can be separated from crystalline compound **III** by washing with water on a Schott filter.

A different pattern was observed in the reaction of dibenzylamine with 4,6-dichloro-5,7-dinitrobenzofurazan (**II**). In this case, 4 equiv of the amine was also necessary to ensure complete conversion of **II**. The formation of bisammonium salt **V** via replacement of both chlorine atoms was followed by debenzylation of one dibenzylammonium group and deprotonation of the other to afford compound **VI** (Scheme 2). These processes require two dibenzylamine molecules.

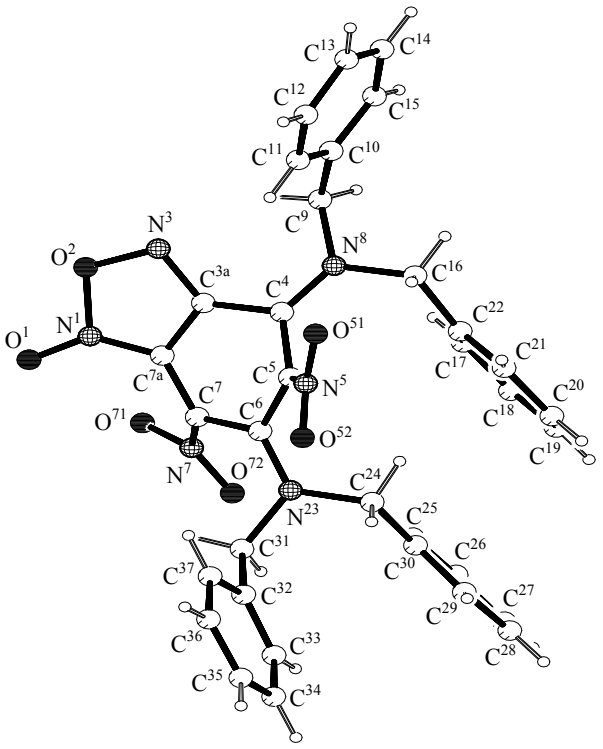


Fig. 2. Structure of the molecule of 4,6-bis(dibenzylamino)-5,7-dinitro-2,1,3-benzoxadiazole 1-oxide (**III**) according to the X-ray diffraction data.

Compound **VI** was isolated as a red crystalline substance. According to the spectral and X-ray diffraction data, molecule **VI** contains one benzyamino group and one dibenzylamino group on the six-membered aromatic ring. In the IR spectrum of **VI** we observed absorption bands typical of nitrobenzofurazans at 1624 (C=N), 1523 (NO_2), and 980 cm^{-1}, as well as a band at 3300 cm^{-1} due to N–H stretching vibration. Simultaneous TG/DSC analysis showed (Fig. 3) that compound **VI** completely decomposes in the temperature range from 144.1 to 182.9°C with a maximum at 175.3°C. The TG/DSC curves for compound **VI** are much more complex than those found for **III** (Fig. 1). The vigorous exothermic effect of sample decompo-

Scheme 2.

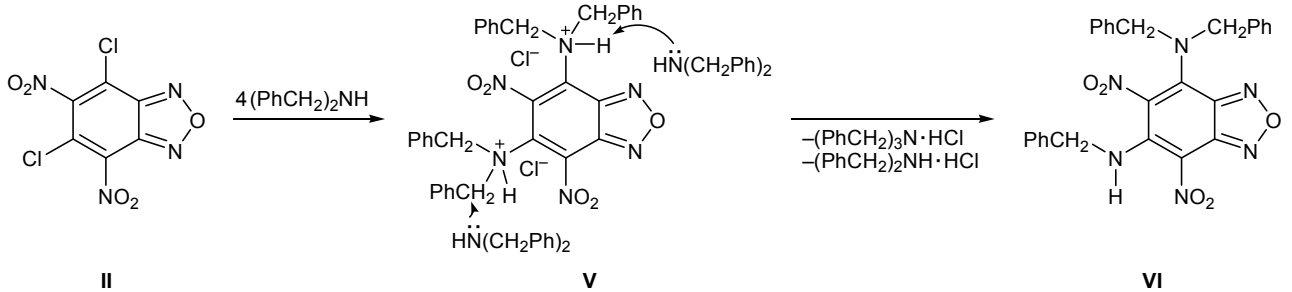


Table 1. Some geometric parameters (bond lengths and bond angles) of molecules **III** and **VI**

Parameter	**III**	**VI**	Parameter	**III**	**VI**
Bond lengths *d*, Å			Bond angles ω, deg		
O^1–N^1	1.202(5)	–	$C^{3a}C^4C^5$	109.8(5)	110.9(3)
N^1–O^2	1.480(5)	1.370(3	$C^4C^5C^6$	120.3(5)	121.8(3)
N^1–C^{7a}	1.309(6)	1.313(4)	$C^4C^5N^5$	115.1(4)	116.7(3)
N^3–O^2	1.391(5)	1.394(3)	$C^6C^5N^5$	121.5(5)	119.2(3)
N^3–C^{3a}	1.371(6)	1.305(3)	$C^5C^6C^7$	116.6(5)	117.6(3)
C^{3a}–C^4	1.449(6)	1.468(4)	$C^5C^6N^{24}$	120.4(5)	121.0(3)
C^{3a}–C^{7a}	1.397(6)	1.422(4)	$C^7C^6N^{24}$	123.0(5)	121.4(3)
C^4–C^5	1.440(6)	1.430(4)	$C^6C^7C^{7a}$	116.4(5)	118.0(3)
C^4–N^8	1.312(5)	1.317(3)	$C^6C^7N^7$	121.3(5)	122.7(3)
C^5–C^6	1.451(5)	1.453(4)	$C^{7a}C^7N^7$	116.8(5)	119.3(3)
C^5–N^5	1.424(5)	1.414(4)	$N^1C^{7a}C^{3a}$	106.9(6)	109.3(3)
C^6–C^7	1.419(6)	1.415(4)	$N^1C^{7a}C^7$	131.1(6)	129.7(3)
C^6–N^{23}	1.338(5)	1.323(4)	$C^{3a}C^{7a}C^7$	121.7(6)	121.0(3)
C^7–C^{7a}	1.412(6)	1.424(4)	$C^4N^8C^9$	123.9(5)	124.3(3)
C^7–N^7	1.437(6)	1.400(4)	$C^4N^8C^{17}$	123.0(5)	124.0(3)
Bond angles ω, deg			$C^9N^8C^{17}$	113.1(4)	111.7(3)
$N^1O^2N^3$	108.9(4)	111.8(2)	$C^5N^5O^{51}$	118.3(5)	119.3(3)
$O^1N^1O^2$	115.6(6)	–	$C^5N^5O^{52}$	118.3(5)	119.5(3)
$O^1N^1C^{7a}$	137.0(7)	–	$O^{51}N^5O^{52}$	123.1(5)	120.8(3)
$O^2N^1C^{7a}$	107.3(5)	104.3(3)	$C^6N^{24}C^{25}$	123.3(4)	128.4(3)
$O^2N^3C^{3a}$	102.7(5)	105.2(3)	$C^6N^{24}C^{32(H)}$	121.3(4)	113(2)
$N^3C^{3a}C^4$	124.8(6)	129.3(3)	$C^{25}N^{24}C^{32(H)}$	115.3(4)	118(2)
$N^3C^{3a}C^{7a}$	114.0(6)	109.4(3)	$C^7N^7O^{71}$	115.7(5)	120.7(3)
$C^{7a}C^{3a}C^4$	120.0(6)	121.3(3)	$C^7N^7O^{72}$	124.1(5)	118.3(3)
$C^{3a}C^4N^8$	123.1(5)	123.5(3)	$O^{71}N^7O^{72}$	120.1(5)	121.0(3)
$C^5C^4N^8$	127.0(5)	125.6(3)			

sition (6.9 mg) was preceded by a weak endothermic effect with its maximum at 151.7°C. The decomposition process is likely to include evolution of small amounts of gaseous products (N_2, O_2, H_2O, NO, CO_2). The overall weight loss at 300°C was 43.76%. In addition, two weak exothermic effects were observed at 209 and 290.1°C; presumably, they reflect complex thermal decomposition process involving profound fragmentation of molecule **VI**.

The structure of compound **VI** was confirmed by analytical and spectral data, including X-ray analysis (Fig. 4). The structure of the benzofurazan fragment in molecule **VI** in crystal is similar to the structure of the benzofuroxan fragment in **III**. The benzene ring in **VI** is distorted to a lesser extent as compared to **III** due to weaker steric effect of less bulky substituent on C^6. The five-membered ring $N^1O^2N^3C^{3a}C^{7a}$ together with the adjacent C^4 and C^7 atoms is planar within 0.053(3) Å, while the C^5 and C^6 atoms deviate from that plane by 0.587(3) and 0.310(3) Å, respectively. The benzene ring in **VI** is more planar than in **III**; the C^4 and C^5 atoms deviate from the mean-square plane by –0.173(3) and 0.187(3) Å, respectively, and the nitrogen atoms in the substituents deviate from that plane by 1.100(3) (N^5), –0.345(3) (N^7), –0.655(3) (N^8), and –0.265(3) Å (N^{23}), i.e., to a considerably lesser extent than in molecule **III**. However, as in **III**, the deviations of the nitro groups are larger than those of the amino groups. All nitrogen atoms in the substituents have trigonal configuration, and their bond planes almost coincide with the bond planes of the corresponding carbon atoms in the benzene ring: the

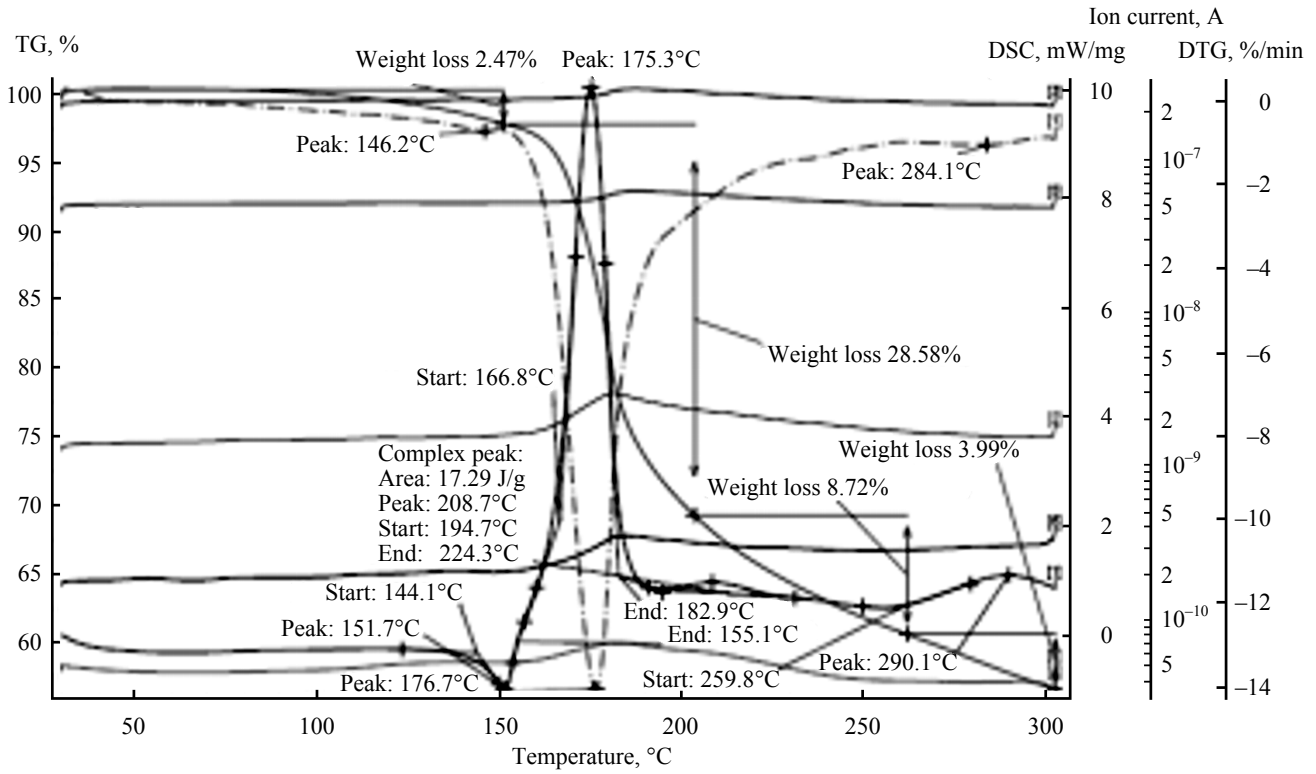


Fig. 3. Simultaneous TG/DSC curves for compound **VI**.

torsion angles are $C^9N^8C^4C^{3a}$ –13.7(5), $C^{24}N^{24}C^6C^5$ 11.8(6), $C^4C^5N^5O^{51}$ 10.9(4), and $C^6C^7N^7O^{71}$ –0.3(5)°. The principal geometric parameters of molecules **III** and **VI** are collected in Table 1. Unlike compound **III**, molecules **VI** in crystal are stabilized by the intramolecular hydrogen bond N^{23}–$H^{23}\cdots O^{71}$ [N^{23}–H^{23} 0.92(4), $H^{23}\cdots O^{71}$ 1.84(4), $N^{23}\cdots O^{71}$ 2.579(4) Å; $\angle N^{23}H^{23}O^{71}$ 137(3)°].

The observed difference in the reactivities of substituted benzofuroxans and benzofurazans **I** and **II** may be related to higher electrophilicity of the former due to the presence of a strong electron-withdrawing *N*-oxide group. This favors increased rate of the amination reaction leading to the disubstituted product. The amination of less electrophilic benzofurazan **II** is accompanied by subsequent debenzylation and deprotonation.

Newly synthesized bisamino benzofuroxan **III** and benzofurazan **VI** showed pronounced antibacterial and antifungal activity (Table 2) in tests on collection strains of pathogenic and opportunistic human and animal microorganisms (provided by the Microbiology Department of the Kazan State Medical Academy): *Staphylococcus aureus* (ATCC 29213), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Proteus mirabilis* (ATCC 12453), and *Candida Albicans* (ATCC 885-653). Compounds **III** and **VI** were dissolved in DMSO immediately before use. Bacterial culture was applied on Müller–Hinton agar (MHA) in a Petri dish; after 5 min, a drop of a solution of a compound to be tested was applied using an inoculating loop. A drop of DMSO as control was also applied onto MHA in each dish. The cultures were incubated for 24 h at 35°C. The results are given in Table 2.

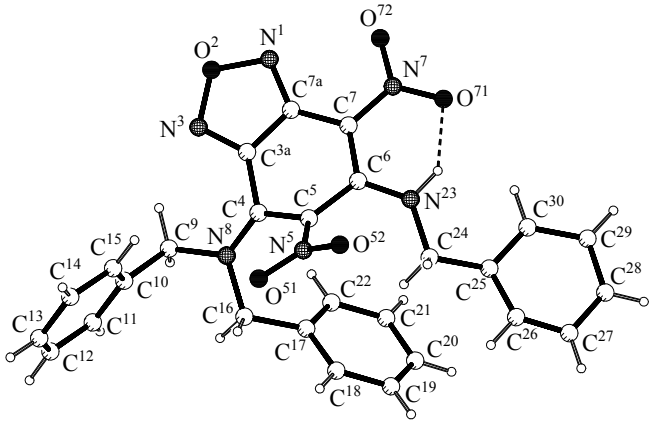


Fig. 4. Structure of the molecule of 6-benzylamino-4-dibenzylamino-5,7-dinitro-2,1,3-benzoxadiazole (**VI**) according to the X-ray diffraction data. The most populated position of the disordered benzene ring C^{25}–C^{30} is shown.

Table 2. Antimicrobial activity (growth inhibition zone, mm) of compounds **III** and **VI** and reference antimicrobial agents (c = 50 μg/0.1 ml)

Compound	*Staphylococcus aureus*	*Escherichia soli*	*Pseudomonas aeruginosa*	*Proteus mirabilis*	*Candida albicans*
III	25±0.2	20±0.1	11±0.15	11±0.4	24±0.1
VI	20±0.3	22±0.3	13.5±0.3	13±0.15	23±0.1
Chlorhexidine	16±0.5	15±0.2	13±0.5	14±0.3	16.5±0.2
Penicillin	23±0.35	16±0.15	8±0.1	10±0.2	–
Griseofulvin	0	0	0	0	19±0.2

EXPERIMENTAL

The IR spectra (400–3700 cm^{-1}) were recorded on a Specord M-80 spectrometer from samples dispersed in mineral oil and placed between KBr plates. The purity and thermal stability of compounds **III** and **VI** were determined by simultaneous TG/DSC analysis on a NETZSCH STA 449C instrument (temperature range 20–400°C, heating rate 10 deg/min, argon atmosphere).

After mixing of compounds **I** and **II** with dibenzylamine at different ratios in ethanol–diethyl ether (1:3) at room temperature under vigorous stirring, the mixture rapidly turned colored. The mixture was kept for two weeks to complete the reaction, the products were purified, and special operations were carried out to obtain single crystals. The solvents were purified according to standard procedures [21]. All initial reactants were distilled just before use, and their purity was checked by comparing their physical constants with published data.

4,6-Bis(dibenzylamino)-5,7-dinitro-2,1,3-benzoxadiazole 1-oxide (III). A solution of 0.5 g (1.7 mmol) of 4,6-dichloro-5,7-dinitrobenzofuroxan in 10 ml of ethanol–diethyl ether (1:3) was added dropwise under stirring to a solution of 1.34 g (6.8 mmol) of dibenzylamine in 10 ml of the same solvent. The originally colorless mixture turned bright red, and dark red fine crystals separated over a period of 24 h. The crystals were filtered off on a Schott filter and washed with ethanol and diethyl ether to remove unreacted initial compounds. Yield 0.83 g (67%), mp 178.5°C (decomp.). IR spectrum, ν, cm^{-1}: 1624 (C=N), 1523 (NO_2), 1492 (C–N), 980 (N–O). Found, %: C 65.92; H 4.28; N 13.55. $C_{34}H_{28}N_6O_6$. Calculated, %: C 66.21; H 4.52; N 13.64.

6-Benzylamino-4-dibenzylamino-5,7-dinitro-2,1,3-benzoxadiazole (VI). A solution of 0.2 g (0.75 mmol) of 4,6-dichloro-5,7-dinitrobenzofurazan in 5 ml of ethanol–diethyl ether (1:3) was added dropwise under stirring to a solution of 0.56 g (3 mmol) of dibenzylamine in 5 ml of the same solvent. The originally yellow mixture turned red, and bright red fine crystals separated over a period of 24 h. After 4 months, a druse of single crystals suitable for X-ray analysis was obtained. The product was filtered off on a Schott filter and washed with ethanol and diethyl ether to remove unreacted initial compounds. Yield 0.27 g (65%), mp 153.4°C (decomp.). IR spectrum, ν, cm^{-1}: 3300 (N–H), 1620 (C=N), 1523 (NO_2), 1492 (C–N), 980 (N–O). Found, %: C 63.56; H 3.45; N 16.14. $C_{27}H_{22}N_6O_5$. Calculated, %: C 63.91; H 3.75; N 16.57.

X-Ray analysis of single crystals of **III** and **VI** was carried out on a Bruker SMART Apex II diffractometer (graphite monochromator, λMoK_α 0.71073 Å). No correction for absorption was applied because of its insignificance. The structures were solved by the direct method and were refined first in isotropic and then in anisotropic approximation using SHELX software [22]. Hydrogen atoms were placed into calculated positions. All calculations were performed with the aid of WinGX [23] and APEX2 [24], and the molecular structures were plotted using PLATON [25]. The X-ray diffraction data for compounds **III** and **VI** were deposited to the Cambridge Crystallographic Data centre (entry nos. CCDC 925345 and 925346, respectively).

Compound **III**. Triclinic crystals, $C_{34}H_{28}N_6O_6$; unit cell parameters (20°C): a = 9.548(5), b = 12.465(7), c = 13.608(7) Å; α = 79.515(7), β = 71.609(6), γ = 79.489(7)°; V = 1497.5(1) $Å^3$; Z = 2; d_{calc} = 1.367 g× cm^{-3}; space group P-1; μMo = 0.93 cm^{-1}. Intensities of 5777 independent reflections were measured, 1628 of which were characterized by $I \geq 2\sigma$. Final divergence factors R = 0.0753, R_w = 0.0999.

Compound **VI**. Triclinic crystals, $C_{27}H_{22}N_6O_5$; unit cell parameters (20°C): a = 7.591(1), b = 13.463(2), c = 13.795(4) Å; α = 114.525(3), β = 99.512(3), γ =

100.451(2)°; V = 1214.9(4) Å^3; Z = 2; d_{calc} = 1.396 g× cm^{-3}; space group P-1; μMo = 0.99 cm^{-1}. Intensities of 4694 independent reflections were measured; 2114 reflections with $I \geq 2\sigma$. Final divergence factors R = 0.0622, R_w = 0.1253. The NH hydrogen atom was localized by the Fourier difference series, and its position was refined in isotropic approximation. The phenyl group in the benzylamino substituent is disordered by two positions with populations of 0.52 and 0.48 due to rotation about the C^{24}–C^{25} bond.

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