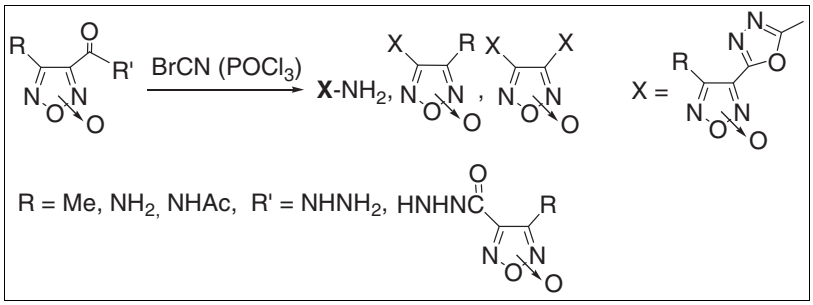
The First Synthesis of Furoxan and 1,3,4-Oxadiazole Ring Ensembles

Aleksey O. Finogenov,[a] Alexander S. Kulikov,[a] Margarita A. Epishina,[a] Igor V. Ovchinnikov,[a] Yu. V. Nelyubina,[b] and Nina N. Makhova[a]*

[a]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation
[b]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation
*E-mail: mnn@ioc.ac.ru

Received June 6, 2011
DOI 10.1002/jhet.1048
View this article online at wileyonlinelibrary.com.



Previously unknown furoxan and 1,3,4-oxadiazole ring ensembles incorporating two, three, and five furoxan and 1,3,4-oxadiazole rings in different combinations were for the first time synthesized from accessible azides and hydrazides of furoxancarboxylic acids. An interdependence of furoxan and 1,3,4-oxadiazole rings on their geometric parameters was revealed by the X-ray diffraction method.

J. Heterocyclic Chem., **50**, 135 (2013).

INTRODUCTION

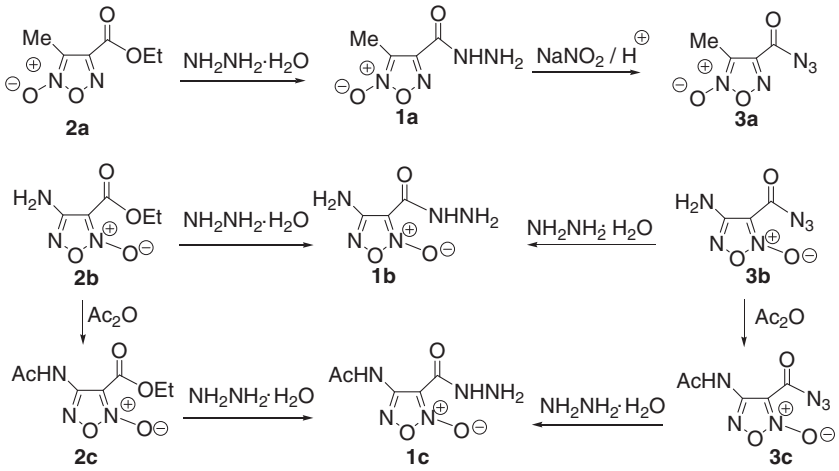
A wide spectrum of biological activity was reported for compounds incorporating oxadiazoles rings. For example, antibacterial, antigelmintic, and fungicidal activities were described for a number of 1,2,5-oxadiazole 2-oxides (furoxans). Some of their phenyl derivatives appeared to have central muscle relaxant and anticonvulsant properties and nitrobenzofuroxans to inhibit nucleic acids and protein biosynthesis [1–3]. Vasodilating and antiaggregatory activity was also reported for the furoxan analog of Nefedipine [4]. Some furoxan derivatives are potential nitric oxide donors [5–7]; various nitrofuroxans can act as propellants and explosives [8]. 1,3,4-Oxadiazole derivatives also display different kinds of biological activity: antibacterial, insecticidal, antifungal, analgesic, anti-inflammatory, anti-HIV, anticonvulsant, *etc*. [9–14]. In addition, 1,3,4-oxadiazole derivatives with an extended conjugated system possess fluorescent properties and can be used as laser dyes, optical brighteners, and scintillators [15,16]. Nitro derivatives of 1,3,4-oxadiazole are also of interest as propellants and explosives. Therefore, a synthesis of previously unknown compounds incorporating furoxan and 1,3,4-oxadiazole rings in one molecule can lead to new biologically active compounds and to new high energetic materials. In this work, a synthesis of ensembles containing two, three, and five furoxan and 1,3,4-oxadiazole rings in different combinations has been presented.

RESULTS AND DISCUSSION

One of the most known approaches to 2,5-disubstituted 1,3,4-oxadiazoles is dehydration of diacyl hydrazines [17,18], and a synthesis of 2-amino-1,3,4-oxadiazoles is based on an interaction of monohydrazide of carboxylic acids with cyanogen bromide [19,20]. The authors of this article have been carrying out investigations in the area of furoxans for many years [8,21a,b]. So, available furoxancarboxylic acids monohydrazides and 1,2-bis (furoxanoyl)hydrazines were selected as basic precursors to synthesize ensembles containing furoxan and 1,3,4-oxadiazole rings in one molecule in different combinations. Hydrazides of isomeric furoxancarboxylic acids **1a–c** of dimeric structure precursors were prepared from corresponding furoxancarboxylic acid esters **2a–c** and hydrazine hydrate [22,23]. Hydrazides **1b**,**c** were also prepared by nucleophilic substitution of the azide group in furoxancarboxylic acid azides **3b**,**c** by the hydrazine group [24]. Initial ester **2c** and azide **3c** were synthesized by acylation of amino groups in ethyl 4-aminofuroxan-3-carboxylate **2b** and furoxancarboxylic acids azide **3b**, accordingly, with acetic anhydride (Scheme 1).

To prepare the simplest ensembles containing two different oxadiazoles in one-molecule hydrazides of isomeric furoxancarboxylic acids **1a–c** were introduced into the heterocyclization reaction with cyanogen bromide in the water–alcohol medium in the presence of $KHCO_3$. It was

Scheme 1



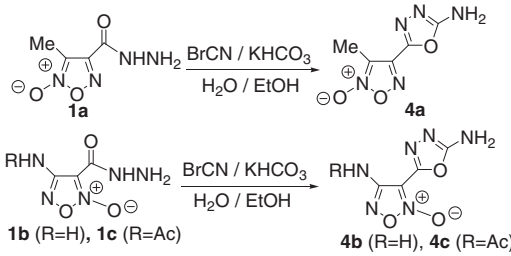
found that all the studied hydrazides had smoothly transformed to 3(4)-R-4(3)-(5-amino-1,3,4-oxadiazol-2-yl)furoxans **4a–c** in high yields (73–84%) (Scheme 2).

To achieve ensembles containing two furoxan and one 1,3,4-oxadiazole rings, it was necessary to synthesize initial 1,2-bis(furoxanoyl)hydrazines **5a–d**. For their preparation acylation of hydrazides **1a–c** with furoxancarboxylic acid azides **3a–c** was performed. This reaction was carried out in mild conditions by stirring of equimolecular amounts of corresponding hydrazides **1a–c** and azides **3a–c** at 20°C in DMSO to result in target 1,2-bis(furoxanoyl)hydrazines **5a–d** in high yields (42–92%). Bis(furoxanoyl)hydrazine **5d** was prepared by two pathways—by an interaction of hydrazide **1a** with azide **3b** and by a reaction of hydrazide **1b** with azide **3a** (Scheme 3).

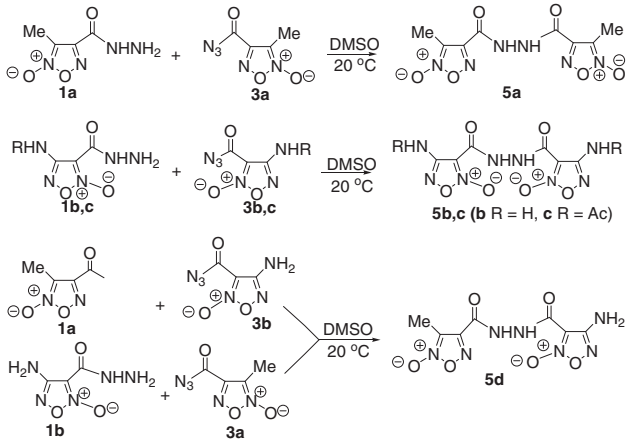
Dehydration of 2,5-bis(furoxanoyl)hydrazines **5a–d** was studied to prepare 2,5-bis(furoxanoyl)-1,3,4-oxadiazoles **6**. For this aim, different dehydrating reagents [19,20] were used: concentrated H_2SO_4, $SOCl_2$, $POCl_3$, and 2-chloro-1,3-dimethylimidazolium chloride [25]. The investigations started with 1,2-bis(3-methylfuroxano-4-yl)hydrazine **5a**. The most suitable conditions for its dehydration proved to be refluxing in $POCl_3$. 2,5-Bis((3-methylfuroxan-4-yl)-1,3,4-oxadiazole **6a** was prepared in 62% yield. The same conditions were used for dehydration of the rest of 1,2-bis (furoxanoyl)hydrazines **5b–d**. However a presence of NH_2 or NHAc groups in these hydrazines posed a significant difficulty for the dehydration course. We managed to introduce only compound **5d** into this reaction, yet the yield of tricyclic product **6d** did not exceed 11% (Scheme 4). Hydrazines **5b**,**c** were decomposed in the reaction conditions. This result is in line with the literature data on the impossibility to dehydrate diaroylhydrazines containing amino or acylamino groups bound to aromatic substituents [26].

3-Methylfuroxan-4-carboxylic acid hydrazide **1a** containing neither NH_2 nor NHAc groups was selected as an initial compound for the preparation of the ensemble with five

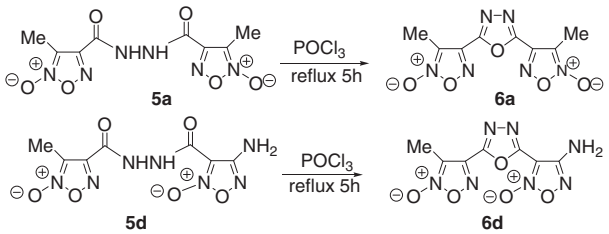
Scheme 2



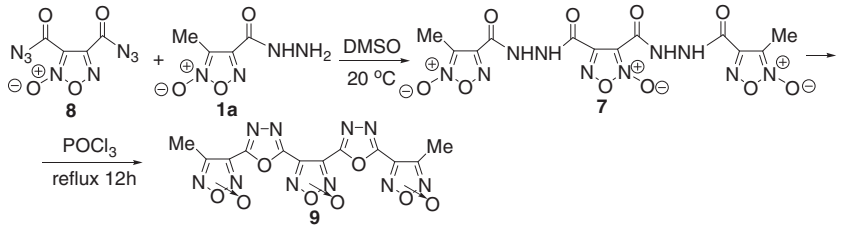
Scheme 3



Scheme 4



Scheme 5



heterocycles in one molecule—three furoxan and two oxadiazole ones. The synthesis of the corresponding precursor, *i.e.*, dihydrazide of furoxan-3,4-dicarboxylic acid acylated at the terminal amino groups by 3-methylfuroxano-4-yl fragments **7**, was based on a reaction of hydrazide **1a** with 0.5 mol of furoxan-3,4-dicarboxylic acid diazide **8** [24] in CCl_4. Refluxing of compound **7** in a $POCl_3$ excess for 12 h resulted in 3,4-bis[2-(3-methylfuroxan-4-yl)-1,3,4-oxadiazol-5-yl)furoxan **9** (Scheme 5). Two pairs of singlets of methyl groups were recorded in the ^{1}H-NMR spectra of this compound—two upfield and two downfield signals. According to literature data [27a], the first pair of signals (2.54 and 2.55 ppm) may belong to C(3) methyl groups and the second one (2.74 and 2.75 ppm) to C(4) methyl groups of the furoxan ring. Evidently, compound **9** is a mixture of isomers, in which two end furoxan rings contain 3- or 4-Me groups. Apparently, heating of compound **7** and final compound **9** in the cyclization conditions led to furoxan rings isomerization [27a]. Considerable number of signals from carbon atoms in the ^{13}C-NMR spectrum of compound **9** and its very low melting point (60–65°C) also evidence to the presence of a mixture of isomers, possibly including isomers of the central furoxan ring. An elemental analysis and especially the mass spectra of compound **9** ascertained its structure. The mass spectra contained a molecule ion and a series of fragment ions constructed as a molecule ion losing one by one six NO fragments (two NO groups from each furoxan ring). Such fragmentation (elimination of two NO groups) under electron impact is typical for furoxan ring mass spectra [27b].

All synthesized compounds were analyzed by the elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry; the structure of compound **4b** crystallized as a molecular complex with DMF (**4b·DMF**) was also supported by X-ray diffraction (XRD) (see Fig. 1). According to the XRD data, the molecule of **4b** is planar within 0.02 Å (the atom with a largest deviation—by 0.07 Å is O(1)), which is indicative of a charge delocalization across the system. As a result, the geometric parameters of 1,3,4-oxadiazole and 1,2,5-oxadiazole 2-oxide (furoxan) moieties markedly altered: in both cases, slight equalization of the bond lengths within the heterocycle is observed. In particular, N C bonds are elongated, O C bonds in one and O N bonds in the other heterocycle equalized and C C and N N ones remain nearly the same as compared to those for the compounds with the methyl group instead of furoxan (refcode WIKQOX in CSD) [28] or 1,3,4-oxadiazole (refcode GAVKIX) [29] fragments, respectively. In turn, the N(1) O(1) bond of the furoxan moiety in **4b** becomes slightly shorter (1.237(2) vs. 1.248 Å in GAVKIX); a similar variation is observed for C(4) N(6) and C(2) N(5) bonds. The latter shortening can be in part a result of the intramolecular N(5) H**…**O(3) bond (N**…**O 3.001(2) Å, NHO 121(1)°); stabilization of the planar conformation of **4b** can be H bond-assisted as well. Both NH_2 groups of **4b** are also involved in the H-bonding with the DMF solvate molecule (N**…**O 2.887 (3)–2.969(3) Å, NHO 162(1)–171(1)°). The resulting infinite layers are additionally stabilized by several N H**…**N (N**…**N 2.992(3)–3.114(2) Å, NHO 144(1)–168(1)°) and N H**…**O (N**…**O 2.946(2) Å, NHO 115(1)°) hydrogen bonds between the product molecules. The formation of the 3D framework from these supramolecular associates is achieved by numerous weak interactions of C H**…**O, C H**…**N, and π**…**π types.

As a result of the researches done using available initial compounds, methods for the preparation of previously unknown polyheterocyclic ensembles incorporating two, three, and five furoxan and 1,3,4-oxadiazole rings in different combinations have been developed. It is important to note that initial hydrazides and azides of furoxancarboxylic acids are interchangeable compounds—hydrazides give azides by

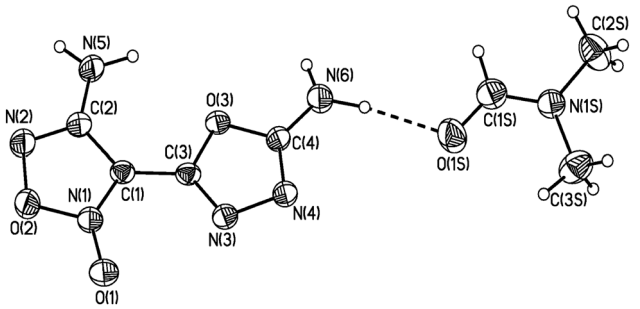


Figure 1. General view of the compound **4b·DMF** in representation of atoms *via* thermal ellispoids at 30% probability level. Selected bond lengths (Å) and angles (°) are: N(1) O(1) 1.237(2), N(1) O(2) 1.406(2), O(2) N(2) 1.402(2), N(2) C(2) 1.314(3), C(1) C(2) 1.429(3), N(1) C(1) 1.319(2), C(1) C(3) 1.430(3), C(3) O(3) 1.364(2), O(3) C(4) 1.368(2), C (4) N(4) 1.303(2), N(3) N(4) 1.410(2), N(3) C(3) 1.283(2); N(1) C(1) C (2) 106.42(18), O(3) C(3) N(3) 113.19(17), C(2) C(1) C(3) 132.55(17).

nitrozation, and azides transform to hydrazides by interacting with hydrazine hydrate in high yields. The interdependence of furoxan and 1,3,4-oxadiazole rings on their geometric parameters was revealed by the XRD method for model dimeric molecule **4b**. The synthesized polyheterocyclic systems are of interest as potential biologically active compounds.

EXPERIMENTAL

Elemental analysis was performed by the CHN Analyzer Perkin-Elmer 2400. The IR spectra (v, cm^{-1}) were measured using a SPECORD-M82 spectrometer. Mass spectra were measured using a Finnigan MAT INCOS-50 instrument. The NMR spectra of all compounds were recorded using a Bruker AM-300 spectrometer at 300 MHz for ^1H and 75.47 MHz for ^{13}C Spectra in $CDCl_3$. The chemical shifts of the signals of $CDCl_3$ residual proton (7.27 ppm) and carbon (77.0 ppm) were used as the internal standard. The spectra were measured at 30° C. Analytical thin-layer chromatography was conducted on silica gel plates (Silufol UV-254). XRD study was carried out on Bruker SMART 1000 CCD diffractometer.

General procedure for the synthesis of ethyl 4-acetylaminofuroxan-3-carboxylate and 4-acetylaminofuroxan-3-carboxylic acid azide (2c and 3c). Three drops of concentrated H_2SO_4 was added to a mixture of ethyl 4-aminofuroxan-3-carboxylate **2b** (1.73 g, 10 mmol) prepared by the procedure [24] or of 4-aminofuroxan-3-carboxylic acid azide **3a** (1.7 g, 10 mmol) prepared by the procedure [30] in 5 mL of acetic anhydride at stirring. The reaction mixture immediately became homogeneous, and in 3 min, a white precipitate was formed. The reaction mixture was stirred for 1 h at room temperature, placed into 25 g of ice, stirred again for 1 h, and the precipitate was filtered, washed with cold water, and dried in air.

2c. Yield 94%, mp 121°C; R_f 0.51 (eluent-$CHCl_3$:$MeCO_2Et$ = 1:1). IR (KBr): 676, 744, 772, 855, 975, 1027, 1115, 1156, 1218, 1265, 1344, 1374, 1447, 1493, 1563, 1618, 1682, 1737, 2992, 3102, 3214 cm^{-1}; ^1H-NMR, δ, ppm: 1.58 (t, 3H, CH_3CH_2); 2.08 (s, 3H, $COCH_3$); 4.55 (q, 2H, CH_2); 11.10 (s, 1H, NH); ^{13}C-NMR, δ, ppm: 15.24 (CH_3CH_2); 22.73 ($COCH_3$); 61.26 (CH_2); 104.80 (C-3 furoxan); 152.68 (C-4 furoxan); 157.34 (COO); 168.18 (CH_3CO); ms (70 eV) *m/z* (I%): 215 (M^+, 11), 174 (39), 173 (M^+ -MeCO + 1, 59), 170 (M^+-OEt, 25), 157 (M^+-AcNH, 72), 143 (34), 132 (76), 115 (EtO_2C-CNO, 67), 113 (48), 101 (100), 97 (100). Anal. Calcd. for $C_7H_9N_3O_5$ (215.164): C, 39.07; H, 4.22; N, 19.53. Found: C, 39.33; H, 4.13; N, 19.29.

3c. Yield 90%, mp 101–102°C; R_f 0.47 (eluent-$CHCl_3$:$MeCO_2Et$ = 1:1). IR (KBr): 640, 672, 680, 728, 752, 844, 872, 976, 1008, 1040, 1112, 1160, 1204, 1218, 1312, 1368, 1440, 1464, 1472, 1532, 1548, 1612, 1648, 1672, 1732, 2180, 2224, 3356 cm^{-1}; ^1H-NMR, δ, ppm: 2.15 (s, 3H, CH_3); 10.85 (s, 1H, NH); ^{13}C-NMR, δ, ppm: 22.98 (CH_3); 106.92 (C-3 furoxan); 149.34 (C-4 furoxan); 161.49 (CON_3); 169.82 (CH_3CO); ms (70 eV) *m/z* (I%): 212 (M^+, 5), 170 (M^+-N_3, 20), 153 (2), 140 (10), 125 (12), 109 (45), 78 (100). Anal. Calcd. for $C_5H_4N_6O_4$ (212.123): C, 28.31; H, 1.90; N, 39.62. Found: C, 28.45; H, 1.82; N, 39.48.

General procedure for the synthesis of furoxancarboxylic acid hydrazides (1a–c) from isomeric ethyl furoxancarboxylate (2a–c). Hydrazine hydrate (0.55 mL, 11 mmol) was added by dropwise to suspension of ethyl furoxancarboxylates (**2a–c**) (10 mmol) in 20 mL of EtOH at 0°C and stirring. Then reaction mixture was stirred for 1 h at 0°C. The precipitate was filtered, washed with cold water, and dried in air. Initial ester (**2a**) was prepared by the procedure [22], ester (**2b**)—by the procedure [24] or [30].

1a. Yield 88%, mp 124–125°C (lit. [22] mp 124–126°C); R_f 0.41 (eluent-$CHCl_3$:MeOH = 4:1); ^{13}C-NMR, δ, ppm: 8.24 (CH_3); 107.08 (C-3 furoxan); 149.81 (C-4 furoxan); 155.05 (CONH).

1b. Yield 97%, mp 260 (lit. [24] m.p.260–261°C).

1c. Yield 84%, mp 174–175°C; R_f 0.15 (eluent-$CHCl_3$:$MeCO_2Et$ = 1:1); IR (KBr): 648, 688, 740, 760, 856, 944, 1000, 1076, 1172, 1224, 1344, 1376, 1440, 1516, 1528, 1584, 1616, 1676, 1712, 3244, 3292, 3344 cm^{-1}; ^1H-NMR, δ, ppm: 2.11 (s, 3H, CH_3); 6.5 (br., s. 3H, $NHNH_2$); 10.75 (s, 1H, NH); ^{13}C-NMR, δ, ppm: 23.21 (CH_3); 106.61 (C-3 furoxan); 150.37 (C-4 furoxan); 153.85 (CONH); 168.78 (CH_3CO); ms (70 eV) *m/z* (I%): 202 (M^+ + 1, 4), 201 (M^+, 8), 172 (M^+-NO + 1, 7), 169 (M^+-NH_2NH_2, 26), 159 (28), 155 (M^+-NO-NH_2, 7), 144 (8), 129 (M^+-NO-Ac + 1, 100), 111 (31), 101 (25), 85 (25). Anal. Calcd. for $C_5H_4N_6O_4$ (201.140): C, 29.86; H, 3.51; N, 34.82. Found: C, 30.00; H, 3.61; N, 34.66.

General procedure for the synthesis of furoxancarboxylic acid hydrazides (1b,c) from furoxancarboxylic acid azides (3b,c). Hydrazine hydrate (1 mL, 20 mmol) was added to suspension of azides (**3b**) or (**3c**) (10 mmol) in 20 mL of water. Reaction mixture was stirred for 1 h at room temperature, precipitate was filtered, washed with cold water, and dried in air. Initial azide **3b** was prepared by the procedure [23], [24].

1b. Yield 85%, mp 260 (lit. [24] mp 260–261°C). The other characteristics are identical to those of compound (**1b**), prepared from ester (**2b**).

1c. Yield 94%, mp 174–175°C. The other characteristics are identical to those of compound (**1c**), prepared from ester (**2c**).

General procedure for the synthesis of 3(4)-R-4(3)-(5-amino-1,3,4-oxadiazol-2-yl)furoxans (4a–c). The solution of 0.5 g (5 mmol) $KHCO_3$ in 3.5 mL of water was added to the suspension of furoxancarboxylic acid hydrazides (**1a–c**) (4 mmol) in 5 mL of ethanol and then cyanogen bromide (0.425 g, 4 mmol) was added in small portions. The reaction mixture was stirred at room temperature until the reaction completion (24–72 h) (TLC control). The precipitates of compounds (**4a–c**) were filtered, washed with cold water, dried in air, and crystallized from ethanol.

4a. Yield 73%, mp 196–197°C; R_f 0.29 (eluent-$CHCl_3$:$MeCO_2Et$ = 1:1); IR (KBr): 636, 656, .700, 716, 744, 848, 944, 980, 1036, 1052, 1100, 1244, 1316, 1376, 1452, 1492, 1596, 1620, 1664, 3108, 3344 cm^{-1}; ^1H-NMR, δ, ppm: 2.33 (s, 3H, CH_3); 7.82 (s, 2H, NH_2); ^{13}C-NMR, δ, ppm: 8.62 (CH_3); 111.89 (C-3 furoxan); 145.40 (C-4 furoxan); 148.07 (C-5 1,3,4-oxadiazole); 164.57 (C-2 1,3,4-oxadiazole); ms (70 eV) *m/z* (I%): 183 (M^+, 73), 167 (M^+-O, 4), 153 (M^+-NO, 9), 123 (M^+-2NO, 61), 110 (3), 79 (100). Anal. Calcd. for $C_5H_5N_5O_3$ (183.125): C, 32.79; H, 2.75; N, 38.24. Found: C, 32.88; H, 2.86; N, 38.07.

4b. Yield 84%, mp 224–225°C. R_f 0.24 (eluent-$CHCl_3$:$MeCO_2Et$ = 1:1). IR (KBr): 624, 656, 712, 740, 864, 944, 972, 1004, 1036, 1088, 1160, 1352, 1424, 1480, 1552, 1592, 1628, 1660, 3224, 3326, 3400 cm^{-1}; ^1H-NMR, δ, ppm: 6.65 (s, 2H, NH_2-furoxan); 7.80 (s, 2H, NH_2-1,3,4-oxadiazole); ^{13}C-NMR, δ, ppm: 100.40 (C-3 furoxan); 146.07 (C-4 furoxan); 155.20 (C-5 1,3,4-oxadiazole); 164.17 (C-2 1,3,4-oxadiazole); ms (70 eV) *m/z* (I%): 168 (M^+-O, 21), 154 (M^+-NO, 49), 124 (M^+-2NO, 50), 111 (95), 83 (85), 80 (100), 68 (100). Anal. Calcd. for $C_4H_4N_6O_3$ (184.113): C, 26.09; H, 2.19; N, 45.65. Found: C, 26.22; H, 2.10; N, 45.45.

4c. Yield 81%; mp 217–218°C; R_f 0.12 (eluent-$CHCl_3$: $MeCO_2Et$ = 1:1); IR (KBr): 620, 680, 712, 736, 780, 856, 928, 956, 996, 1012, 1036, 1100, 1128, 1204, 1268, 1328, 1368, 1424, 1476, 1540, 1560, 1584, 1636, 1668, 1720, 3204, 3264, 3416 cm^{-1}; ^{1}H-NMR, δ, ppm: 2.15 (s, 3H, CH_3); 7.75 (s, 2H, NH_2); 10.90 (s, 1H, AcNH); ^{13}C-NMR, δ, ppm: 22.82 (CH_3); 102.87 (C-3 furoxan); 144.60 (C-4 furoxan); 149.37 (C-5 1,3,4-oxadiazole); 164.40 (C-2 1,3,4-oxadiazole); 169.45 (CO); ms (70 eV) *m/z* (I%): 226 (M^+, 4), 210 (M-O, 5), 195 (12), 181 (M^+-NO_2 + 1, 14), 168 (M^+-AcNH,22), 154 (M^+-NO-Ac + 1, 100), 143 (67), 124 (73), 111 (26), 96 (42), 84 (96). Anal. Calcd. for $C_6H_6N_6O_4$ (226.150): C, 31.87; H, 2.67; N, 37.16. Found: C, 31.65; H, 2.60; N, 37.02.

General procedure for the synthesis of 1,2-bis[4(3)-R-furoxano-3(4)-yl]hydrazines (5a–d). To solution of furoxancarboxylic acids hydrazides (**1a–c**) (10 mmol) in minimum amount of DMSO 10 mmol of 4(3)-R-furoxancarboxylic acid azides (**3a–c**) were added. Reaction mixture was stirred to disappearance of initial compounds (TLC-control) (24–48 h). The formed precipitate was filtered, washed with water and acetone, and dried in air. To isolate compound (**5c**) 10-fold amount of water was added by dropwise to reaction mixture, the precipitate was filtered, washed with cold water, and dried in air.

5a. Compound **5a** was obtained from hydrazide (**1a**) and azide (**3a**) for 24 h, yield 71%, mp 179–180°C; R_f 0.62 (eluent-$CHCl_3$: $MeCO_2Et$ = 1:1). IR (KBr): 628, 680, 808, 852, 868, 904, 980, 1040, 1092, 1244, 1316, 1376, 1440, 1468, 1488, 1540, 1580, 1636, 1680, 1712, 2992, 3200, 3476 cm^{-1}; ^{1}H-NMR, δ, ppm: 2.25 (s, 6H, $2CH_3$); 11.45 (s, 2H, 2NH); ^{13}C-NMR, δ, ppm: 8.21 (CH_3); 112.81 (C-3 furoxan); 150.62 (C-4 furoxan); 156.18 (CO); ms (70 eV) *m/z* (I%): 224 (M^+-2NO, 7), 185 (6), 149 (11), 142 (10), 111 (16), 100 (16), 98 (37), 82 (27), 67 (100). Anal. Calcd. for $C_8H_8N_6O_6$ (284.186): C, 33.81; H, 2.84; N, 29.57. Found: C, 33.63; H, 2.73; N, 29.70.

5b. Compound **5b** was obtained from hydrazide (**1b**) and azide (**3b**) for 48 h in yield 42%, mp 224–227°C (lit. [24] mp 225–228°C).

5c. Compound **5c** was obtained from hydrazide (**1c**) and azide (**3c**) in yield 92%, mp 220–221°C; R_f 0.62 (eluent-$CHCl_3$:$MeCO_2Et$ = 4:1). IR (KBr): 600, 644, 744, 756, 824, 850, 902, 1001, 1035, 1139, 1220, 1306, 1369, 1398, 1431, 1527, 1544, 1598, 1669, 1693, 1714, 3296, 3353, 3431, 3458, 3534 cm^{-1}; ^{1}H-NMR, δ, ppm: 2.10 (s, 6H, $2CH_3$); 10.88 (br., d, 4H, 4NH); ^{13}C-NMR, δ, ppm: 22.84 (CH_3); 106.49 (C-3 furoxan); 149.91 (C-4 furoxan); 152.40 (CONHNHCO); 168.65 (CH_3*C*ONH); ms (70 eV) *m/z* (I%): 292 (31), 252 (M^+-2NO-Ac, 6), 169 (13), 185 (M^+/2, 6), 155 (M^+/2-NO, 36), 144 (31), 129 (12), 125 (50), 112 (M^+/2-NO-Ac, 63), 97 (100) Anal. Calcd. for $C_{10}H_{10}N_8O_8$ (370.236): C, 32.44; H, 2.72; N, 30.27. Found: C, 32.72; H, 2.81; N, 30.12.

5d. Compound **5d** was obtained from hydrazide (**1a**) and azide (**3b**) or from hydrazide (**1b**) and azide (**3a**) in yields 85% and 87%, accordingly; mp 166–167°C; R_f 0.27 (eluent-$CHCl_3$:$MeCO_2Et$ = 1:1).; IR (KBr): 631, 655, 696, 760, 810, 853, 873, 909, 952, 1006, 1036, 1110, 1205, 1325, 1353, 1473, 1535, 1592, 1618, 1633, 1664, 1704, 2987, 3203, 3323, 3438 cm^{-1}; ^{1}H-NMR, δ, ppm: 2.27 (s, 3H, CH_3); 6.60 (s, 2H, NH_2); 10.80 (br., s, 2H, 2NH); ^{13}C-NMR, δ, ppm: 8.70 (CH_3); 104.52 (C-3 furoxan); 112.80 (C-3 furoxan); 150.75 (C-4 furoxan); 155.12 (C-4 furoxan); 156.11 (CO); 156.96 (CO); ms (70 eV) *m/z* (I%): 285 (M^+, 9), 255 (M^+-NO, 25), 209 (7), 198 (17), 184 (29), 168 (6), 154 (11), 143 (11), 124 (58), 101 (44), 100 (73), 79 (57), 69 (61), 68 (83), 67 (100). Anal. Calcd. for $C_7H_7N_7O_6$ (285.174): C, 29.48; H, 2.47; N, 34.38. Found: C, 29.36; H, 2.60; N, 34.22.

General procedure for the synthesis of 2,5-bis[3(4)-R-furoxan-4(3)-yl]-1,3,4-oxadiazoles (6a,d). The mixture of hydrazine (**5a**) or (**5d**) (6 mmol) and 4 mL of $POCl_3$ was refluxed for 5 h. Then reaction mixture was cooled, placed into 60 g of ice, stirred for 1 h, precipitate was filtered, washed with water, and dried in air.

6a. Yield 62%, mp 145–146°C; R_f 0.79 (eluent-$CHCl_3$: $MeCO_2Et$ = 3:1); IR (KBr): 624, 640, 660, 716, 724, 740, 844, 940, 946, 1004, 1036, 1048, 1072, 1192, 1308, 1348, 1380, 1432, 1480, 1568, 1624, 1644, 3420 cm^{-1}; ^{1}H-NMR, δ, ppm: 2.65 (s, CH_3); ^{13}C-NMR, δ, ppm: 8.64 (CH_3); 112.40 (C-3 furoxan); 145.29 (C-4 furoxan); 155.65 (C-2, C-5 1,3,4-oxadiazole); ms (70 eV) *m/z* (I%): 266 (M^+, 22), 236 (M^+-NO, 6), 220 (M^+-NO_2, 6), 206 (M^+-2NO, 48), 176 (M^+-3NO, 46), 146 (M^+-4NO, 70), 111 (13), 107 (14), 101 (41), 89 (68), 67 (100). Anal. Calcd. for $C_8H_6N_6O_5$ (266.171): C, 36.10; H, 2.27; N, 31.57. Found: C, 35.97; H, 2.40; N, 31.44.

6d. Yield 11%, mp 136–137°C; R_f 0.64 (eluent-chloroform: ethyl acetate = 1:1); IR (KBr): 642, 656, 712, 732, 760, 848, 924, 946, 988, 1010, 1044, 1116, 1200, 1254, 1308, 1362, 1418, 1472, 1534, 1620, 1658, 3430 cm^{-1}; ^{1}H-NMR, δ, ppm: 2.30 (s, 3H, CH_3), 6.70 (br., s, 2H, NH_2); ^{13}C-NMR, δ, ppm: 9.21 (CH_3); 106.75 (C-3 furoxan); 112.95 (C-3 furoxan); 145.70 (C-4 furoxan); 153.66 (C-4 furoxan); 155.83, 156.46 (C-2, C-5 1,3,4-oxadiazole); ms (70 eV) *m/z* (I%): 267 (M^+, 15), 207 (M^+-2NO, 35), 177 (M^+-3NO, 60), 147 (M^+-4NO, 74), 112 (28), 89 (68), 67 (100). Anal. Calcd. for $C_7H_5N_7O_5$ (267.159): C, 31.47; H, 1.89; N, 36.70. Found: C, 31.66; H, 2.00; N, 36.50.

Synthesis of 3,4-bis[N^2-(3-methylfuroxano-4-yl)] furoxancarboxylic acid dihydrazide (7). A solution of 3-methylfuroxan-4-carboxylic acid hydrazide (**1a**) (4.74 g, 30 mmol) in 10 mL of DMSO was added by dropwise to solution of furoxan-3,4-dicarboxylic acid diazide (**8**) (3.36 g, 15 mmol) in 10 mL CCl_4 at cooling with ice. Reaction mixture was stirred for 48 h at room temperature and 80 mL of water was slowly added by dropwise. The precipitate was filtered, washed with water, and dried in air. The dry product was stirred in 20 mL of $CHCl_3$, filtered, and dried in air.

Compound **7** was obtained in yield 61%, mp 120–121°C; R_f 0.43 (eluent-chloroform: ethyl acetate = 1:1); IR (KBr): 653, 721, 759, 841, 907, 1038, 1088, 1208, 1247, 1293, 1321, 1382, 1406, 1469, 1520, 1613, 1672, 1708, 2853, 2923, 3224, 3343, 3467 cm^{-1}; ^{1}H-NMR, δ, ppm: 2.24 (s, 3H, CH_3); 2.25 (s, 3H, CH_3); 11.50 (br., s, 4H, 4NH); ^{13}C-NMR, δ, ppm: 8.19 (CH_3); 8.30 (CH_3); 108.76 (C-3 furoxan); 112.75 (C-3 furoxan); 149.50 (C-4 furoxan);150.61 (C-4 furoxan); 152.22, 154.95, 155.56, 156.00 (CO); ms (70 eV) *m/z* (I%): 455 (M^+ + 1, 1), 425 (M^+-NO + 1, 2), 395 (M^+-2NO + 1, 1), 269 (2), 184 (52), 154 (33), 124 (100), 100 (28) Anal. Calcd. for $C_{12}H_{10}N_{10}O_{10}$ (454.269): C, 31.71; H, 2.22; N, 30.83. Found: C, 32.00; H, 2.36; N, 30.97.

Synthesis of 3,4-bis[5-(3(4)-methylfuroxan-4(3)-yl)-1,3,4-oxadiazol-2-yl]furoxan (9). The mixture of compound (**7**) (0.91 g, 2 mmol) and 6 mL of $POCl_3$ was refluxed for 12 h. Then reaction mixture was cooled, placed into 100 g of ice, precipitate was filtered, washed with water, and dried in air. The product obtained was purified by flesh-chromatography (eluent $CHCl_3$), and solvent was evaporated on rotary evaporator.

Compound **9** was obtained in yield 52%, mp 60–61°C. R_f 0.74 (eluent-$CHCl_3$:$MeCO_2Et$ = 3:1). IR (KBr): 633, 664, 749, 813, 850, 944, 968, 1003, 1041, 1081, 1173, 1383, 1491, 1622, 2855, 2926, 3021, 3234, 3431 cm^{-1}; ^{1}H-NMR, $CDCl_3$, δ, ppm:2.54, 2.55 (CH_3 C-3 furoxan); 2.74, 2.75 (CH_3 C-4 furoxan) = 8:5;

ms (70 eV) *m/z* (I%): 418 (M^+, 18), 388 (M^+-NO, 47), 358 (M^+-2NO, 13), 328(M^+-3NO, 24), 298 (M^+-4NO, 34), 268 (M^+-5NO, 6), 238 (M^+-6NO, 67), 206 (13), 193 (82), 163 (82), 149 (32), 146 (42), 133 (52), 124 (100). Anal. Calcd. for $C_{12}H_6N_{10}O_8$ (418.239): C, 34.46; H, 1.45; N, 33.49. Found: C, 34.67; H, 1.40; N, 33.22.

Crystallographic data: Crystals of (**4b·DMFA**) ($C_7H_{11}N_7O_4$, M = 257.23) are orthorhombic, space group Pbca, at RT: a = 10.6121(8), b = 9.2536(7), c = 22.9413(18) Å, V = 2252.8(3) Å^3, Z = 8 (Z' = 2), d_{calc} = 1.517 g cm^{-3}, μ(MoKα) = 1.26 •m^{-1}, F(000) = 1072. Intensities of 21,658 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = 0.71072Å, ω-scans, 2θ < 56°] and 2718 independent reflections [R_{int} = 0.0447] were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The hydrogen atoms of NH_2 groups were found in difference Fourier synthesis. The H(C) atom positions were calculated. All hydrogen atoms were refined in isotropic approximation in riding model with the Uiso(H) parameters equal to 1.2 Ueq(Ci) or 1.2 Ueq(Ni), for methyl groups equal to 1.5 Ueq(Cii), where Ueq(Ci), Ueq(Cii), and Ueq(Ni) are the equivalent thermal parameters of the carbon and nitrogen atoms to which the corresponding H atoms are bonded. For **4b**·DMFA, the refinement converged to wR^2 = 0.1320 and GOF = 1.001 for all independent reflections (R^1 = 0.0423 was calculated against F for 1375 observed reflections with $I > 2\sigma(I)$). All calculations were performed using [31].

REFERENCES AND NOTES

[1] Paton, R. M. In Comprehensive Heterocyclic Chemistry I; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol.6, p393.

[2] Paton, R. M. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol.4, p229.

[3] Nikonov, G.; Bobrov, S. In Comprehensive Heterocyclic Chemistry III;Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2008; Vol.5, p315.

[4] Calvino, R.; Stilo, A. Di.; Fruttero, R.; Gasco, A. M.; Sorba, G.; Gasco, A. IL Farmaco 1993, 48, 321.

[5] Bohn, H.; Brendel, J.; Martorana, B. A.; Schonafinger, K. Br J Pharmacol 1995, 114, 1605.

[6] Gasco, A. M.; Boschi, D.; Gasco, A. J Heterocycl Chem 1995, 32, 811.

[7] Kots, A. Ya.; Grafov, M. A.; Khropov, Yu. V.; Betin, V. L.; Belushkina, N. N.; Busygina, O. G.; Yazykova, M. Yu.; Ovchinnikov, I. V.; Kulikov, A. S.; Makhova, N. N.; Medvedeva, N. A.; Bulargina, T. V.; Severina, I. S. Br J Pharmacol 2000, 129, 1163.

[8] Sheremetev, A. B.; Makhova, N. N.; Friedrichsen, W. Ad Heterocycl Chem 2001, 78, 66.

[9] Hill, J. In Comprehensive Heterocyclic Chemistry I; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol.6, p427.

[10] Hill, J. In Comprehensive Heterocyclic Chemistry II;Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1996; Vol.4, p267.

[11] Suwinski, J.; Szczepankiewicz, W. In Comprehensive Heterocyclic Chemistry III; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2008; Vol.5, p397.

[12] Holla, B. S.; Gonsalves, R.; Shenoy, S. Eur J Med Chem 2000, 35, 267.

[13] Liu, F.; Luo, X.; Song, B.; Bhadury, P. S.; Yang, S.; Jin, L.; Xue, W.; Hu, D. Bioorg Med Chem 2008, 16, 3632.

[14] Narayana, B.; Raj, K. K. V.; Ashalatha, B. V.; Kumary, N. S. Arch Pharm 2005, 338, 373.

[15] Schinzel, E.; Martini, T.; Spatzier, W.; Probst, H. Ger. Offen.3126464, 1983; Schinzel, E.; Martini, T.; Spatzier, W.; Probst, H. Chem Abstr 1983, 98, 199850.

[16] Saitoh, Y.; Matsuoka, M.; Nakao, Y.; Kitao, T. Chem Lett 1991,285.

[17] Khan, M. T. H.; Choudhary, M. I.; Khan, K. M.; Rani, M.; Atta-ur-Rachman. Bioorg Med Chem 2005, 13, 3385.

[18] Pachhamia, V. L.; Parikh, A. R. J Indian Chem Soc 1989, 66, 250.

[19] Kashaev, A. G.; Zimichev, A. V. Russ J Org Chem 2009, 45, 1734.

[20] Shaposhnikov, S. D.; Korobov, N. V.; Sergievskii, A. V.; Pirogov, S. V.; Mei'nikova, S. F.; Tselinskii, I. V. Russ J Org Chem 2002, 38, 1351.

[21] (a) Makhova, N. N.; Godovikova, T. I. Mendeleev Chem J (Engl Transl) 1997, 41, 81; (b) Makhova, N. N.; Ovchinnikov, I. V.; Kulikov, A. S.; Molotov, S. I.; Baryshnikova, E. L. Pure Appl Chem 2004, 76, 1691.

[22] Gasco, A.; Mortarini, V.; Rua, G.; Menziani, E. J Heterocyl Chem 1972, 9, 577.

[23] Ovchinnikov, I. V.; Blinnikov, A. N.; Makhova, N. N.; Khmelnitskii, L. I. Mendeleev Commun 1995, 58.

[24] Kulikov, A. S.; Ovchinnikov, I. V.; Molotov, S. I.; Makhova, N. N. Russ Chem Bull Int Ed 2003,1822.

[25] Isobe, T.; Ishikawa, T. J Org Chem 1999, 64, 6984, 6989.

[26] Chambers, R. D.; Heaton, C. A.; Musgrave, W. K. R. J Chem Soc C 1968, 1933.

[27] Khmel'nitskii, L. I.; Novikov, S. S.; Godovikova, T. I. Chemistry of Furoxans Structure and Synthesis, 2nd ed.; Nauka: Moscow, 1996; (a) p67, (b) 95 (in Russian).

[28] Irrgang, T.; Friedrich, D.; Clemente, R.; Kutlescha, K.; Glatz, G.; Kempe, R. Z Kristallogr-New Cryst Struct 2007, 222, 151.

[29] Ugliengo, P.; Viterbo, D.; Calleri, M. J Chem Soc Perkin Trans 2 1988, 661.

[30] Gasco, A.; Mortarini, V.; Rua, G.; Menziani, E. J Heterocycl Chem 1972, 9, 837.

[31] Sheldrick, G. M, SHELXTL v. 5.10, Structure Determination Software Suit, Bruker AXS: Madison, Wisconsin.