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Dedicated to Full Member of the Russian Academy of Sciences V.A. Tartakovskii on the 70th Anniversary of His Birth

New Heterocycles with a 3-Aminofurazanyl Substituent

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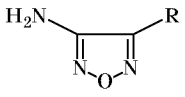
Abstract—New 3-aminofurazans containing 1,2,4- and 1,3,4-oxadiazole, pyridine, and 1,2,4-triazole substituents in the 4-position were synthesized.

Polyheterocyclic compounds having an oxadiazole fragment are potential biologically active compounds. Among isomeric oxadiazoles, 1,2,3- and 1,2,4-oxadiazoles were studied in sufficient detail. Interest in 1,2,5-oxadiazole derivatives as biologically active substances has arisen relatively recently, and some representatives of this series have been found, which exhibit a wide spectrum of biological properties: antimicrobial, antituberculous, spasmolytic, and muscle relaxant activity, etc. [1].

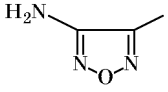
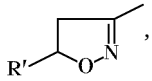
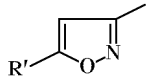
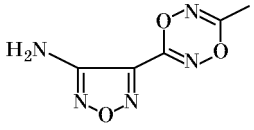
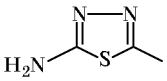
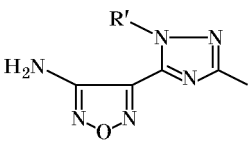
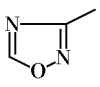
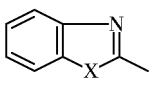
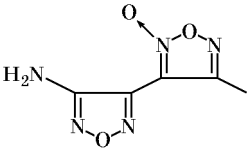
From the viewpoint of synthesis of new biologically active compounds in the series of heteryl-substituted 1,2,5-oxadiazoles, the corresponding amino derivatives attract specific attention as starting compounds. Scheme 1 shows the structures of presently known aminopolyazoles **I** which contain an aminofurazanyl moiety [2–10].

As initial compounds we selected 3-aminofurazan-4-carboxamide oxime (**VII**), 3-aminofurazan-4-carbohydrazide (**VIII**), and 3-aminofurazan-4-carboxamide hydrazone (**IX**), which were synthesized previously [11]. The 1,2,4-oxadiazole fragment in position *4* of the furazan ring in compound **VII** was built up via reaction with nitriles and carboxamides (Scheme 2). Products **X**–**XIII** were obtained by fusion of amide oxime **VII** with carboxamides and nitriles at elevated temperature. Compound **XIV** was synthesized by reaction with cyanogen bromide in aqueous alcohol

Scheme 1.



I

R =  [2, 3],  ,  [4],  [4],  [5],  [6],  [8],  [9],  [10].

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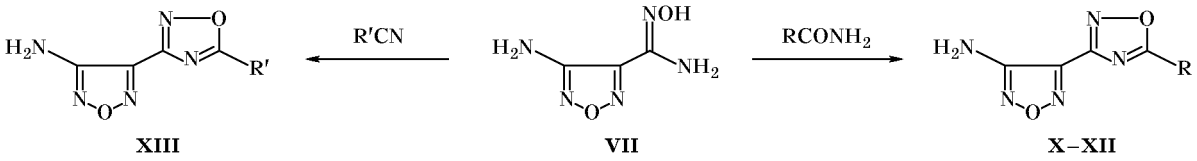
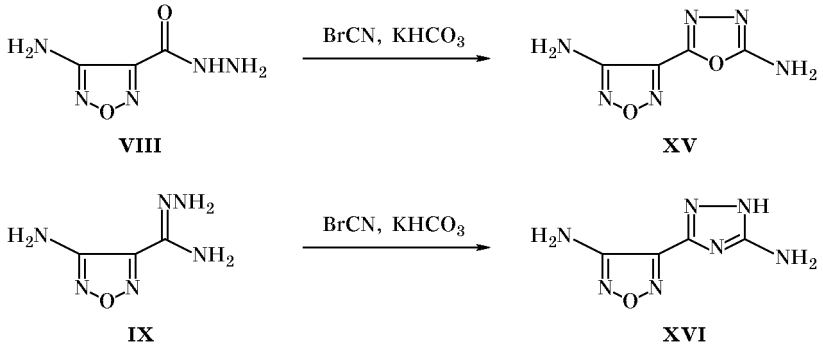
Scheme 2.



XIII, R‘ = 2-pyridyl; **X**, R = CH_3, **XI**, R = 4-pyridyl; **XII**, R = 4-aminofurazan-3-yl.

Scheme 3.

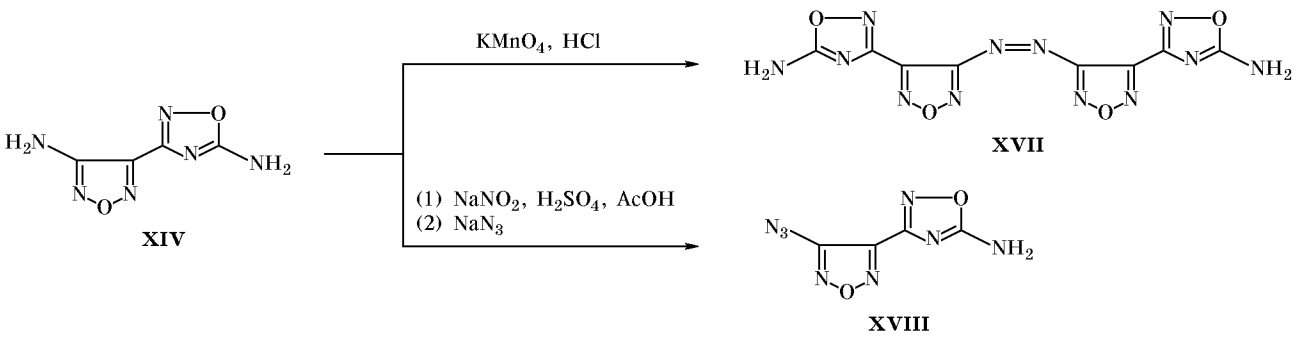


The reaction of amide oxime **VII** with methyl 3-aminofurazan-4-carboxylate or methyl 3-aminofurazan-4-carboximidate afforded product **XII**. It should be noted that fusion of 3-aminofurazan-4-carboxamide oxime **VII** with carboxamides and nitriles occurs in a fairly narrow temperature range. The yields of compounds **X**–**XII** do not exceed 50% because of thermal decomposition of the reactants.

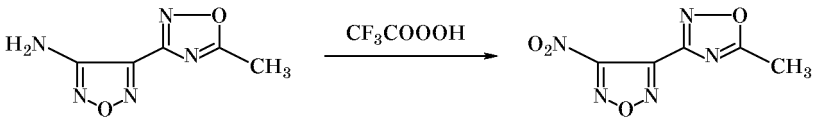
The reactions of 3-aminofurazan-4-carbohydrazide (**VIII**) and amidrazone **IX** with cyanogen bromide resulted in formation of bicyclic 3-amino-4-(aminoazolyl)furazan derivatives, 2-amino-5-(3-amino-1,2,5-oxadiazol-4-yl)-1,3,4-oxadiazole (**XV**) and 3-amino-4-(5-amino-1*H*-1,2,4-triazol-3-yl)-1,2,5-oxadiazole (**XVI**) (Scheme 3).

In the ^{1}H NMR spectra of the products, the chemical shift of protons of the amino group in the furazan ring almost does not depend on the substituent in position *4*; the corresponding signal appears at δ 6.4–6.7 ppm, i.e., in the region typical of aminofurazans. The NH_2 signals in the spectra of isomeric 1,2,4- and 1,3,4-oxadiazoles **XIV** and **XV** and 1,2,4-triazole **XVI** are located in a weaker field: δ 8.35, 7.75, and 12.70 ppm, respectively. These data suggest higher reactivity of the amino group attached to furazan ring. In fact, treatment of 3-amino-4-(5-amino-1,2,4-oxadiazol-3-yl)-1,2,5-oxadiazole (**XIV**) with potassium permanganate in acid medium gave azo derivative **XVII** as a result of oxidative dimerization at the furazan amino groups. The amino group in the furazan ring of **XIV** is selectively diazotized, and subsequent reaction of the diazo compound with sodium azide yields azidofurazan derivative **XVIII** (Scheme 4). Likewise, 3-amino-4-(5-methyl-1,2,4-oxadiazol-3-yl)-

Scheme 4.



Scheme 5.



X **XIX**

1,2,5-oxadiazole (**X**) is readily oxidized at the amino group with trifluoroperoxyacetic acid to give 60% of the corresponding nitro derivative **XIX** (Scheme 5).

EXPERIMENTAL

The IR spectra were recorded on a Perkin–Elmer Spectrum 1000 instrument from samples prepared as thin films on a KBr support. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC-200 spectrometer in DMSO using the solvent signals as reference. The mass spectra (70 eV) were run on a Varian CH-6 mass spectrometer.

The initial compounds, 4-aminofurazan-3-carboxamide oxime (**VII**) [11], 4-aminofurazan-3-carbohydrazide (**VIII**) [6], methyl 4-aminofurazan-3-carboximidate [6], 4-aminofurazan-3-carboxamide hydrazone (**IX**) [7], and methyl 4-aminofurazan-3-carboxylate [11] were synthesized by known methods.

3-Amino-4-(5-methyl-1,2,4-oxadiazol-3-yl)furazan (X). A mixture of 2 g (14 mmol) of amide oxime **VII** and 1.66 g (28.14 mmol) of acetamide was heated for 7 h at 180°C and was then poured into 100 ml of water. The resulting suspension was heated to the boiling point, filtered while hot, and cooled. The precipitate was filtered off and dried at 50°C. Yield 1.27 g (54%), mp 160°C. ^{1}H NMR spectrum, δ, ppm: 2.73 s (3H, CH_3), 6.40 s (2H, NH_2). Found, %: C 36.00; H 2.54; N 50.02. $C_5H_5N_5O_2$. Calculated, %: C 35.93; H 3.02; N 41.90.

3-Amino-4-[5-(3-pyridyl)-1,2,4-oxadiazol-3-yl]-1,2,5-oxadiazole (XI). A mixture of 2 g (14 mmol) of amide oxime **VII** and 3.42 (28 mmol) of nicotinamide was heated for 8 h at 160–165°C. It was then cooled, and the solid material thus obtained was washed with 20 ml of ether, dried in air, washed with 25 ml of hot water, and again dried in air. Yield 1 g (31%), mp 195°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 9.44 s (1H, pyridine), 8.931 (1H, pyridine), 8.65 d (1H, pyridine), 7.73 t (1H, pyridine), 6.64 s (2H, NH_2). Found, %: C 47.22; H 3.08; N 36.33. $C_9H_6N_6O_2$. Calculated, %: C 46.96; H 2.63; N 36.51.

3-Amino-4-[5-(4-amino-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazol-3-yl]-1,2,5-oxadiazole (XII). *a*. An equimolar mixture of amide oxime **VII** and 3-aminofurazan-4-carboxamide was heated for 1 h at 170°C and was then poured into 100 ml of water. The resulting suspension was heated under stirring to the boiling point, filtered while hot, and cooled. The precipitate was filtered off and dried at 50°C. Yield 37%, mp 238°C. IR spectrum, ν, cm^{-1}: 3468, 3359, 1633, 1556, 1499, 1420, 1390, 1157, 1101, 1026, 976. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.70 (2H, NH_2), 6.86 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 166.64, 159.60, 155.76, 155.59, 136.30, 135.06. Found, %: C 30.15; H 2.43; N 47.81. $C_6H_4N_8O_3$. Calculated, %: C 30.52; H 1.71; N 47.45.

b. A mixture of 0.5 g (3.5 mmol) of methyl 3-aminofurazan-4-carboximidate and 0.5 g (3.5 mmol) of amide oxime **VII** was heated for 1–2 min at 220–230°C. It was then cooled, and 25 ml of water was added. The suspension was heated to the boiling point, kept boiling for 5 min, and filtered while hot. The precipitate was dissolved in 3 ml of DMF, the solution was poured into 30 ml of water, and the product was filtered off and dried in air. Yield 0.16 g (19%).

c. A solution of 0.4 g (7.14 mmol) of potassium hydroxide in a minimal volume of water was poured into 40 ml of 1-butanol. The mixture was heated to the boiling point and was kept boiling until the temperature reached 115–118°C. A solution of 1 g (6.9 mmol) of amide oxime **VII** and 2.0 g (0.14 mmol) of methyl 3-aminofurazan-4-carboxylate in 20 ml of butanol was added, and a solid began to separate from the solution almost immediately. The mixture was boiled for 6 h and cooled, and the precipitate was filtered off, washed with a small amount of butanol and 25 ml of hot water, and dried at 60°C. Yield 1.0 g (60%).

3-Amino-4-[5-(4-pyridyl)-1,2,4-oxadiazol-3-yl]-1,2,5-oxadiazole (XIII) was synthesized by fusion of 2 g (13.9 mmol) of amide oxime **VII** with 2.9 g (28 mmol) of 4-cyanopyridine at 130°C. Yield 32%, mp 210–212°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 8.90 s (1H, pyridine), 8.45 d (1H, pyridine), 8.15 t (1H, pyridine), 7.75 t (2H, NH_2). Found, %: C 47.21; H 3.07; N 36.95. $C_9H_6N_6O_2$. Calculated, %: C 46.96; H 2.63; N 36.51.

3-Amino-4-(5-amino-1,2,4-oxadiazol-3-yl)furazan (XIV). A solution of 8 g (80 mmol) of $KHCO_3$ in 30 ml of water was added to a suspension of 10 g (70 mmol) of amide oxime **VII** in 50 ml of alcohol, and 7.42 g (70 mmol) of cyanogen bromide was then added in portions. The mixture was stirred for 24 h at 15–20°C, and the precipitate was filtered off, washed with water, and dried. Yield 10.5 g (89%), mp >275°C (decomp.; from water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.35 s (2H, NH_2), 6.34 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 173.2, 160.0, 156.19, 138.4. Found, %: C 28.51; H 2.48; N 50.08. $C_4H_4N_6O_2$. Calculated, %: C 28.58; H 2.40; N 5.00.

3-Amino-4-(5-amino-1,3,4-oxadiazol-2-yl)furazan (XV). A solution of 8 g (80 mmol) of potassium hydrogen carbonate in 30 ml of water was added to a suspension of 10 g (70 mmol) of hydrazide **VIII** in 50 ml of alcohol, and 7.42 g (70 mmol) of cyanogen bromide was added in portions. The mixture was stirred for 24 h at 15–20°C, and the precipitate was filtered off, washed with water, and dried. Yield 9.9 g (84%), mp 225°C (decomp.; from water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.78 s (2H, NH_2); 6.49 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 165.38, 155.56, 143.12, 135.57. Found, %: C 28.53; H 2.44; N 50.03. $C_4H_4N_6O_2$. Calculated, %: C 28.58; H 2.40; N 50.00.

3-Amino-4-(5-amino-1,2,4-triazol-3-yl)furazan (XVI). A suspension of 1 g (7 mmol) of amidrazone **IX** in 20 ml of water was heated until it became homogeneous, 0.75 g (7 mmol) of cyanogen bromide was added in portions, and 0.7 g (7 mmol) of potassium hydrogen carbonate was then added. The mixture was stirred for 24 h at 15–20°C, and the precipitate was filtered off, washed with water, and dried. Yield 0.5 g (43%), mp 270°C (decomp.; from water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 12.70 s (1H, NH), 6.38 s (2H, NH_2), 6.44 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 158.40, 156.04, 150.07, 140.60. Found, %: C 28.78; H 3.11; N 58.56. $C_4H_5N_7O$. Calculated, %: C 28.75; H 3.02; N 58.67.

3,3′-Azobis[4-(5-amino-1,2,4-oxadiazol-3-yl)-1,2,5-oxadiazole] (XVII). 3-Amino-4-(5-amino-1,2,4-oxadiazol-3-yl)furazan (**XIV**), 4 g (23.8 mmol), was dispersed in a mixture of 80 ml of acetonitrile and 50 ml of concentrated hydrochloric acid, a solution of 3.76 g (23.8 mmol) of potassium permanganate in a minimal amount of water was added dropwise, the mixture was stirred for 15 min and diluted with 300 ml of water, and 5% hydrogen peroxide was added until the solution turned colorless. The precipitate was filtered off and dispersed in 50 ml of acetonitrile, and the suspension was heated to the boiling point and filtered. The product was dried in air. Yield 2.5 g (63%), mp >250°C. ^{1}H NMR spectrum, δ, ppm: 8.37 s (NH_2). ^{13}C NMR spectrum, δ_C, ppm: 173.66, 163.11, 158.33, 142.52. Found, %: C 28.89; H 1.27; N 50.39. $C_8H_4N_{12}O_4$. Calculated, %: C 28.93; H 1.21; N 50.60.

5-Amino-3-(4-azido-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazole (XVIII). Diamine **XIV**, 1 g (5.95 mmol), was added at 0–5°C to a solution of 0.41 g (6.00 mmol) of sodium nitrite in 50 ml of sulfuric acid. The mixture was stirred for 15 min, and 30 ml of acetic acid was added, maintaining the temperature at 0–5°C. The mixture was stirred for 30 min, a solution of 0.78 g (12.0 mmol) of sodium azide in 40 ml of acetic acid was added, and the mixture was stirred for 15 min, poured into 100 ml of water, and extracted with diethyl ether (3×50 ml). The extracts were washed with water until neutral reaction, dried, and evaporated under reduced pressure. Yield 0.7 g (61%), mp 174–175°C (decomp.; from $CHCl_3$). IR spectrum, ν, cm^{-1}: 3401, 3332, 3149, 2159, 2135, 1686, 1673, 1587, 1523, 1493, 1418, 1351, 1206, 972. ^{1}H NMR spectrum, δ, ppm: 8.3 s (NH_2). ^{13}C NMR spectrum, δ_C, ppm: 173.43, 158.45, 153.32, 140.96. Found, %: C 24.81; H 1.12; N 57.67. $C_4H_2N_8O_2$. Calculated, %: C 24.75; H 1.04; N 57.73.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)-3-nitro-1,2,5-oxadiazole (XIX). Trifluoroacetic anhydride, 90 ml, was slowly added (dropwise) at 50°C to 34 g (1 mol) of 30% hydrogen peroxide, and a solution of 5 g (0.03 mol) of oxadiazole **X** in 60 ml of acetonitrile was then added. The mixture was kept for 1 h at 50°C and cooled, and volatile components were evaporated in the cold. Compound **XIX** was isolated as a light brown oily substance. Yield 4 g (60%). ^{1}H NMR spectrum, δ, ppm: 2.81 s (CH_3). ^{13}C NMR spectrum, δ_C, ppm: 180.04, 160.53, 157.51, 141.62, 12.85. Found, %: C 30.92; H 1.21; N 35.82. $C_5H_3N_5O_4$. Calculated, %:C 30.47; H 1.53; N 35.53.

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