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Synthesis and Reactivity of Carbohydroximoyl Azides: II.* 4-Substituted 1,2,5-Oxadiazole-3-carbohydroximoyl Azides and 1-Hydroxy-5-(4-R-1,2,5-oxadiazol-3-yl)tetrazoles**

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Abstract—Diazotization of 4-amino-1,2,5-oxadiazole-3-carbohydroximoyl chloride gave 4-[chloro(hydroxyimino)methyl]-1,2,5-oxadiazole-3-diazonium salt. Treatment of the latter with NaN_3 afforded 4-azido-1,2,5-oxadiazole-3-carbohydroximoyl chloride, and the reaction with $NaNO_2$ yielded 2-cyano-2-hydroxyiminoacetohydroximoyl chloride. By oxidation of 4-amino-1,2,5-oxadiazole-3-carbohydroximoyl azide with $KMnO_4$ in hydrochloric acid 4,4′-dicyano-3,3′-azobis(1,2,5-oxadiazole) was obtained. Azidation of 1,2,5-oxadiazole-3-hydroximoyl chlorides resulted in formation of the corresponding 1,2,5-oxadiazole-3-carbohydroximoyl azides which were brought into reactions with acetic anhydride and acetyl chloride. Decomposition of 4-azido-1,2,5-oxadiazole-3-carbohydroximoyl azide gave 4-azido-1,2,5-oxadiazole-3-carbonitrile; treatment of the same compound with gaseous hydrogen chloride in ether afforded 1-hydroxy-5-(4-azido-1,2,5-oxadiazole-3-yl)tetrazole which was converted into the corresponding acetate by reaction with acetic anhydride.

1-Hydroxytetrazoles having various heterocyclic substituents in position 5 have been studied relatively poorly. The available published data are concerned mainly with the preparation of 5-(3-aminoheteryl)-1-hydroxytetrazoles via isomerization of the corresponding carbohydroximoyl azides by the action of dry hydrogen chloride in an organic solvent. In such a way 5-(3-amino-1,3,4-oxadiazolyl)-1-hydroxytetrazole [2], 5-(3-amino-1,2,5-oxadiazolyl)-1-hydroxytetrazole [3], and 5-(3-amino-1,2,4-oxadiazolyl)-1-hydroxytetrazole [4] were synthesized. Information on the chemical reactivity of these compounds is also limited, although such polycyclic derivatives, as well as their precursors, heterocyclic carbohydroximoyl azides, have several reaction centers which should determine their specific behavior in various reactions.

Using 4-amino-1,2,5-oxadiazole-3-carbohydroximoyl chloride (**Ia**) as starting compound, Andrianov *et al.* previously synthesized 4-amino-1,2,5-oxadiazole-3-carbohydroximoyl azide (**IIa**) and 5-(4-amino-1,2,5-oxadiazol-3-yl)-1-hydroxytetrazole (**IIIa**) [3]. The yield of azide **IIa** can be increased from 67 to 80% by changing the order of mixing of the reactants, i.e., by adding a solution of NaN_3 to a solution of hydroximoyl chloride **Ia**. The best yields of **IIa** were obtained in aqueous ethanol as solvent. It should be noted that azide **IIa** tends to form crystal hydrate; therefore, it is necessary to crystallize the product from organic solvents rather than from water, as was proposed in [3].

Despite low basicity of the amino group which is typical of furazan derivatives [5], oxadiazole **Ia** can be diazotized [6] in sulfuric and acetic acids to form the corresponding diazonium salt. Treatment of the latter with a solution of NaN_3 yields azidofurazan **Ib** (Scheme 1). No replacement of the halogen atom occurs because of the low equilibrium concentration of azide ions in acid medium. However, our attempt to obtain in a similar way 4-nitrooxadiazole **Ic** (by treatment of the diazonium salt with sodium nitrite) was unsuccessful; instead of the expected nitro derivative we isolated 2-cyano-2-hydroxyiminoacetohydroximoyl chloride.

The halogen atom in oxadiazoles **Ia** and **Ib** is smoothly replaced by azido group through the reaction with NaN_3. The resulting carbohydroximoyl azides **IIa** and **IIb** readily undergo isomerization into 1-hydroxytetrazoles **IIIa** and **IIIb** (yield 90%) on

* For communication I, see [1].

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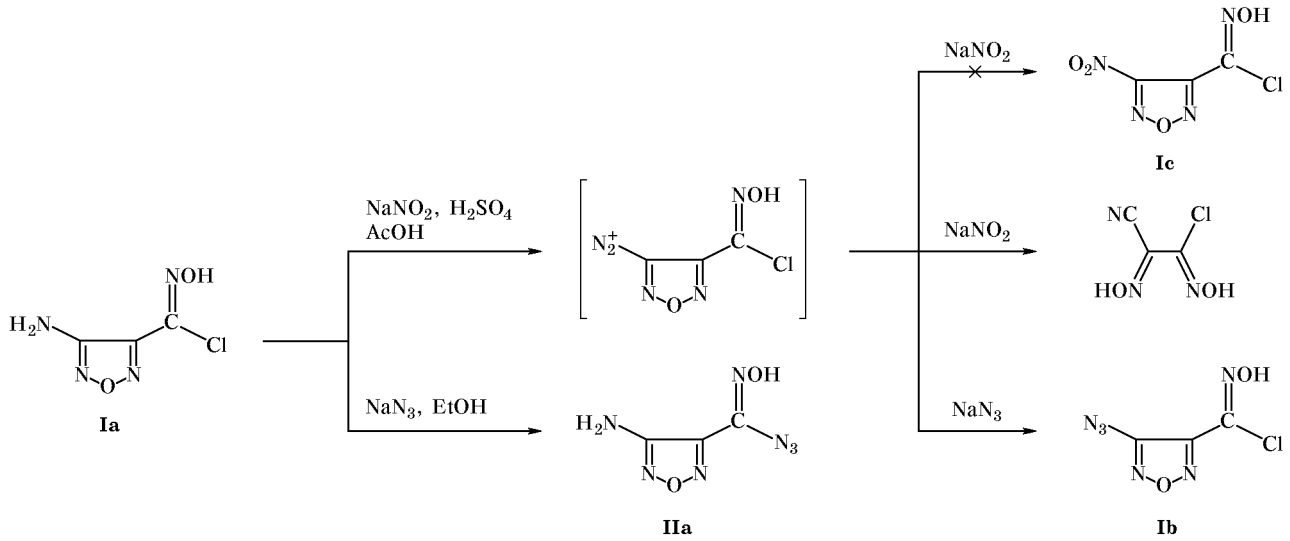
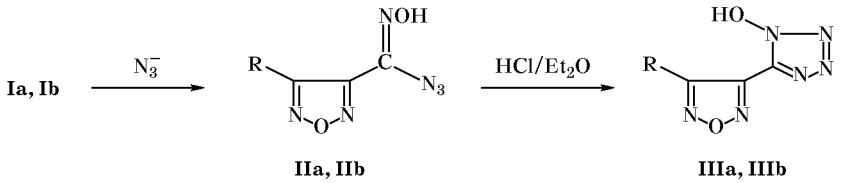
Scheme 1.

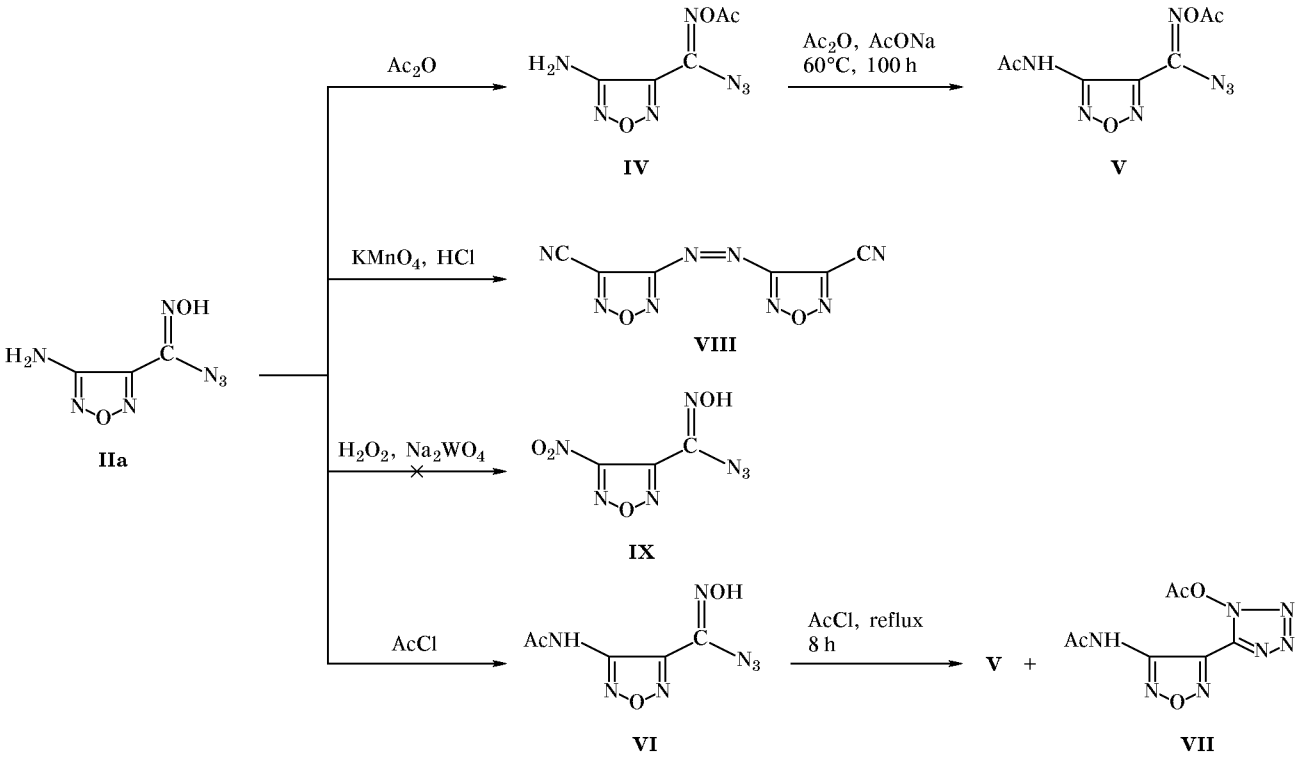


Scheme 2.

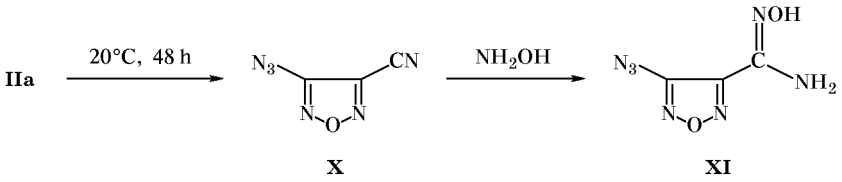


R = NH_2 (**a**), N_3 (**b**).

Scheme 3.



Scheme 4.



X **XI**

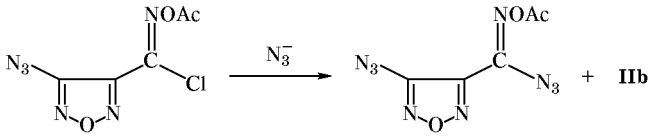
treatment with gaseous hydrogen chloride in ether (Scheme 2). Here, the azido group in position *4* of the furazan ring remains unchanged.

As was shown in [3], in the reaction of aminooxadiazole **Ia** with acetic anhydride the hydroxyimino group is acetylated first, and the subsequent acetylation occurs at the amino group. It was interesting to examine the behavior of hydroximoyl azides **II** in reactions with acetylating agents. Treatment of compound **IIa** with acetic anhydride for 2 h at 45–50°C resulted in formation of *O*-acyl derivative **IV** in almost quantitative yield. Further acetylation at the amino group with formation of *N*-acetylaminofurazan **V** requires considerably more severe conditions: prolonged (about 100 h) heating of a solution of **IV** in acetic anhydride in the presence of anhydrous sodium acetate (Scheme 3). By contrast, acetylation of compound **IIa** with acetyl chloride at 50°C (3 h) occurs first at the amino group, yielding 4-acetylamino-1,2,5-oxadiazole-3-hydroximoyl azide (**VI**); when the reaction mixture was heated for 8 h under reflux, a mixture of *N*,*O*-diacetyl derivative **V** and *N*,*O*-diacetyl derivative **VII** of 1-hydroxy-5-(4-amino-1,2,5-oxadiazol-3-yl)tetrazole was obtained. Compound **VII** is likely to be formed by isomerization of *N*-acetyl derivative **VI** into 5-(4-acetylamino-1,2,5-oxadiazol-3-yl)-1-hydroxytetrazole (as hydrogen chloride accumulates in the reaction mixture) and its subsequent acetylation at the hydroxy group.

Unexpected behavior of oxadiazole **IIa** toward oxidants was revealed. From the product mixture formed in the reaction of **IIa** with $KMnO_4$ in 20% hydrochloric acid we succeeded in isolating only 4,4′-dicyano-3,3′-azodifurazan (**VIII**) in 40% yield. We failed to oxidize compound **IIa** with hydrogen peroxide in the presence of Na_2WO_4: unchanged azide **IIa** was recovered from the reaction mixture. Unlike compound **IIa**, treatment of oxadiazole **IIb** with Ac_2O or AcCl resulted in its complete decomposition; the ability of carbohydroximoyl azides to decompose by the action of acetic acid is known [7]. However, the formation of furazan **X** was observed on exposure of **IIa** to air for 2 days (Scheme 4). The structure of **X** was proved by its transformation into amide oxime **XI** via reaction with hydroxylamine.

Treatment of *O*-acetyl derivative **XII** with sodium azide in acetone gave azide **XIII**. The reaction was accompanied by formation of compound **IIb** as by-product, presumably as a result of hydrolysis of the N−OAc bond in **XIII** (Scheme 5).

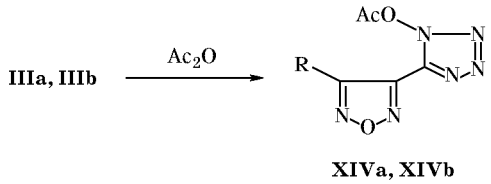
Scheme 5.



XII **XIII**

Oxadiazolyltetrazoles **IIIa** and **IIIb** are readily acetylated with acetic anhydride to afford acetoxytetrazoles **XIVa** and **XIVb** (Scheme 6).

Scheme 6.



XIVa, XIVb

III, **XIV**, R = NH_2 (**a**), N_3 (**b**).

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Perkin–Elmer R12 spectrometer (60 MHz) relative to HMDS as internal reference. The IR spectra were taken on a UR-20 instrument from samples prepared as thin films on NaCl support. TLC was performed on Silufol UV-254 plates using CCl_4–*i*-PrOH–AcOH (16:3:1) as eluent.

4-Azido-1,2,5-oxadiazole-3-carbohydroximoyl chloride (Ib). To a solution of 5 g (0.07 mol) of $NaNO_2$ in 125 ml of concentrated sulfuric acid, prepared at 15–20°C, we added in small portions 10 g (0.06 mol) of compound **Ia**. When the mixture became homogeneous (in ~30 min), 125 ml of acetic

acid was added, maintaining the temperature at 0–5°C. A solution of 26 g (0.4 mol) of NaN_3 in 80 ml of water was then added dropwise at 5–10°C. After 15 min, the mixture was poured into 500 ml of ice water, and the precipitate was filtered off and dried. Yield 7 g (60%). By extraction of the filtrate with diethyl ether an additional amount of product **Ib**, 3.1 g, was isolated. Overall yield 87%. mp 107–108°C. IR spectrum, ν, cm^{-1}: 3320, 2136, 1380, 1136, 1024, 936, 920, 880. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 12.5 (1H, NOH). Found, %: C 19.45; H 0.91; N 44.21. $C_3HClN_6O_2$. Calculated, %: C 19.00; H 0.53; N 44.56.

4-Amino-1,2,5-oxadiazole-3-carbohydroximoyl azide (IIa). To a suspension of 13 g (0.08 mol) of compound **Ia** in 70 ml of ethanol we added with stirring at room temperature a solution of 6.5 g (0.1 mol) of NaN_3 in a minimal amount of water. The mixture was kept until initial compound **Ia** disappeared (TLC) and was poured into 250 ml of water. The precipitate was filtered off, washed with water, and dried in air. Yield 11 g (81%). mp 170–171°C. IR spectrum, ν, cm^{-1}: 3448, 3360, 3256, 2192, 2160, 1136, 1024, 946, 920, 880. ^1H NMR spectrum (acetone-d_6), δ, ppm: 5.75 s (2H, NH_2), 11.3 s (1H, NOH). Found, %: C 21.64; H 1.54; N 58.42. $C_3H_3N_7O_2$. Calculated, %: C 21.30; H 1.77; N 57.99.

4-Azido-1,2,5-oxadiazole-3-carbohydroximoyl azide (IIb) was synthesized as described above for compound **Ib** from 3 g (0.018 mol) of compound **IIa**. Yield 2.2 g (64%). mp 120°C (from ether–hexane, 1:1). IR spectrum, ν, cm^{-1}: 3432, 2320, 2144, 1528, 1508, 1024, 984, 960. ^1H NMR spectrum, δ, ppm: in acetone-d_6: 11.65 s (1H, NOH); in DMSO-d_6: 12.75 s (1H, NOH). Found, %: C 18.23; H 0.67; N 64.99. $C_3HN_9O_2$. Calculated, %: C 18.46; H 0.51; N 64.61.

5-(4-Amino-1,2,5-oxadiazol-3-yl)-1-hydroxytetrazole (IIIa). A stream of gaseous hydrogen chloride was passed through a suspension of 1 g (0.006 mol) of azide **IIa** in 20 ml of diethyl ether until compound **IIa** disappeared completely (TLC). The solvent was removed to leave 1 g of a solid which was dried by azeotropic distillation of water with benzene. mp 184°C. IR spectrum, ν, cm^{-1}: 3450, 3300, 3200, 1640, 1445, 1400, 1290, 1150, 1080, 987. ^1H NMR spectrum (acetone-d_6), δ, ppm: 6.58 s (2H, NH_2), 11.2 s (1H, OH). Found, %: C 21.52; H 1.85; N 58.52. $C_3H_3N_7O_2$. Calculated, %: C 21.30; H 1.77; N 57.99.

5-(4-Azido-1,2,5-oxadiazol-3-yl)-1-hydroxytetrazole (IIIb) was synthesized as described above for compound **IIIa**. Yield 85%. mp 73–80°C (hydrate). ^1H NMR spectrum (acetone-d_6), δ, ppm: 8.45 br.s (1H, OH and H_2O). We failed to remove crystallization water by azeotropic distillation with benzene. Found, %: C 16.85; H 1.52; N 58.85. $C_3HN_9O_2 \cdot H_2O$. Calculated, %: C 16.90; H 1.40; N 59.15.

***O*-Acetyl-4-amino-1,2,5-oxadiazole-3-carbohydroximoyl azide (IV).** A solution of 1 g of compound **IIa** in 10 ml of acetic anhydride was stirred for 2 h at 45°C, and excess acetic anhydride was distilled off. Yield 1.17 g (97%). mp 102–103°C (from CCl_4). IR spectrum, ν, cm^{-1}: 3456, 2128, 1784, 1696, 1632, 1572, 1524, 1368, 1248, 1172, 956. ^1H NMR spectrum (acetone-d_6), δ, ppm: 2.25 s (3H, CH_3), 6.05 s (2H, NH_2). Found, %: C 29.05; H 2.55; N 46.55. $C_5H_5N_7O_3$. Calculated, %: C 28.44; H 2.37; N 46.45.

***O*-Acetyl-4-acetylamino-1,2,5-oxadiazole-3-carbohydroximoyl azide (V).** A mixture of 0.5 g (2.4 mmol) of compound **IV**, 10 ml of acetic anhydride, and a few crystals of calcined sodium acetate was heated for 100 h at 60°C. The mixture was cooled, 50 ml of ether was added, the precipitate was filtered off, and the filtrate was evaporated to dryness. Yield of product **V** 0.47 g (78%). mp 111–113°C (from CCl_4). IR spectrum, ν, cm^{-1}: 3296, 2160, 1788, 1720, 1540, 1368, 1300, 1236, 1172, 1000. ^1H NMR spectrum (acetone-d_6), δ, ppm: 2.20 s (3H, CH_3), 2.25 s (3H, CH_3), 9.7 s (1H, NH). Found, %: C 32.96; H 3.04; N 38.03. $C_7H_7N_7O_4$. Calculated, %: C 33.20; H 2.77; N 38.73.

4-Acetylamino-1,2,5-oxadiazole-3-carbohydroximoyl azide (VI). A mixture of 0.7 g (4.1 mmol) of compound **IIa** and 15 ml of acetyl chloride was heated for 3 h at 40–45°C. The mixture was then cooled, and the precipitate was filtered off to obtain 0.5 g (57%) of compound **V** with mp 173–174°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3768, 3328, 2184, 1740, 1724, 1528, 1304, 1040, 980. ^1H NMR spectrum (acetone-d_6), δ, ppm: 2.37 s (3H, CH_3), 10.0 s (1H, NH), 12.6 s (1H, NOH). Found, %: C 28.67; H 2.47; N 46.62. $C_5H_5N_7O_3$. Calculated, %: C 28.44; H 2.37; N 46.45.

1-Acetoxy-5-(3-acetylamino-1,2,5-oxadiazol-3-yl)tetrazole (VII). A suspension of 0.4 g (2.4 mmol) of compound **IIIa** in 10 ml of acetyl chloride was stirred at room temperature until the precipitate dissolved completely (about 30 min), and excess acetyl chloride was distilled off to leave 0.4 g (67%) of product **VII**. mp 123–124°C (from CCl_4). IR spectrum, ν, cm^{-1}: 1840, 1728, 1572, 1524, 1104, 992. ^1H NMR spectrum (acetone-d_6), δ, ppm: 2.3 s (3H, CH_3), 2.63 s (3H, CH_3), 10.0 s (1H, NH). Found, %:

C 33.12; H 3.04; N 38.95. $C_7H_7N_7O_4$. Calculated, %: C 33.20; H 2.07; N 38.73.

3,3′-Dicyano-4,4′-azobis(1,2,5-oxadiazole) (VIII). A solution of 2.5 g (0.015 mol) of $KMnO_4$ in 60 ml of water was added dropwise with stirring at 15–20°C to a solution of 2 g (0.012 mol) of compound **IIa** in 40 ml of 20% hydrochloric acid. The mixture was kept for 1 h, oxalic acid was added to decolorize it, the mixture was cooled to 5°C, and the precipitate was filtered off. We obtained 0.5 g (39%) of compound **VI** with mp 155–156°C (from $CHCl_3$). The product showed no depression of the melting point on mixing with an authentic sample prepared as described in [8].

4-Azido-1,2,5-oxadiazole-3-carbonitrile (X). Compound **IIb**, 1 g, was kept for 48 h at 20°C on exposure to air. As a result, 0.3 g (40%) of compound **X** was obtained. mp 50–52°C (from ether–hexane, 1:1). IR spectrum, ν, cm^{-1}: 3568, 2352, 2336, 2312, 2144, 1948, 1636, 976. Found, %: C 26.11; N 61.16. C_3N_6O. Calculated, %: C 26.47; N 61.76.

4-Azido-1,2,5-oxadiazole-3-carboxamide oxime (XI). Sodium hydroxide, 0.68 g (0,017 mol), was added to a suspension of 1.2 g (0.017 mol) of hydroxylamine hydrochloride in 20 ml of ethanol. The mixture was stirred for 30 min, and inorganic precipitate was filtered off. Compound **IX**, 0.1 g, was added to the filtrate, and the mixture was kept for 24 h. The solvent was removed to isolate compound **XI** as yellow needles with mp 150–151°C. IR spectrum, ν, cm^{-1}: 2128, 1660, 1520, 1388, 1224, 980, 964, 888. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 5.75 s (2H, NH_2), 9.9 s (1H, NOH). Found, %: C 21.12; H 1.96; N 57.84. $C_3H_3N_7O_2$. Calculated, %: C 21.30; H 1.77; N 57.99.

***O*-Acetyl-4-azido-1,2,5-oxadiazole-3-carbohydroximoyl chloride (XII).** A mixture of 1 g (5.3 mmol) of compound **Ib** and 10 ml of acetic anhydride was stirred at room temperature until the initial compound disappeared (~30 min; TLC). Excess acetic anhydride was distilled off to obtain 1.1 g (90%) of solid product **XII**. mp 50–51°C (after treatment with charcoal of a solution in CCl_4). IR spectrum, ν, cm^{-1}: 2136, 1800, 1592, 1488, 1300, 1168, 1144, 1000. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.35 s (3H, CH_3). Found, %: C 26.27; H 1.85; N 36.90. $C_5H_3ClN_6O_3$. Calculated, %: C 26.00; H 1.30; N 36.52.

***O*-Acetyl-4-azido-1,2,5-oxadiazole-3-carboximoyl azide (XIII).** A solution of 0.42 g (6.5 mmol) of NaN_3 in 10 ml of water was added with stirring at room temperature to a solution of 1 g (4.3 mmol) of compound **XII** in 10 ml of acetone. The mixture was kept until a negative Beilstein test for chlorine was obtained and was poured into water. The precipitate was filtered off, dried in air, and dissolved in CCl_4. The solution was refluxed until gaseous products no longer evolved, cooled, and evaporated. Yield 0.17 g (17%) of solid product **XIII** with mp 38–41°C. IR spectrum, ν, cm^{-1}: 2144, 1796, 1600, 1504, 1368, 1256, 1180, 1004, 960. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.2 s (3H, CH_3). Found, %: C 25.45; H 1.50; N 53.47. $C_5H_3N_9O_3$. Calculated, %: C 25.32; H 1.27; N 53.16.

1-Acetoxy-5-(4-R-1,2,5-oxadiazol-3-yl)tetrazoles XIVa and XIVb (*general procedure*). A mixture of 1 g of compound **IIIa** or **IIIb** and 15 ml of acetic anhydride was stirred at room temperature until the initial compound disappeared completely (TLC). Excess acetic anhydride was distilled off.

1-Acetoxy-5-(4-amino-1,2,5-oxadiazol-3-yl)tetrazole (XIVa). Yield 70%. mp 118–119°C (from CCl_4). IR spectrum, ν, cm^{-1}: 3300, 1728, 1640, 1445, 1400, 1290, 1150, 1080, 987. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.6 s (3H, CH_3), 6.25 s (2H, NH_2). Found, %: C 28.47; H 2.70; N 46.07. $C_5H_5N_7O_3$. Calculated, %: C 28.44; H 2.37; N 46.45.

1-Acetoxy-5-(4-azido-1,2,5-oxadiazol-3-yl)tetrazole (XIVb). Yield 70%. mp 89–90°C (from heptane–ether, 1:1). IR spectrum, ν, cm^{-1}: 2136, 1852, 1836, 1564, 1552, 1460, 1448, 1164, 1132, 1044, 992, 840. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.65 s (3H, CH_3). Found, %: C 24.89; H 1.35; N 52.97. $C_5H_3N_9O_3$. Calculated, %: C 25.32; H 1.27; N 53.16.

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