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Dedicated to the Corresponding Member of the Russian Academy of Sciences B. V. Gidaspov on occasion of his 70th anniversary

Synthesis and Reactivity of Azidoximes: III.* 1-Azido(4-amino-1,2,5-oxadiazol-3-yl)aldoxime in the Cycloaddition Reaction

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Abstract—By 1,3-dipolar addition of 1-azido(4-amino-1,2,5-oxadiazol-3-yl)aldoxime to propargyl alcohol and phenylacetylene bicyclic 4-amino-1,2,5-oxadiazol-3-yl(4-R-1,2,3-triazol-1-yl)ketoximes were obtained which in reaction with acetic anhydride afforded the corresponding O-acyl derivatives. Diazotization of 4-amino-1,2,5-oxadiazol-3-yl(4-R-1,2,3-triazol-1-yl)ketoximes furnished 4-azido derivatives. The treatment of 4-amino-1,2,5-oxadiazol-3-yl(4-hydroxymethyl-1,2,3-triazol-1-yl)ketoxime with $SOCl_2$ resulted in 4-amino-1,2,5-oxadiazol-3-yl(4-chloromethyl-1,2,3-triazol-1-yl)ketoxime, whose chlorine atom was readily replaced by azide ion affording 4-amino-1,2,5-oxadiazol-3-yl(4-azidomethyl-1,2,3-triazol-1-yl)ketoxime.

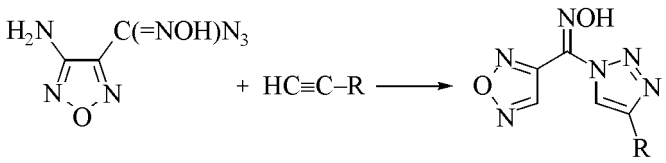
1,3-Dipolar addition of azido derivatives to unsaturated compounds is a well-known preparation method of 1-substituted 1,2,3-triazoles [2]. Recently aiming at the synthesis of substances possessing wide range of biological activity a reaction of 1,3-dipolar cycloaddition of 3-azido-4-R-1,2,5-oxadiazoles to substituted acetylenes was investigated, and bicyclic compounds were obtained having in their structure 1,2,3-triazole and 1,2,5-oxadiazole rings connected by an N–C bond [3, 4]. The reaction is accompanied by isomeric mixture formation, and only in individual cases regioselective processes were observed.

In the 3,4-diazido-1,2,5-oxadiazole both azido groups react with the propargyl alcohol. 3-Azido-4-R-1,2,5-oxadiazoles also react with olefins, in particular, with 1-morpholinyl-2-nitroethene affording 3-(4-nitro-1*H*-1,2,3-triazol-1-yl)-4-R-1,2,5-oxadiazoles [5].

To extend the range of bicyclic compounds, potential biologically active substances containing 1,2,5-oxadiazole and 1,2,3-triazole rings, we investigated a reaction of 1-azido(4-amino-1,2,5-oxadiazol-3-yl)aldoxime with monosubstituted olefins (propargyl alcohol and phenylacetylene).

3-Azidooximes of 4-R-1,2,5-oxadiazoles are still poorly understood. They are only known to smoothly undergo acylation with acetic anhydride, at treating with gaseous HCl in organic solvent (ether) to suffer intramolecular cyclization into 1-hydroxy-5-(4-R-1,2,5-oxadiazolyl)tetrazoles [6, 7], and to decompose into nitriles under action of acetic acid [8].

We demonstrated that the azido group in azidoxime **I** is also capable to add across a triple acetylene bond to furnish 4-amino-1,2,5-oxadiazol-3-yl(4-R-1,2,3-triazol-1-yl)ketoximes (**IIa, b**) where the oxadiazole and triazole rings are connected by hydroximinomethylene bridge.



I **IIa, b**

R = CH_2OH (**a**), Ph (**b**).

In contrast to 3-azido-4-R-1,2,5-oxadiazoles compound **I** reacted with acetylenes only in excess of the latter at elevated temperature (~100°C); in organic solvents (acetone, chloroform, methanol) no reaction is observed. Yield of compounds **IIa, b** attained ~50%. The reaction is regioselective: According to TLC, and ^1H and ^{13}C NMR spectroscopy the reaction products **IIa, b** are individual compounds. In their spectra appear proton signals from a CH group in 8.51–8.80 ppm region; in keeping with [3] it means

* For communication II see [1].

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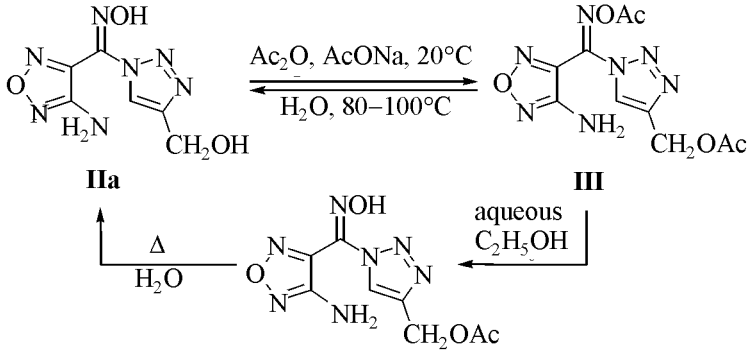
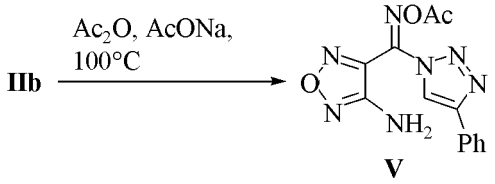
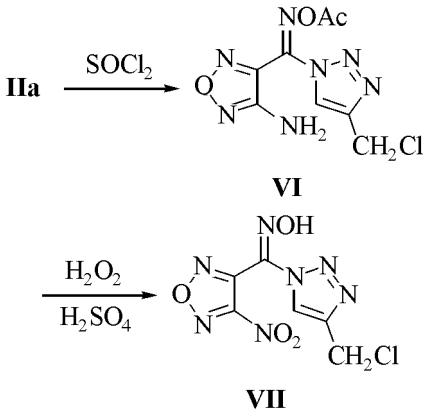
that the substituent is attached to position 4 of the triazole ring. The presence of several reactive substituents in the molecules of compounds **IIa, b** resulted in specific reactivity of these substances. For instance, at treating compound **IIa** with acetic anhydride only oxime and hydroxymethyl groups undergo acylation while the amino group attached to the 1,2,5-oxadiazole ring remains intact.



However the *O,O*-diacetate **III** posesses a low stability against hydrolysis, and at dissolution in aqueous ethanol it is completely transformed into monoacyl derivative **IV**, and at treatment with hot water the initial compound **IIa** is recovered. In phenyl derivative **IIb** the oxime group is not acylated under above conditions, and the acyl derivative **V** is obtained at prolonged heating of the components at ~100°C.



The behavior of bis(heteryl)ketoximes in oxidation was not unambiguous. The oxidation of compound **IIa** in systems H_2O_2 + $(CF_3CO)_2O$ or H_2O_2 + H_2SO_4 gave rise to a mixture of water-soluble oxidation products that we failed to isolate and identify. The complicated pattern of oxidation process is apparently due to intramolecular hydrogen bonds between the oxime, amine, and hydroxy groups. This is indirectly confirmed by easy oxidation with H_2O_2 in H_2SO_4 medium of amine group into a nitro group in a chloromethyl derivative **VI** prepared by reaction of compound **IIa** with $SOCl_2$ at 40–45°C.

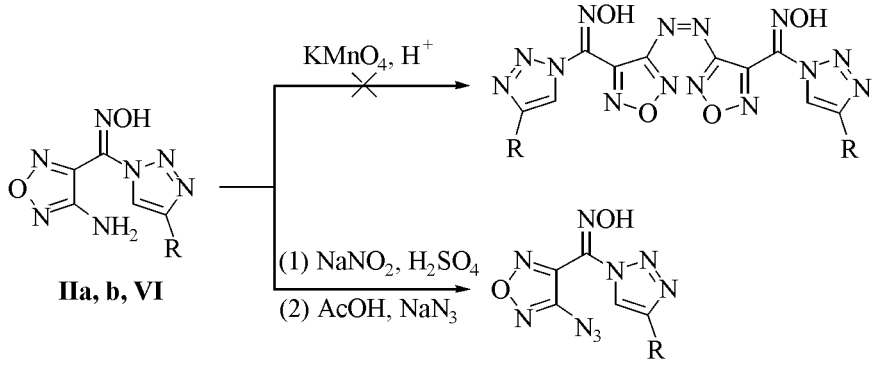


In ^1H NMR spectra of chloromethyl derivatives **VI** and **VII** the proton signals of the CH group appear in the region 8.5 and 9.30 ppm proving the position of the substituent in the 1,2,3-triazole ring. Interestingly the oxime group remains unchanged on oxidation as shows the signal at 13.2 ppm. However we failed to oxidize the amino group into azo derivatives in compounds **IIa, b** and **VI** with $KMnO_4$ in acid medium as is common for the other amino-1,2,5-oxadiazoles [8]: Compounds **IIa, b, VI** were recovered from the reaction mixture unchanged (Scheme 1).

At the same time similarly to the other amino-1,2,5-oxadiazoles [9] compounds **IIb** and **VI** readily undergo diazotization affording diazonium salts which on treating with NaN_3 furnish the corresponding azido derivatives **VIIIb, c**. The halogen atom in compounds **VI, VII, VIIIc** is relatively labile and suffers a nucleophilic substitution with azide ion under common conditions (in acetone at heating or in DMF at room temperature) (Scheme 2).

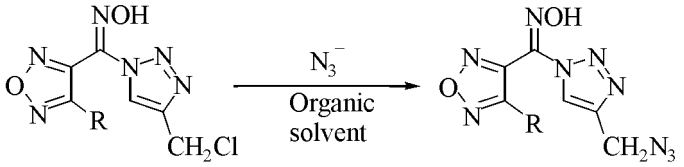
The low reactivity of the ketoxime group in compounds under study has engaged our attention. We

Scheme 1.



R = CH_2OH (**IIa**), Ph (**IIb, VIIIb**), CH_2Cl (**VI, VIIIc**).

Scheme 2.



R = NH_2 (**VI, IXa**), N_3 (**VIIIc, IXb**), NO_2 (**VII, IXc**).

believe that the problem would be cleared by the X-ray diffraction study of the structure of the ketoximes synthesized. The results of the study will be published elsewhere.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on spectrometer Bruker AC-300 in DMSO-d_6, as internal reference served the solvent signals. IR spectra were recorded on Shimadzu FTIR 8400 instrument from thin film on KBr sublayer.

4-Amino-1,2,5-oxadiazol-3-yl(4-hydroxymethyl-1,2,3-triazol-1-yl)ketoxime (IIa). A mixture of 5 g (0.03 mol) of azidoxime (**I**) in 10 ml of propargyl alcohol was heated to 80–85°C at stirring for 3–4 h till complete consumption of azidoxime (TLC monitoring). On cooling the separated precipitate was filtered off, washed with ether. Yield 3.5 g (53%), mp 174–175°C (from H_2O). IR spectrum, cm^{-1}: 3416, 1640 (NH_2), 1532 (C=N), 1244, 1040, 992. ^1H NMR spectrum, δ, ppm: 4.63 (2H, CH_2), 5.4 (1H, OH), 6.39 (2H, NH_2), 8.51 (1H, CH), 13.45 (1H, NOH). ^{13}C NMR spectrum, δ, ppm: 154.86, 147.354, 140.78, 133.76, 124.78, 54.62. Found, %: C 32.43; N 43.00; H 3.48. $C_6H_7N_7O_3$. Calculated, %: C 32.01; N 43.54; H 3.13.

4-Amino-1,2,5-oxadiazol-3-yl(4-phenyl-1,2,3-triazol-1-yl)ketoxime (IIb). A mixture of 2 g (0.012 mol) of azidoxime **I**, 10 ml of phenylacetylene and several crystals of hydroquinone were mixed at 100°C for 10–12 h at 100°C till complete consumption of azidoxime (TLC monitoring). On cooling the separated precipitate was filtered off, washed with 5–10 ml of petroleum ether, and dried in air. Yield 1.7 g (53%), mp 223–225°C (from dichloroethane). IR spectrum, cm^{-1}: 3463, 3337, 1633, 1531, 1423, 1247, 1084, 1003, 945. ^1H NMR spectrum, δ, ppm: 6.10 (2H, NH_2), 7.45 (3H, CH), 7.9 (2H, CH), 8.80 (1H, CH), 12.60 (1H, NOH). Found, %: C 48.47; H 3.30; N 35.92. $C_{11}H_9N_7O_2$. Calculated, %: C 48.70; H 3.30; N 36.16.

O-Acetyl(4-amino-1,2,5-oxadiazol-3-yl)(4-acetoxymethyl-1,2,3-triazol-1-yl)ketoxime (III). A mixture of 1 g (4.5 mmol) of compound **IIa**, 10 ml of Ac_2O, and a little of anhydrous AcONa was stirred at room temperature for 20 h. Then 10 ml of ether was added, the separated precipitate was filtered off, the mother liquor was evaporated in air. Yield 1.1 g (83%), mp 108–109°C (from 70% ethanol). IR spectrum, cm^{-1}: 3458, 3330, 3155, 1805, 1737, 1529, 1367, 1251, 1224, 1164, 1124, 1026, 962. ^1H NMR spectrum, δ, ppm: 8.75 (1H, CH), 6.12 (2H, NH_2), 5.25 (2H, CH_2), 2.25 (3H, CH_3), 2.0

(3H, CH_3). Found, %: C 38.56; H 3.13; N 32.51. $C_{10}H_{11}N_7O_5$. Calculated, %: C 38.84; H 3.59; N 31.71.

4-Amino-1,2,5-oxadiazol-3-yl(4-acetoxymethyl-1,2,3-triazol-1-yl)ketoxime (IV). Diacetate **III** (1 g, 3.4 mmol) was crystallized from aqueous ethanol (20 ml of ethanol + 30 ml of H_2O). We obtained 0.7 g (77%) of compound **V**, mp 169–170°C (decomp.). IR spectrum, cm^{-1}: 3317, 3190, 1730, 1625, 1521, 1369, 1272, 1090, 1058, 1033, 987, 920. ^1H NMR spectrum, δ, ppm: 12.50 (1H, NOH), 8.50 (1H, CH), 5.90 (2H, NH_2), 5.25 (2H, CH_2), 2.25 (3H, CH_3), 2.00 (3H, CH_3). Found, %: C 36.34; H 3.64; N 36.85. $C_8H_9N_7O_4$. Calculated, %: C 35.96; H 3.39; N 36.69.

***O*-Acetyl(4-amino-1,2,5-oxadiazol-3-yl)(4-phenyl-1,2,3-triazol-1-yl)ketoxime (V).** A suspension of 0.5 g (2 mmol) of compound **IIb** in 30 ml of Ac_2O was stirred for 3 h at heating on a boiling water bath (till complete homogenizing of the solution), and then the reaction mixture was evaporated at reduced pressure. The residual oily solid was reprecipitated from dichloromethane solution with carbon tetrachloride. We obtained 0.2 g (34%) of compound **V**, mp 204–205°C. ^1H NMR spectrum, δ, ppm: 9.35 (1H, CH), 8.05 (2H, CH), 7.5 (3H, CH), 5.90 (2H, NH_2), 2.40 (3H, CH_3). Found, %: C 52.34; H 3.84; N 32.25. $C_{13}H_{11}N_7O_2$. Calculated, %: C 52.52; H 3.70; N 32.99.

4-Amino-1,2,5-oxadiazol-3-yl(4-chloromethyl-1,2,3-triazol-1-yl)ketoxime (VI). A mixture of 5 ml $SOCl_2$, 2–3 drops of DMF, and 2 g (0.009 mol) of compound **IIa** was cautiously heated at stirring first to 30°C, then after the end of vigorous gas liberation the reaction mixture was kept for 30 min at 40–45°C, cooled to 0°C, diluted with 20–25 ml of water, cooled again to 0°C, the separated precipitate was filtered off, washed with water till neutral washings, and dried in air. Yield 1.7 g (80%), mp 165–166°C (decomp.). IR spectrum, cm^{-1}: 3467, 3331, 3174, 1624, 1526, 1444, 1265, 1110, 1049, 949. ^1H NMR spectrum, δ, ppm: 12.30 (1H, NOH), 8.50 (1H, CH), 5.60 (2H, NH_2), 4.85 (2H, CH_2). Found, %: C 30.13; H 2.76; Cl 14.90; N 39.76. $C_6H_6ClN_7O_2$. Calculated, %: C 29.58; H 2.48; Cl 14.55; N 40.25.

4-Amino-1,2,5-oxadiazol-3-yl(4-chloromethyl-1,2,3-triazol-1-yl)ketoxime (VII). To a mixture of 15 ml of concn. H_2SO_4 and 15 ml of 30% H_2O_2 was added at 40°C by small portions 1.5 g (6 mmol) of compound **V**, and the reaction mixture was kept at this temperature till the green color of the mixture disappeared. On cooling the reaction mixture was poured into 100 ml of ice water. The separated precipitate was filtered off, washed with water till neutral washings, and dried in air. Yield 1.1 g (66%), mp 149–150°C. IR spectrum, cm^{-1}: 3180, 2831, 1582, 1552, 1423, 1341, 1267, 1111, 1047, 991, 947. ^1H NMR spectrum, δ, ppm: 13.20 (1H, NOH), 9.30 (1H, CH), 4.90 (2H, CH_2). Found, %: C 26.43; H 1.07; Cl 13.11; N 35.28. $C_6H_4ClN_7O_4$. Calculated, %: C 26.34; H 1.47; Cl 12.96; N 35.84.

4-Azido-1,2,5-oxadiazol-3-yl(4-chloromethyl-1,2,3-triazol-1-yl)ketoxime (VIIIc). To a solution of 0.95 g (1.8 mmol) $NaNO_2$ in 30 ml of conc. H_2SO_4 at 10–15°C while stirring was added 3 g (1.2 mmol) of compound **VI**. After its complete dissolution the reaction mixture was cooled to 0°C, diluted with 30 ml of glacial acetic acid, and a solution of 4 g (5.7 mmol) NaN_3 in 15 ml of water was added maintaining the temperature at the level of 5–10°C. The reaction mixture was left standing for 15 min, and then poured into 200 ml of ice water. The separated precipitate was filtered off and reprecipitated from acetic acid solution with water. Yield 2.4 g (72%), mp 150°C (decomp.). IR spectrum, cm^{-1}: 3419, 3151, 2980, 2654, 2140, 1515, 1489, 1279, 1068, 1057, 1002, 941. ^1H NMR spectrum, δ, ppm: 12.75 (1H, NOH), 8.80 (1H, CH), 4.80 (2H, CH_2). ^{13}C NMR spectrum, δ, ppm: 152.47, 143.29, 143.05, 130.99, 126.35, 39.55. Found, %: C 27.01; H 1.67; Cl 13.01; N 46.95. $C_6H_4ClN_9O_2$. Calculated, %: C 26.73; H 1.50; Cl 13.15; N 46.76.

General azidation procedure for 4-R-1,2,5-oxadiazole-3-yl(4-chloromethyl-1,2,3-triazol-1-yl)ketoxymes (VI), (**VII**), (**VIIIc**). A mixture of 1 mmol of chloromethyl derivative **VI**, **VII** or **VIIIc**, 1.5 mmol of NaN_3 in 20–25 ml of DMF was stirred at room temperature till negative reaction toward halogen. Then the reaction mixture was poured into 100 ml of water and extracted with ether (2×50 ml). The solvent was evaporated in air. We obtained compound **IXa**, yield 90%, mp 171°C. IR spectrum, cm^{-1}: 3312, 2128, 1646, 1616, 1536, 1448, 1256, 1120, 1048, 992. ^1H NMR spectrum, δ, ppm: 12.30 (1H, NOH), 8.45 (1H, CH), 5.80 (2H, NH_2), 4.55 (2H, CH_2). Found, %: C 29.29; H 1.90; N 56.05. $C_6H_6N_{10}O_2$. Calculated, %: C 28.81; H 1.90; N 55.99; compound **IXb**, yield 80%, mp 125–126°C. IR spectrum, cm^{-1}: 3430, 3169, 2719, 2153, 2095, 1513, 1482, 1356, 1296, 1249, 1161, 1054, 1002, 939. ^1H NMR spectrum, δ, ppm: 12,90 (1H, NOH), 8.85 (1H, CH), 4.65 (2H, CH_2). Found, %: C 26.30; H 1.70; N 60.53. $C_6H_4N_{12}O_2$. Calculated, %: C 26.09; H 1.60; N 60.86; compound **IXc**, Yield 20%, mp 123–125°C. IR spectrum, cm^{-1}: 2848, 2144, 1512, 1312, 1200,

1160, 1052, 1016, 960, 944. 1H NMR spectrum, δ, ppm: 13.1 (1H, NOH), 9.15 (1H, CH), 4.65 (2H, CH_2). Found, %: C 26.01; H 1.10; N 50.69. $C_6H_4N_{10}O_4$. Calculated, %: C 25.72; H 1.44; N 50.00.

4-Azido-1,2,5-oxadiazol-3-yl(4-phenyl-1,2,3-triazol-1-yl)ketoxime (VIIIb) was obtained similarly to compound **VIIIc** from compound **IIb**. Yield 75–80%, mp 173°C (decomp.) (from dichloroethane). IR spectrum, cm–1: 3808, 2864, 2136, 1616, 1512, 1008. ^{1}H NMR spectrum, δ, ppm: 12.65 (1H, NOH), 9.06 (1H, CH), 7.90 m (2H arom), 7.3 m (3H arom). Found, %: C 44.03; H 2.89; N 42.01. $C_{11}H_7N_9O_2$. Calculated, %: C 44.45; H 2.37; N 42.41.

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