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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 70th Anniversary

Some Reactions of 3,6-Bis(4-amino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine

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Abstract—Diazotization and nitration of 3,6-bis(4-amino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine gave, respectively, 3,6-bis(4-azido-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine and 3,6-bis(4-nitroamino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine. The latter reacted with nitrogenous bases to form the corresponding salts.

1,4,2,5-Dioxadiazine derivatives have been studied very poorly. The first representative of this class of heterocycles, Schmitz' compound, was obtained by treatment of nitromethyl glyoxime with aqueous sodium hydrogen carbonate [1]. Its structure has long been a matter of discussions [2, 3], and only in 1988 it was unambiguously proved using ^{13}C NMR spectroscopy [4].

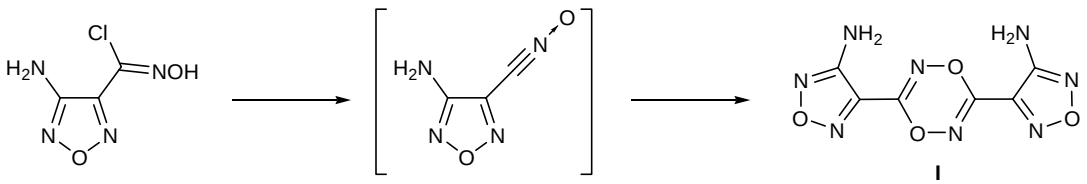
Like 1,2,5-oxadiazole 1-oxides, 1,4,2,5-dioxadiazine ring is formed by dimerization of nitrile oxides generated from such precursors as α-halo oximes, nitrolic acids, etc., but in a more acidic medium [5]. The synthesis of 3,6-bis(aryl-1,4,2,5-dioxadiazines) has been reported [6], and later 3,6-bis(4-amino-1,2,5-oxadiazol-3-yl)-1,4,2,5-di-oxadiazine was prepared by dimerization of 4-amino-1,2,5-oxadiazole-3-carbonitrile oxide [7, 8] (Scheme 1).

There are almost no published data on the reactivity of 1,4,2,5-dioxadiazine derivatives. Exception are successful nitration of 3,6-bis(1-hydroxyiminoethyl)-1,4,2,5-dioxadiazine with nitrogen oxides to the corresponding 3,6-bis(1,1-dinitroethyl) derivative [4] and reduction of 3,6-bis(4-amino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine (**I**) to 4-amino-1,2,5-oxadiazole-3-carboxamide [7].

We examined the behavior of 3,6-bis(4-amino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine (**I**) in the nitration and diazotization reactions. Diamine **I** is poorly soluble in most organic solvents; it is soluble in DMF and acetic anhydride and insoluble in cold acetone, diethyl ether, alcohols, acetonitrile, and dioxane. It can be recrystallized from a large volume of dioxane (solubility 0.4% at the boiling point) or acetonitrile (1.0% at the boiling point) or reprecipitated from DMF with water; however, losses of the product attain 30%. Compound **I** is stable in 60–98% H_2SO_4 even on heating. After heating for 2 h in 98% H_2SO_4, 93–94% of dioxadiazine **I** can be recovered, its melting point remaining unchanged.

The basicity of the amino group in amino-substituted 1,2,5-oxadiazoles is reduced due to electron-acceptor effect of the heteroring [9, 10], which is

Scheme 1.



I

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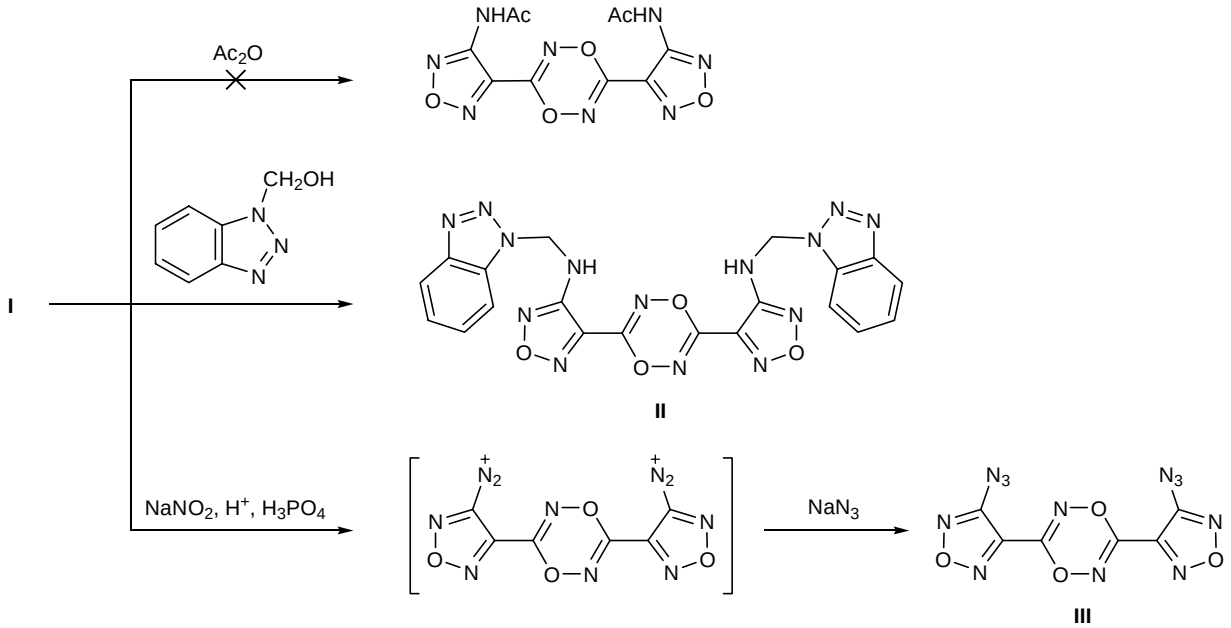
Scheme 2.



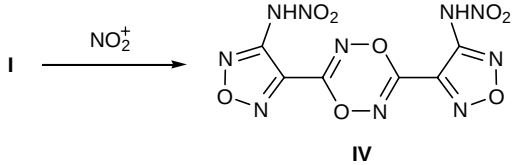
responsible for its specific behavior in reactions with various electrophiles. Information on electronic properties of the 1,4,2,5-dioxadiazine ring is absent at all. Therefore, in order to estimate the effect of the 1,4,2,5-dioxadiazine ring, we examined the behavior of 3,6-bis(4-amino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine (**I**) in some reactions typical of amino-1,2,5-oxadiazoles.

Unlike amino-1,2,5-oxadiazoles, diamine **I** was not acylated with acetic anhydride even on heating. However, it reacted with 1-hydroxymethylbenzotriazole to give compound **II** (Scheme 2). Treatment of **I** with nitrosylsulfuric acid afforded the corresponding diazonium salt which was converted into diazide **III** by the action of sodium azide. Diamine **I** was smoothly nitrated at reduced temperature (–5 to –15°C) with both concentrated nitric acid and its mixtures with sulfuric acid (according to the TLC data); however, only in the first case we succeeded in isolating *N*,*N*′-dinitroamine **IV** by diluting the reaction mixture with a large amount of trifluoroacetic acid (Scheme 3).

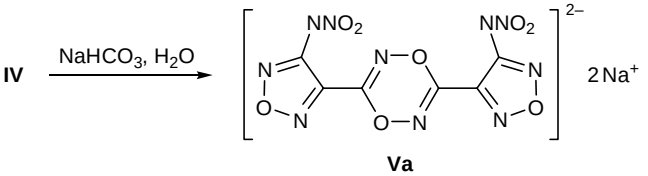
The nitration of **I** under heterogeneous conditions with the use of chlorinated organic solvents at room temperature occurs at a very low rate. No less than 5 days is necessary to complete the reaction in methylene chloride, and change of the precipitate was observed: the initial amine disappeared, and bis(nitroamine) **IV** precipitated. According to the TLC data, a part of the nitration product remained in the solution. An attempt to wash the organic phase with water to remove residual acid resulted in decomposition of **IV**. The nitration in dichloroethane was even slower. After stirring of the reaction mixture for 2 days at room temperature, 90% of the initial diamine was recovered.

N,*N*′-Dinitroamine **IV** is stable in acidic and weakly basic media (within pH range from 1 to 8.5), which is important for the preparation of its salts. Disodium salt **Va** was obtained in 62% yield by treatment of nitroamine **IV** with an aqueous solution of $NaHCO_3$ (Scheme 4) while the use of aqueous Na_2CO_3 led to decomposition of the initial *N*-nitroamine.

Scheme 3.

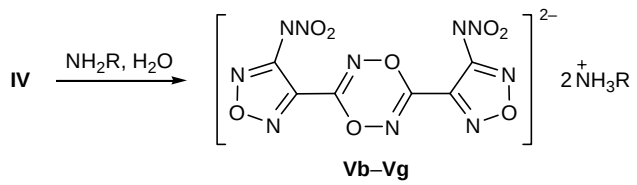


Scheme 4.



Taking the above results into account, stronger nitrogenous bases, namely hydroxylamine, hydrazine, guanidine, and aminoguanidine, were used as the corresponding hydrochlorides, while weak bases like 4-amino-1,2,4-triazole and 1,5-diaminotetrazole were taken as such (Scheme 5).

Scheme 5.



R = OH (**b**), NH_2 (**c**), C(=NH)NH_2 (**d**), NHC(=NH)NH_2 (**e**), 1,2,4-triazol-4-yl (**f**), 5-aminotetrazol-1-yl (**g**).

In these reactions, two equivalents of the base should be applied. Salts **Vb**–**Vg** are sparingly soluble in water, and they do not form crystal hydrates, except for hydroxylammonium salt **Vb** which crystallizes with two water molecules. According to the data of differential thermal analysis, onium salts **Vb**–**Vg** are considerably more stable than the initial *N*-nitroamine (**IV**); they decompose in one step within a narrow temperature range (150–165°C), and the cation nature has no effect on the stability of these salts.

EXPERIMENTAL

CAUTION! *Derivatives of (1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine are explosive; they should be handled with care!*

The IR spectra were recorded on a Shimadzu FTIR 8400 spectrometer in KBr. The ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX-500 instrument in DMSO-d_6 using the solvent signals as reference.

3,6-Bis[4-(1,2,3-benzotriazol-1-ylmethylamino)-1,2,5-oxadiazol-3-yl]-1,4,2,5-dioxadiazine (II). A solution of 2.5 g (10 mmol) of amine **I** in 50 ml of 50% aqueous dioxane was heated to the boiling point, 3.1 g (21 mmol) of 1-hydroxymethylbenzotriazole [11] and one drop of concentrated hydrochloric acid were added in succession, and the mixture was heated for 30 min under reflux. It was then cooled, and the precipitate was filtered off, washed with water, and dried in air. Yield 4.3 g (84%), colorless crystals, mp 197–198°C (from 50% aqueous dioxane). ^1H NMR spectrum, δ, ppm: 8.35 t (2H, NH), 8.00 m (4H, Ph), 7.50 m (4H, Ph), 6.30 d (4H, CH_2). Found, %: C 46.94; H 3.00; N 37.95. $C_{20}H_{14}N_{14}O_4$. Calculated, %: S 46.80; H 2.74; N 38.12.

3,6-Bis(4-azido-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine (III). A suspension of 3 g (12 mmol) of amine **I** in 50 ml of 98% H_2SO_4 was heated under stirring until it became homogeneous. The solution was cooled to 0–5°C, and a solution of nitrosylsulfuric acid prepared from 2.5 g (36 mmol) of $NaNO_2$ and 20 ml of H_2SO_4 was added under continuous stirring, maintaining the temperature at about 0°C. The mixture was stirred for 20 min at that temperature, 80 ml of concentrated phosphoric acid was added at 0–10°C, the mixture was stirred for 10 min, and 7 g (101 mmol) of sodium azide was added at such a rate that the temperature did not exceed 0–5°C. The mixture was stirred for 20 min at 0–5°C, allowed to warm up to room temperature, and poured into 200 ml of ice water. The precipitate was filtered off and recrystallized from carbon tetrachloride. Yield 3 g (83%), colorless crystals, mp 107–109°C (with vigorous decomposition). IR spectrum, ν, cm^{-1}: 2150, 1636, 1515, 1352, 1192, 1085, 1025, 1005, 891, 776. ^{13}C NMR spectrum, δ_C, ppm: 153.50, 153.14, 137.42. Found, %: C 23.92; N 55.00. $C_6N_{12}O_4$. Calculated, %: C 23.69; N 55.26.

3,6-Bis(4-nitroamino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine (IV). *a.* Diamine **I**, 2 g (8 mmol), was added in portions under vigorous stirring to 20 ml of concentrated nitric acid cooled to –5 to –15°C, maintaining the temperature below –5°C. The mixture was stirred for 10 min at –5°C, allowed to slowly warm up to room temperature, and diluted with 70–100 ml of trifluoroacetic acid. The precipitate was filtered off, thoroughly washed with trifluoroacetic acid, and dried in air. Yield 2.6 g (95%), colorless crystals, mp 95°C (with vigorous decomposition). IR spectrum, ν, cm^{-1}: 3280, 1696, 1644, 1632, 1612, 1532, 1440, 1312, 1140, 1120, 1052, 1032, 1024, 1016, 944. ^1H NMR spectrum ($CDCl_3$–DMSO-d_6), δ, ppm: 10.25 (NH). Found, %: C 20.84; H 1.00; N 41.05. $C_6H_2N_{10}O_8$. Calculated, %: C 21.06; H 0.59; N 40.94.

b. Compound **I**, 1 g (4 mmol), was added in small portions under stirring to a solution of 3 g (48 mmol) of concentrated nitric acid in 50 ml of methylene chloride, maintaining the temperature at 20°C. The resulting suspension was stirred for 5 days, and

gradual change of the precipitate was observed. The precipitate was filtered off, washed on a filter with several small portions of trifluoroacetic acid, and dried in air. Yield 0.6 g (45%), mp 95°C (decomp.). No depression of the melting point was observed on mixing with a sample prepared as described in *a*.

3,6-Bis(4-nitroamino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine disodium salt (Va). Sodium hydrogen carbonate, 1 g (12 mmol), was added to a solution of 1 g (3 mmol) of nitroamine **IV** in 20 ml of water. A solid separated immediately. The mixture was stirred for 1 h, and the precipitate was filtered off and dried at 60°C. Yield 0.95 g (62%), mp 163–164°C (decomp.). IR spectrum, ν, cm^{-1}: 3537, 3406, 1672, 1629, 1531, 1492, 1425, 1313, 1132, 1035, 1008, 941, 889, 869, 827, 773. ^{13}C NMR spectrum, δ_C, ppm: 159.18, 155.51, 141.75. Found, %: C 17.91; N 35.22. $C_6N_{10}Na_2O_8$. Calculated, %: C 18.66; N 36.28.

General procedure for the preparation of salts Vb–Vd. Appropriate nitrogenous base hydrochloride, 12 mmol, was added to a solution of 1 g (3 mmol) of nitroamine **IV** in 20 ml of water. The mixture was stirred for 1 h at room temperature, and the precipitate was filtered off, washed in succession with 20 ml of water and 20 ml of acetone, and dried at 60°C.

Bis(hydroxylammonium) salt Vb. Yield 90%, mp 137–138°C (decomp.). IR spectrum, ν, cm^{-1}: 3535, 3344, 3176, 1687, 1629, 1540, 1517, 1488, 1359, 1166, 1122, 1029, 1002, 943, 889, 771. Found, %: C 16.32; H 2.69; N 38.55. $C_6H_8N_{12}O_{10}\cdot 2H_2O$. Calculated, %: C 16.22; H 2.72; N 37.84.

Bis(hydrazinium) salt Vc. Yield 87%, mp 138–139°C (decomp.). IR spectrum, ν cm^{-1}: 1612, 1531, 1487, 1419, 1311, 1107, 1033, 968. Found, %: C 17.32; H 2.69; N 48.65. $C_6H_{10}N_{12}O_{10}$. Calculated, %: C 17.74; H 2.48; N 48.27.

Bis(guanidinium) salt VId. Yield 83%, mp 147–148°C (decomp.). IR spectrum, ν, cm^{-1}: 3529, 3408, 3348, 3251, 3199, 1658, 1635, 1558, 1525, 1487, 1288, 1120, 1010, 941, 877, 858, 804, 777. ^{13}C NMR spectrum, δ_C, ppm: 159.2, 158.8, 155.4, 141.8. Found, %: C 21.07; H 2.23; N 50.05. $C_8H_{12}N_{16}O_8$. Calculated, %: C 20.88; H 2.63; N 48.69.

3,6-Bis(4-nitroamino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine bis(aminoguanidinium) salt (Ve). Compound **I**, 1 g (4 mmol), was added in small portions to a solution of 3 g (48 mmol) of concentrated nitric acid in 50 ml of methylene chloride, stirred at 20°C. The resulting suspension was stirred for 5 days, and gradual change of the precipitate was observed. The precipitate was filtered off, washed with several small portions of trifluoroacetic acid, and dissolved in 20 ml of ethyl acetate, and 0.7 g of aminoguanidine hydrochloride was added to the solution. The suspension was stirred at room temperature until the initial nitroamine disappeared (TLC). The mixture was evaporated in air to dryness, and the residue was washed with water until neutral washings (to remove excess aminoguanidine hydrochloride), and dried in air. Yield 0.7 g (95%), mp 150–152°C (decomp.). IR spectrum, ν, cm^{-1}: 3423, 3384, 3336, 1683, 1659, 1623, 1553, 1533, 1488, 1420, 1403, 1309, 1145, 1125, 1027, 1006, 966, 932, 875, 854, 809, 801, 772, 753. ^1H NMR spectrum, δ, ppm: 6.9 (NH_2), 8.5 (NH). Found, %: C 20.09; H 2.85; N 50.97. $C_8H_{14}N_{18}O_8$. Calculated, %: C 19.59; H 2.85; N 51.42

Salts **Vf** and **Vg** were synthesized in a similar way using 2 equiv of the corresponding free base, 4-amino-1,2,4-triazole or 1,5-diaminotetrazole [12]). Before filtration, 1 ml of trifluoroacetic acid was added to the mixture, and the product was filtered off, washed on a filter in succession with 20 ml of water and 20 ml of acetone, and dried at 60°C.

Bis(1,2,4-triazol-4-ylammonium) salt Vf. Yield 95%, mp 153–154°C (decomp.). IR spectrum, ν, cm^{-1}: 3275, 3101, 1637, 1560, 1537, 1490, 1440, 1213, 1178, 1126, 1078, 1031, 1010, 937. Found, %: C 23.09; H 1.85; N 50.07. $C_{10}H_{10}N_{18}O_8$. Calculated, %: C 23.54; H 1.98; N 49.41

Bis(5-aminotetrazol-1-ylammonium) salt Vg. Yield 87%, mp 145–146°C. IR spectrum, ν, cm^{-1}: 3375, 3346, 3236, 3199, 1699, 1637, 1622, 1537, 1494, 1421, 1352, 1321, 1294, 1130, 1051,1029, 1010, 937. Found, %: C 18.09; H 1.85; N 56.97. $C_8H_{10}N_{22}O_8$. Calculated, %: C 17.72; H 1.86; N 56.82

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