ISSN 1070-3632, Russian Journal of General Chemistry, 2013, Vol. 83, No. 9, pp. 1779–1786. © Pleiades Publishing, Ltd., 2013.
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On the 100th anniversary of V.V. Perekalin

New Representatives of Nitroamine-Containing 1,2,4-Triazoles: Synthesis and Structure

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Received April 22, 2013

Abstract—The interaction of 1-methyl-1-nitroso-2-nitroguanidine with carboxylic acid hydrazides results in formation of *N*-(2-nitroguanidino)amides that easily give 3(5)-nitroamino-5(3)-alkyl(aryl)-1,2,4-triazoles under refluxing in aqueous alkaline medium. We have developed a one-pot method to prepare such heterocyclic structures; the synthesis of one of the sample compound has given an example of the method applicability. The compounds structures have been confirmed by UV, IR, ^{1}H, and $^{13}C–\{^{1}H\}$ NMR spectroscopy.

DOI: 10.1134/S1070363213090259

An increased interest to functionalized 1,2,4-triazoles is due to the high practical importance of many representatives of this class. They are used in medicine (for instance, antifungal and antiviral agents Fluconazole and Ribavirin [1]), as plant growth regulators [2, 3], herbicides and fungicides (for example, Impact® and Bayleton® [4]), and in photographic industry.

One of the methods to prepare the nitroamino-containing 1,2,4-triazoles is cyclization of acyl derivatives of nitroaminoguanidine [5, 6]. We have developed a convenient method leading to new representatives of nitroamino-containing 1,2,4-triazoles, based on condensation of 1-methyl-1-nitroso-2-nitroguanidine with the carboxylic acid hydrazides.

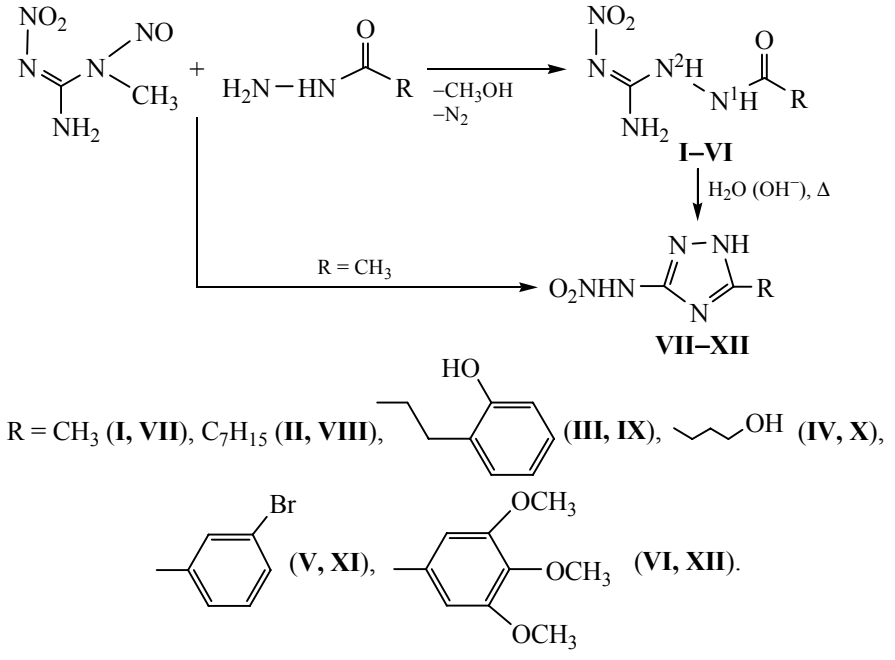
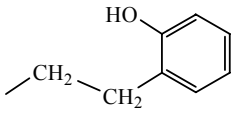
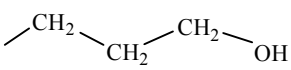
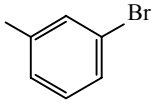
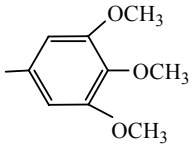


Table 1. Yields, melting points and spectroscopic characteristics of carboxylic acids *N*-(2-nitroguanidino)amides **I–VI**

Comp. no.	R	mp, °C	Yield, %	IR, ν, cm^{-1} (vaseline oil)		^1H NMR (DMSO-d_6), δ, ppm			
				NH	C=O	NH^1	NH^2	NH_2	R
I	$-CH_3$	191–192	66	3386 3239	1700	9.84	9.56	8.19 8.59	1.83 s
II	$-C_7H_{15}$	156–158	65	3275 3193	1711	9.80	9.55	8.15 8.60	0.81 m 1.2 m 1.6 m 2.18 m
III		175–176	74	3388[a] 3335 3248	1694	9.85 c	9.60 s	8.15 8.62	6.60–7.15 m 9.38 s
IV		108–110	73	3477[a] 3445 3220	1692	9.85 c	9.57 s	8.12 8.60	1.70 m 2.20 m 3.38 m 4.60 s
V		179–180	95	3308 3170	1676	10.70 c	9.90 s	8.45 8.70	7.50–8.25 m
VI		216–217	63	3385 3334 3199	1663	10.43 c	9.78 s	8.34 8.63	3.68 s 3.80 s 7.22 s

[a] In the cases of compounds **III** and **IV**, the absorption bands of NH and OH groups were observed in that spectral region.

Reactions of 1-methyl-1-nitroso-2-nitroguanidine with hydrazides of aliphatic and aromatic carboxylic acids performed in aqueous alcohol medium at 80–90°C gave *N*-(2-nitroguanidino)amides of the corresponding acids **I–VI** with yields up to 95%.

Refluxing of the obtained polynitrogen compounds **I–VI** in aqueous alkaline medium resulted in their intramolecular heterocyclization and thus formation of 3-nitroamino-5-alkyl(aryl)-1,2,4-triazoles **VII–XII** with yields up to 92%. Noteworthily, the cyclization of compounds **I–VI** occurred generally slower (within several hours) than in the case of *N*-(2-nitroguanidino)-amidooxalate (within 20 min, [7]).

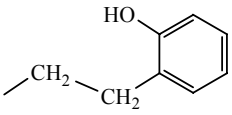
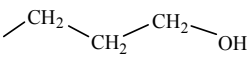
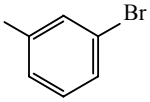
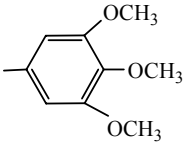
A possibility of one-pot synthesis of 5(3)-methyl-3(5)-nitroamino-1,2,4-triazole **VII** was demonstrated using condensation of 1-methyl-1-nitroso-2-nitroguanidine with *N*-(2-nitroguanidino)acetamide **I** as an example. The reaction was performed by refluxing the reagents mixture in aqueous alkaline medium for 2 h. The so prepared 5(3)-alkyl(aryl)-3(5)-nitroamino-1,2,4-triazoles were colorless high-melting crystalline substances.

The structures of **I–XII** were confirmed by ^1H, ^{13}C–{^1H} NMR, IR, and UV spectroscopy (Tables 1 and 2) as well as by comparison of the melting point of **VII** with that of the reference sample prepared previously by another method [8].

In the ^1H NMR spectra of the compounds, the signals of all structural fragments were identified.

For example, in the ^1H NMR spectrum of **VI** (Fig. 1), the broad signals of magnetically nonequivalent protons of primary NH_2 (8.34 and 8.63 ppm) and secondary NH^1, NH^2 (9.78 and 10.43 ppm) groups were observed in the weak field [9], being characteristic of the aminonitroguanidine structure. The spectrum contained the singlet signals of aromatic ring protons at 7.22 ppm and of those of methoxy groups at 3.68 and 3.80 ppm as well. The validity of the signals assignment was confirmed by ^1H–^{13}C HMQC and HMBC experiments [10, 11].

Table 2. Yields, melting points and spectral characteristics of 5(3)-alkyl(aryl, amino)-3(5)-nitroamino-1,2,4-triazoles **VII**–**XII**

Comp. no.	R	mp, ºC	Yield %	^{1}H NMR (DMSO-d_6), δ, ppm		Electronic spectra (ethanol)	
				NH	R	λ_{max}, nm	ε
VII	$-CH_3$	209–210	60	13.64 s	2.25	291	13000
VIII	$-C_7H_{15}$	185–186	75	13.90 s	0.65 m, 1.3 m, 1.6 m, 2.65 m	287	17000
IX		214–215	75	13.90 s	2.95 s, 6.65–7.15 m, 9.40 s	283	14500
X		196–199	65	13.90 s	1.80 t, 2.45 m, 2.70 m, 3.40 s	287	16000
XI		197–199	71	13.95 s	7.80–8.00 m	291	16500
XII		210–212	92	14.29 s	3.68 s, 3.81 s, 7.23 s	298	16500

In particular, the HMQC spectrum of **VI** (Fig. 2) contained the cross-peaks of proton signals at 3.68 ppm (3H, *p*-OCH_3) and 3.80 ppm (6H, *m*-OCH_3) with the carbon signals of *p*- and *m*-methoxy groups at 60.69 and 56.62 ppm, respectively, as well as of aromatic *ortho*-protons singlet at 7.22 ppm (2H) with the carbons signal at 106.03 ppm ($C^{2'}$, $C^{6'}$). In the HMBC spectrum of **VI** (Fig. 3), the cross-peaks of protons signal at 3.68 (*p*-OCH_3) with carbon signal at 141.15 ppm ($C^{4'}$, ^3J), 3.80 (*m*-OCH_3) with 153.08 ppm ($C^{3'}$, $C^{5'}$, ^3J), and 7.22 (*ortho*-H) with 153.08 ppm ($C^{3'}$, $C^{5'}$, ^2J) were observed. At the same time, the proton signal at 7.22 ppm gave rise to three additional cross-peaks, with the carbons signals at 127.65 ($C^{1'}$, ^2J), 141.15 ($C^{4'}$, ^3J), and 166.29 ppm (C=O, ^3J). The carbon signal with δ_C of 161.92 ppm with no cross-peaks in both HMQC and HMBC spectra was assigned to the $C{=}NNO_2$ carbon atom.

In the ^{1}H NMR spectra of **VII**–**XII** (Fig. 4), there were no proton signals of nitroguanidine fragment, the only downfield broad singlet observed in the range of 13.90–14.29 ppm was assigned to the NH group of triazole ring. Apparently, the signal of $NHNO_2$ group was absent due to its exchange, especially when DMSO-d_6 contained water admixture [12]. The chemical shifts of alkyl and aryl protons of **VII**–**XII** were close to those in the spectra of the starting compounds **I**–**VI**. In the $^{13}C-\{^1H\}$ NMR spectra of **VII** and **XII**, the ^{13}C signals of all structural fragments were identified. In particular, C^5 and C^3 atoms of triazole ring (Fig. 5) were assigned to the signals at 148.30 (**VII**), 148.87 (**XII**) and 153.12 (**VII**), 153.72 ppm (**XII**), respectively. The validity of their assignments was confirmed by the HMBC experiments. In the HMBC spectra, the cross-peak of the methyl group signal at 2.25 ppm with the signal at 148.30 ppm (**VII**) was present, along with the cross-peak of the aromatic ring *ortho*-protons signals (7.23 ppm) with the signal at 148.87 ppm (**XII**), thus, those signals could be assigned to C^5 of triazole ring. Analysis of other cross-peaks in the **XII** spectrum allowed accurate assignment of all the carbon atoms, similarly to the above-described for compound **VI**.

In the IR spectra of heterocycles **VII**–**XII**, a set of intense absorption bands was observed in the range of 1250–1630 cm^{-1}. The strong band at 1600–1630 cm^{-1} could be probably assigned to the combination of stretching of C=N and deformation of N–H bonds [13]. The absorption bands at 1550–1580 and 1260–1320 cm^{-1} were due to stretching of NO_2 group [14, 15]. The N–H valence vibrations were observed in the range of 3100–3600 cm^{-1}. In the cases of **III** and **IV**,

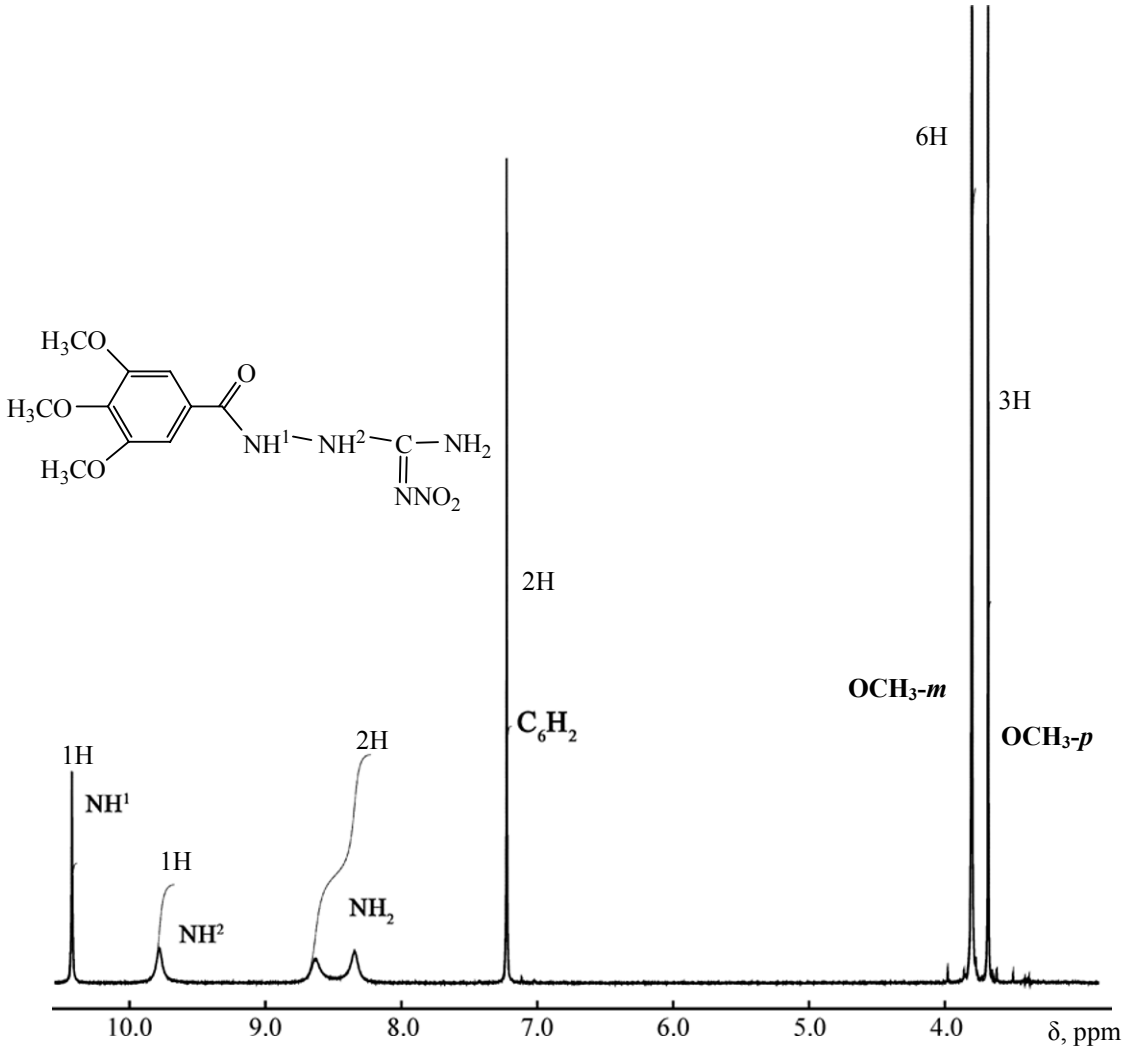


Fig. 1. ^{1}H NMR spectrum of compound **VI** in DMSO-d_6.

the absorption band assigned to OH group was observed in that region.

Electronic spectra of triazoles **VII**–**XII** contained an absorption band at 283–298 nm (ε = 13000–17000), being consistent with the data reported for the structurally similar compounds [7, 9].

To conclude, the studied reactions of 1-methyl-1-nitroso-2-nitroguanidine with carboxylic acid hydrazides were convenient methods to prepare the previously unknown 3(5)-5-nitroamino-5(3)-alkyl(aryl)-1,2,4-triazoles, compounds of potential interest for the medical applications. The obvious advantages of the developed method were availability of the starting materials, high yields of the target products, and possibility of one-pot synthesis under conditions of "green" chemical processes [16].

EXPERIMENTAL

The ^{1}H, ^{13}C–{^{1}H}, ^{1}H–^{13}C HMQC, and HMBC NMR spectra were recorded with Jeol ECX400A spectrometer [399.78 (^{1}H), 100.525 (^{13}C) MHz] in DMSO-d_6; the signals of residual non-deuterated solvent being the internal standard. The IR spectra were recorded with IRPrestige-21 Fourier-spectrometer in KBr pellets. The electronic spectra were recorded with Shimadzu UV2401PC spectrophotometer in quartz cuvettes (l = 0.1 cm, $c \sim 1.0\times10^{-3}$ mol l^{-1} in ethanol). Elemental analysis was performed with Eurovector EA 3000 (CHN Dual mode) analyzer.

1-Methyl-1-nitroso-2-nitroguanidine was prepared as described in [17]. Commercially available hydrazides of octanoic, 4-hydroxybutanoic, 3-(2-hydroxyphenyl)propanoic, 3-bromobenzoic, and 3,4,5-trimethoxybenzoic acids were used.

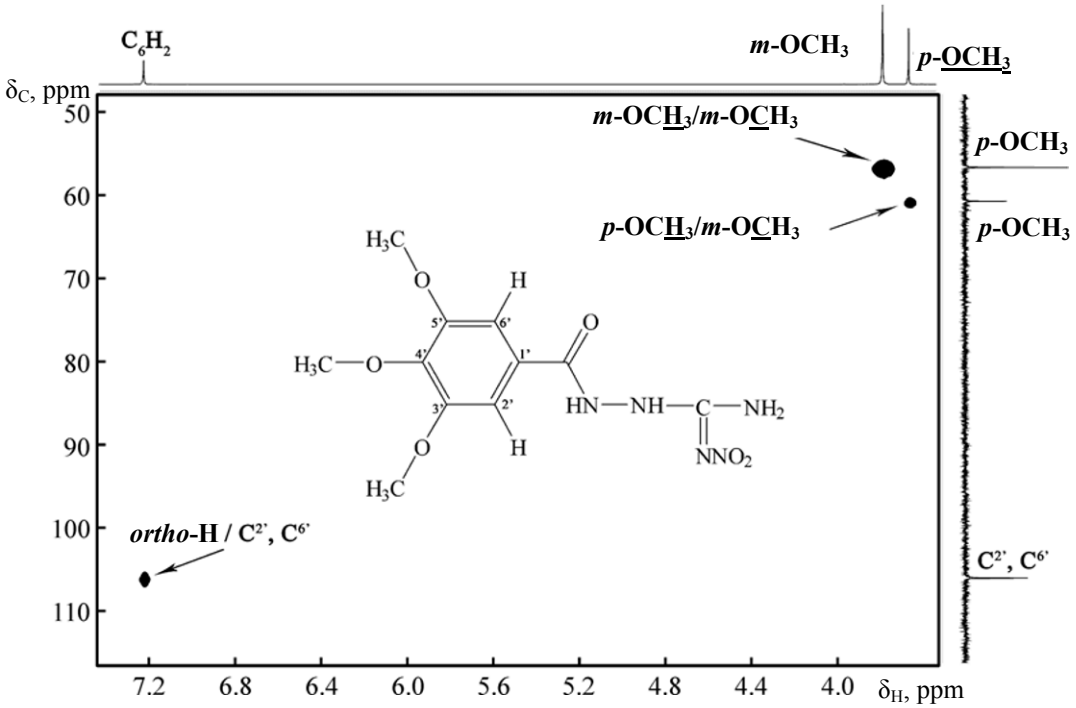


Fig. 2. $^{1}H–^{13}C$ HMQC spectrum of compound **VI** DMSO-d_6.

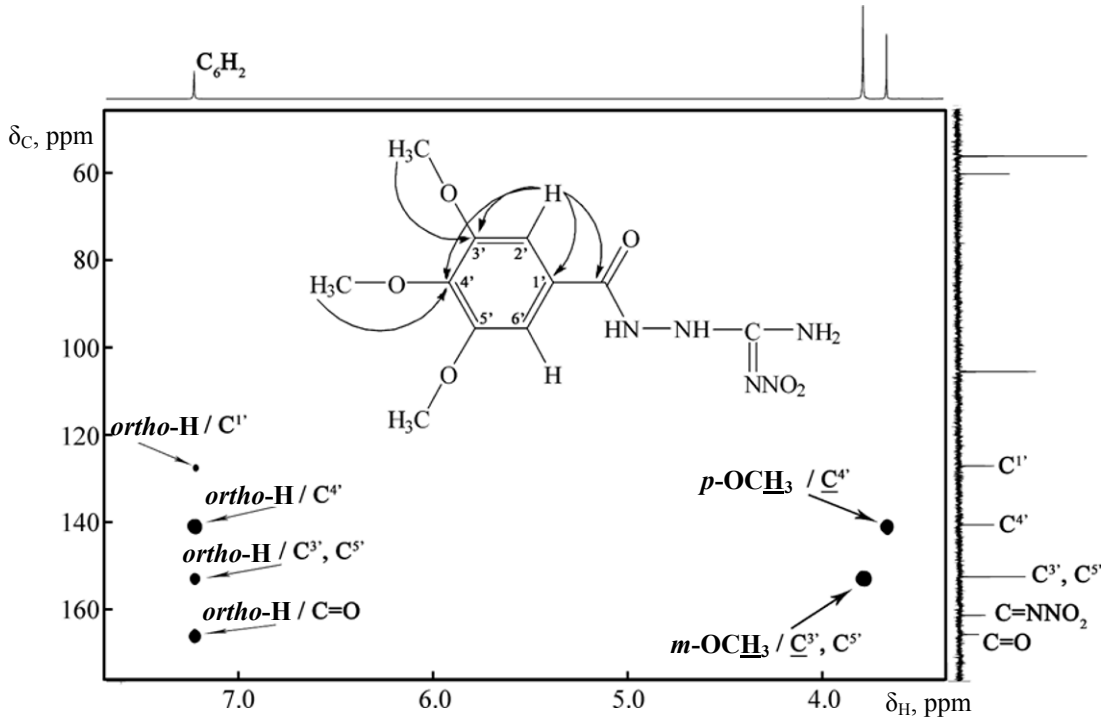


Fig. 3. $^{1}H–^{13}C$ HMBC spectrum of compound **VI** in DMSO-d_6.

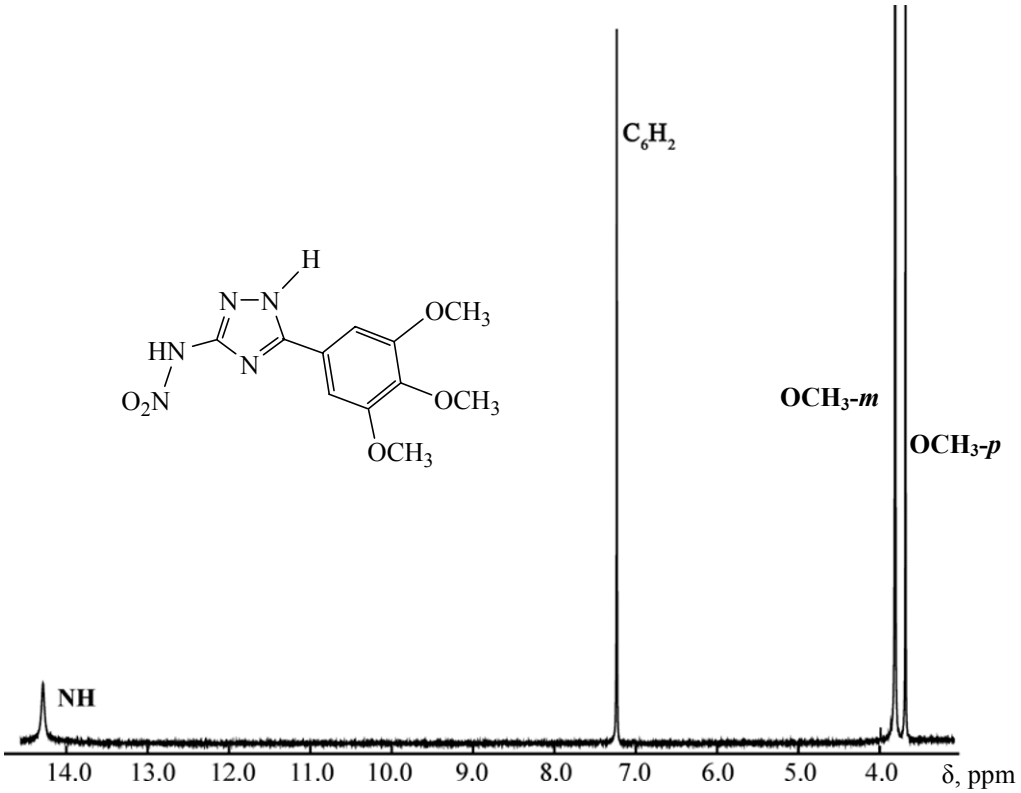


Fig. 4. [1]H NMR spectrum of compound **XII** in DMSO-d_6.

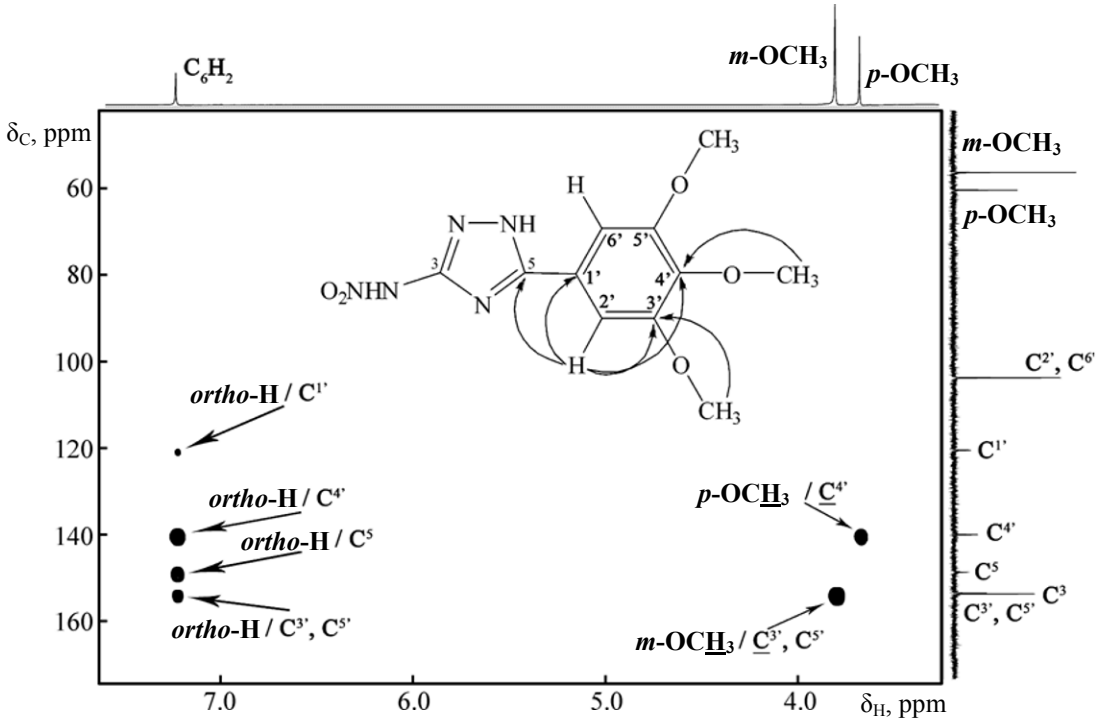


Fig. 5. [1]H–[13]C HMBC spectrum of compound **XII** in DMSO-d_6.

***N*-(2-Nitroguanidino)amide of acetic acid (I).** 23.52 g of 1-methyl-1-nitroso-2-nitroguanidine was added in small portions to a solution of 12.39 g of acetic acid hydrazide in 30 ml of water. The reaction mixture was heated to 80°C. When the precipitate was formed, the reaction mixture was kept for 10–15 h till the reaction completion. The resulting precipitate was filtered off, washed sequentially with cold water, ethanol, ether, and dried in air. Yield 17 g (66%), mp 191–192°C (water). Found, %: C 26.25; H 4.05; N 49.50. $C_3H_7N_5O_3$. Calculated, %: C 22.36; H 4.35; N 43.48.

***N*-(2-Nitroguanidino)amide of octanoic acid (II)** was prepared similarly from 2.07 g of octanoic acid hydrazide and 1.92 g of 1-methyl-1-nitroso-2-nitroguanidine. Yield 2.07 g (65%), mp 156–158°C (isopropanol–water, 1:1). Found, %: C 44.24; H 8.73; N 27.78. $C_9H_{19}N_5O_3$. Calculated, %: C 44.00; H 7.90; N 27.50.

***N*-(2-Nitroguanidino)amide of 3-(2-hydroxyphenyl)propanoic acid (III)** was prepared similarly from 2.6 g of 3-(2-hydroxyphenyl)propionic acid hydrazide and 1.92 g of 1-methyl-1-nitroso-2-nitroguanidine. Yield 2.6 g (75%), mp 175–176°C (isopropanol–water, 1:1). Found N, %: 26.21. $C_{10}H_{13}N_5O_4$. Calculated N, %: 26.20.

***N*-(2-Nitroguanidino)amide of 4-hydroxybutanoic acid (IV)** was prepared similarly from 1.56 g of 4-hydroxybutanoic acid hydrazide and 1.95 g of 1-methyl-1-nitroso-2-nitroguanidine. Yield 1.94 g (73%), mp 108–110°C (water). Found, %: H 5.22; N 34.44. $C_5H_{11}N_5O_4$. Calculated, %: H, 5.36; N 34.14.

***N*-(2-Nitroguanidino)amide of 3-bromobenzoic acid (V)** was prepared similarly from 0.52 g of 3-bromobenzoic acid hydrazide and 0.35 g of 1-methyl-1-nitroso-2-nitroguanidine. Yield 0.69 g (95%), mp 179–180°C (isopropanol–water, 1:1). Found, %: C 32.02; H 2.63; N 23.63. $C_9H_{11}N_5O_3Br$. Calculated, %: C 31.78; H 2.64; N 23.17.

***N*-(2-Nitroguanidino)amide of 3,4,5-trimethoxybenzoic acid (VI)** was prepared similarly from 1.26 g of 3,4,5-trimethoxybenzoic acid hydrazide and 0.82 g of 1-methyl-1-nitroso-2-nitroguanidine. Yield 1.15 g (63%), mp 216–217°C (isopropanol–water, 1:1). Found, %: C 42.36; H 4.77; N 21.96. $C_{12}H_{17}N_5O_6$. Calculated, %: C 42.10; H 4.70; N 22.3.

5(3)-Methyl-3(5)-nitroamino-1,2,4-triazole (VII). *a*. A solution of 0.4 g of sodium hydroxide in 5 ml of water was added to a solution of 1.61 g of acetic acid *N*-(2-nitroguanidino)amide I in 30 ml of water, and the reaction mixture was refluxed for 1–2 h till decolouration of the solution. Then the reaction mixture was cooled down to room temperature and acidified with concentrated hydrochloric acid to pH ~ 5. The resulting precipitate was filtered off and washed with water. Yield 1.14 g (60%), decomp. 212–213°C (water) {decomp. 208°C (water) [7]}.

b. 5.88 g of 1-methyl-1-nitroso-2-nitroguanidine was added in small portions to a solution of 3.31 g of acetic acid hydrazide in 50 ml of water. The reaction mixture was heated at 80ºC for 2 h. Then 2.24 g of sodium hydroxide was added to the mixture. The reaction mixture was heated for 1 h. After cooling down to room temperature, the reaction mixture was acidified with concentrated hydrochloric acid to pH ~ 5. The resulting precipitate was filtered off and washed with water. Yield 3.14 g (55%), decomp. 209–210°C (water). Melting point of the mixture of samples prepared by the both methods was not depressed. Found, %: C 25.17; H 3.49; N 48.95. $C_3H_5N_5O_2$. Calculated, %: C 25.46, H 3.96; N 47.87.

5(3)-Heptyl-3(5)-nitroamino-1,2,4-triazole (VIII). A solution of 0.4 g of sodium hydroxide in 5 ml of water was added to a solution of 2.27 g of octanoic acid *N*-(2-nitroguanidino)amide **II** in 20 ml of water. The reaction mixture was refluxed for 1–2 h till decolouration of the solution. The reaction mixture was cooled down to room temperature and acidified with concentrated hydrochloric acid to pH ~ 5. The resulting precipitate was filtered off and washed with water. Yield 1.53 g (75%), mp 185–186°C (water). Found, %: H 7.10; N 30.90. $C_9H_{17}N_5O_2$. Calculated, %: H 7.48; N 30.83.

5(3)-(2-Hydroxyphenyl)-3(5)-nitroaminoethyl-1,2,4-triazole (IX) was prepared similarly from 2.49 g of 3-(2-hydroxyphenyl)propanoic acid *N*-(2-nitroguanidino)-amide **III** and 0.4 g of sodium hydroxide. Yield 1.68 g (75%), mp 214–215°C (water). Found, %: C 42.36; H 4.77; N 21.96. $C_{10}H_{11}N_5O_3$. Calculated, %: C 42.1; H 4.7; N 22.3.

5(3)-(3-Hydroxypropyl)-3(5)-nitroamino-1,2,4-triazole (X) was prepared similarly from 1.88 g of 4-hydroxybutanoic acid *N*-(2-nitroguanidino)amide **IV** and 0.4 g of sodium hydroxide. Yield 1.1 g (65%), mp 197–199°C (water). Found, %: H 4.74; N 37.34. $C_5H_{10}N_5O_3$. Calculated, %: H 4.81; N 37.43.

3(5)-Nitroamino-5(3)-(3-bromophenyl)-1,2,4-triazole (XI) was prepared similarly from 2.99 g of 3-bromobenzoic acid *N*-(2-nitroguanidino)amide **V** and 0.4 g of sodium hydroxide. Yield 1.91 g (71%), mp 198–199°C (water).

3(5)-Nitroamino-5(3)-(3,4,5-trimethoxyphenyl)-1,2,4-triazole (XII) was prepared similarly from 3.09 g of 3,4,5-trimethoxybenzoic acid *N*-(2-nitroguanidino)-amide **VI** and 0.4 g of sodium hydroxide. Yield 2.56 g (92%), mp 210–212°C (water). Found, %: C 44.76; H 4.55; N 23.64. $C_{12}H_{15}N_5O_5$. Calculated, %: C 44.74; H 4.40; N 23.72.

Physico-chemical studies were performed in the Center for Collective Use in Herzen State Pedagogical University of Russia.

ACKNOWLEDGMENTS

This work was financially supported by the Government of St. Petersburg (diplomas PSP no. 11035, PSP no. 11036, 2011).

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