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β-Nitro- and β-Bromo-β-nitrostyrenes in the Reactions with Aminonitroguanidine

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Abstract—The conditions for the reactions of β-nitro- and β-bromo-β-nitrostyrenes with 1-amino-2-nitroguanidine resulting in the amination products, 1-nitro- and 1-bromo-1-nitro-2-aryl-2-(2-nitroguanidino-amino)ethanes, were found. Under the action of the basic catalysts or prolonged boiling, the adducts derived from the *gem*-bromonitrostyrenes undergo decomposition to form *N*-arylmethylidene-*N*-(2-nitroguanidino)amines.

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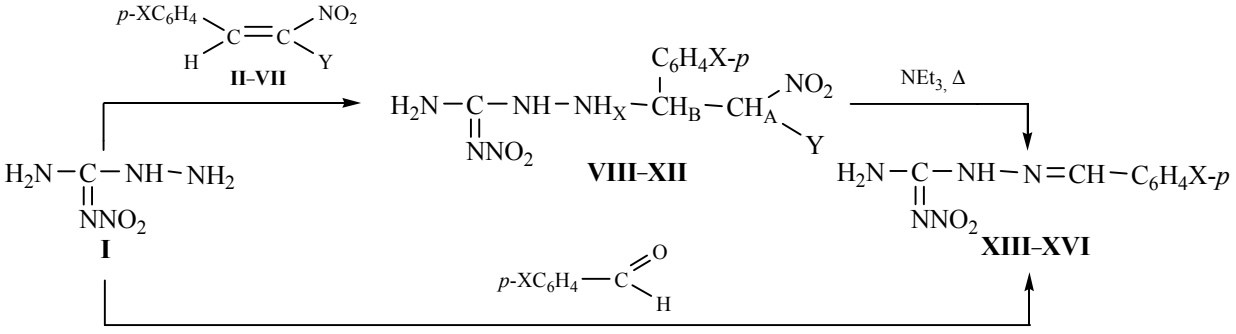
Guanidine and its derivatives are promising reagents for the synthesis of cyclic and open-chain polynitrogen systems, which have found application in many fields of science and technology. Some substituted guanidines have proven to be biologically active compounds with anticancer, antituberculosis, analgesic, fungicidal, and herbicidal activities, and are used in medicine and agriculture [1]. At the present time in medical practice drugs are used containing the guanidine fragment in the structure and possessing antihypertensive (guanfacine, guanabenz), antibacterial (sulginum), antimalarial (bigumalum) and hypoglycemic (phenformin, metformin, buformin) properties [2–4].

1-Amino-2-nitroguanidine behaves as an active nucleophile in the reactions with carbonyl compounds [5, 6], carboxylic acids and their derivatives [7–9]. The reaction of guanidine with the electron deficient alkenes such as β-nitro- and β-bromo-β-nitrostyrenes can be considered as another utilization of the nucleophilic activity of this compound.

The reaction of β-nitro- and β-bromo-β-nitrostyrenes with *N*,*N*-binucleophiles like semicarbazide, thiosemicarbazide, carboxylic acids hydrazides, and phenylhydrazine [10–12] have been reported, but the data on the reactions of nitroalkenes with aminonitroguanidin are absent.

We performed for the first time the reactions of β-nitro- and β-bromo-β-nitrostyrenes **II–VII** with 1-amino-2-nitroguanidine **I**. The reactions were found to proceed successfully in a water–alcohol medium at 60°C within 1–2 h to give the Ad_N products **VIII–XII** in 65–85% yields.

In the investigated reactions the β-bromo-β-nitrostyrenes are more active than β-nitrostyrenes. The reaction with the unsubstituted β-nitrostyrene did not occur even under the more rigid conditions (increase in



Y = H; X = NO_2 (**II, VIII**); Cl (**III, IX**); Y = Br; X = H (**IV, X, XIII**); NO_2 (**V, XI, XIV**); Cl (**VI, XII, XV**); Br (**VII, XVI**).

the reaction time and temperature). We succeeded in obtaining only adducts **VIII** and **IX** in the reaction of aminonitroguanidine with the substituted β-nitrostyrene containing in the *para*-position the electron-withdrawing groups (NO_2, Cl). β-Bromo-β-nitrostyrene **IV** and its derivatives **V** and **VI** also react with aminonitroguanidine to give the adducts **X**–**XII**, but in the presence of the basic reagents (triethylamine, potassium acetate) under short heating these compounds undergo cleavage accompanied by the elimination of the bromonitromethane anion to form the corresponding *N*-arylmethylidene-*N*-(2-nitroguanidino)amines **XIII**–**XV** in 70–80% yields.

A possibility to realize this tandem process (Ad_N–E) also in the one-pot reaction was shown by an example of the reaction of 1-bromo-2-(*p*-bromophenyl)-1-nitroethene **VII** with 1-amino-2-nitroguanidine **I**. The reaction proceeds successfully in 5 h at refluxing the reagents in isopropanol even in the absence of an additional catalyst and results in the corresponding aldimine **XVI**. Probably the adducts easily transform into the corresponding *N*-arylmethylidene-*N*-(2-nitroguanidino)amines due to the high stability of the leaving resonance-stabilized bromonitromethane anion and the formation of the conjugated system of favorable energy. Similar results were obtained in the reactions of *gem*-acetylnitroethenes with hydrazine and acetylhydrazine [13].

The physical characteristics of the obtained arylmethylidene guanidinoamines **XIII**–**XVI** coincide with those of the model compounds synthesized by the authentic synthesis starting from aromatic aldehydes and 1-amino-2-nitroguanidine; for the samples obtained the melting point depression was not observed.

The structure of all the newly synthesized compounds was confirmed by the ^{1}H NMR, IR and electronic spectroscopy data (Tables 1, 2).

The ^{1}H NMR spectra of compounds **VIII**–**XVI** contain the proton signals of the structural fragments. Thus, in the spectrum of compound **IX** (Fig. 1) the methine and methylene protons form an ABX spin system, which leads to the registration of their signals as characteristic multiplets in the range of 4.61–4.92 ppm (a nonequivalence of the methylene protons of CH_2NO_2-moiety is due to the vicinity of the chiral center). In the weaker field there are the broadened signals of the magnetically nonequivalent protons of the primary NH_2- group at 7.69 and 8.41 ppm, and the secondary NH_X- and NH-groups of aminonitroguanidine fragment at 5.83 and 9.38 ppm (this pattern of the proton signals is characteristic of the majority of the aminonitroguanidine derivatives [14]). The aromatic proton signals appear as the doublets at 7.40 and 7.50 ppm.

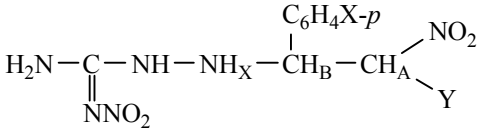
The spectra of compounds **X**–**XII** contain a double set of signals indicating their existence in a DMSO-d_6 as mixtures of diastereomers. Thus, the ^{1}H NMR spectrum of compound **X** (Fig. 2) is a multispin system of the H_B, NH_X and H_A protons of two diastereomers **a** and **b** in the ratio of 3:1. The spectrum of the diastereomer **Xa** contains the corresponding multiplets at 4.79, 6.11, 6.86 ppm, the spectrum of **Xb**, at 4.76, 5.95, 6.87 ppm. In the weak field there are the signals of the aromatic protons as multiplets at 7.35 and 7.43 ppm, as well as the broadened proton signals of NH_2- (7.40, 8.46 ppm) and NH-moieties (9.34, 9.39 ppm) of aminonitroguanidine fragment of two diastereomers.

The IR spectra of adducts **VIII**–**XII** contain the absorption bands of the primary and secondary amino groups in the region of 3450–3200 cm^{-1}, of the C=N bond (1630–1600 cm^{-1}), nonconjugated (1570–1560, 1370–1350 cm^{-1}) and conjugated nitro groups (1520, 1320 cm^{-1}) in the case of compounds **IX** and **XI**. The electronic spectra of compounds **VIII**–**XII** contain the characteristic absorption band of the nitroguanidine fragment at 269 nm [14].

In the ^{1}H NMR spectra of *N*-arylmethylidene-*N*-(2-nitroguanidino)amines **XIII**–**XVI** the protons of =CH, NH_2, and NH moieties resonate in a weak field at 8.10–8.20, 8.54–8.93, 11.80–12.02 ppm, respectively. The signals of aromatic protons appear at 7.39–8.22 ppm (Table 2). The IR spectral data of compounds **XIII**–**XVI** correspond to those of the related compounds [15]. The electronic spectra of compounds **XIII**–**XVI** contain the intensive longwave absorption bands (315–341 nm) originating from the chromophore system of these structures [16].

Therefore, β-nitrostyrenes containing a halogen atom or nitro group, and also β-bromo-β-nitrostyrenes add aminonitroguanidine when heated in a water–alcohol medium in the absence of a catalyst. The presence of the basic catalysts (triethylamine, potassium acetate) in the reaction mixture and the heating produce further transformation of the nucleophilic addition products derived from bromonitrostyrenes into the corresponding aldimines via the bromonitromethane elimination. The latter were shown to be available also through the one-pot synthesis by boiling

Table 1. Physicochemical characteristics of 1-nitro- and 1-bromo-1-nitro-2-aryl-2-(2-nitroguanidinoamino)ethanes **VIII–XII**



Comp. no.	Y	X	mp,[a] °C (**a**:**b**)	IR spectrum (KBr), ν, cm^{-1}		^{1}H NMR spectrum (DMCO-d_6), δ, ppm (J, Hz)						Electronic spectrum (ethanol)	
				NO_2	NH	H_A ($H_A H_{A'}$)	H_B	NH_X	NH	NH_2	Ar	λ_{max}, nm	ε
VIII	H	NO_2	173–175	1550 1535 1380 1350	3440 3370 3300 3200	(4.99 d.d 4.85 d.d) $^2J_{AAm}$ 13.50 $^3J_{AB}$ 5.88 $^3J_{A'B}$ 6.12	4.75 d.d	6.02 s	9.36 s	8.42 s 7.74 s	7.74 d 8.17 d	269	19000
IX	H	Cl	150–153	1560 1380	3430 3308 3207	(4.92 d.d 4.77 d.d) $^2J_{AA'}$ 13.02 $^3J_{AB}$ 6.30 $^3J_{A'B}$ 6.72 $^3J_{BX}$ 6.30	4.61 d.d	5.83 d	9.38 s	8.41 s 7.69 s	7.50 d 7.40 d	269	21000
Xa[b]	Br	H	132–135 (3:1)	1570 1380	3400 3325 3200	6.86 d $^3J_{AB}$ 8.06 $^3J_{BX}$ 3.91	4.79 d.d	6.11 d	9.34 s	7.36	7.35–7.43 m		
Xb[b]						6.87 d $^3J_{AB}$ 7.33 $^3J_{BX}$ 3.17	4.76 d.d	5.95 d	9.39 s	8.46 s	7.35–7.43 m	269	16000
XIa[b]	Br	NO_2	120–122 (1:1)	1570 1520 1350 1320	3440 3275 3210	6.95 d $^3J_{AB}$ 8.00 $^3J_{BX}$ 4.40	4.99 d.d	6.27 d	9.34 s	7.34 s 7.54 s	7.77 d 8.20 d	269	26000
XIb[b]						6.97 d $^3J_{AB}$ 6.59 $^3J_{BX}$ 3.42	4.98 d.d	6.17 d	9.42 s	8.52 s	7.77 d 8.22 d		
XIIa[b]	Br	Cl	122–125 (3:2)	1560 1370	3435 3410 3320 3200	6.85 d $^3J_{AB}$ 8.00 $^3J_{BX}$ 4.30	4.81 d.d	6.13 d	9.33 s	7.47	7.44d 7.46d		
XIIb[b]						6.87 d $^3J_{AB}$ 7.15 $^3J_{BX}$ 3.30	4.79 d.d	5.99 d	9.39 s	8.47 s	7.44 d 7.47 d	269	25000

[a] The melting points of compounds **X**–**XII** are given for the corresponding diastereomers mixtures (**a** and **b**). [b] For compounds **Xa**, **Xb**–**XIIa**, **XIIb** the diastereomer **a** contains in the spectrum the signal of H_A proton in the stronger field and the signals of H_B and H_X protons in a weaker field.

a mixture of bromonitrostyrene and aminonitroguanidine in an aqueous alcohol medium.

EXPERIMENTAL

The ^{1}H NMR spectra were taken from DMSO-d_6 solutions on a Jeol JNM-ECX400A spectrometer operating at 400 MHz relative to the residual protons of a deuterated solvent. The IR spectra were obtained on a Shimadzu IR Prestige-21 Fourier spectrometer from KBr pellets. The electronic spectra were registered on a Shimadzu UV-2401 PC spectrophotometer using quartz cells (l 0.1 cm, c 0.001 M) and

Table 2. Physicochemical characteristics of *N*-arylmethylidene-*N*-(2-nitroguanidino)amines **XIII–XVI**

$H_2N-C(=NNO_2)-NH-N=CH-C_6H_4X$-*p*

Comp. no.	X	mp, °C	IR spectrum (KBr), ν, cm^{-1}			^{1}H NMR spectrum (DMCO-d_6), δ, ppm				Electronic spectrum (ethanol)	
			NO_2[a]	C=N	NH	NH	NH_2	CH	X	λ_{max}, nm	ε
XIII	H	182–185	1445	1629	3454	11.80 s	8.81	8.11 s	7.82 m	221	13000
			1326	1613	3382		8.54		7.39 m	315	27500
					3245						
					3215						
XIV	NO_2	240–242	1514	1633	3457	12.02 s	8.93	8.20	8.22 d	218	7500
			1345	1611	3330		8.78	(Ar)	8.11 d	341	21500
			1417		3212						
			1344								
XV	Cl	210–211	1443	1628	3467	11.82 s	8.82	8.09 s	7.88 d	223	9000
			1323	1612	3241		8.60		7.46 d	319	26500
					3200						
					3171						
XVI	Br	219–220	1445	1628	3461	11.83 s	8.82	8.08 s	7.82 d	225	10000
			1325	1612	3241		8.61		7.61 d	322	29000
					3202						
					3174						

[a] The N–NO_2 absorption bands were assigned according to the published data [15].

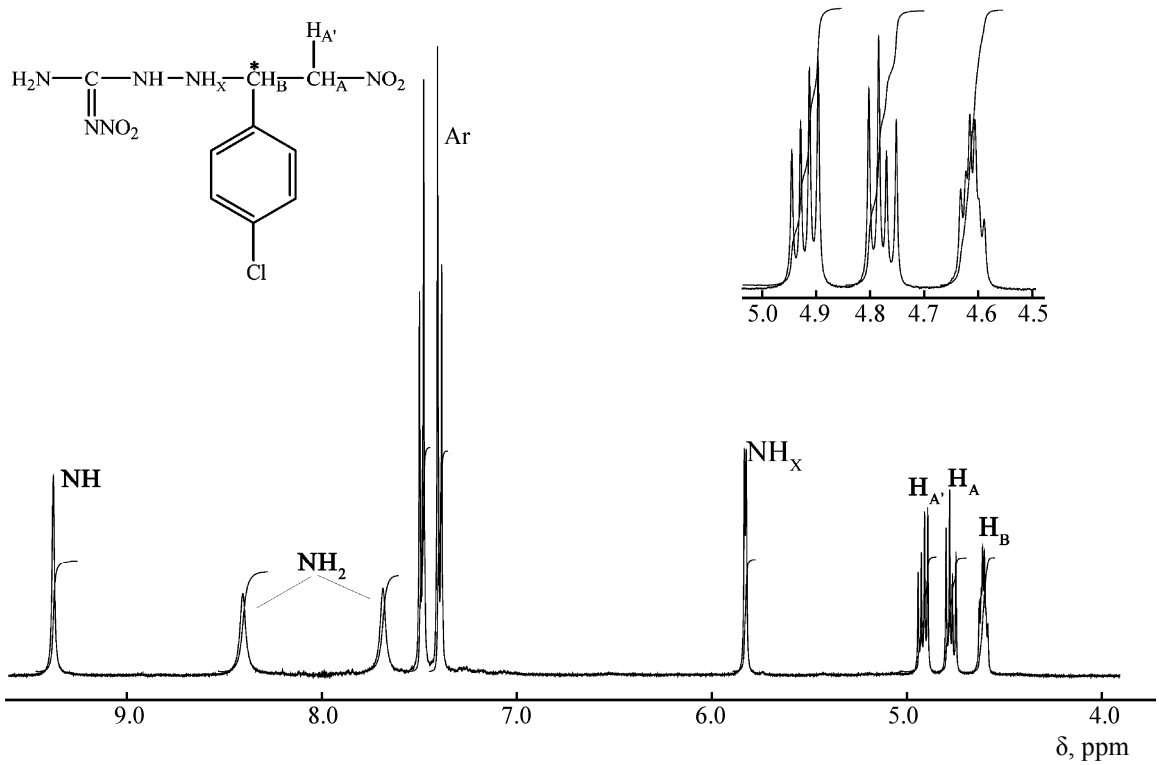


Fig. 1. ^{1}H NMR spectrum of compound **IX** in DMSO-d_6.

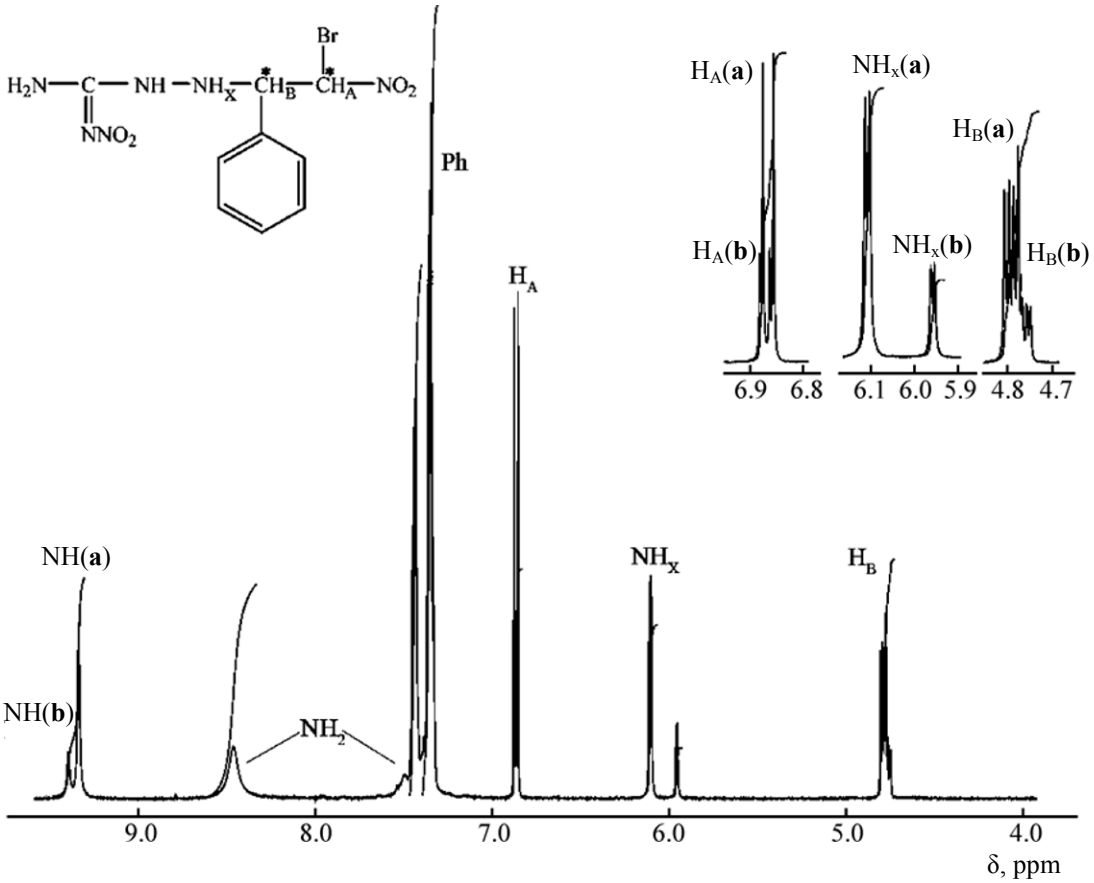


Fig. 2. ^{1}H NMR spectrum of a diastereomers mixture (**a**:**b** = 3:1) of compound **X** in DMSO-d_6.

ethanol as a solvent. The elemental analysis was performed on a Euro Vector (EA 3022 CHN Dual) analyzer. The homogeneity of the products obtained and the reaction progress were monitored by thin layer chromatography (TLC) on Silufol UV 254 plates eluting with a hexane–acetone mixture (3:2) and detecting with UV (254 nm) irradiation.

Aminonitroguanidine **I** and β-nitro- and β-bromo-β-nitrostyrenes **II**–**VII** were obtained according to the procedures [17] and [18–22], respectively.

1-Nitro-2-(2-nitroguanidinoamino)-2-(4-nitrophenyl)ethane (VIII). To a solution of 0.3 g of 1-nitro-2-(4-nitrophenyl)ethene **II** in 30 ml of isopropanol was added a solution of 0.18 g of 1-amino-2-nitroguanidine **I** in 10 ml of water. The reaction mixture was heated to 60°C and stirred for 1.5 h, then cooled to 18–20°C. The crystalline precipitate was filtered off, washed with water, ethanol, ethyl ether, and dried in air. Yield 0.48 g (57%), mp 173–175°C (isopropanol). Found, %: C 34.92; H 3.66; N 31.68. $C_9H_{11}N_7O_6$. Calculated, %: C 34.50; N 31.30; H 3.51.

1-Nitro-2-(2-nitroguanidinoamino)-2-(4-chlorophenyl)ethane (IX) was obtained similarly from the 0.51 g of 1-nitro-2-(4-chlorophenyl)ethene **III** and 0.33 g of 1-amino-2-nitroguanidine **I**. Yield 0.60 g (74%), mp 150–153°C (isopropanol). Found N, %: 28.70. $C_9H_{11}N_6O_4Cl$. Calculated N, %: 27.81.

1-Bromo-1-nitro-2-(2-nitroguanidinoamino)-2-phenylethane (X) (diastereomers mixture, **a:b** = 3:1**).** To a solution of 0.55 g of β-bromo-β-nitrostyrene **IV** in 35 ml of isopropanol was added a solution of 0.27 g of 1-amino-2-nitroguanidine **I** in 10 ml of water. The reaction mixture was heated to 60°C and stirred for 1 h, then cooled to 18–20°C. The crystalline precipitate was filtered off, washed with water, ethanol, ethyl ether, and dried in air. Compound **X** was isolated as a diastereomers mixture (**a:b** = 3:1). Yield 0.70 g (84%), mp 132–135°C (isopropanol). Found, %: C 31.98; H 3.29; N 24.12. $C_9H_{11}N_6O_4Br$. Calculated, %: C 31.12; H 3.17; N 24.20.

1-Bromo-1-nitro-2-(2-nitroguanidinoamino)-2-(4-nitrophenyl)ethane (XI) was obtained similarly

from 0.37 g of 1-bromo-1-nitro-2-(4-nitrophenyl)ethene **V** and 0.16 g of 1-amino-2-nitroguanidine **I**. Compound **XI** was isolated as a diastereomers mixture (**a:b** = 1:1). Yield 0.48 g (51%), mp 120–122°C (isopropanol). Found, %: C 34.92; H 3.66; N 31.68. $C_9H_{10}N_7O_6Br$. Calculated, %: C 34.50; H 3.51; N 31.30.

1-Bromo-1-nitro-2-(2-nitroguanidinoamino)-2-(4-chlorohenyl)ethane (XI) was obtained similarly from 0.4 g of 1-bromo-1-nitro-2-(4-chlorophenyl) ethene **VI** and 0.18 g of 1-amino-2-nitroguanidine **I**. Compound **XII** was isolated as a diastereomers mixture (**a:b** = 3:2). Yield 0.56 g (62%), mp 122–125°C (isopropanol). Found, %: C 35.98; H 3.64; N 28.70. $C_9H_{10}N_6O_4ClBr$. Calculated, %: C 35.76; H 4.12; N 27.81.

***N*-Benzylidene-*N*-(2-nitroguanidino)amine (XIII).** *a*. To a solution of 0.25 g of 1-bromo-1-nitro-2-(2-nitroguanidinoamino)-2-phenylethane **X** in 25 ml of isopropanol was added 0.1 ml of triethylamine at 70°C. The mixture was boiled for 10 min, and then poured into the cold water. The crystalline precipitate was filtered off and washed with water. Yield 0.03 g (21%) mp 182–185°C (isopropanol–water, 2:1) (mp 188°C [23]). Found, %: C 47.05; H 4.50; N 34.17. $C_8H_9N_5O_2$. Calculated, %: C 46.37; H 4.34; N 33.81.

b. To a solution of 0.15 g of 1-bromo-1-nitro-2-(2-nitroguanidinoamino)-2-phenylethane **X** in 25 ml of isopropanol was added a solution of 0.062 g of potassium acetate in 2 ml of water at 70°C. The mixture was heated at 80°C for 10 min and poured into the crushed ice. The crystalline precipitate was filtered off. Yield 0.03 g (37%), mp 181–183°C (isopropanol–water, 2:1).

c. To a solution of 0.265 g of benzaldehyde in 10 ml of ethanol was added a solution of 0.3 g of 1-amino-2-nitroguanidine **I** in 10 ml of water. The mixture was heated at 80°C for 5 min and cooled. The crystalline precipitate was filtered off. Yield 0.5 g (95%), mp 180–183°C (isopropanol–water, 2:1). For all samples the melting point depression was not observed.

***N*-(2-Nitroguanidine)-*N*-(4-nitrophenylmethylidene)amine (XIV)** was obtained similarly by the *a* method from 0.98 g of **XI**. Yield 0.49 g (79%), mp 240–242°C (isopropanol–water, 2:1). Found N, %: 32.57. $C_8H_8N_6O_4$. Calculated N, %: 33.33.

The synthesis by the *c* method from 0.54 g of *p*-nitrobenzaldehyde and 0.42 g of 1-amino-2-nitroguanidine **I** yielded 0.86 g (95%) of compound **XIV**, mp 240–243°C (isopropanol–water, 2:1). For two samples the melting point depression was not observed.

***N*-(2-Nitroguanidino-*N*-(4-chlorophenylmethylidene)amine (XV)** was obtained similarly by the *a* method from 0.95 g of **XII**. Yield 0.4 g (65%), mp 210–211°C (isopropanol–water, 2:1). Found N, %: 29.18. $C_8H_8N_5O_2Cl$. Calculated N, %: 29.04.

The synthesis by the *c* method from 0.54 g of *p*-chlorobenzaldehyde and 0.42 g of 1-amino-2-nitroguanidine **I** yielded 0.56 g (93%) of compound **XV**, mp 210–212°C (isopropanol–water, 2:1). For two samples the melting point depression was not observed.

***N*-(4-Bromophenylmethylidene)-*N*-(2-nitroguanidino)amine (XVI).** To a hot solution of 0.3 g of 1-bromo-2-(4-bromophenyl)-1-nitroethene **VII** in 15 ml of isopropanol was added a solution of 0.115 g of 1-amino-2-nitroguanidine **I** in 10 ml of water. The mixture was boiled for 5 h and cooled to 18–20°C. The crystalline precipitate was filtered off, washed with alcohol, ether, and dried in air. Yield 0.02 g (71%), mp 219–220°C (isopropanol–water, 2:1). Found N, %: 24.31. $C_8H_8N_5O_2Br$. Calculated N, %: 24.47.

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