4-Substituted 2-nitrophenylguanidines
I. Synthesis and cyclization of 4-substituted 2-nitrophenylguanidines

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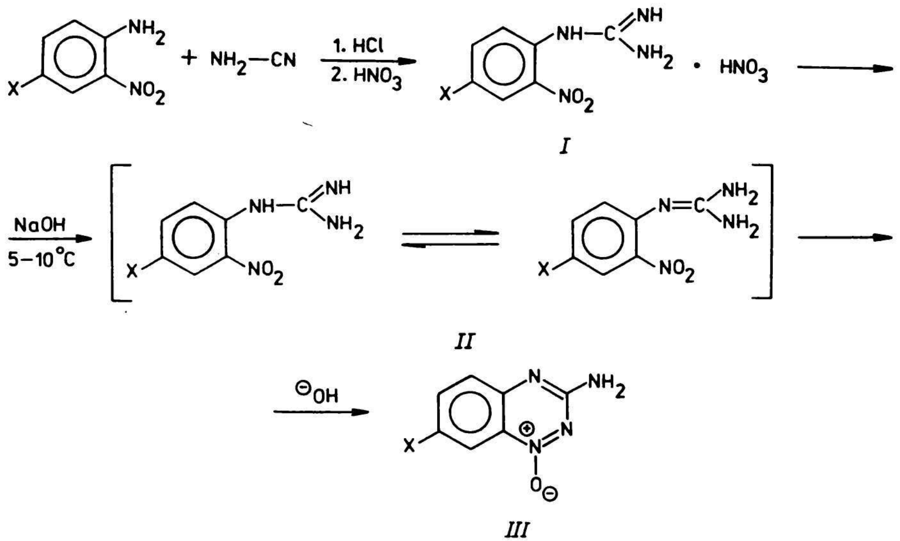
Dedicated to Professor RNDr. J. Hadáček, in honour of his 80th birthday

4-Substituted 2-nitrophenylguanidines were prepared by either an acid-catalyzed addition of 4-substituted 2-nitroanilines to cyanamide or a nucleophilic substitution of chlorine atom in 1-chloro-2,4-dinitrobenzene and 4-chloro-3-nitrobenzonitrile with guanidine. The products were isolated and identified as nitrates. 4-Substituted 2-nitrophenylguanidines nitrates under basic catalysis were cyclized to 3-amino-7-substituted 1,2,4-benzotriazine-1-oxides.

Получены замещенные в положении 4 2-нитрофенилгуанидины как путем кислотно катализируемого присоединения замещенных в положении 4 2-нитроанилинов к цианамиду, так и путем нуклеофильного замещения атома хлора в 1-хлор-2,4-динитробензоле и 4-хлор-3-нитробензонитриле гуанидином. Продукты были выделены и идентифицированы в форме нитратов. Нитраты замещенных в положении 4 2-нитрофенилгуанидинов в условиях щелочного катализа были подвержены циклизации в 3-амино-7-замещенные 1,2,4-бензотриазин-1-оксиды.

Substituted 2-nitrophenylguanidines are the starting compounds for the preparation of 3-amino-1,2,4-benzotriazine derivatives. These substances due to their physiological effect found broad application as bacteriostats, antimalarials, fungicides or growth stimulators [1].

2-Nitrophenylguanidine in a form of slightly soluble nitrate *Ia* was first prepared by *Arndt* [2] by the reaction of 2-nitroaniline with cyanamide under catalysis of hydrochloric acid smelting. By the treatment with alkaline hydroxide the compound *Ia* was converted to the free base *IIa*, which was identified as 2-nitrophenylguanidine hydrate (Scheme 1, X = H). An anhydrous product was isolated as an oily substance which was not possible to be converted into a crystalline form.



	X		X
a	H	*e*	Cl
b	CH_3	*f*	OPh
c	OCH_3	*g*	CN
d	Br	*h*	NO_2

Ia—IIIa [2, 11], *Ih—IIIh* [9, 12], *IIIb* [3, 6, 11], *IIIc* [3, 6, 7, 11], *IIId* [3], *IIIe* [3, 11].

Scheme 1

Later on the reaction of 4-substituted 2-nitroanilines with cyanamide, sodium cyanamide or chloride, was used for the synthesis of substituted 3-amino-1,2,4-benzotriazine-1-oxides (*III*) [3—12]. 2-Nitrophenylguanidines, which were formed there as intermediates, started immediately in the presence of alkaline hydroxide the cyclization reaction to the corresponding derivatives *III* (Scheme 1).

Results and discussion

The information mentioned above was used for the preparation of new compounds *Ib—If* and *IIb—IIf* so far not described in literature.

Compounds *II* were isolated from the reaction mixture as slightly soluble nitrates and recrystallized from diluted nitric acid with addition of charcoal to separate them from unreacted aniline, cyanamide and products of its hydrolysis as well as from 4-substituted 2-nitrophenylbiguanidine. Even so, as the results of TLC showed, the nitrates were contaminated after crystallization by starting anilines. These were successfully separated from nitrates *I* by extraction with boiling chloroform.

Attempts to synthesize 2,4-dinitrophenylguanidine (*IIh*) smelting 2,4-dinitroaniline with cyanamide in the presence of a strong mineral acid failed probably due to low basicity of 2,4-dinitroaniline. A reaction of cyanamide with 2,4-dinitroaniline in boiling acetic acid in the presence of a strong mineral acid lasting several hours was unsuccessful, too. Therefore the compound *IIh* was prepared by a nucleophilic substitution of the chlorine atom in the molecule of 1-chloro-2,4-dinitrobenzene by guanidine. This substitution reaction carried out in either ethanolic or butanolic solution was accompanied by the cyclization of the compound *IIh* to 3-amino-7-nitro-1,2,4-benzotriazine-1-oxide (*IIIh*).

It was shown to be advantageous to carry out the nucleophilic substitution in a mixture of butanol—benzene starting from guanidinium chloride, which was then converted in the reaction mixture to the free base by sodium butoxide. Benzene in the reaction mixture caused the precipitation of the forming 2,4-dinitrophenylguanidine and so suppressed its following cyclization and increased the reaction yield.

The compound *IIg* was prepared analogously with *IIh* from 4-chloro-3-nitrobenzonitrile.

After crystallization from 1—2 M nitric acid nitrates *Ia*—*Ih* formed hydrates which already standing in air were losing part of water of crystallization (its content was not determined) and under drying at the temperature over 105 °C were converted into anhydrous compounds.

The conversion of nitrates into free bases had to be carried out by 10 % aqueous solution of sodium hydroxide at the temperature of 5—10 °C to prevent a higher contamination of the product with compound *III*.

The purity of the compounds *IIa*—*IIh* was examined by the TLC. It was found that the unreacted nitrate *I* as well as the product *III* of the cyclization reaction were impurities and contained a changeable amount of water of crystallization. An attempt to get anhydrous compounds by their recrystallization from anhydrous ethanol failed. But crystallization from dried aprotic solvents was shown to be successful.

A cyclization of compounds *II* to products *III* was carried out in two preparative ways. Compounds *IIg* and *IIh* having a strong electron-attracting group undergo the following rearrangement to derivatives of benzotriazole [8] after cyclization upon treatment of alkaline hydroxide in the reaction mixture. In order to suppress this reaction the products of cyclization *IIIg* and *IIIh* were prepared from the starting material by the reaction in a suspension.

In other cases the cyclization may be carried out so that the corresponding nitrate is dissolved in a hot aqueous solution of sodium hydroxide and this is heated to reflux for several minutes.

The structure and the purity of the prepared compounds were proved by elemental analysis, IR and NMR spectra, and TLC on Silufol (the mobile phase was ether or a mixture ethyl acetate—ethanol (volume ratio $\varphi_r = 2:1$)).

A series of compounds *II* and *III* were prepared for a kinetic investigation of a reaction pathway of cyclization of *II* to *III* (see the following papers).

IR and ^{1}H NMR spectra are discussed in the following papers in connection with the kinetic study of the cyclization.

The correlation of the chemical shift in ^{13}C NMR spectra of the C-7 carbon atom in guanidine group (Table 3) with σ_p Hammett substituent constants is expressed by the following equation

$$\delta_{\text{C-7}} = (5.141 \pm 0.222) \cdot \sigma_p + (152.02 \pm 0.88) \qquad r = 0.919$$

Experimental

Melting points were measured on a Kofler hot-stage VEB Wägetechnik Rapido 79-2106. Elemental analysis was performed with an elemental analyzer CHN C. Erba 1102.

Solvents, melting points, yields, elemental analyses, and spectral characteristics of the synthesized compounds are presented in Tables 1 and 2.

TLC was performed on Silufol UV 254 (Kavalier, Votice), the detection carried out with Fluotest Universal, Quarzlampen Hanau.

Infrared spectra were taken on a Unicam SP 1000 spectrophotometer (compounds *I* in KBr pellets, compounds *II* in a bromoform solution, compounds *III* in a bromoform suspension). ^{13}C NMR spectra of compounds *II* were recorded in DMSO-d_6 with Tesla BS 567 (25 MHz) spectrophotometer using HMDSO as an internal standard (Table 3). ^{1}H NMR spectra are presented in [13].

4-X-2-Nitrophenylguanidinium nitrate (Ia—If)

Compounds *Ia—If* were prepared in accordance with [2]; the isolation was modified in the following way:

The reaction mixture was cooled down to room temperature and then nitric acid (80 cm^3; $c = 2$ mol dm^{-3}) was added. A several hours standing at the temperature of 5—10 °C allowed to crystallize *I*.

After washing with cold water (20 cm^3) the product was recrystallized from 1—2 M nitric acid with charcoal and dried at 105 °C. The dried stuff was suspended and refluxed for about 10 min in 200 cm^3 of chloroform. The solid stuff was filtered off.

4-Cyano-2-nitrophenylguanidinium nitrate (Ig)

Sodium (2.6 g; 0.11 mol) was added into a mixture of ethanol (50 cm^3) and benzene (50 cm^3) and left to react under a cooler with a potassium hydroxide stopper. Afterwards guanidinium chloride (9.55 g; 0.11 mol) was added into the reaction mixture and stirring

Table 1

Characteristics of the synthesized compounds

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield/%	M.p./°C Solvent
			C	H	N		
Ia	$C_7H_9N_5O_5$	243.18	34.58	3.73	28.80	47	159
			34.26	3.71	28.79		
Ib	$C_8H_{11}N_5O_5$	257.21	37.36	4.31	27.23	58	238—239
			37.23	4.29	27.11		
Ic	$C_8H_{11}N_5O_6$	273.21	35.17	4.06	25.63	49	189
			35.21	3.94	25.54		
Id	$C_7H_8N_5O_5Br$	322.08	26.11	2.50	21.74	56	225
			26.14	2.40	21.75		
Ie	$C_7H_8N_5O_5Cl$	277.65	30.28	2.90	25.22	59	230
			30.15	2.82	25.24		
If	$C_{13}H_{13}N_5O_6$	335.31	46.57	3.91	20.89	57	162—163
			46.48	3.85	20.70		
Ig	$C_8H_8N_6O_5$	268.19	35.83	3.01	31.34	38	238—239
			35.81	2.98	31.26		
Ih	$C_7H_8N_6O_7$	288.19	29.18	2.80	29.16	70	237—238
			29.02	2.80	29.08		

Table 1 (Continued)

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield/%	M.p./°C Solvent
IIa	$C_7H_8N_4O_2$	180.17	46.67 46.42	4.48 4.43	31.10 31.03	61	138–139 Benzene
IIb	$C_8H_{10}N_4O_2$	194.20	49.48 49.33	5.19 5.25	28.85 28.66	52	154 Chloroform
IIc	$C_8H_{10}N_4O_3$	210.20	45.72 45.55	4.80 4.77	26.65 26.57	46	143–144 Toluene
IId	$C_7H_7N_4O_2Br$	259.07	32.46 32.18	2.77 2.68	21.63 21.38	61	192–193 Benzene
IIe	$C_7H_7N_4O_2Cl$	214.61	39.18 39.04	3.28 3.25	26.10 26.00	59	199–201 Toluene
IIf	$C_{13}H_{12}N_4O_3$	272.29	57.35 57.20	4.44 4.41	20.58 20.46	65	159–160 Xylene
IIg	$C_8H_7N_5O_2$	205.18	46.83 46.79	3.44 3.44	34.14 34.00	89	186–187 Benzene
IIh	$C_7H_7N_5O_4$	225.16	37.34 37.26	3.13 3.11	31.10 30.94	70	206 Benzene : nitrobenzene ($\varphi_r = 2:1$)

Table 1 (Continued)

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield/%	M.p./°C Solvent
IIIa	$C_7H_6N_4O$	162.15	51.85	3.73	34.55	98	270
			51.62	3.60	34.46		Methylcellosolve
IIIb	$C_8H_8N_4O$	176.16	54.59	4.58	31.80	96	282
			54.51	4.50	31.78		Methylcellosolve
IIIc	$C_8H_8N_4O_2$	192.16	50.00	4.20	29.15	92	271 274
			49.85	4.15	28.96		Pyridine
IIId	$C_7H_5N_4OBr$	241.05	34.88	2.09	23.24	98	311 312
			34.84	2.06	23.12		Pyridine
IIIe	$C_7H_5N_4OCl$	196.59	42.76	2.56	28.50	95	306 308
			42.70	2.54	28.52		Acetic acid
IIIf	$C_{13}H_{10}N_4O_2$	254.27	61.41	3.96	22.04	96	269 270
			61.35	3.92	21.98		Dioxan
IIIg	$C_8H_5N_5O$	187.16	51.34	2.69	37.42	96	252 253
			51.30	2.59	37.36		Acetone + water
IIIh	$C_7H_5N_5O_3$	207.15	40.61	2.43	33.81	95	290
			40.46	2.41	33.72		Pyridine + ethanol

Table 2

IR spectral characteristics of the synthesized compounds

Compound	$\tilde{\nu}$/cm^{-1}					
	$\nu_s(NO_2)$	$\nu_{as}(NO_2)$	$\nu_{as}(NO_3^-)$	$\nu(C{=}N^+)$	$\nu(NH)$	$\nu(C{\equiv}N)$
Ia	1345	1530	1390	1670	3300	
Ib	1350	1545	1395	1685	3300	
Ic	1345	1540	1390	1680	3310	
Id	1340	1540	1385	1685	3300	
Ie	1340	1540	1390	1685	3300	
If	1340	1530	1390	1680	3320	
Ig	1360	1540	1385	1700	3300	2240
Ih	1350	1535	1385	1680	3280	

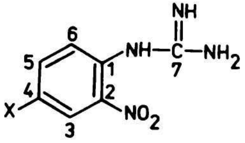
Compound	$\tilde{\nu}$/cm^{-1}						
	$\nu_s(NO_2)$	$\nu_{as}(NO_2)$	$\nu(C{=}N^+)$	$\nu(NH)$			$\nu(C{\equiv}N)$
IIa	1335	1550	1650	3320	3380	3450	
IIb	1335	1550	1650	3320	3360	3430	
IIc	1345	1530	1655	3330	3380	3440	
IId	1335	1540	1640	3320	3380	3450	
IIe	1335	1545	1645	3300	3400	3460	
IIf	1350	1530	1650	2290	3380	3440	
IIg	1335	1535	1645	3300	3390	3460	2230
IIh	1330	1540	1635	3280	3360	3420	

Compound	$\tilde{\nu}$/cm^{-1}						
	$\nu(N{-}O)$	$\nu(C{=}N^+)$	$\nu_s(NH_2)$	$\nu_{as}(NH_2)$	$\nu(CN)$	$\nu_s(NO_2)$	$\nu_{as}(NO_2)$
IIIa	1365	1650	3170	3330			
IIIb	1350	1635	3120	3300			
IIIc	1360	1640	3125	3300			
IIId	1350	1650	3160	3320			
IIIe	1350	1645	3160	3310			
IIIf	1350	1635	3140	3300			
IIIg	1355	1640	3135	3300	2230		
IIIh	1350	1650	3160	3310		1350	1530

left for 20 min at room temperature. Finally 4-chloro-3-nitrobenzonitrile (9.1 g; 0.05 mol) was added to the reaction mixture and dried tetrahydrofuran (20 cm^3) dropped in. The mixture became dark red and its temperature rose by about 10—15 °C. After 6 h standing at room temperature, the solid was filtered off and then extracted with 3 portions of 50 cm^3 of hot ethanol. The filtrate and the ethanolic extract were collected and concentrated to 1/3 of the whole volume with a vacuum rotating evaporator. Nitric acid (60 cm^3; w = 25 %) was added to the rest and the mixture left to crystallize at 5—10 °C shaking it from time to time. Crystals of nitrate were filtered off and worked up by the method mentioned above.

Table 3

^{13}C NMR spectral characteristics of the compounds *II*



Compound	δ/ppm							
	$\delta_{C\text{-}1}$	$\delta_{C\text{-}2}$	$\delta_{C\text{-}3}$	$\delta_{C\text{-}4}$	$\delta_{C\text{-}5}$	$\delta_{C\text{-}6}$	$\delta_{C\text{-}7}$	$\delta_{C\text{-}X}$
IIa	142.06 (s)	143.56 (s)	130.72	124.11	121.91	117.43	152.62 (s)	
IIb	141.24 (s)	141.77 (s)	124.08 (d)	126.83 (s)	131.63 (d)	121.83 (d)	151.47 (s)	17.84 (q) CH_3
IIc	136.43 (s)	141.76 (s)	125.53 (d)	150.69 (s)	128.43 (d)	116.00 (d)	152.00 (s)	53.71 (q) OCH_3
IId	127.35 (s)	142.17 (s)	126.12 (d)	143.11 (s)	133.22 (d)	124.22 (d)	151.81 (s)	
IIe	129.61 (s)	141.89 (s)	126.37 (d)	144.21 (s)	134.00 (d)	124.40 (d)	152.18 (s)	
IIf	140.00 (s)	141.66 (s)	123.78 (d)	146.51 (s)	125.91 (d)	114.45 (d)	151.99 (s)	155.21 (s) 115.89 (d) 128.11 (d) 121.32 (d) OPh
IIg	134.17 (s)	139.32 (s)	123.29 (d)	144.57 (s)	125.62 (d)	119.32 (d)	155.58 (s)	115.90 (s) CN
IIh	132.98 (s)	138.17 (s)	121.98 (d)	150.47 (s)	124.93 (d)	118.25 (d)	157.14 (s)	

2,4-Dinitrophenylguanidinium nitrate (Ih)

Sodium (4.84 g; 0.21 mol) was left to react in absolute butanol (80 cm^3) under stirring. After the reaction ceased more butanol (40 cm^3) was added. Then guanidinium chloride (20 g; 0.21 mol) was added into the reaction mixture under vigorous stirring and the mixture was stirred for another 30 min at room temperature. Then dried benzene (50 cm^3) was poured in and 1-chloro-2,4-dinitrobenzene (20.2 g; 0.1 mol) was added step by step under permanent stirring. The reaction mixture got thicker after 2 h at 40 °C. After cooling to 10 °C the solid was filtered off and then dissolved in hot water (200 cm^3), the solution being filtered with charcoal. Nitric acid (30 cm^3; $w = 40$ %) was added into the filtrate and the mixture left to crystallize for 3 h at 5—10 °C; the product was filtered off. Another portion of the product was obtained from the benzene—butanol mother liquor so that it was shaken with nitric acid (50 cm^3; $c = 2$ mol dm^{-3}) and the aqueous layer was separated. After 12 h standing nitrate fell out and was collected and washed with water. Both portions were recrystallized from 2 M nitric acid with charcoal. The product was dried at 105 °C and extracted with boiling chloroform (300 cm^3).

4-X-2-Nitrophenylguanidine (IIa—IIh)

Finely ground nitrate *Ia—Ih* (0.05 mol) was mixed with sodium hydroxide aqueous solution (50 cm^3; $w = 10$ %) cooled to the temperature of 5—10 °C. A yellowish matter rubbing with the hydroxide solution turned to dark red and was filtered off. After washing with ice water (3 × 25 cm^3) the crystals were dried at 40 °C in a vacuum oven. The dried product was recrystallized from a dried organic solvent.

3-Amino-7-X-1,2,4-benzotriazine-1-oxide (cyclization of the compounds Ia—If)

A suspension of compound *I* (0.05 mol) in sodium hydroxide aqueous solution (100 cm^3; $w = 10$ %) was heated to the boiling point. During 2—10 min of boiling the red solution became yellow under formation of a yellow precipitate of the product. The mixture was cooled to the room temperature, the product filtered off and washed with water. After drying at 105 °C the compound *III* was recrystallized from an organic solvent.

3-Amino-7-Y-1,2,4-benzotriazine-1-oxide
(cyclization of the compounds IIg and IIh)

A suspension of 4-Y-2-nitrophenylguanidine (0.1 mol) and concentrated hydrochloric acid (1 cm^3) in boiling water (50 cm^3) was heated till a solution was formed. Then sodium hydroxide aqueous solution (25 cm^3; $c = 2$ mol dm^{-3}) was added to this hot solution. The orange suspension during 2—5 min turned yellow; the mixture was boiled for another 1—2 min. Then the reaction mixture was cooled to room temperature, the separated product filtered off and worked up as mentioned in the preceding paragraph.

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