N-Ethyl substituted 2-nitrophenylguanidines
I. Synthesis and properties

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New *N*-mono-, di-, and triethyl substituted 2-nitrophenylguanidines with the ethyl group situated at nitrogen atom which does not adjoin 2-nitrophenyl group were prepared. Dissociation constants of the synthesized compounds were determined by spectrophotometry. The structure of the most stable tautomer under conditions of measurement was proved by IR, ^{1}H, and ^{13}C NMR spectroscopy.

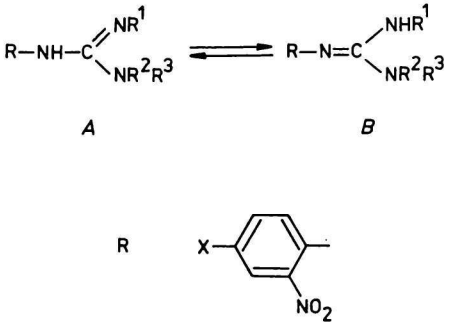
Синтезированы новые *N*-моно-, ди- и триэтил замещенные 2-нитрофенилгуанидины, в которых этильная группа находится на атоме азота, к которому не присоединена 2-нитрофенильная группа. С помощью спектрофотометрических методов определены константы диссоциации полученных соединений. Строение наиболее стабильного в условиях измерения таутомера было подтверждено методами ИК-, ^{1}H ЯМР и ^{13}C ЯМР спектроскопии.

Substituted 2-nitrophenylguanidines are starting stuffs for the preparation of 3-amino-1,2,4-benzotriazine derivatives, which found their practical use especially in pharmacy or as growth stimulators and dyes [1]. 1,2,4-Benzotriazine derivatives are prepared from 2-nitrophenylguanidines by the reaction of cyclization when the guanidine group enters into interaction with nitro group under either a base catalysis [2] or an electrochemical initiation [3, 4].

In order to study further the cyclization reaction pathway in connection with papers [5, 6] we tried to prepare a series of *N*-ethyl substituted 2-nitrophenylguanidines.

In literature [7] there is mentioned a preparation of *N*-phenyl-*N'*-(2-nitrophenyl)guanidine by the desulfuration of 1-phenyl-3-(2-nitrophenyl)thiourea with mercuric oxide in the presence of ammonia in ethanol. This method of preparation was applied to the synthesis of our *N*-ethyl substituted derivatives. Similarly, *N*-phenyl-*N'*-(2-nitrophenyl)guanidine, which was prepared in order to complete the series and to determine its structure, was synthesized.

One can expect the existence of substituted guanidines in tautomeric structures. In dependence on a substitution one of the tautomeric structures will be preferred (Scheme 1).



Scheme 1

As it was found in [5], there are in case of 4-X-2-nitrophenylguanidines, where X = H, CH_3, OCH_3, Br, Cl, OPh, CN, NO_2, preferred tautomers with 2-nitrophenyl system bound at the nitrogen atom of the amino group of the guanidine part of the molecule (Scheme 1, structure *A*, R^1, R^2, R^3 = H). The reason for this seems to be a relatively strong hydrogen bond between oxygen atom of the nitro group and the hydrogen atom of the amino group connected with 2-nitrophenyl system.

The aim of this work is — in addition to the synthesis of the mentioned compounds — also a determination of the structure of the most stable tautomer under laboratory conditions and a study of deprotonation equilibria.

Experimental

Melting points of synthesized compounds were measured on a Kofler hot-stage (VEB Wägetechnik Rapido 79-2106). TLC was carried out on Silufol UV 254 (Kavalier, Votice). Elution was performed by chloroform, benzene, ether or ethyl acetate; compounds were detected with the instrument Fluotest Universal (Quarzlampen, Hanau). Elemental analyses were measured on an elemental analyzer CHN C. Erba 1102.

Table 1

Values of the decadic logarithms of the dissociation constants in the system 2-propanol—sodium 2-propoxide determined by spectrophotometry

Compound	pK_a	Compound	pK_a
IV	13.43 ± 0.09	*VII*	16.60 ± 0.12
V	13.80 ± 0.10	*IX*	16.25 ± 0.12
VI	16.43 ± 0.11		

Dissociation constants (Table 1) were determined by the spectrophotometric method as mentioned in paper [5]. Electronic spectra were measured with the instrument Unicam SP 1800 and are presented in Table 2. Values of molar absorption coefficients of 2-nitrophenylguanidines *IV*—*VII* and *IX* and their deprotonated forms at the wavelength used for the determination of the dissociation constants are given in Table 3.

Table 2

Electronic spectra of compounds *IV*—*VII* and *IX* in the mixture ethanol—water ($\varphi_r = 1:3$)

Compound	λ_{max}/nm ($10\varepsilon/(m^2\,mol^{-1})$)		
IV	205 (5.380)	228 (3.689)	346 (0.418)
V	207 (0.964)	230 (0.953)	337 (0.128)
VI	210 (2.091)	240 (0.626)	370 (0.088)
VII	208 (0.961)	232 (0.714)	405 (0.065)
IX	216 (1.965)	256 (0.581)	350 (0.062)

Table 3

Values of the molar absorption coefficients of compounds *IV*—*VII* and *IX* in 2-propanol (ε_{HG}) and their deprotonated forms in 1 M solution of sodium 2-propoxide in 2-propanol (ε_{G^-}) at wavelength of the maximum of the absorbance of deprotonated form

Compound	λ_{max} / nm	$\varepsilon_{HG}\ 10^{-2}$ / $m^2\,mol^{-1}$	$\varepsilon_{G^-}\ 10^{-2}$ / $m^2\,mol^{-1}$
IV	356	1.020	26.312
V	352	0.618	2.002
VI	398	0.428	2.564
VII	425	0.581	2.683
IX	372	0.326	2.116

IR spectra of the synthesized compounds (Table 4) were measured with spectrophotometer Unicam SP 1000 in bromoform suspension or in bromoform solution (w = 5, 2.5, 1, and 0.5 %); liquid samples neat. ^1H and ^{13}C NMR spectra of 1 M solutions of compounds were recorded with Tesla BS 567 instrument; internal standard HMDSO in hexadeuterodimethyl sulfoxide. NMR spectral characteristics are summarized in Table 5.

Compounds *I*, *III*, and *IV* were prepared in accordance with [7].

1-Ethyl-3-(2-nitrophenyl)thiourea (II)

2-Nitrophenyl isothiocyanate (3.6 g; 0.02 mol) was mixed with 40 % ethanolic solution of ethylamine (50 cm^3) and refluxed for 5 min. A blood-red solution was then

evaporated under vacuum to dryness and the yellowish-brown rest recrystallized from ethanol. Yield = 4 g (88 %), m.p. = 113 °C.

For $C_9H_{11}N_3O_2S$ ($M_r = 225.27$) w_i(calc.): 47.99 % C, 4.92 % H, 18.65 % N; w_i(found): 48.01 % C, 4.86 % H, 18.60 % N.

Table 4

IR spectral characteristics of synthesized compounds

Compound	$\tilde{\nu}$/cm^{-1}				
	ν(NH)	ν(NO_2)	ν(C=C)	ν(C=N)	ν(C=S)
I	3260, 3360, 3440	1340, 1530	1620		1250, 1495
II	3280, 3360	1335, 1530	1610		1260, 1515
III	3270, 3330	1350, 1525	1610		1245, 1505
IV	3290, 3340, 3420	1345, 1505	1585	1650	
V	3330, 3380, 3440	1340, 1520	1600	1640	
VI	3380	1340, 1520	1605	1630	
VII	3380	1345, 1515	1600	1620	
VIII	3250	1330, 1530	1610		
IX	3380, 3460	1340, 1525	1595	1625	

Table 5

^{1}H and ^{13}C NMR characteristics of synthesized compounds

Compound	δ/ppm	
	^{1}H	^{13}C
IV	5.43 (s, 2H, NH), 8.25 (s, 1H, NH), 6.75—7.81 (m, 9H, Ar-H)	114.23, 117.00, 117.40, 120.04, 121.89, 124.00, 130.20, 130.90, 136.28, 135.31, 144.00, 142.12, 150.67 (C=N)
V	1.12 (t, 3H, CH_3), 3.22 (q, 2H, CH_2), 3.95 (s, 3H, NH), 6.90—7.85 (m, 4H, Ar-H)	13.07, 33.44, 117.36, 122.21, 124.11, 130.83, 141.84, 144.16, 150.47 (C=N)
VI	0.75 (t, 6H, CH_3), 2.81 (q, 4H, CH_2), 3.77 (s, 2H, NH), 6.30—7.68 (m, 4H, Ar-H)	13.10, 34.08, 116.39, 122.51, 123.96, 130.91, 140.84, 144.61, 150.62 (C=N)
VII	0.92 (t, 3H, CH_3), 1.02 (t, 6H, CH_3), 2.89 (q, 2H, CH_2), 3.21 (q, 4H, CH_2), 4.54 (s, 1H, NH), 6.53—7.92 (m, 4H, Ar-H)	9.83, 13.07, 35.83, 37.66, 115.00, 122.28, 122.81, 131.09, 138.30, 145.02, 153.19 (C=N)
IX	1.10 (t, 6H, CH_3), 3.32 (q, 4H, CH_2), 2.96 (s, 2H, NH_2), 6.48—7.92 (m, 4H, Ar-H)	6.98, 36.73, 117.23, 123.03, 124.78, 130.57, 131.40, 136.46, 149.27 (C=N)

1-Ethyl-3-(2-nitrophenyl)guanidine (V)

a) Compound *II* (1 g; 0.004 mol) was under boiling dissolved in ethanol (50 cm^3) and then cooled down to 15 °C. Into this stirred solution at the mentioned temperature yellow mercuric oxide (3 g; 0.013 mol) and saturated ethanolic solution of ammonia (20 cm^3) were added. After 15 min charcoal was added, the mixture filtered and then under vacuum concentrated to an oily consistence. The product crystallized from toluene. Yield = 0.73 g (79 %).

b) 2-Nitrophenyl cyanamide (1.6 g; 0.01 mol) was under stirring dissolved in 40 % ethanolic solution of ethylamine (75 cm^3) and the stirring continued for another 20 min at room temperature. Then the mixture was filtered with charcoal, concentrated under vacuum and crystallized from toluene. Yield = 1.68 g (80.7 %), m.p. = 87—88 °C.

For $C_9H_{12}N_4O_2$ (M_r = 208.22) w_i(calc.): 51.92 % C, 5.81 % H, 26.91 % N; w_i(found): 52.00 % C, 5.75 % H, 26.88 % N.

1,3-Diethyl-2-(2-nitrophenyl)guanidine (VI)

1-Ethyl-3-(2-nitrophenyl)thiourea (2 g; 0.009 mol) was dissolved in ethanol (80 cm^3) and cooled down to 15 °C. Under vigorous stirring yellow mercuric oxide (5 g; 0.023 mol) was added and the mixture stirred for another 10 min at the mentioned temperature. Then 40 % ethanolic ethylamine solution (20 cm^3) was added and the stirring continued for further 20 min. Reaction mixture with charcoal was then filtered and the solvent and unreacted ethylamine on a rotating evaporator was distilled off. Yield = 1.95 g (93 %) of dark orange oily compound.

For $C_{11}H_{16}N_4O_2$ (M_r = 236.28) w_i(calc.): 55.92 % C, 6.82 % H, 23.71 % N; w_i(found): 55.96 % C, 6.75 % H, 23.67 % N.

1,1,3-Triethyl-2-(2-nitrophenyl)guanidine (VII)

The compound was prepared analogously like *VI*. Yield = 90 % of orange-red oily substance.

For $C_{13}H_{20}N_4O_2$ (M_r = 264.33) w_i(calc.): 59.07 % C, 7.63 % H, 21.20 % N; w_i(found): 59.10 % C, 7.60 % H, 21.15 % N.

2-Nitrophenyl cyanamide (VIII)

The compound was prepared by the desulfuration of 2-nitrophenylthiourea in ethanol at room temperature. Yield = 85 % of light yellow crystals, m.p. = 152—153 °C (ethanol), Ref. [8] gives m.p. = 152 °C.

1,1-Diethyl-2-(2-nitrophenyl)guanidine (IX)

2-Nitrophenyl cyanamide (1 g; 0.006 mol) was dissolved in 20 % ethanolic solution of diethylamine (50 cm^3) at room temperature and left to stand for about 10 min. Then the product was isolated similarly as compound *VI*. Yield = 1.28 g (90 %) of orange oily compound.

For $C_{11}H_{16}N_4O_2$ (M_r = 236.28) w_i(calc.): 55.92 % C, 6.82 % H, 23.71 % N; w_i(found): 55.86 % C, 6.78 % H, 23.69 % N.

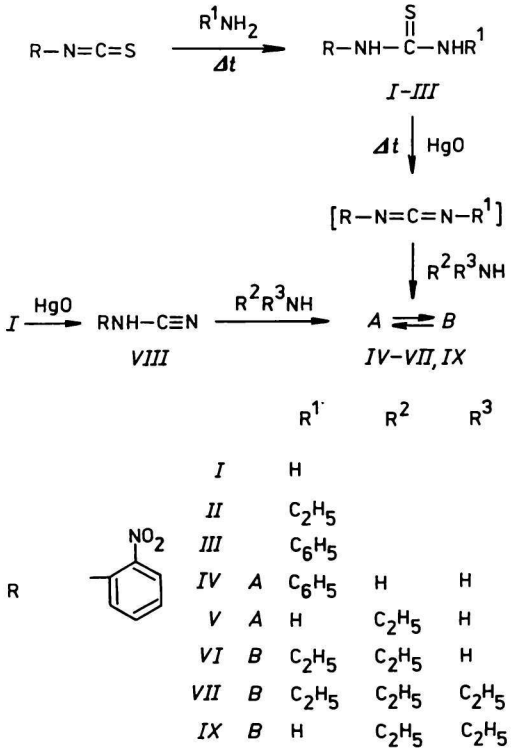
Results and discussion

By the reaction of thiophosgene with 2-nitroaniline [7] we prepared 2-nitrophenyl isothiocyanate. This was used as a substrate for addition of either ammonia forming 2-nitrophenylthiourea (*I*) or ethylamine in ethanol forming 1-ethyl-3-(2-nitrophenyl)thiourea (*II*) (Scheme 2). During the preparation of compound *II* due to an excess of ethylamine the reaction mixture turned to a blood-red colour and we were not able to isolate compound *II* for its high solubility. The high solubility and the colour were caused by the proton abstraction from the nitrogen atom bound at 2-nitrophenyl in the molecule, as we know it from the behaviour of 4-substituted 2-nitrophenylguanidines [5]. In the case of derivative *II* the stability of the anion formed is given by the possibility of delocalization of the negative charge also at sulfur atom which shows higher polarizability than that of imino group in 2-nitrophenylguanidine. Therefore ethylamine as base is here strong enough for a proton abstraction. In order to isolate the product we distilled off the solvent and excessive ethylamine under vacuum and the rest was recrystallized from ethanol. When aniline in excess was added to 2-nitrophenyl isothiocyanate at the temperature of a boiling water bath 1-phenyl-3-(2-nitrophenyl)thiourea (*III*) [7] was formed (Scheme 2).

Compound *II* was treated by mercuric oxide at the temperature of 15—20 °C in ethanol under formation of *N*-ethyl-*N'*-(2-nitrophenyl)carbodiimide which *in situ* added either ammonia forming 1-ethyl-3-(2-nitrophenyl)guanidine (*V*) or ethylamine forming 1,3-diethyl-2-(2-nitrophenyl)guanidine (*VI*). The addition of diethylamine to the mentioned carbodiimide led to 1,1,3-triethyl-2-(2-nitrophenyl)guanidine (*VII*).

The reaction of desulfuration of thiourea *II* had to be carried out at the mentioned low temperature as an increase of the temperature to 50—60 °C, at which the desulfuration of *III* was carried out, resulted here in the decomposition of *N*-ethyl-*N'*-(2-nitrophenyl)carbodiimide to 2-nitroaniline. This was proved by TLC on Silufol using standard in a number of eluents. 2-Nitroaniline so formed complicated the isolation of the pure ethyl substituted 2-nitrophenylguanidines *V*, *VI*, *VII* besides lowering the yield.

Compound *V* was prepared besides the mentioned way also by the addition of ethylamine to 2-nitrophenyl cyanamide (*VIII*). That was obtained by the desulfuration of *I* with mercuric oxide in ethanol. Similarly, 1,1-diethyl-2-(2-nitrophenyl)guanidine (*IX*) was prepared by the addition of diethylamine to compound *VIII*.



Scheme 2

Compounds *VI*, *VII*, and *IX* are oily compounds which at distillation already before the boiling point at a high vacuum start a decomposition to 2-nitroaniline.

We tried to prepare 1-ethyl-1-(2-nitrophenyl)guanidine by the addition of *N*-ethyl-2-nitroaniline to cyanamide under acid catalysis. The reaction was carried out similarly like the addition of 4-substituted 2-nitroanilines to cyanamide [9], it means smelting in the presence of concentrated hydrochloric acid or in acetic acid solution in the presence of catalytic amount of *p*-toluenesulfonic acid. In both cases the unreacted *N*-ethyl-2-nitroaniline was isolated from the reaction mixture only. We suppose that the reason was a steric hindrance of the nitrogen atom of the secondary amino group in *N*-substituted 2-nitroaniline

during its addition to cyanamide as it was observed in the addition of 2-nitrodiphenylamine [7].

In the series of substituted 2-nitrophenylguanidines (compounds *IV*—*VII*, *IX*) we measured the electronic spectra in 2-propanol and searched for their dependence on the concentration of sodium 2-propoxide. We found that these compounds behave similarly like 4-substituted 2-nitrophenylguanidines [5], *i.e.* that by the treatment of a base they lose proton. This was reflected in the electronic spectrum by the bathochromic and hyperchromic shift of the longwavelength band. Thus the values of equilibrium constants of the mentioned compounds were determined (Table 1) by the spectrophotometry in the 2-propanol—sodium 2-propoxide system.

The found values are in good agreement with the observed reality that while compounds *IV* and *V* are soluble in a strong basic solution, the compounds *VI*, *VII*, and *IX* are not. All these facts may be explained by the structure analysis based on IR and NMR spectra.

IR spectra of compounds *IV* and *V* (Table 4) show the existence of an intramolecular hydrogen bridge between the hydrogen atom bound at nitrogen in the neighbourhood of 2-nitrophenyl and the oxygen atom of the nitro group, as it was similarly found in the case of 4-substituted 2-nitrophenylguanidines [5]. In view of the influence of phenyl group (compound *IV*) the wavenumber of vibration of the N—H bond bound at 2-nitrophenyl is shifted to the lower values of wavenumber (3290 cm^{-1}). The hydrogen bond is here stronger than that of unsubstituted 2-nitrophenylguanidine ($\tilde{\nu} = 3320\ cm^{-1}$). The opposite is true with compound *V* where the value of the wavenumber of vibration of the N—H bond is shifted to a higher value (3330 cm^{-1}). The hydrogen bond is here weaker and the hydrogen atom is less acidic (Table 1).

All the mentioned facts as well as the evaluation of the position of the band of the N—H bond stretching vibration using the relation [10]

$$\tilde{\nu}(\nu_s(NH_2)) = 345.53\ cm^{-1} + 0.876\quad \tilde{\nu}(\nu_{as}(NH_2))$$

led us to the structure given in Scheme 2 and so to the conclusion that the remaining two vibrations of N—H bonds in IR spectrum belong to either a primary amino group or two secondary —NH— groups.

In case of compound *IV* the calculated value $\tilde{\nu}(\nu_s) = 3341\ cm^{-1}$ is nearly equal to the value known from the spectrum (3340 cm^{-1}). In ^1H NMR spectrum we found two signals corresponding to hydrogen atoms bound at nitrogen atom. The first of them corresponds to the hydrogen atom at a secondary amino group ($\delta = 8.25$ ppm, relative integral intensity equal to 1) and the second one to the hydrogen atom at a primary amino group ($\delta = 5.43$ ppm, relative integral intensity equal to 2).

For 1-ethyl-3-(2-nitrophenyl)guanidine (*V*) the value $\tilde{\nu}(\nu_s) = 3350\ cm^{-1}$ was calculated. It differs from the experimental value $\tilde{\nu}(\nu_s(NH_2)) = 3380\ cm^{-1}$. This indicates that the ethyl group is bound to nitrogen atom in sp^3-hybrid state. To this finding corresponds also the value of chemical shift of the carbon atom in a methylene group bound at nitrogen atom in sp^3-hybrid state ($\delta = 33.44$ ppm).

^1H NMR spectra in this case could not be used for the identification due to the existence of a fast hydrogen atoms exchange in the guanidine group which manifested itself by the only one signal with integral intensity equal to 3.

From the position of the band corresponding to N—H bonds vibrations in IR spectra of di- and triethyl substituted 2-nitrophenylguanidines *VI* and *IX* it resulted that no hydrogen bond exists in these molecules contrary to the previous cases.

Compounds *VI*, *VII*, and *IX* are at room temperature in the thermodynamically more stable tautomeric form *B* shown in Scheme 1. The stability is given by the lowering of the energy of the system due to the conjugation of the guanidine group with the 2-nitrophenyl rest.

From IR, ^1H and ^{13}C NMR spectra of 1,3-diethyl derivative *VI* an equivalence of both ethylamine groups in guanidine rest can be observed.

For 1,1-diethyl-2-(2-nitrophenyl)guanidine (*IX*) we calculated from the mentioned relation [10] using wavenumber of vibration $\nu_{as}(NH_2)$ a position of band at $\tilde{\nu}(\nu_s(NH_2)) = 3376\ cm^{-1}$, which is very close to the experimental value $\tilde{\nu}(\nu_s(NH_2)) = 3380\ cm^{-1}$

Similarly we estimated the structure of compound *VII*.

An anion formed by the dissociation of proton from guanidine amino group (primary amino group at compound *IX*, secondary at compounds *VI* and *VII*) cannot be stabilized by the delocalization of the negative charge at nitrogen of guanidine group probably due to cross conjugation between 2-nitrophenyl system and either diethylamino group or ethylamino group. This explains the fact that in these cases a stronger base is needed for proton abstraction than the hydroxide ion in aqueous solution.

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