N-Ethyl substituted 2-nitrophenylguanidines II. Cyclization

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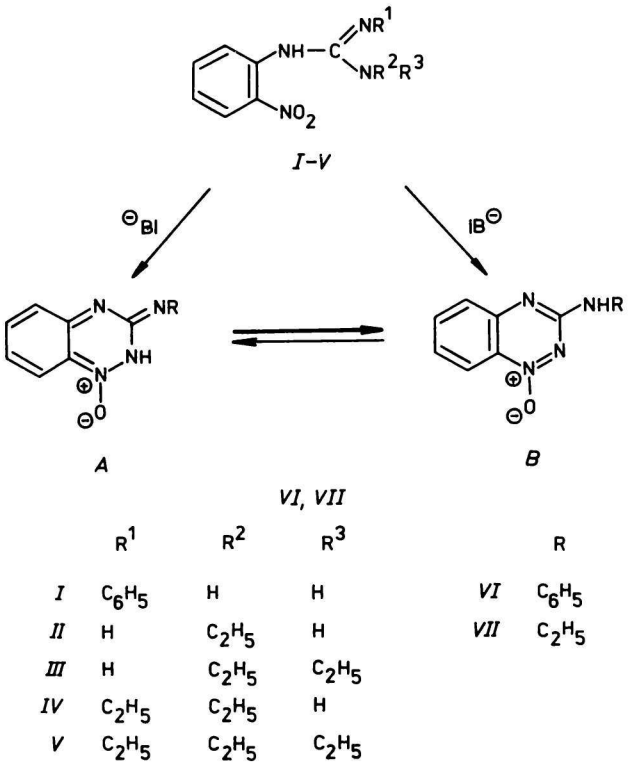
N-Ethyl substituted 2-nitrophenylguanidines underwent under treatment with a base either in a boiling aqueous medium or in DMF at the temperature of 100 °C cyclization, to corresponding substituted 1,2,4-benzotriazine 1-oxides. The products the structure of which was proved by the comparison with compounds synthesized in independent synthesis and by spectral methods, showed that the cyclization can proceed only when an unsubstituted amino or imino group of the guanidine part of molecule is at disposal to the interaction with nitro group.

N-Этилзамещенные 2-нитрофенилгуанидины претерпевали под действием оснований в водной среде при кипении или в среде безводного ДМФ при температуре 100 °C циклизацию в соответствующие замещенные 1,2,4-бензотриазин-1-оксиды. Продукты данной реакции, строение которых было установлено путем сравнения с веществами, синтезированными независимо, а также с помощью спектральных методов, показали, что циклизация может происходить лишь в том случае, если для взаимодействия с нитрогруппой имеется незамещенная амино- или иминогруппа в гуанидиновой части молекулы.

A cyclization of 2-nitrophenylguanidines under a base catalysis leads to derivatives of 1,2,4-benzotriazine 1-oxide [1—3]. After activation of the substrate by a base the cyclization may generally proceed as a nucleophilic attack of the nitrogen atom of the nitro group either by the amino or the imino group of the guanidine part of the molecule forming substituted 3-amino-1,2,4-benzotriazine 1-oxide (Scheme 1).

In the case, when in Scheme 1 R^1, R^2, $R^3 = H$, it is not possible to prove whether the cyclization proceeds through the amino or the imino group by the method based only on a structure analysis of the cyclization product because of the tautomeric equilibrium shifted to the more stable tautomer *B*.

A completely different situation may be in the case of the substituted derivative *I* (Scheme 1) when a substituent different from the hydrogen atom will be bound in the product of the cyclization in an entirely definite position in dependence on which nitrogen atom entered into interaction with the nitro group.



	R^1	R^2	R^3		R
I	C_6H_5	H	H	*VI*	C_6H_5
II	H	C_2H_5	H	*VII*	C_2H_5
III	H	C_2H_5	C_2H_5		
IV	C_2H_5	C_2H_5	H		
V	C_2H_5	C_2H_5	C_2H_5		

Scheme 1

Arndt and *Rossenau* [4] assumed that product *B* is formed under consideration about the attack by an unsubstituted end nitrogen atom of the guanidine group.

The aim of our work is to prove whether the cyclization reaction proceeds through the nitrogen atom of the substituted or the unsubstituted amino or imino group, or in both ways.

Therefore the cyclization of compounds *I*—*V* (Scheme 1) described in paper [5] was followed and the structure of the cyclization products was determined by the comparison with compounds that were prepared by an independent synthesis.

Experimental

Melting points were measured on a Kofler hot-stage (VEB Wägetechnik Rapido 79-2106). TLC was carried out on Silufol UV 254 (Kavalier, Votice); eluent chloroform

or ether, detection was carried out with Fluotest Universal (Quarzlampen, Hanau). Elemental analyses were performed with an elemental analyzer CHN C. Erba 1102. IR spectra measured with the instrument Unicam SP 1000 in suspension or in solution of bromoform are presented in Table 1. Electronic spectra measured with the spectrophotometer Unicam SP 1800 are presented in Table 2. ^{1}H NMR spectra of 1 M solutions of compounds were measured with Tesla BS 567 in DMSO-d_6, internal standard HMDSO. NMR characteristics are summarized in Table 3.

Syntheses of *N*-ethyl substituted 2-nitrophenylguanidines *I*—*V* are described in paper [5].

Table 1

Elemental analyses and IR spectral characteristics of the synthesized compounds

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			$\tilde{\nu}$/cm^{-1}		
			C	H	N	ν(NO)	ν(C=N)	ν(NH)
VI	$C_{13}H_{10}N_4O$	238.25	65.54	4.23	23.52	1350	1620	3250
			65.60	4.15	23.40			
VII	$C_9H_{10}N_4O$	190.21	56.83	5.30	29.46	1355	1595	3220
			56.70	5.27	29.40			
VIII	$C_{11}H_{14}N_4O$	218.26	60.53	6.46	25.67	1345	1615	—
			60.39	6.40	25.55			

Table 2

Electronic spectra of compounds *VI*—*VIII* in aqueous solution

Compound	λ_{max}/nm ($\varepsilon \cdot 10^{-3}$/(m^2 mol^{-1}))			
VI	224 (1.132)	—	276 (2.753)	450 (0.294)
VII	216 (2.143)	244 (2.375)	262 (2.121)	434 (0.331)
VIII	214 (1.196)	248 (2.569)	—	430 (0.402)

Table 3

^{1}H NMR characteristics of compounds *VI*—*VIII*

Compound	δ/ppm
VI	9.42 (s, 1H, NH), 6.95—8.28 (m, 9H, Ar-H)
VII	7.24—8.12 (m, 4H, Ar-H), 6.95 (s, 1H, NH), 3.10 (q, 2H, CH_2, J = 7.5 Hz), 0.95 (t, 3H, CH_3, J = 7.5 Hz)
VIII	7.18—8.06 (m, 4H, Ar-H), 2.95 (q, 4H, CH_2, J = 7.5 Hz). 0.84 (t, 6H, CH_3, J = 7.5 Hz)

3-Phenylamino-1,2,4-benzotriazine 1-oxide (VI)

a) Cyclization of compound *I* was carried out according to paper [4]. Brick red plates, m.p. = 201—202 °C (literature gives m.p. = 197 °C) (ethanol), yield = 95 %.

b) A mixture of 3-chloro-1,2,4-benzotriazine 1-oxide (1.5 g; 0.008 mol) and aniline (1.7 g; 0.018 mol) was heated at the temperature of 135—140 °C on an oil bath for 6 h. Then the reaction mixture was cooled down to room temperature and after solidification rubbed with 16 % hydrochloric acid solution (20 cm^3). The crystals so formed were filtered off and washed with hot water and ethanol. Yield = 1.3 g (68 %), m.p. = 199—201 °C (ethanol).

c) A mixture of 3-methylthio-1,2,4-benzotriazine 1-oxide (1.9 g; 0.01 mol) and aniline (1.8 g; 0.02 mol) was heated for 3 h on an oil bath at the temperature of 140—150 °C. Then the reaction mixture was worked up similarly as in *b*). Yield = 1.9 g (80 %), m.p. = 200—201 °C.

3-Ethylamino-1,2,4-benzotriazine 1-oxide (VII)

a) The cyclization was carried out similarly as with compound *VI*. Yellow needles, m.p. = 192—193 °C (ethanol), yield = 84 %.

b) In a pressure container of volume 200 cm^3 a mixture of 3-chloro-1,2,4-benzotriazine 1-oxide (1.5 g; 0.008 mol) and 30 % ethanolic ethylamine solution (20 cm^3) was heated for 20 h at the temperature of 80 °C. After cooling down to room temperature the content of the container was washed with hot ethanol (50 cm^3) and filtered with charcoal. After condensation yellow crystals were formed. Yield = 0.9 g (59 %), m.p. = 191—193 °C.

c) A mixture of 3-methylthio-1,2,4-benzotriazine 1-oxide (1.9 g; 0.01 mol) and 30 % ethanolic ethylamine solution (20 cm^3) was heated for 10 h in a pressure container of the 200 cm^3 volume at the temperature of 80 °C. After cooling down to room temperature the mixture was worked up similarly as in *b*). Yield = 1.5 g (79 %), m.p. = 190—192 °C.

3-Diethylamino-1,2,4-benzotriazine 1-oxide (VIII)

a) Compound *III* (1.5 g; 0.006 mol) was dissolved in anhydrous DMF (20 cm^3) and to this solution a filtered mixture of anhydrous DMF (10 cm^3), *terț*-butanol (5 g), and sodium hydride (0.1 g; 0.004 mol) was added. The mixture was then heated at a boiling water bath for 5 min. Then the solvent was removed on a rotating evaporator, the rest refluxed with absolute benzene (50 cm^3) and filtered. To the filtrate acetyl chloride (0.4 cm^3; 0.006 mol) was added and heated to reflux. The unreacted acetyl chloride was decomposed boiling the reaction mixture with water (1 cm^3). The product of the cyclization was 3 times extracted from the benzene solution with 20 % hydrochloric acid (10 cm^3) and the extract was finally made alkaline with 10 % aqueous sodium hydroxide

solution. The crude product was obtained after extraction by ether and its evaporation. Yield = 0.35 g (27 %), m.p. = 81—84 °C (chloroform).

b) A mixture of 3-chloro-1,2,4-benzotriazine 1-oxide (1.5 g; 0.008 mol) and 50 % ethanolic diethylamine solution (10 cm^3) in a calorimetric bomb was heated for 8 h at the temperature of 80 °C. Then the mixture was evaporated to dryness, washed with water and the product crystallized from ethanol. Yield = 1.42 g (81 %), m.p. = 80—82 °C.

c) A mixture of 3-methylthio-1,2,4-benzotriazine 1-oxide (1.9 g; 0.01 mol) and 20 % ethanolic diethylamine solution (30 cm^3) was refluxed for 20 h. The product was isolated analogously as in *b*). Yield = 1.6 g (73 %), m.p. = 81—83 °C.

Results and discussion

The cyclization of compounds *I* and *II* was carried out in 10 % aqueous sodium hydroxide solution under reflux [4]. During the reaction compounds *I* and *II* dissolving formed a red solution that after a long boiling gave a precipitation of the product. The dark red colour of the reaction mixture is characteristic of the formation of an anion that originates from the starting substance by splitting off a proton from the amino group in the neighbourhood of 2-nitrophenyl of the guanidine part of molecule [5].

As products were isolated compounds *VI* and *VII* (Scheme 1, *B*) which were shown to be identical with the compounds prepared by a nucleophilic substitution of the chlorine atom in 3-chloro-1,2,4-benzotriazine 1-oxide or substitution of the methylthio group in 3-methylthio-1,2,4-benzotriazine 1-oxide by either aniline or ethylamine. A formation of an isomeric 2-phenyl- or 2-ethyl-3--imino-1,2,4-benzotriazine 1-oxide was not observed in the reaction mixture.

3-Chloro-1,2,4-benzotriazine 1-oxide was prepared by the reaction of phosphoryl chloride with 1,2,4-benzotriazin-3-one 1-oxide in dimethylaniline according to paper [6]. Starting 1,2,4-benzotriazin-3-one 1-oxide was gained by the cyclization of 2-nitrophenylurea in 15 % aqueous sodium hydroxide solution under reflux [7] besides 2-nitroaniline as a product of hydrolysis. 3-Methylthio--1,2,4-benzotriazine 1-oxide was prepared in 80 % yield by the cyclization of 1-benzoyl-3-(2-nitrophenyl)thiourea in the aqueous sodium hydroxide solution [8] followed by the methylation of so formed 1,2,4-benzotriazine-2-thione 1-oxide with dimethyl sulfate.

An identification of compounds *VI* and *VII* was carried out by the comparison with standards using TLC (in ether), melting points, mixed melting points, IR and electronic spectra.

An attempt at cyclization of compounds *III*—*V* (Scheme 1) was also carried out in boiling 10 % aqueous sodium hydroxide solution. These compounds dissolved badly in the reaction mixture forming orange solutions but no cycliza-

tion reaction took place. As a side reaction the hydrolysis of compounds to 2-nitroaniline was observed.

The mentioned used derivatives of 2-nitrophenylguanidine are very little acidic as was shown in paper [5] and therefore in aqueous sodium hydroxide solution do not split off proton and this is probably the reason why they do not cyclize. So we carried out an attempt at cyclization in nonaqueous medium — in anhydrous DMF under catalysis of sodium *tert*-butoxide.

Under these conditions we observed only the cyclization of compound *III* to compound *VIII*. Its formation was accompanied again by the formation of 2-nitroaniline as a side product of the decomposition. The formation of 2-nitroaniline was observed also during attempts at cyclization of compounds *IV* and *V* under the same conditions but here the cyclization did not proceed.

The identity of compound *VIII* was proved by the comparison with a standard which was prepared by the substitution of the chlorine atom in the molecule of 3-chloro-1,2,4-benzotriazine 1-oxide or by the substitution of methylthio group in 3-methylthio-1,2,4-benzotriazine 1-oxide with diethylamine. The comparison was carried out using TLC (in chloroform and ether), melting points, mixed melting points, IR and electronic spectra.

From all experimental data we concluded that the cyclization reaction proceeds as a nucleophilic attack of the nitro group nitrogen atom of the 2-nitrophenylguanidine molecule only in that case if in the molecule which should undergo the cyclization an unsubstituted amino or imino group is present.

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