Acta Poloniae Pharmaceutica – Drug Research. Vol. 56 No. 3 pp. 201–206. 1999

ISSN 0001-6837
Polish Pharmaceutical Society

DRUG SYNTHESIS

STUDIES ON QUINOXALINE DERIVATIVES. SYNTHESIS OF QUINOXALYLAMINO–1,3–DIAZACYCLOALKANES WITH POTENTIAL HYPOTENSIVE ACTIVITY

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Abstract: A series of quinoxalylamino–1,3–diazacycloalkanes was obtained by the reaction of the corresponding substituted aminoquinoxalines with alcohols and amines. The effect of selected compounds on the blood pressure of anaesthesized normotensive rats was studied.

Keywords: quinoxaline derivatives, synthesis, hypotensive activity.

The present paper reports on results of our studies on the synthesis of new quinoxaline derivatives with a potential pharmacological activity. The reactants for the preparation of the title quinoxalylamino–1,3–diazacycloalkanes were the corresponding substituted aminochloro–quinoxalines [**Ia–d**] (1–3), which were treated with some alcohols and amines. The following alcohols were used: 2–phenylethanol as well as benzyl–, 4–chlorobenzyl–, 4–fluorobenzyl–, 4–methoxybenzyl–, 2,4–dichlorobenzyl–, and 2,6–dichlorobenzyl–alcohol. The amines used were: benzylamine, 1–(2–aminoethyl)–piperazine, 4–(2–aminoethyl)–morpholine, 4–(3–aminopropyl)–morpholine, 4–benzylpiperidine and 1–phenylpiperazine. The series of aminoquinoxalines [**IIa–p, IIIa–m**] were treated with benzoylisothiocyanate to give 1–quinoxalyl–3'–benzoylthioureas [**IVa–f**], which were hydrolyzed to the corresponding thioureas [**Va–j**]. *S*–methylisothioureas [**VIa–f**] were obtained in a reaction of appropriate quinoxalylthioureas with methyl iodide. Cyclization of the imidazoline ring [**VIIa–f**] was carried out on heating the hydroiodides of *S*–methylquinoxalylthioureas [**VIa–f**] with ethylenediamine.

RESULTS AND DISCUSSION

The characteristics of quinoxalylamino–1,3–diazacycloalkanes [**VIIa–f**] and of the intermediate products are given in Table 1. The structure of the newly synthesized compounds was confirmed by spectral (IR, NMR) analyses.

The influence of the selected quinoxaline derivatives [**VIIa–c, f, g**] on the blood pressure of anaesthesized normotensive rats was studied. The compounds were administered i.v. at doses limited by their solubility in physiologically compatible aqueous solvents. Thus, the maximum doses ranged from 0.04 and 2.5 mg/kg. The results obtained are collected in Table 2.

At the doses applied the blood pressure lowering effects of the agents studied was relatively low. Only in the case of compound [**VIIc**] a 38 ± 4% decrease in the blood pressure of rats was observed. However, the dose required is relatively high as compared with that of the existing antihypertensive drugs.

The effects of the most active compound [**VIIc**] in the beating rate and amplitude of isolated rat heart atria was also been studied. The preparation was assumed to reflect the activity of this compound with respect to β–adrenergic receptors. Derivative [**VIIc**] elicited some antagonistic effects towards the chronotropic and inotropic action of ISO on isolated rat heart atria. When added to the bath at a concentration of 7.5×10^{-7} mol/dm^3, the compound decreased the beating rate and amplitude of the atria by 73 ± 12% and 19 ± 8%, respectively. The some compound added to the bath at cumulative concentrations of 7.5 ± 10^{-1} – 7.5×10^{-6} mol/dm^3 decreased the beating rate of atria and had no significant effect on the amplitude of the atria. At the concentration of 7.5×10^{-6} mol/dm^3 of [**VIIc**], the decrease of the beating rate was minimum, 62 ± 14%.

The antagonistic effect of derivative [**VIIc**] forwards the inotropic action of ISO on the rat heart atria and thus confirms its β–adrenolytic activity.

Table 1. Characteristics of the newly synthesized quinoxaline derivatives

Comp. No	M.p. °C (solvent)	Yield %	Formula Molecular weight
IIa	143–145 (CH_3OH)	25	$C_{15}H_{13}N_3O$ 251.3
IIb	138–140 (CH_3OH)	68	$C_{16}H_{15}N_3O$ 265.3
IIc	130–132 (acetone)	24	$C_{15}H_{12}ClN_3O$ 285.7
IId	172–174 (CH_3OH)	72	$C_{16}H_{14}ClN_3O$ 299.8
IIe	138–143 (CH_3OH)	70	$C_{16}H_{14}ClN_3O$ 299.8
IIf	136–141 (CH_3OH)	44	$C_{15}H_{12}FN_3O$ 269.3
IIg	155–159 (CH_3OH)	64	$C_{16}H_{14}FN_3O$ 283.3
IIh	185–190 (CH_3OH)	43	$C_{17}H_{16}FN_3O$ 297.3
IIi	139–143 (CH_3OH)	21	$C_{16}H_{15}N_3O_2$ 281.3
IIj	169–172 (CH_3OH)	30	$C_{17}H_{17}N_3O_2$ 295.3
IIk	189–193 (CH_3OH)	46	$C_{18}H_{19}N_3O_2$ 309.3
III	197–201 (CH_3OH)	31	$C_{15}H_{11}Cl_2N_3O$ 320.2
IIm	174–176 (acetone/H_2O)	53	$C_{15}H_{11}Cl_2N_3O$ 320.2
IIn	130–132 (CH_3OH)	15	$C_{16}H_{15}N_3O$ 265.3
IIo	134–136 (C_2H_5OH)	36	$C_{17}H_{17}N_3O$ 279.3
IIp	143–145 petroleum ether	29	$C_{18}H_{19}N_3O$ 293.3
IIIa	263–268 (acetone)	56	$C_{15}H_{14}N_4$ 250.3
IIIb	146–149 (CH_3OH)	33	$C_{17}H_{18}N_4$ 278.4
IIIc	164–168 (CH_3OH/H_2O)	38	$C_{15}H_{21}N_5$ 271.4
IIId	250–255 (CH_3OH)	81	$C_{14}H_{19}N_5O$ 273.3
IIIe	202–203 (CH_3OH)	42	$C_{15}H_{21}N_5O$ 287.4
IIIf	226–229 (CH_3OH)	49	$C_{17}H_{25}N_5O$ 315.4
IIIg	200–204 (CH_3OH)	62	$C_{20}H_{22}N_4$ 318.4
IIIh	179–181 (CH_3OH)	62	$C_{22}H_{26}N_4$ 346.5
IIIi	224–227 (CH_3OH)	88	$C_{18}H_{19}N_5$ 305.4
IIIj	204–207 (C_2H_5OH)	64	$C_{19}H_{21}N_5$ 319.4
IIIk	241–246 (C_2H_5OH)	31	$C_{19}H_{21}N_5$ 319.4
IIIl	239–242 (acetone)	38	$C_{20}H_{23}N_5$ 333.4
IIIm	243–247 (CH_3OH)	35	$C_{18}H_{18}N_6O_2$ 350.4
IVa	166–168 (acetone)	69	$C_{23}H_{19}N_4O_2S$ 415.5
IVb	178–182 (acetone)	59	$C_{24}H_{20}N_4O_2S$ 428.5
IVc	174–176 (acetone/H_2O	50	$C_{23}H_{17}ClN_4O_2S$ 448.9
IVd	167–169 (acetone/H_2O	63	$C_{24}H_{19}ClN_4O_2S$ 462.9
IVe	169–171 (acetone)	58	$C_{23}H_{16}Cl_2N_4O_2S$ 483.4
IVf	188–190 (acetone/H_2O)	86	$C_{23}H_{16}Cl_2N_4O_2S$ 483.4
Va	205–208 (CH_3OH)	62	$C_{16}H_{14}N_4OS$ 310.4
Vb	213–215 (acetone)	81	$C_{17}H_{16}N_4OS$ 324.4
Vc	180–182 (CH_3OH)	79	$C_{16}H_{13}ClN_4OS$ 344.8
Vd	216–220 (CH_3OH)	74	$C_{17}H_{15}ClN_4OS$ 358.8
Ve	151–153 (CH_3OH/H_2O)	53	$C_{16}H_{12}Cl_2N_4OS$ 379.3
Vf	177–179 (CH_3OH)	74	$C_{16}H_{12}Cl_2N_4OS$ 379.3
Vg	175–177 (CH_3OH)	62	$C_{25}H_{30}N_6S$ 446.5
Vh	262–267 (CH_3OH)	56	$C_{25}H_{24}N_6S$ 440.5
Vi	165–170 (CH_3OH)	68	$C_{26}H_{26}N_6S$ 454.5
Vj	307–310 (CH_3OH)	64	$C_{25}H_{23}BrN_6S$ 519.5
VIa	128–130 (acetone/H_2O)	80	$C_{17}H_{17}IN_4OS$ 452.3
VIb	170–173 (acetone)	40	$C_{18}H_{19}IN_4OS$ 466.3
VIc	144–146 (acetone/H_2O)	25	$C_{17}H_{16}ClIN_4OS$ 486.7
VId	168–171 (acetone)	44	$C_{18}H_{18}ClIN_4OS$ 500.8
VIe	182–184 (acetone)	23	$C_{17}H_{15}Cl_2IN_4OS$ 521.2
VIf	175–178 (acetone/H_2O)	26	$C_{17}H_{15}Cl_2IN_4OS$ 521.2
VIIa	170–173 (CH_3OH)	54	$C_{18}H_{17}N_5O$ 319.4

Comp. No	M.p. °C (solvent)	Yield %	Formula Molecular weight
VIIb	163–166 (CH_3OH)	30	$C_{19}H_{19}N_5O$ 333.4
VIIc	98–100 (CH_3OH)	55	$C_{18}H_{16}ClN_5O$ 353.8
VIId	186–190 (CH_3OH)	35	$C_{19}H_{18}ClN_5O$ 367.8
VIIe	217–219 (toluene)	46	$C_{18}H_{15}Cl_2N_5O$ 388.3
VIIf	189–192 (CH_3OH/H_2O)	36	$C_{18}H_{15}Cl_2N_5O$ 388.3

Table 2. Influence of the compounds studied on the blood pressure of normotensive rats.

Compound	Dose mg/kg	Maximum change of blood pressure, %
VIIa	1.25	-28 ± 5
VIIb	0.04	-13 ± 6
VIIc	0.3	-38 ± 7
VIIf	0.25	-12 ± 3
VIIg	2.5	-26 ± 2

However, the effect observed appeared to be relatively weak as compared with that of the existing β–adrenolytics.

The model for studying peripheral α–adrenoceptor mediated reactions was an isolated rat tail artery preparation. Compound [**VIIc**] added to the perfusing fluid in concentration of 5 x 10^{-4} mol/dm^3 decreased the maximum NA vasoconstrictory effect of 45 ± 6%. This observation confirms its weak α–adrenolytic properties.

EXPERIMENTAL

Chemistry

Melting points (uncorrected) were determined with a Boëtius apparatus. IR spectra were taken with a Perkin–Elmer 257 spectrophotometer and the NMR spectra with a BS 487 50 MHz apparatus, using TMS as an external standard. All compounds were analyzed for C, H and N. The analytical results were within ± 0.3% of the theoretical values.

Synthesis of aminoquinoxalines [**IIa–p**]

Ilustrative synthesis: anhydrous dioxane, 5 cm^3, and 0.06 mol (1.5 g) of a 50% suspension of sodium hydride in paraffin oil and 0.02 mol (3.8 g) of 2–amino–3–chloroquinoxaline [**Ib**] were added to a solution of 0.03 mol (4.6 g) of 4–chlorobenzyl alcohol. The reaction mixture was heated for 1 h, then a volatile material was evaporated under a reduced pressure. The solid residue was recrystallized from methanol. The reaction yielded 4.3 g (72%) for [**IId**], m.p. 172–174°C.

For compounds [**IIa–p**]: IR(cm^{-1}): 3200–3400 (NH); 3050–3100 (CH aromat.); 2950–2980 (CH aliphat.).

^{1}H–NMR (d_6-DMSO or $CDCl_3$); 2.3–2.7 (s, 3 (or 6) H, n x CH_3, n = 1, 2); 5.3–5.6 (s, 2H, CH_2); 7.2–7.5 (m, aromatic protons).

Synthesis of aminoquinoxalines [**IIIa–m**]

Ilustrative synthesis: a mixture of 0.0065 mol (2 g) of compound [**Ia**] and 0.04 mol (6 cm^3) of 4–phenylpiperazine was heated for 3 h. The resulting precipitate was recrystallized from methanol (the salt insoluble in methanol was filtered off). The reaction yielded 2.9 g (88%) of [**IIIi**], m.p. 224–227°C.

For compounds [**IIIa–m**]: IR(cm^{-1}): 3440–3490 (NH); 3040–3080 (CH aromat.); 2930–2980 (CH aliphat.).

^{1}H–NMR (d_6-DMSO or $CDCl_3$): 2.5–2.6 (m (d) 10H piperidine or 8H morpholine); 3.6–3.7 (s (d) 4H, $2CH_2$); 4.7 (d, 2H, CH_2); 7.2–7.4 (m, aromatic protons).

Synthesis of 1–quinoxalyl–3'–benzoylthioureas [**IVa–f**]

Ilustrative synthesis: to a solution of benzoylisothiocyanate obtained by mixing 1.5 cm^3 benzoyl chloride with 0.96 g ammonium isothiocyanate in 150 cm^3 anhydrous acetone, 0.012 mol (3.8 g) of [**IId**] in 300 cm^3 of anhydrous acetone was added. The reaction mixture was heated for 1 h. After cooling, the reaction mixture was poured into cold water. The resulting precipitate was collected by filtration and recrystallized from acetone. The reaction yielded 3.5 g (63%) of [**IVd**], m.p. 167–169°C.

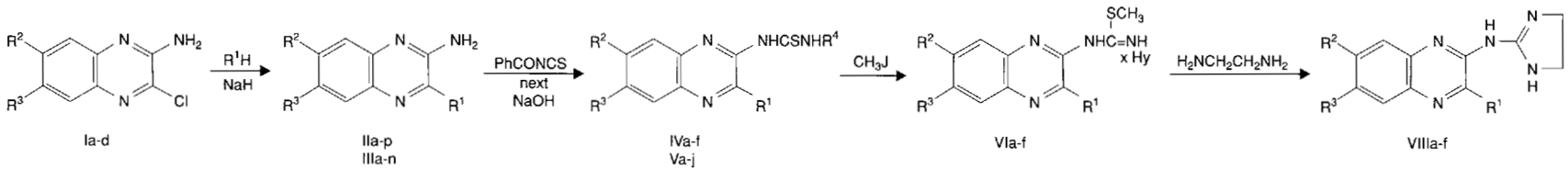
For compounds [**IVa–f**]: IR(cm^{-1}): 3200–3400 (NH); 3050–3080 (CH aromat.); 2920–2960 (CH aliphat.); 1590–1650 (C=O); 1500, 1480, 1440 (CH aromat.).

^{1}H–NMR (d_6-DMSO or $CDCl_3$): 4.5–4.8 (d, 2H, CH_2); 7.2–7.6 (m, aromatic protons).

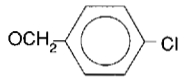
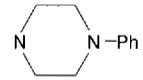
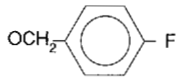
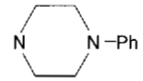
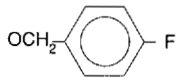
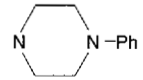
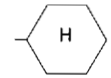
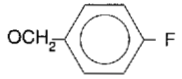
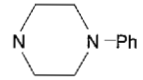
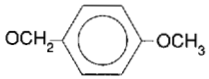
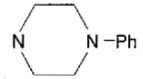
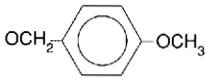
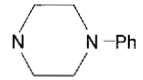
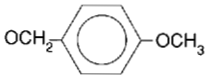
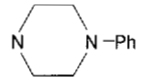
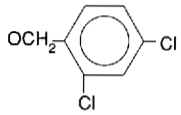
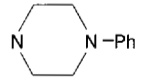
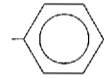
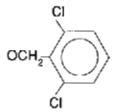
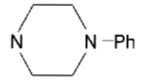
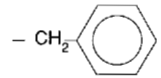
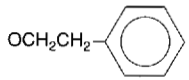
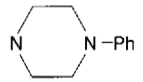
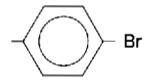
Synthesis of quinoxalylthioureas [**Va–j**]

Ilustrative synthesis: compound [**IVd**] 0.006 mol (2.7 g) was heated for 0.5 h with 70 cm^3 of 10% aqueous sodium hydroxide. After cooling, the resulting precipitate was collected by filtration and

Scheme 1.



No.	R^1	R^2	R^3	R^4	No	R^1	R^2	R^3	R^4
Ia	–	H	H	–	**IIo**	OCH_2CH_2–	CH_3	H	–
Ib	–	H	CH_3	–	**IIp**	OCH_2CH_2–	CH_3	CH_3	–
Ic	–	CH_3	CH_3	–	**IIIa**	$NHCH_2Ph$	H	H	–
Id	–	NO_2		–	**IIIb**	$NHCH_2Ph$	CH_3	CH_3	–
IIa, IVa, Va, VIa, VIIa	OCH_2–	H	H	COPh, H	**IIIc**	$NHCH_2CH_2$–N	H	H	–
IIb, IVb, Vb, VIb, VIIb	OCH_2–	H	CH_3	COPh, H	**IIId**	$NHCH_2CH_2$–N O	H	H	–
IIc, IVc, Vc, VIc, VIIc	OCH_2– Cl	H	H	COPh, H	**IIIe**	$NHCH_2CH_2CH_2$–N O	H	H	–
IId, IVd, Vd, VId, VIId	OCH_2– Cl	H	CH_3	COPh, H	**IIIf**	$NHCH_2CH_2CH_2$–N O	CH_3	CH_3	–

IIe		CH_3	H	–	**IIIg**		H	H	–
IIf		H	H	–	**IIIh**		CH_3	CH_3	–
IIg		CH_3	H	–	**IIIi, Vg**		H	H	
IIh		CH_3	CH_3	–	**IIIj**		H	CH_3	–
IIi		H	H	–	**IIIk**		CH_3	H	–
IIj		CH_3	H	–	**IIIl**		CH_3	CH_3	–
IIk		CH_3	CH_3	–	**IIIm**		NO_2	H	–
IIl, IVl, Ve, VIe, VIIe		H	H	COPh, H	**Vh**		H	H	
IIm, IVf, Vf, VIf, VIIf		H	H	COPh, H	**Vi**		H	H	
IIn		H	H	–	**Vj**		H	H	

recrystallized from methanol. The reaction yielded 1.6 g (74%) of [**Vd**], m.p. 203–205°C.

For compounds [**Va–j**]: IR(cm^{-1}): 3200–3300 (NH); 3040–3080 (CH aromat.); 2920–2940 (CH aliphat.); 1510, 1480, 1450 (CH aromat.).
^{1}H–NMR (d_6-DMSO or $CDCl_3$): 3.5–3.8 (m, 8H piperazine); 4.4–5.5 (s (d) 2H, CH_2); 7.2–7.8 (m, aromatic protons).

Synthesis of hydroiodides of S–methylquinoxalylisothioureas [**VIa–f**]

Ilustrative synthesis: to 0.004 mol (1.6 g) of compound [**Vd**], 0.008 mol methyl iodide dissolved in 170 cm^3 acetone was added. The reaction mixture was refluxed for 1 h. Then acetone was distilled off under a reduced pressure. The resulting precipitate was recrystallized from methanol. The reaction yielded 1.1 g (44%) of [**VId**], m.p. 168–171°C.

For compounds [**VIa–f**]: IR(cm^{-1}): 3200–3450 (NH); 3060–3080 (CH aromat.); 2920–2960 (CH aliphat.).
^{1}H–NMR (d_6-DMSO or $CDCl_3$): 4.3–5.4 (s (d), 2H, CH_2); 7.3–7.8 (m, aromatic protons).

Synthesis of quinoxalylamino–1,3–diazacycloalkanes [**VIIa–f**]

Ilustrative synthesis: to a solution of 0.0016 mol (0.8 g) of compound [**VId**] in 15 cm^3 methanol 0.0035 mol (0.2 g) of ethylenediamine dissolved in 2 cm^3 methanol was added. The reaction mixture was refluxed for 6 h. Then methanol was distilled off under a reduced pressure and 25 cm^3 of water was added to the residue. The resulting precipitate was collected by filtration and recrystallized from methanol. The reaction yielded 0.2 g (35%) of [**VIId**], m.p. 186–190°C.

For compounds [**VIIa–f**]: IR(cm^{-1}): 3200–3400 (NH); 3060–3100 (CH aromat.); 2920–2940 (CH aliphat.).
^{1}H–NMR (d_6-DMSO or $CDCl_3$): 3.4–3.7(d, 4H, CH_2CH_2); 5.4–5.6(s, 2H, CH_2); 7.2–7.8(m, aromatic protons).

Pharmacological Tests

Measurements of the effects on the blood pressure in rats

Male Wistar rats (weight 250–300 g) were anaesthesized with urethane and the trachea was cannulated to allow respiration. Blood pressure was measured in the cannulated carotid artery with a pressure transducer connected to a blood pressure meter (8041, S & W Medico Teknik A/S, Denmark). The agents studied were injected into the left femoral vein. A single dose of a magnitude limited by the solubility of the compound was administered to each animal. Maximum changes of the mean blood pressure were recorded.

Measurements of the effects on isolated rat heart atria

The experiments were performed according to Levy (4). Male Wistar rats (weight 200–250 g) were anaesthesized with urethane. Spontaneously beating atrial pairs were allowed to stabilize in an organ bath containing a modified Krebs solution. After equilibration, the response of the atria to inotropic and chronotropic effects of isoprenaline (ISO) added cumulatively to the bath was recorded.

The compounds under study were added to the bath at a concentration of 7.5 x 10^{-6} mol/dm^3, in the presence of the cumulative concentrations ISO ranging from 10^{-9} to 10^{-5} mol/dm^3.

Changes in the beating rate and amplitude of the atria were expressed as the percentage of the maximum ISO effects.

The effects of the agents tested on isolated rat heart atria were also studied in the absence of ISO in the bath. The compounds under study were added in cumulative concentrations 7.5 x 10^{-11} – 7.5 x 10^{-5} mol/dm^3.

Experiments on isolated rat tail artery

A perfused tail artery preparation according to Nicholas (5) was used. The artery was prepared from male Wistar rats (weight 180–200 g) under the urethane anaesthesia. The cannulated proximal end of the artery was transferred to an organ bath and perfused with the oxygenated Krebs solution. The constrictory activity of the compounds studied was assayed after administration in increasing concentrations. The concentration *vs.* effect curves were plotted, assuming the constriction induced by 10^{-4} mole/dm^3 NA (added in cumulative manner to the bath solution) to be 100%.

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Received: 12.11.1998