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PHARMACOLOGY

ANTIARRHYTHMIC AND ANTIHYPERTENSIVE ACTIVITY OF SOME XANTHONE DERIVATIVES

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Abstract: Some of appropriate aminoisopropanoloxy derivatives of 4-xanthone were tested for their effect on circulatory system (protection against adrenaline-, barium-, and calcium chloride-induced arrhythmias, as well as hypotensive activity and acute toxicity). The most prominent hypotensive activity was demonstrated by (±)-1-[4-(hydroxyethyl)-1-(piperazinyl)]-3-(4-xanthonoxy)-2-propanol dihydrochloride (**II**), which diminished arterial blood pressure by about 40% during one hour observation. The investigated compounds did not prevent adrenaline- and barium-induced arrhythmias. In calcium-induced model of arrhythmia compound **II** slightly intensified blocks (about 7%), but delayed extrasystoles (37%), efficiently prevented bigeminy (70%, $p < 0.01$) and diminished (53%, $p < 0.05$) mortality of animals. All investigated compounds decreased heart rate by 10 – 18%, prolonged P-Q section, QRS complex and Q-T interval. The most potent and significant negative chronotropic effect and markedly prolonged duration of P-Q section was demonstrated by compound **II**. The influence of investigated compounds on ECG components suggests that activity of compound **IV** is similar to class 1a anti-arrhythmic compounds according to Vaughan-Williams classification of antiarrhythmic drugs, because of prolongation of P-Q and Q-T intervals and extension of QRS complex. Compounds **II** and **IV** were also evaluated for anticonvulsant activity in the maximal electroshock seizures (MES) and subcutaneous pentylenetetrazole seizure threshold (ScMet) assays and for neurotoxicity (TOX). The anti-MES activity in mice was found for **IV**, which in a dose of 100 mg/kg within 0.5 h after *ip* administration showed 75% anticonvulsant protection with 50% neurotoxicity.

Keywords: xanthone derivatives, antiarrhythmic activity, arterial blood pressure

Xanthones of natural and synthetic origin are of biological and pharmacological interest. In dependence on the kind and place of substitution in one of the xanthone rings, a large variety of pharmacological activities were reported (1-9). Two synthetic compounds, named xanthonolol (3-[3-(propylamino)-2-hydroxypropoxy]xanthone) and 3-hydroxyxanthone reduced the blood pressure, heart rate, and L-isoproterenol-induced tachycardia in rats (10). We herein report on the preparation and antiarrhythmic, antihypertensive as well as anticonvulsant activity of a few appropriate aminoisopropanoloxy derivatives of 4-xanthone containing 1-(2-hydroxyethyl)-piperazine, ethylpiperazine-1-carboxylate and 1-(benzyl)-piperazine moieties (**II – IV**). Previously, some of appropriate aminoisopropanoloxy derivatives of 2-, 3- or 2-methyl-6-xanthone as well as aminoalkanolic derivatives of 7-chloro-2-methylxanthone had been tested for their effects on the circulatory system, influence on the non-working heart perfusion, antiarrhythmic activity in experimentally adrenaline induced arrhythmia, as well as for anticonvulsant effects (11-14).

EXPERIMENTAL

Chemistry

Apparatus and reagents

Melting points are uncorrected and were determined on a Büchi SMP-20 apparatus. Microanalyses for C, H, N were performed in the Department of Pharmaceutical Chemistry, Medical College, the Jagiellonian University. All the results were within (±) 0.4% of the theoretical values. The IR spectra were recorded on a Perkin-Elmer spectrometer, the samples were prepared as KBr pellets. The ^{1}HNMR spectra were recorded on a Bruker spectrometer with 300 MHz in DMSO-[d_6] using tetramethylsilane (TMS) as an internal standard. TLC was per-

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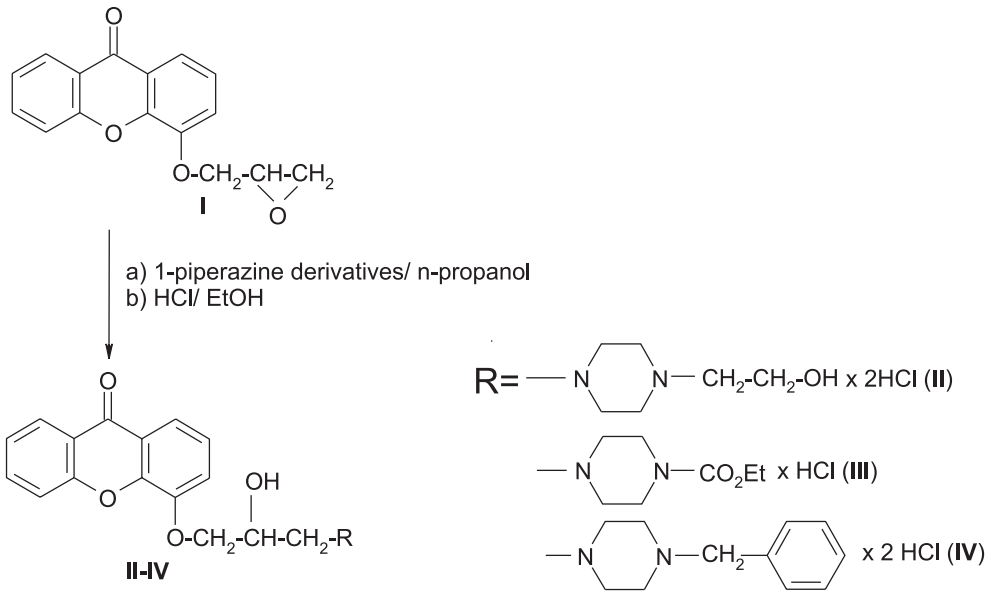

Scheme 1. Synthesis and structures of the title compounds.

formed on silica gel GF_{254} precoated plates (5 × 10 cm, 0.25 mm, Merck) with an appropriate developing system ($CHCl_3$/MeOH, 1 : 1, v/v); spots were visualized with the UV light. The starting compound **(I)** (4-[(2,3-epoxy)propoxy]xanthone) was obtained from 4-hydroxyxanthone, according to the earlier described procedure (15, 16). Reagents and solvents were commercially available materials of reagent grade.

General procedure for the preparation of compounds **II – IV**

Compounds **II – IV** were obtained by amination of **I** with appropriate 1-piperazine derivatives in n-propanol (Scheme 1), according to the earlier published procedures (15, 16). The resulted bases were converted into hydrochloride salts in propanol/acetone (3:1 ,v/v) with an excess of ethanol saturated with HCl.

(±)-1-[4-(Hydroxyethyl)-1-(piperazinyl)]-3-(4-xanthonoxy)-2-propanol dihydrochloride (**II**)

Yield: 62%, m.p. 256-258°C (acetone/ethanol 1 : 1, v/v), R_f = 0.39 (base: m.p. 118-120°C (ethanol)); $C_{22}H_{28}Cl_2N_2O_5$ (471.37). ^{1}H NMR (δ, ppm): 12.62 (2H, bb, NH^+), 8.21 (1H, dd, *J* = 1.7 Hz, *J* = 8.0 Hz, H-8), 7.92-7.12 (6H, m, H-Ar), 6.21 (1H, bs, CHOH), 4.53-4.40 (1H, m, CH), 4.44 (1H, bb, CH_2OH), 4.22-4.12 (2H, m, CH_2OH), 4.08-2.98 (14H, m, $N(CH_2)_6$, OCH_2), IR (ν [cm^{-1}]): 3312, 3007, 2942, 2638, 2440, 1657, 1617, 1607, 1594, 1495, 1451, 1342, 1278, 1232.

(±)-1-[4-(Ethoxycarbonyl)-1-(piperazinyl)]-3-[4-xanthonoxy)-2-propanol hydrochloride (**III**)

Yield: 54%, m.p. 190-192°C (n-propanol), R_f = 0.90 (base: m.p. 138-140°C (ethanol); $C_{23}H_{27}ClN_2O_6$ (462.92). ^{1}H NMR-base (δ, ppm): 8.28 (1H, dd, *J* = 1.6 Hz, *J* = 8.0 Hz, H-8), 7.74-7.28 (6H, m, H-Ar), 5.89 (1H, bs, OH), 4.36-4.24 (1H, m, CH), 4.19 (2H, q, *J* = 7.2 Hz, CH_2(Et)), 4.10-4.05 (2H, m, OCH_2), 3.62-2.64 (10H, m, $N(CH_2)_5$), 1.32 (3H, t, *J* = 7.2 Hz, CH_3(Et)). IR (ν [cm^{-1}]): 3067, 2981, 1711, 1631, 1617, 1593, 1492, 1443, 1269, 1231.

(±)-1-[4-(Benzyl)-1-(piperazinyl)]-3-(4-xanthoxy)-2-propanol dihydrochloride (**IV**)

Yield: 61%, m.p. 247-249°C, R_f = 0.38, $C_{27}H_{30}Cl_2N_2O_4$ (517.44), ^{1}H NMR (δ, ppm): 12.55 (1H, bb, NH^+), 11.6 (1H, bb, NH^+), 8.19-8.13 (1H, m, H-8), 7.88-7.40 (10H, m, H-Ar), 5.76 (1H, bs, OH), 4.51-4.45 (2H, m, CH_2-Ph), 4.40-4.28 (1H, m, CH), 4.12-4.08 (2H, m, OCH_2), 3.86-3.24 (10H, m, $N(CH_2)_5$). IR (ν [cm^{-1}]): 3357, 2991, 2506, 2420, 1642, 1606, 1593, 1494, 1469, 1344, 1284, 1228.

PHARMACOLOGY

Animals

The studies were carried out on male albino Swiss mice weighing 18 – 24 g (purchased from a licensed dealer; Hurlak, Kraków, Poland), normotensive male Wistar rats weighing 170 – 250 g, and guinea-pigs weighing 300 – 350 g. The animals

were kept in plastic cages in a room at a temperature of 20 ± 4°C, under 12/12 h light/dark cycle (light on from 7 a.m. to 7 p.m.). They were fed with granulated feed (standard laboratory pellets; Bacutil, Motycz, Poland) and had free access to water. The control and study groups consisted of 6-8 animals each. Treatment of the used laboratory animals in the present study was in full accordance with the respective Polish and European regulations and was approved by the Local Ethics Committee. The European Convention for protection of the vertebrate animals, used for experimental studies as well as different scientific aims (European Convention) undersigned in Strasburg in 1983, ascertains that in existing conditions is not possible to give up using laboratory animals for the scientific studies. The databases should be created to enable utilization by researches the information from homologous fields in regard to use laboratory audits limitation of the animals' quantity. In our studies comparing pharmacological activities of new compounds, with the well-known drugs used as reference compounds, results of our previous experiments in Department of Pharmacodynamics, Jagiellonian University Medical College were exploited. The utilization of previous results, is postulated by the European Convention – as the *sui generis* database, what is in accord with general recommendations in matter of the vertebrate animals' protection (17).

Drugs

The following drugs were used: adrenaline hydrochloride (Polfa, Poland), thiopental sodium (Spofa, Czech Republic), heparin sodium (Roche, France), propranolol (Polfa, Poland), calcium chloride (POCh, Poland), barium chloride (POCh, Poland), quinidine (Polfa, Poland). The investigated compounds were dissolved or diluted in 0.9% sodium chloride isotonica (Rhone-Poulenc Rorer, France).

Acute toxicity according to Deichmann (18)

The experiments were carried out on male albino Swiss mice (20 – 25 g) The compounds dissolved in 0.9% saline, were injected into the caudal vein (1 mL/kg). Each dose was given to 6 animals. The LD_{50} were calculated acc. to the method of Litchfield and Wilcoxon after 24 h observation period (19).

The effect on normal electrocardiogram

Electrocardiographic studies were carried out on anesthetized rats using a Multicard E-30 apparatus. ECG was recorded from the second extremity lead at a tape speed of 50 mm/s. The influence of the compounds studied on the frequency of myocardiac contraction, the P wave and QRS complex were determined.

Adrenaline-induced arrhythmia according to Szekeres (20)

The arrhythmia was evoked in rats anesthetized with thiopental (75 mg/kg, *ip*) by *iv* injection of adrenaline (20 µg/kg, in a volume of 1 mL/kg of animal weight). The studied compounds were administered intravenously 15 min before adrenaline. Evaluation of the antiarrhythmic activity was made acc. to the time of occurring postadrenaline disorders and the survival time of animals in control and studied group. ECG was recorded on a Multicard E-3 or E-30 apparatus, using the standard limb lead, and the tape speed 50 mm/s.

Calcium chloride-induced arrhythmia according to Szekeres (20)

In order to evoke arrhythmia, calcium chloride in a dose of 150 mg/kg was administered *iv* in a volume of 1 mL/kg. Attenuation or the lack of disturbances and the decreased mortality after calcium chloride were accepted as a criterion of the antiarrhythmic effect of the investigated compounds in comparison with the control group.

Barium chloride-induced arrhythmia according to Szekeres (20)

Barium chloride solution was injected into the caudal vein of rat (32 mg/kg, in a volume of 1 mL/kg). The investigated compound was given *iv* 15 min before the arrhythmogen. The criterion of antiarrhythmic activity was a gradual disappearance of the arrhythmia and restoration of the sinus rhythm in comparison with the control group.

The effect on the arterial blood pressure and respiratory movements

Measurements were carried out on normotensive rats. The animals were anesthetized with *ip*

Table 1. Acute toxicity in mice according to Deichmann and LeBlanc.

Compound	Route	Approx. LD_{50} (mg/kg)
II	*iv*	60.00
III	*iv*	60.00
IV	*iv*	30.00
Quinidine	*iv*	90
Propranolol	*iv*	22

Table 2. Influence of the investigated compounds on ECG parameters.

Compounds	Dose mg/kg	Parameter	Time				
			Before administration	10 sec	5 min	10 min	15 min
II	1/5 LD_{50}	PQ (msec)	37.30 ± 1.25	40.82 ± 0.82	40.17 ± 0.86	39.17 ± 1.04	40.72 ± 1.15
		QRS (msec)	26.07 ± 1.88	27.57 ± 3.06	26.15 ± 3.23	25.25 ± 2.46	28.25 ± 3.14
		QT (msec)	56.50 ± 3.52	56.25 ± 3.30	53.30 ± 3.62	53.37 ± 2.48	54.62 ± 4.45
		Heart rate (beats/min)	356.13 ± 11.07	320.16 ± 9.39[b]	304.61 ± 8,52[d]	302.85 ± 13.42[a]	299.57 ± 9.53[d]
III	1/5 LD_{50}	PQ (msec)	38.25 ± 1.09	40.62 ± 0.82	40.05 ± 0.67	15.62 ± 0.92	40.07 ± 0.87
		QRS (msec)	15.12 ± 1.18	14.27 ± 1.14	15.60 ± 0.71	16.00 ± 1.06	15.75 ± 1.14
		QT (msec)	33.00 ± 1.51	33.80 ± 1.88	32.62 ± 1.65	32.47 ± 2.62	34.60 ± 1.86
		Heart rate (beats/min)	371.31 ± 11.37	340.47 ± 8.60[a]	338.05 ± 11.93[a]	329.32 ± 11.87[b]	319.18 ± 10.67[c]
IV	1/5 LD_{50}	PQ (msec)	39.40 ± 0.88	46.30 ± 2.87	43.10 ± 3.07	42.87 ± 3.21	42.17 ± 2.59
		QRS (msec)	14.37 ± 0.88	15.55 ± 1.04	15.62 ± 0.88	15.30 ± 0.79	15.87 ± 0.71
		QT (msec)	35.87 ± 1.00	34.75 ± 1.41	36.62 ± 1.56	35.02 ± 1.57	33.15 ± 1.80
		Heart rate (beats/min)	339.38 ± 10.00	331.26 ± 17.07	332.16 ± 24.69	318.40 ± 21.04	310.62 ± 20.65

Route: *iv*, anesthesia: thiopental (75 mg/kg *ip*)
The data represent the means ± SEM. Statistical significance was evaluated using a one-way ANOVA test, [a]$p < 0.5$, [b]$p < 0.02$, [c]$p < 0.01$, [d]$p < 0.001$

thiopental administration at a 75 mg/kg dosage. Blood pressures were recorded in the left common carotid artery using an electromanometer of type EK-4 together with a Watanabe recorder WTR-331. The examined compounds dissolved in 0.9% sodium chloride were administered to rat tail vein in a range of dosage 1/20 – 2/5 LD_{50}. Simultaneous blood pressure measurements and changes in respiration were recorded.

Anticonvulsant assays

Antiepileptic activity and neurological toxicity assays were carried out by the Antiepileptic Drug Development Program, Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institute of Health, Bethesda, MD, USA. The compounds were injected *ip* into mice as suspensions in 0.5% methylcellulose at three dosage levels (30, 100 and 300 mg/kg). The MES were elicited by 60 Hz alternating current of 50 mA for 0.2 s via corneal electrodes. A drop of 0.9% NaCl solution was instilled in each eye prior to application of the electrodes. Abolition of the hindlimb tonic extensions component of the seizure was defined as protection in the MES test. The ScMet test was conducted by administering 85 mg/kg of pentylenetetrazole dissolved in 0.9% NaCl solution in the posterior midline of mice. A minimal time 30 min subsequent to *sc* administration of pentylenetetrazole was used for seizure detection. A failure to observe even a threshold seizure (a single episode of clonic spasm of at least 5 s duration) was regarded as protection. Neurological deficit was measured in mice by the rotorod test. The mouse was placed on 1 inch diameter knurled plastic rod rotating at 6 rpm. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of three trials. The more details of the evaluation procedure have been published (22, 23).

Statistical analysis

The data are expressed as the means ± SEM. Student's t-test or Fisher's two-tailed exact probability test were used to determine the significance of differences

Table 3. Anticonvulsant and neurotoxicity screening results of **II**, **IV** and 2-substituted xanthone analogues (**IIa**, **IVa**) of **II** and **IV**.

Compound	Dose	Activity					
		MES[a]		ScMET[b]		Tox[c]	
	mg/kg	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
II	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	0/8	0/4
	300	0/1	0/1	1/5	0/1	2/4	0/2
IIa	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	2/3	0/3	0/1	0/1	0/8	0/4
	300	1/1	0/1	0/1	0/1	4/4	0/2
IV	30	0/1	0/1	1/5	0/1	0/4	0/2
	100	2/3	0/3	0/1	0/1	4/8	1/4
	300	n.t.	0/1	0/1	0/1	2/4	0/2
IVa	30	1/1	1/1	1/1	0/1	0/4	1/2
	100	n.t.	n.t.	n.t.	n.t.	8/8	n.t.
	300	n.t.	n.t.	n.t.	n.t.	4/4	n.t.

[a] number of animals protected/ number of animals tested in the MES test
[b] number of animals protected/ number of animals tested in the scMet test
[c] number of exhibiting toxicity/ number of animals tested in the rotorod test
n.t. – compound was not tested

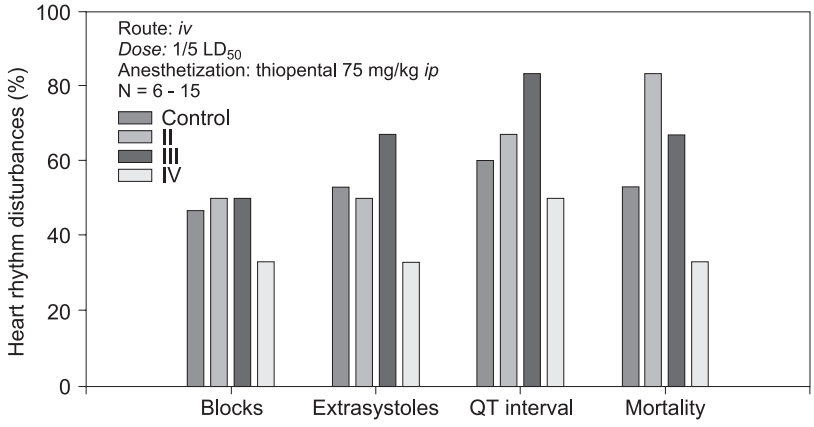

Figure 1. Antiarrhythmic activity of compounds II, III and IV in adrenaline-induced arrhythmia.

between the mean values of the control and treatment groups. Differences were considered significant when p was < 0.05.

RESULTS AND DISCUSSION

Acute toxicity according to Deichmann

The LD_{50} values for investigated aminoalkanolic derivatives **II – IVa**, determined in mice after intravenous administration, are presented in Table 1.

The effect on normal electrocardiogram

All the investigated compounds decreased heart rate by 10 – 18%, prolonged the duration of P-Q section, the QRS complex and the Q-T interval. The strongest negative chronotropic effect ($p < 0.001$) and the most prolonged duration of P-Q section were of compound **II**. In summary, the influence of the investigated compounds on ECG components, suggested that activity of compound **IV** is similar to class 1a antiarrhythmic compounds according to Voughan-Williams, because of the pro-

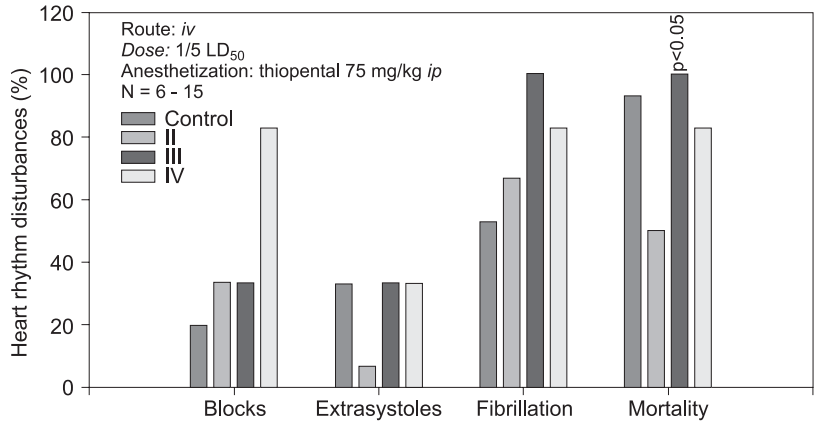

Figure 2. Antiarrhythmic activity of compounds II, III and IV in barium-induced arrhythmia.

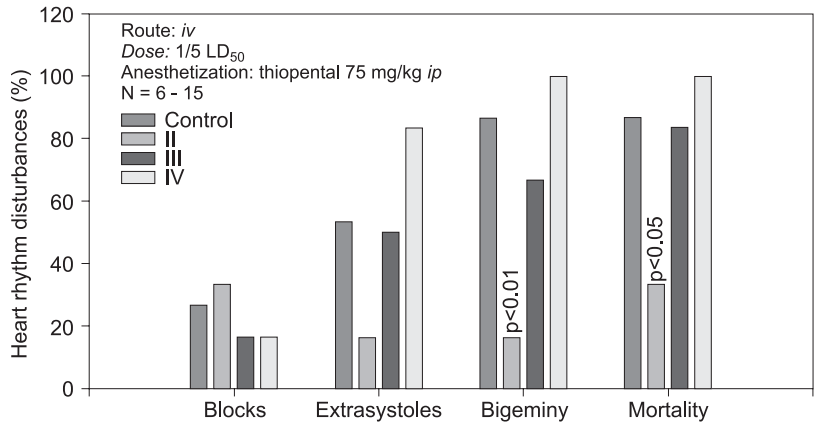

Figure 3. Antiarrhythmic activity of compounds II, III and IV in calcium-induced arrhythmia.

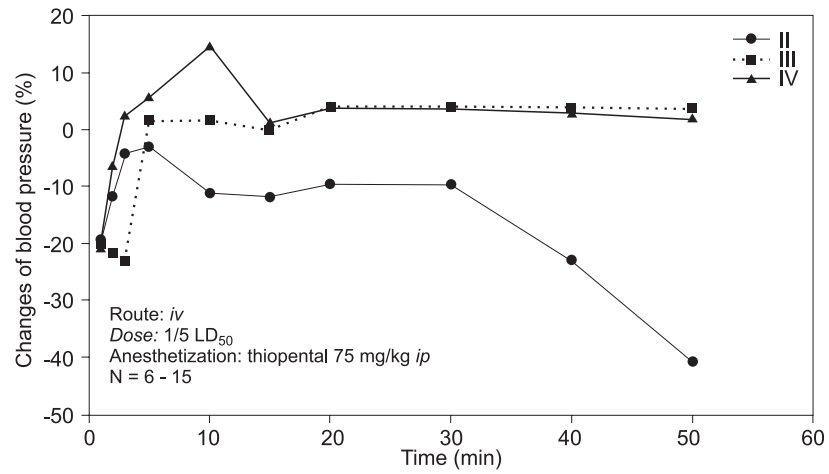

Figure 4. The influence of compounds II, III and IV on blood pressure of anaesthetized rat.

longed P-Q and Q-T intervals and extended QRS complex. (Table 2).

Adrenaline-, barium-, and calcium-induced arrhythmias

The tested compounds did not prevent the adrenaline-induced arrhythmia; but considerably diminished arrhythmia causing blocks and extrasystoles. In adrenaline-induced model of arrhythmia the most effective compound was compound **IV**. The reference compounds – propranolol and quinidine – administered 15 min before adrenaline, showed insignificant preventive activity. In the barium model of arrhythmia, compound **II** diminished mortality by 43%. In calcium-induced model of arrhythmia the strongest activity has also compound **II**. It slightly intensified blocks (about 7%), but delayed the extrasystoles (37%), highly prevented bigeminy (70%, $p < 0.01$) and diminished (by 53%, $p < 0.05$) mortality of animals (Figures 1-3). Propranolol and quinidine used as referenced compounds did not prevent against arrhythmias induced by barium or calcium chlorides.

The effect on the arterial blood pressure and respiratory movements

The investigated compounds had various influence on the blood pressure of normotensive rats. The strongest hypotensive activity was showed by compound **II** which diminished the arterial blood pressure by about 40% during one hour observation. Although immediately after intravenous administrations the new xanthone derivatives weakly activated the respiration, they did not have a significant influence on either the amplitude or frequency of respiratory movements (Figure 4).

Searching for compounds with potential antiepileptic activity we have noticed that several circulatory drugs from the aminoalkanol or aminoalkoxy groups, e.g. β-blockers (propranolol), have also anticonvulsant properties. It is well known that lipophilic drugs exhibit marked central action, with possible indications in neurology and psychiatry. Anticonvulsant effects of propranolol in various seizure models were described (21). The present results suggest that the anticonvulsant activity of compounds **II** and **IV** may be related to their activity in adrenaline- and calcium chloride-induced arrhythmia, but this is probably only one of several factors involved in its activity. These data demonstrated different potency of the new synthesized xanthone derivatives in affecting functions of the CNS and cardiovascular systems, which indicate the importance of pharmacological examination of newly synthesized compounds. The obtained results of pharmacological tests suggest further examinations to establish mechanism(s) of central activity of the examined compounds, 2- and 4-substituted derivatives of xanthone, and to estimate their potential therapeutic value. During the study of antiarrhythmic activity of some new congeners of aminoisopropanoloxy xanthone derivatives the best effect was demonstrated by compound **II**. The lack of electrophysiological studies limited discussion of the mechanism of action displayed by this compound, however, the effect against such an aggressive mediator like adrenaline strongly suggests to extend the antiarrhythmic study of this compound in the other models of arrhythmia and *in situ* and *in vivo* experiments on rat isolated heart.

Anticonvulsant assays

Preliminary anticonvulsant and neurotoxicological tests of compounds **II** and **IV** have been provided by the Antiepileptic Drug Development (ADD) Program (NIH, Bethesda, USA), by their testing procedures which have been described earlier (22, 23). Phase I studies involved three tests in mice: MES (maximal electroshock seizure), ScMet (subcutaneous pentylenetetrazole seizure threshold) and neurotoxicity (TOX). For the tested compounds **II** and **IV** the anticonvulsant activity (MES, mice, *ip*) was found only for **IV**, which in a dose of 100 mg/kg within 0.5 h after injection showed 75% anticonvulsant protection with a 50% neurotoxicity. In the ScMet screen for both compounds in the dose of 300 mg/kg within 0.5 h after administration, 20% anticonvulsant protection was accompanied by neurotoxic signs (50% for **II** and 100% for **IV**). When comparing the anticonvulsant activity of compounds **II** and **IV** with previously described 2-substituted xanthones (**IIa** and **IVa**) containing the same 1-piperazine moiety (12) we observed that these latter were more active at appropriate doses (Table 3).

CONCLUSIONS

Based on the *in vivo* experiments, it seems that (±)-1-[4-(hydroxyethyl)-1-(piperazinyl)]-3-(4-xanthonoxy)-2-propanol dihydrochloride (**II**) and (±)-1-[4-(Benzyl)-1-(piperazinyl)]-3-(4-xanthoxy)-2-propanol dihydrochloride (**IV**) are the most promising compounds, from which **II** demonstrated hypotensive and antiarrhythmic activity (calcium-induced model of arrhythmia). Compound **IV** caused the significant anticonvulsant protection in the MES screen mice in a dose of 100 mg/kg within 0.5 h after *ip* administration.

The obtained preliminary *in vivo* results encourage further search in the group of xanthone derivatives as the agents possessing interesting biological activity.

Acknowledgment

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