4-(3-ALKYLAMINO-2-HYDROXYPROPOXY)-3-(ALKOXYMETHYL)ACETOPHENONES

Ružena ČIŽMÁRIKOVÁ[a], Alois BOROVANSKÝ[b], Ján KOZLOVSKÝ[c], Eva BÉDEROVÁ[c] and Anna DINGOVÁ[c]

[a] *Department of Inorganic and Organic Chemistry,*
[b] *Department of Pharmaceutical Chemistry and*
[c] *Department of Pharmacology and Toxicology,*
Faculty of Pharmacy, Comenius University, 832 32 Bratislava

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A series of new beta-adrenolytics derived from *p*-hydroxyacetophenone was synthesized by four methods. The most advantageous was found to be the five-step synthesis *via* reaction of the intermediate oxirane with amines. The selected compounds reveal a beta-adrenolytic and antiarrhythmic activities.

3-Alkylamino-1-(substituted aryloxy)-2-propanols form a group of medicaments employed not only in treatment of cardiovascular disorders but in many other indications. Beta-adrenolytics are reported[1] to be used in 30 indications of the cardiovascular system and in 20 others of extracardiovascular origin. Although a good deal of beta-adrenolytics are being used, their investigation is still in progress aiming to found compounds with an enhanced selectivity to heart receptors and having the least possible unwanted effects[2,3].

A study concerning the action of beta-adrenolytica showed a positive influence of substituted aromatic ring by electron-donating groups, mainly by alkyls and cycloalkyls[4,5]. Substitution of the aromatic ring by alkoxymethyl and aryl groups and its influence on the effect has not been examined. This prompted us to prepare 4-(3-alkylamino-2-hydroxypropoxy)-3-(alkoxymethyl)acetophenones and investigate their pharmacological effects.

Compounds *I*–*XXVI* were obtained by a 5-step synthesis from *p*-hydroxyacetophenone prepared according to[6]. 4-Hydroxy-3-chloromethylacetophenone prepared by chloromethylation[7] was reacted with the respective alcohols in the presence of sodium hydrogen carbonate according to the modified procedure[7] to yield 3-alkoxymethyl-4-hydroxyacetophenones. The final products were tried to obtain by methods *A*–*D* refs[8–12] of which method *A* was the most advantageous: 3-alkoxymethyl-4-hydroxyacetophenones were treated with chloromethyloxirane in the presence of potassium hydroxide. The oxirane formed gave with isopropylamine and tert-butylamine final products *I*–*XXVI* (Table 1). These were isolated in form of salts with

TABLE I

4-(3-Alkylamino-2-hydroxypropoxy)-3-(alkoxymethyl)acetophenones and their salts prepared by method *A*

Compound	R^1 R^2	Form	Formula M_r	Calculated/Found % C	% H	% N	M.p., °C solvent	Yield, % R_F
I	CH_3 $CH(CH_3)_2$	base	$C_{16}H_{25}NO_4$	—	—	4·74	52—54	—
			295·4	—	—	4·71	*a*	—
		fumarate	$C_{36}H_{54}N_2O_{12}$	61·17	7·70	3·96	150—152	42
			706·8	61·51	8·03	4·20	*b*	0·67
		oxalate	$C_{34}H_{52}N_2O_{12}$	59·98	7·64	4·12	192—194	40
			680·8	59·64	7·75	4·04	*c*	—
II	CH_3 $C(CH_3)_3$	base	$C_{17}H_{27}NO_4$	—	—	4·53	69—72	—
			309·2	—	—	4·77	*a*	—
		fumarate	$C_{38}H_{58}N_2O_{12}$	62·11	7·96	3·81	188—189	45
			734·9	61·98	8·11	4·00	*d*	0·69
		oxalate	$C_{36}H_{56}N_2O_{12}$	61·00	7·96	3·96	195—198	51
			708·9	61·00	8·23	3·99	*c*	—
III	C_2H_5 $CH(CH_3)_2$	base	$C_{17}H_{27}NO_4$	—	—	4·52	41—42	—
			309·2	—	—	4·33	*a*	—
		fumarate	$C_{38}H_{58}N_2O_{12}$	62·11	7·96	3·81	140—142	40
			734·9	62·32	8·24	3·86	*d*	0·74
		oxalate	$C_{19}H_{29}NO_8$	57·13	7·32	3·51	84—86	43
			399·4	56·94	7·02	3·39	*e*	—
IV	C_2H_5 $C(CH_3)_3$	base	$C_{18}H_{29}NO_4$	—	—	4·33	61—64	—
			323·4	—	—	4·10	*a*	—
		fumarate	$C_{40}H_{62}N_2O_{12}$	62·99	8·14	3·69	170—172	35
			762·9	63·15	8·43	3·81	*b*	0·73
		oxalate	$C_{38}H_{60}N_2O_{12}$	61·92	8·20	3·80	186—188	40
			736·8	61·89	7·96	4·03	*f*	—
V	n-C_3H_7 $CH(CH_3)_2$	fumarate	$C_{40}H_{62}N_2O_{12}$	62·97	8·19	3·67	120—122	40
			762·9	62·63	8·32	3·84	*c*	0·72
		oxalate	$C_{38}H_{60}N_2O_{12}$	61·94	8·21	3·80	145—146	52
			736·9	61·62	7·96	3·69	*f*	—
		tartrate	$C_{40}H_{62}N_2O_{14}$	60·32	8·10	3·52	105—107	35
			796·8	59·91	8·02	3·25	*e*	—
VI	n-C_3H_7 $C(CH_3)_3$	base	$C_{19}H_{31}NO_4$	—	—	4·15	60—62	—
			337·5	—	—	4·02	*a*	—
		fumarate	$C_{42}H_{66}N_2O_{12}$	63·78	8·41	3·54	183—184	43
			791·0	64·00	8·56	3·46	*f*	0·74
		oxalate	$C_{40}H_{64}N_2O_{12}$	62·74	8·36	3·66	176—178	46
			765·0	63·07	8·58	3·61	*f*	—

TABLE I
(*Continued*)

Compound	R^1 R^2	Form	Formula M_r	Calculated/Found % C	% H	% N	M.p., °C solvent	Yield, % R_F
VII	i-C_3H_7 $CH(CH_3)_2$	base	$C_{18}H_{29}NO_4$	—	—	4·33	69—71	—
			323·4	—	—	4·10	*a*	—
		fumarate	$C_{40}H_{62}N_2O_{12}$	62·97	8·19	3·67	150—151	40
			762·9	62·14	8·47	3·50	*e*	0·68
VIII	i-C_3H_7 $C(CH_3)_3$	base	$C_{19}H_{31}NO_4$	—	—	4·15	80—93	—
			337·5	—	—	4·19	*a*	—
		fumarate	$C_{42}H_{66}N_2O_{12}$	63·78	8·41	3·54	193—194	35
			791·0	64·10	8·54	3·61	*e*	0·69
IX	n-C_4H_9 $CH(CH_3)_2$	fumarate	$C_{42}H_{66}N_2O_{12}$	63·78	8·41	3·54	117—120	37
			791·0	63·87	8·54	3·30	*e*	0·73
X	n-C_4H_9 $C(CH_3)_3$	fumarate	$C_{44}H_{70}N_2O_{12}$	64·52	8·61	3·42	171—173	39
			818·5	64·30	8·51	3·22	*e*	0·76
XI	s-C_4H_9 $CH(CH_3)_2$	fumarate	$C_{23}H_{35}NO_8$	60·91	7·78	3·09	138—140	34
			453·5	60·95	7·72	3·21	*f*	0·76
XII	s-C_4H_9 $C(CH_3)_3$	fumarate	$C_{44}H_{70}N_2O_{12}$	64·52	8·61	3·42	187—189	37
			818·5	64·27	8·65	3·45	*b*	0·68
XIII	i-C_4H_9 $CH(CH_3)_2$	fumarate	$C_{42}H_{66}N_2O_{12}$	63·78	8·41	3·54	150—153	13
			791·0	63·27	8·55	3·61	*e*	0·66
XIV	i-C_4H_9 $C(CH_3)_3$	fumarate	$C_{44}H_{70}N_2O_{12}$	64·52	8·61	3·42	197—198	36
			818·5	64·30	8·70	3·20	*b*	0·67
XV	n-C_5H_{11} $CH(CH_3)_2$	base	$C_{20}H_{33}NO_4$	—	—	3·98	58—59	—
			351·5	—	—	3·80	*a*	—
		fumarate	$C_{44}H_{70}N_2O_{12}$	64·52	8·61	3·42	133—134	32
			818·5	64·25	8·60	3·28	*e*	0·68
XVI	n-C_5H_{11} $C(CH_3)_3$	base	$C_{21}H_{35}NO_4$	—	—	3·83	58—59	—
			365·5	—	—	3·60	*a*	—
		fumarate	$C_{44}H_{70}N_2O_{12}$	64·52	8·61	3·42	133—134	35
			818·5	64·25	8·60	3·28	*e*	0·66
XVII	i-C_5H_{11} $CH(CH_3)_2$	fumarate	$C_{44}H_{70}N_2O_{12}$	64·52	8·61	3·42	131—132	40
			818·5	64·42	8·51	3·24	*e*	0·73
XVIII	i-C_5H_{11} $C(CH_3)_3$	base	$C_{21}H_{35}NO_4$	—	—	3·83	82—85	—
			365·5	—	—	3·86	*a*	—
		fumarate	$C_{46}H_{74}O_{12}$	65·22	8·81	3·31	181—183	42
			847·1	64·88	8·79	3·37	*b*	0·71

TABLE I
(*Continued*)

Compound	R^1 R^2	Form	Formula M_r	Calculated/Found % C	% H	% N	M.p., °C solvent	Yield, % R_F
XIX	n-C_6H_{13} $CH(CH_3)_2$	base	$C_{21}H_{35}NO_4$	—	—	3·83	38–39	—
			365·5	—	—	3·60	[a]	—
		fumarate	$C_{46}H_{74}N_2O_{12}$	65·22	8·81	3·31	123–125	51
			847·1	65·54	8·98	3·26	[e]	0·85
XX	n-C_6H_{13} $C(CH_3)_3$	base	$C_{22}H_{37}NO_4$	—	—	3·69	74–75	—
			379·5	—	—	3·50	[a]	—
		fumarate	$C_{48}H_{78}N_2O_{12}$	65·87	8·98	3·20	170–171	50
			875·1	65·50	8·95	2·94	[e]	0·81
XXI	n-C_7H_{15} $CH(CH_3)_3$	base	$C_{22}H_{37}NO_4$	—	—	3·69	85–88	—
			379·5	—	—	3·59	[a]	—
		fumarate	$C_{48}H_{78}N_2O_{12}$	65·88	8·98	3·20	124–126	42
			875·2	65·95	8·96	3·07	[e]	0·80
XXII	n-C_7H_{15} $C(CH_3)_3$	base	$C_{23}H_{39}NO_4$	—	—	3·56	53–55	—
			393·6	—	—	3·50	[a]	—
		fumarate	$C_{50}H_{82}N_2O_{12}$	66·49	9·15	3·10	171–173	30
			903·2	66·77	9·13	3·30	[e]	0·77
XXIII	n-C_8H_{17} $CH(CH_3)_2$	fumarate	$C_{50}H_{82}N_2O_{12}$	66·49	9·15	3·10	115–117	36
			903·2	66·59	9·35	3·35	[e]	0·73
XXIV	n-C_8H_{17} $C(CH_3)_3$	fumarate	$C_{52}H_{86}N_2O_{12}$	67·07	9·31	3·01	166–168	33
			931·3	67·30	9·21	3·12	[e]	0·67
XXV	n-C_9H_{19} $CH(CH_3)_2$	fumarate	$C_{52}H_{86}N_2O_{12}$	67·07	9·31	3·01	112–113	40
			931·3	67·20	9·20	3·02	[e]	0·70
XXVI	n-C_9H_{19} $C(CH_3)_3$	fumarate	$C_{54}H_{90}N_2O_{12}$	67·61	9·46	2·92	159–161	38
			959·3	67·45	9·70	3·00	[e]	0·69

[a] Heptane, [b] 2-propanol, [c] ethanol, [d] ethanol–ether, [e] ethyl acetate, [f] ethanol – ethyl acetate

organic acids, especially with fumaric acid in a predominantly base to acid 2 : 1 ratio. Bases were freed from salts with ammonia. Purity of salts was checked by thin-layer chromatography and their structure was corroborated by IR, UV, ^{1}H NMR and mass spectrometric methods.

The IR spectra of salts are characteristic of OH, COO^-, C_{alkoxy}—O—C_{aryl}, and C=C stretching vibrations (Table II). The UV spectra of fumarates (Table II) display bands of $\pi \rightarrow \pi^*$ transitions; these do not undergo alterations with the change of pH.

The ^{1}H NMR spectra of bases (Table III) showed proton signals of the aminopropanol chain. Electron impact mass spectra were recorded for two fumarates: *XI* and *XII* with the base to fumaric acid ratio 1 : 1 and 2 : 1, respectively. Both fumarates lose fumaric acid upon electron impact, and fumarate *XI* reveals a little intense molecular peak of the base. Fumarate *XII* does not display the molecular ion peak, but the $[M-15]^{+\bullet}$ radical ion and species $CH_2{=}\overset{(+)}{N}H{-}CH(CH_3)_2$ and $CH_2{=}\overset{(+)}{N}H{-}C(CH_3)_3$.

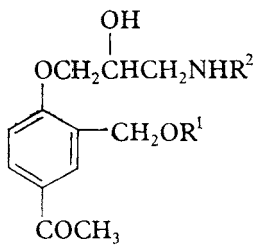
The selected products were tested on beta-adrenolytic and antiarrhythmic effects. The *in vitro* evaluation of anti-isoprenaline activity on spontaneously beating atria of guinea-pig indicates that all compounds under study are able to block the isoprenaline effect. The measure of ability to occupy beta-receptors of heart is expressed as the pA_2 value which is the mean effective dose of the respective compound shifting the dose-response curve for isoprenaline effect on the heart rate twice to the right.

TABLE II
IR and UV spectra of fumarates

Compound	ν(OH)[a]	ν(C=O)[a]	ν(C=C)[a]	$\nu_{as}(COO^-)$[a]	$\nu_{as}(C_{alkoxy}O_{Ar})$[a]	λ_{max}[b] log ε		
VI	3 390	1 678	1 628 1 605	1 576	1 266	203 3·65	221 3·56	274 3·54
X	3 415	1 679	1 634 1 605	1 552	1 260	204 3·62	220 3·53	274 3·51
XII	3 400	1 678	1 633 1 603	1 560	1 270	203 3·49	221 3·47	274 3·32
XVIII	3 416	1 676	1 628 1 603	1 574	1 253	204 3·74	220 3·67	274 3·60
XIX	3 388	1 675	1 628 1 603	1 574	1 253	205 3·58	222 3·62	276 3·60
XX	3 415	1 675	1 630 1 603	1 575	1 260	205 3·58	222 3·62	278 3·63
XXIV	3 403	1 683	1 630 1 607	1 575	1 260	205 3·44	222 3·49	278 3·40
XXVI	3 404	1 678	1 628 1 605	1 575	1 260	204 3·43	222 3·40	274 3·47

[a] IR spectral bands in cm^{-1}, [b] UV λ_{max} in nm, log ε in mol^{-1} m^2

The pA_2 values (Table IV) approaching that of the metipranolol reference are lower than that of metoprolol. The highest pA_2 values had compound *XIX* with hexyloxymethyl group in position 3; higher homologues revealed only little changes in the pA_2 values.



I – XXVI

$R^1 = C_nH_{2n+1}$, $n = 1 - 9$

$R^2 = CH(CH_3)_2$, $C(CH_3)_3$

Decrease of the heart rate (Table IV) showed that all compounds under investigation possess a negative chronotropic effect, which gradually increased with the increasing number of carbon atoms in the alkoxyl groups. Drop of the heart rate increased also in time and the commencement of activity was successive.

TABLE III

^1H NMR spectra of bases, δ (ppm)

Compound	Ar—O—CH_2—CH		—CH_2—NH—C(H)—OH		—$CH(CH_3)_2$ —$C(CH_3)_2$	
I	3·95	3 H, b[a]	2·75	5 H, m	0·95	6 H, d
II	3·95	3 H, b	2·60	4 H, m	1·00	9 H, s
III	3·95	3 H, n	2·65	5 H, m	0·95	6 H, d
IV	3·95	3 H, b	2·60	4 H, m	1·00	9 H, s
VII	3·95	3 H, b	2·60	5 H, m	0·95	6 H, d
VIII	3·95	3 H, n	2·60	4 H, m	1·00	9 H, s
XV	4·05	3 H, b	2·75	5 H, m	0·95	6 H, d
XVIII	4·00	3 H, b	2·67	4 H, m	1·02	9 H, s
XIX	4·05	3 H, b	2·75	5 H, m	0·95	6 H, d
XX	4·00	3 H, b	2·70	4 H, m	1·02	9 H, s
XXI	4·00	3 H, b	2·72	5 H, m	0·95	6 H, d
XXII	3·95	3 H, b	2·70	4 H, m	1·00	9 H, s

[a] Broad band

Investigation of the antiarrhythmic activity (Table V) of selected compounds confirmed that all substances are antiarrhythmic effective in doses 4–8 times higher than the atenolol reference. The highest inhibition of adrenaline arrhythmogeneity displayed compound *V* with propoxymethyl group lowering the percentage of extrasystole to 5·38 in a 8 mg kg^{-1} dose.

The acute toxicity (LD_{50}) values of salts determined orientatively (*cf.* the experimental section) showed that the majority of compounds had a lower acute toxicity when compared with metipranolol and close or higher one in relation to metoprolol. The LD_{50} value changes very little with the alteration of both the alkoxy-chain length and the acid moiety of the base. Small differences in toxicity were observed upon changes at the basic nitrogen. In accordance with the reported data[13] also in this series the tert-butyl analogues had a somewhat higher toxicity than the corresponding isopropyl derivatives.

EXPERIMENTAL

The melting points were determined with a Kofler micro hot-stage, the IR spectra of nujol suspensions were recorded with a Specord IR 75 (Zeiss, Jena) spectrophotometer, the UV spectra

TABLE IV

Relative changes in heart rate (%) after administration of compounds tested and their pA_2 values characterizing the antiisoprenaline effect on the isolated atria of guinea-pigs

Compound[a]	1′	5′	10′	15′	pA_2
I	95·9 ± 1·2	92·8 ± 2·1	90·0 ± 2·9	89·3 ± 2·5	7·74
III	89·1 ± 1·6	88·3 ± 1·4	84·2 ± 2·1	81·7 ± 1·7	6·65
V	94·5 ± 1·7	93·1 ± 0·5	91·7 ± 1·0	90·4 ± 1·7	6·78
VI	99·4 ± 0·6	97·1 ± 0·9	93·6 ± 0·8	92·7 ± 1·1	7·22
VII	96·6 ± 5·7	91·7 ± 4·1	87·9 ± 4·2	85·1 ± 4·7	5·89
XV	100·0 ± 0·0	98·7 ± 1·2	98·7 ± 1·2	92·7 ± 3·4	6·22
XIX	97·4 ± 2·6	93·8 ± 6·1	87·0 ± 5·0	80·5 ± 3·6	7·90
XXI	92·1 ± 5·9	86·4 ± 4·6	74·8 ± 7·1	66·5 ± 9·8	6·62
XXIII	99·2 ± 1·5	98·8 ± 1·3	97·6 ± 2·5	97·1 ± 2·1	6·72
XXV	97·8 ± 0·96	96·9 ± 1·1	93·8 ± 3·4	92·3 ± 3·5	7·42
Metoprolol	95·7 ± 1·0	89·4 ± 1·2	87·5 ± 1·6	85·1 ± 1·2	8·81
Metipranolol	98·6 ± 1·3	80·5 ± 4·6	76·8 ± 3·2	76·8 ± 3·2	7·61

[a] Compounds *I*, *III*, *V*, *VI*, *VII*, *XXIII*, and *XXV* and references: concentration 10^{-6} mol dm^{-3}; compounds *XV*, *XIX* and *XXI*: concentration 10^{-5} mol dm^{-3}. Changes of heart rate were measured with an isometric transducer and recorded with a linear recorder (Kutezs). The effect of compounds on isoprenaline positive chronotropic effect was recorded and the pA_2 values were estimated by analysis of dose-response curves.

of aqueous solutions were measured with a Specord UV VIS apparatus (Zeiss, Jena), the ^{1}H NMR spectra of deuteriochloroform solutions were run with a Tesla BS 487 A instrument operating at 80 MHz hexamethyldisiloxane being the internal reference. The mass spectra were recorded on a JMS-D 100 (Jeol) spectrometer at 70 eV ionization energy and 300 mA trap current. The purity of fumarates was checked by thin-layer chromatography on Silufol UV 245 sheets in a solvent system 1-propanol–diethylamine 9 : 1.

4-(Alkylamino-2-hydroxypropoxy)-3-(alkoxymethyl)acetophenones

Method A: Chloromethyloxirane (5·3 g, 57 mmol) was gradually added to a solution of 3-alkoxymethyl-4-hydroxyacetophenone (55 mmol) in potassium hydroxide (3·3 g, 59 mmol) dissolved in water (50 ml). The stirred mixture was left to react at room temperature for 24 h, the product was extracted with ether or chloroform, the extract was washed with a 5% sodium hydroxide and water. The organic layer was dried with magnesium sulfate and the solvent was evaporated. The residue formed by 4-(2,3-epoxypropoxy)-3-(alkoxymethyl)acetophenone (*c.* 60% yield) was dissolved without previous purification in ethanol or 1-propanol (50 ml) and reacted with the respective amine (10 ml). The mixture was kept at 30°C for 3 h and then at a reflux for 4 h. The solvent and the unreacted amine was removed under diminished pressure, the residue was diluted with water (25 ml) and the base was taken into ether. The extract was dried with potassium carbonate. Addition of an ethereal solution of fumaric or other organic acid resulted in separation of the salt which was crystallized from an appropriate solvent. The base was freed from the salt

TABLE V

Antiarrhythmic antiadrenaline activity

Compound	Dose mg kg^{-1}	% Extrasystoles[a]
I	4·0	23·95
	8·0	13·88
V	4·0	23·61
	8·0	5·38
XV	4·0	13·72
	8·0	14·76
XXI	4·0	23·09
	8·0	17·45
XVI	4·0	31·65
	8·0	15·07
Atenolol	0·5	20·66
	1·0	3·30
	5·0	7·29

[a] Compounds were tested in the given doses by the method of repeated adrenaline doses (20 + + 20 μg kg^{-1} in 30 s intervals). The ECG was recorded in one-minute time intervals; these served for estimation of complexes of ectoptic origin up to the 3rd minute expressed by the number of ventricular extrasystoles the sum of which is the measure of adrenaline arrhythmogeneity.

by dissolving in a small amount of water and addition of 25% ammonia to pH = 8—9 and won by extraction with ether. The crude product was crystallized from a suitable solvent. Yields and constants of salts and bases are listed in Table I.

Method B: 3-Alkoxymethyl-4-hydroxyacetophenone (40 mmol), chloromethyloxirane (100 ml) and piperidine (0·5 ml) were heated on a steam bath for 10 h. The unreacted chloromethyloxirane was distilled off under diminished pressure, the residue was dissolved in chloroform and extracted with dilute hydrochloric acid. The chloroform layer was washed with water, dried and the solvent was removed *in vacuo*. The crude 4-(2-hydroxy-3-chloropropoxy)-3-(alkoxymethyl)acetophenone, obtained in *c.* 65% yield, was dissolved in 2-propanol (50 ml). The respective amine (10 ml) was added and the mixture was refluxed for 24 h, cooled and the solvent with the unreacted amine was distilled off under reduced pressure. The residue was dissolved in dilute hydrochloric acid, washed three times with ether, the aqueous layer was made alkaline and the base was taken into ether. The extract was dried with magnesium sulfate and treated with an ethereal solution of fumaric acid. The separated fumarate was crystallized from a suitable solvent. Yields of *V* and *XXI* were 31 and 34%, respectively.

Method C: A solution of 3-alkoxy-4-hydroxyacetophenone (20 mmol) and 1-tert-butylamino--2,3-epoxypropane prepared according to[13] in dilute sodium hydroxide (20 ml) was stirred at room temperature for 6 h. The required base was obtained from the oily layer by extraction with ether. The extract was dried and treated with an ethereal solution of fumaric acid. The separated fumarate was crystallized from a suitable solvent. Yields of *IV* and *XX* were 10 and 11%, respectively.

Method D: A 4% sodium hydroxide (60 ml) was added to 3-alkoxymethyl-4-hydroxyacetophenone (20 mmol) and 1-chloro-3-tert-butylamino-2-propanol[9] (3·7 g, 20 mmol) and stirred at an ambient temperature for 24 h. The base was taken into ether and worked up as with method *C*. Yields of *VI* and *IV* were 10 and 14%, respectively.

Pharmacological Tests

The majority of compounds was tested on acute toxicity on white mice by *s.c.* application of 1% solutions; the mortality was determined after 24 h. Following LD_{50} values (mg kg^{-1}) were found for fumarates: *I* > 600; *III*, *VI*, *VIII*, *XVI*, *XIX*, *XXIII* 300—400; *IV*, *V*, *XI*, *XV* 300—500; *VII* 500—600; *IX* 200—500; *X* 200—300, *XXI* 400—500; for oxalates: *II* 500—600; *IV* 200—500; for tartrate: *V* 300—500; for metipranolol 250—300; for metoprolol > 600.

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