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SYNTHESIS AND STUDY OF THE PHARMACOLOGICAL PROPERTIES OF 2-AMINOMETHYL AND 2,4-, 2,5-, AND 2,6-DIAMINOMETHYL DERIVATIVES OF 3-ARYLBENZOFURANS

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Continuing a search for cardiovascular agents in the benzofuran series, we have carried out the synthesis and have studied the pharmacological properties of 2-aminomethyl and 2,4-, 2,5-, and 2,6-diaminomethyl derivatives of 3-arylbenzofurans.

Using a published method, from α-phenoxypropiophenones (I-VI) we obtained 2-methyl-3-arylbenzofurans with substituents in position 5 (VII-X) or position 6 (XI-XIII) [1]. 2-Methyl-5-nitro-3-phenylbenzofuran (XIV) was obtained by nitrating the known 2-methyl-3-phenylbenzofuran [2].

As reported previously, 2-methylbenzofuran derivatives are brominated by N-bromosuccinimide in the methyl group [2]. In the present work we obtained a series of 2-bromomethyl derivatives of benzofuran which, without isolation, were converted into the 2-aminomethyl derivatives (XV-XXXII) under the action of secondary amines — diethylamine, piperidine, morpholine, and N-phenylpiperazine.

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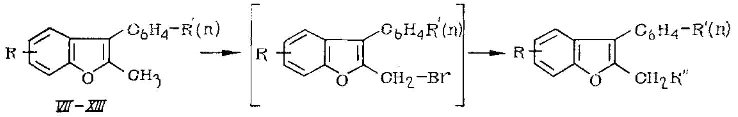
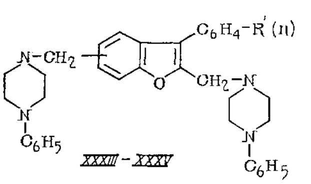
The bromination of 3-(p-chlorophenyl)-2,5-dimethylbenzofuran (VIII), 3-(p-methoxyphenyl)-2,5-dimethylfuran (IX), and 3-(p-chlorophenyl)-2,6-dimethylfuran (XIII) with 2 moles of N-bromosuccinimide gave 2,5- and 2,6-di(bromomethyl)-3-arylbenzofurans which, again without isolation, were converted by the action of N-phenylpiperazine into 3-(p-chlorophenyl)-2,5-di(N-phenylpiperazinomethyl)-benzofuran (XXXIII), 3-(p-methoxyphenyl)-2,5-di(N-phenylpiperazinomethyl)-benzofuran (XXXIV), and 3-(p-chlorophenyl)-2,6-di(N-phenylpiperazinomethyl)benzofuran (XXXV).

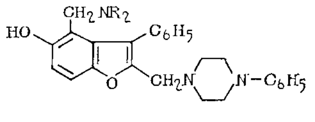
The bromination of 5-acetoxy-2-methyl-3-phenylbenzofuran (XXXVI), obtained by the acetylation of the corresponding 5-hydroxy derivative [3], gave the 2-bromomethyl derivative. The latter was converted under the action of N-phenylpiperazine into 5-acetoxy-3-phenyl-2-(N-phenylpiperazinomethyl)-benzofuran (XXXVII). The hydrolysis of compound (XXXVII) gave 5-hydroxy-3-phenyl-2-(N-phenylpiperazinomethyl)benzofuran (XXXVIII). The aminomethylation of (XXXVIII) with various derivatives of bisdimethylaminomethane led to: 4-dimethylaminomethyl (XXXIX), 4-(N-phenyl piperazinomethyl) (XL), and 4-piperidinomethyl (XLI) derivatives of 5-hydroxy-3-phenyl-2-(N-phenylpiperazinomethyl)benzofuran.



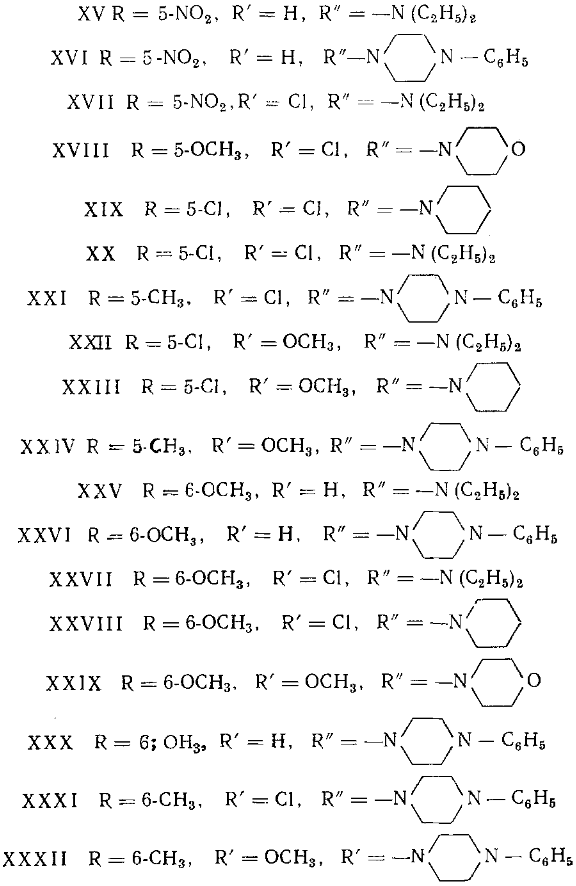
VIII-XIII



XXXIII-XXXV



XXXIX-XLI



XV $R = 5\text{-}NO_2,\ R' = H,\ R'' = —N(C_2H_5)_2$

XVI $R = 5\text{-}NO_2,\ R' = H,\ R''—N\bigcirc N—C_6H_5$

XVII $R = 5\text{-}NO_2, R' = Cl,\ R'' = —N(C_2H_5)_2$

XVIII $R = 5\text{-}OCH_3,\ R' = Cl,\ R'' = —N\bigcirc O$

XIX $R = 5\text{-}Cl,\ R' = Cl,\ R'' = —N\bigcirc$

XX $R = 5\text{-}Cl,\ R' = Cl,\ R'' = —N(C_2H_5)_2$

XXI $R = 5\text{-}CH_3,\ R' = Cl,\ R'' = —N\bigcirc N—C_6H_5$

XXII $R = 5\text{-}Cl,\ R' = OCH_3,\ R'' = —N(C_2H_5)_2$

XXIII $R = 5\text{-}Cl,\ R' = OCH_3,\ R'' = —N\bigcirc$

XXIV $R = 5\text{-}CH_3,\ R' = OCH_3,\ R'' = —N\bigcirc N—C_6H_5$

XXV $R = 6\text{-}OCH_3,\ R' = H,\ R'' = —N(C_2H_5)_2$

XXVI $R = 6\text{-}OCH_3,\ R' = H,\ R'' = —N\bigcirc N—C_6H_5$

XXVII $R = 6\text{-}OCH_3,\ R' = Cl,\ R'' = —N(C_2H_5)_2$

XXVIII $R = 6\text{-}OCH_3,\ R' = Cl,\ R'' = —N\bigcirc$

XXIX $R = 6\text{-}OCH_3,\ R' = OCH_3,\ R'' = —N\bigcirc O$

XXX $R = 6;\ OH_3,\ R' = H,\ R'' = —N\bigcirc N—C_6H_5$

XXXI $R = 6\text{-}CH_3,\ R' = Cl,\ R'' = —N\bigcirc N—C_6H_5$

XXXII $R = 6\text{-}CH_3,\ R' = OCH_3,\ R' = —N\bigcirc N—C_6H_5$

TABLE 1. Toxicity at a Single Injection and Anti-arrhymic Activity of Benzofuran Derivatives

Compound	Method of administration	Toxicity indices			Toxic symptoms	Number of anti-arrhymic effects	
		MTD*	LD_{50}	LD_{100}		positive	negative
XV	Intragastrically	300	460	600	Convulsions	0	7
XVI	"		1000		Causes no toxic symptoms	0	7
XXV	Intraperitoneally	100	150	300	Convulsions	2	11
XXVI	Intragastrically		1000		Causes no toxic symptoms	2	7
XXVIII	"	900	1195	1300	Depression	0	8
XXX	"	1000	1570	2000	"	0	7
XXXII	"	800	1170	1300	"	0	8
XXXV	"		1000		Causes no toxic symptoms	1	7
XXXIX	Intraperitoneally						2
		250	307,5	450	Convulsions	1	7
XL	"	500	710	1000	Depression	0	7
XLI	"	250	345	450	"	1	7
Novocainamid						4	6

*Minimum dose causing a toxic effect.

TABLE 2. Local Anesthetic Activity of Benzofuran Derivatives and of Dicain and of Novocain (M ± m)

Compound	Superficial anesthesia		Infiltration anesthesia	
	concentration of the solution, %	anesthetic index	concentration of the solution, %	anesthetic index
XXV	0,5	418,2±28,11	0,25	51,8±4,27
XXXIX	0,5	734±49,98	0,25	71,2±3,87
XLI	0,5	680,1±78,88	0,25	67±3,27
Dicain	0,5	826,6±28,24	—	—
Novocaine	—	—	0,25	26,3±3,57

EXPERIMENTAL PHARMACOLOGICAL PART

Toxicity was determined on white mice of both sexes weighing 18-28 g. Water-soluble compounds were administered intraperitoneally and insoluble compounds in the form of suspensions in 2% starch paste. Each dose was administered to five animals. The LD_{50} values were calculated by the method of G. N. Pershin [4].

Anti-arrythmic activity was investigated on white rats using the aconitine model of rhythm disturbance [5]. Aconitine was administered intravenously in a dose of 30 μg/kg. The compounds investigated were injected intravenously (water-soluble compounds) in doses of 10% of the LD_{50} value immediately after the appearance of arrhythmia and intragastrically (water-insoluble compounds) 30-40 min after the administration of the aconitine. Compounds (XVI), (XXVI), and (XXXII) were administered in a dose of 150 mg/kg. In this way we determined the arrhythmia-arresting and arrhythmia-preventing action. The novocainamid used for comparison was injected in a dose of 50 mg/kg in order to arrest the arrhythmia.

The local anesthetic action was determined by the terminal method of anesthesia on rabbits according to Renier (each preparation on eight eyes) and by the infiltration method of anesthesia using the Bulbring-Wade procedure on guinea-pigs (each preparation on twelve areas, observation during 1 h). The results obtained were compared with the effect of dicain (terminal anesthesia) and novocaine (infiltration anesthesia) taking in the same concentration [6]. Stimulating action was investigated by Veis's method [7].

The influence on the tonus of an isolated section of rabbit small intestine was investigated by the usual Magnus method.

TABLE 3. Characteristics of the Substances Synthesized

Compound	R	R¹	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
					C	H	Cl		C	H	Cl
I	p-Cl	Cl	84,5	94—5	61,13	4,00	23,91	$C_{15}H_{12}Cl_2O_2$	61,07	4,10	24,03
II	p-CH_3	Cl	90,5	95—6	70,50	5,71	13,12	$C_{16}H_{15}ClO_2$	70,13	5,51	12,94
III	p-CH_3	OCH_3	90	84—6	75—86	6,48	—	$C_{17}H_{17}O_3$	75,90	6,36	—
IV	p-Cl	OCH_3	85,5	93—4	66,21	5,26	12,33	$C_{16}H_{15}ClO_3$	66,26	5,21	12,22
V	m-CH_3	Cl	92,5	85—6	70,06	5,49	12,90	$C_{16}H_{15}ClO_2$	69,95	5,50	12,90
VI	m-CH_3	OCH_3	85	78—9	75,53	6,60	—	$C_{17}H_{18}O_3$	75,53	6,71	—
VII	5-Cl	Cl	85,5	155—6	65,25	3,82	25,80	$C_{15}H_{10}Cl_2O$	65,04	3,63	25,60
VIII	5-CH_3	Cl	96	99—101	74,78	5,02	13,81	$C_{16}H_{13}ClO$	74,86	5,10	13,81
IX	5-CH_3	OCH_3	65,5	68—9	80,60	6,32	—	$C_{17}H_{16}O_2$	80,93	6,39	—
X	5-Cl	OCH_3	85	104—6	70,48	4,82	13,30	$C_{16}H_{13}ClO_2$	70,47	4,80	13,03
XI	6-CH_3	H	44	156—8	86,20	6,38	—	$C_{16}H_{14}O$	86,45	6,35	—
XII	6-CH_3	OCH_3	74	50—2	81,00	6,35	—	$C_{17}H_{16}O_2$	80,93	6,39	—
XIII	6-CH_3	Cl	71	57	74,29	5,00	13,91	$C_{16}H_{13}ClO$	74,85	5,10	13,81

TABLE 4. Characteristics of the 2-Aminomethyl-3-arylbenzofurans Synthesized (XV-XXV)

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
XV	48	237—9	63,10	5,70	10,03	—	$C_{19}H_{20}N_2O_3 \cdot HCl$	63,24	5,87	9,83	—
XVI	60,6	173—4	72,88	5,40	—	10,08	$C_{25}H_{23}N_3O_3$	72,62	5,61		10,16
XVII	53,2	199—201	62,85	5,90	18,55	3,54	$C_{20}H_{22}ClNO_2 \cdot HCl$	63,16	6,10	18,66	3,68
XVIII	68	146—7	67,41	5,59	9,98	—	$C_{20}H_{20}ClNO_3$	67,28	5,63	9,93	—
XIX	55,5	134—6	66,46	5,44	19,76	—	$C_{20}H_{19}Cl_2NO$	66,72	5,32	19,69	—
	94,8	236—8	59,20	5,57	25,79	—	$C_{20}H_{19}Cl_2NOHCl \cdot {}^1/_2H_2O$	59,21	5,23	26,21	—
XX	31,6	90—2	65,63	5,50	20,55	—	$C_{19}H_{19}Cl_2NO$	65,57	5,50	20,37	—
	93	224—6	59,35	5,20	27,77	—	$C_{19}H_{19}Cl_2NO \cdot HCl$	59,43	5,24	27,65	—
XXI	82	110—1	74,84	6,15	8,50	6,72	$C_{26}H_{25}ClN_2O$	74,90	6,04	8,50	6,72
XXII	63,5	214—6	61,85	6,04	18,33	—	$C_{20}H_{22}ClNO_2 \cdot HCl \cdot {}^1/_2H_2O$	61,75	6,21	18,22	—
XXIII	62	112—3	70,90	6,25	9,76	—	$C_{21}H_{22}ClNO_2$	70,89	6,23	9,96	—
XXIV	59,3	150—1	78,70	7,00	—	7,14	$C_{27}H_{28}N_2O_2$	78,61	6,84	—	6,79
XXV	52	158—60	70,26	7,06	10,69	—	$C_{20}H_{23}NO_2HCl$	70,45	6,99	10,25	—
XXVI	21,2	173—5	64,26	6,11	14,83	5,99	$C_{26}H_{26}N_2O_22HCl \cdot H_2O$	63,80	6,18	14,50	5,72
XXVII	16	91—3	63,10	6,58	17,91	—	$C_{20}H_{22}ClNO_2 \cdot HCl$	63,16	6,10	18,65	—
XXVIII	51	217—8	64,04	5,96	18,49	—	$C_{21}H_{22}ClNO_2 \cdot HCl$	64,29	5,91	18,07	—
XXIX	57	110—1	71,57	6,57	—	—	$C_{21}H_{23}NO_4$	71,37	6,56	—	—
XXX	34,5	155—6	81,83	7,04	—	7,73	$C_{26}H_{26}N_2O$	81,64	6,85	—	7,32
XXXI	33,6	168—70	61,61	5,59	21,11	5,77	$C_{26}H_{25}ClN_2O \cdot 2HCl \cdot H_2O$	61,49	5,75	20,94	5,52
XXXII	22,8	142—3	78,45	6,63	—	—	$C_{27}H_{28}N_2O_2$	78,61	6,84	—	—
XXXIII	35	161—3	75,02	6,00	6,26	9,58	$C_{36}H_{37}ClN_4O$	74,94	6,46	6,14	9,71
XXXIV	26,2	146—7	77,59	7,04	—	9,78	$C_{37}H_{40}N_4O_2$	77,49	7,00	—	10,07
XXXV	26	179—80	74,53	6,90	6,04	9,57	$C_{36}H_{37}ClN_4O$	74,91	6,46	6,14	9,71

The toxicities of the compounds investigated, according to the LD_{50} index, covered a wide range of doses. Thus, of the soluble compounds, on intraperitoneal injection the most toxic proved to be compound (XXV) (LD_{50} 150 mg/kg). Compounds (XXXIX) and (XLI) had similar toxicities (LD_{50} 307.5 and 345 mg/kg). Compound (XI) was less toxic (LD_{50} 710 mg/kg). On injection into the stomach in doses of 1000 mg/kg, compounds (XVI), (XXVI), and (XXXV) caused no toxic symptoms whatever. The LD_{50} values of compounds (XXVIII), (XXX), and (XXXII) were between 1170 and 1570 mg/kg. Compound (XV) was more toxic (LD_{50} 460 mg/kg).

The administration to rats of aconitine (0.03 mg/kg intravenously) caused after 4-8 min a prolonged (up to $1^1/_2$ h and more) disturbance of the rhythm of the cardiac contractions. In some of the experiments, compound (XXV) and novocainamid exerted an arresting effect. However, this effect was observed in the first 2-6 min after administration and in then the arrhythmia began again. An action of compound (XXVI) in preventing arrhythmia appeared only in some experiments and was characterized by the fact that after the administration of aconitine the arrhythmia began after 4-8 min and later at the 10th-11th minute. Compounds (XXXV), (XXXIX), and (XLI) gave a weak anti-arrhythmic effect. The other compound investigated exhibited no anti-arrhythmic activity (Table 1).

With respect to local anesthetic activity (Table 2) in the terminal method of anesthesis the compounds investigated were inferior to dicain but they were superior to novocaine in infiltration anesthesia.

At the same time, these compounds (XXXIX and XLI) exhibited a stimulating action – weak for a concentration of 0.25% and moderate for a concentration of 0.5%. Compound (XL) (soluble in water) exhibited no local anesthetic action.

The water-soluble compounds in concentrations of $1 \cdot 10^{-6}$ to $1 \cdot 10^{-5}$ g/ml lowered the tonus of an isolated section of rabbit small intestine. The minimum concentration causing this effect was $1 \cdot 10^{-6}$ g/ml for compound (XXIV), $2 \cdot 10^{-5}$ g/ml for compounds (XXXIX) and (XLI), and $1 \cdot 10^{-5}$ g/ml for (XL).

Thus, some of the compounds investigated exhibit pharmacological activity: anti-arrhythmic, local anesthetic and smooth-musculature-relaxing. However, the compounds studied have no advantages whatever over known drugs with a similar action.

EXPERIMENTAL CHEMICAL PART

General Method of Obtaining the α-Phenoxypropiophenones (I-VI). (Table 3). With stirring, 0.13 mole of potassium carbonate and then 0.122 mole of α-bromopropiophenone was added to a solution of 0.12 mole of a phenol in 120 ml of acetone. The reaction mixture was boiled with stirring for 5 h and it was then filtered and the solvent was distilled off. The residue was recrystallized from ethanol.

General Method of Obtaining the 2-Methyl-3-aryl-benzofurans (VII-XIII) (see Table 3). The polyphosphoric acid obtained from 294 g of phosphorus pentoxide and 140 ml of orthophosphoric acid, heated to 60°C, was added 0.115 mole of an α-phenoxypropiophenone in one portion. The mixture was kept at 60°C with stirring for $3^1/_2$ h, and then it was cooled and poured into water. The product that separated out was purified by recrystallization from ethanol or by redistillation.

2-Methyl-5-nitro-3-phenylbenzofuran (XIV). With stirring at 10-15°C, 1 ml (0.0162 mole) of nitric acid (d 1.42) was added dropwise to a solution of 2.25 g (0.0108 mole) of 2-methyl-3-phenylbenzofuran in 4 ml of glacial acetic acid. The mixture was stirred at the same temperature for 2 h. The precipitate that deposited was separated off and recrystallized from ethanol to give 0.3 g (11%) of the compound (XIV) with mp 124.5-125.5°C. Found, %: C 70.98; H 4.38; N 5.53. $C_{15}H_{11}NO_3$. Calculated, %: C 71.14; H 4.38; N 5.53.

General Method of Obtaining the 2-Aminomethyl-3-arylbenzofurans (XV-XXXII) (Table 4). To a solution of 0.01 mole of a 2-bromomethyl-3-arylbenzofuran in 30 ml of benzene was added 0.02 mole of a secondary amine, and the reaction mixture was left to stand at room temperature for 12 h. The precipitate of amine hydrobromide that had deposited was filtered off, and the solvent was distilled off. The 2-aminomethyl derivative of benzofuran was purified in the form of the base or in the form of a salt.

The 2,5- and 2,6-di(N-phenylpiperazinomethyl)-3-arylbenzofurans (XXXIII-XXXV) were obtained similarly, but by the action of 0.04 mole of N-phenylpiperazine on 0.01 mole of a 2,5- or 2,6-di(bromomethyl)-3-arylbenzofuran.

5-Acetoxy-2-methyl-3-phenylbenzofuran (XXXVI). A solution of 3 g of 5-hydroxy-2-methyl-3-phenylbenzofuran in 18 ml of acetic anhydride at 0.1 ml of triethylamine was boiled for 1 h; the bulk of the acetic anhydride was distilled off in vacuum. Water was added to the residue and the precipitate was separated off. Yield 3 g (84%), mp 95-96°C (from methanol). Found, %: C 77.02; H 5.26. $C_{17}H_{14}O_3$. Calculated, %: C 76.76; H 5.30.

5-Acetoxy-3-phenyl-2-(N-phenylpiperazinomethyl)benzofuran (XXXVII) was obtained similarly to compounds (XV-XXXII); yield 35.2%, mp 163-164°C (from methanol). Found, %: C 76.19; H 6.01; N 6.50. $C_{27}H_{26}N_2O_2$. Calculated, %: C 76.13; H 6.14; N 6.56.

5-Hydroxy-3-phenyl-2-(N-phenylpiperazinomethyl)benzofuran (XXXVIII). A mixture of 1.05 g (0.0025 mole) of (XXXVII) and 0.28 g (0.005 mole) of caustic potash in 10 ml of methanol was boiled for 1.5 h, and then the solvent was distilled off and the residue was dissolved, separated, and recrystallized from methanol. Yield 0.6 g (62.5%) mp 170-172°C. Found, %: C 78.19; H 6.20; N 7.19. $C_{25}H_{24}N_2O_2$. Calculated, %: C 78.19; H 6.30; N 7.29.

5-Hydroxy-4-dimethylaminomethyl-3-phenyl-2-(N-phenylpiperazinomethyl)benzofuran (XXXIX). A mixture of 3.84 g (0.01 mole) of (XXXVIII) and 2.75 ml (0.02 mole) of bisdimethylaminomethane in 40 ml of dioxane was boiled for 3 h. The solvent and the excess of amine were distilled off in vacuum and the residue was recrystallized from isopropanol. Yield 61.3%, mp 153-155°C. Found, %: C 73.55; H 6.95; N 9.20. $C_{28}H_{31}N_3O_2$. Calculated, %: C 73.26; H 7.24; N 9.16.

5-Hydroxyl3-phenyl-2,4-di(N-phenylpiperazinomethyl)benzofuran (XL). A solution of 0.6 g (0.00156 mole) of (XXXVIII) in 10 ml of dioxane was heated with 0.32 ml (0.004 mole) of 34% formalin solution and 0.6 ml (0.004 mole) of N-phenylpiperazine for 4.5 h, and then the solvent was distilled off and the residue was chromatographed on a column of silica gel, the product being eluted with ether. The eluate was evaporated. Yield 0.2 g (23%), mp 164-165°C (from ethanol). Found, %: C 77.29; H 6.89; N 9.84. $C_{36}H_{38}N_4O_2$. Calculated, %: C 77.39; H 6.85; N 10.02.

5-Hydroxy-3-phenyl-2-(N-phenylpiperazinomethyl)-4-piperidinomethylbenzofuran (XLI) was obtained similarly to compound (XXXIX) with a yield of 93.5%, mp 108-109°C (from isopropanol) Found, %: C 76.10; H 7.36; N 7.95. $C_{31}H_{35}N_3O_2 \cdot {}^1/_2\ H_2O$. Calculated, %: C 75.98; H 7.40; N 8.57.

The hydrochloride of compound (XLI) was obtained in the usual way with a yield of 93%; mp 204-207°C (decomp.). Found, %: C 62.94; H 6.67; N 6.96. $C_{31}H_{35}N_3O_2 \cdot 3HCl$. Calculated, %: C 63.00; H 6.43; N 7.11.

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