

of warm 1 N HCl. The remaining solid was dissolved in hot DMF, treated with decolorizing charcoal, filtered through supercell, treated with about 15 mL of 3.5 N NH₄OH, and chilled to give 0.84 g of crude product. Recrystallization from 33% aqueous HOAc afforded 0.7 g (19.5%) of the desired product, mp 303-305 °C dec.

N⁶-(9-Anthracenylmethyl)-N⁶-methyl-2,4,6-pteridinetriamine 0.7-Hydrate (13, Table I). A mixture of 2.5 g (0.0127 mol) of 6-chloro-2,4-pteridinediamine and 9.6 g (0.0434 mol) of N-methyl-9-anthracenemethanamine was stirred at 170 °C for 8 h, allowed to cool, and triturated first with ether, then with MeOH, and finally with warm 0.5 N HCl. The resulting dark solid was extracted 3 times with 150-mL portions of boiling EtOH. The extracts were combined, concentrated to 200 mL, and cooled to afford 1.36 g of precipitate. This material was triturated with warm DMF and then recrystallized from DMF containing a few drops of concentrated NH₄OH to give 0.25 g (5%) of the title compound, mp 277-281 °C dec.

6-(1-Piperidinyl)-2,4-pteridinediamine Hydrochloride 1.8-Hydrate (20, Table I). A mixture of 0.4 g (0.002 mol) of 6-chloro-2,4-pteridinediamine and 6 mL (7 g, 0.082 mol) of piperidine was heated under reflux for 21 h, cooled, and diluted with about 30 mL of ether. The precipitate that formed was washed with water and recrystallized from 1 N HCl to give 0.45 g (71.4%) of the product, mp >300 °C.

4-Methoxy-N-methyl-1-naphthalenemethanamine (29, Table II). A mixture of 50.53 g (0.272 mol) of 4-methoxy-1-naphthaldehyde and 28 mL (0.36 mol) of 40% aqueous methanamine in 500 mL of MeOH was hydrogenated at room temperature over 2 g of 5% platinum on carbon for 0.7 h at an initial pressure of 50.5 psi. The decrease in pressure was 22 psi (100% of theoretical). The mixture was filtered and the solvent removed in vacuo from the filtrate. The resulting oil was distilled to give 31.15 g (57%) of the product, bp 131-136 °C (0.6 mm). Compounds 21, 22, 24-28, and 30 were prepared similarly.

4-Fluoro-N-methylbenzenemethanamine¹⁸ (23). A mixture of 289 g (2 M) of 1-(chloromethyl)-4-fluorobenzene and 290 g (9.6 M) of methanamine in 400 mL of THF was placed in a sealed vessel at room temperature and under 30 psi. The temperature and pressure of the mixture rapidly increased to 88 °C and 135 psi. After 2 h, the mixture was diluted with MeOH and filtered to collect 77 g of solid. The filtrate was diluted with ether, again filtered to collect 100 g of solid, and then concentrated to dryness. The residue was combined with the solids and dissolved in water. The solution was made basic with NaOH and extracted with ether. The extract was dried over magnesium sulfate, filtered, concentrated under vacuum, and distilled to afford 185 g (66.5%), bp 73-75 °C (9 mm). A 10-g sample was converted to its HCl salt

and recrystallized from 2-propanol-MeOH/ether (charcoal) to afford 10 g, mp 193-195 °C.

2-(4-Chlorophenyl)pyrrolidine.¹⁰ To a stirring mixture of 24.3 g (1.0 mol) of magnesium turnings and a crystal of iodine in 75 mL of anhydrous ether was added dropwise a solution of 191.5 g (1.0 mol) of 1-bromo-4-chlorobenzene in 1 L of ether. After the addition was complete, the mixture was stirred for 0.5 h. A solution of 103.6 g (1.0 mol) of 4-chlorobutanenitrile in 100 mL of ether was added dropwise to the 4-chlorophenylmagnesium bromide, and the mixture was stirred under reflux for 1 h. Then, the reflux condenser was reversed and the ether allowed to distill off, keeping the volume constant by addition of xylene. When the temperature of the mixture reached 135 °C, the mixture was heated under reflux for 2 h and allowed to cool overnight. To the stirred mixture was added dropwise 130 mL of saturated NH₄Cl solution. The mixture was filtered and the filter cake was washed with xylene and water. The filtrate and washes were combined and the layers separated. The water layer was extracted with xylene. The xylene fractions were combined, washed with water, dried over anhydrous K₂CO₃ in the presence of decolorizing charcoal, filtered through supercell, and evaporated to dryness under vacuum. The residue was recrystallized from petroleum ether to give 72.6 g (40.5%) of 5-(4-chlorophenyl)-3,4-dihydro-2H-pyrrole, mp 64-66 °C.

A mixture of 72.5 g (0.403 mol) of 5-(4-chlorophenyl)-3,4-dihydro-2H-pyrrole and 2 g of 5% platinum on carbon in 350 mL of toluene was hydrogenated under an initial pressure of 50.5 psi and an average temperature of 28 °C for 21.8 h. An additional gram of 5% platinum on carbon was added and hydrogenation was continued for 23.1 h. The total decrease in pressure was 29.0 psi, 90% of theoretical. The reaction mixture was filtered and the solvent was removed under vacuum. The residual oil was distilled to yield 66.7 g, bp 130 °C (7 mm). VPC demonstrated a 15% contamination with starting material. The hydrogenation was repeated using 59.1 g of this mixture. After filtration and removal of the toluene, distillation gave two fractions: 16.2 g (25% yield), bp 144-151 °C (14 mm) 91% by VPC, and 26.7 g (41% yield), bp 150-151 °C (14 mm) (97% by VPC).

Acknowledgment. The authors are indebted to Dr. M. W. Fisher and Dr. C. L. Heifitz of Warner-Lambert Co. for the antibacterial studies. We also thank William Pearlman for conducting the hydrogenations, C. E. Childs and associates for the microanalyses, Dr. J. M. Vandenberg and co-workers for the determination of spectral data, and Ms. Jeanne Hoftiezer and Ms. Georgianna Hill for preparing many of the intermediates.

Synthesis and Antidepressant Activity of Substituted (ω -Aminoalkoxy)benzene Derivatives

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A series of substituted (ω -aminoalkoxy)benzene derivatives has been synthesized and screened for potential antidepressant activities. The effect of structural variation of these molecules has been systematically examined. Antidepressant activity was clearly displayed by 2-benzyl-1-[4-(methylamino)butoxy]benzene (7), 2-(2-hydroxybenzyl)-1-[4-(methylamino)butoxy]benzene (19), 1-[4-(methylamino)butoxy]-2-phenoxybenzene (29), and 1-[4-(methylamino)butoxy]-2-(phenylthio)benzene (31) in further pharmacological studies. These compounds did not possess the anticholinergic, antihistaminic, and muscle-relaxant side effects common to tricyclic antidepressants.

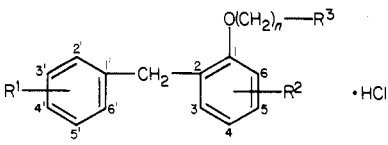
In spite of their clinical usefulness, the tricyclic antidepressants, such as amitriptyline and imipramine, cause varying degrees of side effects mainly originating from anticholinergic actions.¹⁻³ Routine pharmacological

screening in our laboratories of compounds, directed toward new psychotropic agents, has shown that some 1-(4-aminobutoxy)-2-phenylbenzene derivatives antagonize the reserpine-induced hypothermia in mice. These observations prompted us to synthesize a wide variety of related compounds to find a new type of antidepressant

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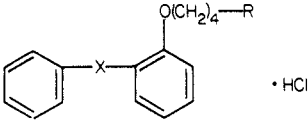
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Table I. 2-Benzyl-1-(ω -Aminoalkoxy)benzene Derivatives


no.	R ¹	R ²	R ³	n	mp, °C	formula ^a	antireserpine, rel potency ^b
1	H	H	NHCH ₃	2	185-190	C ₁₆ H ₂₂ ClNO	0
2 ^c	H	H	N(CH ₃) ₂	2	117-120	C ₁₇ H ₂₂ ClNO	0
3	H	H	NHCH ₃	3	148-152	C ₁₇ H ₂₂ ClNO	0.56
4 ^c	H	H	N(CH ₃) ₂	3	163-165	C ₁₈ H ₂₄ ClNO	0
5	H	H	NHC ₂ H ₅	3	153-154	C ₁₈ H ₂₄ ClNO	0
6	H	H	NH ₂	4	112-113	C ₁₇ H ₂₂ ClNO	0
7	H	H	NHCH ₃	4	117-121	C ₁₈ H ₂₄ ClNO	0.78 ^f
8	H	H	N(CH ₃) ₂	4	135-138	C ₁₉ H ₂₆ ClNO	0
9	H	H	NHC ₂ H ₅	4	104-106	C ₁₉ H ₂₆ ClNO	0.53
10	H	H	c-NC ₂ H ₁₀	4	139-142	C ₂₁ H ₃₀ ClNO	0.41
11	H	H	c-N(CH ₂ CH ₂) ₂ O	4	173-177	C ₂₁ H ₂₈ ClNO	0.30
12	H	H	c-N(CH ₂ CH ₂) ₂ N-CH ₃	4	129-133	C ₂₂ H ₃₂ Cl ₂ N ₂ O	0
13 ^d	H	H	NHCH ₃	5	87.5-89.5	C ₁₆ H ₂₆ ClNO	0.57
14	H	H	N(CH ₃) ₂	5	87-91	C ₂₀ H ₂₈ ClNO	0.23
15	4'-CH ₃	H	NHCH ₃	4	90-92	C ₁₉ H ₂₆ ClNO	0.44
16	4'-CH ₃	H	N(CH ₃) ₂	4	138-143	C ₂₀ H ₂₈ ClNO	0.18
17	H	6-CH ₃	NHCH ₃	4	94-96	C ₁₉ H ₂₆ ClNO	0.56
18	H	6-CH ₃	N(CH ₃) ₂	4	152-157	C ₂₀ H ₂₈ ClNO	0.66
19 ^e	2'-OH	H	NHCH ₃	4	187-188	C ₁₉ H ₂₄ NO ₄	0.99
20	2'-OH	H	N(CH ₃) ₂	4	160	C ₁₉ H ₂₆ ClNO ₂	0.77 ^f
21	H	4-OH	NHCH ₃	4	121-122	C ₁₈ H ₂₄ ClNO ₂	0.31
22	2'-OCH ₃	H	NHCH ₃	4	141	C ₁₉ H ₂₆ ClNO ₂	0.85
23	4'-OCH ₃	H	NHCH ₃	4	96-98	C ₁₉ H ₂₆ ClNO ₂	0
24	4'-OCH ₃	H	N(CH ₃) ₂	4	140-143	C ₂₀ H ₂₈ ClNO ₂	0
25	4'-Cl	H	NHCH ₃	4	113-114.5	C ₁₈ H ₂₃ Cl ₂ NO	0.27
26	4'-Cl	H	N(CH ₃) ₂	4	127.5-129.5	C ₁₉ H ₂₅ Cl ₂ NO	0.17
27	H	4-Cl	NHCH ₃	4	149-153	C ₁₈ H ₂₃ Cl ₂ NO	0.17
28	H	4-Cl	N(CH ₃) ₂	4	117-121	C ₁₉ H ₂₅ Cl ₂ NO	0.26

^a Analysis for C, H, and N are within $\pm 0.4\%$ of the theoretical values. ^b Prevention of reserpine-induced hypothermia. Figures indicate relative potency to amitriptyline (amitriptyline = 1.00). ^c References 4 and 5. ^d Dihydrochloride. ^e 0.5-Oxalic acid. ^f The activity of 7 was not statistically significant from that of 20.

Table II. 1-(4-Aminobutoxy)benzenes



no.	X	R	mp, °C	formula ^a	antireserpine, rel potency ^b
29	O	NHCH ₃	112-116	C ₁₇ H ₂₂ ClNO ₂	1.10
30	O	N(CH ₃) ₂	131-135	C ₁₈ H ₂₂ ClNO ₂	0.58
31	S	NHCH ₃	143-147	C ₁₇ H ₂₂ ClNOS	0.89
32	S	N(CH ₃) ₂	140-146	C ₁₈ H ₂₄ ClNOS	0.70
33	CH(CH ₃)	NHCH ₃	155-158	C ₁₉ H ₂₆ ClNO	0.66
34	CH(CH ₃)	N(CH ₃) ₂	117.5-119	C ₂₀ H ₂₈ ClNO	0.36
35	CH ₂ CH ₂	NHCH ₃	106-111	C ₁₉ H ₂₆ ClNO	0
36	SO	NHCH ₃	150-154	C ₁₇ H ₂₂ ClNO ₂ S	0.49
37	SO ₂	NHCH ₃	178-182	C ₁₇ H ₂₂ ClNO ₃	0.17
38	CH ₂ O	NHCH ₃	126-128	C ₁₈ H ₂₄ ClNO ₂	0
39 ^c	CO	NHCH ₃	172-173	C ₂₀ H ₂₃ NO ₅	0
40	CH(OH)	NHCH ₃	88-91	C ₁₈ H ₂₄ ClNO ₂	0
41 ^c	NH	NHCH ₃	183-185	C ₁₉ H ₂₄ N ₂ O ₄	0.29
42	NHCO	NHCH ₃	131.5-133.5	C ₁₈ H ₂₃ ClN ₂ O ₂	0.36

^{a, b} As in Table I. ^c Oxalic acid.

with fewer side effects. This paper describes the synthesis and primary pharmacological studies of substituted (ω -aminoalkoxy)benzene derivatives.

Chemistry. The various substituted (ω -aminoalkoxy)benzenes (V), found in Tables I-III, were prepared by the general reaction sequence shown in Scheme I. ω -Bromoalkylation of substituted phenols (I) with α, ω -dibromoalkanes (II) in alcoholic KOH gave substituted (ω -bromoalkoxy)phenols (III). Substituted (ω -aminoalk-

Scheme I

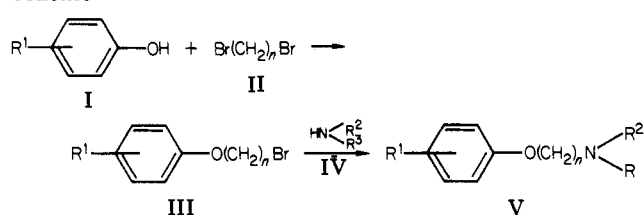
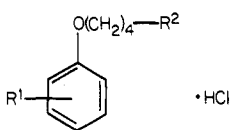


Table III. 1-(4-Aminobutoxy)benzenes



no.	R ¹	R ²	mp, °C	formula ^a	antireserpine, rel potency ^b
43	4-OCH ₃	NHCH ₃	188-190	C ₁₂ H ₂₀ ClNO ₂	0
44	2-OC ₂ H ₅	NHCH ₃	106-110	C ₁₃ H ₂₂ ClNO ₂	0
45	2-Cl	NHCH ₃	137-141	C ₁₁ H ₁₇ Cl ₂ NO	0
46	2-Cl	N(CH ₃) ₂	133-137	C ₁₂ H ₁₉ Cl ₂ NO	0.47
47	2-(<i>c</i> -C ₆ H ₁₁)	NHCH ₃	134-136	C ₁₇ H ₂₈ ClNO	0.28
48	4-(C ₆ H ₅ CH ₂)	NHCH ₃	178-181	C ₁₈ H ₂₄ ClNO	0

^{a, b} As in Table I.

Table IV. Pharmacology

no.	reversal of reserpine-induced hypothermia: ED ₁₀ , mg/kg po	antimuricide effect at 30 mg/kg ip	antiphyso-stigmine effect: ED ₅₀ , mg/kg po	muscle-relaxant action: ED ₅₀ , mg/kg po	toxicity: LD ₅₀ , mg/kg po
7	12.5 (10.3-15.2) ^a	+++	>200	>200	1000 (833-1200)
19	15.0 (12.0-18.7)	++	>200	>200	750 (528-1065)
29	8.8 (6.6-11.7)	++	>200	>200	600 (441-816)
31	15-20	+	>200	>200	980 (766-1254)
imipramine	11.0 (7.7-15.7)	+	120 (63-228)	190 (111-323)	400 (308-520)
amitriptyline	5.8 (3.6-9.3)	+++	35 (27-46)	40 (29-56)	300 (268-336)

^a 95% confidence limits.

oxy)benzenes (V) were prepared by the amination of III with the appropriate amines (IV).

Pharmacological Activity Results and Discussion

The compounds listed were evaluated for their ability to prevent the reserpine-induced hypothermia in mice. Among 2-benzyl-1-(ω -aminoalkoxy)benzene derivatives with no substituents in the benzene ring (Table I, 1-14), compound 7 with a 4-(methylamino)butoxy side chain exhibited the highest antireserpine activity, whereas the compounds with dimethylamino (2, 4, 8, and 14) or cyclic imino (10-12) terminations to the side chain showed very weak activity. The potency changed greatly according to the side-chain length in the (methylamino)alkoxy-type compounds. Namely, by decreasing the length from four (7) to two (1) carbon atoms, the activity completely disappeared. The less potent activity was also observed for compounds where the carbon chain was three (3) or five (13) atoms (compare 7 with 3 and 13). Considering the above experimental results, the optimum side-chain structure for the antireserpine activity is suggested to be 4-(methylamino)butoxy [O(CH₂)₄NHCH₃]. Subsequently, the effect of substitution on the benzene ring in 2-benzyl-1-(4-aminobutoxy)benzene derivatives was examined (Table I, 15-28). The substitution with 2'-OH (19) and 2'-OCH₃ (22) groups on the benzene ring (R¹) of 7 resulted in an increased activity. Concerning the other substituted (methylamino)butoxy-type compounds, the potency decreased in the order of 6-CH₃ (17, 0.56), 4'-CH₃ (15, 0.44), 4-OH (21, 0.31), 4'-Cl (25, 0.27), 4-Cl (27, 0.17), and 4'-OCH₃ (23, 0.00). Although compound 8 with a (dimethylamino)butoxy side chain was inactive in the antireserpine activity, the introduction of various substituents on the benzene ring of 8 produced varying degrees of the activity. Among them, 18 (6-CH₃) and 20 (2'-OH) were relatively active. As shown in Table II, replacement of the bridging methylene (CH₂) group in 7 by oxygen (O, 29) and sulfur (S, 31) resulted in higher potency, while CH(CH₃) (33), SO (36), and NHCO (42) resulted in a reduced activity. Compounds with such bridging groups as

Table V. Antihistaminic Activity

no.	IC ₅₀ , g/mL
7	1.1 × 10 ⁻⁶
19	2.5 × 10 ⁻⁶
29	1.6 × 10 ⁻⁶
31	2.2 × 10 ⁻⁶
imipramine	3.2 × 10 ⁻⁸
amitriptyline	8.3 × 10 ⁻⁹
phenyltoloxamine (2)	10 ⁻⁹

(CH₂)₂ (35), CH₂O (38), CO (39), and CH(OH) (40) were inactive.

In Table III are listed the activities of miscellaneous compounds. Introduction of alkoxy (43, 44), chloro (45, 46), and cyclohexyl (47) groups at R¹ did not give rise to remarkable activity. Indeed, 43-45 had no activity. Compound 48, which was the positional isomer of 7, also showed no activity. Among the active compounds, 7, 19, 29, and 31 were further examined for their pharmacological activities in comparison with those of imipramine and amitriptyline. Compounds 20 and 22, which were as active as 7 in the antireserpine activity, were excluded from further studies because of high acute toxicity. In reversal of reserpine-induced hypothermia and antimuricide effect, both indicative of antidepressant actions, compounds 7 and 29 exhibited potent activities comparable to those of imipramine in antireserpine action and amitriptyline in antimuricide effect, respectively. Four compounds showed no anticholinergic (antiphyso-stigmine effect) and muscle-relaxant actions up to doses as high as 200 mg/kg po in contrast to the potent actions of the reference drugs (Table IV).

Although compound 2 (phenyltoloxamine), which was chemically related to 7, was inactive in antireserpine activity, it had already been reported to have a strong antihistaminic activity by Cheney et al.⁴ Therefore, the

(4) L. C. Cheney, R. R. Smith, and S. B. Binkley, *J. Am. Chem. Soc.*, 71, 60 (1949).

antihistaminic activity of 7 was compared with that of 2. The actions of amitriptyline, imipramine, and three other selected compounds were also examined. All of four compounds, including 7, were shown to be very weak in this antihistaminic assay. In contrast, amitriptyline, imipramine, and 2 exhibited potent antagonistic action at concentrations of 3.2×10^{-8} to 10^{-9} g/mL. It is thus suggested that antihistaminic action is not involved in the antidepressant action of the selected compounds. Judging from the results of brief pharmacological evaluations on the selected four compounds, they may be expected to have a clinical antidepressant action with fewer side effects.

Experimental Section

Chemistry. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. All compounds were analyzed for C, H, and N, and analytical results were within $\pm 0.4\%$ of the theoretical values. Compounds were checked by IR on a JASCO IR-A2, and the spectral data were consistent with the assigned structure in all cases. For purity tests, TLC was performed on fluorescent silica gel plates (Merck) developed in three different solvents (benzene–diethylamine, 2:1; ethyl acetate–acetic acid–water, 35:10:2; chloroform–methanol–concentrated ammonia water 75:25:1). For all compounds, only one spot (visualized by UV light and sulfuric acid) was obtained. In the following paragraph, details are presented for typical examples of the synthetic method (Scheme I).

2-Benzyl-1-[4-(methylamino)butoxy]benzene Hydrochloride (7). To a solution of KOH (13 g, 0.23 mol) and 2-benzylphenol (36.8 g, 0.20 mol) in MeOH (500 mL), 1,4-dibromobutane (90 g, 0.42 mol) was added and the mixture was refluxed for 8 h. Precipitation of KBr gradually took place. The reaction mixture was concentrated in vacuo, and the residue was extracted with benzene (300 mL) and washed (2 N NaOH and saturated NaCl), dried (Na_2SO_4), and distilled to give 45 g (70%) of 1-benzyl-2-(4-bromobutoxy)benzene: bp 160–170 °C (2 mm). To a solution of 1-benzyl-2-(4-bromobutoxy)benzene (10 g, 0.031 mol) in EtOH (100 mL) was added methylamine (50 mL of a 40% aqueous solution). The reaction mixture was stirred for a day at room temperature and evaporated in vacuo. To the oily residue was added 2 N NaOH (100 mL), and the mixture was extracted with Et_2O (100 mL \times 2). After the evaporation of the Et_2O , EtOH (50 mL) and HCl (50 mL of a 15% anhydrous EtOH solution) were added. The solvent was evaporated, and the residue was purified by recrystallization from acetone to give 6.92 g (73.0%) of 2-benzyl-1-[4-(methylamino)butoxy]benzene hydrochloride: mp 117–121 °C. Anal. ($\text{C}_{18}\text{H}_{24}\text{ClNO}$) C, H, N.

Pharmacology. Prevention of Reserpine-Induced Hypothermia. Groups of six male mice (ddy strain, 20–23 g) were simultaneously treated with reserpine (5 mg/kg ip, as an aqueous solution) and the test compounds (10 mg/kg ip, as an aqueous solution). Rectal temperature was measured 4 h after the treatment using an electronic thermister. Percent inhibition of the hypothermia was determined by the formula $(A - B)/A \times 100$ (%), where A = the fall of body temperature in mice treated with 0.9% saline plus reserpine and B = the fall of body temperature in mice treated with the test compounds plus reserpine.

The results were expressed as a relative potency in comparison with the effect of amitriptyline (relative potency of amitriptyline = 1.00).

Reversal of Reserpine-Induced Hypothermia. Groups of six male mice were pretreated with 2 mg/kg sc of reserpine and 18 h later with the test compounds (po). Rectal temperatures were recorded immediately before dosing with the test compound (t_0) and at intervals of 1, 2, and 4 h thereafter (t_1 to t_4). The cumulative temperature rise (T) was calculated according to the following formula: $T = (t_1 + t_2 + t_4) - 3t_0$. The results were expressed as the ED_{10} value in which the compound produced a cumulative temperature difference of 10 °C greater than the controls.⁵

Antimuricide Effect. Antimuricide effect was observed in the olfactory-bulb removed rats (Wistar strain male rats, 250–300 g), which killed mice within 1 min after confrontation. Six or more animals were used for each group, and the behavior was checked 30 min after the test compounds (30 mg/kg ip). The number of animals which showed no muricidal response during 10 min after confrontation was recorded. The results were expressed as the percent antagonism of the muricide: 0–10% = 0; 11–30% = \pm ; 31–50% = +; 51–70% = ++; 71–100% = +++.

Antiphysostigmine Effect. Antiphysostigmine effect was observed as an index of anticholinergic action. Eight mice were used for each group. The test compounds were given orally 2 h prior to administration of physostigmine sulfate (0.5 mg/kg iv, 100% lethal dose, as an aqueous solution). Deaths were recorded over a period of 24 h. The ED_{50} was defined as the dose which reduced the mortality by 50%.

Muscle-Relaxant Action (Traction Test in Mice). Forepaws of mice (eight per group) were placed on a horizontal wire bar of 30 cm in height at 1 h after administration of the test compounds (po). Failure to place the hind feet on to the wire within 5 s was judged to have a muscle-relaxant action. The ED_{50} was defined as the dose which caused muscle relaxation in 50% of the animals used.

Antihistaminic Activity. Male guinea pigs (300–350 g) fasted overnight were killed and the ileum was removed. The ileum was suspended in a 10-mL organ bath containing tyrode solution, which was bubbled with 95% O_2 + 5% CO_2 at 37 °C. The changes of the contraction in response to histamine (10^{-7} g/mL) were isometrically recorded with a force-displacement transducer. The test compounds were introduced 5 min before histamine and the results were expressed as concentrations (IC_{50} , g/mL) reducing the induced contraction by 50%.

Acute Toxicity. Eight mice were used for each group and the test compounds were administered orally. The LD_{50} was calculated according to the method of Litchfield and Wilcoxon.⁷

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