20, 101915-13-3; 21, 101835-77-2; 22, 101835-78-3; 23, 101835-79-4; 24, 101835-80-7; 25, 33507-63-0; [D-Pro^2, D-Trp^{7,9}]-SP, 80434-86-2; SP(6–11)-hexapeptide, 51165-07-2; (S)-(−)-*i*-PrCH$_2$CH(Br)CO$_2$H, 28659-87-2; (*R*)-(+)-*i*-PrCH$_2$CH(Br)CO$_2$H, 429890-28-3; H-Glyψ(CH$_2$S)-D-Leu-OH, 66386-09-2; H-Glyψ(CH$_2$S)Leu-OH, 61844-81-3; Boc-Glyψ(CH$_2$S)Leu-OH, 101835-81-8; Boc-Glyψ(CH$_2$S)-D-Leu-OH, 101835-83-0; carbachol, 51-83-2; L-glutamate, 56-86-0; histamine, 51-45-6; 2-aminoethanethiol, 60-23-1.

Synthesis of 2-(4-Substituted-1-piperazinyl)benzimidazoles as H_1-Antihistaminic Agents

Ryuichi Iemura,* Tsuneo Kawashima, Toshikazu Fukuda, Keizo Ito, and Goro Tsukamoto

Pharmaceuticals Research Center, Kanebo Ltd., 5-90, Tomobuchi-cho 1-Chome, Miyakojima-ku, Osaka, 534, Japan.
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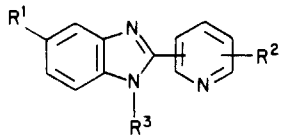
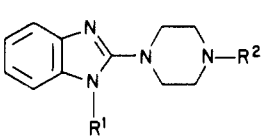
A series of 2-(4-substituted-1-(homo)piperazinyl)benzimidazoles was prepared and tested for H_1-antihistaminic activity in vitro and in vivo. Most of the compounds showed antihistaminic activity and some of the 1-[2-(substituted-oxy)ethyl] derivatives exhibited potent activity. In a structure–activity comparison it was found that the oxygen atom in the 2-(substituted-oxy)ethyl group at the 1-position of the benzimidazole nucleus played an important role for potent antihistaminic activity, especially in vivo. One of the most potent compounds, 1-(2-ethoxyethyl)-2-(4-methyl-1-homopiperazinyl)benzimidazole (**69**), was 39 times more potent than chlorpheniramine maleate in H_1-antihistaminic activity in vivo and was selected for clinical evaluation. The structure of compound **69** is of interest because it provides only a single aromatic unit linked through a chain to a basic nitrogen, while most H_1-antihistaminic agents have structures that comprise a double-aromatic unit linked through a chain to a basic tertiary amino group.

In the previous paper[1] from our laboratory, we reported the synthesis and biological evaluation of 2-(substituted-pyridinyl)benzimidazoles (1) as a novel type of nonacidic antiinflammatory agent. In continuing our study we found a patent[2] concerning the synthesis of 2-(4-substituted-1-piperazinyl)benzimidazole derivatives (**2**), some of which possessed antiinflammatory and analgesic activity.



1



2

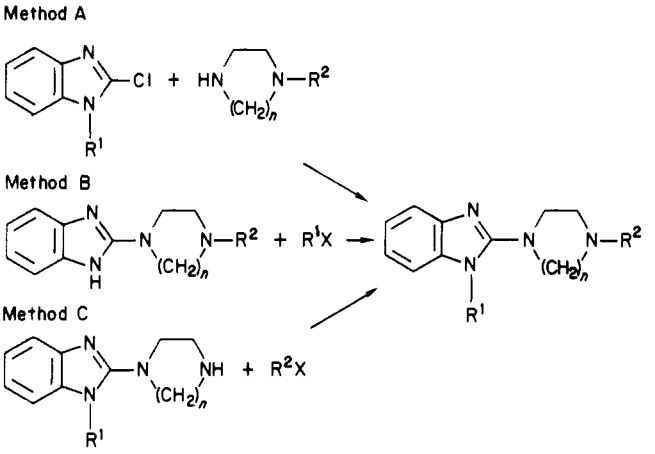
The similarity of structures and pharmacological activities between compounds 1 and **2** urged us to evaluate pharmacological profiles of compounds **2** and compare them with ours. To our surprise, results of our pharmacological screening tests revealed that some of the compounds possessed potent H_1-antihistaminic activity in addition to antiinflammatory activity.

We were interested in the combination of the structure and H_1-antihistaminic activity of compounds **2** and planned to synthesize the derivatives in order to investigate a new type of H_1-antihistaminic agent; the structure of compounds **2** was appreciably different from that of typical H_1-antihistaminic agents, and only a few derivatives were mentioned in the patent.

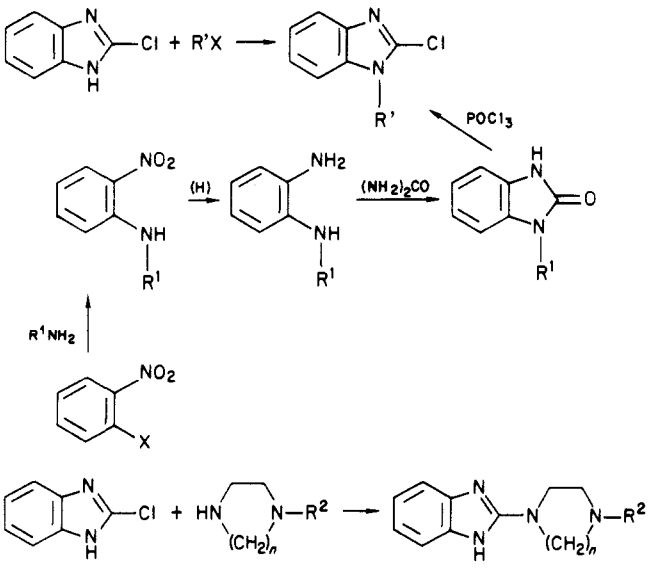
In this paper we report the synthesis of 2-(4-substituted-1-(homo)piperazinyl)benzimidazoles and the results of their pharmacological screening tests for H_1-antihistaminic activity in guinea pigs. Structure–activity relationships are also discussed.

Chemistry. Test compounds (Table II) were for the most part prepared by methods A, B, or C, as shown in Scheme I. In method A, 1-substituted-2-chlorobenzimidazoles were treated with appropriate (homo)piperazine derivatives to give the desired compounds. In method B,

Scheme I



Scheme II



2-(4-substituted-1-(homo)piperazinyl)benzimidazoles were alkylated at the 1-position of the benzimidazole nucleus to afford the desired compounds. And in method C, the desired compounds were prepared by alkylation at the

(1) Tsukamoto, G.; Yoshino, K.; Kohno, T.; Ohtaka, H; Kagaya, H.; Ito, K. *J. Med. Chem.* **1980**, *23*, 734.
(2) Kodama, T.; Takai, A.; Nakabayashi, M.; Watanabe, I.; Sadaki, H.; Kodama, T.; Abe, N.; Kurokawa, A. (Toyama Chemical Co.) Japan Kokai Patent 126 682, 1975; *Chem. Abstr.* **1976**, *84*, 44060h.

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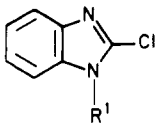
Table I. 2-Chlorobenzimidazoles from 2-Chlorobenzimidazole and Alkyl Halides



no.	R^1	reagent	bp, °C (mmHg)	yield, %	formula	anal.
3	CH_3	CH_3I	107–113.5[a]	79	$C_8H_7ClN_2$	C, H, N
4	$(CH_2)_2CH_3$	$CH_3(CH_2)_2Br$	110.5–111.5 (0.35)	85	$C_{10}H_{11}ClN_2$	C, H, Cl, N
5	$(CH_2)_3CH_3$	$CH_3(CH_2)_3Cl$	128–130 (0.90)	63	$C_{11}H_{13}ClN_2$	C, H, Cl, N
6	$(CH_2)_4CH_3$	$CH_3(CH_2)_4Br$	137–139 (0.65)	70	$C_{12}H_{15}ClN_2$	C, H, Cl, N
7	$(CH_2)_5CH_3$	$CH_3(CH_2)_5Cl$	134–136 (0.30)	71	$C_{13}H_{17}ClN_2$	C, H, Cl, N
8	$(CH_2)_6CH_3$	$CH_3(CH_2)_6Br$	138–140 (0.20)	67	$C_{14}H_{19}ClN_2$	C, H, Cl, N
9	$(CH_2)_9CH_3$	$CH_3(CH_2)_9Br$	159–162 (0.17)	61	$C_{17}H_{25}ClN_2$	C, H, Cl, N
10	Ph		66–68[b]	50[c]	$C_{13}H_9ClN_2$	C,[d] H, N
11	CH_2Ph	$PhCH_2Cl$	108–111[e]	65	$C_{14}H_{11}ClN_2$	C, H, N
12	$(CH_2)_2Ph$	$Ph(CH_2)_2Br$	86–88[f]	62	$C_{15}H_{13}ClN_2$	C, H, N
13	$(CH_2)_2OCH_2CH_3$		132–133.5 (0.65)	80[g]	$C_{11}H_{13}ClN_2O$	C, H, Cl, N
14	$(CH_2)_2OCH{=}CH_2$	$CH_2{=}CHO(CH_2)_2Cl$	140–141.5 (0.60)	60	$C_{11}H_{11}ClN_2O$	C, H, Cl, N
15	$(CH_2)_2O(CH_2)_2CH_3$	$CH_3(CH_2)_2O(CH_2)_2Br$	128.5–130 (0.27)	57	$C_{12}H_{15}ClN_2O$	C, H, Cl, N
16	$(CH_2)_2OCH_2CH{=}CH_2$	$CH_2{=}CHCH_2O(CH_2)_2Br$	149–150 (0.20)	52	$C_{12}H_{13}ClN_2O$	C, H, Cl, N
17	$(CH_2)_2O(CH_2)_3CH_3$	$CH_3(CH_2)_3O(CH_2)_2Br$	161–162 (1.9)	52	$C_{13}H_{17}ClN_2O$	C,[h] H, Cl, N
18	$(CH_2)_2OPh$	$PhO(CH_2)_2Br$	97.5–98.5[i]	64	$C_{15}H_{13}ClN_2O$	C, H, Cl, N

[a] Melting point, recrystallization from ligroin (ref 6, mp 114–116 °C). [b] Melting point, recrystallization from AcOEt/hexane (ref 7, mp 67–68 °C). [c] Yield from 1-phenyl-2-benzimidazolone. [d] C: calcd, 68.28; found, 68.86. [e] Melting point, recrystallization from benzene/hexane (ref 8, 102–105 °C). [f] Melting point, recrystallization from AcOEt/hexane. [g] Yield from 1-(2-ethoxyethyl)-2-benzimidazolone. [h] C: calcd, 61.78; found, 61.21. [i] Melting point, recrystallization from benzene/hexane.

piperazine 4-nitrogen of 1-substituted-2-(1-(homo)-piperazinyl)benzimidazoles.

Starting materials of method A and B were prepared as shown in Scheme II. 1-Substituted-2-chlorobenzimidazoles (Table I) were obtained from alkylation of 2-chlorobenzimidazole or from chlorination of 1-substituted-2-benzimidazolones. The 2-(4-substituted-1-(homo)piperazinyl)benzimidazoles were prepared by reacting 2-chlorobenzimidazole with (homo)piperazine derivatives.

The (ethylamino)ethyl derivative **46** was prepared from 2-chloro-1-(2-chloroethyl)benzimidazole (**24**), by treatment with *N*-methylpiperazine, followed by amination with ethylamine. Preparation of the hydroxyethyl derivative **47** was accomplished by acid hydrolysis of the ethoxyethyl derivative **44**. The 2-(1-piperazinyl) derivative **57** was obtained by hydrogenolysis of the 2-(4-benzyl-1-piperazinyl) derivative **64**. Synthetic details are given in the Experimental Section.

Results and Discussion

All the compounds were tested for H_1-antihistaminic activity in vitro (guinea pig ileum), and the compounds that exhibited potent activity were further tested in vivo (histamine-induced mortality in guinea pigs). The results are listed in Table III.

In the in vitro test of the compounds in which the alkyl, phenyl, or aralkyl group is substituted at the 1-position of the benzimidazole nucleus (**26–39**), **30** (*n*-amyl), **31** (*n*-hexyl), and **38** (benzyl) exhibit potent antihistaminic activity. Those activities are comparable to that of chlorpheniramine maleate, which is one of the potent H_1-antihistaminic agents. The optimum length for unbranched alkyl groups is C_5 and the branched amyl or hexyl-substituted compounds (**34–36**) are less active than the corresponding straight-chain analogues (**30**, **31**).

Among the compounds in which a heteroatom (O, S, or N) is introduced in the straight-chain alkyl group at the 1-position of the benzimidazole nucleus (**40–46**), **41** (2-(ethylthio)ethyl), **43** (*n*-propoxymethyl), and **44** (2-ethoxyethyl) show potent antihistaminic activity in vitro.

Among the compounds that exhibit potent antihistaminic activity in vitro (**30**, **38**, **41**, **43**, **44**), **44** shows the most potent activity in vivo. Its activity in vivo is 25 times more potent than that of chlorpheniramine maleate. These facts suggest that both the presence and the position of the oxygen atom in the alkyl group of the 1-position of the benzimidazole nucleus seem to play an important role for the occurrence of potent H_1-antihistaminic activity, especially in vivo.

On the basis of the above results, the activities of the compounds that had differently substituted oxyethyl groups at the 1-position (**47–56**) were examined. Replacement of the ethyl group in the ethoxyethyl compound **44** by an allyl or propargyl group (**52**, **53**) leads to the retention of good antihistaminic activity in vivo. The vinyl, *n*-propyl, or phenyl group (**49**, **51**, **55**) can be replaced with a slight decrease in activity in vivo. Replacement by a hydrogen atom, methyl, *n*-butyl, or benzyl group (**47**, **48**, **54**, **56**) leads to a considerable fall in antihistaminic activity, especially in vivo.

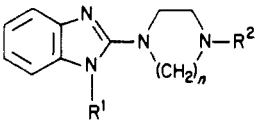
As for the substituent on the piperazine 4-nitrogen, the following structure–activity relationships are observed. Replacement of the piperazine 4-methyl group in **44** by a hydrogen atom and alkyl, benzyl, or phenethyl group (**57–62**, **64**, **65**) leads to good antihistaminic activity in vitro, but in the in vivo test higher alkyl ($>C_3$) substituents decrease the activity. Replacement by a phenyl, diphenylmethyl, or formyl group (**63**, **66**, **67**) leads to a sharp fall in antihistaminic activity. This indicates that the bulky substituents or the substituents that reduce the basicity of the nitrogen atom at the piperazine 4-position have a tendency to diminish the antihistaminic activity.

Similar structure–activity relationships are observed for the compounds in which the piperazine moiety is replaced with the homopiperazine ring (**68–79**).

We have shown that some compounds with structure I have potent antihistaminic activity. Generally the antihistaminic agents (H_1-antagonists) comprise a double-aromatic unit linked through a chain to a basic tertiary amino group[3,4] as shown in structure II. Therefore our compounds (structure I) are of interest because they

(3) Beaven, M. A. *Histamine: Its Role in Physiological and Pathological Process*; Karger: New York, 1978; Chapter 4.
(4) Silva, M. R. *Handbook of Experimental Pharmacology: Histamine II and Anti-Histaminics*; Springer-Verlag: New York, 1978; Chapter 2, Section A.

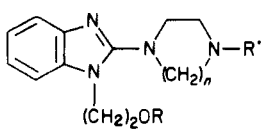
Table II. 2-(4-Substituted 1-piperazinyl)benzimidazoles



no.	*n*	R^1	R^2	mp, °C	recrystn solvent[a]	yield,[b] %	formula[c,d]	method of prepn
26	2	H	CH_3	225.5–228[e]	C	74	$C_{12}H_{16}N_4$	A
27	2	CH_3	CH_3	160.5–163	A	48	$C_{13}H_{18}N_4 \cdot 2HMl$	A
28	2	$(CH_2)_2CH_3$	CH_3	162.5–164	A	74	$C_{15}H_{22}N_4 \cdot 2HFu$	A
29	2	$(CH_2)_3CH_3$	CH_3	156–158.5	A	80	$C_{16}H_{24}N_4 \cdot 2HMl$	A
30	2	$(CH_2)_4CH_3$	CH_3	161.5–163.5	A	90	$C_{17}H_{26}N_4 \cdot 1.5HFu$	A
31	2	$(CH_2)_5CH_3$	CH_3	164–165	A	89	$C_{18}H_{28}N_4 \cdot 1.5HFu$	A
32	2	$(CH_2)_6CH_3$	CH_3	152.5–153.5	A	89	$C_{19}H_{30}N_4 \cdot 1.5HFu$	A
33	2	$(CH_2)_9CH_3$	CH_3	151.5–153	A	90	$C_{22}H_{36}N_4 \cdot 2HFu$	A
34	2	$(CH_2)_2CH(CH_3)_2$	CH_3	81.5–83	H	79	$C_{17}H_{26}N_4$	B
35	2	$CH(CH_3)(CH_2)_2CH_3$	CH_3	168.5–171.5	A	38	$C_{17}H_{26}N_4 \cdot 2HFu$	B
36	2	$CH_2CH(CH_3)(CH_2)_2CH_3$	CH_3	175–176.5	B	62	$C_{18}H_{28}N_4 \cdot 2HFu$	B
37	2	Ph	CH_3	194.5–197	A	80	$C_{18}H_{20}N_4 \cdot 1.5HFu$	A
38	2	CH_2Ph	CH_3	159–160	A	75	$C_{19}H_{22}N_4 \cdot 2HMl$	A
39	2	$(CH_2)_2Ph$	CH_3	172.5–174	A	97	$C_{20}H_{24}N_4 \cdot 1.5HFu$	A
40	2	$CH_2S(CH_2)_2CH_3$	CH_3	72.5–74	D	63	$C_{16}H_{24}N_4S$	B
41	2	$(CH_2)_2SCH_2CH_3$	CH_3	70–72	E	58	$C_{16}H_{24}N_4S$	B
42	2	$(CH_2)_3SCH_2CH_3$	CH_3	48–51	E	74	$C_{17}H_{26}N_4S$	B
43	2	$CH_2O(CH_2)_2CH_3$	CH_3	153–154.5	A	64	$C_{16}H_{24}N_4O \cdot 1.5HFu$	B
44	2	$(CH_2)_2OCH_2CH_3$	CH_3	167.5–168.5	B	96	$C_{16}H_{24}N_4O \cdot 1.5HFu$	A
45	2	$(CH_2)_3OCH_3$	CH_3	148–150.5	A	25	$C_{16}H_{24}N_4O \cdot 2HFu$	B
46	2	$(CH_2)_2NHCH_2CH_3$	CH_3	182–183.5	F	28	$C_{16}H_{25}N_5 \cdot 2HMl$	D
47	2	$(CH_2)_2OH$	CH_3	121–123	A	61	$C_{14}H_{20}N_4O \cdot 2HMl$	E
48	2	$(CH_2)_2OCH_3$	CH_3	111–112.5	B	45	$C_{15}H_{22}N_4O \cdot 2HMl$	B
49	2	$(CH_2)_2OCH{=}CH_2$	CH_3	116–118	G	30	$C_{16}H_{22}N_4O$	A
50	2	$(CH_2)_2O(CH_2)_2OH$	CH_3	175–176.5	B	41	$C_{16}H_{24}N_4O_2 \cdot HFu$	B
51	2	$(CH_2)_2O(CH_2)_2CH_3$	CH_3	165–166	A	87	$C_{17}H_{24}N_4O \cdot 1.5HFu$	A
52	2	$(CH_2)_2OCH_2CH{=}CH_2$	CH_3	161.5–164	A	76	$C_{17}H_{24}N_4O \cdot 1.5HFu$	A
53	2	$(CH_2)_2OCH_2C{\equiv}CH$	CH_3	145–146.5	A	73	$C_{17}H_{22}N_4O \cdot 1.5HFu$	B
54	2	$(CH_2)_2O(CH_2)_3CH_3$	CH_3	148.5–150	A	83	$C_{18}H_{28}N_4O \cdot 1.5HFu$	A
55	2	$(CH_2)_2OPh$	CH_3	152–153.5	A	86	$C_{20}H_{24}N_4O \cdot 1.5HFu$	A
56	2	$(CH_2)_2OCH_2Ph$	CH_3	174–175	B	57	$C_{21}H_{26}N_4O \cdot HFu \cdot 0.5H_2O$	B
57	2	$(CH_2)_2OCH_2CH_3$	H	167–169	A	69	$C_{15}H_{22}N_4O \cdot 1.5HFu$	F
58	2	$(CH_2)_2OCH_2CH_3$	CH_2CH_3	134–135.5	A	92	$C_{17}H_{26}N_4O \cdot 1.5HFu$	C
59	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2CH_3$	142.5–144	A	79	$C_{18}H_{28}N_4O \cdot 2HMl$	C
60	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_3CH_3$	144.5–145.5	A	82	$C_{19}H_{30}N_4O \cdot 2HMl$	C
61	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_4CH_3$	149–150	A	89	$C_{20}H_{32}N_4O \cdot 2HMl$	C
62	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_5CH_3$	143.5–144.5	B	77	$C_{21}H_{34}N_4O \cdot 2HMl$	C
63	2	$(CH_2)_2OCH_2CH_3$	Ph	112–113	G	19	$C_{21}H_{26}N_4O$	A
64	2	$(CH_2)_2OCH_2CH_3$	CH_2Ph	144–145	A	98	$C_{22}H_{28}N_4O \cdot 2HMl$	A
65	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2Ph$	162–163.5	B	99	$C_{23}H_{30}N_4O \cdot 2HMl$	C
66	2	$(CH_2)_2OCH_2CH_3$	$CHPh_2$	91–93	H	47	$C_{28}H_{32}N_4O \cdot 2HMl \cdot H_2O$	C
67	2	$(CH_2)_2OCH_2CH_3$	CHO	113–114	A	47	$C_{16}H_{22}N_4O_2 \cdot HMl$	A
68	3	$(CH_2)_2OCH_2CH_3$	H	85–88	A	60	$C_{16}H_{24}N_4O \cdot 1.5HFu \cdot 0.5H_2O$	A
69	3	$(CH_2)_2OCH_2CH_3$	CH_3	148–151	B	81	$C_{17}H_{26}N_4O \cdot 2HFu$	A
70	3	$(CH_2)_2OCH_2CH_3$	CH_2CH_3	146–147.5	B	76	$C_{18}H_{28}N_4O \cdot 2HFu$	C
71	3	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2CH_3$	125.5–127.5	A	65	$C_{19}H_{30}N_4O \cdot 2HMl$	C
72	3	$(CH_2)_2OCH_2CH_3$	$(CH_2)_3CH_3$	135.5–137	A	86	$C_{20}H_{32}N_4O \cdot 2HMl$	C
73	3	$(CH_2)_2OCH_2CH_3$	$(CH_2)_4CH_3$	145.5–146.5	A	86	$C_{21}H_{34}N_4O \cdot 2HMl$	C
74	3	$(CH_2)_2OCH_2CH_3$	CH_2Ph	127.5–130	A	50	$C_{23}H_{30}N_4O \cdot 2HMl$	C
75	3	$(CH_2)_2O(CH_2)_2CH_3$	CH_3	159.5–160.5	A	74	$C_{18}H_{28}N_4O \cdot 2HFu$	A
76	3	$(CH_2)_2OCH_2CH{=}CH_2$	CH_3	144.5–146.5	A	67	$C_{18}H_{26}N_4O \cdot 2HFu$	A
77	3	$(CH_2)_2OCH_2C{\equiv}CH$	CH_3	122–124.5	A	71	$C_{18}H_{24}N_4O \cdot 2HFu$	B
78	3	$(CH_2)_2O(CH_2)_3CH_3$	CH_3	149.5–154.5	A	97	$C_{19}H_{30}N_4O \cdot 2HFu$	A
79	3	$(CH_2)_2OPh$	CH_3	167–168	B	78	$C_{21}H_{26}N_4O \cdot 2HFu$	A

[a] Solvents: A, EtOH/AcOEt; B, EtOH; C, acetone; D, petroleum ether; E, cyclohexane; F, EtOH/MeOH; G, benzene/hexane; H, AcOEt/hexane. [b] Yield of free base. [c] Analytical results are within ±0.4% of the theoretical values in C, H, N analyses. [d] Abbreviations used are as follows: HFu, hydrogen fumarate; HMl, hydrogen maleate. [e] Reference 2, mp 220–221 °C.

provide only a single aromatic unit (= benzimidazole nucleus) linked through a chain to a basic nitrogen.



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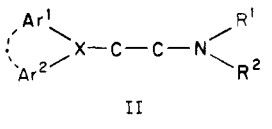
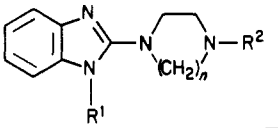


II

One of the most potent compounds, 1-(2-ethoxyethyl)-2-(4-methyl-1-homopiperazinyl)benzimidazole (**69**) (KB-2413), was 39 times more potent than chlorpheniramine maleate in H_1-antihistaminic activity in vivo. KB-2413 also showed antiallergic and antiasthmatic effects[5] and was selected for clinical evaluation.

(5) (a) Fukuda, T.; Saito, T.; Tajima, S.; Shimohara, K.; Ito, K. *Arzneim.-Forsch./Drug Res.* **1984**, *34*(II), 805. (b) Fukuda, T.; Saito, T.; Ito, K. *Arzneim.-Forsch./Drug Res.* **1984**, *34*(II), 811.
(6) Harrison, D.; Ralph, J. T.; Smith, A. C. B. *J. Chem. Soc.* **1963**, 2930.

Table III. Antihistaminic Activity of 2-(4-Substituted-1-piperazinyl)benzimidazoles



no.	n	R^1	R^2	antihistaminic activity[a] in vitro: IC_{50}, μM	antihistaminic activity[a] in vivo: ED_{50}, mg/kg
26	2	H	CH_3	>3.0	NT[b]
27	2	CH_3	CH_3	0.32(0.14–0.58)[c]	NT
28	2	$(CH_2)_2CH_3$	CH_3	0.38(0.28–0.52)	NT
29	2	$(CH_2)_3CH_3$	CH_3	0.050(0.037–0.067)	NT
30	2	$(CH_2)_4CH_3$	CH_3	0.019(0.015–0.026)	0.19(0.12–0.31)
31	2	$(CH_2)_5CH_3$	CH_3	0.026(0.019–0.037)	NT
32	2	$(CH_2)_6CH_3$	CH_3	0.15(0.11–0.21)	NT
33	2	$(CH_2)_9CH_3$	CH_3	4.2(3.3–5.4)	NT
34	2	$(CH_2)_2CH(CH_3)_2$	CH_3	1.4 (0.82–2.6)	NT
35	2	$CH(CH_3)(CH_2)_2CH_3$	CH_3	1.4 (0.88–2.2)	NT
36	2	$CH_2CH(CH_3)(CH_2)_2CH_3$	CH_3	1.5 (1.2–2.1)	NT
37	2	Ph	CH_3	0.76 (0.38–2.4)	NT
38	2	CH_2Ph	CH_3	0.017 (0.0081–0.030)	>0.050
39	2	$(CH_2)_2Ph$	CH_3	0.24 (0.16–0.37)	NT
40	2	$CH_2S(CH_2)_2CH_3$	CH_3	0.068 (0.052–0.099)	NT
41	2	$(CH_2)_2SCH_2CH_3$	CH_3	0.019 (0.013–0.034)	0.28(0.19–0.40)
42	2	$(CH_2)_3SCH_2CH_3$	CH_3	0.53 (0.31–2.3)	NT
43	2	$CH_2O(CH_2)_2CH_3$	CH_3	0.018 (0.011–0.029)	>0.10
44	2	$(CH_2)_2OCH_2CH_3$	CH_3	0.010 (0.0079–0.013)	0.0070 (0.0040–0.011)
45	2	$(CH_2)_3OCH_3$	CH_3	0.86 (0.44–1.9)	>0.10
46	2	$(CH_2)_2NHCH_2CH_3$	CH_3	0.29 (0.21–0.44)	NT
47	2	$(CH_2)_2OH$	CH_3	0.41 (0.32–0.54)	NT
48	2	$(CH_2)_2OCH_3$	CH_3	0.013 (0.011–0.015)	>0.050
49	2	$(CH_2)_2OCH{=}CH_2$	CH_3	0.010 (0.0078–0.015)	0.023 (0.0085–0.044)
50	2	$(CH_2)_2O(CH_2)_2OH$	CH_3	0.042 (0.033–0.054)	0.051[d]
51	2	$(CH_2)_2O(CH_2)_2CH_3$	CH_3	0.020 (0.0092–0.19)	0.015 (0.011–0.020)
52	2	$(CH_2)_2OCH_2CH{=}CH_2$	CH_3	0.017 (0.012–0.025)	0.0058 (0.0028–0.010)
53	2	$(CH_2)_2OCH_2C{\equiv}CH$	CH_3	0.012 (0.0098–0.015)	0.0047 (0.0033–0.0068)
54	2	$(CH_2)_2O(CH_2)_3CH_3$	CH_3	0.038 (0.019–0.070)	>0.10
55	2	$(CH_2)_2OPh$	CH_3	0.0069 (0.0036–0.013)	0.017 (0.0075–0.086)
56	2	$(CH_2)_2OCH_2Ph$	CH_3	0.43 (0.24–0.76)	>0.10
57	2	$(CH_2)_2OCH_2CH_3$	H	0.011 (0.0081–0.015)	0.011 (0.0081–0.016)
58	2	$(CH_2)_2OCH_2CH_3$	CH_2CH_3	0.018 (0.011–0.031)	0.013 (0.0080–0.022)
59	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2CH_3$	0.016 (0.012–0.023)	0.021 (0.016–0.030)
60	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_3CH_3$	0.015 (0.0096–0.024)	>0.10
61	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_4CH_3$	0.030 (0.024–0.039)	>0.10
62	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_5CH_3$	0.0086 (0.0016–0.018)	>0.10
63	2	$(CH_2)_2OCH_2CH_3$	Ph	>10	NT
64	2	$(CH_2)_2OCH_2CH_3$	CH_2Ph	0.027 (0.019–0.037)	0.039 (0.029–0.054)
65	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2Ph$	0.031 (0.022–0.041)	>0.10
66	2	$(CH_2)_2OCH_2CH_3$	$CHPh_2$	>3.0	NT
67	2	$(CH_2)_2OCH_2CH_3$	CHO	>3.0	NT
68	3	$(CH_2)_2OCH_2CH_3$	H	0.025 (0.017–0.047)	0.041 (0.023–0.095)
69	3	$(CH_2)_2OCH_2CH_3$	CH_3	0.0061 (0.0043–0.0086)	0.0044 (0.0027–0.0071)
70	3	$(CH_2)_2OCH_2CH_3$	CH_2CH_3	0.016 (0.011–0.023)	0.032 (0.018–0.088)
71	3	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2CH_3$	0.0084 (0.0044–0.035)	>0.10
72	3	$(CH_2)_2OCH_2CH_3$	$(CH_2)_3CH_3$	0.0084 (0.0066–0.010)	0.12 (0.070–0.22)
73	3	$(CH_2)_2OCH_2CH_3$	$(CH_2)_4CH_3$	0.0074 (0.0060–0.0089)	>0.05
74	3	$(CH_2)_2OCH_2CH_3$	CH_2Ph	0.015 (0.012–0.018)	>0.10
75	3	$(CH_2)_2O(CH_2)_2CH_3$	CH_3	0.016 (0.0089–0.044)	0.0095 (0.0012–0.075)
76	3	$(CH_2)_2OCH_2CH{=}CH_2$	CH_3	0.010 (0.0078–0.013)	0.0088 (0.0050–0.015)
77	3	$(CH_2)_2OCH_2C{\equiv}CH$	CH_3	0.0099 (0.0075–0.013)	0.0046 (0.0030–0.0076)
78	3	$(CH_2)_2O(CH_2)_3CH_3$	CH_3	0.010 (0.0045–0.018)	>0.10
79	3	$(CH_2)_2OPh$	CH_3	0.0091 (0.0060–0.014)	0.014 (0.0084–0.022)
chlorpheniramine maleate				0.012 (0.0094–0.015)	0.17 (0.11–0.27)

[a] See Experimental Section. [b] NT = not tested. [c] 95% confidence limits are included in parentheses. [d] Estimated ED_{50}. 95% confidence limits not given because of poor dose dependency.

Experimental Section

Melting points were taken on a capillary melting point apparatus (Yamato MR-21) and are uncorrected. The structures of all compounds were supported by their IR (Shimadzu IR-440) and ^1H NMR (Hitachi R-24A, Nihon Denshi JNM-PS-100) spectra. Elemental analyses were performed by the Analytical Department of Kyoto University or Kanebo Research Center.

1-*n*-Amyl-2-chlorobenzimidazole (6). A mixture of 2-chlorobenzimidazole (14.0 g, 92 mmol), *n*-amyl bromide (15.0 g, 99 mmol), and 33% w/w aqueous NaOH (15 g) in DMF (100 mL) was stirred at 60 °C for 3.5 h. The reaction mixture was concentrated in vacuo, and the residue was diluted with water (50 mL) and extracted with AcOEt (30 mL × 3). The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo.

(7) Simonov, A. M.; Pozharskii, A. F. *Zh. Obshch. Khim.* **1963**, *33*, 2350; *Chem. Abstr.* **1963**, *59*, 13968a.
(8) Hunger, A.; Kebrle, J.; Rossi, A.; Hoffmann, K. *Helv. Chim. Acta* **1961**, *44*, 1273.

The residue was distilled under reduced pressure to give **6** (14.2 g, 69%) as a colorless liquid, bp 137–139 °C (0.65 mmHg). Anal. ($C_{12}H_{15}ClN_2$) C, H, Cl, N.

***N*-(2-Ethoxyethyl)-*o*-nitroaniline (19).** A mixture of *o*-nitrochlorobenzene (33.0 g, 209 mmol) and 2-ethoxyethylamine (51.0 g, 572 mmol) was refluxed with stirring for 3 h. After cooling, the reaction mixture was diluted with AcOEt (150 mL). The mixture was washed with saturated NaCl, dried over $MgSO_4$, and evaporated in vacuo. The resulting oil was distilled under reduced pressure to give **19** (34.4 g, 78%) as an orange liquid, bp 144–145.5 °C (1.0 mmHg). Anal. ($C_{10}H_{14}N_2O_3$) C, H, N.

***N*-(2-Ethoxyethyl)-*o*-phenylenediamine (20).** A mixture of **19** (42.9 g, 204 mmol) and 10% w/w aqueous NaOH (30 g) in EtOH (100 mL) was stirred vigorously and heated on a water bath until the solution boiled gently. The bath was removed, and to this mixture was added zinc dust (52.0 g, 795 mmol) in several portions frequently enough to keep the solution boiling. After the addition of the zinc dust was completed, the mixture was filtered and the filtrate was poured into water (200 mL) and was extracted with AcOEt. The dried ($MgSO_4$) extract was evaporated in vacuo and the residue was distilled under reduced pressure to give **20** (28.3 g, 77%) as a brown liquid, bp 122–124 °C (0.85 mmHg). Anal. ($C_{10}H_{16}N_2O$) C, H, N.

1-(2-Ethoxyethyl)-2-benzimidazolone (21). A mixture of **20** (34.0 g, 189 mmol) and urea (23.0 g, 383 mmol) was heated with stirring at 150 °C for 5 h. To the cooled mixture was added water (100 mL) and the mixture was extracted with AcOEt. The extract was washed with 2 N HCl and water, dried ($MgSO_4$), and evaporated in vacuo. The residue was recrystallized from *i*-PrOH to give **21** (26.9 g, 69%) as colorless crystals, mp 86–88 °C. Anal. ($C_{11}H_{14}N_2O_2$) C, H, N.

2-Chloro-1-(2-ethoxyethyl)benzimidazole (13). A mixture of **21** (26.0 g, 126 mmol) and phosphorus oxychloride (64.3 g, 419 mmol) was refluxed with stirring for 30 min and then allowed to cool. The reaction mixture was poured into ice-cold water (350 mL). To this mixture was added 4 N NaOH (450 mL) and the mixture was extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was distilled under reduced pressure to give **13** (23.2 g, 82%) as a colorless liquid, bp 132–133.5 °C (0.65 mmHg). Anal. ($C_{11}H_{13}ClN_2O$) C, H, Cl, N.

2-(4-Methyl-1-piperazinyl)benzimidazole (22). A mixture of 2-chlorobenzimidazole (10.0 g, 66 mmol) and *N*-methylpiperazine (20.0 g, 200 mmol) was stirred at 125 °C for 5 h. To the reaction mixture was added 2.5 N NaOH (100 mL), and the resulting precipitate was separated by filtration. The filtrate was extracted with $CHCl_3$ and the dried ($MgSO_4$) extract was evaporated in vacuo. The residue and the precipitate were combined and recrystallized from acetone to give **22** (10.5 g, 74%) as colorless needles, mp 225.5–228 °C. Anal. ($C_{12}H_{16}N_4$) C, H, N.

2-(4-Methyl-1-homopiperazinyl)benzimidazole (23). Reaction of 2-chlorobenzimidazole (6.1 g, 40 mmol) with *N*-methylhomopiperazine (12.0 g, 105 mmol) as described for **22** afforded 3.5 g (38%) of the title compound with mp (acetone) 197–198.5 °C. Anal. ($C_{13}H_{18}N_4$) C, H, N.

2-Chloro-1-(2-chloroethyl)benzimidazole (24). A mixture of 2-chlorobenzimidazole (12.5 g, 82 mmol), 1-bromo-2-chloroethane (12.5 g, 87 mmol), and 33% w/w aqueous NaOH (15 g) in DMF (100 mL) was stirred at room temperature for 13 h. Water (300 mL) was added to the reaction mixture and the mixture was extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on Merck silica gel 60 (100 g). Elution with $CHCl_3$ furnished 10.1 g of a white solid. This solid was recrystallized from benzene/hexane to give **24** (7.47 g, 42%) as colorless plates, mp 67–70 °C. Anal. ($C_9H_8Cl_2N_2$) C, H, N.

1-(2-Chloroethyl)-2-(4-methyl-1-piperazinyl)benzimidazole (25). A mixture of **24** (5.0 g, 23 mmol) and *N*-methylpiperazine (5.0 g, 50 mmol) was stirred at 60 °C for 16.5 h. To the reaction mixture was added 1 N NaOH (50 mL), and the mixture was extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on Merck silica gel 60 (80 g). Elution with $CHCl_3$, $CHCl_3$/MeOH (20:1) furnished 1.39 g (21%) of almost-pure **25**, which crystallized as the hydrogen maleate from EtOH. Recrystallization from EtOH gave **25** (1.53 g, 13%) as colorless scales, mp 141–143.5 °C. Anal. ($C_{14}H_{19}ClN_4 \cdot 2C_4H_4O_4$) H, N; C: calcd, 51.72; found, 52.21.

1-*n*-Amyl-2-(4-methyl-1-piperazinyl)benzimidazole (30). Method A. A mixture of **6** (7.20 g, 32 mmol) and *N*-methylpiperazine (7.00 g, 70 mmol) was stirred at 120 °C for 4 h. To the reaction mixture was added 1 N NaOH (70 mL) and the mixture was extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on Merck silica gel 60 (150 g). Elution with $CHCl_3$, $CHCl_3$/MeOH (20:1) furnished 8.36 g (90%) of almost-pure **30**, which crystallized as the hydrogen fumarate from EtOH. Recrystallization from EtOH/AcOEt gave **30** (6.43 g, 43%) as colorless scales, mp 161.5–163.5 °C.

1-(2-Ethoxyethyl)-2-(4-methyl-1-piperazinyl)benzimidazole (44). Method A. Reaction of **13** (5.00 g, 22 mmol) with *N*-methylpiperazine (4.5 g, 45 mmol) as described for **30** afforded 6.17 g (96%) of **44** as a colorless liquid, which crystallized as the hydrogen fumarate from EtOH. Recrystallization from EtOH gave **44** (7.40 g, 72%) as colorless plates, mp 167–168.5 °C.

1-(3-Methyl-1-butyl)-2-(4-methyl-1-piperazinyl)benzimidazole (34). Method B. A mixture of **22** (2.20 g, 10 mmol), isoamyl chloride (1.60 g, 15 mmol), and NaH (ca. 60%, in oil) (0.70 g, 18 mmol) in DMF (30 mL) was stirred at 60 °C for 5.5 h. The reaction mixture was poured into water (70 mL) and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on Merck silica gel 60 (100 g). Elution with $CHCl_3$, $CHCl_3$/MeOH (20:1) furnished almost-pure **34** (2.30 g, 79%). Recrystallization from AcOEt/hexane gave **34** (1.20 g, 41%) as colorless needles, mp 81.5–83 °C.

1-(2-Ethoxyethyl)-2-(1-piperazinyl)benzimidazole (57). Method F. A solution of 2-(4-benzyl-1-piperazinyl)-1-(2-ethoxyethyl)benzimidazole (**64**) (11.6 g, 32 mmol), prepared by method A, in 80% AcOH (100 mL) was hydrogenolyzed over 5% Pd/C (4.0 g) at 60 °C (50 psi) for 8 h. After removal of the catalyst and evaporation to dryness, the residue was diluted with 2.5 N NaOH (100 mL) and extracted with $CHCl_3$. The resulting oil was purified by column chromatography on Merck silica gel 60 (30 g). Elution with $CHCl_3$, $CHCl_3$/MeOH (7.5:1) furnished almost-pure **57** (7.74 g, 89%) as a pale yellow liquid, which crystallized as the hydrogen fumarate from EtOH. Recrystallization from EtOH/AcOEt gave **57** (4.69 g, 33%) as colorless needles, mp 167–169 °C.

1-(2-Ethoxyethyl)-2-(4-*n*-propyl-1-piperazinyl)benzimidazole (59). Method C. A mixture of **57** (2.00 g, 7.3 mmol), *n*-propyl bromide (1.0 g, 8.9 mmol), and K_2CO_3 (0.55 g, 4.0 mmol) in EtOH (10 mL) was stirred at 65 °C for 5 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on Merck silica gel 60 (30 g). Elution with $CHCl_3$, $CHCl_3$/MeOH (30:1) furnished almost-pure **59** (1.83 g, 79%) as a pale yellow liquid, which crystallized as the hydrogen maleate from EtOH. Recrystallization from EtOH/AcOEt gave **59** (1.99 g, 50%) as colorless needles, mp 142.5–144 °C.

1-[2-(Ethylamino)ethyl]-2-(4-methyl-1-piperazinyl)benzimidazole (46). Method D. A mixture of **25** (2.00 g, 7.2 mmol) and ethylamine (70% aqueous solution, 5 mL) in EtOH (15 mL) was heated at 125 °C in a sealed tube for 3 h. The reaction mixture was evaporated in vacuo and to this residue was added 2 N NaOH (10 mL). The mixture was extracted with $CHCl_3$ and the extract was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on Merck silica gel 60 (30 g). Elution with $CHCl_3$, $CHCl_3$/MeOH (4:1) furnished 1.20 g (58%) of almost-pure **46**, which crystallized as the hydrogen maleate from EtOH. Recrystallization from MeOH/EtOH gave **46** (0.90 g, 24%) as colorless needles, mp 182–183.5 °C.

1-(2-Hydroxyethyl)-2-(4-methyl-1-piperazinyl)benzimidazole (47). Method E. A solution of **44** (5.00 g, 17 mmol) in 30 mL of hydrobromic acid (48%) was refluxed for 3 h. After cooling, the reaction mixture was made basic (pH 12) with 5 N NaOH. The mixture was extracted with *n*-BuOH and the extract was washed with saturated NaCl and concentrated in vacuo. The resulting liquid (3.73 g, 83%) was crystallized as the hydrogen maleate from EtOH. Recrystallization from EtOH/AcOEt gave **47** (4.12 g, 48%) as colorless crystals, mp 121–123 °C.

H_1-Antihistaminic Activity: Contraction of Isolated Ileum from Guinea Pigs Induced by Histamine (in Vitro). A study of the interaction with histamine was carried out with isolated ileum from guinea pigs according to the usual method. The segments (1 cm) of ileum were suspended in an organ bath containing Tyrode solution (ventilation, 32 °C). The contractile responses to histamine (5.4×10^{-7} mol/L) were measured with an isotonic transducer (TD-112S, Nihon Koden, Tokyo, Japan). Each test compound was added in the organ bath 5 min before the addition of histamine. IC_{50} values of the test compounds were calculated by the probit method.[9]

Histamine-Induced Mortality in Guinea Pigs (in Vivo). Histamine-induced mortality in guinea pigs was performed according to the method of Labelle and Tislow.[10] Groups of six to ten animals (250–350 g) were fasted for 20–24 h. Each test compound was administered orally, and 1 h later, histamine (1.1 mg/kg) was injected iv. The number of animals dying within 1 h after the injection of histamine was recorded. ED_{50} values of the test compounds were calculated by the probit method.[9]

Registry No. **3**, 1849-02-1; **4**, 80841-35-6; **5**, 101953-54-2; **6**, 101953-55-3; **7**, 101953-56-4; **8**, 101953-57-5; **9**, 72816-83-2; **10**, 24547-45-3; **11**, 43181-78-8; **12**, 101953-58-6; **13**, 87233-54-3; **14**, 101953-59-7; **15**, 87233-55-4; **16**, 87233-53-2; **17**, 101953-60-0; **18**, 87233-56-5; **19**, 95893-88-2; **20**, 95893-89-3; **22**, 57897-93-5; **23**, 101953-62-2; **24**, 55754-08-0; **25**, 101953-64-4; **27**, 101953-65-5; **27** (free base), 57897-97-9; **28**, 101953-67-7; **28** (free base), 101953-66-6; **29**, 101953-69-9; **29** (free base), 101953-68-8; **30**, 101953-71-3; **30** (free base), 101953-70-2; **31**, 101953-73-5; **31** (free base), 101953-72-4; **32**, 101953-75-7; **32** (free base), 101953-74-6; **33**, 101953-77-9; **33** (free base), 101953-76-8; **34**, 101953-78-0; **35**, 101953-80-4; **35** (free base), 101953-79-1; **36**, 101953-82-6; **36** (free base), 101953-81-5; **37**, 101953-84-8; **37** (free base), 101953-83-7; **38**, 101953-85-9; **38** (free base), 57897-96-8; **39**, 101953-87-1; **39** (free base), 101953-86-0; **40**, 101953-88-2; **41**, 101953-89-3; **42**, 101953-90-6; **43**, 101953-92-8; **43** (free base), 101953-91-7; **44**, 87233-66-7; **44** (free base), 87233-65-6; **45**, 101953-94-0; **45** (free base), 101953-93-9; **46**, 101953-96-2; **46** (free base), 101953-95-1; **47**, 101979-22-0; **47** (free base), 101954-34-1; **48**, 101953-98-4; **48** (free base), 101953-97-3; **49**, 101953-99-5; **50**, 101954-01-2; **50** (free base), 101954-00-1; **51**, 101954-02-3; **51** (free base), 87233-75-8; **52**, 87233-64-5; **52** (free base), 87233-63-4; **53**, 87233-60-1; **53** (free base), 87233-59-8; **54**, 101954-04-5; **54** (free base), 101954-03-4; **55**, 87233-78-1; **55** (free base), 87233-77-0; **56**, 101954-06-7; **56** (free base), 101954-05-6; **57**, 87233-70-3; **57** (free base), 87233-69-0; **58**, 87233-72-5; **58** (free base), 87233-71-4; **59**, 101954-08-9; **59** (free base), 101954-07-8; **60**, 101954-10-3; **60** (free base), 101954-09-0; **61**, 101954-12-5; **61** (free base), 101954-11-4; **62**, 101954-14-7; **62** (free base), 101954-13-6; **63**, 101954-15-8; **64**, 87233-80-5; **64** (free base), 87233-79-2; **65**, 101954-17-0; **65** (free base), 101954-16-9; **66**, 101954-19-2; **66** (free base), 101954-18-1; **67**, 87233-82-7; **67** (free base), 87233-81-6; **68**, 101954-21-6; **68** (free base), 101954-20-5; **69**, 87233-62-3; **69** (free base), 87233-61-2; **70**, 101954-23-8; **70** (free base), 101954-22-7; **71**, 101954-25-0; **71** (free base), 101954-24-9; **72**, 101954-27-2; **72** (free base), 101954-26-1; **73**, 101954-29-4; **73** (free base), 101954-28-3; **74**, 101954-31-8; **74** (free base), 101954-30-7; **75**, 87250-52-0; **75** (free base), 87233-83-8; **76**, 87233-68-9; **76** (free base), 87233-67-8; **77**, 87233-58-7; **77** (free base), 87233-57-6; **78**, 101954-33-0; **78** (free base), 101954-32-9; **79**, 87233-74-7; **79** (free base), 87233-73-6; $CH_3(CH_2)_2Br$, 106-94-5; $CH_3(CH_2)_3Cl$, 109-69-3; $CH_3(CH_2)_4Br$, 110-53-2; $CH_3(CH_2)_5Cl$, 544-10-5; $CH_3(CH_2)_6Br$, 629-04-9; $CH_3(CH_2)_9Br$, 112-29-8; $PhCH_2Cl$, 100-44-7; $Ph(CH_2)_2Br$, 103-63-9; $CH_2{=}CHOCH_2CH_2Cl$, 110-75-8; $CH_3(CH_2)_2O(CH_2)_2Br$, 64994-49-6; $CH_2{=}CHCH_2OCH_2CH_2Br$, 15424-04-1; $CH_3CH_2CH_2OCH_2CH_2Br$, 6550-99-8; $PhO(CH_2)_2Br$, 589-10-6; $HNCH_2CH_2CH_2N(CH_3)CH_2CH_2$, 4318-37-0; $Ph\text{-}NCH_2CH_2NH\text{-}CH_2CH_2$, 92-54-6; $Ph\text{-}CH_2\text{-}NCH_2CH_2NHCH_2CH_2$, 2759-28-6; $OHC\text{-}NCH_2CH_2NH\text{-}CH_2CH_2$, 7755-92-2; $HNCH_2CH_2CH_2NHCH_2CH_2$, 505-66-8; 2-chlorobenzimidazole, 4857-06-1; *N*-methylpiperazine, 109-01-3; 1-(2-ethoxyethyl)-2-benzimidazolone, 101953-61-1; 2-ethoxy ethylamine, 110-76-9; isoamyl chloride, 107-84-6; 1-phenyl-2-benzimidazolone, 14813-85-5; *o*-nitrochlorobenzene, 100-00-5; 1-bromo-2-chloroethane, 107-04-0.

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Two Stereoisomeric Imidazoline Derivatives: Synthesis and Optical and α_2-Adrenoceptor Activities

Jürgen Biedermann,* Alicia León-Lomelí, Harald O. Borbe, and Gerrit Prop

Departments of Chemical, Biochemical, and Pharmacological Research, A. Nattermann & Cie. GmbH, D-5000 Cologne 30, FRG. *Received July 31, 1985*

Two eight-step pathways for synthesizing the stereoisomeric compounds (-)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline hydrochloride ("levlofexidine" hydrochloride; (-)-lofexidine hydrochloride) and (+)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline hydrochloride ("dexlofexidine" hydrochloride; (+)-lofexidine hydrochloride) and the optical resolution of (±)-lofexidine are described. (-)-Lofexidine, a stereoselective α_2-adrenoceptor agonist, due to its center of asymmetry, is demonstrated to be a potent drug for the treatment of hypertension (doses 0.561 μg/kg) and to have the highest affinity and a concentration dependency for α_2-adrenoceptors in direct binding studies (0.36 nmol/L). (+)-Lofexidine is 10 times less potent.

Drugs with α_2-agonistic properties show a remarkable range of pharmacodynamic activities. This group of drugs comprises, in addition to clonidine and guanfacine representing the oldest and most completely investigated compounds, a series of newer compounds.[1] One of these drugs is another imidazoline compound, lofexidine hydrochloride[2-37] ((±)-1). The α_2-adrenoceptor agonists are clinically useful drugs for the treatment of hypertension. This blood pressure lowering effect is based on the stim-

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