struments supported by a grant from the National Institutes of Health (Grant PHS GM 27029).

**Registry No.** **1a**, 98541-32-3; **1b**, 98541-33-4; **2**, 98632-84-9; **3a**, 98632-85-0; **3b**, 98632-86-1; **4a**, 98541-34-5; **4b**, 98541-35-6; **5c**, 84110-38-3; **5d**, 90084-26-7; **5e**, 98541-36-7; **5f**, 98541-37-8; **6a**, 78902-03-1; **6b**, 76110-79-7; **6c**, 85167-12-0; **6d**, 89618-77-9; **6e**, 98541-38-9; **7a**, 88824-38-8; **7b**, 98541-39-0; **7c**, 98541-40-3; **7d**, 94242-79-2; **7e**, 98541-41-4; (*R*)-PhCO-ID, 98541-42-5; (*R*)-Z-Ala-ID, 98541-43-6; (*R*)-Z-Ala-IID, 98541-44-7; (*R*)-Z-Ala-IIID, 98541-45-8; (*R*)-Z-Ala-IVD, 98541-46-9; (*R*)-Z-Ala-VD, 98541-47-0; Rh-CO-IA, 98541-48-1; (*R*)-PhCO-IA, 98632-87-2; (*R*)-Z-Ala-IA, 98541-49-2; (*R*)-Z-Ala-IVA, 98541-50-5; (*R*)-Z-Ala-Va, 98541-51-6; PhCO-IB, 98541-52-7; Z-Gly-IB, 98541-53-8; Ac-IB, 98541-54-9; PhCO-IIB, 98541-55-0; Z-Gly-IIB, 98541-56-1; (*R*)-Z-Ala-IIB, 98541-57-2; (*R*)-PhCO-IB, 98632-88-3; (*R*)-Z-Ala-IB, 98541-58-3; (*R*)-Ac-IB, 98632-89-4; (*R*)-Z-Ala-IIIB, 98541-59-4; (*R*)-Z-Ala-IVB, 98576-62-6; (*R*)-Z-Ala-VB, 98576-63-7; Z-Gly-IA, 98541-60-7; Ac-IA, 98632-90-7; Ph-CO-IIA, 98541-61-8; Z-Gly-IIA, 98541-62-9; (*R*)-Z-Ala-IIA, 98541-63-0; (*R*)-Ac-ID, 78902-05-3; MeBr, 74-83-9; $B(OMe)_3$, 121-43-7; $LiN(SiMe_3)_2$, 4039-32-1; $PhCH_2Br$, 100-39-0; $LiCHCl_2$, 2146-67-0; *i*PrBr, 75-26-3; EtBr, 74-96-4; $PhCO_2Cs$, 17265-04-2; Z-Ala-OH·Cs, 61543-49-5; *dil-threo*-2,3-butanediol, 6982-25-8; pinanediol, 18680-27-8; phenylboronic acid, 98-80-6; phenyllithium, 591-51-5; chymotrypsin, 9004-07-3; elastase, 9004-06-2.

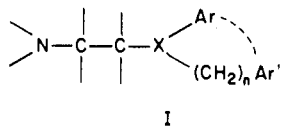
# New Antihistaminic N-Heterocyclic 4-Piperidinamines. 1. Synthesis and Antihistaminic Activity of *N*-(4-Piperidinyl)-1*H*-benzimidazol-2-amines

Frans Janssens,* Joseph Torremans, Marcel Janssen, Raymond A. Stokbroekx, Marcel Luyckx, and Paul A. J. Janssen

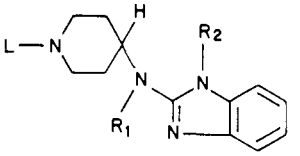
*N. V. Janssen Pharmaceutica, Research Laboratories, B-2340 Beerse, Belgium.* *Received February 4, 1985*

The synthesis of a series *N*-(4-piperidinyl)-1*H*-benzimidazol-2-amines and the preliminary evaluation of their in vitro and in vivo antihistaminic activity are described. Cyclodesulfurization of (2-aminophenyl)thioureas with mercury(II) oxide resulted in 2-aminobenzimidazole intermediates, which were monoalkylated on the *endo*-nitrogen atom. After deprotection of the piperidine nitrogen atom with 48% aqueous hydrobromic acid solution, the title compounds were obtained by three different methods, viz. alkylation, reductive amination, or oxirane ring-opening reactions. The in vivo antihistaminic activity was evaluated by the compound 48/80 induced lethality test in rats and histamine-induced lethality test in guinea pigs after oral and/or subcutaneous administration. The duration of action, for a selected number of compounds, was studied in the guinea pig. The phenylethyl derivatives showed the most potent antihistamine properties after oral administration in both animal species.

Since the beginning of antihistamine research in the Pasteur Institute in France in 1937, many new antihistamines have been discovered.[1] Nearly all the antihistamine drugs that have been developed may be represented by the general formula I, where Ar and Ar′ represent an




I




II

aryl group, $n = 0$ or 1, and X represents a nitrogen, oxygen, or carbon atom connecting the aminoalkyl chain to the aromatic nucleus. In I X–C< may also be replaced by a carbon–carbon double bond. The mean N–X distance is 4.1 ± 0.6 Å.[2]

The terminal nitrogen can be part of a tertiary acyclic or alicyclic amine, and the two aromatic nuclei may be bridged to form tricyclic derivatives.[3] These antihistamines exhibit, in varying degrees, local anaesthetic, adrenergic blocking, antispasmodic, sympathomimetic, analgesic, and antiserotonin activity.[4,5] Moreover, many antihistamines exert some depressant activity on the central nervous system and cause sedation.[6] Peripheral side effects such as gastrointestinal complaints or dry mouth may be due to anticholinergic properties.

Finally, most antihistamines have a short duration of action of only a few hours.[4] In some cases, this drawback can be remedied with a galenic sustained-release form. The side effects and short duration of action limit the use of high oral doses for the treatment of asthma where high tissue levels of antihistamines may be required to prevent allergen-induced bronchospasm.

In light of these facts, it was reasoned that compounds with a long duration of action, a high safety index, and a very low risk of provoking central and anticholinergic side effects would have a broad range of therapeutic applications in diseases, characterized by a prolonged stimulation of histamine $H_1$ receptors.

In this paper, we report the synthesis of a series of new *N*-(4-piperidinyl)-1*H*-benzimidazol-2-amines (II), which are structurally unrelated to any known antihistamine.

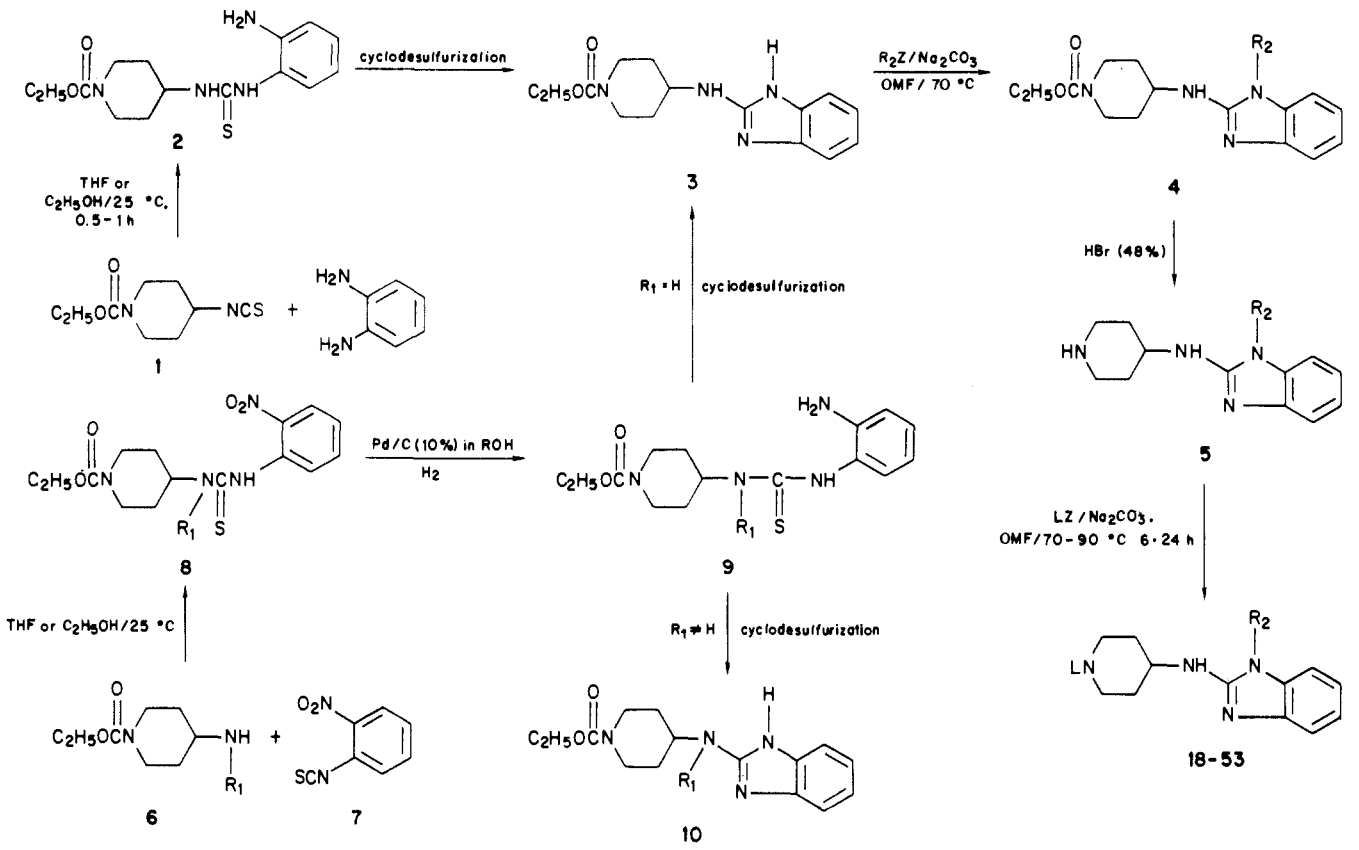
Some of these compounds are long-acting antihistamines by either subcutaneous or oral administration.

**Chemistry.** The synthesis and chemical properties of 2-aminobenzimidazoles were recently reviewed.[7,8] The cyclodesulfurization (Scheme I) of the (2-aminophenyl)-thioureas **2** and **9** resulted in the 2-aminobenzimidazoles **3** and **10** in moderate to excellent yields. Although many cyclodesulfurization agents are available, e.g. alkyl halides, dialkyl sulfates, mercury(II) chloride or acetate, lead(II)

(1) Bovet, D.; Staub, A. M. *C. R. Hebd. Seances Acad. Sci.* **1937**, *124*, 547.
(2) Tollenaere, J. P.; Moereels, H.; Raymaekers, L. A. "Atlas of Three-Dimensional Structure of Drugs", Janssen Research Foundation Series; Elsevier: Amsterdam, 1979; Vol. 1, p 4.
(3) Casy, A. F. "Handbook of Experimental Pharmacology"; Rocha, E., Silva, M., Eds.; Springer-Verlag: Berlin, 1978; Vol. XVIII/2, pp 175–214.
(4) Bovet, D.; Bovet-Nitti, F. "Medicaments du Systeme Nerveux Vegetatif"; Karger, S., Ed.; Basel, 1948; p 741.
(5) Wade, A., Ed. "The Extra Pharmacopeia", 27th ed; The Pharmaceutical Press: London, 1978; pp 1287–1309.
(6) Green, A. F.; Garland, L. G.; Hodson, H. F. "Antiinflammatory Drugs"; Vane, J. R., Ferreira, S. H., Eds.; Springer-Verlag: Berlin, 1979; pp 415–466.
(7) Simonov, A. M.; Anisimova, V. A. *Chem. Heterocycl. Compd.* **1979**, *15*, 705.
(8) Rastogi, R.; Sharma, S. *Synthesis* **1983**, 861.

0022-2623/85/1828-1925$01.50/0 

**Scheme I**




oxide,[9,10] and dicyclohexylcarbodiimide,[11] we mainly used mercury(II) oxide in tetrahydrofuran or ethanol, catalyzed by a small amount of sulfur powder.

On treatment of the isothiocyanate **1** with *o*-phenylenediamine in ethanol or tetrahydrofuran at room temperature, **2** was obtained almost quantitatively. Addition of 2-nitrophenyl isothiocyanate **7** to the 4-aminopiperidines **6**, prepared by reductive amination of 1-carboethoxy-4-piperidone[12] with the appropriate amines, afforded the (2-nitrophenyl)thioureas **8**, which were readily converted to **9** by catalytic hydrogenation of the nitro function with palladium on charcoal. Alkylation of the monosubstituted 2-aminobenzimidazole **3** with the appropriate alkylating agent $R_2Z$ under neutral or weakly basic reaction conditions afforded **4**. NMR spectroscopy revealed that the alkylation reaction proceeded selectively on the *endo*-nitrogen, in accord with the literature.[8] Deprotection of **4** was accomplished by heating at reflux in 48% aqueous hydrogen bromide solution (Scheme I).

The title compounds (Table I) were obtained by introduction of the L substituent onto **5** via Scheme I: (a) alkylation with alkyl halides or alkyl sulfonates in DMF (**18–21**, **23–27**, **29–33**, **35–46**, **48**, **50**, **52**, **53**); (b) catalytic reductive amination with the appropriate ketone (**22**, **34**, **51**); (c) reaction with *N*-[dihydro-3,3-diphenyl-2(3*H*)-furanylidene]-*N*-methylmethanaminium bromide[13] in 4-methyl-2-pentanone (**28** and **47**); (d) ring opening of (phenoxymethyl)oxirane in a mixture of methanol and benzene (**49**).

The 2-aminobenzimidazoles **54–105** (Table II) were prepared by three different methods (Scheme II).

Analogous to the method described in Scheme I, **5** or its free base can be coupled with the appropriate phenylethyl halide (Method I). Deprotection of **10** in refluxing 48% aqueous hydrogen bromide solution gave **11**, which was readily converted to **12** by reacting with the appropriate phenylethyl halide in dimethylformamide in the presence of sodium carbonate. Ring alkylation of **12** with $R_2Z$ occurred under weak basic conditions ($Na_2CO_3$, DMF) for $R_1$ = H and under strong basic conditions (NaH 50%, $Me_2SO$, $C_6H_6$) for $R_1$ = H (Method II).

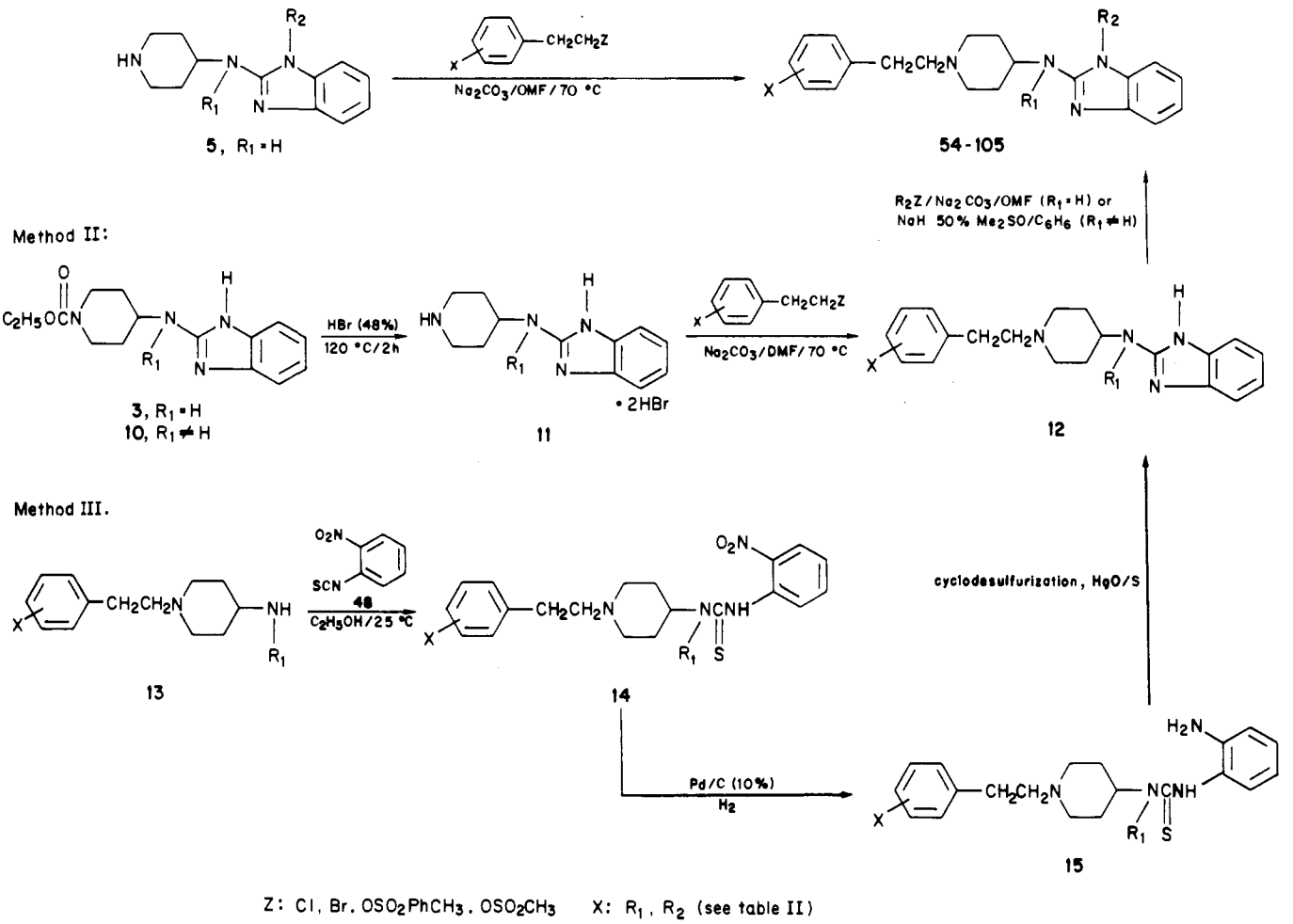
The phenethyl moiety could also be introduced in an earlier stage of the synthesis (Method III). Thus, addition of **7** to the amines **13** afforded the (2-nitrophenyl)thioureas **14**, which were reduced to **15**. Cyclodesulfurization of **15** with mercury(II) oxide, followed by endo *N*-alkylation with $R_2Z$ resulted in the title compounds.

The 1-(phenylethyl)-4-aminopiperidines **13** were prepared as outlined in Scheme III. Alkylation of 1,4-dioxa-8-azaspiro[4.5]decan (**12**)[14] with the corresponding phenylethyl halides yielded **16**, which were hydrolyzed in acidic medium to the appropriate 4-piperidones **17**, reductive amination of **17** with the corresponding amines afforded **13**.

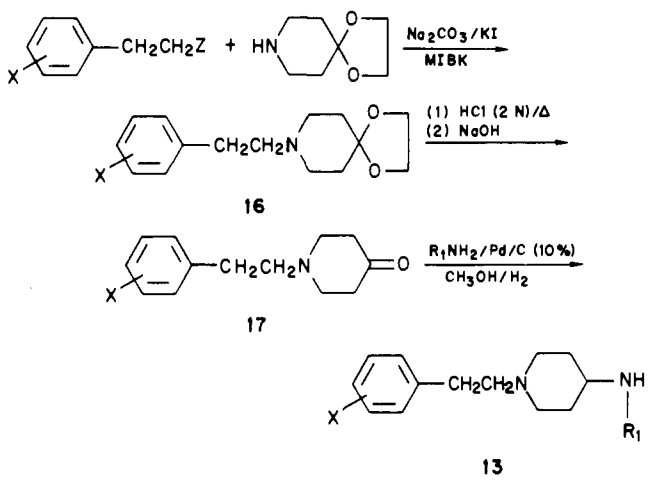
**Pharmacology.** The in vitro antihistaminic activity was evaluated by measuring inhibition of histamine- ($H_1$-) induced contraction of guinea pig ileum. Drug effects were expressed as $A_{10}$ values (the concentration of the antagonist needed to induce a 10-fold shift of the dose–response curve

(9) Mohsen, A.; Omar, M. E.; Ragab, M. S.; Farghaly, A. M.; Barghash, A. M. *Pharmazie* **1975**, *30*, 83.
(10) Mohsen, A.; Omar, M. E.; Ragab, M. S.; Farghaly, A. M.; Barghash, A. M. *Pharmazie* **1976**, *31*, 348.
(11) Mohsen, A.; Omar, M. E.; Habib, N. S.; Abouluafa, O. M. *Synthesis* **1977**, 864.
(12) Eenkhoorn, J. A.; De Silva, O.; Snieckus, V. *Can. J. Chem.* **1973**, *51*, 792.
(13) Stokbroekx, R. A.; Vandenberk, J.; Van Heertum, A. H. M. T.; van Laar, G. H. L. W.; Van der Aa, M. J. M. C.; Van Bever, W. F. M.; Janssen, P. A. J. *J. Med. Chem.* **1973**, *16*, 782.
(14) Stach, K.; Thiel, M.; Bickelhaugt, F. *Monatsh. Chem.* **1962**, *93*, 1090.

**Scheme II**




**Scheme III**




of histamine to the right) and are recorded in Table I and II.[15]

The in vivo antihistamine activity was evaluated by the compound 48/80-induced lethality test in rats[16-18] and the histamine-induced lethality test in guinea pigs[19] after oral and/or subcutaneous administration.

The test animals were inbred Wistar rats (230–270 g) and albino guinea pigs (280–360 g). The results of the compound 48/80 lethality test for a selected number of compounds are summarized in Table III.

In the histamine lethality test in guinea pigs, the dose–response curves were used to determine $PD_{50}$ values.[17] To study the duration of action, 2-fold increments of the test substance were administered orally 3, 24, and 48 h prior to intravenous histamine challenge.

The results of the intravenous histamine lethality in guinea pigs for a selected number of compounds are summarized in Table IV.

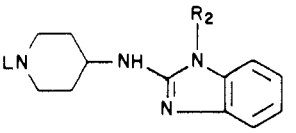
## Results and Discussion

Maximum in vitro antihistaminic activity is found in compounds **31**, **64**, and **75**. Somewhat reduced potency is shown by an extended group of compounds. It soon became apparent that the main subclass consists of *N*-(phenylethyl)piperidines with the benzimidazole moiety substituted on the *endo*-nitrogen atom with either a lower alkyl (**19**, **25**, **57**, **76**) or a 4-fluorobenzyl group (**64**, **65**, **67**).

The in vitro antihistaminic activity is not influenced by introduction of a small alkyl group onto the *exo*-nitrogen

(15) Van Nueten, J. M.; Janssen, P. A. J. *Arch. Int. Pharmacodyn.* **1973**, *204*, 37.
(16) Niemegeers, C. J. E.; Awouters, F.; Van Nueten, J. M.; De Nollin, S.; Janssen, P. A. J. *Arch. Int. Pharmacodyn. Therap.* **1978**, *234*, 164.
(17) Awouters, F.; Niemegeers, C. J. E.; Janssen, P. A. J. *Drug. Dev. Res.* **1981**, *1*, 107.
(18) Awouters, F.; Niemegeers, C. J. E.; Janssen, P. A. J. *Drug. Dev. Res.* **1982**, *2*, 559.
(19) Van Wauwe, J.; Awouters, F.; Niemegeers, C. J. E.; Janssens, F.; Van Nueten, J. M.; Janssen, P. A. J. *Arch. Int. Pharmacodyn. Ther.* **1981**, *251*, 39.

**Table I**



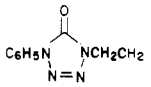
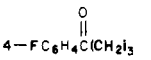
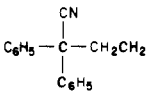
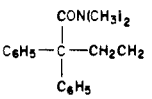
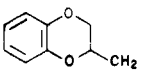
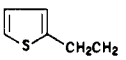
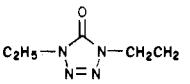
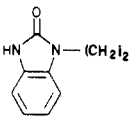
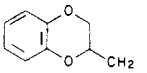
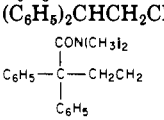
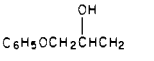
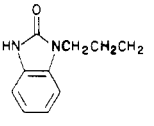
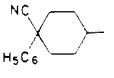
| compd | L | $R_2$ | formula | mp, °C | yield,[a] % | cryst solv[b] | anal. | in vitro antihistamine act.: $A_{10}$, mg/L |
|---|---|---|---|---|---|---|---|---|
| 18 | $CH_3$ | $CH_3$ | $C_{14}H_{20}N_4 \cdot 2HCl \cdot 2H_2O$ | 300.6 | 62 | A | C, H, N, Cl | >0.04[c] |
| 19 | $C_6H_5CH_2CH_2$ | $CH_3$ | $C_{21}H_{26}N_4 \cdot 2HCl \cdot 0.5H_2O$ | 298.3 | 49 | D | C, H, N, Cl | 0.005 |
| 20 |  | $CH_3$ | $C_{22}H_{26}N_8O \cdot 2HCl \cdot 0.5H_2O$ | 279.7 | 40 | D | C, H, N, Cl | 0.02 |
| 21 | $(4\text{-}FC_6H_4)_2CH(CH_2)_3$ | $CH_3$ | $C_{29}H_{32}F_2N_4 \cdot 2HCl \cdot H_2O$ | 271.7 | 47.8 | D | C, H, N, Cl | >0.04 |
| 22 | $i\text{-}C_3H_7$ | $C_2H_5$ | $C_{17}H_{26}N_4$ | 156.6 | 35 | C–E | C, H, N | >0.04 |
| 23 | $CH_2{=}CHCH_2$ | $C_2H_5$ | $C_{17}H_{24}N_4 \cdot 2HNO_3 \cdot 0.5H_2O$ | 258.1 | 24 | D | C, H, N | 0.04 |
| 24 |  | $C_2H_5$ | $C_{24}H_{29}FN_4O \cdot 2HCl$ | 293.1 | 21 | D | C, H, N, Cl | 0.01 |
| 25 |  | $C_2H_5$ | $C_{30}H_{33}N_5 \cdot 2HNO_3 \cdot 0.5H_2O$ | 240.5 | 42 | D | C, H, N | >0.04 |
| 26 | $C_6H_5CH{=}CHCH_2$ | $C_2H_5$ | $C_{23}H_{28}N_4 \cdot 2HNO_3 \cdot 2H_2O$ | 136.0 | 30 | D | C, H, N | >0.04 |
| 27 | $C_6H_5CH_2CH_2$ | $C_2H_5$ | $C_{22}H_{28}N_4$ | 192.8 | 37.5 | C | C, H, N | 0.0063 |
| 28 |  | $C_2H_5$ | $C_{32}H_{39}N_5O$ | 199.4 | 26 | C–E | C, H, N | >0.04 |
| 29 |  | $C_2H_5$ | $C_{23}H_{28}N_4O_2 \cdot 2HNO_3 \cdot H_2O$ | 266.5 | 48 | D | C, H, N | ≥0.04 |
| 30 | $(4\text{-}FC_6H_4)_2CH(CH_2)_3$ | $C_2H_5$ | $C_{30}H_{34}F_2N_4 \cdot 2HCl \cdot 2H_2O$ | 208.6 | 53.5 | D | C, H, N, F | 0.025 |
| 31 | $CH_3$ | $C_6H_5CH_2$ | $C_{20}H_{24}N_4 \cdot 2HCl \cdot H_2O$ | 191.1 | 36.6 | A | C, H, N, Cl | 0.0025 |
| 32 | $n\text{-}C_4H_9$ | $C_6H_5CH_2$ | $C_{23}H_{30}N_4 \cdot 2HCl \cdot H_2O$ | 273.3 | 68.9 | D | C, H, N | 0.0063 |
| 33 | $CH_2{=}CHCH_2$ | $C_6H_5CH_2$ | $C_{22}H_{26}N_4 \cdot 2HCl \cdot H_2O$ | 261.9 | 59 | D | C, H, N, Cl | 0.0063 |
| 34 |  | $C_6H_5CH_2$ | $C_{25}H_{32}N_4$ | 143.0 | 38.5 | A–E | C, H, N | 0.01 |
| 35 | $C_6H_5CH_2$ | $C_6H_5CH_2$ | $C_{26}H_{28}N_4 \cdot 2HNO_3 \cdot 2H_2O$ | 147.2 | 64 | D | C, H, N | 0.01 |
| 36 | $4\text{-}FC_6H_4CH_2$ | $C_6H_5CH_2$ | $C_{26}H_{27}FN_4$ | 152.2 | 16 | A–E | C, H, N, F | 0.01 |
| 37 | $(C_6H_5)_2CH$ | $C_6H_5CH_2$ | $C_{32}H_{32}N_4$ | 203.7 | 21 | E | C, H, N | 0.04 |
| 38 | $C_6H_5CH(CH_3)$ | $C_6H_5CH_2$ | $C_{27}H_{30}N_4$ | 154.0 | 32.5 | A–E | N | 0.0063 |
| 39 |  | $C_6H_5CH_2$ | $C_{25}H_{28}N_4S \cdot 2HCl \cdot H_2O$ | 202 | 28.5 | A | C, H, N, Cl | 0.0063 |
| 40 |  | $C_6H_5CH_2$ | $C_{24}H_{30}N_8O \cdot 2HCl \cdot H_2O$ | 170.9 | 28 | A | C, H, N | 0.025 |
| 41 |  | $C_6H_5CH_2$ | $C_{28}H_{30}N_6O$ | 237.5 | 61.5 | F | C, H, N | 0.025 |
| 42 |  | $C_6H_5CH_2$ | $C_{28}H_{30}N_4O_2$ | 210.2 | 22 | A | C, H, N | 0.01 |
| 43 | $C_6H_5OCH_2CH_2$ | $C_6H_5CH_2$ | $C_{27}H_{30}N_4O \cdot 2HCl \cdot H_2O$ | 197.6 | 70 | D | C, H, N, Cl | 0.01 |
| 44 | $C_6H_5CH_2CH_2CH_2$ | $C_6H_5CH_2$ | $C_{28}H_{32}N_4 \cdot 2HCl \cdot H_2O$ | 197.1 | 60 | D | C, H, N, Cl | 0.01 |
| 45 | $C_6H_5CH{=}CHCH_2$ | $C_6H_5CH_2$ | $C_{28}H_{30}N_4 \cdot 2HCl \cdot H_2O$ | 192.4 | 40 | D | C, H, N, Cl | 0.025 |
| 46 | $(C_6H_5)_2CHCH_2CH_2$ | $C_6H_5CH_2$ | $C_{34}H_{36}N_4$ | 173.8 | 50 | D | C, H, N | 0.04 |
| 47 |  | $C_6H_5CH_2$ | $C_{37}H_{41}N_5O \cdot 0.5H_2O$ | 223.2 | 60 | A | C, H, N | 0.04 |
| 48 | $C_6H_5OCH_2CH_2CH_2$ | $C_6H_5CH_2$ | $C_{28}H_{32}N_4O \cdot 2HCl \cdot 0.5H_2O$ | 208.8 | 44.8 | D | C, H, N, Cl | 0.01 |
| 49 |  | $C_6H_5CH_2$ | $C_{28}H_{32}N_4O_2$ | 146.6 | 44 | A–E | C, H, N | 0.03 |
| 50 |  | $C_6H_5CH_2$ | $C_{29}H_{32}N_6O$ | 243.1 | 45.7 | B | C, H, N | >0.01 |
| 51 |  | $C_6H_5CH_2$ | $C_{32}H_{35}N_5$ | 106.7 | 35.7 | | C, H, N | 0.025 |

Table I (Continued)

| compd | L | $R_2$ | formula | mp, °C | yield,[a] % | cryst solv[b] | anal. | in vitro antihistamine act.: $A_{10}$, mg/L |
|---|---|---|---|---|---|---|---|---|
| 52 | 4-FC$_6$H$_4$C(=O)(CH$_2$)$_3$ | C$_6$H$_5$CH$_2$ | C$_{29}$H$_{31}$FN$_4$O·2HCl·0.5H$_2$O | 269.1 | 18.5 | D | C, H, N, Cl | 0.025 |
| 53 | (4-FC$_6$H$_4$)$_2$CH(CH$_2$)$_3$ | C$_6$H$_5$CH$_2$ | C$_{35}$H$_{36}$F$_2$N$_4$·2HNO$_3$·H$_2$O | 230.9 | 15.4 | D | C, H, N, F | >0.04 |

[a] Based on immediate precursor, after recrystallization. Generally no attempts made to optimize yields. [b] Key: A, 2-propanol; B, ethanol; C, 4-methyl-2-pentanone; D, acetone; E, diisopropyl ether; F, methanol. [c] The symbol > (greater than) indicates that the compound is inactive at the highest dose tested.

atom of the 2-aminobenzimidazole system, as illustrated by **75**, **76**, **79–81**, and **83**. Isosteric replacements in distinct areas of the active structure are also allowed as shown by **39** and **74**. Substitution of the *N*-phenylethyl moiety for a lower alkyl or alkenyl group results in no loss of activity (**30**, **32**, **33**, **91**).

However, compound **95** represents an exception in this active series, since it has the benzyl substituent on the *exo*-nitrogen instead of on the *endo*-nitrogen of the benzimidazole nucleus.

With respect to in vivo antihistaminic activity in the rat after subcutaneous administration, **74** is the most potent compound (Table III) in the compound 48/80 lethality test. Fairly high potency is also found with **31**, **32**, **40**, **41**, and **67**. All these compounds have an arylmethyl substituent on the *endo*-nitrogen atom of the 2-aminobenzimidazole moiety ($R_2$ = $ArCH_2$) and a monosubstituted *exo*-nitrogen ($R_1$ = H). Disubstitution on the *exo*-nitrogen strongly reduces the activity as is illustrated for **77** in comparison with **64**.

Three main clusters can be distinguished for optimal substitution on the piperidine nitrogen: (1) alkyl-substituted compounds (**31–34**); (2) a second group where the aromatic nucleus is linked to the piperidine nitrogen atom, either via an ethylene bridge as in **39–41** or via an aliphatic ether bridge as in **48**; (3) the most important subclass consisting of phenylethyl analogues as illustrated by **67**, **74**, **101**, **102**, and **105**. The better oral activity distinguishes this group from the former two.

Maximum oral activity in the rat is found when the following structural conditions are fulfilled: (1) a phenylethyl group substituted on the piperidine nitrogen; (2) a monosubstituted *exo*-nitrogen ($R_1$ = H) in the 2-aminobenzimidazole moiety; (3) a benzyl or isosteric 2-pyridylmethyl group as a substituent on the *endo*-nitrogen of the 2-aminobenzimidazole moiety.

Electron-donating substituents on the benzene ring of the phenylethyl group such as 3-methyl (**99**) and particularly 3-methoxy (**102**), 4-methoxy (**98**), and 4-ethoxy (**103**) significantly enhanced oral activity. Comparison of **98**, **101**, and **102** shows that meta and para substitution are most advantageous, and from the series **98**, **104**, and **105** it is concluded that one methoxy group is optimal.

Branching of the benzyl group (**72**) is not compatible with oral activity. Although no clear-cut relationship is found between (oral) activity and substitution of the benzyl group, the introduction of a fluoro atom particularly in the 4-position clearly promotes oral activity (**64**, **65**, **67**).

The 3-h results after oral administration show **74** to be the most active compound in the guinea pig model. The relative potencies are less differentiated in the guinea pig than in the rat (oral administration) as illustrated by **64**, **67**, **74**, and **98**. However, the 24–48-h results are more relevant as to duration of action and total potency.

On the basis of the 24-h results, at least seven out of eight compounds are more potent than azatadine, and 48 h after oral administration **64**, **67**, and **98** are at least 10 times as potent as azatadine.

After 24 and 48 h, respectively, **67** and **98** are 4.5 and 1.5–2 times, respectively, more potent than **64**. Again, it can be concluded that introduction of a methoxy substituent on the phenylethyl fragment or a fluoro substituent on the benzyl group results in an enhanced duration of activity.

Applications of the structure–activity relationship, deduced from the above data, to the development of further novel, orally active, specific $H_1$ antagonists are described in the following paper.

## Experimental Section

Melting points are determined with a Mettler $FP_1$ melting point apparatus and are uncorrected. Elemental analyses were performed by the analytical department of Janssen Pharmaceutica Laboratories. Mass spectra were measured with a Varian Mat 311-eV emission spectrometer. NMR spectra were measured with either a Brucker HX 60-12 or a Brucker WP 80-DS instrument (internal standard $Me_4Si$). UV and IR spectra were determined with a Beckman DK-2A and a Perkin–Elmer 421 or 225 spectrometer. Where indicated, GC was measured with a Varian 2100 gas chromatograph (column 2 m, 3% OV 17). Analytical TLC was performed on silica 60 $F_{254}$ (Merck), and the spots were made visible by a UV lamp or iodine vapor.

**Ethyl 4-Isothiocyanato-1-piperidinecarboxylate** (1). To a cooled solution (<10 °C) of sodium hydroxide (4 g, 0.1 mol) in water (60 mL) were added carbon disulfide (7.9 g, 0.1 mol) and ethyl 4-amino-1-piperidinecarboxylate (17.2 g, 0.1 mol). After the mixture was stirred for 30 min below 10 °C, ethyl chloroformate (10.9 g, 0.1 mol) was added dropwise to the reaction mixture while the temperature rose to 35 °C. The mixture was kept at 60 °C for 2 h, cooled, and extracted twice with toluene. The extract was dried ($MgSO_4$) and filtered. The filtrate was evaporated in vacuo, and the residual oil (GC 90%) was used without purification (yield 91%). This oil could be purified by distillation: bp (0.1 mm) 115 °C. Anal. ($C_9H_{14}N_2O_2S$) S: calcd, 14.96; found, 13.10.

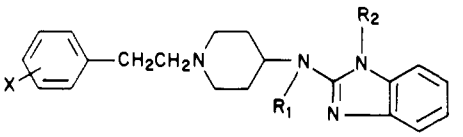
**Ethyl 4-[[[(2-Aminophenyl)amino]thioxomethyl]amino]-1-piperidinecarboxylate** (2). A mixture of *o*-phenylenediamine (10.8 g, 0.1 mol) and of 1 (21.4 g, 0.1 mol) in ethanol (300 mL) was stirred overnight at room temperature. The solvent was evaporated in vacuo, giving 2 in almost quantiative yield. An analytical sample was obtained by crystallization from 2-propanol; mp 239 °C. Anal. ($C_{15}H_{22}N_4O_2S$) C, H, N.

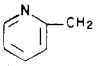
**Ethyl 4-[(1*H*-Benzimidazol-2-yl)amino]-1-piperidinecarboxylate** (3). **Cyclodesulfurization Method A.** A solution of 2 (25.7 g, 0.08 mol) and iodomethane (112 g, 0.8 mol) in ethanol (300 mL) was stirred and refluxed for 8 h. The solvent was evaporated, the residual solid was basified with $NH_4OH$, and the product was extracted with dichloromethane. The combined organic extracts were dried, filtered, and evaporated. The residue was crystallized from a mixture of 2-propanol and diisopropyl ether to yield 3: 7 g (28%); mp 240.6 °C. Anal. ($C_{15}H_{20}N_4O_2$) C, H, N.

**Cyclodesulfurization Method B.** A suspension of 2 (16.1 g, 0.05 mol), yellow HgO (21.6 g, 0.1 mol), and 0.3 g of sulfur powder in ethanol (300 mL) was stirred and refluxed for 2 h. The reaction mixture was filtered over Decalite and the filtrate evaporated. Crystallization of the residue from 4-methyl-2-pentanone yielded 3, 8 g (55.5%).

**Ethyl 4-[(1-Methyl-1*H*-benzimidazol-2-yl)amino]-1-**

**Table II**



| compd | X | $R_1$ | $R_2$ | formula | mp, °C | yield,[a] % | cryst solv[b] | anal. | in vitro antihistamine act.: $A_{10}$, mg/L |
|---|---|---|---|---|---|---|---|---|---|
| **54** | H | H | H | $C_{20}H_{24}N_4$ | 192.1 | 54.6 | C | C, H, N | 0.01 |
| **55** | H | H | *n*-$C_3H_7$ | $C_{23}H_{30}N_4 \cdot 2HCl \cdot 0.5H_2O$ | 278.8 | 24 | D | C, H, N, Cl | 0.02 |
| **56** | H | H | *i*-$C_3H_7$ | $C_{23}H_{30}N_4 \cdot 2HCl$ | 295.8 | 18.5 | A | C, H, N, Cl | >0.04[c] |
| **57** | H | H | *n*-$C_4H_9$ | $C_{24}H_{32}N_4 \cdot 2HCl \cdot 0.5H_2O$ | 274.4 | 37 | D | C, H, N, Cl | 0.0051 |
| **58** | H | H | *n*-$C_5H_{11}$ | $C_{25}H_{34}N_4 \cdot 2HCl \cdot H_2O$ | 243.5 | 21.5 | D | C, H, N, Cl | 0.011 |
| **59** | H | H | *n*-$C_6H_{13}$ | $C_{26}H_{36}N_4 \cdot 2HCl \cdot H_2O$ | 224.2 | 38.7 | D | C, H, N, Cl | 0.025 |
| **60** | H | H | *n*-$C_7H_{15}$ | $C_{27}H_{38}N_4 \cdot 2HCl \cdot H_2O$ | 212.8 | 59.5 | D | C, H, N, Cl | >0.04 |
| **61** | H | H |  | $C_{25}H_{32}N_4 \cdot 2HCl \cdot 0.5H_2O$ | 285.6 | 34 | C | C, H, N, Cl | >0.04 |
| **62** | H | H | $C_6H_5CH_2CH_2$ | $C_{28}H_{32}N_4$ | 136.1 | 28.5 | A–E | C, H, N | 0.0075 |
| **63** | H | H | $C_6H_5CH(CH_3)CH_2$ | $C_{29}H_{34}N_4$ | 144.5 | 23.2 | D–E | C, H, N | >0.04 |
| **64** | H | H | $C_6H_5CH_2$ | $C_{27}H_{30}N_4$ | 141.9 | 24 | C–E | C, H, N | 0.003 |
| **65** | H | H | 2-$FC_6H_4CH_2$ | $C_{27}H_{29}FN_4$ | 138.6 | 40.5 | D | N | 0.0063 |
| **66** | H | H | 2-$ClC_6H_4CH_2$ | $C_{27}H_{29}ClN_4 \cdot 2HCl \cdot 0.5H_2O$ | 244.4 | 64.3 | D | C, H, N, Cl | 0.01 |
| **67** | H | H | 4-$FC_6H_4CH_2$ | $C_{27}H_{29}FN_4 \cdot 2HCl$ | 271.5 | 70 | A | C, H, N, Cl | 0.0063 |
| **68** | H | H | 4-$ClC_6H_4CH_2$ | $C_{27}H_{29}ClN_4 \cdot 2HCl \cdot 0.5H_2O$ | 277.1 | 67.8 | D | C, H, N, Cl | 0.01 |
| **69** | H | H | 4-$BrC_6H_4CH_2$ | $C_{27}H_{29}BrN_4 \cdot 2HCl \cdot H_2O$ | 251.5 | 87 | A | C, H, N, Br, Cl | 0.025 |
| **70** | H | H | 4-$CH_3C_6H_4CH_2$ | $C_{28}H_{32}N_4 \cdot 2HCl \cdot H_2O$ | 191.4 | 55 | A | C, H, N | 0.020 |
| **71** | H | H | $C_6H_5CH(CH_3)$ | $C_{28}H_{32}N_4 \cdot 2HCl \cdot H_2O$ | 239.9 | 38.8 | D | C, H, N, Cl | 0.025 |
| **72** | H | H | 4-$FC_6H_4CH(CH_3)$ | $C_{28}H_{31}FN_4$ | 161.7 | 40.7 | E | C, H, N, F | >0.01 |
| **73** | H | H | $(4\text{-}FC_6H_4)_2CH$ | $C_{33}H_{32}F_2N_4$ | 172.5 | 19 | D–E | C, H, N, F | >0.04 |
| **74** | H | H |  | $C_{26}H_{29}N_5$ | 127.6 | 24.3 | D–E | C, H, N | 0.0063 |
| **75** | H | $CH_3$ | $C_2H_5$ | $C_{23}H_{30}N_4 \cdot 2HCl \cdot H_2O$ | 243.1 | 78 | D | C, H, N, Cl | 0.0025 |
| **76** | H | $CH_3$ | *n*-$C_4H_9$ | $C_{25}H_{34}N_4 \cdot 2HCl$ | 257.9 | 60.5 | A | N, Cl | 0.0063 |
| **77** | H | $CH_3$ | $C_6H_5CH_2$ | $C_{28}H_{32}N_4 \cdot 2HCl$ | 243.1 | 34 | A | C, H, N, Cl | 0.005 |
| **78** | H | $CH_3$ | 2-$ClC_6H_4CH_2$ | $C_{28}H_{31}ClN_4 \cdot 2HCl$ | 251.2 | 18.5 | D | C, H, N, Cl | 0.01 |
| **79** | H | $CH_3$ | 2-$CH_3OC_6H_4CH_2$ | $C_{29}H_{34}N_4O \cdot 2HNO_3$ | 169.7 | 43 | D | C, H, N | 0.0063 |
| **80** | H | $CH_3$ | 4-$FC_6H_4CH_2$ | $C_{28}H_{31}FN_4 \cdot 2HCl$ | 246.6 | 54.4 | A | C, H, N, Cl | 0.0063 |
| **81** | H | $CH_3$ | 4-$ClC_6H_4CH_2$ | $C_{28}H_{31}ClN_4 \cdot 2HCl$ | 251.3 | 34 | | C, H, N, Cl | 0.0063 |
| **82** | H | $CH_3$ | 4-$BrC_6H_4CH_2$ | $C_{28}H_{31}BrN_4 \cdot 2HCl \cdot H_2O$ | 187.1 | 43 | D | C, H, N, Br, Cl | 0.04 |
| **83** | H | $CH_3$ | 4-$CH_3C_6H_4CH_2$ | $C_{29}H_{34}N_4 \cdot 2HNO_3$ | 175.3 | 85 | D | C, H, N | 0.0063 |
| **84** | H | $CH_3$ | 4-$CH_3OC_6H_4CH_2$ | $C_{29}H_{34}N_4O \cdot 2HNO_3$ | 163.5 | 69 | D | C, H, N | 0.01 |
| **85** | H | $C_2H_5$ | H | $C_{22}H_{28}N_4$ | 204.9 | 43 | C | C, H, N | 0.029 |
| **86** | H | $C_2H_5$ | $C_6H_5CH_2$ | $C_{29}H_{34}N_4$ | 115.8 | 27.4 | E | C, H, N | 0.017 |
| **87** | H | *n*-$C_3H_7$ | $C_6H_5CH_2$ | $C_{30}H_{36}N_4 \cdot 2HCl \cdot H_2O$ | 159.4 | 46 | D | C, H, N | >0.01 |
| **88** | H | *i*-$C_3H_7$ | $C_2H_5$ | $C_{25}H_{34}N_4 \cdot 2HCl \cdot 0.5H_2O$ | 206.8 | 54.5 | D | C, H, N, Cl | >0.01 |
| **89** | H | *i*-$C_3H_7$ | $C_6H_5CH_2$ | $C_{30}H_{36}N_4 \cdot C_2H_2O_4$ | 215.6 | 26.7 | D | C, H, N | >0.01 |
| **90** | H |  | H | $C_{23}H_{28}N_4$ | 193.5 | 18 | C | C, H, N | >0.04 |
| **91** | H | $C_6H_5CH_2$ | $C_2H_5$ | $C_{29}H_{34}N_4 \cdot 2HCl \cdot 2H_2O$ | 157.2 | 49 | D | C, H, N, Cl | 0.016 |
| **92** | H | $C_6H_5CH_2$ | $C_6H_5CH_2$ | $C_{34}H_{36}N_4 \cdot 2HNO_3$ | 156.9 | 24 | D | C, H, N | >0.04 |
| **93** | H | $CH_3$ | H | $C_{21}H_{26}N_4 \cdot 2HCl$ | 299.6 | 52 | A | C, H, N, Cl | 0.02 |
| **94** | H | *n*-$C_4H_9$ | H | $C_{24}H_{32}N_4$ | 184.4 | 46.5 | A–E | C, H, N | 0.03 |
| **95** | H | $C_6H_5CH_2$ | H | $C_{27}H_{30}N_4$ | 191.5 | 50 | F | C, H, N | 0.0076 |
| **96** | 4-F | H | $C_6H_5CH_2$ | $C_{27}H_{29}FN_4$ | 112.5 | 38.9 | E | N, F | 0.01 |
| **97** | 4-Cl | H | $C_6H_5CH_2$ | $C_{27}H_{29}ClN_4$ | 183.9 | 33 | A | C, H, Cl | 0.025 |
| **98** | 4-$CH_3O$ | H | $C_6H_5CH_2$ | $C_{28}H_{32}N_4O \cdot 2HCl \cdot H_2O$ | 274.7 | 29 | D | C, H, N, Cl | >0.01 |
| **99** | 3-$CH_3$ | H | $C_6H_5CH_2$ | $C_{28}H_{32}N_4 \cdot 2HCl \cdot H_2O$ | 235.7 | 30 | D | C, H, N, Cl | >0.01 |
| **100** | 3-$CF_3$ | H | $C_6H_5CH_2$ | $C_{28}H_{29}F_3N_4$ | 140.3 | 15.3 | E | C, H | >0.04 |
| **101** | 2-$CH_3O$ | H | $C_6H_5CH_2$ | $C_{28}H_{32}N_4O \cdot 2HCl \cdot 2H_2O$ | 186.1 | 18.2 | D | C, H, N, Cl | 0.01 |
| **102** | 3-$CH_3O$ | H | $C_6H_5CH_2$ | $C_{28}H_{32}N_4O$ | 128.6 | 22.7 | D–E | C, H, N | 0.0063 |
| **103** | 4-$C_2H_5O$ | H | $C_6H_5CH_2$ | $C_{29}H_{34}N_4O$ | 128.5 | 22.2 | D–E | C, H, N | 0.0063 |
| **104** | 3,4-$(CH_3O)_2$ | H | $C_6H_5CH_2$ | $C_{29}H_{34}N_4O_2$ | 149.8 | 21 | D–E | C, H, N | >0.01 |
| **105** | 3,4,5-$(CH_3O)_3$ | H | $C_6H_5CH_2$ | $C_{30}H_{36}N_4O_3$ | 156.6 | 20 | D–E | C, H, N | >0.01 |
| oxatomide | | | | | | | | | 0.014 |
| diphenydramine | | | | | | | | | 0.66 |

[a] Based on immediate precursor, after recrystallization. Generally no attempts made to optimize yields. [b] Key: A, 2-propanol; B, ethanol; C, 4-methyl-2-pentanone; D, acetone; E, diisopropyl ether; F, methanol. [c] The symbol > (greater than) indicates that the compound is inactive at the highest dose tested.

**piperidinecarboxylate (4; $R_2$ = $CH_3$).** A solution of 3 (22 g, 0.08 mol), iodomethane (11.4 g, 0.08 mol), and sodium carbonate (8.5 g, 0.08 mol) in dimethylformamide (500 mL) was stirred overnight at 70 °C. After cooling, the reaction mixture was poured into water and extracted three times with toluene. The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was purified on silica ($CHCl_3$–$CH_3OH$, 96:4 (v/v)) and the pure product crystallized from 4-methyl-2-pentanone to yield 4 ($R_2$ =

**Table III.** Protection from Compound 48/80 Induced Lethality in Rats after Subcutaneous (1 h) and Oral (2 h) Administration

| compd | $ED_{50}$, mg/kg sc | oral |
|---|---|---|
| **18** | >2.5 | – |
| **27** | 2.5 | – |
| **31** | 0.31 | >2.5 |
| **32** | 0.31 | >2.5 |
| **33** | 0.63 | 0.63 |
| **34** | 0.63 | >2.5 |
| **36** | 2.5 | – |
| **38** | 1.25 | >2.5 |
| **39** | 0.63 | – |
| **40** | 0.31 | >2.5 |
| **41** | 0.31 | 2.5 |
| **42** | 2.5 | – |
| **44** | 2.5 | – |
| **45** | 1.25 | >2.5 |
| **48** | 0.63 | 0.63 |
| **49** | 1.25 | 0.63 |
| **50** | 1.25 | 2.5 |
| **51** | 2.5 | – |
| **52** | 2.5 | – |
| **57** | 2.5 | – |
| **58** | 2.5 | – |
| **62** | >2.5 | – |
| **63** | 2.5 | – |
| **64** | 0.63 | 3.5 |
| **65** | 1.25 | 2.5 |
| **67** | 0.31 | 0.63 |
| **68** | 2.5 | – |
| **69** | 1.25 | – |
| **70** | 1.25 | 2.5 |
| **71** | 2.5 | – |
| **72** | 1.25 | >2.5 |
| **74** | 0.16 | 2.5 |
| **75** | 0.63 | >2.5 |
| **76** | 2.5 | – |
| **77** | 2.5 | – |
| **80** | 1.25 | 1.25 |
| **82** | 2.5 | – |
| **83** | 2.5 | – |
| **91** | >2.5 | – |
| **94** | 2.5 | – |
| **96** | 1.25 | >2.5 |
| **97** | 2.5 | – |
| **98** | 1.25 | 0.63 |
| **99** | 1.25 | 2.5 |
| **100** | 2.5 | – |
| **101** | 0.63 | 1.25 |
| **102** | 0.63 | 0.31 |
| **103** | 1.25 | 0.63 |
| **104** | 1.25 | >2.5 |
| **105** | 0.63 | 1.25 |
| oxatomide | – | 5.37 (4.34–6.65)[b] |
| azatadine | 0.049 (0.036–0.066)[b] | 0.48 (0.32–0.70)[b] |
| chlorpheniramine | 0.770 (0.480–1.25)[b] | 37.4 (25.0–56.0)[b] |
| diphenhydramine | 4.090 (2.73–6.12)[b] | 37.4 (21.8–48.8)[b] |

[a] The estimated $ED_{50}$ values are used whenever possible so that a comparison of the relative potencies of the compounds can be made. For inactive compounds the highest dose tested is preceded by the symbol > (greater than). Compounds that are not tested are designated with the symbol –. [b] Confidence limits.

$CH_3$), 16 g (66%). Anal. ($C_{16}H_{22}N_4O_2$) C, H, N.

**1-Methyl-*N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine Dihydrobromide** (5; $R_2 = CH_3$). A solution of 4 ($R_2 = CH_3$) (25 g, 0.083 mol) in 48% hydrobromic acid solution (700 mL) was stirred and refluxed for 3 h. The solvent was evaporated in vacuo, and the solid residue was suspended in ethanol (300 mL), filtered off and air-dried to yield 5 ($R_2 = CH_3$), (29 g (89%). Anal. ($C_{13}H_{18}N_4 \cdot 2HBr$) Br: calcd. 40.86; found, 39.96.

**Ethyl 4-(Methylamino)-1-piperidinecarboxylate** (6; $R_1 = CH_3$). A mixture of ethyl 4-oxo-1-piperidinecarboxylate (17.1 g, 0.1 mol) and methylamine (14.5 g, 0.5 mol) in methanol (300 mL) was hydrogenated at normal pressure and room temperature over Pd/C 10% (5 g). After uptake of 1 equiv of hydrogen, the catalyst was filtered off and the filtrate was evaporated to yield 6 ($R_1 = CH_3$): 17 g (91.4%) as an oil. The oil 6 thus obtained was shown by GC and NMR to be of about 97% purity.

**Table IV.** Protection against Intravenous Histamine Lethality in Guinea Pigs after Oral Administration

| compd | estd $PD_{50}$ values, mg/kg 3 h[a] | 24 h | 48 h |
|---|---|---|---|
| **41** | 0.35 | >0.6 | –[c] |
| **44** | 0.35 | 0.35 | >0.6 |
| **49** | 0.35 | 0.6 | >0.6 |
| **50** | 0.16 | 0.6 | >0.6 |
| **64** | 0.25 | 0.35 | 0.25 |
| **67** | 0.45 | 0.08 | 0.12 |
| **74** | 0.12 | 0.12 | >0.16 |
| **98** | 0.25 | 0.08 | 0.16 |
| oxatomide | 0.18 (0.10–0.31)[b] | >5 | – |
| azatadine | 0.014 (0.011–0.018)[b] | 1.36 (1.04–1.78)[b] | >2.5 |
| diphenhydramine | >2.5 | – | – |

[a] Hours after administration. [b] Confidence limits. [c] –, not tested.

**Ethyl 4-[Methyl[[(2-nitrophenyl)amino]thioxomethyl]amino]-1-piperidinecarboxylate** (8; $R_1 = CH_3$). A solution of 6 ($R_1 = CH_3$) (18 g, 0.1 mol) and 1-isothicyanato-2-nitrobenzene (7; 18 g, 0.1 mol)[20] in ethanol (300 mL) was stirred overnight at room temperature. The precipitate was collected and recrystallized from 2-propanol to yield 8 ($R_1 = CH_3$): 26 g (71%); mp 144.8 °C. Anal. ($C_{16}H_{12}N_4O_4S$) C, H, N, S.

**Ethyl 4-[Methyl[[(2-aminophenyl)amino]thioxomethyl]amino]-1-piperidinecarboxylate** (9; $R_1 = CH_3$). A solution of 8 ($R_1 = CH_3$) (13 g, 0.035 mol) in methanol (250 mL) saturated with ammonia was hydrogenated at normal pressure and room temperature over Pd/C 10% (10 g). After uptake of 3 equiv of hydrogen, the catalyst was filtered off and the filtrate was evaporated to afford 9 ($R_1 = CH_3$): 11.2 g (95%); TLC purity 99%.

**Ethyl 4-[(1*H*-Benzimidazol-2-yl)methylamino]-1-piperidinecarboxylate** (10; $R_1 = CH_3$). The cyclodesulfurization of 9 ($R_1 = CH_3$) in methanol by method B afforded 10: 84%; mp 253.0 °C. Anal. ($C_{16}H_{22}N_4O_2$) C, H, N.

***N*-Methyl-*N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine Dihydrobromide Monohydrate** (11; $R_1 = CH_3$). Decarboxylation of 10 ($R_1 = CH_3$) (4.5 g, 0.015 mol) with 48% aqueous hydrobromic acid solution (50 mL) as mentioned before yielded 11 ($R_1 = CH_3$): 5.8 g (95%); mp 260 °C. Anal. ($C_{13}H_{18}N_4 \cdot 2HBr \cdot H_2O$) Br: calcd, 38.96; found, 38.02.

***N*-Methyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-1*H*-benzimidazol-2-amine Dihydrochloride** (12; X = H, $R_1 = CH_3$). A suspension of 11 ($R_1 = CH_3$) (4 g, 0.01 mol), phenylethyl bromide (1.9 g, 0.01 mol), and sodium carbonate (3.2 g, 0.03 mol) in dimethylformamide (150 mL) was stirred overnight at 70 °C. After cooling, the reaction mixture was poured into water and extracted three times with toluene. The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The solid residue was crystallized from 2-propanol acidified with HCl to yield 12 (X = H, $R_1 = CH_3$): 2.1 g (53%); mp 299.6 °C. Anal. ($C_{21}H_{26}N_4 \cdot 2HCl$) C, H, N, Cl.

***N*-(1-Methylethyl)-1-(2-phenylethyl)-4-piperidinamine** (13; X = H, $R_1 = i\text{-}C_3H_7$). (i) A suspension of phenylethyl bromide (97 g, 0.525 mol), 1,4-dioxa-8-azaspiro[4.5]decane (71.6 g, 0.5 mol),[14] sodium carbonate (140 g, 1.3 mol), and potassium iodide (0.1 g) in 4-methyl-2-pentanone (2000 mL) was stirred and refluxed for 18 h. The mixture was filtered while warm, the filtrate was evaporated in vacuo, and the residual oil was dissolved in diisopropyl ether. The hydrogen chloride salt was formed and the solid filtered off and dried in vacuo to give 16 (X = H), 140 g (87.5%). Crystallization from a methanol/diethyl ether mixture afforded an analytical sample, mp 208 °C. Anal. ($C_{15}H_{21}NO_2 \cdot HCl$) C, H, N, Cl.

(ii) A solution of 16 (X = H; 140 g, 0.57 mol) in 2 N HCl in acetic acid (750 mL) was stirred and refluxed overnight. The cooled reaction mixture was basified with dilute sodium hydroxide and extracted twice with toluene. The combined organic layers

(20) Harter, M. P.; Strauss, U.; Schindler, O. *Helv. Chim. Acta* 1971, *54*, 2114.

were dried ($MgSO_4$) and evaporated, and the residue was triturated with petroleum ether yeilding 17 (X = H): 106.4 g (92%); mp 60 °C. The solid 17 thus obtained was shown by GC and TLC to be of 99% purity.

(iii) A mixture of 17 (X = H; 25 g, 0.12 mol) and isopropylamine (25 g, 0.42 mol) in methanol (400 mL) was hydrogenated over Pd/C 10% (2 g) at normal pressure and room temperature. After the usual workup 13 (X = H, $R_1$ = $i$-$C_3H_7$) was obtained: 28 g (95%); GC purity 99.7%.

***N*-(1-Methylethyl)-*N'*-(2-nitrophenyl)-*N*-[1-(2-phenylethyl)-4-piperidinyl]thiourea (14; X = H, $R_1$ = $i$-$C_3H_7$).** A solution of 7 (21.6 g, 0.12 mol) and 13 (X = H, $R_1$ = $i$-$C_3H_7$) (28.5 g, 0.12 mol) in tetrahydrofuran (200 mL) and ethanol (50 mL) was stirred overnight at room temperature. The residue obtained after evaporation of the solvent was crystallized from 2-propanol to afford 14 (X = H, $R_1$ = $i$-$C_3H_7$): 34 g (84%); mp 100.6 °C. Anal. ($C_{23}H_{30}N_4O_2S$) C, H, N.

***N'*-(2-Aminophenyl)-*N*-(1-methylethyl)-*N*-[1-(2-phenylethyl)-4-piperidinyl]thiourea (15; X = H, $R_1$ = $i$-$C_3H_7$) and *N*-(1-Methylethyl)-*N*-[1-(2-phenylethyl)-4-piperidinyl]-1*H*-benzimidazol-2-amine (12; X = H, $R_1$ = $i$-$C_3H_7$).** (i) Hydrogenation of 14 (X = H, $R_1$ = $i$-$C_3H_7$) (43 g, 0.1 mol) as described for 9 with Pd/C 5% in methanol saturated with ammonia quantitatively afforded 15 (X = H, $R_1$ = $i$-$C_3H_7$): 39 g (98.4%); TLC purity 100%.

(ii) The catalysts were filtered off, and the resulting solution of 15 (X = H, $R_1$ = $i$-$C_3H_7$) was immediately cyclodesulfurized with mercury oxide to yield 12 (X = H, $R_1$ = $i$-$C_3H_7$): 7 g (18%); mp 228.4 °C. Anal. ($C_{23}H_{30}N_4$) C, H, N.

**1-Ethyl-*N*-[1-(1-methylethyl)-4-piperidinyl]-1*H*-benzimidazol-2-amine (22).** A solution of acetone (0.6 g, 0.01 mol), 5·2HBr ($R_2$ = $C_2H_5$; 4 g, 0.01 mol), and sodium methoxide (1.6 g, 0.03 mol) in ethanol (150 mL) was hydrogenated at normal pressure and 25 °C over Pd/C 10% (2 g). The catalyst was filtered off after uptake of 1 equiv of hydrogen, and the filtrate was evaporated. The residue was treated with water and extracted twice with chloroform (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Recrystallization from a mixture of 4-methyl-2-pentanone and diisopropyl ether afforded 22: 1 g (35%); mp 156 °C. Anal. ($C_{17}H_{26}N_4$) C, H, N.

**4-[(1-Ethyl-1*H*-benzimidazol-2-yl)amino]-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidinebutanamide (28).** A suspension of *N*-[dihydro-3,3-diphenyl-2(3*H*)-furanylidene]-*N*-methylmethanaminium bromide[13] (3.5 g, 0.01 mol), 5·2HBr ($R_2$ = $C_2H_5$) (4 g, 0.01 mol), sodium carbonate (3.2 g, 0.03 mol), and a catalytic amount of potassium iodide in 4-methyl-2-pentanone (150 mL) was stirred and refluxed overnight. The water was removed with the aid of a Dean–Stark trap. After cooling, the reaction mixture was poured into water. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified on silica ($CHCl_3$–$CH_3OH$, 97:3 (v/v)). Crystallization of the pure fraction from a mixture of 4-methyl-2-pentanone and diisopropyl ether yielded 28: 1.3 g (26%); mp 199.4 °C. Anal. ($C_{32}H_{39}N_5O$) C, H, N.

**1-(Phenylmethyl)-*N*-[1-[2-(2-thienyl)ethyl]-4-piperidinyl]-1*H*-benzimidazol-2-amine Dihydrochloride Monohydrate (39).** A mixture of 2-(2-thienyl)ethanol 4-methylbenzenesulfonate (ester) (2.8 g, 0.01 mol),[21] 5 ($R_2$ = $C_6H_5CH_2$, 3 g, 0.01 mol), and sodium carbonate (2.1 g, 0.02 mol) in dimethylformamide was heated overnight at 70 °C. The usual workup afforded a solid residue, which was acidified with hydrogen chloride in 2-propanol and was crystallized to yield 39: 1.7 g (28.5%); mp 259–273 °C. Anal. ($C_{25}H_{28}N_4S$·2HCl·$H_2O$) C, H, N, Cl, $H_2O$.

**1-Ethyl-1,4-dihydro-4-[2-[4-[[1-(phenylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-5*H*-tetrazol-5-one Dihydrochloride Monohydrate (40).** A suspension of 1-(2-chloroethyl)-4-ethyl-1,4-dihydro-5*H*-tetrazol-5-one (2.7 g, 0.015 mol),[22] the dihydrobromide salt 5 ($R_2$ = $C_6H_5CH_2$; 7 g, 0.015 mol), and sodium carbonate (4.6 g, 0.045 mol) was allowed to react in dimethylformamide (150 mL) as described for 39. The hydrogen chloride salt was crystallized from 2-propanol to afford 40: 2.2 g (28%); mp 171 °C. Anal. ($C_{24}H_{30}N_8O$·2HCl·$H_2O$) C, H, N, $H_2O$.

**α-(Phenoxymethyl)-4-[[1-(phenylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidineethanol (49).** A suspension of (phenoxymethyl)oxirane (2.25 g, 0.015 mol), 5·2HBr ($R_2$ = $C_6H_5CH_2$; 7 g, 0.015 mol), and sodium carbonate (3.2 g, 0.03 mol) in benzene (150 mL) and methanol (50 mL) was refluxed and stirred overnight. After cooling, the reaction mixture was poured into water and extracted with toluene. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was crystallized from a mixture of methanol and diisopropyl ether to yield 49: 3 g (44%); mp 146.6 °C. Anal. ($C_{28}H_{32}N_4O_2$) C, H, N.

**1-Phenyl-4-[4-[[1-(phenylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]cyclohexanecarbonitrile (51).** A suspension of 4-oxo-1-phenylcyclohexanecarbonitrile (4 g, 0.02 mol),[23] 5·2HBr ($R_2$ = $C_6H_5CH_2$; 9.4 g, 0.02 mol), and sodium carbonate (3.4 g) in methanol (250 mL) was hydrogenated over Pd/C (10%; 5 g) at 70 °C. The catalyst was poisoned by adding 1 mL of a 4% solution of thiophene in methanol (v/v). After uptake of 1 equiv of hydrogen, the catalyst was filtered off, the solvent was evaporated, and the residue was crystallized from a small volume of methanol to afford 51: 3.5 g (35.7%); mp 106 °C. Anal. ($C_{32}H_{35}N_5$) C, H, N.

***N*-[1-(2-Phenylethyl)-4-piperidinyl]-1*H*-benzimidazol-2-amine (54).** This compound was prepared by the same method as described for 39. The reaction of phenylethyl bromide (22.2 g, 0.12 mol) and 5·2HBr ($R_2$ = H; 45 g, 0.12 mol) yielded 54: 21 g (54.6%); mp 192 °C, after crystallization from 4-methyl-2-pentanone. Anal. ($C_{20}H_{24}H_4$) C, H, N.

***N*-[1-(2-Phenylethyl)-4-piperidinyl]-1-(2-pyridinylmethyl)-1*H*-benzimidazol-2-amine (74).** A suspension of 54 (3.2 g, 0.01 mol), 2-picolyl chloride hydrochloride (1.64 g, 0.01 mol), and sodium carbonate (2.1 g, 0.02 mol) in 4-methyl-2-pentanone (150 mL) was refluxed, and the water was removed with the aid of a Dean–Stark trap. After 24 h, the reaction mixture was cooled and poured into water. The organic layer was separated, dried ($MgSO_4$), and filtered, and the filtrate was evaporated. The residue was purified on silica ($CHCl_3$–$CH_3OH$ 98:2 (v/v)). The product was collected, the solvent was evaporated, and the residue was crystallized from a mixture of acetone and diisopropyl ether to yield 74: 1 g (24.3%); mp 127 °C. Anal. ($C_{26}H_{29}N_5$) C, H, N.

**1-[(4-Fluorophenyl)methyl]-*N*-methyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-1*H*-benzimidazol-2-amine Dihydrochloride (80).** To a cooled solution (<5 °C) of 12 (X = H, $R_1$ = $CH_3$; 3.3 g, 0.1 mol) in dimethyl sulfoxide (100 mL) and benzene (100 mL) was added sodium hydride (50%, 0.5 g). After the mixture was stirred at this temperature for 30 min, 4-fluorobenzyl chloride (1.5 g, 0.01 mol) was added dropwise. The reaction mixture was stirred overnight, while the temperature raised spontaneously to room temperature. After addition of water (200 mL), the reaction mixture was extracted twice with toluene (150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was acidified with hydrogen chloride in acetone; the precipitate was collected and crystallized from 2-propanol to yield 80: 2.8 g (54.4%); mp 246.6 °C. Anal. ($C_{28}H_{31}FN_4$·2HCl) C, H, N, $H_2O$, Cl.

***N*-[1-[2-(Methoxyphenyl)ethyl]-4-piperidinyl]-1-(phenylmethyl)-1*H*-benzimidazol-2-amine Dihydrochloride Monohydrate (102).** A suspension of (3-methoxyphenyl)ethanol methanesulfonate (ester)[24] (2.3 g, 0.01 mol), 5·2HBr ($R_2$ = $C_6H_5CH_2$; 4.7 g, 0.01 mol), and sodium carbonate (3.2 g, 0.03 mol) in dimethylformamide (150 mL) was stirred at 70 °C for 24 h. Usual workup, purification on silica ($CHCl_3$–$CH_3OH$ 98:2 (v/v)), and crystallization from a mixture of acetone and diisopropyl ether yielded 102: 1 g (22.7%); mp 128.6 °C. Anal. ($C_{28}H_{32}N_4O$) C, H, N.

**Pharmacological Testing. In Vitro Screening: Inhibition of Histamine- ($H_1$-) Induced Contraction of Guinea Pig Ileum.** Nonterminal segments, 5 cm long, of the ileum of the

(21) Van Daele, P. G. H.; De Bruyn, M. F. L.; Boey, J. M.; Sanczuk, S.; Agten, J. T. M.; Janssen, P. A. J. *Arzneim-Forsch.* **1976**, *26*, 1521.

(22) Denecker, G.; Smets, G.; L'Abbé, G. *Tetrahedron* **1975**, *31*, 765.

(23) Abe, Y.; Harakuwa, T.; Ishikawa, M.; Miki, T.; Sumi, M. *J. Pharm. Soc. Jpn.* **1953**, *73*, 36.

(24) Ebnoether, A.; Bastian, J. M.; Rissi, E. *Chem. Abstr.* **1978**, *78*, P136082*w*.

guinea pig (400–500 g, fasted overnight) were vertically suspended with a preload of 0.75 g in a 100 mL tyrode bath, gassed with a mixture of 95% $O_2$ and 5% $CO_2$ (37.5 °C). Contractions were recorded isotonically (HP 7 DCDT-1000, JSI displacement transducer control unit, Bryans pen-recorder XY 26128). At intervals of 5 min, cumulative dose–response curves were made by adding logarithmically increasing doses of histamine ($5.4 \times 10^{-8}$, $1.6 \times 10^{-7}$, $5.4 \times 10^{-7}$ M, ...) until a maximal contraction was obtained. It took 2 min to complete a dose–response curve. The total volume added to the bath was less than 2% of the bath volume. The procedure was repeated in the presence of the antagonist (contact time 5 min). After the drug was washed out, two other curves were made.[15] The highest test dose normally was 0.04 mg/L.

**In Vivo Screening: (A) Protection of Rats from Compound 48/80 Induced Lethality.** Compound 48/80, a mixture of oligomers obtained by condensation of 4-methoxy-*N*-methylbenzeneethanamine and formaldehyde has been described as a potent histamine-releasing agent.[17,18] The protection from compound 48/80 induced lethal circulatory collapse appears to be a simple way of evaluating quantitatively the antihistaminic activity of test compounds. Male rats of an inbred Wistar strain, weighing 240–260 g, were used in the experiment. After overnight starvation the rats were transferred to conditioned laboratories (temperature 21 ± 1 °C, relative humidity (65 ± 5%).

The rats were treated subcutaneously or orally with a test compound or with the solvent (NaCl solution, 0.9%). One hour after treatment there was injected intravenously compound 48/80, freshly dissolved in water, at a dose of 0.5 mg/kg (0.2 mL/100 g of body weight). In control experiments, wherein 250 solvent-treated animals were injected with the standard dose of compound 48/80, not more than 2.8% of the animals survived after 4 h. Survival after 4 h is therefore considered to be a safe criterion of a protective effect of drug administration. Calculated $ED_{50}$ values with confidence limits, according to Finney,[25] were obtained on the basis of test results on five animals for each of at least three doses from the geometrical series 0.0025, 0.005, 0.01, ..., 10.0, 20.0, and 40.0 mg/kg. Estimated $ED_{50}$-values were based on at least two animals per test dose.

**(B) Protection of Guinea Pigs from Histamine-Induced Lethality.** The 50% protective dose ($PD_{50}$) values against a lethal intravenous dose of histamine were determined by the following method. Male albino guinea pigs (280–360 g) were challenged with an intravenous injection of 1.25 mg/kg of histamine dihydrochloride solution. As all control animals died witin 5 min, survival after 1 h was considered to be a safe criterion of protection from histamine-induced death.[19] $PD_{50}$ values with confidence limits were computed according to Finney.[25] Four to six guinea pigs per dose and time point were used for each of at least three doses from the geometrical series 0.0025, 0.005, 0.01, ..., 2.5, 5 mg/kg. Estimated $PD_{50}$ values were based on at least two animals per test dose. Azatadine maleate (Schering), oxatomide (Janssen), chlorpheniramine hydrochloride (Schering), and diphenylhydramine hydrochloride (Parke-Davis) were used as reference compounds.

**Acknowledgment.** The authors thank the "Instituut to aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw" for financial support. The authors thank Dr. R. Boar for helpful discussions and S. Daniels for typing the manuscript.

(25) Finney, D. J. "Probit Analysis"; University Press: Cambridge, 1962.

**Registry No.** 1, 73733-70-7; 2, 73733-81-0; 3, 73734-07-3; 4 (R = $CH_3$), 73788-44-0; 5 ($R_2$ = $CH_3$), 75970-51-3; 5·2HBr($R_2$ = $C_2H_5$), 73734-17-5; 5·2HBr($R_2$ = $CH_2Ph$), 75970-53-5; 5·2HBr($R_2$ = H), 75970-47-7; 6 ($R_1$ = $CH_3$), 73733-69-4; 7, 2719-30-4; 8 ($R_1$ = $CH_3$), 98267-83-5; 9 ($R_1$ = $CH_3$), 98245-12-6; 10 ($R_1$ = $CH_3$), 98245-13-7; 11 ($R_1$ = $CH_3$), 75970-60-4; 12 (X = H, $R_1$ = *i*-$C_3H_7$), 73736-03-5; 12 (X = H, $R_1$ = $CH_3$) (free base), 75971-16-3; 12 (X = H, $R_1$ = $CH_3$), 73734-39-1; 13 (X = H, $R_1$ = *i*-$C_3H_7$), 73733-91-2; 14 (X = H, $R_1$ = *i*-$C_3H_7$), 73733-92-3; 15 (X = H, $R_1$ = *i*-$C_3H_7$), 73733-96-7; 16 (X = H), 24089-69-8; 16 (X = H) (free base), 16771-89-4; 17 (X = H), 39742-60-4; 18, 73735-91-8; 18 (free base), 98244-74-7; 19, 73734-29-9; 19 (free base), 79278-73-2; 20, 73755-80-3; 20 (free base), 98244-75-8; 21, 73734-94-8; 21 (free base), 98244-76-9; 22, 73735-92-9; 23, 73734-56-2; 23 (free base), 73734-55-1; 24, 73734-80-2; 24 (free base), 98244-77-0; 25, 75970-94-4; 25 (free base), 75970-93-3; 26, 73734-77-7; 26 (free base), 73734-76-6; 27, 73734-30-2; 28, 98244-78-1; 29, 73735-02-1; 29 (free base), 73735-01-0; 30, 73734-95-9; 30 (free base), 98244-79-2; 31, 73735-87-2; 31 (free base), 75971-14-1; 32, 73734-64-2; 32 (free base), 98244-80-5; 33, 73734-57-3; 33 (free base), 98244-81-6; 34, 73735-96-3; 35, 73734-83-5; 35 (free base), 73734-82-4; 36, 73734-84-6; 37, 73734-67-5; 38, 73734-68-6; 39, 73735-66-7; 39 (free base), 98244-82-7; 40, 73755-79-0; 40 (free base), 98244-83-8; 41, 73734-96-0; 42, 73735-03-2; 43, 73734-28-8; 43 (free base), 75970-77-3; 44, 73734-54-0; 44 (free base), 98244-84-9; 45, 73755-77-8; 45 (free base), 98244-85-0; 46, 73734-63-1; 47, 98244-86-1; 48, 73734-58-4; 48 (free base), 98244-87-2; 49, 75971-03-8; 50, 73735-30-5; 51, 73735-97-4; 52, 73735-18-9; 52 (free base), 98244-88-3; 53, 73734-93-7; 53 (free base), 73734-92-6; 54, 73734-45-9; 55, 73734-31-3; 55 (free base), 98244-89-4; 56, 73734-38-0; 56 (free base), 98244-90-7; 57, 73734-35-7; 57 (free base), 98244-91-8; 58, 73734-33-5; 58 (free base), 98244-92-9; 59, 73734-36-8; 59 (free base), 98244-93-0; 60, 73734-34-6; 60 (free base), 98244-94-1; 61, 73734-37-9; 61 (free base), 98244-95-2; 62, 73736-15-9; 63, 73736-17-1; 64, 73734-32-4; 65, 73734-44-8; 66, 73734-40-4; 66 (free base), 98244-96-3; 67, 73734-43-7; 67 (free base), 98088-84-7; 68, 73734-85-7; 68 (free base), 98244-97-4; 69, 73734-41-5; 69 (free base), 98244-98-5; 70, 73734-42-6; 70 (free base), 98244-99-6; 71, 73736-19-3; 71 (free base), 98245-00-2; 72, 75971-18-5; 73, 73736-20-6; 74, 73736-18-2; 75, 73736-32-0; 75 (free base), 98245-01-3; 76, 73736-31-9; 76 (free base), 98245-02-4; 77, 73736-27-3; 77 (free base), 98245-03-5; 78, 73755-94-9; 78 (free base), 98245-04-6; 79, 73736-23-9; 79 (free base), 73736-22-8; 80, 73736-06-8; 80 (free base), 75971-17-4; 81, 73736-30-8; 81 (free base), 98245-05-7; 82, 73736-24-0; 82 (free base), 98245-06-8; 83, 73736-29-5; 83 (free base), 73736-28-4; 84, 73736-26-2; 84 (free base), 73736-25-1; 85, 73736-02-4; 86, 73736-33-1; 87, 73736-35-3; 87 (free base), 98245-07-9; 88, 73755-97-2; 88 (free base), 98245-08-0; 89, 73736-38-6; 89 (free base), 73736-37-5; 90, 73736-04-6; 91, 73736-13-7; 91 (free base), 98245-09-1; 92, 73736-48-8; 92 (free base), 73736-47-7; 93, 73734-39-1; 93 (free base), 75971-16-3; 94, 73755-76-7; 95, 73736-05-7; 96, 73734-87-9; 97, 73735-53-2; 98, 73735-52-1; 98 (free base), 73735-61-2; 99, 73735-51-0; 99 (free base), 98245-10-4; 100, 73734-88-0; 101, 73735-50-9; 101 (free base), 98245-11-5; 102, 73735-48-5; 103, 73735-49-6; 104, 73735-45-2; 105, 73735-54-3; ethyl 4-amino-1-piperidine carboxylate, 58859-46-4; *o*-phenylenediamine, 95-54-5; ethyl 4-oxo-1-piperidinecarboxylate, 29976-53-2; 1,4-dioxa-8-azaspiro[4.5]decane, 177-11-7; *N*-[dihydro-3,3-diphenyl-2(3*H*)-furanylidene-*N*-methylmethanaminium bromide, 37743-18-3; 2-(2-thienyl)ethanol 4-methylbenezenesulfonate(ester), 40412-06-4; 1-(2-chloroethyl)-4-ethyl-1,4-dihydro-5*H*-tetrazol-5-one, 69049-03-2; (phenoxymethyl)oxirane, 122-60-1; 4-oxo-1-phenylcyclohexanecarbonitrile, 25115-74-6; 2-picolyl hydrochloride, 6959-47-3; 4-fluorobenzyl, 352-11-4; (3-methoxyphenyl)ethanol methanesulfonate (ester), 40759-46-4.