3,4-Di-*O*-acetyl-2-bromo-2-deoxy-L-fucopyranose (8b). Bromination of di-*O*-acetylfucal (**5**; 1.0 g) was carried out by the same procedure outlined above for chlorination. TLC (eluant: benzene–ether, 2:1) of the crude dibromo addition product showed four distinct spots. Dry column chromatography was carried out (eluant: benzene–ether, 2:1). The combined fractions corresponding to the spot on TLC which had the highest R_f value yielded 0.38 g (26%) of white crystals. Recrystallization from ether gave **8b**: mp 180–182 °C; $[\alpha]^{22}_D$ −131° (*c* 0.1, H_2O). Anal. ($C_{10}H_{15}BrO_6$) C, H, Br.

2-Bromo-2-deoxy-α-L-fucopyranose (9b). Di-*O*-acetylfucal (**5**; 2.09 g) was brominated as described above, and the crude dibromo product was refluxed in 0.1 N HCl for 6 h, neutralized with Ag_2CO_3, filtered, and evaporated to give a syrupy residue. TLC (eluant: acetone–benzene 2:1) gave two spots, which were separated by dry column chromatography. The component of lower mobility crystallized. Recrystallization from acetonitrile with charcoal treatment gave 187 mg (9%) of **9b** as white crystals: mp 135–137 °C; $[\alpha]^{22}_D$ −90.8° (*c* 0.13, H_2O, equil); NMR, see Table I. Anal. ($C_6H_{11}BrO_4$) C, H, Br.

Methyl 3,4-Di-*O*-acetyl-2-deoxy-2-iodo-β-L-fucopyranoside (10) and Methyl 3,4-Di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-talopyranoside (11). Di-*O*-acetylfucal (**5**; 2.14 g) in 70 mL of dry methanol was mixed with 2.35 g of silver acetate and cooled to 0 °C. Iodine (3.58 g) was added; after 1 h, the silver salts were filtered off and the methanolic filtrate was evaporated in vacuo. The syrupy residue was dissolved in chloroform and washed successively with aqueous sodium bicarbonate and sodium thiosulfate solutions. The chloroform solution was evaporated to dryness in vacuo, and the residue was dry column chromatographed (eluant: petroleum ether–ether, 2:1). Collected were 2.37 g (64%) of methyl 3,4-diacetyl-2,6-dideoxy-2-iodo-α-L-talopyranoside (**11**), 0.31 g (8%) of methyl 2-deoxy-3,4-diacetyl-2-iodo-β-L-fucopyranoside (**10**), and 0.43 g (11%) of an unresolved mixture of **11** and **10**.

Physical constants and analyses are as follows. For **11**: mp 40–42 °C; $[\alpha]^{22}_D$ −37.0 (*c* 0.53, methanol); NMR ($CDCl_3$) δ 5.22 (s, 1, H-1, $J_{1,2}$ = 1.0 Hz), 4.31 (d, 1, H-2, $J_{2,3}$ = 5.0 Hz), 4.90 (t, 1, H-3, $J_{3,4}$ = 3.6 Hz), 5.25 (s, 1, H-4, $J_{4,5}$ = 1.7 Hz), 4.19 (d, 1, H-5, $J_{5,6}$ = 6.7 Hz), 1.22 (d, 3, 5-CH_3), 3.40 (s, 3, 1-OCH_3), 2.08, 2.22 (s, 3, Ac, $J_{2,4}$ = 1.0 Hz). Anal. ($C_{11}H_{17}IO_6$) C, H, I.

For **10**: mp 111–112 °C; $[\alpha]^{22}_D$ −38.3 (*c* 0.12, methanol); NMR ($CDCl_3$) δ 4.34 (d, 1, H-1, $J_{1,2}$ = 8.9 Hz), 4.04 (q, 1, H-2, $J_{2,3}$ = 12.5 Hz), 5.10 (d, 1, H-3, $J_{3,4}$ = 3.2 Hz), 5.09 (s, 1, H-4, $J_{4,5}$ = 1 Hz), 3.85 (q, 1, H-5, $J_{5,6}$ = 6.5 Hz), 1.23 (d, 3, 5-CH_3), 3.59 (s, 1, OCH_3), 2.07, 2.16 (s, 3, Ac, $J_{2,4}$ = 1.1 Hz). Anal. ($C_{11}H_{17}IO_6$) C, H, I.

Methyl 2-Deoxy-2-iodo-β-L-fucopyranoside (12). The iodofucose derivative (**10**; 150 mg) was dissolved in 0.1 M methanolic sodium methoxide solution (20 mL) and allowed to stand at room temperature for 1 h. Neutralization with ion-exchange resin (Amberlite IR 120, H^+) and filtration, followed by evaporation, yielded a syrup, which was dissolved in hot ethyl acetate, decolorized with charcoal, filtered, and evaporated to give 80 mg (61%) of crystals: mp 114–116 °C; $[\alpha]^{22}_D$ −33.1° (*c* 0.13, methanol); NMR ($CDCl_3$) δ 4.46 (d, 1, H-1, *J* = 8.5 Hz), 3.56 (s, 1, OCH_3), 1.37 (d, 3, 5-CH_3). Anal. ($C_7H_{13}IO_4$) C, H, I.

2-Deoxy-2-iodo-L-fucopyranose (13). A solution of 74 mg of methyl 2-deoxy-2-iodo-β-L-fucopyranoside in 0.05 M H_2SO_4 (10 mL) was heated at 100 °C for 2 h, cooled, and neutralized with aqueous $Ba(OH)_2$ solution. Filtration and evaporation in vacuo was followed by dry column chromatography (eluant: ethyl acetate–ethanol, 3:1), which yielded a light yellow syrup. Crystallization was induced by slow evaporation from an acetonitrile–chloroform solution, giving 20 mg (30%) of yellow powder: mp 54–55 °C; $[\alpha]^{22}_D$ −91° (*c* 0.1, H_2O). Anal. ($C_6H_{11}IO_4$) C, H.

Acknowledgment. We thank Dr. E. Mihich for his active encouragement of the program. This study was supported by Grants CA-08793, CA-15757, and CA-13038 from the National Cancer Institute (USPHS). The NMR facility used in this study is supported by the Institute Core Grant CA-16056 from the National Cancer Institute. We also thank Mrs. Onda Dodson Simmons for determining the NMR spectra and to Ms. Nancy Porter and Ms. Patricia Dix for excellent technical assistance.

Synthesis and Psychoanaleptic Properties of New Compounds Structurally Related to Diphenhydramine

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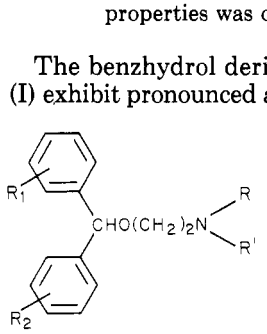
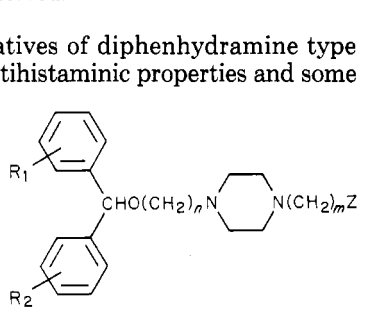
A new series of benzhydryloxyalkylpiperazines carrying a trivalent function has been synthesized and studied for its effects on the central nervous system. Most of the compounds exhibit unexpected nonamphetaminic psychoanaleptic properties. The structure–activity studies revealed the importance of the nature and the position of the substituents on the phenyl rings. However, no significant correlation between atropinic or antihistaminic effects and psychoanaleptic properties was observed.

The benzhydrol derivatives of diphenhydramine type (I) exhibit pronounced antihistaminic properties and some



I



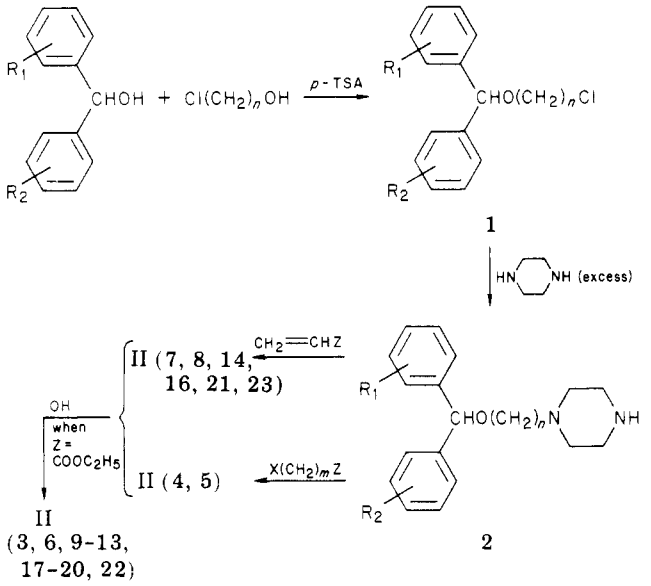
II, n = 2,3; m = 1–4; Z = CN, $COOC_2H_5$, COOH, $CONR_2$

atropinic effects.[1,2] It is also well known that these H_1 antagonists may exert both stimulating and sedative effects on the CNS.[3] This central excitation is associated with overdosage, as shown for pyribenzamine-induced activation of the EEG,[4] and is usually a stimulation of the convulsion type. However, the sedative effect appears mainly at therapeutic doses.

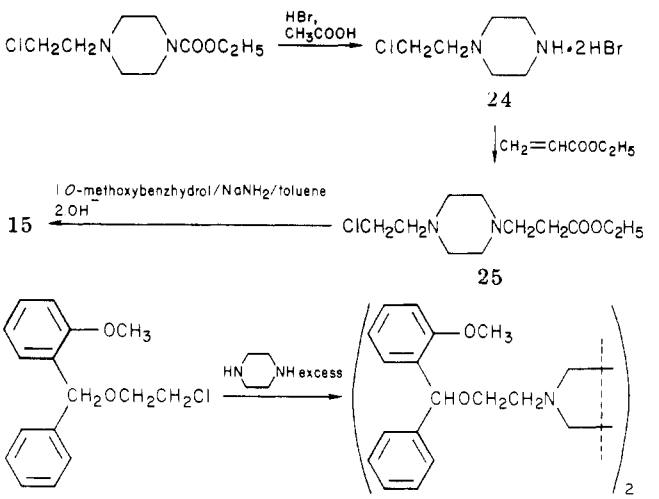
(1) G. Ehrhart and H. Ruschig in "Arzneimittel", Verlag Chemie, Weinheim, Germany, 1972, Chapter 8.
(2) A. Burger in "Medicinal Chemistry", 3rd ed, Part II, Wiley-Interscience, New York, 1969, Chapter 65.
(3) L. S. Goodman and A. Gilman in "Basis of Therapeutics", 5th ed, Macmillan, New York, 1975, Chapter 29.
(4) G. Kings and S. D. Weeks, *Electroenceph. Clin. Neurophysiol.*, **18**, 503 (1965).

0022-2623/80/1823-0149$01.00/0

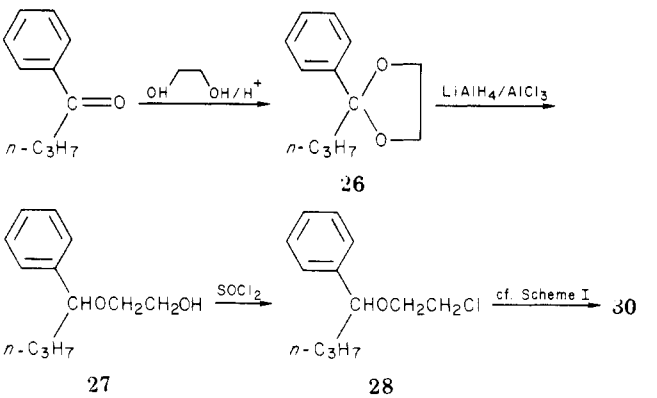
Scheme I



Scheme II



Scheme III



In the attempt to prepare a new type of diphenhydramine derivatives, devoid of sedative side effects, we have synthesized a series of benzhydryloxyalkylpiperazines carrying a chain with a trivalent function (II).

Surprisingly, some of the new compounds prepared, although structurally related to diphenhydramine, show novel, nonamphetaminic psychoanalpetic properties and lack pronounced peripheral anticholinergic activity.

Chemistry. Most compounds were prepared according to Scheme I. The benzhydryl-ω-chloroethyl or -propyl ethers 1 were synthesized by a modification of Sugasawa's method,[5] condensation of the appropriate benzhydrols with the chlorhydrins in the presence of *p*-TSA with azeotropic removal of the water. Treatment of these ethers with an excess of piperazine according to Morren et al.[6] afforded the compounds **2**. The monosubstituted piperazines were finally treated either with acrylic acid derivatives to give the required products II (m = 2; method A) or with ω-halogeno compounds to give the required products II (m = 1, 3, or 4; method B). The free carboxylic acids or their sodium salts were obtained by alkaline hydrolysis of the corresponding ethyl esters (method C).

Compound **15** was prepared by a different process since the general method afforded only a symmetrically disubstituted piperazine derivative irrespective of the reagents ratio used (Scheme II).

When one of the benzene rings in the benzhydrol moiety was replaced by an alkyl group, as in the case of α-propylbenzyl alcohol, the reaction with chlorhydrin led to the dehydration product only. Therefore, compound **30** was prepared via Eliel's dioxolane opening method[7] using butyrophenone (Scheme III).

Compounds **29** and **31** were prepared according to Scheme I but using benzyl alcohol or 9-fluorenol, respectively. The chemical data for all compounds studied are summarized in Tables I and II.

Pharmacology. All compounds were found to increase the exploratory behavior of mice, when tested according to the method of Boissier.[8] The ED_{50} and the LD_{50} obtained are presented in Tables I and II.

Specific tests for characterization of typical psychoanaleptic activity and probable antihistaminic and anticholinergic properties in vitro were performed with the most interesting compounds only and are listed in Table III.

Structure–Activity Relationships. The structure–activity relationships of the psychoanaleptic activity show a significant effect caused by the modification of the length of both aliphatic chains. Increasing n from 2 to 3 (compounds **6** and **14**) doubles the activity without improving the therapeutic index, however. The increase of m from 1 to 2 leads to an increase of the activity, while further increase of the chain's length does not cause any additional effect. On the other hand, the nature and the position of the substituents on the phenyl rings exhibit a profound effect. Compounds **11** and **19**, carrying a 4-F and 4-Cl substituent, accordingly, were found to be the most active ones. Replacement of the halogen by a methyl radical (**20**) decreases the activity, while substitution by a 4-NO_2 group (**21**) almost cancels the stimulating action. Similar results were obtained by changing the position of the substituent on the phenyl ring: the corresponding ortho derivatives **15** and **16** are weakly active. Symmetric aromatic disubstitution (**22** and **23**), as compared to monosubstitution, does not lead to any change in activity. Replacement of one of the phenyl groups by an alkyl radical (**30**) maintains the activity, while the replacement by a hydrogen atom leads to its considerable decrease (**29**). The fluorene de-

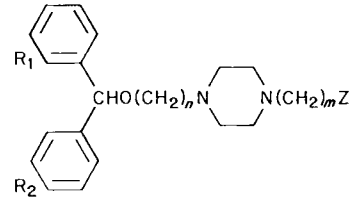
(5) S. Sugasawa and K. Fujiwara, *Yakugaku Zasshi*, **71**, 365 (1951); S. Sugasawa and K. Fujiwara, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1963, p 72.

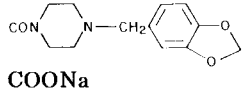
(6) H. Morren, R. Denamer, R. Linz, J. Mathieu, H. Strubbe, and S. Trolin, *Ind. Chim. Belge*, **22**, 409 (1957).

(7) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Am. Chem. Soc.*, **84**, 2371 (1962); R. A. Daignauld and E. L. Eliel, "Organic Syntheses", Collect. Vol. V., Wiley, New York, 1973, p 303.

(8) J. R. Boissier and P. Simon, *Arch. Int. Pharmacodyn.*, **158**, 212 (1965).

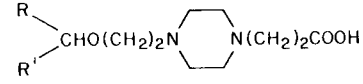
Table I

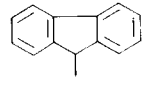


no.	Z	R_1	R_2	n	m	mp, °C	salt	crystn[a] solvent	emp formula	anal.	M	tox-icity: LD_{50}[f]	incr of explor behav: ED_{50}[f]	LD_{50}/ED_{50}
3	COONa	H	H	2	1	234	base	D	$C_{21}H_{25}N_2O_3Na\cdot0.5H_2O$	C,[b] H, N	385.4	4.3	0.5[c]	
4		H	H	2	1	205	trimaleate	E	$C_{25}H_{33}N_3O_3\cdot2C_4H_4O_4$	C, H, N	655.77	1.2	0.15	8
5		H	H	2	1	190	dimaleate	E	$C_{33}H_{40}N_4O_4\cdot3C_4H_4O_4\cdot H_2O$	C, H, N	922.5	0.7	0.03	23
6	COONa	H	H	2	2	260	base	D	$C_{22}H_{27}N_2O_3Na\cdot0.5H_2O$	C, H, N	399.5	3.6	0.21	17
7	CN	H	H	2	2	160	2HCl	E	$C_{22}H_{27}N_3O\cdot2HCl$	C,[d] H, N	422.4	0.7	0.1	7
8	$CONH_2$	H	H	2	2	180	2HCl	F	$C_{22}H_{29}N_3O_2\cdot2HCl\cdot1.5H_2O$	C, H, N	467.4	2.1	0.17	12
9	COOH	H	H	2	3	116	HCl	F	$C_{23}H_{30}N_2O_3\cdot2HCl\cdot2H_2O$	C, H, N	491.4	3.4	0.17	20
10	COOH	4-F	H	2	1	148	dimaleate	E	$C_{21}H_{25}FN_2O_3\cdot2C_4H_4O_4\cdot1.5H_2O$	C, H, N	631.6	2.8	0.1	28
11	COOH	4-F	H	2	2	173	dimaleate	E	$C_{22}H_{27}FN_2O_3\cdot2C_4H_4O_4$	C, H, N	618.6	1.3	0.04	37
12	COOH	4-F	H	2	3	170	dimaleate	E	$C_{23}H_{29}FN_2O_3\cdot2C_4H_4O_4$	C, H, N	632.6	1.9	0.06	34
13	COOH	4-F	H	2	4	176	dimaleate	E	$C_{24}H_{31}FN_2O_3\cdot2C_4H_4O_4$	C, H, N	646.6	2.2	0.05	40
14	$COOC_2H_5$	H	H	3	2	220	2HCl	F	$C_{25}H_{34}N_2O_3\cdot2HCl$	C, H, Cl, N	483.5	1.8	0.1	18
15	COOH	2-OCH_3	H	2	2	175	dimaleate	F	$C_{23}H_{30}N_2O_4\cdot2C_4H_4O_4$	C, H, N	630.6	2.2	0.5[c]	
16	$COOC_2H_5$	2-Cl	H	2	2	180	2HCl	D	$C_{24}H_{31}ClN_2O_3\cdot2HCl$	C, H, Cl, N	503.9	3.2	0.5[c]	
17	COOH	3-CF_3	H	2	2	178	dimaleate	E	$C_{23}H_{27}F_3N_2O_3\cdot2C_4H_4O_4$	C,[e] H, N	668.6	1.8	0.3	6
18	COOH	3,4,5-$(OCH_3)_3$	H	2	2	168	dimaleate	E	$C_{25}H_{34}N_2O_6\cdot2C_4H_4O_4$	C, H, N	690.7	2.3	0.5[c]	
19	COOH	4-Cl	H	2	2	174	dimaleate	E	$C_{22}H_{27}ClN_2O_3\cdot2C_4H_4O_4$	C, H, Cl, N	635	1.6	0.05	32
20	COOH	4-CH_3	H	2	2	180	dimaleate	E	$C_{23}H_{30}N_2O_3\cdot2C_4H_4O_4$	C, H, N	614.6	2.3	0.16	14
21	$COOC_2H_5$	4-NO_2	H	2	2	180	2HCl	F	$C_{24}H_{31}N_3O_5\cdot2HCl$	C, H, Cl, N	514.4	3	0.5[c]	
22	COOH	4-F	4-F	2	2	180	dimaleate	D	$C_{22}H_{26}F_2N_2O_3\cdot2C_4H_4O_4$	C, H, N	636.6	1.1	0.05	23
23	$COOC_2H_5$	4-F	4-F	2	2	190	2HCl	F	$C_{24}H_{30}F_2N_2O_2\cdot2HCl$	C, H, N	505.5	1.2	0.06	20

[a] D = 2-propanol, E = methanol, F = ethanol. [b] C: calcd, 65.43; found, 64.81. [c] No definite dose-effect relationship was observed at this dose level. [d] C: calcd, 62.55; found, 61.94. [e] C: calcd, 55.68; found, 56.20. [f] In mice, mol/kg po.

Table II



no.	R	R'	mp, °C	salt	crystn solvent	emp formula	anal.	M	toxicity: LD_{50} (mice), mol/kg po	increase of exploratory behavior: ED_{50} (mice), mol/kg po	LD_{50}/ED_{50}
29	Ph	H	100	base	EtOAc	$C_{16}H_{24}N_2O_3\cdot0.5H_2O$	C, H, N	301.4	>5.5	0.5[a]	
30	Ph	n-C_3H_7	163	dimaleate	EtOH	$C_{19}H_{30}N_2O_3\cdot2C_4H_4O_4$	C, H, N	566.6	>2.8	0.1	>28
31			160	dimaleate	CH_3OH	$C_{22}H_{26}N_2O_3\cdot2C_4H_4O_4$	C, H, N	598.6	2.3	0.23	10

[a] No definite dose-effect relationship was observed at this dose level.

Table III[a]

compd	group toxicity (mice)[b]	anorexic act. ED_{50} (rats), μmol/kg	narcosis antag ED_{50} (mice), μmol/kg	sympathomimetic act.[c] (dog)	in vitro interact.[d] AcCh pA_2	in vitro interact.[d] histamine pA_2
6	0.6 (0.4-0.8)		>500	0 (50)[e]	3.94 (3.50-4.38)	6.12 (5.85-6.39)
11	1.7 (1.4-2.0)	>60[f]	>650	0 (50)[e]	5.14 (5.00-5.28)	6.65 (5.42-7.88)
16					6.78 (6.45-7.11)	7.25 (7.18-7.32)
23	0.4 (0.3-0.5)		~200	0 (50)[e]	6.51 (6.23-6.79)	8.14 (7.99-8.29)
30					5.71 (5.05-6.37)	5.45 (5.05-5.85)
dl-amphetamine sulfate	5.3 (4.5-6.1)	13 (10-17)	20 (18-22)	50%[g] 30%[h] (0.5)	<3	4.87 (4.68-5.06)
atropine sulfate					9.06 (8.95-9.17)	6.22 (5.82-6.62)
mepyramine maleate					5.40 (5.29-5.51)	9.38 (9.25-9.51)

[a] Data in parentheses are confidence limits for $p = 95\%$. [b] Ratio of LD_{50} isolated/LD_{50} aggregated. [c] Hypertension and tachycardia after iv administration. [d] $n = 12$ (number of experiments). [e] At this dose, changes were less than 10% (values in parentheses in μmol/kg). [f] No activity at this dose. [g] Blood pressure increase. [h] Cardiac rhythm increase.

rivative **31**, whose phenyl rings are coplanar, is moderately psychoanaleptic. Analogous substituent effects were observed in the anti-H_1 diphenhydramine series.[2] A limited number of compounds (Table III) was chosen for further investigation. Compounds **6**, **11**, and **30** act as weak antihistaminics devoid of atropinic activity. Compared to amphetamine, they lack group toxicity, anorexic activity, cardiovascular sympathomimetic action, and narcosis–antagonism. The ortho-substituted compound **16** exerts the strongest peripheral anticholinergic activity, and compound **23** possesses the strongest antihistaminic property. Compound **11**, the most promising candidate, based on potency and minimum side effects, is currently being studied in man. It exhibits an excellent attention-mobilizing activity.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. Analytical results for the elements indicated are within ±0.4% of the theoretical values except when noted. The structures of all compounds were supported by TLC, IR, and NMR spectra. TLC were performed on $60F_{254}$ silica gel plates (Merck), developed with CH_3OH–CH_2Cl_2 (1:10), and detected by UV or Draggendorf's reagent. Spectral data were obtained with a Perkin-Elmer Model 257 IR spectrophotometer (neat or KBr) and an Hitachi Perkin-Elmer R24B NMR spectrometer ($CDCl_3$ solvent and Me_4Si as internal standard).

General Procedure for the Preparation of 1. 1-[(4-Fluorobenzhydryl)oxy]-2-chloroethane (R_1 = *p*-F; R_2 = H). A solution of 4-fluorobenzhydrol (190 g, 0.94 mol), 2-chloroethanol (133 mL, 2 mol), and *p*-TSA·H_2O (12 g) in toluene (1 L) was refluxed (about 1 h), the water formed being removed by azeotropic distillation. The cold solution was washed with water (500 mL), 5% bicarbonate solution (2 × 200 mL), water again (500 mL), dried, and evaporated to yield 244 g (98%) of an oil, which was used in the next step.

General Procedure for the Preparation of 2. 1-[2-[(4-Fluorobenzhydryl)oxy]ethyl]piperazine (R_1 = *p*-F; R_2 = H). A solution of crude **1** (R_1 = *p*-F; R_2 = H; 192 g, 0.725 mol) in toluene (200 mL) was added slowly to a stirred refluxing solution of anhydrous piperazine (252 g, 2.9 mol) in toluene (1 L). The mixture was refluxed for 15 h, cooled to 70 °C, and treated with water (500 mL). The organic phase was washed twice with water (500 mL) and then extracted with 10% acetic acid (2 × 500 mL). The combined aqueous acidic solutions were washed with toluene (3 × 400 mL). The base was liberated with aqueous NaOH and extracted with toluene (3 × 400 mL). The combined organic solutions were washed with water, dried (Na_2SO_4), and evaporated in vacuo to yield a pale yellow oil (191 g, 84%). This crude product was used for the final step.

Method A. 1-[2-[(2-Chlorobenzhydryl)oxy]ethyl]-4-(2-carbethoxyethyl)piperazine Dihydrochloride (16). A solution of **2** (R_1 = *o*-Cl; R_2 = H; 16.5 g, 0.05 mol) and ethyl acrylate (10 g, 0.1 mol) in benzene (150 mL) was refluxed for 4 h. The cold solution was washed with 2% aqueous acetic acid (20 mL), 5% bicarbonate solution (50 mL), water (50 mL), dried (Na_2SO_4), and evaporated to yield 16.5 g (77%) of an oil. It was dissolved in 2-propanol and transformed into the dihydrochloride.

Method B. 1-[2-(Benzhydryloxy)ethyl]-4-(2-morpholino-2-oxoethyl)piperazine Dimaleate (4). A mixture of **2** (R_1 = R_2 = H; 8.9 g, 0.03 mol), 4-(chloroacetyl)morpholine[9] (5 g, 0.03 mol), and $NaHCO_3$ (3.5 g) in EtOH (50 mL) was refluxed with stirring for 8 h. The residue left after the evaporation of the solvent was dissolved in CH_2Cl_2 (150 mL)–H_2O (50 mL). The organic phase was washed with water, dried (Na_2SO_4), and evaporated to give an oil (12 g, 95%), which was transformed into its maleate salt.

Method C. 1-[2-[(4-Fluorobenzhydryl)oxy]ethyl]-4-(2-carboxyethyl)piperazine Dimaleate (11). A solution of **2** (R_1 = *p*-F; R_2 = H; 157 g, 0.5 mol) and ethyl acrylate (65 mL, 0.6 mol) in benzene (300 mL) was refluxed for 4 h. The residue left after the evaporation of the solvent was dissolved in ethanol (200 mL) and 4 N NaOH (150 mL), and this solution was refluxed for 2 h. The cooled solution was neutralized with 4 N HCl (150 mL). The residue obtained after the removal of the solvents in vacuo was suspended in $CHCl_3$ (500 mL). This mixture was washed with water (2 × 250 mL), dried (Na_2SO_4), and evaporated to yield an oil (184 g, 95%). The free base was converted into the dimaleate salt in $CH_3COOC_2H_5$–C_2H_5OH (5:1).

1-(2-Chloroethyl)piperazine Dihydrobromide (24). A stream of dry HBr was passed during 8 h into a hot (80–90 °C) solution of 1-(2-chloroethyl)-4-carbethoxypiperazine hydrochloride[10] (72 g, 0.28 mol) in acetic acid (500 mL). The precipitate formed was filtered from the cold solution and washed twice with ethanol to give **24**: yield 70 g (80%); mp 220 °C.

1-(2-Chloroethyl)-4-(2-carbethoxyethyl)piperazine (25). A solution of **24** (70 g, 0.22 mol), ethyl acrylate (50 g, 0.5 mol), and triethylamine (23 g, 0.226 mol) in benzene (500 mL) was refluxed for 4 h. The filtered cold solution was evaporated to dryness and the residue obtained was dissolved in 10% HCl (450 mL). The aqueous solution was washed with benzene (2 × 100 mL), covered with the same solvent (300 mL), and basified carefully with concentrated NaOH. The aqueous phase was separated and extracted with benzene (2 × 100 mL), and the combined organic solutions were dried and evaporated in vacuo to give an oil (51 g, 92%), which was immediately used in the following step.

1-[2-[(2-Methoxybenzhydryl)oxy]ethyl]-4-(2-carboxyethyl)piperazine Dimaleate (15). A solution of 2-methoxybenzhydrol (10 g, 0.05 mol) in toluene (50 mL) was slowly added to a stirred suspension of $NaNH_2$ (2 g) in toluene (50 mL), and the mixture obtained was refluxed for 1 h. After the addition of a solution of **25** (15 g, 0.06 mol) in toluene (80 mL), the mixture was refluxed for an additonal 3 h. After cooling, the reaction mixture was poured into water (200 mL). The organic phase was extracted with 10% HCl (2 × 100 mL). The acidic aqueous solution was washed with benzene (2 × 50 mL) and then treated with NaOH with cooling. The base (11 g, 54%), an oil, isolated by extraction with ether (3 × 100 mL) and evaporation of the solvent, was saponified (method C) and converted into the dimaleate salt.

(9) W. F. Bruce and J. Seifter, U.S. Patent 2568141 (1951).
(10) M. Herfenist, *J. Am. Chem. Soc.*, 76, 4991 (1954).

2-Phenyl-2-propyl-1,3-dioxolane (26). A solution of butyrophenone (148 g, 1 mol), 1,2-ethanediol (124 g, 2 mol), and *p*-TSA·H_2O (0.5 g) in dry benzene (1 L) was refluxed overnight, the water formed being removed by azeotropic distillation. During the following 8 h, from time to time part of the solvent was distilled off (~100 mL) and replaced by dry benzene (distilled over P_2O_5). The cold reaction mixture was washed successively with 10% NaOH (200 mL) and water (5 × 100 mL) and dried (Na_2SO_4). The residue left after the evaporation of the solvent was fractionated to yield a colorless liquid: yield 163 g (86%); bp 120 °C (14 mm).

2-[(1-Phenylbutyl)oxy]ethanol (27) [bp 140 °C (12 mm)] was prepared according to the method of Eliel[7] in 80% yield.

1-[(1-Phenylbutyl)oxy]-2-chloroethane (28). Compound **27** (132.5 g, 0.7 mol) was dissolved in a cooled solution of $SOCl_2$ (100 mL, 1.4 mol) in pyridine (500 mL), and the resulting solution was heated at 90 °C for 5 h. The cold reaction mixture was poured into ice–water (1 L), carefully acidified (concentrated HCl), and extracted with ether (3 × 300 mL). The combined organic solutions were washed with 5% $NaHCO_3$ (3 × 150 mL) and water (2 × 150 mL), dried (Na_2SO_4), and evaporated to give an oil (102 g, 68%), which was used without further purification in the preparation of compound **30**.

Animals and Drugs. Male Swiss mice (18–20 g), male Wistar rats (100–120 g), guinea pigs (250–300 g), and mongrel dogs of both sexes were used. All compounds and reference drugs were dissolved or suspended in 0.5% aqueous carboxymethylcellulose and administered orally to mice and rats and intravenously to dogs. Control groups were treated with the vehicle only.

Toxicity. LD_{50} values were evaluated from mortality observed in groups of four animals administered with doses of 200, 400, 800, and 1600 mg/kg.

Exploratory Behavior. Its increase was measured by Boissier's[8] method. At the onset of activity, the mice were individually housed in photobeam boxes (20 × 25 × 10 cm) with two crossed beams. The number of beam interruptions was recorded during the first 5-min period. The ED_{50} values (dose increasing by 50% the performance of control animals) were calculated by the least-squares method from the results of four groups (10 mice) administered with increasing doses in geometrical scale (ratio 2).

Group toxicity was determined by Chance's[11] method. Immediately after administration of the compound under study, groups of 10 mice, called "grouped mice", were housed in boxes of reduced dimensions (8.5 × 18 × 8.5 cm) with four aeration holes. The mortality, after 6 h, was compared with that of "isolated mice" treated simultaneously and kept under usual conditions (10 mice in a box of 19 × 29 × 14 cm covered with wire netting). Group toxicity is the ratio of the LD_{50} values of isolated mice to that of grouped mice, based on the administration of six increasing doses in geometrical scale (ratio 2) and computed by Kärber's[12] method.

Anorexic Activity. Roszkowski's[13] method was used in the determination of the anorexic activity, the original diet being substituted by chocolate milk. The animals were allowed to drink this diet, for 6 h, once a week, during 6 weeks. During the last 4 weeks, before each drinking session, the rats were treated with the compounds investigated according to the latin square method.[14] The ED_{50} (dose lowering by 50% the consumption of control group) was computed with the least-squares method from the results of three groups (24 rats) administered with increasing doses in geometrical scale (ratio 2).

Narcosis-Antagonism. Groups of 10 mice were induced to sleep by an ip injection of sodium pentobarbital (160 μmol/kg), 2 h after administration of the compounds investigated. Duration of narcosis was estimated from the loss of wrighting reflex (30 to 60 min in control animals). The ED_{50} values (doses lowering by 50% the duration of narcosis observed in control groups) were computed by the least-squares method from the results obtained by the administration of increasing doses in geometrical scale (ratio 2) to four groups.

Sympathomimetic action was evaluated from the increase (at least 10%) of the femoral arterial blood pressure and of the cardiac rhythm, after iv injection of the compounds to glucochloralose-anesthetized dogs (380 μmol/kg iv).

In Vitro Interactions. The in vitro antihistaminic and anticholinergic activities were investigated by histamine or acetylcholine-induced contractions of guinea pig ileum. After killing the guinea pig by a blow on the neck, longitudinal fragments of the terminal ileum were removed and suspended in 40-mL baths containing Tyrode solution aerated with a gas mixture (95% O_2/5% CO_2) and kept at 32 °C. The contractions were measured isometrically and recorded on smoked cylinders. Cumulative concentration–response to histamine or acetylcholine curves were made before and after the addition of antagonist. Van Rossum's[15] method of data evaluation was used for computing the pA_2, characterizing the affinity of the compounds for different receptor sites.

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(11) M. R. A. Chance, *J. Pharmacol.*, 87, 214 (1946).
(12) G. Kärber, *Arch. Exp. Pathol. Pharmakol.*, 162, 480 (1931).
(13) A. P. Roszkowski and N. M. Kelley, *J. Pharmacol. Exp. Ther.*, 140, 367 (1963).
(14) J. Lellouch and P. Lazar, "Méthode Statistique en Expérimentation Biologique", Flammarion, Paris, 1974, Chapter 8.
(15) J. M. Van Rossum, *Arch. Int. Pharmacodyn.*, 143, 299 (1963).