Synthesis and Central Nervous System Depressant Activity of New Piperazine Derivatives and Related Compounds. II

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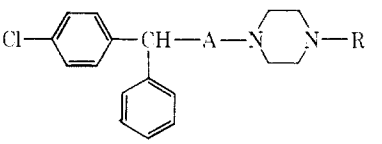
Ninety-three N^1,N^4-disubstituted piperazine derivatives in which the N^1 substituents are 3-(*p*-chlorophenyl)-3-phenylpropionyl, 3-(*p*-chlorophenyl)-3-phenylpropyl, ω-(*p*-chloro-α-phenylbenzyloxy)alkyl, β-(*p*-chloro-α-phenylbenzylmercapto)ethyl, β-(*p*-chloro-α-phenylbenzylamino)ethyl, or β-(1,2-diphenethylamino)ethyl and the N^4 substituents are methyl, 2-hydroxypropyl, 2-(2'-hydroxyethoxy)ethyl, cyclohexyl, benzyl, *m*-methyl- and *p*-*t*-butylbenzyl, *p*-chloro-α-phenylbenzyl, phenethyl, phenyl, chloro- and methoxyphenyl, tolyl, 2-pyridyl, 2-pyrimidyl, or 2-thiazolyl have been synthesized. So have some N,N'-disubstituted ethylenediamines in which the substituent is *p*-chloro-α-phenylbenzyl and N' substituents are alkyl groups or N' is a part of morpholine or piperidine. Screening for CNS activity revealed that some compounds possessed significant CNS depressant activity. A few compounds exhibited promising antihistaminic activity in experimental animals.

Basic benzhydryl ethers,[2] thioethers,[3] and ethylenediamine derivatives[4] in which one of the N atoms is part of a heterocyclic ring are important classes of compounds with CNS activities such as sedative, tranquilizing, antihistaminic, antitussive, and antispasmodic. A number of diphenylpropylamines have been reported to possess analgetic,[5a,b] spasmolytic,[5c-e] and vasodilatory[5f-i] activities. Interest in piperazine-containing molecules has continued to grow in recent years because of the broad spectrum of pharmacological activities found among this group of compounds.[2a,6] It is also known that the mild sedative property exhibited by antihistaminic compounds could be potentiated by the chemical modification to obtain useful antianxiety or tranquilizing substances.[2a,7] We have, therefore, undertaken the synthesis and pharmacological study of a series of compounds, in which *p*-chlorobenzhydryl and various N-monosubstituted piperazines are linked by a connecting chain A as shown in the following general formula I.



I

A = CH_2CO, CH_2CH_2, $O(CH_2)_2$, $O(CH_2)_3$, $S(CH_2)_2$, $NH(CH_2)_2$, or $N(CH_3)CH_2CH_2$

R = alkyl, cycloalkyl, aralkyl, aryl, and heterocyclic groups

In view of the significant CNS depressant activity displayed by some of the ethylenediamine derivatives (I, A = $NHCH_2CH_2$), additional compounds wherein the piperazine part was replaced by other pharmacologically active amines were also synthesized.

To extend the structure-activity relationships in the same series (I, A = $NHCH_2CH_2$), the *p*-chlorobenzhydryl group was replaced by 1,2-diphenylethyl since a

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number of 1,2-diphenylethylamines have shown analgetic and CNS depressant activities.[8]

Chemistry.—N^1-[3-(*p*-Chlorophenyl)-3-phenylpropyl]-N^4-(substituted)piperazines (I, A = CH_2CH_2) were synthesized by the condensation of 3-(*p*-chlorophenyl)-3-phenylpropionyl chloride with different N-monosubstituted piperazines followed by the reduction with LAH.

N^1-[ω-(*p*-Chloro-α-phenylbenzyloxy)alkyl]-N^4-(substituted)piperazines [I, A = $O(CH_2)_2$, $O(CH_2)_4$], N^1-[β-(*p*-chloro-α-phenylbenzylmercapto)ethyl]-N^4-(substituted)piperazines (I, A = SCH_2CH_2), and N^1-[β-(*p*-chloro-α-phenylbenzylamino)ethyl]-N^4-(substituted) piperazines (I, A = $NHCH_2CH_2$) were prepared by condensing ω-(*p*-chloro-α-phenylbenzyloxy)ethyl or -butyl chloride, β-(*p*-chloro-α-phenylbenzylmercapto)ethyl chloride, and β-(*p*-chloro-α-phenylbenzylamino)ethyl chloride hydrochloride, respectively, with various N-monosubstituted piperazines in the presence of Et_3N in EtOH.

N-(*p*-Chloro-α-phenylbenzyl)-N'-(substituted)ethylenediamines and N^1-[β-(1,2-diphenylethylamino)ethyl]-N^4-(substituted)piperazines were prepared by the condensation of β-(*p*-chloro-α-phenylbenzylamino)ethyl chloride hydrochloride or β-(1,2-diphenylethylamino)-ethyl chloride hydrochloride with various amines.

The physical constants, yields, recrystallization solvents and analytical data of the compounds synthesized are given in Tables I–III.

Pharmacology.—The gross observation of intact mice, the spontaneous motor activity, and potentiation of barbital hypnosis revealed that some of the compounds in these series possessed good CNS depressant activity. None of the compounds had any significant analgetic activity (narcotic or nonnarcotic). A few compounds exhibited significant antihistaminic activity.

The results of the pharmacological evaluations, including cardiovascular study and antihistaminic activity of the compounds tested, are given in colums 5–8 of Tables I–III.

Results and Discussion

In general, the CNS depressant activity as seen by the decrease in motor activity was in the following descending order according to the nature of the bridge –A– joining *p*-chloro-α-phenylbenzyl and piperazine moieties in the general formula I: $NHCH_2CH_2 > CH_2CH_2 > CH_2CO > SCH_2CH_2 > OCH_2CH_2CH_2CH_2 > OCH_2CH_2$. The substituents R on the N^4 position of the piperazine also influenced the depressant activity. In the ethylenediamine series (I, A = $NHCH_2CH_2$), compounds **73** and **80–82** exhibited significant CNS depressant activity. The replacement of the piperazine group either by a heterocyclic amine like morpholine, piperidine, or alkyl- or dialkylamine reduced the activity. When *p*-chloro-α-phenylbenzyl moiety was replaced by 1,2-diphenylethyl, the activity was considerably reduced.

Diphenylpropionamides (I, A = CH_2CO) and the corresponding diphenylpropylamines (I, A = CH_2CH_2) exhibited mild to marked CNS depressant activity. The reduction of the amide to the corresponding amine increased the activity. The benzhydryl ethers (I, A = OCH_2CH_2) showed a lower order of depressant activity as compared to the benzhydryl thioethers. In the thioether series (I, A = SCH_2CH_2) the activity was found to be of higher order when the N^4 substituents were aryl (**57** and **61**) and 2-pyrimidyl (**65**). The length of the carbon chain [I, A = $O(CH_2)_4$] had no significant effect on the activity.

In vitro antihistaminic action on guinea pig ileum showed seven compounds (**27**, **34**, **36–38**, **44**, and **52**) to possess significant antihistaminic activity. However, when tested for antihistaminic activity *in vivo* by the aerosol method in the guinea pig, only **27**, **34**, and **38** showed marked antihistaminic activity.

Experimental Section

Pharmacological Methods.—CNS activity of the compounds was evaluated by methods described earlier.[6a] The compounds being insoluble were administered intraperitoneally as an aqueous suspension with 0.5% carboxymethylcellulose.

Cardiovascular effects of some selected compounds were studied in normotensive dogs under pentobarbital anesthesia. The effects of the compounds on pressure response produced by the injection of 2–4 μg/kg of epinephrine, 3–4 μg/kg of acetylcholine, and 3–5 μg/kg of histamine were recorded. The test compounds were generally given in a dose of 5 mg/kg and the effect was studied repeatedly at 10 min, 1 hr, 2 hr, and 4 hr after drug administration.

Antihistaminic activity *in vitro* of the compounds was investigated on the guinea pig ileum against contraction produced by histamine and the results were compared with the inhibition produced by diphenhydramine (10^{-8} g/ml producing 50% inhibition).

In vivo **antihistaminic activity** (guinea pig) was studied by the degree of protection against histamine aerosol (2%). Gasping, head movements, and the appearance of asphyxial convulsion were taken as the end point. The animals which responded to the histamine aerosol (2%) within 2 min were taken for the test. After the rest period (2 days) the test compounds were given intraperitoneally at $0.1LD_{50}$, 0.5 hr before the challenging dose of histamine aerosol. Animals treated with 0.5% vehicle alone served as controls. Absence of above reactions during the exposure period (2 min) was considered as the positive antihistaminic activity.

Chemical Methods.[9] **N-Monosubstituted Piperazines.**—The following N-monosubstituted piperazines required for the present work were prepared according to the literature methods: N-methyl,[10a] N-(2-hydroxypropyl),[10b] N-[2-(2'-hydroxyethoxy)-ethyl],[10c] N-cyclohexyl,[10d] N-benzyl,[10e] N-(*m*-methylbenzyl),[10f] N-(*p*-*t*-butylbenzyl),[10f] N-(*p*-chloro-α-phenylbenzyl),[10g] N-(2-phenethyl),[10f] N-phenyl,[10b] N-*o*- and -*p*-chlorophenyl,[10j] N-*o*- and -*p*-methoxyphenyl,[10j] N-*o*-, -*m*-, and -*p*-tolyl,[10i] N-(2-pyridyl),[10k] N-(2-pyrimidyl),[10k] and N-(2-thiazolyl).[10k]

***p*-Chloro-α-phenylbenzylmalonic Acid.**—*p*-Chloro-α-phenylbenzyl chloride[11] (1.0 mole) was condensed with diethyl malonate (1.1 moles) in the presence of NaOEt (1.1 moles) in EtOH follow-

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(9) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points and boiling points are uncorrected. Melting points were taken in capillary tubes in a sulfuric acid bath with a partial immersion thermometer.

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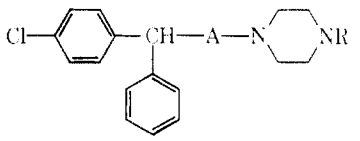
TABLE I

N^1,N^4-DISUBSTITUTED PIPERAZINES



No.	A	R	Crystn solvent[a]	% yield[b]	Mp or bp (mm), °C	Formula	Analysis	Mouse LD_{50}, mg/kg ip	CNS depression,[c] mg/kg ip	↑ / ↓ motor act.,[d] mice	Antihistaminic act.[e]
1	CH_2CO	2-Hydroxypropyl	H	52	123–126	$C_{22}H_{27}ClN_2O_2$	C, H, N	800	100	68	
2	$(CH_2)_2$	2-Hydroxypropyl	A	61	180–182	$C_{22}H_{29}ClN_2O \cdot$ dimaleate	C, H, N	150	(−)[f]	(−)	
3	CH_2CO	Benzyl	P	66	120–122	$C_{26}H_{27}ClN_2O$	C, H, N	800	50	(−)	
4	$(CH_2)_2$	Benzyl	A–W	59	218–220 dec	$C_{28}H_{29}ClN_2 \cdot$ dimaleate	C, H, N	150	(−)[f]	(−)	(−)
5	CH_2CO	*m*-Methylbenzyl	H	78	123–124	$C_{27}H_{29}ClN_2O$	C, H, N	800	100[f]	(−)	
6	$(CH_2)_2$	*m*-Methylbenzyl	E	59	200–202 dec	$C_{27}H_{31}ClN_2 \cdot$ dimaleate	C, H, N	600	50[f]	62	(−)
7	CH_2CO	*p*-*t*-Butylbenzyl	H	61	120–121	$C_{30}H_{35}ClN_2O$	C, H, N	800	200[f]	(−)	
8	$(CH_2)_2$	*p*-*t*-Butylbenzyl	E	61	204–206 dec	$C_{30}H_{37}ClN_2 \cdot$ dimaleate	C, H, N	800	100[f]	56	
9	CH_2CO	2-Phenethyl	H	53	114–116	$C_{27}H_{29}ClN_2O$	C, H, N	800	100[f]	82	
10	$(CH_2)_2$	2-Phenethyl	E	65	260–265 dec	$C_{27}H_{31}ClN_2 \cdot 2HCl$	C, H, N	300	50	(−)	
11	CH_2CO	*o*-Chlorophenyl	P	59	140–142	$C_{25}H_{24}Cl_2N_2O$	C, H, N	800	50[f]	(−)	
12	$(CH_2)_2$	*o*-Chlorophenyl	E–Et	61	178–180	$C_{25}H_{26}Cl_2N_2 \cdot$ maleate	C, H, N	800	100	(−)	
13	CH_2CO	*o*-Methoxyphenyl	P	62	129–130	$C_{26}H_{27}ClN_2O_2$	C, H, N	800	50	(−)	
14	$(CH_2)_2$	*o*-Methoxyphenyl	E	54	182–184	$C_{26}H_{29}ClN_2O \cdot$ maleate	C, H, N	800	50[f]	75	
15	CH_2CO	*o*-Tolyl	P	65	154–156	$C_{26}H_{27}ClN_2O$	C, H, N	800	50[f]	(−)	
16	$(CH_2)_2$	*o*-Tolyl	E–Et	59	180–182	$C_{28}H_{29}ClN_2 \cdot$ maleate	C, H, N	800	100[f]	68	(−)
17	CH_2CO	*m*-Tolyl	H	53	115–117	$C_{26}H_{27}ClN_2O$	C, H, N	800	100[g]	(−)	
18	$(CH_2)_2$	*m*-Tolyl	E–Et	72	200–201	$C_{28}H_{29}ClN_2 \cdot$ maleate	C, H, N	800	100	(−)	
19	CH_2CO	*p*-Tolyl	H	77	126–128	$C_{26}H_{27}ClN_2O$	C, H, N	800	50[f]	75	
20	$(CH_2)_2$	*p*-Tolyl	E–Et	61	162–164	$C_{28}H_{29}ClN_2 \cdot$ maleate	N	800	100[f]	(−)	(−)
21	CH_2CO	2-Pyridyl	P–H	62	150–151	$C_{24}H_{24}ClN_3O$	C, H, N	800	100	(−)	
22	$(CH_2)_2$	2-Pyridyl	P–Et	88	153–154	$C_{24}H_{26}ClN_3 \cdot$ maleate	C, H, N	600	50	72	(−)
23	CH_2CO	2-Pyrimidyl	P	71	175–178	$C_{23}H_{23}ClN_4O$	C, H, N	800	100	(−)	
24	$(CH_2)_2$	2-Pyrimidyl	E–Et	65	173–175	$C_{23}H_{25}ClN_4 \cdot$ maleate	C, H, N	800	100	56	
25	CH_2CO	2-Thiazolyl	P	75	161–162	$C_{22}H_{22}ClN_3OS$	N, S	800	100	(−)	
26	$(CH_2)_2$	2-Thiazolyl	E–Et	52	154–157	$C_{22}H_{24}ClN_3S \cdot$ maleate	N, S	800	(−)	(−)	
27	$O(CH_2)_2$	2-Hydroxypropyl	E	50	194–196 dec	$C_{22}H_{29}ClN_2O_2 \cdot$ oxalate	N	150	(−)	(−)	(+)[b,f]
28	$O(CH_2)_2$	Cyclohexyl	E	70	200–201[i] dec	$C_{25}H_{29}ClN_2O \cdot$ dimaleate	C, H, N	100	40[f]	51	(−)
29	$O(CH_2)_2$	2-Phenethyl	A–Et	68	208–201[k] dec	$C_{27}H_{31}ClN_2O \cdot 2HCl$	N				
			E		198–199	$C_{27}H_{31}ClN_2O \cdot$ dimaleate	N	200	(−)	(−)	(−)
30	$O(CH_2)_2$	Phenyl	E–Et	49	152–153	$C_{28}H_{27}ClN_2O \cdot$ maleate	N	800	200	52	(−)
			E		164–166	$C_{25}H_{27}ClN_2O \cdot$ oxalate	C, H, N				
31	$O(CH_2)_2$	*o*-Chlorophenyl	E	57	170–172 dec	$C_{25}H_{26}Cl_2N_2O \cdot$ oxalate	C, H, N	100	(−)	(−)	
32	$O(CH_2)_2$	*p*-Chlorophenyl	E–Et	55	164–165	$C_{28}H_{28}Cl_2N_2O \cdot$ oxalate	C, H, N	600	100[f]	(−)	
33	$O(CH_2)_2$	*o*-Methoxyphenyl	E–Et	42	168–169	$C_{26}H_{29}ClN_2O_2 \cdot$ oxalate	C, H, N	400	50[f]	(−)	
34	$O(CH_2)_2$	*p*-Methoxyphenyl	E–Et	40	172–173	$C_{26}H_{29}ClN_2O_2 \cdot$ oxalate	C, H, N	400	200	(−)	(+)[b,f]
35	$O(CH_2)_2$	*o*-Tolyl	E–Et	60	182–186 dec	$C_{26}H_{29}ClN_2O \cdot$ oxalate	C, H, N	100	(−)[f]	(−)	
36	$O(CH_2)_2$	*m*-Tolyl	E–Et	63	173–174	$C_{28}H_{29}ClN_2O \cdot$ oxalate	C, H, N	800	200[f]	58	(+)[b,f]
37	$O(CH_2)_2$	2-Pyridyl	E–Et	55	162–164	$C_{24}H_{26}ClN_3O \cdot$ maleate	C, H, N	100	200[f]	(−)	(+)[b]
38	$O(CH_2)_2$	2-Pyrimidyl	E–Et	53	174–175	$C_{25}H_{25}ClN_4O \cdot$ oxalate	C, H, N	150	60	(−)	(+)[b,c,h]
39	$O(CH_2)_2$	2-Thiazolyl	E–Et	59	164–165	$C_{22}H_{24}ClN_3OS \cdot$ oxalate	C, H, N, S	400	50	(−)	(−)
40	$O(CH_2)_3$	2-Hydroxypropyl	E–Et	57	164–166	$C_{23}H_{31}ClN_2O_2 \cdot$ dimaleate	N	100	40	(−)	(−)
			E–Et		214–215 dec	$C_{24}H_{32}ClN_2O_2 \cdot$ dioxalate	N				
41	$O(CH_2)_4$	Benzyl	E–W	58	204–205	$C_{25}H_{33}ClN_2O \cdot$ maleate	N	300	100	62	
42	$O(CH_2)_4$	*m*-Methylbenzyl	P	63	216–220	$C_{29}H_{38}ClN_2O \cdot 2HCl$	C, H, N	600	100[f]	60	(−)[c]
43	$O(CH_2)_4$	*p*-*t*-Butylbenzyl	E	56	198–200	$C_{32}H_{43}ClN_2O \cdot$ dimaleate	C, H, N	600	(−)	(−)	(−)
44	$O(CH_2)_4$	2-Phenethyl	P	71	234–236 dec	$C_{29}H_{38}ClN_2O \cdot 2HCl$	C, H, N	200	50	(−)	(−)[b]
45	$O(CH_2)_4$	Phenyl	E	71	195–197	$C_{25}H_{35}ClN_2O \cdot$ oxalate	C, H, N	500	200	(−)	
46	$O(CH_2)_4$	*p*-Chlorophenyl	E–Et	50	151–153	$C_{25}H_{36}Cl_2N_2O \cdot$ oxalate	C, H, N	300	100	(−)	(−)
47	$O(CH_2)_4$	*o*-Methoxyphenyl	P	48	146–148	$C_{28}H_{39}ClN_2O_2 \cdot$ oxalate	C, H, N	300	(−)	(−)	(−)
48	$O(CH_2)_4$	*p*-Methoxyphenyl	E–Et	50	166–168	$C_{28}H_{39}ClN_2O_2 \cdot$ oxalate	C, H, N	600	100	(−)	
49	$O(CH_2)_4$	*o*-Tolyl	E–Et	55	144–145	$C_{28}H_{38}ClN_2O \cdot$ oxalate	N	75	30	(−)	(−)
50	$O(CH_2)_4$	*m*-Tolyl	E	71	183–184 dec	$C_{28}H_{39}ClN_2O \cdot$ oxalate	C, H, N	600	100[f]	(−)	
51	$O(CH_2)_4$	2-Pyridyl	E	55	184–185 dec	$C_{26}H_{38}ClN_3O \cdot$ oxalate	C, H, N	300	(−)	(−)	(−)
52	$O(CH_2)_4$	2-Pyrimidyl	E	65	182–184 dec	$C_{25}H_{29}ClN_4O \cdot$ oxalate	C, H, N	150	(−)	(−)	(+)[b]
53	$O(CH_2)_4$	2-Thiazolyl	E	53	175–177 dec	$C_{24}H_{28}ClN_3OS \cdot$ oxalate	N, S	200	80[f]	(−)	
54	$S(CH_2)_2$	2-Hydroxypropyl	E	61	222–224	$C_{22}H_{29}ClN_2OS \cdot$ dioxalate	C, H, N, S	600	(−)	(−)	(−)
55	$S(CH_2)_2$	*p*-*t*-Butylbenzyl	E–W	75	202–203	$C_{30}H_{37}ClN_2S \cdot$ dimaleate	C, H, N, S	800	100[f]	(−)	(−)
56	$S(CH_2)_2$	Phenethyl	E	64	192–193	$C_{27}H_{31}ClN_2S \cdot$ dimaleate	C, H, N, S	600	(−)	(−)	(−)
57	$S(CH_2)_2$	Phenyl	E	45	97–98	$C_{25}H_{27}ClN_2S$	C, H, N				
			E–W		208–209 dec	$C_{25}H_{27}ClN_2S \cdot$ oxalate	N, S	600	100	66	
58	$S(CH_2)_2$	*o*-Chlorophenyl	E–W	51	194–195	$C_{25}H_{26}Cl_2N_2S \cdot$ oxalate	C, H, N, S	800	(−)[f]	(−)	
59	$S(CH_2)_2$	*o*-Methoxyphenyl	E–W	59	200–201 dec	$C_{28}H_{29}ClN_2OS \cdot$ oxalate	C, H, N, S	800	100	(−)	(−)[c]
60	$S(CH_2)_2$	*p*-Methoxyphenyl	E–W	41	200–202 dec	$C_{28}H_{29}ClN_2OS \cdot$ oxalate	C, H, N, S	800	200[f]	(−)	
61	$S(CH_2)_2$	*o*-Tolyl	E	53	203–204 dec	$C_{28}H_{29}ClN_2S \cdot$ oxalate	C, H, N, S	800	100[g]	60	(−)
62	$S(CH_2)_2$	*m*-Tolyl	E	55	193–194 dec	$C_{29}H_{29}ClN_2S \cdot$ oxalate	C, H, N, S	800	100	(−)	(−)
63	$S(CH_2)_2$	*p*-Tolyl	E–W	42	212–214 dec	$C_{28}H_{29}ClN_2S \cdot$ oxalate	C, H, N, S	800	100	52	
64	$S(CH_2)_2$	2-Pyridyl	E–W	56	199–201	$C_{24}H_{28}ClN_3S \cdot$ oxalate	C, H, N, S	600	(−)	(−)	(−)
65	$S(CH_2)_2$	2-Pyrimidyl	E	51	185–186	$C_{23}H_{25}ClN_4S \cdot$ maleate	C, H, N, S	800	100[f]	57	(−)[c]
66	$S(CH_2)_2$	2-Thiazolyl	E–Et	42	195–197 dec	$C_{22}H_{24}ClN_3S \cdot$ oxalate	C, H, N, S	800	(−)	0	(−)
			E–W		149–150	$C_{22}H_{24}ClN_3S_2 \cdot$ maleate	N				
67	NH_2CH_2	Methyl	E–Et	39	262–264 dec	$C_{20}H_{26}ClN_3 \cdot 3HCl$	C, H, N				
			E		164–166	$C_{20}H_{26}ClN_3 \cdot$ trimaleate	N	600	200	(−)	(−)
68	$NH(CH_2)_2$	2-Hydroxypropyl		49	240–245 (11)	$C_{22}H_{30}ClN_3O$	N				

Table I (*Continued*)

No.	A	R	Crystn solvent[a]	% yield[b]	Mp or bp (mm), °C	Formula	Analyses	Mouse LD_{50}, mg/kg ip	CNS depression,[c] mg/kg	% ↓ in motor act. of mice[d]	Antihistaminic act.[e]
			E–A		165–168 dec	$C_{22}H_{30}ClN_3O$·dioxalate	C, H, N				(−)
69	$NH(CH_2)_2$	2-(2′-Hydroxyethoxy)ethyl		58	275–285 (10)	$C_{23}H_{32}ClN_3O_2$	C, H, N	400	(−)		
70	$NH(CH_2)_2$	Benzyl	E	64	210–211 dec	$C_{26}H_{30}ClN_3$·dioxalate	C, H, N				
			E–W		188–190	$C_{26}H_{30}ClN_3$·dimaleate	N	300	(−)	(−)	
71	$N(CH_3)(CH_2)_2$	Benzyl	E	54	205–206 dec	$C_{27}H_{32}ClN_3$·dimaleate	N	400	50	(−)	(−)
			E		208–210 dec	$C_{27}H_{32}ClN_3$·dioxalate	C, H, N				
72	$NH(CH_2)_2$	*m*-Methylbenzyl		40	250–270 (6)	$C_{27}H_{32}ClN_3$	N	60	(−)	(−)	
			E		168–170 dec	$C_{27}H_{32}ClN_3$·dimaleate	C, H, N				
73	$NH(CH_2)_2$	*p*-*t*-Butylbenzyl		59	290–296 (12)	$C_{30}H_{38}ClN_3$	C, H, N				
			E		180–182	$C_{30}H_{38}ClN_3$·dimaleate	N	162	60	70	(−)
74	$N(CH_3)(CH_2)_2$	*p*-*t*-Butylbenzyl		49	245–255 (7)	$C_{31}H_{40}ClN_3$	C, H, N				
			E_{90}		212–214 dec	$C_{31}H_{40}ClN_3$·dimaleate	N	800	100	(−)	
75	$NH(CH_2)_2$	*p*-Chooro-α-phenylbenzyl		62	245–255 (7)	$C_{32}H_{33}Cl_2N_3$	C, H, N				
76	$NH(CH_2)_2$	*o*-Chlorophenyl	P–Et	51	159–160 dec	$C_{25}H_{27}Cl_2N_3$·dimaleate	C, H, N	800	100	(−)	(−)[r]
77	$NH(CH_2)_2$	*o*-Methoxyphenyl		49	260–270 (5)	$C_{26}H_{30}ClN_3O$	C, H, N				
78	$NH(CH_2)_2$	*p*-Methoxyphenyl		43	274–285 (3)	$C_{26}H_{30}ClN_3O$	N				
79	$NH(CH_2)_2$	*o*-Tolyl		46	280–295 (9)	$C_{26}H_{30}ClN_3$	N				
80	$NH(CH_2)_2$	2-Pyridyl	H	48	106–107	$C_{24}H_{27}ClN_4$	C, H, N	800	135	92	(−)
81	$NH(CH_2)_2$	2-Pyrimidyl	H	49	88–89	$C_{23}H_{26}ClN_5$	C, H, N				
			E		170–171	$C_{23}H_{26}ClN_5$·dimaleate	N	150	60	65	(−)
82	$NH(CH_2)_2$	2-Thiazolyl		43	265–280 (1)	$C_{22}H_{25}ClN_4S$	N, S	800	60[f]	70	(−)
			E–Et		163–165	$C_{22}H_{25}ClN_4S$·dimaleate	C, H, N, S				

[a] A, Me_2CO; E, EtOH; E_{90}, 90% EtOH; Et, Et_2O; H, *n*-C_6H_{14}; P, *i*-PrOH; W, H_2O. [b] Yields reported are the results of single experiments and are based on 3-(*p*-chlorophenyl)-3-phenylpropionyl chloride (in case of the compounds of odd numbers from **1–25**), N-monosubstituted piperazines (in case of **27–67**), β-(*p*-chloro-α-phenylbenzylamino)ethyl chloride hydrochloride (in case of **67–100**), and β-(1,2-diphenylethylamino)ethyl chloride hydrochloride (in case of **101–111**). Yields are calculated for the materials melting not less than 2–3° below the highest melting point obtained. [c] Mice were observed during the toxicity tests. The lowest dose at which significant depression was noted in mice is recorded in this column. Depression at doses greater than 40% of the LD_{50} is not considered to be significant and is indicated as negative (−). [d] The study of motor activity of a group of six mice was done on an actophotometer for 10 min before and 1, 2, and 4 hr after administration of the compound (dose $0.1LD_{50}$). The peak effect is given here. Less than 50% decrease in motor activity was not considered to be significant and is indicated as negative (−). [e] The negative, moderate, and marked antihistaminic activity of the compounds tested in dogs is noted as (−), (+), and (++), respectively, in this column. The other significant effects on blood pressure of dogs were also given in this column as footnotes. [f] Produced 60% potentiation of barbital hypnosis at $0.1LD_{50}$ dose. [g] Produced 80% potentiation of barbital hypnosis at $0.1LD_{50}$ dose. [h] Showed significant antihistaminic activity when tested *in vitro* on guinea pig ileum. [i] Showed significant antihistaminic activity *in vivo* in the guinea pig by the aerosol method. [j] H. G. Morren, R. Denayer, S. Trolin, E. Grivsky, H. Strubbe, G. Dony, and J. Maricq [*Ind. Chim. Belge*, **19**, 1176 (1954); *Chem. Abstr.*, **53**, 2240 (1959)] reported base bp 205° (0.2 mm.). [k] A. Sacha [*Acta Polon. Pharm.*, **21**, 347 (1965); *Chem. Abstr.*, **64**, 8180*g* (1966)] reported mp 209–212°. [l] 40% inhibition of ACh response after 1 hr; the effect lasted for 4 hr. [m] 80% inhibition of epinephrine response after 10 min; the effect lasted for 3 hr. [n] 70% inhibition of ACh response after 10 min; the effect lasted for 1 hr. [o] 50% inhibition of epinephrine response after 10 min; the effect lasted for 1 hr. [p] 50% inhibition of ACh response after 1 hr; the effect lasted for 2 hr. [q] Produced 32% increase in motor activity at 40 mg/kg. [r] 70% inhibition of ACh response after 1 hr; the effect lasted for 4 hr.

ing the method of Henderson[12] for the preparation of diphenylisosuccinic acid; yield 62%, crystallized from H_2O, mp 178–179° dec. *Anal.* ($C_{16}H_{13}ClO_4$) C, H.

3-(*p*-Chlorophenyl)-3-phenylpropionic Acid. A.—*p*-Chloro-α-phenylbenzylmalonic acid (160 g) was partially decarboxylated by heating at 180° for 2 hr. The desired acid was obtained following the usual technique and recrystallized from H_2O, yield 85 g (62%), mp 108–109°. *Anal.* ($C_{15}H_{13}ClO_2$) C, H.

B.—*p*-Chloro-α-phenylbenzylmalonic acid (20 g) in glacial AcOH (100 ml) was refluxed for 2 hr and then poured over crushed ice. The solid thus obtained on recrystallization (H_2O) gave 9.9 g (58%) of the desired compound in pure form, mp 108–109°, undepressed by admixture of the compound obtained by method A.

3-(*p*-Chlorophenyl)-3-phenylpropionyl chloride was prepared from 3-(*p*-chlorophenyl)-3-phenylpropionic acid by the action of $SOCl_2$; yield 65%, bp 180–186° (6 mm). *Anal.* ($C_{15}H_{12}Cl_2O$) C, H.

N¹-[3-(*p*-Chlorophenyl)-3-phenylpropionyl]-N⁴-phenethylpiperazine (9).—A solution of 3-(*p*-chlorophenyl)-3-phenylpropionyl chloride (5.58 g, 0.02 mole) in anhydrous $CHCl_3$ (25 ml) was added slowly to a solution of N-phenethylpiperazine (3.8 g, 0.02 mole) and Et_3N (4 g, 0.04 mole) in anhydrous $CHCl_3$ (25 ml), and the mixture was refluxed for 7 hr. It was then cooled, washed (H_2O), dried (Na_2SO_4), and concentrated. The resulting solid was crystallized twice.

The other members of this series (I, A = CH_2CO) were prepared similarly. Absorption peaks of ir spectra were as expected.

N¹-[3-(*p*-Chlorophenyl)-3-phenylpropyl]-N⁴-phenethylpiperazine Dihydrochloride (10).—A solution of the above amide (2.16 g, 0.05 mole) in Na-dried THF (175 ml) was added dropwise to a suspension of LAH (1.0 g) in dry Et_2O (200 ml) at such a rate that a gentle reflux was maintained. After addition, the reaction mixture was refluxed for 16 hr, cooled in ice, and decomposed by dropwise addition of ice–H_2O. The inorganic material was filtered off and the organic phase was dried (Na_2SO_4) and concentrated. The residue was taken up in 15 ml of Me_2CO and was added to 10 ml of 5 *N* 2-propanolic HCl. The white solid thus obtained was recrystallized.

The rest of the amides were reduced similarly to the corresponding amines. Absorption peaks of ir spectra were as expected.

δ-(*p*-Chloro-α-phenylbenzyloxy)butyl Chloride.—The procedure followed was analogous to that described by Morren[13] for the preparation of δ-(*o*-chloro-α-phenylbenzyloxy)butyl chloride; yield 60%, bp 186–194° (5 mm). *Anal.* ($C_{17}H_{18}Cl_2O$) C, H.

β-(*p*-Chloro-α-phenylbenzylmercapto)ethyl Alcohol.—*p*-Chloro-α-phenylbenzyl mercaptan[3a] (94 g, 0.4 mole) was added dropwise to an equimolar quantity of $NaOC_2H_5$ in 200 ml of EtOH, followed by ethylene chlorohydrin (32 ml, 0.4 mole) and refluxed for 2 hr. The reaction mixture was poured over ice and extracted with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and the solvent was removed. The residual oil was subjected to fractional distillation under reduced pressure and the fraction distilling at 216–224° (11 mm) was collected as a bluish oil, yield 57 g (51%). *Anal.* ($C_{15}H_{15}ClOS$) C, H, S.

β-(*p*-Chloro-α-phenylbenzylmercapto)ethyl chloride was prepared from the corresponding alcohol with $SOCl_2$ in $CHCl_3$, bp 208–218° (13 mm), yield 63%. *Anal.* ($C_{15}H_{14}Cl_2S$) C, H, S.

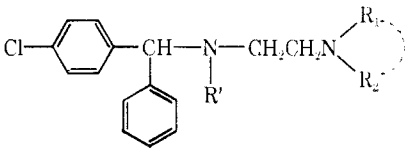
β-(*p*-Chloro-α-phenylbenzylamino)ethyl Alcohol.—A solution of *p*-chloro-α-phenylbenzyl chloride (119 g, 0.5 mole) in pyridine

(12) G. G. Henderson, *J. Chem. Soc.*, **59**, 731 (1891).

(13) H. G. Morren, Belgian Patent 551,032 (March 14, 1957); *Chem. Abstr.*, **53**, 20101*i* (1959).

TABLE II

N,N'-DISUBSTITUTED ETHYLENEDIAMINES

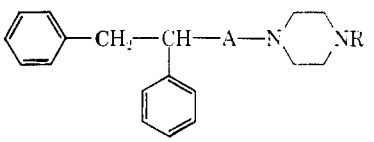


No.	R'	-N(R1)(R2)	Crystn solvent[a]	% yield[b]	Mp or bp (mm), °C	Formula	Analyses	Mouse LD50, mg/kg ip	CNS depression,[c] mg/kg	% ↓ in motor act. of mice[d]	Antihistaminic act.[e]
83	H	NH_2		62	204–210 (4)	$C_{15}H_{17}ClN_2$	C, H, N	450	135[f]	[illegible]	
84	H	Me_2N	E	52	180–181[g]	$C_{17}H_{21}ClN_2$·dioxalate	C, H, N	150	(−)		
85	Me	Me_2N	E	48	136–138	$C_{18}H_{23}ClN_2$·dioxalate	C, H, N	100	(−)		
86	H	Et_2N		41	176–184 (8)	$C_{19}H_{25}ClN_2$	N	100	(−)		
			E		184–185	$C_{19}H_{25}ClN_2$·dipicrate	N				
87	H	n-Pr_2N		41	175–187 (1)	$C_{21}H_{29}ClN_2$	N	250	(−)	(−)	
88	H	n-Bu_2N		56	190–205 (8)	$C_{23}H_{33}ClN_2$	N	250	60[f]	52	
89	H	$(PhCH_2)_2N$		40	255–270 (7)	$C_{29}H_{29}ClN_2$	N				
			E-Et		172–173	$C_{29}H_{29}ClN_2$·oxalate	C, H, N	200	60		
90	H	C_5H_5NH		69	200–205 (9)	$C_{18}H_{19}ClN_2$	C, H, N	60	(−)	(−)	
			A		164–165	$C_{18}H_{21}ClN_2$·dimaleate	N				
91	H	n-PrNH		58	170–176 (8)	$C_{18}H_{23}ClN_2$	C, H, N				
			E		216–217 dec	$C_{18}H_{23}ClN_2$·dioxalate	N	150	(−)	(−)	(−)
92	Me	n-PrNH	E	39	204–205	$C_{19}H_{25}ClN_2$·oxalate	N	250	90	(−)	
93	H	i-PrNH		56	170–180 (10)	$C_{18}H_{23}ClN_2$	N	150	60	(−)	
			A		151–152	$C_{18}H_{23}ClN_2$·dimaleate	C, H, N				(−)
94	Me	i-PrNH		42	184–194 (8)	$C_{19}H_{25}ClN_2$	N				
95	H	i-BuNH		49	200–205 (9)	$C_{19}H_{26}ClN_2$	N	800	90		(−)
			E-Et		167–168 dec	$C_{19}H_{25}ClN_2$·dimaleate	C, H, N				
96	H	Cyclohexylamino		46	223–236 (4)	$C_{21}H_{27}ClN_2$	N	200	(−)		
97	H	2,6-Xylidino		49	232–242 (7)	$C_{23}H_{25}ClN_2$	N				
			E		171–172	$C_{23}H_{25}ClN_2$·maleate	C, H, N	800	(−)	(−)	
98	H	Morpholino		56	190–200 (3)	$C_{19}H_{23}ClN_2O$	N,	200	60	56	
			A		193–194 dec	$(C_{19}H_{23}ClN_2O)_2$·trioxalate	C, H, N			67	
99	Me	Morpholino		48	210–212 (7)	$C_{20}H_{25}ClN_2O$	C, H, N	800	135[f]		
			A		161–162	$(C_{20}H_{25}ClN_2O)_2$·trioxalate	C, H, N				
100	H	Piperidino	51		215–224 (10)	$C_{20}H_{25}ClN_2$	N	200	40	67	
			E		170–171	$C_{20}H_{25}ClN_2$·dioxalate	N				

[a–f] See corresponding footnotes in Table I. [g] V. D. Amato [*Boll. Soc. Ital. Biol. Sper.*, **27**, 426 (1951); *Chem. Abstr.*, **48**, 866*d* (1954)] reported the dihydrochloride of base (hygroscopic).

TABLE III

1,2-DIPHENYLETHYLAMINES



No.	A	R	Crystn solvent[a]	% yield[b]	Mp or bp (mm), °C	Formula	Analyses	Mouse LD50, mg/kg ip	CNS depression,[c] mg/kg	% ↓ in motor act. of mice[d]	Antihistaminic act.[e]
101	$NH(CH_2)_2$	Me		54	210–215[h] (7)	$C_{21}H_{29}N_3$	N	300	(−)[f]	(−)	(−)
102	$NH(CH_2)_2$	$PhCH_2$	E	53	170–171	$C_{27}H_{33}N_3$·dimaleate	C, H, N	75	30	56	
			E		258–260 dec	$C_{27}H_{33}N_3$·3HCl	C, H, N				
103	$NH(CH_2)_2$	m-Methylbenzyl		47	255–265 (5)	$C_{28}H_{35}N_3$	N	250	60	70	
104	$NH(CH_2)_2$	p-t-Butylbenzyl	H	53	88–89	$C_{31}H_{41}N_3$	C, H, N	800	100	56	(−)
105	$NH(CH_2)_2$	p-Chloro-α-phenylbenzyl		43	260–275 (7)	$C_{33}H_{36}ClN_3$	N				
106	$NH(CH_2)_2$	o-Methoxyphenyl	E-Et	46	126–128	$C_{27}H_{33}N_3O$·dimaleate	C, H, N				
			E-Et		208–210	$C_{27}H_{33}N_3O$·HCl	C, H, N	150	(−)[g]	(−)	
107	$NH(CH_2)_2$	p-Methoxyphenyl	H	53	99–101	$C_{27}H_{33}N_3O$	C, H, N	300	(−)	52	
108	$NH(CH_2)_2$	2-Pyridyl	H	62	112–113	$C_{25}H_{30}N_4$	C, H, N	450	90[f]	62	(−)[f]
109	$NH(CH_2)_2$	2-Pyrimidyl	H	65	113–114	$C_{24}H_{29}N_5$	C, H, N	100	(−)	(−)	
110	$N(CH_3)(CH_2)_2$	2-Pyrimidyl	E	56	226–232 dec	$C_{26}H_{31}N_5$·3HCl	C, H, N	75	(−)	(−)	
111	$NH(CH_2)_2$	2-Thiazolyl	H	51	84–85	$C_{23}H_{28}N_4S$	C, H, N, S	75	(−)	(−)	

[a–g] See corresponding footnotes in Table I. [h] Compounds solidified on standing. [i] 50% inhibition of ACh response after 10 min; the effect lasted for 2 hr.

(120 ml) was added dropwise with stirring to an ice-cooled solution of monoethanolamine (61 g, 1 mole) in pyridine (75 ml). Stirring was continued for 6 hr at room temperature and the mixture was then heated on a steam bath for 10 hr. Pyridine was distilled off under diminished pressure, and the residue was treated with ice–H_2O and extracted with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and concentrated, and the resulting oil was distilled *in vacuo*. The fraction distilling at bp 202–212° (6 mm) was collected, yield 79 g (60%). *Anal.* ($C_{15}H_{16}ClNO$) N. The oxalate was crystallized (EtOH–Me_2CO), mp 191–192°.[14a] *Anal.* ($C_{17}H_{18}ClNO_5$) N.

(14) (a) E. Gwynnp and F. Colin [British Patent 1,109,502 (April 10, 1968); *Chem. Abstr.*, **69**, 35937*m* (1968)] prepared this compound by the catalytic reduction of the Schiff base obtained from *p*-chlorobenzophenone and monoethanolamine. (b) B·HCl lit.[14a] mp 230–232°.

β-(p-Chloro-α-phenylbenzylamino)ethyl chloride hydrochloride was obtained in 71% yield by the action of $SOCl_2$ on β-(p-chloro-α-phenylbenzylamino)ethyl alcohol in $CHCl_3$ following the usual techniques; it was crystallized from EtOH, mp 230–232°.[14b] *Anal.* ($C_{15}H_{16}Cl_3N$) C, H, N.

β-[N-(Methyl)-N-(p-chloro-α-phenylbenzyl)amino]ethyl Alcohol.—A mixture of β-(p-chloro-α-phenylbenzylamino)ethyl alcohol (26.15 g, 0.1 mole), HCOOH (10 ml, 98%), and HCHO (41 ml, 37–41%) was refluxed for 6 hr. Most of the HCHO and HCOOH were removed by distillation under diminished pressure. The residue was made alkaline with cold 5 *N* NaOH and extracted with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and concentrated and the residue was distilled *in vacuo*. The fraction distilling at 184–190° (6 mm) was collected, yielded 18 g (65%). *Anal.* ($C_{16}H_{18}ClNO$) N.

β-[N-(Methyl)-N-(p-chloro-α-phenylbenzyl)amino]ethyl chloride hydrochloride was obtained as an oil by the action of $SOCl_2$ on the corresponding alcohol and was used directly for further condensation.

β-(1,2-Diphenylethylamino)ethyl chloride hydrochloride was prepared in 91% yield by the action of $SOCl_2$ on the corresponding alcohol[15] as usual and crystallized (EtOH), mp 212–213° dec. *Anal.* ($C_{16}H_{19}Cl_2N$) N.

β-[N-(Methyl)-N-(1,2-diphenethyl)amino]ethyl chloride hydrochloride was prepared from β-(1,2-diphenylethylamino)ethyl alcohol hydrochloride, following the method described by Kerwin, *et al.*[16]

N^1-[β-(p-Chloro-α-phenylbenzyloxy)ethyl]-N^4-(2-pyridyl)piperazine Maleate (37).—To a mixture of N-(2-pyridyl)piperazine (1.63 g, 0.01 mole) and Et_3N (2.0 g, 0.02 mole) in EtOH (20 ml), was added a solution of β-(p-chloro-α-phenylbenzyloxy)ethyl chloride[17] (3.09 g, 0.11 mole) in EtOH (10 ml) and the reaction mixture was refluxed for 25 hr. The solvent was distilled off, and the residue was treated with cold 40% NaOH till alkaline and extracted with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and concentrated. The resulting oil was taken up in 20 ml of EtOH and added to a solution of maleic acid in EtOH. The solid thus obtained was crystallized.

N-(p-Chloro-α-phenylbenzyl)-N'-(2,6-xylidino)ethylenediamine (97) was prepared by the condensation of β-(p-chloro-α-phenylbenzylamino)ethyl chloride [obtained by the basification of 9.5 g, 0.03 mole, of β-(p-chloro-α-phenylbenzylamino)ethyl chloride hydrochloride] with 2,6-xylidine (3.63 g, 0.03 mole) following the method described for **37**. The resulting oil was distilled *in vacuo* and the fraction distilling at bp 230–242° (7 mm) was collected. The free base was converted to its maleate salt.

N-(p-Chloro-α-phenylbenzyl)ethylenediamine (83).—A solution of p-chloro-α-phenylbenzyl chloride (23.7 g, 0.1 mole) in pyridine (25 ml) was added dropwise with stirring to an ice-cooled solution of ethylenediamine (24 g, 0.4 mole) in pyridine (50 ml). The reaction mixture was stirred at room temperature for 16 hr and then heated on a steam bath for 1 hr. Pyridine was distilled off at diminished pressure, cold H_2O was added to the residue, and the residue was extracted with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and concentrated. The residual oil was distilled *in vacuo* and the portion distilling between 176 and 182° (2 mm) was collected.

The other compounds reported in Tables I–III were obtained by the condensation of appropriate halides with various N-monosubstituted piperazines or appropriate amines, following the method described for **37**. In case of amines having low boiling points, excess of amines was taken, eliminating the use of triethylamine. The resulting products were crystallized when solid or converted into the appropriate salts or distilled under vacuum when an oil.

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Synthesis and Central Nervous System Depressant Activity of New Piperazine and Related Derivatives. III

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Several N^1,N^4-disubstituted piperazine derivatives, in which N^1 substituents are 3,4,5-trimethoxybenzoylacetyl, 3,4,5-trimethoxycinnamoyl or -hydrocinnamoyl, 3,4,5-trimethoxyphenylpropyl, and 3,4,5-trimethoxybenzoylalkyl and N^4 substituents are benzyl, *m*-methyl- or *p*-*t*-butylbenzyl, *p*-chloro-α-phenylbenzyl, phenyl, chloro-, fluoro-, or methoxyphenyl, tolyl, α,α,α-trifluorotolyl, 2-pyridyl, 2-pyrimidyl, or 2-thiazoyl groups, have been synthesized. Analogous compounds with other alkyl and heterocyclic amines in place of piperazine have also been synthesized. All these compounds have been screened for CNS activity. A few of these compounds exhibited significant CNS depressant activity. The 3,4,5-trimethoxyphenyl moiety was found to be the most essential for CNS activity as stepwise omission of the methoxy groups of most active compounds resulted in loss of activity.

We have recently reported[2] the synthesis and CNS depressant activity of compounds incorporating 3,4,5-trimethoxyphenyl and piperazine groupings into a single molecule with appropriate variations in the connecting bridge and at the N^4 position of piperazine ring. In that series the $-COCH_2CH_2-$ linkage was found to furnish the most active compounds. The work has now been extended to include new linkages, restricting the length of the bridge to three carbon atoms. Analogous compounds replacing the piperazine with other biologi-

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