a Grignard solution prepared from Mg (4.7 g) and 4-(cyclopent-1-enyl)bromobenzene (38 g) in a mixture of Et_2O (235 ml) and THF (95 ml), a solution of 2,3-epoxypropyl chloride (31.5 g) in Et_2O (40 ml) was added during 30 min with stirring at room temperature. After stirring for a further 30 min the mixture was decomposed by the addition of 5 *N* HCl. The ether layer was separated, washed (H_2O), and dried (Na_2SO_4) and the ether was distilled. The residual oil was distilled to yield a fraction (18.5 g), bp 120–155° (0.1 mm), which solidified and had mp 100–101° (from ligroin).

(c) **1-Cyano-3-[*p*-(cyclopent-1-enyl)phenyl]propan-2-ol.**—A solution of the foregoing chlorohydrin (14.8 g) in EtOH (150 ml) was treated with a solution of 96% KCN (5.1 g) in H_2O (11 ml) and the mixture was heated under reflux for 90 min. It was then cooled and diluted with iced H_2O and the product was isolated with $CHCl_3$. It (12 g) had mp 77–78° [from C_6H_6–petroleum ether (bp 60–80°)].

(d) **Ethyl 4-[*p*-(cyclopent-1-enyl)phenyl]-3-hydroxybutyrate** was obtained when a solution of the foregoing nitrile (7.5 g) in EtOH (75 ml) and H_2O (2 ml) was saturated with HCl gas and then heated under reflux for 12 hr. The ester (4.4 g) isolated with $CHCl_3$ had bp 165–169° (0.15 mm).

(e) **4-[*p*-(Cyclopent-1-enyl)phenyl]-3-hydroxybutyric Acid.**—A solution of the foregoing ester (2.2 g) in 50% EtOH–H_2O (25 ml) containing NaOH (0.4 g) was heated under reflux for 1 hr. It was then cooled slightly and poured with stirring into excess warm, dilute HCl. The mixture was cooled and the acid was collected. It (1.7 g) had mp 153–156° (from MeOH–H_2O).

4-(Cyclohept-1-enyl)bromobenzene, prepared as described for 4-(cyclopent-1-enyl)bromobenzene, using cycloheptanone in place of cyclopentanone, had mp 51–53° (from MeOH). *Anal.* ($C_{13}H_{15}Br$) C, H, Br.

N-(β-Hydroxyethyl)-4-(*p*-biphenylyl)-3-hydroxybutyramide.—A mixture of ethyl 4-(*p*-biphenylyl)-3-hydroxybutyrate (10 g) and ethanolamine (10 ml) was heated on the steam bath for 2 hr when it was cooled and stirred with dilute HCl. The amide (8 g) had mp 130–131° (from EtOH). *Anal.* ($C_{18}H_{21}NO_3$) C, H, N.

N-(β-Hydroxyethyl)-4-(*p*-biphenylyloxy)-3-hydroxybutyramide had mp 181–183° (from EtOH). *Anal.* ($C_{18}H_{21}NO_4$) C, H, N.

N-(β-Hydroxyethyl)-3-hydroxy-4-(2-naphthyloxy)butyramide had mp 161–163° (from EtOH). *Anal.* ($C_{16}H_{19}NO_4$) C, H, N.

Acknowledgments.—The authors are indebted to Dr. P. Feather, A.R.I.C., Mr. D. F. Hayman, A.R.I.C., and Dr. G. B. Jackman, A.R.I.C., for the preparation of some of the compounds listed in Table II and to Mr. G. Vincent for technical assistance.

Potential Antihypertensive Agents. II.[1] Unsymmetrically 1,4-Disubstituted Piperazines. I

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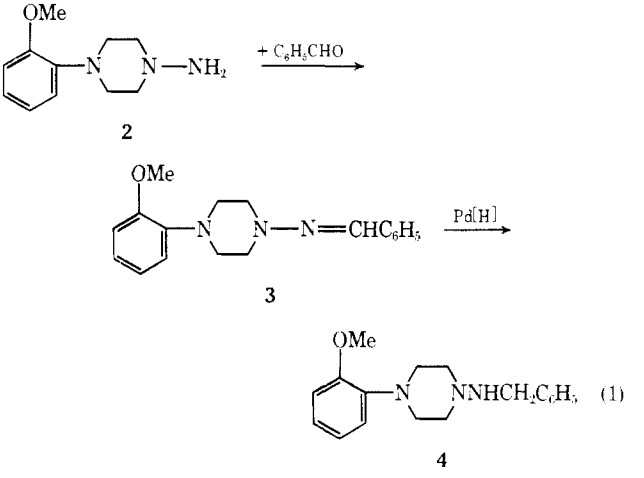
Several unsymmetrically 1,4-disubstituted piperazines have been prepared by reducing 1-acyl-4-substituted piperazines, the latter having been obtained by the acylation of 1-alkyl- or 1-arylpiperazines. Alkylation of 1-amino-4-(*o*-methoxyphenyl)piperazine (**2**) gives 1-amino-1-alkyl-4-(*o*-methoxyphenyl)piperazinium halide (**5–8, 12**). Some of the 4-substituted derivatives of 1-phenyl- or 1-(*o*-methoxyphenyl)piperazines show appreciable antihypertensive activities, but the 1-methyl-4-substituted piperazines cause no significant fall in blood pressure.

In continuation of our studies of compounds having antihypertensive properties, we have prepared and tested a large number of unsymmetrically 1,4-disubstituted piperazines.

Chemistry.—The unknown 1-phenyl-4-aminopiperazine (**1**) was prepared by refluxing bis-β-chloroethyl aniline with hydrazine in ethanol. Preparation of 1-(*o*-methoxyphenyl)-4-aminopiperazine (**2**) was similarly achieved. These compounds could also be prepared by nitrosating the corresponding 1-substituted piperazine with sodium nitrite and hydrochloric acid and reducing the 4-nitrosopiperazine derivative with zinc dust in acetic acid.

Reaction of **2** with aromatic aldehydes resulted in the formation of the corresponding Schiff bases, *e.g.*, **3** (eq 1). Hydrogenation of **3** in the presence of 10% Pd-C gave **4**. Attempted reduction of **3** ($NaBH_4$ or $LiAlH_4$), or hydrogenation in the presence of PtO_2, failed to give **4**.

The reaction of **2** with benzyl chloride or benzyl iodide resulted in substitution on the 1-nitrogen atom to yield **5** and **6** (eq 2). Compound **7** (and **8**) was similarly obtained. Proof for the assignment of the structure of **5** (and **6**) was found in the reaction of benzylhydrazine and bis(β-chloroethyl)-*o*-anisidine (**9**) which yielded the hydrochloride **10** and could be converted to **5** by treatment with $NaHCO_3$ (eq 2).

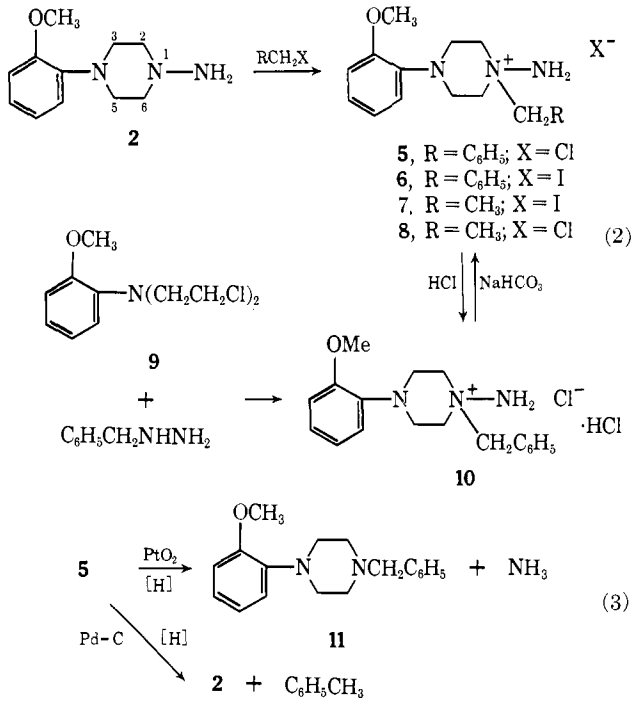


(1)

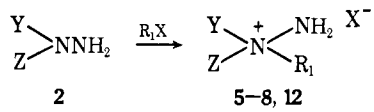
Hydrogenolysis of **5** (eq 3) in the presence of PtO_2 gave 1-benzyl-4-(*o*-methoxyphenyl)piperazine (**11**) and ammonia. On the other hand, hydrogenolysis in the presence of 10% Pd-C gave 1-amino-4-(*o*-methoxyphenyl)piperazine (**2**) and toluene.

Substitution on the N-1 position of 1-amino-4-(*o*-methoxyphenyl)piperazine (**2**) may be explained by the assumption that N-1 has the highest nucleophilic activity of the three nitrogen atoms in the molecule. The amino group in compound **2** can be visualized as a

(1) F. Fried, R. N. Prasad, and A. P. Gaunce, *J. Med. Chem.*, **10**, 279 (1967), may be considered as paper 1.

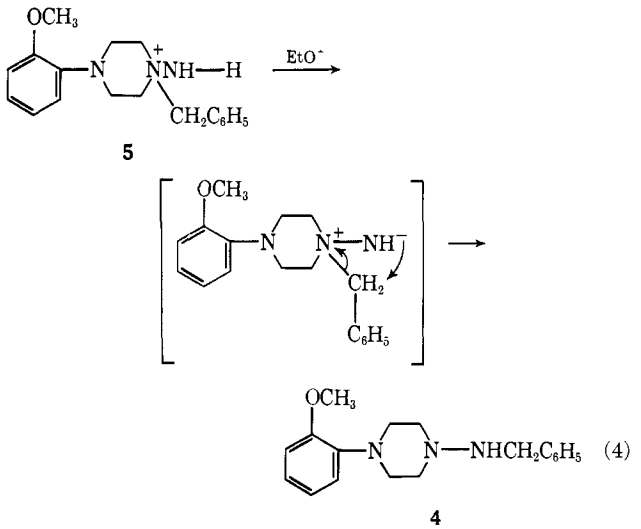


part of the unsymmetrically disubstituted hydrazine. Y and Z may be considered as the alkyl groups which



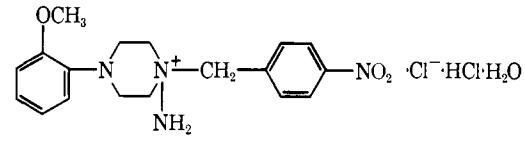
tend to increase the availability of the electron pair on the N-1 nitrogen, making it the center of highest nucleophilic reactivity.[2]

When **5** was heated with sodium ethoxide in absolute ethanol, it underwent a rearrangement to give **4** (eq 4), which may be postulated as analogous to the Steven rearrangement.[3,4]



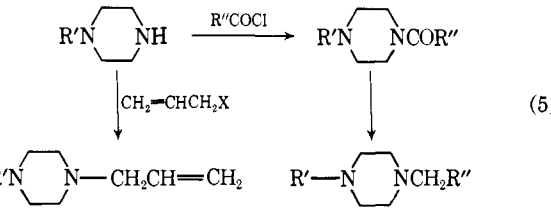
Treatment of **2** with a large excess of MeI gave a monomethiodide (**7**), which was also prepared from **8** (obtained from methylhydrazine and **9**) and KI. The product **7** (and **8**) is thus considered to be the N-1 methyl derivative.

A study of the nmr data of **2**–**12** shows that the four aromatic protons of *o*-methoxyphenyl ring in **4**–**11** appear between 455 and 463 Hz as a relatively broad single peak in the aromatic region. This assignment is based on the spectrum of **12**.[5]



Reaction of phenylpiperazine with ethylenimine in refluxing ethanol, containing a catalytic amount of H_2SO_4, gave 1-(β-aminoethyl)-4-phenylpiperazine[6] (**13**) in 76% yield. Other (β-aminoethyl)-4-substituted piperazines (**14**, **15**) were made similarly. This method was found to be more convenient than the two-step method[7] from 1-substituted piperazine *via* 1-substituted piperazine–acetonitrile.[8,9]

The amides (Table IV, and partly in Tables III and I), in general, were prepared from the corresponding piperazines by treatment with the appropriate acid chloride in the presence of a proton acceptor (eq 5). An excess of the piperazine usually served this purpose. Some of the amides on reduction with $LiAlH_4$ or diborane gave rise to 1-aralkyl-4-substituted piperazines (Table V). Preparation of 1-allyl- or 1-propargyl-4-substituted piperazines was achieved by the reaction of allyl or propargyl bromide with the desired substituted piperazines (eq 5).



Pharmacology.—The antihypertensive activity of the compounds was measured as described before.[1] In most cases, the effect of the compounds on pressor responses to epinephrine and bilateral carotid occlusion were also noted. The results are given in Tables I–V.

A general study of the structural features of the piperazines tested for their effect on blood pressure of experimental animals led to the following observations. None of the 1-methyl-4-substituted piperazines showed any significant activity. Only the 4-substituted derivatives of 1-phenyl- or 1-*o*-methoxyphenylpiperazines showed appreciable and sustained fall in blood pressure. Of these, the most active ones were **1**, **2**, **41**, **84**, **88**, and **97**.

Substitution of a methoxy group in the *ortho* position of the phenyl ring in 1-benzoyl-4-phenylpiperazine[10]

(2) B. M. Bloom, *Ann. N. Y. Acad. Sci.*, **107**, 878 (1963).

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 523.

(4) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, p 266.

(5) The *p*-nitrobenzylic ring of **12** gave the expected $A_2'B_2'$ pattern at lower field (474–506 Hz).

(6) E. Cerkovnikov and P. Stern, *Arhiv. Kem.* (Zagreb), **18**, 12 (1946).

(7) J. H. Short, U. Biermacher, D. A. Dunnigan, and T. D. Leth, *J. Med. Chem.*, **6**, 275 (1963).

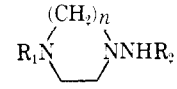
(8) R. P. Mull, R. M. Mizzoni, M. R. Dapero, and M. E. Egbert, *ibid.*, **5**, 944 (1962).

(9) D. E. Adelson and C. B. Pollard, *J. Amer. Chem. Soc.*, **57**, 1430 (1935).

(10) V. Prelog and G. J. Driza, *Collect. Czech. Chem. Commun.*, **5**, 497 (1933); *Chem. Abstr.*, **28**, 1347 (1934).

Table I

1-Alkyl- or 1-Aralkyl-4-(substituted)aminopiperazines and -homopiperazines

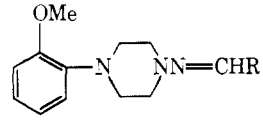


No.	R_1	R_2	n	Yield,[a] %	Bp (bath) or mp, °C	Salt[b]	Method[c]	Formula	Analyses	Activity[d]
1	C_6H_5	H	2	50[e]	108–110 (0.17)			$C_{10}H_{15}N_3$	C, H, N	A – – –
					57–60					
2	o-$CH_3OC_6H_4$	H	2	75[f]	144–149 (0.5)			$C_{11}H_{17}N_3O$	C, H, N	B – – –
					101–104	E + M				
					206–209 dec	M + E		$C_{11}H_{17}N_3O \cdot 2HCl$		
4	o-$CH_3OC_6H_4$	$CH_2C_6H_5$	2	35	210.5–211.5	A + E		$C_{18}H_{23}N_3O \cdot HCl$	C, H, Cl, N	+ –
19	CH_3	H	3	60	94–96 (18)[g]			$C_6H_{15}N_3$	C, H, N	+ –
24	CH_3[h]	$COCH{=}CHC_6H_5$	2	15	225–227 dec	M + E	F(18)	$C_{14}H_{19}N_3O \cdot 2HCl$	C, H, Cl, N	+ –
25	CH_3	$COCH{=}CHC_6H_5$	3	39	124–126	B + P	D(1)	$C_{15}H_{21}N_3O$	C, H, N, O	–
26	C_6H_5	COC_6H_5	2	76	235–236	A	D(2)	$C_{17}H_{19}N_3O$	C, H, N	+
27	o-$CH_3OC_6H_4$	COC_6H_5	2	63	193–195	A	D(2)	$C_{18}H_{21}N_3O_2$	C, H, N	+
28	o-$CH_3OC_6H_4$	$COC_6H_4OCH_3$-p	2	75	219–220.5	A	D(2)	$C_{19}H_{23}N_3O_3$	C, H, N	+

[a] Yields given are those of crude solid or once distilled liquid. [b] Recrystallization solvents: A = EtOH, B = C_6H_6, E = Et_2O, M = MeOH, P = petroleum ether (bp 30–60°). [c] Reaction period indicated in hours in parentheses. [d] Yield 64% from 1-nitroso-4-phenylpiperazine and 50% from bis(β-chloroethyl)aniline and hydrazine. [e] Yield 75% from 1-o-methoxyphenyl-4-nitrosopiperazine, 66% from N-[bis(β-chloroethyl)]-o-anisidine and hydrazine. [f] $n^{30}D$ 1.4898. [g] The starting amine, 1-amino-4-methylpiperazine, bp 73–80° (18 mm), $n^{30}D$ 1.4813, was prepared according to the method reported: E. A. Conroy, U. S. Patent 2,663,706 (Dec 1953) (lit. bp 118–120° (25 mm)). [h] + –, inactive; +, rise in blood pressure; X, sustained fall in blood pressure, but marked decrease in epinephrine and/or carotid occlusion; XX, sustained fall in blood pressure, but reversal of epinephrine response; –, transient fall in blood pressure or insufficient activity; – –, unsustained fall in blood pressure; – – –, mean blood pressure lowered by 30–60 mm for 1 hr or longer; A, B, or C, (A) decrease in epinephrine and carotid occlusion, (B) decrease in epinephrine only, (C) increase in epinephrine and decrease in carotid occlusion.

Table II

1-o-Methoxyphenyl-4-substituted Benzylideneaminopiperazines

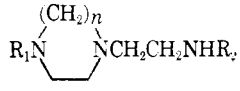


No.	R	Yield, %[a]	Mp, °C	Salt[b]	Formula	Analyses	Activity[c]
3	C_6H_5	51.5	93–94	A	$C_{18}H_{21}N_3O$	C, H, N, O	+
20	$C_6H_3Cl_2$-3,4	32	137–138	A	$C_{18}H_{19}Cl_2N_3O$	C, H, Cl, N	+
21	$C_6H_3(OCH_3)_2$-3,4	75	145–146.5	A	$C_{20}H_{25}N_3O_3$	C, H, N	+
22	$C_6H_4N(CH_3)_2$-p	70	132–133.5	A	$C_{20}H_{26}N_4O$	C, H, N	+ –
23		88	87–88.5	E + P	$C_{17}H_{20}N_4O$	C, H, N	+

[a] Yields given are those of crude solids. [b] Recrystallization solvents: A = EtOH, E = Et_2O, P = petroleum ether. [c] See footnote *h* in Table I.

Table III

1-Alkyl- or 1-Aryl-4-(β-substituted amino)ethylpiperazines and -homopiperazines



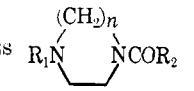
No.	R_1	R_2	n	Yield, %[a]	Mp, °C	Salt[b]	Method[c]	Formula	Analyses	Activity[d]
29	CH_3	COC_6H_4Cl-o	3	38	109–111	M + E	F(18)	$C_{15}H_{22}ClN_3O \cdot 0.5H_2O \cdot 2HCl$	C, H, Cl, N	+ –
30	CH_3	$COCH{=}CHC_6H_5$	2	31	254–256	M + E	A(11)	$C_{16}H_{23}N_3O \cdot 2HCl$	C, H, Cl, N	+ –
31	C_6H_5	$CH_2CH_2CONHNH_2$	2	*d*	225–227 dec	M + E	*e*	$C_{15}H_{25}N_5O \cdot 3HCl$	C, H, Cl, N	–

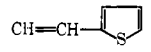
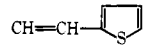
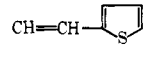
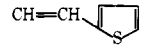
[a] Yields given are those of crude solid. [b] Recrystallization solvents: M = MeOH, E = Et_2O. [c] Reaction period in hours indicated in parenthesis. [d] Over-all yield 10% starting from **13**. [e] Prepared by the reaction of 1-(β-aminoethyl)-4-phenylpiperazine (**13**) (0.1 mole) with ethyl acrylate (0.12 mole) at room temperature for 72 hr, complete removal of the solvent and excess ester under reduced pressure, and subsequent refluxing with 95% hydrazine (0.12 mole) in EtOH for 3 hr. Ethanol was removed and the product was isolated as a trihydrochloride. [f] See footnote *h* in Table I.

(which caused a sustained fall in blood pressure) gave **57**, which caused an unsustained fall in blood pressure. However, if the methoxy group was attached to the *ortho* position of the benzoyl group, as in **41**, the product so obtained produced a sustained fall in blood pressure. The corresponding *p*-methoxybenzoyl derivative (**42**) caused a large unsustained fall in blood pressure, whereas the *m*-methoxybenzoyl derivative (**43**) was inactive.

There was no consistent change in antihypertensive

TABLE IV: 1-ALKYL- OR 1-ARALKYL-4-ACYLPIPERAZINES AND -HOMOPIPERAZINES

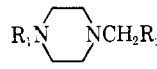


No.	R_1	R_2	n	Yield,[a] %	Mp, °C	S[b]	Method[c]	Formula	Analyses	Activity[h]
32	o-$CH_3OC_6H_4$	p-ClC_6H_4	2	85	125–127	B + P	E(20)	$C_{18}H_{19}ClN_2O_2$	C, H, Cl, N	X
33	CH_3	p-ClC_6H_4	2	81	279–281	M + E	F(20)	$C_{12}H_{15}ClN_2O \cdot HCl$	C, H, Cl, N	− −
34	CH_3	p-ClC_6H_4	3	53	183–185	M + E	F(20)	$C_{13}H_{17}ClN_2O \cdot HCl$	C, H, Cl, N	−
35	CH_3	o-ClC_6H_4	2	82	292–294 dec	M + E	A(1)	$C_{12}H_{15}ClN_2O \cdot HCl$	C, H, Cl, N	+
36	CH_3	o-ClC_6H_4	3	83	253–255 dec	M	A(1)	$C_{13}H_{17}ClN_2O \cdot HCl$	C, H, Cl, N	+
37	o-$CH_3OC_6H_4$	o-ClC_6H_4	2	78	164–166	B + P	D(1)	$C_{18}H_{19}ClN_2O_2$	C, H, Cl, N, O	− −
38	o-$CH_3OC_6H_4$	o-$CH_3OC_6H_4$	2	87	91– 93	E	D(0.5)	$C_{19}H_{22}N_2O_3$	C, H, N	− −
39	CH_3	o-$CH_3OC_6H_4$	2	57	268–270	M + E	F(20)	$C_{13}H_{18}N_2O_2 \cdot HCl$	C, H, Cl, N	−
40	CH_3	o-$CH_3OC_6H_4$	3	55	262–264	M + E	F(20)	$C_{14}H_{20}N_2O_2 \cdot HCl$	C, H, Cl, N	+ −
41[d]	C_6H_5	o-$CH_3OC_6H_4$	2	99	103–104	Ea	A(3)	$C_{18}H_{20}N_2O_2$	C, H, N, O	B− − −
42	C_6H_5	p-$CH_3OC_6H_4$	2	81	128–129.5	E	E(20)	$C_{18}H_{20}N_2O_2$[e]	C, H, N	− −
43	C_6H_5	m-$CH_3OC_6H_4$	2	46	208–210[e] dec	E + W	B(1)	$C_{18}H_{20}N_2O_2 \cdot HCl$	C, H, Cl, N	+ −
44	CH_3	p-$CH_3OC_6H_4$	2	97	241–243	M + E	A(2)	$C_{13}H_{18}N_2O_2 \cdot HCl$	C, H, Cl, N	−
45	o-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	2	97	122–123	B + P	D(1)	$C_{19}H_{22}N_2O_3$	C, H, N	−
46	CH_3	o-$CH_3C_6H_4$	2	74	286–288 dec	M + E	B(0.5)[f]	$C_{13}H_{18}N_2O \cdot HCl$	C, H, Cl, N	+ −
47	CH_3	o-$CH_3C_6H_4$	3	55	264–266 dec	M + E	B(1)[f]	$C_{14}H_{20}N_2O \cdot HCl$	C, H, Cl, N	+ −
48	C_6H_5	o-$CH_3C_6H_4$	2	33.5	200–202	M + E	B(0.5)[f]	$C_{18}H_{20}N_2O \cdot HCl$	C, H, Cl, N	X
49	C_6H_5	m-$CH_3C_6H_4$	2	74.5	198–200	M + E	B(0.5)[f]	$C_{18}H_{20}N_2O \cdot HCl$	C, H, Cl, N	− −
50	C_6H_5	p-$NO_2C_6H_4$	2	95	119–121	M	E(20)	$C_{17}H_{17}N_3O_3$	C, H, N	− −
51	CH_3	p-$NO_2C_6H_4$	2	96	98–100	C + H	D(2)	$C_{12}H_{15}N_3O_3$	C, H, N, O	+ −
52	o-$CH_3OC_6H_4$	p-$NO_2C_6H_4$	2	62	128–130	C + M	D(0.5)[g]	$C_{18}H_{19}N_3O_4$	C, H, N, O	− −
53	C_6H_5	m-$NO_2C_6H_4$	2	82	93– 95	M	E(20)	$C_{17}H_{17}N_3O_3$	C, H, N	+ −
54	o-$CH_3OC_6H_4$	m-$NO_2C_6H_4$	2	90	109–111	M	E(20)	$C_{18}H_{19}N_3O_4$	C, H, N	−
55	o-$CH_3OC_6H_4$	3,5-$(NO_2)_2C_6H_3$	2	53	154–156	C + M	E(20)	$C_{18}H_{18}N_4O_6$	C, H, N	− −
56	CH_3	C_6H_5	3	50	210–212	M + E	A(4)	$C_{13}H_{18}N_2O \cdot HCl$	C, H, Cl, N	+
57	o-$CH_3OC_6H_4$	C_6H_5	2	20	98– 99	C + H	A(2)	$C_{18}H_{20}N_2O_2$	C, H, N, O	− −
58[d]	C_6H_5	c-C_3H_5	2	73	63– 64[h]	E + P	E(4)	$C_{14}H_{18}N_2O$	C, H, N, O	−
59	C_6H_5	$CH(C_6H_5)_2$	2	65	164–166	B + P	C(0.5)[f]	$C_{24}H_{24}N_2O$	C, H, N	− −
60	CH_3	$CH(C_6H_5)_2$	3	82	170–172	M + E	B(0.5)	$C_{20}H_{24}N_2O \cdot HCl$	C, H, Cl, N	− −
61	CH_3	$CH_2OC_6H_5$	2	64	182–183	M + E	F(20)	$C_{13}H_{18}N_2O_2 \cdot HCl$	C, H, Cl, N	+ −
62	C_6H_5	$CH_2OC_6H_5$	2	67	179–181	M	F(20)	$C_{18}H_{20}N_2O_2 \cdot HCl$	C, H, Cl, N	− −
63	C_6H_5	$CH(CH_3)OC_6H_5$	2	84	214–216	M + W	F(20)	$C_{19}H_{22}N_2O_2 \cdot HCl$	C, H, Cl, N	− −
				72	104–105.5	E		$C_{19}H_{22}N_2O_2$	C, H, N	
64	CH_3	$CH(CH_3)OC_6H_5$	3	71	210–212	M + E	F(20)	$C_{15}H_{22}N_2O_2 \cdot HCl$	C, H, Cl, N	+ −
65	CH_3		2	86	216–218	M + E	B(0.5)	$C_{12}H_{16}N_2OS \cdot HCl$	C, H, Cl, N	−
66	CH_3		3	43	117–119	M + E	B(0.5)	$C_{13}H_{18}N_2OS \cdot HCl$	C, H, Cl, N, S	+ −
67	C_6H_5		2	86	157–159	C + M	B(0.5)	$C_{17}H_{18}N_2OS$	C, H, N, S	−
68	o-$CH_3OC_6H_4$		2	22	184–186	M + E	B(0.5)	$C_{18}H_{20}N_2O_2S \cdot HCl$	C, H, Cl, N, S	+ −
69	o-$CH_3OC_6H_4$	$CH{=}CHC_6H_5$	2	89	112–114	B + P	D(0.5)	$C_{20}H_{22}N_2O_2$	C, H, N	−
70	o-$CH_3OC_6H_4$	$CH{=}CH_2$	2	66	81.5–83	B + P	E(48)	$C_{14}H_{18}N_2O_2$	C, H, N	−
71	C_6H_5	$CH{=}CH_2$	2	48	210 dec	M	F(48)	$C_{13}H_{16}N_2O \cdot HCl$	C, H, Cl, N	+ −
72	o-$CH_3OC_6H_4$	$CH_2OC_6H_3Cl_2$-2,4	2	75	129–131	B + P	C(0.5)	$C_{19}H_{20}Cl_2N_2O_3$	C, H, Cl, N	X
73	CH_3	$CH_2OC_6H_3Cl_2$-2,4	2	62	195–196	M	B(0.5)	$C_{13}H_{16}Cl_2N_2O_2 \cdot HCl$	C, H, Cl, N	−
74	CH_3	$CH_2OC_6H_3Cl_2$-2,4	3	63	208–210	M	B(0.5)	$C_{14}H_{18}Cl_2N_2O_2 \cdot HCl$	C, H, Cl, N	−
75	CH_3	3,4-$Cl_2C_6H_3$	2	68	298–300	M	A(1)	$C_{12}H_{14}Cl_2N_2O \cdot HCl$	C, H, Cl, O	−
76	CH_3	3,4-$Cl_2C_6H_3$	3	89	235–237	M + E	A(1)	$C_{13}H_{16}Cl_2N_2O \cdot HCl$	C, H, Cl, N	− −
77	o-$CH_3OC_6H_4$	3,4-$Cl_2C_6H_3$	2	55	132–134	M	D(1)	$C_{18}H_{18}Cl_2N_2O_2$	C, H, Cl, N	−
78	CH_3	2,4-$Cl_2C_6H_3$	2	83	289–291	M	A(1)	$C_{12}H_{14}Cl_2N_2O \cdot HCl$	C, H, Cl, N	+ −
79	CH_3	2,4-$Cl_2C_6H_3$	3	66	233–234	M + E	A(1)	$C_{13}H_{16}Cl_2N_2O \cdot HCl$	C, H, Cl, N	−
80	C_6H_5	3,4-$(CH_3O)_2C_6H_3$	2	57	198–200	M	B(0.5)	$C_{19}H_{22}N_2O_3 \cdot HCl$	C, H, Cl, N	− −
81	CH_3	3,4-$NO_2ClC_6H_3$	2	86	110–112	C + P	D(1)	$C_{12}H_{14}ClN_3O_3$	C, H, Cl, N	+ −
82	C_6H_5	CH_2N_3[i]	2	96	95.5–96.5	M		$C_{12}H_{15}N_5O$	C, H, N	−
83	CH_3	CH_2N_3[j]	2	23	209–210 dec	A		$C_7H_{14}ClN_5O$	C, H, Cl, N	+
84	o-$CH_3OC_6H_4$	CH_2N_3[k]	2	75	172–173 dec	A + E		$C_{13}H_{18}ClN_5O_2$	C, H, Cl, N	A− − −
85	o-$CH_3OC_6H_4$	CH_2I[l]	2	75	101.5–103	A		$C_{13}H_{17}IN_2O_2$	C, H, I, N	+
86	o-$CH_3OC_6H_4$	CH_2Cl[m]	2	58	98–99	B + P		$C_{13}H_{17}ClN_2O_2$	C, H, Cl, N	

[a] Yields given are those of crude solid. [b] Recrystallization solvents: A = EtOH, Ac = Me_2CO, B = C_6H_6, C = $CHCl_3$, E = Et_2O, Ea = EtOAc, H = hexane, M = MeOH, P = petroleum ether (30–60°), W = water. [c] Reaction period indicated in hours in parentheses. [d] Compound prepared by Dr. F. Fried of these laboratories. [e] J. R. Boissier, R. Ratouis, and C. Dumont, *J. Med. Chem.*, **6**, 541 (1963), reported the dihydrochloride of p-methoxybenzoyl (mp 224°) and m-methoxybenzoyl (mp 196°) derivatives. [f] The acid chloride was prepared by stirring thionyl chloride with the corresponding acid, containing DMF, at room temperature. [g] Instead of C_6H_6, the reaction solvent used was $CHCl_3$. [h] Bp 179–182° (0.9 mm). [i] Yield (i) 28% on reaction of ethyl azidoacetate and phenylpiperazine and (ii) 96% on reaction of 1-chloroacetyl-4-piperazine [preparation reported by H. P. Dalalian and S. Kushner, U. S. Patent 2,807,617 (Sept 1957); *Chem. Abstr.*, **52**, 3875 (1958)] and sodium azide. [j] Prepared from ethyl azidoacetate and methylpiperazine. [k] Prepared from NaN_3 and 1-iodoacetyl-4-o-methoxyphenylpiperazine. [l] Prepared from 1-chloroacetyl-4-o-methoxyphenylpiperazine (0.057 mole) and KI (0.085 mole). [m] Prepared from 1-o-methoxyphenylpiperazine and chloroacetyl chloride in Et_2O. [n] See footnote *h* in Table I.

TABLE V

1-ALKYL OR 1-ARALKYL-4-ALKYL- OR -ARALKYLPIPERAZINES



No.	R_1	R_2	Yield,[a] %	Bp (mm) or mp, °C	S[b]	Method	Formula	Analyses	Activity[c]
87	CH_3	$CH_2=CH_2$	45	268 dec	M	A	$C_5H_{16}N_2 \cdot 2HCl$[d]	C, H, Cl, N	+ –
88	o-$CH_3OC_6H_4$	$CH_2=CH_2$	83	117 (0.5)		B	$C_{14}H_{20}N_2O$	C, H, N	– – –
				222 dec	M + A		$C_{14}H_{20}N_2O \cdot 2HCl$	C, H, Cl, N	
89	C_6H_5	$CH_2=CH_2$	69	110–114 (0.8)		B[e]	$C_{12}H_{18}N_2$	C, H, N	X
90	o-$CH_3OC_6H_4$	$C\equiv CH$	74	128 (0.5)		C	$C_{14}H_{18}N_2O$	C, H, N	–
				205	W		$C_{14}H_{18}N_2O \cdot 2C_6H_3N_3O_7$[e]	C, H, N	
91	C_6H_5	$C\equiv CH$	78	118 (0.7)		C	$C_{12}H_{16}N_2$[f]	C, H, N	XX
				177–178	W		$C_{12}H_{16}N_2 \cdot 2C_6H_3N_3O_7$[e]	C, H, N	
92	CH_3	$C\equiv CH$	50	252 dec	W	C	$C_8H_{14}N_2 \cdot 2C_6H_3N_3O_7$[e]	C, H, N	±
93	C_6H_5	c-C_3H_5	73	120 (0.3), 35–36		D	$C_{13}H_{20}N_2$	C, H, N	X
				170	E		$C_{14}H_{20}N_2 \cdot 2C_6H_3N_3O_7$[e]	C, H, N	
94	C_6H_5	2,4-$Cl_2C_6H_3$	53	66–68	M	E	$C_{17}H_{18}Cl_2N_2$	C, H, Cl, N	– –
95	CH_3	2,4-$Cl_2C_6H_3$	90	238.5–239	E + Et	E	$C_{12}H_{16}Cl_2N_2 \cdot 2HCl$[g]	C, H, Cl, N	+
96	C_6H_5	o-$CH_3OC_6H_4$	46.5	103.5–105	E	D	$C_{18}H_{22}N_2O$	C, H, N	+
97	C_6H_5	p-$CH_3OC_6H_4$	35	107.5–108.5	E	D	$C_{18}H_{22}N_2O$[h]	C, H, N	– – –
98	C_6H_5	$CH(C_6H_5)_2$	76	115–116	E	F	$C_{24}H_{26}N_2$	C, H, N	–
99	C_6H_5	$CH(CH_3)OC_6H_5$	60	190–196	E + Et	D	$C_{19}H_{24}N_2O \cdot 2HCl$	C, H, Cl, N	+ –
100	C_6H_5	3,4-$(OCH_3)_2C_6H_3$	85	205–207	M + Et	F	$C_{19}H_{24}N_2O_2 \cdot HCl$	C, H, Cl, N	–
101	C_6H_5	m-$CH_3C_6H_4$	50	184–185	E + Et	F	$C_{18}H_{22}N_2 \cdot HCl$	C, H, Cl, N	
102	C_6H_5	m-$CH_3OC_6H_4$	54.5	201–203	E + Et	F	$C_{18}H_{22}N_2O \cdot 2HCl$[h]	C, H, Cl, N	–

[a] Yields given are those of the crude solids or once-distilled liquid. [b] Recrystallization solvents: A = Me_2CO, E = EtOH, Et = Et_2O, W = H_2O, M = MeOH. [c] O. Hromatka, I. Grass, and F. Sauter, *Monatsh. Chem.*, **87**, 701 (1956); *Chem. Abstr.*, **51**, 8109 (1957), reported the picrate of 1-allyl-4-methylpiperazine (prepared by a different route). [d] T. Cuvigny and H. Normant, *J. Organometal. Chem.* (Amsterdam), **1**, 120 (1963); *Chem. Abstr.*, **60**, 4165 (1964), reported the preparation of 1-allyl-4-phenylpiperazine by a different route. [e] Analyzed as a dipicrate. [f] N. D. Dawson, U. S. Patent 2,993,899; *Chem. Abstr.*, **56**, P3492 (1962), prepared 1-phenyl-4-propargylpiperazine, bp 147° (4 mm), from aniline and $CH\equiv C-CH_2N(CH_2CH_2Cl)_2 \cdot HCl$. [g] The product had to be heated *in vacuo* at 160–170° (3 hr) to get rid of all traces of EtOH. [h] J. R. Boissier, R. Ratouis, and C. Dumont, *J. Med. Chem.*, **6**, 541 (1963), prepared 1-(*p*-methoxybenzyl)-4-phenylpiperazine dihydrochloride (mp 224°) and 1-(*m*-methoxybenzyl)-4-phenylpiperazine dihydrochloride (mp 196°) from phenylpiperazine and the corresponding benzyl chloride. [i] Boissier, *et al.*,[h] reported the preparation of 1-(3,4-dimethoxybenzyl)-4-phenylpiperazine from phenylpiperazine and 3,4-dimethoxybenzyl chloride. [j] See footnote *h* in Table I.

activity in passing from the amides (Tables I and IV) to the amines (Table V).

The amides **70**, **71**, and **58** had relatively weak hypotensive properties, whereas the corresponding amines **88**, **89**, and **93** lowered the blood pressure of experimental animals by 50–80 mm for over 30 min.

The amide **42** caused a large unsustained fall in blood pressure, but the corresponding amine, **97**, caused a fall in blood pressure which was sustained for 40 min. The amides **59**, **63**, and **80** also produced a large unsustained fall in blood pressure, but the amines **98**, **99**, and **100** were essentially inactive. 1-Benzoyl-4-phenylpiperazine[10] caused a sustained fall in blood pressure, but 1-benzyl-4-phenylpiperazine[10] produced a large unsustained fall in blood pressure.

Experimental Section[11]

1-Nitroso-4-phenylpiperazine (16).—1-Phenylpiperazine[12] (48.6 g, 0.3 mole) was mixed with H_2O (400 ml) and concentrated HCl was added dropwise until the pH was 5–6. A solution of $NaNO_2$ (20.7 g, 0.3 mole) in H_2O (150 ml) was added over a period of 20 min maintaining a pH of 5–6 by dropwise addition of 15% HCl to the center of the reaction vessel. (While adding the acid, care was taken to see that it did not fall on the sides of the reaction vessel, otherwise the color of the reaction mixture changed from orange to dark green with signs of decomposition.) The orange precipitate was filtered below 15°, washed (H_2O), and dissolved in Et_2O. The product was crystallized from the dry Et_2O solution by the addition of petroleum ether (bp 30–60°); yield 26.3 g (46%), mp 65–67°. *Anal.* ($C_{10}H_{13}N_3O$) C, H, N.

1-(*o*-Methoxyphenyl)piperazine was nitrosated similarly at 70–75° (1 hr). The product **1-(*o*-methoxyphenyl)-4-nitrosopiperazine (17)** was isolated from the reaction mixture by basification (NaOH) and subsequent extraction ($CHCl_3$) in 56.5% yield, bp 185–200° (0.5–0.8 mm), mp 62–64° (MeOH–H_2O). *Anal.* ($C_{11}H_{15}N_3O_2$) C, H, N.

1-Methyl-4-nitrosohomopiperazine (18) was prepared from 1-methylhomopiperazine[13] (40 g, 0.35 mole) at −5 to 0° by the method described for the preparation of **17**, in 78% yield, bp 140–143° (17 mm). This product was reduced to **19** without any further purification.

1-Amino-4-phenylpiperazine (1, Table I). Method A.—A mixture of N,N-bis(β-chloroethyl)aniline[14] (109 g, 0.5 mole) and 99–100% $(NH_2)_2H_2O$ (110 g, 2.2 moles) in EtOH (900 ml) was heated under reflux. After 2 hr there was separation of layers in the reaction mixture and H_2O (170 ml) was added to render it homogeneous. Refluxing was continued for 22 hr. Most of the EtOH was then removed under reduced pressure, and the residue was basified with 20% NaOH. The basic solution was extracted ($CHCl_3$, five 100-ml portions) and the extract was dried. After removal of the solvent, 59.0 g (66%) of the product boiling at 118–127° (0.7 mm) was obtained. The distillate, which solidified (mp 45–50°) on cooling, was recrystallized from petroleum ether (60–80°) and redistilled to give the pure product. 1-Amino-4-(*o*-methoxyphenyl)piperazine (**2**) was prepared similarly from hydrazine and the corresponding *o*-anisidine (**9**).[15]

Method B.—Zinc dust (26.8 g, 0.41 mole) was added over a period of 20 min to **16** (26 g, 0.136 mole) in 50% aqueous AcOH (200 ml) at 20–30°. The mixture was heated to 50° and, after 1 hr at this temperature, filtered. The filtrate was cooled and

(11) Boiling points are uncorrected. Melting points were determined in open capillary tubes with a Thomas–Hoover capillary melting point apparatus, which was calibrated against known standards. Unless otherwise stated, the ir spectra of crystalline solids were of Nujol mulls. The microanalyses were provided by Messrs. Orville Kolsto and Victor Rauschel and staff of Abbott Microanalytical Laboratory, North Chicago, Ill. The nmr spectra of all the compounds were taken in D_2O containing DCl, on a Varian A-60 instrument using 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (TPS) as internal standard. They were kindly provided by Dr. M. Levenberg and R. Egan, of the Chemical Physics Department, Abbott Laboratories, North Chicago, Ill., and are reported in hertz from TPS. Unless specially noted, uv, ir, and nmr spectra were as expected.

(12) C. B. Pollard and L. G. MacDowell, *J. Amer. Chem. Soc.*, **56**, 2199 (1934).

(13) A. H. Sommers, R. J. Michaels, Jr., and A. W. Weston, *ibid.*, **76**, 5805 (1954).

(14) R. C. Elderfield, I. S. Covey, J. B. Geiduschek, W. L. Meyers, A. B. Ross, and J. H. Ross, *J. Org. Chem.*, **23**, 1749 (1958).

(15) A. H. Sommers, U. S. Patent 2,891,063 (1959); *Chem. Abstr.*, **53**, 22028 (1959).

strongly basified with 50% NaOH, followed by NaOH pellets, until the separated precipitate had redissolved. The product was extracted ($CHCl_3$), the extract was washed (H_2O), dried, and concentrated, and the residue was distilled *in vacuo* to give 15.3 g (64%) of the product boiling at 108–110° (0.17 mm), mp 57–60°.

1-Amino-4-methylhomopiperazine (19) and 1-amino-4-(*o*-methoxyphenyl)piperazine (2) were prepared similarly.

1-Benzylideneamino-4-(*o*-methoxyphenyl)piperazine (3, Table II).—A mixture of benzaldehyde (7.7 g, 0.072 mole) and **2** (15 g, 0.072 mole) in toluene (200 ml) was refluxed, using a water separator, until the theoretical amount of H_2O had been collected (1.3 ml, 1.5 hr). The reaction solution was cooled and diluted with petroleum ether (30–60°) to give 11.0 g (51%) of the crude product (mp 88–99°). Recrystallization from absolute EtOH gave the analytically pure product, mp 93–94°. The ir spectrum showed no primary or secondary amine peak.

Other benzylideneamino derivatives (**20–23**) were prepared similarly and are entered in the table.

1-Benzylamino-4-(*o*-methoxyphenyl)piperazine Monohydrochloride (4). Method A.—A solution of **3** (10 g, 0.034 mole) in DMF (50 ml) and 10% Pd–C (0.3 g) was hydrogenated in a Parr shaker at room temperature at an initial pressure of 3.66 kg/cm². After 0.5 hr the hydrogenation mixture was filtered and the filtrate was poured into cold H_2O and extracted (Et_2O). The extract was dried and concentrated to give an oil, which was converted to the hydrochloride (mp 209.5–211°). Two recrystallizations (EtOH–Et_2O) gave the analytically pure product melting at 210.5–211.5° in 35% yield. *Anal.* ($C_{18}H_{23}N_3O \cdot HCl$) C, H, Cl, N.

Method B.—Metallic Na (0.72 g, 0.0315 g-atom) was dissolved in absolute EtOH (50 ml) and **5** (10.5 g, 0.0315 mole) was added. The clear solution was heated in a pressure bottle on the steam bath for 4 hr, and allowed to cool to room temperature. The mixture was diluted (EtOH) and filtered (1.8 g of NaCl, 100%). The filtrate was evaporated and the oily residue was taken up in Et_2O, filtered, and evaporated again (7.5 g). This compound had no Cl, did not form an embonate salt, and was insoluble in H_2O. The product was distilled twice in a collar flask (oil bath, *ca.* 190°, 0.5 mm) and analyzed as 1-benzylamino-4-*o*-methoxyphenylpiperazine (**4**). *Anal.* ($C_{18}H_{23}N_3O$) C, H, N. A part of the product was converted to its monohydrochloride (mp 209–212° dec, from EtOH–Et_2O) which was identical with the product made by method A.

1-Amino-1-benzyl-4-(*o*-methoxyphenyl)-1-piperazinium Chloride (5). Method A.—A solution of NaI (29.5 g, 0.198 mole) in absolute EtOH (1000 ml) was added to 1-amino-4-(*o*-methoxyphenyl)piperazine (41 g, 0.198 mole) in EtOH (200 ml) followed by K_2CO_3 (27.3 g, 0.198 mole) in H_2O (25 ml) and benzyl chloride (25 g, 0.198 mole). The mixture was refluxed for 19 hr and filtered hot to give 45.5 g (84%) of 1-amino-1-benzyl-4-(*o*-methoxyphenyl)-1-piperazinium iodide (**6**), mp 174° dec. Recrystallization (H_2O) raised the melting point to 176° dec. *Anal.* ($C_{18}H_{24}IN_3O$) C, H, I, N, O.

A solution of **6** in MeOH was passed through a column of IRA-400 (Cl^- form). The eluate was concentrated and the residue was diluted (Et_2O) to give **5** (hydrated form) in 70% over-all yield. The hydrated product melted at *ca.* 140°, then resolidified and melted at 198–199°. The analysis for this product corresponded to ($C_{18}H_{24}ClN_3O \cdot 0.5H_2O$) C, **H**, Cl, N, O. The water of crystallization could be removed by heating at 150° for 15 min, giving the pure product (**5**), mp 201–202°. *Anal.* ($C_{18}H_{24}ClN_3O$) C, H, N.

A sample of **5** was converted to a monohydrochloride (**10**), mp 167–168° (from EtOH–Et_2O). *Anal.* ($C_{18}H_{24}ClN_3O \cdot HCl \cdot H_2O$) C, H, Cl, N.

Another sample of the quaternary chloro compound **5** was converted to its embonate salt, by dissolving it in H_2O and adding a hot saturated solution of sodium embonate to it. The embonate salt of **5** was filtered and washed (H_2O), mp 141°. *Anal.* ($C_{59}H_{62}N_6O_8 \cdot 2H_2O$) C, H, N, O.

Method B.—A mixture of **2** (12 g, 0.058 mole) and benzyl chloride (3.6 g, 0.029 mole) in toluene was refluxed for 5 hr. The reaction mixture was cooled and filtered. The filtrate was evaporated and the residue (3.4 g, 35%) was crystallized (EtOH–Et_2O) to give **5**.

Method C.—A solution of benzyl hydrazine[16] (9.3 g, 0.0763 mole) in absolute EtOH (100 ml) and bis(β-chloroethyl)-*o*-anisidine[15] (**9**) (18.9 g, 0.0763 mole) was refluxed under N_2 for 21 hr. At the end of this period, the reaction mixture was concentrated and the residue was washed (Et_2O). The remaining oil was treated with methanolic HCl and Et_2O to give **10** (8 g). An aqueous solution of **10** was basified (cold $NaHCO_3$) and extracted ($CHCl_3$). The extract was concentrated and the residue was recrystallized (MeOH–C_6H_6–Et_2O) to give pure **5** (mp 201–202°).

1-Amino-4-(*o*-methoxyphenyl)-1-methylpiperazinium Iodide (7).—1-Amino-4-(*o*-methoxyphenyl)-1-methylpiperazinium chloride (**8**) (mp 211–213°, EtOH–Et_2O) was prepared by refluxing equivalent amounts of methyl hydrazine and **9** in EtOH, as described for the preparation of **5** (method C). *Anal.* ($C_{12}H_{20}ClN_3O$) C, H, Cl. Treatment of **8** with NaI in absolute MeOH gave **7**, mp 176–178° dec. *Anal.* ($C_{12}H_{20}IN_3O$) C, H, I, N.

Compound **7** was also prepared by refluxing **2** with excess MeI in MeOH for 4 hr. The solvent was removed and the residue on trituration (Et_2O) gave the methiodide (mp 174–175° dec) in 81% yield.

1-Amino-1-(*p*-nitrobenzyl)-4-(*o*-methoxyphenyl)-1-piperazinium Chloride Hydrochloride Monohydrate (12).—1-Amino-4-(*o*-methoxyphenyl)piperazine (8.0 g, 0.0386 mole) and α-chloro-*p*-nitrotoluene (6.6 g, 0.0386 mole) in C_6H_6 were refluxed for 5 hr. The reaction mixture was cooled, filtered, and concentrated. The yellow oily residue was dissolved in MeOH and triturated (Et_2O) until a solid formed (8.0 g). A small sample was converted to the hydrochloride and recrystallized (EtOH–Et_2O), mp 165–166° dec. *Anal.* ($C_{18}H_{23}ClN_4O_3 \cdot HCl \cdot H_2O$) C, H, Cl, N.

Hydrogenations. Reduction of 1-Amino-1-benzyl-4-(*o*-methoxyphenyl)piperazinium Chloride. (a) With 10% Pd–C.—A solution of **5** (10 g, 0.0296 mole) in 100 ml of EtOH and 100 mg of Pd–C was hydrogenated at 3.5 kg/cm² for 1 hr. The mixture was filtered. The presence of toluene in the filtrate was shown by glpc using a silicone SE-30 column. The filtrate was evaporated to near dryness and Et_2O was added. The product (5.5 g, mp 199–201°) which was filtered and recrystallized from EtOH–Et_2O was identified as the hydrochloride salt of 1-amino-4-(*o*-methoxyphenyl)piperazine (**2**).

(b) With PtO_2.—A solution of **5** (10 g, 0.0296 mole) in absolute EtOH (100 ml) and *ca.* 100 mg of PtO_2 were hydrogenated at 3.5 kg/cm². After 1 hr the mixture was filtered. The odor of NH_3 was noticed. The filtrate was evaporated and the residue was taken up in C_6H_6. The extract was concentrated and the oil remaining (5.5 g) was distilled in a collar flask. This product was identified as 1-benzyl-4-(*o*-methoxyphenyl)piperazine (**11**). *Anal.* ($C_{18}H_{22}N_2O$) C, H, N, O.

1-Benzyl-4-(*o*-methoxyphenyl)piperazine (11) was synthesized by refluxing benzyl chloride (6.3 g, 0.05 mole) and *o*-methoxyphenylpiperazine (19.2 g, 0.1 mole) in xylene for 2.5 hr. The reaction mixture was cooled, filtered, and concentrated. The oily residue was converted to the dihydrochloride, yield 13.2 g (75%), mp 202–203° dec. Recrystallization from EtOH–Et_2O containing a little C_6H_6 raised the melting point to 206–207° dec. *Anal.* ($C_{18}H_{22}N_2O \cdot 2HCl$) C, H, N.

The hydrated hydrochloride had a melting point of 162–167° dec. The free base (mp 50° from petroleum ether), prepared from the aqueous solution of its dihydrochloride and $NaHCO_3$ solution, separated as an oil which crystallized slowly on standing. *Anal.* ($C_{18}H_{22}N_2O$) C, H, N.

1-(β-Aminoethyl)-4-phenylpiperazine (13, Table III).—A solution of 1-phenylpiperazine (53.5 g, 0.33 mole) in EtOH (220 ml) containing concentrated H_2SO_4 (3 ml) was refluxed with ethylenimine (13.0 g, 0.3 mole) for 24 hr. After this period, EtOH was removed by distillation. The residue was mixed with solid KOH (15 g) and the mixture distilled under reduced pressure. After an initial fraction of 1-phenylpiperazine (27.1 g, 0.167 mole), the product distilled at 116–120° (0.1 mm) and solidified on cooling; yield 78%, on the basis of 1-phenylpiperazine used. It was identified by formation of its picrate, mp 199–201° dec, lit.[6] 203–204° dec.

1-(β-Aminoethyl)-4-methylpiperazine (14),[7] bp 89–92° (9.5 mm), $n^{25}D$ 1.4785, and **1-(β-aminoethyl)-4-methylhomopiperazine (15),**[7] bp 103–105° (9.5 mm), were obtained similarly from the corresponding methylpiperazine or methylhomopiperazine and ethylenimine in 43 and 35% yields, respectively.

Preparation of Amides (Table IV and part of Tables I and III).—The following methods indicate the general procedure followed in the preparation of the amides. The period of refluxing is indicated in Table I.

Method A. 1-(3,4-Dichlorobenzoyl)-4-methylpiperazine Hy-

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drochloride (75).—A solution of 1-methylpiperazine (20.0 g, 0.20 mole)[17] in C_6H_6 (400 ml) was treated with small portions of 3,4-dichlorobenzoyl chloride (20.95 g, 0.10 mole) and the resulting hot mixture refluxed for 1 hr. The cooled mixture was washed successively with H_2O (five 50-ml portions), 1 *N* NaOH solution (two 30-ml portions), and H_2O (three 30-ml portions). The organic layer was dried and concentrated. The residual oil was dissolved in MeOH (100 ml) and dry HCl gas was bubbled through the cooled solution to give 21.0 g (68%) of the crude product, mp 298–300°.[18] Two recrystallizations (MeOH) gave 43% of the analytically pure product with no change in the melting point.

Method B. 1-(2,4-Dichlorophenoxyacetyl)-4-methylpiperazine Hydrochloride (73).—A mixture of 2,4-dichlorophenoxyacetic acid (22.1 g, 0.1 mole) and $SOCl_2$ (40 ml) was refluxed for 0.5 hr (reaction period indicated in the table). The excess reagent was removed under reduced pressure. The residue was dissolved in C_6H_6 (60 ml) and cautiously added to a solution of 1-methylpiperazine (20.0 g, 0.2 mole) in C_6H_6 (200 ml). The mixture was stirred overnight, at room temperature, and then washed successively with H_2O (three 20-ml portions), 1 *N* NaOH (30 ml), and H_2O (two 30-ml portions). The organic layer was dried and concentrated under reduced pressure. The residual oil was taken up in Et_2O (100 ml) and ethereal HCl (60 ml) was added to give 21.0 g (62%) of the product, mp 195–196°. Recrystallization (MeOH) did not raise the melting point.

Method C.—This method is essentially the same as method B except that the product was isolated as the free base without conversion to the hydrochloride. One or two recrystallizations from a suitable solvent gave the analytical sample.

Method D was identical with method A, except that the product was isolated as the free base without conversion to the hydrochloride. Recrystallization from a suitable solvent gave the analytically pure product.

Method E was the same as method D, above, except that the reaction was carried on at room temperature for a period indicated in the table.

Method F was the same as method E, except that the product was isolated as a hydrochloride.

1-Alkyl- or 1-Aryl-4-alkyl- or -aralkylpiperazines (Table V).—Compounds in this series were prepared by the following general methods.

Method A. 1-Allyl-4-methylpiperazine Dihydrochloride (87).—Allyl bromide (90 g, 0.74 mole) was added to a solution of N-methylpiperazine (150.3 g, 1.5 moles) in toluene (300 ml) at 10–20° under N_2. The mixture was stirred overnight at room temperature, refluxed for 1 hr, cooled, and filtered and the filtrate was washed (15% NaOH, saturated NaCl). The organic layer was dried and concentrated. The oily residue was distilled, bp 45° (4.0 mm), yield 48.8 g (46.5%). The distillate was taken up in MeOH, converted to the hydrochloride salt, and recrystallized (MeOH).

Method B. 1-Allyl-4-phenylpiperazine (89).—The reaction was carried out exactly as in method A, except that the mixture was refluxed for 30 min only. The product was distilled twice and isolated as a free base, $n^{25}D$ 1.5603.

Method C. 1-(*o*-Methoxyphenyl)-4-propargylpiperazine (90) was prepared as described in method A, except that the reaction mixture was refluxed for 30 min as soon as the addition of propargyl bromide was complete. The product was isolated by distillation.

Method D. 1-Cyclopropylmethyl-4-phenylpiperazine (93).—A solution of **58** (49.4 g, 0.215 mole) in Et_2O (600 ml) was added over 30 min to a suspension of $LiAlH_4$ (9.0 g, 0.236 mole) in Et_2O (500 ml), at 10°. The mixture was then refluxed for 3 hr, cooled to 10°, and hydrolyzed by cautious addition of EtOAc (5.3 g, 0.06 mole), followed by H_2O (80 ml). The precipitate was filtered and the filtrate was dried and concentrated. The the residue, on distillation, gave the product.

Compound **96** was also prepared by this method, except that THF was used as the solvent. In the preparation of **97** and **99** by this method, $LiAlH_4$ was dissolved in Et_2O and the amide was dissolved in THF.

Method E. 1-(2,4-Dichlorobenzyl)-4-phenylpiperazine (94).—A mixture of N-phenylpiperazine (32.4 g, 0.2 mole) and α-2,4-trichlorotoluene (19.5 g, 0.1 mole) was refluxed in xylene (200 ml) for 4 hr and filtered. The filtrate was evaporated, and the residue crystallized (MeOH).

In the case of **95**, the residue was distilled [bp 110–112° (0.1 mm)] and the distillate was converted to a hydrochloride.

Method F. 1-Phenyl-4-(*m*-tolyl)piperazine (101).—A solution of **49** (as a free base) in THF was added dropwise to a 2.5% solution of diborane in THF (120 ml), at −10° under N_2. After the addition was complete, the well-stirred mixture was allowed to warm slowly to room temperature and then refluxed for 2 hr. The reaction mixture was cooled and hydrolyzed by dropwise addition of 10% HCl (80 ml), and the solvent was removed by concentration. The residue was basified with aqueous KOH and extracted ($CHCl_3$) and the extract was dried and concentrated. The residue was converted to the hydrochloride and recrystallized (EtOH–Et_2O).

1-(β-Diphenylethyl)-4-phenylpiperazine (98) was prepared similarly by the reduction of the corresponding amide (**59**) with diborane. The product (**98**) was isolated as the free base.

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(18) In some cases the hydrochloride was reconverted to the free base and purified as such.