

a Grignard solution prepared from Mg (4.7 g) and 4-(cyclopent-1-enyl)bromobenzene (38 g) in a mixture of Et₂O (235 ml) and THF (95 ml), a solution of 2,3-epoxypropyl chloride (31.5 g) in Et₂O (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 (H₂O), and dried (Na₂SO₄) 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 H₂O (11 ml) and the mixture was heated under reflux for 90 min. It was then cooled and diluted with iced H₂O and the product was isolated with CHCl₃. It (12 g) had mp 77–78° [from C₆H₆-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 H₂O (2 ml) was saturated with HCl gas and then heated under reflux for 12 hr. The ester (4.4 g) isolated with CHCl₃ 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-H₂O (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-H₂O).

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.* (C₁₃H₁₃Br) C, H, Br.

N-(β-Hydroxyethyl)-4-(p-biphenyl)-3-hydroxybutyramide.—A mixture of ethyl 4-(p-biphenyl)-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.* (C₁₅H₂₁NO₄) C, H, N.

N-(β-Hydroxyethyl)-4-(p-biphenyloxy)-3-hydroxybutyramide had mp 181–183° (from EtOH). *Anal.* (C₁₅H₂₁NO₄) C, H, N.

N-(β-Hydroxyethyl)-3-hydroxy-4-(2-naphthyloxy)butyramide had mp 161–163° (from EtOH). *Anal.* (C₁₈H₁₉NO₄) C, H, N.

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

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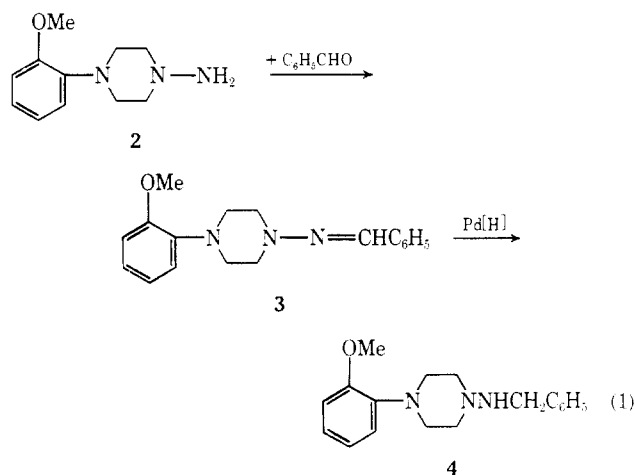
Several unsymmetrically 1,4-disubstituted piperazines have been prepared by reducing 1-acyl-4-substituted piperazines, the latter having been obtained by the acylation of 1-alkyl- or 1-arylpiperazines. Alkylation of 1-amino-4-(*o*-methoxyphenyl)piperazine (**2**) gives 1-amino-1-alkyl-4-(*o*-methoxyphenyl)piperazinium 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** (NaBH₄ or LiAlH₄), or hydrogenation in the presence of PtO₂, 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

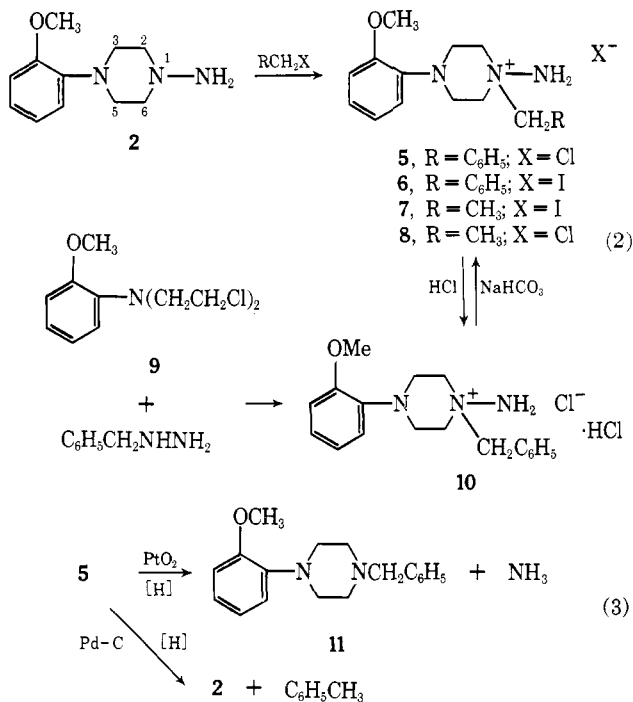


converted to **5** by treatment with NaHCO₃ (eq 2).

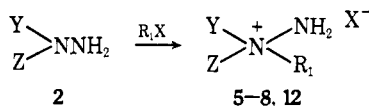
Hydrogenolysis of **5** (eq 3) in the presence of PtO₂ gave 1-benzyl-4-(*o*-methoxyphenyl)piperazine (**11**) and ammonia. On the other hand, hydrogenolysis in the presence of 10% Pd-C gave 1-amino-4-(*o*-methoxyphenyl)piperazine (**2**) and toluene.

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 I.

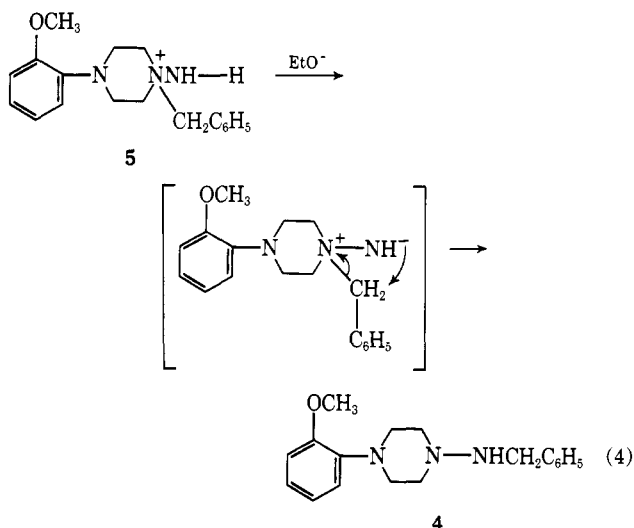


part of the unsymmetrically disubstituted hydrazine. Y and Z may be considered as the alkyl groups which



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

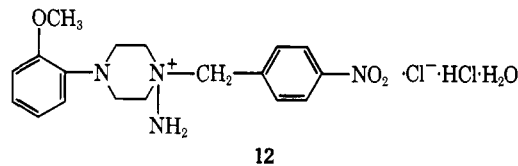
(2) B. M. Bloom, *Ann. N. Y. Acad. Sci.*, **107**, 878 (1963).

(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.

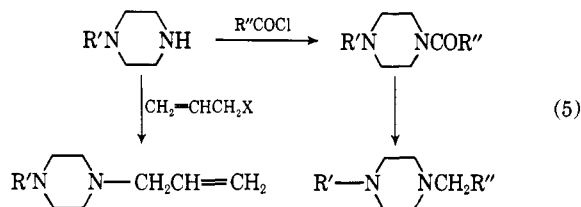
product **7** (and **8**) is thus considered to be the N-1 methyl derivative.

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 H₂SO₄, gave 1-(β-aminoethyl)-4-phenylpiperazine (**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 method⁷ 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 LiAlH₄ or diborane gave rise to 1-alkyl-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-phenylpiperazine¹⁰

(5) The *p*-nitrobenzyl ring of **12** gave the expected A₂B₂ pattern at lower field (474–506 Hz).

(6) E. Cerkovnikov and P. Stern, *Archiv. 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).

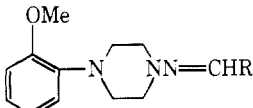
(10) V. Prelog and G. J. Driza, *Collect. Czech. Chem. Commun.*, **5**, 497 (1933); *Chem. Abstr.*, **28**, 1347 (1934).

TABLE I
 1-ALKYL- OR 1-ARYL-4-(SUBSTITUTED)AMINOPIPERAZINES AND -HOMOPIPERAZINES

No.	R ₁	R ₂	n	Yield, ^a		Bp (mm) or mp, °C	S ^b	Method ^c	Formula	Analyses	Activity ^d
				%							
1	C ₆ H ₅	H	2	50 ^d		108-110 (0.17) 57-60			C ₁₀ H ₁₅ N ₃	C, H, N	A - - -
2	<i>o</i> -CH ₃ OC ₆ H ₄	H	2	75 ^e		144-149 (0.5) 101-104 206-209 dec	E + M M + E		C ₁₁ H ₁₇ N ₃ O C ₁₁ H ₁₇ N ₃ O·2HCl	C, H, N	B - - -
4	<i>o</i> -CH ₃ OC ₆ H ₄	CH ₂ C ₆ H ₅	2	35		210.5-211.5	A + E		C ₁₃ H ₂₃ N ₃ O·HCl	C, H, Cl, N	+ -
19	CH ₃	H	3	60		94-96 (18) ^f			C ₆ H ₁₅ N ₃	C, H, N	+ -
24	CH ₃ ^g	COCH=CHC ₆ H ₅	2	15		225-227 dec	M + E	F(18)	C ₁₄ H ₁₉ N ₃ O·2HCl	C, H, Cl, N	+ -
25	CH ₃	COCH=CHC ₆ H ₅	3	39		124-126	B + P	D(1)	C ₁₅ H ₂₁ N ₃ O	C, H, N, O	-
26	C ₆ H ₅	COC ₆ H ₅	2	76		235-236	A	D(2)	C ₁₇ H ₁₉ N ₃ O	C, H, N	+
27	<i>o</i> -CH ₃ OC ₆ H ₄	COC ₆ H ₅	2	63		193-195	A	D(2)	C ₁₅ H ₂₁ N ₃ O ₂	C, H, N	+
28	<i>o</i> -CH ₃ OC ₆ H ₄	COC ₆ H ₄ OCH ₃ - <i>p</i>	2	75		219-220.5	A	D(2)	C ₁₇ H ₂₃ N ₃ O ₃	C, H, N	+

^a Yields given are those of crude solid or once distilled liquid. ^b Recrystallization solvents: A = EtOH, B = C₆H₆, E = Et₂O, 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_D²⁰ 1.4898. ^g The starting amine, 1-amino-4-methylpiperazine, bp 73-80° (18 mm), n_D³⁰ 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	S ^b	Formula	Analyses	Activity ^c
3	C ₆ H ₅	51.5	93-94	A	C ₁₅ H ₂₁ N ₃ O	C, H, N, O	+
20	C ₆ H ₃ Cl ₂ -3,4	32	137-138	A	C ₁₈ H ₁₉ Cl ₂ N ₃ O	C, H, Cl, N	+
21	C ₆ H ₃ (OCH ₃) ₂ -3,4	75	145-146.5	A	C ₂₀ H ₂₅ N ₃ O ₃	C, H, N	+
22	C ₆ H ₄ N(CH ₃) ₂ - <i>p</i>	70	132-133.5	A	C ₂₀ H ₂₆ N ₄ O	C, H, N	+ -
23		88	87-88.5	E + P	C ₁₇ H ₂₆ N ₄ O	C, H, N	+

^a Yields given are those of crude solids. ^b Recrystallization solvents: A = EtOH, E = Et₂O, 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	S ^b	Method ^c	Formula	Analyses	Activity ^d
				%							
29	CH ₃	COC ₆ H ₄ Cl- <i>o</i>	3	38		109-111	M + E	F(18)	C ₁₅ H ₂₂ ClN ₃ O· 0.5H ₂ O·2HCl	C, H, Cl, N	+ -
30	CH ₃	COCH=CHC ₆ H ₅	2	31		254-256	M + E	A(1)	C ₁₆ H ₂₃ N ₃ O·2HCl	C, H, Cl, N	+ -
31	C ₆ H ₅	CH ₂ CH ₂ CONHNH ₂	2	<i>d</i>		225-227 dec	M + E	<i>e</i>	C ₁₅ H ₂₅ N ₃ O·3HCl	C, H, Cl, N	-

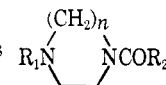
^a Yields given are those of crude solid. ^b Recrystallization solvents: M = MeOH, E = Et₂O. ^c Reaction period in hours indicated in parenthesis. ^d Over-all yield 10% starting from **13**. ^e Prepared by the reaction of 1-(β-aminoethyl)-4-phenylpiperazine (**13**) (0.1 mole) with ethyl acrylate (0.12 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 ^m
32	<i>o</i> -CH ₃ OC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	2	85	125-127	B + P	E(20)	C ₁₈ H ₁₉ ClN ₂ O ₂	C, H, Cl, N	X
33	CH ₃	<i>p</i> -ClC ₆ H ₄	2	81	279-281	M + E	F(20)	C ₁₂ H ₁₃ ClN ₂ O · HCl	C, H, Cl, N	—
34	CH ₃	<i>p</i> -ClC ₆ H ₄	3	53	183-185	M + E	F(20)	C ₁₃ H ₁₇ ClN ₂ O · HCl	C, H, Cl, N	—
35	CH ₃	<i>o</i> -ClC ₆ H ₄	2	82	292-294	M + E	A(1)	C ₁₂ H ₁₃ ClN ₂ O · HCl	C, H, Cl, N	+
36	CH ₃	<i>o</i> -ClC ₆ H ₄	3	83	253-255 dec	M	A(1)	C ₁₃ H ₁₇ ClN ₂ O · HCl	C, H, Cl, N	+
37	<i>o</i> -CH ₃ OC ₆ H ₄	<i>o</i> -ClC ₆ H ₄	2	78	164-166	B + P	D(1)	C ₁₈ H ₁₉ ClN ₂ O ₂	C, H, Cl, N, O	—
38	<i>o</i> -CH ₃ OC ₆ H ₄	<i>o</i> -CH ₃ OC ₆ H ₄	2	87	91-93	E	D(0.5)	C ₁₅ H ₂₀ N ₂ O ₃	C, H, N	—
39	CH ₃	<i>o</i> -CH ₃ OC ₆ H ₄	2	57	268-270	M + E	F(20)	C ₁₃ H ₁₈ N ₂ O ₂ · HCl	C, H, Cl, N	—
40	CH ₃	<i>o</i> -CH ₃ OC ₆ H ₄	3	55	262-264	M + E	F(20)	C ₁₄ H ₂₀ N ₂ O ₂ · HCl	C, H, Cl, N	+-
41 ^d	C ₆ H ₅	<i>o</i> -CH ₃ OC ₆ H ₄	2	99	103-104	Ea	A(3)	C ₁₈ H ₂₀ N ₂ O ₂	C, H, N, O	B- - -
42	C ₆ H ₅	<i>p</i> -CH ₃ OC ₆ H ₄	2	81	128- 129.5	E	E(20)	C ₁₈ H ₂₀ N ₂ O ₂ ^e	C, H, N	—
43	C ₆ H ₅	<i>m</i> -CH ₃ OC ₆ H ₄	2	46	208-210 ^e dec	E + W	B(1)	C ₁₈ H ₂₀ N ₂ O ₂ · HCl	C, H, Cl, N	+-
44	CH ₃	<i>p</i> -CH ₃ OC ₆ H ₄	2	97	241-243	M + E	A(2)	C ₁₃ H ₁₈ N ₂ O ₂ · HCl	C, H, Cl, N	—
45	<i>o</i> -CH ₃ OC ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄	2	97	122-123	B + P	D(1)	C ₁₈ H ₂₂ N ₂ O ₃	C, H, N	(-)
46	CH ₃	<i>o</i> -CH ₃ C ₆ H ₄	2	74	286-288 dec	M + E	B(0.5) ^f	C ₁₃ H ₁₈ N ₂ O · HCl	C, H, Cl, N	+-
47	CH ₃	<i>o</i> -CH ₃ C ₆ H ₄	3	55	264-266 dec	M + E	B(1) ^g	C ₁₄ H ₂₀ N ₂ O · HCl	C, H, Cl, N	+-
48	C ₆ H ₅	<i>o</i> -CH ₃ C ₆ H ₄	2	33.5	200-202	M + E	B(0.5) ^f	C ₁₈ H ₂₀ N ₂ O · HCl	C, H, Cl, N	X
49	C ₆ H ₅	<i>m</i> -CH ₃ C ₆ H ₄	2	74.5	198-200	M + E	B(0.5) ^f	C ₁₈ H ₂₀ N ₂ O · HCl	C, H, Cl, N	—
50	C ₆ H ₅	<i>p</i> -NO ₂ C ₆ H ₄	2	95	119-121	M	E(20)	C ₁₇ H ₁₇ N ₂ O ₃	C, H, N	—
51	CH ₃	<i>p</i> -NO ₂ C ₆ H ₄	2	96	98-100	C + H	D(2)	C ₁₂ H ₁₅ N ₃ O ₃	C, H, N, O	+-
52	<i>o</i> -CH ₃ OC ₆ H ₄	<i>p</i> -NO ₂ C ₆ H ₄	2	62	128-130	C + M	D(0.5) ^g	C ₁₈ H ₁₉ N ₃ O ₄	C, H, N, O	—
53	C ₆ H ₅	<i>m</i> -NO ₂ C ₆ H ₄	2	82	93-95	M	E(20)	C ₁₇ H ₁₇ N ₃ O ₃	C, H, N	+-
54	<i>o</i> -CH ₃ OC ₆ H ₄	<i>m</i> -NO ₂ C ₆ H ₄	2	90	109-111	M	E(20)	C ₁₈ H ₁₉ N ₃ O ₄	C, H, N	—
55	<i>o</i> -CH ₃ OC ₆ H ₄	3,5-(NO ₂) ₂ C ₆ H ₃	2	53	154-156	C + M	E(20)	C ₁₈ H ₁₇ N ₃ O ₆	C, H, N	—
56	CH ₃	C ₆ H ₅	3	50	210-212	M + E	A(4)	C ₁₃ H ₁₈ N ₂ O · HCl	C, H, Cl, N	+
57	<i>o</i> -CH ₃ OC ₆ H ₄	C ₆ H ₅	2	20	98-99	C + H	A(2)	C ₁₈ H ₂₀ N ₂ O ₂	C, H, N, O	—
58 ^d	C ₆ H ₅	<i>c</i> -C ₆ H ₅	2	73	63-64 ^h	E + P	E(4)	C ₁₄ H ₁₈ N ₂ O	C, H, N, O	—
59	C ₆ H ₅	CH(C ₆ H ₅) ₂	2	65	164-166	B + P	C(0.5) ^f	C ₂₄ H ₃₄ N ₂ O	C, H, N	—
60	CH ₃	CH(C ₆ H ₅) ₂	3	82	170-172	M + E	B(0.5)	C ₂₆ H ₃₄ N ₂ O · HCl	C, H, Cl, N	—
61	CH ₃	CH ₂ OC ₆ H ₅	2	64	182-183	M + E	F(20)	C ₁₃ H ₁₈ N ₂ O ₂ · HCl	C, H, Cl, N	+-
62	C ₆ H ₅	CH ₂ OC ₆ H ₅	2	67	179-181	M	F(20)	C ₁₈ H ₂₀ N ₂ O ₂ · HCl	C, H, Cl, N	—
63	C ₆ H ₅	CH(CH ₃)OC ₆ H ₅	2	84	214-216 105.5	M + W	F(20)	C ₁₉ H ₂₃ N ₂ O ₂ · HCl	C, H, Cl, N	—
				72	104- 105.5	E		C ₁₉ H ₂₂ N ₂ O ₂	C, H, N	
64	CH ₃	CH(CH ₃)OC ₆ H ₅	3	71	210-212	M + E	F(20)	C ₁₃ H ₂₂ N ₂ O ₂ · HCl	C, H, Cl, N	+-
65	CH ₃	CH=CH-	2	86	216-218	M + E	B(0.5)	C ₁₂ H ₁₆ N ₂ OS · HCl	C, H, Cl, N	-
66	CH ₃	CH=CH-	3	43	117-119	M + E	B(0.5)	C ₁₃ H ₁₅ N ₂ OS · HCl	C, H, Cl, N, S	+-
67	C ₆ H ₅	CH=CH-	2	86	157-159	C + M	B(0.5)	C ₁₇ H ₁₈ N ₂ OS	C, H, N, S	-
68	<i>o</i> -CH ₃ OC ₆ H ₄	CH=CH-	2	22	184-186	M + E	B(0.5)	C ₁₈ H ₂₀ N ₂ O ₂ S · HCl	C, H, Cl, N, S	+-
69	<i>o</i> -CH ₃ OC ₆ H ₄	CH=CHC ₆ H ₅	2	89	112-114	B + P	D(0.5)	C ₂₀ H ₂₂ N ₂ O ₂	C, H, N	-
70	<i>o</i> -CH ₃ OC ₆ H ₄	CH=CH ₂	2	66	81.5-83	B + P	E(48)	C ₁₄ H ₁₈ N ₂ O ₂	C, H, N	—
71	C ₆ H ₅	CH=CH ₂	2	48	210 dec	M	F(48)	C ₁₃ H ₁₆ N ₂ O · HCl	C, H, Cl, N	+-
72	<i>o</i> -CH ₃ OC ₆ H ₄	CH ₂ OC ₆ H ₄ Cl ₂ -2,4	2	75	129-131	B + P	C(0.5)	C ₁₉ H ₂₀ Cl ₂ N ₂ O ₃	C, H, Cl, N	X†
73	CH ₃	CH ₂ OC ₆ H ₄ Cl ₂ -2,4	2	62	195-196	M	B(0.5)	C ₁₃ H ₁₆ Cl ₂ N ₂ O ₂ · HCl	C, H, Cl, N	-
74	CH ₃	CH ₂ OC ₆ H ₄ Cl ₂ -2,4	3	63	208-210	M	B(0.5)	C ₁₄ H ₁₈ Cl ₂ N ₂ O ₂ · HCl	C, H, Cl, N	-
75	CH ₃	3,4-Cl ₂ C ₆ H ₃	2	68	298-300	M	A(1)	C ₁₂ H ₁₄ Cl ₂ N ₂ O · HCl	C, H, Cl, O	-
76	CH ₃	3,4-Cl ₂ C ₆ H ₃	3	89	235-237	M + E	A(1)	C ₁₃ H ₁₆ Cl ₂ N ₂ O · HCl	C, H, Cl, N	—
77	<i>o</i> -CH ₃ OC ₆ H ₄	3,4-Cl ₂ C ₆ H ₃	2	55	132-134	M	D(1)	C ₁₈ H ₁₈ Cl ₂ N ₂ O ₂	C, H, Cl, N	-
78	CH ₃	2,4-Cl ₂ C ₆ H ₃	2	83	289-291	M	A(1)	C ₁₂ H ₁₄ Cl ₂ N ₂ O · HCl	C, H, Cl, N	+-
79	CH ₃	2,4-Cl ₂ C ₆ H ₃	3	66	233-234	M + E	A(1)	C ₁₃ H ₁₆ Cl ₂ N ₂ O · HCl	C, H, Cl, N	-
80	C ₆ H ₅	3,4-(CH ₂ O) ₂ C ₆ H ₃	2	57	198-200	M	B(0.5)	C ₁₉ H ₂₂ N ₂ O ₃ · HCl	C, H, Cl, N	—
81	CH ₃	3,4-NO ₂ ClC ₆ H ₃	2	86	110-112	C + P	D(1)	C ₁₂ H ₁₄ ClN ₃ O ₃	C, H, Cl, N	+-
82	C ₆ H ₅	CH ₂ N ₃ ⁱ	2	96	95.5-96.5	M		C ₁₂ H ₁₆ N ₅ O	C, H, N	+
83	CH ₃	CH ₂ N ₃ ^j	2	23	209-210 dec	A		C ₇ H ₁₄ ClN ₅ O	C, H, Cl, N	+
84	<i>o</i> -CH ₃ OC ₆ H ₄	CH ₂ N ₃ ^k	2	75	172-173 dec	A + E		C ₁₃ H ₁₈ ClN ₅ O ₂	C, H, Cl, N	A- - -
85	<i>o</i> -CH ₃ OC ₆ H ₄	CH ₂ I ^l	2	75	101.5-103	A		C ₁₃ H ₁₇ IN ₅ O ₂	C, H, I, N	+
86	<i>o</i> -CH ₃ OC ₆ H ₄	CH ₂ Cl ^m	2	58	98-99	B + P		C ₁₃ H ₁₇ ClN ₅ O ₂	C, H, Cl, N	+

^a Yields given are those of crude solid. ^b Recrystallization solvents: A = EtOH, Ac = Me₂CO, B = C₆H₆, C = CHCl₃, E = Et₂O, 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 C₆H₅, the reaction solvent used was CHCl₃. ^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 NaN₃ 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 Et₂O. ⁿ See footnote h in Table I.

TABLE V
 1-ALKYL OR 1-ARALKYL-4-ALKYL- OR -ARALKYLPYPERAZINES

		$\begin{array}{c} \diagup \quad \diagdown \\ \text{R}_1\text{N} \quad \text{NCH}_2\text{R}_2 \\ \diagdown \quad \diagup \end{array}$									
No.	R ₁	R ₂	Yield, ^a %	Bp (mm) or mp, °C	s ^b	Method	Formula	Analyses	Activity ^c		
87	CH ₃	CH=CH ₂	45	268 dec	M	A	C ₈ H ₁₆ N ₂ ·2HCl ^f	C, H, Cl, N	++		
88	<i>o</i> -CH ₃ OC ₆ H ₄	CH=CH ₂	83	117 (0.5) 222 dec	M + A	B	C ₁₄ H ₂₀ N ₂ O C ₁₄ H ₂₀ N ₂ O·2HCl	C, H, N C, H, Cl, N	---		
89	C ₆ H ₅	CH=CH ₂	69	110-114 (0.8)		B ^d	C ₁₃ H ₁₅ N ₂	C, H, N	X		
90	<i>o</i> -CH ₃ OC ₆ H ₄	C≡CH	74	128 (0.5) 205	W	C	C ₁₄ H ₁₅ N ₂ O C ₁₄ H ₁₅ N ₂ O·2C ₆ H ₅ N ₃ O ₇ ^e	C, H, N C, H, N	-		
91	C ₆ H ₅	C≡CH	78	118 (0.7) 177-178	W	C	C ₁₃ H ₁₆ N ₂ ^f C ₁₃ H ₁₆ N ₂ ·2C ₆ H ₅ N ₃ O ₇ ^e	C, H, N C, H, N	XX		
92	CH ₃	C≡CH	50	252 dec	W	C	C ₈ H ₁₄ N ₂ ·2C ₆ H ₅ N ₃ O ₇ ^e	C, H, N	±		
93	C ₆ H ₅	<i>c</i> -C ₃ H ₅	73	120 (0.3), 35-36		D	C ₁₄ H ₂₆ N ₂	C, H, N	X		
94	C ₆ H ₅	2,4-Cl ₂ C ₆ H ₃	53	66-68	E	E	C ₁₄ H ₂₀ N ₂ ·2C ₆ H ₅ N ₃ O ₇ ^e	C, H, N	-		
95	CH ₃	2,4-Cl ₂ C ₆ H ₃	90	238.5-239	E + Et	E	C ₁₇ H ₁₈ Cl ₂ N ₂ C ₁₇ H ₁₆ Cl ₂ N ₂ ·2HCl ^g	C, H, Cl, N C, H, Cl, N	+		
96	C ₆ H ₅	<i>o</i> -CH ₃ OC ₆ H ₄	46.5	103.5-105	E	D	C ₁₅ H ₂₂ N ₂ O	C, H, N	+		
97	C ₆ H ₅	<i>p</i> -CH ₃ OC ₆ H ₄	35	107.5-108.5	E	D	C ₁₅ H ₂₂ N ₂ O ^h	C, H, N	---		
98	C ₆ H ₅	CH(C ₆ H ₅) ₂	76	115-116	E	F	C ₂₄ H ₂₆ N ₂	C, H, N	-		
99	C ₆ H ₅	CH(CH ₃)OC ₆ H ₅	60	190-196	E + Et	D	C ₁₅ H ₂₄ N ₂ O·2HCl	C, H, Cl, N	++		
100	C ₆ H ₅	3,4-(OCH ₃) ₂ C ₆ H ₃	85	205-207	M + Et	F	C ₁₅ H ₂₄ N ₂ O ₂ ·HCl ⁱ	C, H, Cl, N	-		
101	C ₆ H ₅	<i>m</i> -CH ₃ C ₆ H ₄	50	184-185	E + Et	F	C ₁₅ H ₂₂ N ₂ ·HCl	C, H, Cl, N	-		
102	C ₆ H ₅	<i>m</i> -CH ₃ OC ₆ H ₄	54.5	201-203	E + Et	F	C ₁₅ H ₂₂ N ₂ O·2HCl ^h	C, H, Cl, N	-		

^a Yields given are those of the crude solids or once-distilled liquid. ^b Recrystallization solvents: A = Me₂CO, E = EtOH, Et = Et₂O, W = H₂O, 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 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≡C-CH₂N(CH₂CH₂Cl)₂·HCl. ^f The product had to be heated *in vacuo* at 160-170° (3 hr) to get rid of all traces of EtOH. ^g 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. ^h Boissier, *et al.*,^h reported the preparation of 1-(3,4-dimethoxybenzyl)-4-phenylpiperazine from phenylpiperazine and 3,4-dimethoxybenzyl chloride. ⁱ 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-phenylpiperazine¹⁰ caused a sustained fall in blood pressure, but 1-benzyl-4-phenylpiperazine¹⁰ produced a large unsustained fall in blood pressure.

Experimental Section¹¹

1-Nitroso-4-phenylpiperazine (16).—1-Phenylpiperazine¹² (48.6 g, 0.3 mole) was mixed with H₂O (400 ml) and concentrated HCl was added dropwise until the pH was 5-6. A solution of NaNO₂ (20.7 g, 0.3 mole) in H₂O (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

(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 D₂O 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).

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 (H₂O), and dissolved in Et₂O. The product was crystallized from the dry Et₂O solution by the addition of petroleum ether (bp 30-60°); yield 26.3 g (46%), mp 65-67°. *Anal.* (C₁₀H₁₃N₃O) 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 (CHCl₃) in 56.5% yield, bp 185-200° (0.5-0.8 mm), mp 62-64° (MeOH-H₂O). *Anal.* (C₁₁H₁₃N₃O₂) C, H, N.

1-Methyl-4-nitrosopiperazine (18) was prepared from 1-methylhomopiperazine¹³ (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)aniline¹⁴ (109 g, 0.5 mole) and 99-100% (NH₂)₂H₂O (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 H₂O (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 (CHCl₃, 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

(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 (CHCl₃), the extract was washed (H₂O), 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 H₂O 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 H₂O and extracted (Et₂O). The extract was dried and concentrated to give an oil, which was converted to the hydrochloride (mp 209.5–211°). Two recrystallizations (EtOH–Et₂O) gave the analytically pure product melting at 210.5–211.5° in 35% yield. *Anal.* (C₁₈H₂₃N₃O·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 Et₂O, filtered, and evaporated again (7.5 g). This compound had no Cl, did not form an embonate salt, and was insoluble in H₂O. 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.* (C₁₈H₂₃N₃O) C, H, N. A part of the product was converted to its monohydrochloride (mp 209–212° dec, from EtOH–Et₂O) 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 K₂CO₃ (27.3 g, 0.198 mole) in H₂O (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 (H₂O) raised the melting point to 176° dec. *Anal.* (C₁₈H₂₄IN₃O) 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 (Et₂O) 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 (C₁₈H₂₄ClN₃O·0.5H₂O) 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.* (C₁₈H₂₄ClN₃O) C, H, N.

A sample of **5** was converted to a monohydrochloride (**10**), mp 167–168° (from EtOH–Et₂O). *Anal.* (C₁₈H₂₄ClN₃O·HCl·H₂O) C, H, Cl, N.

Another sample of the quaternary chloro compound **5** was converted to its embonate salt, by dissolving it in H₂O and adding a hot saturated solution of sodium embonate to it. The embonate salt of **5** was filtered and washed (H₂O), mp 141°. *Anal.* (C₁₈H₂₂N₃O₂·2H₂O) 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–Et₂O) to give **5**.

Method C.—A solution of benzyl hydrazine¹⁶ (9.3 g, 0.0763 mole) in absolute EtOH (100 ml) and bis(β -chloroethyl)-*o*-

anisidine¹⁶ (**9**) (18.9 g, 0.0763 mole) was refluxed under N₂ for 21 hr. At the end of this period, the reaction mixture was concentrated and the residue was washed (Et₂O). The remaining oil was treated with methanolic HCl and Et₂O to give **10** (8 g). An aqueous solution of **10** was basified (cold NaHCO₃) and extracted (CHCl₃). The extract was concentrated and the residue was recrystallized (MeOH–C₆H₆–Et₂O) 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–Et₂O) was prepared by refluxing equivalent amounts of methyl hydrazine and **9** in EtOH, as described for the preparation of **5** (method C). *Anal.* (C₁₂H₂₀ClN₃O) C, H, Cl. Treatment of **8** with NaI in absolute MeOH gave **7**, mp 176–178° dec. *Anal.* (C₁₂H₂₀IN₃O) 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 (Et₂O) 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 C₆H₆ were refluxed for 5 hr. The reaction mixture was cooled, filtered, and concentrated. The yellow oily residue was dissolved in MeOH and triturated (Et₂O) until a solid formed (8.0 g). A small sample was converted to the hydrochloride and recrystallized (EtOH–Et₂O), mp 165–166° dec. *Anal.* (C₁₈H₂₃ClN₃O₂·HCl·H₂O) 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 Et₂O was added. The product (5.5 g, mp 199–201°) which was filtered and recrystallized from EtOH–Et₂O was identified as the hydrochloride salt of 1-amino-4-(*o*-methoxyphenyl)piperazine (**2**).

(b) **With PtO₂.**—A solution of **5** (10 g, 0.0296 mole) in absolute EtOH (100 ml) and *ca.* 100 mg of PtO₂ were hydrogenated at 3.5 kg/cm². After 1 hr the mixture was filtered. The odor of NH₃ was noticed. The filtrate was evaporated and the residue was taken up in C₆H₆. 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.* (C₁₈H₂₂N₂O) 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–Et₂O containing a little C₆H₆ raised the melting point to 206–207° dec. *Anal.* (C₁₈H₂₂N₂O·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 NaHCO₃ solution, separated as an oil which crystallized slowly on standing. *Anal.* (C₁₈H₂₂N₂O) 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 H₂SO₄ (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*_D²⁰ 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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dichloride (75).—A solution of 1-methylpiperazine (20.0 g, 0.20 mole)¹⁷ in C₆H₆ (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 H₂O (five 50-ml portions), 1 *N* NaOH solution (two 30-ml portions), and H₂O (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°. 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 SOCl₂ (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 C₆H₆ (60 ml) and cautiously added to a solution of 1-methylpiperazine (20.0 g, 0.2 mole) in C₆H₆ (200 ml). The mixture was stirred overnight, at room temperature, and then washed successively with H₂O (three 20-ml portions), 1 *N* NaOH (30 ml), and H₂O (two 30-ml portions). The organic layer was dried and concentrated under reduced pressure. The residual oil was taken up in Et₂O (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 N₂. 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*_D²⁵ 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 Et₂O (600 ml) was added over 30 min to a suspension of LiAlH₄ (9.0 g, 0.236 mole) in Et₂O (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 H₂O (80 ml). The precipitate was filtered and the filtrate was dried and concentrated. 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, LiAlH₄ was dissolved in Et₂O 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 N₂. 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 (CHCl₃) and the extract was dried and concentrated. The residue was converted to the hydrochloride and recrystallized (EtOH–Et₂O).

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.