methoxyamine gave 22.8 g. (95%) of the oxime O-methyl ether, b.p. 70–75° (0.1 mm.).

Anal. Calcd. for $C_{10}H_{12}ClNO$: C, 60.8; H, 6.1; N, 7.1. Found: C, 61.0; H, 6.2; N, 6.9.

Catalytic hydrogenation of this compound gave **11** in 29% yield.

***dl*-1-(4-Methylphenyl)-2-hydroxyaminopropane (5).**—1-*p*-Tolyl-2-propanone,[23] b.p. 62–67° (0.5 mm.) [lit.[23] 92–94° (3 mm.)], was obtained in 79% yield by reduction of 1-*p*-tolyl-2-nitro-1-propene[24] with iron and HCl.

The oxime of this ketone, m.p. 84–85° (lit.[23] 88–89°), was obtained in 87% yield. Catalytic hydrogenation gave **5** in 74% yield.

***dl*-1-(4-Methylphenyl)-2-methoxyaminopropane (12).**—1-*p*-Tolyl-2-propanone oxime O-methyl ether was an oil, b.p. 82–84° (1.3 mm.), obtained in 95% yield by treatment of 1-*p*-tolyl-2-propanone with methoxyamine.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.6; H, 8.5; N, 7.9. Found: C, 74.3; H, 8.2; N, 7.7.

Catalytic hydrogenation afforded **12** in 42% yield.

***dl*-N-[β-(1,2,3,4-Tetrahydronaphthyl)]hydroxylamine (6).**—β-Tetralone oxime[25] (8.6 g.) in 150 ml. of ethanol containing 1.8 g. of HCl was hydrogenated over 0.25 g. of platinum oxide catalyst at 3.5 kg./cm.² (50 p.s.i.g.) until 1 mole equiv. of hydrogen was absorbed. The reaction mixture was processed as described previously, and **6** was isolated as the oxalate, m.p. 183–184°; yield, 3.4 g. (30%).

***dl*-1-(3-Indolyl)-2-hydroxyaminopropane (7).** Crude 1-(3-indolyl)-2-propanone oxime (8 g.), obtained from 3-indoleacetone[26] and hydroxylamine, in 200 ml. of ethanol containing 1.6 g. of HCl was hydrogenated over 0.2 g. of platinum oxide catalyst at 3.5 kg./cm.² (50 p.s.i.g.) until 1 mole equiv. of hydrogen was absorbed. The hydroxyamino compound **7** was isolated as the oxalate, m.p. 180–181°.

***dl*-1-(4-Chlorophenyl)-2-aminopropane (15).**—To a cooled and stirred mixture of 23 g. of lithium aluminum hydride and 500 ml. of anhydrous ether was added gradually a solution of 29.6 g. of 1-(*p*-chlorophenyl)-2-nitro-1-propene[27] in 100 ml. of dry reagent benzene. The reaction mixture was stirred and heated under reflux for 1 hr., cooled, and decomposed with ice water. After filtration from inorganic material, the dried solution was treated with HCl gas to precipitate **15** as the hydrochloride; yield, 25.7 g. (83%); m.p. 163–165°, after recrystallization from ethanol–ethyl acetate–ether.

***dl*-1-(4-Tolyl)-2-aminopropane (16).**—Reduction of 23 g. of 1-(*p*-tolyl)-2-nitro-1-propene with 17 g. of lithium aluminum hydride gave 16.7 g. (70%) of **16** as the hydrochloride, m.p. 158–159°, after recrystallization from ethanol–ethyl acetate–ether.

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Synthesis and Pharmacological Study of New Piperazine Derivatives. II. Phenethylpiperazines

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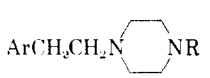
Thirty-eight 1,4-disubstituted piperazines have been prepared, in which the 1-substituents are phenethyl or its mono- or dimethoxy derivatives, and the 4-substituents are phenyl, mono-, or polysubstituted phenyl, pyridyl, methylpyrazinyl, chloro-, or methoxypyridazinyl. They have been studied systematically for potency against epinephrine and histamine on the isolated guinea pig seminal vesicle, in comparison with ergotamine and promethazine.

In the preceding paper of this series[1] the synthesis and the adrenolytic and antihistaminic activities of a number of benzylpiperazines have been described. We now wish to report the study of phenethylpiperazines of type I, where Ar = phenyl, mono- or dimethoxyphenyl, and R = phenyl, mono-, or polysubstituted phenyl, pyridyl, methylpyrazinyl, chloro- or methoxypyridazinyl.



I

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Although a variety of 1,4-disubstituted piperazines are known, only some derivatives of the same general formula have been described specifically.[2]

Phenethylpiperazine derivatives (Table I) were prepared by condensation of the relevant monosubstituted piperazine with the appropriate phenethylhalide in the presence of a twofold excess of the piperazine in xylene (methods A and B) or in the presence of anhydrous potassium carbonate in butanol (method C). The aminophenylpiperazine derivative was obtained

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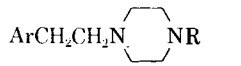
TABLE I



Compd.	Ar	R	Method[a]	Yield crystallized, %	Crystn. solvent[b]	M.p., °C.[c] of amine or salt	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H	Pharmacological data[d] Adrenolytic activity EC_{50}, γ/ml.[e]	Pharmacological data[d] Anti-histaminic activity EC_{50}, γ/ml.[e]	LD_{50}, mg./kg., mice i.p.[f]
1	C_6H_5	C_6H_5[g]	F	32	IE	78+	$C_{18}H_{22}N_2$	81.15	8.33	81.0	8.3	0.2	0.05	75
2	3-$CH_3OC_6H_4$	C_6H_5	F	35	PE I	65+	$C_{19}H_{24}N_2O$	76.98	8.16	76.9	8.0	1	0.2	300
3	4-$CH_3OC_6H_4$	C_6H_5	E	77	E 96	97+	$C_{19}H_{24}N_2O$	76.98	8.16	77.1	8.2	...	...	...
4	3,4-$(CH_3O)_2C_6H_3$	C_6H_5	E	50	E 90	94+	$C_{20}H_{26}N_2O_2$	73.58	8.03	73.5	8.1	0.02	0.02	150
5	3,4-$(CH_3O)_2C_6H_3$	2-FC_6H_4	G	54	IE	90	$C_{20}H_{25}FN_2O_2$	69.74	7.32	69.7	7.3	0.05	0.05	75
6	3,4-$(CH_3O)_2C_6H_3$	2-ClC_6H_4	G	73	IE	94	$C_{20}H_{25}ClN_2O_2$	66.56	6.98	66.6	7.0	0.01	0.5	100
7	3,4-$(CH_3O)_2C_6H_3$	3-ClC_6H_4	E	70	PE III	82	$C_{20}H_{25}ClN_2O_2$	66.56	6.98	66.7	7.0	0.2	0.2	75
8	3,4-$(CH_3O)_2C_6H_3$	4-ClC_6H_4	E	71	H	111	$C_{20}H_{25}ClN_2O_2$	66.56	6.98	66.5	7.3	0.5	0.05	75
9	3,4-$(CH_3O)_2C_6H_3$	2-BrC_6H_4	E	66	H	105	$C_{20}H_{25}BrN_2O_2$	59.26	6.22	59.3	6.1	0.02	0.1	75
10	3,4-$(CH_3O)_2C_6H_3$	2-OHC_6H_4	E	77	H	111	$C_{20}H_{26}N_2O_3$	70.15	7.65	70.2	7.7	0.1	0.1	50
11	3,4-$(CH_3O)_2C_6H_3$	2-$NO_2C_6H_4$	E	54	H	73	$C_{20}H_{25}N_3O_4$	64.67	6.78	64.8	6.8	0.2	0.2	75
12	3,4-$(CH_3O)_2C_6H_3$	2-$NH_2C_6H_4$	H	78	P	114	$C_{20}H_{27}N_3O_2$	70.35	7.97	70.4	8.3	0.05	0.01	75
13	3,4-$(CH_3O)_2C_6H_3$	2-$CH_3CONHC_6H_4$	I	80	H	117	$C_{22}H_{29}N_3O_3$	68.90	7.63	68.9	7.9	1	2	75
14	3,4-$(CH_3O)_2C_6H_3$	2-$CH_3C_6H_4$	E	60	H	92	$C_{21}H_{28}N_2O_2$	74.08	8.29	74.1	8.5	0.05	0.05	100
15	3,4-$(CH_3O)_2C_6H_3$	3-$CH_3C_6H_4$	E	63	PE III	60	$C_{21}H_{28}N_2O_2$	74.08	8.29	73.9	8.1	0.2	0.1	100
16	3,4-$(CH_3O)_2C_6H_3$	4-$CH_3C_6H_4$	E	63	H	87	$C_{21}H_{28}N_2O_2$	74.08	8.29	74.0	8.3	0.2	0.1	150
17	3,4-$(CH_3O)_2C_6H_3$	2-$CH_3OC_6H_4$	E	67	H	101	$C_{21}H_{28}N_2O_3$	70.76	7.92	70.9	7.8	0.002	0.05	50
18	3,4-$(CH_3O)_2C_6H_3$	3-$CH_3OC_6H_4$	E	49	H	81	$C_{21}H_{28}N_2O_3$	70.76	7.92	71.0	7.9	0.2	0.01	100
19	3,4-$(CH_3O)_2C_6H_3$	4-$CH_3OC_6H_4$	E	56	PE III	110	$C_{21}H_{28}N_2O_3$	70.76	7.92	70.6	7.8	0.2	0.2	100
20	3,4-$(CH_3O)_2C_6H_3$	2-$C_2H_5OC_6H_4$	E	45	H	63	$C_{22}H_{30}N_2O_3$	71.32	8.16	71.2	7.9	0.005	0.01	150
21	3,4-$(CH_3O)_2C_6H_3$	2-$CH_3SC_6H_4$	E	24	PE I	79	$C_{21}H_{28}N_2O_2S$	67.70	7.58	67.9	7.7	0.005	0.5	100
22	3,4-$(CH_3O)_2C_6H_3$	2,4-$Cl_2C_6H_3$	E	46	H	80	$C_{20}H_{24}Cl_2N_2O_2$	60.76	6.12	60.9	6.2	0.1	0.05	75
23	3,4-$(CH_3O)_2C_6H_3$	2,5-$Cl_2C_6H_3$	E	78	H	100	$C_{20}H_{24}Cl_2N_2O_2$	60.76	6.12	60.6	5.9	0.05	1	50
24	3,4-$(CH_3O)_2C_6H_3$	2,3-$(CH_3)_2C_6H_3$	G	60	PE III	85	$C_{22}H_{30}N_2O_2$	74.54	8.53	74.5	8.4	0.1	0.01	75
25	3,4-$(CH_3O)_2C_6H_3$	2,4-$(CH_3)_2C_6H_3$	G	48	IE	80	$C_{22}H_{30}N_2O_2$	74.54	8.53	74.6	8.5	0.1	0.05	75
26	3,4-$(CH_3O)_2C_6H_3$	2,5-$(CH_3)_2C_6H_3$	G	61	H	78	$C_{22}H_{30}N_2O_2$	74.54	8.53	74.6	8.6	0.1	...	...
27	3,4-$(CH_3O)_2C_6H_3$	2,6-$(CH_3)_2C_6H_3$	G	50	H	96	$C_{22}H_{30}N_2O_2$	74.54	8.53	74.5	8.6	0.05	5	150
28	3,4-$(CH_3O)_2C_6H_3$	3,4-$(CH_3)_2C_6H_3$	G	53	H	115	$C_{22}H_{30}N_2O_2$	74.54	8.53	74.6	8.5	0.02	0.1	100
29	3,4-$(CH_3O)_2C_6H_3$	2,5-$(CH_3O)_2C_6H_3$	E	65	AE	215	$C_{22}H_{30}N_2O_4 \cdot HCl$	62.47	7.39	62.2	7.4	0.2	0.05	100
30	C_6H_5	2-C_5H_4N[h]	F	23	M	49	$C_{17}H_{21}N_3$	76.36	7.92	76.4	7.9	3	0.2	...
31	4-$CH_3OC_6H_4$	2-C_5H_4N[h,i]	E	50	M	99	$C_{18}H_{23}N_3O$	72.69	7.79	72.9	7.7	0.4	0.05	100
32	2,4-$(CH_3O)_2C_6H_3$	2-C_5H_4N[h]	E	44	AE	136	$C_{19}H_{25}N_3O_2 \cdot 2HCl$	57.00	6.80	56.5	7.1	0.1	0.05	150
33	2,5-$(CH_3O)_2C_6H_3$	2-C_5H_4N[h]	E	60	P	210+	$C_{19}H_{25}N_3O_2 \cdot 2HCl$	57.00	6.80	56.85	6.85	0.5	0.2	300
34	3,4-$(CH_3O)_2C_6H_3$	2-C_5H_4N[h]	E	78	H	74	$C_{19}H_{23}N_3O_2$	69.69	7.69	69.7	7.5	0.5	0.2	300
35	3,4-$(CH_3O)_2C_6H_3$	4-C_5H_4N[h]	E	50	H	134	$C_{19}H_{25}N_3O_2$	69.69	7.69	69.5	7.9	>5	>5	...
36	3,4-$(CH_3O)_2C_6H_3$	2-$C_5H_5N_2$[j]	E	71	PE II	66	$C_{19}H_{26}N_4O_2$	66.64	7.65	66.4	7.6	2	0.5	...
37	3,4-$(CH_3O)_2C_6H_3$	3-$C_4H_2ClN_2$[k]	E	53	H	120	$C_{18}H_{23}ClN_4O_2$	59.58	6.39	59.7	6.4	>5	>5	...
38	3,4-$(CH_3O)_2C_6H_3$	3-$C_5H_5N_2O$[l]	E	68	H	113	$C_{19}H_{26}N_4O_3$	63.66	7.31	63.3	7.5	>5	0.5	...

[a] See Experimental section. [b] AE, absolute ethanol; E 96, 96% ethanol; E 90, 90% ethanol; H, heptane; IE, isopropyl ether; M, methanol; P, 2-propanol; PE, petroleum ether (I, b.p. 35–50°; II, b.p. 50–60°; III, b.p. 60–70°). [c] Melting points were determined on a Kofler hot stage microscope or (for compounds marked with +) in open capillaries and are uncorrected. [d] Compounds prepared as bases were dissolved in dilute acetic acid. [e] EC_{50} is the concentration which inhibited the normal contraction of either adrenaline (2 γ/ml.) and histamine (2 γ/ml.) by 50%; > means that the compound was inactive up to the concentration of 5 γ/ml. [f] See ref. 1. [g] Lit.[2a] m.p. 77–78°. [h] C_5H_4N, pyridyl. [i] Lit.[2c] m.p. 92–94°. [j] $C_5H_5N_2$, 3-methylpyrazinyl. [k] $C_4H_2ClN_2$, 6-chloropyridazinyl. [l] $C_5H_5N_2O$, 6-methoxypyridazinyl.

TABLE II[a]

Compd.	R	Method[b]	Yield, %	B.p. (mm.)[c] or m.p., °C.[d]	Salts for analyses: Formula	M.p., °C.[e]	Crystn. solvent[e]	Calcd., % C	Calcd., % H	Found, % C	Found, % H
39	2-FC_6H_4	A	25	93 (0.5)	$C_{10}H_{13}FN_2 \cdot HCl$	187	P	55.42	6.51	55.7	6.6
40	2-BrC_6H_4[f]	B	55	114 (0.2)	$C_{10}H_{13}BrN_2 \cdot HBr$	180	AE	37.29	4.38	37.4	4.5
41	2-OHC_6H_4	B	33	127	$C_{10}H_{14}N_2O \cdot HBr$	204	P	46.34	5.83	46.4	5.8
42	2-$CH_3SC_6H_4$[g]	B	42	120 (0.2)	$C_{11}H_{16}N_2S \cdot HBr$	205	AE	45.67	5.92	45.9	6.1
43	2,4-$Cl_2C_6H_3$	C	27	125 (0.2)	$C_{10}H_{12}Cl_2N_2 \cdot HBr$	202	P	38.48	4.20	38.6	4.0
44	2,5-$Cl_2C_6H_3$[h]	C	48	128 (0.2)	$C_{10}H_{12}Cl_2N_2 \cdot HBr$	226	P	38.48	4.20	38.2	4.1
45	2,3-$(CH_3)_2C_6H_3$[i]	A	37	94 (0.3)	$C_{12}H_{18}N_2 \cdot HCl$	294	E 96	63.56	8.44	63.6	8.4
46	2,4-$(CH_3)_2C_6H_3$[j]	A	41	153 (10)	$C_{12}H_{18}N_2 \cdot HCl$	236	P	63.56	8.44	63.5	8.3
47	2,5-$(CH_3)_2C_6H_3$[k]	A	40	154 (10) 40	$C_{12}H_{18}N_2 \cdot HCl$	279	E 96	63.56	8.44	63.8	8.3
48	2,6-$(CH_3)_2C_6H_3$[l]	A	15	148 (10)	$C_{12}H_{18}N_2 \cdot HCl$	240	P	63.56	8.44	63.7	8.6
49	3,4-$(CH_3)_2C_6H_3$	A	36	175 (10) 62	$C_{12}H_{18}N_2 \cdot HCl$	173	P	63.56	8.44	63.4	8.3
50	2,5-$(CH_3O)_2C_6H_3$[m]	B	57	133 (0.2)	$C_{12}H_{18}N_2O_2 \cdot HCl$	169	AE	55.70	7.40	55.5	7.5
51	4-C_5H_4N[n]	D	85	140	$C_9H_{13}N_3$[o]	...	...	66.23	8.03	66.1	8.0

[a] Purities of all distilled monosubstituted piperazines were determined by gas chromatography using a Prolabo apparatus with a thermal conductivity detector (column: 4 m. long, 6-mm. diameter, packed with C 22 firebrick coated with 20% by weight of Rhodorsil silicone oil, temperature 240°, carrier gas hydrogen). Retention time was 8 to 10 min. With compounds prepared from anilines, chromatograms showed a trace of these materials even after three rectifications (retention time about 2 min.). [b] See Experimental section. [c] Uncorrected. [d] Uncorrected, taken on a Kofler-type hot stage. [e] AE, absolute ethanol; E 96, 96% ethanol; P, 2-propanol. [f] R. F. Parcell [U. S. Patent 2,833,770 (1958)] reported b.p. 109–113° (0.35 mm.). [g] R. F. Parcell [U. S. Patent 2,836,594 (1958)] reported b.p. 123–126° (0.2 mm.). [h] Parke, Davis and Co. [British Patent 850,663 (1960)] reported b.p. 125–128° (0.5 mm.). [i] Lit.[b] b.p. 110–113° (1 mm.). [j] H. G. Morren, Belgian Patent 614,177 (1962), no data. [k] R. F. Parcell [U. S. Patent 2,922,788 (1960)] reported 105–108° (1 mm.). [l] H. P. Dalalian, L. N. Starker, and L. Goldman, U. S. Patent 2,909,524 (1959), no data. [m] Lit.[b] b.p. 127–132° (0.5 mm.). [n] C_5H_4N, pyridyl. [o] Base.

from the nitrophenylpiperazine derivative by catalytic reduction (method D) and the acetylaminophenylpiperazine derivative by treating the amino derivative with acetyl chloride (method E).

Many of the 1-monosubstituted piperazines used in this work are known compounds. In Table II, descriptive and analytical data are listed for 13 additional compounds of this type. Synthetic details for those derivatives are given in the Experimental part; most of them have been described in the patent literature (see footnotes to Table II).

The compounds have been tested on the isolated guinea pig seminal vesicle according to the method of Stone and Loew.[3] The results of this investigation appear in Table I. Several compounds possess a potent activity against epinephrine.[4] The observed histaminolytic effect is relatively weak in comparison to promethazine.[4] Compound **6** was retained for a more extensive pharmacological examination. It exhibits adrenolytic, hypotensive, and neuroleptic properties in laboratory animals.[5]

Experimental

Melting points (uncorrected) were determined using a Kofler micro hot stage.

1-Monosubstituted Piperazines.—The following compounds were prepared as described in the literature: 1-phenyl-,[6a] 1-[*m*-(*o*- and *p*-)chlorophenyl]-,[6b] 1-[*m*-(*o*- and *p*-)tolyl]-,[6b] 1-(*o*-nitrophenyl)-,[6c] 1-[*m*-(*o*- and *p*-)methoxyphenyl]-,[6d] 1-(*o*-ethoxyphenyl)-,[6e] 1-(2-pyridyl)-,[6e] 1-(3-methyl-2-pyrazinyl)-,[1] 1-(6-chloro-3-pyridazinyl)-,[1] and 1-(6-methoxy-3-pyridazinyl)piperazines.[1] The remainder of the 1-monosubstituted piperazines (Table II) were obtained by one of the following methods for which representative procedures are given.

A. 1-(2-Fluorophenyl)piperazine (39).—A mixture of 24.4 g. (0.22 mole) of 2-fluoroaniline, 21 g. (0.2 mole) of diethanolamine, and 40 ml. of HCl (sp. gr. 1.19) was immersed in an oil bath preheated to 125° and heated slowly to 170°. The temperature of the bath was maintained at 170° for 7 hr. and at 240° for 7 hr. After cooling, the residual dark oil was taken up in water and NaOH (20 g.) was added to the solution. Extraction with benzene, concentration, and distillation afforded 9 g. of **39** after removal of a forerun of 10 g. of 2-fluoroaniline.

B. 1-(2-Bromophenyl)piperazine (40).—A solution of 77.5 g. (0.45 mole) of 2-bromoaniline, and 46.8 g. (0.15 mole) of bis(β-bromoethyl)amine hydrobromide in 150 ml. of 2-butanone was refluxed for 3 hr. Upon cooling for 15 hr. at 0°, a mixture of hydrobromide salts crystallized as white granules. The solid was collected, taken up in water, and treated as in method A to give 19.8 g. of **40** after removal of a forerun of 45.2 g. of 2-bromoaniline.

C. 1-(2,4-Dichlorophenyl)piperazine (43).—The procedure used was a modification of method A to avoid excessive sublimation. The mixture of 2,4-dichloroaniline, diethanolamine, and HCl was heated at 140° for 5 hr. After cooling, it was dissolved in water, made alkaline, and then extracted with hot benzene. Upon cooling overnight at 0°, the solid was filtered and dried to give **N-(2,4-dichlorophenyl)-N'-(2-hydroxyethyl)-ethylenediamine** (53%). The analytical sample was produced by one more recrystallization from benzene, m.p. 81°.

Anal. Calcd. for $C_{10}H_{14}Cl_2N_2O$: C, 48.20; H, 5.66. Found: C, 48.2; H, 5.6.

A solution of 24.9 g. (0.1 mole) of the above ethylenediamine in 20 ml. of HCl (sp. gr. 1.19) was concentrated *in vacuo*. The residue was heated at 240° for 8 hr. and then treated as in method A to give 11.8 g. of **43** (27% yield from diethanolamine).

(3) C. A. Stone and E. R. Loew, *J. Pharmacol. Exptl. Therap.*, **106**, 226 (1952).

(4) For comparative purposes, with the same conditions, EC_{50} for ergotamine against epinephrine was found to be 0.02 γ/ml. and EC_{50} for promethazine against histamine was 0.001 γ/ml.

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The same procedure was used to obtain **N-(2,5-dichlorophenyl)-N'-(2-hydroxyethyl)ethylenediamine.** For analysis a sample was recrystallized from toluene, m.p. 95°.

Anal. Calcd. for $C_{10}H_{14}Cl_2N_2O$: C, 48.20; H, 5.66. Found: C, 48.5; H, 5.6.

D. 1-(4-Pyridyl)piperazine (51).—A solution of 1-benzyl-4-(4-pyridyl)piperazine[1] (25.33 g., 0.1 mole) in 100 ml. of 2 *N* HCl and 500 ml. of methanol was hydrogenated with 10 g. of palladium-on-charcoal catalyst (5% by wt.) at room temperature under atmospheric pressure. The theoretical amount of hydrogen was taken up in 3 hr. The catalyst was filtered and the filtrate was concentrated *in vacuo* on a rotary evaporator. The resulting white solid was taken up in water, and the solution was made alkaline with KOH. The precipitate was collected and dried to give **51** in nearly quantitative yield. It was recrystallized from heptane.

E and F. 1-(3,4-Dimethoxyphenethyl)-4-(2-pyridyl)piperazine (34).—A solution of 113 g. (0.46 mole) of 3,4-dimethoxyphenethyl bromide[7] and 150 g. (0.92 mole) of 1-(2-pyridyl)-piperazine in 1 l. of anhydrous xylene was refluxed for 10 hr. with stirring. After cooling, the mixture was filtered to remove 1-(2-pyridyl)piperazinium bromide (the solid was dried, yield 111 g.) and the filtrate was extracted with 500 ml. of 5% HCl. This solution was immediately made basic at 10–20°. The white solid which formed was collected, washed with water, and dried to give 138 g. (92%) of **34**. Recrystallization from 3 l. of heptane produced pure product.

1-(2,5-Dimethoxyphenethyl)-4-(2-pyridyl)piperazine Hydrochloride (33).—Following the same procedure, 1-(2,5-dimethoxyphenethyl)-4-(2-pyridyl)piperazine was obtained as an oil after extraction with ether of the basic solution and concentration *in vacuo* of the dried extracts. To a solution of 16.35 g. (0.05 mole) of this base in 50 ml. of absolute ethanol was added 0.1 mole of 2 *N* absolute ethanolic HCl. The solvent was evaporated *in vacuo* and crude **33** was crystallized.

In method F, the above procedure was carried out for aralkyl chlorides, the solution being stirred under reflux for 24 hr.

G. 1-(3,4-Dimethoxyphenethyl)-4-(2-chlorophenyl)piperazine (6).—A solution of 120 g. (0.49 mole) of 3,4-dimethoxyphenethyl bromide and 98 g. (0.5 mole) of 1-(2-chlorophenyl)piperazine in 1 l. of 1-butanol was stirred at 105–110° for 15 hr. in the presence of 76 g. of anhydrous potassium carbonate. The mixture was filtered while hot and the filtrate was kept at 0° overnight to give colorless crystals; yield, 150 g. (84%). Recrystallization from 1.2 l. of isopropyl ether gave pure 6.

H. 1-(3,4 Dimethoxyphenethyl)-4-(2-aminophenyl)piperazine (12).—A sample of 18.55 g. (0.05 mole) of 1-(3,4-dimethoxyphenethyl)-4-(2-nitrophenyl)piperazine (11) in 300 ml. of ethanol was hydrogenated in the presence of platinum oxide catalyst at room temperature under atmospheric pressure. The calculated amount of hydrogen was taken up in 15 min. and the temperature was raised to 40–50°. The catalyst was removed while warm and a slow crystallization in the refrigerator of the filtrate afforded 14.1 g. (82.5%) of white crystals. Recrystallization from 50 ml. of 2-propanol gave pure **12**.

I. 1-(3,4-Dimethoxyphenethyl)-4-(2-acetylaminophenyl)-piperazine (13).—Acetyl chloride (7.85 g., 0.1 mole) was added slowly to a stirred solution of 6.8 g. (0.02 mole) of the above amine (**12**) in 75 ml. of toluene under anhydrous conditions. After refluxing for 1 hr., the solid was collected and dried to give 7.55 g. (90%) of **1-(3,4-dimethoxyphenethyl)-4-(2-acetylaminophenyl)piperazine hydrochloride**, m.p. 200–205°. For analysis, a sample was recrystallized from 2-propanol, m.p. 215°.

Anal. Calcd. for $C_{22}H_{29}N_3O_3 \cdot HCl$: Cl, 8.44. Found: Cl, 8.3.

A 5-g. finely ground sample of the above hydrochloride was suspended in 100 ml. of dry ether and treated with gaseous ammonia with stirring. After 15 min., the inorganic salt was filtered and the filtrate was concentrated *in vacuo* to yield a white solid. It was recrystallized from 150 ml. of heptane to give 4.05 g. (80%) of **13**.

(7) The necessary phenethyl halides were obtained according to literature methods: 3-methoxyphenethyl chloride, W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1533 (1935); 4-methoxyphenethyl bromide, J. B. Shoesmith and R. J. Connor, *ibid.*, 2230 (1927); 3,4-dimethoxyphenethyl bromide, S. Sugasawa, *J. Pharm. Soc. Japan*, **57**, 296 (1937); 2,5-dimethoxyphenethyl bromide, R. A. Barnes, *J. Am. Chem. Soc.*, **75**, 3004 (1953); 2,4-dimethoxyphenethyl bromide was prepared in 70% yield from 2-(2,4-dimethoxyphenyl)ethanol by the method used for 2,5-dimethoxyphenethyl bromide, b.p. 116–119° (0.3 mm.). *Anal.* Calcd. for $C_{10}H_{13}BrO_2$: Br, 32.60. Found: Br, 32.4.

p-Amino-N-[2-(substituted amino)ethyl]benzamides. Potential Antifibrillatory Drugs

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The alkylation of amines with 1-*p*-nitrobenzoylethylenimine has been studied. The *p*-nitro-N-[2-(substituted amino)ethyl]benzamides were readily hydrolyzed to N-substituted ethylenediamines. The *p*-nitrobenzamides were hydrogenated catalytically and a series of analogs of procaine amide were obtained. These analogs were screened for antifibrillatory activity in the rabbit heart and in the dog heart. Several of the compounds showed high activity.

Numerous drugs have been used to some extent in the treatment of the heart's rate and rhythm. However, only quinidine and *p*-amino-N-(2-diethylaminoethyl)-benzamide (procaine amide) are drugs of sufficient selectivity and specificity of action to be classified as antiarrhythmic and antifibrillatory agents. Fibrillation is a state of rapid, tremulous, and ineffective contractions of the atrial or ventricular muscle. In 1918 quinidine was reported to be the most effective antiarrhythmic agents among the cinchona alkaloids.[1] 2-Diethylaminoethyl *p*-aminobenzoate (procaine) had been reported to have some activity by Shen and Simon.[2] In 1951, procaine amide was shown to be effective in the treatment of cardiac arrhythmias.[3] This compound has cardiac actions essentially identical with those of quinidine.[4]

Although very useful, both quinidine and procaine amide may at times precipitate ventricular fibrillation or respiratory collapse.[5] Thus it was felt that the synthesis and study of the cardiac action of a series of

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