those of the parent substance.[3] One of the routes chosen was the preparation of nitro compounds, reduction to the amino compounds, diazotization, and finally replacement of the diazonium group by hydroxyl. One of the methyls in the dimethylamino group was split off in some cases to form monomethylamino compounds. The compositions of the latter compounds differed so little from the expected dimethylamino compound that the loss of the methyl group was detected by infrared or n.m.r. observations, not by analytical data.[4] In a few instances it was found convenient to couple a hydroxylepidine with a suitable aldehyde or to prepare a methoxy dimethylaminostyrylquinoline and hydrolyze it to the hydroxy compound. Some 4-(4-dimethylamino-2-methoxystyryl)-quinoline was recovered unhydrolyzed after 4 hr. in boiling sulfuric acid (60% by wt.) along with a small yield of the desired 2-hydroxy product. The latter was obtained more conveniently from 4-dimethylamino-2-hydroxybenzaldehyde and lepidine hydrochloride.

Like many other hydroxy heterocyclic substances[5] most of these hydroxy compounds were not readily soluble in oil. Perhaps for this reason, they did not show much biological activity when administered in this way. It is interesting to note that the melting points of the 3′-amino and 3′-hydroxy compounds were lower than those of the other hydroxy and amino compounds listed. Fifteen of the compounds listed in Table I were tested by single i.p. injection in oil, against Walker 256 tumors in rats, at the Chester Beatty Research Institute. None of the hydroxy compounds tested showed antitumor activity, but the 8-amino, the 2-dimethylamino, and all four monomethoxy compounds showed clear-cut activity. The most potent of the fifteen compounds were the 3′-ethyl and the 2′-methoxy.

Experimental

All styryl compounds were prepared by reaction of the aldehyde with the lepidine hydrochloride unless otherwise indicated.

2-Dimethylaminolepidine Hydrochloride.—A solution of 2-chlorolepidine hydrochloride in dimethylformamide was refluxed for 3 hr. The white crystals that separated on cooling were collected and dried; m.p. 330°. This material was used for the preparation of **11**.

Anal. Calcd. for $C_{12}H_{14}N_2 \cdot HCl$: neut. equiv., 222.7. Found: neut. equiv. (titration using pH meter), 223.0.

4-(4-Hydroxystyryl)quinoline.—A solution of 2.5 g. (0.01 mole) of 4-(4-aminostyryl)quinoline in 500 ml. of 40% H_2SO_4 was diazotized with 1.09 g. of sodium nitrite (0.01 mole) at 0–5° The diazotized salt was slowly added to boiling water, then the solution was boiled an additional 5 min. The acid mixture was neutralized using NaOH initially and completing the neutralization with Na_2CO_3. The precipitate was filtered, dried, and recrystallized from octane until the compound appeared chromatographically pure; m.p. 259–261°, yield 0.58 g. (23%).

Anal. Calcd. for $C_{17}H_{13}NO$: C, 82.55; H, 5.71. Found: C, 82.42, 82.37; H, 5.5, 5.7.

(3) C. T. Bahner, L. M. Rives, E. B. Senter, W. Longmire, H. Kinder, D. B. Bales, F. Hannan, B. Pettyjohn, W. K. Easley, L. Free, and H. Free, *J. Org. Chem.*, **27**, 2233 (1962); C. T. Bahner, *Acta Unio Intern. Contra Cancrum*, **20**, 253 (1964).

(4) We are grateful to Dr. Clarence Cook of the Research Triangle Institute for obtaining and interpreting infrared and n.m.r. curves on selected compounds.

(5) A. Albert, "Heterocyclic Chemistry," University of London, London, 1959, p. 44.

Synthesis and Pharmacological Study of New Piperazine Derivatives. III. Phenoxyalkylpiperazines

R. RATOUIS,

Société Centrale de Recherches & d'Applications Techniques, Paris

J. R. BOISSIER,

Institut de pharmacologie, Faculté de Médecine, Paris

AND C. DUMONT

Laboratoires DIAMANT, La Plaine-Saint-Denis (Seine)

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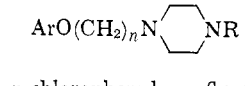
Early pharmacologic studies demonstrated that phenoxyethylamine and some of its derivatives were sympatholytic.[1] In our search for new structures with such useful activities,[2] it was considered of interest to introduce phenoxyethyl and more generally aryloxyalkyl groupings into the 4-position of a series of 1-phenylpiperazines and some of their congeners. In this investigation, we decided to prepare unsymmetrical piperazines (I) and to vary the substituents Ar and R, and the size of the alkylene unit. The following compounds were prepared.



I, Ar = phenyl, *p*-chlorophenyl, *p*-fluorophenyl, *o*-tolyl, *p*-methoxyphenyl, 2,6-xylyl, 3,4-dimethoxyphenyl
R = phenyl, *o*- or *p*-chlorophenyl, *o*-methoxyphenyl, 2,3-xylyl, 2-pyridyl
n = 2 to 10

To our knowledge, the synthesis of only one compound of formula I (Ar = R = C_6H_5; n = 2) has been reported[3]; recently Abood and co-workers[4] have synthesized and tested for their psychotropic properties, a large number of aryloxyalkylpiperazines of type I but with R = H or $CO_2C_2H_5$ (n = 2 to 7).

In Table I descriptive and analytical data are listed for compounds of formula I. They were obtained from the corresponding aryloxyalkyl bromides by treatment with the appropriate monosubstituted piperazine in the presence of anhydrous potassium carbonate in butanol. The desired products were isolated either directly as bases or the bases were converted to hydrochloride salts.

The aryloxyalkyl bromides required (Table II) were prepared from phenoxides and polymethylene dibromides according to previously reported procedures.[5] The use of water as a reaction medium led to the formation of symmetrical bisaryloxyalkanes as side products (method A). No side product was isolated when absolute ethanol and excess dibromide (method B) was used. Synthetic details are given for these methods

(1) D. Bovet and F. Bovet-Nitti, "Medicaments du système nerveux végétatif," S. Karger, S.A., Bâle, 1948, p. 222.

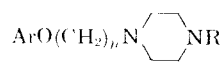
(2) Previous paper in this series: R. Ratouis, J. R. Boissier, and C. Dumont, *J. Med. Chem.*, **8**, 104 (1965).

(3) A. P. Swain and S. K. Naegele, *J. Am. Chem. Soc.*, **76**, 5091 (1954).

(4) L. G. Abood, L. Brady, E. Boulton, V. Lipman, and M. Fishman, *Arch. Intern. Pharmacodyn.*, **134**, 106 (1961).

(5) See for examples Table II, footnotes *c* to *i*.

TABLE I



Compd.	Ar	R	n	Yield crystallized, %	Crystn.[a] solvent	M.p.,[b] °C., of amine or salt	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H	LD_{50}, mg./kg., mice i.p.[c]
1	C_6H_5	2-ClC_6H_4	2	51	IE	76	$C_{18}H_{21}ClN_2O$	68.23	6.68	68.21	6.70	100
2	4-ClC_6H_4	C_6H_5	2	57	E 96	84–85	$C_{18}H_{21}ClN_2O$	68.23	6.68	68.60	6.58	150
3	4-ClC_6H_4	2-ClC_6H_4	2	63	PE	67–68	$C_{18}H_{20}Cl_2N_2O$	61.54	5.74	61.68	5.62	800
4	4-ClC_6H_4	4-ClC_6H_4	2	70	E 96	118–119	$C_{18}H_{20}Cl_2N_2O$	61.54	5.74	61.62	5.75	800
5	4-ClC_6H_4	2-C_5H_4N[d]	2	81	H	110	$C_{17}H_{20}ClN_3O$	64.24	6.34	64.21	6.28	300
6	3,4-$(CH_3O)_2C_6H_3$	2-ClC_6H_4	2	62	IE	81–82	$C_{20}H_{25}ClN_2O_3$	63.74	6.69	63.77	6.80	150
7	3,4-$(CH_3O)_2C_6H_3$	2-$CH_3OC_6H_4$	2	67	H	70	$C_{21}H_{28}N_2O_4$	67.72	7.58	67.90	7.61	150
8	C_6H_5	2-ClC_6H_4[e]	3	72	P	188–190	$C_{19}H_{23}ClN_2O \cdot HCl$	62.13	6.58	62.32	6.69	75
9	C_6H_5	2-ClC_6H_4	4	62	P	156–157	$C_{20}H_{25}ClN_2O \cdot HCl$	62.99	6.87	62.72	7.10	75
10	4-FC_6H_4	4-ClC_6H_4	4	64	E 96	121	$C_{20}H_{24}ClFN_2O$	66.16	6.67	66.38	6.78	600
11	4-FC_6H_4	2-$CH_3OC_6H_4$	4	78	H	77–78	$C_{21}H_{27}FN_2O_2$	70.36	7.59	70.76	7.54	600
12	4-FC_6H_4	2-C_5H_4N[d]	4	61	H	62	$C_{19}H_{24}FN_3O$	69.27	7.34	69.39	7.40	150
13	4-ClC_6H_4	C_6H_5	4	54	PE	53	$C_{20}H_{25}ClN_2O$	69.65	7.31	69.73	7.58	600
14	4-ClC_6H_4	2-ClC_6H_4	4	64	P	155	$C_{20}H_{24}Cl_2N_2O \cdot HCl$	57.77	6.06	57.86	5.91	75
15	4-ClC_6H_4	3-ClC_6H_4	4	55	P	155–156	$C_{20}H_{24}Cl_2N_2O \cdot HCl$	57.77	6.06	58.00	6.13	100
16	4-ClC_6H_4	4-ClC_6H_4	4	76	E 96	102–103	$C_{20}H_{24}Cl_2N_2O$	63.32	6.38	63.51	6.53	800
17	4-ClC_6H_4	2-$CH_3OC_6H_4$	4	65	H	55–56	$C_{21}H_{27}ClN_2O_2$	67.27	7.26	67.66	7.23	75
18	4-ClC_6H_4	2,3-$(CH_3)_2C_6H_3$	4	56	AE	203–205	$C_{22}H_{29}ClN_2O \cdot HCl$	64.54	7.39	64.57	7.32	600
19	4-ClC_6H_4	2-C_5H_4N[d]	4	89	H	61–62	$C_{19}H_{24}ClN_3O$	65.98	6.99	65.84	6.96	150
20	2-$CH_3C_6H_4$	C_6H_5	4	63	P	129–130	$C_{21}H_{28}N_2O \cdot HCl$	69.88	8.10	69.72	8.01	300
21	2-$CH_3C_6H_4$	4-ClC_6H_4	4	74	H	62–64	$C_{21}H_{27}ClN_2O$	70.27	7.58	70.13	7.87	400
22	2-$CH_3C_6H_4$	2-C_5H_4N[d]	4	52	AE	175	$C_{20}H_{27}N_3O \cdot 2HCl$	60.29	7.34	60.31	7.32	100
23	4-$CH_3OC_6H_4$	4-ClC_6H_4	4	66	E 96	86–87	$C_{21}H_{27}ClN_2O_2$	67.27	7.26	67.50	7.34	150
24	4-$CH_3OC_6H_4$	2-C_5H_4N[d]	4	54	AE	198	$C_{20}H_{27}N_3O_2 \cdot 2HCl$	57.97	7.05	58.03	7.31	150
25	2,6-$(CH_3)_2C_6H_3$	C_6H_5	4	53	P	193–195	$C_{22}H_{30}N_2O \cdot HCl$	70.47	8.33	70.04	8.39	300
26	2,6-$(CH_3)_2C_6H_3$	4-ClC_6H_4	4	70	H	88–89	$C_{22}H_{29}ClN_2O$	70.85	7.84	70.64	7.83	800
27	2,6-$(CH_3)_2C_6H_3$	2-C_5H_4N[d]	4	61	E 96	184–186	$C_{21}H_{29}N_3O \cdot 2HCl$	61.16	7.58	61.08	7.59	375
28	3,4-$(CH_3O)_2C_6H_3$	2-ClC_6H_4	4	69	H	66	$C_{22}H_{29}ClN_2O_3$	65.25	7.22	65.51	7.50	150
29	3,4-$(CH_3O)_2C_6H_3$	2-ClC_6H_4	6	80	IE	85	$C_{24}H_{33}ClN_2O_3$	66.57	7.68	66.79	7.73	100
30	C_6H_5	2-ClC_6H_4	10	61	P–Et	165	$C_{26}H_{37}ClN_2O \cdot HCl$	67.08	8.23	66.95	8.25	...
31	3,4-$(CH_3O)_2C_6H_3$	2-ClC_6H_4	10	50	IE	78–79	$C_{28}H_{41}ClN_2O_3$	68.76	8.45	68.72	8.65	...

[a] AE, absolute ethanol; E 96, 96% ethanol; Et, ether; H, heptane; IE, isopropyl ether; P, 2-propanol; PE, petroleum ether (b.p. 60–75°). [b] Uncorrected, measured on a Kofler hot stage microscope. [c] Acute toxicity determined by intraperitoneal injection of increasing doses (25, 50, 100, 200, 400, and 800 mg./kg.) to pairs of mice according to W. G. Smith in "Progress in Medicinal Chemistry," G. P. Ellis and G. B. West, Ed., Butterworths, London, 1961, p. 1. The LD_{50} is approximately the dose killing one out of two mice or the average of the two successive doses for which mortalities of 0/2 and 2/2 have been observed. [d] C_5H_4N = pyridyl. [e] 1-(3-Phenoxypropyl)-4-(2-chlorophenyl)piperazine was recrystallized from petroleum ether (b.p. 60–75°), m.p. 49°.

TABLE II

$ArO(CH_2)_nBr$

Compd.	Ar	n	Method	Yield, %	B.p., °C. (mm.)[a]	M.p., °C.[b]	Formula	% Br Calcd.	% Br Found
32	C_6H_5[c]	2	A	45	128–129 (20)	30			
33	4-ClC_6H_4[d]	2	A	55	134–135 (8)	34–38			
34	3,4-$(CH_3O)_2C_6H_3$	2	A	50	123–128 (0.1)	60	$C_{10}H_{13}BrO_3$	30.60	30.14
35	C_6H_5[e]	3	A	58	146–150 (20)				
36	C_6H_5[f]	4	A	56	155–157 (18)	43			
37	4-FC_6H_4	4	B	68	87–92 (0.1)	34–36	$C_{10}H_{12}BrFO$	32.34	32.41
38	4-ClC_6H_4[g]	4	B	77	110–112 (0.2)	31–33			
39	2-$CH_3C_6H_4$	4	B	58.5	98–100 (0.2)		$C_{11}H_{15}BrO$	32.87	32.75
40	4-$CH_3OC_6H_4$[h]	4	B	72	113–115 (0.1)	37			
41	2,6-$(CH_3)_2C_6H_3$	4	B	51	98–101 (0.1)		$C_{12}H_{17}BrO$	31.08	31.32
42	3,4-$(CH_3O)_2C_6H_3$	4	A	57	150–155 (0.1)		$C_{12}H_{17}BrO_3$	27.64	27.34
43	3,4-$(CH_3O)_2C_6H_3$	6	B	75	175–185 (0.5)	48	$C_{14}H_{21}BrO_3$	25.19	25.15
44	C_6H_5[i]	10	B	53	150–155 (0.4)	31			
45	3,4-$(CH_3O)_2C_6H_3$	10	B	61	194–200 (0.1)	44	$C_{18}H_{29}BrO_3$	21.41	21.43

[a] Uncorrected. [b] Uncorrected, determined on a Kofler hot stage microscope without recrystallization. [c] C. S. Marvel and A. L. Tanenbaum "Organic Syntheses," Coll.Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 436, reported b.p. 125–130° (18 mm.). [d] B. Belleau, *J. Med. Pharm. Chem.*, **1**, 327 (1959), reported b.p. 140° (0.5 mm.). [e] C. S. Marvel and A. L. Tanenbaum, footnote *b*, p. 435, reported b.p. 136–142° (20 mm.). [f] C. S. Marvel and A. L. Tanenbaum, *J. Am. Chem. Soc.*, **44**, 2645 (1922), reported b.p. 153–156° (18 mm.), m.p. 41°. [g] Y. M. Beasley, V. Petrow, and O. Stephenson, *J. Pharm. Pharmacol.*, **10**, 47 (1958), reported b.p. 198–200° (20 mm.). [h] N. J. Leonard, D. L. Felley, and E. D. Nicolaides, *J. Am. Chem. Soc.*, **74**, 1700 (1952), reported b.p. 125–130° (1.5 mm.), m.p. 42°. [i] M. R. Lehman, C. D. Thompson, and C. S. Marvel, *ibid.*, **55**, 1977 (1933), reported b.p. 170–176° (3 mm.) m.p. 32.5°.

in the Experimental part. N-Monosubstituted piperazines were prepared according to literature methods.[6]

The compounds were studied for acute toxicity (Table I). They were tested for antihypertensive activity in chloralose-anesthetized dogs under the conditions of Boissier and co-workers.[7] A prolonged drop of blood pressure and an inhibition or reversal of epinephrine response was generally observed. Compounds **3**, **5**, **7**, **11**, and **28** appeared to possess the most interesting hypotensive and adrenolytic effects at doses of 0.1–2 mg./kg. i.v.

By gross observation of intact mice, some compounds (**6, 7, 8, 28, 29**) were found to be CNS depressants after an i.p. injection of 20 mg./kg. This was confirmed by the tests commonly used in our laboratory[8] (chimney test, traction test, and barbiturate narcosis potentiation).

Experimental

Phenols.—4-Chloro-, 4-fluoro-, and 2,6-dimethylphenols were obtained commercially (Fluka A.G., Buchs, S. G., Switzerland). 3,4-Dimethoxyphenol was prepared by peracetic acid oxidation of veratraldehyde according to the procedure of Meltzer and Doczi.[9] The yield of 3,4-dimethoxyphenyl formate boiling at 98–100° (0.1 mm.) was 76%; the yield of 3,4-dimethoxyphenol boiling at 120–122° (0.2 mm.) was 80%.

A. 4-(3,4-Dimethoxyphenoxy)butyl Bromide (42).—A suspension of 1,4-dibromobutane (86.4 g., 0.4 mole) and 3,4-dimethoxyphenol (30.8 g., 0.2 mole) in 100 ml. of water was heated under reflux with stirring. A solution of NaOH (8.0 g., 0.2 mole) in 25 ml. of water was added dropwise and the reactants were refluxed for 3 hr. After cooling, the organic layer was extracted into ether, and the extract was washed with water. After removal of the solvent the product was distilled *in vacuo*.

Bis-1,4-(3,4-dimethoxyphenoxy)butane was obtained by recrystallization of the distillation residue from heptane (6 g.), m.p. 109–110°.

Anal. Calcd. for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66, 24; H, 7.11.

The same procedure was used to obtain **2-(3,4-dimethoxyphenoxy)ethyl bromide (34)**[10] and **bis-1,2-(3,4-dimethoxyphenoxy)-ethane.** For analysis a sample of the latter compound was recrystallized from heptane, m.p. 106°.

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.90; H, 6.78.

B. 6-(3,4-Dimethoxyphenoxy)hexyl Bromide (43).—A solution of 1,6-dibromohexane (195.2 g., 0.8 mole) and 3,4-dimethoxyphenol (30.8 g., 0.2 mole) in 250 ml. of ethanol was refluxed, and 13.2 g. (0.2 mole) of 85% KOH in 50 ml. of methanol was added dropwise. The mixture was refluxed for 5 hr. with stirring. During this process, KBr crystallized. After cooling, the solid was collected by filtration. The filtrate was concentrated *in vacuo*, washed with water, and distilled under reduced pressure.

General Procedure for Preparation of Compounds I.—A mixture of aryloxyalkyl bromide (0.1 mole), 1-monosubstituted piperazine (0.115 mole), and anhydrous K_2CO_3 (0.115 mole) in 1-butanol (200 ml.) was heated at 100° for 15 hr. After filtration of inorganic salts, the 1-butanol was removed under reduced pressure and the dark oil was taken up in 200 ml. of ether. The ether solution was filtered and extracted with 1 *N* HCl. The acidic solution, after being washed with ether, was treated with 2 *N* aqueous NaOH and extracted with ether. Removal of the solvent afforded crude I. The resulting product was either recrystallized, when solid, from the appropriate solvent or converted to a hydrochloride salt by addition of the calculated amount of 2 *N* absolute ethanolic HCl, isolation, and recrystallization. The physical constants, yields, solvents, and analytical data are given in Table I.

(6) (a) 1-Phenylpiperazine: K. Fujii, K. Tomino, and H. Watanabe *J. Pharm. Soc. Japan*, **74**, 1052 (1954); (b) chlorophenylpiperazines: C. B. Pollard and T. H. Wicker, *J. Am. Chem. Soc.*, **76**, 1853 (1954); (c) methoxyphenylpiperazines: C. B. Pollard and J. B. Christie, *J. Org. Chem.*, **23**, 1333 (1958); (d) 1-(2,3-dimethylphenyl) piperazine: ref. 2; (e) 1-(2-pyridyl)piperazine: K. L. Howard, H. W. Stewart, E. A. Conroy, and J. J. Denton, *J. Org. Chem.*, **18**, 1484 (1953).

(7) J. R. Boissier, R. Ratouis, and C. Dumont, *Therapie*, **18**, 1499 (1963).

(8) J. R. Boissier, C. Dumont, R. Ratouis, and J. Pagny, *Arch. Intern. Pharmacodyn.*, **133**, 29 (1961).

(9) R. I. Meltzer and J. Doczi, *J. Am. Chem. Soc.*, **72**, 4986 (1950).

(10) Since our work was completed this compound has been reported: D. J. Drain, J. G. B. Howes, R. Lazare, A. M. Salaman, R. Shadbolt, and H. W. R. Williams, *J. Med. Chem.*, **6**, 63 (1963), give b.p. 122–126° (0.05 mm.), m.p. 58–59°.