N-[2-(α-Phenyl-*o*-tolyloxy)ethyl]-2-indanamine (49), bp 238–248° (0.36–0.50 mm), yield 51%, hydrochloride mp 172–173°, was prepared similarly from 2-aminoindane[26] and α-phenyl-*o*-tolyloxyacetic acid ethyl ester (III) *via* N-(2-indanyl)-(α-phenyl-*o*-tolyloxy)acetamide, mp 188–192.8°, yield 80%.

N-(2-indanyl)-(α-phenyl-*o*-tolyloxy)acetamide, mp 188–192.8°, yield 80%.

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 79.78; H, 6.49; N, 4.04.

2-(α-Phenyl-*o*-tolyloxy)ethylamine.—A solution of 34.6 g (0.155 mole) of (α-phenyl-*o*-tolyloxy)acetonitrile[2h,27] in 200 ml of dry ether was slowly added to 11.7 g (0.308 mole) of $LiAlH_4$ suspended in 200 ml of dry ether with efficient stirring. The mixture was refluxed for 13 hr and, after cooling, treated with 10.1 ml of water, 7.5 ml of 30% NaOH, and finally 34.2 ml of water. After stirring for 1 hr, the precipitate was filtered and washed thoroughly with ether. The combined filtrate was dried ($MgSO_4$), the solvent was removed, and the residue (35.2 g) was distilled *in vacuo*. The fraction boiling at 149.5–162° (0.38–0.52 mm) was redistilled, yielding 28.2 g (80%) of V, bp 148.5–151° (0.48–0.52 mm).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.25; H, 7.54; N, 6.16. Found: C, 79.40; H, 7.75; N, 5.74.

N-[2-(α-Phenyl-*o*-tolyloxy)ethyl]-*p*-hydroxyphenylacetamide.—A mixture of 23.4 g (0.103 mole) of 2-(α-phenyl-*o*-tolyloxy)-ethylamine (V) and 17.1 g (0.103 mole) of *p*-hydroxyphenylacetic acid methyl ester[12] was heated to 140° for 30 min, then to 200° for 3 hr, while the alcohol formed during the reaction escaped. The syrupy residue was recrystallized from alcohol; mp 126.6–131.6°, yield 24.4 g (65%). A sample prepared for analysis melted at 131–132.8°.

Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.40; H, 6.47; N, 3.82.

N-[2-(α-Phenyl-*o*-tolyloxy)ethyl]-*p*-hydroxyphenethylamine Hydrochloride (50).—In the upper part of a Soxhlet apparatus was placed 21.6 g (0.06 mole) of N-[2-(α-phenyl-*o*-tolyloxy)ethyl]-*p*-hydroxyphenylacetamide. In the bottom flask a suspension of 11.4 g (0.6 mole) of $LiAlH_4$ in 600 ml of dry ether was prepared, and the extraction continued under reflux until the amide had disappeared (162 hr). To the cooled, stirred suspension was added in succession 11.2 ml of water, 8.6 ml of 20% NaOH, and 58.4 ml of water. The precipitate was filtered and washed with ether and then suspended in 400 ml of 3 *N* HCl. Extraction with three 100-ml portions of chloroform followed by filtration of the insoluble product gave 6.64 g of the crude product, mp 150–155°. Recrystallization from ethanol yielded 4.28 g, mp 160.4–163.6°, which on further purification gave a final yield of 3.2 g (14%) of the analytically pure hydrochloride.

N-*p*-Tolylsulfonyl-N-[2-(*p*-tolylsulfonyloxy)ethyl]-α-methylphenethylamine (VI).—To a solution of 35.9 g (0.2 mole) of 2-(α-methylphenethylamino)ethanol in 240 ml of dry pyridine was added in small portions 85.4 g (0.5 mole) of *p*-tolylsulfonyl chloride with efficient stirring and cooling in an ice–salt mixture. The temperature was kept below 10°, then poured on 1 l. of ice-water, and the organic phase was extracted with two 500-ml portions of ether. The ether layer was decolorized and freed from black, tarry impurities by washing twice with 250-ml portions of 3 *N* HCl, separating, and drying ($MgSO_4$). Removal of the solvent left a yellow syrup (55.6 g, 57%) that resisted all attempts of crystallization. Elemental analysis (*Anal.* Calcd for $C_{25}H_{29}NO_5S_2$: N, 2.87; S, 13.15. Found: N, 2.64; S, 12.61.) showed the material to be sufficiently pure for use in the next step.

N-(α-Methylphenethyl)-N-[2-(*o*-benzoylphenoxy)ethyl]-*p*-toluenesulfonamide (VII).—2-Hydroxybenzophenone (21.2 g, 0.1 mole) was added to a solution of 2.46 g (0.1 g-atom) of Na in 50 ml of alcohol. To this, 52.1 g (0.1 mole) of VI dissolved in 100 ml alcohol was added, and the mixture was heated in an autoclave to 160° for 24 hr. The solvent was then removed *in vacuo*, and the residue was treated with 300 ml of 10% NaOH. Extraction of the oily precipitate with ether, and evaporation of the solution to dryness gave 50 g (91%) of a syrup that could not be crystallized.

Anal. Calcd for $C_{31}H_{31}NSO_4$: N, 2.73; S, 6.24. Found: N, 2.60; S, 6.09.

2-[2-(α-Methylphenethylamino)ethoxy]benzophenone Hydrochloride (51).—A mixture of 22.4 g (0.04 mole) of VII, 100 g of 36.7% dry HBr in glacial acetic acid, and 8.23 g (0.08 mole) of phenol was left standing at room temperature for 6 days. The dark solution was evaporated to dryness *in vacuo* and the residue was distributed between 200 ml of 15% NaOH and 200 ml of ether. The ether phase was washed with 15% NaOH and water, dried ($MgSO_4$), and treated with dry HCl. The resulting oily suspension was evaporated to dryness *in vacuo*, and the residue was recrystallized from acetonitrile; yield 10.8 g, mp 134–137°. Repeated recrystallizations from acetonitrile and 2-propanol gave the analytically pure hydrochloride **51** (7.23 g, 42%), mp 142.5–147°.

Acknowledgment.—The skilful and devoted technical assistance of Miss J. Christiansen, Mrs. E. Kaastrup, Mrs. D. Kondrup Pedersen, Mrs. B. Petersen, and Miss A. Schytt is acknowledged.

(26) 2-Aminoindane was prepared in practically quantitative yield by a Schmidt reaction on indane-2-carboxylic acid chloride.

(27) R. B. Burtner, U. S. Patent 2,676,968 (1954).

Serotonin Inhibitors. III.[1] Compounds Related to 2′-(3-Dimethylaminopropylthio)cinnamanilide[2,3]

JOHN KRAPCHO AND CHESTER F. TURK

The Squibb Institute for Medical Research, New Brunswick, New Jersey

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The preparation of 24 compounds related to 2′-(3-dimethylaminopropylthio)cinnamanilide and their antiserotonin activity on the rat uterus are reported. Four of these compounds are highly active in this test procedure.

We have previously reported the synthesis and antiserotonin activity of I[3] and several of its analogs. Following the pharmacological studies of this series of compounds,[4–7] I was selected for evaluation in man.

Preliminary clinical studies have shown that I exhibits antidepressant action, is effective in the treatment of spastic bronchial disease and gastrointestinal hyperfunctioning states, and apparently possesses

(1) Previous paper: J. Krapcho, E. R. Spitzmiller, C. F. Turk, and J. Fried, *J. Med. Chem.*, **7**, 376 (1964).

(2) Presented in part before the Division of Medicinal Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(3) Cinanserin is the approved generic name for 2′-(3-dimethylaminopropylthio)cinnamanilide (I).

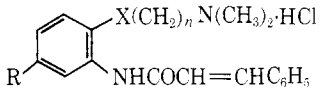
(4) B. Rubin, J. J. Piala, J. C. Burke, and B. N. Craver, *Arch. Intern. Pharmacodyn.*, **152**, 132 (1964).

(5) A. R. Furgiuele, J. P. High, and Z. P. Horovitz, *ibid.*, **155**, 225 (1965).

(6) B. Rubin and M. H. Waugh, *Proc. Soc. Exptl. Biol. Med.*, **119**, 438 (1965).

(7) B. Rubin, J. Krapcho, and J. P. High, *Life Sci.*, **5**, 845 (1966).

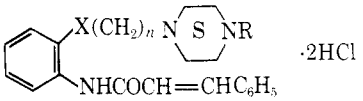
TABLE I



No.	X	n	R	Mp, °C[a]	Yield, %	Formula	% chlorine Calcd	% chlorine Found	% nitrogen Calcd	% nitrogen Found	Antiserotonin activity[b]
1[c]	...	1	H	131–133	43	$C_{20}H_{22}N_2O_5$[d,e]			7.56	7.47	++
2	...	2	H	189–191	40	$C_{18}H_{23}ClN_2O$	10.72	10.65	8.47	8.18	+++
3[c]	...	3	H	123–125	54	$C_{20}H_{25}ClN_2O$	10.28	10.57	8.12	8.36	−
4[c]	CO	2	H	156–158	15	$C_{20}H_{23}ClN_2O_2 \cdot 0.5H_2O$[f]	9.64	9.65	7.62	7.52	− − − − −
5	CO	3	H	185–187	13	$C_{21}H_{25}ClN_2O_2$	9.51	9.72	7.51	7.23	+ −
6	CONH	2	H	165–167	78	$C_{20}H_{24}ClN_3O_2$	9.48	9.75	11.24	11.43	−
7	$CON(CH_3)$	2	H	183–185	23	$C_{21}H_{26}ClN_3O_2$	10.83	11.11	9.14	9.36	+ −
8	COO	2	H	190–192[g]	39	$C_{20}H_{23}ClN_2O_3$	9.46	9.35	7.47	7.21	+ −
9	NHCO	2	H	194–196	34	$C_{20}H_{24}ClN_3O_2$	9.48	9.31	11.24	11.07	+
10	$N(CH_3)$	3	H	177–179	78	$C_{21}H_{28}ClN_3O$	9.48	9.45	11.24	10.98	+
11	O	3	CF_3	125–127	55	$C_{20}H_{24}ClF_3N_2O_2$	8.27	8.33	6.53	6.40	+
12	O	3	NO_2	247–249	44	$C_{20}H_{24}ClN_3O_4$	8.74	8.96	10.35	10.58	+
13	3-Cinnamamido-2-(3-dimethylaminopropoxy)-pyridine·HCl			202–204	26	$C_{19}H_{24}ClN_3O_2$	9.80	9.70	11.61	11.42	+

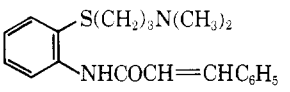
[a] These salts were crystallized from acetonitrile except **1** (methanol–ether), **3** (acetone), **4** and **5** (ethanol), **12** (methanol). [b] Activity measured on isolated rat uterus:[4] BAS = 1: >64X = +++++, 16–64X = ++++, 4–16X = +++, 1–4X = ++, 0.25–1X = +. Reference material I was assayed directly against BAS and found to be 157 times more potent in this test. [c] The amine used in this preparation has been described: **1**, E. Stedman, *J. Chem. Soc.*, 1904 (1927); **3**, J. v. Braun, *Ber.*, **43**, 2875 (1910); **4**, H. Takahashi, *J. Japan. Biochem. Soc.*, **26**, 154 (1954); *Chem. Abstr.*, **49**, 11575 (1955). [d] Oxalate salt. [e] *Anal.* Calcd: C, 64.85; H, 5.99; Found: C, 64.70; H, 6.29. [f] *Anal.* Calcd: C, 65.30; H, 6.58. Found: C, 65.34; H, 6.70. [g] Base melted at 75–77° (hexane). *Anal.* Calcd: N, 8.28. Found: N, 8.44.

TABLE II



No.	X	n	R	Mp, °C[a]	Yield, %	Formula	% chlorine Calcd	% chlorine Found	% nitrogen Calcd	% nitrogen Found	Antiserotonin activity[b]	CNS depressant activity[c]
14[d]	S	3	H	160–162	10	$C_{22}H_{29}Cl_2N_3OS$	15.61	15.37	9.25	8.98	++	++
15	S	3	CH_2CH_2OH	222–224	23	$C_{24}H_{33}Cl_2N_3O_2S$	14.22	14.37	8.43	8.35	+++	++
16[e]	S	3	$CH_2C_6H_5$	222–224	18	$C_{29}H_{35}Cl_2N_3OS$	13.02	13.16	7.72	7.54	++++++	++
17	S	3	$(CH_2)_2C_6H_5$	219–221	31	$C_{30}H_{37}Cl_2N_3OS$	12.69	12.88	7.52	7.31	++++++	++
18	S	3	C_6H_5	208–210	37	$C_{28}H_{32}ClN_3OS$[f]	7.18	7.06	8.50	8.44	++++	+
19	S	3	2-$(CH_3O)C_6H_4$	191–193	47	$C_{29}H_{34}ClN_3O_2S$[f]	6.77	6.68	8.02	8.07	+++	+++
20	S	2	2-$(CH_3O)C_6H_4$	197–199	38	$C_{28}H_{34}ClN_3O_2S$[f]	6.95	7.19	8.24	8.16	++	+
21	O	3	2-$(CH_3O)C_6H_4$	235–237	61	$C_{29}H_{34}ClN_3O_3$[f]	6.98	7.08	8.27	8.32	+++	+++
22	S	3	2-pyridyl	194–196	14	$C_{27}H_{32}Cl_2N_4OS$	13.34	13.15	10.54	10.54	++++++	+
23	2′-[3-(Methylphenethylamino)propylthio]-cinnamanilide			138–140	28	$C_{29}H_{32}N_2O_2S$[g,h]			5.38	5.29	++++	−
24	2′-[3-Bis(2-hydroxyethylamino)propylthio]-cinnamanilide			117–119	33	$C_{22}H_{29}ClN_2O_3S$[f]	8.11	8.13	6.41	6.68	+++	++

[a] These salts were crystallized from ethanol except **14** (methanol–ether), **17, 19,** and **24** (acetonitrile), **18** and **21** (methanol). [b] See footnote *b* in Table I. Most of the compounds were tested as aqueous solutions; the water-insoluble materials were dissolved in dimethylacetamide (**18** and **20**), DMF (**21**), or propylene glycol (**23**) and then diluted with water. [c] CNS depressant activity observed in rats (intraperitoneal) at the following dose range (mg/kg): 6–25 = +++, 25–100 = ++, and 100–400 = +. In general, compounds were administered as aqueous solutions; however, **18–21** and **23** were tested as suspensions in 0.25% agar solution. [d] Prepared by addition of 2′-(3-chloropropylthio)cinnamanilide to a suspension of 3 equiv of piperazine in xylene and refluxing the mixture for 7 hr. [e] Obtained as the major product of the reaction of 2,3-dihydro-2-phenyl-1,5-benzothiazepin-5(4H)-one with sodamide and 4-benzyl-1-(3-bromopropyl)piperazine according to a procedure described in ref 12. [f] Monohydrochloride. [g] Oxalate salt. [h] *Anal.* Calcd: C, 66.90; H, 6.20. Found: C, 66.83; H, 6.39.



I

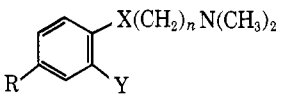
the capacity for completely controlling the manifestations of the carcinoid syndrome.[8]

(8) Information kindly provided by Dr. C. K. Gorby, Director of Clinical Pharmacology of The Squibb Institute for Medical Research.

We now wish to report the preparation and antiserotonin activities of compounds related to I in which the sulfur is removed or replaced by CO, CONH, $CONCH_3$, COO, NHCO, and NCH_3 groupings, in addition to the three oxa analogs (**11–13**) (Table I).

Since the modification of I, in which the dimethylamino group was replaced by 4-methylpiperazino (II),[1] showed definite activity as a CNS depressant, analogs of II (Table II) having in the 4 position substituents such as 2-hydroxyethyl, phenyl, *o*-methoxy-

TABLE III



No.	X	Y	n	R	Bp, °C (mm)	Yield,[a] %	Formula	% nitrogen—Calcd	% nitrogen—Found
A[b]	...	NO_2	2	H	100–105 (0.5)	78	$C_{10}H_{14}N_2O_2$	14.43	14.14
B	...	NH_2	2	H	90–95 (0.3)	76	$C_{10}H_{16}N_2$	17.06	16.90
C[c]	CO	NO_2	3	H	125–140 (0.3)	32	$C_{12}H_{16}N_2O_3$	11.86	11.38
D	CO	NH_2	3	H	*d*	95	$C_{12}H_{18}N_2O$	13.58	12.64[a]
E[e]	CONH	NO_2	2	H	*e*	64	$C_{11}H_{16}ClN_3O_3$	15.35	14.98
F	CONH	NH_2	2	H	154–159 (0.1)	85	$C_{11}H_{17}N_3O$	20.27	20.08
G[e]	$CON(CH_3)$	NO_2	2	H	*e*	71	$C_{12}H_{18}ClN_3O_3$	14.60	14.91
H	$CON(CH_3)$	NH_2	2	H	69–71[f]	45	$C_{12}H_{19}N_3O$	18.99	19.24
I[g]	COO	NH_2	2	H	119–122 (0.2)	75	$C_{11}H_{16}N_2O_2$	13.45	13.26
J[h]	NHCO	NO_2	2	H	*d*	70	$C_{11}H_{15}N_3O_3$	17.71	17.94
K	NHCO	NH_2	2	H	80–82[f]	84	$C_{11}H_{17}N_3O$	20.27	19.98
L[i]	$N(CH_3)$	NO_2	3	H	121–123 (0.1)	66	$C_{12}H_{19}N_3O_2$	17.71	17.86
M	$N(CH_3)$	NH_2	3	H	98–100 (0.1)	89	$C_{12}H_{21}N_3$	20.27	20.35
N[j]	O	NO_2	3	CF_3	129–131 (0.1)	46	$C_{12}H_{15}F_3N_2O_3$	9.59	9.41
O	O	NH_2	3	CF_3	109–114 (0.1)	93	$C_{12}H_{17}F_3N_2O$	10.68	10.30
P[k]	O	NH_2	3	NO_2	185–195 (0.3)	15	$C_{11}H_{17}N_3O_3$	17.56	17.32
Q[l]	3-Amino-2-(3-dimethylaminopropoxy)pyridine				108–115 (0.2)	24	$C_{10}H_{17}N_3O$	21.52	21.40

[a] Since the compounds listed in this table are intermediates, further purifications were not carried out. The low nitrogen value of D indicated the presence of entrained solvent. All of the amino compounds were treated with cinnamoyl chloride to give the appropriate cinnamanilides (Table I). [b] Prepared by heating *o*-nitrophenethyl bromide with excess dimethylamine in ethanol. [c] Obtained by addition of *o*-nitroacetophenone to isopropyl alcohol containing 1 equiv of sodium methoxide, followed by a slight excess of 2-dimethylaminoethyl chloride and heating for 7 hr. [d] Material was not distilled. [e] Product of the reaction of *o*-nitrobenzoyl chloride with the appropriately substituted ethylenediamine in chloroform. Materials were isolated in the form of hydrochloride salts and purified by crystallization from acetonitrile: E, mp 151–153°; G, mp 179–181°. [f] Melting point of free base: H (cyclohexane), K (benzene–hexane). [g] Prepared by treatment of sodium anthranilate in isopropyl alcohol with 2-dimethylaminoethyl chloride and refluxing the mixture for 2 hr. [h] Obtained by treatment of 2′-nitro-2-chloropropionanilide with NaI and excess dimethylamine. The above nitro compound was obtained in 85% yield by interaction of *o*-nitroaniline with 3-chloropropionyl chloride in benzene, mp 86–88° (ethanol). *Anal.* Calcd for $C_9H_9ClN_2O_3$: Cl, 15.51. Found: Cl, 15.50. [i] A mixture of equivalent quantities of *o*-chloronitrobenzene and N,N,N′-trimethyl-1,3-propanediamine in toluene was refluxed for 8 hr. [j] A suspension of the sodium salt of 3-dimethylaminopropanol in toluene was heated with an equivalent quantity of 4-chloro-3-nitrobenzotrifluoride for 4.5 hr. [k] Prepared by heating the sodium salt of 2-amino-4-nitrophenol and 3-dimethylaminopropyl chloride in a mixture of isopropyl alcohol and dimethylformamide for 5 hr. [l] Product obtained by addition of a toluene solution of 3-amino-2-chloropyridine to a hot solution of the sodium salt of 3-dimethylaminopropanol in toluene. The mixture was refluxed for 7 hr.

phenyl, benzyl, phenethyl, and 2-pyridyl were also prepared and evaluated for both antiserotonin and CNS activity.

The preparation of compounds of Table I usually involved the catalytic reduction of the nitro intermediates of Table III to give the corresponding amines (also in Table III) and the latter reacted with cinnamoyl chloride in chloroform solution as described in the synthesis of I.[1] Most of the products of Table II were obtained by interaction of 2′-(ω-iodoalkylthio)- or 2′-(3-iodopropoxy)cinnamanilides with the appropriately substituted piperazine (or a secondary amine in the case of **23** and **24**).

Four of the 24 compounds showed a high order of activity in inhibiting the spasmogenic effect of serotonin in the excised rat uterus test procedure;[4] **16** and **17** had essentially the same activity as I, while **4** and **22** were about three times more potent in this test. When compared against the bronchoconstrictor effect of serotonin in the dog,[4,9] the latter two compounds were equipotent with I. All of the piperazino compounds (**14–22**) were tested for CNS depressant activity in rats by the intraperitoneal route, and the most effective of these compounds were **19** and **21**. Further studies of **19** showed that this material caused depression in the rodent comparable to chlordiazepoxide in tests such as rotarod, septal rat,[10] and pole climb when administered intraperitoneally; unfortunately, the compound is not well absorbed by the oral route.

(9) J. Krapcho, B. Rubin, A. M. Drungis, E. R. Spitzmiller, C. F. Turk, J. Williams, B. N. Craver, and J. Fried, *J. Med. Chem.*, **6**, 219 (1963).

Experimental Section[11]

2′-(3-Chloropropylthio)cinnamanilide (III).—A suspension of 71.0 g (0.28 mole) of 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one[12] in 130 ml of isopropyl alcohol was added to a stirred solution of 15.0 g (0.28 mole) of sodium methoxide in 400 ml of isopropyl alcohol and the mixture was refluxed for 20 min. The orange-red solution was cooled to 40° and treated with 52.0 g (0.33 mole) of 1-bromo-3-chloropropane, and the mixture was refluxed for 5 hr. The bulk of the solvent was removed under reduced pressure; the residue was cooled, treated with 1 l. of water and 400 ml of hexane, and filtered to give 92.0 g of solid, mp 110–112°. After crystallization from 650 ml of isopropyl alcohol, the colorless product weighed 71.0 g (77%), mp 114–116°.

Anal. Calcd for $C_{18}H_{18}ClNOS$: Cl, 10.68; N, 4.22. Found: Cl, 10.37; N, 4.17.

By substituting an equivalent quantity of 1-bromo-2-chloroethane for the 1-bromo-3-chloropropane in the above preparation, a 58% yield of **2′-(2-chloroethylthio)cinnamanilide** was obtained; mp 110–112° (acetonitrile).

Anal. Calcd for $C_{17}H_{16}ClNOS$: Cl, 11.16; N, 4.41. Found: Cl, 10.95; N, 4.60.

(10) L. O. Randall, W. Schallek, G. A. Heise, F. F. Keith, and R. E. Bagdon, *J. Pharmacol. Exptl. Therap.*, **129**, 163 (1960).

(11) Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected.

(12) J. Krapcho, E. R. Spitzmiller, and C. F. Turk, *J. Med. Chem.*, **6**, 544 (1963).

2′-(3-Chloropropoxy)cinnamanilide.—Interaction of 18.0 g (0.75 mole) of *o*-hydroxycinnamanilide[13] with equivalent quantities of sodium methoxide and 1-bromo-3-chloropropane in isopropyl alcohol according to the above procedure gave 24.0 g of product, mp 115–119°. After crystallization from ethanol, the nearly colorless solid weighed 16.0 g (67%), mp 118–120°.

Anal. Calcd for $C_{18}H_{18}ClNO_2$: Cl, 11.23; N, 4.44. Found: Cl, 11.08; N, 4.55.

2′-{3-[4-(*o*-Methoxyphenyl)-1-piperazinyl]propylthio}cinnamanilide Hydrochloride (19).—A solution of 28.0 g (0.084 mole) of III in 200 ml of acetone was added to a stirred solution of 13.0 g (0.085 mole) of NaI in 150 ml of acetone and the mixture was refluxed for 6 hr. The solvent was removed under reduced pressure and the residue was digested with 500 ml of warm toluene and filtered, and the filtrate was treated with 32.0 g (0.17 mole) of 1-(*o*-methoxyphenyl)piperazine. This mixture was refluxed for 5 hr, cooled, and filtered to remove the hydriodide salt of the starting piperazine (14.0 g). The filtrate was washed with 100 ml of water and then stirred with 150 ml of 1 *N* HCl. The hydrochloride which separated from the mixture was filtered, dried (25.0 g), and crystallized from 550 ml of isopropyl alcohol to give 20.5 g (47%) of colorless product, mp 191–193°.

(13) V. R. Huisgen, H. Eder, L. Blazejewicz, and E. Mergenthaler, *Ann.*, **573**, 137 (1951).

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Some Cardiovascular Effects of a Series of Aryloxyalkylamines. II[1]

J. AUGSTEIN, W. C. AUSTIN,[2] C. A. BARTRAM, AND R. J. BOSCOTT

Chemical Research Department, Pfizer Ltd., Sandwich, Kent, England

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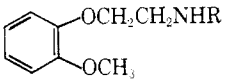
A number of N-substituted phenoxyethylamines have been prepared and their antihypertensive activity examined in anesthetized normotensive cats and neurogenically hypertensive dogs. Examination of the structure–activity relationships shows that the 2-(2-methoxyphenoxy)ethylamino moiety is necessary for maximum effect. The structural requirements in further N substitution are much less specific. A summary of the results of clinical trials with three compounds is included.

In a previous series of phenoxyethylamines[1] a high level of antihypertensive activity was observed which was the result of a classical adrenolytic action, the blockade of α receptors. The preparation of a number of analogous N-aralkyl, N-alkyl, N-alkenyl, and N-alkynyl derivatives (Tables I–XIII) was therefore undertaken. Some of these compounds were found to be potent antihypertensives with a long duration of action when tested in anesthetized normotensive cats and neurogenically hypertensive dogs.

The structure–activity relationships were determined on the basis of the results obtained using normotensive cats anesthetized with chloralose, the blood pressure changes being traced on a kymograph. The compounds were administered intravenously. The activities of individual compounds are related to that of N-[3-(2,5-dimethoxyphenoxy)propyl]-2-(2-methoxyphenoxy)ethylamine[1] (VI) which is given the arbitrary activity of 100, and which at a dose of 100 mg/kg produced a fall in mean arterial pressure of 60 mm, which lasted from 20 to 90 min and usually from 60 to 90. The comparison is of both potency and duration of action and is therefore a comparison of the areas given by the curves on the kymograph tracings under the straight line given by the normal blood pressure.

The effects of the more active compounds on the pressor responses of injected epinephrine and norepinephrine were examined. In contrast to the N-aryloxyalkylphenoxyethylamines of part I[1] where, in the fashion of typical adrenolytic agents, the pressor responses to norepinephrine were abolished and those to epinephrine were reversed, varying effects were observed, suggesting that the modes of action were only partly those of an adrenolytic agent.

In agreement with previous findings on structure–activity relationships, it was established that the 2-(2-methoxyphenoxy)ethylamino moiety was necessary for a maximum antihypertensive effect when the compounds were administered intravenously to anesthetized cats. In contrast, the structural requirements for the rest of the molecule were much less specific. For example, high levels of activity have been demonstrated for such diverse structures as I–V.



I, R = $CH_2CHOHCH_2OCH_2CH{=}CH_2$ (Table II, **28**)
II, R = $(CH_2)_3OCH_2CH{=}CH_2$ (Table III, **68**)
III, R = $(CH_2)_5CN$ (Table X, **104**)
IV, R = $(CH_2)_6OCOCH_3$ (Table XII, **110**)
V, R = $(CH_2)_4C_6H_4OCH_3$-*p* (Table XIII, **119**)
VI, R = $(CH_2)_3OC_6H_3$-2,5-$(OCH_3)_2$

Compound I, unlike most other *o*-methoxyphenoxyethylamine derivatives of this series, potentiated the pressor effects of epinephrine and norepinephrine in dogs and was shown to act predominantly by a central mechanism. Compound III, however, reversed the pressor response to epinephrine without altering that to norepinephrine. Further work was precluded by the fact that toxic symptoms were observed at therapeutic doses and that the activity apparent after intravenous administration was not reproduced orally.

(1) Part I: J. Augstein, W. C. Austin, R. J. Boscott, S. M. Green, and C. R. Worthing, *J. Med. Chem.*, **8**, 356 (1965).

(2) To whom enquiries should be sent.