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]

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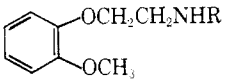
A number of N-substituted phenoxyethylamines have been prepared and their antihypertensive activity examined in anesthetized normotensive cats and neurogenically hypertensive dogs. Examination of the structure–activity relationships shows that the 2-(2-methoxyphenoxy)ethylamino moiety is necessary for 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.



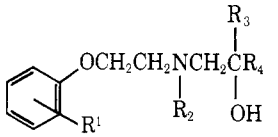
I, R = $CH_2CHOHCH_2OCH_2CH{=}CH_2$ (Table II, **28**)
II, R = $(CH_2)_3OCH_2CH{=}CH_2$ (Table III, **68**)
III, R = $(CH_2)_5CN$ (Table X, **104**)
IV, R = $(CH_2)_6OCOCH_3$ (Table XII, **110**)
V, R = $(CH_2)_4C_6H_4OCH_3$-*p* (Table XIII, **119**)
VI, R = $(CH_2)_3OC_6H_3$-2,5-$(OCH_3)_2$

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.

TABLE I
N-HYDROXYALKYL-2-(SUBSTITUTED PHENOXY)ETHYLAMINES



No.	R_1	R_2	R_3	R_4	Bp, °C (mm)	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
1	*o*-OCH_3	H	H	H	170 (1.3)[b]	B	$C_{11}H_{17}NO_3$	62.54	8.11		62.50	8.01		10
2	*o*-OCH_3	H	CH_3	H	143 (1)	B	$C_{12}H_{19}NO_3$	63.97	8.50	6.22	63.98	8.46	6.20	0
3	*o*-OCH_3	H	CH_3	CH_3	128–130 (0.3)	A	$C_{13}H_{21}NO_3$	65.24	8.85	5.85	64.97	8.70	5.64	0
4	*o*-OCH_3	H	CH_3	C_2H_5	146–149 (2)	A	$C_{14}H_{23}NO_3$	66.37	9.15	5.53	66.25	9.40	5.03	10
5	*o*-OCH_3	H	CH_3	*n*-C_3H_7	146–148 (0.3)	B	$C_{15}H_{25}NO_3$[c]	67.38	9.43	5.24	67.57	9.37	5.56	20
6	*o*-OCH_3	H	CH_3	*n*-C_4H_9	158–160 (0.005)	A	$C_{16}H_{27}NO_3$	68.29	9.67	4.98	68.41	9.67	4.73	15
7	*o*-OCH_3	H	CH_3	*n*-C_6H_{13}	154–156 (0.002)	A	$C_{18}H_{31}NO_3$	69.86	10.10	4.53	69.74	10.37	4.42	0
8	*o*-OCH_3	H	CH_3	$CH_2CH{=}CH_2$	129–130 (0.001)	A	$C_{16}H_{23}NO_3$	67.94	8.68	5.28	68.29	8.64	5.22	10
9	*o*-OCH_3	H	C_2H_5	C_2H_5	124 (0.002)	A	$C_{15}H_{25}NO_3$	67.38	9.43	5.24	67.44	9.30	4.80	10
10	*o*-OCH_3	CH_2CH_2OH	H	H	165–170 (0.1)	B	$C_{12}H_{21}NO_4$	61.15	8.29	5.49	61.60	8.59	5.60	0
11	*o*-OCH_3	C_2H_5	CH_3	*n*-C_3H_7	146–150 (0.6)	C	$C_{17}H_{29}NO_3$	69.11	9.90	4.74	69.13	9.79	4.30	0
12	*o*-OCH_3	CO-*n*-C_3H_7	CH_3	*n*-C_3H_7	194–198 (1)	B	$C_{33}H_{37}NO_6$[d]	67.78	9.15	3.44	68.02	9.38	3.88	0
13	H	H	CH_3	*n*-C_3H_7	130 (0.5)	B	$C_{14}H_{23}NO_2$	70.85	9.77	5.90	70.70	10.15	5.65	0
14	*m*-OCH_3	H	CH_3	*n*-C_3H_7	140 (0.1)	B	$C_{15}H_{25}NO_3$	67.38	9.43	5.24	68.00	9.58	5.24	10
15	*p*-OCH_3	H	CH_3	*n*-C_3H_7	158–160 (0.5)	B	$C_{15}H_{25}NO_3$	67.38	9.43		67.67	9.70		0
16	*o*-Cl	H	CH_3	*n*-C_3H_7	176 (1)	B	$C_{14}H_{22}ClNO_2$	61.86	8.12	5.12	61.76	8.56	5.09	0
17	3,4-$(CH_3)_2$	H	CH_3	*n*-C_3H_7	136 (0.25)	B	$C_{16}H_{27}NO_2$	72.41	10.26	5.28	71.97	10.36	5.59	0

[a] The antihypertensive activities are related to the compound N-[3-(2,5-dimethoxyphenoxy)propyl]-2-(2-methoxyphenoxy)ethylamine, which is given the arbitrary activity of 100. At 100 μg/kg, this compound produces a fall in mean arterial pressure of 60 mm, which lasted for 20–90 min and usually 60–90 min. [b] W. S. Gump and E. J. Nikawitz [*J. Am. Chem. Soc.*, **72**, 3846 (1950)] reported bp 181–186° (4 mm). [c] Hydrochloride mp 77.5–78°. [d] O-Butyryl derivative. O,N acylation with butyryl chloride.

Compounds IV and V, in the fashion of a typical adrenolytic, both reverse the pressor effects of epinephrine while abolishing those due to norepinephrine. Compound IV like III, was not active after oral administration, although highly active by the intravenous route. Compound V, in dogs, appears, however, to act mainly by a central effect. At an oral dose of 2.5 mg/kg in dogs a sustained antihypertensive response was elicited which lasted more than 20 hr.

At various stages, I, V, and VI were submitted to clinical trial. In hypertensive patients, I produced a variable fall in blood pressure, lasting 0.5 hr, which was accompanied by an associated central depressive effect. Compound VI produced a predictable fall in blood pressure lasting 3–4 hr, accompanied by tachycardia which was sufficient to preclude its use as an antihypertensive agent. Compound V produced a fall in blood pressure of similar duration. This is in contrast with the longer duration shown in dogs and was accompanied by a considerable feeling of depression.

Experimental Section

Preparation of the Secondary Amines. A.—One molecular equivalent of substituted alkyl halide was added slowly to an excess of the required phenoxyalkylamine (2–4 moles) while stirring at 100°. When the addition was complete, heating and stirring were continued for a further 2 hr. The mixture was cooled, basified with dilute NaOH solution, and extracted with chloroform or methylene chloride. After drying and removing the solvent, the residue was distilled *in vacuo*. After recovery of excess starting amine, the products were usually obtained as colorless oils.

B.—As in A, except that a substituted alkylamine is treated with the requisite phenoxyalkyl halides.

C.—Equimolar quantities of amine and halide were mixed with an equivalent of Na_2CO_3 or $NaHCO_3$ in alcohol, and the resultant mixture was refluxed while stirring for 16–24 hr. The mixture was then cooled, inorganic salts were removed by filtration, the alcohol distilled, and the residue distilled *in vacuo*. The products were obtained as colorless oils, some of which solidified on standing.

D.—Some derivatives containing ester groupings were prepared from the N-benzylphenoxyethylamine and the requisite chloro compound followed by debenzylation of the product in acetic acid using hydrogen in the presence of 10% Pd–C catalyst at atmospheric pressure and room temperature.

E.—Other ester derivatives were prepared by esterification with the N-(ω-hydroxyalkyl)-2-phenoxyethylamine of the required acid as follows. The acid (1.5 moles), the alcohol (1 mole), *p*-toluenesulfonic acid (1.25 moles), and dry benzene were mixed and refluxed under a Dean–Stark trap, the theoretical quantity of water usually being obtained in 16–24 hr. The mixture was then cooled, excess acid was recovered by shaking with cold, dilute NaOH solution, it was washed with water and dried, and the solvent was removed. The products were then converted to, and purified as, the acid maleate.

N-[4-(4-Trimethylacetoxyphenyl)butyl]-2-(2-methoxyphenoxy)ethylamine Acid Maleate (15).—N-[4-(*p*-Hydroxyphenyl)-butyl]-N-benzyl-2-(2-methoxyphenoxy)ethylamine (5 g) and pivalyl chloride (1.4 g) were mixed together with dry pyridine (15 ml), the resultant mixture being heated on the steam bath for 1.5 hr. After cooling, the mixture was poured into ice water, then treated with Na_2CO_3 solution, the resultant mixture being extracted with chloroform.

The residue (2.5 g) was then debenzylated by hydrogenation at atmospheric pressure and room temperature using 10% Pd–C catalyst (0.5 g) in glacial acetic acid (15 ml). The product was obtained as the acid maleate which after several recrystallizations from ethyl acetate gave colorless needles, mp 114–115°.

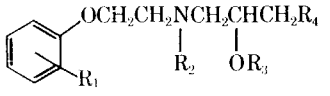
N-(3,4-Dimethoxyphenethyl)-2-(2-hydroxyphenoxy)ethylamine Acid Maleate (24).—N-(3,4-Dimethoxyphenethyl)-2-(2-benzyloxyphenoxy)ethylamine (**25**) (4 g) was debenzylated by hydrogenation in 95% alcohol (30 ml) in the presence of 10% Pd–C catalyst (1 g) at atmospheric pressure and room temperature. The product was isolated as the acid maleate, which was recrystallized several times from alcohol–ether and obtained as colorless needles, mp 138–139°.

N-[4-(4-Hydroxyphenyl)butyl]-2-(2-hydroxyphenoxy)ethylamine Hydrobromide.—N-[4-(4-Methoxyphenyl)butyl]-2-(2-methoxyphenoxy)ethylamine (5 g) was mixed with concentrated HBr (15 ml) and the mixture refluxed for 18 hr. On cooling, the resultant solid was filtered off, washed with cold water, and recrystallized several times from water. The product was obtained as colorless fine crystals, mp 219–220°.

Acknowledgment.—The authors wish to thank Mr. P. R. Wood for microanalytical data and Dr. H. Reinert for permission to quote pharmacological results and to acknowledge the technical contributions of Mr. A. L. Ham, Mr. A. B. Plane, and Miss M. J. Rasor.

TABLE II

N-ALKYL-2-(SUBSTITUTED PHENOXY)ETHYLAMINES



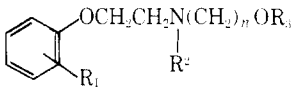
No.	R_1	R_2	R_3	R_4	Bp (mm) or mp, °C	$n^{25}D$ or other data	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
18	*o*-OCH_3	H	H	OH	86–87	Needles (EtOAc)	B	$C_{12}H_{19}NO_4$	59.73	7.94	5.81	59.82	7.82	5.72	0
19	*o*-OCH_3	H	H	OCH_3	68.5–70	Cryst (petr ether, 40–60°)	A	$C_{13}H_{21}NO_4$	61.15	8.29	5.49	61.53	8.39	5.48	0
20	*o*-OCH_3	H	H	OC_3H_7-*n*	158–161 (0.2)										
21	*o*-OCH_3	H	H	OC_4H_9-*n*	160 (0.005), 52–54		A	$C_{16}H_{25}NO_4$	63.58	8.89	4.94	63.06	8.93	5.23	20
22	*o*-OCH_3	H	H	OC_5H_{11}-*n*	166–168 (0.2)		A	$C_{16}H_{27}NO_4$	64.62	9.15	4.71	64.37	8.94	4.83	20
23	*o*-OCH_3	H	H	OC_6H_{13}-*n*	180–182 (0.2)		A	$C_{17}H_{29}NO_4$	65.56	9.39	4.50	65.36	9.52	4.57	20
24	*o*-OCH_3	H	H	OC_7H_{15}-*n*	188 (0.007)		A	$C_{18}H_{31}NO_4$	66.43	9.60	4.30	66.45	9.61	4.17	0
25	*o*-OCH_3	H	H	OC_8H_{17}-*n*	193–194 (0.3)		A	$C_{19}H_{33}NO_4$	67.22	9.80	4.13	66.97	9.97	4.13	0
							A	$C_{24}H_{36}NO_4$	67.95	9.98	3.96	67.59	9.92	4.20	0
26	*o*-OCH_3	H	H	$OCH(CH_2)_4$	178–180 (0.1), 71.5–72.5	Needles (petr ether)	A	$C_{17}H_{27}NO_4$	65.99	8.80	4.53	66.00	8.68	4.31	10
27	*o*-OCH_3	H	H	$OCH(CH_2)_5$	176 (0.2)		A	$C_{18}H_{29}NO_4$	66.84	9.04	4.33	67.15	9.12	4.19	0
28	*o*-OCH_3	H	H	$OCH_2CH=CH_2$	164 (0.3)	1.5254	B	$C_{16}H_{23}NO_4$	64.03	8.24	4.98	63.92	8.07	4.96	50
						B·HCl, mp 79.5–80° (EtOAc)	B	$C_{16}H_{24}ClNO_4$	56.69	7.61	4.41	56.46	7.38	4.47	
						B·AM, mp 85–86° (EtOAc)	B	$C_{19}H_{27}NO_5$	57.42	6.85	3.52	57.42	6.83	3.67	
29	*o*-OCH_3	H	H	$OCH_2CH=CHCH_3$	181–186 (0.4)		A	$C_{16}H_{25}NO_4$	65.06	8.53	4.74	65.12	8.43	4.73	50
30	*o*-OCH_3	H	H	$OCH_2CH_2CH=CH_2$	162–163 (0.01)		A	$C_{16}H_{25}NO_4$	65.06	8.53	4.74	64.92	8.59	4.55	20
31	*o*-OCH_3	H	H	$O(CH_2)_3CH=CH_2$	168–171 (0.0006)	1.5205	A	$C_{17}H_{27}NO_4$	65.99	8.80	4.53	65.66	8.80	4.35	15
32	*o*-OCH_3	H	H	$O(CH_2)_2CH=CHCH_2CH_3$	169–171 (0.002)		A	$C_{18}H_{29}NO_4$	66.84	9.04	4.33	66.59	8.95	4.14	10
33	*o*-OCH_3	H	H	$OCH_2(CH=CH)_2CH_3$	178–181 (0.02)		A	$C_{18}H_{27}NO_4$	67.26	8.47	4.36	66.83	8.28	4.80	15
34	*o*-OCH_3	H	H	$CH_2-CHCHCH-CHCH_3$ (with =O)	172–176 (0.1)	1.5240	A	$C_{18}H_{27}NO_4$	67.26	8.47	4.36	67.30	8.56	4.31	0
35	*o*-OCH_3	H	H	$OC(CH_3)_2C=CH$ (with =O)	152–154 (0.2)		A	$C_{17}H_{25}NO_4$	66.42	8.20	4.56	66.36	8.27	4.47	10
36	*o*-OCH_3	H	H	$C_6H_5C(CH_3)C=CH$ (with =O)	162–166 (0.0006)		A	$C_{18}H_{25}NO_4$	67.26	8.47	4.36	67.23	8.70	4.13	20
37	*o*-OCH_3	H	H	$(CH_2)_3CHC=CH$ (with =O)	160–164 (0.005)	1.5213	A	$C_{18}H_{25}NO_4$	67.26	8.47	4.36	67.34	8.44	4.09	10

No.	R_1	R_2	R_3	R_4	Bp (mm) or mp, °C	$n^{20}D$ or other data	Method	Formula	Caled, % C	Caled, % H	Caled, % N	Found, % C	Found, % H	Found, % N	Activity[a]
38	*o*-OCH_3	H	H	$OCH_2CH_2OCH_3$	188–190 (0.35)		A	$C_{16}H_{25}NO_5$	60.18	8.42	4.68	60.43	8.42	4.91	0
39	*o*-OCH_3	H	H	$OCH_2CH_2OC_4H_9$-*n*	170–172 (0.006)		A	$C_{18}H_{31}NO_5$	63.31	9.15	4.10	63.20	9.09	4.20	0
40	*o*-OCH_3	H	H	$OC(CH_3)_2COCH_3$	145 (0.02)		A	$C_{17}H_{27}NO_5$	62.75	8.36	4.30	62.54	8.33	4.18	10
41	*o*-OCH_3	H	H	$SCH_2CH=CH_2$	196 (0.8)		A	$C_{15}H_{23}NO_3S$	60.59	7.80	4.71	60.52	7.93	4.60	20
42	*o*-OCH_3	H	$CH_2CH=CH_2$	$OCH_2CH=CH_2$	151 (0.2)		A	$C_{18}H_{27}NO_4$	67.26	8.47	4.36	67.25	8.59	4.13	0
43[b]	*o*-OCH_3	H	$COCH_3$	$OCH_2CH=CH_2$	204–206 (0.3)			$C_{17}H_{25}NO_5$	63.14	7.79	4.33	62.87	7.91	4.86	0
44[c]	*o*-OCH_3	$COCH_3$	$COCH_3$	$OCH_2CH=CH_2$	Decompd	Purified by chromatog		$C_{19}H_{27}NO_6$	62.45	7.45	3.83	62.29	7.55	3.95	0
45[d]	*o*-OCH_3	COC_3H_7-*n*	COC_3H_7-*n*	$OCH_2CH=CH_2$	182–184 (0.005)			$C_{23}H_{35}NO_6$	65.53	8.37	3.32	65.49	8.47	3.26	0
46	*o*-OCH_3	CH_3	H	$OCH_2CH=CH_2$	156–157 (0.25)	1.5169		$C_{16}H_{23}NO_4$	65.06	8.53	4.74	65.07	8.45	5.05	20
47	*o*-OCH_3	*n*-C_4H_9	H	$OCH_2CH=CH_2$	170 (0.3)		A	$C_{19}H_{31}NO_4$	67.62	9.26	4.15	67.63	9.20	3.99	0
48[e]	*o*-OCH_3	$COOC_2H_5$	H	$OCH_2CH=CH_2$	174–176 (0.0008)		A	$C_{18}H_{27}NO_6$	61.17	7.70	3.96	60.95	7.66	3.74	0
49[f]	*o*-OCH_3	NO	H	$OCH_2CH=CH_2$	Not distilled			$C_{15}H_{24}N_2O_5$	58.05	7.15	9.03	58.02	7.04	9.11	0
50[g]	*o*-OCH_3	NH_2	H	$OCH_2CH=CH_2$	168–172 (0.0006)			$C_{15}H_{24}N_2O_4$	60.79	8.16	9.45	60.23	7.81	9.45	10
51	*o*-OC_2H_5	H	H	$OCH_2CH=CH_2$	198 (1)		B	$C_{16}H_{25}NO_4$	65.06	8.53	4.74	64.98	8.62	4.96	0
52	*m*-OCH_3	H	H	$OCH_2CH=CH_2$	187 (0.75)		B	$C_{16}H_{23}NO_4$	64.03	8.24	4.98	63.74	8.40	4.71	
53	*p*-OCH_3	H	H	$OCH_2CH=CH_2$	178–180 (0.5), 63–65		B	$C_{16}H_{23}NO_4$	64.03	8.24	4.98	64.19	8.32	4.92	10
54	*o*-CH_3	H	H	$OCH_2CH=CH_2$	182–184 (2), 50–52		B	$C_{18}H_{23}NO_3$	67.89	8.74		67.82	8.64	Not detd	10
55	*o*-Cl	H	H	$OCH_2CH=CH_2$	160–162 (0.15), 38–40		B	$C_{14}H_{24}ClNO_3$	58.83	7.05	4.90	58.88	7.06	5.35	0
56	*m*-CF_3	H	H	$OCH_2CH=CH_2$	124–128 (0.0006)	1.4825	B	$C_{15}H_{24}F_3NO_3$	56.42	6.31	4.39	56.30	6.39	4.33	0
57	*o*-CH_3	H	H	OC_5H_{11}-*n*	B·HCl 108.5–109.5		B	$C_{17}H_{34}ClNO_3$[h]	61.70	8.83	4.23	61.93	9.15	4.39	0
58	*o*-$OCH_2C_6H_5$	H	H	OC_5H_{11}-*n*	B·HCl 95–96		B	$C_{23}H_{34}ClNO_4$[h]	65.15	8.08	3.33	65.34	8.13	3.57	0
59[i]	*o*-OH	H	H	OC_5H_{11}-*n*	B·HCl 182.5–183.5	EtOAc–EtOH (10:1)		$C_{16}H_{28}ClNO_4$[h]	57.55	8.45	4.20	57.41	8.52	4.61	10
60	2,3-$(OCH_3)_2$	H	H	$OCH_2CH=CH_2$	194–198 (0.6)		B	$C_{16}H_{25}NO_5$	61.71	8.09	4.50	61.70	8.26	4.60	15
61	2,4-$(OCH_3)_2$	H	H	$OCH_2CH=CH_2$	198–200 (0.7)		B	$C_{16}H_{25}NO_5$	61.71	8.09	4.50	61.51	8.27	5.09	0
62	2,5-$(OCH_3)_2$	H	H	$OCH_2CH=CH_2$	164–166 (0.0006), 45–46	1.5252	B	$C_{16}H_{25}NO_5$	61.71	8.09	4.50	61.81	8.13	4.51	10
63	2,6-$(OCH_3)_2$	H	H	$OCH_2CH=CH_2$	208–210 (2)		B	$C_{16}H_{25}NO_5$	61.71	8.09	4.50	61.75	7.99	4.69	0
64	2-OCH_3-4-CH_3	H	H	$OCH_2CH=CH_2$	175–176 (0.2), 40–43		B	$C_{16}H_{25}NO_4$	65.06	8.53	4.74	64.80	8.44	4.80	0

[a] See footnote *a*, Table I. [b] Prepared by acetylation of the hydrochloride of **28** with 1 mole of acetic anhydride and extraction of the product with cold dilute acid to separate from the N-acetylated material. [c] Normal acetylation of **28** with 2 moles of acetic anhydride. [d] Prepared by standard reaction of butyryl chloride with **28**. [e] Prepared by standard reaction of ethyl chloroformate with **28**. [f] Prepared by standard N nitrosation of **28**. [g] Prepared by reduction of **49** with $LiAlH_4$. [h] Hydrochloride analyzed. [i] Prepared by hydrogenolysis of **58** using 5% Pd-C at atmospheric pressure and room temperature. [j] B = base, AM = acid maleate.

TABLE III

N-ALKYL-2-(SUBSTITUTED PHENOXY)ETHYLAMINES

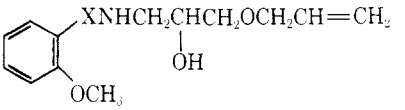


No.	R_1	R_2	R_3	n	Bp, °C	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
65	*o*-OCH_3	H	*n*-C_4H_9	2	134–136 (0.7)	A	$C_{15}H_{25}NO_3$	67.38	9.43	5.24	67.56	9.26	4.94	10
66[b]	*o*-OCH_3	H	CH_3	3	139–140 (0.6)	B	$C_{13}H_{21}NO_3$	65.24	8.85	5.85	65.28	9.09	5.69	10
67	*o*-OCH_3	H	*n*-C_3H_7	3	149–151 (0.6)	A	$C_{15}H_{25}NO_3$	67.38	9.43	5.24	67.57	9.46	5.28	10
68[c]	*o*-OCH_3	H	$CH_2CH{=}CH_2$	3	137–139 (0.35)	A	$C_{15}H_{23}NO_3$	67.94	8.68	5.28	68.19	8.76	5.19	60
							$C_{15}H_{23}NO_7$	59.83	7.14	3.67	59.87	7.00	3.79	
69	*o*-OCH_3	H	$CH_2CH{=}CHCH_3$	3	128–132 (0.01)	A	$C_{16}H_{25}NO_3$	68.82	8.95	5.02	69.00	8.89	4.93	10
70[d]	*o*-OCH_3	$COOC_2H_5$	$CH_2CH{=}CH_2$	3	145–146 (0.0001)		$C_{15}H_{27}NO_6$	64.07	8.06	4.15	63.97	8.04	4.19	0
71	2-OCH_3-4-CH_3	H	CH_3	3	142–144 (0.25)	B	$C_{14}H_{23}NO_2$	66.37	9.15	5.53	66.27	9.07	5.35	0
72	2,6-$(OCH_3)_2$	H	CH_3	3	154–156 (0.3)	B	$C_{14}H_{23}NO_3$	62.43	8.61	5.20	62.59	8.67	5.10	0
73[e]	*o*-OCH_3	H	*n*-C_4H_9	5	144 (0.003)	A	$C_{15}H_{25}NO_2$	69.86	10.10	4.53	69.71	10.08	4.80	10
74	*o*-OCH_3	H	$CH_2CH{=}CH_2$	6	156–158 (0.002)	C	$C_{15}H_{23}NO_2$	70.32	9.51	4.56	70.31	9.47	4.65	10
75	*o*-OCH_3	H	*n*-C_4H_9	6	167–168 (0.3)	C	$C_{19}H_{33}NO_2$	70.55	10.28	4.33	70.44	10.22	4.07	20
76	*o*-OCH_3	H	H	6	166–168 (0.2)	A	$C_{18}H_{29}NO_2$	67.38	9.43	5.24	67.30	9.57	4.77	20

[a] See footnote *a*, Table I. [b] Ciba Ltd., South African Patent 59/3531 (1959). [c] Acid maleate, mp 69.5–70° (EtOH–Et_2O). [d] Prepared by reaction of ethyl chloroformate with **68**. [e] $n^{20}D$ 1.4990.

TABLE IV

N-SUBSTITUTED 3-ALLYOXY-2-HYDROXYPROPYLAMINES

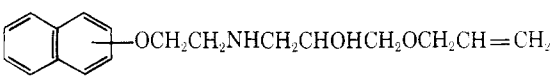


No.	X	Bp, °C (mm)	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
77	$-O(CH_2)_3-$	186–187 (0.9)	B	$C_{16}H_{25}NO_4$	65.06	8.53		65.04	8.53		0
78	$-OCH_2C(CH_3)H-$	156 (5.4×10^{-3})	B	$C_{16}H_{25}NO_4$	65.06	8.53	4.74	64.79	8.50	4.40	0
79	$-OCH_2C(OH)HCH_2$	210 (4×10^{-3})	B	$C_{16}H_{25}NO_5$	61.71	8.09	4.50	62.12	8.04	4.27	0
80	$-(CH_2)_3-$	168–170 (2)	B	$C_{16}H_{25}NO_3$	68.78	9.02	5.01	68.76	8.97	4.99	10
81	$-SCH_2CH_2-$	177 (0.3)	B	$C_{15}H_{23}NO_3S$	60.59	7.80	4.71	60.32	7.89	4.38	10
82	$-NHCH_2CH_2-$	174–176 (0.25×10^{-2})	B	$C_{15}H_{24}N_2O_3$	64.26	8.63	9.99	64.15	8.77	9.78	0

[a] See footnote *a*, Table I.

TABLE V

N-(3-ALLYLOXY-2-HYDROXYPROPYL)NAPHTHYLOXYETHYLAMINES

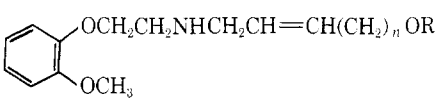


No.	Substitution	Bp (mm) or mp, °C	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
83	α	182–184 (0.005)	B	$C_{18}H_{23}NO_3$	71.73	7.69	4.65	71.66	7.95	5.04	25
84	β	186–188 (0.01)	B	$C_{18}H_{23}NO_3$	71.73	7.69	4.65	71.91	7.89	4.62	0
85	4-OCH_3-α	75.5–77[b]	B	$C_{19}H_{25}NO_4$	68.86	7.60	4.23	68.91	7.70	4.15	0

[a] See footnote *a*, Table I. [b] Needles from petroleum ether.

TABLE VI

N-ALKOXYALKENYL-2-(2-METHOXYPHENOXY)ETHYLAMINES

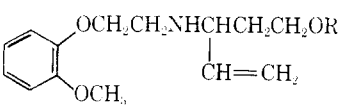


No.	n	R	Bp, °C (mm)	Other data	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
86	1	*n*-C_4H_9	138–140 (0.0001)		A	$C_{17}H_{27}NO_3$	69.59	9.28	4.77	69.76	9.12	4.81	10
87	1	$CH_2CH{=}CHCH_3$	144–145 (0.006)		A	$C_{17}H_{25}NO_3$	70.07	8.65	4.81	69.96	8.59	5.04	20
88	2	CH_3		Acid maleate, mp 89.5–90°	A	$C_{19}H_{27}NO_7$[b]	59.83	7.14	3.67	60.08	7.03	3.56	10
89	2	*n*-C_3H_7	140–142 (0.004)	$n^{20}D$ 1.5108	A	$C_{17}H_{27}NO_3$	69.59	9.28		69.58	9.28	Not detd	10
90	2	*n*-C_4H_9	137 (0.0006)		A	$C_{15}H_{29}NO_3$	70.32	9.51	4.56	70.46	9.35	4.43	10
91	2	*n*-C_5H_{11}	138–141 (0.0008)	$n^{20}D$ 1.4986	A	$C_{19}H_{31}NO_3$	70.99	9.72	4.36	71.20	9.38	4.43	10

[a] See footnote *a*, Table I. [b] Analysis of acid maleate.

TABLE VII

N-(3-ALKOXY-1-VINYLPROPYL)-2-(2-METHOXYPHENOXY)ETHYLAMINES

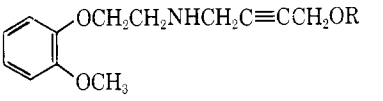


No.	R	Bp, °C (mm)	$n^{20}D$	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
92	CH_3	163 (0.7)	1.5174	A	$C_{15}H_{23}NO_3$	67.89	8.74	5.28	67.85	8.51	5.34	10
93	C_2H_5	110 (0.03)	1.5126	A	$C_{16}H_{25}NO_3$	68.78	9.02	5.01	68.48	8.91	4.77	10
94	*n*-C_3H_7	134–138 (0.003)	1.5122	A	$C_{17}H_{27}NO_3$	69.59	9.28	4.77	69.84	9.12	4.73	10
95	*n*-C_4H_9	136 (0.0001)	1.5049	A	$C_{18}H_{29}NO_3$	70.32	9.51	4.56	70.52	9.33	4.40	10

[a] See footnote *a*, Table I.

TABLE VIII

N-(4-ALKOXYBUT-2-YNYL)-2-(2-METHOXYPHENOXY)ETHYLAMINES

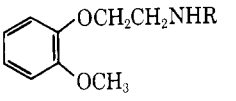


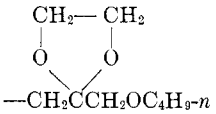
No.	R	Bp, °C (mm)	$n^{20}D$	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
96	CH_3	128–132 (0.002)	1.5351	A	$C_{14}H_{19}NO_3$	67.44	7.68	5.62	67.35	7.62	5.47	0
97	C_2H_5	138–142 (0.002)		A	$C_{15}H_{21}NO_3$	68.41	8.04	5.32	68.16	7.90	4.76	10
98	n-C_3H_7	154 (0.005)	1.5260	A	$C_{16}H_{23}NO_3$	69.28	8.36	5.05	69.25	8.35	4.95	0

[a] See footnote *a*, Table I.

TABLE IX

N-SUBSTITUTED 2-(2-METHOXYPHENOXY)ETHYLAMINES

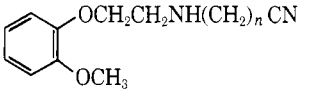


No.	R	Bp, °C (mm)	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
99	$(CH_2)_2CHOHCH_2OCH_2CH{=}CH_2$	164–168 (0.3)	A	$C_{16}H_{25}NO_4$	65.06	8.53	4.74	65.13	8.56	5.08	25
100		160 (0.2)	A	$C_{18}H_{29}NO_5$	63.69	8.61	4.13	63.63	8.69	4.39	10

[a] See footnote *a*, Table I.

TABLE X

N-ω-CYANOALKYL-2-(2-METHOXYPHENOXY)ETHYLAMINES

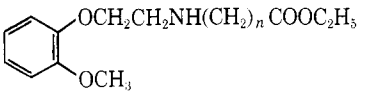


No.	n	Bp, °C (mm)	Acid maleate mp, °C (solvent)	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
101	2	...	119–121 (MeOH)	C	$C_{16}H_{20}N_2O_6$[b]	57.13	5.99	8.33	57.20	5.97	8.43	10
102	3	...	109.5–111 (MeOH)	C	$C_{17}H_{22}N_2O_6$[b]	58.27	6.33	8.00	58.25	6.27	7.91	50
103	4	174 (0.7)	97–99.5 (MeOH–Et_2O)	C	$C_{18}H_{24}N_2O_6$[b]	59.33	6.64	7.69	59.65	6.65	7.50	90
104	5	176–180 (0.5)		B	$C_{15}H_{22}NO_2$	68.67	8.45	10.68	68.76	8.41	10.68	120
105	6	185–188 (0.35)	78.5–80 (MeOH–Et_2O)	C	$C_{20}H_{28}N_2O_6$[b]	61.21	7.19	7.14	60.93	7.13	7.04	50

[a] See footnote *a*, Table I. [b] Analysis of acid maleate.

TABLE XI

N-ω-CARBETHOXYALKYL-2-(2-METHOXYPHENOXY)ETHYLAMINES

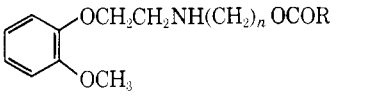


No.	n	Acid maleate mp, °C (solvent)	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
106	1	91.5–93 (MeOH–Et_2O)	A	$C_{17}H_{23}NO_8$[b]	55.28	6.28	3.79	55.49	6.25	3.67	0
107	2	94–95.5 (MeOH–Et_2O, EtOAc)	A	$C_{18}H_{25}NO_8$[b]	56.39	6.57	3.65	56.63	6.40	4.13	0

[a] See footnote *a*, Table I. [b] Analysis of acid maleate.

TABLE XII

N-ω-(ACYLOXYALKYL)-2-(2-METHOXYPHENOXY)ETHYLAMINES

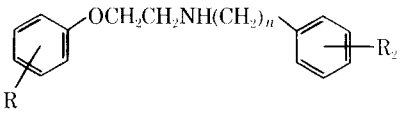


No.	R	n	Bp, °C (mm)	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
108	CH_3	4	140–144 (0.002)	A	$C_{15}H_{23}NO_4$	64.03	8.24	4.98	63.89	8.24	5.49	25
109	CH_3	5	150–154 (0.0003)	A	$C_{16}H_{25}NO_4$	65.06	8.53	4.74	64.69	8.61	4.48	25
110	CH_3	6	158–162 (0.0006)	A	$C_{17}H_{27}NO_4$	65.99	8.80	4.53	66.09	8.87	4.83	100
111	C_2H_5	5	148–152 (0.002)	A	$C_{17}H_{27}NO_4$	65.99	8.80	4.53	66.01	8.76	4.56	25
			N-acetyl, 181–185 (5.4×10^{-3})		$C_{19}H_{29}NO_5$	64.93	8.32	3.99	64.76	8.35	3.95	0
112	$CH{=}CHCH_3$	4	140–144 (0.6)	A	$C_{17}H_{25}NO_4$	66.42	8.20	4.56	66.67	8.22	4.49	0

[a] See footnote *a*, Table I.

TABLE XIII

N-ω-(SUBSTITUTED PHENYLALKYL)-2-(2-METHOXYPHENOXY)ETHYLAMINES



No.	n	R_1	R_2	Bp, °C (mm)	Derivative mp, °C (solvent)	Method	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Activity[a]
113	4	*o*-OCH_3	H	164–166 (0.02)	AM[d] 117–118 (EtOAc)	A	$C_{23}H_{29}NO_6$[b]	66.49	7.04	3.37	66.69	7.04	3.47	45
114	2	*o*-OCH_3	*o*-OCH_3	166–168 (0.002)	AM 117–118.5 (EtOH–Et_2O)	A	$C_{18}H_{23}NO_3$	71.73	7.69	4.65	71.91	7.84	4.49	
							$C_{29}H_{27}NO_7$[b]	63.30	6.52	3.36	63.22	6.81	2.96	
115	3	*o*-OCH_3	*o*-OCH_3		AM 104–105.5 (EtOH–Et_2O)	A	$C_{23}H_{29}NO_7$[b]	64.02	6.77	3.25	64.28	6.86	3.15	60
116	4	*o*-OCH_3	*o*-OCH_3		AM 86–87 (EtOAc, EtOH–Et_2O)	B	$C_{23}H_{31}NO_7$[b]	64.70	7.01	3.14	64.72	6.95	3.00	30
117	2	*o*-OCH_3	*p*-OCH_3	194 (0.01)	AM 128.5–129.5 (EtOAc)	A	$C_{22}H_{27}NO_7$[b]	63.30	6.52	3.36	62.88	6.40	3.47	60
118	3	*o*-OCH_3	*p*-OCH_3	195 (0.008)	AM 109–111 (EtOAc)	A	$C_{23}H_{29}NO_7$[b]	64.02	6.77	3.25	64.10	6.56	3.02	30
119	4	*o*-OCH_3	*p*-OCH_3	180–182 (0.006)	AM 99.5–100.5 (EtOAc, EtOH–Et_2O)	A	$C_{20}H_{27}NO_3$	72.92	8.26	3.86	72.73	8.23	4.25	130
							$C_{24}H_{31}NO_7$[b]	64.70	7.01	3.14	64.58	7.03	2.93	
120	5	*o*-OCH_3	*p*-OCH_3		AM 91–92 (EtOAc, EtOH–Et_2O)	A	$C_{25}H_{33}NO_7$[b]	65.34	7.24	3.05	65.46	7.24	3.03	30
121	3	*o*-OCH_3	*p*-OC_2H_5	196–200 (0.002)	AM 114–115 (EtOH–Et_2O)	A	$C_{24}H_{31}NO_7$[b]	64.70	7.01	3.14	64.63	7.19	2.97	0
122	4	*o*-OCH_3	*p*-OC_2H_5		B·HCl 104 (EtOAc)	A	$C_{24}H_{30}ClNO_3$[c]	66.40	7.90	3.69	66.01	7.94	3.55	60
					AM 101.5–102 (EtOAc)		$C_{25}H_{33}NO_7$[b]	65.34	7.24	3.05	65.32	7.33	3.06	
123	4	*o*-OCH_3	*p*-OC_3H_7-*n*		B·HCl 104.5–106 (EtOAc)	A	$C_{25}H_{32}ClNO_3$[c]	67.07	8.11	3.56	67.20	8.06	3.51	60
124	4	*o*-OCH_3	*p*-OC_4H_9-*n*		AM 121–122 (EtOAc)	A	$C_{27}H_{37}NO_7$[b]	66.51	7.65	2.87	66.68	7.72	2.80	0
125	4	*o*-OCH_3	*p*-OH	210 (0.0006)		A	$C_{19}H_{25}NO_3$	72.35	7.99	4.44	72.09	8.09	4.49	100
126	4	*o*-OCH_3	*p*-$OCOCH_3$		B·HCl 90.5–91.5 (EtOAc)	A	$C_{21}H_{28}ClNO_4$[c]	64.03	7.17	3.56	64.03	7.20	3.70	120
127	4	*o*-OCH_3	*p*-$OCOC(CH_3)_3$		AM 144–145 (EtOAc)		$C_{28}H_{37}NO_8$[b]	65.22	7.23	2.72	65.57	7.27	2.88	90
128	4	*o*-OCH_3	*p*-CH_3	189–191 (0.3)		A	$C_{20}H_{27}NO_2$	76.64	8.68	4.47	76.82	8.83	4.53	90
129	4	*o*-OCH_3	*p*-Cl	198–204 (0.3)	AM 108–109 (EtOAc)	A	$C_{23}H_{28}ClNO_6$[b]	61.40	6.27	3.11	61.38	6.30	3.35	40
130	4	*o*-OCH_3	*p*-$COCH_3$		B·HCl 110–110.5 (EtOH–Et_2O)	A	$C_{21}H_{28}ClNO_3$[c]	66.74	7.47	3.71	66.73	7.64	3.83	50
131	4	*o*-OCH_3	2,5-$(OCH_3)_2$	204–208 (0.01)[e]		A	$C_{21}H_{29}NO_4$	70.17	8.13	3.90	70.41	7.94	3.51	40
132	4	*o*-OCH_3	2,4-$(OCH_3)_2$		AM 85–86 (EtOAc–Et_2O)	A	$C_{25}H_{33}NO_8$	63.14	7.00	2.95	62.91	7.02	3.14	0
133	2	*o*-OCH_3	3,4-$(OCH_3)_2$	*Ca.* 185 (0.004)	AM 106–106.5 (EtOH–Et_2O)	B	$C_{23}H_{29}NO_8$[b]	61.73	6.53	3.13	61.91	6.41	3.12	70
134	4	*o*-OCH_3	3,4-$(OCH_3)_2$	196–198 (0.002)	B·HCl 201 (EtOH–Et_2O)	A	$C_{21}H_{29}NO_4$	70.17	8.13	3.90	70.02	8.09	4.05	45
							$C_{21}H_{30}ClNO_4$[c]	63.71	7.64	3.54	63.77	7.53	3.64	45
135	2	*p*-OCH_3	3,4-$(OCH_3)_2$		AM 123–125.5 (MeOH–Et_2O)	B	$C_{23}H_{29}NO_8$	61.73	6.53	3.13	61.94	6.62	2.84	25
136	2	*o*-OH	3,4-$(OCH_3)_2$		AM 138–139 (EtOH–Et_2O)		$C_{22}H_{27}NO_8$[b]	60.96	6.28	3.23	61.25	6.57	3.15	
137	2	*o*-$OCH_2C_6H_5$	3,4-$(OCH_3)_2$		AM 114–116 (MeOH–Et_2O)	B	$C_{29}H_{33}NO_8$[b]	65.52	6.35	2.68	66.11	6.48	2.63	0
138	2	*o*-CH_3	3,4-$(OCH_3)_2$	184–185 (0.0006)	AM 108.5–110 (MeOH–Et_2O)	B	$C_{23}H_{29}NO_7$	64.02	6.77	3.25	63.96	6.53	3.10	0
139	2	*o*-Cl	3,4-$(OCH_3)_2$	186–190 (0.001)	AM 120.5–122 (MeOH–Et_2O)	B	$C_{22}H_{26}ClNO_7$[b]	58.47	5.80	3.10	58.40	5.90	2.84	20
140	2	*p*-Cl	3,4-$(OCH_3)_2$		AM 132–134 (MeOH–Et_2O)	B	$C_{22}H_{26}ClNO_7$[b]	58.47	5.80	3.10	58.45	5.74	2.99	0

[a] See footnote *a*, Table I. [b] Analysis of acid maleate. [c] Analysis of hydrochloride. [d] AM = acid maleate, B = base. [e] $n^{25.5}D$ 1.5562.