Some Cardiovascular Effects of a Series of Aryloxyalkylamines. I

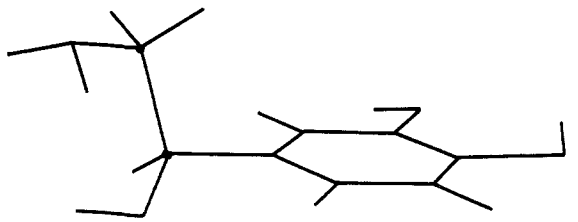
J. AUGSTEIN,[1] W. C. AUSTIN, R. J. BOSCOTT, S. M. GREEN, AND C. R. WORTHING

Chemical Research Department, Pfizer Limited, Sandwich, Kent, Great Britain

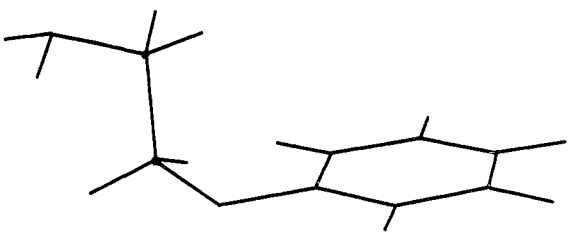
Received December 24, 1964

N-Substituted phenoxyalkylamine derivatives (**128**) have been prepared and tested for their antihypertensive activity. Observations on structure–activity relationships show that the 2-(2-methoxyphenoxy)ethylamine moiety is essential to obtain maximum activity; structural requirements of the group attached to the nitrogen atom are less specific. Maximum activity, as measured by fall in blood pressure, was obtained with the following N-substituted 2-(2-methoxyphenoxy)ethylamines: 3-(2,5-dimethoxyphenoxy)propyl- (**23**), 3-(2,4-dimethoxyphenoxy)propyl- (**24**), 3-(2-methoxy-5-acetylphenoxy)propyl- (**32**), 3-(2,4,5-trimethoxyphenoxy)propyl- (**50**), and 3-(4-methoxyphenoxy)-2-hydroxypropyl- (**109**). These five structurally closely related compounds represent, among others of outstanding activity, the optimum substitution pattern with respect to antihypertensive activity displayed. A high degree of activity was accompanied by tachycardia, indicating a failure to block β-receptors in the heart. An attempt is made to correlate the difference in affinity for α- and β-adrenergic receptors with chemical structures.

Bioisosteres of norepinephrine (A) such as 2-phenoxyethylamine (B) have been described for the first



A



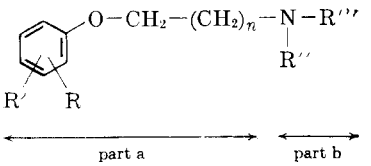
B

time in a comprehensive form by Bovet and coworkers.[2] They discussed, among other aspects, the affinity of 2-phenoxyethylamines for adrenergic structures as expressed by their effects on the blood pressure of anesthetized animals and various other organ preparations. Some N-substituted 2-phenoxyethylamines, like all classical "antiadrenaline" compounds, antagonize and abolish pressor effects of norepinephrine and reverse those of epinephrine.[3]

Excitation of vasoconstrictor receptors in the vascular smooth muscle is best achieved by a transmitter with a small (unsubstituted) cationic head as is present in norepinephrine, favoring effective charge "neutralization" between transmitter cation and receptor anion.[4] Substitution on the nitrogen atom of a transmitter (agonist) or transmitter analog by larger substituents increases the bulk around the charge carrier. This may give rise to incomplete charge "neutralization" and reduced excitatory response. Alternatively, competition between the sympathetic transmitter and the antagonist at receptor level produces an inhibition of the sympathomimetic effects of the natural transmitter. As a consequence of this, effective sympathetic tone is reduced which results in a fall of arterial pressure. The magnitude of this inhibition depends, according to definition, upon the degree of α-receptor blockade.[5]

A number of compounds described in this paper produced a marked and prolonged reduction of mean arterial blood pressure in normotensive and hypertensive animals which resulted from a classical adrenolytic action (blockade of α-receptors[6]). This was demonstrated with the most active compounds of this series by their antagonism to the effects of injected norepinephrine and by determination of their pA_2 values. These compounds did not annul the positive inotropic and chronotropic effects of epinephrine and of sympathetic stimulation, effects which are mediated through β-receptors.[7]

Structure–Activity Relationship.[8]—The large variety of compounds prepared enabled us to make several generalizations pertaining to the general structure C.



C

Part a.—A high degree of specificity seems essential for part a of the molecule, requiring 2-(2-methoxyphenoxy)ethyl for optimum α-receptor blocking activity. Removal of the substituent from the *ortho* position, replacement by other radicals (**77–80**), or substitution in positions other than *ortho* (**75** and **76**) resulted in a decline of activity in otherwise optimal structures. Similar results were obtained on disubstitution of the benzene ring in various positions (**82–84**). On replacement of the benzene ring by **1**- or 2-naphthyl radicals (**126**) all activity was lost. Branching of the

(1) Inquiries should be addressed to Dr. J. Augstein.

(2) D. Bovet and F. Bovet-Nitti, "Structure et Activité Pharmacodynamique des Médicaments du Système Nerveux Vegetatif," Verlag S. Karger A.-G., Basel, 1948, p. 170.

(3) (a) E. Kahane and J. Lévy, *Bull. Soc. Chim. Biol.*, **27**, 256 (1945); *Chem. Abstr.*, **41**, 1755e (1947); (b) C. Heymans, C. R. de Vleeschhouwer, and G. van den Heuvel-Heymans, *Arch. Intern. Pharmacodyn.*, **85**, 188 (1951); (c) P. E. Moore, A. W. Richardson, and H. D. Green, *J. Pharmacol. Exptl. Therap.*, **106**, 14 (1952).

(4) B. Belleau, Ciba Foundation Symposium on Adrenergic Mechanisms, J. R. Vane, G. E. W. Wolstenholme, and M. O'Connor, Ed., J. and A. Churchill Ltd., London, 1960, p. 223.

(5) E. J. Ariëns, ref. 4, p. 253.

(6) R. P. Ahlquist, *Am. J. Physiol.*, **153**, 586 (1948).

(7) E. J. Ariëns, ref. 4, p. 264.

(8) Further results obtained by us, supporting these interpretations, will be published shortly.

ethylene chain (**63**–**65**), increase in chain length (**85**–**86**), or substitution of the secondary nitrogen atom (**97**–**106**) reduced or abolished activity. The complete loss in activity (with the exception of **98**) on substitution of the secondary nitrogen atom appears to be of significance with regard to the observation that effective charge "neutralization" between active cation and anion receptor or competitive block are favored by a nitrogen carrying hydrogen atoms.[4]

Part b.—Specificity appears to be less pronounced in part b of the molecule for effective α-receptor blockade. The optimum distance in part b between nitrogen and an aromatic nucleus is provided by an unbranched C_3 chain, in addition to which there may be incorporated a polar function such as an oxygen atom, in the form of an ether linkage, a sulfamoyl, an amido, or an ester group.

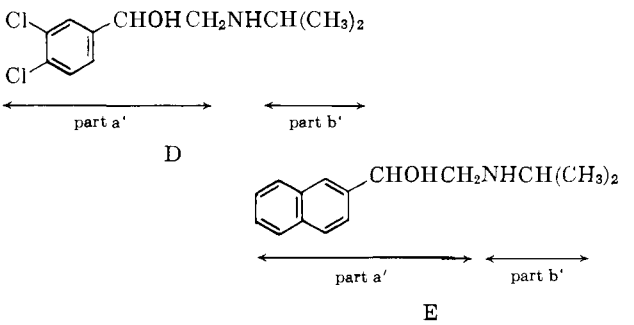
Increase (**54**) or decrease (**1**) in chain length, branching in any position (**66**–**68**), or introduction of a multiple bond into a C_4 unit (**69** and **70**) decreased activity. Introduction of a hydroxyl group into the side chain generally lowered the activity; compound **109** represented an exception. Replacement of the ether bridge by sulfamoyl (**89**–**92**) or imido (**94**) groups increased activity while amides (**93** and **116**–**118**) were of low potency with the exception of **115**. The ester **81** produced significant activity.

Replacement of the benzene ring by 4-substituted benzyl (**73**) improved the activity, while **1**- or 2-naphthyl (**124** and **125**), alicyclic (**112** and **113**), or heterocyclic (**114**) radicals gave rise to weakly active or inactive compounds.

The results obtained support the view that attachment to α-receptors requires that part a of the compounds described be structurally closely related to the agonist (norepinephrine), while the bulk of part b around the charge-carrying nitrogen atom contributes to drug effectiveness in various less specific structures as represented by parts b of compounds **23**–**25**, **32**, **49**, **50**, **73**, **81**, **89**, **92**, and **109**. Out of these, the most active α-receptor blockers were structurally closely related, the benzene ring being substituted in the 4-position (**109**), in the 2,4-positions (**24**), in the 2,5-positions (**23** and **32**), or in the 2,4,5-positions (**50**) both by electron-withdrawing or electron-donating groups. The fact that these agents do not block the β-receptors of the heart and smooth muscles adds evidence to the assumption that β-receptors possess different features to α-receptors at the molecular level.

Two compounds, recognized to block β-receptors, N-isopropyl-2-(3,4-dichlorophenyl)ethanolamine[9] (DCI) (D) and N-isopropyl-2-(2-naphthyl)ethanolamine[10] (E), are very similar in size with regard to their aromatic systems (where two chlorine atoms in D are equivalent to an additional benzene ring in E) and identical with regard to their N-isopropylethanolamine moiety.

A comparison of model C and compounds D and E reveals structural features which may be characteristic of compounds with specific affinity for either α- or β-receptors. Thus van der Waals forces of part a in model C and its surface area are reduced compared with part a′ in D and E, while part b in C is bulky and very



different in chemical nature compared with part b′ in D and E.

This difference in physical and chemical nature may account for the exclusive affinity of the compounds described here for α-receptors and that of D and E for β-receptors.

Pharmacology.—The pharmacological effects on adrenergic neuroeffector transmission of the compounds described were studied in cats and dogs anesthetized with chloralose. All active compounds antagonized both the contractions of the cat nictitating membrane in response to pre- and postganglionic stimulation of the cervical sympathetic trunk and those to injected epinephrine and norepinephrine. The pressor effects of injected norepinephrine were abolished, and the pressor effects of epinephrine were reversed. These compounds abolished the biphasic pressor response evoked by electrical stimulation of the distal end of the divided right splanchnic nerve. They antagonized the effects of sympathetic nerve stimulation at the same concentration as that required to antagonize the effects of exogenous epinephrine and norepinephrine.

The positive inotropic and chronotropic effects of epinephrine and isoprenaline and stimulation of the accelerans nerve were not altered by those compounds which produced a satisfactory fall in blood pressure. These results show that the compounds described antagonized the effects of the sympathetic transmitter on α-adrenergic receptors but not those on β-adrenergic receptors.

A quantitative estimation of the adrenolytic properties of a number of these compounds was obtained by determining the pA_2 values against epinephrine at 2 min. using strips of rabbit uterine horn suspended in oxygenated Tyrode's solution at 34° (Table I).

TABLE I

pA_2 VALUES OF SOME N-SUBSTITUTED PHENOXYETHYLAMINES

No.	pA_2
5	6.57
6	6.32
7	6.47
23	7.48
60	6.25
61	6.24
89	7.10
Tolazoline	5.73
Dibenamine	6.36

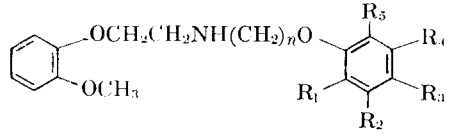
Chemistry.—Compounds tested for antihypertensive activity are listed in Tables II–VII. Most of these were prepared by conventional methods, thus treating primary amines with suitable aryloxyalkyl halides as listed in Table VIII by one of two general procedures (**1** or **2**). The halogen compounds were prepared by

(9) C. E. Powell, I. H. Slater, L. Le Compte, Jr., and J. E. Waddell, *J. Pharmacol. Exptl. Therap.*, **122**, 480 (1958).

(10) J. W. Black and J. S. Stephenson, *Lancet*, II, 311 (1962).

TABLE II

N-[2-(2-METHOXYPHENOXY)ETHYL]ARYLOXYALKYLAMINES[a]



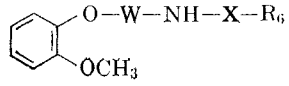
No.	n	R_4	R_2	R_3	R_4	R_5	M.p., °C.[b]	B.p. (mm.), °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Yield, %[c]	Recrystn. solvent[d]	Activity,[e] %
1	2	OCH_3	H	H	H	H	91–92 B	196 (0.3)[f]	$C_{18}H_{23}NO_4$	68.12	7.31	4.41	68.29	7.27	4.46	60	Ea–P	30
2	2	H	Cl	Cl	H	H	139 M		$C_{21}H_{23}Cl_2NO_7$	53.39	4.99	2.96	53.39	5.11	3.04	54	E	0
3	2	OCH_3	H	H	OCH_3	H	131–132.5 M		$C_{25}H_{29}NO_9$	59.60	6.31	3.02	59.55	6.27	3.19	33	E	0
4	3	H	H	H	H	H	47–49 B	197–199 (0.85)	$C_{18}H_{23}NO_3$	71.73	7.69	4.65	71.81	7.73	4.43	10	P	30
5	3	OCH_3	H	H	H	H	73–74 B	190–200 (0.3)	$C_{19}H_{25}NO_4$	68.86	7.60	4.23	68.64	7.42	4.02	45	Ea or P	40
6	3	H	OCH_3	H	H	H	117–118 H	203–210 (0.5)	$C_{19}H_{26}ClNO_4$	62.03	7.13	3.81	62.18	7.12	3.67	3	M–Et	20
7	3	H	H	OCH_3	H	H	133–135 M	204–206 (0.3)	$C_{19}H_{25}NO_4$	68.86	7.60		68.89	7.66		43.5	E	50
8	3	CH_3	H	H	H	H		175 (0.1)[g]	$C_{19}H_{25}NO_3$	72.35	7.99		72.28	8.05		38		20
9	3	H	CH_3	H	H	H	42.5–43.5 B	183–184 (0.1)[h]	$C_{19}H_{25}NO_3$	72.35	7.99	4.41	72.26	8.07	4.43	26	P	30
10	3	H	H	CH_3	H	H	106.5–108 H	183–184 (0.2)	$C_{19}H_{26}ClNO_3$	64.85	7.45	3.98	64.88	7.42	3.91	14	Ea	40
11	3	Cl	H	H	H	H	113–115 Mm	191–193 (0.25)	$C_{30}H_{46}Cl_2N_2O_6$	61.00	6.14		61.17	6.00		10	Ea	20
12	3	H	H	Cl	H	H	112–113 H		$C_{18}H_{23}Cl_2NO_3$	58.09	6.23	3.76	58.24	6.20	3.56	8	M–Et	30
13	3	NO_2	H	H	H	H	94–95 M[i]		$C_{22}H_{26}N_2O_5$	57.13	5.67	6.06	57.19	5.74	5.90	6.5	M–Et	20
14	3	H	H	NO_2	H	H	56.5–57.5 B[j]		$C_{18}H_{22}N_2O_5$	62.41	6.40	8.09	62.53	6.24	8.26	74	P	40
15	3	H	H	NH_2	H	H	75.5–76.5 B[k]	214–220 (0.1)	$C_{18}H_{24}N_2O_3$	68.33	7.65	8.86	68.36	7.68	8.56	60	Ea	30
16	3	$CONH_2$	H	H	H	H	127–129.5 B		$C_{19}H_{24}N_2O_4$	66.25	7.02	8.14	65.92	7.12	7.78	27	Ea	40
17	3	H	CF_3	H	H	H		169 (0.1)[b]	$C_{19}H_{22}F_3NO_3$	61.77	6.00		61.66	5.88		27		20
18	3	H	H	$C(CH_3)_3$	H	H	93.5–95.5 H	198–200 (0.2)[l]	$C_{22}H_{32}ClNO_3$	67.05	8.19	3.56	67.20	8.19	3.29	10	Ea	10
19	3	H	H	C_6H_5	H	H	161–163 H[n]		$C_{24}H_{28}ClNO_3$	69.63	6.82	3.39	69.56	6.81	3.40	25	E	30
20	3	H	H	$OCH_2C_6H_5$	H	H	154–156 M		$C_{29}H_{33}NO_8$	66.53	6.35		66.73	6.25		...	M	0
21	3	H	H	C_6H_{11}	H	H	140–142 M		$C_{28}H_{37}NO_7$	67.31	7.47	2.80	67.06	7.27	2.61	52	E	0
22	3	OCH_3	H	H	H	OCH_3		205–206 (0.3)	$C_{26}H_{37}NO_6$	66.46	7.53	3.88	66.31	7.73	3.82	37		0
23	3	OCH_3	H	H	OCH_3	H	64–66 B[m]	228–230 (0.5)	$C_{26}H_{37}NO_6$	66.46	7.53	3.88	66.29	7.66	3.65	59	P	100
24	3	OCH_3	H	OCH_3	H	H	87–89 M		$C_{26}H_{37}NO_6$	60.36	6.54	2.93	60.34	6.48	2.80	55.5	E	100
25	3	OCH_3	OCH_3	H	H	H	99–100.5 M		$C_{24}H_{31}NO_5$	60.36	6.54	2.93	60.23	6.48	3.08	57	E–Et	90
26	3	H	OCH_3	OCH_3	H	H	118–120 M		$C_{24}H_{31}NO_5$	60.36	6.54	2.93	60.50	6.64	3.15	69	E	30
27	3	H	OCH_3	H	OCH_3	H	107–109 M		$C_{24}H_{31}NO_5$	60.36	6.54	2.93	60.23	6.35	3.08	61	E	10
28	3	OCH_3	H	H	OCH_2CH_3	H	107–109.5 M		$C_{25}H_{33}NO_5$	61.09	6.77		61.27	6.43		19	E	30
29	3	OCH_2CH_3	H	H	OCH_3	H	114–116 M		$C_{25}H_{33}NO_5$	61.09	6.77	2.86	61.09	6.57	2.90	13	E	20
30	3	OCH_2CH_3	H	H	OCH_2CH_3	H	115–118 M		$C_{26}H_{35}NO_5$	61.77	6.98	2.77	62.11	7.20	2.58	38	E	10
31	3	$O(CH_2)_3CH_3$	H	H	$O(CH_2)_3CH_3$	H	88–90 M		$C_{30}H_{43}NO_5$	64.15	7.72	2.49	64.07	7.87	2.56	48	E	10
32	3	OCH_3	H	H	$COCH_3$	H	130–132 M		$C_{26}H_{35}NO_6$	61.33	6.38	2.85	61.56	6.50	2.58	7	E	100
33	3	OCH_3	H	$COCH_3$	H	H	126–128 M[n]		$C_{25}H_{33}NO_6$	61.33	6.38	2.85	61.48	6.51	2.98	...	E–Et	40

No.	n	R_1	R_2	R_3	R_4	R_5	M.p., °C.[b]	B.p. (mm.), °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Yield, %[c]	Recrystn. solvent[d]	Activity,[e] %
34	3	OCH_3	H	CN	H	H	58–60 B[a,o]		$C_{20}H_{24}N_2O_4$	67.39	6.79	7.86	67.33	6.81	7.91	50	P	10
35	3	OCH_3	H	H	CN	H	115–117 M		$C_{24}H_{28}N_2O_8$	61.01	5.97	5.93	61.01	5.99	5.79	21	E	0
36	3	OCH_3	H	H	CH_3	H	110–112 M		$C_{24}H_{31}NO_8$	62.45	6.77	3.04	62.38	6.91	3.10	62	E	10
37	3	OCH_3	H	H	Br	H	114–115 M		$C_{23}H_{28}BrNO_8$	52.46	5.38	2.66	52.45	5.33	2.71	59	E	10
38	3	Cl	H	H	Cl	H	114–116 M[n]		$C_{22}H_{25}Cl_2NO_7$	54.31	5.18	2.88	54.51	5.14	2.98	12	Ea	10
39	3	$CH(CH_3)_2$	H	H	CH_3	H		190–191 (0.3)	$C_{22}H_{31}NO_3$	73.89	8.74	3.92	73.60	8.69	3.90	39		0
40	3	H	CH_3	H	$CH(CH_3)_2$	H		188.5–189.5 (0.07)[p]	$C_{22}H_{31}NO_3$	73.89	8.74	3.92	74.06	8.78	3.73	42		10
41	3	CH_3	H	H	H	CH_3	104–106 M	192–194 (0.25)	$C_{24}H_{31}NO_7$	64.70	7.01	3.14	64.97	6.91	3.12	58	E-Et	40
42	3	CH_3	H	H	CH_3	H	125–127 M	185–186 (0.25)	$C_{24}H_{31}NO_7$	64.70	7.01	3.14	64.83	6.93	3.23	42	E	30
43	3	H	CH_3	H	CH_3	H	57–58 B		$C_{20}H_{27}NO_3$	72.93	8.26	4.25	72.91	8.38	4.35	55	Ea	20
44	3	OCH_3	H	$CH_2CH{=}CH_2$	H	H	50–52 B	202 (0.2)	$C_{22}H_{29}NO_4$	71.13	7.87	3.77	71.25	8.05	3.85	8	P	0
45	3	OCH_3	H	$CH{=}CHCH_3$	H	H	109–110 M		$C_{26}H_{33}NO_8$	64.07	6.82	2.87	64.16	6.61	2.95	...	E	10
46	3	CH_3	H	H	CH_3	CH_3	119–120 M	202–203 (0.3)	$C_{25}H_{33}NO_7$	65.34	7.24	3.05	65.24	7.20	3.12	49	E	40
47	3	CH_3	H	CH_3	CH_3	H	127–128 M	197–198 (0.2)	$C_{25}H_{33}NO_7$	65.34	7.24	3.05	65.39	7.18	2.91	8	E	30
48	3	CH_3	CH_3	H	CH_3	H	70–71 B	197 (0.25)	$C_{21}H_{29}NO_3$	73.41	8.51	4.08	73.41	8.37	4.42	18	Ea	0
49	3	CH_3	H	CH_3	H	CH_3	118–119 M	194–200 (0.25)	$C_{25}H_{33}NO_7$	65.34	7.24	3.05	65.28	7.12	2.82	41	E	70
50	3	OCH_3	H	OCH_3	OCH_3	H	49–51.5 B		$C_{21}H_{29}NO_6$	64.43	7.47	3.58	64.16	7.62	3.64	...	Et-P	110
51	3	OCH_3	H	Cl	OCH_3	H	105–107 M[p]		$C_{24}H_{30}ClNO_9$	56.30	5.90	2.73	56.26	6.01	2.69	...	E-Et	20
52	3	CH_3	CH_3	H	CH_3	CH_3	137–139 M		$C_{26}H_{35}NO_7$	65.94	7.45	2.96	65.83	7.36	2.90	48	E	20
53	3	CH_3	CH_3	CH_3	CH_3	CH_3	150–152 M		$C_{27}H_{37}NO_7$	66.51	7.65	2.87	66.51	7.90	2.87	60	E	20
54	4	OCH_3	H	H	H	H	54–55.5 B		$C_{20}H_{27}NO_4$	69.54	7.88	4.06	69.68	7.93	3.90	...	Ea-P	30
55	4	H	H	OCH_3	H	H	119–120 H		$C_{20}H_{28}ClNO_4$	62.90	7.39	3.67	62.88	7.38	3.80	...	M-Et	40
56	4	H	H	CH_3	H	H	116–118 M	195–196 (0.2)[q]	$C_{24}H_{31}NO_7$	64.70	7.01	3.14	64.79	7.01	3.07	36	E	0
57	4	OCH_3	H	H	OCH_3	H	120–122 M		$C_{25}H_{33}NO_9$	61.09	6.77	2.85	61.16	6.88	2.78	54	E	0
58	5	OCH_3	H	H	H	H	85–86 B		$C_{21}H_{29}NO_4$	70.15	8.13	3.90	70.28	8.11	3.87	10	Ea	30
59	5	OCH_3	H	H	OCH_3	H	73–74 B		$C_{22}H_{31}NO_5$	67.84	8.02	3.60	67.99	8.13	3.66	23	E	30
60	6	OCH_3	H	H	H	H	119–120 H		$C_{22}H_{32}ClNO_4$	64.43	7.87	3.42	64.51	7.73	3.08	9	M-Et	20
61	6	H	H	OCH_3	H	H	114–116 M		$C_{26}H_{35}NO_8$	63.78	7.21	2.86	63.83	7.31	3.14	...	E	20
62	8	OCH_3	H	H	H	H	61–62 B		$C_{24}H_{35}NO_4$	71.80	8.79	3.49	71.76	8.62	3.44	15	B-P	0

[a] See Experimental part. All compounds were prepared from amine X by general procedure 1, except **19**, which was prepared by general procedure 2, and **15**, which was obtained by hydrogenation of **14**. [b] Melting points given for B = free base, M = hydrogen maleate, Mm = maleate, H = hydrochloride. [c] Yields refer to analytically pure material and are probably not optimum. [d] E = ethanol, E-Et = ethanol–ether, Ea = ethyl acetate, Ea-P = ethyl acetate–petroleum ether, P = petroleum ether, M = methanol, M-Et = methanol–ether, Et-P = ether–petroleum ether, B-P = benzene–petroleum ether, A-Et = acetone–ether, A = acetone, Et = ether. [e] Tests in normotensive cats (halothane, N_2O, O_2 anesthesia, followed by 70 mg./kg. i.v. of chloralose). [ECG], venous, and arterial pressure were measured by insertion of catheters into the *Vena cava caudalis* and *Arteria iliaca communis*. Standard ECG leads were recorded with subcutaneous needle electrodes. The arterial and venous pressure as well as respiration were recorded *via* membrane pressure transducers on an ultraviolet galvanometer recorder. The compound (100 γ/kg.) was administered intravenously. The hypotensive activity of the compounds was recorded as the mean fall in arterial blood pressure measured from the time of administration until return to pre-administration levels. An arbitrary approximate scale of relative activities, expressed as per cent of three standard activities, was adopted to reproduce the results obtained. Compound **23** (serving as standard = 100%) produced a fall of mean arterial blood pressure of 60 mm. lasting, in several experiments, from at least 20 min. up to 90 min. The antihypertensive effects of **23** (and of other compounds of considerable activity) were much more pronounced than the hypotensive effects produced in normotensive animals. In acute neurogenic hypertensive dogs under nembutal anesthesia (30 mg./kg. i.v.), 50 γ/kg. of compound **23** produced a fall of mean arterial blood pressure of 55 mm. lasting for more than 6 hr. Compound **89** (serving as standard = 70%) produced a fall in mean arterial blood pressure in the normotensive animal of approximately 45 mm. lasting for approximately 60 min. Compound **5** (serving as standard = 40%) produced a fall in mean arterial blood pressure in the normotensive animal of approximately 35 mm. lasting for approximately 35 min. 0 = no activity at dose level administered. [f] See ref. 3a. [g] $n^{20}D$ 1.5543. [h] $n^{20}D$ 1.5554. [i] Purified through the hydrogen oxalate. [j] A compound analyzing as an isomer was also obtained and proved to be inactive. [k] $n^{20}D$ 1.5186. [l] $n^{20}D$ 1.5448. [m] Hydrogen maleate m.p. 121–123°. [n] Insoluble hydrohalide separated during work-up procedure. [o] Hydrogen maleate m.p. 130–132°. [p] $n^{20}D$ 1.5446. [q] $n^{20}D$ 1.5524.

TABLE III

N-SUBSTITUTED 2-(2-METHOXYPHENOXY)ALKYLAMINES[a]

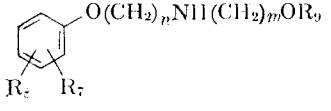


No.	W	X	R6	M.p., °C.[b]	B.p. (mm.), °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Yield, %[c]	Recrystn. solvent[d]	Activity, %
63	$CH_2CH(CH_3)$	$(CH_2)_3$	2-$CH_3OC_6H_4O$	130–132 H	167–180 (0.1)[f]	$C_{20}H_{28}ClNO_4$	62.91	7.39	3.67	63.10	7.37	3.94	7	M–Et	20
64	$CH_2CH(CH_3)$	$(CH_2)_3$	2,5-$(CH_3O)_2C_6H_3O$	66–68 B[g]	224 (0.2)[h]	$C_{21}H_{29}NO_5$	67.18	7.79	3.73	67.11	8.10	3.72	9	Et–P	30
65	$CH(CH_3)CH_2$	$(CH_2)_3$	2,5-$(CH_3O)_2C_6H_3O$	76–78 M[h]		$C_{25}H_{33}NO_9$	61.09	6.77	2.85	60.81	6.70	2.89	4	E–Et	30
66	$(CH_2)_7$	$CH(CH_3)CH_2CH_2$	2,5-$(CH_3O)_2C_6H_3O$	99–101 M	234–240 (0.5)[i]	$C_{25}H_{33}NO_9$	61.09	6.77	2.85	60.95	6.86	3.07	21	E–Et	20
67	$(CH_2)_2$	$CH_2CH(CH_3)CH_2$	2,5-$(CH_3O)_2C_6H_3O$	114–115 M[i]		$C_{25}H_{33}NO_9$	61.09	6.77	2.85	61.05	6.65	3.06	11	E	20
68	$(CH_2)_2$	$CH_2CH_2CH(CH_3)$	2,5-$(CH_3O)_2C_6H_3O$	96–98 M[i]		$C_{25}H_{33}NO_9$	61.09	6.77	2.85	61.25	6.66	3.06	45	E–Et	10
69	$(CH_2)_2$	$CH_2CH{=}CHCH_2$	2,5-$(CH_3O)_2C_6H_3O$	112–115 M[i]		$C_{25}H_{31}NO_9$	61.34	6.38	2.86	61.51	6.67	2.57	28	E	10
70	$(CH_2)_2$	$CH_2C{\equiv}CCH_2$	2-$CH_3OC_6H_4O$	115–117 M[i,j]		$C_{24}H_{27}NO_8$	63.01	5.95	3.06	63.03	5.99	3.14	4	E	0
71	$(CH_2)_2$	$(CH_2)_3$	$C_6H_5CH_2O$		186 (0.3)[i]	$C_{19}H_{25}NO_3$	72.35	7.99	4.44	72.49	7.91	4.10	..		30
72	$(CH_2)_2$	$(CH_2)_3$	2-$CH_3OC_6H_4CH_2O$		164–168 (2.4×10^{-3})[i]	$C_{20}H_{27}NO_4$	69.54	7.88	4.05	69.66	7.61	4.01	..		30
73	$(CH_2)_2$	$(CH_2)_3$	4-$CH_3OC_6H_4CH_2O$	70–71 M[i]		$C_{24}H_{31}NO_8$	62.45	6.77	3.04	62.41	6.69	2.72	15	A–Et	70
74	$(CH_2)_2$	$CH_2CH(OH)CH_2$	$C_6H_5CH_2O$		204 (0.003)[i]	$C_{19}H_{25}NO_4$	68.89	7.61	4.23	68.19	7.61	4.36	..		30

[a] All compounds were prepared according to general procedure I except **64**, which was obtained by reductive amination (see Experimental). [b] Footnote *b*, Table II. [c] Footnote *c*, Table II. [d] Footnote *d*, Table II. [e] Footnote *e*, Table II. [f] Prepared from amine XII. [g] Purified through hydrogen oxalate. [h] Prepared from amine XI. [i] Prepared from amine X. [j] Reaction performed with cooling and the product was purified through hydrogen oxalate; m.p. 172–173°.

TABLE IV

N-SUBSTITUTED ARYLOXYALKYLAMINES[a]

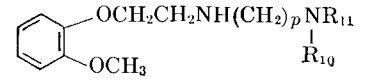


No.	R7	R8	n	m	R9	M.p., °C.[b]	B.p. (mm.), °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Yield, %[c]	Recrystn. solvent[d]	Activity,[e] %
75	3-OCH_3	H	2	3	2-$CH_3OC_6H_4$	108–110 H	186 (6×10^{-4})[f]	$C_{19}H_{25}ClNO_4$	62.03	7.13	3.81	62.16	7.11	3.63	8	Ea	0
76	4-OCH_3	H	2	3	2-$CH_3OC_6H_4$	129–130 H	196–198 (0.1)[f]	$C_{19}H_{26}ClNO_4$	62.03	7.13	3.81	61.79	7.02	3.74	23	Ea	0
77	2-CH_3	H	2	3	2-$CH_3OC_6H_4$	99–101 H	181–186 (0.35)[f]	$C_{19}H_{25}NO_3$	72.36	7.99	4.44	72.09	7.85	4.24	10	E–Et	20
78	2-$CONH_2$	H	2	3	2-$CH_3OC_6H_4$	103–104 B[f]		$C_{19}H_{24}N_2O_4$	66.25	7.02	8.14	66.18	6.91	8.43	9	Ea–P	0
79	2-$CH(CH_3)_2$	H	2	3	2-$CH_3OC_6H_4$	96–97 M	191.5–192.5 (0.25)[f,g]	$C_{25}H_{33}NO_7$	65.34	7.24	3.05	65.39	7.15	2.63	7	E	20
80	2-C_6H_5	H	2	3	2,5-$(CH_3O)_2C_6H_3$	115–116 M[h]		$C_{29}H_{33}NO_8$	66.52	6.35	2.68	66.39	6.41	2.80	69	E	10
81	2-OCH_3	H	2	3	3,4,5-$(CH_3O)_3C_6H_2CO$	91–93 M[i]		$C_{26}H_{35}NO_{11}$	58.32	6.21	2.62	58.33	6.47	2.52	38	M–Et	70
82	2-OCH_3	6-OCH_3	2	3	2-$CH_3OC_6H_4$	90–92 M[f]		$C_{24}H_{31}NO_9$	60.36	6.55	2.93	60.45	6.62	2.89	8	Ea	0
83	2-OCH_3	5-OCH_3	2	3	2,5-$(CH_3O)_2C_6H_3$	89–91 B[h]		$C_{21}H_{29}NO_6$	64.43	7.47	3.58	64.36	7.50	3.57	66	Ea–P	30
84	3-Cl	4-Cl	2	3	2,5-$(CH_3O)_2C_6H_3$	155–157 M[h]		$C_{33}H_{27}Cl_2NO_8$	53.51	5.27	2.71	53.97	5.30	2.49	52	E	0
85	2-OCH_3	H	3	3	2-$CH_3OC_6H_4$	120–122 H[f]		$C_{20}H_{25}ClNO_4$	62.91	7.39	3.67	62.92	7.16	3.55	10	M–Et	20
86	2-OCH_3	H	4	4	4-$CH_3OC_6H_4$	106–107 H[j]		$C_{22}H_{32}ClNO_4$	64.43	7.87	3.42	64.27	7.79	3.39	10	E	0

[a] All compounds were prepared by general procedure I, except 81 (see Experimental). [b] Footnote *b*, Table II. [c] Footnote *c*, Table II. [d] Footnote *d*, Table II. [e] Footnote *e*, Table II. [f] Prepared from amine XII. [g] $n^{20}D$ 1.5472. [h] Prepared from amine XI. [i] Prepared from amine XLVIII. [j] Prepared from amine XIII.

TABLE V

N-SUBSTITUTED 2-(2-METHOXYPHENOXY)ETHYLAMINES[a]

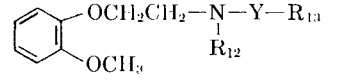


No.	p	R_{10}	R_{11}	M.p., °C.[b]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Yield, %[c]	Recrystn. solvent[d]	Activity,[e] %
87	2	H	4-$CH_3C_6H_4SO_2$	119–120 M	$C_{22}H_{28}N_2O_3S$	54.99	5.87	5.83	55.21	5.82	5.81	55	E-Et	20
88	3	H	$C_6H_5SO_2$	105–107 M	$C_{22}H_{28}N_2O_3S$	54.99	5.87	5.83	54.88	6.17	5.85	16	E	30
89	3	H	4-$CH_3C_6H_4SO_2$	108–110 M	$C_{23}H_{30}N_2O_3S$	55.85	6.12	5.67	55.84	6.18	5.68	67	M-Et	70
90	3	CH_3	4-$CH_3C_6H_4SO_2$	118–120 M	$C_{24}H_{32}N_2O_3S$	56.66	6.34	5.51	56.83	6.55	5.79	35	E	30
91	3	H	2,5-$(NO_2)ClC_6H_3SO_2$	112–114 M	$C_{22}H_{26}ClN_3O_{10}S$	47.18	4.68	7.50	47.36	4.56	7.35	4	Ea	30
92	3	H	2,5-$(NH_2)ClC_6H_3SO_2$	121–123 M[f]	$C_{22}H_{28}ClN_3O_3S$	49.84	5.32	7.93	50.08	5.37	7.86	20	Ea	70
93	3	H	4-$CH_3C_6H_4CO$	123–125 M	$C_{24}H_{30}N_2O_7$	62.87	6.60	6.11	62.65	6.59	5.85	28	Ea	30
94	3		$C_6H_4(CO)_2$	149–151 H[g]	$C_{20}H_{23}ClN_2O_4$	61.45	5.93	7.17	61.19	6.27	6.95	12	E	40
95	2	H	2-$CH_3OC_6H_4$	97–98 B[h]	$C_{18}H_{24}N_2O_3$	68.36	7.62	8.86	68.31	7.53	8.48	12	P or A	30
96	3	H	2-$CH_3OC_6H_4OCH_2CH_2$	62–63 B[h,i]	$C_{21}H_{30}N_2O_4$	67.33	8.07	7.48	67.16	8.10	7.43	13	P	20

[a] All compounds except **92** were prepared according to general procedure 1. During the work-up procedure compounds **87–93** were washed with $KHCO_3$ solution instead of 2 *N* NaOH. Amine X was used for the preparation of compounds, **87**, **91**, and **93–95**. [b] Footnote *b*, Table II. [c] Footnote *c*, Table II. [d] Footnote *d*, Table II. [e] Footnote *e*, Table II. [f] Prepared by reduction of compound **91**. [g] Purified through the hydrogen oxalate. [h] During the work-up procedure the final product was extracted into hydrochloric acid from the chloroform solution. [i] Amine III was used.

TABLE VI

TERTIARY AMINES OR AMIDES[a]

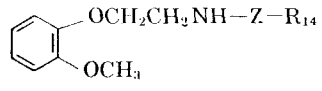


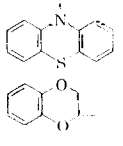
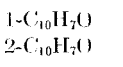
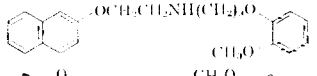
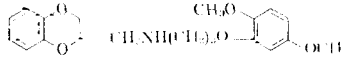
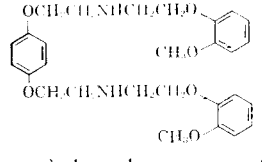
No.	R_{12}	Y	R_{13}	M.p., °C.[b]	B.p. (mm.), °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Yield, %[c]	Recrystn. solvent[d]	Activity,[e] %
97	CH_3CO	$(CH_2)_3$	2-$CH_3OC_6H_4O$	65–66[a]		$C_{21}H_{27}NO_5$	67.54	7.29	3.75	67.45	7.02	3.63	23	P	0
98	NH_2	$(CH_2)_3$	2-$CH_3OC_6H_4O$	109–111 M	194–210 (0.3)[f]	$C_{23}H_{30}N_2O_8$	59.71	6.54	6.06	59.84	6.61	6.07	8	E	20
99	$CH_3(CH_2)_3$	$(CH_2)_3$	2-$CH_3OC_6H_4O$	93–95 H	194–203 (0.12)[g]	$C_{23}H_{34}ClNO_4$	65.13	8.08	3.30	65.16	8.27	3.13	20	M-Et	0
100	$CH_3(CH_2)_3$	$CH_2C{\equiv}CCH_2$	2-$CH_3OC_6H_4O$	65–66 M[g,h]		$C_{28}H_{35}NO_8$	65.48	6.87	2.73	65.31	6.86	2.95	20	M-Et	0
101	$HO(CH_2)_2$	$(CH_2)_3$	2-$CH_3C_6H_4O$		198–199 (0.15)[h,i]	$C_{21}H_{29}NO_4$	70.15	8.13	3.90	70.18	8.03	3.82	20		0
102	$Cl(CH_2)_2$	$(CH_2)_3$	2-$CH_3C_6H_4O$	115–117 H[a]		$C_{21}H_{29}Cl_2NO_3$	60.85	7.05	3.38	60.70	6.85	3.33	20	M-Et	0
103	CH_3CO	$(CH_2)_3$	2,5-$(CH_3O)_2C_6H_3O$	47–50[a]		$C_{22}H_{29}NO_6$	65.49	7.25	3.47	65.36	7.47	3.28	34	M	0
104	CH_3CH_2OCO	$(CH_2)_3$	2,5-$(CH_3O)_2C_6H_3O$	61–63	234 (0.15)[a]	$C_{23}H_{31}NO_7$	63.72	7.21	3.23	63.89	7.22	3.26	42	Et	0
105	$C_6H_5CH_2$	$(CH_2)_3$	2,5-$(CH_3O)_2C_6H_3O$	90–91 M	254–262 (0.25)[j]	$C_{31}H_{37}NO_9$	65.59	6.57	2.47	65.70	6.52	2.38	67	E-Et	0
106	CH_3	$CH(CH_3)CO$	2-$CH_3OC_6H_4NH$	148–150 M[k]		$C_{24}H_{30}N_2O_8$	60.75	6.37	5.90	60.89	6.07	5.77	52	E	0

[a] Compounds **99** and **100** were prepared by general procedure 1; **98**, **101**, **105**, and **106** by general procedure 2; **97**, **103**, and **104** by acylation of compounds **5** and **23**; **102** by chlorination of **101** (see Experimental). [b] Footnote *b*, Table II. [c] Footnote *c*, Table II. [d] Footnote *d*, Table II. [e] Footnote *e*, Table II. [f] Prepared from hydrazine IV. [g] Prepared from amine II. [h] Unreacted secondary amine was removed as the *p*-toluenesulfonamide. [i] $n^{20}D$ 1.5508; prepared from compound **8**. [j] Prepared from amine I. [k] Prepared from compound **115**.

TABLE VII

N-SUBSTITUTED 2-(2-METHOXYPHENOXY)ETHYLAMINES[a]



No.	Z	R_{14}	M.p., °C.[b]	Formula	Calcd., %			Found, %			Yield, %[c]	Recrystn. solvent[d]	Activity,[e] %
					C	H	N	C	H	N			
107	$CH_2CH(OH)CH_2$	C_6H_5O	102–103 B	$C_{18}H_{23}NO_4$	68.10	7.30	4.42	68.22	7.23	4.73	17	B–P	30
108	$CH_2CH(OH)CH_2$	$2\text{-}CH_3OC_6H_4O$	93–94 B	$C_{19}H_{25}NO_5$	65.69	7.25	4.03	65.51	7.22	4.20	10	Ea	30
109	$CH_2CH(OH)CH_2$	$4\text{-}CH_3OC_6H_4O$	100–101 H	$C_{19}H_{26}ClNO_5$	59.40	6.83	3.63	59.60	6.89	3.35	..	Ea	100
110	$CH_2CH(OH)CH_2$	$2\text{-}CH_3C_6H_4O$	74–75 B	$C_{19}H_{25}NO_4$	68.88	7.61	4.23	68.74	7.52	4.13	12	P	0
111	$CH_2CH(OH)CH_2$	$2,5\text{-}(CH_3O)_2C_6H_3O$	101–102 M	$C_{24}H_{31}NO_{10}$	58.41	6.33	2.84	58.42	6.21	2.63	5	E Et	0
112	$CH_2CH(OH)CH_2$	C_5H_9O	70–71 B	$C_{17}H_{27}NO_4$	65.98	8.80	4.53	66.18	8.76	4.31	5	P	30
113	$CH_2CH(OH)CH_2$	$C_6H_{11}O$		$C_{18}H_{29}NO_4$[f]	66.85	9.04	4.33	67.15	9.12	4.49	..		0
114	$CH_2CH(OH)CH_2$	$2\text{-}(C_4H_7O)CH_2O$	117–119[g]	$C_{38}H_{58}N_2O_{16}$	57.12	7.32		56.85	7.30		..	E	0
115	$CH(CH_3)CO$	$2\text{-}CH_3OC_6H_4NH$	160–163 H[h]	$C_{19}H_{25}ClN_2O_4$	59.91	6.62	7.36	59.85	6.57	6.93	12	E Et	40
116	$CH(CH_3)CO$	$2,5\text{-}(CH_3O)_2C_6H_3NH$	130–132 M[h]	$C_{24}H_{30}N_2O_9$	58.76	6.17	5.71	58.97	6.24	5.48	62	E	20
117	CH_2CH_2CO	$2\text{-}CH_3OC_6H_4NH$	133–135 M[h]	$C_{23}H_{28}N_2O_8$	59.99	6.13	6.08	59.78	6.04	6.09	33	E	10
118	$CH_2CH_2CH_2CO$	$2\text{-}CH_3OC_6H_4NH$	110–112 M[h]	$C_{24}H_{30}N_2O_8$	60.75	6.37	5.90	60.51	6.48	6.07	4	E	10
119	CH_2CH_2CO	$C_6H_5CH_2NH$	148–150 H[h]	$C_{19}H_{25}ClN_2O_3$	62.54	6.91	7.68	62.56	6.87	7.54	5	A	20
120	CH_2CH_2CO	$2\text{-}CH_3OC_6H_4OCH_2CH_2NH$	104–106 M[h]	$C_{25}H_{32}N_2O_9$	59.50	6.40	5.55	59.12	6.53	5.48	9	M Et	30
121	$(CH_2)_3$	$4\text{-}CH_3C_6H_4S$	126–128 M	$C_{23}H_{29}NO_6S$	61.73	6.53	3.13	61.66	6.64	2.84	32	E	20
122	$(CH_2)_3$		132–134 M	$C_{28}H_{30}N_2O_6S$	64.35	5.79	5.36	64.36	5.81	5.27	78	E	20
123	CH_2		116–118 M	$C_{22}H_{25}NO_5$	61.25	5.84	3.25	60.99	5.86	3.45	..	M–Et	10
124	$(CH_2)_3$	$1\text{-}C_{10}H_7O$	62–63 B	$C_{22}H_{25}NO_3$	75.18	7.17	3.99	75.15	7.21	4.41	5	P	0
125	$(CH_2)_3$	$2\text{-}C_{10}H_7O$	73–74 B	$C_{22}H_{25}NO_3$	75.18	7.17	3.99	75.15	7.28	4.27	..	P	0
126			190–192 H	$C_{22}H_{26}ClNO_3$	68.11	6.76	3.61	68.23	6.66	3.18	15	E	0
127			116–118 M	$C_{24}H_{29}NO_9$	60.62	6.15	2.95	61.01	6.08	2.83	7	E	30
128			196–198 H	$C_{28}H_{38}Cl_2N_2O_6$	59.05	6.73		59.16	6.90		..	M–Et	0

[a] All compounds have been prepared according to general procedure 1, except compounds **109**, **110**, **112**–**115**, and **119**, where general procedure 2 was employed (see Experimental). In all cases amine X was used except for compound **126** (amine XII) and **127** (amine XI). [b] Footnote *b*, Table II. [c] Footnote *c*, Table II. [d] Footnote *d*, Table II. [e] Footnote *e*, Table II. [f] B.p. 176° (0.2 mm.). [g] Dihydroxy maleate. [h] Washed with $KHCO_3$ solution instead of 2 *N* NaOH during the work-up procedure.

standard procedures either from a phenol and an alkylene α,ω-dihalide, or by halogenation of the corresponding alcohols. Some of the primary amines used were prepared by an improved Gabriel method from the corresponding bromo compounds.

The tertiary nitrogen derivatives listed in Table VI were obtained by alkylation or acylation of the corresponding secondary amines. General methods of preparation and any deviations from them are fully described in the Experimental part.[11]

Experimental[12]

Aryloxyalkyl Halides (Table VIII). General Procedure.[13]—The appropriate phenol (0.20 mole) and the alkylene α,ω-dihalide (0.25 mole) (in the case of ethylene 1,2-dibromide, 0.40 mole) were heated to 100° with vigorous stirring, and 125 ml. of 1.6 *N* NaOH was added to the mixture during 30 min. Vigorous stirring and heating were continued until the pH approached 7. The The cold reaction mixture, consisting of two layers, was taken up in ether or chloroform, the aqueous layer separated (up to 80% of unreacted phenol can be recovered from the aqueous phase), and the organic phase thoroughly was washed with 2 *N* NaOH (in some cases 20% NaOH solution was necessary to remove unreacted phenol) and once with saturated NaCl solution and dried ($MgSO_4$), and the solvent was evaporated. The product was obtained by distillation; unreacted alkylene α,ω-dihalide was collected in the forerun.

N-Substituted Aryloxyalkylamines (Tables II-VII). General Procedure 1.—The appropriate amine (0.40 mole) was heated at 50° in an oil bath. During an interval of 20–30 min., 0.10 mole of the corresponding substituted alkyl bromide was added with stirring, keeping the bath temperature between 45–55°. Generally at the end of the addition the mixture became viscous and an amine hydrohalide separated out. The mixture was stirred and heated for another 1–1.5 hr. and, after cooling, was dissolved in the appropriate amount of chloroform. The chloroform solution was extracted several times with 2 *N* HCl to remove excess primary amine,[14] washed with 100 ml. each of 2 *N* NaOH and saturated NaCl solution, and dried (K_2CO_3 or $MgSO_4$). The solvent was evaporated and the residue was distilled, crystallized, or converted into a suitable salt. The use of a substituted alkyl chloride required bath temperatures of 120–130° and a reaction time of up to 4 hr.

General Procedure 2.—The appropriate amine (0.10 mole), a substituted alkyl halide (0.10 mole), and K_2CO_3 (0.10 mole) (or $KHCO_3$) were refluxed in 250 ml. of ethanol for 18 hr.; the mixture was cooled and filtered, and the solvent was removed by distillation (**19** crystallized on cooling from the ethanolic solution). The residual material was purified as described in general procedure 1.

N-[2-(2-Methoxyphenoxy)ethyl]-N-[3-(2-methylphenoxy)propyl]-2-hydroxyethylamine (**101**) was prepared by general procedure 2 from amine **8** and chloroethanol. Unreacted secondary amine was removed *via* the *p*-toluenesulfonamide.

N-[2-(2-Methoxyphenoxy)ethyl]benzylamine (I) was prepared by general procedure 1 from benzylamine and bromide **129** (bath temperature 90–110°); b.p. 160–161° (0.3 mm.), $n^{20}D$ 1.5699, yield 79%.

N-[2-(2-Methoxyphenoxy)ethyl]-*n*-butylamine (II) was prepared by general procedure 1 from *n*-butylamine and bromide **129**; b.p. 107° (0.15 mm.), $n^{20}D$ 1.5108, yield 71%, hydrochloride m.p. 138–139° (acetone–ether).

Anal. Calcd. for $C_{13}H_{22}ClNO_2$: C, 60.10; H, 8.54; N, 5.39. Found: C, 59.78; H, 8.28; N, 5.21.

N-[2-(2-Methoxyphenoxy)ethyl]propylenediamine (III) was prepared according to general procedure 1 from propylenediamine and bromide **129**. During the work-up procedure the whole product was basified with 20% NaOH solution and extracted with ether. The product had b.p. 142° (0.6 mm.), yield 21%.

Anal. Calcd. for $C_{12}H_{20}N_2O_2$: N, 12.44. Found: N, 12.53.

2-(2-Methoxyphenoxy)ethylhydrazine (**IV**).—Bromide **129** (34.6 g., 0.15 mole) in 250 ml. ethanol was added over a period of 1 hr. to a solution of hydrazine hydrate (75 g., 1.50 moles) in 150 ml. of ethanol. The solution was refluxed for 16 hr. The solvent and excess hydrazine were evaporated under reduced pressure, and a small quantity of water and solid NaOH were added to the residue until two layers appeared. The product was extracted with chloroform and dried (K_2CO_3), and the solvent was evaporated. The residue was distilled, b.p. 146–150° (3 mm.), yield 20.7 g. (76%), hydrochloride m.p. 108–110°.

N-[2-(2-Methoxyphenoxy)ethyl]phthalimide (**V**).[15]—Bromide **129** (36 g., 0.156 mole) and phthalimide (27.3 g., 0.186 mole) in 100 ml. of dimethylacetamide were heated to 90° and a solution of KOH (10.45 g., 0.186 mole) in 30 ml. of methanol was added over a period of 25 min. The mixture was stirred and heated further for 1.5 hr. The cold mixture was poured into 300 ml. of water and the slowly solidifying material was filtered; the filter cake was treated with aqueous K_2CO_3 (200 ml., 10%) with heating and vigorous stirring for 10 min. The warm slurry was filtered, washed thoroughly with water, dried, and recrystallized from ethanol to give the product, m.p. 102–104.5°, yield 23 g. (57%).

N-[3-(2-Methoxyphenoxy)propyl]phthalimide (**VI**) was prepared similarly; m.p. 89–90°, yield 69% (from bromide **139**).

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.45; H, 5.50. Found: C, 69.23; H, 5.46.

N-[3-(2,5-Dimethoxyphenoxy)propyl]phthalimide (**VII**) was also prepared similarly; m.p. 130–132° (propanol), yield 75% (from bromide **160**).

N-(3-Bromopropyl)phthalimide (**VIII**).[16]—Potassium phthalimide (70 g., 0.378 mole) and 1,3-trimethylenedibromide (310 g., 1.534 moles) were heated for 1.5 hr. at 180°. Excess trimethylene dibromide was blown off with steam, the remaining mixture was filtered, and the solid was triturated with ethanol and filtered. The solid obtained by evaporation of the ethanol was extracted in a Soxhlet with petroleum ether (b.p. 40–60°). From the extract 16 g. of material was obtained which after recrystallization from petroleum ether (b.p. 40–60°) had m.p. 70–72°, yield 15 g. (14%).

4-(2-Methoxyphenoxy)butyronitrile (**IX**).—Sodium (34.6 g., 1.50 g.-atoms) was finely powdered in 300 ml. of boiling toluene. Guaiacol (186 g., 1.50 moles) in 200 ml. of dimethylacetamide was slowly added, followed by 4-chlorobutyronitrile (162 g., 1.57 moles). The mixture was stirred vigorously and the temperature was kept at 115° for 4 hr. The cold mixture was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform, the solution was washed with water and dried ($MgSO_4$), and the solvent was evaporated. The product had b.p. 113–116° (0.25 mm.), m.p. 31–33°, yield 212 g. (74%).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 68.89; H, 6.74.

2-(2-Methoxyphenoxy)ethylamine (**X**).[3a]—Phthalimide V (21 g., 0.071 mole) and hydrazine hydrate (3.55 g., 0.071 mole) in 70 ml. of absolute ethanol were heated on the steam bath for 45 min. A thick white precipitate appeared, to which 20 ml. of 18% HCl was added. Heating was continued for 1 hr.; solid material was filtered off and washed with ethanol, the solvent was evaporated from the filtrate, and the residue was basified with a 20% NaOH solution. The mixture was extracted with chloroform and dried (K_2CO_3), and the solvent was evapo-

(11) Methods of preparation of a few halogen compounds not mentioned in this publication will be described in the forthcoming publication.[8] N-(3-Chloropropionyl)benzylamine was obtained from Rona Laboratories, London, W.1; 2-(2-chloroethoxy)naphthalene was prepared according to G. R. Clemo and W. H. Perkin, Jr., *J. Chem. Soc.*, 642 (1922); 2-(bromomethyl)-1,4-benzodioxane was prepared according to C. Milani, R. Landi-Vittory, and G. B. Marini-Bettòlo, *Rend. Ist. Super Sanità*, **22**, 207 (1959); *Chem. Abstr.*, **54**, 1522*h* (1960); 10-(3-bromopropyl)phenothiazine was prepared according to O. Hromatka, F. Sauter, and L. H. Schlager, *Monatsh. Chem.*, **88**, 193 (1957); E. F. Godefroi and E. L. Wittle, *J. Org. Chem.*, **21**, 1163 (1956).

(12) Melting points are corrected. Most of them were taken on an Electrothermal apparatus, Series 1A.

(13) C. S. Marvel and A. L. Tanenbaum, *J. Am. Chem. Soc.*, **44**, 2647 (1922); "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 435.

(14) In some cases this separation was not possible because the final product was extractable with HCl from chloroform. This is indicated in the tables. In other cases the extraction with 2 *N* HCl produced a proportion of a hydrohalide which was insoluble in chloroform. It was filtered, crystallized, and identified separately, or basified and combined with the residue obtained at the end of the original work-up procedure.

(15) H. K. Müller and G. Rieck, *J. prakt. Chem.*, **9**, 30 (1959).

(16) An improved method has been published since by C.-Y. Yüan, C.-T. Lin, and J.-H. Liu, *Hua Hsüeh Hsueh Pao*, **25**, 183 (1959); *Chem. Abstr.*, **54**, 4405*c* (1960).

TABLE VIII
PHYSICAL PROPERTIES OF ARYLOXYALKYL HALIDES
Ar—O—$(CH_2)_n$—X

No.	Ar	n	X	Yield, %[a]	B.p. (mm.), °C.[b]	M.p., °C.[b]	$n^{20}D^{b}$
129	2-$CH_3OC_6H_4$	2	Br	60	151–152 (18.5)[c]	38–41	
130	3-$CH_3OC_6H_4$	2	Br	22	95–96 (0.35)		
131	4-$CH_3OC_6H_4$	2	Br	48	102–104 (0.25)[d]	47–49 (methanol)	
132	2-$(CH_3)_2CHC_6H_4$	2	Br	16	84–86 (0.3)		1.5346
133	2-$C_6H_5C_6H_4$	2	Br	25	121–124 (0.2)		
134	2,6-$(CH_3O)_2C_6H_3$	2	Br	46	117 (0.8)[e]		
135	2,5-$(CH_3O)_2C_6H_3$	2	Br	46	117 (0.15)[e]		
136	3,4-$(CH_3)_2C_6H_3$	2	Br	12	100–102 (0.5)		
137	3,4-$Cl_2C_6H_3$	2	Br	50	140–142 (0.05)		1.5830
138	C_6H_5	3	Br	45	136 (18)[g,h]		
139	2-$CH_3OC_6H_4$	3	Br	74	104–114 (0.3)[i,j]		
140	3-$CH_3OC_6H_4$	3	Br	68	113–114 (0.5)		
141	4-$CH_3OC_6H_4$	3	Br	39	98 (0.3)[k,l]		
142	2-ClC_6H_4	3	Br	49	89–96 (0.2)[m,n]		
143	4-ClC_6H_4	3	Br	64	110–111 (0.3)[k,o]		1.5584
144	2-$CH_3C_6H_4$	3	Br	44	90 (0.3)[p]		
145	3-$CH_3C_6H_4$	3	Br	64	88–90 (0.2)[k,q]		1.5395
146	4-$CH_3C_6H_4$	3	Br	61	100–102 (0.6)[p]		
147	2-$NO_2C_6H_4$	3	Br	41	144–152 (0.5)[m]	36.5–37.5 (methanol or petr. ether)	
148	4-$NO_2C_6H_4$	3	Br	34	150–151 (0.2)[m,o,r]		1.5943
149	3-$CF_3C_6H_4$	3	Br	61	78 (0.25)[s]		
150	4-$C_6H_{11}C_6H_4$	3	Br	32	150–154 (0.3)	40–42	
151	4-$(CH_3)_3CC_6H_4$	3	Br	33	118–120 (0.4)		1.5269
152	4-$C_6H_5C_6H_4$	3	Br	38	165–168 (0.4)	67–69 (ethanol)	
153	4-$C_6H_5CH_2OC_6H_4$	3	Br	51	170–174 (0.35)	59–60 (ethanol)	
154	1-$C_{10}H_7$	3	Br	12	144 (0.55)		
155	2-$C_{10}H_7$	3	Br	31	152–154 (0.35)	53–54 (methanol)[t]	
156	2,4-$(CH_3O)(CH_2{=}CHCH_2)C_6H_3$	3	Br	40	124–125 (0.4)		
157	2,4-$(CH_3O)(CH_3CH{=}CH)C_6H_3$	3	Br	40	134–135 (0.12)		1.5742
158	2,3-$(CH_3O)_2C_6H_3$	3	Br	38	140–141 (0.25)		
159	2,4-$(CH_3O)_2C_6H_3$	3	Br	55	132–134 (0.5)		1.5470
160	2,5-$(CH_3O)_2C_6H_3$	3	Br	61	125–126 (0.3)	58–61 (methanol)[f]	
161	2,6-$(CH_3O)_2C_6H_3$	3	Br	25	116–118 (0.5)		
162	3,4-$(CH_3O)_2C_6H_3$	3	Br	41	149 (0.25)		1.5524
163	3,5-$(CH_3O)_2C_6H_3$	3	Br	32	132–142 (0.25)		1.5508[u]
164	2,5-$(CH_3)_2C_6H_3$	3	Br	49	104–109 (0.7)		1.5372
165	2,6-$(CH_3)_2C_6H_3$	3	Br	33	97–100 (0.45)		1.5336[v,n]
166	3,5-$(CH_3)_2C_6H_3$	3	Br	55	100–104 (0.4)		1.5381
167	2,4-$[(CH_3)_2CH]CH_3C_6H_3$	3	Br	19	102–104 (0.2)		1.5277
168	3,5-$CH_3[(CH_3)_2CH]C_6H_3$	3	Br	44	97 (1)		1.5293
169	2,5-$(CH_3O)BrC_6H_3$	3	Br	57	140–142 (0.35)	55–59[f]	
170	2,4-$(CH_3O)(CH_3CO)C_6H_3$	3	Br	45	150–160 (5×10^{-3})		1.5733[y]
171	2,5-$Cl_2C_6H_3$	3	Br	52	170–174 (14)		
172	2,5-$(CH_3O)CH_3C_6H_3$	3	Br	51	114–116 (0.3)		1.5450[z]
173	2,5-$(CH_3CH_2O)_2C_6H_3$	3	Br	26	140 (0.25)		1.5302[f]
174	2,5-$(CH_3CH_2O)(CH_3O)C_6H_3$	3	Br	43	158 (2)		1.5377[f]
175	2,5-$(CH_3O)(CH_3CH_2O)C_6H_3$	3	Br	58	130 (0.25)		1.5414[f]
176	2,5-$(CH_3O)(CH_3CO)C_6H_3$	3	Br	32	156–160 (3×10^{-3})	80–84[aa]	
177	2,4-$(CH_3O)(CN)C_6H_3$	3	Br	22	150–166 (8×10^{-3})	98–99[bb]	
178	2,3,6-$(CH_3)_3C_6H_2$	3	Br	18	96–97 (0.3)		
179	2,4,6-$(CH_3)_3C_6H_2$	3	Br	21	102–106 (0.7)		1.5272
180	2,4,5-$(CH_3)_3C_6H_2$	3	Br	32	120–123 (0.8)		
181	2,3,5-$(CH_3)_3C_6H_2$	3	Br	33	109–111 (0.25)		
182	2,4,5-$(CH_3O)_3C_6H_2$	3	Br	25	152 (0.4)	83–85[f]	
183	2,5,4-$(CH_3O)_2ClC_6H_2$	3	Br	39	140–142 (5×10^{-3})	104–107 (ethanol)[f]	
184	2,4,5,6-$(CH_3)_4C_6H$	3	Br	9	168–170 (10)	49–50 (methanol)	
185	2,3,4,5,6-$(CH_3)_5C_6$	3	Br	12	130–140 (0.3)	54–56 (methanol)	
186	2-$CH_3OC_6H_4$	4	Br	74	118–124 (0.35)	62–63 (methanol)	
187	4-$CH_3OC_6H_4$	4	Br	28	123 (0.4)	42–43.5 (methanol)[cc]	
188	4-$CH_3C_6H_4$	4	Br	73	108–110 (0.25)	29–31	
189	2,5-$(CH_3O)_2C_6H_3$	4	Br	34	150–152 (0.3)		
190	2-$CH_3OC_6H_4$	5	Br	30	114–117 (0.1)[dd]		
191	2,5-$(CH_3O)_2C_6H_3$	5	Br	58	148–150 (0.2)		1.5405
192	2-$CH_3OC_6H_4$	6	Cl	40	122–127 (0.15)		
193	4-$CH_3OC_6H_4$	6	Cl	35	130–132 (0.2)		
194	2-$CH_3OC_6H_4$	8	Br	49	149–152 (0.1)		

TABLE VIII (*Continued*)

Ar—O—R—X

No.	Ar	R	X	Yield, %[a]	B.p. (mm.), °C.[b]	M.p., °C.[b]
195	2,5-$(CH_3O)_2C_6H_3$	$CH_2CH{=}CHCH_2$	Cl	7	131–151 (0.35)[ee]	
196	2-$CH_3OC_6H_4$	$CH_2C{\equiv}CCH_2$	Cl	48	124–130 (0.45)[ff]	61–62 (methanol)
197	2,5-$(CH_3O)_2C_6H_3$	$CH_2CH(CH_3)CH_2$	Halogen	18	128–135 (0.3)[gg]	

[a] Yields are not necessarily optimum. [b] These constants do not refer to analytically pure materials. [c] A. Wohl and E. Berthold, *Chem. Ber.*, **43**, 2175 (1910). [d] B. Belleau, *J. Med. Pharm. Chem.*, 1, 327 (1959). [e] A. P. Swain and S. K. Naegele, *J. Am. Chem. Soc.*, **76**, 5091 (1954). [f] For starting phenol see ref. 23. [g] See ref. 13. [h] P. Rumpf, *Bull. soc. chim. France*, [5] **5**, 871 (1938). [i] Y. M. Beasley, V. Petrow, and O. Stephenson, *J. Pharm. Pharmacol.*, **10**, 47 (1958). [j] E. Merck, German Patent 184,968 (1902); *Chem. Zentr.*, II, 861 (1907). [k] N. J. Leonard and W. C. Wildman, *J. Am. Chem. Soc.*, **71**, 3089 (1949). [l] A. W. Nineham, *J. Chem. Soc.*, 2601 (1953). [m] P. E. Gagnon, O. Nadeau, and R. Coté, *Can. J. Chem.*, **30**, 592 (1952). [n] J. D. Genzer, C. P. Huttrer, and G. C. Van Wessem, *J. Am. Chem. Soc.*, **73**, 3159 (1959). [o] P. E. Gagnon, J. L. Boivin, and J. Giguère, *Can. J. Res.*, **28B**, 352 (1950). [p] R. E. Rindfusz, P. M. Ginnings, and N. L. Harnack, *J. Am. Chem. Soc.*, **42**, 157 (1920). [q] P. A. Boivin, P. E. Gagnon, E. Renaud, and W. A. Bridgeo, *Can. J. Chem.*, **30**, 994 (1952). [r] J. N. Ashley, R. F. Collins, M. Davis, and N. E. Sirett, *J. Chem. Soc.*, 3298 (1958). [s] Phenol bought from Maumee Chemical Co., Toledo 5, Ohio. [t] P. M. Pope and D. Woodcock, *J. Chem. Soc.*, 1721 (1954). [u] Phenol prepared according to K. Freudenberg, H. Fikentscher, and W. Weiner, *Ann. Chem.*, **442**, 309 (1925). [v] V. Petrow, O. Stephenson, and A. J. Thomas, *J. Pharm. Pharmacol.*, **8**, 666 (1956). [w] J. P. Ryan and P. R. O'Connor, *J. Am. Chem. Soc.*, **74**, 5866 (1952). [x] Phenol prepared according to E. M. Hindmarsh, I. Knight, and R. Robinson, *J. Chem. Soc.*, 940 (1917). [y] Phenol prepared according to A. Y. Berlin, S. M. Sherlin, and T. A. Serebrennikova, *Zh. Obshch. Khim.*, **19**, 759 (1949); *Chem. Abstr.*, 44, 1058 (1950). [z] Phenol prepared according to A. A. Goldberg and H. S. Turner, *J. Chem. Soc.*, 111 (1946). [aa] Phenol prepared according to R. Schwarz and K. Cpaek, *Monatsh.*, **83**, 883 (1952). [bb] Phenol prepared according to E. Marcus, *Chem. Ber.*, **24**, 3650 (1891). [cc] N. J. Leonard, D. L. Felley, and E. D. Nicolaides, *J. Am. Chem. Soc.*, **74**, 1700 (1952). [dd] C. L. Leese and R. A. Raphael, *J. Chem. Soc.*, 2725 (1950); see also footnotes *i*, *j*, and *l*. [ee] As starting material 1,4-dichloro-2-butene was used. [ff] As starting material 1,4-dichloro-2-butyne was used. [gg] 1-Chloro-2-methyl-3-bromopropane was used to give a mixed halide.

rated. The residual oil was distilled, b.p. 96–98° (0.4 mm.), $n^{20}D$ 1.5462, yield 9.4 g. (79%). The free base readily formed a carbonate on exposure to air; hydrogen maleate, m.p. 100–101° (ethanol).

Anal. Calcd. for $C_9H_{13}NO_2{\cdot}C_4H_4O_4$: C, 55.09; H, 6.05; N, 4.94. Found: C, 54.98; H, 6.11; N, 4.72.

The following amines (XI and XII) were prepared in the same way: **3-(2,5-dimethoxyphenoxy)propylamine** (**XI**), b.p. 128–131° (0.12 mm.), $n^{20}D$ 1.5384, yield 65% (from phthalimide VII); **3-(2-methoxyphenoxy)propylamine** (**XII**), b.p. 108–111° (0.8 mm.), yield 87% (from phthalimide VI).

Compound XII was also prepared by catalytic hydrogenation of 3-(2-methoxyphenoxy)propionitrile[17] in glacial acetic acid over platinum oxide or 10% palladium–charcoal under 10 atm. pressure. It had b.p. 97–99° (0.15 mm.), $n^{20}D$ 1.5403, yield 85%.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 66.28; H, 8.35. Found: C, 66.53; H, 8.23.

4-(2-Methoxyphenoxy)butylamine (**XIII**) was prepared in the same way as XII by catalytic hydrogenation from nitrile IX; it had b.p. 122° (0.75 mm.), yield 70%.

N-(3-Bromopropionyl)-*o*-anisidine (**XIV**).—To *o*-anisidine (43 g., 0.350 mole) in 125 ml. of dry ether was added with cooling and stirring 3-bromopropionyl chloride[18] (30 g., 0.175 mole) in 30 ml. of dry ether over a period of 45 min. The mixture was stirred for 15 min. at 40–45° and cooled, the solid was filtered and washed with ether, and the combined ethereal solutions were evaporated to leave a dark oil which was crystallized from petroleum ether (b.p. 60–80°) to give the product, m.p. 82–84°, yield 31.9 g. (71%).

Compounds XV–XVIII were prepared in the same way: **N-(4-chlorobutyryl)-*o*-anisidine** (**XV**), b.p. 166–168° (0.6 mm.), yield 53% (from *o*-anisidine and 4-chlorobutyryl chloride); **N-(2-bromopropionyl)-*o*-anisidine** (**XV**), m.p. 64–65° (petroleum ether, b.p. 60–80°), yield 66% (from *o*-anisidine and 2-bromopropionyl bromide); **N-(2-bromopropionyl)-2,5-dimethoxyaniline** (**XVII**) (chloroform was used as reaction solvent), m.p. 66–68° (petroleum ether, b.p. 60–80°), yield 71% (from 2,5-dimethoxyaniline and 2-bromopropionyl bromide).

N-(3-Hydroxypropyl)benzenesulfonamide (**XVIII**).—Benzenesulfonyl chloride (52.8 g., 0.3 mole) was added with cooling and stirring over a period of 1.5 hr. to 3-aminopropanol (90 g., 1.2 moles). The mixture was then heated to 70° for 1 hr. with stirring. After cooling it was poured into water, extracted twice with chloroform, the chloroform extract was washed with 2 *N* HCl and saturated NaCl solution and dried ($MgSO_4$), and the solvent was evaporated. The remaining oil was distilled, b.p. 198–200° (0.2 mm.), $n^{20}D$ 1.5488, yield 24.5 g. (38%).

Compounds XIX and XX were prepared in the same way: **N-(2-hydroxyethyl)-*p*-toluenesulfonamide** (**XIX**),[19] b.p. 192–196° (0.2 mm.), yield 77% (from *p*-toluenesulfonyl chloride and 2-aminoethanol); **N-(3-hydroxypropyl)-*p*-toluenesulfonamide** (**XX**), b.p. 194–195° (0.25 mm.), $n^{20}D$ 1.5478, m.p. 52–55° (chloroform–petroleum ether, b.p. 40–60°) (lit.[20] m.p. 55–56°), yield 68% (from *p*-toluenesulfonyl chloride and 3-aminopropanol).

N-(3-Hydroxypropyl)-*p*-toluamide (**XXI**) was prepared from *p*-toluoyl chloride and 3-aminopropanol. It had b.p. 175–180° (0.2 mm.), $n^{20}D$ 1.5592, yield 63%.

N-(3-Hydroxypropyl)-2-nitro-5-chlorobenzenesulfonamide (**XXII**) was prepared from 2-nitro-5-chlorobenzenesulfonyl chloride[21] and 3-aminopropanol. During the period of addition the temperature was kept at 10°. The mixture was stirred for a further 30 min. at room temperature. The product crystallized from the ether extract upon evaporation and was recrystallized from ether. It had m.p. 74–75°, yield 35%.

Anal. Calcd. for $C_9H_{11}ClN_2O_5S$: C, 36.68; H, 3.76; N, 9.51; S, 10.88. Found: C, 36.66; H, 3.89; N, 9.16; S, 10.57.

N-Methyl-N-(3-hydroxypropyl)-*p*-toluenesulfonamide (**XXIII**).—Sulfonamide XX (34.4 g., 0.15 mole) and methyl iodide (25 g., 0.177 mole) were heated to reflux temperature. Aqueous NaOH (100 ml., 6%) was added to the mixture during 1 hr. The reaction was refluxed for a further 30 min., cooled, and extracted with chloroform, the extract was washed with 4 *N* NaOH and water and dried ($MgSO_4$), and the solvent was evaporated. The product had b.p. 176° (0.2 mm.), yield 30 g. (83%).

N-(3-Bromopropyl)benzenesulfonamide (**XXIV**).—Sulfonamide XVIII (24.5 g., 0.123 mole) in 110 ml. of dichloroethane was treated with phosphorus tribromide (39.8 g., 0.147 mole) with stirring at a bath temperature of 80° over a period of 1 hr. The solution was heated for a further 30 min. at 90°. When cold, the mixture was poured onto ice, the organic layer was separated, washed with water, and dried ($MgSO_4$), and the solvent was evaporated. The crude material (25.5 g.) was obtained as a viscous oil which was used without further purification.

Compounds XXV–XXIX were prepared by a similar procedure: **N-(2-bromoethyl)-*p*-toluenesulfonamide** (**XXV**), from sulfonamide XIX, m.p. 92–94° (chloroform–petroleum ether, b.p. 60–80°) (lit.[22] m.p. 88–90°), yield 47%; **N-(3-bromopropyl)-*p*-toluenesulfonamide** (**XXVI**), from sulfonamide XX with or without solvent, m.p. 62–65° (chloroform–petroleum ether, b.p. 60–80°), yield 61% (alternatively, reaction of XX with a 36%

(17) Prepared according to J. Colonge and A. Guyot, *Bull. soc. chim. France*, 1228 (1957). As a catalyst a 40% solution of trimethylbenzylammonium hydroxide in methanol (Triton B) was used, giving yields of 35–45%.

(18) Prepared from β-bromopropionic acid (0.2 mole), thionyl chloride (1.3 moles), and a few drops of dimethylformamide; b.p. 82–85° (14 mm.), yield 89%.

(19) See also A. E. Kretov and G. V. Tikhonova, *Zh. Obshch. Khim.*, **29**, 412 (1959); *Chem. Abstr.*, **54**, 369c (1960), who obtained a 47.5% yield.

(20) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, **26**, 138 (1961).

(21) Prepared according to Schering Corp., U. S. Patent 2,986,573 (May 30, 1961); *Chem. Abstr.*, **56**, 4875 (1962).

(22) D. H. Peacock and U. C. Dutta, *J. Chem. Soc.*, 1303 (1934).

solution of hydrogen bromide in glacial acetic acid yielded 62% of XXVI); **N-methyl-N-(3-bromopropyl)-*p*-toluenesulfonamide XXVII**, from sulfonamide XXIII in benzene as reaction solvent, b.p. 212–220° (1.3 mm.), yield 33%; **N-(3-bromopropyl)-2-nitro-5-chlorobenzenesulfonamide (XXVIII)**, from sulfonamide XXII in tetrachloroethane as reaction solvent at 5°; the mixture was heated for 30 min. at 40–50°, yield 56% of crude material; **N-(3-bromopropyl)-*p*-toluamide (XXIX)**, from amide XXI, yield 45% of crude material.

N-[2-(2-Methoxyphenoxy)ethyl]-3-chloropropionamide (XXX).—Amine X (16.7 g., 0.1 mole) and NaOH solution (80 ml., 5%) were stirred with ice cooling and 3-chloropropionyl chloride (12.7 g., 0.1 mole) added over a period of 30 min. Stirring was continued for a further 30 min., the mixture was filtered, and the solid obtained was recrystallized from aqueous ethanol. It had m.p. 64.5–65.5°, yield 8.8 g. (34%).

Methyl 3-(2,5-Dimethoxyphenoxy)crotonate (XXXI).—2,5-Dimethoxyphenol[23] (30 g., 0.195 mole) in 50 ml. anhydrous dimethylacetamide was heated to 80° when sodium (2.24 g., 0.098 g.-atom) was introduced in small pieces with vigorous stirring. After the sodium had dissolved, methyl 3-chlorocrotonate[24] (13.1 g., 0.098 mole) was added over a period of 30 min. at 130–140°, when a reaction took place. Further heating was continued at 140° for 30 min.

The solvent was evaporated under reduced pressure, and the remaining oil was poured onto ice and extracted with ether. The extract was washed with 1 *N* NaOH and water and dried (Na_2SO_4), and the solvent was removed by distillation. The remaining oil was distilled, b.p. 137–140° (0.15 mm.), yield 15.4 g. (63%).

Methyl 3-(2,5-Dimethoxyphenoxy)butyrate (XXXII).—Ester XXXI (15.4 g., 0.061 mole) was dissolved in 100 ml. of methanol and reduced catalytically over palladium-charcoal (3 g., 10%) at normal temperature and pressure, yielding an oil which was distilled, b.p. 133–134° (0.25 mm.), $n^{20}D$ 1.5136, yield 11 g. (71%).

3-(2,5-Dimethoxyphenoxy)butanol (XXXIII).—Ester XXXII (11 g., 0.043 mole) was reduced with $LiAlH_4$ (2 g., 0.053 mole) in 75 ml. of ether, by heating the reaction mixture to 50° for 30 min. The reaction was worked up in the usual way and the product distilled, b.p. 132–136° (0.2 mm.), yield 7.8 g. (80%).

Ethyl 2-(2-Methoxyphenoxy)propionate (XXXIV).—Guaiacol (41.3 g., 0.33 mole) and $KHCO_3$ (33.3 g., 0.33 mole) in 170 ml. dimethylacetamide were stirred and heated to 90°. Ethyl 2-bromopropionate (59.7 g., 0.33 mole) was introduced over 65 min. with stirring. The mixture was stirred and heated at 110° for a further 3 hr. After cooling, the reaction mixture was filtered, the solvent was evaporated under reduced pressure, the residue was treated with water and extracted with ether, the extract was washed with 1 *N* NaOH and water and dried ($MgSO_4$), and the solvent was evaporated. The residual oil was distilled, b.p. 113–115° (0.5 mm.), $n^{20}D$ 1.5024, yield 46.1 g. (62%).

2-(2-Methoxyphenoxy)propanol (XXXV).—Ester XXXIV (46.1 g., 0.205 mole) was reduced with $LiAlH_4$ (8.6 g., 0.226 mole) in ether at room temperature. The product was worked up in the usual manner and had b.p. 96° (0.1 mm.), $n^{20}D$ 1.5303, yield 33.8 g. (90%).

3-Hydroxypropyl *p*-Tolyl Thioether (XXXVI).—*p*-Tolylthiol (12.4 g., 0.1 mole) and 3-chloropropanol (9.4 g., 0.1 mole) were heated to 100° and NaOH solution (100 ml., 4%) was added to the mixture during 45 min. with vigorous stirring. On further refluxing and stirring for 1.25 hr. the pH approached 7. The cold reaction product was separated from the aqueous layer, the organic layer was taken up in ether, extracted several times with 2 *N* NaOH, washed with saturated NaCl solution, and dried ($MgSO_4$), and the solvent was evaporated. The residue was distilled yielding the product, b.p. 126–128° (0.35 mm.), $n^{20}D$ 1.5704, yield 13.2 g. (73%).

4-(2,5-Dimethoxyphenoxy)butan-2-ol (XXXVII) was prepared by a similar method from 2,5-dimethoxyphenol and 4-chlorobutan-2-ol.[25] It had b.p. 141° (0.2mm.), $n^{20}D$ 1.5267, yield 64%.

N-(2-Chloroethyl)-*o*-anisidine Hydrochloride (XXXVIII).—N-(2-Hydroxyethyl)-*o*-anisidine[26] (17.7 g., 0.1 mole) was dissolved in chloroform and the hydrochloride was prepared by introduction of the appropriate amount of HCl gas. The solvent was evaporated and replaced by fresh chloroform, and thionyl chloride (13.1 g., 0.11 mole) was added over 15 min. The mixture was refluxed for 1 hr., and the solvent was evaporated. The residue was recrystallized from acetone. It had m.p. 146–148°, yield 54%.

3-(2-Methoxy-5-cyanophenoxy)propyl Bromide (XXXIX).—2-Methoxy-5-cyanophenol[27] (37.8 g., 0.254 mole), K_2CO_3 (35 g., 0.254 mole), and 1,3-trimethylene dibromide (79.5 g., 0.394 mole) in 250 ml. of acetone were stirred under reflux for 36 hr. The cold mixture was filtered, the filtrate was evaporated, the remaining product was dissolved in chloroform, the solution was washed with 4 *N* NaOH and water and dried ($MgSO_4$), and the solvent was evaporated. The product was distilled and had b.p. 142–146° (3×10^{-3} mm.). After two recrystallizations from ethanol it had m.p. 77–79°, yield 16 g. (23%).

3-(2,5-Dibutoxyphenoxy)propyl Bromide (XL).—To sodium (0.88 g., 0.038 g.-atom) dissolved in 25 ml. of absolute ethanol, was added 2,5-dibutoxyphenol[28] (9.1 g., 0.038 mole), and the solution was evaporated to dryness. The sodium salt was dissolved in dimethylformamide and, after addition of 1,3-trimethylene dibromide (13.2 g., 0.065 mole), the mixture was refluxed for 4 hr. The solvent was evaporated under reduced pressure and, after addition of water, the aqueous layer extracted with chloroform. The extract was washed with 4 *N* NaOH and water and dried ($MgSO_4$), and the solvent was evaporated. The oil obtained was distilled, b.p. 168° (0.45 mm.), $n^{20}D$ 1.5089, yield 9.6 g. (71%).

***o*-Bromoethoxybenzamide[28] (XLI).**—Salicylamide (41 g., 0.299 mole) and ethylene dibromide (114 g., 0.605 mole) were heated to reflux in 500 ml. of ethanol. Sodium (6.9 g., 0.300 g.-atom) dissolved in 150 ml. of ethanol was added over a period of 1 hr. Heating was continued until the pH of the solution was 7.5. On cooling, a white precipitate appeared which was filtered off, and the mother liquor was concentrated until the precipitate, crystallizing from the solution, had m.p. below 112°. Water was then added, the mixture was extracted with chloroform, the extract was washed with 2 *N* NaOH and water and dried ($MgSO_4$), and the solvent was evaporated. The residue was crystallized from chloroform–petroleum ether (b.p. 60–80°); it had m.p. 111–112.5°, yield 24 g. (33%).

3-Bromopropyloxy-*o*-benzamide (XLII).—This was prepared in the same way from salicylamide and 1,3-trimethylene dibromide; it had m.p. 126–128° [chloroform–petroleum ether (b.p. 40–60°)], yield 15%.

N-[2-(2-Methoxyphenoxy)ethyl]-N-(2-chloroethyl)-3-(2-methylphenoxy)propylamine (102).—Amine **101** (11.8 g., 0.033 mole) was dissolved in 50 ml. of chloroform, and thionyl chloride (5.4 g., 0.045 mole) in 25 ml. of chloroform was added with stirring and ice cooling. The mixture was left to stand for 15 hr. at room temperature. The solvent was evaporated, ethanol was added and evaporated to dryness. The residue was dissolved in 30 ml. of boiling ethanol, 150 ml. of dry ether was added, and the mixture was allowed to crystallize (see Table VI).

3-Chloropropyl *p*-Tolyl Thioether (XLIII).—Thioether XXXVI (13.2 g., 0.073 mole) was dissolved in dry pyridine (5.7 g., 0.073 mole). Thionyl chloride (11.1 g., 0.082 mole) was added with stirring and cooling over a period of 30 min. The mixture was stirred for 1.25 hr. at room temperature and for 2.5 hr. at 70–80°, cooled, poured onto ice, and extracted with chloroform. The extract was washed with saturated $KHCO_3$ solution and water and dried ($MgSO_4$), and the solvent was evaporated. The residue was distilled, b.p. 94° (0.15 mm.), yield 9 g. (62%).

Compounds XLIV–XLVI were prepared according to the same method: **4-(2,5-dimethoxyphenoxy)-2-chlorobutane (XLIV)**, from XXXVII, b.p. 144–147° (0.4 mm.), yield 26%; **2-(2-methoxyphenoxy)propyl chloride (XLV)**, from XXXV, b.p. 90–91° (0.4 mm.), $n^{20}D$ 1.5267, yield 51%. *Anal.* Calcd. for $C_{10}H_{13}ClO_2$: C, 59.84; H, 6.53. Found: C, 59.96; H, 6.63.); **3-(2,5-dimethoxyphenoxy)butyl chloride (XLVI)**, from XXXIII, b.p. 134–135° (0.2 mm.), $n^{20}D$ 1.5264, yield 41%.

N-[2-(2-Methoxyphenoxy)ethyl]-3-hydroxypropylamine (XLVII) was prepared by general procedure 1 from propanolamine and bromide **129**. It had b.p. 148–150° (0.15 mm.), $n^{20}D$ 1.5380, yield 54%.

(23) C. A. Bartram, D. A. Battye, and C. R. Worthing, *J. Chem. Soc.*, 4691 (1963).

(24) D. E. Jones, R. O. Morris, C. A. Vernon, and R. F. M. White, *ibid.*, 2349 (1960); H. Scheibler and J. Voss, *Chem. Ber.*, **53**, 379 (1920).

(25) Prepared from methylmagnesium iodide and β-chloropropionaldehyde [see R. L. Shriner, H. A. Rendleman, and A. Berger, *J. Org. Chem.*, **4**, 103 (1939)] in a yield of 5%, b.p. 58–61° (13 mm.), $n^{20}D$ 1.4437. *Anal.* Calcd. for C_4H_9ClO: C, 44.25; H, 8.35. Found: C, 44.20; H, 8.51.

(26) J. v. Braun and J. Seemann, *Chem. Ber.*, **55**, 3818 (1922).

(27) F. Fallix, L. Holzinger, P. Ita, and R. Schwarz, *ibid.*, **74**, 79 (1941).

(28) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 403 (1915).

N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]-3-hydroxypropylamine (XLVIII) was prepared according to general procedure 2 from amine XLVII and benzyl chloride. It had b.p. 191–193° (0.25 mm.), $n^{20}D$ 1.5605, yield 88%.

N-Benzyl-N-[2-(-methoxyphenoxy)ethyl]-3-aminopropyl 3,4,5-Trimethoxybenzoate (XLIX).—Amine XLVIII (7.4 g., 0.055 mole) was dissolved in pyridine (100 ml.) and 3,4,5-trimethoxybenzoyl chloride[29] (25.5 g., 0.111 mole) was added with cooling. The solution was left to stand for 15 hr., poured into ice-cold 2 *N* NaOH, and extracted with benzene. The extract was washed with water and dried ($NaSO_4$), and the solvent was evaporated. The residue was crystallized from dibutyl ether or ethyl ether and had m.p. 77–78°, yield 17.8 g. (63%).

Anal. Calcd. for $C_{29}H_{35}NO_7$: C, 68.35; H, 6.92; N, 2.75. Found: C, 68.39; H, 6.69; N, 2.88.

3-[2-(2-Methoxyphenoxy)ethylamino]propyl 3,4,5-Trimethoxybenzoate (81).—Compound XLIX (8.9 g., 0.017 mole) in 100 ml. of glacial acetic acid was hydrogenated at normal temperature and pressure with prehydrogenated 10% palladium–charcoal (1 g.). The catalyst was filtered off, the solvent was evaporated, 2 *N* NaOH was added, and the solution was extracted with ether. The extract was washed with saturated NaCl solution and dried ($NaSO_4$), and the solvent was evaporated. A hydrogen maleate was prepared from the residue (see Table IV).

N-{3-[2-(2-Methoxyphenoxy)ethylamino]propyl}-2-amino-5-chlorobenzenesulfonamide (92).—Compound **91** (1 g., 0.002 mole) was stirred and refluxed in aqueous methanol (4.5 ml., 67%); ammonium chloride (0.8 g., 0.015 mole) and, over a period of 30 min., iron filings (0.8 g., 0.014 g.-atom) in portions were added. Heating and stirring were continued for a further 30 min. The cold mixture was filtered, the solvent was evaporated, potassium bicarbonate solution was added, and the solution was extracted with chloroform. The extract was dried ($MgSO_4$), and the solvent was evaporated. The residual oil was converted into a hydrogen maleate (see Table V).

N-[2-(2-Methoxyphenoxy)isopropyl]-3-(2,5-dimethoxyphenoxy)propylamine (64).—2-Methoxyphenoxyacetone[30] (20 g., 0.111 mole) and amine XI (64 g., 0.303 mole) were hydrogenated in 200 ml. of methanol over 8 ml. of Raney nickel at 110 atm. and normal temperature for 22 hr. The catalyst was filtered off, the solvent was evaporated, the residue was dissolved in chloroform, the solution was washed with 2 *N* hydrochloric acid, 2 *N* sodium hydroxide, and water and dried (K_2CO_3), and the solvent was evaporated. The residue was purified by distillation (see Table III).

N-[2-(2-Methoxyphenoxy)ethyl]-3-(*p*-aminophenoxy)propylamine (15).—Compound **14** (23 g., 0.067 mole) was hydrogenated in 310 ml. of absolute ethanol over platinum oxide (0.3 g.) at 8 atm. and normal temperature. The catalyst was filtered off and the solvent evaporated. The residue was basified with 2 *N* NaOH, extracted with chloroform, the extract was washed with water and dried (K_2CO_3), and the solvent was evaporated. The residue was purified by distillation (some decomposition occurred) (see Table II).

N-[2-(2-Methoxyphenoxy)ethyl]-N-[3-(2,5-dimethoxyphenoxy)propyl] Ethyl Carbamate (104).—Compound **23** (10 g., 0.028 mole) was dissolved in pyridine (15 ml.) and ethyl chloroformate (3.3 g., 0.030 mole) was added with stirring over 20 min. The solution was heated to 60° for 2 hr. The cold mixture was poured into ice water and extracted with benzene. The extract was washed with 2 *N* HCl and water and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by distillation (see Table VI).

N-[2-(2-Methoxyphenoxy)ethyl]-N-[3-(2-methoxyphenoxy)propyl]acetamide (97).—Compound **5** (5 g., 0.015 mole) was dissolved in pyridine (50 ml.), and acetyl chloride (3 g., 0.039 mole) was added over 15 min. The solution was stirred for a further 30 min. Ice water was added and the mixture was extracted with ether. The ether was washed with 2 *N* HCl and water and dried ($MgSO_4$), and the solvent was evaporated. The remaining oil was crystallized from petroleum ether (b.p. 40–60°) (see Table VI).

N-[2-(2-Methoxyphenoxy)ethyl]-N-[3-(2,5-dimethoxyphenoxy)propyl]acetamide (103).—Compound **23** (10 g., 0.028 mole) in acetic anhydride was refluxed for 16 hr. Excess acetic anhydride was evaporated, the residue was dissolved in ether, the solution was washed with 2 *N* HCl, 2 *N* NaOH, and water and dried ($MgSO_4$), and the solvent was evaporated. The residue gave the pure product after low-temperature crystallization from methanol (see Table VI).

Acknowledgment.—The authors are indebted to Mr. P. Wood and his staff for the microanalyses, to Mr. V. Voss for his technical assistance, and to Dr. A. M. Monro for his help in the preparation of the manuscript. The authors also wish to express their thanks to their colleagues in the Pharmacology Department who carried out all pharmacological evaluations.

(29) Prepared according to A. Lasslo and W. D. Jordan, *J. Org. Chem.*, **21**, 805 (1956).

(30) Prepared according to C. D. Hurd and P. Perletz, *J. Am. Chem. Soc.*, **68**, 38 (1946), in 66% yield, b.p. 89–91° (0.2 mm.), $n^{20}D$ 1.5293.