[CONTRIBUTION FROM THE RESEARCH DIVISION, SMITH, KLINE AND FRENCH LABORATORIES]

Adrenergic Blocking Agents. III. N-(Aryloxyisopropyl)-β-haloethylamines[1]

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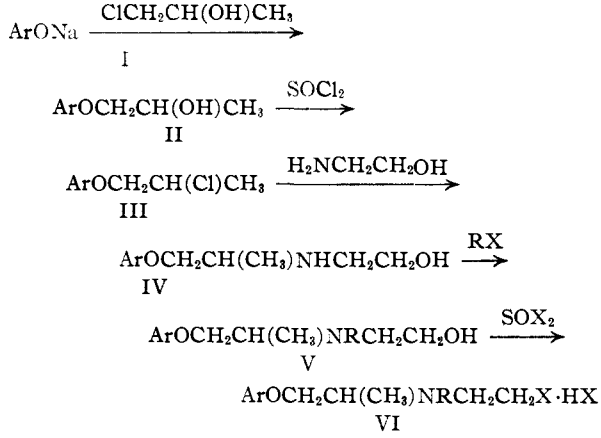
A series of thirty-three N-(R)-N-(β-phenoxyisopropyl)-β-haloethylamines, the intermediates for their preparation and methods of synthesis are described. Preliminary pharmacological data indicate that these β-haloethylamines are potent adrenergic blocking agents following intravenous administration and that some are effective orally. Structural and chemical factors which may influence blocking ability are discussed.

During the investigation of the adrenergic blocking action of N,N-disubstituted-β-haloethylamines,[3] one of our major objectives has been the development of an orally active agent since such a compound would be of major importance as a potentially useful therapeutic substance. It was felt that structural modifications of intravenously active compounds might lead to increased oral efficacy.

In the sympathomimetic amine series, the introduction of an α-methyl group to convert phenethylamine into phenylisopropylamine results in an orally active drug.[4,5] This result appears to be associated with the ability of the β-methyl group to protect the amine from attack by amine oxidase.[6] Although the modes of action of the β-haloamines and the sympathomimetic amines are probably quite different[3,7] the introduction of an α-methyl group to convert N-benzyl-N-phenylethyl-β-chloroethylamine into the corresponding N-(β-phenylisopropyl)-β-chloroethyl compound markedly enhances intravenous activity.[3b] We have extended our study of the effect of the α-methyl modification to N-(phenoxyethyl)-β-haloethylamines since a number of these have been reported[8] to be active adrenergic blocking agents when administered intravenously to animals.

We have found that N-(β-phenoxyisopropyl)-β-haloethylamines are also active after intravenous administration and some members of the series have an enhanced ability to produce, in animals, a prolonged block after oral administration. For example, N-(β-phenoxyisopropyl)-N-benzyl-β-chloroethylamine is more active than the β-phenoxyethyl homolog when oral potencies are compared, although the two are approximately equal in activity by the intravenous route.

Most of the β-haloethylamine hydrohalides listed in Table V were prepared from phenols or α-naphthol by the following method



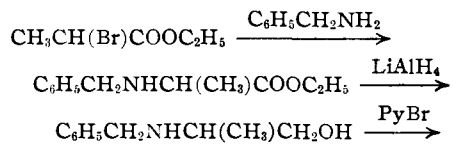
Addition of propylene chlorohydrin to the sodium phenates in refluxing alcohol gave satisfactory yields of the ether alcohols (II) which were converted to the chloro compounds by the method of Libermann[9] or by Darzens' procedure.[10] Alkylation of 2-benzylaminoethanol with 1-phenoxy-2-chloropropane without a solvent at 160° formed the desired tertiary amine (V, Ar = phenyl, R = benzyl) in poor yield. Better results were obtained according to the scheme shown above in which ethanolamine was first monoalkylated and the group R was then introduced by reaction of IV with benzyl or substituted benzyl halides, β-phenoxyethyl bromide, allyl bromide or ethyl iodide. Interaction of the aminoethanols (V) with thionyl chloride or thionyl bromide proceeded smoothly in chloroform solution. N-(β-Phenoxyisopropyl)-ethanolamine (IV, Ar = phenyl) was also prepared by reductive amination of phenoxyacetone with ethanolamine.

Alkylation of isopropanolamine with 1-phenoxy-2-chloropropane produced two diastereoisomeric racemic forms

$$C_6H_5OCH_2CH(Cl)CH_3 + H_2NCH_2CH(OH)CH_3 \longrightarrow C_6H_5OCH_2CH(CH_3)NHCH_2CH(OH)CH_3$$

These were separated by crystallization of the solid isomer from petroleum ether and the two forms were benzylated and the tertiary aminopropanols treated with thionyl chloride.

The pyridyl analog of the parent compound was synthesized by the series of reactions



(1) Presented before the Division of Medicinal Chemistry at the 118th Meeting of the American Chemical Society in Chicago, Illinois, September, 1950.

(2) Deceased.

(3) (a) Kerwin, Herdegen, Heisler and Ullyot, THIS JOURNAL, **72**, 940 (1950); (b) Kerwin, Herdegen, Heisler and Ullyot, *ibid.*, **72**, 3983 (1950); Abstracts 116th Meeting American Chemical Society, page 23 L, 1949.

(4) Piness, Miller and Alles, *J. Am. Med. Assoc.*, **94**, 790 (1930).

(5) Chen, Wu and Henriksen, *J. Pharmacol. Expt. Therap.*, **36**, 363 (1929).

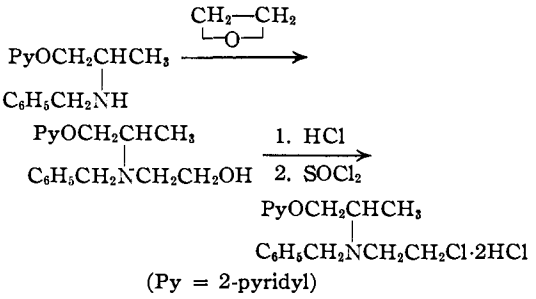
(6) Beyer, *ibid.*, **71**, 151 (1941).

(7) Nickerson, *ibid.*, **95**, (Part II), 27 (1949).

(8) (a) Rieveschl, Fleming and Coleman, Abstracts 112th Meeting American Chemical Society, page 17 K, 1947. (b) Nickerson and Gump, *J. Pharm. Expt. Therap.*, **97**, 25 (1949). (c) Henderson and Chen, *Fed. Proc.*, **8**, 301 (1949). (d) Gump and Nikawitz, THIS JOURNAL, **72**, 3846 (1950).

(9) Libermann, *Nature*, **160**, 903 (1947).

(10) Darzens, *Compt. rend.*, **152**, 1314 (1911).



Since the β-phenoxyisopropyl group appears to produce desirable effects it was of interest to test a β-chloroamine containing two of these groups. The bis compound was prepared by hydrogenating the crude ketimine formed from β-phenoxyisopropylamine and phenoxyacetone. The N-(β-hydroxyethyl) group was introduced by treating the secondary amine with ethylene oxide.

Pharmacological Results.—Table V gives the adrenergic blocking action of the β-haloethylamines after both intravenous and oral administration. Intravenous activity was determined in cats as previously described.[3a]

In oral experiments 10 mg./kg. of the compound was given to cats and after three hours a test dose (12.5 micrograms) of epinephrine was injected. If a depressor response occurred, three successive test doses (50 mμ., 500 μg. and 1 mg./kg.) were given. The numerical rating assigned as a measure of blocking ability is a summation proportional to the amount of epinephrine reversed or blocked divided by the number of animals employed. When the pressor effect of a given test dose of epinephrine was blocked but not reversed, the numerical value assigned was one-half the micrograms of epinephrine administered. Experience has shown that compounds with oral ratings below 1000 are not consistently effective adrenergic blocking agents following administration by this route. The values recorded in Tables V and VI have been rounded to the nearest hundred. While these ratings express the relative order of activity they cannot be considered to denote an absolute value.

Previous work has shown that marked adrenergic blocking ability following intravenous administration is manifested in the N-benzyl-N-(β-phenoxyethyl)-β-chlorethylamine series.[3b] A few of these compounds have been tested in these laboratories in order to compare their blocking ability with that of our compounds. The intravenous and oral ratings are recorded in Table VI. Complete pharmacological data will be reported elsewhere.

Discussion of Relationship of Structure to Activity.—The lack of correlation between intravenous and oral activity, as shown by the data for 861 (Table VI), 688 and 806 (Table V), demonstrates that factors other than blocking ability alone play an important role in oral effectiveness.

On comparison of N-benzyl-N-phenoxyethyl-β-chlorethylamine (513, Table VI) with N-benzyl-N-(β-phenoxyisopropyl)-β-chloroethylamine (688, Table V) it appears that α-methyl substitution in the former has resulted in a compound with enhanced oral activity and that even the intravenous activity has been somewhat increased. While substitution of a 2-methyl or a 2-isopropyl group in the phenoxy ring of 513 resulted in compounds (674, 861, Table VI) ranking among the more potent intravenously active adrenergic blocking agents of the β-haloamine type, these compounds were practically inactive orally. Alkyl substitution in the phenoxy ring of the 688 series either markedly lowered or destroyed oral activity. However the effect on intravenous potency was variable. Thus those substitutions which had little effect are 2-methyl (783), 3-methyl (845), 2-isopropyl (1001), 2-isopropyl-5-methyl (973), and 3,4-dimethyl (883); however a 2-isopropyl group appeared to be optimum. Decreased activity resulted from 4-methyl (730), 2-*s*-butyl (793), 4-*s*-butyl (901) and 4-*t*-butyl (974) substitutions. Large substituents such as a 4-phenyl (945), a 4-cyclohexyl (924) or a 2-benzyl (1002) markedly lowered intravenous activity and resulted in orally inactive compounds. Substitution of the phenoxy ring of 688 by 4-hydroxy (972), 4-methoxy (784) or 4-benzyloxy (835) had little effect on intravenous activity but oral activity was markedly lowered or destroyed. Chlorine substitution in the 2- or 4-positions (1025 and 853) lowered intravenous activity somewhat and oral activity was no longer apparent.

In the phenoxyethyl series substitution in the benzyl ring by a 2-methyl (790, Table VI) had little effect on intravenous activity and if anything slightly decreased oral potency. On the other hand substitution in the benzyl group of the phenoxyisopropyl series by a 2-methyl markedly lowered oral activity but only slightly decreased intravenous effectiveness. Chlorine substitution, 4-chloro (804), 2,4-dichloro (805), 3,4-dichloro (803) destroyed oral activity but only the 2,4-substitution markedly lowered intravenous activity. Methoxyl substitution in the 4-, or 3,4-positions of the benzyl of this series had little effect on intravenous activity but essentially eliminated oral activity.

Substitution on the β-chloroethyl of 688 by a β-methyl resulted in two diastereoisomers (781 and 974, Table V). Both of these were only slightly less active than 688 intravenously but they were orally ineffective.

Replacement of the phenoxy ring of 688 by α-naphthoxy or 2-pyridyloxy (907 and 1137, Table V) decreased intravenous and eliminated oral activities.

Replacement of the benzyl group of 688 by: (a) phenoxyethyl (806), if anything, increased intravenous and slightly lowered oral activities; (b) allyl (833) slightly lowered intravenous and oral activities; (c) ethyl (1370) markedly lowered intravenous and eliminated oral activities and (d) β-phenoxyisopropyl to give the bis-(β-phenoxyisopropyl) compound (1273) had no effect on intravenous but markedly lowered oral activity.

On the basis of these results it appears that the α-methyl group in 688 contributes to oral activity. Furthermore, the requirements for oral activity seem to be rather precise since there is no correlation between intravenous and oral activity. This is further emphasized by the fact that in the phenoxyisopropyl series the substitutions in the phenoxy or benzyl groups markedly lowered or de-

TABLE I

1-PHENOXY-2-PROPANOLS R—C$_6$H$_4$—OCH$_2$CHCH$_3$ (OH)

R =	B.p. or m.p., °C.	Press., mm.	n^{20}D	Yield, %	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2-CH$_3$[a]	86–88	2	1.5199	64	$C_{10}H_{14}O_2$	72.26	8.49	71.99	8.76
3-CH$_3$	114	5	1.5211	84	$C_{10}H_{14}O_2$	72.26	8.49	72.37	8.38
4-CH$_3$	101–106	4		82	$C_{10}H_{14}O_2$	72.26	8.49	72.34	8.35
2-(CH$_3$)$_2$CH	98	3	1.5118	68	$C_{12}H_{18}O_2$	74.19	9.34	74.14	9.36
4-(CH$_3$)$_3$C	105–110[b]	2		76	$C_{13}H_{20}O_2$	74.96	9.68	75.03	9,57
2-C$_6$H$_5$CH$_2$	56.5–57[c]			72	$C_{16}H_{18}O_2$	79.31	7.49	79.20	7.45
2-(CH$_3$)$_2$CH-5-CH$_3$	94–97	2	1.5100	72	$C_{13}H_{20}O_2$	74.96	9.68	75.18	9.58
3,4-diCH$_3$	110–113	3	1.5226	80	$C_{11}H_{16}O_2$	73.30	8.95	73.30	9.09
4-CH$_3$O	63–64[d]			73	$C_{10}H_{14}O_3$	65.91	7.74	65.80	7.57
4-C$_6$H$_5$CH$_2$O	104–105[e]			60	$C_{16}H_{18}O_3$	74.39	7.02	74.25	6.86
2-Cl[f]	109–114	3	1.5382	69	$C_9H_{11}O_2Cl$	57.92	5.94	58.63	5.93
4-Cl[g]	125–130	6	1.5378	63	$C_9H_{11}O_2Cl$	57.92	5.94	58.17	6.04
α-C$_{16}$H$_7$OCH$_2$CH(OH)CH$_3$	59–63[c]			55	$C_{13}H_{14}O_2$	77.20	6.98	77.31	6.76

[a] The *p*-nitrobenzoate ester melted at 95.5–96°. *Anal.* Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43. Found: C, 64.51; H, 5.50. [b] M.p. 44–46° from petroleum ether. [c] Recrystallized from Esso hexane. [d] Recrystallized from benzene and petroleum ether. [e] Recrystallized from benzene. [f] The *p*-nitrobenzoate ester melted at 97–97.5°. *Anal.* Calcd. for $C_{16}H_{14}NO_5Cl$: C, 57.23; H, 4.20. Found: C, 57.52; H, 4.46. [g] The *p*-nitrobenzoate ester melted at 76.6–77°. *Anal.* Calcd. for $C_{16}H_{14}NO_5Cl$: C, 57.23; H, 4.20. Found: C, 57.19; H, 4.03.

TABLE II

1-PHENOXY-2-CHLOROPROPANES R—C$_6$H$_4$—OCH$_2$CH(Cl)CH$_3$

R =	B.p. or m.p., °C.	Press., mm.	n^{20}D	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
H	94–95	5	1.5207	66	$C_9H_{11}OCl$	63.35	6.50	63.30	6.95
2-CH$_3$	94–95	3	1.5160	70	$C_{10}H_{13}OCl$	65.04	7.10	65.02	7.17
3-CH$_3$	96.5–98	5	1.5166	72	$C_{10}H_{13}OCl$	65.04	7.10	65.03	7.10
4-CH$_3$	76.5–77	2	1.5199	75	$C_{10}H_{13}OCl$	Cl, 19.20		Cl, 19.03	
2-(CH$_3$)$_2$CH	76–78	2	1.5100	74	$C_{12}H_{17}OCl$	67.75	8.06	67,90	8.22
2-C$_2$H$_5$CH(CH$_3$)	118–124	4		69	$C_{13}H_{19}OCl$	Cl, 15.64		Cl, 15.63	
4-C$_2$H$_5$CH(CH$_3$)	104–110	2	1.5070	78	$C_{13}H_{19}OCl$	68.86	8.45	69.23	8.54
4-(CH$_3$)$_3$C	100–103	0.3	1.5071	43	$C_{13}H_{19}OCl$	68.86	8.45	68.99	8.96
4-C$_6$H$_5$	75–76[a]			81	$C_{15}H_{15}OCl$	73.02	6.13	73.52	6.15
4-C$_6$H$_{11}$	46–46.5[a]			61	$C_{15}H_{21}OCl$	71.27	8.37	71.11	8.13
2-C$_6$H$_5$CH$_2$	80.5–81[a]			58	$C_{16}H_{17}OCl$	73.69	6.57	74.04	6.93
2-(CH$_3$)$_2$CH-5-CH$_3$	90–91	3	1.5090	53	$C_{13}H_{19}OCl$	68.86	8.45	68.98	8.35
3,4-diCH$_3$	96–98	3	1.5197	97	$C_{11}H_{15}OCl$	66.49	7.61	66.49	7.65
4-CH$_3$O	91–95.5	1	1.5243	83	$C_{10}H_{13}O_2Cl$	59.85	6.53	60.10	6.38
4-C$_6$H$_5$CH$_2$O	66–67.5[a]			83	$C_{16}H_{17}O_2Cl$	69.43	6.19	69.80	6.18
2-Cl	112–114	5	1.5346	67	$C_9H_{10}OCl_2$	52.71	4.92	52.95	4.86
4-Cl	37–39[b]			73	$C_9H_{10}OCl_2$	52.71	4.92	52.73	5.14
α-C$_{10}$H$_7$OCH$_2$CH(Cl)CH$_3$	117–120	0.2	1.5962	70	$C_{13}H_{13}OCl$	Cl, 16.07		Cl, 16.11	

[a] Recrystallized from alcohol. [b] Recrystallized from petroleum ether after distillation, b.p. 84–90° at 2 mm.

stroyed the ability to produce an adrenergic block after oral administration while in the phenoxyethyl series substitution of a 2-methyl in the benzyl group (compound 790) if anything only slightly decreased oral activity. One additional fact is noteworthy. Replacement of the β-chlorine by bromine (1000, Table V) essentially eliminated oral effectiveness. While this may at first appear startling it may be associated with the greater reactivity of the β-bromo compound which could result in its being destroyed before it can be absorbed into the blood stream from the gastrointestinal tract and distributed in the body. It has been amply demonstrated here and in previous work,[3,7,8] that structural factors are exceedingly important in contributing to blocking ability *per se* once the agent gets into the blood stream. However, we feel that it is probable that rather exacting requirements regarding solubility and chemical reactivity must be met to attain oral effectiveness.

Experimental[11]

Generous samples of 1-phenoxy-2-propanol, 1-(2-*s*-butylphenoxy)-2-propanol, 1-(4-*s*-butylphenoxy)-2-propanol, 1-(4-biphenyloxy)-2-propanol and 1-(4-cyclohexylphenoxy)-2-propanol were supplied by the Dow Chemical Company. *p*-Methoxybenzyl chloride[12] and 3,4-dimethoxybenzyl bromide[13] were prepared by methods described in the literature.

1-Aryloxy-2-propanols.—All the compounds listed in Table I were prepared by essentially the procedure described for 1-(3,4-dimethylphenoxy)-2-propanol.

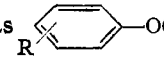
A solution of 112 g. (2.8 moles) of sodium hydroxide in 125 ml. of water was added to 350 g. (2.8 moles) of 3,4-di-

(11) Melting points are corrected, boiling points are uncorrected.

(12) Haller and Bauer, *Compt. rend.*, **153**, 23 (1911).

(13) Haworth, Perkin and Rankin, *J. Chem. Soc.*, **127**, 1444 (1925).

TABLE III

N-(β-ARYLOXYISOPROPYL)-AMINO ALCOHOLS 

R =	M.p., °C.	Yield, %	Recry.[a] solvn.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H	M.p.,[b] °C.	Hydrochloride Formula	Cl⁻ analyses Calcd.	Found
H	70.5-72	58	H	$C_{11}H_{17}NO_2$	67.66	8.77	67.60	9.02	103.5-104.5	$C_{11}H_{18}NO_2Cl$	15.30	15.18
2-CH_3	57.5-59	62	B, P	$C_{12}H_{19}NO_2$	68.86	9.15	69.02	9.12	101.5-102.4	$C_{12}H_{20}NO_2Cl$	14.43	14.39
3-CH_3	57-58	69	B, P	$C_{12}H_{19}NO_2$	68.86	9.15	68.82	8.60	84-86	$C_{12}H_{20}NO_2Cl$	14.43	14.36
4-CH_3	69-71	75	B, H	$C_{12}H_{19}NO_2$	68.86	9.15	68.78	8.99	100-102	$C_{12}H_{20}NO_2Cl$	14.43	14.43
2-$(CH_3)_2CH$	52-54	46	H	$C_{14}H_{23}NO_2$	70.85	9.77	70.94	9.75				
2-$C_2H_5CH(CH_3)$	69.5-71.5	59	H	$C_{15}H_{25}O_2N$	71.67	10.02	71.73	9.79				
4-$C_2H_5CH(CH_3)$	[c]	62		$C_{15}H_{25}NO_2$	71.67	10.02	71.63	9.88	95-97	$C_{15}H_{24}NOCl_2$	12.32	12.38
4-$(CH_3)_3C$	49-50	74	H	$C_{15}H_{25}NO_2$	71.67	10.02	72.03	9.94				
4-C_6H_5	141-142	89	E	$C_{17}H_{21}NO_2$	75.24	7.80	75.24	7.79				
4-C_6H_{11}	45-46	53	P	$C_{17}H_{27}NO_2$	73.60	9.81	73.72	9.91	134-135	$C_{17}H_{28}NO_2Cl$	11.30	11.40
2-$C_6H_5CH_2$	76.5-77	29	B, P	$C_{18}H_{23}NO_2$	75.75	8.12	75.75	8.23				
2-$(CH_3)_2CH$-5-CH_3	[d]	34		$C_{15}H_{25}NO_2$	71.67	10.03	71.51	10.03	118-120	$C_{15}H_{26}NO_2Cl$	12.32	12.23
3,4-di-CH_3	60-61.5	68	B, P	$C_{13}H_{21}NO_2$	69.92	9.48	69.97	9.42				
4-CH_3O	53-55	57	B, P	$C_{12}H_{19}NO_3$	63.97	8.50	64.04	8.35	108.5-109.5	$C_{12}H_{20}NO_3Cl$	13.55	13.50
4-$C_6H_5CH_2O$	121-122	76	B	$C_{18}H_{23}NO_3$	71.73	7.67	71.70	7.56				
2-Cl	[e]	52		$C_{11}H_{16}NO_2Cl$	57.51	7.02	58.01	7.45	115-117	$C_{11}H_{17}NO_2Cl_2$	13.32	13.35
4-Cl	63.5-64	62	B, P	$C_{11}H_{16}NO_2Cl$	57.51	7.02	57.77	7.26	77-78	$C_{11}H_{17}NO_2Cl_2$	[f]	
Other N-aryloxy amino alcohols												
α-$C_{10}H_7OCH_2CH(CH_3)NH$-CH_2CH_2OH	70-71.5	60	B, P	$C_{15}H_{19}NO_2$	73.44	7.81	73.42	7.90	119-121.5	$C_{15}H_{20}NO_2Cl$	12.58	12.57
$C_6H_4OCH_2CH(CH_3)$-$NHCH_2CH$-$(CH_3)OH$[g]	69.5-71(A) [h] (B)	22 19	H	$C_{12}H_{19}NO_2$ $C_{12}H_{19}NO_2$	68.86 68.86	9.15 9.15	68.88 68.71	9.05 8.89	135-136 97-99[i]	$C_{12}H_{20}NO_2Cl$ $C_{12}H_{20}NO_2Cl$	14.43 14.43	14.55 14.48

[a] Solvents as follows: H = Esso hexane, B = benzene, P = petroleum ether, E = ethanol, combinations denote recrystallization from mixed solvents. [b] Hydrochlorides were recrystallized from alcohol and ether unless noted otherwise. [c] B.p. 166–178° (3 mm.). [d] B.p. 127–128° (0.4 mm.). [e] B.p. 136–141° (0.7 mm.). [f] *Anal.* Calcd. for $C_{11}H_{17}NO_2Cl_2$: C, 49.63; H, 6.44. Found: C, 49.75; H, 6.27. [g] Racemates A and B. [h] B.p. 114–115° (0.7 mm.); $n^{20}D$ 1.5182. [i] Recrystallized once from acetone and thrice from alcohol and ether.

methylphenol dissolved in 400 ml. of alcohol. The solution was stirred and refluxed while 263 g. (2.8 moles) of propylene chlorohydrin was added dropwise over a two-hour interval. After an additional three hours of refluxing, the reaction mixture was allowed to cool and filtered. The salt cake was washed with a little alcohol, most of the alcohol was removed from the filtrate under reduced pressure and the crude product was dissolved in approximately an equal volume of benzene. The benzene solution was extracted with 10% sodium hydroxide solution, washed with water and distilled.

Some of the solid ether alcohols separated from the reaction mixture when it was allowed to cool; these were collected, washed with water and recrystallized.

1-Aryloxy-2-chloropropanes.—The general procedure is illustrated by the following preparation.

1-(3-Methylphenoxy)-2-propanol (272 g., 1.64 moles) was placed in a one-liter flask provided with a gas delivery tube dipping beneath the surface of the liquid, dropping funnel and condenser. The alcohol was cooled by an ice-bath and a slow stream of dry air was introduced while 146 g. (1.23 moles) of thionyl chloride was added over a two-hour period. Air was bubbled through the dark solution for three hours at room temperature and then another 146 g. of thionyl chloride was added over a half-hour interval.

The next morning two ml. of dry pyridine was added and the solution was heated on the steam-bath for three hours. The cooled reaction mixture was poured into a liter of water, 300 ml. of benzene was added and the aqueous phase was withdrawn. Sodium bicarbonate solution was used to wash the benzene solution free of acid. After a final wash with water, the solution was dried over magnesium sulfate, filtered and distilled.

Comparable yields were obtained when one mole of pyridine per mole of alcohol was employed. For example, 198 g. (1.7 moles) of thionyl chloride was added dropwise to a stirred cooled solution of 277 g. (1.4 moles) of 1-(2-isopropyl-5-methylphenoxy)-2-propanol and 134 g. (1.7 moles) of dry pyridine in 300 ml. of chloroform. After the addition was completed, the solution was refluxed for 1.5 hours, cooled and poured into water. The chloroform layer was separated, washed with sodium bicarbonate solution and water, dried and distilled.

Solid ether alcohols were treated in the same manner with dry benzene or chloroform as solvent. The yields, physical constants and analyses of the 2-chloropropanes are given in Table II.

2-(β-Aryloxyisopropylamino)-ethanols. Method A.—In a typical experiment 88 g. (1.44 moles) of ethanolamine was heated to boiling in a 500-ml. flask equipped with stirrer, dropping funnel and condenser while 89 g. (0.48 mole) of 1-(2-methylphenyl)-2-chloropropane was added dropwise with stirring. During the latter part of the addition two phases were formed. After the addition of the chloro compound the reaction mixture was refluxed for three hours, then cooled and poured into 300 ml. of water. The water-insoluble oil was extracted into 400 ml. of ether and the ether solution was extracted with 2 *N* hydrochloric acid until a clear solution was obtained when a sample of the extract was made basic. The combined extracts were made strongly alkaline with sodium hydroxide solution and extracted with three portions of ether. After the solution was dried over anhydrous potassium carbonate, the solvent was distilled. As the last traces of ether were being removed under reduced pressure, the amine solidified.

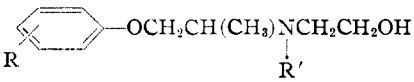
Method B.—A solution of 50 g. (0.33 mole) of phenoxyacetone and 20 g. (0.33 mole) of ethanolamine in alcohol No. 30 was shaken with Raney nickel under a hydrogen pressure of 3 atmospheres. Approximately 0.23 mole of hydrogen was absorbed. The solution was filtered, the alcohol evaporated under reduced pressure and the residue diluted with water. The organic layer was extracted into ether, and the ether removed *in vacuo*. Recrystallization of the solid from Esso hexane yielded 26 g. of product, m.p. 65–69°. Purification by formation of the hydrochloride, recrystallization and liberation of the free base gave 18.8 g. (25%) of material melting at 70.5–72°.

N-(β-Phenoxyisopropyl)-1-amino-2-propanol.—The reaction of 0.75 mole of 1-phenoxy-2-chloropropane with 2.25 moles of isopropanolamine was conducted as described in Method A above. The crude product was taken up in ether, dried and distilled to yield 87 g. (56%) of oil, b.p. 120–125° (3 mm.).

Anal. Calcd. for $C_{12}H_{19}O_2N$: C, 68.86; H, 9.15. Found: C, 68.59; H, 8.95.

A solution of the distillate in petroleum ether was cooled to −20°, whereupon the solid racemic form (Isomer A) crystallized. A second recrystallization from petroleum ether produced 35 g. (22%) of crystals, m.p. 69.5–71°.

TABLE IV

N,N-DISUBSTITUTED AMINO ALCOHOLS  —$OCH_2CH(CH_3)NCH_2CH_2OH$

R' = benzyl R =	B.p. or m.p., °C.	Press., mm.	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Formula	Hydrochloride[a] M.p., °C.	Cl⁻ analyses Calcd.	Cl⁻ analyses Found
H	150–151	0.25	85	$C_{18}H_{23}NO_2$	75.75	8.12	75.34	8.26				
2-CH_3	157–163	.2	66	$C_{19}H_{25}NO_2$	76.22	8.42	75.76	6.33	$C_{19}H_{26}NO_2Cl$	98–99.5	10.56	10.55
3-CH_3	154–161	.2	19						$C_{19}H_{26}NO_2Cl$	85.87	10.56	10.54
4-CH_3	159–163	.2	82	$C_{19}H_{25}NO_2$	76.22	8.42	75.90	8.61	$C_{19}H_{26}NO_2Cl$	112.5–114.5	10.56	10.44
2-$(CH_3)_2CH$	183–186	.7	68	$C_{21}H_{29}NO_2$	77.02	8.93	76.98	9.00				
2-$C_2H_5CH(CH_3)$	172	.35	55	$C_{22}H_{31}NO_2$	77.38	9.15	77.37	8.91				
4-$C_2H_5CH(CH_3)$	165–172	.25	81	$C_{22}H_{31}NO_2$	77.38	9.15	77.55	9.21				
4-$(CH_3)_3C$	66.5–67.5[b]		63	$C_{22}H_{31}NO_2$	77.38	9.15	77.33	9.26				
4-C_6H_5	222–232	.3	29	$C_{24}H_{27}NO_2$	79.74	7.53	79.76	7.63				
4-C_6H_{11}	215–216	.5	70	$C_{24}H_{33}NO_2$	78.43	9.05	78.51	8.91				
2-$C_6H_5CH_2$	211–216	.2	42	$C_{25}H_{29}NO_2$	79.96	7.79	79.99	8.02				
2-$(CH_3)_2CH$-5-CH_3	170–174	.4	69	$C_{22}H_{31}NO_2$	77.38	9.15	77.26	9.16	$C_{22}H_{32}NO_2Cl$	96–98	9.38	9.24
3,4-diCH_3	163.5–166[c]		81	$C_{20}H_{27}NO_2$	76.64	8.50	76.64	8.06	$C_{20}H_{28}NO_2Cl$	121–123	10.13	10.15
4-CH_3O	171–177	.2	61	$C_{19}H_{25}NO_3$	72.35	7.99	71.99	7.67	$C_{19}H_{26}NO_3Cl$	104.5–106	10.08	9.97
4-$C_6H_5CH_2O$			47[d]						$C_{25}H_{30}NO_3Cl$	110–111.5	8.29	8.44
2-Cl	170–179	.5	17						$C_{18}H_{23}NO_2Cl_2$	146–148	[e]	[e]
4-Cl	174–177	.2	60	$C_{18}H_{22}NO_2Cl$	67.59	6.93	67.40	6.94				
R = H, R' =												
4-$ClC_6H_4CH_2$	165–170	.3	75	$C_{18}H_{22}NO_2Cl$	67.59	6.93	67.49	6.68				
2,4-$Cl_2C_6H_3CH_2$			62	$C_{18}H_{21}NO_2Cl_2$	61.02	5.98	61.15	6.01				
3,4-$Cl_2C_6H_3CH_2$			66	$C_{18}H_{21}NO_2Cl$	[f]							
4-$CH_3OC_6H_4CH_2$	142–157	.2	70	$C_{19}H_{25}NO_3$	[f]							
3,4-$(CH_3O)_2C_6H_3CH_2$	188–189	.8	34	$C_{20}H_{27}NO_4$	69.64	7.88	69.40	8.23				
$C_6H_5OCH_2CH_2$	160–167	.2	87	$C_{19}H_{25}NO_3$	72.35	7.99	72.15	7.82				
$C_6H_5OCH_2CH(CH_3)$	180–183	.2	39	$C_{20}H_{27}NO_3$	72.92	8.26	72.91	8.35				
$CH_2=CHCH_2$	122–124	.7	36	$C_{14}H_{21}NO_2$	71.45	9.00	70.88	9.09				
C_2H_5	121–122	.8	51	$C_{13}H_{21}NO_2$	69.92	9.48	70.02	9.22				
$C_6H_5CH_2N(R)CH_2CH(R')OH$ R = R' =												
α-$C_{10}H_7OCH_2CH(CH_3)$ H	195–198	.2	50	$C_{22}H_{25}NO_2$	78.77	7.51	78.71	7.63				
$C_6H_5OCH_2CH(CH_3)$ CH_3 A	142–149	.2	81	$C_{19}H_{25}NO_2$	76.22	8.42	76.62	8.17				
CH_3 B	148–152	.2	68	$C_{19}H_{25}NO_2$	76.22	8.42	76.13	8.76				
$(2\text{-}C_5H_4N)OCH_2CH(CH_3)$[g] H	138–146	.3–.5	48	$C_{17}H_{22}N_2O_2$	71.30	7.74	70.70	7.64				

[a] Hydrochlorides were recrystallized from alcohol and ether. [b] Recrystallized from alcohol. [c] Recrystallized from Esso hexane. [d] Isolated as the hydrochloride salt. [e] Calcd.: C, 60.68; H, 6.51. Found: C, 60.68; H, 6.33. [f] Distilled base was not analyzed but was used directly to prepare the β-chloroethylamine. [g] The dipicrate, recrystallized from alcohol, melted at 131–132°. *Anal.* Calcd. for $C_{29}H_{28}N_6O_{16}$: C, 46.78; H, 3.79; N, 15.05. Found: C, 47.00; H, 4.32; N, 15.17.

The original petroleum ether filtrate was diluted with diethyl ether and saturated with dry hydrogen chloride. The salt was collected, recrystallized from acetone and then three times from alcohol and ether to yield 35 g. (19%) of Isomer B hydrochloride. The purified hydrochloride was converted to the free base which distilled as a colorless viscous oil, b.p. 114–115° (0.7 mm.), $n^{20}D$ 1.5182.

N,N-Disubstituted Amino Alcohols.—Most of the compounds listed in Table IV were prepared in the same manner as follows:

A mixture of 78.7 g. (0.35 mole) of 2-[β-(4-methoxyphenoxy)-isopropylamino]-ethanol, 24.2 g. (0.175 mole) of anhydrous potassium carbonate, 44 g. (0.35 mole) of benzyl chloride and 150 ml. of alcohol was stirred and refluxed for nine hours. Approximately 100 ml. of alcohol was removed by distillation, the concentrated mixture was refluxed an additional five hours and then diluted with 300 ml. of water. The organic layer was extracted into ether, the solution was dried over anhydrous magnesium sulfate, filtered and distilled.

The 4-benzyloxy compound was not distilled. The hydrochloride was formed by passing dry hydrogen chloride into a dried ether solution of the crude product. The other hydrochlorides in Table IV were prepared from the distilled bases.

The 4-methoxybenzyl, 3,4-dimethoxybenzyl and β-phenoxyethyl compounds were prepared by a slightly different procedure as illustrated by the following typical experiment.

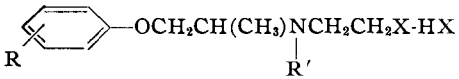
A solution of 28 g. (0.12 mole) of 3,4-dimethoxybenzyl bromide, 48 g. (0.24 mole) of 2-(β-phenoxyisopropylamino)-ethanol and 100 ml. of toluene was refluxed for two hours. The cooled mixture was diluted with 200 ml. of ether, the oil which separated gradually solidified and was removed by filtration. The filtrate was shaken with 100 ml. of 5% sodium hydroxide solution, washed with water, dried over anhydrous potassium carbonate and distilled.

Ethyl α-Benzylaminopropionate.—Three moles (321 g.) of benzylamine was heated to its boiling point while 271 g. (1.5 moles) of ethyl α-bromopropionate was added with stirring over a three-hour interval. The mixture was refluxed an additional 1.5 hours, poured into ice and water and made basic with 40% sodium hydroxide solution. The organic layer was extracted into ether, dried and distilled to yield 115 g. (37%) of product, b.p. 116–117.5° (5 mm.). *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.47; H, 8.30; N, 6.94.

2-Benzylamino-1-propanol.—Twenty-one grams (0.55 mole) of lithium aluminum hydride and 750 ml. of ether was stirred in a flask equipped with mercury sealed stirrer, dropping funnel and condenser while 115 g. (0.55 mole) of ethyl α-benzylaminopropionate in 200 ml. of ether was added dropwise at a rate to cause gentle refluxing. After the addition was completed, the mixture was refluxed for 45 minutes, cooled and 100 ml. of water added cautiously. The reaction mixture was then poured into 2 liters of 10% sulfuric acid, the ether layer was separated and discarded. The aqueous acid solution was made strongly basic with 40% sodium hydroxide solution and extracted twice with 150-ml. portions of benzene. Removal of the solvent left a solid which weighed 55 g. and melted at 64–66° after recrystallization from hexane. The slightly colored material was converted to the hydrochloride in ether solution and the salt was recrystallized from alcohol and ether. Conversion of the hydrochloride to the free base and recrystallization from hexane gave 41 g. (45%) of colorless crystals, m.p. 68–68.5°. *Anal.* Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.60; H, 9.05.

TABLE V

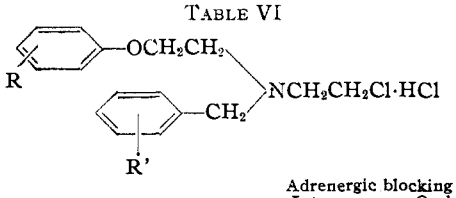
N,N-DISUBSTITUTED β-HALOETHYLAMINE HYDROHALIDES [a]



No.	R' = benzyl, X = Cl; R =	R' =	M.p., °C.	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. X⁻	Found C	Found H	Found X⁻	Adrenergic Blocking Action: Intravenous dose in mg./kg. [b]	Adrenergic Blocking Action: Oral rating at 10 mg./kg. [c]
688	H		137.5–140	60	$C_{18}H_{23}NOCl_2$	63.58	6.91	10.42	63.35	7.02	10.39	1–2.5	1600
783	2-CH_3		153.5–154.5	61	$C_{19}H_{25}NOCl_2$	64.40	7.11	10.01	64.48	6.99	9.98	1–2.5	600
845	3-CH_3		133–134	71	$C_{19}H_{25}NOCl_2$	64.40	7.11	10.01	64.50	6.89	9.97	2.5	100
730	4-CH_3		138–140	76	$C_{19}H_{25}NOCl_2$	64.40	7.11	10.01	64.31	7.02	10.02	10	Inactive
1001	2-$(CH_3)_2CH$		113.5–115.5	43	$C_{21}H_{29}NOCl_2$	65.96	7.65		65.99	7.43		1.0	0
793	2-$C_2H_5CH(CH_3)$		142–143.5	76	$C_{22}H_{31}NOCl_2$	66.66	7.88	8.94	66.79	7.54	8.86	5	100
901	4-$C_2H_5CH(CH_3)$		131–132	52	$C_{22}H_{31}NOCl_2$	66.66	7.88	8.94	66.79	7.95	8.92	>20	Not tested
974	4-$(CH_3)_3C$		158.5–159	50	$C_{22}H_{31}NOCl_2$	66.66	7.88	8.94	66.65	8.11	8.72	>20	Not tested
945	4-C_6H_5		182.5–183	90	$C_{24}H_{27}NOCl_2$	69.23	6.54	8.52	69.38	6.42	8.59	Insoluble	Inactive
924	4-C_6H_{11}		189.5–190.5	93	$C_{24}H_{33}NOCl_2$	68.23	7.87	8.39	68.10	7.84	8.58	>20	Not tested
1002	2-$C_6H_5CH_2$		134.5–136.5	46	$C_{25}H_{29}NOCl_2$	69.76	6.79	8.24	69.79	6.54	7.99	10	Inactive
973	2-$(CH_3)_2CH$-5-CH_3		107–109	61	$C_{22}H_{31}NOCl_2$	66.66	7.88		66.68	7.96		2.5	Inactive
883	3,4-$(CH_3)_2$		143–145	82	$C_{20}H_{27}NOCl_2$	65.21	7.39	9.63	65.25	7.22	9.58	2.5	Inactive
784	4-CH_3O		152–153	91	$C_{19}H_{25}NO_2Cl$	61.62	6.81	9.57	61.85	6.77	9.61	2.5–5	700
835	4-$C_6H_5CH_2O$		152–154	68	$C_{25}H_{29}NO_2Cl_2$	67.26	6.55	7.96	67.27	6.60	7.98	5	Inactive
972	4-HO		139–141	66	$C_{18}H_{23}NO_2Cl_2$	60.68	6.51	9.95	60.66	6.42	9.75	1–2.5	400
1025	2-Cl		164–166	71	$C_{18}H_{22}NOCl_3$			9.46			9.30	5	100
853	4-Cl		158.5–159	50	$C_{18}H_{22}NOCl_3$	57.69	5.92	9.46	57.80	6.11	9.46	10	100
1040	H X = Br		134.5–136.5	65	$C_{18}H_{22}NOBr_2$			18.62			18.72	1.0	100
	R = H, X = Cl; R' =												
804	4-$ClC_6H_4CH_2$		143–144	66	$C_{18}H_{22}NOCl_3$	57.69	5.92	9.46	57.67	6.30	9.79	10	300
805	2,4-$Cl_2C_6H_3CH_2$		116–118.5	55	$C_{18}H_{21}NOCl_4$	52.83	5.17	8.66	52.94	5.20	8.65	Inactive at 20	Not tested
803	3,4-$Cl_2C_6H_3CH_2$		145–146	54	$C_{16}H_{21}NOCl_4$	52.83	5.17		52.82	5.25		5	Inactive
854	4-$CH_3OC_6H_4CH_2$		146.5–147.5	38	$C_{19}H_{25}NO_2Cl_2$	61.62	6.81	9.58	61.75	6.78	9.31	5	100
880	3,4-$(CH_3O)_2C_6H_3CH_2$		128.5–129.5	54	$C_{20}H_{27}NO_3Cl_2$	60.00	6.80	17.72[d]	60.17	6.89	17.87[d]	1–2.5	500
806	$C_6H_5OCH_2CH_2$		99.5–100.5	40	$C_{19}H_{25}NO_2Cl_2$	61.62	6.80	9.58	61.67	7.07	9.73	0.5–1	1200
1273	$C_6H_5OCH_2CH(CH_3)$[e]		167–168.5	56	$C_{20}H_{28}NO_6ClS$			7.95[f]			7.74[f]	1–2.5	500
833	$CH_2=CHCH_2$		75–77	47	$C_{14}H_{21}NOCl_2$	57.93	7.29	12.22	57.94	7.55	12.31	5	1200
1370	C_2H_5[g]			35	$C_{13}H_{20}NOCl$	64.58	8.34		64.57	8.17		10+	Inactive
752	2-$CH_3C_6H_4CH_2$		118		$C_{19}H_{25}NOCl_2$			10.01			9.6	2.5–5	800
	$C_6H_5CH_2N(R)CH_2CH(R')Cl \cdot HCl$; R =	R' =				C	H	Cl⁻	C	H	Cl⁻		
907	α-$C_{10}H_7OCH_2CH(CH_3)$	H	172–175	70	$C_{22}H_{25}NOCl_2$	67.69	6.46	9.08	67.47	6.44	8.99	10–15	Not tested
781	$C_6H_5OCH_2CH(CH_3)$	CH_3 A	146–147	65	$C_{19}H_{25}NOCl_2$	64.40	7.11	10.01	64.20	7.32	10.02	2.5	600
947		CH_3 B	104–106.5	42	$C_{19}H_{25}NOCl_2$	64.40	7.11		64.54	7.00		2.5–5	Inactive
1137	(2-$C_5H_4N)OCH_2CH(CH_3)$[h]	H	138–139	73	$C_{17}H_{23}N_2OCl_3$	54.05	6.14	18.77	54.07	6.27	18.63	5	Inactive
	$(C_6H_5CH_2)_2NCH_2CH_2Cl$[i]											10	800

[a] Hydrohalides were recrystallized from alcohol and ether. [b] Amount of drug which when injected into cats causes a fall in blood pressure after 1 mg./kg. of epinephrine. [c] See text for explanation of numbering system. [d] Total chlorine. [e] Acid sulfate salt, recrystallized from alcohol and ether. [f] Organic chlorine. [g] Free base was liberated from its hydrochloride and distilled, b.p. 113–116° (0.2 mm.). [h] Dihydrochloride. [i] Dibenamine–Smith, Kline and French Laboratories trademark for N,N-dibenzyl β-chloroethylamine hydrochloride.

TABLE VI



No.	R	R	Adrenergic blocking action Intravenous dose in mg./kg.	Oral rating at 10 mg./kg.
513	H	H	2.5–5	1200
674	2-CH_3	H	1	400
861	2-$(CH_3)_2CH$	H	1–2.5	100
790	H	2-CH_3	2.5–5	1000

2-Benzylamino-1-(2-pyridyloxy)-propane.—Sodium (5.5 g., 0.24 mole) was added to a solution of 39 g. (0.24 mole) of 2-benzylamino-1-propanol and 250 ml. of dry xylene. When the initial reaction had subsided, the mixture was refluxed for three hours until all the sodium had reacted. Thirty-nine grams (0.24 mole) of 2-bromopyridine was added to the cold mixture which was heated slowly and finally refluxed for four hours. The cold xylene solution was extracted with water and then with 2 *N* hydrochloric acid. Sodium hydroxide was added to the acid solution and the base was extracted into ether. Thirty-seven grams (64%) of product, b.p. 104–116° (0.2–0.3 mm.), was obtained on distillation. A portion of the liquid was redistilled and the fraction boiling at 137–139° (1 mm.); $n^{20}D$ 1.5518 was analyzed.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49. Found: C, 74.10; H, 7.65.

N-[β-(2-Pyridyloxy)-isopropyl]-N-benzylethanolamine.—A mixture of 28.5 g. (0.12 mole) of 2-benzylamino-1-(2-pyridyloxy)-propane, 10.5 g. (0.24 mole) of ethylene oxide and 2.1 g. (0.12 mole) of water was heated in a closed vessel at 100° for four hours and then at 120° for another four hours. Ether was added, the solution was dried and distilled.

β-Phenoxyisopropylamine.—A solution of 75 g. (0.5 mole) of phenoxyacetone, 53 g. (0.5 mole) of benzylamine in 100 ml. of alcohol was hydrogenated over platinum oxide catalyst at approximately 3 atmospheres pressure. The calculated amount of hydrogen was absorbed in three hours at room temperature. The N-benzyl-β-phenoxyisopropylamine was not isolated, but to the filtered solution was added 0.5 mole of concentrated hydrochloric acid and 10% palladium-on-charcoal catalyst. Further hydrogenation at 3 atmospheres and room temperature removed the benzyl group. The filtered solution was concentrated to dryness, the residual hydrochloride was dissolved in water and the base liberated with sodium carbonate. The amine was extracted in ether, dried over potassium carbonate and distilled to give 90% of colorless liquid, b.p. 55–62° (0.3 mm.); $n^{20}D$ 1.5227.[14]

N,N-Bis-(β-phenoxyisopropyl)-amine.—Twenty-four grams (0.16 mole) of *p*-phenoxyisopropylamine and 24 g. (0.16 mole) of phenoxyacetone were heated at 110–120° (inside temperature) for two hours. The crude imine was dissolved in alcohol and hydrogenated over platinum oxide catalyst at 65° and 50 lb. After filtering, the solution was distilled to yield 30 g. (66%) of secondary amine, b.p. 160–162° (0.2–0.3 mm.).

The picrate was prepared in alcohol solution and was recrystallized from acetone, m.p. 159–162°.

Anal. Calcd. for $C_{24}H_{26}N_4O_9$: N, 10.89. Found: N, 11.07.

(14) Hurd and Perlitz, THIS JOURNAL, **68**, 38 (1946), report b. p. 117–120° (13 mm.); $n^{20}D$ 1.5237.

A solid isomer of N,N-bis-(β-phenoxyisopropyl)-amine was obtained in the following manner. The amine (124 g.) was converted into the neutral sulfate in alcohol solution and the salt was recrystallized twice from alcohol. Seventeen and one-half grams of the less soluble isomer, m.p. 172.5–174°, was collected and converted to the free base. Evaporation of an ether solution of the base left 14 g. of solid which melted at 46.5–47.5° after recrystallization from petroleum ether.

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.68; H, 7.75.

N,N-Bis-(β-phenoxyisopropyl)-ethanolamine.—Thirty-two grams (0.11 mole) of N,N-bis-(β-phenoxyisopropyl)-amine, 10 g. (0.22 mole) of ethylene oxide and 2 g. (0.11 mole) of water were heated in a sealed vessel at 100° for seven hours and then at 120° for six hours. The reaction mixture was dissolved in ether, dried over potassium carbonate and distilled. The tertiary amine distilled as a viscous oil, b.p. 180–183° (0.2 mm.), wt. 14 g. (39%). The picrate, recrystallized from alcohol, melted at 141–142°.

Anal. Calcd. for $C_{26}H_{30}N_4O_{10}$: H, 10.03. Found: N, 10.01.

N,N-Disubstituted-β-haloethylamine Hydrochloride.—The preparation of N-(β-phenoxyisopropyl)-N-benzyl-β-chloroethylamine hydrochloride serves to illustrate the general method.

Dry hydrogen chloride was introduced into 20 g. (0.067 mole) of N-(β-phenoxyisopropyl)-N-benzylethanolamine dissolved in 50 ml. of dry chloroform until the solution was acid to moistened congo paper. Nine grams (0.076 mole) of thionyl chloride in 50 ml. of chloroform was added slowly while the solution was cooled in an ice-bath. The solution was then heated on a water-bath at 50–60° for two hours after which the solvent was removed under reduced pressure. Crystallization of the oily residue was induced by trituration with ether and the hydrochloride was recrystallized from alcohol and ether.

The N-(β-phenoxyisopropyl)-N-benzyl-β-bromoethyl hydrobromide was prepared in the same manner from thionyl bromide.

N-[β-(4-Hydroxyphenoxy)-isopropyl]-N-benzyl-β-chloroethylamine hydrochloride was prepared by debenzylation[15] of the corresponding 4-benzyloxy compound as follows. Four grams (0.009 mole) of N-[β-(4-benzyloxyphenoxy)-isopropyl]-N-benzyl-β-chloroethylamine hydrochloride was refluxed for 3 hours in 13 cc. of concentrated hydrochloric acid and 13 cc. of alcohol No. 30. Removal of the solvent under reduced pressure left an oil which solidified on trituration with ether. Recrystallization of the solid from alcohol and ether gave 2 g. (66%) of the 4-hydroxy compound.

N,N-Bis-(phenoxyisopropyl)-β-chloroethylamine hydrochloride was not obtained in solid form. The oily salt was extracted with sodium bicarbonate solution and ether, the organic layer was separated and dried over potassium carbonate. Addition of the ethereal sulfuric acid to the ether solution of the free base precipitated a crystalline acid sulfate which was recrystallized from alcohol and ether.

Acknowledgments.—The authors are indebted to Ruth Savacool, Rita Fox and Frances McCarron for the analyses. We are also grateful to Dr. William Gump of Givaudan-Delawanna, Inc., for supplying us with compounds 752, 674, 861 and 790 and for his kind permission to include these compounds in this report.

PHILADELPHIA, PENNA. RECEIVED FEBRUARY 14, 1951

(15) Druey, *Bull. soc. chim.*, [5] **2**, 1737 (1935).