nitroölefins, which contain no hydrogen atom alpha to the nitro group, with diazomethane and diazoacetic ester has been shown to be a useful preparative scheme for the otherwise difficultly accessible 3,4-disubstituted pyrazoles and the corresponding 5-carboxylic esters.

2. The condensation of nitroölefins with diazomethane results in the formation of products (presumably nitropyrazolines) which yield 3,4-disubstituted pyrazoles in good yields when treated with mineral acids, alkali or heat. Four new pyrazoles of this type have been prepared and characterized. In one case, the intermediate nitropyrazoline was obtained in excellent yield as a crystalline solid. Evidence is presented for its structure. Attempts to isolate the pure nitropyrazolines obtained from aliphatic nitroölefins resulted in the isolation of pyrazoles.

3. Nitroölefins were observed to react with diazoacetic ester only at elevated temperatures (boiling petroleum ether, 100–140°). Oxides of nitrogen were eliminated during the course of the reaction. The products were substituted 5-carbethoxypyrazoles. Four new pyrazoles of this type were prepared and characterized.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GIVAUDAN-DELAWANNA, INC.]

Adrenergic Blocking Agents. II. N-(2-Chloroethyl)-N-(2-phenoxyethyl)-amine Hydrochlorides[1]

BY WILLIAM S. GUMP AND EDWARD J. NIKAWITZ

The important discovery by Nickerson and Goodman[2] that N-(2-chloroethyl)-dibenzylamine ("Dibenamine")[3] hydrochloride is a specific and potent adrenergic blocking agent was followed by the syntheses and pharmacological studies of other tertiary N-(2-chloroethyl) amines.

Without reviewing here the extended literature[4] on the subject, we wish to refer only to two types of compounds which are related to the series described in this paper. Rieveschl, Fleming and Coleman[5] synthesized N-[2-(2-biphenylyloxy)-ethyl]-N-(2-chloroethyl)-alkylamines, found to be moderately active adrenergic blocking substances,[6] and Henderson and Chen[7] reported on the strong epinephrine antagonism of N-(2-*o*-benzylphenoxyethyl)-N-(2-chloroethyl)-ethylamine hydrochloride. These compounds contain either phenyl or benzyl in the ortho position of the benzene ring of the phenoxyethyl moiety; we undertook the preparation of a series of N-(2-chloroethyl)-N-(2-phenoxyethyl)-amine hydrochlorides having alkyl, dialkyl, methoxy or chlorine as ring substituents, in an attempt to find substances of higher potency and to acquire further knowledge on the relationship between structure and activity.

Our new amines belong mainly to three groups (listed in Tables IX to XI) of the configurations:

Groups I and II $ROCH_2CH_2\diagdown\!\!\diagup NCH_2CH_2Cl\cdot HCl$ (R' = C_2H_5 (I), $C_6H_5CH_2$ (II))

R = phenyl or phenyl substituted by alkyl, dialkyl, methoxy

Group III $(ROCH_2CH_2)_2NCH_2CH_2Cl\cdot HCl$

R = phenyl or phenyl substituted by alkyl, dialkyl, methoxy, chlorine

The properties of other tertiary N-(2-chloroethyl)-amine hydrochlorides closely related, but not exactly belonging to the types of Groups I to III, are described in Table XII.

The N-(2-chloroethyl)-amine hydrochlorides of our series are crystalline white substances, soluble in alcohols and glycols; they are practically insoluble in water, with the exception of the N-ethyl derivatives which show slight solubility. The 2-chloroethyl compounds were obtained from the corresponding N,N-disubstituted 2-aminoethanols on treating them with thionyl chloride. The 2-aminoethanols (Tables V–VIII) were synthesized in satisfactory yields by the condensation of 2-ethylaminoethanol, 2-benzylaminoethanol and 2-aminoethanol with the appropriate β-halogen phenetoles. The introduction of two phenoxyethyl groups into 2-aminoethanol required the use of the more reactive β-bromophenetoles.

In the case of some of the alcohols listed in Tables VI and VII, it was found preferable to carry out the synthesis in two steps. The secondary amino alcohols (Table IV) were prepared first and then condensed with benzyl chloride or a substituted β-halogen phenetole.

For the synthesis of the compounds listed in Table XII, the same general procedures were employed and the steps involved are evident from the formulas.

The preparation of di-(2-*o*-tóloxyethyl)-amine hydrochloride (Table XIII, No. 3) was first tried

(1) Presented before the Division of Medicinal Chemistry at the 116th Meeting of the American Chemical Society, Atlantic City, September 21, 1949.

(2) Nickerson and Goodman, *Federation Proc.*, **5**, 194 (1946); *J. Pharmacol. Exp. Therap.*, **89**, 167 (1947).

(3) Trade-mark of Smith, Kline & French Laboratories, Philadelphia, Pa.

(4) Nickerson, *Pharmacological Reviews*, *J. Pharmacol. Exp. Therap.*, **95**, 27 (part 2, April, 1949).

(5) Rieveschl, Fleming and Coleman, Abstracts of Papers 112th Meeting, A. C. S., Sept. 1947.

(6) Achenbach and Lowe, *Federation Proc.*, **6**, 304 (1947); *J. Pharmacol. Exp. Therap.*, **95**, 448 (1949).

(7) Henderson and Chen, *Federation Proc.*, **8**, 301 (1949).

by the reaction of β-bromo-*o*-methylphenetole with ammonia in an autoclave, as mentioned by Kahane and Lévy.[8] However, this method was found to be unsatisfactory; therefore, we condensed *o*-cresol with N-benzyl-di-(2-chloroethyl)-amine hydrochloride in alkaline solution and removed the benzyl group from the resulting N-benzyl-di-(2-*o*-toloxyethyl)-amine by catalytic hydrogenation.

TABLE I

2-PHENOXYETHANOLS, $ROCH_2CH_2OH$

R	B. p., °C. (4 mm.)	$n^{20}D$	Purity,[a] %
o-Ethylphenyl	116–120	1.5180	99
o-Isopropylphenyl	119–125	1.5200	101
o,-*n*-Amylphenyl	136–141	1.5312	98.5
m,*m*-Dimethylphenyl	130–133	....	100

[a] Determined by acetylation.

TABLE II

β-CHLOROPHENETOLES, $ROCH_2CH_2Cl$

R	Empirical formula	B. p., °C. (4 mm.)	$n^{20}D$	Chlorine, % Calcd.	Found
o-Tolyl[a,c]	$C_9H_{11}OCl$	90–94	1.5270	20.8	20.9
m-Tolyl[c]	$C_9H_{11}OCl$	98–100	1.5288	20.8	21.0
p-Tolyl[c]	$C_9H_{11}OCl$	91–94	Mushy crystals	20.8	20.9
o-Ethylphenyl	$C_{10}H_{13}OCl$	103–106	....	19.2	19.0
o-Isopropylphenyl	$C_{11}H_{15}OCl$	105–109	1.5180	17.9	17.8
o-*n*-Amylphenyl	$C_{13}H_{19}OCl$	130–133	1.5151	15.6	15.9
m,*p*-Dimethylphenyl	$C_{10}H_{13}OCl$	116–118	1.5198	19.2	19.2
Thymyl	$C_{12}H_{17}OCl$	115–119	1.5160	16.7	16.5
o-Methoxyphenyl[c]	$C_9H_{11}O_2Cl$	123–128	M. p. 41–43°	19.0	19.2
o-Chlorophenyl[b,c]	$C_8H_9OCl_2$	111–114	1.5500	37.2	37.1
p-Chlorophenyl[b]	$C_8H_9OCl_2$	115–117	M. p. 41°	37.2	36.9

[a] Clemo and Perkin, *J. Chem. Soc.*, **121**, 642 (1922). [b] Coleman and Stratton, U. S. Patent 2,186,367 (Jan. 9, 1940). [c] Harris and Stewart *Can. J. Research*, **27B**, 739 (1949).

TABLE III

β-BROMOPHENETOLES, $ROCH_2CH_2Br$

R	Empirical formula	B. p., °C. (5 mm.)	$n^{20}D$	Bromine, % Calcd.	Found
o-Allylphenyl	$C_{11}H_{13}OBr$	133–136	1.5528	33.2	33.0
p-Allyl-*o*-methoxyphenyl	$C_{12}H_{15}O_2Br$	160–162	1.5525	29.4	29.0
sym.-Xylyl	$C_{10}H_{13}OBr$	120–121	1.5408	34.8	34.5
2,5-Xylyl	$C_{10}H_{13}OBr$	124–125	1.5408	34.8	34.3
o-Isopropylphenyl	$C_{11}H_{15}OBr$	123–127	1.5350	32.9	32.7

Condensation of *o*-cresol with N-ethyl-di-(2-chloroethyl)-amine hydrochloride and with N-(2-chloroethyl)-diethylamine hydrochloride yielded compounds 4 and 6 (Table XIII).

Pharmacological Results

Adrenergic blocking activity and toxicity of this series of compounds was determined[9] as outlined in our previous paper[10] and as described in detail by Nickerson and Gump.[11]

The compounds are listed as active or inactive. Those compounds which are distinctly more or less active than Dibenamine (designated as ++) are marked +++ and +, respectively. It will be noted that the N-ethyl derivatives (Table IX) are quite toxic and not particularly active. The N-benzyl compounds with methoxy or low alkyl substituents (Table X) are highly potent; for example, N-benzyl-N-(2-chloroethyl)-2-*o*-toloxyethylamine hydrochloride (Table X, No. 2) is about five times as active as Dibenamine hydrochloride when administered intravenously.[12] These substances also show a favorable therapeutic index, with the exception of the rather toxic methoxy derivative. The di-(2-phenoxyethyl)-amines containing *o*-methyl and *o*-methoxy groups (Table XI) follow a similar pattern. In contrast to the very potent N-(2-chloroethyl)-N-ethyl-1-naphthalenemethylamine hydrochloride,[13] the 2-(α-naphthoxyethyl) analog (Table XII, No. 1) is almost void of adrenergic blocking activity.

Kahane and Lévy[8] who had carried out extensive studies on the sympatholytic effects of primary and secondary substituted 2-phenoxyethylamines found the ortho derivatives, such as the hydrohalides of N-(2-*o*-toloxyethyl)-2-aminoethanol and of di-(2-*o*-toloxyethyl)-amine to be the most active compounds. We prepared the hydrochlorides of these two amines and a few substances of similar configuration (Table XIII). All these amines are closely related to potent compounds (Table IX, no. 3 and Table XI, no. 2) of our series and exhibit adrenergic blockade. However, it should be emphasized that their blocking action is of a very different type from that characteristic of Dibenamine and of the substances listed in Tables IX–XII. The blockade is transitory and is not significantly altered by the presence of sodium thiosulfate[14] whereas prior administration of this chemical will prevent the typical epinephrine-reversal of Dibenamine and its congeners.[15]

(8) Kahane and Lévy, *Bull. soc. chim. biol.*, **27**, 562 (1945).

(9) The authors are greatly indebted to Dr. M. Nickerson of the University of Utah for the pharmacological testing of the chemicals.

(10) Gump and Nikawitz, THIS JOURNAL, **72**, 1309 (1950).

(11) Nickerson and Gump, *J. Pharmacol. Exp. Therap.*, **97**, 25 (1949).

(12) Ref. 4, p. 42.

(13) Loew and Micetich, *J. Pharmacol. Exp. Therap.*, **93**, 434 (1948).

(14) Ref. 11, p. 45.

(15) Nickerson and Goodman, *Federation Proc.*, **7**, 399 (1948).

TABLE IV

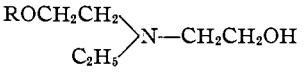
N-(2-PHENOXYETHYL)-2-AMINOETHANOLS: $ROCH_2CH_2NHCH_2CH_2OH$, R = PHENYL OR SUBSTITUTED PHENYL

No.	Substituent in phenyl group	Empirical formula	B. p. °C.	Mm.	$n^{20}D$	Yield,[a] %	Purity,[b] %
1	.....	$C_{10}H_{15}NO_2$	172–178	4	1.5373	60	102
2	*o*-Methyl	$C_{11}H_{17}NO_2$	168–170	4	1.5340	73	100
3	*o*-Isopropyl	$C_{13}H_{21}NO_2$	177–183	4	1.5252	61	99
4	*o*-Methoxy	$C_{11}H_{17}NO_3$	181–186	4	1.5386	74	99.5
5	*p*-Methoxy	$C_{11}H_{17}NO_3$	200–205	4	....	63	100

[a] Yields are based on β-halogen phenetoles. [b] Determined by potentiometric titration.

TABLE V

N-ETHYL-N-(2-PHENOXYETHYL)-2-AMINOETHANOLS R = MONO- OR DISUBSTITUTED PHENYL

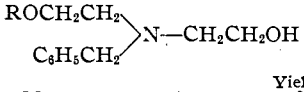


No.	Substituent in phenyl group	Empirical formula	B. p. °C.	Mm.	$n^{20}D$	Yield,[a] %	Purity,[b] %
1	.....	$C_{12}H_{19}NO_2$	152–158	4	1.5195	64	99.5
2	*p*-Methyl	$C_{13}H_{21}NO_2$	164–170	3	1.5158	66	101
3	*o*-Methyl	$C_{13}H_{21}NO_2$	166–170	4	1.5200	75	100.5
4	*o*-Methoxy	$C_{13}H_{21}NO_3$	177–180	4	1.5245	35	101
5	*o*-Ethyl	$C_{14}H_{23}NO_2$	168–170	4	1.5188	40	100
6	*o*-Isopropyl	$C_{15}H_{25}NO_2$	168–175	4	1.5113	83	100.5
7	*m,p*-Dimethyl	$C_{14}H_{23}NO_2$	192–195	6	1.5192	58	100
8	*o*-Methoxy-*p*-allyl	$C_{16}H_{25}NO_3$	201–208	4	1.5260	45	99

[a] Yields are based on β-halogen phenetoles. [b] Determined by potentiometric titration.

TABLE VI

N-BENZYL-N-(2-PHENOXYETHYL)-2-AMINOETHANOLS R = MONO- OR DISUBSTITUTED PHENYL



No	Substituent in phenyl group	Empirical formula	B. p. °C.	Mm.	$n^{20}D$	Yield,[a] %	Purity,[b] %
1	.....	$C_{17}H_{21}NO_2$	207–213	6	1.5599	41	96
2	*o*-Methyl	$C_{18}H_{23}NO_2$	215–222	4	1.5590	64	101
3	*o*-Methoxy	$C_{18}H_{23}NO_3$	238–244	4	1.5640	39	101
4	*p*-Methoxy	$C_{18}H_{23}NO_3$	246–250	4	1.5605	41	100
5	*o*-Ethyl	$C_{19}H_{25}NO_2$	225–227	5	1.5548	50	101
6	*o*-Isopropyl	$C_{20}H_{27}NO_2$	232–238	4	1.5500	64	101
7	*o*-*n*-Amyl	$C_{22}H_{31}NO_2$	244–249	4	1.5560	44	97
8	*m,p*-Dimethyl	$C_{19}H_{25}NO_2$	248–250	6	1.5572	31	102

[a] Yields are based on β-halogen phenetoles. [b] Determined by potentiometric titration.

TABLE VII

N,N-DI-(2-PHENOXYETHYL)-2-AMINOETHANOLS, $(ROCH_2CH_2)_2NCH_2CH_2OH$, R = MONO- OR DISUBSTITUTED PHENYL

No.	Substituent in phenyl group	Empirical formula	B. p. °C.	Mm.	$n^{20}D$[a]	Yield,[b] %	Purity,[c] %
1	.....	$C_{18}H_{23}NO_4$	245–250	5	1.5548	46	99
2	*o*-Methyl	$C_{20}H_{27}NO_3$	250–255	5	1.5540	57	101
3	*m*-Methyl	$C_{20}H_{27}NO_3$	278–285	7	....	33	100
4	*p*-Methyl	$C_{20}H_{27}NO_3$	242–248	3	....	39	100
5	*o*-Methoxy	$C_{20}H_{27}NO_5$	260–269	4	....	24	97
6	*o*-Chloro	$C_{18}H_{21}NO_3Cl$	265–273	4	....	21	97
7	*p*-Chloro	$C_{18}H_{21}NO_3Cl$	269–278	4	....	30	102
8	2,5-Dimethyl	$C_{22}H_{31}NO_3$	257–264	4	1.5479	49	101
9	3,5-Dimethyl	$C_{22}H_{31}NO_3$	254–261	3	....	42	100.5
10	3-Methyl-6-isopropyl	$C_{26}H_{39}NO_3$	252–258	4	1.5348	35	102

[a] No determination of the refractive index of substances being very viscous or partly solid at room temperature. [b] Yields are based on β-halogen phenetoles. [c] Determined by potentiometric titration.

Experimental

A. β-Halophenetoles

(a) **β-Chlorophenetoles.**—β-Chlorophenetole was obtained from Eastman Kodak Co. The substituted β-chlorophenetoles were prepared by condensing the corresponding sodium phenolates with ethylene chlorohydrin and treating the resulting 2-phenoxyethanols with thionyl chloride in the presence of pyridine[16]; the over-all yields amounted to 45–70%. The substituted 2-phenoxyethanols have been described in the literature with the exception of the compounds listed in Table I.

(16) Kirner, THIS JOURNAL, **48**, 2748 (1926).

TABLE VIII

COMPOUNDS OF THE GENERAL STRUCTURE $\begin{matrix} R \\ R' \end{matrix}\!\!>\!NCH_2CH_2OH$

No.	R	R′	Empirical formula	B. p. °C.	Mm.	$n^{20}D$	Yield, %	Purity,[d] %
1	C_2H_5	α-$C_{10}H_7OCH_2CH_2$	$C_{16}H_{21}NO_2$	211–221	5	1.5820	60[a]	98
2	C_2H_5	β-$C_{10}H_7OCH_2CH_2$	$C_{16}H_{21}NO_2$	215–220	4	1.5810	53[a]	100
3	C_2H_5	o-$CH_3C_6H_4OCH_2OCH_2CH_2CH_2$	$C_{15}H_{25}NO_3$	195–203	4	1.5085	65[a]	99.5
4	α-$C_{10}H_7CH_2$	o-$CH_3C_6H_4OCH_2CH_2$	$C_{22}H_{25}NO_2$	275–285	4	....	56[b]	102
5	o-$CH_3OC_6H_4OCH_2CH_2$	o-$CH_3C_6H_4OCH_2CH_2$	$C_{20}H_{27}NO_4$	256–269	4	....	33[c]	96

[a] Yields are based on β-halogen phenetoles. [b] On 1-naphthalenemethyl chloride. [c] On β-bromo-2-methylphenetoles. [d] Determined by potentiometric titration.

TABLE IX

N-(2-CHLOROETHYL)-N-(2-PHENOXYETHYL)-ETHYLAMINE HYDROCHLORIDES $\begin{matrix} ROCH_2CH_2 \\ C_2H_5 \end{matrix}\!\!>\!N\cdot CH_2CH_2Cl\cdot HCl$
R = MONO- OR DISUBSTITUTED PHENYL

No.	Substituent in phenyl group	Empirical formula	M. p., °C.	Yield,[a] %	Chlorine, % Chloride Calcd.	Chloride Found	Total Calcd.	Total Found	Toxicity[b] (approx. L. D. 50) mg./kg.	Adrenergic[b] blocking activity
1	.....	$C_{12}H_{19}NOCl_2$	103–105	29	13.5	13.7	26.8	26.5	35	+
2	p-Methyl	$C_{13}H_{21}NOCl_2$	105–107	24	12.8	13.0	25.5	25.6	. . .	±
3	o-Methyl	$C_{13}H_{21}NOCl_2$	126–128	69	12.8	12.6	25.5	25.4	40	++
4	o-Methoxy	$C_{13}H_{21}NO_2Cl_2$	127–129	69	12.0	11.9	24.1	24.2	25	++
5	o-Ethyl	$C_{14}H_{23}NOCl_2$	106–108	29	12.2	12.1	24.3	24.6	70	++
6	o-Isopropyl	$C_{15}H_{25}NOCl_2$	130–132	54	11.6	11.7	23.2	23.2	100	++
7	m,p-Dimethyl	$C_{14}H_{23}NOCl_2$	135–136	68	12.2	12.0	24.3	24.2	400	−
8	o-Methoxy-p-allyl	$C_{16}H_{25}NO_2Cl_2$	124–126	30	10.6	10.3	21.2	21.4	<15	−
	"Dibenamine" hydrochloride								800	++

[a] Yields are based on N-ethyl-N-(2-phenoxyethyl)-2-aminoethanols. [b] See text for explanation.

TABLE X

N-(2-CHLOROETHYL)-N-(2-PHENOXYETHYL)-BENZYLAMINE HYDROCHLORIDES $\begin{matrix} ROCH_2CH_2 \\ C_6H_5CH_2 \end{matrix}\!\!>\!N\cdot CH_2CH_2Cl\cdot HCl$
R = MONO- OR DISUBSTITUTED PHENYL

No.	Substituent in phenyl group	Empirical formula	M. p., °C.	Yield,[a] %	Chlorine, % Chloride Calcd.	Chloride Found	Total Calcd.	Total Found	Toxicity (approx. L. D. 50) mg./kg.	Adrenergic blocking activity
1	.....	$C_{17}H_{21}NOCl_2$	106–108	37	10.9	11.2	21.8	21.6	125	++
2	o-Methyl	$C_{18}H_{23}NOCl_2$	142–144	61	10.4	10.5	20.8	21.1	>1000	+++
3	o-Methoxy	$C_{18}H_{23}NO_2Cl_2$	127–129	13	10.0	10.3	19.9	19.5	50	+++
4	p-Methoxy	$C_{18}H_{23}NO_2Cl_2$	140–142	75	10.0	9.9	19.9	19.9	<100	+++
5	o-Ethyl	$C_{19}H_{25}NOCl_2$	117–119	20	10.0	10.3	20.0	20.2	1000	+++
6	o-Isopropyl	$C_{20}H_{27}NOCl_2$	127–128	55	9.7	9.6	19.3	19.2	1000	+++
7	o-n-Amyl	$C_{22}H_{31}NOCl_2$	136–138	13	9.0	9.1	18.0	18.3	>1000	+
8	m,p-Dimethyl	$C_{19}H_{25}NOCl_2$	150–152	66	10.0	10.1	20.0	19.8	1000	+ (weak)

[a] Yields are based on N-benzyl-N-(2-phenoxyethyl)-2-aminoethanols.

TABLE XI

N-(2-CHLOROETHYL)-DI-(2-PHENOXYETHYL)-AMINE HYDROCHLORIDES, $(ROCH_2CH_2)_2NCH_2CH_2Cl\cdot HCl$, R = MONO- OR DISUBSTITUTED PHENYL

No.	Substituent in phenyl group	Empirical formula	M. p., °C.	Yield,[a] %	Chlorine, % Chloride Calcd.	Chloride Found	Total Calcd.	Total Found	Toxicity (approx. L. D. 50) mg./kg.	Adrenergic blocking activity
1	.....	$C_{18}H_{23}NO_2Cl_2$	130–131	48	10.0	10.2	19.9	19.9	35	++
2	o-Methyl	$C_{20}H_{27}NO_2Cl_2$	140–142	34	9.3	9.5	18.5	18.6	>1000	+++
3	m-Methyl	$C_{20}H_{27}NO_2Cl_2$	99–100	39	9.3	9.3	18.5	18.5	....	+
4	p-Methyl	$C_{20}H_{27}NO_2Cl_2$	148–151	41	9.3	9.5	18.5	18.1	....	+
5	o-Methoxy	$C_{20}H_{27}NO_4Cl_2$	109–111	15	8.5	8.6	17.1	17.4	50	+++
6	o-Chloro	$C_{18}H_{21}NO_2Cl_4$	150–153	18	8.5	8.2	33.4	33.2	1000	+ (slight)
7	p-Chloro	$C_{18}H_{21}NO_2Cl_4$	141–144	12	8.5	8.7	33.4	33.1	....	−
8	2,5-Dimethyl	$C_{22}H_{31}NO_2Cl_2$	151–154	60	8.6	8.5	17.2	17.0	> 500	−
9	3,5-Dimethyl	$C_{22}H_{31}NO_2Cl_2$	146–148	30	8.6	8.2	17.2	16.9	....	−
10	3-Methyl-6-isopropyl	$C_{26}H_{39}NO_2Cl_2$	124–126	19	7.6	7.8	15.2	15.0	>1000	−

[a] Yields are based on N,N-di-(2-phenoxyethyl)-2-aminoethanols.

TABLE XII

COMPOUNDS OF THE GENERAL STRUCTURE $\begin{matrix}R\\R'\end{matrix}\rangle NCH_2CH_2Cl\cdot HCl$

No.	R	R′	Empirical formula	M. p., °C.	Yield,[a] %	Chlorine, % Chloride Calcd.	Chloride Found	Total Calcd.	Total Found	Toxicity (approx. L. D. 50) mg./kg.	Adrenergic blocking activity
1	C_2H_5	α-$C_{10}H_7OCH_2CH_2$	$C_{16}H_{21}NOCl_2$	131–133	44	11.3	11.3	22.6	22.7	60	+ (very slight)
2	C_2H_5	β-$C_{10}H_7OCH_2CH_2$	$C_{16}H_{21}NOCl_2$	132–134	35	11.3	11.3	22.6	22.5	75	−
3	C_2H_5	o-$CH_3C_6H_4OCH_2CH_2OCH_2CH_2$	$C_{15}H_{25}NO_2Cl_2$	96–98	54	11.0	11.1	22.0	22.0	70	−
4	α-$C_{10}H_7CH_2$	o-$CH_3C_6H_4OCH_2CH_2$	$C_{22}H_{25}NOCl_2$	173–176	32	9.1	9.3	18.0	18.0	>1000	++
5	o-$CH_3OC_6H_4OCH_2CH_2$	o-$CH_3C_6H_4OCH_2CH_2$	$C_{20}H_{27}NO_3Cl_2$	122–124	35	8.9	8.8	17.7	17.7	100	+++

[a] Yields are based on the corresponding aminoethanols (Table VII).

The properties of the β-chlorophenetoles are summarized in Table II.

(b) **β-Bromophenetoles.**—The β-bromoethers were obtained from the reaction of the substituted sodium phenolates with ethylene bromide[17]; the yields were rather low (30–55%). A series of β-bromophenetoles had been prepared by Kahane and Lévy[8] in connection with their syntheses of substituted phenoxyethylamines. Compounds not reported in the literature are listed in Table III.

B. **2-Phenoxyethylaminoethanols.**—(a) Secondary amines (Table IV).: The secondary amino alcohols were prepared by condensation of the substituted β-halogen phenetoles with an excess of 2-aminoethanol. The following example shows the method employed:

N-(2-*o*-Toloxyethyl)-2-aminoethanol (IV, 2).—2-Aminoethanol (366 g., 6 moles) was stirred, heated to 100–110°, and β-chloro-*o*-methylphenetole (171 g., 1 mole) was added dropwise during two hours. After the mixture had been stirred and heated to 120° for three hours, it was cooled to about 70° and a solution of 40 g. of sodium hydroxide in 40 ml. of water and 500 ml. of alcohol was added. After cooling, the solution was filtered from the formed salt and the alcohol removed by distillation. The residual oil was distilled at 4 mm. pressure, yielding 281 g. of recovered 2-aminoethanol, an intermediate fraction of 26 g., b. p. 66–165°, and a main fraction of 165 g., b. p. 165–175°. The latter was redistilled, resulting in 145 g. of pure N-(2-*o*-toloxyethyl)-2-aminoethanol.

(b) **N-Ethyl-N-(2-phenoxyethyl)-2-aminoethanols (Table V).**—The N-ethyl-2-(2-phenoxyethyl)-2-aminoethanols were obtained from 2-ethylaminoethanol and the β-halogen phenetoles; the preparation of one of these amino alcohols is described to illustrate the procedure:

N-Ethyl-N-(2-*p*-toloxyethyl)-2-aminoethanol (V, 2).—2-Ethylaminoethanol (89 g.) was stirred, heated to 100–110°, and 85 g. of β-chloro-*p*-methylphenetole was added dropwise during one hour. The mixture was stirred and heated at 120° for four hours, cooled to about 80° and made alkaline with sodium hydroxide solution. The oil was extracted from the cold mixture with benzene, the benzene solution washed with water and dried with anhydrous sodium sulfate. After removal of the solvent, the product (83 g.) boiled at 165–172° (3 mm.). Redistillation yielded the pure substance (74 g.) boiling at 166–169° (3 mm.). In the case of compounds 4, 6 and 7 (Table V) better results were obtained on heating the reactants at 160–170° instead of 120°.

(c) **N-Benzyl-N-(2-phenoxyethyl)-2-aminoethanols (Table VI).**—These amino alcohols were prepared in the same manner as the N-ethyl compounds (B, b), 2-benzylaminoethanol being employed instead of 2-ethylaminoethanol. An alternate method was used for compounds 4 and 6 (Table VI); the secondary alcohols (B, a) were treated with benzyl chloride in the presence of anhydrous potassium carbonate:

N-Benzyl-N-(2-*o*-isopropylphenoxyethyl)-2-aminoethanol (VI, 6).—Benzyl chloride (24 g.) was dropped during thirty minutes into a mixture of 40 g. of N-(2-*o*-isopropylphenoxyethyl)-2-aminoethanol (IV, 3) and 50 g. of anhydrous potassium carbonate which was stirred and heated to 110°. Heating was continued for six hours at 150°. After cooling, the mixture was made alkaline with sodium hydroxide solution and the oil extracted with benzene. The benzene layer was washed with water and dried with anhydrous sodium sulfate; after removal of the benzene, the amino alcohol (29 g.) boiled at 230–250° (5 mm.). On redistillation, 22 g., boiling at 232–238° (4 mm.), were obtained.

(d) **N,N-Di-(2-phenoxyethyl)-2-aminoethanols (Table VII).** Method I: 2-Aminoethanol (1 mol.) was condensed with the appropriate β-bromophenetole (1 mol.) at 150–160°, following the procedure given under (b).

Method II: Secondary aminoethanols (Table IV) were reacted with the corresponding β-bromophenetoles in the

(17) Marvel and Tannenbaum, "Org. Syntheses," Coll. Vol. I, 2nd ed., p. 436.

TABLE XIII

N-(2-*o*-TOLOXYETHYL)-AMINE HYDROCHLORIDES *o*-$CH_3C_6H_4OCH_2CH_2N(R)(R')\cdot HCl$

No.	R	R'	Empirical formula	M. p., °C.	Chlorine, % Calcd.	Found	Toxicity (approx. L. D. 50) mg./kg.	Adrenergic blocking (activity of short duration)
1[a]	H	$HOCH_2CH_2$	$C_{11}H_{18}NO_2Cl$	141–142	15.3	15.3	>500	+
2	H	$ClCH_2CH_2$	$C_{11}H_{17}NOCl_2$	199–200	28.4	28.7	>500	++
					Cl^- 14.2	14.2		
3[b]	H	*o*-$CH_3C_6H_4OCH_2CH_2$	$C_{18}H_{24}NO_2Cl$	168–170	11.0	11.0	...	++
4	C_2H_5	*o*-$CH_3C_6H_4OCH_2CH_2$	$C_{20}H_{28}NO_2Cl$	144–145	10.2	10.3	100	+
5	CH_2CH_2OH	*o*-$CH_3C_6H_4OCH_2CH_2$	$C_{20}H_{28}NO_3Cl$	138–139	9.7	9.6	>500	+
6	C_2H_5	C_2H_5	$C_{13}H_{22}NOCl$	139–141	14.5	14.6	...	+

[a] Ref. 8 (m. p. 139°). [b] Ref. 8 (hydrobromide, m. p. 145°).

presence of anhydrous potassium carbonate in the same manner as benzyl chloride was employed in procedure c.

C. 2-Chloroethylamine Hydrochlorides (Tables IX-XII).—The amino alcohols were treated with thionyl chloride as illustrated by the example given:

N-(2-Chloroethyl)-N-(2-*o*-methoxyphenoxyethyl)-ethylamine Hydrochloride (IX, 4).—A solution of 20.0 g. of thionyl chloride in 100 ml. of chloroform was dropped during two hours into a solution of 30.8 g. of the amino alcohol (V, 4) in 100 ml. of chloroform which was stirred and cooled in an ice-bath. After a few hours at room temperature, the solvent was distilled off and the residue refluxed for fifteen minutes with 80 cc. of absolute alcohol in the presence of 5 g. of decolorizing carbon. The filtered solution was mixed with 300 cc. of ether and put into the refrigerator for crystallization. The purification process was repeated using 100 cc. of abs. alcohol, 5 g. of carbon and 200 cc. of ether; yield, 26 g. of white crystals.

In some cases, three or four recrystallizations from alcohol–ether were necessary in order to obtain colorless, crystalline substances.

N-(2-*o*-Toloxyethyl)-amine Hydrochlorides (Table XIII)

Di-(2-*o*-Toloxyethyl)-amine Hydrochloride (XIII, 3): (a) **N-Benzyl-di-(2-*o*-toloxyethyl)-amine.**—A solution of 40 g. of sodium hydroxide in 50 ml. of water was added to 108 g. of *o*-cresol in 400 ml. of alcohol. The mixture was refluxed under stirring and solutions of 135 g. of N-benzyl-di-(2-chloroethyl)-amine hydrochloride[18] in 400 ml. of alcohol and of 20 g. of sodium hydroxide in 40 ml. of water and 200 ml. of alcohol were dropped in simultaneously during two hours. Refluxing and stirring was continued overnight. The formed sodium chloride was filtered off and washed with a small amount of alcohol. Removal of the alcohol and distillation of the residue at 4 mm. pressure yielded 112 g., boiling at 235–280°. Redistillation resulted in 94 g. of N-benzyl-di-(2-*o*-toloxyethyl)-amine; b. p. 245–265° (4 mm.); $n^{20}D$ 1.5675; purity 95% (determined by potentiometric titration).

(b) **Di-(2-*o*-toloxyethyl)-amine.**—Thirty-six grams of N-benzyl-di-(2-*o*-toloxyethyl)-amine was dissolved in 500 ml. of methanol and this solution hydrogenated for four hours in a rocking autoclave at 56° and 200 lb. pressure in the presence of 1.5 g. of palladium black. After filtration and removal of the methanol, the residue was fractionally distilled at 4 mm. pressure. Twelve grams collected from 220–250° was redistilled, yielding 7 g. of the desired amine, b. p. 221–230° (4 mm.); $n^{20}D$ 1.5535; purity 96% (determined by potentiometric titration). A solution of the amine in ether was treated with hydrogen chloride, the precipitate filtered and purified by crystallization from a small amount of alcohol.

N-Ethyl-di-(2-*o*-toloxyethyl)-amine Hydrochloride (XIII, 4).—N-Ethyl-di-(2-*o*-toloxyethyl)-amine was prepared from *o*-cresol and N-ethyl-di-(2-chloroethyl)-amine hydrochloride by the same procedure as has been described for the preceding compound. The yellow oil boiled at 215–223° (5 mm.); yield 60%; $n^{20}D$ 1.5422; purity 100.5% (by potentiometric titration). The base (20 g.) was dissolved in 300 ml. of ether and hydrogen chloride passed through the solution under cooling. The hydrochloride which formed was filtered, dissolved in 90 ml. of absolute alcohol and precipitated with 600 ml. of ether; yield 22 g. In a similar manner, N-(2-*o*-toloxyethyl)-2-aminoethanol hydrochloride (XIII, 1) and N,N-di-(2-*o*-toloxyethyl)-2-aminoethanol hydrochloride (XIII, 5) were prepared from the corresponding bases (IV, 2 and VII, 2).

N-(2-*o*-Toloxyethyl)-diethylamine Hydrochloride (XIII, 6).—The free base, obtained from *o*-cresol and N-(2-chloroethyl)-diethylamine hydrochloride, boiled at 121–125° (4 mm.); $n^{20}D$ 1.5020; yield 45%; purity 97% (by potentiometric titration). Treatment of the ethereal solution of the base with hydrogen chloride resulted in the formation of the hydrochloride.

(18) Office of the Publication Board, Department of Commerce, Report PB 6810, p. 7.

Summary

The synthesis of a series of N-(2-chloroethyl)-N-(2-phenoxyethyl)-ethylamines, N-(2-chloroethyl)-N-(2-phenoxyethyl)-benzylamines, N-(2-chloroethyl)-di-(2-phenoxyethyl)-amines and various related amines in form of their hydrochlorides has been described. A large number of these compounds show adrenergic blocking activity, some of them being considerably more potent than N-(2-chloroethyl)-dibenzylamine ("Dibenamine") hydrochloride.

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