tion 3, $n^{22}D$ 1.5404, was analyzed and found to be a hydrocarbon mixture (IV and V).

Anal. Calcd. for $C_{14}H_{18}$: C, 90.3; H, 9.68. Found: C, 90.2; H, 9.79.

Ozonolysis of 1.76 g. (0.008 mole) of this fraction according to the method of Whitmore and Church[15] gave 0.001 mole of formaldehyde, 0.0039 mole of acetophenone 3,4-dinitrophenylhydrazone and 0.004 mole of cyclohexyl phenyl ketone 2,4-dinitrophenylhydrazone. The yield of fraction 3 varied from 7–20% of theory, depending, apparently, on the conditions of distillation. The residue 4 which appeared to be polymerized hydrocarbon material increased with the decreased yields of fraction 3.

Cyclohexyl *p*-Anisyl Ketone.[16]—This substance, b. p. 125–135° (2 mm.), m. p. 58–59° (re-crystallized from ligroin) was isolated by distillation from the dehydration of crude cyclohexyl-*p*-anisylmethylcarbinol. The 2,4-dinitrophenylhydrazone prepared in the usual way melted at 115.5–116°.

Cyclohexyl *p*-tolyl ketone was isolated from the dehydration product of cyclohexyl-*p*-tolylmethylcarbinol by distillation (b. p. 105–110° at 2 mm.) and recrystallization, m. p. 64–65°. This substance does not appear to have been reported previously.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.1; H, 8.90. Found: C, 83.0; H, 8.71.

(15) Whitmore and Church, THIS JOURNAL, **54**, 3710 (1932).

(16) Hughes and Lions, *Chem. Abst.*, **33**, 589 (1939).

The 2,4-dinitrophenylhydrazone melted at 166.5°.

Anal. Calcd. for $C_{20}H_{22}N_4O_4$: C, 62.9; H, 5.79; N, 14.6. Found: C, 63.2; H, 6.01; N, 14.1.

Isobutyrophenone was isolated from the dehydration products of 10 g. isopropylphenylmethylcarbinol in the form of its 2,4-dinitrophenylhydrazone. There was obtained 1.6 g., m. p. 162°,[17] after recrystallization from alcohol.

Valerophenone was isolated from the dehydration products of 15 g. of *n*-butylmethylphenylcarbinol in the form of its 2,4-dinitrophenylhydrazone. After recrystallization from acetic acid there was obtained 0.17 g., m. p. 166.[15]

Summary

Cyclohexylmethylphenylcarbinol prepared from cyclohexylmagnesium chloride and acetophenone has been found to contain 1,3-diphenyl-1-cyclohexyl-1,3-butanediol.

The anomalous behavior of cyclohexylmethylphenylcarbinol and some analogous carbinols on dehydration has been interpreted on the basis of the presence of 1,3-diols in these preparations.

(17) Evans, *J. Chem. Soc.*, **138**, 788 (1936).

NEW HAVEN, CONNECTICUT
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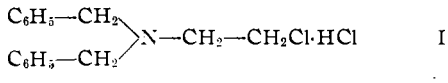
[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

o-Benzylphenyl Derivatives. IV.[1] β-Chloroethylamines

BY WILLIAM B. WHEATLEY, WILLIAM E. FITZGIBBON, LEE C. CHENEY AND S. B. BINKLEY

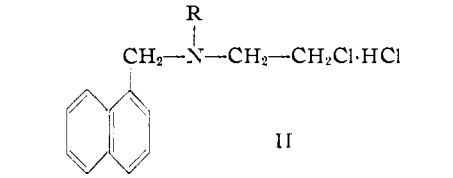
The discovery of Nickerson and Goodman[2a] that dibenzyl β-chloroethylamine hydrochloride (Dibenamine, I) blocks, or in higher doses, reverses the pressor effect of epinephrine has stimu-



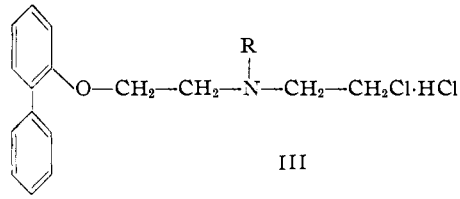
I

lated extensive research in the field of β-haloethylamines. An excellent review of sympatholytics, both of the β-haloethylamine and of other types, was presented by Nickerson at the Medicinal Chemistry Symposium of the American Chemical Society which was held at Ann Arbor, June 17–19, 1948.[2c] Published data indicate that the β-haloethylamine moiety is essential to sympatholytic activity in compounds related to Dibenamine, as increasing the distance between nitrogen and halogen or replacement of the halogen by other groups results in complete loss of activity.[2b] It has been stated that at least one benzyl-on-nitrogen group is also essential for activity in this series.

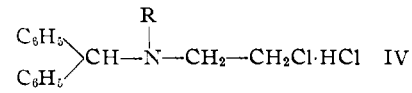
More recent work has substantiated the statement that the β-haloethylamine moiety is essential, but has shown that certain groups may replace the benzyl radical without inactivation. Several new series of sympatholytics have been disclosed: for example, the α-naphthylmethyl (II), 2-biphenoxyethyl (III) and benzohydryl series (IV).[3]



II



III



IV

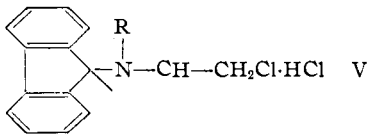
Many of the members of these series are potent epinephrine antagonists, and some possess antihistaminic properties in varying degrees. Even more recently, a series of fluorene sympatho-

(1) For the preceding paper in this series, see Wheatley, Cheney and Binkley, THIS JOURNAL, **71**, 3795 (1949).

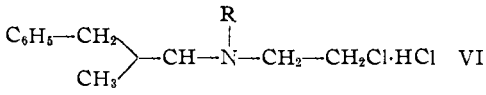
(2)(a) Nickerson and Goodman, *Fed. Proc.*, **5**, 194 (1946); (b) Nickerson, Nomaguchi and Goodman, *ibid.*, **5**, 195 (1946); (c) *cf.* Nickerson, *J. Pharmacol.*, **95**, 27 (1949).

(3) (a) Achenbach and Loew, *ibid.*, **6**, 304 (1947); Rieveschl and Fleming, paper presented at the Division of Medicinal Chemistry of the A. C. S., New York Meeting, Sept. 17, 1947; (b) Hunt, *J. Pharmacol.*, **95**, 177 (1949).

lytics (V) has been announced,[4] several of this series are comparable in activity to Dibenamine. A series of N-phenylisopropyl β-haloethylamines

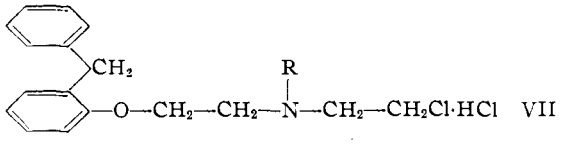


(VI) has been prepared, and sympatholytic activity has been found here also.[5]

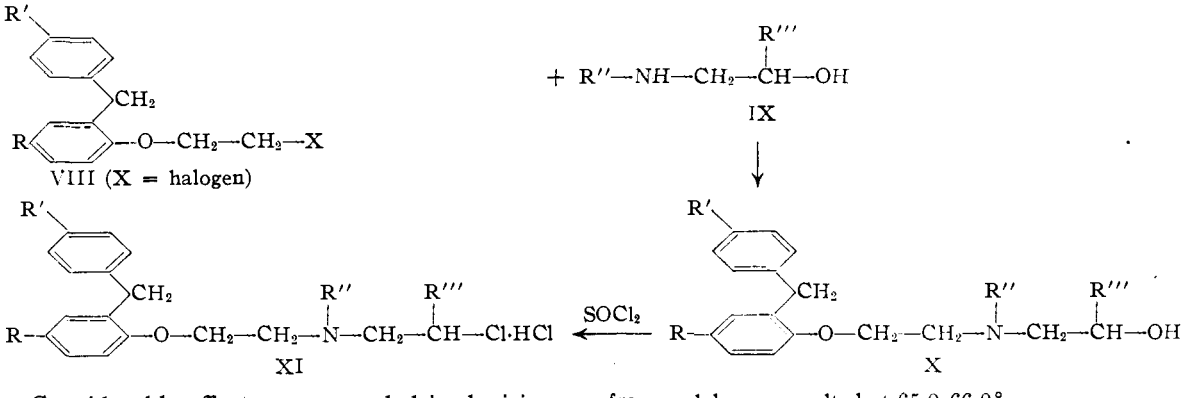


It is obvious that of these series, II, IV and V contain a benzyl type group on nitrogen, while in series III and VI this would be true only where R represents benzyl. Pharmacological results have demonstrated definite sympatholytic properties in series III, when R is lower alkyl, and in series VI, when R is allyl or isobutyl. Thus the hypothesis, based on the Dibenamine series, that a benzyl-on-nitrogen is essential, cannot be extended to all other series.

Investigation in the field of sympatholytics has been underway in this laboratory for some time. A series of β-(*o*-benzylphenoxy)-ethyl-β-chloroethylamines (VII) has been prepared, and it has been found that certain of these compounds possess marked sympatholytic and antihistaminic properties. This observation has been confirmed in another laboratory, as Henderson and Chen have stated that VII (R = C_2H_5) is 7.5 times as potent as Dibenamine.[6]



An outline of the preparation of these compounds is given



Considerable effort was expended in devising a practical synthesis of the requisite β-benzylphenoxyethyl halide (VIII). Sodium *o*-benzylphenoxide and ethylene dibromide reacted to give a product which was essentially β-(*o*-benzylphenoxy)-ethyl bromide. It could not be obtained in a pure state, however, and the yields from a number of experiments never exceeded 50%. Thionyl chloride converted β-(*o*-benzylphenoxy)-ethanol, prepared by the reaction of sodium *o*-benzylphenoxide and ethylene chlorohydrin, to β-(*o*-benzylphenoxy)-ethyl chloride, but the over-all yield was less than 10%. It was finally found that the use of β-chloroethyl *p*-toluenesulfonate[7] made possible the preparation of β-(*o*-benzylphenoxy)-ethyl chloride in excellent yield and of high purity.

One β-alkylaminoethanol, β-(2-phenylisopropylamino)-ethanol, could not be made to react with β-(*o*-benzylphenoxy)-ethyl chloride under conditions which were satisfactory for other alkylaminoethanols. The corresponding iodide (VIII, R,R′ = H, X = I) was therefore prepared,[8] and this reacted smoothly with the β-alkylaminoethanol (IX).

Experimental[9]

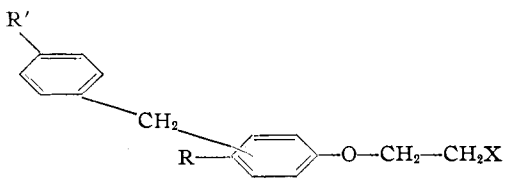
β-(Benzylphenoxy)-ethyl Halides (VIII)

β-(*o*-Benzylphenoxy)-ethyl Chloride (VIII, R, R′ = H, X = Cl).—To a stirred suspension of 36 g. (1.5 moles) of sodium hydride in 300 ml. of toluene, under a nitrogen atmosphere, was added dropwise a solution of 276 g. (1.5 moles) of *o*-benzylphenol[10] in 600 ml. of toluene. After the addition had been completed, the mixture was refluxed for thirty minutes. To the clear solution, stirred and maintained at reflux, was added dropwise 368 g. (1.57 moles) of β-chloroethyl *p*-toluenesulfonate. A white precipitate appeared at once. After sixteen hours of refluxing, 45 ml. of 56% potassium hydroxide was added and the mixture subjected to steam distillation until no more toluene appeared in the distillate. Basification at this point insures saponification during the steam distillation of any unreacted β-chloroethyl *p*-toluenesulfonate to compounds which will not contaminate the desired product. The two-phase residue was poured into a beaker and stirred vigorously while cooling. The oily layer solidified, and was collected by filtration. Recrystallization of the crude product from cyclohexane gave 330 g. (89% yield) of β-(*o*-benzylphenoxy)-ethyl chloride, m. p. 62–65°. An analytical sample, recrystallized several times from cyclohexane, melted at 65.0–66.0°.

(4) Kerwin, Ullyot, Fellows and Macko, *Fed. Proc.*, **8**, 308 (1949).
(5) Ullyot, Kerwin, Fellows and Macko, *ibid.*, **8**, 340 (1949).
(6) Henderson and Chen, *ibid.*, **8**, 301 (1949).
(7) Clemo and Perkin, *J. Chem. Soc.*, **121**, 642 (1922).
(8) Finkelstein, *Ber.*, **43**, 1528 (1910).
(9) All melting points are uncorrected.
(10) Cheney, Smith and Binkley, THIS JOURNAL, **71**, 60 (1949).

TABLE I

β-(BENZYLPHENOXY)-ETHYL HALIDES

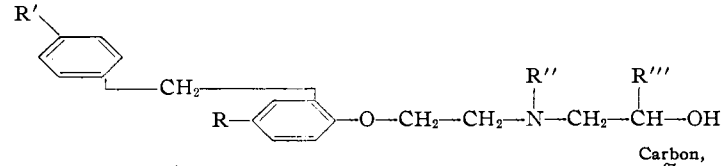


R	R′	X	Position of benzyl group	Yield, %	M. p., °C. or b. p., °C.	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	H	Cl	Ortho	89	65.0–66.0[a]		$C_{15}H_{15}OCl$	73.0	73.0	6.1	6.1
H	H	I	Ortho	88	95.0–98.0[a]		$C_{15}H_{15}OI$	53.3	55.5	4.5	4.2
	H	Cl	Para	94	64.0–65.0[b]		$C_{15}H_{15}OCl$	73.0	73.2	6.1	6.1
H	Cl	Cl	Ortho	91	148	1	$C_{15}H_{14}OCl_2$	64.1	61.3	5.0	5.3
Cl	H	Cl	Ortho	98	46.5–48.5[c]		$C_{15}H_{14}OCl_2$	64.1	64.4	5.0	5.1
H	F	Cl	Ortho	97	144–147	2	$C_{15}H_{14}OClF$	68.1	66.8	5.3	5.5

[a] Recrystallized from cyclohexane. [b] Recrystallized from methanol. [c] Recrystallized from Skellysolve B.

TABLE II

β-HYDROXYETHYLAMINES



R	R′	R″	R‴	Halide[a]	Reaction solvent[b]	Time of reflux, hr.	Yield, %	B. p., °C.	Mm.	$n^{25}D$ or m. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	H	$-CH_3$	H	Br	T	6	84	203–204	2.4	1.5628	$C_{18}H_{23}O_2N$	75.8	75.3	8.1	8.4
H	H	$-C_2H_5$	H	Cl	T	15	88	178	1	1.5363	$C_{19}H_{25}O_2N$	76.2	76.1	8.4	8.6
H	H	$-CH(CH_3)_2$	H	Br	T	16	50	181–186	2	1.5500	$C_{20}H_{27}O_2N$	76.6	76.3	8.7	8.6
H	H	$-(CH_2)_3-CH_3$	H	Br	T	7	92	199–205	1.5	1.5460	$C_{21}H_{29}O_2N$	77.0	77.0	8.9	9.0
H	H	$-CH(CH_3)-C_2H_5$	H	Cl	X	24	45	189	1	1.5462	$C_{21}H_{29}O_2N$	77.0	77.1	8.9	8.9
H	H	$-CH_2-CH(CH_3)_2$	H	Br	T	16	73	184–188	1	1.5438	$C_{21}H_{29}O_2N$	77.0	77.2	8.9	9.0
H	H	$-CH_2-CH(C_2H_5)-C_4H_9$	H	Br	T	34	76	224–235	2	1.5310	$C_{25}H_{37}O_2N$	78.3	78.2	9.7	9.4
H	H	$-CH_2-C_6H_5$	H	Br	T	16	70	230–235	1	1.5836	$C_{24}H_{27}O_2N$	79.7	79.6	7.5	7.6
H	H	$-CH<(CH_2-CH_2)>CH_2$	H	Br	T	8	69	223–233	1.5	52.0–53.0[c]	$C_{22}H_{31}O_2N$	78.1	78.1	8.8	9.0
H	H	$-CH(CH_2-C_6H_5)-CH_2$	H	I	T	16	82	220–221	1	1.5734	$C_{26}H_{31}O_2N$	80.1	79.1	8.0	7.8
H	H	$-CH_2-CH_2OH$	H	Br	T	16	60	224–225	1	1.5644	$C_{19}H_{25}O_3N$	72.4	72.3	8.0	8.3
H	H	$-CH(CH_3)_2$	$-CH_3$	Cl	X	48	76	167–171	1	1.5400	$C_{21}H_{29}O_2N$	77.0	77.0	8.9	8.9
H	H	$-CH(CH_3)_2$	$-CH=CH_2$	Cl	X	16	26	187–190	1	1.5466	$C_{22}H_{29}O_2N$	77.8	77.8	8.6	8.6
H	H	$-CH(CH_3)_2$	$-C_6H_5$	Cl	X	48	62[e]	.....		178.5–179.5	$C_{26}H_{32}O_2NCl$	73.3	72.3	7.6	7.6
H	Cl	$-CH(CH_3)_2$	H	Cl	X	20	29	188–190	1	1.5556	$C_{20}H_{26}O_2NCl$	69.1	69.2	7.5	7.7
Cl	H	$-CH(CH_3)_2$	H	Cl	T	48	52	180–184	1	56.5–57.5	$C_{20}H_{26}O_2NCl$	69.1	69.1	7.5	7.4
H	F	$-CH(CH_3)_2$	H	Cl	X	30	74	191–196	1	1.5376	$C_{20}H_{26}O_2NF$	72.5	72.5	7.9	7.4
H	H	$-CH(CH_3)_2$	H[d]	Cl	T	54	52	206–213	1	1.5488	$C_{20}H_{27}O_2N$	76.6	76.3	8.7	8.8

[a] β-(Benzylphenoxy)-ethyl halide used (VIII, X = Br, Cl, I). [b] T = toluene, X = xylene. [c] Recrystallized from Skellysolve B. [d] The benzyl group is para to the oxygen instead of ortho as in all others. [e] These data are for the hydrochloride of the hydroxyethylamine, which crystallized out of water during working up of the reaction mixture. It was recrystallized from dilute isopropyl alcohol.

Anal. Calcd. for $C_{15}H_{15}OCl$: C, 73.0; H, 6.1. Found: C, 73.0; H, 6.1.

β-(*o*-Benzylphenoxy)-ethyl Iodide (VIII, R, R′ = H, X = I).—A solution of 61.1 g. (0.25 mole) of β-(*o*-benzylphenoxy)-ethyl chloride and 37.7 g. (0.25 mole) of sodium iodide in 250 ml. of acetone was refluxed for sixteen hours. The cooled reaction mixture was filtered to remove sodium chloride, and the filtrate concentrated to about 100 ml. The concentrate was poured into 500 ml. of cold water, whereupon a solid formed. Ten milliliters of saturated sodium bisulfite solution was added and the mixture stirred for some thirty minutes to thoroughly break up lumps, then filtered. Recrystallization of the crude product from cyclohexane gave 74 g. of material, m. p. 88–95°, which was pure enough for the subsequent reaction. An analytical sample melted at 95.0–98.0°.

Anal. Calcd. for $C_{15}H_{15}OI$: C, 53.3; H, 4.5. Found: C, 55.5; H, 4.2.

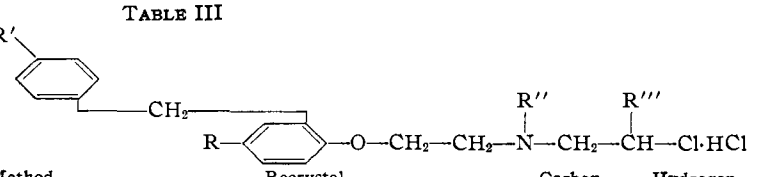
The range of melting and analysis prove that the product was still contaminated with the chloro compound.

In Table I are summarized the β-(benzylphenoxy)-ethyl halides which were prepared. The last four halides in the table were prepared from β-chloroethyl *p*-toluenesulfonate and the appropriate benzylphenol: *p*-benzylphenol,[10] *o*-(*p*-chlorobenzyl)-phenol,[11] *o*-benzyl-*p*-chlorophenol,[11] and *o*-(*p*-fluorobenzyl)-phenol.[1] In two cases,

(11) Huston, *et al.*, THIS JOURNAL, **55**, 4639 (1933).

TABLE III

β-CHLOROETHYLAMINE HYDROCHLORIDES



R	R′	R″	R‴	Method of prepn.	Yield, %[a]	M. p., °C.	Recrystallization solvent[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	H	—CH_3	H	A	78	115.0–118.0	*i*-PrOH	$C_{18}H_{22}ONCl_2$	63.5	63.5	6.8	6.8
H	H	—C_2H_5	H	B	71	161.0–163.5	*i*-PrOH–EtOAc	$C_{19}H_{24}ONCl_2$	64.4	64.5	7.1	7.1
H	H	—$CH(CH_3)_2$	H	B	78	138.0–139.0	*i*-PrOH–SSB	$C_{20}H_{27}ONCl_2$	65.2	65.2	7.4	7.5
H	H	—$(CH_2)_3CH_3$	H	B	76	110.0–111.0	EtOAc–Et_2O	$C_{21}H_{29}ONCl_2$	66.0	65.9	7.7	7.6
H	H	—$CH(CH_3)C_2H_5$	H	C	63	107.0–110.0	*i*-PrOH–Et_2O	$C_{21}H_{29}ONCl_2$	66.0	65.9	7.7	7.7
H	H	—$CH_2CH(CH_3)_2$	H	C	80	101.0–103.0	EtOAc	$C_{21}H_{29}ONCl_2$	66.0	66.0	7.7	7.9
H	H	—$CH_2CH(C_2H_5)C_4H_9$	H	A	72	82.5–84.5	MIBK-SSB	$C_{25}H_{37}ONCl_2$	68.5	68.5	8.5	8.7
H	H	—$CH_2C_6H_5$	H	C	67	151.0–153.5	*i*-PrOH	$C_{24}H_{23}ONCl_2$	69.2	69.2	6.5	6.8
H	H	—CH(cyclohexyl)	H	A	87	108.5–110.0	MIBK	$C_{23}H_{31}ONCl_2$	67.6	67.6	7.7	7.7
H	H	—$CH(CH_3)CH_2C_6H_5$	H	A	73	153.0–155.0	MIBK	$C_{26}H_{31}ONCl_2$	70.3	70.3	7.0	7.1
H	H	—CH_2CH_2Cl	H	C	54	155.0–158.0	*i*-PrOH	$C_{19}H_{24}ONCl_3$	58.7	58.8	6.2	6.2
H	H	—$CH(CH_3)_2$	—CH_3	B	61	117.0–118.5	MIBK	$C_{21}H_{29}ONCl_2$	66.0	65.9	7.7	7.5
H	H	—$CH(CH_3)_2$	—$CH{=}CH_2$	A	31	97.0–102.0	MIBK	$C_{22}H_{29}ONCl_2$	67.0	67.0	7.4	7.4
H	H	—$CH(CH_3)_2$	—C_6H_5	C	62	124.5–127.0	MIBK–Et_2O	$C_{26}H_{31}ONCl_2$	70.3	69.7	7.0	7.0
H	Cl	—$CH(CH_3)_2$	H	A	69	131.0–133.5	EtOAc	$C_{20}H_{26}ONCl_3$	59.6	59.7	6.5	6.6
Cl	H	—$CH(CH_3)_2$	H	B	76	146.0–147.0	*i*-PrOH	$C_{20}H_{26}ONCl_3$	59.6	59.7	6.5	6.5
H	F	—$CH(CH_3)_2$	H	C	83	136.0–138.5	*i*-PrOH–SSB	$C_{20}H_{26}ONCl_2F$	62.2	62.3	6.8	6.8
H	H	—$CH(CH_3)_2$	H[c]	C	49	106.0–109.5	MIBK	$C_{20}H_{27}ONCl_2$	65.2	65.5	7.4	7.3

[a] These yields represent those of recrystallized products. [b] Solvents: MIBK-methyl isobutyl ketone, SSB or SSC—Skellysolve B or C (petroleum ether fractions of b. p. 60–71° and 85–100°, respectively). [c] The benzyl group is para to the oxygen, instead of ortho as in all others.

where R′ = Cl or F, the crude products did not solidify when the residue from steam distillation was cooled. The mixtures, therefore, were extracted with ether; the combined ether extracts dried, stripped and residues distilled *in vacuo* to give the β-(benzylphenoxy)-ethyl chlorides.

β-Alkylaminoethanols (IX)

The following β-alkylaminoethanols were prepared by reductively alkylating the appropriate carbonyl compound (in parentheses) with ethanolamine after the procedure described by Cope and Hancock[12]: isopropyl (acetone), *n*-butyl (*n*-butyraldehyde), isobutyl (isobutyraldehyde), *s*-butyl (methyl ethyl ketone), 2-ethylhexyl (2-ethylhexaldehyde), cyclohexyl (cyclohexanone), benzyl[13] (benzaldehyde).

β-(2-Phenylisopropylamino)-ethanol (IX, R‴ = H, R″ = $C_6H_5CH_2CH(CH_3)$—).—A mixture of 30.5 g. (0.5 mole) of ethanolamine and 87.2 g. (0.65 mole) of phenylacetone was hydrogenated over platinum catalyst in absolute ethanol solution.[12] There was obtained 75.7 g. (84% yield) of material boiling at 115–117° (0.7 mm.). Poor analyses were obtained on this product, the carbon values being consistently low. Therefore, the hydrochloride was prepared; it melted at 106.5–108.5° after recrystallization from isopropyl alcohol–ether.

Anal. Calcd. for $C_{11}H_{18}ONCl$: C, 61.2; H, 8.4. Found: C, 61.3; H, 8.4.

1-Isopropylamino-2-propanol (IX, R‴ = CH_3, R″ = $(CH_3)_2CH$—).—A mixture of 116 g. (2.0 moles) of propylene oxide and 177 g. (3.0 moles) of isopropylamine was allowed to stand at room temperature for eighteen days, then refluxed for forty-eight hours. Distillation gave 165 g. (71% yield) of 1-isopropylamino-2-propanol, b. p. 76–78° (21 mm.); Cope and Hancock[14] prepared this compound in 97% yield by reductively alkylating acetone with 1-amino-2-propanol; b. p. 75.5–76° (22 mm.).

α-Vinyl-β-isopropylaminoethanol (IX, R‴ = CH_2=CH—, R″ = $(CH_3)_2CH$—).—A mixture of 140 g. (2.0 moles) of 3,4-epoxy-1-butene and 177 g. (3.0 moles) of isopropylamine was allowed to stand at room temperature for fourteen days, then refluxed for twenty hours and finally distilled. There was obtained 194 g. (75% yield) of α-vinyl-β-isopropylaminoethanol, b. p. 89–94° (21 mm.), $n^{25}D$ 1.4508.

Anal. Calcd. for $C_7H_{15}ON$: C, 65.1; H, 11.7. Found: C, 65.0; H, 11.7.

α-Phenyl-β-isopropylaminoethanol (IX, R‴ = C_6H_5, R″ = $(CH_3)_2CH$—).—A mixture of 60 g. (0.5 mole) of styrene oxide and 45 g. (0.75 mole) of isopropylamine was allowed to stand at room temperature in a stoppered flask. After one week the mixture had set to a mass of crystals. After another week 30 ml. of petroleum ether (b. p. 28–38°) was added and the crystals collected by filtration. The product amounted to 64 g. (71% yield); m. p. 91.0–92.5°.

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.7; H, 9.6. Found: C, 73.8; H, 9.6.

β-Hydroxyethylamines (X)

N-β-(*o*-Benzylphenoxy)-ethyl-N-β-hydroxyethyl-ethylamine (X, R, R′, R‴ = H, R″ = C_2H_5).—A solution of 239 g. (0.97 mole) of β-(*o*-benzylphenoxy)-ethyl chloride and 181 g. (2.03 moles) of β-ethylaminoethanol in 300 ml. of toluene was refluxed, with stirring, for fifteen hours. The reaction mixture was cooled, diluted with one liter of ether, and the β-ethylaminoethanol hydrochloride removed by filtration. The filtrate was washed several times with water, then with three portions of dilute hydrochloric acid. Basification of the combined acid extracts liberated the amine, which was extracted into ether. The ether extracts were shaken with saturated sodium chloride solution, filtered through anhydrous sodium sul-

(12) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).
(13) Cromwell and Fitzgibbon, *ibid.*, **70**, 387 (1948).
(14) Cope and Hancock, *ibid.*, **66**, 1453 (1944).

fate, stripped and the residue distilled *in vacuo*. There was obtained 255 g. (88% yield) of the hydroxyamine, b. p. 178° (1 mm.).

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.2; H, 8.4. Found: C, 76.1; H, 8.6.

In Table II are analogs which were prepared in a similar manner. In cases where the alkylaminoethanol hydrohalides were oils, the supernatant liquid was decanted and worked up as described above. In several cases, the hydrochlorides of the products were so water insoluble that three layers formed on extraction with dilute hydrochloric acid. If this happened, the two lower layers were drawn off together as the acid extract.

β-Chloroethylamine Hydrochlorides (XI)

Method A.—To an ice-cold, well-stirred solution of 0.1 mole of the β-hydroxyethylamine (X) in 100 ml. of chloroform was added dropwise 15 ml. of thionyl chloride. After the addition was complete, the mixture was allowed to come to room temperature and finally refluxed for one hour. The solvent and excess thionyl chloride were evaporated under reduced pressure. The residual oil was taken up in 50 ml. of benzene and the solvent again evaporated under reduced pressure. This treatment with benzene was repeated and the residue then crystallized from a suitable solvent.

Method B.—A solution of 0.1 mole of the β-hydroxyethylamine in 100 ml. of ether was added dropwise to an ice-cold, stirred solution of 15 ml. of thionyl chloride in 100 ml. of ether. After the addition was complete, the mixture was refluxed one to three hours. In most cases, the product had solidified at this point, so it was collected by filtration and recrystallized. If the product remained an oil, it was worked up as described under method A.

Method C.—This method differed from method B only in the order of addition; thionyl chloride was added to the solution of the β-hydroxyethylamine.

The data on the β-chloroethylamine hydrochlorides are contained in Table III.

Pharmacology.—A detailed report on the pharmacology of these compounds will be published by S. Loewe and L. S. Goodman. The most active compounds are those in which R, R′ and R‴ represent hydrogen and R″ is ethyl or isopropyl. These compounds are about five times as active as "Dibenamine" as sympatholytics and more active than "Benadryl" as antihistaminics.

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Summary

A series of N-β-(benzylphenoxy)-ethyl-N-β-chloroethylalkylamine hydrochlorides has been prepared. Certain members of this series display sympatholytic activity or antihistaminic activity in animals.

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Halogen Containing Ketones, Esters and Carbinols Related to Methadone

BY M. E. SPEETER, L. C. CHENEY AND S. B. BINKLEY

The acylation of carbinols derived from the synthetic analgesics methadone, isomethadone and related ketones has been reported earlier from these laboratories.[1] Studies of other workers with some of these derivatives have appeared[2,3] and the properties of some of the optically active forms given.[4] This paper reports the high analgesic potency of some halogen containing esters of carbinols derived from methadone and related ketones.

The potentiating effect of halogen substitution when present in the acyl group made it of interest to determine the effect of halogen substitution in the phenyl ring. The increase in activity afforded by halogen substitution in the antimalarials[5,6] and the antihistaminics[7] has been established. In the O.P.B. 981[8] it is stated that for maximum activity the two phenyl groups in compounds of the methadone series must not be sub-

TABLE I

HALOGEN CONTAINING ESTERS $(C_6H_5)_2C(R_1)(R_2O{-}CH{-}C_2H_5)$

R_1	R_2	M. p., °C., uncor.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Yield, %	LD_{50}[a]	Analgesia[b]	Activity index[c]
CH_2-$CH(CH_3)N(CH_3)_2$	$ClCH_2CO$-[d]	195–196	$C_{23}H_{30}ClNO_2 \cdot HCl$	65.08	64.80	7.36	7.43	47	13.3 ± 2	0.75	18
CH_2-$CH(CH_3)N(CH_3)_2$	$BrCH_2CO$[e]	190–191	$C_{23}H_{30}BrNO_2 \cdot HBr$	53.80	53.60	6.08	6.25	73	23 ± 2	5.0	4.0
$CH(CH_3)$-$CH_2N(CH_3)_2$	$ClCH_2CO$-[d]	205–206	$C_{23}H_{30}ClNO_2 \cdot HCl$	65.08	65.05	7.36	7.37	39	ca. 70	8.0	8.7
$-CH(CH_3)-CH_2N(CH_3)_2$	$ClCH_2CH_2OCO$-[d]	188–189	$C_{24}H_{32}ClNO_3 \cdot HCl$	63.43	63.40	7.32	7.28	62	220 ± 10	25	9.0
$-CH_2-CH_2-NC_4H_8O$[f]	$ClCH_2CO$-[e]	229–231	$C_{24}H_{30}NO_3 \cdot HCl$	63.71	63.70	6.91	6.97	65	105 ± 15	3	35
$-CH_2-CH(CH_3)NC_4H_8O$	$ClCH_2CO$-[g]	195–196	$C_{25}H_{32}ClNO_3 \cdot HCl$	64.36	63.90	7.13	7.28	..	77 ± 11	1	77

[a] Intraperitoneal LD_{50} in the mouse in mg./kg. [b] Subcutaneous minimal analgesic dose in guinea pig in mg./kg. [c] For comparison the activity index (LD_{50} ÷ effective dose) for methadone measured by the same pharmacological methods is 2.3. [d] Recryst. from isopropyl alcohol. [e] Recryst. from ethanol. [f] $-NC_4H_8O$ represents morpholinyl. [g] Recryst. from methyl isobutyl ketone; yield not recorded.

These esters, shown in Table I, were prepared by the procedures developed earlier.[1]

(1) Speeter, Byrd, Cheney and Binkley, THIS JOURNAL, **71**, 57 (1949).

(2) May and Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(3) May and Mosettig, *ibid.*, **13**, 663 (1948).

(4) Pohland, Marshall and Carney, THIS JOURNAL, **71**, 460 (1949).

(5) Board for Coördination of Malarial Studies, *Science*, **103**, 8 (1946).

(6) Gurd, *Nature*, **158**, 707 (1946).

(7) Tislow, LaBelle, Makovsky, Reed, Cunningham, Emele, Grandage and Roggenhofer, *Federation Proc.*, **8**, 338 (1949).

(8) Kleiderer, Rice, Conquest and Williams, Report No. P. B. 981, Office of the Publication Board, Department of Commerce, Washington, D. C., p. 93.