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

Adrenergic Blocking Agents. II. N-Aralkyl-β-haloethylamines[1]

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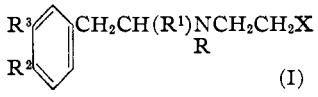
In continuation of our studies[2] on the relation of structure of N,N-disubstituted β-haloethylamines to adrenergic blocking activity, we have prepared a series of β-haloethylamines (I).



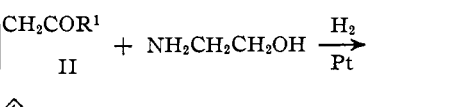
(I)

R = CH_3, C_2H_5, *i*-C_3H_7, *i*-C_4H_9, allyl, $C_6H_5CH_2$
R^1 = H, CH_3, C_6H_5, $C_6H_5CH_2$
R^2, R^3 = H, OH, OCH_3
X = Cl, Br

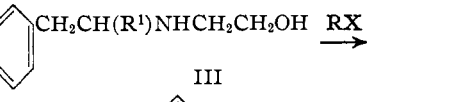
All of the β-chloroethylamine hydrochlorides (see Table I) were formed from the corresponding N,N-disubstituted ethanolamines and thionyl chloride. The two hydroxy substituted β-bromoethylamine hydrobromides in Table I were prepared by heating N-(*p*-methoxyphenylisopropyl)-N benzylethanolamine (or the 3,4-dimethoxy compound) with concentrated hydrobromic acid to effect simultaneous demethylation and replacement of the aliphatic hydroxyl group.

Three general procedures were employed to synthesize the intermediate ethanolamine hydrochlorides listed in Table II. In method A, N-aralkylethanolamines (III) were formed by reductive amination of aralkyl ketones (II) with ethanolamine. The secondary ethanolamines were then benzylated or alkylated to form IV. The N-benzyl-N-(β-phenylethyl)-ethanolamine resulted from the alkylation of N-benzylethanolamine with β-phenylethyl bromide.

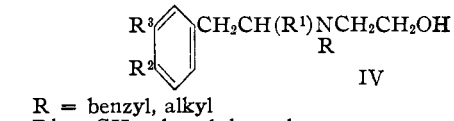
(A)



II



III



IV

R = benzyl, alkyl
R^1 = CH_3, phenyl, benzyl
R^2, R^3 = H, OCH_3

The dextro isomer of IV (R = $C_6H_5CH_2$, R^1 = CH_3, R^2, R^3 = H) was prepared by reducing the N-benzal derivative of *d*-β-phenylisopropylamine and treating the resulting secondary amine with ethylene bromohydrin (method B).

(B) $C_6H_5CH_2CH(CH_3)NH_2 + C_6H_5CHO \xrightarrow[Pt]{H_2}$

$C_6H_5CH_2CH(CH_3)NHCH_2C_6H_5 \xrightarrow{BrCH_2CH_2OH}$
$C_6H_5CH_2CH(CH_3)N(CH_2C_6H_5)CH_2CH_2OH$

As an example of the third procedure, N-isopropyl-β-phenylisopropylamine was formed by reductive amination of benzyl methyl ketone with isopropylamine. Ethylene bromohydrin was employed to introduce the β-hydroxyethyl group (method C).

(C) $C_6H_5CH_2COCH_3 + (CH_3)_2CHNH_2 \xrightarrow[Pt]{H_2}$

$C_6H_5CH_2CH(CH_3)NHCH(CH_3)_2 \xrightarrow{BrCH_2CH_2OH}$
$C_6H_5CH_2CH(CH_3)NCH(CH_3)_2$
$|$
CH_2CH_2OH

Pharmacology.—In Table I are recorded the adrenergic blocking activities of the β-haloethylamines with "Dibenamine"[3] included for comparison. We are indebted to Dr. Edwin J. Fellows of these laboratories for these data which will be reported in more detail elsewhere.

All except three (408, 502, 528) of the compounds reported equal or exceed "Dibenamine" in activity. N-Benzyl-N-(β-phenylisopropyl)-β-chloroethylamine hydrochloride (194) is approximately twice as active as N-benzyl-N-(β-phenylethyl)-β-chloroethylamine hydrochloride (195). This effect of the α-methyl group is reminiscent of that produced by the introduction of an α-methyl into a β-phenylethylamine in the sympathomimetic series.[4,5] In the latter type of compound, the α-methyl group appears to enhance activity by protecting the molecule from the action of amine oxidase.[6] However, it is unlikely that the α-methyl group in our compounds plays the same role as in the sympathomimetic amines since the modes of action of the two types of drugs appear to be quite different. A β-haloamine, or more probably an imonium ion formed therefrom, appears to be reversibly adsorbed at or near the site of action of epinephrine, after which chemical interaction with a tissue component occurs and results in an adrenergic blockade of long duration.[7] Thus it may be expected that chemical and steric factors inherent in the β-haloamine will affect the ability of the agent to reach the site of action and its power to alkylate the epinephrine "receptor

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

(2) Kerwin, Herdegen and Ullyot, THIS JOURNAL, **72**, 940 (1950).

(3) Smith, Kline & French trademark for N,N-dibenzyl-β-chlorethylamine hydrochloride.

(4) Piness, Miller and Alles, *J. A. M. A.*, **94**, 790 (1930).

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

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

(7) Nickerson, *J. Pharmacol. Expt. Therap.*, **95** (Part II), 27 (1949).

TABLE I

N,N-DISUBSTITUTED-β-HALOETHYLAMINE HYDROHALIDES

SKF no.	$C_6H_5CH_2NCH_2CH_2Cl\cdot HCl$ R	Yield, %	M. p., °C.	Recryst. solvent	Empirical formula	Calcd. C	Calcd. H	Calcd. Cl⁻ or Br⁻	Analyses, % Found C	Found H	Found Cl⁻ or Br⁻	Adrenergic blocking dose in mg./kg.[a]
195	$C_6H_5CH_2CH_2-$	77	103.5–105.5	Acetone	$C_{17}H_{21}Cl_2N$	65.79	6.82	11.43	65.58	6.90	11.33	10
194	$C_6H_5CH_2CH(CH_3)-$	94	145–147.5	Alcohol–ether	$C_{18}H_{23}Cl_2N$	66.66	7.14	10.93	66.27	7.30	10.81	5
194A	(d)-$C_6H_5CH_2CH(CH_3)$-[b]	79	131.5–133	Alcohol–ether	$C_{18}H_{23}Cl_2N$	66.66	7.14	10.93	66.70	6.97	10.92	5
443	p-$(CH_3O)C_6H_4CH_2CH(CH_3)-$	45	122–123	Acetone–ether	$C_{19}H_{25}Cl_2NO$	64.12	7.11	10.01	64.45	7.27	9.80	5
625A	3,4-$(CH_3O)_2C_6H_3CH_2CH(CH_3)-$	52	149–151	Acetone–ether	$C_{20}H_{27}Cl_2NO_2$	62.49	7.08	9.22	62.55	6.84	9.36	2.5
408	$C_6H_{11}CH_2CH(CH_3)-$	67	145–147	Alcohol–ether	$C_{18}H_{29}Cl_2N$	65.44	8.84	21.48[c]	65.72	8.98	21.29[c]	15
	$C_6H_5CH_2NCH_2CH_2Br\cdot HBr$ R											
594A	p-$(OH)C_6H_4CH_2CH(CH_3)-$	71	179–181	Alcohol–ether	$C_{18}H_{23}Br_2NO$	50.37	5.40	18.62	50.65	5.57	18.87	2.5–5
669C	3,4-$(OH)_2C_6H_3CH_2CH(CH_3)-$	32	170–172	Alcohol–ether	$C_{18}H_{23}Br_2NO_2$	48.56	5.21	17.95	48.75	5.58	18.12	1–2.5
	$C_6H_5CH_2CH(R^1)NCH_2CH_2Cl\cdot HCl$ R											
	R^1 R											
502	CH_3 C_2H_5-	86	160–160.5	Alcohol–ether	$C_{13}H_{21}Cl_2N$	59.54	8.07	13.52	59.62	8.00	13.39	10–20[d]
528	CH_3 $CH_3CH(CH_3)-$	48	128–129.5	Alcohol–ether	$C_{14}H_{23}Cl_2N$	60.86	8.39	12.84	60.75	8.16	12.69	10+[e]
561	CH_3 $CH_2=CHCH_2-$	85	163–163.5	Alcohol–ether	$C_{14}H_{21}Cl_2N$	61.31	7.72	12.93	61.24	7.96	12.83	10
570	CH_3 $CH_3CH(CH_3)CH_2-$	70	138–139	Alcohol–ether	$C_{15}H_{25}Cl_2N$	62.06	8.68	12.21	62.31	9.04	12.22	10
658A	C_6H_5 CH_3-	73	175.5–177.5	Alcohol–ether	$C_{17}H_{21}Cl_2N$	65.81	6.82	11.43	65.78	7.23	11.48	10
541	$CH_2C_6H_5$ CH_3-	75	184–185	Alcohol–ether	$C_{18}H_{23}Cl_2N$	66.86	7.15	10.93	66.93	7.45	10.80	10
"Dibenamine"												10

[a] Weight of compound (in mg. per kg. of animal weight) which when administered intravenously in cats blocks or reverses pressor response to four test doses of epinephrine, the last and largest of which is 1 mg./kg. [b] $[\alpha]^{20}D$ +37.9 (C = 8.00 in ethanol). [c] Total chlorine. [d] Reverses the pressor response to test doses I and II only. Too toxic to test at higher dosage. [e] Ten mg./kg. blocks and reverses pressor response to test doses I, II and III consistently, but only occasionally that of test dose IV.

substance." Perhaps the α-methyl group of compound 194 has a stabilizing influence on the reactive intermediate and thereby increases its adsorption at the site of action, or affects the alkylating ability of the agent in such a manner as to produce a greater specificity for certain chemical groups at its site of action.

A comparison of the compound 194 with "Dibenamine" indicates a two-fold increase in activity due to the β-phenylisopropyl group. This effect is lost by reduction of the phenyl ring as in 408. Hydroxyl groups on the phenyl ring increase the activity, the 3,4-dihydroxy compound 669C being four to ten times as active as "Dibenamine."

In correlating the structure of β-haloethylamines with adrenergic blocking action Nickerson[7] states that an active compound must have a β-haloalkyl group capable of forming an active intermediate (ethylenimonium ion or vinylamine) and, furthermore, the compound must include an unsaturated ring structure attached to the nitrogen in such a way that hyperconjugation will act to stabilize the reactive intermediate. It is noteworthy that compounds 528, 570 and 541 do not fulfill this last requirement and yet are effective blocking agents. In these compounds both of the benzyl groups of "Dibenamine" have been replaced by groups of different chemical characteristics and ones which cannot be considered equivalent to benzyl groups[8] or capable of forming a resonating, conjugated system which Nickerson[9,10] postulates is necessary for adrenergic blocking action. It would appear that such a concept is not adequately definitive for agents of this type. Whether the greater

(8) Nickerson and Goodman, *Fed. Proc.*, **5**, 194 (1946).

(9) Nickerson, Abstracts of First Medicinal Chemistry Symposium of the Division of Medicinal Chemistry of the American Chemical Society, pages 70–80 (1948).

(10) Nickerson and Gump, *J. Pharmacol. Expt. Therapy*, **97**, 42 (1949).

TABLE II

N,N-DISUBSTITUTED ETHANOLAMINE HYDROCHLORIDES

$C_6H_5CH_2N(R)CH_2CH_2OH\cdot HCl$ R	Method of prepn.	Yield, %	Recryst. solvent	M. p., °C.	Empirical formula	Analyses, % Calcd.	Found
$C_6H_5CH_2CH_2$—	1	65	Alcohol–acetone	146–149	$C_{17}H_{22}ClNO$	C, 69.96	69.75
						H, 7.63	7.78
$C_6H_5CH_2CH(CH_3)$—	1	53	Alcohol	201.5–203.5	$C_{18}H_{24}ClNO$	Cl, 11.60	11.50
(*d*)-$C_6H_5CH_2CH(CH_3)$[a]	3	33	Alcohol–ether	137–139	$C_{18}H_{24}ClNO$	Cl, 11.60	11.53
p-$(CH_3O)C_6H_4CH_2CH(CH_3)$[b]	1	45	Alcohol–ether	143–144	$C_{19}H_{26}ClNO$	C, 67.94	68.37
						H, 7.80	7.64
3,4-$(CH_3O)_2C_6H_3CH_2CH(CH_3)$—[c]	1	61			$C_{20}H_{27}NO_3$	C, 72.92	72.59
						H, 8.26	8.46
$C_6H_{11}CH_2CH(CH_3)$—[d]	1	70	Acetone–ether	121.5–123	$C_{18}H_{30}ClNO$	Cl, 11.37	11.31

$C_6H_5CH_2CH(R^1)NRCH_2CH_2OH\cdot HCl$

R^1	R						
—CH_3	C_2H_5—	1	45	Alcohol–ether	110–112	$C_{13}H_{22}ClNO$	Cl, 14.59	14.41
—CH_3[e]	$CH_3CH(CH_3)$—	3	56	Acetone–ether	74–75	$C_{14}H_{24}ClNO$	Cl, 13.75	13.61
—CH_3	$CH_2=CHCH_2$—	1[f]	71	Alcohol–ether	89–91	$C_{14}H_{22}ClNO$	Cl, 13.86	13.78
—CH_3	$CH_3CH(CH_3)CH_2$—	1[g]	15	Alcohol–ether	119–121	$C_{15}H_{26}ClNO$	Cl, 13.04	12.97
—C_6H_5	CH_3—	2	70	Alcohol–ether	158.5–160	$C_{17}H_{22}ClNO$	Cl, 12.15	12.25
—$CH_2C_6H_5$	CH_3—	2	73	Alcohol–ether	157.5–159	$C_{18}H_{24}ClNO$	Cl, 11.59	11.73

[a] $[\alpha]^{20}D$ +34.4 (*C* = 8.00 in ethanol). [b] The hydrobromide melted at 120–122°. *Anal.* Calcd. for $C_{19}H_{26}BrNO_2$: Br, 21.01. Found: Br, 21.18. [c] Free base, b. p. 198–200° (1 mm.). [d] The *p*-nitrobenzoate ester hydrochloride melted at 155.5–157.° *Anal.* Calcd. for $C_{25}H_{33}ClN_2O_4$: Cl, 7.47. Found: Cl, 7.61. [e] The hydrobromide melted at 104–106°. *Anal.* Calcd. for $C_{14}H_{24}BrNO$: Br, 26.44. Found: Br, 26.26. [f] A 15% excess of alkyl bromide was used and the reaction mixture refluxed without a solvent. [g] A 30% excess of isobutyl bromide was used and the mixture refluxed without a solvent.

TABLE III

N-SUBSTITUTED ETHANOLAMINES

$RCH_2CH(R^1)NHCH_2CH_2OH$ R	R^1	B. p. °C.	Mm.	Yield, %	Salt	M. p., °C.	Empirical formula	Analyses, % Calcd.	Found
C_6H_5—	—CH_3	118–122	3	81	Hydrochloride	110–111	$C_{11}H_{18}ClNO$	Cl, 16.45	16.36
p-$(CH_3O)C_6H_5$—	—CH_3	154–157	2	76	Hydrochloride	106–107	$C_{12}H_{20}ClNO_2$	Cl, 14.43	14.36
3,4-$(CH_3O)_2C_6H_4$—	—CH_3			80		77.5–78[a]	$C_{13}H_{21}NO_3$	C, 65.24	65.12
								H, 8.84	8.96
C_6H_{11}—	—CH_3	98–102	3	62			$C_{11}H_{23}NO$	C, 70.91	70.59
								H, 12.98	12.73
					Hydrochloride	102–104	$C_{11}H_{24}ClNO$	Cl, 15.99	16.24
C_6H_5—	—C_6H_5			59		65–66[b]	$C_{16}H_{19}NO$	C, 79.63	79.63
								H, 7.94	8.26
C_6H_5—	—$CH_2C_6H_5$	195–197	3	62	Hydrochloride	97–98.5	$C_{17}H_{22}ClNO$	Cl, 12.15	11.92

[a] Free base, recrystallized from hexane. [b] Free base, recrystallized from aqueous alcohol.

blocking activity of those compounds which do have an N-benzyl group, or its equivalent, is a consequence of a resultant ability to form a resonating conjugated system or is associated with other chemical and steric factors must, for the present, remain an open question.

Dr. Fellows has demonstrated that the blocking action of compound 528 is eliminated by prior administration of thiosulfate as is also true for "Dibenamine."[11] Thus, compound 528 and "Dibenamine" behave similarly *in vivo*, a fact which suggests that their blocking action is brought about by the same sequence of events; *i.e.*, formation of a reactive intermediate, which can be destroyed by interaction with thiosulfate, and subsequent alkylation of cellular material by the intermediate.

(11) Nickerson, Nomaguchi and Goodman, *Fed. Proc.*, **5**, 195 (1946).

Experimental[12,13]

N-Substituted Ethanolamines.—Reductive alkylation of ethanolamine with an aldehyde or ketone[14,15] was employed. The method is illustrated by the following example.

One-half mole (82 g.) of freshly distilled *p*-methoxyphenylacetone was added to a cooled solution of 30.5 g. (0.5 mole) of ethanolamine in 75 ml. of alcohol. The solution was shaken at room temperature under a pressure of 3–4 atmospheres of hydrogen in the presence of 0.3 g. of pre-reduced Adams platinum oxide (American Platinum Works). Over a period of four hours, 0.45 mole of hydrogen was absorbed. The catalyst was filtered off, the alcohol distilled and the remainder poured into 200 ml. of 3 *N* hydrochloric acid. Acid insoluble material was extracted into ether, the aqueous solution was made basic with sodium hydroxide solution and the amine layer was

(12) Microanalyses were performed by Ruth Savacool, Rita Fox and Mrs. Lillian S. Shreve of these Laboratories.

(13) All melting points are corrected.

(14) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).

(15) Cromwell and Fitzgibbon, *ibid.*, **70**, 387 (1948).

extracted into ether. The ether solution was dried over potassium carbonate, filtered and distilled. In some instances, it was necessary to heat the solution to 70° to attain substantially complete reduction.

The solid amino alcohols were recrystallized after removal of the alcohol solvent. The hydrochlorides were prepared in ether solution and, unless otherwise noted, were recrystallized from mixtures of alcohol and ether. The properties, yields and analyses of the new amino alcohols are listed in Table III.

d-**N-Benzyl-β-phenylisopropylamine.**—One mole (106 g.) of benzaldehyde was added to a cooled solution of 135 g. (1 mole) of *d*-β-phenylisopropylamine[16] and 100 ml. of alcohol. The solution was shaken with hydrogen in the presence of 0.2 g. of platinum oxide at 500 lb. initial pressure and room temperature. Over a three-hour period, 0.85 mole of hydrogen was absorbed. The catalyst was removed by filtration and the solvent was distilled at atmospheric pressure. Distillation of the residue *in vacuo* yielded 190 g. of colorless liquid boiling at 163–173° (8 mm.). Ten grams of the distillate was converted to the hydrochloride in ether and the salt was recrystallized from alcohol, wt. 8.5 g.; m. p. 176°; $[\alpha]^{20}D$ +20.3° (C = 8.00 in ethanol). *Anal.* Calcd. for $C_{16}H_{20}ClN$: Cl, 13.53. Found: Cl, 13.50.

N-Isopropyl-β-phenylisopropylamine.[17]—A solution of 201 g. (1.5 mole) of benzyl methyl ketone, 88.5 g. of isopropylamine, 150 ml. of alcohol and 0.5 g. of platinum oxide catalyst were shaken at room temperature under 500 lb. hydrogen pressure. The calculated amount of hydrogen was absorbed over a period of two and one-half hours. After the catalyst was filtered off, the solution was distilled, first at atmospheric pressure and then under reduced pressure. The amine was collected at 60–65° (3 mm.); yield 180 g. (65%). It formed a hydrochloride which, after recrystallization from alcohol and ether, melted at 157–157.5°. *Anal.* Calcd. for $C_{12}H_{20}ClN$: Cl, 16.59. Found: Cl, 16.46.

N,N-Disubstituted-ethanolamines.—Three general methods were employed: alkylation or benzylation of an N-substituted ethanolamine; (2) methylation of an N-substituted ethanolamine with formaldehyde and formic acid according to the procedure of Clarke, *et al.*,[18] and (3) reaction of two moles of a secondary amine with one mole of ethylene bromohydrin. The following preparations illustrate these methods.

(1) **N-(*p*-Methoxyphenylisopropyl)-N-benzylethanolamine.**—In this method equimolar proportions of secondary amine and halide were used in the presence of potassium carbonate. In a one-liter, 3-necked flask equipped with mercury-sealed stirrer and condenser were placed 105 g. (0.5 mole) of N-*p*-methoxyphenylisopropyl)-ethanolamine, 63 g. (0.5 mole) of benzyl chloride, 35 g. (0.25 mole) of anhydrous potassium carbonate and 150 ml. of alcohol. The mixture was stirred and heated under reflux for nine hours. Water was added to the cooled reaction mixture and the organic layer was extracted into ether. The ether layer, after drying and distillation, yielded 115 g. of heavy viscous oil; b. p. 190–195° (1 mm.).

(2) **N-(1,2-Diphenylethyl)-N-methylethanolamine.**—In a 250-ml. flask equipped with mercury-sealed stirrer, condenser and dropping funnel were placed 17.3 g. (0.07 mole) of N-(1,2-diphenylethyl)-ethanolamine and 7.8 g. of 90% formic acid. Twenty-nine grams of 35% formaldehyde was added with stirring and the solution was refluxed for six hours. Most of the formaldehyde and formic acid were removed by distillation at reduced pressure; water and sodium hydroxide was added to the residue and the amine extracted into ether. The ether solution was dried over magnesium sulfate, filtered and treated with anhydrous hydrogen chloride. Two recrystallizations from alcohol gave 14.8 g. (71%) of hydrochloride, m. p. 158.5–160°.

(3) **N-(β-Phenylisopropyl)-N-isopropylethanolamine Hydrochloride.**—One-half mole (138 g.) of N-isopropyl-β-phenylisopropylamine and 31 g. (0.25 mole) of ethylene bromohydrin were heated at 150–155° for six hours. On cooling, a mass of crystals formed in the red solution. After addition of 300 cc. of ether, the solid was filtered and washed with ether. The ether was removed by distillation and the residue distilled to give 31 g. of amino alcohol; b. p. 142–145° (5 mm.).

The hydrochlorides were prepared from the free bases and anhydrous hydrogen chloride in ether solution. The properties, methods of preparation, yields and analyses of the ethanolamine hydrochlorides are listed in Table II.

N,N-Disubstituted-β-chloroethylamine Hydrochlorides.—The procedure for converting the amino alcohols to the corresponding β-chloroethylamines is illustrated by the following preparation. A solution of 46.5 g. (0.19 mole) of N-(β-phenylisopropyl)-N-ethylethanolamine hydrochloride and 75 ml. of chloroform was cooled in an ice bath while 35 g. (0.29 mole) of thionyl chloride in 75 ml. of chloroform was added. The solution was allowed to come to room temperature and then was heated by a water-bath at 50° for two hours. The solvent and excess thionyl chloride were removed at reduced pressure and the residual oil was stirred with 150 ml. of ether. The β-chloroethylamine hydrochloride crystallized after a few minutes and was recrystallized twice from alcohol and ether.

N,N-Disubstituted-β-bromoethylamine Hydrobromides.—Nineteen grams (0.05 mole) of N-[β-(*p*-methoxyphenyl)-isopropyl]-N-benzylethanolamine hydrobromide, 50 ml. of 48% hydrobromic acid and 0.5 ml. of hypophosphorous acid were heated under a reflux condenser at 100–110° (inside temperature) for an hour until methyl bromide was no longer evolved. The reflux condenser was replaced by a stillhead and a condenser set for downward distillation. The inside temperature was raised to 126° and the water allowed to distil slowly. After six hours, a portion of the acid was distilled and the remainder was removed at reduced pressure. Alcohol was added and distilled several times to aid the removal of the last traces of hydrobromic acid. Finally the amine hydrobromide was dissolved in alcohol; the slow addition of ether, with cooling, caused the salt to separate as colorless crystals.

The dihydroxy compound (Table III) was prepared in a similar manner from N-[β-(3,4-dimethoxyphenyl)-isopropyl]-N-benzylethanolamine.

Summary

The synthesis of a series of N-(β-phenylisopropyl)-N-benzyl(or alkyl)-β-haloethylamines has been described and their adrenergic blocking activity has been reported. N-Benzyl-N-[β-(3,4-dihydroxyphenyl)-isopropyl]-β-bromoethylamine hydrobromide is five to ten times as active as "Dibenamine." Factors bearing on adrenergic blocking ability have been discussed.

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(16) Nabenhauer, U. S. Patent 2,276,509 (1942).

(17) Jacobsen, Wollstein and Christensen, *Klin. Wochschr.*, **17**, 1580 (1938); *C. A.*, **33**, 1041 (1939).

(18) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).