Synthesis and α-Adrenolytic Activity of Chiral β-Haloethylamines

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Abstract □ Several series of *N,N*-diaralkyl- and *N*-aryloxyalkyl-*N*-aralkyl-β-haloethylamines were synthesized containing centers of chirality in the aralkyl substituent and in the β-haloethyl moiety to study the stereoselectivity of α-adrenolytic activity of the β-haloethylamines. These compounds were synthesized from starting materials of known absolute configuration *via* synthetic schemes that did not alter the stereochemical integrity of the chiral centers. Evaluation of the α-adrenolytic activities of these β-haloethylamines on rat vas deferens indicated a variable degree of stereoselectivity of adrenergic blockade, which is interpreted in terms of drug–receptor interactions.

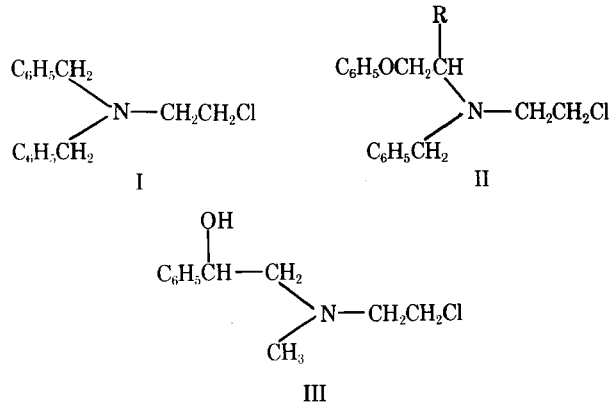
Keyphrases □ β-Haloethylamines, chiral—synthesis, stereoselectivity of α-adrenolytic activity studied, rats □ Enantiomers—β-haloethylamines, synthesis, stereoselectivity of α-adrenolytic activity studied, rats □ α-Adrenolytic activity—stereoselectivity of β-haloethylamines, rats □ Drug–receptor interactions—β-haloethylamines, stereoselectivity of α-adrenolytic activity studied, rats □ Structure–activity relationships—series of β-haloethylamines, stereoselectivity of adrenolytic activity studied, rats

The β-haloethylamines have found utility as therapeutic agents in the treatment of occlusive peripheral vascular disease and, primarily, as pharmacological tools in investigations of the α-adrenergic receptor (1, 2). The β-haloethylamines that produce a highly selective, irreversible antagonism of the α-adrenergic receptor can be structurally classified as either *N,N*-diaralkyl-β-haloethylamines (*e.g.*, dibenamine, I) or *N*-aralkyl-*N*-aryloxyalkyl-β-haloethylamines (*e.g.*, phenoxybenzamine, II, R = CH_3) (3).

While there is considerable information regarding the effect of structural modification on α-adrenolytic activity of the β-haloethylamines, only recently has evidence been obtained indicating that the α-receptor is stereoselective in its interaction with chiral β-haloethylamines. (*R*)-Phenoxybenzamine was reported to be approximately twice as active as the racemate and 14.5 times more potent than the (*S*)-antipode (4). The stereoselectivity of the α-adrenolytic activity of isomers of phenoxybenzamine was proposed to be due to an affinity difference for the receptor by the enantiomers as a result of conformational factors that influence the binding of the C-methyl group.

McLean *et al.* (5) reported on a series of α-adrenolytics containing the β-haloethylamine moiety incorporated into the structure of an agonist ligand, *N*-methyl-β-phenylethanolamine (III) (5). While these compounds were significantly less potent than phenoxybenzamine, their α-adrenolytic activity was characterized by a certain degree of stereoselectivity; (*S*)-III was approximately six times more potent than (*R*)-III. This stereoselectivity of action was opposite to that found in the interaction of β-phenylethanolamine agonists at the α-adrenergic receptor.

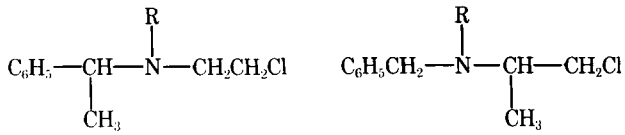
The objective of this study was to investigate more fully the stereochemical requirements for β-haloethylamine antagonism of the α-adrenergic receptor. The approach chosen was to design β-haloethylamines containing centers of chirality in the *N*-benzyl and the *N*-β-chloroethyl substituents of these compounds. Hence, β-haloethylamines IV and V were designed by introducing a center of chirality *via* α-methylation of the *N*-benzyl substituent of dibenamine and desmethylphenoxybenzamine (II, R=H). Similarly, β-haloethylamines VI and VII were designed by incorporation of an α-methyl group into the *N*-β-chloroethyl substituent of dibenamine and desmethylphenoxybenzamine. Hence, interpretation of the relative α-adrenolytic potencies of isomers IV–VII should provide useful information regarding both the structural and stereochemical requirements for β-haloethylamine antagonism of the α-adrenergic receptor.



EXPERIMENTAL[1]

Chemistry—The syntheses of the desired chiral β-haloethylamines (IV–VII) were carried out in such a manner that the absolute configurations of the enantiomers were unequivocally determined. This objective was accomplished by utilizing starting materials of known absolute configuration and by utilizing synthetic reactions that maintained the stereochemical integrity of the chiral center.

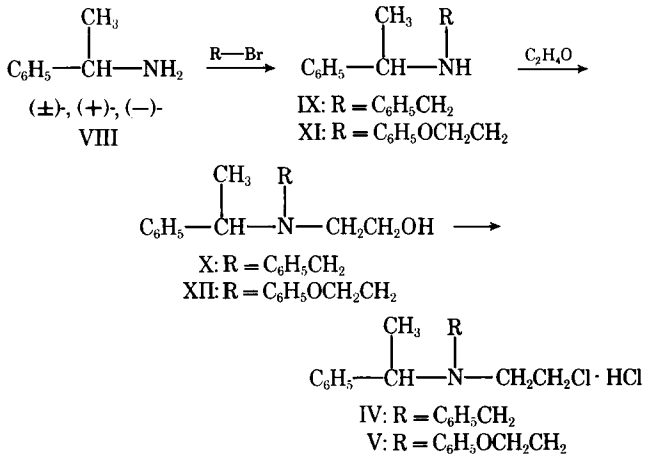
The racemate and enantiomers of IV and V were synthesized utilizing the racemate and (*R*)-(+)- and (*S*)-(−)-antipodes of α-



IV: R = $C_6H_5CH_2$
V: R = $C_6H_5OCH_2CH_2$

VI: R = $C_6H_5CH_2$
VII: R = $C_6H_5OCH_2CH_2$

[1] All melting points were determined with a Mel-Temp melting-point apparatus and are uncorrected. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. The IR spectra were obtained using a Perkin-Elmer 257 or a Beckman model 33 spectrophotometer. NMR spectra were obtained with a Jeolco C-60-HL spectrometer. Optical rotations were measured with a Perkin-Elmer 114 polarimeter, using a 5% sample concentration in 95% ethanol.



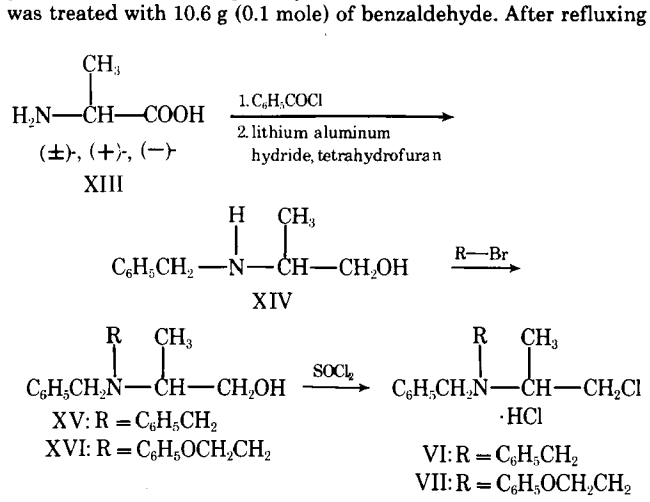
Scheme I

methylbenzylamine (VIII) (Scheme I). Benzylation of VIII was performed by condensation of VIII with benzaldehyde followed by borohydride reduction (Method A) or by treatment of VIII with benzyl bromide (Method B). It was recognized that synthesis by Method A could lead to racemization of the chiral center *via* tautomerization of the intermediate imine. However, a comparison of the optical rotations of the product, α-methyldibenzylamine (IX), obtained by treatment of the enantiomers of VIII according to either Method A or B, showed these values to be essentially identical, thereby indicating that racemization had not occurred in Method A.

The secondary amine (IX) was converted to the amino alcohol (X) by treatment with ethylene oxide, and X was converted to the β-chloroethylamine hydrochloride (IV) using thionyl chloride. Treatment of the racemate and enantiomers of VIII with 2-phenoxyethyl bromide gave the desired secondary amine (XI) in yields of approximately 75%. Hydroxyethylation of XI with ethylene oxide gave the amino alcohol (XII), which was converted to the β-chloroethylamine hydrochloride (V) using thionyl chloride in chloroform.

The racemate and enantiomers of VI and VII were synthesized from the racemate and (*R*)-(−)-alanine and (*S*)-(−)-alanine (XIII) (Scheme II). Alanine was benzoylated and reduced to *N*-benzylalaninol (XIV) by standard procedures (4). *N*-Benzylation of XIV using benzyl bromide in triethylamine gave good yields of the desired amino alcohol (XV), which was readily converted to the β-chloroethylamine analog (VI) upon treatment with thionyl chloride. *N*-2-Phenoxyethylation of XIV was carried out using 2-phenoxyethyl bromide in triethylamine; the resulting amino alcohol (XVI), upon treatment with thionyl chloride, gave the β-chloroethylamine analog (VII).

α-Methyldibenzylamine (IX)—*Method A*—A solution of 12.1 g (0.1 mole) of α-methylbenzylamine in 200 ml of dried benzene was treated with 10.6 g (0.1 mole) of benzaldehyde. After refluxing



Scheme II

for 12 hr under a Dean–Stark apparatus, the solution was concentrated *in vacuo* to a yellow oil. This oil then was dissolved in 200 ml of an ethanolic suspension of 7.8 g (0.2 mole) of sodium borohydride. The reaction was refluxed overnight, treated with 25 ml of water, and filtered. The filtrate was concentrated *in vacuo;* the residue was dissolved in ether, dried (sodium sulfate), and concentrated *in vacuo;* and the light-yellow oil was distilled to yield 9.8 g (44%) of (±)-VIII, bp 118–121° (0.75 mm).

Treatment of (±)-VIII with ethereal hydrochloric acid followed by recrystallization from ethyl acetate provided (±)-VIII-HCl, mp 181–183° [lit. (6) mp 184°]; (*R*)-VIII, bp 110–115° (0.2 mm), $[\alpha]_D^{25}$ +52.0° [lit. (6) bp 171° (15 mm), $[\alpha]_D^{20}$ +29.7°]; and (*S*)-VIII, bp 112–115° (0.2 mm), $[\alpha]_D^{25}$ −53.2° [lit. (6) bp 171° (15 mm), $[\alpha]_D^{20}$ −39.9°]. The hydrochloride salts of (*R*)- and (*S*)-VIII were prepared in ethereal hydrochloric acid and recrystallized from ethyl acetate, mp 176–177° [lit. (6) mp 177°].

Method B—An ice-cooled solution of 12.1 g (0.1 mole) of α-methylbenzylamine in 200 ml of dry toluene was treated with 17.1 g (0.1 mole) of benzyl bromide added dropwise in a 20-ml solution of dry toluene. The reaction was refluxed for 3 hr and then concentrated *in vacuo*. The resulting oil was distilled to give 10.2 g (49%) of (±)-VIII. Similar treatment of (+)- and (−)-α-methylbenzylamines gave products whose physical data were identical to those obtained by Method A.

***N*-(2-Hydroxyethyl)-α-methyldibenzylamine (X)**—In an ice-cooled metal reaction bomb, 40.1 g (0.19 mole) of (±)-IX was treated with 9.7 g (0.22 mole) of ethylene oxide and 2 ml of water. The reaction mixture was heated at 110° for 12 hr and yielded an extremely viscous oil. Following distillation, 24 g (51%) of (±)-X was obtained, bp 150° (0.4 mm); (*R*)-X, bp 156–159° (0.15 mm), $[\alpha]_D^{25}$ + 27.4°; and (*S*)-X, bp 155–160° (0.15 mm), $[\alpha]_D^{25}$ −26.5°.

Anal.—Calc. for $C_{17}H_{21}NO$: C, 69.97; H, 7.60; N, 4.80. Found (±): C, 70.46; H, 7.82; N, 4.76; (*R*): C, 69.81; H, 7.60; N, 4.63; (*S*): C, 70.18, H, 7.77; N, 4.42.

***N*-(2-Chloroethyl)-α-methyldibenzylamine Hydrochloride (IV)**—An ice-cooled solution of 19 g (0.075 mole) of (±)-X in 100 ml of chloroform, previously saturated with dry hydrogen chloride gas, was treated with 11.0 g (0.1 mole) of thionyl chloride in 50 ml of chloroform. The reaction mixture was refluxed for 12 hr and then concentrated *in vacuo* to a viscous amber oil. A crystalline product was obtained by crystallization of the oil from ethyl acetate; 16.4 g (72%) of (±)-IV, mp 143–145°, was obtained after three recrystallizations from ethyl acetate. The enantiomers of X were obtained by an identical procedure: (*R*)-X, mp 176–177°, $[\alpha]_D^{25}$ + 18.2°; and (*S*)-X, mp 177–178°, $[\alpha]_D^{25}$ −18.1°.

Anal.—Calc. for $C_{17}H_{20}ClN{\cdot}HCl$: C, 65.81; H, 6.82; N, 4.51. Found (±): C, 65.79; H, 7.04; N. 4.24; (*R*): C, 65.79; H, 6.98; N, 4.65; (*S*): C, 65.77; H, 7.09; N, 4.13.

α-Methyl-*N*-(2-phenoxyethyl)benzylamine (XI)—A mixture of 12.1 g (0.1 mole) of (±)-VIII, 20 g (0.1 mole) of 2-phenoxyethyl bromide (prepared by treatment of 2-phenoxyethanol with phosphorus tribromide), and 10 g (0.1 mole) of triethylamine was prepared in a 45-ml metal reaction vessel. The sealed reaction vessel was heated at 100° for 12 hr, and a viscous oil was obtained. This oil was dissolved in chloroform and extracted with three 50-ml portions of water. The chloroform solution was dried (sodium sulfate) and concentrated *in vacuo*, and the resultant oil was distilled to give 18.4 g (75%) of (±)-XI, bp 120–127° (0.1 mm).

The enantiomers of VIII were treated in the same manner, providing (*R*)-XI, bp 126–129° (0.2 mm), $[\alpha]_D^{25}$ + 31.5°; and (*S*)-XI, bp 120–126° (0.1 mm), $[\alpha]_D^{24}$ −30.6°. The hydrochloride salts of the isomers of XI were prepared in ethereal hydrochloric acid providing (±)-XI-HCl, mp 151–153°; (*R*)-XI-HCl, mp 125–126°, $[\alpha]_D^{25}$ −10.5°; and (*S*)-XI-HCl, mp 124–126°, $[\alpha]_D^{25}$ + 10.0°.

Anal.—Calc. for $C_{16}H_{19}NO{\cdot}HCl$: C, 69.18; H, 7.26; N, 5.04. Found (±): C, 69.22; H, 7.06; N, 4.98; (*R*): C, 69.19; H, 7.18; N, 4.95; (*S*): C, 69.19; H, 7.30; N, 5.00.

***N*-(2-Hydroxyethyl)-*N*-(2-phenoxyethyl)-α-methylbenzylamine (XII)**—A mixture of 18.4 g (0.076 mole) of (±)-XI, 3.5 g (0.08 mole) of ethylene oxide, and 2 ml of water was prepared and sealed in a 45-ml metal reaction vessel. The vessel was heated at 120° for 17 hr, and the contents were distilled to afford 14.9 g (69%) of (±)-XII, bp 181–184° (0.2 mm). The enantiomers of XII were prepared in an identical manner, giving (*R*)-XII, bp 170–174° (0.12 mm), $[\alpha]_D^{25}$ +11.6°; and (*S*)-XII, bp 174–177° (0.16 mm), $[\alpha]_D^{25}$ −11.9°.

Anal.—Calc. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found

(±): C, 75.04; H, 8.01; N, 5.15; (*R*): C, 75.39; H, 8.26; N, 5.14; (*S*): C, 75.32; H, 7.92; N, 4.88.

***N*-(2-Chloroethyl)-*N*-(2-phenoxyethyl)-α-methylbenzylamine Hydrochloride (V)**—Addition of 15 g (0.13 mole) of thionyl chloride to 10 g (0.035 mole) of (±)-XII in an ice-cooled chloroformic hydrochloric acid solution, followed by a 2-hr reflux period and workup as described in the preparation of (±)-IV, gave 4.8 g (40%) of (±)-V, mp 84–86°, after three recrystallizations from ethyl acetate. The enantiomers of V were similarly prepared, giving (*R*)-V, mp 106–107°, $[\alpha]_D^{25}$ +24.6°; and (*S*)-V, mp 106–108°, $[\alpha]_D^{25}$ −25.0°.

Anal.—Calc. for $C_{18}H_{22}ClNO{\cdot}HCl$: C, 63.53; H, 6.81; N, 4.12. Found (±): C, 63.57; H, 6.86; N, 3.83; (*R*): C, 63.87; H, 7.17; N, 3.93; (*S*): C, 63.50; H, 7.02; N, 4.35.

***N,N*-Dibenzyl-2-amino-1-propanol (XV)**—A solution of 13.7 g (0.08 mole) of benzyl bromide in 50 ml of dry toluene was added dropwise at room temperature to a stirred 250-ml solution of 10 g (0.06 mole) of (±)-XIV [prepared by lithium aluminum hydride in tetrahydrofuran reduction of (±)-*N*-benzoylalanine according to published procedures] (4) in dry toluene and 6 g of sodium carbonate in suspension. After addition of the benzyl bromide, the reaction was refluxed for 24 hr and filtered. Then the filtrate was concentrated *in vacuo* and the residue was distilled to afford 10.1 g (64%) of (±)-XV, bp 143–148° (0.1 mm).

The enantiomers of XV were prepared similarly from the enantiomers of XIV, providing (*R*)-XV, bp 144–149° (0.1 mm), $[\alpha]_D^{25}$ −34.8°; and (*S*)-XV, bp 142–148° (0.1 mm), $[\alpha]_D^{25}$ +35.1°. The hydrochloride salts of the isomers of XV were prepared in ethyl acetate saturated with hydrochloric acid. The salts were recrystallized to a stable melting point from ethyl acetate, providing (±)-XV-HCl, mp 181–183° [lit. (7) mp 180.5–182.5°]; (*R*)-XV-HCl, mp 140–142°; and (*S*)-XV-HCl, mp 142–144°.

Anal.—Calc. for $C_{17}H_{21}NO{\cdot}HCl$: C, 69.97; H, 7.60; N, 4.80. Found (±): C, 69.83; H, 7.85; N, 4.66; (*R*): C, 69.99; H, 7.38; N, 4.86; (*S*): C, 70.13; H, 7.61; N, 4.71.

***N*-(2-Chloro-1-methylethyl)dibenzylamine Hydrochloride (VI)**—A solution of 5.3 g (0.021 mole) of (±)-XV in 200 ml of dry, distilled benzene, previously saturated with hydrochloric acid, was cooled in an ice bath. Then 5.3 g (0.045 mole) of thionyl chloride in 50 ml of benzene was added. The reaction was allowed to warm to room temperature and then was refluxed for 12 hr. The solution was concentrated *in vacuo*, treated with three portions of 95% ethanol to destroy the unreacted thionyl chloride, and further concentrated *in vacuo*. A dark viscous oil, which crystallized on standing for 2 hr, was obtained. Recrystallization of the solid yielded 2.8 g (45%) of (±)-VI, mp 136–138° [lit. (8) mp 137–139°]. The enantiomers of XV were treated in an identical manner to provide (*R*)-VI, mp 167–168°, $[\alpha]_D^{25}$ −28.5°; and (*S*)-VI, mp 166–168°, $[\alpha]_D^{25}$ +26.2°.

Anal.—Calc. for $C_{17}H_{21}ClN{\cdot}HCl$: C, 65.81; H, 6.82; N, 4.51. Found (±): C, 66.35; H, 6.95; N, 4.53; (*R*): C, 65.74; H, 6.75; N, 4.54; (*S*): C, 65.98; H, 6.81; N, 4.42.

***N*-(2-Hydroxy-1-methylethyl)-*N*-(2-phenoxyethyl)benzylamine (XVI)**—A solution of 16.4 g (0.1 mole) of (±)-XIV in 200 ml of triethylamine was treated with 24 g (0.12 mole) of 2-phenoxyethyl bromide. The reaction was refluxed for 24 hr, after which the solvent was removed *in vacuo* and the resultant oil was distilled to provide 12.7 g (44%) of (±)-XVI, bp 190–198° (0.22 mm). The enantiomers of XIV were treated in an identical manner to yield (*R*)-XVI, bp 180–184° (0.08 mm), $[\alpha]_D^{25}$ −38.8°; and (*S*)-XVI, bp 186–190° (0.2 mm), $[\alpha]_D^{25}$ +39.5°.

Anal.—Calc. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.13; N, 4.91. Found (±): C, 75.52; H, 8.37; N, 4.97; (*R*): C, 76.61; H, 8.11; N, 5.10; (*S*): C, 75.92; H, 8.45; N, 4.91.

***N*-(2-Chloro-1-methylethyl)-*N*-(2-phenoxyethyl)benzylamine Hydrochloride (VII)**—A solution of 7 g (0.025 mole) of XVI and 3.6 g (0.03 mole) of thionyl chloride was prepared in chloroform, previously treated with hydrochloric acid. The solution was refluxed for 3 hr, concentrated *in vacuo*, and treated with three portions of ethanol with alternate *in vacuo* concentration. The resulting dark gummy material was crystallized from ethyl acetate to yield 3.7 g (44%) of (±)-VII which, after three recrystallizations from ethyl acetate, gave a white solid, mp 116–117°. The enantiomers of VII were likewise prepared from the enantiomers of XIV, giving (*R*)-VII, mp 122–124°, $[\alpha]_D^{25}$ +23.2°; and (*S*)-VII, mp 124–125°, $[\alpha]_D^{25}$ −22.5°.

Anal.—Calc. for $C_{18}H_{22}ClNO{\cdot}HCl$: C, 63.53; H, 6.81; N, 4.12. Found (±): C, 63.77; H, 6.88; N, 4.05; (*R*): C, 63.58; H, 6.72; N, 4.11; (*S*): C, 63.90; H, 7.12; N, 4.26.

Table I—α-Adrenolytic Activities of Chiral β-Chloroethylamines

Compound	Configuration	ED_{50}, mmole/ml
(±)-IV	—	12.0×10^{-8}
(+)-IV	*R*	7.0×10^{-8}
(−)-IV	*S*	22.0×10^{-8}
(±)-V	—	6.4×10^{-8}
(+)-V	*R*	6.1×10^{-8}
(−)-V	*S*	6.8×10^{-8}
(±)-VI	—	Inactive[a]
(−)-VI	*R*	Inactive[a]
(+)-VI	*S*	Inactive[a]
(±)-VII	—	75.0×10^{-8}
(+)-VII	*R*	34.0×10^{-8}
(−)-VII	*S*	24.0×10^{-8}
(±)-Phenoxybenzamine	—	1.5×10^{-8}

[a] The isomers of VI were deemed inactive in this study because they did not produce significant blockade of the contractile response of levarterenol of the rat vas deferens up to a concentration of 9.2×10^{-6} mmole/ml.

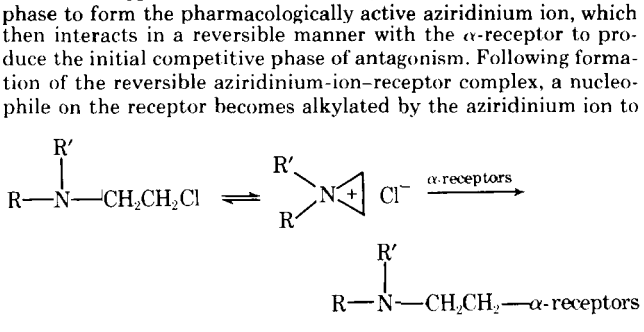
Pharmacology—Male, white rats, 200–375 g, were sacrificed with a sharp blow to the head. The vas deferens was removed in 2–3-cm strips and immediately placed in a bath of modified Krebs–Henseleit solution aerated by 95% oxygen and 5% carbon dioxide. In the test procedure, the vas deferens was mounted in a 25-ml bath of aerated Krebs–Henseleit solution and maintained at 37°. Tissues were allowed to equilibrate at least 30 min prior to the beginning of any experiment.

Contractile responses were recorded by means of a physiograph[2] with a chart speed of 0.01 cm/sec. The first step in the test procedure involved obtaining a contractile response to 5×10^{-5} *M* levarterenol [(−)-norepinephrine] (95% of maximum contraction). The next response to levarterenol was recorded after the tissue had stabilized, as indicated by a flat baseline. A given dose of β-haloethylamine was then added to the bath fluid; after 5 min, the tissue was washed, levarterenol was added, and the response was recorded. The percent decrease in the contractile response was calculated and represents the degree of adrenergic blockade.

A graphical correlation of percent blockade *versus* log concentration of the β-haloethylamine was then prepared, and the ED_{50} concentrations were taken from the graph. The ED_{50} values representing the concentration of β-haloethylamines (in millimoles per milliliter) required to reduce by 50% the response of the rat vas deferens to 5×10^{-5} *M* levarterenol after a 5-min exposure of the tissue to the antagonist are presented in Table I.

RESULTS AND DISCUSSION

The blockade of α-adrenergic receptors by β-haloethylamines has been characterized as being competitive irreversible in nature (9). To account for the biphasic nature of β-haloethylamine antagonism, Nickerson (10) proposed Scheme III for the mechanism of action of these agents. This proposal, later substantiated by Graham (11), suggests that the β-haloethylamine cyclizes in the biophase to form the pharmacologically active aziridinium ion, which then interacts in a reversible manner with the α-receptor to produce the initial competitive phase of antagonism. Following formation of the reversible aziridinium-ion–receptor complex, a nucleophile on the receptor becomes alkylated by the aziridinium ion to



Scheme III

[2] DMP-4A.

establish irreversible blockade. Hence, the production of adrenergic antagonism by a β-haloethylamine is a function of the chemical reactivity of the molecule, which is of importance in the formation of the aziridinium ion, and the degree of structural and stereochemical complementarity of the aziridinium ion for the components of the α-receptor.

Hypothetical representations of the complex formed between the aziridinium ion and the α-receptor inferred a primary receptor binding role for the aryloxyalkyl substituent of the *N*-aryloxyalkyl-β-haloethylamines (12, 13). Similar descriptions of the interaction of an *N,N*-diaralkyl-β-haloethylamine with the α-receptor implicated a primary binding site on the receptor for the *N*-aralkyl substituent. However, it would appear that in the case of an *N*-aryloxyalkyl-*N*-aralkyl-β-haloethylamine (II), its primary interaction with the α-receptor involves preferential binding of the aryloxyalkyl substituent as opposed to binding of the aralkyl group. This conclusion is based upon the greater antagonistic potencies of the *N*-aryloxyalkyl-β-haloethylamines as compared to their *N*-aralkyl analogs (*e.g.*, phenoxybenzamine *versus* dibenamine) and confirmed by the results of this study that indicate greater potency for the *N*-phenoxyethyl-β-haloethylamines (V and VII) as compared to their *N*-benzyl analogs (IV and VI).

In addition, the lack of stereoselectivity of antagonistic action of the isomers of V suggests that the achiral phenoxyethyl substituent is primarily involved in receptor binding to the exclusion of an interaction of the chiral *N*-α-methylbenzyl substituent in these isomers. One would reasonably expect to observe a significant degree of stereoselectivity in the actions of the isomers of V if the *N*-α-methylbenzyl moiety was involved in binding the aziridinium ion of V to receptor components. Similarly, the relatively low level of stereoselectivity of α-antagonism exhibited by the isomers of IV [(*R*)/(*S*) ratio of 3.1] suggests that there is no great preference in binding of either the *N*-benzyl or the chiral *N*-α-methylethyl substituents of this β-haloethylamine at the receptor.

Previous studies of the effect of the α-methylation of the β-chloroethyl substituent of dibenamine indicated no change in potency as a result of this structural modification. However, a similar structural change in the phenoxybenzamine series is associated with a loss of antagonistic activity (14). The findings of this study are somewhat opposed to the literature reports in that the isomers of VI do not possess significant α-adrenolytic activity whereas the isomers of VII exhibit a fair degree of potency. The earlier studies of the effect of this structural modification on α-adrenolytic activity were carried out in whole animals (cat blood pressure changes), and the isomers of the dibenamine and phenoxybenzamine analogs were not studied.

Based upon the results obtained in this study, the general effect of α-methylation of the β-chloroethyl substituent in the β-haloethylamines is deleterious with regard to α-adrenolytic potency. The effect of this structural modification is so significantly deleterious to potency that VII is even less active than IV. The stereoselectivity of antagonistic potencies of the isomers of VII may be indicative of differences in receptor affinities for these compounds. However, numerous other factors may play a role in producing potency differences between enantiomeric β-haloethylamines (4, 5). These factors include differing modes of binding to the receptor, which could result in differing rates of receptor nucleophile alkylation; differences in rates of inhibition of levarterenol uptake sites; and the possibility of at least two different receptor subsites, which mediate the antagonism of β-haloethylamines at the adrenergic receptor.

Further, a comparison of the potencies of one series of isomers with a structurally related series of isomers is complicated by the possibility of differing rates of cyclization of the β-haloethylamines to the aziridinium ions. Additional study is required prior to explaining the nature of the stereoselectivity of α-adrenolytic potencies of the isomers of VII.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 19, 1975, from the *Department of Medicinal Chemistry, University of Mississippi, University, MS 38677*

Accepted for publication June 26, 1975.

Adapted in part from a thesis submitted by F. W. Crawford to the Graduate School, University of Mississippi, in partial fulfillment of the Master of Science degree requirements.

Supported by the Mississippi Heart Association and the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

The authors acknowledge the assistance of Dr. James C. Murphy and Mr. Joseph M. Mauldin in carrying out the pharmacological evaluation of the compounds.

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