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Synthesis and Adrenoreceptor Blocking Action of Aziridinium Ions Derived from Phenoxybenzamine and Dibenamine[†]

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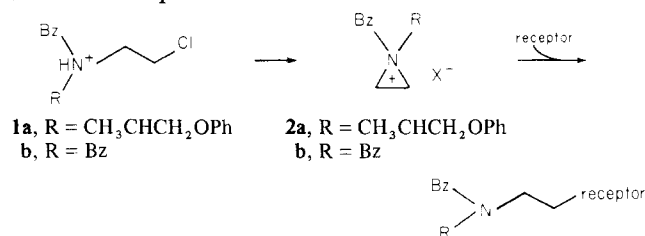
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Crystalline perchlorate salts of aziridinium ions derived from phenoxybenzamine and dibenamine were prepared. Both aziridinium ions were tested on the rat vas deferens and found to possess α -adrenergic potencies which were nearly identical with those of the parent compounds. The hydrolysis rates of phenoxybenzamine and dibenamine aziridinium ions (**2a,b**) in physiological medium were found to be 6.04×10^{-4} and $8.35 \times 10^{-4} \text{ sec}^{-1}$, respectively. The rates of cyclization of the parent amines to **2a** and **2b** in aqueous medium were 1.9×10^{-2} and $7.2 \times 10^{-3} \text{ sec}^{-1}$, respectively. The potencies and kinetic profiles indicate that the aziridinium ion is the only active species in α -adrenergic blockade. Moreover, differences in potency between phenoxybenzamine and dibenamine appear to be exclusively to a difference in receptor affinity rather than to a difference in intrinsic alkylating ability.

Phenoxybenzamine (**1a**) and dibenamine (**1b**) are employed extensively as tools in pharmacologic studies. Although it has been generally accepted that the nonequilibrium blockade of α -adrenergic receptors by these drugs is mediated through the corresponding aziridinium species (**2a,b**), no unequivocal evidence has been reported which establishes the intermediacy of this reactive intermediate.^{1,2} The acceptance of the mechanism for receptor inactivation is based principally on an extensive collection of indirect evidence compiled since Nickerson and Goodman³ first proposed the formation of an aziridinium ion as a prerequisite for covalent bond formation with the receptor.



Historically, the approach taken for the study of the activities of ions related to **2** has been by the use of solutions containing predicted concentrations of both parent amine and the intermediate.⁴⁻⁶ The levels of intermediate were estimated by sequential titrimetric determinations of hydrogen ion and chloride ion concentrations. Since the time frames of such methods might not be sensitive enough to accurately measure the rapid dynamic processes taking

place in these systems, a more definitive study of the kinetic and pharmacologic behavior of **1** and **2** would be instructive.

The most apparent manner in which to test the activities of **2** is to quantitatively convert **1** into **2**. Unfortunately, the isolation and testing of an aziridinium ion intermediate for pharmacologic activity have been accomplished in only one previous case. Allen and Chapman⁷ and Graham⁸ found that the in vivo activities of ions derived from several *N*-ethyl-*N*-chlorobenzyl-2-chloroethylamines (as the picrylsulfonate salts) were roughly parallel to their concentration. To our knowledge, no detailed investigation has been published on the isolated aziridinium ion (**2**) derived from phenoxybenzamine or dibenamine. Because of their extensive use in pharmacology, we have undertaken a study which includes the synthesis and characterization of **2a** and **2b**, their rates of formation and decomposition under physiological conditions, and their in vitro activities.

Chemistry. The aziridinium compounds **2a** and **2b** were synthesized and isolated as the stable perchlorate salts ($\text{X} = \text{ClO}_4^-$) by the use of AgClO_4 , according to the method of Leonard and Paukstelis.⁹ Thus, the free base of racemic **1a** was treated with excess anhydrous AgClO_4 in acetone resulting in the formation of **2a** and AgCl . As expected,¹⁰ the aziridinium salt underwent decomposition when stored for extended periods in acetone solution but was stable in, and recrystallizable from, CH_2Cl_2 . Similarly, treatment of the free base of **1b** with anhydrous AgClO_4 in acetone afforded salt **2b**, which was also recrystallizable from CH_2Cl_2 .

A careful proof of structure for **2a** and **2b** was undertaken, to eliminate the possibility of the piperazinium dimer **3**, although such compounds have been shown to be

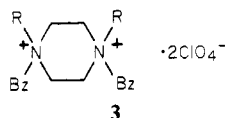
[†] This paper is dedicated to the memory of Edward E. Smissman.

Table I. Rates of Cyclization of Phenoxybenzamine and Dibenamine at 37°C^a

Compd	Solvent	k (sec ⁻¹) × 10 ³ (95% confidence limits)	$T_{1/2}$, min
1a	80% aq Me ₂ CO	4.98 (±0.20)	2.3
	H ₂ O ^b	19	0.61
1b	80% aq Me ₂ CO	1.88 (±0.07)	6.1
	H ₂ O ^b	7.2	1.6

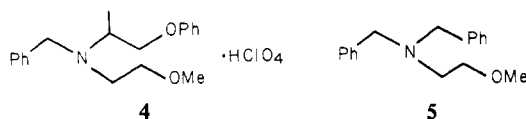
^a 0.025 M NaHCO₃, ca. 5×10^{-4} M 1a and 1b. ^b Extrapolated from 80% aqueous Me₂CO according to A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, 78, 2770 (1956).

inactive as α -adrenergic blocking agents in all cases.¹¹ Since 2 and 3 have identical elemental composition, NMR



spectroscopy and chemical reactivity were the primary criteria used. The NMR spectrum of 2b exhibits a singlet absorption at δ 3.38, which is diagnostic for aziridinium ring protons.⁹ On the other hand, the ring protons of 3 would be expected⁹ to show an absorption in the range of δ 4.0–4.1, a region which is devoid of any absorption in our sample. Similarly, the spectrum of 2a showed no absorption in the δ 4.0–4.2 region, ruling out the possibility of 3 as an alternative to 2. The dissymmetry of the molecule greatly complicated the spectrum of 2a, and the multiplet at δ 3.0–3.6 precluded the assignment of a characteristic chemical shift for the ring protons.

The existence of 2a was further confirmed by a study of its solvolytic reactivity. By heating 2a at reflux in excess MeOH for 30 min, a single product was produced, identified as the perchlorate salt of *N*-phenoxyisopropyl-*N*-benzyl-2-methoxyethylamine (4) by NMR and microanalysis. The corresponding free base of 4 was identical with the product resulting from the reaction of 1a·HCl with NaOMe in MeOH. Under the above methanolysis conditions, 3 would not be expected to exhibit such high reactivity. Unfortunately, methanolysis of 2b afforded



an oil which was uncrystallizable. However, spectroscopic (NMR, ir) analysis of the resulting free base clearly supported the existence of di-*N*-benzyl-2-methoxyethylamine (5). This product was identical with the product formed by the reaction of 1b·HCl with excess NaOMe. GC analysis confirmed the presence of only one compound in each case.

Kinetic Studies. The kinetic profiles were determined for both 1a and 1b by studying first the rates of cyclization to 2a and 2b, respectively, and then the rates of hydrolysis of synthesized 2a and 2b in physiological medium. The rates of formation of 2a,b were determined potentiometrically in 80% aqueous acetone, using a Cl⁻ electrode. The results of these determinations are shown in Table I, along with values extrapolated to pure water. It can be noted that phenoxybenzamine (1a) cyclizes to the aziridinium ion approximately 2.5 times more rapidly than dibenamine (1b).

The respective hydrolysis rates of 2a and 2b were determined in modified Kreb's solution at 37°C. The product amino alcohols were quantified by GC analysis, using methyl ether 4 as an internal standard. The results (Table II) indicate that the rates of hydrolysis of both 2a

Table II. Hydrolysis Rates of Aziridinium Ions 2a and 2b at 37°C^a

Compd	k (sec ⁻¹) × 10 ⁴ (95% confidence limits)	$T_{1/2}$, min
2a	6.04 (±0.24)	19
2b	8.35 (±0.51)	14

^a Determined in modified Kreb's solution, 0.025 M NaHCO₃, ca. 0.003 M 2a and 2b.

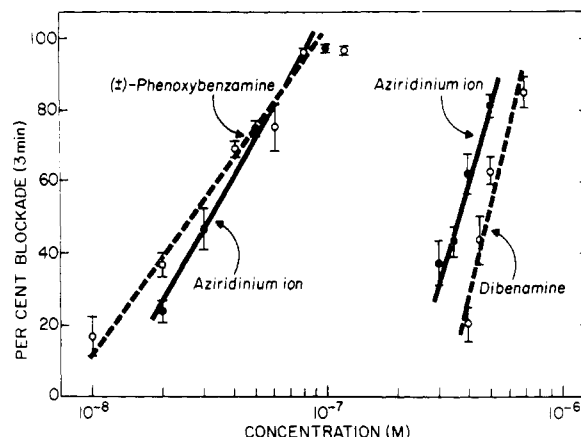


Figure 1. The percent blockade of the response to norepinephrine (5×10^{-5} M) on the vas deferens of the rat after a 3-min exposure to the parent amines and their derived aziridinium salts.

and 2b are slower than their rates of formation and are of comparable magnitude with respect to each other.¹²

Pharmacology. A comparison of the relative potencies of 1a,b and their respective aziridinium ions to block norepinephrine contractions of the vas deferens after 3 min is shown Figure 1. It can be seen that both 1a and its ion 2a were more potent than either 1b or 2b. In each case, the activity of the aziridinium ion was quite similar to that of the parent compound. For 1b, the ion was slightly more potent, while the potencies were virtually the same for 1a and 2a.

Graphs of the exposure times necessary to produce 50% blockade with varying concentrations of antagonist are presented in Figure 2. For 1a and 2a, the curves were essentially the same over the times used in the study. However, for 1b and 2b, the ion is again more potent at all times, with the curves tending to converge toward a larger time interval. It should be noted that the early points (1-min range) for these systems are difficult to obtain and are not as reliable as the remaining points.

In other studies, the existence of nonequilibrium blockade for all compounds was confirmed by the fact that the activities were not reversible by washing over the time span of the experiment. However, the blockade was reduced 30–40% after standing for 3 hr. All substances were found to antagonize serotonin to about the same degree. It may be noted that drug vehicles and salts were tested and found to be inactive at the concentrations reached in these studies.

Discussion

It should first be stated that the high blocking activity of 2a and 2b clearly implicates the aziridinium ion as the active species. The accepted pathway for blockade¹³ (Scheme I) begins by cyclization at a rate k_1 , followed by formation of a reversible complex with receptor M. Alkylation then follows at a rate determined by k_2 to establish the nonequilibrium blockade. By utilizing the pure aziridinium intermediate, k_1 has been removed from the rate expression, thus simplifying the analysis of subsequent steps. In order to deal with the reversible equilibrium step,

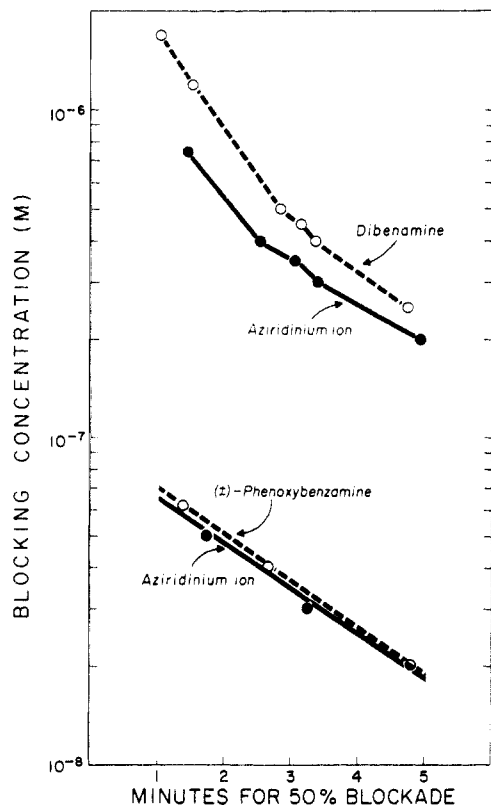
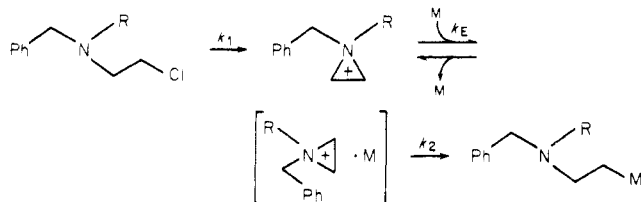


Figure 2. Time to produce 50% blockade of the response of the vas deferens to norepinephrine ($5 \times 10^{-5} M$) after exposure to various concentrations of parent amines or aziridinium salts.

Scheme I



we have utilized the data shown in Figure 2 and the results of a previous study.

Portoghesi et al.¹⁴ found that the optical antipodes of phenoxybenzamine exhibited alkylating behavior consistent with the interpretation that the enantiomeric alkylating agents differed substantially in receptor affinity but alkylated the receptor at similar rates, once the reversible complex was formed. Thus the difference in potency was attributed to an affinity difference rather than to a difference in intrinsic alkylating activity. Consistent with this interpretation was the fact that parallel slopes were obtained when concentration was plotted against "minutes for 50% blockade", analogous to Figure 2.

By following the potencies of the ions at 50% blockade (Figure 2), the activities at each time interval were determined at equal concentrations of alkylated receptor; i.e., the graphs represent the change in concentration of the alkylated receptor with time. If it is assumed that slopes of the linear portions of the curves are proportional to the rates of receptor alkylation, then it follows from the previous results¹⁴ that a comparison of these slopes can provide information regarding the relative rates of receptor alkylation by **2a** and **2b**. When the linear portions of the curves are compared, **2a** is found to have a slope of $0.130 \pm 0.007 \text{ min}^{-1}$ while **2b** has a slope of $0.126 \pm 0.010 \text{ min}^{-1}$. Clearly, the slopes are statistically indistinguishable, implying that the rates of receptor alkylation are indis-

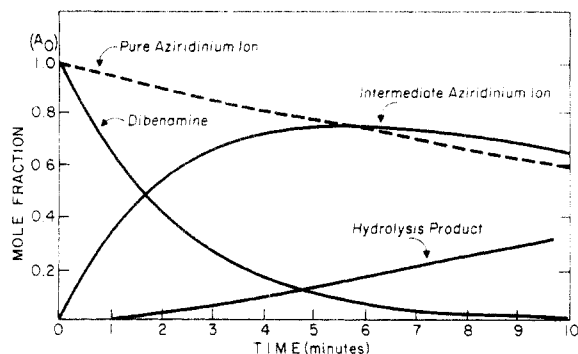


Figure 3. Kinetic profile at 37°C of dibenamine hydrochloride (**1b**) and its derived aziridinium perchlorate (**2b**).

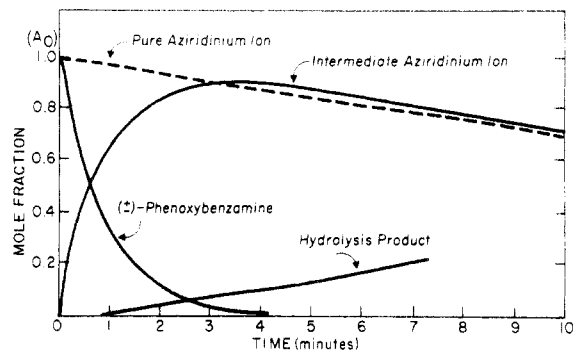


Figure 4. Kinetic profile at 37°C of phenoxybenzamine hydrochloride (**1b**) and its derived aziridinium perchlorate (**2a**).

tinguishable, and the differences in potency between phenoxybenzamine and dibenamine are due principally to transport and affinity differences.

The results of this study also provide information as to whether or not the parent compounds **1a** and **1b** alkylate adrenergic receptors. Calculations based on the above results strongly indicate that they do not. These conclusions are based on comparison of the combined kinetic profiles of each system and the respective activity profiles. The kinetic profiles are presented in Figures 3 and 4 as consecutive first-order reactions,¹⁵ based on the rate constants at 37°C in buffered medium.

For dibenamine (Figure 3), the rate of cyclization is such that the maximum ion concentration occurs at about 6 min after dissolution, with a gradual hydrolysis occurring after that point. The level of aziridinium ion **2b** derived from **1b** intersects the first-order decay curve of pure **2b** at 5.5 min, at which point the blocking activities of the two solutions should be indistinguishable if **2b** is the only active species. The dose-response curves in Figure 2 are in reasonably good agreement with this figure, considering that the rates of cyclization are extrapolated values and there is room for experimental error. The extrapolated point of intersection of the curves for **1b** and **2b** is 6.25 min, an error of 12%. If **1b** were to have significant alkylating activity, the curves of **1b** and **2b** would be expected to intersect at a time shorter than that predicted by Figure 3, not longer.

Reasonably consistent behavior was also observed for phenoxybenzamine (Figure 4). Since the cyclization rate of **1a** is approximately 2.5 times as fast as **1b** and the rate of hydrolysis of **2a** is slightly slower than **2b**, the maximum ion concentration is reached in about 3 min and the levels remain relatively high for several minutes. This is effectively illustrated by the calculation that 80% of the theoretical maximum concentration of **2a** is still present after 10 min. At 3 min, solutions of **1a** and **2a** should be pharmacologically indistinguishable, and this is observed

in Figure 1. The close agreement of the curves of **1a** and **2a** in Figure 2 at early times (1–2 min) could be interpreted as due to some activity of the parent compound, although we attribute it to the previously mentioned difficulties in the experimental method. At 2 min, the levels of aziridinium ion derived from **1a** are calculated to be 92% of the level resulting from hydrolysis of **2a**. It is unlikely that differences of this magnitude can be distinguished pharmacologically.

Finally, results of the present study suggest that the α -adrenergic receptors are located primarily on the exterior cell surface in the vas deferens, since the active intermediates **2a** and **2b** are ionic compounds, and should be incapable of facile penetration through the cell membranes.

In summary, the results presented here strongly support the existence of the aziridinium ion intermediates derived from phenoxybenzamine and dibenamine as the sole active species in α -adrenergic blockade. The parent amines are seen to have little or no receptor alkylating ability. The observed differences in potency between phenoxybenzamine and dibenamine are indicated to be due primarily to transport and receptor affinity differences rather than to differences in alkylating ability.

Experimental Section

All melting points were determined by the capillary method and are uncorrected. Microanalyses were performed by MHW Laboratories, Garden City, Mich., and were within $\pm 0.2\%$ of the calculated values. Ir spectra were determined on a Perkin-Elmer 237B grating spectrophotometer; NMR spectra were determined at ambient temperature on a Varian A-60D or XL-100 spectrometer, using Me₄Si as internal standard. GC analyses were performed on a Perkin-Elmer 900 instrument equipped with an Autolab 6300 digital integrator.

N-Phenoxyisopropyl-N-benzylaziridinium Perchlorate (2a). To an ice-cold, stirred mixture of 0.681 g (0.002 mol) of phenoxybenzamine hydrochloride (**1a**), 20 ml of H₂O, and 30 ml of Et₂O was added dropwise 20.0 ml of 0.10 N NaOH (0.002 mol). The Et₂O layer was separated and the aqueous layer washed with two additional portions of Et₂O. The extracts were combined, dried over Na₂SO₄, and evaporated under reduced pressure to yield 0.638 g of colorless oil. The crude product was taken up in 10 ml of dry Me₂CO, cooled to 0°, and treated with 0.65 g (0.0032 mol) of anhydrous AgClO₄ in 10 ml dry Me₂CO. A precipitate formed immediately. After 10 min, the precipitate was filtered and the resulting solution was evaporated under reduced pressure to afford a gummy white solid. The product was taken up in CH₂Cl₂, leaving behind the remaining Ag salts. The filtered solution was concentrated under N₂ and then cooled to afford 0.703 g (94%) of white crystals. Traces of Ag remained in the product, as evidenced by slight darkening upon standing in light. Further recrystallization afforded white needles: mp 155–156°C dec; ir (Nujol mull) 3120, 1585, 1450, 1370, 1220, 1060, 750, 690 cm⁻¹; NMR (CD₃COCD₃) δ 7.7–6.9 (m, 10 H, aromatic CH), 4.80 (s, 2 H, benzylic CH₂), 4.50 (d, 2 H, CH₂), 4.0–3.0 (m, 5 H, aziridinium ring CH, methine CH), 1.68 (d, 3 H, CH₃). Anal. (C₁₈H₂₂ClNO₅) C, H, N, Cl.

N-Phenoxyisopropyl-N-benzyl-2-methoxyethylammonium Perchlorate (4-HClO₄). To 10 ml of anhydrous MeOH was added 0.308 g (0.84 mmol) of **2a**. The stirred solution was heated at reflux for 30 min, cooled, and evaporated under reduced pressure to afford a white solid. This solid was taken up in more dry CH₃OH, concentrated under N₂, and allowed to cool, affording 0.272 g of crystalline 4-HClO₄: mp 135–136°C dec; ir (Nujol mull) 3160, 1570, 1450, 1370, 1235, 1075 cm⁻¹. Anal. (C₁₉H₂₅ClNO₆) C, H, N.

To 0.502 g of 4-HClO₄ in a separatory funnel was added 5 ml of H₂O and 15 ml of 0.1 N NaOH. A quantity of Et₂O was added and the mixture was shaken until the crystals had reacted. The Et₂O layer was separated and the H₂O layer washed twice more with Et₂O. The extracts were combined, dried over MgSO₄, and evaporated under reduced pressure to afford 0.373 g of **4** as a colorless liquid. Ir and NMR spectra were identical with that of a sample prepared as follows. Into 50 ml of dry MeOH which

had been reacted with 0.120 g of Na (0.0052 g-atom) was placed 0.637 g of **1a**·HCl (1.87 mmol). The stirred solution was heated at reflux for 3 hr, cooled, and evaporated to afford 0.560 g (99%) of **4**: ir (neat) 1601, 1490, 1235 cm⁻¹; NMR (CDCl₃) δ 7.40–6.67 (m, 10 H, aromatic CH), 4.17–3.60 (m, 2 H, NCH₂CH₂), 3.73 (s, 2 H, PhCH₂), 3.48–3.00 (m, 3 H, methine and MeOCH₂), 3.22 (s, 3 H, OCH₃), 2.80 (d, 2 H, CH₂OPh), 1.13 (d, 3 H, CHCH₃).

N,N-Dibenzylaziridinium perchlorate (2b) was prepared in a manner analogous to **2a**, utilizing 1.185 g (0.004 mol) of **1b**·HCl and 1.327 g (0.0064 mol) of anhydrous AgClO₄. Recrystallization from CH₂Cl₂ afforded 0.929 g (72%) of white crystals: mp 126–128°C; NMR (CD₃COCD₃) δ 7.53 (s, 10 H, aromatic), 4.60 (s, 4 H, benzyl CH₂), 3.38 (s, 4 H, aziridinium CH₂). Anal. (C₁₆H₁₈ClNO₄) C, H, N.

N,N-Dibenzyl-2-methoxyethylamine (5). To 10 ml of anhydrous MeOH was added 0.300 g (0.927 mmol) of **2b**. The stirred solution was heated at reflux for 30 min, cooled, and evaporated under reduced pressure to afford a hygroscopic oil which resisted crystallization. The oil was placed in a separatory funnel, to which was added 10 ml of H₂O and 10 ml of 0.1 N NaOH. The mixture was extracted with three portions of Et₂O. The extracts were combined, dried over MgSO₄, and evaporated to afford 0.214 g of **7** as a colorless liquid. Ir and NMR spectra were identical with that of a sample prepared as follows. Into 50 ml of dry MeOH which had been reacted with 0.130 g of Na (0.0057 g-atom) was placed 0.554 g (1.87 mmol) of dibenamine hydrochloride. The stirred solution was heated at reflux for 3 hr, cooled, and evaporated under reduced pressure. A quantity of H₂O was added and the product extracted with Et₂O. The Et₂O solution was evaporated to afford 0.47 g of **7**: ir (neat) 3025, 1490, 1450, 110, 740, 690 cm⁻¹; NMR (CDCl₃) δ 7.47–7.07 (m, 10 H, aromatic CH), 3.62 (s, 4 H, Bz), 3.43 (t, 2 H, MeOCH₂), 3.22 (s, 3 H, CH₃), 2.65 (t, 2 H, NCH₂).

Cyclization Kinetics. A chloride ion selective silver billet combination electrode (Beckman no. 39517) was calibrated with standard solutions of NaCl in 80% aqueous Me₂CO at 37°C containing 25 mM NaHCO₃. Into a stirred solution of 10 ml of buffered 80% aqueous Me₂CO at 37°C, in which the electrode was immersed, was injected 40 μ l of ca. 0.1 M solution of **1a**·HCl or **1b**·HCl in dry Me₂CO. Initial concentration of salt was ca. 4×10^{-4} M. Readings of Cl⁻ concentration were taken every 12 sec using the calibrated electrode. Rate constants were determined from a plot of log (moles of amine) vs. time, using PLSTSQR,¹⁶ an interactive regression analysis computer program. Confidence limits (95% level) were determined by standard statistical methods.¹⁷

Hydrolysis Kinetics. Into a 5-ml volumetric flask was weighed 31.78 mg of **2b** and 8.337 mg of 4-HClO₄ as an internal standard. Anhydrous Me₂CO was added to a volume of 5.0 ml. After solution, 0.80-ml aliquots were withdrawn and placed in each of six vials containing 5.0 ml of magnetically stirred modified Kreb's solution, containing 25 mM NaHCO₃ buffer, and maintained at 37.0°C. Each injection was made at measured time. After a predetermined variable time interval, each vial was removed from the bath and immediately frozen by immersion in a dry ice–2-propanol mixture and then stored at –20°C until the infinity sample had been removed.

The contents of each vial were isolated as follows. The contents were allowed to thaw slightly and then transferred to a beaker containing ca. 9 g of ice and 5 ml of 10% Na₂CO₃ solution. The resulting mixture was then transferred to a 30-ml separatory funnel and quickly extracted with three portions of Et₂O. The combined extracts were dried over MgSO₄ and concentrated under N₂. The concentrated solutions were then used directly for GC analysis.

Analysis was performed utilizing a 6 ft \times 1/8 in. glass column packed with 3% OV-17 on Chromosorb W, oven temperature 240°, N₂ flow ca. 30 ml/min. The area of the peak due to the hydrolysis product, N-benzyl-N-phenoxyisopropyl-2-aminoethanol, was followed, relative to that of the corresponding methyl ether **4**. A plot of the log (moles of aziridinium ion) vs. time showed good pseudo-first-order kinetics through 2 half-lives. Each rate constant was determined using PLSTSQR.¹⁶

Pharmacologic testing was carried out on the rat vas deferens as previously described.¹⁴ Each point on the dose–response curve represents the average of six determinations.

Acknowledgment. We wish to express our appreciation to Dr. G. Ulyott of Smith Kline & French Laboratories who provided us with **1a** and **1b** for this study.

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Importance of the Aromatic Ring¹ in Adrenergic Amines. 2. Synthesis and Adrenergic Activity of Some Nonaromatic Six- and Eight-Membered Ring Analogs of β -Phenylethanolamine^{2,3,†}

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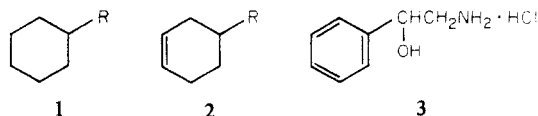
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The synthesis of β -phenylethanolamine analogs in which the phenyl ring is replaced by cyclohexyl, cyclohexen-4-yl, cyclooctyl, cyclooctenyl, cycloocta-1,3-dien-2-yl, cycloocta-1,5-dienyl, and cyclooctatetraenyl was accomplished by conversion of the corresponding aldehydes to the cyanohydrins followed by reduction with lithium aluminum hydride. A preparatively useful synthesis of 1-formylcyclooctatetraene is described utilizing the photocycloaddition of methyl propiolate to benzene followed by reduction to the alcohol and oxidation with MnO_2 . All compounds, as their hydrochloride salts, exhibited indirect adrenergic activity on the rat vas deferens. On the reserpinized rat vas deferens all compounds potentiated the effects of exogenous norepinephrine. The results are in agreement with the conclusion that the more saturated the ring moiety, the greater the affinity for the amine uptake site of the vas deferens and suggest that there is no important interaction between the drug and this uptake site that involves π -complex formation.

The presence of an aromatic ring in a variety of drug molecules has led to speculations regarding the contribution of interactions between the aromatic ring and the pharmacological site of action to the overall observed pharmacological activity of the given drug. In the case of adrenergic amines and the α -adrenergic receptor site, an interaction between the electron-rich π cloud of the aromatic ring and an electron-deficient area of the receptor has been suggested in a number of theories and receptor models.⁴⁻⁷

In this paper we shall describe the synthesis and preliminary adrenergic evaluation of two series of β -phenylethanolamine analogs in which there is a varying degree of ring unsaturation. The first series of six-

membered ring analogs of β -phenylethanolamine (**3**) consists of the fully saturated cyclohexylethanolamine (**1a**), the partially saturated cyclohexen-4-ylethanolamine (**2a**), and the parent aromatic β -phenylethanolamine (**3**).



a, R = $CH(OH)CH_2NH_2 \cdot HCl$
b, R = $CH(OH)CN$
c, R = CHO

The second series consists of eight-membered ring analogs of **3** and ranges from the fully saturated cyclooctylethanolamine (**4a**), through the monounsaturated cyclooctenylethanolamine (**5a**), to more unsaturated derivatives, cycloocta-1,3-dien-2-ylethanolamine (**6a**) and cycloocta-1,5-dienylethanolamine (**7a**), and to the fully

† This paper is dedicated to the memory of Edward E. Smissman, a trusted friend whose inspiration and encouragement will not be forgotten.