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Inhibition of Uptake of Catecholamines by Benzylamine Derivatives[1]

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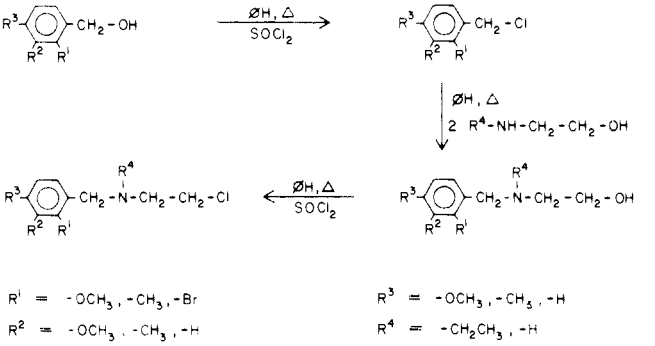
Eight benzylamine analogues of bretylium were synthesized, including *N*-(2-chloroethyl)-*N*-ethyl-2-methylbenzylamine (5), and evaluated as inhibitors of accumulation of norepinephrine and dopamine in rat brain homogenates. All compounds gave an I_{50} value (concentration of inhibitor that causes 50% reduction in control accumulation) considerably lower against norepinephrine in cortex than against dopamine in striatum. High potency (low I_{50}) and high specificity (preference for inhibition of norepinephrine transport compared to dopamine transport) are associated with a (2-chloroethyl) moiety, tertiary amino center, and ortho substitution of the aromatic function in the benzylamino group. 5 also inhibited the uptake of norepinephrine in rabbit aorta, indicating its effect against the uptake process in general. Cocaine protects against the effects of 5 in coincubation studies when compared to the appropriate controls, indicating that 5 acts at or close to the site of action of cocaine which is thought to be the uptake carrier site.

The catecholamines, norepinephrine and dopamine, are neurotransmitters whose action at the postsynaptic receptor is thought to be terminated by return to the presynaptic terminal.[2] This movement from extracellular to intracellular compartments, or uptake, is achieved by a specific carrier transport system.[2] Inhibition of this uptake process would be expected to have profound effects on neuronal activity, and this is the proposed mechanism of action of central nervous system stimulants such as cocaine,[3] amphetamine,[4] and tricyclic antidepressants.[5] A specific irreversible inhibitor would be a potent tool in the study of the transport system, since it would allow labeling of the carrier. This report describes the synthesis, structure-activity relations, and preliminary pharmacology of a series of benzylamine derivatives that inhibit norepinephrine uptake into brain and vascular tissue, probably irreversibly.

The compounds studied here are methyl- and methoxy-substituted (β-haloethyl)- and (β-hydroxyethyl)-benzylamines and are related to the (β-haloethyl)-benzylamines described by Ross and his co-workers.[6] These investigators found *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine to be a long-lasting, irreversible inhibitor of norepinephrine uptake in intact animals.[7,8] In the studies described here, the inhibitory activity was investigated by in vitro procedures, primarily in rat brain preparations enriched in synaptosomes or nerve-ending particles. The results show that some of these compounds are potent inhibitors that might be useful in studies of neuronal uptake.

Synthesis. The synthesis of all compounds followed the general scheme illustrated in Scheme I. The appropriate benzyl alcohol was converted to the chloride with thionyl chloride, followed by reaction with the necessary amino alcohol to yield the corresponding (2-hydroxyethyl)benzylamine. This amino alcohol was treated with thionyl chloride to yield the appropriate (2-chloroethyl)benzylamine, which could be isolated as the hydrochloride or oxalate salts. The structures of the compounds and their physical properties are summarized in Table I.

Scheme I. Synthesis of Uptake Inhibitors



Results

A summary of the I_{50} values determined as described in the biochemical procedures of the Experimental Section is found in Table II for rat brain. Bretylium (1) and three other *o*-bromo compounds were examined to allow comparison with compounds described by Ross et al.[6] In these initial experiments the proposed inhibitor was coincubated with the substrate catecholamine so that the observed

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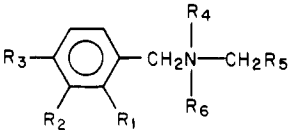
Table I. Derivatives of Benzylamine



compd	R_1	R_2	R_3	R_4	R_5	R_6	mp, °C	yield, %	formula	anal.
1	Br	H	H	CH_2CH_3	H	CH_3 OTS^-	94-96		$C_{18}H_{24}BrNO_3S$	*a*
2	Br	H	H	H	CH_2Cl	HCl	178-180	29	$C_9H_{12}Cl_2BrN$	C, H, N
3	Br	H	H	CH_2CH_3	CH_2Cl	HCl	147-149	90	$C_{11}H_{16}Cl_2BrN$	C, H, N
4	Br	H	H	CH_2CH_3	CH_2OH		>250[b]	99	$C_{11}H_{16}BrNO \cdot 0.5H_2O$	C, H, N, Br
5	CH_3	H	H	CH_2CH_3	CH_2Cl	HCl	146.5-148.5	30	$C_{11}H_{19}Cl_2N$	C, H, N
6	CH_3	H	H	CH_2CH_3	CH_2OH		>250[b]	70	$C_{12}H_{19}NO \cdot 0.5H_2O$	C, H, N
7	H	CH_3	H	CH_2CH_3	CH_2Cl	HCl	158-159.5	15	$C_{12}H_{19}Cl_2N$	C, H, N
8	H	CH_3	H	CH_2CH_3	CH_2OH		>250[b]	65	$C_{12}H_{19}NO \cdot 0.5H_2O$	C, H, N
9	H	H	CH_3	CH_2CH_3	CH_2Cl	HCl	172.5-175	72	$C_{12}H_{19}Cl_2N$	C, H, N
10	OCH_3	H	H	CH_2CH_3	CH_2Cl	$(CO_2H)_2$	45-49	60	$C_{14}H_{20}ClNO_5 \cdot 0.25H_2O$	C, H, N[c]
11	H	OCH_3	H	CH_2CH_3	CH_2Cl	$(CO_2H)_2$	75-78	37	$C_{14}H_{20}ClNO_5$	C, H, Cl[d]
12	H	H	OCH_3	CH_2CH_3	CH_2Cl	$0.5(CO_2H)_2$	108-111	46	$C_{13}H_{19}ClNO_3 \cdot 2H_2O$	C, H, N[e]

[a] Commercial bretylium tosylate from Burroughs-Wellcome Corp. [b] Boiling point, 1 atm. [c] H: calcd, 6.41; found, 5.77. [d] Cl: calcd, 11.16; found, 10.17. [e] N: calcd, 4.54; found, 3.76.

Table II. Inhibition of Synaptosomal Uptake[a]

compd	I_{50}, μM[b] cortex[c]	striatum[d]	selectivity[e]
1	3.43	149	43.4
2	50.2	326	6.5
3	0.05	5.87	117.4
4	78.0	640	8.2
5[f]	0.08	6.09	76.1
6	137	1050	7.7
7	0.77	28.6	37.1
8	49.0	250	5.1
9	3.05	78.4	25.7
10	31.1	303	9.7
11	23.2	127	5.5
12	29.8	147	4.9

[a] Synaptosome-enriched subcellular fractions of rat brain. [b] Average of two or more independent determinations; each in triplicate; variations were less than 25% between each multiple measurement. [c] Cortical synaptosomal uptake; norepinephrine concentration 0.1 μM. [d] Striatal synaptosomal uptake; dopamine concentration 0.1 μM. [e] Ratio of I_{50}, striatum, to I_{50}, cortex. [f] I_{50} for NE uptake by rabbit aortic rings 0.1 μM.

inhibition was the result of a competitive interaction between the substrate and inhibitor for the transport carrier. The most potent inhibitors were the ortho-substituted tertiary compounds **3** and **5**. These two molecules are also the most selective in the inhibition of uptake of norepinephrine compared to dopamine (Table II). Meta-substituted tertiary amines **7** and **11** were considerably less potent as uptake inhibitors than their ortho counterparts **5** and **10**. Para-substituted compounds **9** and **12** also had higher I_{50} values as uptake inhibitors than the corresponding ortho derivatives. The 2-hydroxyethyl derivatives **4**, **6**, and **8** were very weak inhibitors compared to their corresponding 2-chloroethyl derivatives **3**, **5**, and **7**. Bretylium (**1**, a quaternary benzylamine) and **2** (a secondary benzylamine) both exhibited lower potency and selectivity than their tertiary counterpart, **3**.

The effectiveness of **5** as an inhibitor was examined by preincubation with brain minces followed by homogenization and subcellular fractionation. These procedures would remove nonbound inhibitor so that uptake inhibition would likely be due to irreversibly bound material only. The results of these studies, shown in Figures 1 and 2, indicate that noncompetitive inhibition results with a reduction in apparent V_{max} and no change in K_M. These effects at 10^{-7} M could be blocked by coincubation with cocaine at 10^{-5} M (not shown). Compound **5** also inhibited

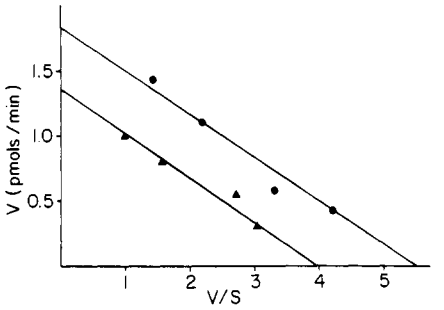


Figure 1. Irreversible inhibition of norepinephrine uptake in cortical synaptosomes. Kinetic parameters (compound **5**). Average kinetic parameters (K_M, μM; three independent determinations) were 0.317 ± 0.07, control; 0.310 ± 0.06, inhibited. V_{max} values (pmol/min) were 2.32 ± 0.30, control; 1.68 ± 0.30, inhibited.

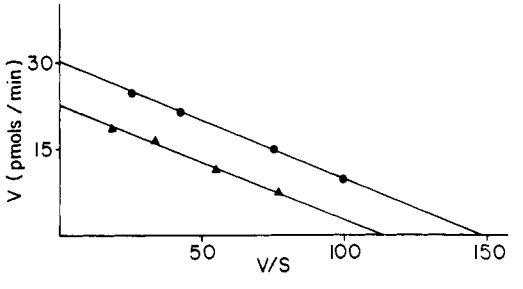
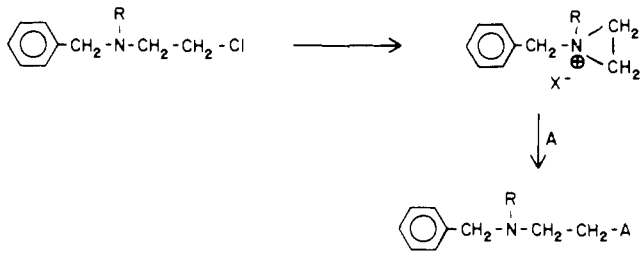


Figure 2. Irreversible inhibition of dopamine uptake in striatal synaptosomes. Kinetic parameters (compound **5**). Average kinetic parameters (K_M, μM; three independent determinations) were 0.248 ± 0.05, control; 0.240 ± 0.09, inhibited. V_{max} values (pmol/min) were 37.71 ± 5.10, control; 21.91 ± 3.35, inhibited.

Scheme II. Possible Mode of Action of "2-Chloroethylamino" Alkylating Inhibitors[a]

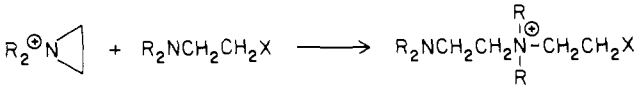


[a] A = nucleophile; i.e., water, receptor, etc.

norepinephrine uptake in rabbit aorta preparations[9] with an I_{50} (0.1 μM) essentially equal to that for rat cortex (Table II).

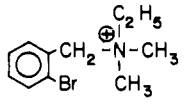
Discussion

It has been known for sometime[10] that tertiary 2-haloalkylamines cyclize to form reactive aziridinium derivatives (see Scheme II), which have been shown to be the moiety responsible for these compounds' adrenergic blocking actions.[11] The rate of formation of the aziridinium ion from β-haloethylamines is dependent on the nature of the leaving halide, the conjugative effects of the alkyl substituents, and the basicity of the nitrogen.[12] The level of aziridinium ion from **5** after a 35-min incubation at pH 7.4 has been estimated at 40%, and it appears to remain at that level for an additional 40 min.[13] Maintenance of the ion at this level for a significant time period is presumably due to its slow rate of decomposition relative to its rate of formation. This rate difference has been documented for the two postsynaptic adrenergic blocking agents, phenoxybenzamine and dibenamine.[11] The aziridinium ion decomposes for the most part by hydrolysis and by reaction with tissue nucleophiles. In addition, it

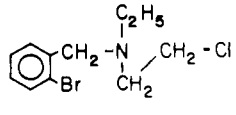


is possible that the reaction of the aziridinium ion with another molecule to form a dimer could also be a reactive alkylating species. At the I_{50} concentration of the more potent inhibitors studied here (8×10^{-8} M), however, it seems unlikely that the dimer would be a statistically significant species.

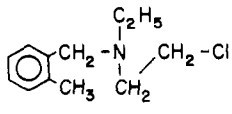
The most potent inhibitors of all the compounds studied were the ortho-substituted benzylamines **3** and **5**. **3**



Bretylium **1**



3



5

exhibited more than an order of magnitude greater inhibition potency and more than three times greater selectivity for the cortical transport system than did the secondary analogue, **2**, the (2-hydroxyethyl)amino compound, **4**, or the quaternary bretylium (**1**). These results indicate three structural features in determining potency of in vitro inhibition of uptake in these benzylamines: i.e., ortho-substitution, a (2-chloroethyl)amino moiety, and a tertiary amino function.

The *o*-methyl compound, **5**, is comparable to the *o*-bromo, **3**, in potency, and the I_{50} values increased progressively as the methyl group was attached at the 2, 3, and 4 positions. The methoxy series was nonselective, as evidenced by the high I_{50} values and the low selectivity. The low activity of the alcohols **4**, **6**, and **8** could reflect the requirement for the aziridinium ion in an effective inhibitor. In these initial screening experiments, the inhibitors and catecholamine were coincubated so that the inhibition observed represents a competitive one. Thus, the relative potency of the alcohols compared to the β-halo compound is a measure of affinity for the carrier system. High potency and specificity are associated with a 2-chloroethyl or aziridinium precursor moiety, a tertiary amino center, and ortho substitution of the aromatic ring. The subsequent experiments with **5**, in which the compound was preincubated with tissue prior to its homogenization and fractionation, reflect its actions as a potentially irreversible inhibitor.

Inhibition of norepinephrine uptake by compound **5** in rabbit aorta, in addition to rat brain, indicates that its inhibitory effect is generally against the uptake process and not confined to a single in vitro system. The fact that cocaine protects against the effects of the inhibitor in coincubation studies when compared to the appropriate controls indicates that the inhibitor acts at or very close to the site of action of cocaine which is thought to be the uptake carrier site.

These experiments have shown that these (β-haloethyl)benzylamines are effective and probably irreversible inhibitors of norepinephrine uptake with some degree of selectivity. As in most studies comparing dopamine and norepinephrine uptake inhibition, the NE system is inhibited at lower concentrations than the dopamine system. The tissue studies show that inhibition can be demonstrated by in vitro techniques that will allow manipulations directed at selectivity and labeling. These experiments are now in progress.

Experimental Section

All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Mass spectra were obtained on a Hewlett-Packard 5981A GC–MS system, using a direct-probe inlet. Elemental analyses were performed by Chemalytics Inc., Tempe, Ariz. Yields, melting points, and elemental analyses results of all compounds are summarized in Table I.

Materials. 2-Bromobenzyl bromide, 2-methylbenzyl bromide, 3-methylbenzyl bromide, 4-methylbenzyl bromide, 2-methoxybenzyl alcohol, 3-methoxybenzyl alcohol, 4-methoxybenzyl alcohol, ethanolamine, and 2-(ethylamino)ethanol were purchased from Aldrich Chemical Co., Milwaukee, Wis., and all were ≥95% pure by GLC. Tritiated dopamine (1 mCi/mL; 0.018 mg/mL) and tritiated *l*-norepinephrine (1 mCi/2 mL; 0.029 mg/2 mL) were purchased from New England Nuclear, Boston, Mass., as was the tissue solubilizer Protosol®. 3-Hydroxytyramine hydrochloride (dopamine) and *l*-arterenol bitartrate hydrate (norepinephrine) were obtained from Calbiochem, La Jolla, Calif. Bretylium tosylate was a gift from Burroughs-Wellcome Co., Tuckahoe, N.Y. Nialamide was a gift from Pfizer Laboratories, Brooklyn, N.Y.

Krebs–Ringer phosphate (pH 7.4) containing 1.1 mM *l*-ascorbic acid, 8.4 mM dextrose, 12 μM nialamide, 0.9 mM Ca^{2+}, 2.5 mM Mg^{2+}, 4.2 mM K^+, 123 mM Na^+, and 0.02 M sodium phosphate (pH 7.4) buffer was prepared using AR salts from the J. T. Baker Co., Philipsburg, N.J. Bray's scintillation solution was prepared according to the method of Bray.[14] Sucrose, oxalic acid, benzene, hydrochloric acid, and sodium carbonate were also purchased from Baker Chemical Co. and were reagent grade; Millipore filters (0.8 μM) were purchased from the Millipore Corp., Boston. White New Zealand male rabbits (2.5–3.5 kg) and male Sprague–Dawley rats (160–220 g) were purchased from the Curd Co., Los Angeles.

Synthesis. Synthetic methods are outlined in Scheme I. **Method A.** Compounds **2** through **9** of Table I were prepared by the following general procedure. A solution of the appropriate benzyl bromide (0.1 mol) and amino alcohol (0.22 mol) in 100 mL of benzene was stirred for 12 h at room temperature and then refluxed for 2 h. The organic layer was extracted three times with 50 mL of 1 N HCl; the acid extracts were combined, washed with 40 mL of ether three times, and then made alkaline with Na_2CO_3. The amino alcohols separated as oils and were extracted with ether. The extracts were dried and evaporated to yield off-white viscous oils (e.g., compounds **4**, **6**, and **8**). To the appropriate amino alcohol (0.1 mol) in 100 mL of dry $CHCl_3$ was then added excess (0.15 mol) $SOCl_2$, and the mixture was stirred for 2 h and refluxed for an additional 1 h. It was then evaporated under vacuum, and 25 mL of cold water was added. After three washes with 50 mL of ether, the pH was raised by adding solid Na_2CO_3, and the solution was extracted three times with ether (50 mL). After drying the solution over Na_2SO_4, an ethereal solution of hydrogen chloride was slowly added to precipitate the corresponding *N*-(2-chloroethyl)amine as a hydrochloride salt (i.e., compounds **2**, **3**, **5**, **7**, and **9**). Representative compounds gave the expected mass spectra, e.g., compound **3**: *m/e* 169, 171 (40%), 226, 228 (25%), and 276 parent (0.2%). Compounds **5**, 7, and **9** gave somewhat similar spectra, i.e., *m/e* 105 (100%), 162 (75%), and small parent ions at 211 (2%).

Method B. Compounds **10–12** of Table I were prepared by the following procedure: 0.1 mol of the appropriately substituted benzyl alcohol was dissolved in 100 mL of dry benzene, and 0.15 mol of $SOCl_2$ was added. The solution was stirred at room temperature for 3 h and then refluxed for 1 h. It was then evaporated in vacuo to complete dryness, and the residue was then subjected to the same scheme as in method A to yield the appropriately substituted (2-chloroethyl)amino derivatives, except that oxalate salts were isolated instead of hydrochlorides by addition of an ether solution of oxalic acid to the ether solution of the (2-chloroethyl)amino derivative.

Biochemical Procedures. Preparation of Cortical and Striatal Synaptosome Fractions (P_2). Male Sprague–Dawley rats (180–220 g) were sacrificed by decapitation, and striata and cerebral cortices were immediately dissected and added to separate 10-mL portions of 0.32 M sucrose (0 °C). The tissues were gently homogenized with a Teflon pestle and centrifuged at 1100*g* for 10 min. In all subsequent procedures, solutions and equipment were maintained at 0 °C. The supernatant was transferred to another centrifuge tube, 1 mL of 0.32 M sucrose was added, and the suspension was centrifuged at 11000*g* for 20 min. The supernatant from this step was discarded and 10 mL of sucrose solution was added to the pellet, which was resuspended by gentle homogenization and centrifuged at 11000*g* for 20 min. The supernatant was again discarded and 1 mL of sucrose solution was added to the pellet, which was resuspended, poured into a 10-mL glass mortar, and diluted to 3 mL. The preparation was stored at 0 °C and used as soon as possible.

Accumulation of Catecholamines by Synaptosomes. Synaptosomal incubations were carried out in glass scintillation vials containing 20 μL of nialamide (0.47 mM solution; 12.5 μM in final incubation), 100 μL of synaptosomal suspension prepared as described, and 0.58 mL of Krebs–Ringer phosphate containing the inhibitor. After a 5-min preincubation of the mixture at 37 °C for equilibration, 50 μL of tritiated substrate (~200 000 cpm) was added, and the mixture was incubated for 3 min. Final volume of all samples was 0.75 mL, and substrate concentration was 0.1 μM.

At the end of 3 min, uptake was quenched by the addition of 5 mL of 0.9% NaCl containing 100 μM nonradioactive substrate. The quenched medium was then filtered through Millipore filters (0.8 μM), and the vials were washed with an additional 5 mL of saline. The filters were then dissolved in 10 mL of Bray's solution[14] and counted by liquid scintillation spectrometry.

I_{50} Determination in Synaptosomes. Each inhibitor was tested at three different concentrations, such that the I_{50} (concentration of an inhibitor that causes a 50% reduction in control accumulation) value fell between the highest and lowest concentration tested. These concentrations were chosen by preliminary approximating experiments in which a concentration range of 10^4 was used. I_{50} values were calculated by a linear regression analysis of a plot of A_0/A_1 vs. inhibitor concentration, where A_0 is the control accumulation (no inhibitor) and A_1 is the accumulation in the presence of the inhibitor. The point at which $A_0/A_1 = 2$ is the I_{50} value. Both A_0 and each A_1 were determined in triplicate, and the mean was used in the plot. "Blanks" in which uptake is measured at 0 °C were subtracted from both control and inhibited accumulation to correct for diffusion and nonspecific binding.

Irreversible Inhibition of Brain Tissue Uptake. Two male Sprague–Dawley rats were sacrificed by decapitation, and striata or cerebral cortices were immediately dissected and added to 4.5 mL of Krebs phosphate solution at 0 °C. The tissue was then cut in a fine mince with scissors (approximately 2 mm), and 0.5 mL of a solution of compound **5** was added such that the final concentration was 8×10^{-8} M. The suspension was then incubated for 15 min at 37 °C with shaking in a metabolic incubator. At the end of the incubation, the tissue suspensions were poured into centrifuge tubes and centrifuged at 3000*g* for 5 min. The Krebs supernatant was removed, and the tissues were suspended in 0.32 M sucrose for homogenization as described in method A. Incubations of the P_2 fraction from each mince were then carried out as described in method B for a 3-min uptake in the presence of different concentrations of substrate.

Aorta Preparations and Incubations. The thoracic aorta was removed from male white New Zealand rabbits killed by exsanguination, and excess fatty tissue was trimmed. The aorta was then cut into 2-mm (ca. 5 mg) rings and grouped together in lots of five rings on pieces of thread. After a 30-min preincubation at 37 °C in Krebs solution–bicarbonate (or appropriate inhibitor in Krebs solution), the rings were washed in fresh Krebs solution for 30 min, and then tritiated norepinephrine (0.2 μM final concentration) was added. The mixture was incubated for 60 min. The rings were then removed, blotted, and individually weighed. Each ring was then incubated at 40 °C overnight with 1 mL of Protosol® (tissue solubilizer) in a scintillation vial. Toluene-based scintillation fluid[15] (10 mL) was then added, and the samples were counted on a Mark III liquid scintillation spectrometer.

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