Synthesis and Pharmacology of Potential β-Blockers

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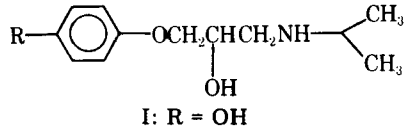
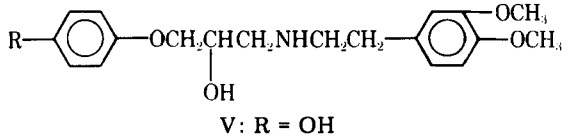
Abstract □ Several 1-(4-substituted phenoxy)-2-hydroxy-3-isopropylaminopropanes and 1-(4-substituted phenoxy)-2-hydroxy-3-[3,4-dimethoxyphenethyl]aminopropanes were synthesized for possible β-adrenergic receptor blockade. The compounds were synthesized by reaction of the 4-substituted phenol with epichlorohydrin and subsequent opening of the resulting epoxide with either *N*-isopropylamine or *N*-3,4-dimethoxyphenethylamine. Preliminary biological testing indicated a decrease in the β-blocking potency and the duration of action.

Keyphrases □ β-Adrenergic blockers—synthesis and pharmacology, substituted aminopropanes, structure–activity relationships □ Aminopropanes, substituted—synthesis and pharmacology as potential β-adrenergic blockers, structure–activity relationships □ Structure–activity relationships—substituted aminopropanes as potential β-adrenergic blockers, synthesis and pharmacology

Several β-adrenergic receptor blocking drugs currently under clinical investigation differ pharmacologically on the basis of potency, selectivity, intrinsic sympathomimetic activity, membrane-stabilizing activity, and duration of action. Previous reports (1–3) indicated that polar substitution on the ring of aryloxypropanolamines increases intrinsic molecular activity while increased molecule lipophilicity enhances membrane-stabilizing activity. Furthermore, *para* substitution of phenoxypropanolamines enhances cardioselectivity (1, 2, 4, 5). Clearly defined structural requirements for modification of the duration of β-blocking activity have not been identified. The present study examined the effects of polar substitution in the *para* position of phenoxypropanolamines on several characteristics of β-receptor blockade.



I: R = OH
II: R = CH_2OH
III: R = CO_2CH_3
IV: R = CO_2H



V: R = OH
VI: R = CH_2OH
VII: R = CO_2CH_3
VIII: R = CO_2H

Two series of compounds were synthesized and evaluated. The first series consisted of 1-(4-substituted phenoxy)-2-hydroxy-3-isopropylaminopropanes having structural properties similar to previously synthesized β-blockers. In the second series, the structural importance of the *N*-isopropyl group for β_1 *versus* β_2 adrenergic receptor blocking activity was explored by replacing it with a *N*-3,4-dimethoxyphenethyl group. As in the first series, polar substitutents were incorporated into the phenoxy ring system.

RESULTS AND DISCUSSION

Chemistry—Compounds I–IV were synthesized using a modification of established literature procedures (6). The synthetic route to VII utilized the approach developed by Hoefle *et al.* (7), wherein the methyl 4-hydroxybenzoate (IX) served as the starting material. Thus, condensation of IX with epichlorohydrin gave the requisite epoxide X (Scheme I) which, due to its instability, was rapidly opened with *N*-3,4-dimethoxyphenethylamine to give VII. Reduction of the ester VII provided the benzyl alcohol VI, while hydrolysis of VII with 2.0 *N* NaOH gave the acid VIII. 4-(Benzyloxy)phenol was converted to XIII (Scheme II) using the standard two-step procedure. Subsequent hydrogenolysis of the benzyl protecting group provided V.

Biology—Chronotropic ID_{25} and ID_{50} values for each compound and for propranolol are contained in Table I. All compounds except IV and VII appeared to have blocking activity but were considerably less potent than propranolol in blocking the heart rate effects of isoproterenol. A comparison of the relative potencies revealed that the compounds were five to 52 times less potent than propranolol on the heart. The methylene hydroxy derivatives of both series of compounds had potencies that approached those of propranolol. Propranolol produced 51, 61, and 59% inhibition of the diastolic pressure response to isoproterenol infusions at 0.008, 0.024, and 0.072 mg/kg, respectively. All compounds except I were, in general, much less effective than propranolol in blocking diastolic pressure, producing <26% inhibition at any dose. Compound I produced 68.8% inhibition at 10.0 mg/kg.

Table II summarizes the data on the duration of chronotropic block induced by the active compounds and propranolol. Duration of action has been normalized to equivalent pharmacological effect as described

Table I—Chronotropic Blocking Potency [a]

Compound	*n*	ID_{25} moles/kg × 10^{-8}	ID_{25} Relative Potency	ID_{50} moles/kg × 10^{-7}	ID_{50} Relative Potency
Propranol	10	3.3 ± 0.03 [b]	1	1.1 ± 0.2 [b]	1
I	3	28.0 ± 7.6	0.12	— [c]	— [c]
II	3	172.0 ± 54.9	0.019	166.0 ± 90.2	0.006
III	5	59.3 ± 9.9	0.056	15.7 ± 2.9	0.067
IV	3		Not active		
V	4	36.6 ± 6.6	0.093	8.6 ± 1.3	0.122
VI	3	15.1 ± 4.5	0.22	4.8 ± 1.8	0.22
VII	3	51.7 ± 11.8	0.064	11.1 ± 3.3	0.095
VIII	3		Not active		

[a] ID_{25} and ID_{50} refer to 25 and 50% inhibition of the chronotropic response to isoproterenol hydrochloride infusion at 1.0 μg/kg/min. [b] Values are means ± *SEM*. [c] Fifty-percent inhibition was not attained with this agent.

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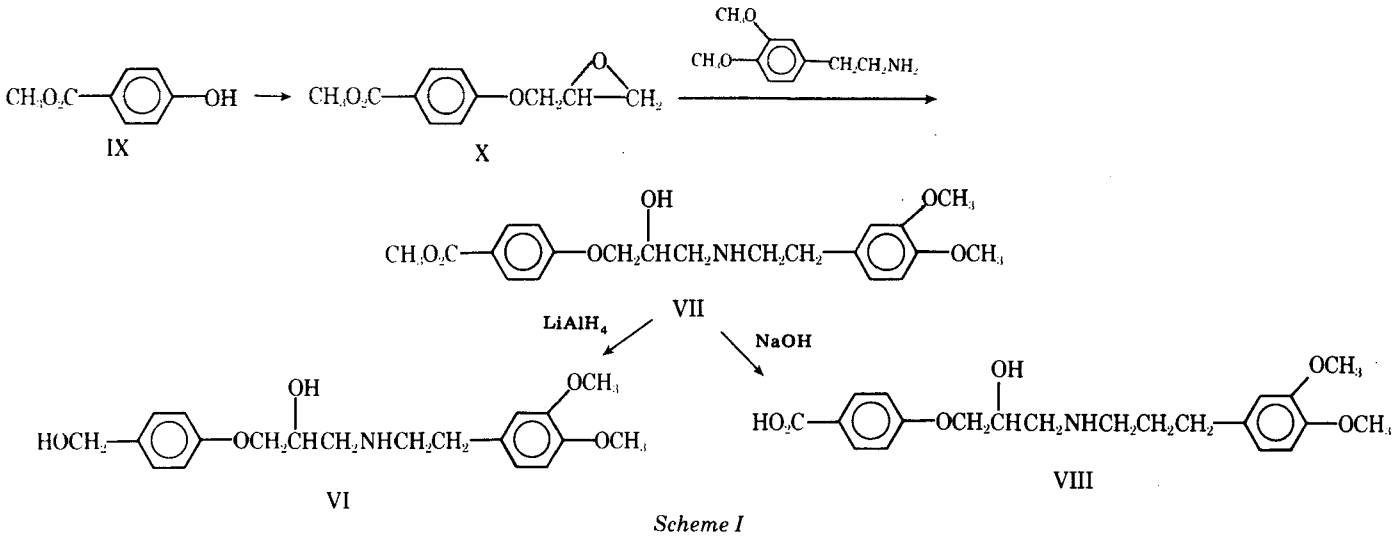
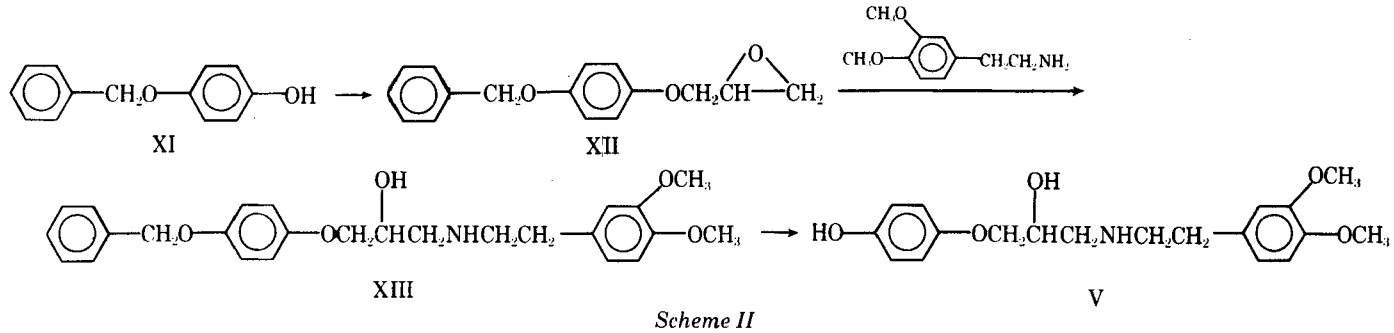
Table II—Duration of Chronotropic Block (Minutes) [a]

Inhibition	Propranolol	I	II	III	V	VI	VII
ID_{25} [b]	14.8 ± 2.4	14.4 ± 1.2	6.0 ± 1.2	4.4 ± 1.4	3.5 ± 0.4	3.5 ± 1.1	4.5 ± 0.5
ID_{50} [b]	20.4 ± 2.4	—[c]	31.1 ± 10.2	9.5 ± 2.8	7.8 ± 0.7	6.7 ± 2.4	7.7 ± 1.4

[a] Duration was measured as the time associated with 50% recovery of the heart rate after dosing with the blocking agent. [b] Duration was normalized to doses producing 25 and 50% inhibition of the heart rate response to isoproterenol infusion. [c] Fifty-percent inhibition was not attained with this agent.



Scheme I



Scheme II

under *Experimental* to facilitate comparison. With two exceptions, the duration of block was considerably shorter with the polar-substituted compounds than with propranolol. Compound I, which has a hydroxy group in the *para* position of the ring, had a duration of action at the I_{25} level that approached that of propranolol. Compound II was peculiar. At low doses (I_{25}), it produced a significantly shorter blocking effect than propranolol; but at higher doses (I_{50}), its duration of action was equivalent to that of propranolol.

The isoproterenol infusion model used for compound evaluation is not appropriate for quantitative analysis of cardioselective properties. Nevertheless, the fact that all compounds except I caused considerably less diastolic pressure inhibition than did propranolol suggests that these agents are somewhat cardioselective. Indeed, *para* substitution (1, 2, 4, 5), especially with hydrogen bond acceptor groups (1), is thought to be favorable to the development of cardioselective properties. *N*-Substitution with the 3,4-dimethoxyphenethyl system also has been shown to impact on cardioselectivity (8); as shown by Hoefle *et al.* (7), combination of this end group with *para* substitution in the ring results in remarkable cardioselectivity.

The present findings indicate that *para* substitution of phenoxypropanolamines with polar substituents appears, in general, to produce β-receptor antagonists with a shorter duration of action than that of propranolol. The potency of these compounds, however, is considerably less than that of propranolol. This latter finding supports previous reports (1, 2), which indicated that *para* substitution almost universally lowers potency relative to both propranolol and to *ortho*-substituted derivatives. However, the potency was somewhat improved when *para* substitution was coupled with the *N*-3,4-dimethoxyphenethyl substituent. This effect was obvious with *p*-hydroxy and *p*-methylene hydroxy substitution but was less clear with the methyl esters. A similar phenomenon was reported by Hoefle *et al.* (7) for nonring-substituted and *para*-substituted amide compounds.

EXPERIMENTAL[1]

Methyl 4-(2,3-Epoxypropoxy)benzoate (X)—To 75 ml of methanol containing 2.4 g (0.06 mole) of NaOH were added 7.6 g (0.05 mole) of methyl 4-hydroxybenzoate and 30 ml (0.4 mole) of epichlorohydrin. The reaction mixture was stirred at room temperature for 20 hr and then was concentrated to a residual oil partitioned between 50 ml of chloroform and 25 ml of 1 *N* NaOH. The organic phase was separated, washed twice with 25-ml portions of water and once with 25 ml of saturated sodium chloride, and dried over magnesium sulfate. The chloroform was evaporated, and the product was obtained as a colorless oil in 99% yield; NMR (CDCl): δ 7.2 (m, 4H, Ar*H*) and 3.45 (s, 3H, $-OCH_3$).

1-(4-Methoxycarbonylphenoxy)-2-hydroxy -3- (3,4-dimethoxyphenethylamino)propane (VII)—A reaction mixture containing 6.24 (0.03 mole) of X and 5.5 g (0.03 mole) of 3,4-dimethoxyphenethylamine in 50 ml of methanol was refluxed for 2.0 hr. After the volatiles were removed, a viscous oil resulted and then solidified upon standing to yield 81% of theory. Recrystallization from ethyl acetate afforded an analytical sample, mp 117–118°.

[1] Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. IR absorption spectra were recorded on a Beckman model 18A spectrophotometer on either liquid films or potassium bromide pellets. NMR spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as the internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

The hydrochloride salt was obtained by acidifying an ethanolic solution of the base with anhydrous hydrochloric acid (93% yield). Recrystallization from 2-propanol afforded an analytical sample, mp 166–167°; IR (KBr): 1695 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 6.7–8.0 (m, 7H, Ar*H*), 3.80 (s, 9H, $-OCH_3$), and 2.9–4.0 (m, 9H, $-CH_2$ and –CH).

Anal.—Calc. for $C_{21}H_{28}ClNO_6$: C, 59.19; H, 6.63; N, 3.29. Found: C, 59.10; H, 6.58; N, 3.24.

1-(4-Hydroxymethylphenoxy)-2-hydroxy -3- (3,4-dimethoxyphenethylamino)propane Hydrochloride (VI)—To a suspension of 5.3 g (0.015 mole) of VII in 150 ml of dry tetrahydrofuran was added 4.0 g of lithium tetrahydroaluminate in small portions. The resulting reaction mixture was refluxed overnight. After cooling, the excess lithium tetrahydroaluminate was decomposed by careful addition of 5 ml of 2 *N* NaOH. The white precipitate which formed was removed by filtration and discarded. The filtrate was dried over anhydrous magnesium sulfate and acidified with anhydrous hydrochloride. The volatiles were removed, and the residue was recrystallized twice from 2-propanol, yielding 4.0 g (66% yield) of product, mp 110° dec.; NMR (CF_3COOH): δ 6.9 (m, 7H, Ar*H*) and 3.9 (s, 6H, $-OCH_3$).

Anal.—Calc. for $C_{20}H_{28}ClNO_5$: C, 60.37; H, 7.10; N, 3.52. Found: C, 60.44; H, 7.14; N, 3.54.

1-(4-Hydroxycarbonylphenoxy)-2-hydroxy -3- (3,4-dimethoxyphenethylamino)propane (VIII)—A suspension of VII (1.95 g, 0.005 mole) in 15 ml of 2 *N* NaOH was refluxed for 1.5 hr. After the reaction mixture was cooled and acidified with concentrated hydrochloric acid (2 ml), the desired product precipitated as the hydrochloride salt. Recrystallization of the salt from methanol afforded an analytical sample (78% yield), mp 224–225°; IR (KBr): 3370 (–OH) and 1670 (CO_2H) cm^{-1}; NMR (CF_3COOH): δ 6.9–8.0 (m, 7H, Ar*H*), 3.8 (s, 6H, $-OCH_3$), 4.3, and 3.0–3.5 (m, 9H, $-CH_2$).

Anal.—Calc. for $C_{20}H_{26}ClNO_6$: C, 58.36; H, 6.36; N, 3.51. Found: C, 58.46; H, 6.40; N, 3.40.

3-(4-Benzyloxy)phenoxy-1,2-epoxypropane (XII)—A methanolic solution (250 ml) containing *p*-(benzyloxy)phenol (20.0 g, 0.1 mole), sodium hydroxide (4.0 g, 0.1 mole), and epichlorohydrin (0.5 mole) was stirred at room temperature for 18 hr. The reaction mixture was filtered, and the filtrate was concentrated under vacuum. The resulting residue was partitioned between 100 ml of chloroform and 40 ml of 0.1 *N* NaOH. The organic phase was dried over magnesium sulfate. Solvent removal under a vacuum afforded the product as a semisolid, which was recrystallized from methanol (21.3-g yield, 82%), mp 69–71°; NMR ($CDCl_3$): δ 6.9–7.4 (m, 9H, Ar*H*), 5.0 (s, 2H, ArCH_2), and 2.8–4.2 (m, 5H, $-CH_2$ and –CH).

1-(4-Benzyloxy)phenoxy-2-hydroxy -3- (3,4-dimethoxyphenethylamino)propane (XIII)—A solution of XII (6.45 g, 0.025 mole) and 3,4-dimethoxyphenethylamine (4.65 g, 0.025 mole) in 40 ml of methanol was refluxed for 2.0 hr, followed by evaporation of the solvent under reduced pressure. The residue was made basic with 3 *N* NaOH, and the basic solution was extracted with two 50-ml portions of chloroform. The organic phase was dried over magnesium sulfate, and the volatiles were removed under reduced pressure. The residue was recrystallized from ethyl acetate (8.2-g yield, 73%), mp 103–106°; NMR ($CDCl_3$): δ 6.8–7.4 (m, 9H, Ar*H*), 5.0 (s, 2H, ArCH_2), 3.8 (s, 6H, $-OCH_3$), and 2.7 (m, 9H, $-CH_2$ and –CH).

Anal.—Calc. for $C_{26}H_{32}NO_5$: C, 71.23; H, 7.30; N, 3.19. Found: C, 71.41; H, 7.23; N, 3.01.

1-(4-Hydroxyphenoxy)-2-hydroxy -3- (3,4-dimethoxyphenethylamino)propane Hydrochloride (V)—A methanolic solution (250 ml) containing 9.5 g (0.022 mole) of XIII was hydrogenated over 200 mg of 10% palladium-on-charcoal on a Parr hydrogenator until hydrogen uptake ceased. The catalyst was removed by filtration, and the filtrate was evaporated to give an oily residue. An ethanolic solution of the residue was acidified with anhydrous hydrochloric acid. The resulting white precipitate was recrystallized from ethanol (6.2-g yield, 74%), mp 180–182°; NMR (CF_3COOH): δ 6.9 (n, 7H, Ar*H*) and 3.9 (s, 6H, $-OCH_3$).

Anal.—Calc. for $C_{19}H_{26}ClNO_5$: C, 59.44; H, 6.82; N, 3.67. Found: C, 59.59; H, 6.97; N, 3.70.

Biology—The β-blocking activity of the eight experimental compounds and propranolol was assessed in vagotomized, pentobarbital-anesthetized dogs (30 mg/kg), prepared for measurement of pulsatile aortic blood pressure (carotid cannula) and heart rate[2]. β-Blocking activity was measured as the percent inhibition of the heart rate and diastolic blood pressure response produced by continuous isoproterenol hydrochloride infusion at 1.0 μg/kg/min. A continuous isoproterenol infusion was chosen to measure the duration of β-blockade associated with each compound studied. Preliminary studies indicated that the heart rate and diastolic pressure response to continuous isoproterenol infusion were stable for 4 hr.

Each experimental compound was tested at four dose levels: 0.01, 0.1, 1.0, and 10.0 mg/kg; propranolol was tested at 0.008, 0.024, and 0.072 mg/kg. All blockers were administered intravenously over a 15-sec period. Blocker administration commenced with the lowest dose first, and subsequent doses were administered 15 min after the effects of the previous dose had disappeared. Each animal received only one blocking drug.

Compound potency was compared with that of propranolol on the basis of doses (moles per kilogram) required to produce 25 and 50% inhibition (ID_{25} and ID_{50}, respectively) of the isoproterenol-induced heart rate change. These values were obtained from log dose–response curves for each agent. The duration of β-blockade was measured as the time associated with 50% recovery of the heart rate after dosing with blocking agents. Plots were then constructed of duration of action *versus* percent inhibition. An approximately linear relation existed between the two variables over the linear portion of the dose–response curve. Estimation of the 50% recovery times associated with 20 and 50% inhibition allowed normalization of the duration of action to the pharmacological effect.

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