Synthesis of 4′- and 5′-Hydroxyoxprenolol: Pharmacologically Active Ring-Hydroxylated Metabolites of Oxprenolol

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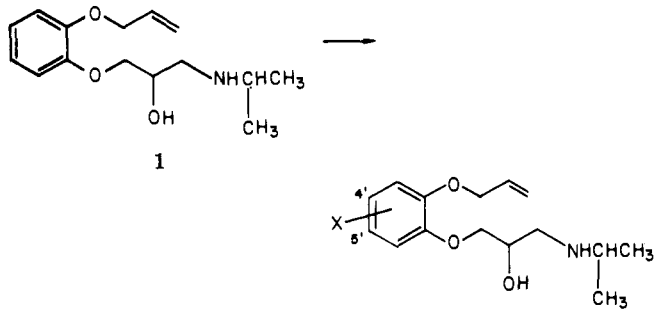
Synthesis and preliminary pharmacological activity data for 4′- and 5′-hydroxyoxprenolol (2 and 3) are reported. The synthetic routes make use of the isomeric 2-pyranyl monoether derivatives of 4-hydroxysalicylaldehyde and 2,5-dihydroxyacetophenone. The corresponding *O*-allyl ethers were converted to substituted phenols by Baeyer–Villiger oxidation and the propanolamine side chain elaborated using epichlorohydrin, followed by oxirane ring opening with isopropylamine. Each of the hydroxylated metabolites is about ten times less potent than oxprenolol as an antagonist to the isoproterenol-induced relaxation of guinea pig tracheal strips.

The metabolic disposition of oxprenolol, 1-(isopropylamino)-3-[2-(allyloxy)phenoxy]-2-propanol (1), an important aryloxypropanolamine β-adrenergic antagonist, has been widely studied.[1-6] A variety of metabolic processes have been reported to occur, including oxidation of the propanolamine side chain, glucuronidation, and aromatic hydroxylation.[1,2,5] In an earlier paper, we demonstrated that aromatic hydroxylation of oxprenolol in man and in the rat occurs principally at C-4′ and less frequently at C-5′, producing **2** and **3**, respectively.[7,8] These hydroxylated metabolites are produced by way of one or more arene oxides which undergo NIH-shift processes.[9] Since these metabolites might potentially contribute to the pharmacological and therapeutic properties of oxprenolol in a way similar to that suggested for the hydroxylated metabolites of propranolol[10] and alprenolol,[12-14] we set out to prepare quantities of them to allow for pharmacological evaluation. In this paper, we report the synthesis of the isomeric 4′- and 5′-hydroxylated metabolites of oxprenolol (**2** and **3**) and initial observations of their β-adrenergic antagonist activity.



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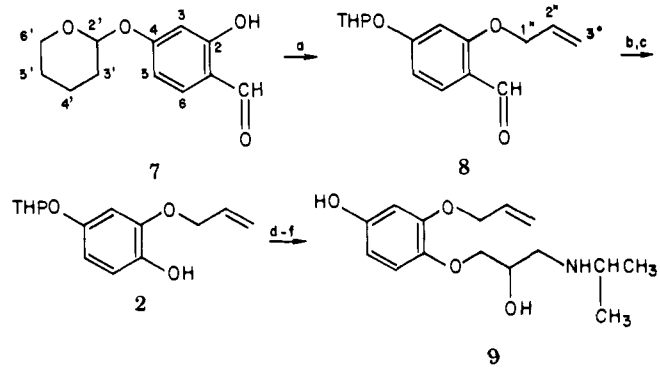
2, X = 4′-OH
3, X = 5′-OH

Synthesis. A general synthetic route was devised which allowed the facile preparation of 4′- and 5′-hydroxyoxprenolol (**2** and **3**). The primary features of this route are the selective protection of the non-hydrogen-bonded phenolic hydroxyl group of a hydroxysalicylaldehyde (or dihydroxyacetophenone) as a tetrahydropyranyl ether and the use of a Baeyer–Villiger oxidation process to convert aryl carbonyl compounds to phenols. The phenolic hydroxyl group was then elaborated into the propanolamine side chain characteristic of the β-adrenergic antagonists.

The synthesis of 4′-hydroxyoxprenolol is outlined in Scheme I. 2,4-Dihydroxybenzaldehyde was converted to its 4-tetrahydropyranyl ether (**7**). Selective protection of phenolic hydroxyl groups not adjacent to carbonyl groups has previously been reported, principally by ether formation.[15,16] O-Allylation of the remaining hydroxyl group was accomplished with allyl bromide (K_2CO_3/DMF), producing **8** in excellent yield. Baeyer–Villiger oxidation, followed by alkaline hydrolysis of the formate ester, produced a quantitative yield of phenol **9**, which was converted to **2** in two steps: O-alkylation with epichlorohydrin and oxirane ring opening with isopropylamine. A series of similar synthetic procedures were used for formation of the 5′-hydroxyoxprenolol (**3**), starting from 2,5-dihydroxyacetophenone.

Scheme I. Synthesis of 4′-Hydroxyoxprenolol (2)



a, allyl bromide (K_2CO_3/DMF); b, *m*-$ClC_6H_4CO_3H$; c, NaOH, H_2O; d, epichlorohydrin, K_2CO_3/acetone; e, isopropylamine, Δ; f, H_3O^+

Pharmacology. The compounds were tested for their ability to block the isoproterenol-induced relaxation of guinea pig tracheal smooth muscle. The K_B values for **1–3** are summarized in Table I. The 4′- and 5′-hydroxy metabolites (**2** and **3**) are about equally potent but are about 10 times less potent than oxprenolol (**1**). For all three antagonists, the K_B values were found to be concentration dependent; i.e., the calculated K_B values increased with antagonist concentration. For other antagonists, this phenomenon has been demonstrated to be related to the presence of saturable uptake and/or metabolic processes for the agonist in the tissue and does not represent an aberrant type of antagonism.[17,18] It seems likely the same factors are responsible for the concentration-dependent antagonism produced by oxprenolol and its hydroxylated metabolites.

The tenfold reduced activity of **2** and **3** vs. oxprenolol (**1**) indicates decreased affinity of these compounds at this β-adrenergic receptor. Although increased affinity might be expected on the basis of adding phenolic hydroxyl substituents similar to the aromatic ring substitution of the agonists norepinephrine and isoproterenol, for most β-receptor antagonists this does not hold. It has previously been shown in homologous series of β-adrenergic receptor

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Table I. Apparent Dissociation Constants (K_B) for Oxprenolol and Derivatives in Isolated Guinea Pig Tracheal Strips Using Isoproterenol as the Agonist

agonist concn, M	K_B values[a] (SEM)		
	oxprenolol (1)	4'-hydroxyoxprenolol (2)	5'-hydroxyoxprenolol (3)
10^{-8}	$2.05 (\pm 0.23) \times 10^{-9}$		
10^{-7}	$2.61 (\pm 0.24) \times 10^{-9}$	$2.65 (\pm 0.52) \times 10^{-8}$	$3.48 (\pm 0.39) \times 10^{-8}$
10^{-6}	$5.81 (\pm 1.29) \times 10^{-9}$	$4.55 (\pm 0.29) \times 10^{-8}$	$3.79 (\pm 0.53) \times 10^{-8}$
10^{-5}		$1.22 (\pm 0.04) \times 10^{-7}$	$1.01 (\pm 0.53) \times 10^{-7}$

[a] Each value represents the average of four experiments.

antagonists that lipophilicity is an important parameter. Greater lipophilicity increases receptor affinity in several assays, although not always consistently.[19] Contrary to extending this observation to a general rule are observations that aromatic ring hydroxylated metabolites of propranolol and alprenolol show about equal β-antagonism effects as their respective parent drugs, although they demonstrate some differences in other pharmacological properties.[10,13] The small difference in activity between 4'- and 5'-hydroxyoxprenolol further suggests little regioselectivity for the additional hydroxyl substituent in the drug–receptor interaction, not inconsistent with observations of other β-adrenergic receptor antagonists.

Since quantitation of these metabolites has not yet been reported, it is difficult to speculate in a meaningful way upon their potential contribution to pharmacological effects of oxprenolol. Further testing of these agents in other pharmacological assay systems is needed, as well as more information about blood and tissue level–time relationships in test animals after various routes of administration.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. NMR spectra were recorded on Varian T-60 and EM-360 spectrometers using Me_4Si as internal standard. Notations used in the descriptions are s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England. Where indicated by the symbols of the elements, analyses were within ±0.4% of theoretical values.

4-[(2-Tetrahydropyranyl)oxy]-2-hydroxybenzaldehyde (7). To a solution of 20 mL (18.40 g, 0.22 mol) of dihydropyran maintained at 20 °C (periodic cooling in an ice bath) was added with stirring 5.00 g (36.2 mmol) of 2,4-dihydroxybenzaldehyde (6) and 15 mg (0.097 mmol) of pTsOH. Over the next 5 min an additional 15.0 g (0.11 mol) of aldehyde 6 was added in small amounts as rapidly as it would dissolve maintaining efficient stirring. A total of 20.0 g (0.14 mol) of aldehyde 6 was added. The resulting solution was stirred at room temperature for 3 h and then partitioned between 150 mL of aqueous 10% NaOH and 200 mL of ether. The ether solution was extracted with an additional 50 mL of aqueous 10% NaOH, and the combined NaOH phases were washed with ether (2 × 200 mL). The solution was adjusted to pH 8 with aqueous 37% HCl and extracted with ether (2 × 200 mL). The combined ether extracts were dried (Na_2SO_4) and evaporated, affording 26.80 g (81% yield) of 7 as a clear, brown oil: NMR ($CDCl_3$) δ 9.93 (s, 1, CHO), 7.57 (d, 1 H_6, J = 9 Hz), 6.78 (dd, 1, H_5, J = 9 and 2 Hz), 6.73 (d, 1, H_3, J = 2 Hz), 5.58 (s, 1 $H_{2'}$), 4.03–3.50 (m, 2, 2 $H_{6'}$), 2.07–1.43 (m, 6, 2 $H_{3'}$, 2 $H_{4'}$, 2 $H_{5'}$); IR 3.27, 3.39, 3.91, 6.10, 6.65, 7.45, 7.70, 8.04 μm.

4-[(2-Tetrahydropyranyl)oxy]-2-(allyloxy)benzaldehyde (8). A solution of 26.80 g (0.12 mol) of crude 7 in 30 mL of DMF was added to a mixture of 16.00 g (0.13 mol) of allyl bromide and 16.60 g (0.12 mol) of K_2CO_3. After stirring the mixture at room temperature for 2 days, 200 mL of aqueous 5% NaOH was added and the mixture was extracted with ether (2 × 300 mL). The combined ether extracts were washed with aqueous 5% NaOH (2 × 200 mL), and the solvent was evaporated to yield 30.20 g (95% yield) of crude 8 as an orange oil, which was used without further purification: NMR ($CDCl_3$) δ 10.40 (s, 1, CHO), 7.77 (s, 1, H_6, J = 9 Hz), 6.67 (dd, 1, H_5, J = 9 and 2 Hz), 6.65 (d, 1, H_3, J = 2 Hz), 6.43–5.77 (m, 1, $H_{2''}$), 5.57–5.17 (m, 3, 2 $H_{3''}$, $H_{2'}$), 4.70–4.50 (m, 2, 2 $H_{1''}$), 4.07–3.40 (m, 2, 2 $H_{6'}$), 2.07–1.40 (m, 6, 2 $H_{3'}$, 2 H_4, 2 $H_{5'}$); IR 3.40, 3.50, 5.94, 6.20, 6.95, 7.89, 8.49 μm.

4-[(2-Tetrahydropyranyl)oxy]-2-(allyloxy)phenol (9). A solution of 10.00 g (38.2 mmol) of aldehyde 8 in 100 mL of CH_2Cl_2 was cooled by periodic immersion in an ice bath to maintain 20 °C. *m*-Chloroperoxybenzoic acid (85%), 7.75 g (38.2 mmol), was added. After 30 min, the ice bath was removed and the mixture stirred at room temperature for 3 days. The mixture was partitioned between 200 mL of each of aqueous saturated $NaHCO_3$ and of ether. The aqueous solution was extracted with an additional 200 mL of ether. The combined ether extracts were washed with aqueous saturated $NaHCO_3$ (2 × 200 mL), and the solvent was evaporated, yielding 10.10 g (99% yield) of the crude formate ester. The ester was dissolved in 25 mL of EtOH and stirred with 50 mL of pH 8 carbonate buffer at room temperature for 5 h. Periodic addition of solid Na_2CO_3 was necessary to maintain the solution at pH 8–9. The mixture was diluted with 150 mL of aqueous saturated $NaHCO_3$ and extracted with ether (2 × 200 mL). Evaporation of the ether gave 8.70 g (92% yield) of crude 9, which was used without further purification: NMR ($CDCl_3$) δ 6.92–6.73 (m, 4, 3 Ar H, $H_{2''}$), 5.52–5.13 (m, 3, 2 $H_{3''}$, $H_{2'}$), 4.60–4.40 (m, 2, 2 $H_{1''}$), 4.20–3.27 (m, 2, 2 $H_{6'}$), 2.07–1.30 (m, 6, 2 $H_{3'}$, 2 $H_{4'}$, 2 $H_{5'}$); IR 2.95, 3.40, 3.49, 6.21, 6.60, 8.06, 8.58 μm.

3-[4-[(2-Tetrahydropyranyl)oxy]-2-(allyloxy)phenoxy]-1,2-epoxypropane (10). A solution of 8.70 g (34.8 mmol) of crude phenol 9 in 40 mL of acetone was added to a mixture of 8.00 g (87.0 mmol) of epichlorohydrin and 4.80 g (34.8 mmol) of K_2CO_3. After reluxing, with stirring, for 2 days, the solvent was evaporated to 30 mL, added to 150 mL of aqueous 5% NaOH, and then extracted with ether (2 × 200 mL). The combined ether extracts were washed with aqueous 10% NaOH (2 × 200 mL), and the solvent was evaporated to give 7.10 g (67% yield) of crude 10, obtained as a brown oil: NMR ($CDCl_3$) δ 6.92–6.47 (m, 3, Ar H), 6.37–5.57 (m, 1, $H_{2''}$), 5.53–5.13 (m, 3, H_2, 2 $H_{3''}$), 4.60–4.43 (m, 2, 2 $H_{1''}$), 4.30–3.10 (m, 5, H_2, 2 H_3, 2 $H_{5'}$), 2.90–2.60 (m, 2, 2 H_1), 2.07–1.33 (m, 6, 2 $H_{3'}$, 2 $H_{4'}$, 2 $H_{5'}$); IR 3.40, 3.50, 6.25, 6.67, 7.94, 8.20, 8.51, 8.97, 9.76 μm.

1-(Isopropylamino)-3-[4-hydroxy-2-(allyloxy)phenoxy]-2-propanol (4'-Hydroxyoxprenolol; 2). A solution of 7.10 g (31.5 mmol) of crude epoxide 10 in 75 mL (52.0 g, 88 mmol) of isopropylamine was heated in a bomb at 115 °F for 22 h and cooled, the bomb was opened, and the isopropylamine was evaporated, yielding 8.40 g (99% yield) of the intermediate pyranyl ether 11. The crude pyranyl ether 11 was dissolved in 25 mL of EtOH and stirred for 30 min with 50 mL of aqueous 2 N HCl. The resulting solution was washed with ether (2 × 100 mL) and then made alkaline by the addition of solid NaOH. The mixture was washed with ether (2 × 200 mL), then adjusted to pH 9 (Na_2CO_3), and extracted with ether (2 × 200 mL). Evaporation of the combined ether extracts gave 2.60 g (30% yield) of clear, brown oil: NMR (CDCl) δ 6.65 (d, 1, Ar H_6, J = 8 Hz), 6.38 (d, 1, Ar H_3, J = 3 Hz), 6.22 (dd, Ar H_5, J = 8 and 3 Hz), 6.37–5.73 (m, 1, $H_{2'}$), 5.85–5.10 (m, 2, 2 $H_{3'}$), 4.92 (br s, exchangeable), 4.50–4.37 (m, 2, 2 $H_{1'}$), 3.92 (s, 3, 2 H_3, H_2), 3.00–2.57 (m, 3, 2 H_1, H_α), 1.02 (d, 6, CH_3, J = 6 Hz); IR 3.46, 3.40, 3.47, 6.26, 6.88, 7.81, 8.49, 8.91, 9.82 μm.

The oil was acidified with ethereal HCl and the HCl salt of 21 crystallized from EtOAc/MeOH to give 840 mg (13% yield) of a white solid, mp 94.0–96.5 °C. Anal. ($C_{15}H_{24}NO_4Cl$) C, H, N.

5-[(2-Tetrahydropyranyl)oxy]-2-(allyloxy)acetophenone (13). A solution of 11.0 g (46.6 mmol) of phenol 12, prepared according to the method of Kunze,[20] in 30 mL of DMF, 6.77 g

(56 mmol) of allyl bromide, and 6.40 g (46.6 mmol) of K_2CO_3 was stirred to room temperature for 20 h. Aqueous 5% NaOH (200 mL) was added and the product extracted with ether (2 × 200 mL). The combined ether layers were washed with aqueous 5% NaOH (2 × 200 mL), and the solvent was evaporated to give 11.10 g (86% yield) of **13** as a brown oil: NMR ($CDCl_3$) δ 7.42 (d, 1, Ar H_6, J = 3 Hz), 7.24 (dd, 1, Ar H_4, J = 9 and 3 Hz), 6.86 (d, 1, Ar H_3, J = 9 Hz), 6.38–5.77 (m, 1, $H_{2''}$), 5.53–5.14 (m, 3, 2 $H_{3''}$, $H_{2'}$), 4.62–4.48 (m, 2, 2 $H_{1''}$), 4.00–3.37 (m, 2, 2 H_6), 2.61 (s, 3, CH_3), 1.93–1.33 (m, 6, 2 $H_{3'}$, 2 $H_{4'}$, 2 $H_{5'}$); IR 3.25, 3.39, 3.47, 5.95, 5.95, 6.67, 7.02, 7.76, 8.23 μm.

5-[(2-Tetrahydropyranyl)oxy]-2-(allyloxy)phenol (14). To a solution of 11.10 g (40 mmol) of acetophenone **13** in 60 mL of CH_2Cl_2, cooled to 20 °C by periodic immersion in an ice bath, was added 8.11 g (40 mmol) of 85% *m*-chloroperoxybenzoic acid. After 30 min of cooling, the mixture was stirred at room temperature for 3 days. The resulting white suspension was shaken with 200 mL of aqueous saturated $NaHCO_3$ and then extracted with ether (2 × 200 mL). The combined ether extracts were washed with aqueous saturated $NaHCO_3$ (2 × 200 mL) and the solvent was evaporated to give a quantitative yield of the intermediate acetate ester: IR 3.40, 5.65 μm (C=O).

The ester, 11.00 g (37.5 mmol), was dissolved in 50 mL of EtOH, 35 mL of aqueous 5% NaOH was added, and the mixture was stirred for 30 min. An additional 150 mL of aqueous 5% NaOH was added, and the mixture was washed with ether (2 × 200 mL). The aqueous solution was adjusted to pH 9 (Na_2CO_3) and extracted with ether (2 × 200 mL). Evaporation of the combined ether extracts gave 6.40 g (64% yield) of **14** as a clear, light brown oil: NMR ($CDCl_3$) δ 6.73 (d, 1, Ar H_3, J = 8 Hz), 6.68 (d, 1, Ar H_6, J = 3 Hz), 6.43 (dd, Ar H_4, J = 8 and 3 Hz), 6.12–5.58 (m, 1, $H_{2''}$), 5.47–4.93 (m, 3, 2 $H_{3''}$, $H_{2'}$), 4.50–4.30 (m, 2, 2 $H_{1''}$), 4.07–3.20 (m, 2, 2 $H_{6'}$), 2.13–1.47 (m, 6, 2 $H_{3'}$, 2 $H_{4'}$, 2 $H_{5'}$); IR 2.96, 3.40, 3.50, 6.25, 6.64, 8.10, 8.62, 10.10 μm.

3-[5-[(2-Tetrahydropyranyl)oxy]-2-(allyloxy)phenoxy]-1,2-epoxypropane (15). To a solution of 6.40 g (25.6 mmol) of phenol **14** in 40 mL of acetone was added 5.89 g (64.0 mmol) of epichlorohydrin and 3.53 g (25.6 mmol) of K_2CO_3. The mixture was stirred at reflux for 2 days and then the acetone was evaporated. The residue was added to 150 mL of aqueous 5% NaOH and extracted with ether (2 × 200 mL). The combined ether extracts were washed with aqueous 5% NaOH (2 × 200 mL), and the solvent was evaporated to yield 6.00 g (77% yield) of **15** as a clear yellow oil, which was used without further purification: NMR ($CDCl_3$) δ 6.77–6.37 (m, 3, Ar H), 6.33–5.63 (m, 1, $H_{2''}$), 5.77–4.97 (m, 3, $H_{2'}$, 2 $H_{3''}$), 4.50–4.33 (m, 2, 2 $H_{1''}$), 4.27–3.13 (m, 5, H_2, 2 H_3, 2 $H_{6'}$), 2.90–2.57 (m, 2, 2 H_1), 2.10–1.37 (m, 6, 2 $H_{3'}$, 2 $H_{4'}$, 2 $H_{5'}$); IR 3.40, 3.48, 6.23, 6.63, 7.87, 8.20, 8.47, 8.81 μm.

1-(Isopropylamino)-3-[5-hydroxy-2-(allyloxy)phenoxy]-2-propanol (5'-Hydroxyoxprenolol; 3). A solution of 6.00 g (19.6 mmol) of epoxide **15** in 100 mL (96.0 g, 1.17 mol) of isopropylamine was heated in a bomb at 115 °C for 22 h. After cooling the solution, the excess isopropylamine was evaporated, yielding 7.10 g (98% yield) of crude pyranyl ether **16**, which was dissolved in 20 mL of EtOH and stirred for 1 h with 50 mL of aqueous 2 N HCl. The mixture was diluted with 50 mL of H_2O and washed with ether (2 × 150 mL). The solution was made alkaline with solid NaOH and washed with ether (2 × 150 mL). The solution was adjusted to pH 8.5 by the addition of solid $NaHCO_3$, followed by the dropwise addition of aqueous 37% HCl. The resulting mixture was then extracted with ether (2 × 200 mL). Evaporation of the solvent gave 4.10 g of **3** (73% crude yield) as a clear, orange syrup: NMR ($CDCl_3$) δ 6.07 (d, 1, Ar H_3, J = 8 Hz), 6.40–5.72 (m, 3, Ar H_4 and Ar H_6, $H_{2'}$), 5.40–5.03 (m, 2, 2 $H_{3'}$), 5.30 (s, 3, exchangeable), 4.50–4.33 (m, 2, 2 $H_{1'}$), 3.87 (br s, 3, 2 H_3, H_2), 3.10–2.17 (m, 3, 2 H_1, H_α), 1.04 (d, 6, 2 CH_3, J = 6 Hz); IR 3.15, 3.44, 3.51, 6.27, 6.67, 6.90, 7.81, 8.30, 8.55, 8.97 μm.

The syrup was acidified with etheral HCl. The resulting HCl salt of **3** was crystallized from MeOH–EtOAc, affording 2.40 g (38% yield) of light yellow crystals of **3**·HCl, mp 127.5–128.5 °C. Anal. ($C_{15}H_{24}NO_4Cl$) H, N; C: calcd, 56.69; found, 56.28.

Pharmacology. Guinea pig tracheal strips were suspended in 10-mL tissue baths and responses were recorded as previously described.[17] Cumulative dose–response effects of isoproterenol were obtained in the presence of carbachol, 10^{-7} M. Two dose–response curves to isoproterenol were obtained on each strip, one before and one in the presence of antagonist. The tissue was washed for 1 h after the first dose–response curve and before the addition of an antagonist. The antagonists were added to the bath 1 h prior to obtaining the second dose–response curve. In all cases, there was a parallel shift of the dose–response curve to the right without alteration of the maximum degree of relaxation produced by the agonist. Two consecutive dose–response curves without adding antagonist were reproducible within 0.2 log unit, and dose ratios were not corrected for this slight change.

Effects of the antagonists were analyzed by calculating apparent dissociation constants (K_B values) as described by Furchgott.[21] The dose ratio for an antagonist was calculated as the antilog of the difference between the –log molar ED_{50} for isoproterenol in the control curve and the –log molar ED_{50} for isoproterenol in the treated curve. The K_B values were calculated as: K_B = [B]/(dose ratio – 1), where B refers to the antagonist. Three different concentrations of each antagonist were examined.

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