β-Adrenergic Blockade by 3-[3-(Substituted amino)-2-hydroxypropoxy]-5-hydroxybenzyl Alcohols

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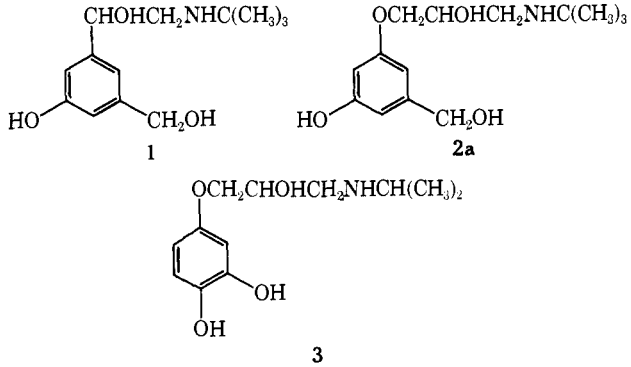
Recently, a new β-sympathomimetic agent, 3-[3-α-(*tert*-butylaminomethyl)]-5-hydroxy-*m*-xylene-α,α′-diol (**1**), was reported which selectively stimulated the β_2-adrenergic receptors.[1] It was of interest to determine the effect on biological activity of replacing the ethanolamino (**1**) side chain by an oxypropanolamino (**2a**) group. A similar modification of isoproterenol gave an analog (**3**) which was reported to possess β-sympathomimetic activity similar to epinephrine.[2]



1 **2a** 3

Chemistry. Reaction of methyl 3,5-dihydroxybenzoate (**4**) with 1 equiv of benzoyl chloride gave the corresponding methyl 3-benzoyloxy-5-hydroxybenzoate (**5**) which was then benzylated using benzyl bromide to give methyl 3-benzoyloxy-5-benzyloxybenzoate (**6**). The benzoyl group of **6** was removed by trans esterification with MeOH and *p*-toluenesulfonic acid and gave methyl 3-benzyloxy-5-hydroxybenzoate (**7**). Reaction of **7** with epichlorohydrin in MeOH containing NaOH gave the intermediate methyl 3-benzyloxy-5-(2,3-epoxypropoxy)benzoate (**8**) which was further reacted with the appropriate amine, such as *tert*-butylamine. The compound obtained, methyl 3-benzyloxy-5-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzoate (**9a**), was reduced with $LiAlH_4$ and gave 3-benzyloxy-5-[3-*tert*-butylamino)-2-hydroxypropoxy]benzyl alcohol as product **10a**. Catalytic debenzylation of **10a** gave the desired product **2a** (Scheme I).

The corresponding 3,4-dimethoxyphenylethyl analog in the benzophenone (**11**) and tetralone (**12**) series of β-blockers was prepared from known epoxide intermediates[3,4] using the method for the preparation of **9b**.

The unusual $CHCl_3$ solubility of the hydrochloride salts of analogs **9b**, **11**, and **12** allowed a method of separation of the product from 3,4-dimethoxyphenylethylamine. After an acid extraction of the crude mixture of amines in $CHCl_3$, the desired product hydrochloride remained in the $CHCl_3$ phase. A basic wash of the $CHCl_3$ phase followed by evaporation of the solvent gave the desired product.

Pharmacology. The β-adrenergic receptor agonist, antagonist, and direct myocardial depressant effects of this series of compounds were evaluated in barbiturate anesthetized, bilaterally vagotomized mongrel dogs. Dogs were generally either pretreated with reserpine (0.5 mg/kg ip for 2 days and used on the day 3) or the ganglion blocker ansolysen (2 mg/kg iv) prior to the experiments. Reserpinization or ganglion blockade suppressed resting sympathetic tone and facilitated evaluation for intrinsic sympathomimetic and direct myocardial depressant actions. Control responses to isoproterenol (0.3 μg/kg iv) were established after which compounds were administered intravenously on a half log dose schedule (0.03–10.0 mg/kg) at 20-min intervals. Isoproterenol challenges were interposed midway between doses of the drug in order to evaluate β-adrenergic blockade of heart rate. Results obtained from one or a small number of dogs were reliable and served as a basis for further studies on selected analogs.

The compounds were also evaluated for antiarrhythmic activity in ouabain-intoxicated dogs. Ouabain was administered in sequential iv doses (40, 20, 10 μg/kg, etc.) at 15- or 30-min intervals until a stable ventricular tachycardia

Scheme I

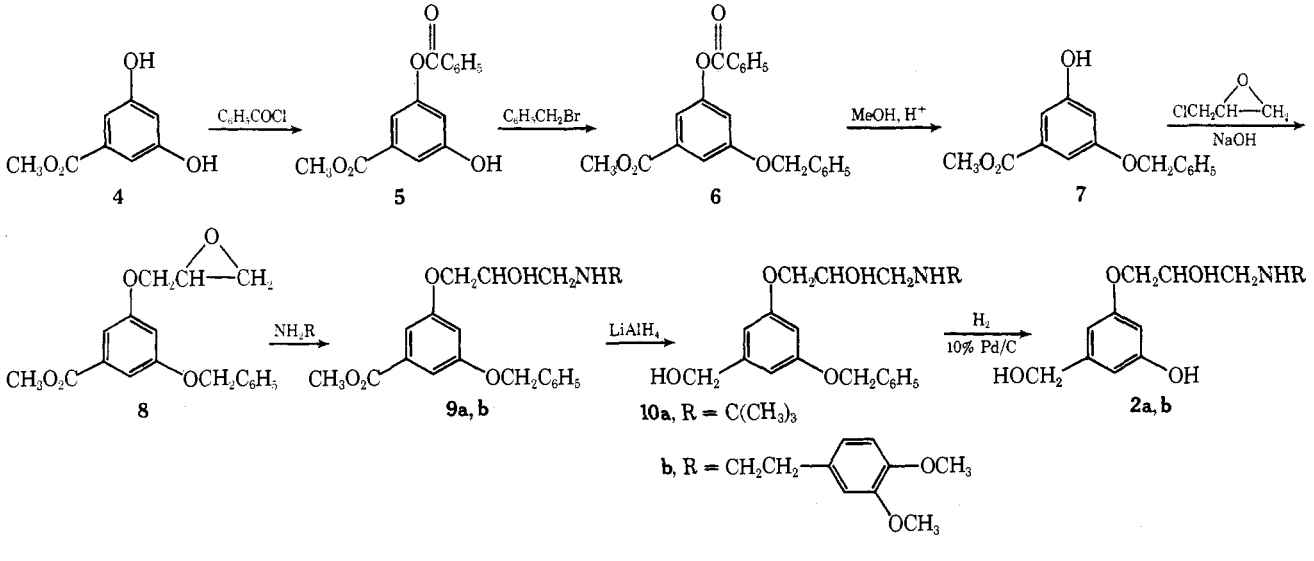
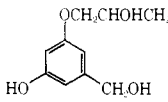
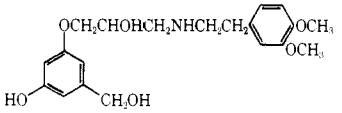
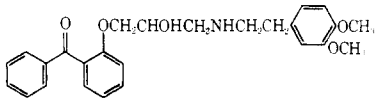
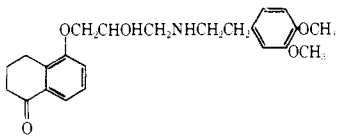
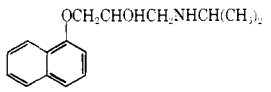


Table I

No.	Compound	Dose,[e] mg/kg; 100% β-blockade	Intrinsic act.	Direct myocardial depression, dose, mg/kg
2a		0.1–0.3	None[a]	>3
2b		0.3–1.0[f]	Yes[b]	10–30
11		1–3	None[c]	1–3
12		1–3	None[d]	1–3
Propranolol		0.3	None[d]	1–3

[a]Ganglion blocker pretreatment. [b]Methods utilizing ganglion blocker and reserpine pretreatment were employed. [c]No pretreatment. [d]Reserpine pretreatment. [e]Dose of antagonist sufficient to block positive chronotropic response to isoproterenol (0.3 μg/kg iv). [f]Compound **2b** was the only analog tested which demonstrated cardioselectivity. Doses causing 100% blockade of heart rate did not block blood pressure.

appeared. The drug was administered at a rate of 1.0 mg/kg min^{-1} to determine its ability to restore normal sinus rhythm.

Discussion

The replacement of the *tert*-butylaminoethanol side chain of a known β_2-sympathomimetic (**1**)[1] by the 3-*tert*-butylamino-2-hydroxypropoxy moiety yielded **2a,** a potent new nonselective β-adrenergic blocking agent without β-sympathomimetic and antiarrhythmic action. A similar modification of isoproterenol resulted in a sympathomimetic agent, **3**, with activity reported to be similar to epinephrine.[2]

When the *tert*-butyl group of **2a** was replaced by the 3,4-dimethoxyphenylethyl group, a β-adrenergic blocker, **2b** was obtained which was similar in potency to propranolol with only low myocardial depressant action. This analog, **2b,** possessed intrinsic β-sympathomimetic action at doses of 0.03 mg/kg or less. Analogs **2a** and **2b** were ineffective in reversing ouabain-induced cardiac arrhythmias. Preliminary studies indicated that **2b** exerted a threefold preference for blockade of myocardial β_1-receptors over β_2-receptors when the relative blockade of isoproterenol effects on heart rate, contractile force, and blood pressure were compared. Similar incorporation of the 3,4-dimethoxyphenylethyl group into the benzophenone (**11**)[3] and tetralone (**12**)[4] series of β-adrenergic blockers failed to yield analogs which were cardioselective or nondepressant.

In the present study, an apparent 3:1 selectivity ratio for **2b** was observed. However, additional experiments are needed to quantitatively compare **2b** with practolol which was reported to exert an eightfold cardioselective response in anesthetized dogs.[5] Unlike the present study, the practolol studies were designed to quantitatively differentiate between the β_1 and β_2 response (Table I).

Experimental Section

Melting points were taken in open capillary tubes on a Mel-Temp and are uncorrected. Each analytical sample was homogeneous by tlc and had ir, uv, and nmr spectra compatible with its structure. Combustion analysis for C, H, N, and Cl gave results within 0.4% of theory.

Methyl 3-Benzoyloxy-5-hydroxybenzoate (5). To a solution of 168 g (1.0 mol) of **4** in 2.0 l. of water was added 30 ml of 10% NaOH until pH 8 was reached. Benzoyl chloride (154 g, 1.1 mol) and 400 ml of 10% NaOH were added simultaneously to the warmed reaction mixture (40°) over a 30-min period. The reaction was stirred at 30–35° for 1 hr and extracted with $CHCl_3$ (2 × 750 ml). The combined $CHCl_3$ extracts were washed with water (1 × 350 ml) and dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave 252 g (92.8%) of the crude **5**. Recrystallization of the material from benzene gave 159 g (58.5%), mp 110–112°, of crystalline **5** which was used without further purification.

Methyl 3-Benzoyloxy-5-benzyloxybenzoate (6). A mixture of **5** (418 g, 1.54 mol), benzyl bromide (387 g, 2.26 mol), K_2CO_3 (310 g, 2.26 mol), and 4.1 l. of acetone was heated at reflux for 3 hr. The mixture was poured onto 3.3 l. of ice and extracted with $CHCl_3$ (2 × 2 l.). The $CHCl_3$ extracts were combined and washed with 10% NaOH (3.3 l.) and water (2 × 1.6 l.). The $CHCl_3$ phase was dried with $MgSO_4$ and evaporated to give an oily residue which was stirred with hexane (1.8 l.) at 10° for 1 hr. Crystalline material was collected by filtration and reslurried with hexane (1.3 l.) for 1 hr at 10°. The crystalline **6** was collected and dried to give 409 g (73.5%), mp 69–70°, used without further purification.

Methyl 3-Benzyloxy-5-hydroxybenzoate (7). A reaction mixture containing 409 g (1.13 mol) of **6**, 102 g (0.55 mol) of *p*-toluenesulfonic acid, and 2.7 l. of MeOH was heated at reflux for 17 hr. The reaction mixture was evaporated to dryness; the crude residue obtained was dissolved in $CHCl_3$ (2.5 l.), washed with aqueous $NaHCO_3$ and water, and dried with $MgSO_4$ before the $CHCl_3$ phase was evaporated *in vacuo* to the crude product as an oil. Trituration of the residue with hexane yielded crystalline **7**: yield 220 g (75.5%); mp 97–98°. *Anal.* ($C_{15}H_{14}O_4$) C, H.

Methyl 3-Benzyloxy-5-(2,3-epoxypropoxy)benzoate (8). A methanolic solution (250 ml) containing 4.26 g (106 mmol) of NaOH, 250 ml of epichlorohydrin, and 25 g (96.8 mmol) of **7** was stirred at room temperature for 18 hr. The reaction mixture was evaporated to a residual oil which was dissolved in 500 ml of $CHCl_3$ and extracted with 10% NaOH (1 × 100 ml) and water (1 × 100 ml) before drying with anhydrous $MgSO_4$. The $CHCl_3$ was evaporated and the crude expected product was obtained as a gum in 98% yield.

Methyl 3-Benzyloxy-5-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzoate Hydrochloride (9a). A reaction mixture contain-

ing 29.9 g (94.8 mmol) of crude 8 and 250 ml of *tert*-butylamine dissolved in 250 ml of methanol was heated at reflux for 1 hr. After evaporation of the volatile components of the reaction mixture, the oily residue which remained was converted to a crystalline hydrochloride salt: yield 30.2 g (75.3%); mp 174–176°. Recrystallization of the product from toluene gave the analytical sample: mp 181–183°. *Anal.* ($C_{22}H_{29}NO_5 \cdot HCl$) C, H, N, Cl.

3-Benzyloxy-5-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzyl Alcohol (10a). To a suspension of 29.1 g (68.5 mmol) of **9a** in 500 ml of THF cooled at 0° was added 5.20 g (137 mmol) of $LiAlH_4$. The resultant mixture was refluxed 18 hr. After the excess $LiAlH_4$ and complex had been destroyed by the addition of water, the reaction mixture was diluted with 500 ml of $CHCl_3$ and the precipitate was removed by filtration. The organic filtrate was washed with water (1 × 500 ml), dried with $MgSO_4$, and evaporated to give the crude solid **10a**: yield 20.7 g (84.0%); mp 99–105°. The analytical sample was obtained from cyclohexane: mp 105–107°. *Anal.* ($C_{21}H_{29}NO_4$) C, H, N.

3-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-5-hydroxybenzyl Alcohol Fumarate (2a). An ethanol solution (250 ml) containing 19.7 g (54.7 mmol) of **10a** was hydrogenated over 8 g of 10% Pd/C catalyst until hydrogen uptake had ceased. The catalyst was removed by filtration through a Celite pad and the filtrate obtained was evaporated to a gummy residue. A crystalline fumerate salt was obtained in analytical purity from MeOH–Et_2O: mp 254–255° dec. *Anal.* ($C_{14}H_{23}NO_4 \cdot 0.5C_4H_4O_4$) C, H, N.

Methyl 3-Benzyloxy-5-[3-(3,4-dimethoxyphenylethylamino)-2-hydroxypropoxy]benzoate (9b). A reaction mixture containing 10.0 g (31.9 mmol) of **8**, 25 g (138 mmol) of 3,4-dimethoxyphenylethylamine, and 100 ml of methanol was heated at reflux for 1 hr. Evaporation of the reaction mixture gave a residual oil which was dissolved in $CHCl_3$ (500 ml), extracted with 1 *N* HCl (2 × 250 ml) and 1 *N* NaOH (500 ml), and dried with anhydrous $MgSO_4$. Evaporation of the $CHCl_3$ gave a residual solid which upon trituration with a Et_2O–hexane mixture gave 14.6 g (92.4%) of crystalline product: mp 75–85°. The analytical material was obtained by recrystallization from toluene: mp 94–95°. *Anal.* ($C_{28}H_{33}NO_7$) C, H, N.

3-[3-(3,4-Dimethoxyphenylethylamino)-2-hydroxypropoxy]-5-hydroxybenzyl Alcohol Fumarate (2b). To a suspension of 3.11 g (82.0 mmol) of $LiAlH_4$ in 250 ml of dry THF was added a THF solution (250 ml) containing 20.3 g (41.0 mmol) of methyl 3-benzyloxy-5-[3-(3,4-dimethoxyphenylethylamino)-2-hydroxypropoxy]benzoate. The resulting reaction mixture was refluxed for 3 hr before the excess $LiAlH_4$ and complex were destroyed by the careful addition of water. The white precipitate which formed was removed by filtration and the filtrate obtained was evaporated *in vacuo* and gave a quantitative yield of the crude **10b** as a straw-colored oil.

An ethanol solution (150 ml) containing 19.6 g (41.2 mmol) of **10b** was hydrogenated over 5.0 g of 10% Pd/C catalyst until hydrogen uptake had ceased. The catalyst was removed by filtration and the filtrate was evaporated to give an oily residue as product. A crystalline fumarate salt was obtained from 1-PrOH: yield 14.1 g; mp 183–186° dec. The analytical sample was obtained by one recrystallization from MeOH–Et_2O: mp 189–191° dec. *Anal.* ($C_{20}H_{27}NO_6 \cdot 0.5C_4H_4O_4$) C, H, N.

2-[3-(3,4-Dimethoxyphenylethylamino)-2-hydroxypropoxy]benzophenone Hydrogen Oxalate (11). A methanolic solution (100 ml) containing 10.0 g (39.3 mmol) of 2-(2,3-epoxypropoxy)benzophenone[3] and 22.6 g (125 mmol) of 3,4-dimethoxyphenylethylamine was heated at reflux for 2 hr. The reaction mixture was evaporated to remove the volatile components and the residue obtained was dissolved in $CHCl_3$ (500 ml). The $CHCl_3$ solution was washed with 3 *N* HCl (3 × 500 ml), 1 *N* NaOH (1 × 500 ml), and H_2O (1 × 500 ml) before being dried with $MgSO_4$ and evaporated to give 15.8 g (92.2%) of the expected product as an oil. The product was purified as an oxalate salt by recrystallization from 2-PrOH: yield 12.4 g (61.1%); mp 129–130°. *Anal.* ($C_{26}H_{29}NO_5 \cdot C_2H_2O_4$) C, H, N.

5-[3-(3,4-Dimethoxyphenylethylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone Hydrogen Oxalate (12). A reaction mixture containing 13.4 g (61.6 mmol) of 3,4-dihydro-5-(2,3-epoxypropoxy)-1(2*H*)-naphthalenone,[4] 100 ml of MeOH, and 53.7 g (295 mmol) of 3,4-dimethoxyphenylethylamine was heated at reflux for 1 hr. The mixture was evaporated to an oily residue which was dissolved in $CHCl_3$ (500 ml) and washed with 3 *N* HCl (3 × 500 ml), 20% NaOH (1 × 100 ml), and H_2O (1 × 500 ml). The $CHCl_3$ solution was dried ($MgSO_4$) and evaporated *in vacuo* to give the expected product as a crude oil: yield 13.5 g (54.9%). The product was purified as an oxalate salt by recrystallization from 2-PrOH: mp 152–154°. *Anal.* ($C_{23}H_{29}NO_5 \cdot C_2H_2O_4$) C, H, N.

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Hashish.[1] Importance of the Phenolic Hydroxyl Group in Tetrahydrocannabinols

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Optically active Δ^9- and Δ^8-tetrahydrocannabinols (THC's), cannabidiol and racemic Δ^9-*cis*-THC, and their corresponding analogs (**1b** → **4b**) in which the positions of the phenolic hydroxyl group and the *n*-C_5 side chain have been interchanged are compared in selected pharmacological tests in mice. The results indicate that the phenolic hydroxyl group in the 1 position in THC's is very important for eliciting activity and that cannabidiol and Δ^9-*cis*-THC possess weak CNS depressant properties.

To date over 30 cannabinoids have been isolated from the plant *Cannabis sativa* and it is generally accepted that the principal compounds of pharmacological interest are Δ^9- and Δ^8-6a,10a-*trans*-tetrahydrocannabinols (THC's). In laboratory animals Δ^9- and Δ^8-THC's cause CNS depression and ataxia. The characteristic effect of THC's, which distinguishes them from all other psychoactive drugs, is a postural arrest phenomenon with relaxed staring associated with hyperexcitability to external stimuli ("popcorn effect").[2] On the basis of behavioral tests in monkeys, Edery, *et al.*,[3] have reported some structure–activity relationships (SAR) in the THC series. However, little is known about the importance of the phenolic hydroxyl group in naturally occurring THC's. In monkeys, the acetates of Δ^9- and Δ^8-THC's have 1/10 to 1/2 the activity of the parent compounds and the methyl ethers are essentially inactive.[3] We have found that the aminoalkyl esters of Δ^9-THC are nearly equiactive with the parent