Ring-Hydroxylated Propranolol: Synthesis and β-Receptor Antagonist and Vasodilating Activities of the Seven Isomers[1]

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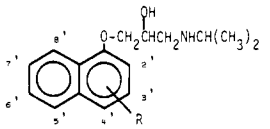
Propranolol (Inderal; 1) is extensively metabolized in man. Metabolites of interest pharmacologically include ring-hydroxylated propranolols (**1a–g**). In order to identify these ring-oxidized products and to study the effect of hydroxyl position on biological activity, we have synthesized all seven isomers. With the exception of **1b** and **1g**, the desired compounds were prepared by alkylation of the respective methoxy-1-naphthols with epichlorohydrin and reaction of the resulting epoxide with isopropylamine. Cleavage of the methyl group in fused pyridine hydrochloride afforded **1a,c–f**. **1g** was prepared by the direct alkylation of 1,8-naphthalenediol (**17**) with epichlorohydrin, followed by reaction with isopropylamine. **1b** was synthesized by treating 2-naphthol (**9**) with chlorine gas and then treating the resulting 1,1-dichloronaphthalen-2(1*H*)-one (**10**) with sodium allyl oxide. Acetylation of the hydroxy function and epoxidation of the allyl group, followed by reaction with isopropylamine, gave 3′-hydroxy-4′-chloropropranolol (**15**). Dechlorination gave **1b**. All of the racemic hydroxylated propranolols produced β blockade and direct vasodilation in anesthetized dogs. The potency is strongly dependent upon the position of the hydroxyl group, i.e., **1e** is 4 times as potent as 1 as a β receptor antagonist, whereas **1a**, **1b**, and **1g** are all significantly less potent than 1. For direct vasodilation, **1a** and **1g** are equipotent to 1, while **1b–f** are much less potent. The potencies of the compounds were also compared with their 1-octanol/pH 7.4 buffer distribution coefficients; the direct vasodilating potency was found to increase with increasing lipophilicity, while the β-adrenergic antagonist potency decreased.

Propranolol (1, R = H) is extensively metabolized in



1, R = H
1a, R = 2′-OH
b, R = 3′-OH
c, R = 4′-OH
1d, R = 5′-OH
e, R = 6′-OH
f, R = 7′-OH
g, R = 8′-OH

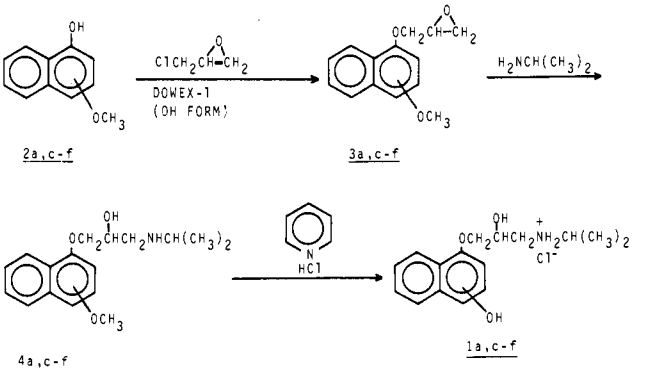
man with only between 0.15 and 0.7% excreted unchanged.[2] Of the many metabolites that have been identified, the ring-hydroxylated products are of particular importance.

Two isomeric monohydroxylated metabolites of propranolol were detected in the urine of man and rats.[3] One of these isomers was tentatively identified as 4′-hydroxypropranolol (**1c**) by various separation and spectroscopic techniques.[3,4] Since a 3′,4′-epoxide was thought,[3] and later demonstrated,[5] to be an intermediate in the oxidation of the ring, the unknown isomer was proposed to be 3′-hydroxypropranolol (**1b**). The detection of two additional monohydroxypropranolol isomers formed by the rat liver 9000*g* supernatant, however, demonstrated a much more complicated oxidation pattern of this drug.[6] This study also emphasized that the previous identification of 4′-hydroxypropranolol[3,4] was by no means unequivocal. In order to understand the ring oxidation of propranolol, the synthesis of all possible isomers is obligatory.

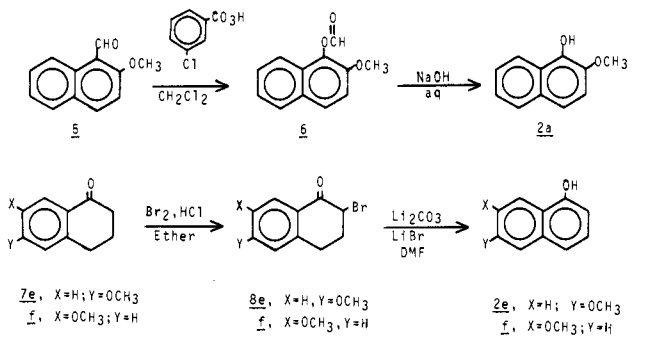
Ring oxidation of propranolol has important pharmacological implications. Thus, 4′-hydroxypropranolol has been demonstrated to be equipotent to propranolol as a β-receptor antagonist[7] and is believed to contribute to the activity of propranolol in man.[8,9] As other monohydroxylated products are also formed[3,6] it is important to determine their biological activity.

This report describes the synthesis of the seven isomeric monohydroxypropranolols. The β-receptor antagonist and the direct vasodilating properties for each of the compounds were determined in the dog and compared to their

Scheme I



Scheme II



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(4) P. A. Bond, *Nature (London)*, 213, 721 (1967).
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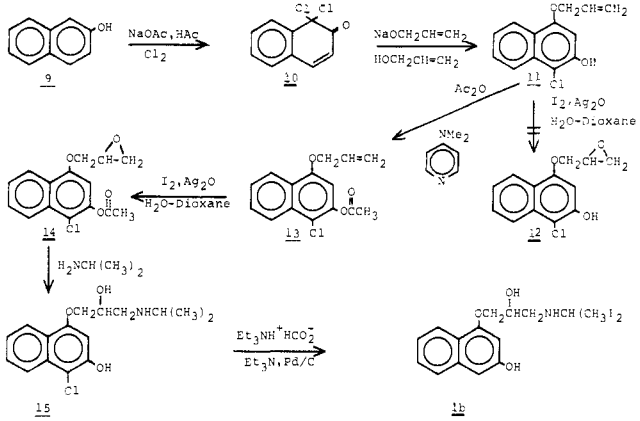
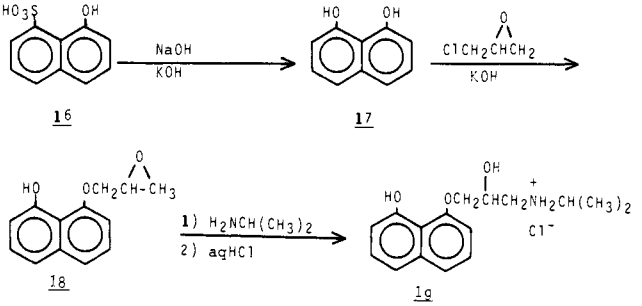
Scheme III



Scheme IV



1-octanol/pH 7.4 buffer distribution coefficients. This work also formed the basis for structure identification of monohydroxylated metabolites of propranolol.[10]

Chemistry. 2′-Hydroxy-, 4′-Hydroxy-, 5′-Hydroxy-, 6′-Hydroxy-, and 7′-Hydroxypropranolol (1a,c–f). Five of the isomers of hydroxypropranolol were prepared from the corresponding methoxynaphthols (**2a,c–f**) by the route shown in Scheme I. Compound **2a** was prepared from 2-methoxy-1-naphthaldehyde (**5**, Scheme II) via a Baeyer–Villiger[11] rearrangement using *m*-chloroperbenzoic acid to form **6**, which upon hydrolysis with aqueous sodium hydroxide gives 2-methoxy-1-naphthol[12] (**2a**).

The 4-methoxy- and the 5-methoxy-1-naphthols can be prepared by simple monoalkylation of the naphthalenediol. In practice, however, it is easier to synthesize 4-methoxy-1-naphthol (**2**) from 1,4-naphthoquinone by reductive methylation with stannous chloride in methanolic HCl.[13] 5-Methoxy-1-naphthol (**2d**) was prepared from the 1,5-naphthalenediol by monomethylation using dimethyl sulfate in aqueous sodium hydroxide.[14]

6-Methoxy- (**2e**) and 7-methoxy-1-naphthol (**2f**) (Scheme II) were synthesized from 6-methoxy- (**7e**) and 7-methoxy-1-tetralone (**7f**), respectively, according to the procedures of Kasturi[15] and Durden[16] by bromination in diethyl ether/hydrogen chloride, followed by dehydrohalogenation/aromatization with lithium carbonate and lithium bromide in refluxing dimethylformamide to give the known 6-methoxy-[15] (**2e**) and 7-methoxy-1-naphthols[17] (**2f**).

With the requisite methoxynaphthols in hand, the final synthesis of the desired propranolols was accomplished (Scheme I), by alkylating **2a,c–f** with epichlorohydrin using Dowex-1 anion-exchange resin (hydroxide form) as catalyst. Gas chromatography–mass spectrometric analysis showed that generally the reaction mixtures contained 80–90% of the epoxide (**3a,c–f**) with the remainder being the chlorohydrin. Amination of this mixture with isopropylamine gave the methoxypropranolols (**4a,c–f**) in good yields. Demethylation with fused pyridine hydrochloride at 155–170 °C gave the 2′-hydroxy- (**1a**), 4′-hydroxy- (**1c**),[18] 5′-hydroxy- (**1d**),[19] 6′-hydroxy- (**1e**),[20] and 7′-hydroxypropranolol (**1f**) hydrochlorides.

3′-Hydroxypropranolol. The synthesis of 3′-hydroxypropranolol (**1b**) presented a considerable problem. Although the 3-methoxy-1-naphthol is a known compound, its synthesis is difficult and the yields are poor.[21] In addition, the instability of this system makes it a poor candidate for the harsh conditions of the last step in Scheme I. Therefore, an alternate synthesis was devised.

The method of Iskander et al.[22] for the synthesis of 1-chloro-4-methoxy-2-naphthol was modified to prepare 1-chloro-4-(allyloxy)-2-naphthol (**11**) as depicted in Scheme III. 2-Naphthol (**9**) was treated with chlorine gas in acetic acid and sodium acetate[23] to give 1,1-dichloronaphthalen-2(1*H*)-one (**10**). Reaction of **10** with sodium allyl oxide in allyl alcohol gave **11**.

Attempts to elaborate the allyl group into the β-blocker side chain by epoxidizing the double bond in **11** or acetate **13** with peracids were unsuccessful. Epoxide **14** was finally prepared by the method of Parrilli et al.[24] by treating **13** with iodine and silver oxide in aqueous dioxane. Interestingly, attempts to use this same procedure with **11** gave no epoxide **12**. Amination of **14** was effected in isopropylamine to give 3′-hydroxy-4′-chloropropranolol (**15**). Efforts to remove the chloro group by catalytic reduction were unsuccessful; therefore, the procedure of Cortese and Heck[25] using Pd/C and triethylammonium formate in triethylamine, followed by aqueous hydrochloric acid, was used to give 3′-hydroxypropranolol (**1b**) as the hydrochloride salt.

8′-Hydroxypropranolol. It has been reported[26] that previous attempts to prepare 1,8-dimethoxynaphthalene gave instead the monoalkylated 8-methoxy-1-naphthol (**2g**). The reason stated for these failures was the

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Table I. Comparative Effects of Compounds as β-Adrenergic Receptor Antagonists and on Hindlimb Perfusion Pressure in Anesthetized Dogs (n = 4)

no.	app pA_2 values, mean ± SE, for blockade of isoproterenol-induced increases in HR and contractile force and isoproterenol-induced vasodilation[a]			dose, mg, mean ± SE, to decrease hindlimb perfusion pressure (55 mmHg)[b]
	heart rate	contractile force	vasodilation	
1	7.43 ± 0.08 (1.00)	7.60 ± 0.08 (1.00)	7.95 ± 0.06 (1.00)	0.55 ± 0.57 (1.00)
1a	5.87 ± 0.12 (0.03)	6.19 ± 0.03 (0.04)	6.33 ± 0.23 (0.02)	0.52 ± 0.36 (1.07)
1b	6.54 ± 0.03 (0.13)	6.97 ± 0.03 (0.23)	7.23 ± 0.20 (0.19)	10.00 ± 2.80 (0.06)
1c	7.34 ± 0.06 (0.81)	7.54 ± 0.07 (0.87)	7.50 ± 0.14 (0.35)	4.35 ± 2.31 (0.13)
1d	7.12 ± 0.11 (0.49)	7.49 ± 0.10 (0.78)	7.68 ± 0.11 (0.54)	1.95 ± 0.82 (0.28)
1e	8.01 ± 0.10 (3.80)	8.36 ± 0.21 (5.75)	8.35 ± 0.17 (2.51)	2.45 ± 0.86 (0.22)
1f	7.25 ± 0.13 (0.66)	7.76 ± 0.06 (1.45)	7.58 ± 0.15 (0.43)	2.80 ± 0.60 (0.20)
1g	6.64 ± 0.06 (0.16)	6.81 ± 0.06 (0.16)	7.26 ± 0.21 (0.20)	0.58 ± 0.36 (0.94)

[a] Numbers in parentheses indicate potency of each compound, as a β-receptor antagonist, relative to propranolol. They were determined by dividing the dose of propranolol (in mol/kg) required to produce a twofold shift in isoproterenol-induced dose-response curves by the dose of each hydroxypropranolol derivative needed to produce a twofold shift in the isoproterenol dose-response curves. [b] Numbers in parentheses indicate vasodilator potency of each compound relative to that of propranolol. They were determined by dividing the doses of propranolol by the dose of each of the other compounds.

"cryptophenolic" nature of 8-methoxy-1-naphthol which makes **2g** only sparingly soluble in aqueous alkali, thus evading further alkylation. Therefore, this insolubility was used in monoalkylating 1,8-naphthalenediol (**17**) by treating **17** (Scheme IV) with 1 equiv of potassium hydroxide and epichlorohydrin to give **18**. Amination with isopropylamine, followed by aqueous hydrochloric acid, afforded 8-hydroxypropranolol (**1g**) as the hydrochloride salt.

Pharmacology. β-Adrenergic receptor antagonist potencies of racemic mixtures of the **1a–g** hydrochlorides were determined in pentobarbital-anesthetized mongrel dogs and compared with **1**·HCl. Dose–response curves were generated to isoproterenol (increases in heart rate, contractile force, and femoral artery flow) before and after three cumulative doses of propranolol or one of the hydroxy derivatives. Shifts in the isoproterenol dose–response curves were used to calculate apparent pA_2 values.

All of the seven monohydroxypropranolols shifted the isoproterenol dose–response curve to the right; thus, all compounds possess β-adrenergic receptor antagonist activity. No selectivity was observed for the β receptors controlling heart rate, contractile force, or vasodilation. The apparent pA_2 values for each of the compounds as indexes of β-receptor blocking potency on each of these three parameters are shown in Table I, as well as the potencies of the hydroxypropranolols relative to propranolol. Compound **1e** is the most potent of the eight compounds studied and is the only compound found to be a more potent β-receptor antagonist than propranolol. On the other hand, **1a**, **1b**, and **1g** were all found to be significantly less potent than propranolol. Compounds **1c** and **1d** have been reported to have similar potency to propranolol for this effect,[8,19] a finding confirmed in this study. Our study demonstrated that **1f** is equipotent to propranolol as a β-receptor antagonist.

All isomers produced direct dose-related vasodilator responses when injected intraarterially into the constant-flow perfused hindlimb of the dog. The vasodilator action of propranolol was originally reported by Shanks[27] and shown to be a non-β-receptor mediated effect. Shanks showed that the d and l isomers of propranolol are equipotent for this effect and that prior administration of propranolol in doses which produced β-receptor blockade did not alter the response. Although all the hydroxypropranolol isomers produce vasodilatation, only **1a** and **1g** are as potent as propranolol for this effect (Table I).

(27) R. G. Shanks, *Br. J. Pharmacol.*, **29**, 204 (1967).

Table II. Comparison of Distribution Coefficients in 1-Octanol/pH 7.4 Buffer (D) and Relative β-Adrenergic Antagonist and Vasodilating Potencies for Monohydroxypropranolols

no.	log D[a]	β-adrenergic antagonist potency rel to propranolol[b]	vasodilator potency rel to propranolol[c]
1	1.25 ± 0.02	1.00	1.00
1a	1.66 ± 0.06	0.03	1.07
1b	0.57 ± 0.02	0.16	0.06
1c	0.53 ± 0.01	0.77	0.13
1d	0.56 ± 0.01	0.56	0.28
1e	0.46 ± 0.02	3.82	0.22
1f	0.62 ± 0.01	0.95	0.20
1g	1.40 ± 0.01	0.17	0.94

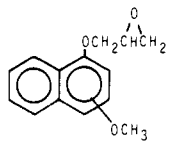
[a] Mean ± SE (n = 3). [b] Composite from pA_2 for heart rate, contractile force, and vasodilation (Table I). Mean relative potencies were determined by calculating a mean of the doses to produce a twofold shift in isoproterenol-induced dose-response curves for each parameter. The mean value for each hydroxypropranolol was then divided into the mean value for propranolol. [c] See Table I.

All other analogues were less potent. While **1a** and **1g** are two of the least potent of the hydroxypropranolols for β-receptor blocking activity, they are the most potent for vasodilator effects. In general, there is no direct relationship between the β-receptor blockade produced by these compounds and their vasodilator potency.

Distribution Coefficients and Relative β-Adrenergic Antagonist and Vasodilating Properties. The logarithms of the distribution coefficients 1-octanol/pH 7.4 phosphate buffer (log D) for the seven monohydroxypropranolols are shown in Table II, together with their relative β-adrenergic antagonist and vasodilating properties. The D values for the **1a** and **1g** isomers are much higher than for the other isomers and also exceed the D value for propranolol. This difference is very likely due to intramolecular hydrogen bonding between the phenolic hydroxyl groups of these isomers and the side chain. The direct vasodilating properties of **1a** and **1g** also clearly exceed those of the other isomers, suggesting lipophilicity as a major contributor to this effect. In contrast, the β-adrenergic antagonist properties of these two isomers are very weak. Whereas the direct vasodilating potency decreases with decreasing lipophilicity (Table II), the β-adrenergic antagonist potency increases. Indeed, the least lipophilic isomer, **1e**, is the most potent antagonist of the β receptors.

Thus, it appears that the direct vasodilating properties of the monohydroxypropranolols are directly related to

Table III



no.	position of methoxy	% yield[a]	mp, °C
3a	2	98	oil
3c	4	100	semisolid
3d	5	70	117-117.5
3e	6	87	oil
3f	7	77	65-66

[a] Including 10-20% chlorohydrin.

their lipophilicity, i.e., their ability to enter tissues or tissue membranes. On the other hand, the ability to produce β blockade for the more lipophilic isomers (**1a** and **1g**) may be limited by nonspecific binding to tissue sites other than the β receptors.

However, when considering the β-receptor antagonist properties of the five isomers with a low and similar lipophilicity (log D ranging from 0.46 to 0.62), it seems evident that the position of the hydroxyl group is crucial for the affinity to the β receptors. Thus, within this group of compounds with similar lipophilicity, **1e** is 4 to 23 times more potent than the other isomers.

Metabolism. Our studies on the metabolism of propranolol in rats and man[10] have confirmed **1a,c,d,f** as the ring-hydroxylated metabolites of propranolol previously detected.[6] Details of this work will be reported separately.

Experimental Section

Chemical Methods. Melting points, determined on a Thomas-Hoover capillary melting point apparatus, are uncorrected. UV spectra were recorded on a Cary 15 scanning spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer, employing Me_4Si as internal standard, and are consistent with assigned structures. Electron-impact mass spectra were obtained at 70 eV on a Finnigan 3200 GC/MS interfaced with a Finnigan 6000 data systems and are consistent with assigned structures. Elemental analyses were performed by Atlanta Microlabs, Atlanta, Ga., and are within ±0.4% of theory. Analytical samples were dried in vacuo at ambient temperature and are free of significant impurities on TLC (Analtech silica gel GF, $CHCl_3$–MeOH–NH_4OH, 60:10:1) and gas chromatography (OV-1) as both bis(trimethylsilyl) and tris(trifluoroacetyl) derivatives.

2-Methoxy-1-naphthol (2a) was prepared according to the procedure of Nelson and Burke[11] in 39.7% yield, mp 53–54 °C (lit.[12] 53.5–54.5 °C).

4-Methoxy-1-naphthol (2c) was prepared in 32% yield from 1,4-naphthoquinone according to the procedure of Walker and Nelson,[13] mp 128–129 °C (lit.[13] 128–129 °C).

5-Methoxy-1-naphthol (2d) was prepared from 1,5-dihydroxynaphthalene in 28.5% yield according to the method of Fierz-David et al.[14] mp 136–137 °C (lit.[14] 135–136 °C).

6-Methoxy-1-naphthol (2e) was prepared from **9e** in 32.6% yield employing the method of Kasturi and Asunachelem,[15] mp 81.5–83.5 °C (lit.[15] 85 °C).

7-Methoxy-1-naphthol (2f) was prepared from **9f** in 84% yield by the method of Durden,[16] mp 102.5–104 °C (lit.[17] 104.5–105 °C).

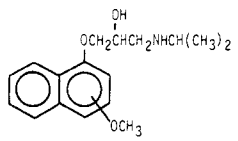
General Procedure for the Synthesis of 1′-(2,3-Epoxypropoxy)-Substituted Methoxynaphthalenes (3a,c–f). To the methoxy-1-naphthol (**2a,c–f**) dissolved in epichlorohydrin (29 mmol/mmol of **2**) was added Dowex-1 resin (hydroxide form; 0.61 mequiv/mmol of the starting naphthol). The reaction mixture was refluxed for 1 h and another portion of resin (0.3 mequiv/mmol of **2**) was added. After another 30-min reflux, the reaction mixture was filtered and the resin washed with CH_2Cl_2. The filtrate was concentrated in vacuo; the residue chromatographed on a short column of silica gel eluting with benzene to give 80–90% of **3a–c–f** and 10–20% of chlorohydrin. Pertinent data are shown in Table III.

General Procedure for the Preparation of Methoxypropranolols (4a,c–f). Isopropylamine (29 mmol/mmol of **3**) was added to the mixture of epoxide (**3a,c–f**) and chlorohydrin, and the reaction mixture was stirred at 30 °C until TLC indicated the absence of starting material. After the excess isopropylamine was removed with reduced pressure, the residue was dissolved in 1 N HCl and washed with ether. The methoxypropranolols were isolated by adjusting the pH to 9.6 and either extracting the resulting oil with EtOAc or filtering the precipitate. The data are shown in Table IV.

General Procedure for the Synthesis of Hydroxypropranolol (1a,c–f) Hydrochlorides. A thick-walled, screw-top test tube containing methoxypropranolol (**4a,c–f**) and pyridine hydrochloride (8 mmol/mmol of **4**) was dried at 30 °C overnight over P_2O_5. The reaction mixture was heated at 155–180 °C under N_2 until the methoxypropranolol was consumed as indicated by GC. The cooled reaction mixture was dissolved in H_2O and washed with ether; the pH was then adjusted to 9.6, and the resulting insoluble material was either filtered or extracted with EtOAc and purified as is shown in Table V. The free base was dissolved in 1 N HCl and lyophilized: NMR (Me_2SO-d_6) average δ 1.33 [d, J = 7 Hz, 6, $CH(CH_3)_2$], 3.2 [m, 7, OH, NH_2, $CH(CH_3)_2$, CH_2N], 4.2 (m, 3, OCH_2CH), 7.2–8.4 (m, 6, aromatic); MS [$(SiMe_3)_2$ derivative], m/z 419 (M^+), 232 [$M - CH_2CHOSiMe_3CH_2 - NHCH(CH_3)_2 + H$], 72 [$CH_2{=}NHCH(CH_3)_2^+$]. Compounds **1a** and **1f** have an additional fragment at m/z 216 [$M - OCH_2CHOSiMe_3CH_2NHCH(CH_3)_2$]; UV (pH 7.4 buffer), **1a**: λ_{max} 227 nm (ϵ 31 300), 267 (sh) 278 (4800), 288 (4300), 317 (sh), 329 (2200); **1c**: 208 (43 100), 239 (19 200), 307 (sh), 315 (5300), 327 (4800); **1d**: 224 (52 400), 285 (sh), 295 (7900), 311 (6300), 325 (5200); **1e**: 218 (38 200), 239 (20 500), 273 (sh), 282 (4700), 293 (sh), 314 (2200), 328 (2400); **1f**: 211 (44 800), 228 (sh), 273 (sh), 281 (5400), 292 (4900), 319 (2300), 331 (2600).

1,1-Dichloronaphthalen-2(1*H*)-one (10) was prepared according to the procedure of Stansfield[22] and Burton.[23] Some purification of **10** was effected by chromatography on a short silica gel column eluting with benzene.

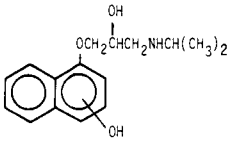
Table IV



no.	position of methoxy	reaction time, h	isolation method	purifn method	mp, °C	% yield[a]
4a	2	90	extracted	recrystallized[a] from hexane	88-89[a]	82
4c	4	172	filtered	washed with ether[b]	163-165 dec[b,c]	68
4d	5	72	filtered	washed with H_2O[a]	183-185.5 dec[b,d]	94
4e	6	94	extracted	recrystallized from i-PrOH[b]	169-170 dec[b,e]	87
4f	7	67	filtered	recrystallized from hexane[a]	90.5-91[a]	90

[a] Free base. [b] HCl salt. [c] Literature[18] mp 168-170 °C. [d] Literature[20] mp 184-186 °C. [e] Literature[20] mp 168-169 °C.

Table V



no.	position of hydroxy	reaction time, h	isolation method	purifn method	mp, °C	% yield[a]
1a	2	4	extract	col chromatography[b]	128-130[a]	34
1c	4	1	filtered	col chromatography[c]	172-174 dec[d]	50
1d	5	5	extract	precipitated from *i*-PrOH-ether	183-185 dec[a]	25
1e	6	15	extract	recrystallized from *i*-PrOH-H_2O[b]	174.5-176 dec[e,f]	57
1f	7	15	filtered	recrystallized from benzene[b]	210-211 dec[a]	54

[a] HCl salt. [b] Free base chromatographed on silica gel; eluted with benzene-acetone (1:1). [c] HCl salt chromatographed on a Avicel F cellulose; eluted with $CHCl_3$-MeOH (7:3) and then recrystallized from *i*-PrOH-ether. [d] Literature[18] mp 176-178 °C. [e] Free base. [f] Literature[20] mp 178-180 °C.

Because of purification difficulties, **10** was used for the subsequent reaction in the semipure form. A sample was purified by column chromatography on silica gel eluting with 40% benzene in CCl_4, mp 46–47 °C (lit.[23] 48–50 °C).

1-Chloro-4-(allyloxy)-2-naphthol (11). Sodium metal (9.0 g, 391 mmol) was added piecewise to 220 mL of allyl alcohol at 10–20 °C. After the solution was cooled to −10 °C, **10** (36.7 g) dissolved in 50 mL of dry dioxane was added over a period of 40 min. The reaction mixture was maintained at −10 °C for 2 h and then 18 mL of HOAc (314 mmol) was added. The dioxane and excess allyl alcohol were removed in vacuo, and the residue was dissolved in 300 mL of $CHCl_3$ and filtered. The filtrate was washed with 3 × 100 mL of saturated $NaHCO_3$, 3 × 100 mL of H_2O, and 1 × 100 mL of saturated NaCl, then dried ($MgSO_4$) and filtered, and the solvent was removed to yield 22.12 g of **11** as a brown tar. The product was dissolved in benzene and chromatographed on an activity II alumina column eluting with benzene. Removal of the solvent gave 8.65 g of **11**. One recrystallization (hexane, 18 mL/g) gave 4.9 g, mp 88–90 °C dec. For analysis, **11** was recrystallized twice from hexanes (10 mL/g): mp 90–91.5 °C; NMR ($CDCl_3$) δ 4.65 (m, 2, OCH_2), 5.28 (m, 1, vinylic), 5.51 (m, 1, vinylic), 6.2 (m, 1, vinylic), 6.60 (s, 1, aromatic, H-3), 7.4 (m, 2, aromatic H-6 and H-7), 8.1 (m, 2, aromatic, H-5 and H-8); MS ($SiMe_3$ derivative), *m/z* 306 (M^+), 265 (M − $CH_2CH{=}CH_2$). Anal. ($C_{13}H_{11}ClO_2$) C, H, Cl.

1-(Allyloxy)-3-acetoxy-4-chloronaphthalene (13). Compound **11** (5.44 g, 23.3 mmol) was dissolved in Ac_2O (16 mL, 17.3 g, 170 mmol) and 180 mg of 4-(*N,N*-dimethylamino)pyridine was added. After the mixture was stirred at 30 °C for 1.5 h, 100 mL of H_2O was added and stirring was continued for another 1.5 h. The resulting solid was filtered, washed with H_2O, and dried to yield 5.53 g of tan solid. Crystallization from hexanes (5.5 mL/g) gave 5.38 g of **13** as a pale yellow solid, mp 61–62 °C. For analysis, the product was recrystallized twice from hexanes: mp 62–62.5 °C; NMR ($CDCl_3$) δ 2.35 (s, 3, $COCH_3$), 4.55 (m, 2, OCH_2), 5.25 (m, 1, vinylic), 5.48 (m, 1, vinylic), 6.1 (m, 1, vinylic), 6.58 (s, 1, aromatic, H-2), 7.5 (m, 2, aromatic, H-6 and H-7), 8.3 (m, 2, aromatic, H-5 and H-8); MS, *m/z* 276 (M^+), 234 (M − CH_2CO), 43 ($COCH_3^+$). Anal. ($C_{15}H_{13}ClO_3$) C, H, Cl.

1′-(2,3-Epoxypropoxy)-3′-acetoxy-4′-chloronaphthalene (14). In a flask flushed with N_2 were placed **13** (2.50 g, 9.03 mmol) and 170 mL of dioxane–H_2O (12:1). To this solution was added I_2 (3.18 g, 12.5 mmol), followed by Ag_2O (2.92 g, 12.6 mmol). The mixture was stirred at 30 °C for 24 h protected from light. Additional I_2 (1.6 g, 6.3 mmol) and Ag_2O (2.92 g, 12.6 mmol) were added, and stirring was continued for 24 h. A final portion of Ag_2O (2.92 g, 12.6 mmol) was added and stirring continued for 24 h.

The solvents were removed in vacuo, and the residue was dissolved in $CHCl_3$ and filtered. The filtrate was evaporated with reduced pressure, and the residue was redissolved in $CHCl_3$, chromatographed on a short column of silica gel, and eluted with $CHCl_3$ to give 2.17 g (82%) of **14** as a white solid: mp 83.5–84.5 °C; NMR ($CDCl_3$) δ 2.35 (s, 3, $COCH_3$), 2.8 (m, 2, $CHCH_2$), 3.4 (m, 1, OCH_2CH), 4.2 (m, 2, OCH_2), 6.61 (s, 1, aromatic, H-2), 7.6 (m, 2, aromatic, H-6 and H-7), 8.2 (m, 2, aromatic, H-5 and H-8); MS, *m/z* 292 (M^+), 250 (M − CH_2O), 194 [M − CH_2CO − $CH_2CH(O)CH_2$ + H], 43 ($COCH_3^+$). Anal. ($C_{15}H_{13}ClO_4$) C, H, Cl.

3′-Hydroxy-4′-chloropropranolol (15). Compound **14** (1.98 g, 6.76 mmol) was stirred at ambient temperature for 26 h in isopropylamine (18 mL, 271 mmol). Excess amine was removed with reduced pressure, and the residue, a red orange tar, was dissolved in 20 mL of 1 N HCl, washed with 8 × 20 mL of ether, and then basified to pH of 9.6 with K_2CO_3. The cream-colored solid was filtered, washed with H_2O, and dried to give 1.83 g. Purification was effected by recrystallization from MeOH (136 mL/g) to yield 1.48 g (71%) of **15** as a white solid: mp >190 °C dec; NMR (Me_2SO-d_6) δ 1.02 [d, *J* = 6 Hz, 6, $CH(CH_3)_2$], 2.8 (m, 3, CH_2NCH), 4.05 (m, 3, OCH_2CH), 4.65 (br, s, 3, OH, NH), 6.78 (s, 1, aromatic, H-2), 7.4 (m, 2, aromatic, H-6 and H-7), 7.98 and 8.18 (m, 2, aromatic, H-5 and H-8); MS [$(SiMe_3)_2$ derivative], *m/z* 453 (M^+), 266 [M − $CH_2CHOSiMe_3CH_2NHCH(CH_3)_2$], 72 [$CH{=}NCH(CH_3)_2^+$]. Anal. ($C_{16}H_{20}ClNO_3$) C, H, N, Cl.

3′-Hydroxypropranolol (1b) Hydrochloride. To a suspension of **15** (620 mg, 2 mmol), 500 mg of 5% Pd/C, and Et_3N (8 mL, 5.82 g, 5.75 mmol) was added HCO_2H (1.6 mL, 1.95 g, 42.4 mmol), and the mixture was heated under N_2 at 60 °C for 5 h. After 1 h, 5% Pd/C (300 mg), Et_3N (8 mL), and HCO_2H (1.6 mL) were added, and additional Et_3N (8 mL) and HCO_2H (1.6 mL) were added at 1.5-h intervals. The excess Et_3N was removed in a stream of N_2, and the residue was extracted with 20 mL of MeOH, filtered, and washed with MeOH. After removal of MeOH with reduced pressure, the pH was adjusted to 9.6 with saturated K_2CO_3 solution. The aqueous insoluble material was extracted with 4 × 50 mL of EtOAc, the combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was removed to yield a tan glass. The glass was dissolved in 25 mL of 1 N HCl, washed with 3 × 25 mL of ether, and lyophilized. The salt was suspended in 5 mL of H_2O and the pH was adjusted to 9.6 with K_2CO_3, yielding an insoluble tar. After the H_2O was decanted, the tar was dried in vacuo to yield 440 mg of a tan glass. The product (390 mg) **14** was dissolved in 1 N HCl and lyophilized to yield 401 mg of solid. Pooled material from another reaction (550 mg) was chromatographed on silica eluting with isopropyl alcohol to give 336 mg of a gray glass. Solidification was effected by suspension in 3 mL of acetonitrile and 100 mL of $CHCl_3$ was added to yield 273 mg of **1b**·HCl as a tan solid: mp >140 °C dec; NMR (Me_2SO-d_6) δ 1.33 [d, *J* = 6 Hz, 6, $CH(CH_3)_2$], 3.3 [m, 7, OH, NH_2, $CH(CH_3)_2$, CH_2N], 4.3 (m, 3, OCH_2CHOH), 6.63 and 6.80 (d, *J* = 2 Hz, 2, aromatic, H-2 and H-4), 7.5 (m, 3, aromatic, H-5, H-6, and H-7), 8.17 (m, 1, aromatic, H-8); MS [$(SiMe_3)_2$ derivative], *m/z* 419 (M^+), 232 [M − $CH_2CHOSiMe_3CH_2NHCH$ − $(CH_3)_2$], 72 [$CH{=}NCH(CH_3)_2^+$]; UV (pH 7.4 buffer) λ_{max} 228 nm (ε 54800), 281 (3300), 291 (3200), 320 (1200), 330 (1300). Because of the instability of the HCl salt, the analysis was obtained on the free base. Anal. ($C_{16}H_{21}NO_3 \cdot 0.75H_2O$) C, H, N.

1,8-Dihydroxynaphthalene (17) was prepared in 35% yield from 8-hydroxy-1-naphthalenesulfonic acid (**16**) according to the procedure of Lurie,[17] mp 141.5–142 °C (lit.[17] 142–143 °C).

8′-Hydroxypropranolol (1g) Hydrochloride. 1,8-Dihydroxynaphthalene (**17**; 800 mg, 5 mmol) was dissolved in 2.3 mL of deoxygenated aqueous 2.2 N KOH and epichlorohydrin (0.5 mL, 590 mg, 6.38 mmol) was added. The solution was refluxed for 20 min during which time an oil formed. The reaction mixture

was cooled to room temperature and extracted with 3 × 5 mL of ether. The combined extracts were evaporated, the residue was dissolved in $CHCl_3$, dried ($MgSO_4$), and filtered, and the solvent was removed to yield 1.20 g of amber oil. This product, which contained >95% of epoxide 18, was aminated at room temperature in isopropylamine (10 mL, 8.9 g, 158 mmol) for 6 days. The excess isopropylamine was removed with reduced pressure, and the residue was dissolved in 12 mL of 1 N HCl. The acidic solution was washed with 6 × 20 mL of ether and then basified to a pH of 9.6 with K_2CO_3. The oil was extracted with EtOAc and dried ($MgSO_4$), and the solvents were removed with reduced pressure. The residue was dissolved in ether and filtered, and the ether was removed with reduced pressure to yield 831 mg of amber oil. The product was purified by silica gel column chromatography, eluting with 15% MeOH in ether to give 510 mg of 8′-hydroxypropranolol as a golden oil. The free base was dissolved in 8 mL of 1 N HCl and lyophilized, and the resulting solid was triturated with 10 mL of $CHCl_3$ to yield 495 mg (31.8%) of **1g**·HCl as a tan solid: mp 183–185 °C; NMR (Me_2SO-d_6) δ 1.32 [d, J = 7 Hz, 6, $CH(CH_3)_2$], 3.2 [m, 7, OH, NH_2, $CH(CH_3)_2$, CH_2N], 4.35 (m, 3, OCH_2, CHOH), 6.7–7.7 (m, 6, aromatic); MS [$(SiMe_3)_2$ derivative], m/z 419 (M^+), 232 [$M - CH_2CHOSiMe_3CH_2NHCH(CH_3)_2$], 216 [$M - OCH_2 - CHOSiMe_3CH_2NCH(CH_3)_2$], 72 [$CH_2{=}NCH(CH_3)_2^+$]; UV (pH 7.4 buffer) λ_{max} 224 nm (ε 56 200), 298 (8300), 314 (7300), 328 (7300). Anal. ($C_{16}H_{21}NO_3$·HCl) C, H, N, Cl.

Pharmacology Methods. β-Receptor Antagonism. The methods used were similar to those reported by others.[28] Mongrel dogs (8–15 kg) of either sex were anesthetized with sodium pentobarbital (30 mg/kg, iv). Through a midcervical incision a cannula was placed in the jugular vein for intravenous (iv) injections, a cannula was inserted in the carotid artery and attached to a Statham pressure transducer for recording arterial pressure, a bilateral vagotomy was performed, the trachea was cannulated, and the dogs were artificially ventilated at 15 mL/kg and 16/min. The right femoral artery was isolated and a Biotronics Laboratories electromagnetic flow probe was placed around the artery. A small branch of the femoral artery was cannulated in a retrograde manner to permit direct intraarterial (ia) injections to be made into the femoral artery. The chest was opened by a midsternal incision, the pericardium was cut to expose the right ventricle, and a Walton–Brodie strain gauge was arch sutured to the ventricle. The arch was stretched to approximately the peak of the length–tension curve. Arterial pressure, myocardial contractile force, heart rate, electrocardiogram, and femoral artery flow were recorded on a Grass Model 7 polygraph.

Initially, dose–response curves to isoproterenol (iv: positive inotropic and positive chronotropic effects; ia: vasodilatation) were generated. Shifts in these curves were determined by repeating the isoproterenol dose–response curves after cumulative doses of 10, 100, and 1000 μg/kg of propranolol or one of the hydroxypropranolol derivatives as the hydrochloride salts. Shifts in the isoproterenol curves were used to calculate apparent pA_2 values,[28,29] an index of receptor antagonism. Potency as β-receptor antagonists of each hydroxypropranolol relative to propranolol was calculated as a ratio of the doses (antilog of $-pA_2$) needed to produce twofold shifts in isoproterenol dose–response curves. Each dog was used to test only one compound and each compound was tested in four dogs.

Vasodilatation. When propranolol is injected directly into the femoral artery it produces vasodilatation.[27] This effect has been shown to be unrelated to the β-receptor blocking effects of propranolol. This property was used as an index to compare the non-β-receptor mediated effects of the hydroxypropranolol compounds with propranolol. For these experiments, mongrel dogs were anesthetized and cannulated as described below. The vascularly isolated pump-perfused hindlimb was used as described by others.[30] Blood flow was kept constant throughout the experiment, and changes in vascular resistance were measured as changes in perfusion pressure. Bolus ia injections of 1 and **1a–g** were made directly into the perfusion system. Dose–response curves were generated to all eight compounds in four dogs. In each dog, lowest doses were injected first, followed by the next highest dose. At each dose level the order of injection of the various compounds was randomized.

Drug Administration. All compounds were weighed for use each day, and the drugs were dissolved in isotonic saline and injected into the dog in small volumes.

Statistics. Data are presented as the mean plus or minus the standard error of the mean for four dogs. Differences in means were analyzed by one-way analysis of variance and Duncan's multiple range test.[31]

1-Octanol/pH 7.4 Phosphate Buffer Distribution Coefficients. Compounds **1a–g** were dissolved in 0.16 M, pH 7.4, phosphate buffer saturated with 1-octanol to a concentration of 10^{-4} M. Ten milliliter volumes of these solutions were shaken for 15 min with equal volumes of 1-octanol, which had previously been saturated with buffer solution. After centrifugation of these solutions at 2600 rpm for 10 min, the absorbance of both phases was measured on a Zeiss spectrophotometer at a suitable wavelength between 278 and 307 nm predetermined on a Cary 15 scanning spectrophotometer. The distribution coefficients were determined in triplicate as the ratios between the absorbance of the 1-octanol phase and the pH 7.4 phosphate buffer phase.

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