into an ice mixture of concentrated HCl to give a solid (mp 173–175 °C) which was recrystallized from ethylene glycol monomethyl ether. There was obtained 90 g of a brown solid, mp 213–214 °C (lit.[3] mp 213–214 °C) (yield 68%).

4-Alkylthiotetrachlorobenzonitriles 24. To a solution of 8.3 g (0.36 g/atom) of sodium metal in 540 mL of dry methanol was added 98 g (0.36 mol) of 4-mercapto-2,3,5,6-tetrachlorobenzonitrile. The resulting dark amber solution was heated at reflux for 3 h. Methanol was removed by distillation with simultaneous addition of toluene from an addition funnel so as to maintain a nearly constant volume. The thick slurry was cooled and filtered, and the filter cake was washed thoroughly with petroleum ether to yield 91 g of pale orange colored solids, mp >360 °C. This product was the sodium 4-cyanotetrachlorophenylmercaptide. The mercaptide was dissolved in 1,2-dimethoxyethane and stirred at room temperature as 2 equiv of the appropriate alkyl halide were added. The reaction mixture was stirred for 2 h, then heated to 60 °C for 1 h, cooled, and concentrated to afford a solid residue which was recrystallized from hot hexane to yield the desired sulfide, **24**.

4-Alkylsulfonyltetrachlorobenzonitriles 25a–j. A mixture of the alkylthiobenzonitrile **24** and acetic acid was treated with 30% aqueous H_2O_2 and refluxed at 100 °C for 2 h. The cooled mixture was poured over ice to form a solid which was recrystallized from isopropyl alcohol, affording analytically pure product.

2-Aminotrifluoroterephthalonitriles 28a–g. To a stirring solution of tetrafluoroterephthalonitrile[13] in acetone was added an aqueous solution of the appropriate amine. The mixture was heated to 55 °C for 4 h. On cooling over ice, a solid formed. It was recrystallized from methanol–H_2O to afford analytically pure product.

Carrageenan-Induced Pedal Edema Assay.[18] Male rats (Long Evans strain) weighing between 130 and 200 g are used in this assay. Five rats each were used in the treatment groups and in the known standard control, whereas ten rats were used in the control edema group. Unless otherwise indicated, phenylbutazone was administered orally at 100 mg/kg to the standard control group. The edema control group was administered the vehicle which consisted of 0.25% methylcellulose solution. All of the rats were fasted for at least 15 h prior to the test. Water was available ad libitum. All of the experimental drugs were given orally and were dissolved or suspended in 0.25% methylcellulose solution. One hour after administration of the test compound, 0.05 mL of a 1% sterile solution of carrageenan was injected into the plantar tissues of the left hind paw of each rat. Three hours after carrageenan administration, the paw volumes of injected paws were measured by means of a water displacement apparatus. The apparatus used is a modification of that described by Adamkiewicz.[26] The amount of edema was calculated and the percent reduction of edema from control values was determined. The mean volume of edema, based on 50 determinations, was 1.25 cm^3 with a standard deviation of 0.226 cm^3. This represents the control value. A reduction on edema greater than 20% of the control value was considered significant. Based on 46 determinations, phenylbutazone produced a mean inhibition of edema of 43.8% with a standard deviation of 13.4%.

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Nondepressant β-Adrenergic Blocking Agents. 1. Substituted 3-Amino-1-(5,6,7,8-tetrahydro-1-naphthoxy)-2-propanols

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A series of 3-amino-1-(5,6,7,8-tetrahydronaphthoxy)-2-propanols was synthesized and investigated for β-adrenergic blocking activity and direct myocardial depressant action. The *cis*- and *trans*-diols **12–15** were found to retain the β-blocking potency of propranolol but to lack its myocardial depressant action. Compound **15** (nadolol) is currently undergoing extensive clinical evaluation as a potential antianginal, antiarrhythmic, and antihypertensive agent.

The clinical utility of propranolol in the treatment of angina pectoris,[1] hypertension,[2,3] and certain arrhythmias[4,5] is well documented. In addition to its β-blocking properties, however, propranolol has exhibited a direct myocardial depressant action,[6] which can precipitate acute congestive heart failure in patients with impaired left ventricular function.[7,8]

Prompted by the discovery of practolol,[9] attempts[10] to

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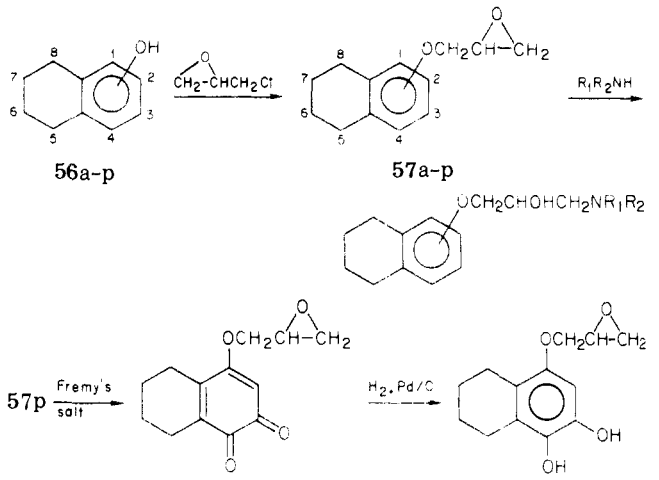
Scheme I



	substituents	position of side chain
a	unsubstituted	1
b	$\Delta^{6,7}$	1
c	6,7-epoxy	1
d	6-OH	1
e	7-OH	1
f	*trans*-6,7-$(OH)_2$	1
g	*cis*-6,7-$(OH)_2$	1
h	*trans*-5-OMe-6-OH	1
i	*cis*-7-OH-8-OMe	1
j	*trans*-5,6-$(OH)_2$	1
k	*cis*-6,7-$(OH)_2$, acetonide	1
l	*cis*-6,7-$(OMe)_2$	1
m	*cis*-6,7-$(OH)_2$	2
n	*trans*-6,7-$(OH)_2$	2
o	*cis*-4,6,7-$(OH)_3$, acetonide	1
p	4-OH	1
q	3,4-$(OH)_2$	1

obtain substances more potent or more selective in action than propranolol have in recent years concentrated on the development of cardioselective β blockers, an approach which has met with limited success with regard to substantially reducing direct myocardial depression.

Herein are described the synthesis and biological activity of a new series of β-adrenergic blocking agents which ultimately led to *cis*-5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-2,3-naphthalenediol [**15**, nadolol (USAN approved name), Table I]. This compound retains the β-blocking potency of propranolol, virtually lacks myocardial depressant action, and possesses antiarrhythmic activity. In addition, it lacks membrane-stabilizing action and intrinsic sympathomimetic activity and does not demonstrate selectivity for either β_1 or β_2 receptors.[11,12] In rats, dogs, and monkeys this compound is not metabolized extensively.[13,14] Nadolol is currently undergoing extensive clinical evaluation as a potential antianginal, antiarrhythmic, and antihypertensive agent.

Chemistry (Tables I–III). 1. General Route. The majority of the compounds listed in Tables I–III were synthesized via the general route illustrated in Scheme I.

(a) Phenolic Precursors 56. Since most of the phenolic precursors **56** had not previously been reported in the literature, methods for their synthesis were developed (see the Experimental Section).

Phenol **56e** was initially prepared from 7-methoxy-1-naphthol[15] by adaptation of the previously described sequence employed in the conversion of 6-methoxy-1-naphthol to 6-hydroxy-5,6,7,8-tetrahydro-1-naphthol (**56d**).[16] Alternatively, and more conveniently, an easily separable 1:1 mixture of **56d** and **56e** was prepared by hydroboration–oxidation of 5,8-dihydro-1-naphthol.[17]

The *cis*-6,7-diols **56g**, **56m**, and **56o** were prepared from 5,8-dihydro-1-naphthol,[17] 5,8-dihydro-2-naphthol,[18] and 1,4-dihydroxy-5,8-dihydronaphthalene,[19] respectively, via sequences involving Woodward's modification of the Prevost reaction as the key cis-hydroxylation step.[20] The *trans*-6,7-diols **56f** and **56n** were likewise prepared from the corresponding known olefins via solvolysis of intermediate epoxides. Phenols **56k** and **56l** were prepared from **56g** via standard methods.

Phenols **56h–j** were prepared along the lines described above via a sequence involving adaptation of the reported base-catalyzed isomerization of 5,8-dihydro-1-naphthol to a mixture of 5,6- and 7,8-dihydro-1-naphthols[16] (**61** and **62**).

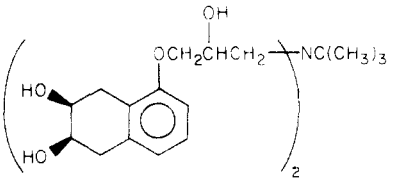
(b) Epoxides 57. The epoxides **57a–p** were prepared by direct alkylation of phenols **56a–p** with epichlorohydrin employing either NaOMe in Me_2SO (method 1) or, more conveniently, NaOH in acetone containing a small amount of water (method 2). In the case of diphenolic precursors **56o** and **56p**, monoalkylation was achieved using 1 equiv of NaOH and a tenfold excess of epichlorohydrin. The desired epoxides **57o** and **57p** were separated from bis-alkylated material by careful base extraction (method 3).

Epoxide **57q** was converted to epoxide **57g** via *o*-quinone **58** using Fremy's salt as the oxidant.

The majority of the epoxides **57** were obtained as mixtures of two racemic diastereomers and were used without extensive purification.

(c) Reaction of Epoxides 57 with Amines. The reaction of epoxides **57** with amines was effected by three general methods (see the Experimental Section, methods 1–3). In the majority of cases, the crude products were 1:1 mixtures of racemic diastereomers and were obtained in analytical purity by recrystallization. The exact diastereomeric compositions of these purified materials were not determined.[21]

The formation of isomeric 2-amino-3-(5,6,7,8-tetrahydronaphthoxy)-1-propanols in these epoxide openings was not observed. This observation is in agreement with epoxide openings in similar systems.[22] In one case, however, a minor component was detected and shown to be identical with the "bis" compound **68** independently synthesized from **57g** and **15**.



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2. Miscellaneous Routes (Tables I–III). Compounds **6** and **26–29** (Table I) were prepared from key epoxide **57c** as depicted in Scheme II. The key to this sequence was the demonstration that the side-chain epoxide could easily be opened in the presence of the 6,7-epoxide.

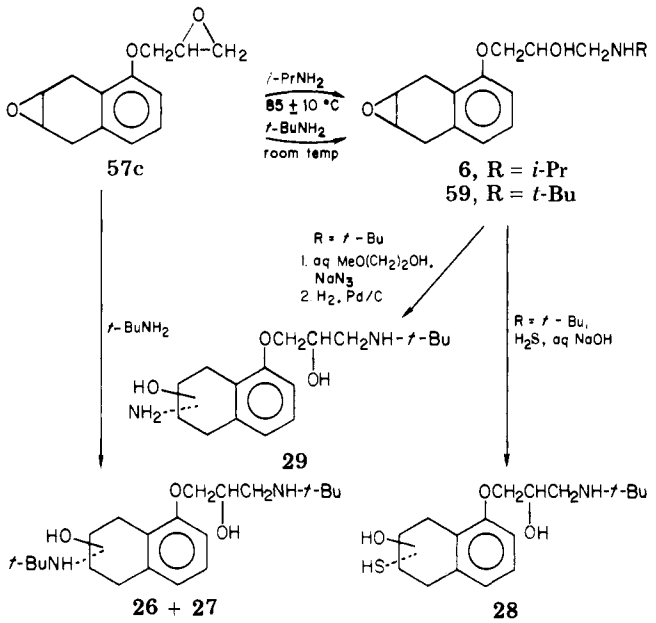
Keto derivative **7** was prepared from **60** via Birch reduction and acid hydrolysis as indicated in Scheme III.

Compound **24** was prepared from **23** via acid hydrolysis. Iodo derivative **25** was prepared via direct iodination of **15** with ICl.

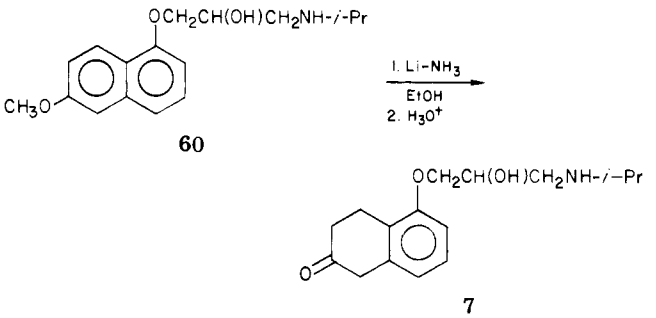
Primary amines **31** and **49** were prepared from epoxides **57g** and **57p**, respectively, via sequences involving epoxide opening with NaN_3 followed by catalytic reduction.

Tertiary amines **40** and **41** were prepared by acylation of **15** followed by metal hydride reduction.

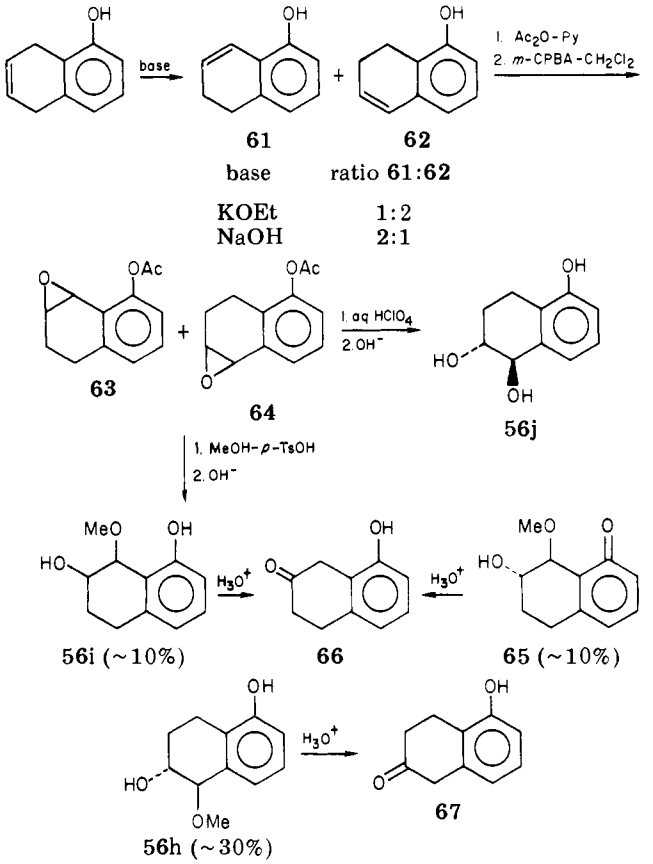
Scheme II



Scheme III



Scheme IV



Preparation of the isomerically substituted tetrahydronaphthols was achieved starting with 5,8-dihydronaphthol as depicted in Scheme IV.

Pharmacology. In vitro β-adrenergic blocking potency was determined in the isoproterenol stimulated guinea pig atrial muscle preparation as previously described.[11] Results are quoted (Tables I–III) as the molar concentration required to give 50% inhibition of the isoproterenol (0.003 × 10^{-3} mg/mL) response (IC_{50}) and are the mean of at least two tissues.

Cardiac depressant activity was assessed in vitro by observing the effects on myocardial contractility of increasing cumulative concentrations of the test compound in the guinea pig atrial muscle preparation as previously described.[11] Results are recorded (Tables I–III) as the highest concentration at which no significant decrease in contractility was observed.

In one case (**25**), β-blocking potency and myocardial depression data were obtained by the same procedure in cat isolated papillary muscle by direct comparison with compound **15**.

Discussion

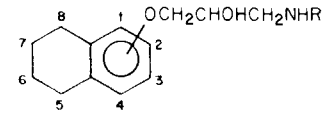
The most commonly employed, and usually most active, amine substituents in β blockers of both the arylethanolamine and aryloxypropanolamine types (e.g., pronethalol and propranolol, respectively) are small branched alkyl groups. Our study of the effects of alicyclic ring substitution in a series of 3-amino-1-(5,6,7,8-tetrahydronaphthoxy)-2-propanols was therefore initiated using amines of this type. The compounds listed in Table I illustrate the effect of alicyclic ring oxygenation in this series on the activities of β blockade and myocardial depression. As is evident, only the *cis*- and *trans*-6,7-diols **12**–**15** combine the β-blocking potency of propranolol with a lack of myocardial depression. Unsubstituted, unsaturated, epoxy, keto, and monohydroxy derivatives and hydroxy ethers are potent β blockers, but all are depressant. The depression observed with the *trans*-5,6-diol **18** is less than that observed with propranolol but is greater than that observed with its regioisomer **13**. Interestingly, ether derivatives (**19** and **20**) of **15** are also depressant. Compounds **21** and **22** dramatically illustrate that potent β-blocking activity is restricted to the 1-naphthoxy-derived system.

The effects of compound **24** on myocardial contractility were somewhat anomalous in that a constant 10% decrease was observed at 0.31 × 10^{-3}–0.31 mg/mL while at 1.0 mg/mL, no decrease was observed; its corresponding acetonide **23** gave unexceptional results. The β-blocking potency of the 4-iodo derivative **25** was equal to that of **15** (cat isolated papillary muscle) but produced a significant decrease in contractile force above 0.31 mg/mL.

Compounds **26**–**29** represent a somewhat limited attempt to determine the effect of replacing one of the hydroxyl groups of the 6,7-diol moiety with other functional groups. Replacement with a primary or secondary amine (**26**, **27**, and **29**) leads to both a decrease in β-blocking activity and marked depression at 0.31–1.0 mg/mL.

The compounds in Table II illustrate the effect of amine variation in the nondepressant *cis*-6,7-diol system of **14** and **15**. Interestingly, the parent primary amine **30** is not without β-blocking activity, an observation which has also been made in the propranolol series.[22] As anticipated, simple tertiary amines are substantially less potent as β blockers than simple secondary amines. As is evident,

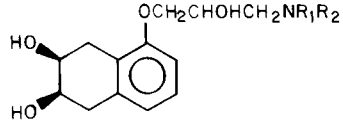
Table I. Substituted 3-Amino-1-(5,6,7,8-tetrahydronaphthoxy)-2-propanols



no.	substituents	R	position of side chain	yield,[a] %	methods of prepn[b,c]	mp, °C	crystn solvent	formula	analyses	guinea pig atrial muscle: IC_{50},[d] (mg/mL) × 10^3	guinea pig atrial muscle: max nondepressant dose,[e] (mg/mL) × 10^3
1	propanolol	*i*-Pr	1							0.01	0.31
2	5-keto (bunolol)	*t*-Bu	1							0.006	1.0
3	none	*i*-Pr	1	45	$G_{1,1}$	83–84	Et_2O	$C_{16}H_{25}NO_2$	C, H, N	0.01	1.0
4	$\Delta^{6,7}$	*t*-Bu	1	80	$G_{1,1}$	60–64	petr ether	$C_{17}H_{25}NO_2$	C, H, N	0.0013[f]	0.3
5	$\Delta^{6,7}$	*i*-Pr	1	75	$G_{1,1}$	85–88	Et_2O	$C_{16}H_{23}NO_2$	C, H, N	0.001	1.0
6	6,7-epoxy	*i*-Pr	1	42[g]	*b*	115–117	Et_2O	$C_{16}H_{23}NO_3$	C, H, N	0.012	31
7	6-keto	*i*-Pr	1	39[h]	*b*	194.5–196	MeOH	$C_{16}H_{23}NO_3$	C, H, N	0.006	3.1 (2)
8	6-OH	*i*-Pr	1	32	$G_{1,1}$	163–164.5	EtOH	$C_{16}H_{25}NO_3 \cdot C_2H_2O_4$	C, H, N	0.002	31
9	6-OH	*t*-Bu	1	66	$G_{1,1}$	139–148	MeCN	$C_{17}H_{27}NO_3$	C, H, N	0.001 (1)	10
10	7-OH	*i*-Pr	1	46	$G_{1,1}$	115–116	C_6H_6	$C_{16}H_{25}NO_3$	C, H, N	0.005	3.1 (2)
11	7-OH	*t*-Bu	1	32	$G_{1,1}$	110–114	MeCN	$C_{17}H_{27}NO_3$	C, H, N	0.0025	1.0
12	*trans*-6,7-$(OH)_2$	*i*-Pr	1	49	$G_{1,1}$	112–127	C_6H_6	$C_{16}H_{25}NO_4$	C, H, N	0.05	>1000
13	*trans*-6,7-$(OH)_2$	*t*-Bu	1	37	$G_{1,1}$	110–129.5	MeCN	$C_{17}H_{27}NO_4$	C, H, N	0.015	>1000
14	*cis*-6,7-$(OH)_2$	*i*-Pr	1	25	$G_{1,1}$	112–120.5	C_6H_6	$C_{16}H_{25}NO_4$	C, H, N	0.1	>1000
15	*cis*-6,7-$(OH)_2$	*t*-Bu	1	74	$G_{1,1}$	124–136	C_6H_6	$C_{17}H_{27}NO_4$	C, H, N	0.03	>1000
16	*trans*-5-OMe-6-OH	*i*-Pr	1	35	$G_{1,1}$	168–169.5	EtOH	$C_{17}H_{27}NO_4 \cdot C_2H_2O_4$	C, H, N	0.05	31
17	*cis*-7-OH-8-OMe	*i*-Pr	1	34	$G_{1,1}$	142–144	EtOH	$C_{17}H_{27}NO_4 \cdot C_2H_2O_4$	C, H, N	0.8 (1)	10
18	*trans*-5,6-$(OH)_2$	*t*-Bu	1	33	$G_{1,1}$	138–169	MeCN	$C_{17}H_{27}NO_4$	C, H, N	0.02	310
19	*cis*-6,7-$(OH)_2$, acetonide	*t*-Bu	1	16	$G_{1,1}$	85–88	Et_2O–C_5H_{12}	$C_{20}H_{31}NO_4$	C, H, N	0.04	3.1
20	*cis*-6,7-$(OMe)_2$	*t*-Bu	1	34	$G_{1,1}$	168–175	*n*-PrOH–Et_2O	$C_{19}H_{31}NO_4 \cdot HCl$	C, H, N, Cl	0.051[f]	100
21	*cis*-6,7-$(OH)_2$	*t*-Bu	2	20	$G_{1,1}$	106–129	MeCN	$C_{17}H_{27}NO_4$	C, H, N	10.0	>1000
22	*trans*-6,7-$(OH)_2$	*t*-Bu	2	37	$G_{1,1}$	138–143	MeCN	$C_{17}H_{27}NO_4$	C, H, N	6	100
23	*cis*-4,6,7-$(OH)_3$, acetonide	*t*-Bu	1	20	$G_{3,3}$	153–161	EtOAc	$C_{20}H_{31}NO_5$	C, H, N	0.3	100
24	*cis*-4,6,7-$(OH)_3$	*t*-Bu	1	38[i]	*b*	178–185	*i*-PrOH	$C_{17}H_{27}NO_5 \cdot HCl$	C, H, N, Cl	0.086	*j*
25	*cis*-6,7-$(OH)_2$-4-I	*t*-Bu	1	45[k]	*b*	140	$CHCl_3$	$C_{17}H_{26}NO_4I$	C, H, N, I	*l*	*l*
26	*trans*-6(7)-OH-7(6)-*t*-BuNH, isomer A	*t*-Bu	1	8[m]	*b*	147–153	$(i\text{-Pr})_2O$–EtOAc	$C_{21}H_{36}N_2O$	C, H, N	1.3	100
27	*trans*-6(7)-OH-7(6)-*t*-BuNH, isomer B	*t*-Bu	1	4[m]	*b*	125–128	$(i\text{-Pr})_2O$–EtOAc	$C_{21}H_{36}H_2O$	C, H, N	9.0 (5)	>1000 (6)
28	*trans*-6(7)-OH-7(6)-SH, isomer A	*t*-Bu	1	19[m]	*b*	186–190	MeOH–$CHCl_3$	$C_{17}H_{27}NO_3S$	C, H, N, S	0.025	310
29	*trans*-6(7)-OH-7(6)-NH_2, isomer mixture	*t*-Bu	1	28[m]	*b*	125–160	EtOH	$C_{17}H_{28}N_2O_3 \cdot 2HCl \cdot H_2O$	C, H, N, Cl	0.5	>1000

[a] Yield refers to overall yield of purified product from phenols 56, unless otherwise indicated. [b] Refer to the Experimental Section. [c] G – general route (Scheme I); subscripts refer to method of phenol alkylation and method of epoxide opening, respectively. [d] Mean of two tissues except when indicated in parentheses. [e] Mean of three tissues except when indicated in parentheses. [f] Determined in rat portal vein. [g] Calculated from 57c. [h] Calculated from 60. [i] Calculated from 57o. [j] At 0.31 × 10^{-3}–0.31 mg/mL, a constant 10–15% depression was observed. At 1.0 mg/mL, no depression was observed. [k] Calculated from 15. [l] Determined in cat isolated papillary muscle. See text. [m] Calculated from 59.

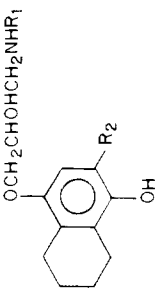
Table II



no.	R_1	R_2	yield,[a] %	method of prepn[b,c]	mp, °C	crystn solvent	formula	analyses	guinea pig atrial muscle: IC_{50},[d] (mg/mL) × 10^3	guinea pig atrial muscle: max nondepressant dose,[e] (mg/mL) × 10^3
30	H	H	28[f]	*b*	180–181	MeOH–MeCN	$C_{13}H_{19}NO_4 \cdot HCl$	C, H, N, Cl	3.8	>1000
31	Me	H	74	2	96–130	MeOH–C_6H_6	$C_{14}H_{21}NO_4$	C, H, N	nd[k]	nd
32	*n*-Bu	H	88	2	107–110	MeCN–C_6H_6	$C_{17}H_{27}NO_4$	C, H, N	0.44[g]	nd
33	$C_6H_5CH_2$–	H	40	2	135–144	MeCN	$C_{20}H_{25}NO_4$	C, H, N	1.0	100
34	$Me_3CCH_2(Me)_2C$–	H	50	2	127–137	MeCN	$C_{21}H_{35}NO_4$	C, H, N	0.78[g]	1.0
35	$C_6H_5CH_2CH_2$–	H	81	2	81–87	C_6H_6	$C_{21}H_{27}NO_4$	C, H, N	0.5	100
36	$C_6H_5CH_2(Me)_2C$–	H	35	2	99–115	C_6H_6–C_6H_{14}	$C_{23}H_{31}NO_4$	C, H, N	0.045[g]	3.1 (2)
37	3,4-$(OMe)_2C_6H_3CH_2CH_2$–	H	60	2	107–111.5	MeCN	$C_{23}H_{31}NO_6$	C, H, N	0.07	>1000
38	2-$OEtC_6H_4OCH_2CH_2$–	H	64	2	105–120	C_6H_6	$C_{23}H_{31}NO_6$	C, H, N	0.31	31
39	[2-OMe-4-(H_2C=$CHCH_2$)-C_6H_3]OCH_2CH_2–	H	40	2	112–131.5	MeCN	$C_{25}H_{33}NO_6$	C, H, N	1.5[g]	3.1 (2)
40	*t*-Bu	Me	46[h]	b	116–131	C_6H_6	$C_{18}H_{29}NO_4$	C, H, N	inactive	>1000
41	*t*-Bu	Et	57[h]	b	120–136	MeCN	$C_{19}H_{31}NO_4$	C, H, N	nd	>1000
42	Et	Et	28	2	108–116	C_6H_6	$C_{17}H_{27}NO_4$	C, H, N	31.0	>1000 (2)
43	$C_6H_5CH_2$–	*i*-Pr	37	2	89–106	Et_2O	$C_{23}H_{31}NO_4$	C, H, N	80.0	310
44	($C_6H_5CH_2$)(*t*-Bu)NCH_2CH_2–	H	14	2	91–95	MeCN	$C_{25}H_{36}N_2O_4$	C, H, N	>8[g]	31
45	(2-$OMeC_6H_4$)$N(CH_2CH_2)_2N$		83	2	148.5–149.5	MeCN–EtOH	$C_{24}H_{32}N_2O_5$	C, H, N	0.46[g]	nd
46	(2-C_5H_4N)$N(CH_2CH_2)_2N$		36	2	128–130	MeCN	$C_{22}H_{29}N_3O_4$	C, H, N	inactive	>310
47	*t*-Bu	$(CH_3)_2I$	86		72–82[i]		$C_{19}H_{32}NO_4I$	C, H, N, I	0.63	1000
48	*t*-Bu[j]	H	40		91–100	Et_2O	$C_{18}H_{29}NO_4$	C, H, N	16	31

[a] Yields refer to purified product obtained from epoxide 57g unless otherwise specified. [b] Refer to the Experimental Section. [c] Refers to method employed in opening of epoxide 57g. [d] See footnote *d*, Table I. [e] See footnote *e*, Table I. [f] Calculated from 57k. [g] Determined in rat portal vein. [h] Calculated from 15. [i] Amorphous solid. [j] Compound also bears a CH_3 on C-2 of side chain. [k] nd = not determined.

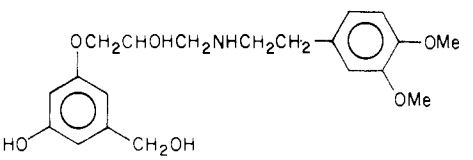
Table III



no.	R_1	R_2	yield,[a] %	method of prepn[b,c]	mp, °C	crystn solvent	formula	analyses	guinea pig atrial muscle: IC_{50},[d] (mg/mL) × 10^3	guinea pig atrial muscle: max nondepressant dose,[e] (mg/mL) × 10^3
49	H	H		*b*	182–186	MeOH–MeCN	$C_{12}H_{19}NO_3 \cdot HCl$	C, H, N, Cl	0.15	31
50	*t*-Bu	H	32	3	127–132	C_6H_6–C_6H_{14}	$C_{17}H_{27}NO_3$	C, H, N	0.01	10 (2)
51	*t*-Bu	OH	49	3	191–194	HOAc–Et_2O	$C_{17}H_{27}NO_4 \cdot C_2H_4O_2$	C, H, N	0.1	10
52	*i*-Pr	H	95	3	119–121	C_6H_6	$C_{16}H_{25}NO_3$	C, H, N	0.004	10
53	*i*-Pr	OH	47	3	89–94[f]	HOAc–Et_2O	$C_{16}H_{25}NO_3 \cdot C_2H_4O_2$	C, H, N	0.11	100
54	3,4-$(OMe)_2C_6H_3CH_2CH_2$	H	7	3	139–141	EtOAc–Et_2O	$C_{23}H_{35}NO_5 \cdot C_2H_4O_2$	C, H, N	0.024	3.1
55	3,4-$(OMe)_2C_6H_3CH_2CH_2$	OH	8	3	130–135	*i*-PrOH–Et_2O	$C_{23}H_{31}NO_6 \cdot HCl$	C, H, N, Cl	5.9	3.1

[a] Yields refer to purified products obtained from epoxides **57p** and **57q**. [b] Refer to the Experimental Section. [c] Refers to method employed in the opening of epoxides **57p** and **57q**. [d] See footnote *d*, Table I. [e] See footnote *e*, Table I. [f] Amorphous solid.

incorporation of amines other than simple alkyl does not favorably effect the activities of β blockade and myocardial depression. The relatively potent β-blocking activity and lack of myocardial depression of the 3,4-dimethoxyphenethylamine **37** are, however, worth mentioning. It is interesting to note that similar incorporation of the 3,4-dimethoxyphenethyl group into the benzophenone and tetralone series of β-adrenergic blockers failed to yield analogues which were either cardioselective or nondepressant.[23] Compound **69**, however, has been reported to



69

be a potent cardioselective β blocker possessing low myocardial depressant action.[23]

The isomeric hydroxy compounds in Table III which lack the 6,7-diol function lend further support to the contention that this functionality prevents myocardial depression.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. All compounds had consistent NMR and IR spectra. Experimental analyses were performed by the Analytical Department of the Squibb Institute for Medical Research. Elements shown analyzed correctly to ±0.4% of calculated values. Each synthetic method is illustrated by a specific example and is accompanied by a list of compounds prepared by this procedure. "Alumina" for chromatography refers to "Woelm neutral or basic for column chromatography" adjusted with water to designated activity. GC was run in a nitrogen steam on a Varian Aerograph 1200. TLC was done in the appropriate solvent using 0.20-mm aluminum oxide neutral type E precoated aluminum sheets with F-254 indicator and visualized under UV light as well as iodine vapors. MCB activated charcoal (Darco) was used as a decolorizing agent.

1. General Route (Tables I–III). (a) Phenolic Precursors 56. 5,6,7,8-Tetrahydro-1,7-naphthalenediol (56e). A solution of 7.85 g (0.045 mol) of 7-methoxy-1-naphthol[15] in 200 mL of NH_3 (liquid) was maintained at −45 to −50 °C while 1.04 g (0.148 g-atom) of Li was added over 20 min. An amount of 7 mL of absolute EtOH was added over 10 min, then the NH_3 was evaporated, and the residue was suspended in 100 mL of H_2O and 50 mL of EtOH. The mixture was cooled, concentrated hydrochloric acid was added until the mixture was acidic to litmus, and then the mixture was stirred for 3 h at room temperature. The mixture was extracted with 3 × 200 mL of $CHCl_3$, which was washed with water and then concentrated in vacuo to give 8.0 g (100%) of 5-hydroxy-1,2-dihydro-3(4*H*)-naphthalenone as a brown solid.

A solution of 8.0 g of the above solid in 200 mL of MeOH was cooled to 0 °C and 2.9 g (0.076 mol) of $NaBH_4$ was added over 3–5 min. After 1 h the mixture was acidified with 10% aqueous HCl, partially evaporated in vacuo to remove the MeOH, and then diluted with H_2O. The solution was extracted with 3 × 150 mL of $CHCl_3$ which was washed with H_2O, dried over $MgSO_4$, filtered, and evaporated in vacuo to give a brown solid. The solid was recrystallized from EtOAc–hexane (Darco) to give 2.7 g of solid, mp 140–150 °C (36.4%). A second recrystallization gave **56e** in two crops of 1.7 (mp 150.5–152 °C) and 0.3 g (mp 149–151 °C).

Hydroboration–Oxidation of 5,8-Dihydro-1-naphthol. 5,6,7,8-Tetrahydro-1,6(7)-naphthalenediol (56d) and 56e. A solution of 35.0 g (0.25 mol) of crude 5,8-dihydro-1-naphthol[17] in 500 mL of THF was hydroborated with 250 mL of 1 N BH_3–THF at 0 °C for 2 h. Water was added cautiously, followed by a solution of 66 g of NaOH in 250 mL of H_2O and 28 mL of 30% H_2O_2. After 1 h at 0 °C the solution was extracted with ether to give 33.6 g of crude product. Chromatography over 700 g of alumina II gave 9.1 g of chromatographically pure **56d** eluted with

1–5% MeOH in $CHCl_3$. Crystallization from 120 mL of 1:1 hexane–EtOAc gave 6.95 g (18%), mp 129–129.5 °C (lit.[16] mp 127–128 °C).

Elution with 5–25% MeOH in $CHCl_3$ gave 8.6 g of chromatographically pure **56e**. Crystallization from 140 mL of 4:1 EtOAc–hexane gave 6.45 g (18%), mp 149–152 °C.

***trans*-5,6,7,8-Tetrahydro-1,6,7-naphthalenetriol (56f).** An amount of 25.0 g (ca. 0.12 mol) of *m*-chloroperbenzoic acid was added over 10 min to an ice-cooled solution of 14.6 g (0.10 mol) of 5,8-dihydro-1-naphthol[17] in 225 mL of EtOAc. After 16 h at ambient temperature the slurry was poured into a cooled, stirred mixture of 300 mL each of ether and 10% aqueous $NaHCO_3$. After 15 min the organic phase was separated, washed with H_2O and saturated aqueous NaCl, and dried. Solvent removal gave an oil which was triturated with two 100-mL portions of boiling hexane. The residue was recrystallized from 150 mL of 1:1 hexane–EtOAc to give 6.6 g (41%) of 5,6,7,8-tetrahydro-6,7-epoxy-1-naphthol, mp 143–146 °C. Two further recrystallizations of a small sample gave the analytical sample, mp 149.5–151 °C. Anal. ($C_{10}H_{10}O_2$) C, H.

A solution of 8.0 g (0.048 mol) of the above in 100 mL of THF was cooled to 0 °C and 20 mL of H_2O and 0.5 mL of 70% perchloric acid were added. After 4 h, a further 1.5 mL of acid was added and the solution stirred for 16 h at ambient temperature and diluted with 100 mL each of ether, 10% aqueous $NaHCO_3$, and saturated aqueous NaCl. The aqueous layer was separated and washed with 150 mL of ether–THF (1:1). The organic phase was washed with saturated aqueous NaCl, dried, and evaporated to give an oil which solidified on trituration with $CHCl_3$. Recrystallization gave, in two crops, 4.85 g of solid which was recrystallized from EtOAc to give 3.84 g (43%), mp 179.5–181.5 °C. Two further recrystallizations of a small sample gave the analytical sample, mp 183–184 °C. Anal. ($C_{10}H_{12}O_3$) C, H.

***cis*-5,6,7,8-Tetrahydro-1,6,7-naphthalenetriol (56g).** A solution of 29.2 g (0.2 mol) of 5,8-dihydro-2-naphthol[17] and 40 mL of acetic anhydride in 100 mL of pyridine was prepared. After 16 h the solvent was removed in vacuo and the residue dissolved in ether, washed with 200 mL of 5% hydrochloric acid, H_2O, 200 mL of 10% aqueous NaOH, and saturated aqueous NaCl, and dried. Solvent removal gave 34.2 g (90.5%) of crude acetate which was dissolved in 900 mL of HOAc and 36 mL of H_2O. An amount of 53.3 g (0.32 mol) of AgOAc was added followed by 40.6 g (0.16 g-atom) of I_2. The slurry was heated with good stirring at 85 ± 10 °C for 3 h under N_2, cooled, and filtered. The filtrate was evaporated in vacuo and the residue dissolved in 250 mL of MeOH and cooled to 0 °C. A solution of 40 g of NaOH in 200 mL of H_2O was added under N_2 and the mixture stirred overnight. The bulk of the MeOH was removed in vacuo whereupon a solid formed. This was filtered, dissolved in 150 mL of H_2O, and acidified with 20 mL of concentrated HCl. Cooling gave a solid which was filtered and pressed dry to give 16.5 g (51%), mp 184.5–187 °C. Recrystallization from absolute EtOH gave the analytical sample, mp 188–188.5 °C. Anal. ($C_{10}H_{12}O_3$) C, H.

3a,9a-*cis*-3a,4,9,9a-Tetrahydro-2,2-dimethyl-2*H*-naphtho[2,3-*d*]-1,3-dioxol-5-ol (56k). A slurry of 90.0 g (0.50 mol) of **56g** in 900 mL of acetone dimethyl ketal was stirred with 0.5 g of *p*-toluenesulfonic acid monohydrate (solution in ca. 15 min). After 2 h the clear solution was diluted with an equal volume of ether and washed with a mixture of 900 mL of saturated aqueous NaCl and 100 mL of saturated aqueous $NaHCO_3$. Drying (Na_2SO_4) and solvent removal gave a solid which was powdered and dried at 50 °C (0.2 mm) to give 112.4 g of **56k** as a tan solid (ca. 100%) essentially homogeneous on TLC [silica gel, hexane–$CHCl_3$ (1:1) eluent].

***cis*-6,7-Dimethoxy-5,6,7,8-tetrahydro-1-naphthol (56l).** A mixture of 10.66 g (0.0485 mol) of **56k** and 2.7 g (0.05 mol) of NaOMe was dissolved in 115 mL of Me_2SO, 50 mL of solvent removed in vacuo, a mixture of 5.64 g (0.048 mol) of benzyl chloride and 30 mL of Me_2SO added, and the mixture stirred at room temperature overnight under N_2.

The solution was poured into a mixture of ether (500 mL), H_2O (1 L), and 10% aqueous NaOH (50 mL). The layers were separated, the aqueous layer was extracted with ether (500 mL), and the combined ether extracts were washed with H_2O and saturated aqueous NaCl, dried, and evaporated in vacuo to give 11.16 g of white solid (72%).

The 11.16 g of solid was dissolved in 100 mL of glacial HOAc, 20 mL of H_2O added, and the mixture heated until a clear solution was obtained. The mixture was stirred at room temperature overnight. The mixture was filtered; the solid was washed with glacial HOAc and ether and dried to give 8.2 g (84.6%) of *cis*-1,2,3,4-tetrahydro-5-benzyloxy-2,3-naphthalenediol as a white solid.

A solution of 8.1 g (0.3 mol) of the above in 80 mL of Me_2SO was cooled to 5 °C under N_2. Methyl iodide (16.8 g, 0.118 mol) was added and then a mineral oil suspension of 1.71 g (0.07 mol) of sodium hydride was added over 10 min. The mixture was stirred for 30 min at 20–22 °C, an additional 6.8 g of methyl iodide and 0.5 g of sodium hydride suspension were added, and the mixture was stirred for 2 h at room temperature. Methanol (20 mL) was cautiously added and the mixture was partitioned between H_2O (500 mL) and ether (200 mL). The aqueous layer was extracted with ether (2 × 200 mL) and the combined ether extracts were washed, dried, and evaporated in vacuo to give 10.2 g of yellow liquid. TLC on alumina and IR spectra indicated a mixture of reactant and product.

The 10.2 g of liquid was dissolved in Me_2SO at room temperature; 22.89 g of methyl iodide was added and then 3.2 g of 57% sodium hydride–mineral oil dispersion. The mixture was stirred for 2 h at room temperature and then worked up as before to give 10.26 g of oil, which by TLC is a mixture of mineral oil and product.

Hydrogenation of the 10.26 g of oil in 100 mL of glacial HOAc with 2 g of 5% Pd/C for 18 h gave only partial debenzylation due apparently to catalyst "poisoning" by the mineral oil. The HOAc solution was filtered and evaporated in vacuo to give an oil which was partitioned between ether and 5% aqueous sodium hydroxide. The basic solution was acidified and extracted with ether to give 1.8 g of the solid phenol. The ether layer was washed with saturated NaCl solution, dried, and evaporated to give 5.95 g of oil, a mixture of reactant and mineral oil. Filtration of this material through alumina II, eluting with hexane–$CHCl_3$ (1:1), gave 3.8 g of starting material. Hydrogenation and workup as before gave 2.18 g of cream-colored solid.

Recrystallization of the 3.98-g (64%) sample of **56l** from hexane–ether gave 3.3 g of solid, mp 122–124 °C, in three crops.

***cis*-1,2,3,4-Tetrahydro-2,3,6-naphthalenetriol (56m).** Following the procedure of Marshall et al.,[18] 25.0 g (0.17 mol) of 2-naphthol afforded 18.9 g of a 3:2 mixture of 5,6,7,8-tetrahydro-2-naphthol and 5,8-dihydro-2-naphthol. This material was used without further purification.

Following the procedure described for the conversion of 5,8-dihydro-1-naphthol to **56g**, 18.9 g of crude 5,8-dihydro-2-naphthol afforded 7.9 g (25% from 2-naphthol) of crude **56m** as a tan solid. Recrystallization from EtOH–EtOAc gave in several crops 4.03 g, mp 193–195.5 °C.

***trans*-1,2,3,4-Tetrahydro-2,3,6-naphthalenetriol (56n).** To a stirred solution of 15.12 g of the acetate ester of crude 5,8-dihydro-2-naphthol (prepared by acylation with acetic anhydride in pyridine) in 160 mL of CH_2Cl_2 at 0–5 °C was added 10.5 g (0.061 mol) of 85% *m*-chloroperbenzoic acid over 10 min. The mixture was stirred overnight at room temperature and then poured into a slurry of 100 g of ice and 50 mL of 10% aqueous NaOH. The layers were separated, the aqueous layer was reextracted with CH_2Cl_2 (2 × 100 mL), and the combined extracts were washed with H_2O, dried, and evaporated in vacuo to give 16 g of yellow liquid.

A solution of the above liquid (16 g) in 120 mL of THF, 50 mL of H_2O, and 1.6 mL of 70% perchloric acid was stirred overnight at room temperature under N_2. A solution of 8.8 g of NaOH in 20 mL of H_2O was added with cooling (<25 °C) and the mixture stirred for 2 h at room temperature. A mixture of 25 mL of concentrated HCl and 30 g of ice was added slowly (<25 °C), with cooling. The solid which formed was collected and dried in vacuo to give 5.7 g of white solid. Recrystallization from EtOAc–MeOH gave 4.41 g (29% from 2-naphthol) of **56n**, mp 241.5–243 °C, in three crops.

Isomerization of 5,8-Dihydro-1-naphthol: 5,6-Dihydro-1-naphthol (61) and 7,8-Dihydro-1-naphthol (62). (a) With KOEt. The isomerization of 5,8-dihydro-1-naphthol with KOEt was accomplished via a slight modification of the procedure of Eastman and Larkin.[16] Thus a mixture of 4.5 g (20.8 mmol) of

Table IV

component (Me_3Si ether)	retention time, min	rel % (from a)	rel % (from b)	m/e
5,6,7,8-tetrahydro-1-naphthol	37.5	40	25	220
5,6-dihydro-1-naphthol	35.0	40	25	218
7,8-dihydro-1-naphthol	37.0	20	50	218

crude phenol and 10.0 g (89.1 mmol) of KO-*t*-Bu in 12 mL of xylene and 3 mL of absolute EtOH was refluxed under N_2 for 16 h. The mixture was poured onto ice, ether was added, the layers were separated, and the organic phase was discarded. The aqueous layer was acidified with 5% aqueous HCl and extracted with ether. The ether extracts were dried and concentrated in vacuo to 4.1 g (91%) of an oil, which was distilled in vacuo to give 2.39 g (53%) of an oil which rapidly solidified. This material analyzed as described in (c).

(b) With NaOH. A mixture of 105.8 g (0.72 mol) of crude 5,8-dihydro-1-naphthol and 480 g of 50% aqueous NaOH was refluxed under N_2 for 2 h, cooled, poured onto 2 kg of ice, and acidified with concentrated HCl. The resulting solid was extracted into ether, the ether extracts were dried and concentrated in vacuo, and the residue was distilled to give 88 g (83%) of a mixture of **61** and **62**, bp 91–95 °C (0.5 mm).

(c) Analysis of Mixtures of Olefins 61 and 62. Both mixtures of olefins **61** and **62** described above in (a) and (b) were converted into their trimethylsilyl ethers with *N,O*-bis(trimethylsilyl)acetamide at room temperature. The mixtures were resolved in a 50-ft Carbowax 20M SCOT GC column held at 160 °C, with the injector at 200 °C and the transfer line at 200 °C at a He pressure of 2 lb. Both samples contained the three components shown in Table IV.

Methanolysis of 63 and 64: *cis*- and *trans*-8-Methoxy-5,6,7,8-tetrahydro-1,7-naphthalenediols (56i and 65) and *trans*-5-Methoxy-5,6,7,8-tetrahydro-1,6-naphthalenediol (56h). (a) 5,6- and 7,8-Epoxy-5,6,7,8-tetrahydro-1-naphthol Acetates (63 and 64). A mixture of olefins **61** and **62** prepared by the method described above in (b) was acetylated following the procedure described in the synthesis of **56g**. A solution of 18.4 g (0.10 mol) of this acetate mixture in 400 mL of CH_2Cl_2 was cooled to 0 °C and 20.0 g (ca. 0.1 mol) of 85% *m*-chloroperbenzoic acid was added with stirring. After 2 h at 0 °C, 100 mL of cold 5% aqueous NaOH was added with good stirring. After 5 min the layers were separated and the organic layer was dried and evaporated to give 19.8 g (ca. 100%) of **63** and **64** as an oil which was used without further purification.

(b) Methanolysis of 63 and 64. The above 19.8 g of epoxide was dissolved in 400 mL of MeOH and stirred overnight with 200 mg of *p*-TsOH. The solution was cooled to 0 °C and 100 mL of 9% aqueous NaOH added. After 2 h at 0 °C the bulk of the MeOH was removed in vacuo and 75 mL of 10% HCl added at 0 °C. Extraction with $CHCl_3$ (5 × 200 mL) gave 19.2 g of oil which showed five major spots on TLC ($CHCl_3$, alumina, I_2). This material was adsorbed onto 150 mL of neutral alumina II, placed on a 550-g column of dry packed alumina II, and eluted (100-mL fractions) with 1400 mL of hexane–$CHCl_3$ (1:1), 700 mL of $CHCl_3$–hexane (2:1), 700 mL of $CHCl_3$–hexane (3:1), 600 mL of $CHCl_3$, and 1500 mL of 5% MeOH in $CHCl_3$.

Fractions 1–6 contained 2.38 g of chromatographically pure 5,6,7,8-tetrahydro-1-naphthol.

Fractions 9–12 contained 0.63 g of a chromatographically pure mixture of olefins **61** and **62**.

Fractions 15–21 contained 1.68 g (10%) of **65** contaminated with **56i**. Recrystallization from EtOAc gave 0.812 g of chromatographically pure **65**, mp 131–135.5 °C.

Fractions 22–28 contained 2.13 g (10%) of **56i** contaminated with **56h**. Recrystallization from EtOAc gave 1.36 g of chromatographically pure **56i**, mp 110.5–113 °C.

Fractions 29–51 contained 8.33 g (30%) of impure **56h**. Recrystallization from EtOAc gave 4.79 g of chromatographically pure **56h**, mp 137.5–139 °C.

Pinacol Rearrangement of 65, 56i, and 56h. A slurry of 0.36 g (1.86 mmol) of **56h** in 5 mL of 10% aqueous H_2SO_4 was refluxed for 2 h and cooled, and the resulting solid was filtered. The solid was taken up in EtOAc, washed with H_2O, dried, and concentrated in vacuo to give 0.285 g of yellow solid. Recrystallization of this material from EtOAc–hexane gave 0.212 g (71%) of solid identical (IR, TLC, and melting point) with an authentic sample of 5-hydroxy-3,4-dihydro-2(1*H*)-naphthalenone (**67**).

Following the method described above, **65** and **56i** were independently converted to the same product, identical (TLC and melting point) with an authentic sample of 8-hydroxy-3,4-dihydro-2(1*H*)-naphthalenone (**66**).

***trans*-1,2,3,4-Tetrahydro-1,2,5-naphthalenetriol (56j).** A solution of 41.3 g (0.20 mol) of a mixture of **63** and **64** (prepared as described above) in 420 mL of THF and 105 mL of H_2O was cooled to 0 °C and 2.4 mL of 70% $HClO_4$ added. After 150 min at 0 °C the solution was partitioned between 600 mL of ether and a mixture of 600 mL of saturated aqueous NaCl and 100 mL of saturated aqueous $NaHCO_3$. The organic layer was separated, dried, and evaporated to give 46.2 g of oily solid. Trituration with 200 mL of boiling ether gave 13.4 g, mp 153–158 °C. Recrystallization from 250 mL of ethyl acetate gave 10.2 g (23%) of chromatographically pure *trans*-1,2,3,4-tetrahydro-1,2,5-naphthalenetriol 5-acetate, mp 161–162.5 °C.

A solution of 13.3 g (0.06 mol) of the above acetate in 500 mL of THF was cooled to 0 °C and 140 mL of 1 N NaOH added under N_2. After 2 h at 0 °C, CO_2 was bubbled through to pH 8, the slurry diluted with 1 L of saturated aqueous NaCl, and the mixture extracted with $CHCl_3$ (3 × 500 mL) to give 9.1 g of solid. Recrystallization from 100 mL of ethyl acetate gave 5.7 g (53%) of **56j**, mp 147.5–149.5 °C.

5,8-Dihydroxy-3a,9a-*cis*-3a,4,9,9a-tetrahydro-2,2-dimethylnaphtho[2,3-*d*]-1,3-dioxole (56o). *cis*-5,6,7,8-Tetrahydro-1,4,6,7-naphthalenetetrol was prepared from 5,8-dihydro-1,4-naphthalenediol[19] by the procedure described in the synthesis of **56g**, with the exception that the product was obtained by extraction with *n*-BuOH. The combined extracts were washed with saturated aqueous NaCl and concentrated to near dryness in vacuo. The resulting product was filtered off and washed well with ether to give tetrol (28%), mp 221–224 °C, which was used without further purification.

Acetonide **56o** was prepared from the above tetrol in 80% yield following the procedure described in the synthesis of **56k**.

(b) Epoxides 57. 2,3-*cis*-1,2,3,4-Tetrahydro-5-(2,3-epoxypropoxy)-2,3-naphthalenediol (57g). Method 1. A solution of 1.20 g (0.03 mol) of sodium methoxide and 5.4 g (0.03 mol) of triol **56g** in 200 mL of MeOH was prepared under N_2. The residue obtained upon solvent removal was stirred overnight with 200 mL of Me_2SO and 4.65 g (0.05 mol) of epichlorohydrin under N_2. The bulk of the solvent was removed at 50 °C (0.1 mm) and the residue dissolved in 500 mL of H_2O. Extraction with $CHCl_3$ (10 × 200 ml) gave 3.46 g of solid which was recrystallized from 150 mL of hexane–EtOAc to give 2.80 g of epoxydiol **57g**, mp 108–111.5 °C.

Method 2. A mixture of 7.26 g (0.04 mol) of triol **56g** in 37.4 mL each of acetone and epichlorohydrin and 4.9 mL of H_2O was heated to reflux under N_2. A solution of 1.6 g (0.04 mol) of NaOH in 9 mL of H_2O was added over 30 min (ca. 1.5 mL every 5 min). The mixture was stirred at reflux for 3.5 h and overnight at room temperature.

The mixture was evaporated in vacuo to give a solid–oil mixture which was partitioned between 100 mL each of H_2O and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ (2 × 100 mL) and the $CHCl_3$ was dried and evaporated in vacuo to give a white solid, 8.75 g (92.8%), mp 72–112 °C.

Method 3. 8-(2,3-Epoxypropoxy)-3a,9a-*cis*-3a,4,9,9a-tetrahydro-2,2-dimethylnaphtho[2,3-*d*]-1,3-dioxol-5-ol (57o). A stirred mixture of 18 g (0.073 mol) of acetonide **56o**, 60 mL of epichlorohydrin (74 g, 0.80 mol), 60 mL of acetone, and 10 mL of H_2O was heated to reflux under N_2. A solution of 3.2 g (0.08 mol) of NaOH in 20 mL of H_2O was then added over 15 min. After the addition was complete, the mixture was refluxed for an additional 45 min.

The reaction mixture was then concentrated in vacuo (care must be exercised to remove all excess epichlorohydrin to avoid further alkylation during base extraction!) and the residue partitioned between H_2O and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$; the combined $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated in vacuo to 28.8 g of a oil.

The above oil was combined with a previously prepared sample (6.1 g, total = 34.9 g), dissolved in ethyl acetate, and thoroughly extracted with *cold* dilute aqueous NaOH.

The combined aqueous base extracts were chilled and acidified with *cold* dilute aqueous HOAc, and the resulting solution was thoroughly extracted with EtOAc. The combined organic extracts were dried and concentrated in vacuo to 11.5 g of oil (43%).

The above oil was taken up in $CHCl_3$ and applied to an alumina column (300 g, activity III, neutral). Fractions 1–3 (250 mL) consisted of nonpolar material. Fractions 3–10 (250 mL) gave 3.1 g of crystalline epoxide **57o**, after combination, concentration in vacuo, and trituration with hexane–isopropyl ether.

(c) Epoxide Openings. Method 1. *cis*-5-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-2,3-naphthalenediol (15). A mixture of 3.0 g (0.013 mol) of epoxydiol **57g** and 22 mL of *tert*-butylamine was heated at 85–95 °C for 15 h in a small Parr bomb. The excess amine was removed in vacuo, the residue triturated with ether, and the resulting solid recrystallized from benzene to give 3.4 g (86%) of **15**, mp 124–136 °C. Anal. ($C_{17}H_{27}NO_4$) C, H, N.

Method 2. 5,5′-[3,3′-(*tert*-Butylnitrilo)bis(2-hydroxy-1,3-propanediyl)dioxy]bis[*cis*-1,2,3,4-tetrahydro-2,3-naphthalenediol] (68). A solution of 2.36 g (0.01 mol) of epoxydiol **57g** and 3.09 g (0.01 mol) of amine **15** in 60 mL of EtOH was refluxed for 50 h under N_2 and the solvent removed in vacuo. Crystallization of the residue from benzene–acetonitrile (5:1) gave 3.3 g of solid in two crops. Recrystallization from 100 mL of acetonitrile gave 2.4 g (40%) of **68**, mp 120–165 °C. Anal. ($C_{30}H_{43}NO_8$) C, H, N.

Method 3. *cis*-4-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-5,6,7,8-tetrahydro-1,6,7-naphthalenetriol Hydrochloride (1:1) (24). A solution of 3.1 g (0.010 mol) of crystalline epoxide **57o** in 50 mL of absolute EtOH, 30 mL of benzene, and 20 mL of *tert*-butylamine was left overnight at room temperature. This solution was then taken to dryness in vacuo to a glass, which was dissolved in 100 mL of 5% hydrochloric acid and left at room temperature for 1 h. This solution was then concentrated in vacuo to a tan foam. This was dissolved in hot 2-propanol, decolorized with Darco, and diluted with ether. The resulting precipitate was subjected to the same treatment to give 1.2 g (38%) of amorphous solid. The amorphous material (1.2 g) was then recrystallized from 2-propanol to give 0.30 g of crystalline solid, mp 178–185 °C. Anal. ($C_{17}H_{27}NO_5$·HCl) C, H, N, Cl.

8-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-3a,9a-*cis*-3a,4,9,9a-tetrahydro-2,2-dimethylnaphtho[2,3-*d*]-1,3-dioxol-5-ol (23). Crude acetal **23** (3.8 g), prepared as described in the synthesis of **24**, was chromatographed on ca. 120 g of activity III basic alumina. Elution with 2–5% MeOH in $CHCl_3$ gave 3.2 g of **23** as a foam. On standing in ether, crystalline material (1.7 g, 50%) was deposited. This was recrystallized from ethyl acetate to give 1.0 g, mp 153–161 °C. Anal. ($C_{20}H_{31}NO_5$) C, H, N.

2. Miscellaneous Methods (Tables I–III). 3,4-Dihydro-5-[2-(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-2(1*H*)-naphthalenone Oxalate Salt (1:1) (7). A solution of 2.99 g (0.01 mol) of **60** in 25 mL each of THF and *t*-BuOH in 200 mL of NH_3(l) was cooled in a −55 to −50 °C bath and 1 in. (ca. 226 mg, ca. 0.03 g-atom) of Li was added. The blue color persisted for 6 min; addition of ca. 70 mg further of Li gave a blue color for 5 min. The NH_3 was evaporated under N_2 and the residue partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extract was dried and evaporated to give 3.16 g of solid which was refluxed for 30 min with 1.0 g (0.011 mol) of oxalic acid in 70 mL of 95% EtOH and allowed to stand overnight. The resulting solid was filtered and recrystallized twice from MeOH to give 1.36 g (39%), mp 194.5–196 °C. Anal. ($C_{18}H_{25}NO_7$) C, H, N.

2,3-Epoxypropyl 6,7-Epoxy-5,6,7,8-tetrahydro-1-naphthyl Ether (57c). To a well-stirred solution of 7.0 g (0.03 mol) of epoxide **57b** in 60 mL of CH_2Cl_2 was added dropwise a solution of 7.1 g (0.03 mol) of 85% *m*-chloroperbenzoic acid in 100 mL of CH_2Cl_2 at such a rate that the temperature was maintained between 25 and 30 °C and the mixture was stirred overnight at room temperature. The precipitate was filtered off; the filtrate was washed with saturated aqueous $NaHCO_3$ and H_2O, dried, and concentrated in vacuo to give 7.2 g (95%) of an oil, which solidified on standing. Recrystallization from ether gave **57c** as colorless needles, mp 85–87 °C. Anal. ($C_{13}H_{14}O_3$) C, H.

2,3-Epoxy-5-[3-(1-methylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydronaphthalene (6). A solution of 4.3 g (0.02 mol) of epoxide **57c** in 34 mL of isopropylamine was heated in a small Parr bomb at 70–80 °C for 10 h. Evaporation of the excess isopropylamine in vacuo yielded 5.3 g of a brown sticky solid. Crystallization from ether–pentane gave 2.0 g (44%) of off-white solid, mp 106–110 °C. A second recrystallization from ether gave 0.60 g of **6** as a white solid, mp 115–117 °C. Anal. ($C_{16}H_{23}NO_3$) C, H, N.

***trans*-3-[(1,1-Dimethylethyl)amino]-5- (or 8-) [3-[(dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-2-naphthalenol, Isomers A and B (26 and 27).** A mixture of 7.5 g (0.034 mol) of epoxide **57c**, 75 mL of *tert*-butylamine, and 2 mL of 2-propanol was charged to a small bomb and heated at 120–140 °C for 5 days. After cooling the mixture was taken to dryness in vacuo. A sample run on thin layer (alumina, developed 5% MeOH in $CHCl_3$, detected iodine) showed that no starting material remained and the product showed two slower moving spots. The material was chromatographed on 470 g of activity III basic alumina. The faster moving material was eluted with $CHCl_3$ (5.9 g, 60%) and was shown by analysis, NMR, and IR to be 1-[(6,7-epoxy-5,6,7,8-tetrahydro-1-naphthyl)oxy]-3-(*tert*-butylamino)-2-propanol (**59**).

The slower moving material was eluted with 2–5% MeOH in $CHCl_3$. On standing in ether 2.1 g (17%) of crystalline material was deposited. Recrystallization from isopropyl ether–ethyl acetate gave isomer mixture A, **26** [crop I, 950 mg (7.6%), mp 147–153 °C. Anal. ($C_{21}H_{36}N_2O_3$) C, H, N], and isomer mixture B, **27** [crop II, 520 mg (4.2%), shrinking at 120 °C, mp 125–128 °C. Anal. ($C_{21}H_{36}N_2O_3$) C, H, N]. The two isomer mixtures had different crystalline form and slightly different IR and NMR spectra but could not be separated on TLC.

1-[(6,7-Epoxy-5,6,7,8-tetrahydro-1-naphthyl)oxy]-3-(*tert*-butylamino)-2-propanol (59). A solution of 10.4 g (0.048 mol) of epoxide **57c** in 60 mL of EtOH and 40 mL of benzene was treated with 20 mL of *tert*-butylamine and left at room temperature. The reaction was monitored by TLC (alumina developed 5% MeOH in $CHCl_3$). At the end of 3 days only a small amount of starting material remained. The mixture was taken to dryness in vacuo leaving 12.6 g of oil. Ether was added and, after standing for several hours in the cold, crystalline **59** (5.8 g, 42%) was harvested.

2,3-*trans*-5- (or 8-) [3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-3-mercapto-2-naphthalenol, Isomer A (28). A well-stirred solution of 1.6 g (0.040 mol) of NaOH in 20 mL of MeOH was saturated with H_2S by bubbling in the gas for 75 min while cooling to −10 to 0 °C. While continuing a slow stream of gas a solution of 5.8 g (0.020 mol) of epoxide **59** in 10 mL of MeOH was added dropwise over a period of 20 min. The gas flow was stopped and after the mixture was stirred an additional hour in the ice bath the mixture was left standing 20 h at room temperature. The mixture was taken to near dryness in vacuo. Water was added to the residue and the pH was adjusted to 8–9 using dilute aqueous HCl. Three $CHCl_3$ extracts were washed with saturated aqueous NaCl and dried, and the solvent was removed in vacuo leaving a tan solid (7.3 g). TLC (5% MeOH in $CHCl_3$, alumina) of this material showed no starting material, two major spots (presumably the two positional isomers), and some slow-moving material. Most of the material was dissolved in hot $CHCl_3$ (some insoluble material removed by filtration). On standing 1.2 g (18.5%) of crystalline material was deposited. TLC showed this to be nearly pure faster moving isomer. This was recrystallized from $CHCl_3$–MeOH to give 400 mg of **28**, shrinking at 180 °C, mp 186–190 °C. Anal. ($C_{17}H_{27}NO_3S$) C, H, N, S.

2,3-*trans*-3-Amino-5- (or 8-) [3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-2-naphthalenol Hydrochloride (1:2) (29). A mixture of 11.3 g (0.039 mol) of epoxide **59**, 10.4 g (0.160 mol) of NaN_3, and 2.3 g (0.043 mol) of NH_4Cl in 105 mL of 2-methoxyethanol and 16 mL of H_2O was heated at 80 ± 5 °C for 18 h. The mixture was then taken to near dryness in vacuo. Water was added to the residue and this was extracted three times with $CHCl_3$. The $CHCl_3$ extracts were dried, filtered, and freed of solvent in vacuo leaving 12.6 g (96%) of crude solid azide.

This was partially dissolved in 200 mL of absolute EtOH, treated with 0.5 g of PtO_2, and hydrogenated on the Parr shaker at up to 50 psi for 24 h. During this time the bottle was vented and refilled with hydrogen several times. The catalyst was removed by filtration and the filtrate was taken to dryness in vacuo leaving a foam which failed to crystallize. It was dissolved in warm *i*-PrOH, treated with charcoal, and filtered. The filtrate was acidified with a solution of HCl in *i*-PrOH. Ether was added, precipitating a mixture of gum and solid. This was twice dissolved in warm *i*-PrOH and precipitated by adding ether. The second time, the first material that precipitated was somewhat gummy. This was removed and addition of more ether to the filtrate gave a near white solid which was dried several days in vacuo over P_2O_5 at 56 °C to give **29**, 4.3 g (28%), softening and decomposition at 125–160 °C. Anal. ($C_{17}H_{28}N_2O_3 \cdot 2HCl \cdot H_2O$) C, H, N, Cl.

2,3-*cis*-5-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-8-iodo-2,3-naphthalenediol (25). To a solution of 25.0 g (0.081 mol) of **15** in a mixture of 250 mL of H_2O and 8.5 mL of concentrated hydrochloric acid at 15 °C was added dropwise over 30 min a solution of 13.2 g of ICl in 17.5 mL of concentrated hydrochloric acid. When approximately 80% of the ICl had been added, the solution became cloudy and an oil precipitated from the reaction mixture. The solution was allowed to warm to room temperature and then stirred for an additional 30 min, during which time the oily precipitate dissolved. The solution was made basic by the addition of 25 mL of 50% aqueous NaOH and then extracted with CH_2Cl_2 (5 × 250 mL). Concentration of the CH_2Cl_2 extracts in vacuo gave an oil which crystallized on standing. Recrystallization from $CHCl_3$ gave 15.8 g (45%) of **25**, mp 140–141 °C. Anal. ($C_{17}H_{26}NO_4I$) C, H, N, I.

4-(2,3-Epoxypropoxy)-5,6,7,8-tetrahydro-1,2-naphthalenediol (57g). To a well-stirred solution of 26.8 g (0.10 mol) of freshly prepared potassium nitrosodisulfonate (Fremy's salt) in 1.80 L of H_2O and 0.18 L of $^1/_6$ M KH_2PO_4 at 0–5 °C was added a solution of 9.24 g (0.042 mol) of epoxide **57p** in 250 mL of ether. The mixture was stirred at 0–5 °C for 30 min, followed by addition (in one portion) of a solution of 26.8 g (0.10 mol) of Fremy's salt in 1.8 L of H_2O and 0.18 L of $^1/_6$ M KH_2PO_4 precooled to 0–5 °C. The mixture was stirred for an additional 30 min, $CHCl_3$ was added, and the layers were separated. The aqueous layer was thoroughly extracted with $CHCl_3$; the combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated in vacuo to give 9.0 g (85%) of solid red-orange quinone **58**.

A suspension of the above quinone **58** (9.0 g) in 250 mL of EtOAc was hydrogenated in the presence of 1.0 g of 5% Pd/C (Parr shaker). After uptake of 1 equiv of H_2 (10 min), the solution was warmed briefly to dissolve precipitated product, the catalyst filtered off (Celite), and the filtrate concentrated in vacuo to an off-white solid. Trituration with ether gave 8.0 g (89%) of crystalline epoxide **57g**.

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Structure–Activity Study of β-Adrenergic Agents Using the SIMCA Method of Pattern Recognition

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The SIMCA method of pattern recognition (PaRC) was used to analyze structure–activity data for a series of phenethylamine agonists and antagonists of the β-adrenergic receptor. On the basis of physicochemical substituent parameters the SIMCA method classified correctly 100% of the agonists and 88% of the antagonists. In addition, parameters derived from the class models were correlated with the biological activities of the agonists and antagonists, respectively. Test compounds not included in the initial data analysis were classified and their activities estimated. The applicability of pattern recognition in structure–activity studies in general is discussed.

Since the early reports of Hansch[2a] and Free and Wilson[2b] using multivariable regression to systematically analyze biological structure–activity data, a field of research interest has developed around the philosophy of relating structural changes within a class of pharmacologically similar agents to changes in biological activity. The work of Hansch and his co-workers is especially significant in that it has shown that structurally and physicochemically similar substances can behave pharmacologically in regular and predictable manners.

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