

temperature of 20 °C. Mice were injected with reserpine 3 mg/kg sc, followed immediately by ip injection of the test compound in normal saline. Control rectal temperatures were taken immediately prior to the injection of reserpine. After 4 h, the rectal temperature of each mouse was measured with a microthermometer. ED₅₀ was defined as the dose that caused 50% inhibition of reserpine-induced decrease in the rectal temperature.

Our modification of the procedure of Askew involves simultaneous injection of reserpine and the test compound without waiting for 17 h after reserpine injection. Hino et al.⁴ have injected the test compound simultaneously with reserpine, and their ED₅₀ value for the imipramine was almost identical to ours. The ED₅₀ of imipramine obtained by Houlihan et al.⁵ was found to be 12.8 mg/kg when imipramine was injected 1 h after reserpine. Unfortunately, no statistics were available to allow comparison with our value. Also, we have noticed the ED₅₀ of imipramine to be 18.5 ± 5.7 mg/kg when it was injected 2 h after reserpine. Furthermore, we have found that the rectal temperature of mice dropped from 37.6 ± 0.53 to 26.2 ± 0.49, 25 ± 0.35 °C, and 22.72 ± 0.45 °C at 4, 5, and 6 h after reserpine injection, respectively. Askew reported that the rectal temperature had fallen to the region of 21–24 °C 17 h after reserpine injection. Therefore, it seems that the need for waiting a period of 17 h is not essential as long as the room temperature is kept at 20 ± 1 °C.

B. LD₅₀. The LD₅₀ was determined according to the procedure described by Turner¹³ by ip injection of the test compound in

normal saline into Swiss-Webster mice weighing 12–23 g. LD₅₀ was defined as the dose that killed 50% of the mice in 48 h.

Registry No. 1, 97633-84-6; 2, 97633-87-9; 2 (free base), 97633-86-8; 3, 97633-89-1; 3 (free base), 97633-88-0; 4, 97633-91-5; 4 (free base), 97633-90-4; 5, 97633-93-7; 5 (free base), 97633-92-6; 6, 97633-95-9; 6 (free base), 97633-94-8; 7, 97633-97-1; 7 (free base), 97633-96-0; 8, 97633-99-3; 8 (free base), 97633-98-2; 9, 72320-58-2; 10, 97634-04-3; 10 (free base), 97634-03-2; 11, 97634-06-5; 11 (free base), 97634-05-4; 12, 97634-02-1; 12 (free base), 97634-01-0; Me₂N(CH₂)₃NH₂, 109-55-7; Me₂N(CH₂)₃NHMe, 4543-96-8; HO-(CH₂)₃NMe₂, 3179-63-3; Cl(CH₂)₃NMe₂, 109-54-6; L₂NiCl₂, 15629-92-2; CH₃MgBr, 75-16-1; 2-chloro-4-phenylquinoline, 5855-56-1; *N,N*-dimethylethylenediamine, 108-00-9; *N,N,N'*-trimethylethylenediamine, 142-25-6; *N,N*-dimethylethanolamine, 108-01-0; 2-mercapto-4-phenylquinoline, 27309-54-2; 2-(dimethylamino)ethyl chloride, 107-99-3; 4-phenylquinaldine, 1721-92-2; 2-(bromomethyl)-4-phenylquinoline, 97634-00-9; diethylamine, 109-89-7; piperazine, 110-85-0; 3-chloro-1-bromopropane, 109-70-6; 2-pyridylhydrazine, 4930-98-7; 2-chloropyridine, 109-09-1; hydrazine, 302-01-2; 1,2,4-triazolo[4,3-*a*]pyridin-3-(2*H*)-one, 6969-71-7; urea, 57-13-6; thiourea, 62-56-6; *S*-(4-phenyl-2-quinolyl)-isothiurea, 97633-85-7.

(13) Turner, R. A. "Screening Methods in Pharmacology"; Academic Press: New York, 1965; 308.

Conformationally Defined Adrenergic Agents. 1. Design and Synthesis of Novel α_2 Selective Adrenergic Agents: Electrostatic Repulsion Based Conformational Prototypes

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A previous report of the adrenergic selectivity of 2- and 6-fluoronorepinephrine prompted us to formulate a hypothesis that accounted for this selectivity on the basis of a conformational preference induced by electrostatic repulsion between the aromatic fluorine atom and the side-chain hydroxyl group. A series of nitrogen-substituted catechol (aminomethyl)benzocyclobutenes, indanes, tetralins, and benzocycloheptenes were prepared, and when their radioligand binding affinities were determined, it was found that the overall pattern of binding affinity results supported the electrostatic repulsion hypothesis. The radioligand binding assay also revealed several highly α_2 selective adrenergic agents among these compounds, with the binding selectivity maximizing for compounds having nitrogen substituted with a group no larger than methyl and having a five-membered carbocyclic ring (i.e., 16, 17, and 19).

Separation of adrenergic effects into two classes mediated by α and β receptors was first suggested by Ahlquist¹ in 1948. Since that time, further work in the area of sympathetic nervous system receptors has led to their subclassification as α_1 , α_2 ² and β_1 , β_2 .³

Compounds possessing selective activity at various of these adrenergic receptors may be expected to be of therapeutic value since they are likely to have enhanced efficacy while minimizing the side effects often encountered with less selective agents.

The preparation of norepinephrine (NE) derivatives that in various in vitro preparations show selective α - or β -adrenergic receptor activity has been reported by Kirk⁴ et al. They found that 2-fluoronorepinephrine (2-FNE) exhibited β -agonistic activity while 6-fluoronorepinephrine (6-FNE) was an α agonist. Noting that the corresponding

fluorinated dopamines did not show adrenergic selectivity,⁵ one of the explanations that they offered for their observations invoked the formation of a hydrogen bond between the benzylic hydroxyl group and the aromatic fluorine atom. This was suggested to result in the stabilization of different rotameric conformations for the different FNEs. When the radioligand binding affinity of these compounds was determined,⁶ it was found that 6-FNE bound to both α_1 and α_2 receptors but did not bind to β receptors. However, 2-FNE bound strongly to β receptors and modestly to the α_2 receptor but did not show significant binding to the α_1 -adrenergic receptor.⁷

It was our belief that the observed adrenergic specificity of the 2- and 6-FNEs may have resulted from a conformational bias induced by the electrostatic repulsion between the side-chain β -hydroxyl group and the fluorine atom attached at the 2- or 6-position of the aromatic ring.

(1) Ahlquist, R. P. *Am. J. Physiol.* 1948, 153, 586.

(2) Starke, K. *Rev. Physiol. Biochem. Pharmacol.* 1977, 77, 1.

(3) Lands, A. M.; Arnold, A.; McAuliff, J. P.; Ludena, F. P.; Brown, T. G. *Nature* 1967, 214, 597.

(4) Kirk, K. L.; Cantacuzene, D.; Nimitkitpaisan, Y.; McCulloh, D.; Padgett, W. L.; Daly, J. W.; Creveling, C. R. *J. Med. Chem.* 1979, 22, 1493.

(5) Goldberg, L. J.; Kohli, J. D.; Cantacuzene, D.; Kirk, K. L.; Creveling, C. R. *J. Pharmacol. Exp. Ther.* 1980, 213, 509.

(6) Nimit, Y.; Cantacuzene, D.; Kirk, K. L.; Creveling, C. R.; Daly, J. W. *Life Sci.* 1980, 27, 1577.

(7) The β -adrenergic activity of the compounds will be dealt with separately.

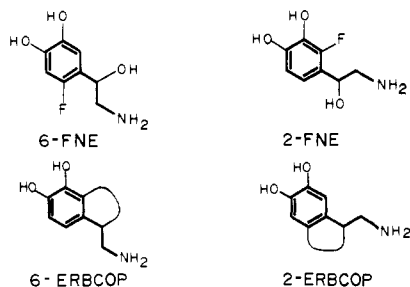


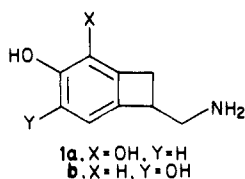
Figure 1. Comparison of the FNEs with their electrostatic repulsion based conformational prototypes (ERBCOPs).

A repulsive interaction of this sort, we reasoned, might be expected to diminish (but not eliminate) the rotational freedom about the C_1-C_α bond.

In an effort to obtain selective adrenergic agents we employed the electrostatic repulsion hypothesis in the design of compounds in which rotation about the NE C_1-C_α bond was restricted through the incorporation of a ring between the side-chain α -carbon and position 2 or 6 of the aromatic ring. As shown in Figure 1 these "electrostatic repulsion based conformational prototypes" (ERBCOPs) use a carbocyclic ring to accomplish the same sort of conformational restriction that had been brought about by the electrostatic repulsion between the aromatic fluorine and the side-chain hydroxyl group in the FNEs. We felt that semirigid molecules of this sort would be a first step toward the production of receptor subtype selective adrenergic agents.

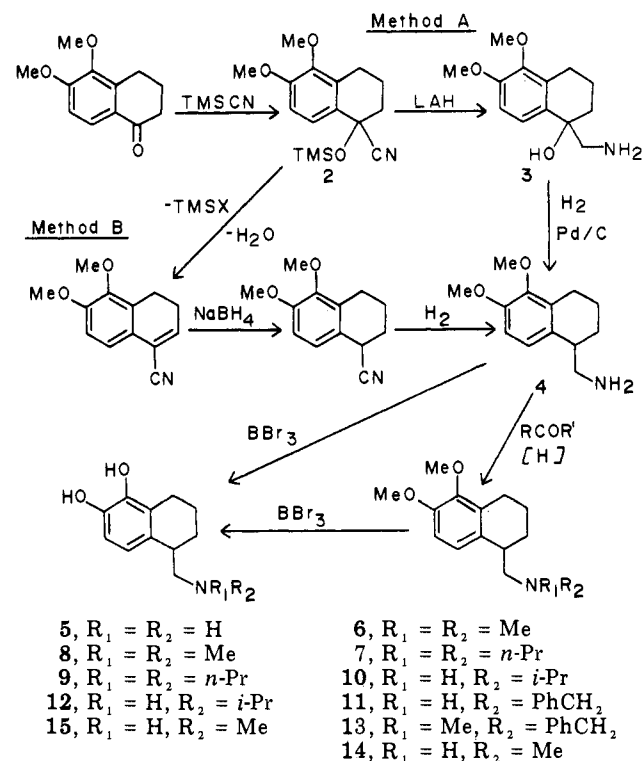
The selection of carbocyclic ring sizes for these semirigid compounds was guided by a desire to systematically investigate the effect of rotational flexibility about the C_1-C_α bond. It was recognized that as the ring size was increased to obtain a greater degree of flexibility, there was necessarily an increase in steric bulk and that at some point this was likely to have a detrimental effect on the ability of the compounds to bind to the adrenergic receptors. With this in mind, we chose to prepare carbocyclic rings of four, five, six, and seven members, in order to investigate their adrenergic receptor interactions.

Chemistry. The benzocyclobutenes **1a,b** were prepared as described by Brown.⁸



Our synthesis⁹ of the (aminomethyl)tetralins by either of the methods outlined in Scheme I is illustrative of the methods used for the remaining compounds. Starting with the known 5,6-dimethoxytetralone,¹⁰ the trimethylsilyl cyanohydrin **2** was prepared, using trimethylsilyl cyanide (TMSCN) with Lewis acid catalysis.¹¹ In our experience, the best results in the TMSCN reactions were obtained when the starting ketone was dried prior to reaction

Scheme I



through azeotropic removal of water with acetonitrile or benzene, both of which are suitable solvents for these reactions. We have also had success using aluminum chloride rather than the usually described zinc iodide although in some system $AlCl_3$ has caused a minor amount of aromatic methyl ether dealkylation. It was desirable, in general, to keep the amount of solvent to a minimum, while the temperature of the reaction could be varied from 50 to 90 °C without adverse effect.

When the route of method A was followed, reduction of **2** to the ethylamine **3** was accomplished with lithium aluminum hydride (LAH), and the isolation of the product **3** was facilitated by employing the granular workup described by Fieser.¹² Removal of the benzylic hydroxyl group was accomplished by catalytic reduction of crude **3** to give the dimethoxy(aminomethyl)tetralin **4** isolated as the hydrochloride salt. From **2** it was also possible to proceed by method B, employing an acid-catalyzed deprotection and dehydration of **2** to the unsaturated nitrile, which was then conjugately reduced with $NaBH_4$ to the aliphatic nitrile and then reduced in a separate step to the (aminomethyl)tetralin **4** by catalytic hydrogenation.

The aromatic methyl ethers of **4** could readily be cleaved with BBr_3 in excess followed by quenching with methanol and removal of the boron as the trimethylborate/methanol azeotrope, to yield the catecholamine hydrobromide **5**. These boron tribromide cleavage reactions (done under inert atmosphere in methylene chloride) were generally started at -78 °C and allowed to warm to ambient temperature overnight, though for sensitive molecules 1 h at -78 °C followed by 1 h at 0 °C was sufficient to produce a clean conversion to the catechol.

Catalytic reductive alkylation using formaldehyde provided the N,N -dimethyl compound **6**, and two cycles of propionic anhydride acylation followed by borane reduction gave the [(N,N -di- n -propylamino)methyl]tetralin **7**.¹³

(8) Brown, K. *European Pat. App.* 43194, 1982.

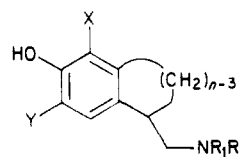
(9) (a) DeBernardis, J. F.; Kyncl, J. J.; Winn, M. U.K. Pat. App. GB2093837A, 1982. (b) Some of these (aminomethyl)tetralins have also been prepared by: Nichols, D. E.; Jadhov, K. P.; Buzdor, R. A. *Acta Pharm. Suecia, Suppl.* 1983, 65.

(10) Oka, Y.; Motohashi, M.; Sugihara, H.; Miyashita, O.; Itoh, K.; Nishikawa, M.; Yurugi, S. *Chem. Pharm. Bull.* 1977, 25, 632.

(11) This type of transformation has been previously reported. For a review of the reactions of TMSCN and its products see: Groutas, W. C.; Felkner, D. *Synthesis* 1980, 861.

(12) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 584.

Table I. Catecholamines Prepared for This Study



compd	X	Y	n	R ₁	R ₂	method ^a	mp ^b	formula	anal. ^c
5	OH	H	6	H	H	A	211–213	C ₁₁ H ₁₆ BrNO ₂	C, H, N
8	OH	H	6	Me	Me	A	246–248	C ₁₃ H ₂₀ BrNO ₂	C, H, N
9	OH	H	6	<i>n</i> -Pr	<i>n</i> -Pr	A ^d	155–160	C ₁₇ H ₂₈ BrNO ₂	C, H, N
12	OH	H	6	<i>i</i> -Pr	H	A	226–229	C ₁₄ H ₂₂ BrNO ₂	C, H, N
15	OH	H	6	Me	H	A	238–240	C ₁₂ H ₁₈ BrNO ₂	C, H, N
16	OH	H	5	H	H	A	252–253	C ₁₀ H ₁₄ BrNO ₂	C, H, N
17	OH	H	5	Me	H	A	215–217	C ₁₁ H ₁₆ BrNO ₂	C, H, N ^e
18	OH	H	5	Et	H	A ^d	215–216	C ₁₂ H ₁₈ BrNO ₂	C, H, N
19	OH	H	5	Me	Me	A ^f	242–243	C ₁₂ H ₁₈ BrNO ₂	C, H, N
20	OH	H	5	Et	Et	A ^g	174–176	C ₁₄ H ₂₂ BrNO ₂	C, H, N
21	OH	H	5	<i>i</i> -Pr	H	A	175–176	C ₁₃ H ₂₀ BrNO ₂ · ¹ / ₄ H ₂ O ^h	C, H, N
22	OH	H	5	<i>n</i> -Pr	<i>n</i> -Pr	A ^h	142–145	C ₁₆ H ₂₆ BrNO ₂	C, H, N
23	H	OH	5	H	H	A	209–210	C ₁₀ H ₁₄ BrNO ₂	C, H, N
24	H	OH	5	Me	Me	A	227–228	C ₁₂ H ₁₈ BrNO ₂	C, H, N
25	H	OH	5	<i>i</i> -Pr	H	A	152–154	C ₁₃ H ₂₀ BrNO ₂ · ¹ / ₄ H ₂ O ^h	C, H, N
26	H	OH	5	<i>n</i> -Pr	<i>n</i> -Pr	A ⁱ	135–155	C ₁₆ H ₂₆ BrNO ₂ ·H ₂ O ^h	C, H, N
27	OH	H	6	Et	H	B ^d	218–220	C ₁₃ H ₂₀ BrNO ₂ · ¹ / ₄ H ₂ O ^h	C, H, N
28	OH	H	6	Et	Et	B ^f	177–178	C ₁₅ H ₂₄ BrNO ₂	C, H, N
29	H	OH	6	H	H	A	98–100	C ₁₁ H ₁₆ BrNO ₂ ·C ₃ H ₈ O ⁱ	C, H, N
30	H	OH	6	Me	H	A	208–209	C ₁₂ H ₁₈ BrNO ₂	C, H, N
31	H	OH	6	Me	Me	A	245–247	C ₁₃ H ₂₀ BrNO ₂	C, H, N
32	H	OH	6	<i>i</i> -Pr	H	A	207–209	C ₁₄ H ₂₂ BrNO ₂	C, H, N
33	H	OH	6	<i>n</i> -Pr	<i>n</i> -Pr	A ^d	^j	C ₁₇ H ₂₈ ClNO ₂ · ¹ / ₄ H ₂ O ^h	C, H, N ^k
34	OH	H	7	H	H	B	235–237	C ₁₂ H ₁₈ BrNO ₂ · ¹ / ₄ H ₂ O ^h	C, H, N
35	H	OH	7	H	H	B	261–263	C ₁₂ H ₁₈ BrNO ₂	C, H, N

^a Refers to method A and method B referred to in Scheme I. ^b The melting point in °C, uncorrected. ^c Combustion analytical data agreed with calculated values within ±0.4% unless otherwise indicated. ^d The reductive amination was done by acylation with the appropriate anhydride followed by diborane reduction, repeating the process a second time if the tertiary amine was desired. ^e C: calcd, 48.19; found, 48.72. ^f The synthesis was conducted on the methylenedioxy compounds rather than the dimethoxy compounds, starting from the corresponding (methylenedioxy)indanes. ^g The reductive amination was done by catalytic hydrogenation in the presence of the appropriate keto compound. ^h This hygroscopic amine salt analyzed correctly only as the indicated hydrate. ⁱ This compound crystallized with an equivalent of 2-propanol, which was verified by ¹H NMR as well as by the combustion analysis. ^j This compound was isolated as an amorphous solid, no melting point was obtained. ^k N: calcd, 4.43; found, 3.98.

These underwent BBr₃ cleavage of the dimethyl ethers to the respective catechols 8 and 9. When the reductive alkylation was done with acetone or benzaldehyde as the carbonyl component, the monoalkylated amines 10 and 11 resulted. The *N*-isopropylamine 10 was cleaved to the catechol 12 as before, while the *N*-benzylamine 11 was further reductively alkylated to the tertiary amine 13 prior to catalytic debenzoylation to 14 and BBr₃ cleavage to the [(*N*-methylamino)methyl]tetralin 15. The compounds listed in Table I were prepared by the synthetic methods indicated.¹⁴

- (13) In some cases the di-*n*-propylamines were prepared by catalytic reductive alkylation of the primary amine in the presence of propionaldehyde. For specific cases, see Table I.
- (14) The synthesis of some of the five-membered ring compounds has been reported previously using a different methodology: Saiino, S.; Yamamine, S.; Saitou, S. *Pat.* J53005146, 1978.
- (15) Because radioligand binding data are log normally distributed,¹⁶ we have reported geometrical mean values of the *K*₁ along with the 90% confidence limits (CL) for each value. To report such data as an arithmetic mean (AM) plus or minus the standard error of the AM is inappropriate since it does not give a true representation of the variance of the data. Furthermore, if one wishes to examine differences in the data, it is important to recall that the usual tests for the statistical significance of such differences¹⁷ assume that a normal distribution exists for the data under consideration, and it would not be valid to apply such tests to the AM of log normally distributed data.
- (16) Bush, E. N., unpublished results. For a description of the analogous case for *in vitro* data see: Fleming, W. W.; Westfall, D. P.; De La Lande, I. S.; Jellet, L. B. *J. Pharmacol. Exp. Ther.* 1972, 181, 339.

Table II. Radioligand Binding Data^a for 6-ERBCOP Type Compounds

	α ₁ (90% CL) ^b	α ₂ (90% CL) ^b
6-FNE	650 (580–720)	35 (4–290)
1a	16000 (11000–24000)	170 (160–180)
36	3300 (2100–5000)	21 (11–41)
16	8600 (6100–12000)	15 (10–23)
17	2000 (1000–4100)	7.0 (3.9–13)
18	2500 (2100–3000)	130 (53–300)
19	6900 (3900–12000)	25 (18–37)
20	3600 (2300–5800)	320 (190–560)
21	4600 (2600–7900)	660 (450–970)
22	7400 (2700–21000)	470 (280–770)
5	13000 (5400–32000)	47 (26–86)
15	7900 (5200–12000)	44 (28–67)
27	7900 (5000–13000)	200 (110–380)
8	13000 (7200–24000)	660 (370–1200)
28	3100 (2000–4800)	250 (130–490)
12	6600 (3900–11000)	4700 (3600–6200)
9	7900 (6400–9700)	180 (80–400)
34	27000 (16000–45000)	880 (530–1500)
clonidine	520 (300–900)	30 (23–40)
UK14,304	740 (150–3700)	30 (25–38)
NE	390 (370–410)	37 (35–39)

^a Values given are nm *K*₁ values. See Experimental Section for radioligand and tissue used. ^b 90% confidence limits shown in parentheses. See ref 15.

Results and Discussion

As we indicated above, our investigation of compounds designed to interact selectively at α-adrenergic receptors

- (17) Youden, W. J. "Statistical Methods for Chemists"; Wiley: New York, 1951.

Table III. Radioligand Binding Data^a for 2-ERBCOP Type Compounds

	α_1 (90% CL) ^b	α_2 (90% CL) ^b
2-FNE	25000 (12000–54000)	1400 (140–14000)
1b	5000 (2100–12000)	200 (100–390)
23	26000 (19000–35000)	520 (260–1000)
24	13000 (12000–15000)	860 (500–1500)
25	11000 (4400–27000)	3800 (1500–9100)
26	29000 (20000–43000)	690 (550–880)
29	15000 (12000–18000)	5100 (2500–10000)
30	8700 (6600–11000)	1300 (1200–1500)
31	13000 (7900–21000)	700 (540–920)
32	14000 (6400–29000)	2500 (1200–5000)
33	16000 (14000–18000)	600 (450–800)
35	11000 (4000–33000)	19000 (8400–44000)

^a See footnote a, Table II. ^b See footnote b, Table II.

Table IV. Comparison of Radioligand Binding Affinity^a of 6-ERBCOP Type Compounds with the Corresponding 2-ERBCOP Type Compounds^b

	α_1 ^c	α_2 ^c
6-FNE (2-FNE)	1600 (25000)	270 (1400)
1a (1b)	16000 (5000)	170 (200)
16 (23)	8600 (26000)	15 (520)
19 (24)	6900 (1300)	25 (860)
21 (25)	4600 (11000)	660 (3800)
22 (26)	7400 (29000)	470 (690)
5 (29)	13000 (15000)	47 (5100)
15 (30)	7900 (8700)	44 (1300)
8 (31)	13000 (13000)	660 (700)
12 (32)	6600 (14000)	4700 (2500)
9 (33)	2900 (16000)	180 (600)
34 (35)	27000 (11000)	880 (19000)

^a See footnote a, Table II. ^b 2-ERBCOP type compounds shown in parentheses. ^c For 90% CL, see Tables II and III.

was based in part on an electrostatic repulsion model associated with the FNEs. The radioligand binding data for a number of 6-ERBCOP type compounds are shown in Table II.¹⁵

Inspection of this data shows that, just as 6-FNE, these compounds exhibit binding to both the α_1 and α_2 receptors, and in every case the binding to the α_2 receptor is better than to the α_1 receptor.

The results of radioligand binding studies of the 2-ERBCOP type compounds are shown in Table III. As can be seen from examination of these data, these compounds, at the α receptors, generally parallel the pattern shown by 2-FNE, i.e., modest binding to the α_2 receptor with poor binding affinity to the α_1 receptor.

While the data in Tables II and III indicate the rough correspondence of the binding affinity of the FNEs with that of the compounds designed to approximate the FNE electrostatic repulsion based conformations, it should also be noted (Table IV) that the 6-ERBCOP type compounds generally demonstrate better binding to the α receptors than do their 2-ERBCOP counterparts.

All of these results lend credibility to the electrostatic repulsion model as a likely explanation for the selectivity of the FNEs. Note that contrary to an electrostatic repulsion model a hydrogen-bonding hypothesis would predict (1) the compounds of Table II would mimic the conformation and binding affinity of 2-FNE, (2) the compounds of Table III would exhibit the same sort of binding affinity as 6-FNE, and (3) the trend in binding potencies would be opposite to that shown in Table IV.

Having recognized that the electrostatic repulsion model satisfactorily accounts for the radioligand binding constants observed for these compounds, we were interested in investigating the effects of carbocyclic ring size and nitrogen substitution (Table V) on binding affinity. The

best binding at both the α_1 and α_2 receptors tends to occur with five-membered ring compounds having nitrogen substituents no larger than methyl. As was mentioned above, the so-called 6-ERBCOP type compounds exhibit better α receptor affinity than their 2-ERBCOP analogues.

Interestingly, the 6-ERBCOP type compounds (cf. Table VI compounds 1a, 5, 15–17, 19, and 36) turn out to be much more α_2 selective (5–30 times) than 6-FNE itself, on the basis of the ratio of the α_1 binding constant to the α_2 binding constant. As can be seen, the best selectivity is observed for compounds having a five-membered ring and nitrogen substituents no larger than methyl, with these compounds showing α_2 selectivities much greater than that of clonidine or UK 14,304-18, which are included as literature examples of α_2 selective compounds. An examination of the binding constants (Table II) reveals that this selectivity is due largely to an increased affinity for the α_2 receptor; however, a modest decrease in the binding affinity at the α_1 receptor also occurs.

Conclusions

We feel that the overall pattern of the results presented herein supports the electrostatic repulsion model as an explanation for the difference in activity observed for the 2- and 6-FNEs. The high affinity for the α_2 receptor of some of the 6-ERBCOP type compounds, which have no benzylic hydroxyl group, suggests that the role of the 6-FNE side-chain hydroxyl group in α_2 receptor binding is to provide a favorable conformation for binding to the receptor rather than to produce a direct interaction with the receptor itself. However, these data do not rule out the possibility that a significant portion of the α_1 receptor binding affinity arises from an interaction of the NE side-chain hydroxyl group with the α_1 receptor protein.

Finally, we have prepared a series of adrenergic agents, a number of which have been shown to be more selective than either clonidine or UK 14,304-18 in binding to the α_2 -adrenergic receptor.

Experimental Section

Tissue Preparation. Twenty male Sprague-Dawley rats weighing 250–350 g were anesthetized with pentobarbital sodium (50 mg/kg, ip), and the brains and livers (α_1) were quickly removed and placed in assay buffer (Tris-HCl, 50 mM, pH 7.7, at 25 °C) at 4 °C. Cerebral cortices (α_2) were separated from the remainder of the brains, and tissues were pooled prior to homogenization. The organs were weighed, and pooled tissues were separately homogenized in 20 volumes of preparation buffer (Tris-HCl, 50 mM, pH 7.7, at 25 °C, containing 5 mM EDTA), in a Tekmar SDT homogenizer at full speed for two 10-s bursts. The homogenates were centrifuged at 50000g (4 °C) for 10 min, and the supernatants were discarded. The pellets were resuspended by homogenization as above in 20 volumes of preparation buffer and recentrifuged for 10 min, and the supernatants were again discarded. Each final pellet was resuspended in 6.25 volumes of assay buffer, flash-frozen in liquid nitrogen, and stored at –70 °C until the day of experiment. Membranes were thawed at room temperature and thereafter maintained at 4 °C.

Assay Methods. All assays were performed in a light-subdued laboratory, with a total incubation volume of 1.0 mL. A 450- μ L portion of radioligand [either [³H]prazosin (sp act. 23 Ci/mmol, Amersham, Arlington Heights, IL) for α_1 or [³H]rauwolscine (sp act. 79 Ci/mmol, New England Nuclear, Boston, MA) for α_2 assays] in assay buffer was incorporated with 50 μ L of 0.3 mM ascorbic acid, containing phentolamine (10^{–5} M, nonspecific binding), varying concentrations of test compounds, or no addition (total binding). Incubation commenced upon the addition of 500 μ L of membrane homogenate in assay buffer, resulting in a final protein concentration of 50–150 μ g/mL, determined by the method of Bradford.¹⁸

Table V. Effects of Carbocyclic Ring Size and Nitrogen Substitution on Radioligand Binding Affinity^a

	<i>n</i> = 4		<i>n</i> = 5		<i>n</i> = 6		<i>n</i> = 7		
	α_1 b	α_2 b	α_1 b	α_2 b	α_1 b	α_2 b	α_1 b	α_2 b	
			 2-ERBCOP Type						
$R_1 = R_2 = H$	16000	170	8600	15	13000	5	47	27000	880
$R_1 = Me, R_2 = H$			2000	7	7900	15	44		
$R_1 = Et, R_2 = H$			2500	130	7900	27	200		
$R_1 = i-Pr, R_2 = H$			4600	660	6600	12	4700		
$R_1 = R_2 = Me$	3300	21	6900	25	13000	8	660		
$R_1 = R_2 = Et$			3600	320	3100	28	250		
$R_1 = R_2 = n-Pr$			7400	470	7900	9	180		
			 6-ERBCOP Type						
$R_1 = R_2 = H$	5000	200	26000	520	15000	29	5100	11000	19000
$R_1 = i-Pr, R_2 = H$			11000	3800	14000	32	2500		
$R_1 = R_2 = Me$			13000	860	13000	31	700		
$R_1 = R_2 = n-Pr$			29000	690	16000	33	600		

^a See footnote a, Table II. ^b For 90% CL, see Tables II and III.

Table VI. α_2 Selectivity of 6-ERBCOP Type Compounds Expressed as the Ratio of the α_1 to α_2 Radioligand Binding Constants

compd	α_1/α_2 (90% CL) ^a	<i>n</i>	R ₁	R ₂
6-FNE	18 (9.2-37)			
1a	98 (76-130)	4	H	H
36	160 (70-360)	4	Me	Me
16	560 (320-990)	5	H	H
17	290 (150-550)	5	Me	H
18	20 (11-36)	5	Et	H
21	6.9 (4.4-11)	5	<i>i</i> -Pr	H
19	270 (160-440)	5	Me	Me
20	11 (6.8-18)	5	Et	Et
22	16 (8.3-31)	5	<i>n</i> -Pr	<i>n</i> -Pr
5	270 (120-630)	6	H	H
15	180 (120-280)	6	Me	H
27	40 (24-68)	6	Et	H
12	1.4 (0.97-2.0)	6	<i>i</i> -Pr	H
8	20 (11-35)	6	Me	Me
28	13 (7.6-22)	6	Et	Et
9	44 (25-77)	6	<i>n</i> -Pr	<i>n</i> -Pr
34	30 (17-53)	7	H	H
clonidine	17 (9.5-31)			
UK 14,304	24 (9.3-64)			

^a See footnote b, Table II.

Equilibrium binding was evaluated after a 50-min incubation at 25 °C for α_1 assays or a 2-h incubation period at 4 °C for α_2 assays. Receptor-bound radioligand was separated from free ligand by filtration under -180 mmHg vacuum through Whatman

934AH filters, which were dried in a hot air oven at 60 °C. Three milliliters of Ready-Solv NA (Beckman) was added, and the solubilized ligand was counted to a 4.5% 2 σ error level in a Beckman LS3800 liquid scintillation counter at approximately 63% counting efficiency. The "added" radioligand tubes were not filtered, but 0.1 mL was dried on a filter, combined with 3 mL of Ready-Solv, and counted. Quenching was determined by the H# method.

In saturation binding experiments, eight concentrations of radioligand between 10⁻¹¹ and 10⁻⁸ M were utilized. Total (buffer control) and nonspecific (10⁻⁵ M phentolamine) binding were determined in triplicate at each concentration of radioligand. The radioligand affinity (K_D) and apparent receptor density (B_{max}) were evaluated, by using the method of Scatchard.¹⁹ Total and nonspecific binding data were also analyzed via the SCAFFIT program of Munson and Rodbard,²⁰ to determine whether the data could be best described by either a one- or two-site model.

In the competition binding assays, total and nonspecific binding were each determined with five replicates. Specific binding was the arithmetic difference between total binding and nonspecific binding. Affinities of each of the tested compounds were evaluated by measuring the percent inhibition of specific binding, from at least four concentrations between 10⁻¹⁰ and 10⁻³ M, with duplicate determinations at each concentration. The concentration at which 50% inhibition of specific binding was observed and the pseudo-Hill coefficient were calculated from the linear relationship between logit % specific bound (log [%/(1 - %)]) vs. log concentration. The dissociation constant (K_i) was derived according to the equation of Cheng and Prusoff, with the assumption that the compounds being tested were competitive with the radioligand being used:²¹

$$K_i = IC_{50} / (1 + [L] / K_D)$$

(19) Scatchard, G. *Ann. N.Y. Acad. Sci.* 1949, 51, 660.

(20) Munson, P. J.; Rodbard, D. *Anal. Biochem.* 1980, 107, 220.

The ligand concentration (L) used in this calculation was the arithmetic difference between the total ligand added to each incubation tube as determined from the counts in the "added" tubes and the radioligand bound at the IC₅₀ concentration. The ligand affinities (K_D) of [³H]prazosin and [³H]rauwolscine were 0.051 and 3.24 nM, respectively.

Synthetic Methods. Melting points were determined on a Thomas-Hoover Unimelt and are uncorrected. Combustion analyses were performed by the Analytical Services Department, Abbott Laboratories, North Chicago, IL. Infrared spectra were obtained on either a Perkin-Elmer 283B or Perkin-Elmer 683 spectrophotometer. ¹H NMR spectra are reported in ppm downfield from internal Me₄Si or DSS and were obtained on either a Varian T-60, a Varian EM-360, a Varian XL-100-15 with a TT 100 computer, a General Electric QE-300, or a Nicolet NT-360 spectrometer. Solvents were reagent grade and were used without additional purification unless otherwise indicated.

1-(Aminomethyl)-5,6-dimethoxytetralin Hydrochloride (4). **Method A.** A mixture of 20 g (0.10 mol) of 5,6-dimethoxy- α -tetralone,¹⁰ 11.5 g (0.12 mol) of trimethylsilyl cyanide (TMSCN), 20 mg (0.1 mmol) of ZnI₂, and 16 mL of benzene was heated at 60 °C under nitrogen for 5 h. The resulting solution was cooled and added dropwise to a mixture of 8.4 g (0.22 mol) of LAH in 250 mL of ether, and the whole was heated under nitrogen at reflux for 2 h. After cooling, the reaction was carefully quenched with 10 mL of 15% aqueous NaOH followed by 15 mL of H₂O. After the resulting slurry was stirred for 20 min, CHCl₃ was added and the solids were filtered off. The organic solution was concentrated before adding ether to complete the crystallization of 21.5 g (93%) of 1-(aminomethyl)-1-hydroxy-5,6-dimethoxytetralin (3): mp 138–140 °C; IR (CDCl₃) 3600, 3400, 2950, 1600, 1490 cm⁻¹; ¹H NMR (CDCl₃) δ 1.65–2.10 (m, 4), 2.60–2.90 (m, 2), 2.92 (s, 1), 3.73 (s, 3), 3.81 (s, 3), 6.84 (d, 1, J = 8 Hz), 7.28 (d, 1, J = 8 Hz). Anal. (C₁₃H₁₉NO₂) C, H, N. A solution of 13.6 g (57 mmol) of 3 in 140 mL of methanol and 8.3 mL of 12 N HCl was then hydrogenated in a Parr shaker in the presence of 5 g of 10% palladium on carbon for 20 h at room temperature. The resulting mixture was filtered, evaporated, and crystallized from 2-propanol/ether to give 13.6 g (92%) of 4: mp 249–251 °C; IR (KBr) 3400, 2950, 1600, 1490 cm⁻¹; ¹H NMR (D₂O) δ 1.65–2.00 (m, 4), 2.54–2.92 (m, 2), 3.17–3.35 (m, 3), 3.76 (s, 3), 3.80 (s, 3), 7.05 (d, 1, J = 8 Hz), 7.16 (d, 1, J = 8 Hz). Anal. (C₁₃H₂₀ClNO₂) C, H, N.

Method B. A 10-g (0.05 mol) portion of 5,6-dimethoxy- α -tetralone¹⁰ was treated with TMSCN as in method A after which the benzene was evaporated and the residue was dissolved in 100 mL of CH₃OH. The solution was cooled in an ice bath, and a stream of HCl gas was bubbled into it for 2.5 h. The solution was then evaporated and the residue dissolved in CHCl₃, washed with H₂O and with saturated potassium bicarbonate, dried over MgSO₄, filtered, evaporated, and crystallized from ether to give 9.4 g (91%) of 1-cyano-3,4-dihydro-5,6-dimethoxynaphthalene: mp 137–139 °C; ¹H NMR (CDCl₃) δ 2.30–3.00 (m, 4), 3.80 (s, 3), 3.90 (s, 3), 6.75 (t, 1, J = 4 Hz), 6.71 (d, 1, J = 8 Hz), 7.21 (d, 1, J = 8 Hz). Anal. (C₁₃H₁₃NO₂) C, H, N. A mixture of 1.0 g (4.7 mmol) of 1-cyano-3,4-dihydro-5,6-dimethoxynaphthalene, 0.9 g (24 mmol) of NaBH₄, and 8 mL of ethanol was heated at reflux for 30 min. The cooled solution was concentrated in vacuo, water was added, and the whole was cooled. The resulting solid was filtered, dissolved in ether, dried over MgSO₄, filtered, evaporated, and crystallized from Skelly B to give 0.83 g (81%) of 1-cyano-5,6-dimethoxytetralin: mp 51–53 °C; ¹H NMR (CDCl₃) δ 1.70–2.20 (m, 4), 2.60–3.00 (m, 2), 3.60–3.80 (m, 1), 3.83 (s, 3), 3.88 (s, 3), 6.83 (d, 1, J = 6 Hz), 7.05 (d, 1, J = 6 Hz). A mixture of 4.9 g (23 mmol) of 1-cyano-5,6-dimethoxytetralin, 2.5 g of Raney nickel, 175 mL of CH₃OH, and 25 mL of NH₄OH was hydrogenated in a Parr shaker for 4 h. The catalyst was filtered off, and the filtrate was evaporated. To a solution of the resulting residue in ethanol was added methanolic HCl followed by ether. The resulting precipitate was filtered, washed with ether, and air-dried to give 5.4 g (93%) of 4.

General Method for Dimethyl Ether Cleavage. 1-(Aminomethyl)-5,6-dihydroxytetralin Hydrobromide (5). To a

mixture of 5.23 g (20 mmol) of 4 and 50 mL of CH₂Cl₂ under nitrogen at -78 °C was added dropwise a solution of 10 mL (106 mmol) of BBr₃ in 50 mL of CH₂Cl₂. After stirring at -78 °C for 0.5 h and at room temperature for 2.5 h, the reaction was quenched at -78 °C with excess CH₃OH and evaporated prior to recrystallization from methanol/ether to give 3.60 g (65%) of 5²² in two crops: IR (KBr) 3400, 3100, 2950, 1600, 1500, 1490 cm⁻¹; ¹H NMR (D₂O) 1.58–1.92 (m, 4), 2.37–2.74 (m, 2), 3.00–3.26 (m, 3), 6.75 (d, 1, J = 9 Hz), 6.84 (d, 1, J = 9 Hz).

1-[(N,N-Dimethylamino)methyl]-5,6-dimethoxytetralin Hydrochloride (6). A mixture of 4.47 g (17.4 mmol) of 4, 4 mL (53 mmol) of 37% formalin, 96 mL of CH₃OH, 2.4 g (17.6 mmol) of NaOAc·3H₂O, and 1.0 g of 5% palladium on carbon was hydrogenated in a Parr shaker overnight at room temperature. After filtration and concentration, there was added aqueous KOH and the aqueous layer was extracted with CHCl₃, which was then dried over K₂CO₃, filtered, and evaporated. The hydrochloride was formed and crystallized from 2-propanol and HCl to give 3.97 g (80%) of 6: mp 243–244 °C; IR (KBr) 3400, 2950, 2700, 1500 cm⁻¹; ¹H NMR (D₂O) δ 1.64–1.92 (m, 4), 2.50–2.82 (m, 2), 3.00 (s, 6), 3.20–3.40 (m, 3), 3.74 (s, 3), 3.86 (s, 3), 7.05 (s, 2). Anal. (C₁₅H₂₄ClNO₂) C, H, N.

1-[(N,N-Dimethylamino)methyl]-5,6-dihydroxytetralin Hydrobromide (8). Cleavage of 2.86 g (10 mmol) of dimethyl ether 6 by the general method above gave 2.94 g (97%) of 8²²: IR (KBr) 3300, 2950, 2756, 1600, 1490 cm⁻¹; ¹H NMR (Me₂SO-*d*₆ + D₂O) δ 1.46–1.74 (m, 4), 2.80 (s, 6), 3.00–3.33 (m, 3), 6.65 (s, 2).

1-[(N,N-Di-n-propylamino)methyl]-5,6-dimethoxytetralin Hydrochloride (7). A suspension of 10.0 g (39 mmol) of 4 in H₂O was made basic with 45% aqueous KOH and extracted with ether, which was dried over Na₂CO₃, filtered, and concentrated to ca. 100 mL. To this solution was added with cooling 9.9 g (76 mmol) of propionic anhydride (exothermic). After stirring at room temperature for 1 h, the solution was cooled and the resulting crystals were filtered off and dissolved in CHCl₃ and then washed with 10% aqueous KOH prior to being dried over MgSO₄, filtered, evaporated, and crystallized from ether/Skelly B to give 9.56 g (89%) of 1-[(N-propionylamino)methyl]-5,6-dimethoxytetralin in two crops; mp 103–105 °C. A solution of 9.56 g (35 mmol) of this amide in 50 mL of tetrahydrofuran (THF) was added at a moderate rate under nitrogen to 87 mL of precooled 1 M BH₃ in THF. The resulting solution was refluxed for 2 h, cooled, and quenched by the dropwise addition of 25 mL of 6 N HCl. This solution was heated at reflux for 10 min, then concentrated, and basified with aqueous KOH. After some insoluble solid that was saved for later processing was filtered off, the filtrate was extracted with ether and the combined ether extracts were dried over K₂CO₃, filtered, and evaporated and their residue was dissolved in 2-propanol and acidified with HCl to give 7.01 g of 1-[(N-n-propylamino)methyl]-5,6-dimethoxytetralin hydrochloride. The solid that had been filtered off after the initial basification was heated at reflux in HCl, CH₃OH, and H₂O and then worked up as above to give an additional 2.34 g of this amine hydrochloride for a total yield of 9.35 g (90%): mp 203–205 °C; IR (KBr) 3450, 2950, 2700, 1480 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 0.82 (t, 3, J = 8 Hz), 1.38–2.00 (m, 6), 2.50–3.33 (m, 5), 3.65 (s, 3), 3.75 (s, 3), 6.95 (d, 1, J = 9 Hz), 7.10 (d, 1, J = 9 Hz). Anal. (C₁₈H₂₆ClNO₂) C, H, N. The above acylation and reduction procedures were repeated using 6.20 g (21 mmol) of this secondary amine hydrochloride to give 4.81 g (68%) of 7 from these two steps: mp 149–151 °C; IR (KBr) 3450, 2950, 2600, 1600, 1480 cm⁻¹; ¹H NMR (D₂O) δ 0.95 (t, 6, J = 8 Hz), 1.55–2.05 (m, 8), 2.50–2.65 (m, 2), 3.00–3.40 (m, 7), 3.78 (s, 3), 3.89 (s, 3), 7.10 (s, 2).

1-[(N,N-Di-n-propylamino)methyl]-5,6-dihydroxytetralin Hydrobromide (9). Cleavage of 3.70 g (10.8 mmol) of the dimethyl ether 7 by the general method above gave 3.83 g (99%) of 9²²: IR (KBr) 3400, 3240, 2970, 1620, 1490 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 0.87 (t, 6, J = 7 Hz), 1.32–2.00 (m, 8), 2.36–2.68 (m, 2), 2.82–3.40 (m, 7), 6.66 (s, 2); mass spectrum m/e 277 (M⁺), 177, 163, 114.

1-[(N-Isopropylamino)methyl]-5,6-dimethoxytetralin Hydrochloride (10). A mixture of 5.05 g (20 mmol) of 4, 0.3 g of PtO₂, 140 mL of CH₃OH, 10 mL (136 mmol) of acetone, and

(21) Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* 1973, 22, 3099.

(22) For melting point and analysis, see Table I.

2.7 g (20 mmol) of NaOAc·3H₂O was hydrogenated in a Parr shaker at room temperature for 1.5 h. After filtration and concentration, there were added aqueous KOH and CHCl₃. The organic layer was separated, dried over K₂CO₃, filtered, evaporated, dissolved in 2-propanol, and acidified with HCl to give 5.78 g (98%) of 10: mp 187–189 °C; IR (KBr) 3450, 2950, 2800, 1600, 1570, 1480 cm⁻¹; ¹H NMR (D₂O) δ 1.33 (d, 3, *J* = 7 Hz), 1.36 (d, 3, *J* = 7 Hz), 1.60–2.00 (m, 4), 2.50–2.80 (m, 2), 3.10–3.30 (m, 3), 3.50 (sept, 1, *J* = 7 Hz), 3.77 (s, 3), 3.89 (s, 3), 7.03 (d, 1, *J* = 7 Hz), 7.17 (d, 1, *J* = 7 Hz). Anal. (C₁₆H₂₆ClNO₂) C, H, N.

1-[(*N*-Isopropylamino)methyl]-5,6-dihydroxytetralin Hydrobromide (12). Cleavage of 3.00 g (10 mmol) of dimethyl ether 10 using the general method above gave 3.01 g (95%) of 12:²² IR (KBr) 3400, 2950, 1600, 1580, 1500 cm⁻¹; ¹H NMR (D₂O) δ 1.29 (d, 6, *J* = 6 Hz), 1.58–2.00 (m, 4), 2.40–2.80 (m, 4), 3.04–3.30 (m, 3), 3.40 (sept, 1, *J* = 6 Hz), 6.80 (s, 2).

1-[(*N*-Benzylamino)methyl]-5,6-dimethoxytetralin Hydrochloride (11). A mixture of 10 g (39 mmol) of 4, 4 mL (39 mmol) of benzaldehyde, 1.5 g of 5% platinum on carbon, 200 mL of CH₃OH, and 5.3 g (39 mmol) of NaOAc·3H₂O was hydrogenated in a Parr shaker at room temperature for 0.5 h, filtered, and concentrated. After aqueous KOH was added, the whole was extracted with CHCl₃ and the combined extracts were dried over K₂CO₃, filtered, and concentrated prior to the addition of 2-propanol and HCl to give 12.1 g (90%) of 11: mp 217–219 °C; IR (KBr) 3450, 2950, 2800, 1600, 1560, 1485 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 1.38–2.00 (m, 4), 2.50–2.70 (m, 2), 3.00–3.30 (m, 3), 3.67 (s, 3), 3.76 (s, 3), 4.05–4.32 (m, 2), 6.90 (d, 1, *J* = 8 Hz), 7.00 (d, 1, *J* = 8 Hz), 7.35–7.85 (m, 5). Anal. (C₂₀H₂₆ClNO₂) C, H, N.

1-[(*N*-Benzyl-*N*-methylamino)methyl]-5,6-dimethoxytetralin Hydrochloride (13). A mixture of 8.83 g (25.4 mmol) of 11, 3.5 g (25.7 mmol) of NaOAc·3H₂O, 3 mL (40 mmol) of 37% formalin, 95 mL of CH₃OH, and 0.8 g of 5% platinum on carbon was hydrogenated in a Parr shaker at room temperature for 1 h, filtered, and concentrated. After the addition of KOH, the mixture was extracted with CHCl₃ and the combined extracts were dried over K₂CO₃, filtered, and concentrated prior to the addition of 2-propanol and HCl to give 8.46 g (92%) of 13: mp 172–174 °C; IR (KBr) 3450, 2920, 2650, 1590, 1480 cm⁻¹; ¹H NMR (D₂O) δ 1.42–1.85 (m, 4), 2.40–2.71 (m, 2), 3.04 (s, 3), 3.25–3.30 (m, 3), 3.70 (s, 3), 3.84 (s, 3), 4.42 (AB, 2, *J* = 14 Hz), 7.06 (s, 1), 7.60 (s, 1). Anal. (C₂₁H₂₈ClNO₂) C, H, N.

1-[(*N*-Methylamino)methyl]-5,6-dimethoxytetralin Hydrochloride (14). A mixture of 6.83 g (18.9 mmol) of 13, 100 mL

of CH₃OH, and 1.4 g of palladium on carbon was hydrogenated in a Parr shaker at room temperature for 2 h. The resulting mixture was filtered and the filtrate concentrated, diluted with 2-propanol, and reconstituted to give 4.57 g (89%) of 14: mp 202–204 °C; IR (KBr) 3400, 2950, 2750, 1600, 1490 cm⁻¹; ¹H NMR (D₂O) δ 1.67–1.92 (m, 4), 2.58–2.95 (m, 2), 2.86 (s, 3), 3.16–3.28 (m, 3), 3.80 (s, 3), 3.90 (s, 3), 7.10 (s, 2). Anal. (C₁₄H₂₂ClNO₂) C, H, N.

1-[(*N*-Methylamino)methyl]-5,6-dihydroxytetralin Hydrobromide (15). Cleavage of 3.44 g (12.7 mmol) of 14 by the general method described above gave 3.54 g (97%) of 15:²² IR (KBr) 3440, 3200, 3050, 2950, 1625, 1580, 1490 cm⁻¹; ¹H NMR (D₂O) δ 1.55–1.83 (m, 4), 2.37–2.75 (m, 2), 2.74 (s, 3), 3.00–3.15 (m, 3), 6.73 (d, 1, *J* = 8 Hz), 6.85 (d, 1, *J* = 8 Hz).

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Registry No. 1a, 97352-01-7; 1b, 81615-40-9; 3, 84854-65-9; 4, 84865-81-6; 5, 84854-75-1; 5 (free base), 97352-16-4; 6, 84854-72-8; 7, 84854-70-6; 8, 97352-02-8; 8 (free base), 97352-17-5; 9, 84854-71-7; 9 (free base), 97352-18-6; 10, 97352-03-9; 11, 97352-04-0; 12, 84854-74-0; 12 (free base), 97352-19-7; 13, 97352-05-1; 14, 84854-66-0; 15, 84854-73-9; 15 (free base), 97352-20-0; 16, 97352-06-2; 16 (free base), 97352-21-1; 17, 66361-26-0; 17 (free base), 97352-22-2; 18, 95860-03-0; 18 (free base), 97352-23-3; 19, 95859-97-5; 19 (free base), 95860-06-3; 20, 95860-05-2; 20 (free base), 97352-24-4; 21, 66361-27-1; 21 (free base), 97352-25-5; 22, 97352-07-3; 22 (free base), 97352-26-6; 23, 87731-06-4; 23 (free base), 97352-27-7; 24, 97352-08-4; 24 (free base), 97352-28-8; 25, 66361-25-9; 25 (free base), 97352-29-9; 26, 97352-09-5; 26 (free base), 97352-30-2; 27, 97352-10-8; 27 (free base), 97352-31-3; 28, 97352-11-9; 28 (free base), 97352-32-4; 29, 84854-55-7; 29 (free base), 80440-58-0; 30, 84854-62-6; 30 (free base), 97352-33-5; 31, 84854-60-4; 31 (free base), 97352-34-6; 32, 84854-56-8; 32 (free base), 97352-35-7; 33, 97352-12-0; 33 (free base), 97352-36-8; 34, 97352-13-1; 34 (free base), 97352-37-9; 35, 97352-14-2; 35 (free base), 97352-38-0; 36, 81615-44-3; 5,6-dimethoxy- α -tetralone, 24039-89-2; 1-cyano-3,4-dihydro-5,6-dimethoxynaphthalene, 89047-59-6; 1-cyano-5,6-dimethoxytetralin, 97352-15-3; 1-[(*N*-propionylamino)methyl]-5,6-dimethoxytetralin, 84854-67-1; 1-[(*N*-propylamino)methyl]-5,6-dimethoxytetralin hydrochloride, 84854-68-2.