2[5] following the procedure outlined for the preparation of 4. Compound 5 was obtained as a light yellow powder: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.32 (s, 6, indole CH_3), 2.16 (d, 3, Ar CH_3), 6.80 (d, 1, Ar H), 6.91 (s, 1, Ar H), 7.20–7.38 (m, 2, Ar H); mass spectrum, *m/e* (relative intensity) 269 (100, M^+). Anal. ($C_{15}H_{15}N_3O_2$) C, H, N.

Pharmacological Methods. Experiments in Anesthetized Dogs. Mongrel dogs of either sex (7–14 kg) were anesthetized with sodium pentobarbital (35 mg/kg, iv). A positive-pressure pump was used to ventilate dogs through an endotracheal tube (18 strokes/min, 20 mL/kg per stroke) and a heating pad maintained body temperature at 37–38 °C. Femoral arterial blood pressure was measured through a polyethylene catheter filled with heparin solution (16 units/mL) and connected to a Statham pressure transducer. The femoral vein was cannulated for iv drug administration. Heart rate was derived by means of a cardiotachometer that was triggered by the arterial pressure pulse. A Walton-Brodie strain-gauge arch sutured to the right ventricle of the heart measured cardiac contractility. Tension on the gauge was adjusted to 50 g, which corresponded to 10 mm of recorder pen deflection. Rapid iv injection of 50 mL of 5% dextran and mechanical compression of the aorta demonstrated that contractility measurements were independent of changes in preload and afterload. Subcutaneous pin electrodes provided a lead II ECG. Increasing doses of test compounds were administered iv in volumes of 0.25–4.0 mL at 5-min intervals; no responses occurred with appropriate vehicle injections. ED_{50} values were determined by linear regression analysis and are reported as the mean ± SEM of experimental values.

Acknowledgment. We thank Patsy Abbett for preparation of the manuscript.

Registry No. 1, 100643-96-7; 2, 100644-04-0; 4, 106500-53-2; 5, 106500-54-3.

Supplementary Material Available: Atomic coordinates, bond lengths, bond angles, anisotropic temperature factors, and hydrogen atom coordinates for 1 (Tables III–VII) (5 pages). Ordering information is given on any current masthead page.

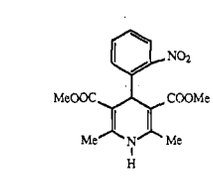
Substituted 1,2,3,4-Tetrahydroaminonaphthols: Antihypertensive Agents, Calcium Channel Blockers, and Adrenergic Receptor Blockers with Catecholamine-Depleting Effects

Karnail S. Atwal,* Brian C. O'Reilly, Eric P. Ruby, Chester F. Turk, Gunnar Aberg, Magdi M. Asaad, James L. Bergey, Suzanne Moreland, and James R. Powell

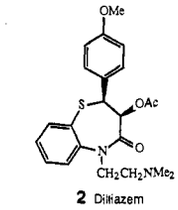
The Squibb Institute for Medical Research, Princeton, New Jersey 08543-4000. *Received August 11, 1986*

Substituted 1,2,3,4-tetrahydroaminonaphthols were found to be calcium channel blockers with antihypertensive properties. These compounds also possessed adrenergic β-receptor blocking activity. From the structure–activity studies, no clear correlation emerged between the in vitro calcium channel blocking activity and the acute antihypertensive activity in cannulated spontaneously hypertensive rats. Extensive pharmacological testing of selected compounds indicated that aminonaphthols are antihypertensive agents with many pharmacological properties. The relative contribution of various pharmacological actions toward the observed antihypertensive activity is unclear. Since the clinically useful calcium channel blocker verapamil is structurally related to these compounds, one of the aminonaphthols, *trans*-3-[(3,3-diphenylpropyl)amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol (12), was compared with verapamil for calcium channel blocking activity, adrenergic blocking activity, and catecholamine-depleting activity. Both compounds were found to be equipotent in these test systems.

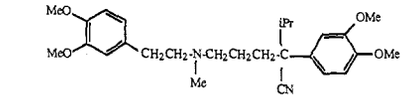
Calcium channel blockers have emerged to be the drugs of choice for treating various cardiac disorders.[1] The drugs commonly used are nifedipine (1), diltiazem (2), and verapamil (3). The last decade has seen an explosion in the synthesis of newer derivatives in each class. Most of this work has revolved around the most potent and vascular selective dihydropyridines. Efforts in the area of verapamil-like compounds are relatively few.[2] This is probably due to the fact that verapamil is a less specific calcium channel blocker than nifedipine. During the course of our own studies directed at the development of novel calcium channel blockers, we have found 1,2,3,4-tetrahydroaminonaphthols (4)[3] to be potent antihypertensive agents. A program was therefore initiated to study these compounds in detail. Some of these molecules display calcium channel blocking activity and β-receptor blocking activity, a combination that may be therapeutically advantageous.[4] In the present paper we disclose the results of our studies aimed at delineating the mechanism of action of aminonaphthols (4). We also describe the



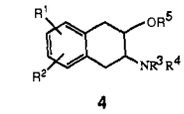
1 Nifedipine



2 Diltiazem



3 Verapamil



4

comparison of one of these compounds, *trans*-3-[(3,3-diphenylpropyl)amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol (12) with verapamil in a variety of pharmacological tests.

Chemistry

The synthesis of the trans amino alcohols (6) was accomplished in a straightforward manner. The epoxides (5)[5] were allowed to react with the appropriate amine under thermal (method A) or Lewis acid catalyzed (method B)[6] conditions (Scheme I). The stereochemistry of the

(1) Mannhold, R. *Drugs Today* **1984**, *20*, 69.
(2) Gualtieri, F.; Teodori, E.; Bellucci, C.; Pesce, E.; Piacenza, G. *J. Med. Chem.* **1985**, *28*, 1621 and references therein.
(3) U.S. Patents 3 930 022 and 4 076 843 assigned to E. R. Squibb & Sons, Inc.; Christova, K.; Dantschev, D. *Arch. Pharm. (Weinheim, Ger.)* **1984**, *317*, 619 and references therein.
(4) Cain, M. E.; Martin, T. C.; Sobel, B. E. *J. Cardiovasc. Med.* **1983**, 485.

(5) In order to simplify product identification, we have restricted our efforts to the synthesis of symmetrically substituted epoxides (7–11). For the synthesis of epoxide 7, see ref 3.

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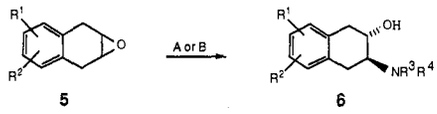
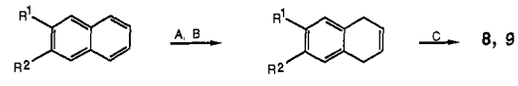
Scheme I[a]



5 6

[a] Key: (A) R_3R_4NH, heat; (B) R_3R_4NH, Et_3Al.

Scheme II[a]



12 $R^1 = R^2 = OH$

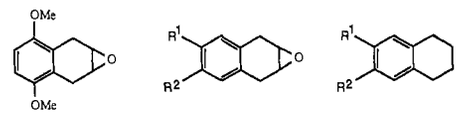
13 $R^1 = R^2 = OH$

14a) $R^1 = R^2 = OMe$

b) $R^1R^2 = OCH_2O$

[a] Key: (A) Li/NH_3; (B) K_2CO_3, MeI; (C) *m*-chloroperoxybenzoic acid.

product was ascertained to be trans by ^1H NMR spectroscopy. The derivatives prepared are listed in Table I along with their physical properties and the method of preparation. The synthesis of the various amines is described in the Experimental Section. The synthesis of 6,7-epoxy-5,6,7,8-tetrahydro-1,4-dimethoxynaphthalene (**7**) was carried out as described in the literature.[3] 6,7-Ep-



7 8 $R^1 = R^2 = OMe$

9 $R^1R^2 = OCH_2O$

10 $R^1 = R^2 = H$

11 $R^1 = R^2 = Me$

15

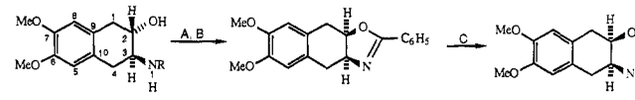
oxy-5,6,7,8-tetrahydro-2,3-dimethoxynaphthalene (**8**) and 6,7-epoxy-5,6,7,8-tetrahydro-2,3-(methylenedioxy)-naphthalene (**9**) were prepared from 2,3-dihydroxynaphthalene in three steps (Scheme II). 2,3-Dihydroxynaphthalene was subjected to dissolving metal reduction and the resulting olefin (**13**) alkylated with the appropriate alkylating agent to provide the intermediate (**14**). Epoxidation with *m*-chloroperbenzoic acid provided the desired epoxide (**8**,**9**) in rather low overall yield. The formation of a substantial amount of the tetrahydro product (**15**), during liquid ammonia reduction, could not be avoided. Some unidentified olefinic products were also formed during the reduction process. The preparation of 2,3-epoxy-1,2,3,4-tetrahydronaphthalene (**10**) has been described previously.[3] 6,7-Epoxy-5,6,7,8-tetrahydro-2,3-dimethylnaphthalene (**11**), prepared from 2,3-dimethylnaphthalene by dissolving metal reduction followed by epoxidation, was used for the next reaction without purification. The entire process is similar to the synthesis of epoxide **8** except that there is no alkylation step involved.

The synthesis of 4-(2-benzothiazolyl)propylamine from 4-chlorobutyryl chloride was fairly straightforward and is described in the Experimental Section. 4,4-Diphenylbutylamine and 5,5-diphenylpentylamine could be prepared from diphenylmethane whereas the 4,4-dicyclohexylamine was prepared from the 3,3-diphenylpropylamine by hydrogenation. The synthesis of the amines used in entries 16–18 (Table I) was carried out from the commercially available ketones and is detailed in the Experimental Section.

The syntheses of the acetate (entry 19), the methyl ether (entry 20), and the *N*-methyl derivative (entry 21) were

(6) Overman, L.; Flippin, L. *Tetrahedron Lett.* **1981**, *22*, 195.

Scheme III[a]



16 R = H

17 $R = COC_6H_5$

18 19

[a] Key: (A) NaOH, C_6H_5COCl; B) $SOCl_2$, heat; (C) 2.5N HCl.

carried out from the amino alcohol (entry 12) by using standard methods. The deshydroxy compound (entry 22) was prepared from 6,7-dimethoxy-2-tetralone by reductive amination.

The cis amino alcohol (entry 23) was obtained from the primary alcohol (**19**), which in turn was obtained from the trans product (**16**) via the benzoate (**17**) (Scheme III). It was at this stage that we had the opportunity to compare the 400-Mz ^1H NMR spectra of the trans (entry 12) and the cis (entry 23) compounds. The coupling constant of 10 Hz between C_2H and C_3H in the trans product (entry 12) is consistent with the trans diequatorial stereochemistry for the hydroxyl and the amino groups. The cis product (entry 23), where C_2H is shifted 0.4 ppm downfield, shows almost no coupling between C_2H and C_3H (for numbering, see formula **12**). This in line with a dihedral angle of nearly 90° and is indicative of axial stereochemistry for the hydroxyl group. The final proof came from the X-ray analysis of a derivative of the trans compound.[7] The acyl derivative (entry 24) was prepared by coupling of the amino alcohol (**16**) with 3,3-diphenylpropionic acid.

Pharmacology

The methods used to study biological activity (Tables II and III) are described in the Experimental Section.

Some of these compounds displayed good antihypertensive activity when given orally to spontaneously hypertensive rats (Table II). Pharmacological studies were therefore designed to elucidate the mechanism of action of these compounds.

Because of their structural similarity to verapamil,[8] we looked for possible calcium channel blocking activity. Calcium channel blocking activity in vitro was studied in a rabbit thoracic aorta preparation that was depolarized with potassium. The IC_{50} values were calculated by linear regression analysis of the dose-response curves. The vasorelaxant activity recorded in this test, according to our experience, is fairly predictable of the calcium channel blocking activity.[9] Potassium-depolarized excitation–contraction coupling is agreed to result from the mobilization of extracellular calcium through the voltage-sensitive calcium channel. Methods similar to ours have been routinely employed to determine the potency of calcium channel blockers in different smooth muscle preparations.[10]

In order to confirm channel blocking activity, we also examined some of these compounds (e.g., entry 12, Table III) by electrophysiological techniques. They were found to produce a selective reduction of the amplitude of Ca^{2+}-dependent slow-response action potentials in canine Purkinje fibers in vitro. No alteration of the Na^+-dependent action potential parameters was found, even at

(7) The X-rays analysis was carried out by Mary Malley.

(8) The compounds described in this paper can be considered to be derivatives of conformationally restricted phenylethylamine. Verapamil, of course, is a derivative of (3,4-dimethoxyphenyl)ethylamine.

(9) Brittain, R. J.; Moreland, S. *Physiologist* **1985**, *24*, 325.

(10) Yousif, F. B.; Triggle, D. J. *Can. J. Physiol. Pharmacol.* **1986**, *64*, 273 and references therein.

concentrations 10 times higher than the IC_{50} for slow-response blockade.

We found that compounds with phenylalkyl side chains (entries 1–3) showed only marginal calcium channel blocking activity and replacement of the phenyl ring with heterocycles (entries 4 and 5) was without any effect. Introduction of a second phenyl group[11] into the alkyl side chain resulted in improvement in the calcium channel blocking activity (entries 6–9), but this improvement was not reflected by increased antihypertensive activity. Hydrogenation of the phenyl rings led to the compound with potent antihypertensive activity (entry 10), but this compound was exceedingly difficult to evaluate for possible calcium channel blocking activity in in vitro test systems due to its poor solubility.

Replacement of the 5,8-dimethoxy groups (entry 7) with hydrogens provided a derivative with improved vasorelaxant activity (entry 11), but this compound remained devoid of any antihypertensive activity. By far the best antihypertensive activity was obtained when the substituents were introduced into the 6- and 7-positions of the naphthol moiety (entries 12–15).[12] With the exception of the catechol derivative (entry 14),[13] all of these compounds showed calcium channel blocking activity quite comparable to that of verapamil.

Modification of the phenyl groups of the side chain did not affect the antihypertensive activity significantly but had some effect on the calcium channel blocking activity (entries 16, 17). Replacement of one of the phenyl rings with an isopropyl group resulted in complete loss of the antihypertensive activity, although this compound still relaxed the vascular smooth muscle in vitro (entry 18).

With the exception of the acetate (entry 19), modification of the amino alcohol functionality led to a considerable drop in the antihypertensive activity (entries 20–23). Interestingly, some of these compounds still relaxed the potassium-contracted rabbit aorta (entries 21–23). It is worth pointing out here that while the relative stereochemistry of the amino alcohol was crucial to the antihypertensive activity, it had no effect on the calcium channel blocking activity recorded in the rabbit aorta test (entry 12 vs. 23). The presence of the basic nitrogen atom was essential for both the antihypertensive affect as well as the smooth muscle relaxing activity in vitro (entry 24).

Since these compounds contain the amino–alcohol arrangement common to adrenoceptor β-blocking agents,[14] we evaluated them for β-blocking activity. ED_{50} values for blockade of β_1- and β_2-receptors were determined in anesthetized pigs challenged with intravenous injections of isoproterenol. As summarized in Table II, some of the compounds showed β-blocking activity with marginal level of selectivity for the β_2-receptor.

Although some of the compounds displayed impressive antihypertensive activity, there did not seem to be a direct correlation between the antihypertensive activity and the calcium channel blocking activity (recorded as smooth muscle relaxing activity in depolarized rabbit aorta). Especially noticeable are entries 11 and 21–23 where the compounds showed good calcium blocking activity but were only marginally active as antihypertensive agents. In order to explore further the mechanism of action of these compounds, we decided to do some additional testing.

The structurally related calcium channel blocking drug verapamil has been reported to possess a variety of pharmacological properties.[15] We evaluated one of the most potent antihypertensive agents of this series, *trans*-3-[(3,3-diphenylpropyl)amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol (entry 12) in some of these test systems along with verapamil. We compared the two compounds for calcium channel blocking activity, for α-receptor blockade, and for effects on catecholamine stores. Rabbit aorta tissue challenged with norepinephrine was used for determining the pA_2 value for α-blockade. For determination of catecholamine depletion, we orally administered the test compounds (45 μmol/kg; twice) to spontaneously hypertensive rats. After 24 h, the rats were sacrificed and the hearts and brains were analyzed for catecholamine levels. As shown in Tables II and III, *trans*-3-[(3,3-diphenylpropyl)amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol (entry 12) and verapamil share several pharmacological properties. Of particular interest was the ability of the aminonaphthol (entry 12) and verapamil to deplete peripheral catecholamine stores. The mechanism for catecholamine depletion may be different for each compound.[16] The degree to which the various activities demonstrated for *trans*-3-[(3,3-diphenylpropyl)amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol contribute to the antihypertensive effect of aminonaphthols (4) is not clear.

We have demonstrated that some of the aminonaphthol analogues are antihypertensive agents with many pharmacological properties. In addition to being calcium channel blockers, they are adrenergic blocking agents and they also deplete catecholamines from peripheral stores. The relative contribution of the various pharmacological actions toward the observed antihypertensive activity, however, remains to be determined. The most active compound in this series, *trans*-3-[(3,3-diphenylpropyl)-amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol, is structurally related to both class II (e.g., verapamil) and class III (e.g., prenylamine) calcium channel blockers. Our results confirm that verapamil, which is a clinically useful calcium channel blocker, also displays several other pharmacological properties.[15] In fact, verapamil and *trans*-3-[(3,3-diphenylpropyl)amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol show very similar potencies for α-receptor blockade and for effects on the catecholamine levels. Both compounds are equipotent as antihypertensive agents in the spontaneously hypertensive rats.

Experimental Section

Chemistry. All melting points were taken on a capillary

(11) It is not surprising that introduction of the second phenyl group improved the calcium channel blocking activity as these compounds are now related to the known calcium channel blockers such as prenylamine; see for example: Janis, R. A.; Triggle, D. J. *J. Med. Chem.* **1983**, *26*, 775.

(12) It is interesting to note that one of the most active compounds (entry 12) has a substitution pattern on the naphthol ring that is very similar to the phenylethylamine portion of verapamil.

(13) Due to its instability in solution, the in vitro testing of this compound could not be carried out properly.

(14) Ahlquist, R. *Prog. Drug. Res.* **1976**, *20*, 27 and references therein.

(15) For calcium channel blocking activity, see reference in note 10. For dopamine antagonistic activity, see: Johnson, C. E.; Steinsland, O. S.; Scriabine, A. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 802. For reserpine-like activity and catecholamine-depletion studies, see: Chaudhry, A.; Vohra, M. M. *Eur. J. Pharmacol.* **1984**, *97*, 156 and references cited therein. For α-blocking activity, see: (a) Beckering, J. J.; Thoolan M. J. M. C.; de Jong, A.; Wilfert, B.; Timmermans, P. B. M. W. M.; van Zwieten, P. A. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 515. (b) Karliner, J. S.; Motulsky, H. J.; Dunlap, J.; Brown, J. H.; Insel, P. A. *Circulation* **1981**, *64* (Suppl. 4), 208. (c) Motulsky, H. J.; Hughes, R. J.; Snavely, M. D.; Insel, P. A. *Circulation* **1981**, *64* (Suppl. 4), 287.

(16) Aberg, G.; Asaad, M. M.; Atwal, K. S.; Bergey, J. L.; Liu, E. C. K.; Zaki, F. G. manuscript in preparation.

Table I. Summary of the Structures of Aminonaphthols and Their Melting Point and Method of Preparation

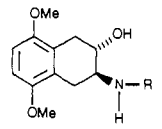
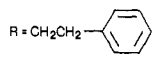
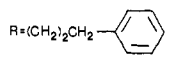
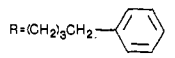
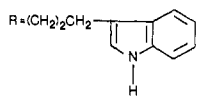
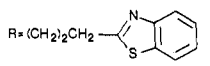
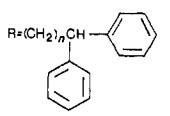
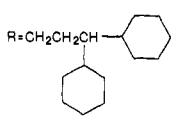
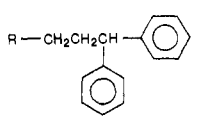
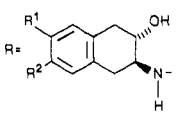
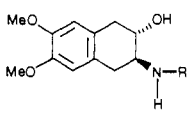
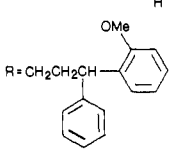
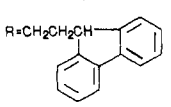
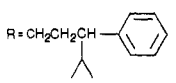
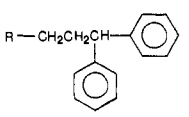
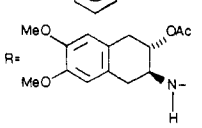
entry	structure	analyses	mp, °C	method	yield, %
					
1		$C_{20}H_{25}NO_3$ (C, H, N)	131–133 (2-propanol)	B	63
2		$C_{21}H_{27}NO_3$·HCl (C, H, N, Cl)	243–244 (ethanol)	B	82
3		$C_{22}H_{29}NO_3$·HCl (C, H, N, Cl)	237–239 (2-propanol/methanol)	A	58
4		$C_{23}H_{28}N_2O_3$·HCl (C, H, N, Cl)	220–222 dec (2-propanol/methanol)	A	63
5		$C_{22}H_{26}N_2O_3S$·HCl (C, H, N, Cl)	250–252 dec (2-propanol/methanol)	A	41
					
6	$n = 1$	$C_{26}H_{29}NO_3$·HCl (C, H, N, Cl)	222–224 (acetonitrile/2-propanol)	A	48
7	$n = 2$	$C_{27}H_{31}NO_3$·HCl (C, H, N, Cl)	249–250 (ethanol)	A	40
8	$n = 3$	$C_{28}H_{33}NO_3$·HCl (C, H, N, Cl)	261–264 (ethanol/methanol)	B	30
9	$n = 4$	$C_{29}H_{35}NO_3$·HCl (C, H, N, Cl)	201–203 (acetonitrile)	A	63
10		$C_{27}H_{43}NO_3$·HCl (C, H, N, Cl)	274–277 (2-propanol/methanol)	B	78
					
					
11	$R^1 = R^2 = H$	$C_{25}H_{27}NO$·HCl (C, H, N, Cl)	239–240 (acetonitrile)	B	51
12	$R^1 = R^2 = OMe$	$C_{27}H_{31}NO_3$·HCl·0.56H_2O (C, H, N, Cl)	224–226 (ethanol)	A	74
13	R^1, $R^2 = OCH_2O$	$C_{26}H_{27}NO_3$·HCl (C, H, N, Cl)	244–246 (2-propanol)	A	73
14	$R^1 = R^2 = OH$	$C_{25}H_{27}NO_3$·HCl (C, H, N, Cl)	>250 (methanol)	A	63
15	$R^1 = R^2 = Me$	$C_{27}H_{31}NO$·HCl (C, H, N, Cl)	197–199 (ether/methanol)	A	15
					
16		$C_{28}H_{33}NO_4$·HCl (C, H, N, Cl)	250–252 (2-propanol/methanol)	A	56
17		$C_{27}H_{29}NO_3$·HCl (C, H, N, Cl)	>275 (methanol)	A	70
18		$C_{24}H_{33}NO_3$·HCl (C, H, N, Cl)	243–245 dec (2-propanol/methanol)	A	68
					
19		$C_{29}H_{33}NO_4$·HCl (C, H, N, Cl)	209–211 (2-propanol)		91

Table I (Continued)

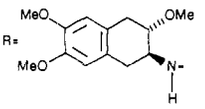
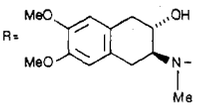
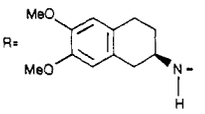
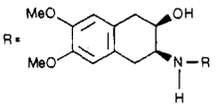
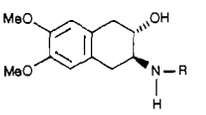
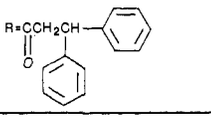
entry	structure	analyses	mp, °C	method	yield, %
20		$C_{28}H_{33}NO_3 \cdot (COOH)_2 \cdot 0.36H_2O$ (C, H, N)	186–188 (ethanol)		64
21		$C_{28}H_{33}NO_3$ (C, H, N)	154–156 (2-propanol)		66
22		$C_{27}H_{31}NO_2 \cdot HCl$ (C, H, N, Cl)	238–239 (acetone)		48
23	 	$C_{27}H_{31}NO_3 \cdot HCl$ (C, H, N, Cl)	257–260 (2-propanol/methanol)		36
24		$C_{27}H_{29}NO_3$ (C, H, N)	171–172 (2-propanol)		80

Table II. Summary of the Antihypertensive Activity, Calcium Blocking Activity, and β-Adrenoceptor Blocking Activity of Aminonaphthols

entry	antihypertensive activity[a] (135 μmol/kg po) (n = 5): decrease in blood pressure		calcium blocking activity (n = 4):	β-blocking activity: ED_{50}, mg/kg (n = 2)	
	% maximum (0–6 h)	% average over 24 h	IC_{50}, μM	β_1	β_2
1	*b*	*b*	21	0.90	0.01
2	14	14	5.5	0.46	0.03
3	26	23	3.6	1.35	0.28
4	23	24	23	0.56	0.08
5	16	16	13.5	0.44	0.03
6	10	16	13.3	>3.0	2.0
7	15	19	1.5	0.22	0.14
8	6	10	0.8	1.50	1.34
9	10	10	2.0	3.0	0.20
10	27	23	*c*	*c*	*c*
11	11	8	0.4	>3.0	3.0
12	32	34	0.4	3.0	1.6
13	25	25	0.3	2.16	0.80
14	29 (45 μmol/kg)	30	19.6	*d*	*d*
15	17 (45 μmol/kg)	32	1.0	*d*	*d*
16	21	28	0.6	*d*	*d*
17	32	34	1.4	*d*	*d*
18	8	10	2.5	*d*	*d*
19	34	34	2.8	>3.0	>3.0
20	*b*	*b*	1.8	>3.0	2.55
21	11	19	0.4	>3.0	1.05
22	11	12	0.2	>3.0	1.19
23	14	19	0.2	*d*	*d*
24	6	16	9.4	>3.0	>3.0
propranolol	*b*	*b*	*d*	0.05	0.1
verapamil	40	32	0.3	>3.0	>3.0

[a] Percent decrease in blood pressure was calculated from the decrease in blood pressure (normally 40–75 mmHg) of the treatment group and the blood pressure (normally 190–200 mmHg) of the control group; 135 μmol/kg usually amounts to 40–50 mg/kg of the test agent. [b] No activity. [c] Could not be tested due to solubility problems. [d] Not tested.

melting point apparatus and are uncorrected. The infrared spectra were recorded with a Perkin-Elmer 983 spectrophotometer in a KBr pellet. NMR spectra were measured on JEOL GX-400 and FX-270 spectrometers with Me_4Si as an internal standard. Flash chromatography was run with Whatman LPS-1 silica gel. Spectral data of only key intermediates and final compounds are included. Microanalyses of all crystalline compounds was within ±0.4% of calculated values.

Method A (Described for the Preparation of *trans*-3-[(3,3-Diphenylpropyl)amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol Hydrochloride, Entry 12). The reaction mixture containing epoxide **8** (10.0 g, 48.5 mmol), 3,3-diphenylpropylamine (10.9 g, 50.0 mmol), and 3-pentanol (2.0 mL) was heated at 160 °C for 4 h. The reaction mixture was allowed to cool and then triturated with 2-propanol to provide a colorless solid (17.8 g). This was dissolved in chloroform and converted into its HCl salt. The resulting product was crystallized from 2-propanol–methanol to yield pure product (16.5 g, 73.6%): mp 224–226 °C; NMR (CH_3COOH-d_4) δ 3.05 (dd, J = 15.5 and 11.0 Hz, C_1-2H), 3.15 (m, C_4H), 3.48 (td, J = 10.0 and 5.3 Hz, C_3H),

Table III. Comparison of Verapamil with *trans*-3-[(3,3-Diphenylpropyl)amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol

entry	antihypertensive activity[a] (45 μmol/kg po) (n = 4): decrease in blood pressure, % maximum (0–6 h)	antihypertensive activity[a] (45 μmol/kg po) (n = 4): decrease in blood pressure, % average (0–24 h)	calcium blocking activity: IC_{50}, μM (n = 4)	α-blocking activity: pA_2 (n = 6)	% catecholamine depletion (SHR) (n = 4; 2 × 45 μmol/kg), brain	% catecholamine depletion (SHR) (n = 4; 2 × 45 μmol/kg), heart	slow action potential blockade (n = 4): IC_{50}, μM
12	21	25	0.4	6.0	0	97	0.27
verapamil	16	21	0.3	6.0	0	75	0.11

[a] Percent decrease in blood pressure was calculated from the decrease in blood pressure (normally 40–75 mmHg) of the treatment group and the blood pressure (normally 190–200 mmHg) of the control group; 45 μmol/kg amounts to 22 mg/kg of verapamil and 21 mg/kg of *trans*-3-[(3,3-diphenylpropyl)amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol.

4.22 (td, J = 10.0 and 6.0 Hz, C_2H), 6.63, 6.62 (s, C_5H and C_6H) (for numbering, see formula 13).

Method B (Described for the Preparation of *trans*-1,2,3,4-Tetrahydro-5,8-dimethoxy-3-[(3-phenylpropyl)-amino]-2-naphthalenol Hydrochloride, Entry 2). The solution of phenylpropylamine (946 mg, 7.0 mmol) in dry dichloromethane (5 mL) under argon was treated dropwise with triethylaluminum solution (3.7 mL of 1.9 M solution in toluene). After the mixture was stirred at room temperature for 30 min, a solution of 6,7-epoxy-5,6,7,8-tetrahydro-1,4-dimethoxynaphthalene (7; 1.44 g, 7.0 mmol) in dichloromethane (2 mL) was added dropwise. The reaction was allowed to stir at room temperature overnight. It was cooled to 0 °C and then treated with 6 N sodium hydroxide (5 mL). The resulting mixture was stirred vigorously at room temperature for 1 h. The organic layer was separated and the aqueous phase was reextracted with dichloromethane. The combined organic extracts were washed with brine, dried over magnesium sulfate, and evaporated to provide a light yellow oil. This was converted to its HCl salt by treatment with ethanolic HCl, and the product was crystallized from acetonitrile to yield a colorless solid (2.17 g, 82.5%); mp 243–244 °C.

Preparation 6,7-Epoxy-5,6,7,8-tetrahydro-2,3-dimethoxynaphthalene (8). A solution of 2,3-dihydroxynaphthalene (12; 48 g, 0.30 mol) in 150 mL of THF was added to 1 L of liquid ammonia at −78 °C under an argon atmosphere. A colorless precipitate formed. To this stirred mixture was added lithium metal (10.5 g, 1.5 mol) in small pieces over the course of 1 h. When addition of the lithium was complete, the reaction was stirred for 45 min. Ethanol was added until the blue color disappeared (200 mL over 20 min). The ammonia was evaporated, and ice, water, and ether were added. The mixture was cooled in an ice/H_2O bath and acidified (to pH 1) with 140 mL of concentrated HCl. The layers were separated, and the aqueous layer was reextracted with ether. The combined organic fractions were washed with brine, dried ($MgSO_4$), and evaporated to give a yellowish oil. This was taken up in acetone (500 mL), and the mechanically stirred solution was treated with ground K_2CO_3 (230 g, 1.7 mol) followed by methyl iodide (75 mL, 1.2 mol). The brown mixture was allowed to stir overnight at room temperature. The reaction mixture was then filtered and evaporated to give a tan solid. This was taken up in 20% CH_2Cl_2 in Et_2O and washed with water, 5 N HCl, 10% $NaHSO_3$, 1 N NaOH, and brine. After drying over $MgSO_4$, the solution was rotary evaporated to give a yellowish solid (52 g). This solid was triturated with ether to give colorless crystals (26 g). The mother liquor was concentrated to a solid (26 g) and triturated with ether/hexane (1/1) to give 6 g of pale yellow crystals. To a stirred solution of the combined solid (29 g) in 500 mL of CH_2Cl_2 under argon at 0 °C was added a slurry of *m*-chloroperbenzoic acid (19.1 g, 85%) in CH_2Cl_2 (200 mL) over the course of 30 min. Solid mCPBA (20 g) was then added portionwise over 50 min (total mCPBA, 39.1 g of 85%). The resulting mixture was allowed to stir for 3 h. The reaction mixture was filtered through Celite and evaporated to a yellow oil. This was taken up in ether and washed with 10% $NaHSO_3$, 1 N NaOH, and brine, dried over $MgSO_4$, and evaporated to give a yellow solid. Chromatography (Waters HPLC, 3% EtOAc in CH_2Cl_2) yielded a yellowish solid (9.6 g). This was combined with 1.2 g from another run and recrystallized from isopropyl ether to give analytically pure pale yellow needles 8 (8.38 g, 14% from 2,3-dihydroxynaphthalene); mp 99–101 °C. The other epoxides (9–11) were prepared in a similar manner.

Preparation of *trans*-7-[(3,3-Diphenylpropyl)amino]-5,6,7,8-tetrahydro-2,3,6-naphthalenetriol Hydrochloride (Entry 14). (a) *trans*-3-[(3,3-Diphenylpropyl)amino]-5,6,7,8-tetrahydro-6,7-bis(phenylmethoxy)-2-naphthalenol hydrochloride was prepared in 70% yield by reacting 6,7-epoxy-5,6,7,8-tetrahydro-2,3-bis(phenylmethoxy)naphthalene (prepared by the same method as described for 8) with 3,3-diphenylpropylamine by method A; mp 218–220 °C (2-propanol/methanol).

(b) A mixture of *trans*-3-[(3,3-diphenylpropyl)amino]-5,6,7,8-tetrahydro-6,7-bis(phenylmethoxy)-2-naphthalenol hydrochloride (1.0 g, 1.65 mmol) and 10% palladium on charcoal (62 mg) in methanol (50 mL) was stirred under hydrogen at atmospheric pressure. The reaction was filtered through Celite and the filtrate was immediately evaporated until cloudy. It was diluted with ether and the resulting solid was filtered to give *trans*-7-[(3,3-diphenylpropyl)amino]-5,6,7,8-tetrahydro-2,3,6-naphthalenetriol hydrochloride (639 mg, 91%) (entry 14); mp above 250 °C.

Preparation of 3-(2-Benzothiazolyl)propanamine for Entry 5. A solution of o-aminothiophenol (4.25 g, 34 mmol) and diisopropylethylamine (4.4 g, 5.9 mL, 34 mmol) in anhydrous tetrahydrofuran (30 mL) was cooled to 0 °C and treated dropwise with 4-chlorobutyryl chloride (4.0 g, 28.4 mmol, 3.3 mL of 97%). After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was continued for 2 h. The reaction was then heated at 80 °C (oil bath) for 14 h. It was cooled to room temperature and diluted with dichloromethane (50 mL). The resulting solution was washed with 2 N HCl, 1 N sodium hydroxide, and brine. After drying over magnesium sulfate, the solvent was evaporated under reduced pressure to give a light brown oil. Purification by flash chromatography (10% ethyl acetate in hexane) gave 3-(benzothiazolyl)propyl chloride (4.40 g, 63.5%) as a light yellow oil.

The reaction mixture containing 3-(2-benzothiazolyl)propyl chloride (2.4 g, 11.34 mmol) in dry Me_2SO (20 mL) was treated with potassium phthalamide (2.50 g, 13.6 mmol), and the resulting suspension was stirred at 80 °C under argon for about 3 h. The reaction mixture was poured into water (75 mL), and the resulting precipitate was filtered off and washed with water and 2-propanol. The yellow solid (3.3 g) was recrystallized from 2-propanol to give 2-[2-(benzothiazolyl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione as pale yellow crystals (2.8 g, 76.7%).

A solution of 2-[2-(benzothiazolyl)ethyl]-1*H*-isoindole-1,3-(2*H*)-dione (3.7 g, 11.5 mmol) in chloroform (30 mL) was treated with hydrazine (552 mg, 17.3 mmol), and the resulting yellow solution was stirred under argon for 4 h. More hydrazine (550 mg) was added and stirring was continued for 16 h. The white solid was filtered off and the solvent was evaporated to give a brown semisolid. The residue was taken up in chloroform and extracted with 2 N HCl (3 × 50 mL). The aqueous extracts were basified with 5 N NaOH to pH 14 and reextracted with chloroform. The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated to give 3-(2-benzothiazolyl)propanamine (1.9 g, 86.4% crude yield) as a thick oil.

Preparation of 4,4-Diphenylpentylamine for Entry 9. A suspension of $NaNH_2$, employing 6.3 g (0.275 g-atom) of Na pellets, in approximately 600 mL of liquid NH_3 was prepared.[17] After all of the Na had been added, about 1 h was required for all of the blue color to disappear to give the dark gray suspension. Addition of diphenylmethane (42 g, 0.25 mol) in ether (20 mL)

(17) Murphy, W. S.; Hamrick, P. J.; Hauser, C. R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 523.

gave a deep orange-brown suspension. After the mixture was stirred for 1 h, 4-bromobutyronitrile (40.7 g, 0.275 mol) in 20 mL of ether was added dropwise. Stirring was continued for 3 h (dry ice condenser) after which the NH_3 was allowed to evaporate overnight. The mixture of a dark oil and solids was stirred for 1 h with 250 mL of ether and 25 mL of EtOH, then cooled, stirred vigorously, and treated portionwise with 150 mL of H_2O. After stirring for an additional 15 min, the layers were separated, and the aqueous phase was extracted with ether (3 × 200 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated to give 52.3 g of a yellow oil. The latter was fractionated and material boiling at 135–165 °C (0.2–0.3 mmHg) was redistilled to yield 21.7 g of 4,4-diphenylbutyronitrile as a light yellow oil; bp 152–160 °C (0.2–0.3 mmHg).

A stirred suspension of lithium aluminum hydride (1.9 g, 50 mmol) in 100 mL of ether was treated dropwise with 4,4-diphenylbutyronitrile (10.0 g, 42 mmol) in 20 mL of ether. After the addition, the mixture was stirred at room temperature for 15 min, heated to reflux for 3 h, and kept overnight at room temperature. The mixture was cooled, stirred vigorously, and treated portionwise (cautiously) with 2.5 mL of H_2O, 2 mL of 20% NaOH, and finally 7 mL of H_2O. The cooling bath was removed, and after the mixture was stirred for 1 h, the solid was filtered off and washed with ether, and the combined filtrates were dried ($MgSO_4$). The solvent was removed on a rotary evaporator and the yellow oily residue (9.3 g) distilled to provide 4,4-diphenylpentylamine as a light yellow oil (8.4 g, 83%); bp 148–153 °C (0.2 mm).

Preparation of 4-Methyl-3-phenylpentylamine for Entry 18. To a solution of *n*-butyllithium in hexane (1.55 M, 21 mL, 33 mmol) at −78 °C under argon was added THF (5 mL), followed by dropwise addition of a solution of acetonitrile (1.6 mL, 30 mmol) in THF (30 mL).[18] A white precipitate formed. This mixture was allowed to stir for 1 h, after which time a solution of isobutyrophenone (4.45 g, 30 mmol) in THF (30 mL) was added dropwise. The cooling bath was removed and the reaction (now a pale yellow solution) was stirred for 15 min before it was poured into ice water/HCl. This mixture was extracted with ether. The combined organic phases were washed with brine, dried over $MgSO_4$, and rotary evaporated to give the crude hydroxy nitrile (6.00 g) as an oil.

To a solution of the crude compound (5.8 g) in dioxane (50 mL) was added 85% H_3PO_4 (10.0 mL) and the solution was refluxed overnight (oil bath temperature 140–160 °C). The solution turned dark brown. The reaction mixture was poured into ice water and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and rotary evaporated to a brown, partly crystalline gum. Chromatography (CH_2Cl_2/hexane, 7/3) gave a cis/trans mixture of the unsaturated nitrile as a yellow oil (2.00 g, 40% from isobutyrophenone).

A mixture of the unsaturated nitrile (1.80 g, 10.5 mmol), PtO_2 (170 mg), acetic anhydride (20 mL), and ethyl acetate (2 mL) was shaken under hydrogen pressure (20 psi) on a Parr hydrogenator for 18 h. The reaction mixture was filtered, rotary evaporated, and coevaporated, with toluene to give an oil (2.37 g).

A mixture of the above *N*-acetyl compound (1.70 g, 7.75 mmol) and 3 N aqueous HCl (25 mL) was refluxed for 24 h. After cooling to room temperature, the mixture was cooled in an ice/H_2O bath and basified to pH 14 with 6 N NaOH. The aqueous phase was extracted with 4 × 50 mL of 20% CH_2Cl_2 in Et_2O. The combined organic extracts were washed with brine, dried over K_2CO_3, and filtered. The filter cake was washed with $CHCl_3$. The filtrate was evaporated to give 4-methyl-3-phenylpentylamine as an oil (1.12 g, 87%).

3-(2-Methoxyphenyl)-3-phenylpropylamine (used in entry 16) and 2-(9-fluorenyl)ethylamine (used in entry 17) were prepared in a similar fashion.

Preparation of *N*-(3,3-Diphenylpropyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenamine Hydrochloride (Entry 22). To a solution of 3,3-diphenylpropylamine (3.1 g, 14.6 mmol) in methanol (12 mL) was added ethanolic hydrochloric acid (1 mL of 5 N solution, 5 mmol) followed by 6,7-dimethoxy-2-tetralone (500 mg, 2.43 mmol). To the dark brown reaction mixture was then added sodium cyanoborohydride (130 mg, 1.96 mmol). The resulting suspension was stirred at room temperature for 48 h whereby the reaction mixture had become a homogeneous red solution. It was diluted with chloroform (50 mL) and washed with 2 N sodium hydroxide and brine. After drying over anhydrous potassium carbonate, the solvent was evaporated to a brown oily residue. It was purified by flash chromatography (1–2% MeOH in CH_2Cl_2) to give a yellow oil (720 mg). This material was taken up in acetone and treated with ethanolic HCl (0.4 mL of 5 N solution) to provide analytically pure product (513 mg, 48.4%); mp 238.5–239.5 °C after crystallization from acetone.

Preparation of *cis*-3-Amino-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol Hydrochloride. To a solution of *trans*-3-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol hydrochloride (1.30 g, 5.0 mmol), prepared by ammonolysis of epoxide **8**, in water (15 mL) at 0 °C was added a solution of benzoyl chloride (0.70 g, 5.0 mmol) in toluene (5 mL). To this vigorously stirred two-phase mixture was added, over the course of 2 h, sufficient 1 N aqueous NaOH to keep the pH between 7 and 9. The mixture was diluted with $CHCl_3$ and 1 N NaOH and filtered, and the filter cake was washed with H_2O. The white solid obtained was recrystallized from CH_3CN to give white crystals (1.30 g), mp 209–211 °C. A second crop was obtained (white crystals, 176 mg, mp partial at 191–193 °C, complete at 209–211 °C) that was identical by TLC. Combined yield: 1.48 g, 90%.

A solution of the above *N*-benzoyl compound (1.15 g, 3.52 mmol) in thionyl chloride (0.7 mL) under argon was heated in an oil bath at 50 °C for 2 h. The brown reaction mixture was diluted with toluene and a colorless precipitate formed. The solvent was evaporated, leaving a pale orange solid. A suspension of the solid in 2.5 N aqueous HCl was refluxed overnight. The solvent was rotary evaporated and the oily residue was triturated with CH_3CN to give an off-white solid, **19** (672 mg, 74%). This product was used for the next reaction without further purification.

Preparation of *cis*-3-[(3,3-Diphenylpropyl)amino]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthalenol Hydrochloride (Entry 23). To a solution of compound **19** (622 mg, 2.4 mmol) in dry CH_3OH (5 mL) under argon was added Et_3N (0.21 mL, 1.5 mmol) followed by a solution of 3,3-diphenylpropionaldehyde (626 mg, 3.0 mmol) in dry CH_3OH (5 mL). Sodium cyanoborohydride (280 mg, 4.5 mmol) was then added and the solution was allowed to stir at room temperature for 2 days. The solution was then cooled in an ice/H_2O bath and treated dropwise with concentrated HCl until the solution reached pH 2. The solvent was evaporated, leaving a colorless solid. To the solid were added ice, $CHCl_3$, and 1 N aqueous NaOH, and this mixture was shaken until the solid dissolved. The layers were separated, and the aqueous phase was extracted again with $CHCl_3$. The combined organic extracts were washed with brine, dried (anhydrous K_2CO_3), filtered, and evaporated to an oil. The oil was chromatographed on silica gel (CH_2Cl_2/CH_3OH/HOAc, 100/1/1, followed by 4% CH_3OH in CH_2Cl_2) to give an oil. This was taken up in CH_2Cl_2, washed with 1 N NaOH and brine, dried (K_2CO_3), filtered, and treated with excess methanolic HCl. The solvent was evaporated and the colorless solid residue was recrystallized from 2-propanol/$CHCl_3$/CH_3OH to give analytically pure white crystals (388 mg, 36%): mp 257.5–260 °C dec; NMR (CH_3COOH-d_4) δ 2.98 (dd, J = 17.5 and 2.6 Hz, C_1-2H), 3.09 (d, J = 7.69 Hz, C_4H), 3.66 (t, J = 8.54 Hz, C_3H), 4.64 (br s, C_2H), 6.59 (s, C_5H, C_8H) (for numbering, see formula **16**).

Preparation of *trans*-3,3-Diphenyl-*N*-(1,2,3,4-tetrahydro-3-hydroxy-6,7-dimethoxy-2-naphthalenyl)propanamide (Entry 24). To a solution of 3,3-diphenylpropionic acid (868 mg, 3.85 mmol) and hydroxybenzotriazole (518 mg, 3.85 mmol) in dimethylformamide (10 mL) was added dicyclohexylcarbodiimide (791 mg, 3.85 mmol). The reaction mixture was stirred under argon for 15–20 min whereby a white precipitate had appeared. It was then treated with amino alcohol **16** (784 mg, 3.5 mmol), and the resulting suspension was stirred at room temperature overnight. The reaction mixture was diluted with chloroform and dicyclohexylurea was filtered off. The solution was thoroughly washed with water, 1 N HCl, sodium bicarbonate, and brine. After drying over anhydrous $MgSO_4$, the solvent was evaporated to provide a semisolid. It was again diluted with chloroform and more dicyclohexylurea was filtered off. The residue, after evaporation of solvent, was purified by flash

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chromatography (2% MeOH in $CHCl_3$) to give a colorless solid (1.32 g). Crystallization from 2-propanol provided colorless crystalline product (1.0 g). The mother liquor was concentrated and crystallized again from 2-propanol to give a second crop (210 mg). The combined yield was 1.21 g: 79.8%. Analytically pure product, mp 171–172 °C, was obtained by recrystallization from absolute ethanol: NMR ($CDCl_3$) δ 2.3 (dd, J = 16.4 and 7.9 Hz, 1 H), 2.6 (dd, J = 16.6 and 8.4 Hz, 1 H), 2.9 (m, 2 H), 3.6 (m, 1 H), 3.82, 3.81 (s, 3 H), 3.90 (m, 1 H), 4.54 (t, J = 7.9 Hz, 1 H), 6.50, 6.44 (s, 1 H), 7.25 (m, 10 H); IR (KBr) 3411, 3346, 1668 cm^{-1}.

Pharmacology. (a) Calcium Blockade IC_{50} and α-Adrenoceptor pA_2 Determination. Male New Zealand rabbits weighing 1.8–2.4 kg were sacrificed by an injection of sodium pentobarbital (50 mg/kg) in the marginal ear vein. A section of the thoracic aorta approximately 3 cm long was removed and placed in a petri dish containing warm normal Krebs (PSS) solution.[19] Excess fat and tissue were removed, and rings of approximately 3 mm were cut and opened to yield strips 3 mm wide and 1 cm long. Strips were then mounted in 50-mL jacketed organ muscle chambers under a 4-g preload that was applied and maintained during a minimum 1-h equilibration period. Bath temperature was maintained at 37 °C and PSS was gassed with 95% O_2 + 5% CO_2 to yield a pH of 7.35. In the Ca^{2+}-blockade experiments, strips were stimulated by replacing the normal Krebs solution with a high K^+ (100 mM) PSS in which Na^+ was reduced by an equimolar amount. After attainment of a steady plateau tension, strips were exposed to increasing concentrations of various agents and relaxant responses were normalized with respect to initial recorded tensions. IC_{50} values were determined by regression analysis of the linear portion of the concentration response curves.[20] The pA_2 values for α_1-adrenoceptor blockade were obtained in strips similarly prepared but bathed in normal Krebs containing cocaine (10 μM) and propranolol (1 μM). Relative shifts in the cumulative concentration response curves to norepinephrine caused by the presence of various concentrations of test agents were used to obtained pA_2 values by a standard Schild analysis.[20]

(b) β-Adrenoceptor Blockade ED_{50}. Weanling pigs of either sex were anesthetized with sodium pentobarbital (40 mg/kg ip), tracheotomized, and respired with room air by a Harvard respirator pump. Blood gases were monitored with a Radiometer automated blood gas analyzer. The left femoral artery and vein were cannulated for the recording of blood pressure and drug administration, respectively. Hexamethonium (10 mg/kg) was given to block possible reflex response blood pressure changes, and atropine (0.2 mg/kg) was given to block the reflex activation of central cholinergic outflow tracts.

Isoproterenol was then given in a dose (0.1 μg/kg iv) that was found to reduce mean arterial blood pressure by approximately 30 mmHg and to increase heart rate at least 50 beats/min. Prior to drug administration, the responses to at least two challenges to isoproterenol were assessed for reproducibility. Test drug was then given iv over 5 min every 15 min; successive doses were increased cumulatively. Five minutes after each dose, an isoproterenol challenge was given to assess the possible blocking effects of drugs on heart rate increases (β_1) and decreases in diastolic blood pressure (β_2). Linear regression analysis of normalized dose–response curves yielded β_1 and β_2 ED_{50} values.

(c) Antihypertensive and Catecholamine-Depleting Effects in Spontaneously Hypertensive Rats (SHR). Male SHR were prepared surgically according to the method of Weeks and Jones,[21] and 3 weeks were allowed for recovery. Blood pressure was recorded directly by the method of Laffin et al.[22] Two oral doses of 45 μmol/kg were given with an interval of 17 h. Four hours after the second dose, the rats were killed by decapitation, and hearts and brains were quickly removed and frozen for tissue catecholamine determinations. Frozen tissues were homogenized in freshly prepared 0.4 N perchloric acid containing 5 mM reduced glutathione and then centrifuged at 0 °C to produce a protein-free supernatant, which was diluted and assayed in duplicate for catecholamine content. The radioenzymatic assay kit used in these experiments was purchased from Upjohn Diagnostics.

(d) Slow-Response Action Potentials. Canine Purkinje fibers were superfused with oxygenated Tyrode's solution with 15 μM atropine sulfate (Sigma) for approximately 30 min, at which time they were superfused with tris-buffer solution for the remainder of the experiment. The composition of the superfusate was as follows (mM): 140.1 tetraethylammonium (TEA) chloride, 8.0 $CaCl_2$, 2.7 KCl, 0.5 $MgCl_2$, 5.0 Tris (Trizma 7.7), 15 μM atropine sulfate. The solution was aerated with 100% O_2 and maintained at 35 ± 0.5 °C. The fiber was placed between the tips of the stimulating electrode and electrically stimulated with 60–90-V pulses of 30-ms duration at a rate of 0.2 Hz. Intracellular action potentials were recorded with glass microelectrodes (15–40 meg ohm) filled with 3 M KCl and coupled to high-impedance, negative-capacitance electrometers (WPI Instruments). Ag/Ag–Cl half cells were used as reference electrodes.

The amplitude of the Ca^{2+}-dependent, slow-response action potential as produced under these experimental conditions was used as an index of the slow inward current and drug-induced changes that were taken as a measure of Ca^{2+}-blockade in cardiac tissue.

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Registry No. **5** (R_1, R_2 = 6,7-$(OCH_2C_6H_5)_2$), 106359-42-6; **6** (R_1, R_2 = 5,8-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_2C_6H_5$), 106359-26-6; **6**·HCl (R_1, R_2 = 5,8-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_3C_6H_5$), 106359-27-7; **6**·HCl (R_1, R_2 = 5,8-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_4C_6H_5$), 106359-28-8; **6**·HCl (R_1, R_2 = 5,8-$(OCH_3)_2$, R_3 = H, R_4 = $CH_2CH(C_6H_5)_2$), 101333-54-4; **6**·HCl (R_1, R_2 = 5,8-$(OCH_3)_2$, R_3 = H, R_4 = $CH_2CH_2CH(C_6H_5)_2$), 101333-52-2; **6**·HCl (R_1, R_2 = 5,8-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_3CH(C_6H_5)_2$), 101333-67-9; **6**·HCl (R_1, R_2 = 5,8-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_4CH(C_6H_5)_2$), 101333-75-9; **6**·HCl (R_1 = R_2 = R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)_2$), 101333-51-1; **6**·HCl (R_1, R_2 = 6,7-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)_2$), 101333-61-3; **6**·HCl (R_1, R_2 = OCH_2O, R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)_2$), 106359-30-2; **6**·HCl (R_1, R_2 = 6,7-$(OH)_2$, R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)_2$), 106359-31-3; **6**·HCl (R_1, R_2 = 6,7-$(CH_3)_2$, R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)_2$), 106359-32-4; **6**·HCl (R_1, R_2 = 6,7-$(OCH_3)_2$, R_3 = H, R_4 = 4-$(CH_2)_2CH(C_6H_5)C_6H_4OCH_3$, 106359-33-5; **6**·HCl (R_1, R_2 = 6,7-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)(CH(CH_3)_2)$), 106359-34-6; **6**·HCl (acetate, R_1, R_2 = 6,7-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)_2$), 101333-72-6; **6** (R_1, R_2 = $(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)_2$), 101333-70-4; *cis*-**6**·HCl (R_1, R_2 = 6,7-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)_2$, 101333-80-6; **6** (R_1, R_2 = 6,7-$(OCH_3)_2$, R_3 = H, R_4 = $COCH_2CH(C_6H_5)_2$), 106375-47-7; **6** (R_1, R_2 = 6,7-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)_2$), 101333-76-0; **6** (R_1, R_2 = 6,7-$(OCH_3)_2$, R_3 = H, R_4 = $(CH_2)_3C_6H_5$), 106359-36-8; **6**·HCl (R_1, R_2 = 6,7-$(OCH_2C_6H_5)_2$, R_3 = H, R_4 = $(CH_2)_2CH(C_6H_5)_2$), 106359-41-5; **6** (R_1, R_2 = 6,7-$(OCH_3)_2$, R_3 = H, R_4 = COC_6H_5), 101334-02-5; **7**, 58851-64-2; **8**, 62946-20-7; **9**, 106359-38-0; **10**, 2461-35-0; **11**, 106359-39-1; **12**, 92-44-4; **13**, 106359-37-9; **14a**, 36230-56-5; **14b**, 106359-40-4; **16**·HCl, 106359-48-2; **18**, 106359-49-3; **19**, 101334-04-7; $H_2N(CH_2)_2CH(C_6H_5)_2$, 5586-73-2; $H_2N(CH_2)_3C_6H_5$, 2038-57-5; $2\text{-}H_2NC_6H_4SH$, 137-07-5; $H_3CCH_2N(CH(CH_3)_2)_2$, 7087-68-5; $Cl(CH_2)_3COCl$, 4635-59-0; $Br(CH_2)_3CN$, 5332-06-9; $(C_6H_5)_2CH_2$, 101-81-5; $(C_6H_5)_2CH(CH_2)_2CN$, 22156-48-5; $(C_6H_5)_2C(CH_3)(CH_2)_3NH_2$, 106359-44-8; $C_6H_5COCH(CH_3)_2$, 611-70-1; CH_3CN, 75-05-8; $H_3CCH(OH)CN$, 78-97-7; (Z)-$C_6H_5((CH_3)_2CH)C{=}CHCH_2NH_2$, 106359-45-9; (E)-$C_6H_5((CH_3)_2CH)C{=}CHCH_2NH_2$, 106359-46-0; $C_6H_5((CH_3)_2CH)C{=}CHCH_2NHCOCH_3$, 106359-47-1; $((CH_3)_2CH)CH(C_6H_5)(CH_2)_2NH_2$, 101334-00-3; $(C_6H_5)_2CHCH_2CHO$, 4279-81-6; $(C_6H_5)_2CHCH_2CO_2H$, 3333-15-1; $H_2N(CH_2)_2C_6H_5$, 64-04-0; $H_2N(CH_2)_4C_6H_5$, 13214-66-9; $H_2NCH_2CH(C_6H_5)_2$, 3963-62-0; $H_2N(CH_2)_3CH(C_6H_5)_2$, 36765-74-9; $2\text{-}H_2N(CH_2)_2CH(C_6H_5)C_6H_4OCH_3$, 106359-50-6; *trans*-1,2,3,4-tetrahydro-5,8-dimethoxy-3-[(3-(3-indolyl)propyl)amino]-2-naphthalenol hydrochloride, 106359-29-9; *trans*-1,2,3,4-tetrahydro-5,8-dimethoxy-3-[(3-benzothiazol-2-ylpropyl)amino]-2-naphthalenol hydro-

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chloride, 101333-64-6; *trans*-1,2,3,4-tetrahydro-5,8-dimethoxy-3-[(3,3-dicyclohexylpropyl)amino]-2-naphthalenol hydrochloride, 101333-60-2; *trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-3-[(2-(9*H*-fluoren-9-yl)ethyl)amino]-2-naphthalenol hydrochloride, 101333-74-8; *trans*-1,2,3,4-tetrahydro-6,7-dimethoxy-3-[(3,3-diphenylpropyl)amino]-2-naphthalenol oxalate, 101333-79-3; 1,2,3,4-tetrahydro-6,7-dimethoxy-3-[(3,3-diphenylpropyl)-amino]naphthalene, 106359-35-7; 3-(benzothiazolyl)propyl chloride, 65655-72-3; potassium phthalimide, 1074-82-4; 2-[2-(benzothiazolyl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione, 106359-43-7; 3-(2-benzothiazoyl)propanamine, 51124-73-3; 6,7-dimethoxy-2-tetralone, 2472-13-1; 3-(3-propylamine)indole, 6245-89-2; 3,3-dicyclohexylpropylamine, 101333-99-7; 2-(9-9*H*-fluorenyl)ethanamine, 21745-79-9.

Synthesis and Biological Activity of Novel Calcium Channel Blockers: 2,5-Dihydro-4-methyl-2-phenyl-1,5-benzothiazepine-3-carboxylic Acid Esters and 2,5-Dihydro-4-methyl-2-phenyl-1,5-benzodiazepine-3-carboxylic Acid Esters

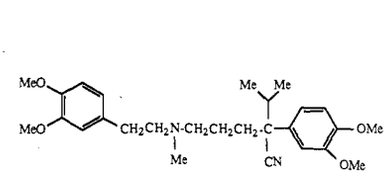
Karnail S. Atwal,* James L. Bergey, Anders Hedberg, and Suzanne Moreland

The Squibb Institute for Medical Research, Princeton, New Jersey 08543-4000. *Received September 6, 1986*

2,5-Dihydro-4-methyl-2-phenyl-1,5-benzothiazepine-3-carboxylic acid esters, based on the structures of dihydropyridines and diltiazem, were synthesized from o-aminothiophenol and 2-(phenylmethylene)-3-oxobutanoic acid esters. Biological evaluation in the potassium-depolarized rabbit aorta suggests that these compounds are calcium channel blockers. The in vitro activity was further confirmed by electrophysiological techniques. Structure–activity studies for the aromatic substitution showed that the 2-nitro derivative was the most potent (IC_{50} = 0.3 μM) compound in vitro while the ethyl ester was slightly better than the corresponding methyl ester. Replacement of sulfur with nitrogen atom provided 2,5-dihydro-4-methyl-2-(3-nitrophenyl)-1,5-benzodiazepine-3-carboxylic acid ethyl ester, which was only slightly less active than the corresponding benzothiazepine. Derivatization of the nitrogen in 2,5-dihydro-4-methyl-2-(3-nitrophenyl)-1,5-benzothiazepine-3-carboxylic acid methyl ester with a (dimethylamino)ethyl group (present in diltiazem) provided 2,5-dihydro-5-[(dimethylamino)ethyl]-4-methyl-2-(3-nitrophenyl)-1,5-benzothiazepine-3-carboxylic acid methyl ester, which was found to be equipotent to diltiazem in vitro. Radioligand binding studies using [^{3}H]nitrendipine and [^{3}H]diltiazem showed that the compound with the free nitrogen binds competitively into the dihydropyridine binding site while the molecule in which the nitrogen is alkylated with a (dimethylamino)ethyl group interacts competitively with both diltiazem and dihydropyridine binding sites. Our results therefore show that 2,5-dihydro-4-methyl-2-phenyl-1,5-benzothiazepine-3-carboxylic ester is a good starting point for designing dihydropyridine as well as diltiazem mimics.

Calcium channel blockers have been proven to be clinically useful agents in treating various cardiovascular disorders.[1] The drugs that are most prescribed in this area are, verapamil (1), diltiazem (2), and nifedipine (3). Because of their potency and their selectivity for the vascular smooth muscle, there has been tremendous activity in the synthesis of new dihydropyridine analogues. Efforts in the area of diltiazem like molecules are relatively few. Verapamil, which possesses a variety of pharmacological properties,[2] has seen very little activity.[3] Considering the diverse pharmacology of verapamil, one is inclined to design novel molecules based on the structures of diltiazem (2) and nifedipine (3); however, such an endeavor is extremely complicated due to the dissimilar nature of the structures of these compounds. In the present paper we describe our approach for designing novel calcium channel blocking agents, e.g., benzothiazepines and benzodiazepines (4).

The structures of compound 4 (X = S) is derived from both diltiazem and a dihydropyridine type calcium channel blocker. With the reasonable assumption that only half of the dihydropyridine molecule is necessary for binding



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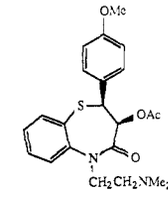

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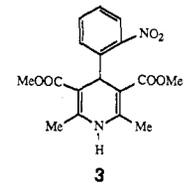

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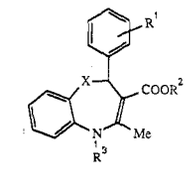

4

into the receptor site,[4] molecules such as 4 (X = S, R^3 = H) were expected to be dihydropyridine mimics. We had also hoped that derivatization of the nitrogen atom in 4 with a (dimethylamino)ethyl group (found in diltiazem structure) might provide us with compounds (4, X = S, R^3 = $CH_2CH_2NMe_2$) that would display diltiazem-like activity. In order to determine if sulfur is necessary for calcium channel blocking activity, we evaluated the corresponding benzodiazepine analogue (4, X = NH, R^3 = H).

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(4) Dihydropyridine type calcium channel blockers having ester on only one side of the molecule have been described; see for example: (a) U.S. Patent 3 910 917, 1975. (b) Jpn. Kokai JP 81,173, 1985. (c) German Offen. 3 234 684 A1, 1984.

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