Molecular Structure of the Dihydropyridazinone Cardiotonic 1,3-Dihydro-3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2*H*-indol-2-one, a Potent Inhibitor of Cyclic AMP Phosphodiesterase

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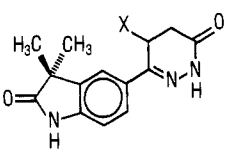
The cardiotonic 1,3-dihydro-3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2*H*-indol-2-one (1, LY195115) is a potent, competitive inhibitor (K_i = 80 nM) of sarcoplasmic reticulum derived phosphodiesterase (SR-PDE). Moreover, the compound is a potent positive inotrope both in vitro and in vivo. To assist further cardiotonic drug-design studies, we have mapped the three-dimensional structure of 1 using X-ray crystallography. From a global viewpoint, this drug was essentially planar, but two small regions of nonplanarity were apparent. These involved the geminal methyl substituents in the indol-2-one moiety and the C5′ methylene unit of the dihydropyridazinone ring. Because of our previous studies involving the bipyridine cardiotonics amrinone and milrinone, the conformational relationship between the plane of the phenyl ring and the horizontal symmetry plane defined by N2′, C3′, and C4′ of 1 was of particular interest. The C6–C5–C3′–C4′ dihedral angle was −2.7°, whereas the C6–C5–C3′–N2′ dihedral angle was 174.6°. Therefore the two rings maintain a high degree of coplanarity. Compound 4, the congener of 1 possessing a completely unsaturated pyridazinone ring was also studied. In terms of inotropic activity, this compound, devoid of any puckering in the pyridazinone moiety, was equipotent with 1. Methyl substitution at the 4-position of the dihydropyridazinone and pyridazinone rings provided disparate results. Compound 2, the 4-methyl analogue of 1, was 2-fold more potent than 1, and the methyl substituent probably caused only minor perturbations in overall molecular topology. However 5, the 4-methyl analogue of the pyridazinone 4, was 4.4-fold less active than 4, perhaps as a result of methyl-induced molecular nonplanarity.

Congestive heart failure (CHF) is a widespread disease, with an estimated three to four million cases in the United States.[1] Moreover, the disease is highly malignant, and the 1-year mortality rate in patients with advanced CHF is 50% or more.[2] From a global viewpoint, it is well-known that coronary, valvular, and myocardial diseases are often etiologically involved in the development of CHF; however, the molecular mechanisms for the initiation and progression of the disease are poorly understood.[3] Consequently, most pharmacologic interventions, including diuretics, vasodilators, and inotropic drugs, have attempted to correct the cardiac and circulatory derangements of CHF rather than intervening in the disease process itself.

Whereas numerous well-tolerated and highly efficacious diuretics and vasodilators are available, the only currently marketed, orally effective positive inotropes are the cardiac glycosides, which are fraught with therapeutic limitations. Therefore the discovery of a new class of nonglycoside positive inotropes, exemplified by milrinone, isomazole, and enoximone, has stimulated considerable research on their structure–activity relationships (SAR), mechanisms of action, and roles in the management of CHF.[4]

We recently described the synthesis and pharmacology of 1,3-dihydro-3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2*H*-indol-2-one (1, LY195115).[5,6] This compound is the most potent and longest acting nonglycoside cardiotonic described to date and is currently undergoing extensive clinical evaluation. Mechanistically, this class



1, X = H
2, X = CH_3

of cardiotonics appears to exert their inotropic effects via selective inhibition of a specific isozyme of cAMP phosphodiesterase, usually referred to as phosphodiesterase III (PDE III).[7] Of all cardiotonics we have examined, 1 is the most selective inhibitor of PDE III (>10 000-fold selectivity relative to other PDE isozymes). Moreover, using 1 as a biochemical tool, we have provided evidence that the subcellular origin of this membrane-bound enzyme is the sarcoplasmic reticulum.[8,9] Steady-state enzyme kinetic studies revealed that 1 is a linear competitive inhibitor of highly purified canine sarcoplasmic reticulum derived phosphodiesterase (SR-PDE). With a K_i of 80 nM the compound is bound more avidly by PDE than cAMP, the enzyme's natural substrate.[9] To assist further cardiotonic drug design studies and to provide knowledge about the possible topology at the catalytic site of SR-PDE, we have mapped the three-dimensional structure of 1 using X-ray crystallography. Moreover, we have conducted some highly focused SAR studies to probe effects of molecular conformation on inotropic activity.

Results and Discussion

X-ray Crystallography. Compound 1 crystallized from acetic acid/water as colorless prisms in the monoclinic space group $C2/c$, and the unit cell constants are summarized in Table I. A total of 1749 unique reflections were measured, and the structure was solved by direct methods. Anisotropic temperature factors were assigned to all nonhydrogen atoms, while the hydrogen atoms were kept isotropic. Full-matrix least-squares refinement of all

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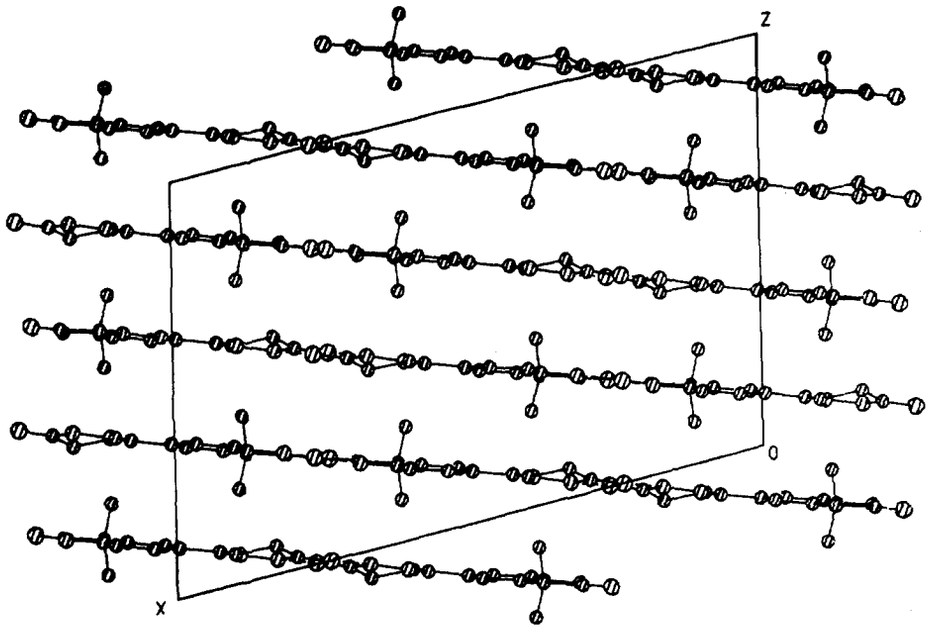


Figure 1. Unit cell contents and molecular packing of 1.

Table I. Crystal Data and Experimental Details for Analysis of 1

analysis	compound 1
formula	$C_{14}H_{15}N_3O_2$
formula wt	257.298
space group	$C2/c$
a, Å	21.850 (6)
b, Å	8.358 (1)
c, Å	14.442 (2)
β, deg	103.069
V, Å^3	2568.90
Z	8
d_{calcd}, g cm^{-3}	1.330
μ (Cu K$_\alpha$), cm^{-1}	23.4
no. of reflections	1749
no. of observed reflections	1400
final R	0.048

non-hydrogen coordinates and thermal parameters provided a final discrepancy index of 0.048 for 1400 observed reflections. Final atomic fractional coordinates and thermal parameters are available as supplementary material. No unusual bond lengths or angles were noted.

Figure 1 depicts the unit cell contents and molecular packing of 1. Each unit cell contains eight molecules arranged in a head-to-head and tail-to-tail orientation. Figure 2 shows a stereoscopic view of 1 as well as the non-hydrogen crystallographic numbering system. From a global perspective, 1 can be considered a planar molecule; however, two small regions of nonplanarity were apparent. As expected, the two indol-2-one C-3 methyl substituents project above and below the indolone horizontal symmetry plane, giving the molecule a symmetrical "butterfly-like" appearance. The symmetry of this portion of the molecule is highlighted by the O2–C2–C3–C3^1 and O2–C2–C3–C3^2 dihedral angles, which are −62.7 and 58.1°, respectively. These geminal methyl substituents increase inotropic potency both in vitro and in vivo and, from a mechanistic viewpoint, enhance the potency of 1 as an inhibitor of SR-PDE.[5,9] For example, the IC_{50} values of 1 and the desmethyl compound 3 (1,3-dihydro-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2*H*-indol-2-one) as inhibitors of SR-PDE are 130 and 380 nM, respectively, indicating that the methyl substituents result in a 3-fold increase in intrinsic potency.[9] As we have previously reported,[5] homologation to alkyl groups larger than methyl results in a decrease in

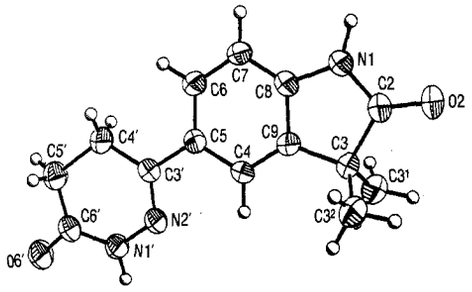


Figure 2. Computer-generated perspective drawing of 1 with crystallographic numbering system.

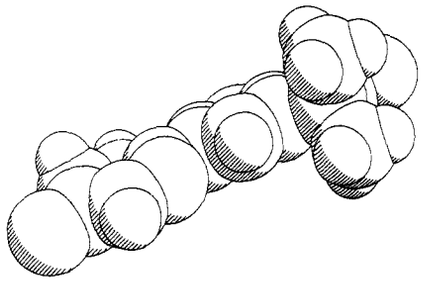


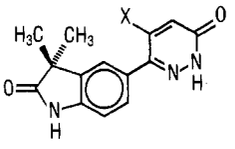
Figure 3. Computer-generated space-filling representation of 1. Note the slight deviation from planarity at C5′ of the dihydropyridazinone ring.

inotropic potency. Presumably, these methyl substituents occupy small, lipophilic, methyl-sized pockets in the active site of SR-PDE.

As is readily apparent from Figure 3, a second point of nonplanarity resides in the dihydropyridazinone ring. This ring adopts a half-chair-like conformation with C5′ projecting slightly out of the molecular plane. This permits, to a certain extent, the thermodynamically preferred staggered conformational relationship between the hydrogens of the juxtaposed dihydropyridazinone methylene units; the H4′A–C4′–C5′–H5′A dihedral angle is 87.9°. The six-membered heterocyclic ring conformation is defined by the following torsional angles: N1′N2′, −10.2°; N1′C6′, −2.3°; C5′C6′, 22.8°; C4′C5′, −30.8°; C3′C4′, 20.4°; N2′C3′, −0.2°.

We have previously described our work on the conformations of the bipyridine cardiotonics amrinone and

milrinone.[10] We reported that the 2-methyl substituent, rather than the 5-cyano moiety, was primarily responsible for the superior potency of milrinone both as an inotrope and as an inhibitor of PDE III. In the solid state, the dihedral angle between the planes formed by the two aromatic rings of amrinone dihydrochloride was 1.3°. The corresponding angle for milrinone hydrochloride was 52.2°, reflecting the steric interaction of the 2-methyl substituent with the 3′,5′-hydrogen atoms of the pyridine moiety. Moreover, ^{1}H NMR studies revealed the anticipated conformational differences in solution.[10] Erhardt and coworkers have recently reported the importance of nonplanarity in benzoylimidazolone cardiotonics.[11] Consequently, in the crystal structure of **1**, the conformational relationship between the plane of the phenyl ring and the horizontal symmetry plane defined by N2′, C3′, and C4′ was of particular interest. The C6–C5–C3′–C4′ dihedral angle was −2.7°, whereas the C6–C5–C3′–N2′ dihedral angle was 174.6°. This high degree of molecular planarity presumably allows conjugative interactions between the imine double bond and the phenyl ring and minimizes steric repulsion between the C6 hydrogen and the two hydrogens of the C4′ dihydropyridazinone methylene unit; the nonbonded distances between hydrogens C4′A and B and H6 are 2.179 and 2.622 Å, respectively.



4, X = H
5, X = CH_3

Conformational SAR Studies. Because of the almost complete molecular planarity of **1**, it was of interest to prepare and examine the inotropic activity of the unsaturated congener **4**. This point of unsaturation would remove the pucker and enforce total planarity of the pyridazinone ring, presumably without altering the coplanar relationship between the pyridazinone and phenyl rings. Sircar and co-workers have reported that in some dihydropyridazinone cardiotonics, oxidation to the pyridazinone ring decreases inotropic potency. For example, after iv administration to pentobarbital-anesthetized dogs, the inotropic ED_{50} values of 4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinone (CI-914) and 6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinone were 45 and 100 μg/kg, respectively,[12] a 100% decrease in inotropic potency. However, in some cases oxidation slightly increased inotropic potency. It should be noted that these pyridazinone data were obtained from only one or two animals.[12] Our interest in **4** was heightened upon its discovery as a metabolite after oral administration of **1** to animals and humans.[13]

Compound **4** was readily prepared from **1** by manganese dioxide oxidation in refluxing DMF, and the compound proved to be essentially equipotent with **1** as a positive inotrope. For example, after iv administration of **1** and **4** to pentobarbital-anesthetized dogs, the inotropic ED_{50} values were 6.8 and 7.4 μg/kg (Table II and Figure 4),

Table II. Cardiovascular Profile of Dihydropyridazinone Cardiotonics in Anesthetized Dogs[a]

no.	ED_{50} for contractility, μg/kg iv	% increase in HR	% decrease in MAP	*n*
1	6.8 ± 1	12 ± 1	15 ± 2	4
2	3.6 ± 1	20 ± 2	31 ± 4	4
4	7.4 ± 4	24 ± 3	18 ± 3	4
5	32.6 ± 7	15 ± 3	20 ± 10	4

[a] ED_{50} values were determined by linear regression analysis and are reported as the mean ± SEM of experimental values. Heart rate and mean arterial blood pressure values are the percent changes recorded at the inotropic ED_{50} values. Control values were contractility, 50 g tension; heart rate (HR), 127 ± 3 beats/min; mean arterial blood pressure (MAP), 99 ± 3 mmHg.

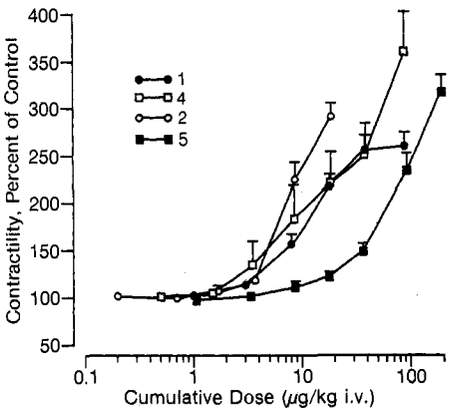


Figure 4. Dose-dependent effects of **1**, **2**, **4**, and **5** on myocardial contractility in pentobarbital-anesthetized dogs. Increasing doses of drug were administered at 5-min intervals and peak responses recorded. Each point is the mean ± SEM of experimental values. Symbols without error bars indicate that errors fell within the area of the symbols. Control (base line) values were as follow: contractility, 50 g tension, heart rate (HR), 127 ± 3 beats/min; mean arterial blood pressure (MAP), 99 ± 3 mmHg.

respectively, indicating that removal of the pucker from the dihydropyridazinone had little impact on inotropic activity in this series. The entire inotropic dose–response curves for **4** and **1** are displayed in Figure 4, whereas effects of the compounds on heart rate and mean arterial blood pressure are compiled in Table II. Effects of the two compounds on mean arterial blood pressure were indistinguishable, whereas **4** appeared to produce more tachycardia than **1**.

We have previously shown that methyl substitution at the 4-position of the dihydropyridazinone (compound **2**) resulted in increased inotropic potency.[5] In anesthetized dogs, the iv ED_{50} of **2** was 3.6 μg/kg, approximately a 2-fold enhancement in potency relative to **1** (Table II, Figure 4). In addition to increasing inotropic potency, the 4-methyl substituent also increased the magnitude of the compound's effect on mean arterial blood pressure at the inotropic ED_{50} (Table II). We have attempted to perform crystallographic analysis of the solid-state conformation of **2**, but were unable to obtain suitable crystals. However, as judged from molecular models, the methyl group would be expected to cause no marked perturbation of the dihydropyridazinone ring conformation or its conformational relationship to the indole moiety, since the methyl substituent can easily be maintained in a pseudoaxial position. Therefore, the methyl-induced increase in inotropic potency may result from a hydrophobic interaction,[14] as has been previously postulated for the geminal methyl sub-

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stituents of the indol-2-one moiety (vide supra).

In the fully unsaturated pyridazinone system (e.g., 4), methyl substituent at the 4-position will cause a marked perturbation in molecular topology, as does the similarly disposed methyl substituent of milrinone.[10] Consequently, 5 was synthesized from 2 by manganese-mediated oxidation. The inotropic ED_{50} of the compound was 32.6 μg/kg after iv administration to pentobarbital-anesthetized dogs (Figure 4, Table II), a 4.4-fold loss in potency relative to 4. Thus, whereas there was a pronounced methyl-induced enhancement of inotropic activity in the bipyridine cardiotonics, a methyl-induced diminution in inotropic activity was observed in pyridazinone cardiotonics. The molecular basis for the disparate effects of analogous methyl substitution in the bipyridine and pyridazinone cardiotonics is an enigma, particularly since the two series of compounds are mechanistically related.[7,9] Although both series are competitive inhibitors of PDE III, the opposite effects on inotropic potency of methyl-induced alterations in three-dimensional topology may imply that the bipyridine and pyridazinone cardiotonics have different modes of binding to the catalytic site of PDE III. The fact that the basic pyridine nitrogen of milrinone is oriented differently than the critical hydrogen-bond acceptor site[5] of the dihydropyridazinone cardiotonics (the amide oxygen or imidazole nitrogen of 1 or CI-914, respectively) lends credence to this hypothesis. In addition to its different orientation, the hydrogen-bond acceptor site of the bipyridine cardiotonics appears to be considerably less important in determining inotropic potency than the hydrogen-bond acceptor site of the dihydropyridazinone cardiotonics. For example, replacement of the monosubstituted pyridine moiety of milrinone with a phenyl ring (3-amino-6-methyl-5-phenyl-2(1*H*)-pyridone, APP 201-533) results in approximately a 4- to 5-fold decrease in inotropic potency,[15,16] whereas removal of the lactam carbonyl group in compounds related to 1 results in a 100-fold decrease in inotropic potency.[5]

Bristol and co-workers have proposed a five-point model to account for the positive inotropic activity of several noncatecholamine, nonglycoside cardiotonics.[14] Because many of these compounds appear to exert their inotropic effects by inhibition of a specific isozyme of phosphodiesterase (PDE III or SR-PDE),[7,9] this model would also relate to the structural features required for optimal interaction with the active site of SR-PDE. Briefly, their five-point model involves "(1) the presence of a strong dipole (carbonyl) at one end of the molecule, (2) an adjacent acidic proton, (3) a methyl-sized lipophilic space, (4) a relatively flat overall topography, and (5) a basic or hydrogen-bond acceptor site opposite the dipole". Compound 1, the most potent noncatecholamine, nonglycoside inotrope and inhibitor of SR-PDE we have examined to date, is a good candidate to test this model. Our X-ray crystallographic analysis of 1, as well as our previously reported classical SAR studies,[5,17] indicates that the Bristol model is valid *for dihydropyridazinone cardiotonics*. However, 1 and related compounds definitely indicate that a basic site (at least in the Lowry–Brønsted sense) opposite the dipole (point 5) is not a prerequisite for potent inotropic activity because either an imidazole nitrogen or an amide oxygen in this region provide potent inotropes. The indol-2-one carbonyl group of 1 may serve as a hydrogen-bond acceptor site, but this function cannot be easily distinguished from the electronic effects the amide substituent has on the phenyl ring of the indole.[5] As a further refinement of the model, effects of the indol-2-one 3,3 geminal methyl substituents indicate that small, lipophilic groups adjacent to the hydrogen-bond acceptor site significantly enhance the ability of the dihydropyridazinone cardiotonics to inhibit SR-PDE and thereby increase inotropic potency.

It should be stressed that while this model is valid for dihydropyridazinone or pyridazinone cardiotonics, it may not be completely applicable to all structural classes of cardiotonics which inhibit PDE III. With respect to point 4 we have described in this paper the disparate effects of methyl-induced nonplanarity in the bipyridine and pyridazinone cardiotonics; this may relate to different modes of binding to the active site of PDE III. Moreover, we have noted that point 5 appears to be less important for bipyridine cardiotonics than for dihydropyridazinone or pyridazinone cardiotonics. Further efforts to define a more generally applicable model are underway.

Experimental Section

Methods. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Proton magnetic resonance (^{1}H NMR) spectra were obtained with a Bruker WM-270 spectrometer. Chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard (δ scale). ^{1}H NMR data are presented in the form: (solvent in which spectra were determined), δ value of signal (peak multiplicity, integrated number of protons, and assignment). Mass spectra were recorded from a Varian MAT CH-5 spectrometer, at the ionization voltage expressed in parentheses. Only peaks of high relative intensity or of diagnostic importance are presented in the form: *m/e* (intensity relative to base peak). Microanalytical data were provided by the Physical Chemistry Department of Lilly Research Laboratories; only symbols of elements analyzed are given and they were within 0.4% of theoretical values unless indicated otherwise.

X-ray Crystallography. Compound 1 crystallized from acetic acid/water as colorless prisms in the monoclinic space group *C*2/*c*, with eight molecules in a unit cell having the dimensions a = 21.850 (6) Å, b = 8.358 (1) Å, c = 14.442 (2) Å, and β = 103.069°; calculated density was 1.330 g cm^{-3}.

Intensities of 1749 unique reflections with 2θ less than 116.0° were measured in the automated θ–2θ scan mode on a Syntex/Nicolet P3 four-angle diffractometer using monochromatic copper radiation. Positions of the atoms were obtained by interpretation of an *E* map phased by the direct methods routine SOLV of the SHELXTL program.[18] The structure was refined by the least-squares method with anisotropic temperature factors for all atoms except hydrogens, which were included at calculated positions with isotropic temperature factors. The final *R* factor was 0.048 for 1400 observed reflections. Tables III–VII (see supplementary material paragraph) contain atomic coordinates, bond lengths, bond angles, anisotropic temperature factors, and hydrogen atom coordinates, respectively.

5-(1,6-Dihydro-6-oxo-3-pyridazinyl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one (4). Manganese dioxide (49.4 g, 56.8 mmol) was added to a solution of 1[5] (14.6 g, 56.8 mmol) in 500 mL of DMF. The mixture was heated at 145 °C for 6 h and stirred at room temperature overnight. The reaction was heated to 120 °C and filtered through Celite, and solvent was removed in vacuo. Recrystallization from DMF provided 11.3 g (78%) of 4 as a light yellow powder: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.30 (s, 6, CH_3), 6.94 and 6.98 (overlapping d's, 2, Ar H), 7.68 (d, 1, Ar H), 7.80 (s, 1, Ar H), 8.02 (d, 1, Ar H); mass spectrum, *m/e* (relative intensity) 255 (100, M^+). Anal. ($C_{14}H_{13}N_3O_2$) C, H, N.

5-(4-Methyl-6-oxo-3-pyridazinyl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one (5). This compound was prepared from

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(18) Purchased from Nicolet, originator: Sheldrick, G. M.

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.

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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

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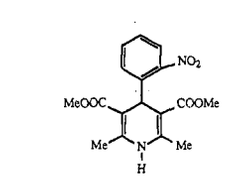
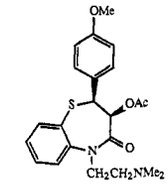
Substituted 1,2,3,4-tetrahydroaminonaphthols were found to be calcium channel blockers with antihypertensive properties. These compounds also possessed adrenergic β-receptor blocking activity. From the structure–activity studies, no clear correlation emerged between the in vitro calcium channel blocking 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.

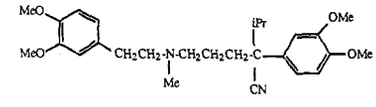
Calcium channel blockers have emerged to be the drugs of choice for treating various cardiac disorders.[1] The drugs commonly used are nifedipine (1), diltiazem (2), and verapamil (3). The last decade has seen an explosion in the synthesis of newer derivatives in each class. Most of this work has revolved 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 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.



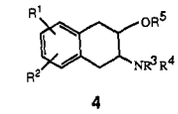
1 Nifedipine



2 Diltiazem



3 Verapamil



4

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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