1.20–3.34 (other aliphatic protons on the pyrrolizidine ring); mass spectrum, m/e 183 (M^+). Anal. ($C_{10}H_{17}NO_2$) C, H, N.

Synthesis of *N*-Aryl-8-pyrrolizidineacetamides (6a–s). Method A. To a stirred suspension of 1.5–2 equiv of sodium hydride (50% dispersion in oil) in 1,4-dioxane was added dropwise a solution of 1.5–2 equiv of the substituted aniline and the mixture was heated at 100 °C for 2 h. A solution of 1 equiv of compound 4 in 1,4-dioxane was added to the above-stirred mixture at room temperature and then heated at 100 °C for 2 h. The reaction mixture was poured into ice–water and extracted with ether. The ether layer was washed with 5% aqueous HCl, and the aqueous layer was neutralized with sodium bicarbonate followed by washing with ether. The resulting aqueous layer was basified with 20% NaOH and extracted with chloroform. The chloroform layer was washed with water, dried over magnesium sulfate, and evaporated to give an oily substance. This material was converted to the corresponding hydrochloride, or picrate, which was recrystallized from ethanol–ether to give colorless crystals (**6a–s**). The structures of the target compounds obtained by the above method were easily confirmed by their mass spectra [correct molecular ion], IR [1665–1685 cm^{-1} (amide C=O)], NMR ($CDCl_3$, as free base) [δ 1.2–4 (pyrrolizidine ring protons), 2.38–2.54 (s, 2 H, CH_2CO), 6.40–8.18 (introduced aromatic ring) are characteristic], and elemental analysis.

The structures, physical properties, and yields of the target compounds are summarized in Table I.

Method B. To a stirred solution of compound **5** (2.03 g, 0.012 mol) in chloroform (100 mL) was added dropwise oxalyl chloride (30 mL, 0.34 mol) at room temperature. The mixture was heated at 40 °C for 1 h and then evaporated under reduced pressure to give solid material. To a stirred solution of this material in chloroform (100 mL) was added at room temperature a substituted aniline (0.020 mol). After stirring for 1 h at room temperature, the solvent was evaporated to leave an oil. The products were purified by recrystallization or by column chromatography. When 2,6-xylidine was used as a substituted aniline, compound **6n**·HCl was obtained as crystals (81%).

***N*-(2,6-Dimethylphenyl)-8-pyrrolizidinecarboxamide (9). Method C.** To a stirred suspension of sodium hydride (50% dispersion in oil) (1.0 g, 0.0208 mol) in 1,4-dioxane was added slowly 2,6-xylidine (2.0 mL, 0.0162 mol) at room temperature, and then the mixture was heated to reflux for 2 h. A solution of compound 8 (2.0 g, 0.0109 mol) in 1,4-dioxane was added dropwise to the above reaction mixture with ice cooling and the mixture was heated under reflux for 5 h. The resulting mixture was poured into ice–water and extracted with ether. The ether layer was evaporated under reduced pressure, and the residue was converted to its hydrochloride. Purification by column chromatography on silica gel using methanol–chloroform (1:10) as eluent gave a solid, which was recrystallized from chloroform to afford compound **9** (2.39 g, 74%): mp 127–130 °C; IR (KBr) 1660 cm^{-1} (amide C=O). The free base gave the following physical data: NMR ($CDCl_3$) δ 2.20 (s, 6 H, protons of two methyl groups), 7.00 (br s, 3 H, aromatic protons), 1.20–3.34 (m, 12 H, other aliphatic protons on the pyrrolizidine ring); mass spectrum, m/e 258 (M^+).

Pharmacological Method. The antiarrhythmic activity of the target compounds in mice was evaluated essentially according to the method described by Lawson.[15]

Groups of 10 male mice (DDY strain) weighing 18–22 g were used and all compounds were injected subcutaneously. The volume of solution injected was 0.1 mL/10 g of body weight. Thirty minutes after drug administration, the mice were exposed to chloroform vapor in a glass beaker until respiratory arrest occurred. The animals were removed from the beaker immediately after respiratory arrest, and a lead II electrocardiogram was used to observe whether ventricular fibrillation took place or not, and then the heart was exposed for visual inspection of ventricular rhythm. At least three to four doses of drug were administered to obtain different degrees of protection against fibrillation. According to the method of Litchfield and Wilkoxon,[16] the antiarrhythmic ED_{50} value was calculated, at which 50% of animals were protected from ventricular fibrillation induced by chloroform. The acute LD_{50} value (24 h) was calculated by the up-and-down method described by Brownlee[17] in order to assess the therapeutic index (LD_{50}/ED_{50}).

Certain members of the series were selected for further testing in dogs with ventricular arrhythmias produced by coronary artery ligation according to the method of Harris.[13]

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Structure–Activity Relationships of Arylimidazopyridine Cardiotonics: Discovery and Inotropic Activity of 2-[2-Methoxy-4-(methylsulfinyl)phenyl]-1*H*-imidazo[4,5-*c*]pyridine[1]

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Recently several noncatecholamine, nonglycoside cardiotonic drugs have been discovered that possess both inotropic and vasodilator activities in experimental animals and man. Prototypical compounds include amrinone, sulmazole, and fenoximone. We investigated the structural requirements necessary for optimal inotropic activity in a series of molecules containing a heterocyclic ring fused to 2-phenylimidazole and discovered that 2-phenylimidazo[4,5-*c*]pyridines were generally 5–10-fold more potent than analogous 2-phenylimidazo[4,5-*b*]pyridines (e.g., sulmazole) or 8-phenylpurines. Furthermore, all imidazo[4,5-*c*]pyridine analogues we tested were orally active; in contrast, only one of the imidazo[4,5-*b*]pyridine derivatives, sulmazole, was significantly active. One of several highly active compounds in the [4,5-*c*] series was **50** (LY175326, 2-[2-methoxy-4-(methylsulfinyl)phenyl]-1*H*-imidazo[4,5-*c*]pyridine hydrochloride). The structure–activity relationship of this series is presented and compared to that of the imidazo[4,5-*b*]pyridine and purine series.

Congestive heart failure (CHF) afflicts approximately 3–4 million Americans, and the 2-year survival rate of patients with severe failure is 30% or less.[2,3] This high incidence and unacceptably poor prognosis underscore the

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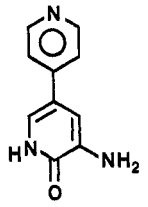
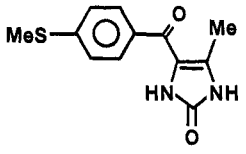
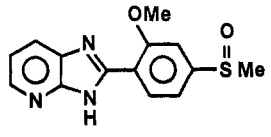
Chart I



amrinone, 1



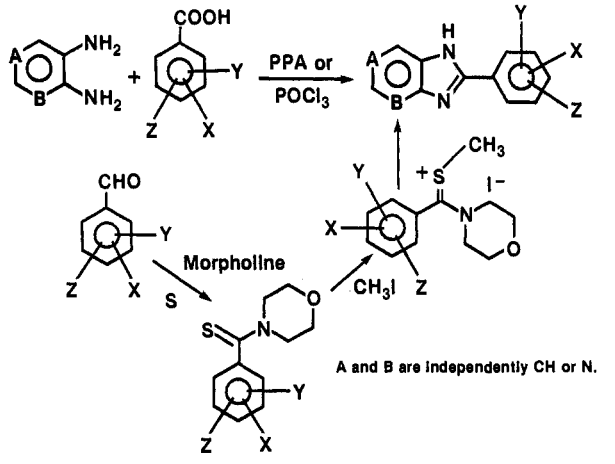
fenoximone, 2



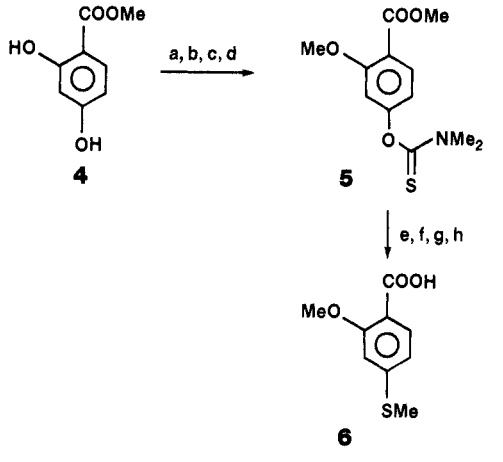
sulmazole, 3

need for new modalities in the treatment of this disease. Since diminished myocardial contractility is the fundamental defect in CHF, positive inotropic drugs have long been used to augment contractility and thereby enhance cardiac performance. Cardiac glycosides such as digoxin and drugs such as dopamine which result in β-adrenoceptor activation are the principal inotropic drugs used in the management of heart failure. Although cardiac glycosides are among the most frequently prescribed drugs and have been used for centuries, they have numerous liabilities such as a therapeutic index of 2–3, somewhat erratic absorption, participation in deleterious drug–drug interactions, and limited efficacy.[4-8] Untoward effects of β-agonists include sinus tachycardia, ventricular tachyarrhythmias, and the precipitation or exacerbation of myocardial ischemia;[9] however, the most significant limitation of these drugs in chronic therapy may be tachyphylaxis resulting from β-receptor "down regulation".[10-14]

Scheme I



Scheme II[a]



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[a] (a) NaH, BzlCl, 79%; (b) NaH, MeI, 95%; (c) 5% Pd/C, H_2, 98%; (d) NaH, $ClC(S)NMe_2$, 86%; (e) 245 °C; (f) NaOH, 86% (two steps); (g) NaH, $MeOSO_2OMe$; (h) NaOH, 86% (two steps).

Recently several noncatecholamine, nonglycoside inotropic drugs have been described (Chart I). Prototypical compounds include amrinone (1),[15,16] fenoximone (2),[17,18] and sulmazole (3).[19] Although the mechanism(s) of action of these compounds has not been well defined, it is clearly different from that of cardiac glycosides or sympathomimetic amines.[20,21] In addition to their inotropic effects, these compounds also dilate the peripheral vasculature;[22-24] consequently, they enhance impaired cardiac performance by simultaneously increasing cardiac contractility and

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reducing impedence to ejection. Accumulating data obtained in experimental animals and man indicate that this combination of augmented myocardial contractility and impedence reduction may provide maximal improvement in cardiac performance.[25-28]

At the outset of our studies, sulmazole appeared to be the most promising agent with combined inotropic/vasodilator activities. This judgement, coupled with the limited published data on 2-arylimidazopyridine structure–activity relationships (SAR), led us to investigate these molecules as a source of novel and therapeutically useful positive inotropic drugs.

Results and Discussion

Chemistry. The 2-phenylimidazopyridines, 2-phenylbenzimidazoles, and 8-phenylpurines employed in this investigation were readily synthesized from the appropriate aryldiamine and benzoic acid (Scheme I; A and B are independently N or CH).[29] When the benzoic acid was unsubstituted or possessed unreactive substituents (e.g., alkyl or halogen), either polyphosphoric acid (PPA) at 180–200 °C or P_2O_5/methanesulfonic acid (1/10) at 100–120 °C were preferred media for formation of the bicyclic heterocycle.[30] When alkoxy substituents were present, PPA sometimes led to dealkylation and phosphorus oxychloride was the condensing reagent of choice.[31] Finally, when labile or reactive substituents were present, a method employing a thiomorpholide iodide was convenient for preparation of the bicyclic heterocycle (Scheme I).[31] Most benzoic acids were obtained by literature methods. Several 2,4-disubstituted benzoic acids were prepared by subjecting the appropriate phenol to a Kolbe–Schmidt reaction and then elaborating the substituted 2-hydroxybenzoic acid. For example, 3-(methylthio)phenol was treated with anhydrous potassium carbonate under a 500-psi carbon dioxide atmosphere to afford a 72% yield of 4-(methylthio)salicylic acid, which was elaborated employing standard chemistry to 4-(methylthio)-2-*n*-propoxybenzoic acid in acceptable yield (see Experimental Section). Unfortunately, the Kolbe–Schmidt reaction was unsuitable for large-scale preparation of 2-methoxy-4-(methylthio)benzoic acid (**6**), and alternate methodology outlined in Scheme II was employed. Although this latter route is somewhat lengthy, it is superior to the one literature method[32] in terms of overall yield and the fact that no chromatographic separations are required.

Structure–Activity Relationships. Heterocyclic Nucleus. In pioneering studies which resulted in the discovery of sulmazole, Kutter and Austel[33] concentrated on 2-(2,4-disubstituted phenyl)imidazo[4,5-*b*]pyridines. We began by synthesizing the parent compound, 2-phenylimidazo[4,5-*b*]pyridine (**7**), and determining the structural features necessary for inotropic and vasodilator activities. We found that **7**, devoid of the sulmazole substituents at positions 2 and 4 of the phenyl ring, possessed little or no inotropic activity in isolated cat papillary muscle (Figure 1 and Table IV). The deaza analogue 2-phenylbenzimidazole (**16**) was also inactive. We then prepared and tested 2-phenylimidazo[4,5-*c*]pyridine (**17**). Much to our surprise, shifting the nitrogen from position 4 to position 5 (benzimidazole numbering) dramatically increased inotropic activity in this series of bicyclic heterocycles (Figure 1 and Table IV). For example, a concentration of 3×10^{-4} M **17** increased contractility by 200% (300% of control).

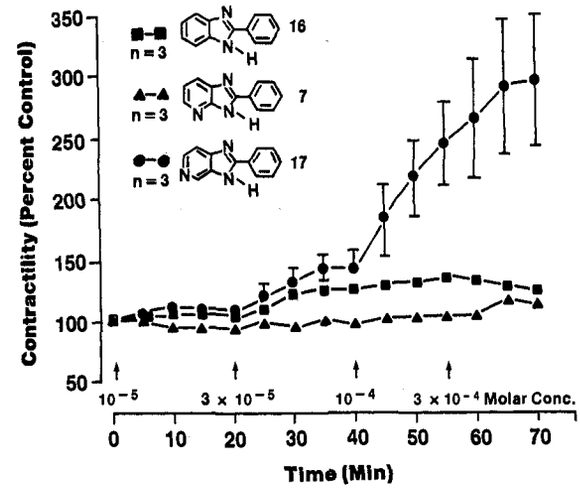

Figure 1. Inotropic activities of a benzimidazole and two imidazopyridines in cat papillary muscle. Cumulative dose-response curves were obtained by adding increasing concentrations of drug to muscle baths at the indicated intervals. Five-minute interval responses are shown and represent the mean ±SEM of three experiments.

Because of the superiority of **17**, we synthesized a series of imidazo[4,5-*b*]- and -[4,5-*c*]pyridines to determine if the [4,5-*c*] compounds are routinely more potent than analogous [4,5-*b*]isomers. Our initial comparison consisted of compounds **7**, **8**, **10**, **11** ([4,5-*b*] isomers) and **17**, **29**, **19**, **25** ([4,5-*c*] isomers). These compounds were studied by intravenous (iv) administration to pentobarbital anesthetized dogs, and the data are presented in Figure 2 and Table IV. These studies confirmed the superior inotropic activity of the [4,5-*c*] series. For example, the ED_{50} for the 4-methoxy-substituted [4,5-*c*] isomer **29** was 1.7 mg/kg while that of the analogous [4,5-*b*] isomer **8** was unobtainable; this latter compound elicited a maximum increase in inotropic activity (dP/dt of LVP) of only 18% at 8 mg/kg. Regardless of the substituents employed within this series, the iv potency of the [4,5-*c*] isomers was always greater than that of analogous [4,5-*b*]isomers (Table IV).

We also briefly investigated the hybrid of the 2-phenylimidazo[4,5-*b*]- and -[4,5-*c*]pyridines—the 8-phenylpurines[34] (Tables III and IV). These compounds were comparably potent with the imidazo[4,5-*b*]pyridines both in vitro and in vivo (Table IV and Figure 4) and offered no apparent advantage.

Structure–Activity Relationships. Optimization of Substituents. After verifying the superior inotropic activity of the imidazo[4,5-*c*]pyridines, we explored the effects of substituents on the phenyl ring of **17** in an attempt to optimize inotropic activity. Compounds that had appreciable inotropic activity in the cat papillary muscle assay were examined in pentobarbital anesthetized dogs

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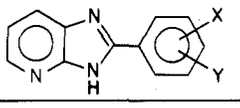
Table I. Structure and Properties of 2-Phenylimidazo[4,5-b]pyridines



no.	X	Y	method[a]	% yield[b]	formula	mp, °C	recrystn solvent	anal.[c]
7	H	H	B	84	$C_{12}H_9N_3$	289–291	MeOH	C, H, N
8	4-OMe	H	A	73	$C_{13}H_{11}N_3O$	230–232	EtOH/H_2O	C, H, N
9	4-SMe	H	A	47	$C_{13}H_{12}ClN_3S$	242–244	EtOH/H_2O	C, H, N, Cl
10	4-SO_2Me	H	B	76	$C_{13}H_{12}ClN_3O_2S$	304–306	EtOH/H_2O	C, H, N, Cl
11	3-Me	H	B	65	$C_{13}H_{11}N_3$	229–230.5	MeOH/(i-Pr)$_2$O	C, H, N
12	3-OMe	4-OMe	A	47	$C_{14}H_{14}ClN_3O_2$	266–267 dec	EtOH/H_2O	C, H, N, Cl
13	2-OMe	4-OMe	A	70	$C_{14}H_{14}ClN_3O_2$	246–248	EtOH/H_2O	C, H, N, Cl
14	2-OMe	4-SOMe	D	82	$C_{14}H_{13}N_3O_2S$	193–195	acetone/hexane	C, H, N
15	2-OMe	4-SO_2Me	E	50	$C_{14}H_{13}N_3O_3S$	220–222	EtOH	C, H, N

[a] Method A: $POCl_3$. Method B: PPA. Method D: MCPBA, EtOH/$CHCl_3$, −40 °C. Method E: CH_3CO_3H, MeOH. [b] Yields are not optimized. Some of the lower yields represent mechanical losses during purification because of the unusual solubility characteristics of these molecules. [c] An extended combustion period (3–5 min) at 950 °C was often required to obtain acceptable analyses.

to study drug effects on contractility, arterial blood pressure, and heart rate; the cardiovascular data are compiled in Table IV. Monosubstituted compounds (**18–32**) were not significantly more potent than **17** and did not present a clear SAR. Kutter and Austel[33] demonstrated that 2,4-dimethoxy substitution in the [4,5-*b*] series increased activity; consequently, we synthesized the 2,4-dimethoxy[4,5-*c*] isomer **38** and observed an increased activity relative to **17**. In the cat papillary muscle, **38** produced 58% and 72% increases in contractility at 10^{-5} and 10^{-4} M, respectively. In anesthetized dogs, administration of 0.30 mg/kg iv resulted in a 50% increase in contractility that was accompanied by a 9% increase in heart rate and a 17% decrease in mean arterial blood pressure. In marked contrast to the analogous [4,5-*b*] isomer **13**, **38** was active after oral administration to conscious, chronically instrumented animals (vide infra). Because of the encouraging preliminary pharmacology of **38**, all possible dimethoxy isomers (**38–43**) were prepared and evaluated to determine the regiospecificity of the dimethoxy substituent effect. As indicated in Table IV, the 2,3-, 2,5-, 2,6-, and 3,5-dimethoxy analogues produced increases in papillary muscle contractility which did not differ dramatically from that of the unsubstituted phenyl compound **17**. However, the 3,4-dimethoxy analogue **42** produced an increase in contractility of 64% at 10^{-5} M, making it essentially equipotent with **38** (58% increase at 10^{-5} M); the equivalent activities of the two compounds were confirmed in anesthetized dogs (Table IV).

Because of the good activity and cardiotonic profile of the 2,4-dimethoxy compound **38**, a series of compounds (**33**, **36–38**, **44–60**) was studied in which 2,4-disubstitution was maintained, but substituents with a wide range of σ constants were employed to alter the electronic nature of the phenyl ring. Replacing the 2-methoxy substituent with a chloro (**33**), methyl (**36**), methylthio (**52**), or methylsulfinyl (**53**) diminished inotropic activity of the compounds at 10^{-5} M (16%, −7%, 14%, 7% increase in contractility, respectively). Preliminary X-ray crystallographic studies[35] on **38** indicate that a hydrogen bond exists between the imidazole hydrogen and the methoxy oxygen, resulting in molecular planarity. The hydrogen bond is not mandatory, however, as evidence by the good inotropic activity of **42**.

The substituent at the 4-position could be widely varied while inotropic activity is still maintained. For example, a concentration of 10^{-5} M of either the 4-chloro (**45**) or

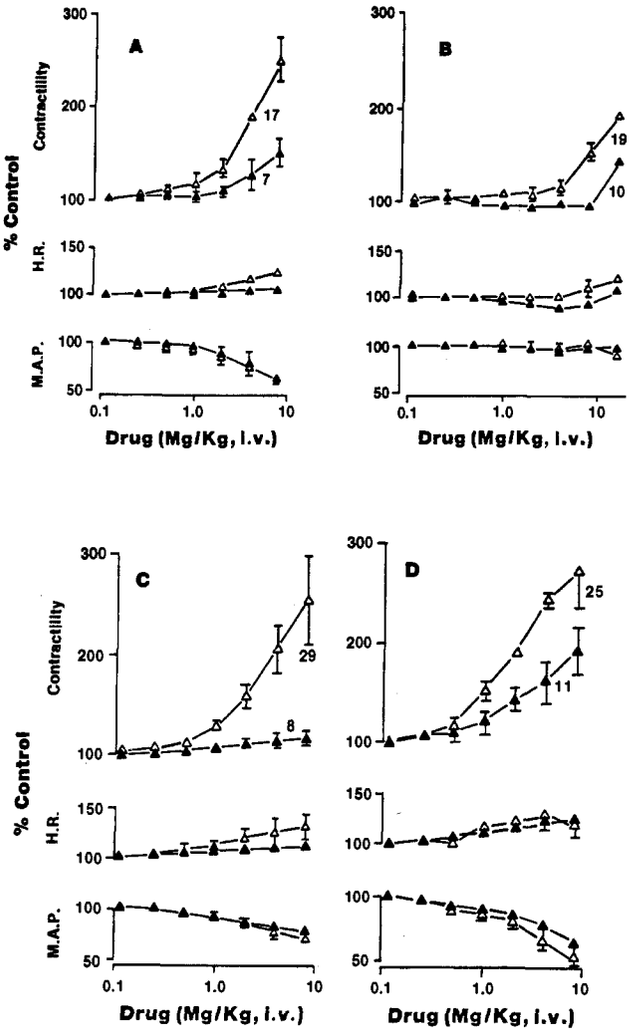


Figure 2. Dose-dependent effects of selected compounds in pentobarbital-anesthetized dogs. Drugs were administered at 5-min intervals and peak responses recorded. Each point is either the mean ± SEM ($n \geq 3$) or mean ± range ($n = 2$) of experimental values. Symbols without error bars indicate that errors fell within the area of the symbols. Control values were as follows: contractility, 35 g tension; heart rate (H.R.) 142 beats/min; mean arterial blood pressure (M.A.P.), 100 mmHg.

4-methylthio (**49**, LY137150) analogues increased contractile force of cat papillary muscles by 62% and 41%, respectively; both agents were also active in the anesthetized dog (Table IV). Oxidation of **49** with MCPBA at low temperatures to form the sulfoxide **50** (LY175326) resulted

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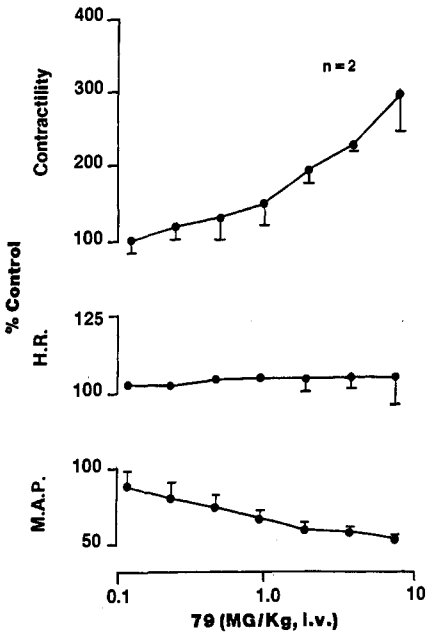

Figure 3. Dose-dependent effects of selected compounds in pentobarbital-anesthetized dogs. Drugs were administered at 5-min intervals and peak responses recorded. Each point is the mean ± range (n = 2) of experimental values. Symbols without error bars indicate that errors fell within the area of the symbols. Control values were as follows: contractility, 35 g tension; heart rate (H.R.) 142 beats/min; mean arterial blood pressure (M.A.P.), 100 mmHg.

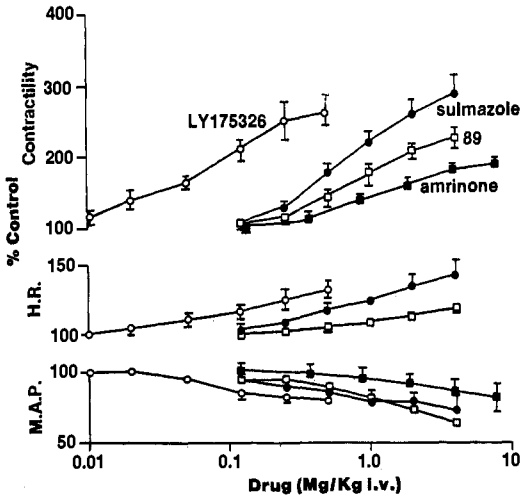

Figure 4. Dose-dependent effects of selected compounds in pentobarbital-anesthetized dogs. Drugs were administered at 5-min intervals and peak responses recorded. Each point is either the mean ± SEM ($n \geq 3$) or mean ± range (n = 2) of experimental values. Symbols without error bars indicate that errors fell within the area of the symbols. Control values were as follows: contractility, 35 g tension; heart rate (H.R.) 142 beats/min; mean arterial blood pressure (M.A.P.), 100 mmHg. The H.R. effects of amrinone are not shown as they were identical with those of **89**.

in a 9-fold increase in potency in anesthetized dogs. As shown in Table IV, **50** is a potent inotrope, with an ED_{50} of 30 μg/kg. Further oxidation of **50** to the sulfone **51** (LY163252) produced a slightly more potent compound (ED_{50} = 20 μg/kg).[36] As expected, all these compounds were more potent than the analogous [4,5-*b*] isomers prepared by Kutter and Austel.[31,33] Several other disubstituted compounds of interest are the nitro compound **56**, the methanesulfonate analogue **57**, and the trifluoromethyl congener **58**; each proved to be a potent inotrope both in vitro and in vivo (iv ED_{50}'s = 15, 6, 9 μg/kg, respectively).

The majority of the more potent compounds in this series (e.g., **50**, **51**, **56–58**) have strong electron-withdrawing substituents in the 4-position of the phenyl ring; the σ_P constants for $S(O)CH_3$, SO_2CH_3, NO_2, OSO_2CH_3, and CF_3 are 0.49, 0.72, 0.78, 0.36, and 0.54, respectively.[37] However, there is no correlation between σ_P and inotropic potency. A comparison of the widely varied 4-substituent σ_P's of **45**, **49**, and **38** (σ_P's of Cl, MeS, and MeO are 0.23, 0.00, and −0.27, respectively) and their almost equivalent inotropic activities (iv ED_{50}'s = 0.23, 0.2, and 0.3 mg/kg, respectively) supports the hypothesis that σ_P does not contribute markedly to inotropic potency in this series. A feature which all optimal substituents have in common is a hydrogen-bond acceptor site two or three atoms removed from the phenyl ring. We are preparing additional compounds to examine whether this hydrogen-bonding site is indeed a major factor in determining the inotropic potency of these molecules.

Several alkyl homologues of **38** and **50** were prepared (e.g., **63–66**, **75–82**) and found to dramatically increase contractility and lower blood pressure without the expected degrees of reflex tachycardia[38] (Table IV). For example, administration of 10 mg/kg of **79** to pentobarbital-anesthetized dogs increased contractility by 200%, reduced mean arterial blood pressure by 45%, and increased heart rate only 10% (Figure 3). The reason for this modest reflex tachycardia is not known; no direct bradycardic activity was observed in isolated guinea pig atria (data not shown). Several trisubstituted compounds were also prepared (**83–86**) and tested for inotropic activity. These specific compounds offered no advantage.

Additional Pharmacological Studies. The cardiovascular profile of **50** after iv administration to pentobarbital-anesthetized dogs was studied and compared to those of sulmazole (**3**), the analogous purine **89**, and amrinone (Figure 4). With all four compounds the most pronounced effect was a dose-related increase in contractility with the principal difference being potency. The ED_{50}'s for **50**, sulmazole, **89**, and amrinone were 0.03, 0.3, 0.6, and 1.3 mg/kg, respectively. A second difference was that **50** decreased mean arterial blood pressure less at its inotropic ED_{50}; the percent decreases (relative to control) produced by **50**, sulmazole, **89**, and amrinone were −1, −10, −14, and −9, respectively. These data may be of clinical significance since a reported side effect of amrinone is hypotension.[39-41] In fact, some investigators have concluded that at pharmacologically relevant doses in congestive heart failure patients, amrinone is strictly a vasodilator.[42-44]

(36) The inotropic activity of the sulfide and sulfone analogues of LY175326 is important since these two compounds are metabolites of LY175326 after oral administration to dogs or rats. Franklin, R. B., unpublished observations.

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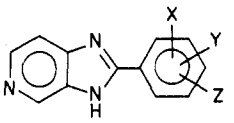
Table II. Structure and Properties of 2-Phenylimidazo[4,5-*c*]pyridines

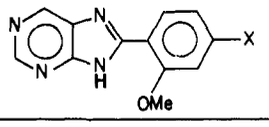


no.	X	Y	Z	method[a]	% yield[b]	formula	mp, °C	recrystn solvent	anal.[c]
17	H	H	H	B	84	$C_{12}H_9N_3$	225–226.5	H_2O	C, H, N
18	4-SMe	H	H	A	51	$C_{13}H_{12}ClN_3S$	307–309	EtOH/H_2O	C, H, N, Cl, S
19	4-SO_2Me	H	H	B	83	$C_{13}H_{12}ClN_3O_2S$	>320	MeOH/H_2O	C, H, N, Cl
20	4-CN	H	H	A	6	$C_{13}H_9ClN_4$	>320	MeOH	C, H, N
21	2-F	H	H	B	90	$C_{12}H_9ClFN_3 \cdot H_2O$	243–245	MeOH	C, H, N
22	3-F	H	H	B	83	$C_{12}H_9ClFN_3$	267–268	EtOH/H_2O	C, H, N, Cl, F
23	4-F	H	H	B	47	$C_{12}H_9ClFN_3$	320 dec	MeOH	C, H, N
24	2-Me	H	H	C	21	$C_{13}H_{12}ClN_3$	262.5–263.5	EtOH	C, H, N, Cl
25	3-Me	H	H	B	56	$C_{13}H_{11}N_3$	202.5–204	MeOH/H_2O	C, H, N
26	4-Me	H	H	C	25	$C_{13}H_{12}ClN_3$	266–267.5	EtOH/H_2O	C, H, N, Cl
27	2-OMe	H	H	A	40	$C_{13}H_{12}ClN_3O$	173–175	EtOH	C, H, N
28	3-OMe	H	H	A	62	$C_{13}H_{12}ClN_3O$	258–260	EtOH	C, H, N, Cl
29	4-OMe	H	H	A	74	$C_{13}H_{12}ClN_3O$	271–273	EtOH	C, H, N, Cl
30	4-O-*n*-Bu	H	H	A	44	$C_{16}H_{18}ClN_3O$	246–248	EtOH	C, H, N, Cl
31	4-NMe_2	H	H	A	48	$C_{14}H_{15}ClN_4$	296–297	EtOH	C, H, N
32	4-SPh	H	H	C	40	$C_{18}H_{14}ClN_3S$	165–167	EtOH	C, H, N, Cl
33	2-Cl	4-Cl	H	B	80	$C_{12}H_7Cl_2N_3$	179–181	EtOH	C, H, N
34	3-Cl	5-Cl	H	B	53	$C_{12}H_8Cl_3N_3$	>320	DMF/H_2O	C, H, N, Cl
35	3-Me	4-Me	H	B	28	$C_{14}H_{14}ClN_3$	286–287	EtOH/H_2O	C, H, N, Cl
36	2-Me	4-Me	H	B	42	$C_{14}H_{14}ClN_3$	295–296	EtOH	C, H, N, Cl
37	2-Me	4-OMe	H	A	49	$C_{14}H_{14}ClN_3O$	272 dec	EtOH/H_2O	C, H, N, Cl
38	2-OMe	4-OMe	H	A	57	$C_{14}H_{14}ClN_3O_2$	231–234	EtOH/H_2O	C, H, N, Cl
39	2-OMe	3-OMe	H	A	26	$C_{14}H_{14}ClN_3O_2$	279–281	EtOH/H_2O	C, H, N, Cl
40	2-OMe	5-OMe	H	A	39	$C_{14}H_{14}ClN_3O_2$	257–259	EtOH	C, H, N, Cl
41	2-OMe	6-OMe	H	A	22	$C_{14}H_{14}ClN_3O_2$	175–177	EtOH/H_2O	C, H, N, Cl
42	3-OMe	4-OMe	H	A	63	$C_{14}H_{14}ClN_3O_2$	263–265	EtOH/H_2O	C, H, N
43	3-OMe	5-OMe	H	A	47	$C_{14}H_{13}N_3O_2$	136–139	EtOH	C, H, N
44	2-OMe	4-F	H	A	53	$C_{13}H_{11}ClFN_3O$	162 dec	EtOH/H_2O	C, H, N
45	2-OMe	4-Cl	H	A	55	$C_{13}H_{11}Cl_2N_3O$	227–228	EtOH/H_2O	C, H, N, Cl
46	2-OMe	4-Br	H	A	38	$C_{13}H_{11}BrClN_3O$	177–182	EtOH/H_2O	C, H, N
47	2-OMe	4-I	H	A	66	$C_{13}H_{11}ClIN_3O$	196–200	EtOH/Et_2O	C, H, N
48	2-OMe	4-Me	H	A	92	$C_{14}H_{14}ClN_3O$	221–222	EtOH/H_2O	C, H, N, Cl
49	2-OMe	4-SMe	H	A	87	$C_{14}H_{14}ClN_3OS$	218–221	DMF/H_2O	C, H, N, Cl, S
50	2-OMe	4-S(O)Me	H	D	88	$C_{14}H_{14}ClN_3O_2S$	210–212	DMF/Et_2O	C, H, N, Cl
51	2-OMe	4-SO_2Me	H	E	92	$C_{14}H_{14}ClN_3O_3S \cdot {}^3/_4H_2O$	218–218.5	EtOH	C, H, N, Cl
52	2-SMe	4-OMe	H	A	47	$C_{14}H_{14}ClN_3OS$	273–274	EtOH	C, H, N, Cl
53	2-S(O)Me	4-OMe	H	D	59	$C_{14}H_{14}ClN_3O_2S$	257–258	DMF/THF	C, H, N
54	2-SMe	4-SMe	H	A	45	$C_{14}H_{14}ClN_3S_2$	283–284.5	EtOH/H_2O	C, H, N, Cl, S
55	2-OMe	4-OPh	H	A	77	$C_{19}H_{15}N_3O_2$	212–213	THF/hex	C, H, N
56	2-OMe	4-NO_2	H	A	37	$C_{13}H_{10}N_4O_3$	220–221.5	THF/hex	C, H, N
57	2-OMe	4-OSO_2Me	H		62	$C_{14}H_{14}ClN_3O_4S$	215–216 dec	DMF	C, H, N, Cl
58	2-OMe	4-CF_3	H	A	16	$C_{14}H_{11}ClF_3N_3O$	210 dec	EtOH/Et_2O	C, H, N, Cl
59	2-OMe	4-NMe_2	H	A	58	$C_{15}H_{17}ClN_4O$	260–263	EtOH/H_2O	C, H, N
60	2-OMe	4-OBzl	H	A	53	$C_{20}H_{17}N_3O_2$	164–164	*d*	C, H, N
61	3-OMe	4-SMe	H	A	28	$C_{14}H_{14}ClN_3OS$	287–288 dec	DMF/THF	C, H, N
62	3-OMe	4-S(O)Me	H	D	79	$C_{14}H_{14}ClN_3O_2S$	252 dec	DMF	C, H, N
63	2-OEt	4-OMe	H	A	63	$C_{15}H_{15}N_3O_2$	157–158	THF/hex	C, H, N
64	2-O-*n*-C_3H_7	4-OMe	H	A	48	$C_{16}H_{17}N_3O_2$	125–126	THF/hex	C, H, N
65	2-O-*n*-C_4H_9	4-OMe	H	A	53	$C_{17}H_{19}N_3O_2$	123–124	THF/hex	C, H, N
66	2-O-*n*-C_5H_{11}	4-OMe	H	A	40	$C_{18}H_{22}ClN_3O_2$	188–189	EtOH	C, H, N
67	2-OC_2H_4OMe	4-OMe	H	A	27	$C_{16}H_{17}N_3O_3$	137–138.5	EtOAc/hex	C, H, N
68	2-OC_3H_6OMe	4-OMe	H	A	76	$C_{17}H_{19}N_3O_3$	123–124.5	THF/hex	C, H, N
69	2-OC_2H_4SPh	4-OMe	H	A	38	$C_{21}H_{19}N_3O_2S$	122–123	THF/hex	C, H, N, S
70	2-OC_2H_4S(O)Ph	4-OMe	H	D	37	$C_{21}H_{19}N_3O_3S$	183–184.5	MeOH/THF	C, H, N, S
71	2-OC_2H_4SMe	4-OMe	H	A	40	$C_{16}H_{17}N_3O_2S$	140–142.5	THF/hex	C, H, N, S
72	2-OC_2H_4S(O)Me	4-OMe	H	D	78	$C_{16}H_{17}N_3O_3S$	196–197	MeOH/THF/hex	C, H, N, S
73	2-OC_2H_4SEt	4-OMe	H	A	50	$C_{17}H_{20}ClN_3O_2S$	153–156	EtOH/H_2O	C, H, N, Cl, S
74	2-OC_3H_6SMe	4-OMe	H	A	55	$C_{17}H_{19}N_3O_2S$	105–107	THF/hex	C, H, N, S
75	2-OEt	4-SMe	H	A	76	$C_{15}H_{15}N_3OS$	136–138	THF/hex	C, H, N
76	2-OEt	4-S(O)Me	H	D	70	$C_{15}H_{16}ClN_3O_2S$	199–200	DMF/THF	C, H, N
77	2-OEt	4-SO_2Me	H	E	26	$C_{15}H_{15}N_3O_3S$	199–200	THF/hex	C, H, N
78	2-O-*n*-C_3H_7	4-SMe	H	A	56	$C_{16}H_{17}N_3OS$	144–145	THF/hex	C, H, N
79	2-O-*n*-C_3H_7	4-S(O)Me	H	D	71	$C_{16}H_{17}N_3O_2S$	98–100	THF/hex	C, H, N
80	2-OMe	4-SEt	H	A	52	$C_{15}H_{16}ClN_3OS$	242–243	EtOH	C, H, N
81	2-OMe	4-S(O)Et	H	D	64	$C_{15}H_{16}ClN_3O_2S$	162–163 dec	EtOH/THF	C, H, N, Cl
82	2-OMe	4-S-*n*-C_3H_7	H	A	57	$C_{16}H_{17}N_3OS$	162–163	THF/hex	C, H, N
83	3-OMe	4-OMe	5-OMe	A	56	$C_{15}H_{16}ClN_3O_3$	248–250	EtOH/H_2O	C, H, N, Cl
84	2-OMe	4-OMe	5-OMe	A	70	$C_{15}H_{16}ClN_3O_3$	247–248	EtOH/H_2O	C, H, N, Cl
85	2-OMe	4-OMe	6-OMe	A	8	$C_{15}H_{15}N_3O_3$	132–133	THF/hex	C, H, N
86	3-Me	4-OMe	5-Me	A	24	$C_{15}H_{16}ClN_3O$	258–259	EtOH	C, H, N, Cl

Footnotes to Table II

[a] Method A: $POCl_3$. Method B: PPA. Method C: $P_2O_5/MeSO_3H$ (1/10). Method D: MCPBA, $EtOH/CHCl_3$, −40 °C. Method E: CH_3CO_3H, MeOH. [b] Yields are not optimized. Some of the lower yields represent mechanical losses during purification because of the unusual solubility characteristics of these molecules. [c] An extended combustion period (3–5 min) at 950 °C was often required to obtain acceptable analyses. [d] Tested and analyzed after chromatography over silica gel.

Table III. Structure and Properties of 8-Phenylpurines



no.	X	method[a]	% yield[b]	formula	mp, °C	recrystn solvent	anal.[c]
87	OMe	A	68	$C_{13}H_{13}ClN_4O_2 \cdot {}^1/_2H_2O$	231–233	EtOH	C, H, N, Cl
88	SMe	A	91	$C_{13}H_{13}ClN_4OS$	227–229 dec	EtOH	C, H, N
89	S(O)Me	D	81	$C_{13}H_{13}ClN_4O_2S$	212–213 dec	DMF	C, H, N

[a] Method A: $POCl_3$. Method D: MCPBA, $EtOH/CHCl_2$, −40 °C. [b] Yields are not optimized. Some of the lower yields represent mechanical losses during purification because of the unusual solubility characteristics of these molecules. [c] An extended combustion period (3–5 min) at 950 °C was often required to obtain acceptable analyses.

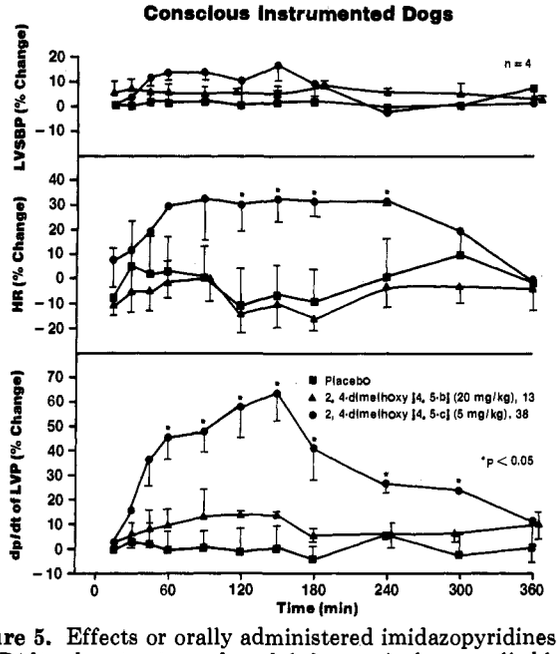


Figure 5. Effects or orally administered imidazopyridines on $LVdP/dt_{60}$, heart rate, and peak left ventricular systolic blood pressure (LVSBP). Chronically instrumented dogs received either drug or placebo (lactose) in 000 gelatin capsules; cardiovascular responses were recorded continuously throughout the experiment. Values are the mean ±SEM of four experiments. Control values were as follows: $LVdP/dt_{60}$, 51 ± 3 s^{-1}; heart rate, 72 ± 4 beats/min; LVSBP, 133 ± 6 mmHg. *, $P < 0.05$ compared to placebo.

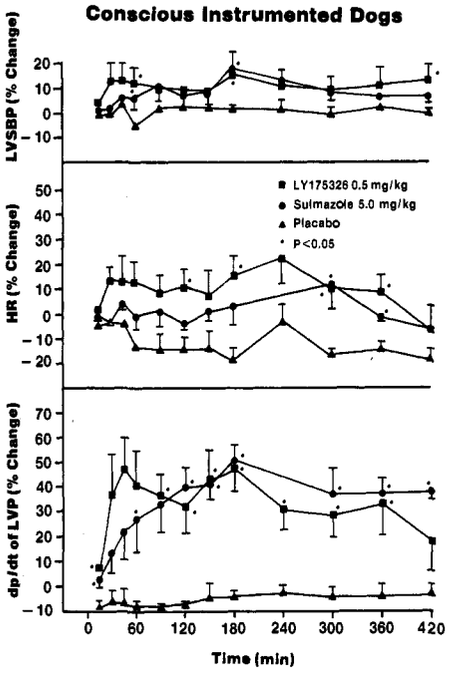


Figure 6. Refer to legend of Figure 5.

Diederen and Kadatz[19] reported that of the imidazo-[4,5-*b*]pyridines they investigated, only sulmazole had sufficient oral activity in dogs to be considered a drug candidate. Therefore, we performed comparative studies on the oral activity of analogous [4,5-*b*] and 4,5-*c*]-imidazopyridines. To our surprise, all imidazo[4,5-*c*]-pyridine derivatives we tested were orally active; in contrast, only one of the imidazo[4,5-*b*]pyridiine derivatives, sulmazole, was significantly active. For example, when 5.0 mg/kg of **38** was administered orally to conscious, chronically instrumented dogs, absorption was rapid and resulted in a 60% increase in $LVdP/dt_{60}$ at 1 h; duration of action was aproximately 4 h (Figure 5). The corresponding [4,5-*b*] isomer **13**, at a 4-fold higher dose, produced only minimal and statistically insignificant increases in $LVdP/dt_{60}$. Similar data were obtained for the 4-(methylsulfonyl)-2-methoxy analogues **15** and **51**; only the [4,5-*c*] isomer **51** was significantly active. Although both 4-(methylsulfinyl)-2-methoxy isomers **50** and sulmazole were orally active, there was a substantial difference in their potencies. As shown in Figure 6, 0.5 mg/kg of **50** caused a 40–50% increase in $LVdP/dt_{60}$ that was associated with a 10–20% increase in heart rate.[45] The heart rate and mean arterial blood pressure effects were near control values of 5 h while contractility remained signif-

(43) Hermiller, J. B.; Leithe, M. E.; Magorien, R. D.; Unverferth, D. V.; Leier, C. V. *J. Pharmacol. Exp. Therap.* **1984**, *228*, 319.
(44) Wilmshurst, P. T.; Walker, J. M.; Fry, C. Hh.; Mounsey, J. P.; Twort, C. H. C.; Williams, B. T.; Davies, M. J.; Webb-Peploe, M. M. *Cardiovas. Res.* **1984**, *18*, 302.

(45) The conscious dogs used in these oral studies are highly conditioned with heart rates of 72 ± 4 beats/min, rendering them extremely sensitive to increases in this parameter.

Table IV. Cardiovascular Activities of Imidazopyridines and Purines

	cat papillary muscle contractility, % of control (response ratio[d])				anesthetized dog			
no.	10^{-6}	10^{-5}	10^{-4}	*n*	ED_{50} for contractility, mg/kg, iv	% change in HR[e]	% change in MAP[e]	*n*
1 (amrinone)		143 (0.61)	190 (1.25)	4	1.3	11	−9	4
7		101 ± 2 (0.01)	112 ± 11 (0.15)	5	8	7	−36	2
8		104 ± 10 (0.06)	173 ± 32 (1.01)	2	*a*	*a*	*a*	3
9		NT[b]	NT		1.9	27	−7	1
10		NT	NT		18.0	8	−2	3
11		NT	NT		2.8	18	−27	3
12		103 ± 2.5 (0.04)	116.5 ± 1.5 (0.22)	2	NT			
13		172 ± 60 (1.00)	264 ± 140 (2.27)	2	0.8	18	−22	4
14		112 ± 3 (0.16)	156 ± 19 (0.78)	8	0.3	13	−10	4
15		120 ± 6 (0.28)	129 ± 8 (0.40)	7	0.4	10	−20	3
16		105 (0.07)	134 (0.47)	2	NT			
17		106 ± 5 (0.08)	242 ± 34 (1.97)	3	2.5	13	−15	3
18		115 ± 9 (0.21)	212 ± 31 (1.55)	3	4	0	−15	2
19		117 ± 16 (0.24)	137 ± 18 (0.51)	4	7.5	10	+2	3
20		112 ± 6 (0.16)	164 ± 29 (0.89)	2	NT			
21		107 (0.10)	145 (0.63)	1	NT			
22		112 ± 10 (0.17)	157 ± 43 (0.79)	2	NT			
23		105 ± 5 (0.06)	163 ± 20 (0.87)	2	NT			
24		106 ± 5 (0.09)	188 ± 22 (1.22)	3	2.2	24	−20	1
25		118 ± 5 (0.25)	195 ± 30 (1.32)	3	1.0	17	−20	3
26		97 ± 8 (−0.04)	169 ± 10 (0.96)	6	NT			
27		120 (0.28)	200 (1.38)	1	NT			
28		115 ± 15 (0.21)	214 ± 29 (1.58)	2	NT			
29		104 ± 2 (0.07)	205 ± 29 (1.46)	3	1.7	17	−14	3
30		114 ± 8 (0.19)	288 ± 78 (2.61)	4	NT			
31		94 ± 7 (−0.08)	175 ± 25 (1.04)	2	*c*			1
32		122 ± 13 (0.31)	124 ± 8 (0.33)	4	NT			
33		116 ± 16 (0.22)	171 ± 44 (0.99)	6	0.7	17	−22	1
34		115 (0.21)	146 (0.64)	1	NT			
35		133 ± 21.2 (0.46)	226 ± 44 (1.75)	4	5.2	0	−53	1
36		93 ± (−0.10)	100 ± 13 (0.0)	4	1.4	12	−24	1
37		119 ± 1.5 (0.26)	145 ± 9 (0.63)	2	NT			
38		158 ± 9 (0.81)	172 ± 0.3 (1.00)	3	0.3	9	−17	4
39		102 ± 3 (0.03)	90 ± 6 (−0.14)	3	NT			
40		110 ± 2 (0.14)	169 ± 33 (0.96)	4	NT			
41		78 ± 4 (−0.31)	184 ± 20 (1.16)	3	NT			
42		164 ± 24 (0.89)	252 ± 26 (2.11)	4	0.4	15	−9	2
43		115 ± 11 (0.21)	179 ± 34 (1.10)	4	NT			
44		120 ± 5.5 (0.28)	142 ± 5.2 (0.58)	3	NT			
45	123 ± 3 (0.32)	162 ± 25 (0.86)	165 ± 27 (0.90)	7	0.23	14	−21	1
46		134 ± 12.0 (0.47)	175 ± 38 (1.04)	6	NT			
47		139 ± 7.3 (0.54)	159 ± 14.3 (0.82)	5	NT			
48		117 ± 11 (0.24)	202 ± 39 (1.42)	4	0.28	8	−7	1
49		143 ± 15 (0.60)	142 ± 18 (0.59)	6	0.2	9	−17	2
50		172 ± 24 (1.00)	268 ± 91 (2.33)	3	0.03	7	−1	6
51		176 ± 18 (1.05)	221 ± 49 (1.68)	3	0.02	8	−5	4
52		114 ± 5.7 (0.19)	204 ± 47.4 (1.44)	5	NT			
53		107 ± 2.5 (0.10)	116 ± 10.5 (0.22)	2	NT			
54		113 ± 3.5 (0.18)	161 ± 4 (0.84)	2	NT			
55		122 ± 4 (0.30)	155 ± 23.5 (0.76)	2	*c*			2
56	127 ± 3.5 (0.38)	142 ± 12.9 (0.58)	144 ± 20.4 (0.61)	4	0.015	5	−23	2
57		240 (1.94)	326 (3.13)	2	0.006	17	−25	2
58		139 ± 12 (0.54)	135 ± 11 (0.49)	6	0.009	10	−12	5
59		102 (0.03)	165 (0.90)	2	NT			
60		112 (0.17)	105 (0.07)	2	NT			
61		NT	NT		NT			
62		111 ± 4 (0.15)	154 ± 17.8 (0.75)	3	NT			
63		108 ± 3 (0.11)	130 ± 9 (0.41)	5	NT			
64		134 ± 13 (0.47)	336 ± 225 (3.27)	3	1.3	−7	−59	2
65		100 ± 4 (0.00)	140 ± 24 (0.55)	4	NT			
66		105 ± 4 (0.07)	81 ± 17 (−0.26)	4	NT			
67		109 ± 8 (0.12)	116 ± 12 (0.22)	4	NT			
68		99 ± 7.3 (−0.01)	147 ± 26.8 (0.65)	4	NT			
69		103 ± 10 (0.04)	109 ± 14 (0.12)	5	NT			
70		107 ± 4 (0.10)	96 ± 17 (−0.05)	2	NT			
71		122 ± 12 (0.30)	140 ± 28 (0.55)	2	1.1	4	−21	3
72		123 ± 5 (0.32)	186 ± 24 (1.19)	6	5.2	−4	−37	2
73		128 ± 13 (0.39)	134 ± 17 (0.47)	2	1.0	20	−21	2
74		118 ± 13 (0.25)	129 ± 13 (0.41)	4	NT			
75		122 ± 6 (0.30)	149 ± 12 (0.68)	6	NT			
76	113 ± 6 (0.18)	183 ± 35 (1.15)	262 ± 45 (2.25)	8	0.1	14	−4	3
77		137 ± 13 (0.51)	198 ± 36 (1.36)	3	0.07	7	−11	2
78		NT	NT		1.2	−3	−62	3

Table IV (Continued)

no.	cat papillary muscle contractility, % of control (response ratio[d]) 10^{-6}	10^{-5}	10^{-4}	n	anesthetized dog ED_{50} for contractility, mg/kg, iv	% change in HR[e]	% change in MAP[e]	n
79		122 ± 6.7 (0.30)	159 ± 2.5 (0.82)	3	1.0	10	−33	2
80		136 ± 15 (0.50)	196 ± 50 (1.33)	5	NT			
81		136 ± 23 (0.50)	170 ± 11.5 (1.00)	2	NT			
82		125 ± 75 (0.35)	139 ± 14.6 (0.54)	4	NT			
83		109 ± 4 (0.12)	151 ± 34 (0.71)	6	NT			
84		108 ± 3 (0.12)	129 ± 13.5 (0.40)	2	NT			
85		103 ± 6.5 (0.04)	137 ± 17 (0.51)	5	NT			
86		121 ± 40 (0.29)	213 ± 39 (1.57)	9	NT			
87		117 ± 12 (0.24)	215 ± 85 (1.59)	2	0.3	7	−15	1
88		109 ± 2 (0.12)	131 ± 10.5 (0.43)	2	NT			
89		115 ± 6.7 (0.21)	142 ± 20.1 (0.58)	3	0.6	8	14	3

[a] ED_{50} not obtainable. Maximum of 18% increase in dP/dt at 8 mg/kg, accompanied with a 10% increase in HR and a 24% decrease in MAP. [b] NT = not tested. [c] Maximum percent increase was less than 50% up to a high dose of 4 mg/kg, iv. [d] Response ratio = (percent increase to drug)/(percent increase to 10^{-6} M isoproterenol). [e] Values are percent changes at the inotropic ED_{50}'s.

icantly increased at 6 h. A tenfold higher dose of sulmazole was required for comparable activity (Figure 6). The reason(s) for the dramatic differences in oral activities of these two heterocylic systems is an enigma. In all species tested, sulmazole is metabolized primarily by hydroxylation at position 3 of the pyridine with subsequent oxidative destruction of the pyridine ring.[46] If this is a facile metabolic pathway for other imidazo[4,5-*b*]pyridines, it may explain their usually poor oral activity.

Conclusions

We have demonstrated that inotropic activity in this series of azabenzimidazoles is exquisitely sensitive to both the number and position of nitrogens in the fused six-membered ring. The benzimidazoles that we investigated did not possess useful inotropic activity while phenylimidazo[4,5-*b*]pyridines and purines, with appropriate substituents on the phenyl moiety, exhibited reasonable inotropic activity. The imidazo[4,5-*c*]pyridines consistently possessed superior activity whether examined in vitro or in vivo. In addition to their potency advantage, the [4,5-*c*] isomers possessed superior oral activity and some had longer durations of action than the analogous [4,5-*b*] isomers. These pharmacological differences may stem from physicochemical and metabolic differences, and we are investigating these possibilities.

In our studies on effects of phenyl ring substituents on inotropic activity, we found in general that the most potent compounds were 2,4-disubstituted and that molecular planarity may be important; the same effects were observed in the [4,5-*b*] series by Kutter and Austel.[33] The substituent at the 4-position could be varied dramatically while inotropic activity is still maintained. Substituents at the 4-position which possessed a hydrogen-bonding site two to three atoms removed from the phenyl ring appeared to be optimal.

Several of these imidazo[4,5-*c*]pyridines, including **50**, were potent and long-acting cardiotonic agents that simultaneously enhanced contractility and reduced vascular resistance. After iv administration to pentobarbital-anesthetized dogs, **50** was 43- and 10-fold more potent than either amrinone or sulmazole, respectively, which could reduce the incidence of side effects. In this regard, canine 90-day toxicology studies with oral doses of 12.5 mg/kg per day of **50** produced no ECG or pathological abnormalities. The wide safety margin, oral efficacy, and long duration of action of **LY175326** suggest it may be useful in the chronic management of congestive heart failure. Further structure–activity relationship, biochemical, and pharmacological studies of this series are in progress and will be reported in due course.[47]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Identity of all compounds was confirmed by ^1H NMR and mass spectra and combustion analysis. All reactions were followed by TLC carried out on Merck F254 silica gel plates. Microanalytical data were provided by the Physical Chemistry Department of the Lilly Research Laboratories; only symbols of elements analyzed are given and they were within 0.4% of theoretical values unless indicated otherwise.

Except where noted, a standard procedure was used for product isolations. This involved quenching by addition to water, filtration or exhaustive extraction with a solvent (washing of extract with aqueous solutions, on occasion), drying over an anhydrous salt, and evaporation of solvent under reduced pressure. Particular solvents, aqueous washes (if used), and drying agents are mentioned in parentheses after the phrase "product isolation".

Synthesis of Imidazopyridines and Purines. Method A is illustrated by the preparation of 2-(2,4-dimethoxyphenyl)-imidazo[4,5-*c*]pyridine hydrochloride (**38**).

A mixture of 3,4-diaminopyridine (10.9 g, 100 mmol) and 2,4-dimethoxybenzoic acid (18.2 g, 100 mmol) was added to 400 mL of phosphorus oxychloride and the resulting mixture was heated to reflux for 4 h. After the mixture cooled, phosphorus oxychloride was removed under reduced pressure and the residue was treated with 200 mL of 1 N hydrochloric acid. The resulting solution was neutralized with 50% aqueous sodium hydroxide and the precipitated product was collected by filtration. Flash chromatography over silica gel (methylene chloride/methanol, 15/1) and recrystallization from ethanol/water saturated with hydrogen chloride gave the title product (16.54 g, 57% yield) as light tan needles; mp 231–234 °C. Anal. ($C_{14}H_{14}ClN_3O_2$) C, H, N, Cl.

Method B is illustrated by the synthesis of 2-(3-fluorophenyl)imidazo[4,5-*c*]pyridine hydrochloride (**22**).

A mixture of 3,4-diaminopyridine (1.09 g, 10 mmol), 3-fluorobenzoic acid (1.40 g, 10 mmol), and polyphosphoric acid (PPA, 40 g) was heated to 200 °C with stirring for 3.5 h. The solution was then carefully added to water and neutralized by addition of 50% aqueous sodium hydroxide, and the resulting precipitate was collected by filtration. Crystallization from ethanol/water/hydrochloric acid resulted in 1.72 g (81% yield) of 2-(3-fluorophenyl)imidazo[4,5-*c*]pyridine hydrochloride; mp

(46) Roth, V. W.; Prox, A.; Reuter, A. ; Schmid, J.; Zimmer, A.; Zipp, H. *Arzneim.-Forsch.* 1981, *31*, 232.

(47) LY175326 and this series of imidazo[4,5-*c*]pyridines were independently discovered by scientists at E. Merck GmBH and the Wellcome Foundation. See European Patent Applications 72926 and 79083, respectively. We congratulate them on their work.

267–268 °C. Anal. ($C_{12}H_9ClFN_3$) C, H, N, Cl, F.

Method C is illustrated by the synthesis of 2-(4-methylphenyl)imidazo[4,5-*c*]pyridine hydrochloride (**26**).

A mixture of 3,4-diaminopyridine (10 g, 92 mmol), *p*-toluic acid (12.5 g, 92 mmol), and 150 mL of phosphorus pentoxide/methanesulfonic acid (1/10) was heated to 100–120 °C for 3.5 h. After cooling, the mixture was poured into 200 mL of ice water and neutralized with 50% sodium hydroxide, and the resulting precipitate was collected by filtration. The precipitate was flash chromatographed over silica gel, eluting with 9/1 methylene chloride/methanol. The product was crystallized from ethanol/water saturated with hydrogen chloride and recrystallized from ethanol/water to yield 5.0 g (22% yield) of the title product as cream-colored fluffy crystals; mp 266–267.5 °C. Anal. ($C_{13}H_{12}ClN_3$) C, H, N, Cl.

Method D is illustrated by the synthesis of 2-[2-methoxy-4-(methylsulfinyl)phenyl]imidazo[4,5-*c*]pyridine hydrochloride (**50**).

Two grams (7.3 mmol) of 2-[2-methoxy-4-(methylsulfenyl)-phenyl]imidazo[4,5-*c*]pyridine (free base of **49**) was dissolved in 50 mL of hot ethanol. One hundred milliliters of chloroform was added and the solution cooled to −30 to −40 °C by means of an external cooling bath. A solution of 1.455 g of 85% *m*-chloroperbenzoic acid (7.2 mmol) in 10 mL of chloroform was added over a 1-h period and the reaction was stirred for 3 h at −30 to −40 °C. The reaction was then warmed to room temperature and evaporated in vacuo, and the resulting foam was dissolved in 20 mL of dimethylformamide; at this point 1.3 mL of concentrated hydrochloric acid was added. Diethyl ether was added to the cloud point and the solution was stirred for 30 min. The suspension was chilled and filtered, affording 2.1 g (90%) of the title product as brown crystals; mp 210–212 °C. Anal. ($C_{14}H_{14}ClN_3O_2S$) C, H, N, Cl.

Method E is illustrated by the synthesis of 2-[2-methoxy-4-(methylsulfonyl)phenyl]imidazo[4,5-*c*]pyridine hydrochloride (**51**).

A solution of 40% peracetic acid (702 g) in 850 mL of methanol was added to a solution of 2-[2-methoxy-4-(methylsulfenyl)-phenyl]imidazo[4,5-*c*]pyridine hydrochloride (527 g, 1.71 mol) in 4.4 L of methanol over 1.5 h; the temperature of this exothermic reaction was not allowed to exceed 45 °C. After 2 h an additional 70 g of peracetic acid was added and the reaction was heated to 45 °C for 1 h. 2-Propanol (5.2 L) was added and the reaction was cooled to 5 °C. The mixture was filtered and dried to yield 627 g (92%) of product as white crystals; mp 218–218.5 °C. Anal. ($C_{14}H_{14}ClN_3O_3S \cdot {}^3/_4H_2O$) C, H, N, Cl.

Synthesis of 4-(Methylthio)-2-methoxybenzoic Acid (6, Scheme II). 4-(Benzyloxy)-2-hydroxybenzoic Acid Methyl Ester. Compound 4 (51 g, 303 mmol), tetrabutylammonium chloride (252 mg), potassium iodide (18.72 g, 112 mmol), potassium carbonate (42 g, 300 mmol), and benzyl chloride (38 mL, 332 mmol) were added to 600 mL of acetone and the mixture was heated to reflux for 4 h. After cooling to room temperature, the mixture was filtered and concentrated under reduced pressure to a solid. Product isolation (ethyl acetate, water, brine, $MgSO_4$) and washing the resulting solid with cold methanol provided 61.62 g (79%) of white crystals. The analytical sample was recrystallized from methanol; mp 93–95 °C. Anal. ($C_{15}H_{14}O_4$) C, H.

4-(Benzyloxy)-2-methoxybenzoic Acid Methyl Ester. 4-(Benzyloxy)-2-hydroxybenzoic acid methyl ester (78.0 g, 302.3 mmol) was added in portions to a suspension of sodium hydride (13.93 g of a 60% suspension in oil, 348.3 mmol) in 700 mL of DMF. After evolution of hydrogen ceased, methyl iodide (129 g, 909 mmol) was added in one portion and the reaction was stirred at room temperature. After 2.5 h, TLC indicated disappearance of starting material, and product isolation (ether, water, brine, $MgSO_4$) and recrystallization afforded 73.59 g of product as white crystals; mp 81–82.5 °C. Anal. ($C_{16}H_{16}O_4$) C, H.

4-Hydroxy-2-methoxybenzoic Acid Methyl Ester. 4-(Benzyloxy)-2-methoxybenzoic acid methyl ester (61.13 g, 224.7 mmol) and 5 g of 5% Pd/C were suspended in 200 mL of THF. After degassing, the mixture was stirred under 35 psi of hydrogen until the theoretical amount had been consumed. The reaction was filtered through Celite. Removal of solvent under reduced pressure yielded 39.73 g of analytically pure product as a white solid; mp 137–140 °C. Anal. ($C_9H_{10}O_4$) C, H.

4-[(Dimethylamino)thioxomethoxy]-2-methoxybenzoic Acid Methyl Ester (5). Sodium hydride (8.91 g of a 60% suspension in oil, 222.7 mmol) was added in portions to a solution of 4-hydroxy-2-methoxybenzoic acid methyl ester (29.96 g, 164.5 mmol) in 800 mL of DMF. After evolution of hydrogen ceased, dimethylthiocarbamoyl chloride (27.53 g, 222.7 mmol) was added to one portion. The mixture was stirred at room temperature overnight and poured into 3 L of water. Product isolation (ethyl acetate, water, brine, $MgSO_4$) and recrystallization from THF/hexane yielded 34.21 g of product as white crystals; mp 93.5–95 °C. Anal. ($C_{12}H_{15}NO_4S$) C, H, N, S.

4-Mercapto-2-methoxybenzoic Acid. Compound **5** (96.5 g, 358 mmol) was heated under nitrogen at 235–245 °C for 1 h, at which time TLC analysis indicated the reaction was complete. The *S*-aryl thiocarbamate product was a dark viscous oil.

A mixture of this oil and 5 N sodium hydroxide (358 mL, 1.79 mol) in 700 mL of methanol was refluxed overnight. Solvent was removed under reduced pressure, the residue was dissolved in water, and the solution was slowly acidified with 6 N hydrochloric acid, which resulted in evolution of gas and formation of a voluminous white precipitate. Product isolation (ethyl acetate, water, brine, $MgSO_4$) and recrystallization from THF/hexane yielded 50.23 g of product as light yellow crystals; mp 100.5–102.5 °C. Anal. ($C_8H_8O_3S$) C, H, S.

4-(Methylthio)-2-methoxybenzoic Acid. 4-Mercapto-2-methoxybenzoic acid (44.78 g, 243 mmol) was added in portions to sodium hydride (21.4 g of a 60% suspension in oil, 535 mmol) in 700 mL of DMF at 0 °C. After evolution of hydrogen ceased, dimethyl sulfate (31.58 g, 250 mmol) was added dropwise. After stirring overnight, the reaction was poured into 1.5 L of water and extracted with hexane (discarded). Acidification of the aqueous layer with dilute hydrochloric acid, product isolation (ethyl acetate, brine, $MgSO_4$), and recrystallization from THF/hexane afforded 45.04 g of product as light yellow crystals; mp 94–96 °C. Anal. ($C_9H_{10}O_3S$) C, H, S.

Kolbe–Schmidt Mediated Synthesis of 2,4-Disubstituted Benzoic Acids. This method is illustrated by the synthesis of 4-(methylthio)-2-propoxybenzoic acid.

2-Hydroxy-4-(methylthio)benzoic Acid. A mixture of 3-hydroxythioanisole (20 g, 143 mmol) and anhydrous potassium carbonate (50 g, 362 mmol) in a 0.5-L stainless steel autoclave under a 500-psi carbon dioxide atmosphere was heated at 200 °C for 5 h. After cooling to room temperature, the mixture was dissolved in 1 L of water, filtered, and extracted with ether (discarded). The aqueous layer was carefully acidified with 6 N hydrochloric acid. Product isolation (ethyl acetate, water, brine, $MgSO_4$) and recrystallization provided 17.7 g (72%) of product as white crystals; mp 178–180 °C. Anal. ($C_8H_8O_3S$) C, H, S.

2-Hydroxy-4-(methylthio)benzoic Acid Methyl Ester. Dimethyl sulfate (11.7 mL, 125 mmol) was added dropwise to a vigorously stirred mixture of 2-hydroxy-4-(methylthio)benzoic acid (23.0 g, 125 mmol) and potassium carbonate (13.0 g, 90 mmol) in 100 mL of Me_2SO at 0 °C. After warming and stirring for 2.5 h at room temperature, the reaction mixture was poured into water and the resulting precipitate filtered. Product isolation (ethyl acetate, water, $MgSO_4$) provided 22.2 g (90%) of product as a white solid; mp 54.5–55.5 °C. Anal. ($C_9H_{10}O_3S$) C, H.

4-(Methylthio)-2-*n*-propoxybenzoic Acid. 2-Hydroxy-4-(methylthio)benzoic acid methyl ester (21.0 g, 110 mmol) was added in portions to a mixture of sodium hydride (5.1 g of a 60% suspension in oil; 130 mmol) in 250 mL of DMF. After the exotherm and hydrogen evolution ceased, *n*-propyl iodide (20.7 mL, 210 mmol) was added in one portion and the reaction was stirred overnight. Dilution with 1 L of water and product isolation (ethyl acetate, water, brine, $MgSO_4$) afforded 26.5 g of an oil.

The oil and 50% sodium hydroxide (28.8 mL, 550 mmol) in 250 mL of methanol were refluxed for 5 min. After cooling, methanol was removed in vacuo, and the residue was dissolved in water, washed with hexanes (discarded), and acidified with 6 N hydrochloric acid. Product isolation (ethyl acetate, water, brine, $MgSO_4$) and recrystallization from THF/hexane yielded 20.5 g (86%) of product as white crystals; mp 75–76 °C. Anal. ($C_{11}H_{14}O_3S$) C, H.

Pharmacological Methods. Isolated Cat Papillary Muscles. Cats of either sex were anesthetized with methoxyflurane, their hearts immediately removed, and papillary muscles dissected and suspended in individual muscle baths. A 27-gauge hook secured the muscle to an electrode mounted in the bottom of the

bath and a silk thread attached the tendon to a Statham isometric transducer. Baths contained Krebs–Henseleit solution (37.5 °C, bubbled with 95% O_2/5% CO_2) of the following millimolar composition: NaCl 118, KCl 4.5, $CaCl_2$ 2.5, KH_2PO_4 1.1, $MgSO_4$ 1.2, $NaHCO_3$ 25, and glucose, 11. A base-line tension of 1.0 g was applied to each tissue. Muscles were stimulated to contract by administering square-wave pulses (2.0 ms in duration, 12 times/min, 20% above threshold voltage) delivered through the hook electrode and a second electrode positioned near the top of the muscle; contractions were recorded on a Beckman polygraph.

Muscles were equilibrated for 60 min prior to drug treatment. In order to assure that muscles were functioning properly, each was exposed to 10^{-6} M isoproterenol for 3 min. If the inotropic response was less than 120% of control, the muscle was rejected. This short-acting standard was washed out of the baths, and the muscles were allowed 30 min to stabilize. Test compounds were added to baths at 10^{-5} M for 30 min followed by 10^{-4} M for an additional 30 min. To establish cumulative dose–response relationships, drugs were added to baths and allowed to produce maximal responses before the addition of the next higher concentration.

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 stokes/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 intravenous drug administration. Heart rate was derived by means of a cardiotachometer which 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 intravenous injection of 50 mL of 5% dextran and mechanical compression of the aorta showed that contractility measurements were independent of changes in preload and afterload. Subcutaneous pin electrodes provided a lead II ECG. Increasing doses of drugs (0.01, 0.02, 0.05, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 mg/kg) were administered intravenously in volumes of 0.25–4.0 mL at 5-min intervals; no responses occurred with appropriate vehicle control injections.

Conscious Dog Studies. Male mongrel dogs weighing 15–36 kg were chronically instrumented to monitor $LVdP/dt_{60}$, peak systolic blood pressure, and heart rate. Under halothane/nitrous oxide anesthesia, a precalibrated Konigsberg P22 pressure transducer was implanted into the left ventricle through a stab wound at the apex. The dogs were allowed to recover from surgery a minimum of 2 weeks before use in a study. The animals were conditioned to the test laboratory and trained to lie quietly for 4-h periods. This conditioning was necessary to obtain stable, reproducible results from day to day. Dogs were fasted 18 h before an experiment and gross behavioral observations of animals were made throughout each study. Drug or placebo (lactose) was administered in 000 gelatin capsules.

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Registry No. **4**, 2150-47-2; **5**, 95420-30-7; **6**, 72856-73-6; **7**, 1016-93-9; **8**, 63581-47-5; **9**, 95420-31-8; **9**·HCl, 57318-26-0; **10**, 95420-32-9; **10**·HCl, 57318-45-3; **11**, 1019-81-4; **12**, 95420-33-0; **12**·HCl, 95420-34-1; **13**, 77303-19-6; **13**·HCl, 53929-89-8; **14**, 77303-19-6; **15**, 77414-24-5; **17**, 75007-92-0; **18**, 89075-44-5; **18**·HCl, 89075-02-5; **19**, 89075-41-2; **19**·HCl, 89074-98-6; **20**, 89075-48-9; **20**·HCl, 89075-07-0; **21**, 89075-43-4; **21**·HCl, 89075-00-3; **22**, 89074-94-2; **22**·HCl, 89074-95-3; **23**, 89075-42-3; **23**·HCl, 89074-99-7; **24**, 89075-53-6; **24**·HCl, 89075-15-0; **25**, 89074-96-4; **26**, 89075-52-5; **26**·HCl, 89075-14-9; **27**, 87359-17-9; **27**·HCl, 87359-18-0; **28**, 89075-49-0; **28**·HCl, 89075-09-2; **29**, 80675-85-0; **29**·HCl, 89075-08-1; **30**, 89075-50-3; **30**·HCl, 89075-11-6; **31**, 80675-86-1; **31**·HCl, 89075-10-5; **32**, 95420-36-3; **32**·HCl, 95420-37-4; **33**, 89075-33-2; **34**, 89075-40-1; **34**·HCl, 89074-97-5; **35**, 89075-57-0; **35**·HCl, 89075-32-1; **36**, 87359-25-9; **36**·HCl, 87359-26-0; **37**, 95420-38-5; **37**·HCl, 95420-39-6; **38**, 87359-11-3; **38**·HCl, 89075-01-4; **39**, 89075-45-6; **39**·HCl, 89075-04-7; **40**, 80675-94-1; **40**·HCl, 89075-18-3; **41**, 89075-54-7; **41**·HCl, 89075-20-7; **42**, 87359-19-1; **42**·HCl, 80675-92-9; **43**, 89075-19-4; **44**, 95420-40-9; **44**·HCl, 95420-41-0; **45**, 87359-22-6; **45**·HCl, 87359-23-7; **46**, 95420-42-1; **46**·HCl, 89075-38-7; **47**, 95420-43-2; **47**·HCl, 95420-44-3; **48**, 95420-45-4; **48**·HCl, 95420-46-5; **49**, 87359-45-3; **49**·HCl, 86315-69-7; **50**, 86315-52-8; **50**·HCl, 87359-33-9; **51**, 87359-43-1; **51**·HCl, 87359-44-2; **52**, 87359-30-6; **52**·HCl, 95420-47-6; **53**, 87359-32-8; **53**·HCl, 87359-31-7; **54**, 95420-48-7; **54**·HCl, 95420-49-8; **55**, 95420-50-1; **56**, 95420-51-2; **57**, 95420-52-3; **57**·HCl, 95420-53-4; **58**, 95420-54-5; **58**·HCl, 95420-55-6; **59**, 95420-56-7; **59**·HCl, 95420-57-8; **60**, 95420-58-9; **61**, 95420-59-0; **61**·HCl, 89075-37-6; **62**, 95420-60-3; **62**·HCl, 89075-39-8; **63**, 86315-28-8; **64**, 89075-16-1; **65**, 89075-17-2; **66**, 89090-06-2; **66**·HCl, 89075-22-9; **67**, 87359-27-1; **68**, 89075-23-0; **69**, 89075-24-1; **70**, 89075-35-4; **71**, 89075-25-2; **72**, 89075-34-3; **73**, 89075-56-9; **73**·HCl, 89075-31-0; **74**, 89075-30-9; **75**, 89075-28-5; **76**, 95420-61-4; **76**·HCl, 95420-62-5; **77**, 95420-63-6; **78**, 89075-29-6; **79**, 89075-36-5; **80**, 95420-64-7; **80**·HCl, 89075-27-4; **81**, 95420-65-8; **81**·HCl, 95420-66-9; **82**, 95420-67-0; **83**, 87359-13-5; **83**·HCl, 89075-03-6; **84**, 89075-55-8; **84**·HCl, 89075-26-3; **85**, 89075-21-8; **86**, 89075-12-7; **86**·HCl, 89686-51-1; **87**, 77456-43-0; **87**·HCl, 95420-68-1; **88**, 77456-44-1; **88**·HCl, 95420-69-2; **89**, 77456-53-2; **89**·HCl, 95420-70-5; $C_6H_5CO_2H$, 65-85-0; 4-OMe-$C_6H_4CO_2H$, 100-09-4; 4-SMe-$C_6H_4CO_2H$, 13205-48-6; 4-SO_2Me-$C_6H_4CO_2H$, 4052-30-6; 3-Me-$C_6H_4CO_2H$, 99-04-7; 3-OMe-4-OMe-$C_6H_3CO_2H$, 93-07-2; 2-OMe-4-OMe-$C_6H_3CO_2H$, 91-52-1; 4-CN-$C_6H_4CO_2H$, 619-65-8; 2-F-$C_6H_4CO_2H$, 445-29-4; 3-F-$C_6H_4CO_2H$, 455-38-9; 4-F-$C_6H_4CO_2H$, 456-22-4; 2-Me-$C_6H_4CO_2H$, 118-90-1; Me-$C_6H_4CO_2H$, 99-94-5; 2-OMe-$C_6H_4CO_2H$, 579-75-9; 3-OMe-$C_6H_4CO_2H$, 586-38-9; 4-oMe-$C_6H_4CO_2H$, 100-09-4; 4-OBu-$C_6H_4CO_2H$, 1498-96-0; 4-NMe_2-$C_6H_4CO_2H$, 619-84-1; 4-SPh-$C_6H_4CO_2H$, 6310-24-3; 2-Cl-4-Cl-$C_6H_3CO_2H$, 50-84-0; 3-Cl-5-Cl-$C_6H_3CO_2H$, 51-36-5; 3-Me-4-Me-$C_6H_3CO_2H$, 619-04-5; 2-Me-4-Me-$C_6H_3CO_2H$, 611-01-8; 2-Me-4-OMe-$C_6H_3CO_2H$, 6245-57-4; 2-OMe-3-OMe-$C_6H_3CO_2H$, 1521-38-6; 2-OMe-5-OMe-$C_6H_3CO_2H$, 2785-98-0; 2-OMe-6-OMe-$C_6H_3CO_2H$, 1466-76-8; 3-OMe-5-OMe-$C_6H_3CO_2H$, 1132-21-4; 2-OMe-4-F-$C_6H_3CO_2H$, 395-82-4; 2-OMe-4-Cl-$C_6H_3CO_2H$, 57479-70-6; 2-OMe-4-Br-$C_6H_3CO_2H$, 72135-36-5; 2-OMe-4-I-$C_6H_3CO_2H$, 89942-34-7; 2-OMe-4-Me-$C_6H_3CO_2H$, 704-45-0; 2-SMe-4-OMe-$C_6H_3CO_2H$, 72856-74-7; 2-SMe-4-SMe-$C_6H_3CO_2H$, 95420-76-1; 2-OMe-4-OPh-$C_6H_3CO_2H$, 95420-77-2; 2-OMe-4-NO_2-$C_6H_3CO_2H$, 2597-56-0; 2-OMe-4-CF_3-$C_6H_3CO_2H$, 448-36-2; 2-OMe-4-NMe_2-$C_6H_3CO_2H$, 95420-78-3; 2-OMe-4-OBzl-$C_6H_3CO_2H$, 85607-79-0; 3-OMe-4-SMe-$C_6H_3CO_2H$, 95420-79-4; 2-OEt-4-OMe-$C_6H_3CO_2H$, 55085-15-9; 2-OPr-4-OMe-$C_6H_3CO_2H$, 87359-70-4; 2-OBu-4-OMe-$C_6H_3CO_2H$, 95420-80-7; 2-O-C_5H_{11}-4-OMe-$C_6H_3CO_2H$, 95420-81-8; 2-OC_2H_4OMe-4-OMe-$C_6H_3CO_2H$, 87359-71-5; 2-OC_3H_6OMe-4-OMe-$C_6H_3CO_2H$, 95420-82-9; 2-OC_2H_4SPh-4-OMe-$C_6H_3CO_2H$, 95420-83-0; 2-OC_2H_4SMe-4-OMe-$C_6H_3CO_2H$, 95420-84-1; 2-OC_2H_4SEt-4-OMe-$C_6H_3CO_2H$, 95420-85-2; 2-OC_3H_6SMe-4-OMe-$C_6H_3CO_2H$, 95420-86-3; 2-OEt-4-SMe-$C_6H_3CO_2H$, 89407-44-3; 2-OMe-4-SEt-$C_6H_3CO_2H$, 95420-87-4; 2-OMe-4-SPr-$C_6H_3CO_2H$, 95420-88-5; 3-OMe-4-OMe-5-OMe-$C_6H_2CO_2H$, 118-41-2; 2-OMe-4-OMe-5-OMe-$C_6H_2CO_2H$, 490-64-2; 2-OMe-4-OMe-6-OMe-$C_6H_2CO_2H$, 570-02-5; 3-Me-4-OMe-5-Me-$C_6H_2CO_2H$, 21553-46-8; 4-(benzyloxy)-2-hydroxybenzoic acid methyl ester, 5427-29-2; 4-(benzyloxy)-2-methoxybenzoic acid methyl ester, 28478-45-7; 4-hydroxy-2-methoxybenzoic acid methyl ester, 28478-46-8; dimethylthiocarbamoyl chloride, 16420-13-6; 4-[(dimethylcarbamoyl)thio]-2-methoxybenzoic acid methyl ester, 95420-71-6; 4-mercapto-2-methoxybenzoic acid, 95420-72-7; 3-hydroxythioanisole, 3463-03-4; 2-hydroxy-4-(methylthio)benzoic acid, 67127-67-7; 2-hydroxy-4-(methylthio)benzoic acid methyl ester, 95420-73-8; 4-(methylthio)-2-*n*-propoxybenzoic acid methyl ester, 95420-74-9; 4-(methylthio)-2-*n*-propoxybenzoic acid, 95420-75-0; 2,3-pyridinediamine, 452-58-4; 3,4-pyridinediamine, 54-96-6; 4,5-pyrimidinediamine, 13754-19-3.