Cardiotonic Agents. 2. Synthesis and Structure-Activity Relationships of 4,5-Dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinones: A New Class of Positive Inotropic Agents[1]

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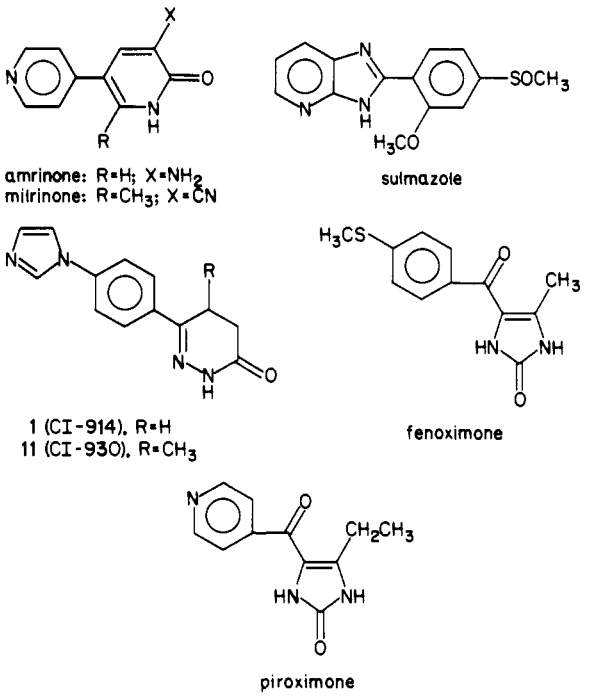
A series of 4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinones and related compounds were synthesized and evaluated for positive inotropic activity. Most members of this series produced dose-related increases in myocardial contractility that were associated with relatively minor increases in heart rate and decreases in systemic arterial blood pressure. Introduction of a methyl substituent at the 5-position of 1 (CI-914) produced the most potent compound in this series (11, CI-930). Compound 1 is more potent than amrinone whereas compound 11 is more potent than milrinone. The inotropic effects of 1 and 11 are not mediated via stimulation of β-adrenergic receptors. Selective inhibition of cardiac phosphodiesterase fraction III represents the principal component of the positive inotropic action of 1 and 11.

For many years digitalis glycosides have been the principal agents used for the treatment of heart failure.[2,3] However, their use is limited by arrhythmogenic liability. Recently, systemic vasodilators, which reduce ventricular afterload and improve cardiac performance, have been increasingly used for the treatment of heart failure.[4,5] An agent that combines reduction in ventricular afterload and positive inotropic activity would provide the most efficient enhancement of cardiac pump function.[5,6] Two sympathomimetic agents, dobutamine and dopamine,[7] have been used successfully in the treatment of acute exacerbations of congestive heart failure; however, chronotropic liability and oral ineffectiveness prevent the use of either drug in chronic treatment of congestive heart failure. Amrinone, a 2(1*H*)-pyridone, produces acute hemodynamic improvement in patients with congestive heart failure;[8-10] however, dose-related thrombocytopenia, fever, and gastrointestinal side effects may limit amrinone's effectiveness.[11,12] Recently milrinone, a more potent analogue of amrinone, has been reported to be effective in patients with severe congestive hart failure.[13-15] Other nonsympathomimetic cardiotonic agents under development include sulmazole,[16,17] MDL-17043 (fenoximone), and MDL-19205 (piroximone)[18-20] (Chart 1).

The considerable therapeutic need and lack of effective agents for the management of congestive heart failure (CHF) prompted the initiation of a program in our laboratory to identify potent, safe, orally active inotropic agents. 6-Phenyl-3(2*H*)-pyridazinones and their 4,5-dihydro analogues are well documented in the literature with various biological properties including reduction of blood pressure,[21-23] inhibition of platelet aggregation,[23,24] and antiinflammation.[25] We have found that 6-phenyl-3-(2*H*)-pyridazinone also possesses weak positive inotropic activity. This led us to search for novel and more potent analogues, which resulted in a new class of positive inotropic agents, 4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)-phenyl]-3(2*H*)-pyridazinones and their derivatives (Tables I–III). Several of these agents including 1 (CI-914) and 11 (CI-930) are more potent than amrinone. In comparison to milrinone compound 11 is approximately 3 times more potent when administered intravenously, and up to 10 times more potent when administered orally, in a dog model.

Chemistry. 4,5-Dihydro-3(2*H*)-pyridazinones (**1–24**; Tables I and II) were prepared by reaction of hydrazine and the appropriate γ-oxobenzenebutanoic acids. The

Chart I



dihydropyridazinones were subsequently converted to the pyridazinones either by bromine/acetic acid (method A)

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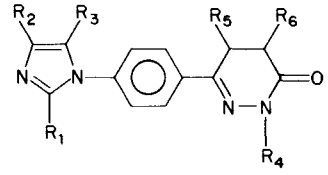
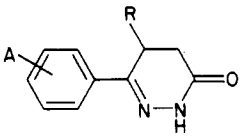
Table I. 4,5-Dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinones



										myocardial contractility	
no.	R_1	R_2	R_3	R_4	R_5	R_6	mp, °C (recrystn solvent)[a]	mol formula	yield,[b] %	iv: dose, mg/kg, to cause 50% inc in dP/dt_{max}[c] (*n*)	po: dose, mg/kg, to cause 40–60% inc in dP/dt_{max}[d]
1	H	H	H	H	H	H	290–291 (A)	$C_{13}H_{12}N_4O \cdot HCl \cdot 0.4H_2O$	80	0.045 ± 0.006 (6)	1.0 (6)
2	CH_3	H	H	H	H	H	168–169 (D)	$C_{14}H_{14}N_4O \cdot 0.4H_2O$	68	0.3 (2)	1.0
3	C_2H_5	CH_3	H	H	H	H	177–178 (A)	$C_{16}H_{18}N_4O$	82	0.1	<3.1
4	H	CH_2OH	H	H	H	H	213.5–215 (A)	$C_{14}H_{14}N_4O_2$	22	0.034 ± 0.01 (4)	
5	SH	H	H	H	H	H	310–312.5 dec (C)	$C_{13}H_{12}N_4OS$	41		>10.0
6	SCH_3	H	H	H	H	H	149–155 (I)	$C_{14}H_{14}N_4OS$	91		10.0
7	$SOCH_3$	H	H	H	H	H	187–188 (A)	$C_{14}H_{14}N_4O_2S$	66	0.3	10.0
8	SO_2CH_3	H	H	H	H	H	199–201 (B)	$C_{14}H_{14}N_4O_3S$	64		>1.0
9	H	H	H	CH_3	H	H	143–144 (E)	$C_{14}H_{14}N_4O$	48	>1.0 (0.2)	
10	H	H	H	CH_2CH_2OA[e]	H	H	123–124 (D)	$C_{17}H_{18}N_4O_3$	59	>1.0	
11	H	H	H	H	CH_3	H	296–298 dec (A)	$C_{14}H_{14}N_4O \cdot HCl$	80	0.013 ± 0.006 (8)	0.1 (6)
12	H	H	H	H	C_2H_5	H	123–125 (A)	$C_{15}H_{16}N_4O$	44	1.0 (2)	
13	H	$-(CH_2)_4-$		H	H	H	296–297 (B)	$C_{17}H_{18}N_4O \cdot 0.1H_2O$	51	0.064 ± 0.016 (3)	>1.0
14	H	$-(CH_2)_4-$		H	CH_3	H	199–200 (A)	$C_{18}H_{20}N_4O$	65	0.02 ± 0.0 (3)	0.3
15	H			H	H	H	262–264 (A)	$C_{17}H_{14}N_4O$	58	0.1 (2)	3.1
16	H			H	H	H	233–234 (A)	$C_{19}H_{18}N_4O$	75		>10 >3.1
17	H	H	H	H	H	CH_3	203–204 (A)	$C_{14}H_{14}N_4O$	50	1.0 (2)	
18	H	H	H	H	$-(CH_2)_4-$		243–244 (A)	$C_{17}H_{18}N_4O$	52	1.0 (2)	
19	H	H	H	CH_2Ph	H	H	130–131 (A)	$C_{20}H_{18}N_4O \cdot 0.1H_2O$	80		10.0

[a] Key: A = EtOH; B = MeOH; C = DMF; D = CH_2Cl_2/isopropyl ether; E = EtOH/isopropyl ether; F = ethyl acetate; G = THF; H = EtOH/$CHCl_3$; I = H_2O. [b] Yield was not optimized. [c] Data are not available for all compounds. Values were obtained from a dose–response curve for soluble compounds only and are expressed as the mean ± SEM. When two determinations were made (designated in parentheses), the value shown is the arithmetic mean. [d] Data shown were obtained from single determination except for compounds 1 and 11.

Table II. 4,5-Dihydro-6-(4-heterocyclylphenyl)-3(2*H*)-pyridazinones



no.	A	R	mp, °C (recrystn solvent)[a]	mol formula	yield,[b] %	myocardial contractility (po): dose, mg/kg to cause 40–60% inc in dP/dt_{max}
20		H	257–258 (C)	$C_{13}H_{12}N_4O$	76	>3.1
21		H	190–190.5	$C_{13}H_{12}N_4O$	57	>1.0[c] (2)
22		H	311–312 (dec) (C)	$C_{12}H_{11}N_5O$	56	1.0
23		H	292.5–293 (dec) (B)	$C_{12}H_{11}N_5O$	7	>3.1
24		H	222–223 (B)	$C_{14}H_{13}N_3O$	50	10.0

[a,b] See corresponding footnotes in Table I. [c] Dose to cause 50% increase in dP/dt_{max} (IV) = 0.3 mg/kg (n = 3). [d] Data shown were obtained from single determinations except for compound **21**.

or by manganese dioxide oxidation (method B) (**25–39**; Table III) as outlined in Scheme I. The synthesis of the key intermediates, γ-oxobenzenebutanoic acids (**40–53**; Table IV), is outlined in Scheme II. Method C involves reaction of 4-halo-γ-oxobenzenebutanoic acids with various azoles under strongly basic conditions such as sodium hydride or *n*-butyllithium. This procedure was more suitable for compounds where R_5 and R_6 were both hydrogen (**40**, **43**, **49**, **51**; Table IV). Method D involves the condensation of the desired azoles with haloacetophenones[26] to give azolylacetophenones, which were converted to the corresponding β-keto esters by reaction with sodium hydride and dimethyl carbonate.[27] Alkylation of these β-keto esters with ethyl bromoacetate followed by acid hydrolysis gave the desired γ-keto acids (**40–42**, **47–48**, **53**; Table IV). Method E involves the addition of an aldehyde anion equivalent to a suitably substituted acrylonitrile followed by hydrolysis to give the desired γ-keto acids (**44-46**; Table IV).[28] This method was preferred for compounds where R_5 and R_6 were methyl.

6-(4-Aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (**54**)[21] was used as the starting material for the synthesis of 2-thioxoimidazole (**5**) as shown in Scheme III. Compound **54** was converted to the corresponding isothiocyanate **55** by reaction with 1,1′-thiocarbonyldiimidazole at 0 °C followed by reaction with aminoacetaldehyde dimethyl acetal to give **5**.[29] Nitric acid oxidation of **5** gave **1**. Compound **5** was converted to the methylthio derivative **6**, which was oxidized with *m*-chloroperbenzoic acid to the methylsulfinyl and methylsulfonyl compounds (**7**, **8**). Compounds **23** and **24** were obtained from **54** by reaction with 1,2-hydrazinedicarboxaldehyde[30] and tetrahydro-2,5-dimethoxyfuran, respectively.

The synthesis of 4-aminopyridazinone (**33**) is outlined in Scheme IV. 1-[4-(1*H*-Imidazol-1-yl)phenyl]ethanone was condensed with diethylketomalonate, and the intermediate keto ester was subsequently treated with hydrazine to yield **34**.[31] Compound **34** was converted to the 4-aminopyridazinone (**33**) via Curtius rearrangement as well as via Hoffman degradation of the corresponding amide (**35**). Compound **33** was also obtained in very high yield (90%) by reacting the parent compound **1** with excess hydrazine hydrate at 100 °C.[32]

Biological Results and Discussion. Compounds in Tables I–III were evaluated intravenously in an acutely instrumented anesthetized dog and/or orally in a conscious dog model[33] for positive inotropic activity as described in the Experimental Section. Heart rate, myocardial con-

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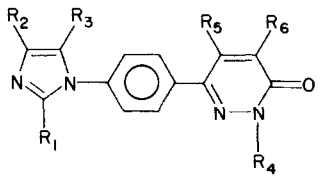
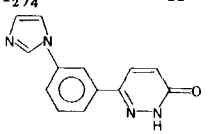
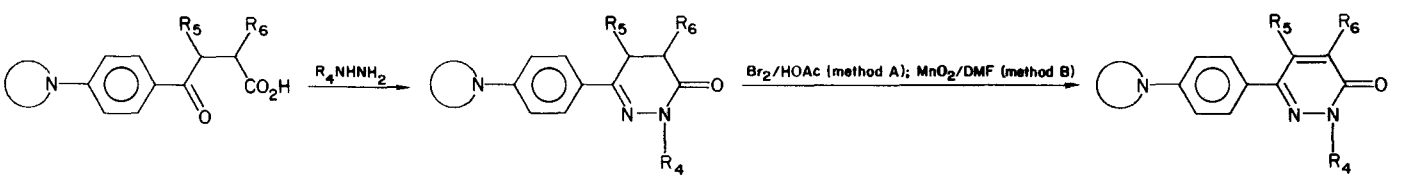
Table III. 6-[4-(1*H*-Imidazol-1-yl)phenyl]-3(2*H*)-pyridazinones



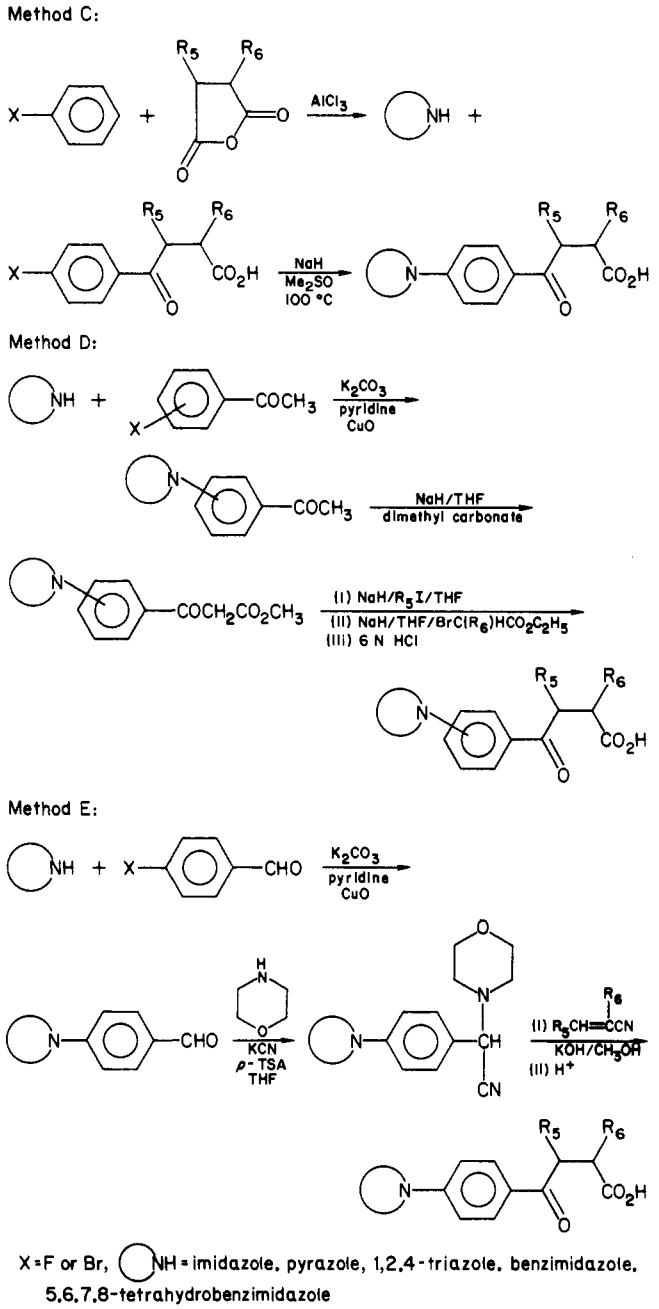
no.	R_1	R_2	R_3	R_4	R_5	R_6	mp, °C (recrystn solvent)[a]	mol formula	yield,[b] %	myocardial contractility: dose to cause 50% inc in dP/dt_{max} (*n*)
25	H	H	H	H	H	H	244-245 (A)	$C_{13}H_{10}N_4O$	75	0.1 (2)
26	CH_3	H	H	H	H	H	220-221 (D)	$C_{14}H_{12}N_4O$	20	0.1 (2)
27	C_2H_5	CH_3	H	H	H	H	215-216 (G)	$C_{16}H_{16}N_4O$	20	0.3
28	C_2H_5	CH_3	Br	H	H	H	186-187 (A)	$C_{16}H_{15}BrN_4O$	69	0.2
29	H	H	H	CH_3	H	H	172-173 (A)	$C_{14}H_{12}N_4O$	25	>1.0
30	H	H	H	CH_2CH_2OH	H	H	212-213	$C_{15}H_{14}N_4O_2$	71	>1.0
31	H	H	H	H	CH_3	H	284-286	$C_{14}H_{12}N_4O$	60	>1.0
32	H	H	H	H	H	CH_3	225-226 (G)	$C_{14}H_{12}N_4O$	23	0.3 (2)
33	H	H	H	H	H	NH_2	323-325 dec	$C_{13}H_{11}N_5O$	80	0.3 (2)
34	H	H	H	H	H	$CONHNH_2$	304-305 dec	$C_{14}H_{12}N_6O_2$	54	1.0
35	H	H	H	H	H	$CONH_2$	332-335 dec	$C_{14}H_{11}N_5O_2$	32	>1.0
36	H	H	H	H	H	CO_2H	290-292 dec	$C_{14}H_{10}N_4O_3 \cdot HCl$	96	>1.0
37	H	$(CH_2)_4$		H	H	H	319-320 (B)	$C_{17}H_{16}N_4O$	25	0.1 (2)
38	H	$(CH_2)_4$		H	CH_3	H	313-314 (B)	$C_{18}H_{18}N_4O$	25	>0.1
39								$C_{13}H_{10}N_4O$	71	0.2

[a-c] See corresponding footnotes in Table I.

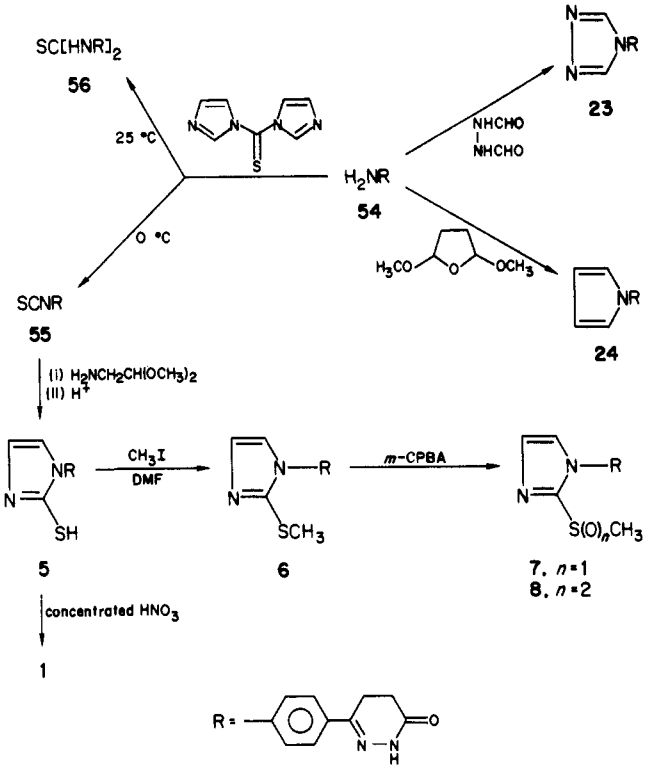
Scheme I



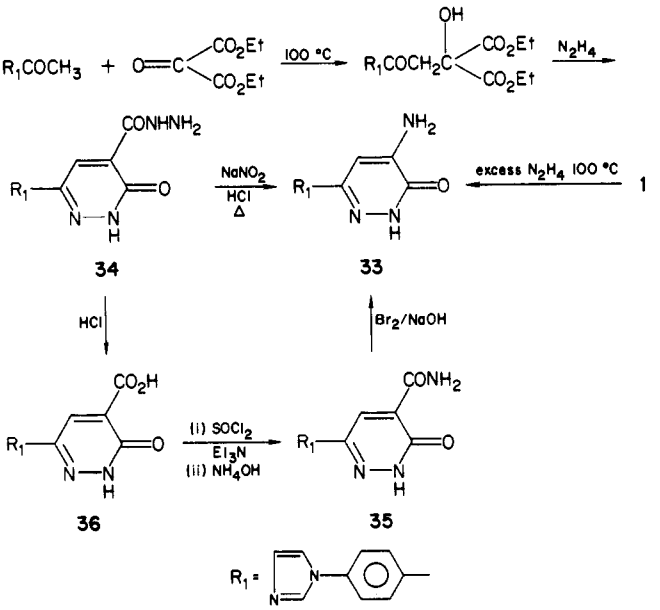
Scheme II



Scheme III



Scheme IV



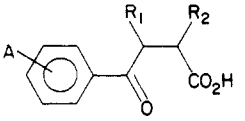
tractility (derived by measuring dP/dt_{max} of left ventricular pressure), and aortic blood pressure were recorded. Intravenous dose–response curves were determined with at least four doses of each compound.

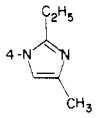
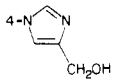
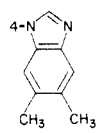
The dose of each compound to increase myocardial contractility by 50% is shown in Tables I and III. Compound **1** produced substantial increases in myocardial contractility. Alkyl substitution of the imidazole moiety (**2** and **3**) did not offer any advantage over **1**, whereas the hydroxymethyl analogue **4** retained the potency of the unsubstituted compound **1**. Compound **7**, in which the imidazole ring was substituted by methylsulfinyl group, retained some of the activity of the parent compound **1**. Compound **13**, in which the imidazole ring has been replaced by tetrahydrobenzimidazole, is equipotent to the imidazole analogue **1**. Considerable loss in activity was observed by substituting the amide nitrogen (**9**, **10**). This finding indicates that a free NH is required for significant positive inotropic activity.

Among the compounds in Table I, it is apparent that 5-methyl-substituted compounds (**11** and **14**) are consistently more potent positive inotropic agents than their normethyl analogues (**1** and **13**), and homologating this 5-substituent to ethyl (**12**) led to diminished activity. By contrast, introduction of a 4-methyl substituent (**17**) leads to a substantial reduction in potency relative to the parent compound. Compound **18**, where R_5 and R_6 taken together form a cyclohexane ring, was considerably less potent than **1**.

Table II lists compounds in which the imidazole moiety has been replaced by other heterocycles. Unfortunately, except for compound **21** the inotropic activity could not be assessed in the anesthetized dog model because limited solubility precluded intravenous administration of the agent. However, the 1,2,4-triazole analogue, **22**, is the only other heterocyclic replacement that retained potent pos-

Table IV. Substituted γ-Oxobenzenebutanoic acids



no.	A	R_1	R_2	mp, °C (recrystn solvent)[a]	mol formula	yield,[b] %
40		H	H	272–273 (C)	$C_{13}H_{12}N_2O_3 \cdot 0.1H_2O$	80
41		H	H	234–235 (C)	$C_{14}H_{14}N_2O_3$	50
42		H	H	188–189	$C_{16}H_{18}N_2O_3$	55
43[c]		H	H	213–218 dec (B)	$C_{14}H_{14}N_2O_4$	26
44		CH_3	H	180–181	$C_{14}H_{14}N_2O_3$	76
45		H	CH_3	200–201 (G)	$C_{14}H_{14}N_2O_3$	75
46		C_2H_5	H	147–149 (J)	$C_{15}H_{16}N_2O_3$	50
47		H	H	140.5–142 (I)	$C_{13}H_{12}N_2O_3$	38
48		H	H	234–235 (B)	$C_{12}H_{11}N_3O_3$	58
49		H	H	185–187 (B)	$C_{13}H_{12}N_2O_3$	50
50		H	H	234–235 (C)	$C_{17}H_{18}N_2O_3$	70
51		CH_3	H	210–211 (A)	$C_{18}H_{20}N_2O_3$	56
52		H	H	232–233 dec (B)	$C_{17}H_{14}N_2O_3$	72
53		H	H	298–300 dec (C)	$C_{19}H_{18}N_2O_3 \cdot 0.05$-DMF	70

[a,b] See corresponding footnote in Table I. [c] N: calcd, 10.21; found, 9.39.

itive inotropic activity when tested orally. Compound **21**, in which the imidazole ring was attached to the 3-position of the phenyl ring, was slightly less active than **1**.

Compounds listed in Table III are the oxidation products of 4,5-dihydropyridazinones. In general, the positive inotropic activity of the dihydropyridazinones is parallel to the pyridazinones with the exception of the 5-methyl analogue. Introduction of a methyl group at the 5-position of the 4,5-dihydropyridazinone led to an increase in potency, whereas the 5-methylpyridazinones **31** and **38**, are considerably less active.

Compounds **1** and **11** were among the most potent positive inotropic compounds tested and were extensively evaluated. The cardiovascular profiles of **1** and **11** in anesthetized dogs are shown in Figures 1 and 2, respectively. Intravenous doses of 0.01–1.0 mg/kg for compound **1** and 0.001–0.1 mg/kg for compound **11** produced dose-related increases in cardiac contractile force (CF). The inotropic effect is associated with small increases in heart rate (HR) and small decreases in blood pressure. Similar dose–response curves were obtained for **1** in anesthetized monkeys.[34] This inotropic effect of **1** was not blocked by a dose of propranolol that produced marked inhibition of an equieffective dose of isoproterenol[34] (Table V). This indicates that these agents are not acting by direct stimulation of β-adrenergic receptors, or indirectly by release of catecholamines. These compounds are selective inhibitors of cardiac phosphodiesterase fraction III (PDE-III), which is believed to be the principal component of the mechanism of action.[35] A complete report of the struc-

(34) Evans, D. B.; Burmeister, W. E.; Eldon, C. M.; McNish, R. W.; Potoczak, R. E.; Schenden, J. A.; Steffen, R. P.; Kaplan, H. R. *Pharmacologist* **1983**, *25* (3), 550.

Table V. Cardiovascular Activity of 1 (CI-914) in the Presence of β-Adrenoceptor Blockade[a-d]

	heart rate (HR)		contractility (CF)		blood pressure S/D (BP)	
	IP	1	IP	1	IP	1
before β-blockade	31 ± 4.3*	24 ± 2.9*	96 ± 6.9*	82 ± 10.8*	−6.6 ± 1.5*/−15.4 ± 1.8*	−4.2 ± 1.2*/−7.0 ± 1.2*
after β-blockade	0.4 ± 0.7°	5.4 ± 1.7*°	10.4 ± 2.8°*	62.4 ± 8.5*	1.0 ± 0.8°/−0.8 ± 0.8°	−2.8 ± 0.7*/−8.2 ± 1.0*

[a] Drug/dose: propranolol/0.5 mg/kg; isoproterenol (IP)/0.31 μg/kg; compound 1/0.31 mg/kg. [b] Route: iv (n = 5). [c] Values are percent change from control ± SEM: *, significant at $p \leq 0.05$ level vs. control; °, significantly different from response before β-blockade at $p < 0.05$ level. [d] Pretreatment CF, HR, and BP values were 3196 ± 2.48 mmHg/s, 148 ± 8 beats/min, and 143 ± 5/111 ± 3 mmHg, respectively.

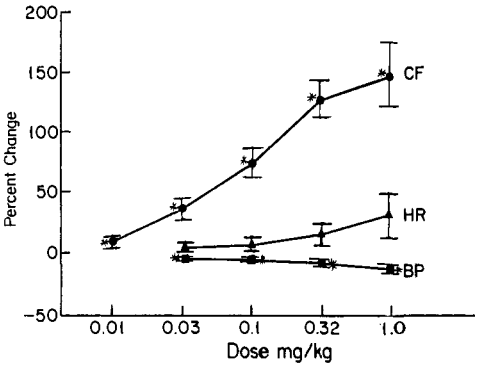


Figure 1. Cardiovascular profile of 4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinone (1) in anesthetized dogs: *, significant at $p < 0.05$ level vs. control; dP/dt = 2215 ± 158 mmHg/s; heart rate 116 ± 7.8 beats/min; MBP 124 ± 3 mmHg.

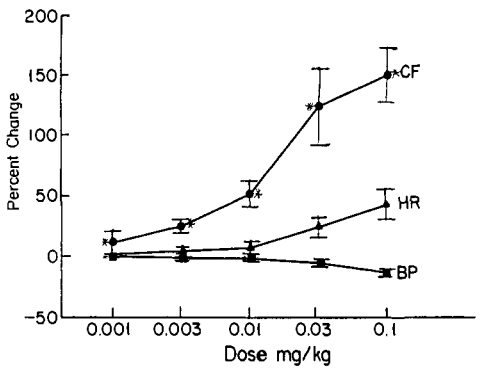


Figure 2. Cardiovascular profile of 4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-5-methyl-3(2*H*)-pyridazinone (11) in anesthetized dogs: *, significant at $p < 0.05$ level vs. control; dP/dt 2676 ± 141 mmHg/s; heart rate 145 ± 8.5 beats/min; MBP = 156 ± 4 mmHg.

ture–activity relationships (PDE-III) of these compounds will be the subject of a future publication.

Table VI shows the comparative inotropic responses of 1 and 11 with amrinone, milrinone, fenoximone, and sulmazole in anesthetized dogs. These results demonstrate that 1 and 11 are more potent than amrinone and 11 is more potent than milrinone. This is also reflected in the inotropic effect of these agents when administered orally to conscious dogs (Table VII).

On the basis of these results, the 4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinones represent a new class of potent, nonsympathomimetic, orally active positive inotropic agents. Detailed studies with two of these compounds (1 and 11) suggest their potential utility in the treatment of congestive heart failure (CHF).

Experimental Section

Melting points were uncorrected and were taken on a Thomas-Hoover capillary melting point apparatus. IR and ^{1}H NMR spectra of all new compounds were consistent with the proposed structures. Each analytical sample was homogeneous by TLC performed on silica gel plates with methylene chloride and methanol (9:1) as eluants. Elemental analyses were within 0.4% of theoretical values unless otherwise stated.

(35) Weishaar, R. E.; Quade, M. M.; Schenden, J. A.; Boyd, D. K.; Evans, D. B. *Pharmacologist* **1983**, *25* (3), 551.

Table VI. Comparative Data for the Inotropic Responses of Cardiotonic Agents in Anesthetized Dog Preparation

compd	dose (n),[a] mg/kg	compd	dose (n),[a] mg/kg
1	0.045 ± 0.006 (6)	amrinone	0.389 ± 0.028 (7)
11	0.013 ± 0.006 (8)	sulmazole	0.435 ± 0.085 (4)
milrinone	0.037 ± 0.014 (5)	fenoximone	0.283 ± 0.020 (2)

[a] Values are dose producing 50% increase in myocardial in contractility from control levels ± SEM. Significant at $p < 0.05$ compared to control.

Table VII. Effect of Cardiotonic Agents on Myocardial Contractility in the Conscious Dog following Oral Administration

		% increase[a]	
compd	dose, mg/kg	contractility	heart rate
1	0.31	10–20	10–15
	1.0	40 ± 6	29 ± 7
11	0.1	42 ± 9	34 ± 14[b]
	0.31	70 ± 23	49 ± 12
amrinone	3.1	6 ± 7	23 ± 9
	10.0	45 ± 22[b]	18 ± 18[b]
milrinone	1.0	45 ± 5	60 ± 13
sulmazole	10.0	57 ± 11	61 ± 14

[a] Values are maximum response from control average (n = 5, 6) ± SEM. Significant at $p < 0.05$ compared to control. [b] Not statistically significant.

General Procedure for the Synthesis of 4,5-Dihydro-6-(substituted phenyl)-3(2*H*)-pyridazinones (Tables I and II). 4,5-Dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinone (1). A solution of 4.5 g (0.018 mol) of 4-(1*H*-imidazol-1-yl)-γ-oxobenzenebutanoic acid (40) in ethanol (60 mL) was heated under reflux with 85% hydrazine hydrate (2.5 mL, 0.045 mol) for 7 h. The solution was concentrated to half its volume and filtered. The crude product was crystallized from ethanol to yield 3.5 g of 1.

Ethanolic HCl was added to a solution of 1 g (0.004 mol) of 1 in 30 mL of ethanol until the pH of the solution was 2. The crystalline precipitate was collected, washed with a small volume of ethanol, and air-dried to give the corresponding monohydrochloride of 1.

General Procedure for the Synthesis of 6-(Substituted phenyl)-3(2*H*)-pyridazinones (Table III). 6-[4-(1*H*-Imidazol-1-yl)phenyl]-3(2*H*)-pyridazinone (25; Table III). Method A. A solution of bromine (0.7 mL, 0.013 mol) in acetic acid (20 mL) was added dropwise to a solution of 2.6 g (0.011 mol) of 1 in acetic acid (85 mL) at 90–95 °C. The reaction mixture was subsequently heated under reflux for 3.5 h. Upon cooling, the solid was filtered, washed with ether, and converted to the free base that was crystallized from ethanol to yield 1.3 g of **25**.

6-[4-(1*H*-Imidazol-1-yl)phenyl]-5-methyl-3(2*H*)-pyridazinone (31; Table III). Method B. A solution of 3.6 g (0.014 mol) of 11 in a mixture of dioxane (100 mL) and *N,N*-dimethylformamide (25 mL) was heated with 12 g (0.14 mol) of MnO_2 at 90 °C overnight. The temperature was raised to 105 °C and maintained there for 4 h. The solid was filtered and washed thoroughly with hot dioxane. The filtrate and the washings were combined and evaporated in vacuo, and the residue was crystallized from methanol/tetrahydrofuran to yield 2.1 g of **30**.

General Procedure for the Synthesis of Substituted γ-Oxobenzenebutanoic Acids (Table IV). 4-(1*H*-Imidazol-1-

yl)-γ-oxobenzenebutanoic Acid (40; Table IV). Method C. A solution of 4-fluoro-γ-oxobenzenebutanoic acid[36] (20 g, 0.1 mol) and imidazole (6.8 g, 0.1 mol) in Me_2SO (50 mL) was added dropwise to a suspension of 50% NaH (9.6 g, 0.2 mol) in toluene (20 mL) with stirring, keeping the temperature around 30 °C. The mixture was stirred at room temperature overnight followed by heating at 100–110 °C for 18 h. The solution was poured into water and extracted with ether. The aqueous solution was adjusted to pH 5; the solid obtained was filtered, washed with water, and crystallized from DMF to give 10 g of **40**.

Method D. A solution of 24.2 g (0.13 mol) of 1-[4-(1*H*-imidazol-1-yl)-phenyl]ethanone in 250 mL of tetrahydrofuran was added to a suspension of 6.7 g (0.14 mol) of 50% NaH in 70 mL of tetrahydrofuran with stirring. After stirring 1 h at room temperature, 30 mL (0.33 mol) of dimethyl carbonate was added followed by heating the mixture under reflux overnight. After cooling, the reaction mixture was filtered, and the residue was suspended in water. Acetic acid was added until pH 6, and the product was filtered and crystallized from methanol/ether to yield 15 g of methyl 4-(1*H*-imidazol-lyl)-β-oxobenzenepropanoate, mp 110–111 °C.

A solution of the above β-keto ester (6.1 g, 0.025 mol) in tetrahydrofuran (65 mL) was added slowly to a stirred suspension of 50% NaH (1.2 g, 0.025 mol) in tetrahydrofuran (20 mL), and the solution was stirred for an additional 1 h. Ethyl bromoacetate (4.5 g, 0.027 mol) was added, followed by heating under reflux for 8 h. The tetrahydrofuran was removed by rotary evaporation; the residue was treated with water and extracted with ether. The solid obtained after removal of ether was hydrolyzed by heating with 6 N HCl for 8 h. The crude acid was crystallized from *N,N*-dimethylformamide to yield 3.3 g of **40**.

4-(1*H*-Imidazol-1-yl)-β-methyl-γ-oxobenzenebutanoic Acid (44; Table IV). Method E. A rapidly stirred mixture of 172.2 g (1.0 mol) of 4-(1*H*-imidazol-1-yl)benzaldehyde,[37] 190.0 g (1.0 mol) of *p*-toluenesulfonic acid, and 480.0 g (5.5 mol) of morpholine in 1800 mL of dry dioxane was heated under reflux in a nitrogen atmosphere for 0.5 h. After the mixture was cooled to 50 °C, a suspension of 65.2 g (1.0 mol) of potassium cyanide in 80 mL of water was added, causing the temperature to rise to 65 °C. The temperature was raised to reflux and maintained there for 1 h. The solution was concentrated to ca. 1000 mL and poured onto 800 mL of 15% aqueous potassium carbonate. The product was extracted with 4 L of dichloromethane, and the extracts were washed successively with 100 mL of saturated aqueous $NaHSO_3$, aqueous $NaHCO_3$, and water. The dried (Na_2SO_4) extracts were concentrated to a small volume to give 230 g of α-[4-(1*H*-imidazol-1-yl)phenyl]-4-morpholineacetonitrile, mp 141–142 °C.

To a stirred solution of 67.0 g (0.25 mol) of the above nitrile in 175 mL of dry tetrahydrofuran containing 4 mL of 30% methanolic potassium hydroxide was added 35.0 g (0.52 mol) of 2-butenenitrile dropwise over 0.25 h and the solution was allowed to stir under nitrogen overnight. The solution was subsequently evaporated, the residue was dissolved in dichloromethane and passed through a column of Florisil (120 g). The eluate (ca. 1800 mL) was evaporated, and the residue was triturated with ethyl acetate/ether to give 58.1 g of 2-[4-(1*H*-imidazol-1-yl)phenyl]-3-methyl-2-(4-morpholinyl)pentanedinitrile as white crystals, mp 165–166 °C.

A solution of 64.5 g (0.192 mol) of the dinitrile in 225 mL of 75% aqueous acetic acid was heated on a steam bath under nitrogen for 3 h. After the solution was evaporated, the residue was taken up in ice water and treated with $NaHCO_3$ to pH 7.5. This solution was extracted twice with 50 mL of dichloromethane, and the combined extracts were dried with Na_2SO_4 and evaporated. Crystallization of the residue from 2-propanol gave 36.5 g (79% yield) of 4-(1*H*-imidazol-1-yl)-β-methyl-γ-oxobenzenebutanenitrile, mp 107–108 °C.

A solution of 36.3 g (0.152 mol) of the above γ-keto nitrile in 120 mL of 1-propanol and 100 mL of 20% aqueous hydrochloric acid was heated under reflux in a nitrogen atmosphere for 7 h. The solution was concentrated to 50 mL, dissolved in ice water, and made basic with potassium carbonate. The nonacidic material (3.9 g), which was extracted with 300 mL of dichloromethane, contained predominantly unchanged γ-keto nitrile derivative. The aqueous alkaline phase was treated slowly with acetic acid to pH 5.0. After standing overnight at 23 °C, a solid was collected and washed successively with cold water and ether, giving 30.9 g of **44**.

4,5-Dihydro-6-[4-[2-(methylthio)-1*H*-imidazol-1-yl]-phenyl]-3(2*H*)-pyridazinone (6). A solution of 10 g (0.053 mol) of 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (**54**) in *N,N*-dimethylformamide (200 mL) was added to an ice-cold solution of 1,1′-thiocarbonyldiimidazole (10 g, 0.056 mol) in *N,N*-dimethylformamide (50 mL) over a 3-h period. The reaction mixture was slowly warmed to room temperature and stirred for an additional 0.5 h. The solution was then diluted with 800 mL of water, cooled, filtered, and air-dried to give 10.8 g of 4,5-dihydro-6-[4-isothiocyanatophenyl]-3(2*H*)-pyridazinone (**55**), mp 111–182.5 °C.

A solution of 10 g (0.053 mol) of **54** in 200 mL of DMF was added to a solution of 10 g (0.056 mol) of 1,1′-thiocarbonyldiimidazole in 50 mL of DMF at ambient temperature over a 3-h period. The reaction mixture was stirred at room temperature for an additional 1 h. The solution was diluted with 800 mL of water, cooled, filtered, and air-dried to yield 10 g of *N,N′*-bis-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]thiourea (**56**).

A solution of 10 g (0.043 mol) of **55** in *N,N*-dimethylformamide (60 mL) was added dropwise to a solution of aminoacetaldehyde dimethyl acetal (7.17 g, 0.068 mol) in *N,N*-dimethylformamide (20 mL) followed by heating for 2 h at 80 °C. The DMF was removed by distillation under reduced pressure, and the residue was heated under reflux with 100 mL of 10% HCl for 0.5 h. Upon cooling, the solid was collected by filtration, washed with water, and crystallized to give 7 g of 6-[4-(2,3-dihydro-2-thioxo-1*H*-imidazol-1-yl)phenyl]-4,5-dihydro-3(2*H*)-pyridazinone (**5**).

A solution of 2.97 g (0.011 mol) of **5** in *N,N*-dimethylformamide (50 mL) was treated with methyl iodide (4.6 g, 0.032 mol). The DMF was removed by distillation, and the residue was treated with water. The solution was made basic, and the crystalline material was collected by filtration to yield 1.75 g of **6**.

A solution of 2.08 g (0.007 mol) of **6** in chloroform (30 mL) was oxidized with *m*-chloroperbenzoic acid (1.56 g, 0.009 mol) at 0 °C to yield 1.45 g of 4,5-dihydro-6-[4-[2-(methylsulfinyl)-1*H*-imidazol-1-yl]phenyl]-3(2*H*)-pyridazinone (**7**).

Similarly, a solution of 1.68 g (0.006 mol) of **6** in chloroform (15 mL) was oxidized with *m*-chloroperbenzoic acid (2.55 g, 0.015 mol) at ambient temperature to yield 1.54 g of 4,5-dihydro-6-[4-[2-(methylsulfonyl)-1*H*-imidazol-1-yl]phenyl]-3(2*H*)-pyridazinone (**8**).

4,5-Dihydro-6-[4-(4*H*-1,2,4-triazol-4-yl)phenyl]-3(2*H*)-pyridazinone (23). A mixture of 3.78 g (0.02 mol) of **54** and 1,2-hydrazinedicarboxaldehyde (1.76, 0.02 mol) was heated together at 220 °C for 6 h. The solid was chromatographed and crystallized from acetonitrile/methanol to yield **23**.

4,5-Dihydro-6-[4-(1*H*-pyrrol-1-yl)phenyl]-3(2*H*)-pyridazinone (24). A mixture of 3.7 g (0.02 mol) of **54** and 2.6 g (0.02 mol) of tetrahydro-2,5-dimethoxyfuran in 37 mL of glacial acetic acid was heated under reflux for 4 h. The reaction mixture was cooled and filtered, and the residue was washed with ethanol and crystallized from methanol to give 1.2 g of **24**.

2,3-Dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3-oxo-4-pyridazinecarboxylic Acid Hydrazide (34). A mixture of diethyl ketomalonate (87.08 g, 0.50 mol) and 1-[4-(1*H*-imidazol-1-yl)phenyl]ethanone (93.1 g, 0.50 mol) was warmed to 95–100 °C with stirring for 3 h. During this time, the original tan slurry was transformed into a black syrup. Anhydrous ethanol (130 mL) was then added with stirring, resulting in a black solution. Upon standing overnight at 8 °C, the solution formed a solid mass that was suspended in absolute ethanol (100 mL) and filtered to obtain 67 g of a brown solid, hydroxy[2-[4-(1*H*-imidazol-1-yl)phenyl]-2-oxoethyl]propanedioic acid diethyl ester. This material is suitable for use without additional purification; however, it can be recrystallized from methanol to give an analytical product, mp 155–156 °C.

A solution of 79.1 g (1.58 mol) of hydrazine hydrate and the above ester (113.7 g, 0.316 mol) in methanol (700 mL) was heated under reflux for 18 h. The reaction mixture was cooled in ice;

(36) Adcock, W.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1967**, 89, 386.
(37) Sitkina, L. M.; Simonov, A. M. *Khim. Geterotrikl. Soedin. Akad. Nauk. Latv. SSR* **1966**, *143*; *Chem. Abstr.* **1966**, *65*, 13686*e*.

the resulting crystalline yellow solid was filtered, washed with methanol (60 mL), and dried to give 80.2 g of **34**.

2,3-Dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3-oxo-4-pyridazinecarboxamide (35). Method F. A slurry of 50.8 g (0.5 mol) of triethylamine, 24 mL (0.33 mol) of thionyl chloride, and 26.3 g (0.08 mol) of **36** in *N*,*N*-dimethylformamide (500 mL) was added with vigorous stirring to *N*,*N*-dimethylformamide (250 mL) through which a stream of gaseous ammonia was introduced. When ammonia ceased to be absorbed, the reaction mixture was evaporated to dryness, filtered through a column (3 × 15 cm) of neutral alumina (activity I), and eluted with CH_2Cl_2/CH_3OH (9:1) to give a tan semisolid. This was triturated with ethanol and filtered to yield 11.6 g of **35**.

2,3-Dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3-oxo-4-pyridazinecarboxylic Acid (36). A suspension of 25.0 g (0.08 mol) of **34** in 2500 mL of 12 N HCl was heated under reflux for 18 h. The reaction mixture was cooled in ice and filtered, and the residue was washed with 6 N HCl followed by diethyl ether. The solid was dried at 45 °C in a vacuum oven for 18 h to yield 22.7 g of **36** as the hydrochloride salt.

4-Amino-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinone (33). Method G. A slurry of 10.0 g (0.034 mol) of **34**, 11 mL of water, and 195 mL of 12 N HCl was cooled to 5 °C with stirring and treated dropwise with a solution of 5.6 g (0.08 mol) of sodium nitrite in 20 mL of water. When the addition was complete, the reaction mixture was warmed to 20 °C, transferred to a large beaker, and warmed on a steam bath. The reaction mixture formed a solution, and a precipitate separated. The cooled reaction mixture was filtered and the filtrate made basic with the addition of concentrated ammonia (250 mL). The resulting suspension was filtered, and the solid was combined with the first crop. The solid was a mixture of the desired amine and starting carboxylic acid. The amine is separated from the acid by silica gel filtration using $CHCl_3/CH_3OH/NH_4OH$ (90:10:1) as the eluent. The elutate was concentrated to a small volume and filtered to give 1.12 g of **33**.

Method H. A suspension of 1.0 g (0.004 mol) of **1** in 5 mL of hydrazine hydrate was heated on a steam bath for 30 h. The reaction mixture was cooled and the product filtered. The residue was washed with water followed by ethanol and air-dried to yield 0.8 g of **33**.

Pharmacological Methods. 1. Anesthetized Dog Model. Adult mongrel dogs of either sex were anesthetized with pentobarbital, 35 mg/kg, iv, and were subsequently maintained under anesthesia with a continuous infusion of pentobarbital, 5 mg/kg per h. The trachea was intubated, but the animals were permitted to breathe spontaneously. A cannula was inserted into the femoral vein for administering test agents. A Millar catheter tip pressure transducer (Model PC-350) was inserted into the ascending aorta via the femoral artery for measuring aortic blood pressure. Another similar transducer was passed into the left ventricle via the left carotid artery for measuring left ventricular blood pressure. Needle electrodes were placed subcutaneously for recording a lead II electrocardiogram (ECG).

Left ventricular and aortic blood pressures were recorded on a strip chart recorder. Heart rate, using a biotachometer triggered from the R wave of the ECG, and the first derivative of left ventricular blood pressure (dP/dt), obtained with a differentiator amplifier coupled to the corresponding pressure amplifier, were also recorded. Data analyses were performed with a digital computer. A period of 30 min was utilized to obtain control data prior to administration of test agent. Depending on solubility of the agent, compounds were dissolved in 0.9% saline solution or in dilute HCl or NaOH (0.1 or 1.0 N) and were diluted to volume with normal saline. Each dose of the test agent was administered in a volume of 0.1 mL/kg over a period of 1 min unless otherwise designated. Limited solubility may require adjustments in the volume of the solution that was administered. The test agents were administered in an ascending dose manner. Usually, half-log intervals were maintained between doses, with typical dosing consisting of four to six doses (for example, 0.01, 0.03, 0.1, 0.3, 1.0 mg/kg) in order to establish any dose–response relationships. A 10–30-min interval was used between doses. Only one compound was administered to any one animal. The inotropic activity of a compound was determined by measuring changes in dP/dt_{max} of left ventricular pressure.

2. Conscious Dog Model. Adult mongrel dogs were prepared by surgically implanting devices for measuring ECG, aortic blood pressure, aortic blood flow, and left ventricular blood pressure. These animals were allowed to recover from surgery for at least 2 weeks prior to undergoing testing. On the day of the test, the dogs were caged and connected to appropriate interfacing for recording the indicated cardiovascular parameters on a strip chart recorder. Heart rate, aortic blood pressure, left ventricular blood pressure, and aortic blood flow were measured directly; myocardial contractility was determined by obtaining dP/dt_{max} of left ventricular blood pressure and dQ/dt_{max} of aortic blood flow. Cardiac output and total peripheral resistance were derived from heart rate, aortic flow, and aortic blood pressure. Data analyses were performed with a digital computer. The test agent was then administered by gavage to the fasted dog either as a solution or as a suspension in a single dose or multiple-dose fashion.

Data are expressed as means ± SEM. Statstical analysis of the data was performed by using a student's t-test for paired or unpaired data. The probability value, $p < 0.05$, was accepted as level of significance.

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Registry No. **1**, 84243-58-3; **1**·HCl, 89198-09-4; **2**, 86798-78-9; **3**, 86798-79-0; **4**, 86798-54-1; **5**, 86798-61-0; **6**, 86798-62-1; **7**, 86798-63-2; **8**, 86798-64-3; **9**, 86798-81-4; **10**, 97150-56-6; **11**, 86798-59-6; **11**·HCl, 90791-23-4; **12**, 88427-75-2; **13**, 86798-69-8; **14**, 97150-57-7; **15**, 86798-56-3; **16**, 97150-58-8; **17**, 88427-72-9; **18**, 97150-59-9; **19**, 97150-60-2; **20**, 97150-61-3; **21**, 86798-67-6; **22**, 86798-72-3; **24**, 86798-73-4; **25**, 84243-59-4; **26**, 86798-87-0; **27**, 86798-88-1; **28**, 97150-62-4; **29**, 86798-94-9; **30**, 97150-63-5; **31**, 86798-76-7; **32**, 97150-64-6; **33**, 97150-65-7; **34**, 97150-66-8; **35**, 97150-67-9; **36**, 97150-80-6; **36**·HCl, 97150-68-0; **37**, 86798-77-8; **38**, 97150-69-1; **39**, 97150-70-4; **40**, 84243-57-2; **41**, 88427-87-6; **42**, 97150-71-5; **43**, 86798-53-0; **44**, 88427-81-0; **45**, 88427-80-9; **46**, 88427-83-2; **47**, 86798-66-5; **48**, 86798-70-1; **49**, 97150-72-6; **50**, 97150-73-7; **51**, 97150-74-8; **52**, 97150-75-9; **53**, 97150-76-0; **54**, 21282-90-6; **55**, 86798-60-9; **56**, 97150-77-1; 4-fluoro-γ-oxobenzenebutanoic acid, 366-77-8; imidazole, 288-32-4; 1-[4-(1*H*-imidazol-1-yl)phenyl]ethanone, 10041-06-2; methyl 4-(1*H*-imidazol-1-yl)-β-oxobenzenepropanoate, 84243-56-1; ethyl bromoacetate, 105-36-2; 4-(1*H*-imidazol-1-yl)benzaldehyde, 10040-98-9; α-[4-(1*H*-imidazol-1-yl)phenyl]-4-morpholineacetonitrile, 86798-58-5; 2-butenenitrile, 4786-20-3; 2-[4-(1*H*-imidazol-1-yl)-phenyl]-3-methyl-2-(4-morpholinyl)pentanedinitrile, 97150-78-2; 4-(1*H*-imidazol-1-yl)-β-methyl-γ-oxobenzenebutanenitrile, 88427-89-8; 1,1′-thiocarbonyldiimidazole, 6160-65-2; aminoacetaldehyde dimethyl acetal, 22483-09-6; 1,2-hydrazinedicarboxaldehyde, 628-36-4; tetrahydro-2,5-dimethoxyfuran, 696-59-3; diethyl ketomalonate, 609-09-6; hydroxy[2-[4-(1*H*-imidazol-1-yl)phenyl]-2-oxoethyl]propanedioic acid diethyl ester, 97150-79-3.