product, AMP, may also be degraded to adenosine, adenine, and inosine. To correct for further hydrolysis of the product, the radioactivity in the remaining portion of the chromatogram was also quantified and included in the calculation of the cAMP phosphodiesterase activity. Drugs were tested in triplicate up to concentrations as high as 100 μM.

Acknowledgment. We appreciate the technical assistance provided by A. Smart and H. Troy.

Registry No. **5**, 104271-32-1; **6**, 104271-38-7; **7**, 104271-43-4; **8**, 104271-33-2; **9**, 104271-34-3; **10**, 104271-50-3; **11**, 104271-44-5; **12**, 104271-51-4; **13**, 107454-13-7; **14**, 107454-22-8; **15**, 107454-17-1; **16**, 107454-18-2; **17**, 107454-18-2; **18**, 108060-51-1; **19**, 108060-52-2; **20**, 108060-53-3; **21**, 107454-23-9; **22**, 107454-26-2; **23**, 107454-24-0; **24**, 108060-54-4; **25**, 108060-55-5; **26**, 108060-56-6; **27**, 108060-57-7; **28**, 108060-58-8; **29**, 108060-59-9; **30**, 107454-29-5; $C_6H_5COnCH_2)_3Cl$, 939-52-6; $4\text{-}H_2NC_6H_4CO(CH_2)_3Cl$, 108060-60-2; $4\text{-}FC_6H_4CO(CH_2)_3Cl$, 3874-54-2; $4\text{-}HOC_6H_4CO(CH_2)_3Cl$, 7150-55-2; $4\text{-}CH_3SO_2NHC_6H_4CO(CH_2)_3Cl$, 108060-61-3; $4\text{-}C_2H_5OC_6H_4CO\text{-}(CH_2)_3Cl$, 75343-08-7; $4\text{-}CH_3CONHC_6H_4CO(CH_2)_3Cl$, 56924-11-9; $ClCOOCCl_3$, 503-38-8; $COCl_2$, 75-44-5; imidazole, 288-32-4; 2-methylimidazole, 693-98-1; 2-ethylimidazole, 1072-62-4.

Cardiotonic Agents. 2.[1] (Imidazolyl)aroylimidazolones, Highly Potent and Selective Positive Inotropic Agents[2]

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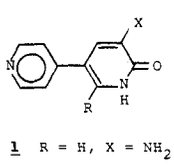
Berlex Laboratories, Inc., Cedar Knolls, New Jersey 07927. *Received August 25, 1986*

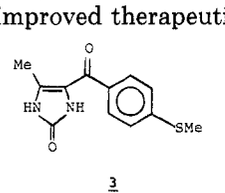
A series of 4-alkyl-1,3-dihydro-5-[(1*H*-imidazolyl)benzoyl]-2*H*-imidazol-2-ones **9** was synthesized and evaluated in vitro for positive inotropic and cyclic AMP phosphodiesterase inhibitory activity. A wide range of inotropic and enzyme-inhibitory potencies was observed, substitution on the imidazolyl moiety being the major determinant of activity. The 4-ethyl-5-[4-(1*H*-imidazol-1-yl)benzoyl] congener **9g** exhibited the highest potency in vitro. Incorporation of a methyl group at the imidazolyl 2-position gave **9h**, which was less potent but remarkably selective in vivo for positive inotropic effects over heart rate and hypotensive effects.

For some 200 years, digitalis and its constituent cardiac glycosides such as digoxin and digitoxin have been used as positive inotropic agents for the treatment of congestive heart failure (CHF). Although these drugs are selective in their inotropic action and exhibit no significant direct effects on the vasculature, their potential for producing cardiac arrhythmia leads to undesirably low therapeutic ratios. This problem and the increasingly high death rate from CHF in developed countries have spurred attempts to find an orally available "digitalis replacement".[3] The discovery[4] of amrinone (**1**) has led to the synthesis of a number of agents that show varying promise for CHF treatment. A few of these compounds are shown in structures **2**–**5** (**2**, milrinone;[5] **3**, enoximone;[6] **4**, pelrinone;[7] **5**, imazodan[8]). Although their mode of action has not been fully elucidated, it differs from that of digitalis and appears to result, in large part, from inhibition of the low-K_m (cyclic AMP specific) phosphodiesterase (PDE).[9] As noted elsewhere,[3] these compounds also have substantial direct vasorelaxant activity and, therefore, are not strict digitalis replacements. Thus, there still exists a need for a selective inotropic agent having an improved therapeutic ratio.[10]



1 R = H, X = NH_2

2 R = Me, X = CN



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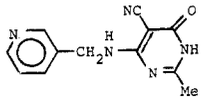

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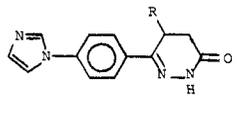

5a R = H

5b R = Me

Recently, we discovered two series of cardioactive compounds, the imidazopyridines **6** and the related imidazopyridinones (e.g., **7**),[1] where the attachment of an imidazolyl substituent to an aromatic ring leads to improved activity. To further explore the generality of this relationship, we thought that it would be useful to examine less rigid versions of **7**. The aroylimidazolones **8**, first prepared by Duschinsky and Dolan[11] (**8a**) and more recently elaborated as cardiotonic agents by Schnettler et al.[6a,12] (**3**), provided a suitable framework on which to test

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(1) For paper 1, see: Davey, D.; Erhardt, P. W.; Lumma, W. C., Jr.; Wiggins, J.; Sullivan, M.; Pang, D.; Cantor, E. *J. Med. Chem.*, preceding paper in this issue.
(2) Presented in part at the 192nd American Chemical Society National Meeting, Anaheim, CA, September 1986 (MEDI 10), and at the IXth International Symposium on Medicinal Chemistry, Berlin (West), September 1986 (Abstract 110).
(3) Erhardt, P. W. *J. Med. Chem.* **1987**, *30*, 231.
(4) Alousi, A. A.; Farah, A. E.; Lesher, G. Y.; Opalka, C. J. *Circ. Res.* **1979**, *45*, 666.
(5) Braunwald, E.; Sonnenblick, E. J.; Chakrin, L. W.; Schwartz, R. P., Eds. *Milrinone: Investigation of New Inotropic Therapy for Congestive Heart Failure*; Raven: New York, 1984.
(6) (a) Schnettler, R. A.; Dage, R. C.; Grisar, J. M. *J. Med. Chem.* **1982**, *25*, 1477. (b) Petein, M.; Levine, T. B.; Weingarten, J.; Cohn, J. N. *Clin. Res.* **1984**, *32*, 198A.
(7) McQuillan, J.; Bagli, J.; Grimes, D.; Lee, D.; Metcalf, G. *Pharmacologist* **1984**, *26*, Abstr 204.
(8) (a) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. *J. Med. Chem.* **1984**, *27*, 1101. (b) Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1985**, *28*, 1405.
(9) Weishaar, R. E.; Cain, M. H.; Bristol, J. A. *J. Med. Chem.* **1985**, *28*, 537 and references therein.
(10) Like digitalis, such an agent could be used independently for its inotropic effect or, when desired, administered with a vascular drug that has been specifically tailored for use in treating CHF. In the latter case, complementary inotropic and vasodilatory effects could then be readily balanced through separate dosage adjustment in order to provide maximum combination therapy.
(11) (a) Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc.* **1945**, *67*, 2079. (b) Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc.* **1946**, *68*, 2350.

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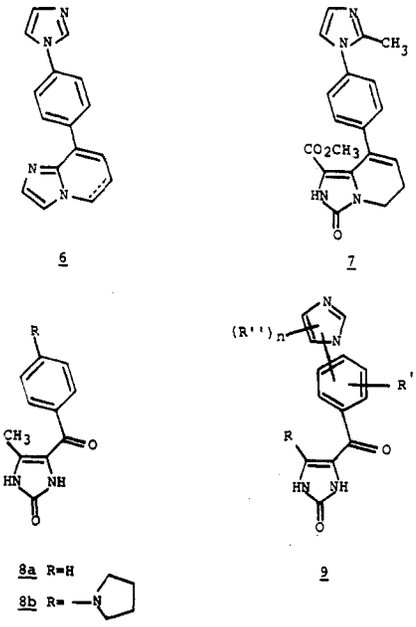


6 7

8a R=H
8b R= —N

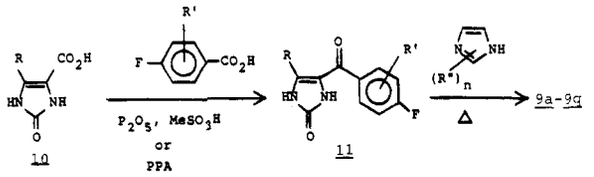
9

this structure–activity relationship (SAR). In addition, because the latter authors found that analogues possessing saturated cyclic amino substituents in the 4-position of the benzoyl group (e.g., **8b**) gave markedly lowered inotropic potency, we regarded this nucleus as a particularly rigorous test of the generality of our phenylimidazole SAR. We report herein the preparation[13] of a number of (imidazolylbenzoyl)imidazolones **9** and the results from evaluation of their positive inotropic activity. During the work we were encouraged by the synthesis[8] of imazodan (**5**), which has an improved cardiotonic profile when compared with related structures lacking the imidazole substituent.[14,15]

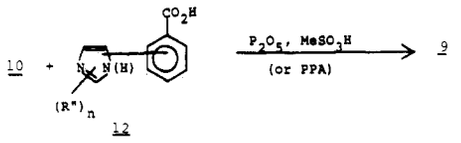
Chemistry

The compounds with an imidazol-1-yl group at the para position of the benzoyl moiety were prepared by nucleophilic displacement of fluoride from the known[6a] 4-fluorobenzoyl intermediates **11** with the appropriate imidazole (Scheme I). The reactions were conducted in molten imidazole or, in a few cases, in the presence of a small amount of a high-boiling, dipolar aprotic solvent (DMF, *N*-methylpyrrolidinone). The reported preparation of the 4-fluoro intermediates employs Friedel–Crafts acylation of 4-alkylimidazolones.[11] We have found that the more easily isolated alkylimidazolonecarboxylic acids (**10**) are excellent substitutes for the imidazolones when the acylation is conducted in polyphosphoric acid (PPA) or P_2O_5–methanesulfonic acid ("Eaton's acid").[16]

Scheme I



Scheme II



As shown in Scheme II, an alternative synthesis was employed for the imidazol-2-yl compounds **9r** and **9s**, the meta-substituted example **9t**, and the imidazolylmethyl compound **9v**. These were prepared by acylation of **10** with the imidazolylbenzoic acids **12**, again in PPA or, preferably, Eaton's acid. This procedure is also applicable to the preparation of the *p*-imidazol-1-yl compounds and, when optimized, is well suited for large-scale preparations. The imidazolylbenzoic acids **12** were prepared by using a variety of procedures, as described in the Experimental Section. A fundamentally different synthesis of the imidazol-2-yl compounds has been reported recently by the Merrell-Dow group.[17] The 2-(hydroxymethyl) compound **9f** was prepared from **9a** by reaction with aqueous formaldehyde at 120 °C,[18] and the imidazolium derivative **9u** was prepared by methylation of **9h** with methyl iodide in DMF.

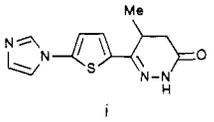
The target compounds were isolated as the free bases, most easily by neutralization of solutions in aqueous acid or base. In some cases, crystallization or chromatography was necessary for purification, but these techniques were hampered by the insolubility of the neutral compounds in water and most organic solvents. A few salts were prepared to aid in purification, but these usually offered no advantages. The compounds prepared and their physical properties are presented in Table I.

Results and Discussion

The in vitro inotropic properties of the compounds were evaluated in isolated ferret papillary muscle (Table II). The concentrations of drug needed for 50% inhibition (IC_{50}) of cyclic AMP hydrolysis by a partially purified canine cardiac phosphodiesterase (PDE) are also shown. The positive inotropic effects of the new compounds were not blocked by 100 μM nadolol (data not shown), indicating that the observed effects were not caused by catecholamine release. Several known positive inotropic agents (**2–5**) of clinical interest were tested for comparison.

The results show that, overall, there is no inherent loss of potency from an imidazolyl substituent: the most potent compounds **9a** and **9g** are nearly 2 orders of magnitude more potent than enoximone (**3**) in the papillary screen and are more potent PDE inhibitors as well. The contrast to the results of Schnettler et al.,[6a] in which cyclic saturated amino substituents greatly lowered potency, is pronounced. This difference seems to be due to some unique feature of the imidazole ring since potency is exquisitely dependent on the nature of its substituents, the positive inotropic effects ranging from insignificant at 100 μM (**9d**, **9u**) to a C_{20} of 63 nM (**9g**).

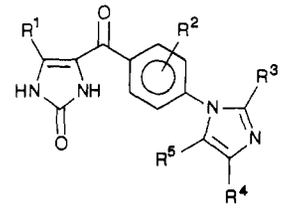
(12) Schnettler, R. A.; Dage, R. C.; Papopoli, F. P. *J. Med. Chem.* **1986**, *29*, 860.
(13) Erhardt, P. W.; Hagedorn, A. A., III; Lumma, W. C., Jr.; Wohl, R. A. U.S. Patent 4 556 665 (to Schering A. G.), 1985.
(14) For example: Thyes, M.; Lehmann, H. D.; Gries, J.; Koenig, H.; Kretzschmar, R.; Kunze, J.; Lebkuecher, R.; Lenke, D. *J. Med. Chem.* **1983**, *26*, 800.
(15) It should be noted that in motapizone, i, vasodilatory properties appear to predominate: Prop, G.; Borbe, H. O.; Hilboll, G. *Drugs Future* **1986**, *11*, 25 and references therein.



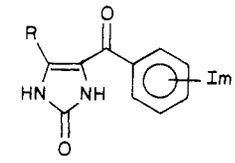
i

(16) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *35*, 4071.
(17) Dage, R. C.; Schnettler, R. A. European Patent Application 0 118 790 (to Merrell-Dow Pharmaceuticals, Inc.), 1984.
(18) For example: Alley, P. W. *J. Org. Chem.* **1975**, *40*, 1837.

Table I. Chemical Data for Imidazolones **9**



9a-q



9r-v

compd	R^1	R^2	R^3	R^4	R^5	% yield (method)[a]	mp, °C (purifn)[b]	formula[c]
9a	Me	H	H	H	H	61 (A)	335–337 dec (A + B)	$C_{14}H_{12}N_4O_2$
9b	Me	H	Me	H	H	86 (A)	339–342 dec (C)	$C_{15}H_{14}N_4O_2$
9c	Me	H	H	Me	H	45 (A)	320–326 dec (D)	$C_{15}H_{14}N_4O_2$
9d	Me	H	Me	Me	Me	20 (A)	325–328 dec (E)	$C_{17}H_{18}N_4O_2$
9e	Me	H	H	benzo		28 (A)	324–332 dec (D)	$C_{18}H_{14}N_4O_2$
9f	Me	H	CH_2OH	H	H	15 (B)	308–310 dec (F + D)	$C_{15}H_{14}N_4O_3$
9g	Et	H	H	H	H	89 (A)	313–315 dec (G)	$C_{15}H_{14}N_4O_2$
9h	Et	H	Me	H	H	88 (A), 63 (C)	>320 dec[d] (G)	$C_{16}H_{16}N_4O_2$
9i	Et	H	Et	H	H	63 (A)	>300 (G)	$C_{17}H_{18}N_4O_2$
9j	Et	H	Pr	H	H	23 A)	172–174 (G)	$C_{18}H_{20}N_4O_2$
9k	Et	H	$CHMe_2$	H	H	32 (A)	260–262 dec (E)	$C_{18}H_{20}N_4O_2$
9l	Et	H	$(CH_2)_2CHMe_2$	H	H	27 (A)	279–281 dec (E)	$C_{20}H_{24}N_4O_2$
9m	Et	H	Et	Me	H	38 (A)	180–182 (G + E)	$C_{18}H_{20}N_4O_2$
9n	Et	2-Me	H	H	H	33 (A)	288–290 dec (G)	$C_{16}H_{16}N_4O_2$
9o	Et	2-Me	Me	H	H	31 (A)	>300 (C)	$C_{17}H_{18}N_4O_2$
9p	Et	3-Me	H	H	H	47 (A)	294–296 dec (G)	$C_{16}H_{16}N_4O_2$
9q	Et	3-Me	Me	H	H	32 (A)	>300 (H)	$C_{17}H_{18}N_4O_2$
9r	R = Me, Im = 4-(1*H*-imidazol-2-yl)					5 (D)	>350 dec[d] (B + D)	$C_{14}H_{12}N_4O_2$
9s	R = Et, Im = 4-(1*H*-imidazol-2-yl)					6 (D)	301–304 dec (D)	$C_{15}H_{14}N_4O_2 \cdot H_2O$
9t	R = Et, Im = 3-(1*H*-imidazol-1-yl)					2 (D)	293–295 dec (F + I)	$C_{15}H_{14}N_4O_2 \cdot 0.15NaOAc$[e]
9u	R = Et, Im = 4-(2,3-Me_2-1*H*-imidazolium)[f]					19 (E)	268–271 dec (E)	$C_{17}H_{19}N_4O_2I$[g]
9v	R = Et, Im = 4-[(1*H*-imidazol-1-yl)methyl]					28 (D)	253–255 dec (B)	$C_{16}H_{16}N_4O_2$

[a] Isolated yields of analytically pure material. Except for **9a**, **9b**, **9g**, and **9h** (both methods), yields were not optimized. Synthetic methods: A, fluoride displacement; B, reaction of **9a** with CH_2O; C, Friedel–Crafts acylation in Eaton's acid; D, Friedel–Crafts acylation in polyphosphoric acid; E, quaternization of **9h** with methyl iodide. [b] Purification methods; A, HCl salt crystallized from H_2O; B, precipitated from aqueous NaOH with CO_2; C, crude product washed with boiling H_2O; D, recrystallized from 2-propanol + H_2O; E, recrystallized from MeOH; F, chromatographed on silica gel; G, precipitated from aqueous HCl with NH_4OH; H, recrystallized from EtOH; I, precipitated from aqueous NaOH with acetic acid. [c] Satisfactory elemental analyses (C, H, N) were obtained for all compounds except where notted; the IR and ^1H NMR spectra were in accord with the assigned structures. [d] Decomposed without melting. [e] Presence of NaOAc in thoroughly washed **9t** confirmed by NMR. [f] Systematic name: 1-[4-[(5-ethyl-1,3-dihydro-2-oxo-2*H*-imidazol-4-yl)carbonyl]phenyl]-2,3-dimethyl-1*H*-imidazolium iodide. [g] N: calcd, 12.78; found, 12.36.

A structure–activity relationship paralleling that seen in vivo for other benzoylimidazolones[6a] is observed for the imidazolone 5-alkyl substituent, potency increasing as this group is changed from methyl to ethyl. For the *p*-imidazolyl compounds, it appears that introduction of a methyl substituent on the benzene ring does not seriously affect potency: a methyl group ortho to the carbonyl reduces potency slightly, and a *m*-methyl has no significant effect. The single *m*-imidazolyl compound (**9t**) shows inotropic potency significantly lower than the para isomer **9g**. Direct connection of the imidazole and benzene rings is not required for activity, as demonstrated by the results for **9v**.

In contrast, with regard to the substituents on the imidazole ring, it appears that the presence of an alkyl group anywhere on the ring decreases positive inotropy and potency for PDE inhibition. A single methyl group has a 5–10-fold effect, while the potencies of the more heavily substituted compounds are lowered drastically. There are only relatively slight differences among the effects of methyl, ethyl, propyl, and isopropyl groups, at least at the 2-position of the imidazole. Interestingly, the isopentyl group of **9l** restores most of the PDE inhibition lost by introduction of smaller groups (**9h–k**); the low potency seen in the papillary muscle may reflect different transport or distribution of this highly lipophilic compound in the tissue. The inactivity of the quaternized derivative **9u** strongly suggests that a neutral imidazole moiety is necessary for both PDE inhibition and positive inotropy.

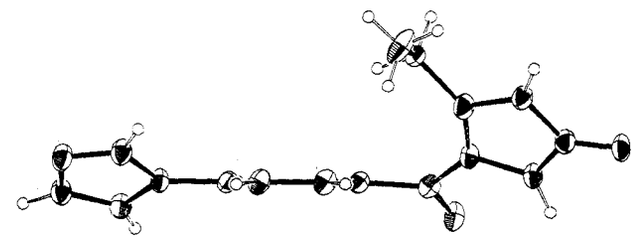


Figure 1. Molecular structure of **9g** from single-crystal X-ray diffraction analysis.

Some insight into origins of the observed substituent effects is provided by considering the three-dimensional structure of **9g**, shown in Figure 1. Increasing the bulk of the imidazolone 5-alkyl substituent would be expected to increase the deviation from coplanarity of the imidazolone and phenyl rings; substituents ortho to the carbonyl group are expected to have an even greater effect. We propose that noncoplanarity of the benzene and imidazolone rings is desirable for activity, but that complete deconjugation of the benzene and carbonyl reduces activity.[19]

Substitution at the 2-position of the imidazole ring would be expected to move the imidazole and benzene rings further from coplanarity. It is tempting to interpret

(19) Erhardt, P. W.; Hagedorn, A. A., III; Lampe, J. W.; Sabio, M. IXth International Symposium on Medicinal Chemistry, Berlin (West), September 1986 (Abstract 111).

Table II. Biological Data: Equieffective Concentrations for Imidazolones **9** and Comparison Compounds **2–5**

compd	canine cardiac cAMP-PDE inhibn: IC_{50},[a] μM	ferret papillary muscle contractility 20% increase: C_{20},[b] μM
9a	6	0.1, 0.1
9b	30	1, 2
9c	65	11, 27
9d	>100	NR[c]
9e	20	11, 20
9f	49	0.4, 2.5
9g	2	0.063 (3; 0.01–0.13)
9h	37	0.7 (5; 0.14–2)
9i	25	0.1, 0.5
9j	29	1, 2
9k	40	16.3 (3; 3–39)
9l	7	21.7 (3; 9–46)
9m	19	21, 23
9n	4	0.2, 0.3
9o	73	1.3, 2.7
9p	2	0.05, 0.1
9q	2	0.2, 0.3
9r	27	1.1 (3; 0.3–2)
9s	15	0.4 (4; 0.3–0.6)
9t	23	0.1, 5
9u	>100	NR[c]
9v	30	4 (3; 4–4)
2	6	0.57 (6; 0.1–2)
3	5	3.18 (4; 0.2–10)
4	4	0.23 (3; 0.2–0.3)
5	6	0.30 (3; 0.1–0.4)

[a] Determined by interpolation of the mean dose–response curves from three to six series of measurements. In all cases, the range of inhibition at each dose of test compound was less than ±10%. [b] Determined by interpolation; when ≥3 determinations were made, the value shown is the mean (number of determinations; range) of the interpolated C_{20} values. [c] Not reached; $C_{20} \approx 100$ μM in one tissue, negative inotropy observed in another.

the decreased potency accompanying imidazole alkylation as reflecting this reorientation (e.g., the diminished potency of the 2-isopropyl compound **9k** compared with its straight chain analogue **9j**). However, a similar conformational change should result from placing a methyl group on the benzene ring in the position meta to the carbonyl, and the insignificant loss of potency accompanying this substitution suggests that other factors are involved. Furthermore, the imidazolylmethyl compound **9v** exhibits appreciable activity in both screens, suggesting considerable tolerance for the orientation of the imidazole ring in the binding site. It is possible that the lowered potency of the 2-alkylimidazol-1-yl compounds may simply reflect their greater basicity. Supporting this view is the inactivity of the imidazolium compound **9u**. Alternatively, the binding site for these agents may have a lipophilic region that accepts the imidazolone alkyl group. If a methyl group at the 3-position of the benzoyl group interacts with this region (which would require that the benzene ring be oriented so as to place the methyl syn to the imidazolone), loss of potency from increased torsion about the benzene–imidazole bond may be largely balanced. The restoration of PDE inhibitory potency by the large isopentyl group of **9l** may also be explained on this basis—small groups interact only weakly with this lipophilic region, whereas larger chains bind more strongly. Molecular modelling shows that the isopentyl group can, in fact, reach the same region occupied by the imidazolone ethyl group in the X-ray structure of **9g**. Furthermore, the low potency of the hydroxymethyl compound **9f** lends support to this hypothesis. We are now engaged in theoretical and spectroscopic investigation of the conformational surface in an attempt to assess the importance of these influences.

A regression analysis of the PDE inhibition data and the ferret papillary data gives a correlation coefficient of 0.61. This implies that while PDE inhibition may be an important factor in determining positive inotropic potency, other factors also may be involved.

To define further the biological profiles for some of the compounds, the separation of their inotropic from chronotropic and hypotensive effects was examined in normal, pentobarbital-anesthetized dogs. Table III presents, for some of the compounds with high in vitro potency, the doses that strengthen contractility (measured by left ventricular dP/dt) by 50%, which increase heart rate by 15%, and which decrease mean blood pressure by 20%. The data for standards **2–5** are included for comparison. In general, the effects on contractility in vivo parallel those observed in the ferret papillary screen. Again, the positive inotropic effects were not affected by high doses of β-adrenergic blockers. The effects of a 2-methyl substituent become highly significant in vivo: for the pair of compounds **9g–h**, the 2-methyl analogue **9h** has significantly less depressor and tachycardic properties. In fact, three of the five dogs receiving **9h** did not reach a 20% drop in pressure, even at doses increasing dP/dt by well over 100%. At this time, we can provide no convincing explanation for this selectivity. Speculatively, the differences may be due to slightly different structural requirements for binding to the PDEs from cardiac and vascular tissues or for transport of the drugs into the tissues. Alternatively, there may be some other mechanism contributing to the positive inotropic effects of the methylated species. In this regard, it should be noted that **9h** is substantially more potent in vivo than might be predicted on the basis of the in vitro papillary muscle data.

The specificity for positive inotropy exhibited by **9h** is striking. The search along the cAMP cascade for new cardiotonics has not, to our knowledge, led to any other compounds of comparable selectivity. Alternatively, the more typical profile of an inotropic agent with hypotensive

Table III. Effects of Selected Compounds in Anesthetized Dogs

compd	no. of dogs	maximum dose, mg/kg	equieffective dose,[a] mg/kg iv: contractility (LV dP/dt), +50%	heart rate, +15%	mean arterial pressure, −20%
9a	6	3.0	≤0.1[b] [1]	0.1 (0.05–0.2) [2]	0.9 (0.2–2.4) [0]
9b	9	3.0	0.3 (0.1–0.4) [1]	0.8 (0.7–2) [1]	0.6 (0.1–1.4)[c]
9g	4	0.1	0.02 (0.005–0.07) [0]	0.016 (0.009–0.02) [0]	0.03 (0.02–0.04) [1]
9h	5	1.0	0.03 (0.02–0.05) [0]	0.3 (0.01–0.8) [1]	0.3 (0.2, 0.4) [3]
2	6	0.3	0.09 (0.01–0.2) [1]	0.06 (0.02–0.2) [1]	0.2 (0.07–0.3) [2]
3	4	3.0	0.7 (0.2–1.0) [0]	0.6 (0.3–1.0) [0]	2.0 (2.0) [3][d]
4	6	1.0	0.04 (0.03–0.07) [1]	0.1 (0.04–0.3) [0]	0.4 (0.04–1.0) [0]
5	5	3.0	0.3 (0.05–0.9) [1]	0.3 (0.08–0.6) [0]	1.0 (0.6–1.5) [0]

[a] Reported as the means of the interpolated equieffective doses for the individual dogs. Shown are the mean, the range for the interpolated equieffective doses (in parentheses), and the number of dogs *not* reaching the indicated response at the highest dose administered [in brackets]. [b] Doses below 0.1 mg/kg were not studied. [c] Mean for five dogs. Three exhibited biphasic responses, pressure increasing to ca. 12% at 0.1–0.3 mg/kg and then declining to near or somewhat below control values. One dog showed little response, pressure declining 15% at 3.0 mg/kg. [d] Responses at 3.0 mg/kg were 13%, 19%, and 19% for these three dogs.

properties is exhibited by **9g**. The latter compound appears to be one of the most potent compounds of this type when assessed in vitro and in vivo. Thus, our imidazolone–benzoyl–imidazole series has provided two compounds of high interest. Their detailed hemodynamic properties in normal and heart-failure animals will be published separately, along with ancillary pharmacology indicating their promise as clinical candidates for CHF treatment.

Experimental Section

General Procedures. Samples for analysis and biological testing were dried in vacuo at 100 °C. NMR spectra were recorded on a Varian XL-300 spectrometer using $(CH_3)_4Si$ as internal standard; samples were dissolved in Me_2SO-d_6. IR spectra were determined on a Sargent-Welch 3-300 spectrometer on samples in KBr disks. UV spectra were determined on a Hewlett-Packard 8450A diode array spectrophotometer. Elemental analyses agreed within 0.4% of the theoretical values for C, H, and N and for any other elements determined. Melting points, determined on a Thomas-Hoover apparatus, are uncorrected. Commercial alkylimidazoles were recrystallized before use to remove small amounts of contaminating higher and lower homologues; all other reagents were used as received.

Method A. 1,3-Dihydro-4-[4-(1*H*-imidazol-1-yl)benzoyl]-5-methyl-2*H*-imidazol-2-one (9a). 4-(4-Fluorobenzoyl)-1,3-dihydro-5-methyl-2*H*-imidazol-2-one[6a] (24.0 g, 0.11 mol) and imidazole (88.5 g, 1.3 mol) were combined in a 250-mL round-bottom flask containing a magnetic stir bar, and the flask was immersed up to the joint in an oil bath at 140 °C. When a clear melt had been obtained, the flask was stoppered and kept at 140 °C for 16 h and then heated further at 155 °C for 24 h. The suspension was cooled and stirred with H_2O (300 mL) containing K_2CO_3 (15 g) and the crude product filtered and washed with H_2O. The solid was dissolved in 0.5 M HCl (300 mL) at 80 °C, and the solution was filtered and cooled to 5 °C overnight. The salt was mixed with H_2O (ca. 3.5 L) and sufficient 5 M NaOH was added to dissolve the solid. The product was precipitated by passing CO_2 through the filtered solution. Filtration, stirring with H_2O (300 mL) and boiling 1:1 2-propanol + H_2O (1 L), filtration, and drying afforded 18.1 g (61%) of a light yellow product, mp 335–337 °C dec. Anal. ($C_{14}H_{12}N_4O_2$) C, H, N.

2-(3-Methylbutyl)-1*H*-imidazole. 1-(Diethoxymethyl)-imidazole (40.5 g, 0.31 mol) was lithiated and alkylated with 1-iodo-3-methylbutane by the general procedure of Curtis and Brown.[20] The crude product (47% crude yield) was purified by conversion into the hydrochloride and recrystallization from EtOAc + CH_3CN: mp 122–123 °C. Anal. ($C_8H_{15}ClN_2$) C, H, N. The free base, obtained by neutralization of the salt and extraction into ether, was used in the preparation of **9l** without further purification.

Method B. 1,3-Dihydro-4-[4-[2-(hydroxymethyl)-1*H*-imidazol-1-yl]benzoyl]-5-methyl-2*H*-imidazol-2-one (9f). A mixture of **9a** (5.85 g, 21.8 mmol) and 37% aqueous formaldehyde (300 mL) was heated at 120 °C in a pressure tube for 17 h. The tube was cooled to room temperature, and the contents were filtered, washed with Et_2O (2 × 600 mL, 1 × 300 mL), and evaporated to dryness. Chromatography of the residue on silica gel, first with a gradient of NH_4OH (2–4%) in 2-propanol and then twice with a gradient of NH_4OH (5–20%) in CH_3CN, afforded the title compound. Two recrystallizations from 2-propanol + H_2O afforded 0.96 g (14.8%) of pure material, mp 308–310 °C dec. Anal. ($C_{15}H_{14}N_4O_3$) C, H, N. The location of the hydroxymethyl group was confirmed by the NMR spectrum (Me_2SO-d_6): δ 1.91 (s, 3), 4.44 (d, 2), 5.50 (t, 1), 7.05 (s, 1), 7.50 (s, 1), 7.74 (m, 4), 10.4 (s, 1), and 10.98 (s, 1).

Method C. 4-Ethyl-1,3-dihydro-5-[4-(2-methyl-1*H*-imidazol-1-yl)benzoyl]-2*H*-imidazol-2-one (9h). A mixture of ethyl 4-fluorobenzoate (245 g, 1.46 mol), 2-methylimidazole (300 g, 3.66 mol) (Aldrich, recrystallized from acetone to remove ca. 1% imidazole), Me_2SO (500 mL), and finely ground K_2CO_3 (320 g) was stirred overnight at 120 °C. The mixture was diluted with water (1 L) and extracted with CH_2Cl_2 (1.5 L). The product was isolated from the organic layer by extraction into aqueous HCl, basification of the aqueous acid, extraction into CH_2Cl_2, drying (Na_2SO_4), and evaporation. The crude residue was heated with aqueous NaOH (6 M, 250 mL) at 90 °C until a clear solution was obtained, and the solution was cooled and neutralized to pH 7 with acetic acid. The product was collected, stirred with hot water, filtered, washed with acetone and ether, and dried. The yield of white 4-(2-methyl-1*H*-imidazol-1-yl)benzoic acid was 53.2 g (18%), mp 300–305 °C dec. Anal. ($C_{11}H_{10}N_2O_2$) C, H, N.

A mixture of P_2O_5 (14 g) and CH_3SO_3H (140 g) was stirred at 100 °C until homogeneous and then cooled to 60 °C. 4-(2-Methyl-1*H*-imidazol-1-yl)benzoic acid (11.0 g, 54.4 mmol) and 5-ethyl-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxylic acid (10.0 g, 64 mmol) were added, and the mixture was stirred at 60–65 °C until a clear solution resulted. The solution was then heated at 110–115 °C for 5 h, cooled to room temperature, and mixed with ice (400 g). The resulting red-brown slush was cooled in ice while 50% aqueous NaOH was added to give a pH of 8–9, and the resulting suspension was stirred for 1 h at room temperature. The crude product was collected, stirred with 2% aqueous $NaHCO_3$ (100 mL) for 30 min, collected, boiled briefly with DMF (30 mL), filtered, and washed with water and MeOH. After drying, the off-white product, dec without melting >300 °C, weighed 10.16 g (63.5%). Anal. ($C_{16}H_{16}N_4O_2$) C, H, N.

Method D. 4-Ethyl-1,3-dihydro-5-[4-(1*H*-imidazol-1-ylmethyl)benzoyl]-2*H*-imidazol-2-one (9v). 4-(Chloromethyl)-benzoyl chloride (35 g, 0.18 mol) was added in one portion to a solution of imidazole (124 g, 1.8 mol) in DMF (260 mL), and the solution was stirred at room temperature overnight. Water (25 mL) was added, the mixture was stirred at room temperature for 1 h, the pH was adjusted to 7.0 with concentrated HCl, and the suspension was kept at room temperature overnight. The solid was collected and washed with water, MeOH, and Et_2O to give 20 g (55%) of crude 4-(1*H*-imidazol-1-ylmethyl)benzoic acid suitable for the preparation of **9v**. An analytical sample was obtained by recrystallization from MeOH–H_2O, mp 267–268 °C. Anal. ($C_{11}H_{10}N_2O_2$) C, H, N.

A mixture of the above acid (15.6 g, 77 mmol), 5-ethyl-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxylic acid (18.7 g, 110 mmol), and polyphosphoric acid (266 g) was heated slowly (gas evolution) to 105 °C with manual stirring, and the resulting solution was maintained at that temperature for 6 h. The reaction mixture was quenched with ice, the pH was adjusted to 7 with NaOH, and the suspension was stirred overnight. The sticky solid was collected, washed extensively with water, and dissolved in aqueous NaOH. Passage of a stream of CO_2 through the filtered solution precipitated 6.38 g (28%) of a light yellow product, mp 253–255 °C dec. Anal. ($C_{16}H_{16}N_4O_2$) C, H, N.

4-(1*H*-Imidazol-2-yl)benzoic Acid. Dropwise addition of glyoxal (40% in water, 21.5 mL, ca. 0.15 mol) to a solution of 4-formylbenzoic acid (15 g, 0.1 mol) in concentrated aqueous ammonia (65 mL) at room temperature followed by stirring overnight and neutralization afforded the title compound (18.55 g, 98.6% crude yield). A portion was recrystallized from DMF to give the analytical sample, mp >350 °C. Anal. ($C_{10}H_8N_2O_2$) C, H, N.

3-(1*H*-Imidazol-1-yl)benzoic Acid. Without purification of intermediates, 3-isothiocyanatobenzoic acid[21] was converted into 3-(2,3-dihydro-2-thioxo-1*H*-imidazol-1-yl)benzoic acid by the general sequence of Johnson et al.[22] Oxidation with 25% HNO_3 afforded, after neutralization, the title compound in 72% overall yield: mp 203–205 °C (from H_2O) (lit.[23] mp 144–146 °C). Anal. ($C_{10}H_8N_2O_2$) C, H, N.

Method E. 1-[4-[(5-Ethyl-1,3-dihydro-2-oxo-2*H*-imidazol-4-yl)carbonyl]phenyl]-2,3-dimethyl-1*H*-imidazolium Iodide (9u). A mixture of **9h** (1.0 g, 3.3 mmol) and NaH (from 0.135 g of a 60% dispersion in oil, 3.4 mmol) in DMF (20 mL) was stirred at room temperature under N_2 until a clear

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yellow solution was obtained. Iodomethane (0.21 mL, ca. 3.4 mmol) was added and the solution was kept at 70 °C overnight. The reaction mixture was filtered to remove ca. 100 mg of **9h** and the filtrate was evaporated to dryness. Recrystallization of the residue from MeOH afforded 0.28 g (19%) of the title salt, mp 268–271 °C dec. Anal. ($C_{17}H_{19}N_4O_2I$) C, H; N: calcd, 12.78; found, 12.36.

Preparation and Assay of cAMP Phosphodiesterase. These studies were conducted according to previously published methods.[1]

Determination of Effects on Ferret Papillary Muscle Contractility. Ferrets (600–1200 g, unselected for sex) were anesthetized with sodium pentobarbital (50 mg/kg, ip) and the hearts quickly removed and rinsed in room-temperature physiological salt solution. Papillary muscles ≤ 1 mm in largest diameter and ≥ 3 mm in length were removed with the chordae tendonae and some muscle wall intact. The muscles were attached at the distal end to a gold clamp and mounted in vertical tissue baths of 20-mL volume. The baths were perfused with physiological saline solution containing 123 mM NaCl, 4 mM KCl, 2.5 mM $CaCl_2$, 1.05 mM $MgCl_2$, 25 mM $NaHCO_3$, 1.8 mM NaH_2PO_4, and 5.5 mM dextrose at 35 °C; the solution was equilibrated with a mixture of 95% O_2 and 5% CO_2, giving a pH of 7.3–7.5. The muscle was stretched, applying ca. 300 mg of resting tension and stimulated through Pt point electrodes imbedded in the bottom muscle clamp. Constant current pulses of 1-ms duration and approximately 10–20% above threshold at 0.2-Hz frequency were used for stimulation. The muscles were gradually stretched to the peaks of their length–tension relations and allowed to equilibrate for ca. 30 min. Only those muscles that developed at least 300 mg of tension at the end of this equilibration period and that increased developed force by at least 50% upon paired electrical stimulation were used.

After equilibration, the infusion was stopped and the test compound, dissolved with 1.1 equiv of CH_3SO_3H in water or physiological saline, was injected directly into the bath. The muscle performance was followed for at least 5 min, all data being recorded on a laboratory computer. The tissue bath was washed every 15–20 min to remove the previous concentration of drug and to provide fresh saline. The concentrations of drug were typically 0.1–100 μM in half-log increments, except for some of the more potent compounds, which were studied at lower concentrations. When only weak responses to test compounds were observed, the muscle was challenged (after washout) with 300 nM *N*-isopropyloctopamine to ascertain normal function.

At the end of the experiment, the length (at optimal stretching) and weight of muscle between the clamps were measured, and muscle cross-sectional area was calculated. Force measurements were corrected for muscle size by dividing force and maximum rate of force development by cross-sectional area. Only those data from muscles that developed a force of at least 0.5 g/mm^2 were retained. C_{20} values were obtained by interpolation of the dose–response curves.

Hemodynamic Measurements. These studies were conducted in pentobarbital-anesthetized dogs according to previously published methods.[1]

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Registry No. **2**, 78415-72-2; **3**, 77671-31-9; 4, 94386-65-9; **5**, 84243-58-3; **9a**, 101183-98-6; **9b**, 101184-01-4; **9c**, 101184-03-6; **9d**, 101986-50-9; **9e**, 101184-05-8; **9f**, 101184-06-9; **9g**, 101183-99-7; **9h**, 101184-07-0; **9i**, 108035-32-1; **9j**, 108035-33-2; **9k**, 108035-34-3; **9l**, 101184-02-5; **9m**, 108035-35-4; **9n**, 108035-36-5; **9o**, 108035-37-6; **9p**, 108035-37-6; **9q**, 108035-38-7; **9r**, 108035-39-8; **9s**, 94444-69-6; **9t**, 108035-40-1; **9u**, 108035-41-2; **9v**, 108035-42-3; **10** (R = Me, R^1 = H), 77671-25-1; **10** (R = Et, R^1 = 2 - Me), 108058-65-7; **10** (R = Et, R^1 = 3 - Me), 108035-48-9; 4-(4-fluorobenzoyl)-1,3-dihydro-5-methyl-2*H*-imidazol-2-one, 77671-25-1; 1-(diethoxymethyl)imidazole, 61278-81-7; 2-(3-methylbutyl)-1*H*-imidazole, 16245-88-8; 2-(3-methylbutyl)-1*H*-imidazole hydrochloride, 108035-43-4; ethyl 4-fluorobenzoate, 451-46-7; ethyl 4-(2-methyl-1-imidazolyl)benzoate, 108035-44-5; 4-(2-methyl-1*H*-imidazol-1-yl)benzoic acid, 101184-11-6; 5-ethyl-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxylic acid, 101184-10-5; 4-(1*H*-imidazol-1-yl)methyl benzoic acid, 94084-75-0; 4-(1*H*-imidazol-2-yl)benzoic acid, 108035-45-6; 3-isothiocyanatobenzoic acid, 2131-63-7; 3-(2,3-dihydro-2-thioxo-1*H*-imidazol-1-yl)benzoic acid, 108035-46-7; 3-(1*H*-imidazol-1-yl)benzoic acid, 108035-47-8; 5-methyl-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxylic acid, 101184-09-2; canine cardiac phosphidiesterase, 9036-21-9; imidazole, 288-32-4; 1-iodo-3-methylbutane, 541-28-6; formaldehyde, 50-00-0; 2-methylimidazole, 693-98-1; 4-(chloromethyl)benzoyl chloride, 876-08-4; glyoxal, 107-22-2; 4-formylbenzoic acid, 619-66-9; 4-methylimidazole, 822-36-6; 2,4,5-trimethylimidazole, 822-90-2; benzimidazole, 51-17-2; 2-ethylimidazole, 1072-62-4; 2-propylimidazole, 50995-95-4; 2-isopropylimidazole, 36947-68-9; 2-ethyl-4-methylimidazole, 931-36-2.

Supplementary Material Available: Results from X-ray crystallographic analysis of **9g** (17 pages); table of observed and calculated structure factors (4 pages). Ordering information is given on any current masthead page.