Cardiotonic Agents. 7. Prodrug Derivatives Of 4-Ethyl-1,3-dihydro-5-[4-(2-methyl-1*H*-imidazol-1-yl)benzoyl]-2*H*-imidazol-2-one

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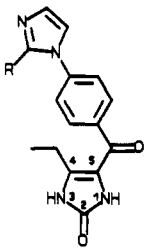
The cardiotonic agent 4-ethyl-1,3-dihydro-5-[4-(2-methyl-1*H*-imidazol-1-yl)benzoyl]-2*H*-imidazol-2-one (1) was found to have low bioavailability when administered orally to rats and dogs. A series of *N*-acyl derivatives, an underutilized prodrug of acidic NH compounds, has been synthesized and tested for their ability to improve the oral bioavailability of 1. Reaction of the monosodium salt of 1 with various anhydrides afforded the N-1 monoacylimidazolones with surprisingly high regioselectivity. In addition to the prodrugs, acylation of 1 with propionic or phenylacetic anhydride led to the novel 3*H*-pyrrolo[1,2-*c*]imidazole-3,5(2*H*)-diones 6. The prodrugs showed a significant increase in the partition coefficients with a minor decrease in the aqueous solubility. The benzoyl derivative 4b exhibited the highest stability in both pH 1.5 and 7.4 buffer solutions. Further evaluation of 4b showed rapid conversion to 1 in canine plasma ($t_{1/2}$ = 38 min), and human plasma ($t_{1/2}$ = 10 min). Oral studies indicated that the bioavailability of 4b was increased to >75% (compared to <20% for 1), and hemodynamic studies demonstrated that the selective inotropic profile of 1 was retained.

Compound 1 is a selective inotropic agent, which after intravenous administration to dogs increased the force of cardiac contraction without affecting heart rate and blood pressure.[1] It represents a unique tool that could be used to assess the specific value of positive inotropy during therapy of congestive heart failure.[2] However, 1 was found to have low bioavailability (<20%) when administered orally to rats and dogs.[5] Interestingly, its close structural analogues 2 and 3 exhibit good bioavailability (>80%) but lack the high degree of selectivity for inotropic activity. Initial attempts to improve the bioavailability of 1 through formulation and dosage regimen studies were unsuccessful.[5] These results prompted an investigation into potential prodrugs designed to deliver effective plasma levels of 1 upon oral administration.[6,7]

Although a biological mechanism responsible for the low oral bioavailability of 1 was not apparent, the higher



1 R = CH_3
2 R = H
3 R = CH_2CH_3

bioavailability of 2 and 3 led us to believe that slight structural modifications would change the absorption properties and potentially alleviate the bioavailability problem. Furthermore, if nonpolar substituents were chosen, then the lipophilicity of the resulting prodrugs would be increased and their ability to penetrate biological membranes might be enhanced. Addition of nonpolar functionalities was also viewed as superior to polar functionalities because they represent better candidates for subsequent enzymatic removal.[8] Concerning the stability of the prodrugs, we felt that it was important for the substituents to be stable in the GI tract but extremely labile after absorption. A short systemic half-life would diminish any biological activity that might be inherent to the prodrug and preclude other metabolic conversions that could compete with liberation of 1.

Typically, NH acidic compounds have been converted to useful prodrug candidates through formation of *N*-Mannich bases, hydroxymethyl derivatives, or *N*-[(acyloxy)alkyl] analogues. Surprisingly, formation of prodrugs from acidic NH compounds through N-acylation has received little attention in the past.[9] Since the acidity of an imidazolone is similar to catechol,[10] and because drugs

(1) Hagedorn, A. A., III; Erhardt, P. W.; Lumma, W. C., Jr.; Wohl, R. A.; Cantor, E.; Chou, Y.-L.; Ingebretsen, W. R.; Lampe, J. W.; Pang, D.; Pease, C. A.; Wiggins, J. Cardiotonic Agents. 2. (Imidazolyl)aroylimidazolones, Highly Potent and Selective Positive Inotropic Agents. *J. Med Chem.* 1987, *30*, 1342-1347.

(2) The recent ("second generation"[3]) cardiotonic agents as typified by milrinone generally possess positive inotropic activity in combination with significant vasodilatory properties (e.g. "inodilators" able to "reduce after-load"). The complex etiology of congestive heart failure coupled with the lack of an appropriately selective and nontoxic drug has complicated attempts to definitively answer long-standing questions about the nature of the efficacy for the cardiac glycosides and the general therapeutic role of positive inotropic agents in this clinical syndrome.[4] It should be noted that a selective drug such as compound 1 would allow for assessing both specific inotropic therapy and combination therapy since it can be administered either alone or in combination with additional drugs such as a vasodilator.

(3) Erhardt, P. W. Second Generation Phosphodiesterase Inhibitors: Structure-Activity Relationships and Receptor Models. In *Isoenzymes of Cyclic Nucleotide Phosphodiesterases*; Beavo, J., Houslay, M. D., Eds.; John Wiley and Sons: New York, 1990; p 317-333.

(4) Erhardt, P. W. In Search of the Digitalis Replacement. *J. Med. Chem.* 1987, *30*, 231-237.

(5) Additional information pertaining to oral and intraduodenal bioavailability, formulation, and dosage regimen studies is available as supplementary material.

(6) Several review articles and books are available. For a recent review see: Waller, D. G.; George, C. F. Prodrugs. *Br. J. Clin. Pharamcol.* 1989, *28*, 497-507.

(7) Erhardt, P. W.; Hagedorn, A. A., III. U.S. Patent 4,743,612, 1988.

(8) Williams, R. T. Species Variations in Drug Biotransformations. In *Fundamentals of Drug Metabolism and Drug Disposition*; LaDu, B. N.; Mandel, H. G.; Way, E. L., Eds.; Williams and Wilkins Co.: Baltimore, 1971; pp 187-205.

(9) Bundgaard, H. Design of Prodrugs: Bioreversible Derivatives for Various Functional Groups and Chemical Entities. In *Design of Prodrugs*; Bundgaard, H., Ed.; Elsevier: New York, 1985; pp 1-92.

(10) We have determined that the pK_a = 10.6 for removal of a proton from one of the imidazolone nitrogens in structures 1 and 2. This value is similar to that for typical phenols and catechols.

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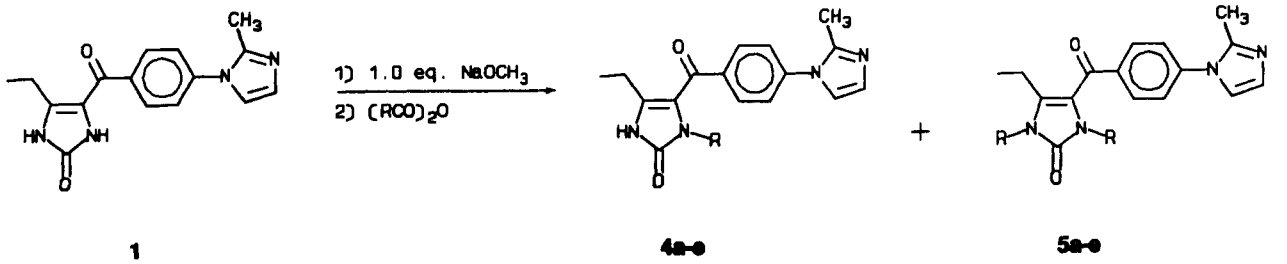
Scheme I



a: R = $COCH_3$
b: R = COC_6H_5
c: R = $COCH_2CH_3$
d: R = $COCH(CH_3)_2$
e: R = $COCH_2C_6H_5$

possessing a catechol moiety have been successfully converted to prodrugs by acylation,[11] we decided to investigate simple acyl groups on 1. A few symmetrical diacylated analogues of structurally related cardiotonic imidazolones have been reported.[12] These compounds retained some or all of the activity of the unsubstituted analogues, and it was noted that their activity may have resulted from their deacylation in vivo. These results further encouraged our interest in acylated derivatives of 1. However, to avoid compounds with severely limited water solubility, only the monoacylated systems were studied. In addition, monoacylated prodrugs would have the advantage of being only a single metabolic step away from producing the parent system 1. The N-1 acylated regioisomers were of particular interest since this would block any intramolecular hydrogen bonding between the imidazolone NH and the ketone carbonyl and, thereby, potentially enhance the water solubility. Our final consideration was to ensure that the prodrug substituent, after metabolic liberation, would not possess significant biological activity or toxicity. In this regard, simple acetyl and benzoyl[13] groups seemed like ideal substituents for initial combination with 1. The results from our studies in which an efficient prodrug of 1 was obtained through N-acylation of the imidazolone are reported herein. In addition, the benzyl analogue 7 was prepared as a stable (non-prodrug) version of **4b** to help assess the biological activity that might be inherent to the N-1-substituted imidazolone system.

Chemistry

The acylimidazolones 4 (Table I) were prepared by the general method illustrated in Scheme I. Reaction of the isolated monosodium salt of 1 with 1.5 equiv of an anhydride in DMF afforded the acylated adducts 4. In addition to 4, diacylated imidazolones 5, starting imidazolone 1, and in some cases minor amounts (<1%) of the other monoacylated regioisomers could be isolated. The regiochemistry of the acylation has been established by NMR NOE studies[14] and X-ray crystallographic analysis (Figure 1).

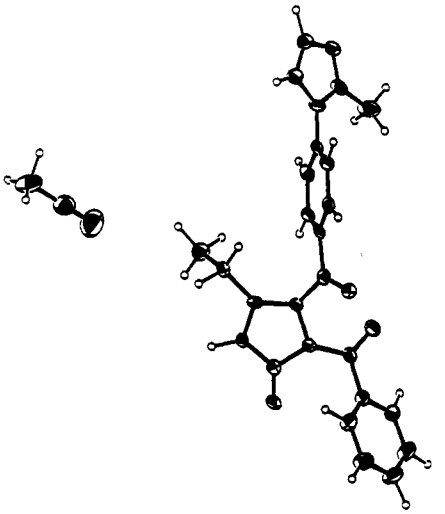
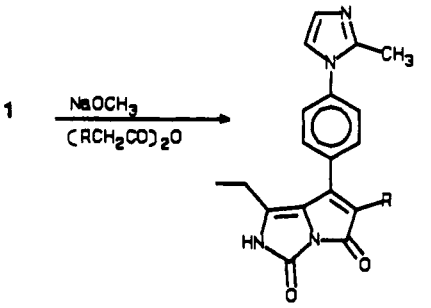


Figure 1. ORTEP drawing of the X-ray structure of compound **4b**.

Scheme II



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The regioselectivity can be explained by an equilibrium in which the predominant regioisomer 4 results from the selective deacylation of the diacylated imidazolone 5. Steric factors would seen to render acyl groups at the N-3 position of the imidazolone more labile and account for the observed product selectivity. Consistent with this explanation, higher yields of the monacylimidazolones 4 have been obtained in two steps by first forming the bis adducts 5 followed by a selective deacylation with triethylamine in refluxing 2-propanol.

Reaction of 1 with propionic or phenylacetic anhydride under standard conditions afforded low yields of 4c and 4e due to the competing formation of 3*H*-pyrrolo[1,2-*c*]-imidazole-3,5(2*H*)-diones 6 (Scheme II). These novel

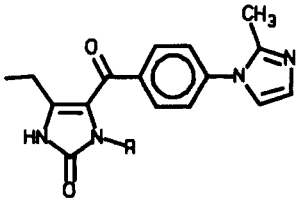
(11) McClure, D. A. The Effect of a Prodrug of Epinephrine (Dipivalyl Epinephrine) in Glaucoma-General Pharmacology, Toxicology, and Clincal Experience. In *Prodrugs as Novel Drug Delivery Systems*; Higuchi, T.; Stella, V., Eds.; American Chemical Society: Washington, DC 1975; p 224–235.

(12) Schnettler, R. A.; Dage, R. C.; Grisar, J. M. 4-Aroyl-1,3-dihydro-2*H*-imidazol-2-one, a New Class of Cardiotonic Agents. *J. Med. Chem.* **1982**, *25*, 1477–1481.

(13) Robinson, C. P. Sodium Benzoate/Sodium Phenylacetate. *Drugs Today (Barcelona)* **1987**, *23*, 501–503.

(14) NOE difference experiment with irradiation of the imidazolone NH protons of **4a–e** showed enhancement of the methylene protons of the ethyl substituents.

Table I. Physical and Biological Properties of Cardiotonic Imidazolones



compd	R	solubility pH 7.4 (μM)[a]	partn coefft[b]	conversion to 1[c] pH 1.5 $t^{1/2}$ (h)	conversion to 1[c] pH 7.4 $t^{1/2}$ (h)	conversion to 1[c] plasma $t^{1/2}$ (min)	ferret papillary muscle contractility 20% increase: C_{20} (μM)[d]	mp (°C)
1	H	44	7				0.5	>320
4a	$COCH_3$	40	26	21	8	30	0.2	240–242
4b	COC_6H_5	23	92	263	25	38	0.2	218–220
4c	$COCH_2CH_3$	30	52	17	6	30	0.3	216–218
4d	$COCH(CH_3)_2$	10	>200	132	8	47	0.3	255–257
4e	$COCH_2C_6H_5$	25	NT[e]	39	1.5	NT	0.2	178–179
7	$CH_2C_6H_5$	NT	NT	NA[f]	NA	NA	13	87–93

[a] Measured in pH 7.4 phosphate buffer and determined by HPLC. [b] Determined in an octanol/pH 7.4 phosphate buffer system. [c] Half-life measurements of drug consumed, described in the Experimental Section. [d] Drug concentration (μM) causing a 20% increase in contractile force of ferret papillary muscle. Data represent the mean from at least two determinations. Range from all data were within ±10%. For all compounds the inotropic effect was not altered by coadministration of 1 μM propranolol, thus ruling out the possibility that the observed responses were mediated through β-adrenergic receptors. [e] Not tested. [f] Not applicable.

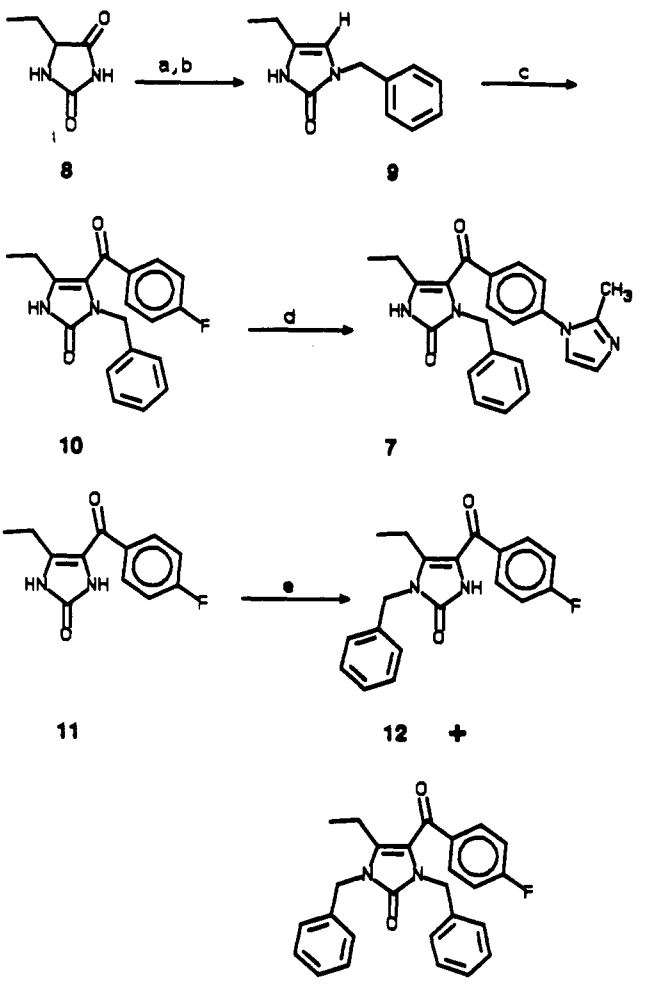
heterocyclic compounds maintain some of the inotropic effects characteristic of the parent imidazolones. A short series of these compounds has been prepared, and their synthesis and biological activities will be reported elsewhere.[15]

The synthesis of benzylimidazolone 7 is outlined in Scheme III. Alkylation of hydantoin 8 with NaOH and benzyl bromide,[16] followed by reductive dehydration with LAH[17] afforded the desired regioisomer 9. Friedel–Crafts acylation with *p*-fluorobenzoic acid at 85 °C in a 1:1 mixture of PPA–CH_3SO_3H gave the imidazolone 10. Nucleophilic displacement with 2-methylimidazole afforded 7. Interestingly, alkylation of imidazolone 11[1] with benzyl bromide gave little of the monobenzyl analogue 10. Instead, the alternate regioisomer 12 and dibenzylated analogue 13 were the predominant products isolated from the reaction. Thus, it appears that the N-3 position of the imidazolone is the kinetically favored site for alkylation, and is consistent with the regiochemistry of the acylimidazolones 4a–e resulting from a thermodynamic equilibrium of the anions.

Results and Discussion

A number of screens were used to help select a prodrug for in vivo studies (Table I). First, the solubilities and partition coefficients were determined to evaluate the differences in the physical properties of the prodrugs relative to 1. Second, inotropic activity was measured in an in vitro tissue perfusion assay that would measure the contractility independent of any specific mechanism. Finally, HPLC monitoring of the compounds in dog plasma and pH 1.5 and 7.4 buffer solutions was used to measure the half-life conversion rates of the prodrugs to 1.

Scheme III[a]



[a] (a) $NaOH/C_6H_5CH_2Br/EtOH/H_2O$; (b) LAH/THF; (c) *p*-fluorobenzoic acid/PPA/CH_3SO_3H, 85 °C; (d) 2-methylimidazole, 150 °C; (e) $NaH/C_6H_5CH_2Br$.

The partition coefficients for 4a–d followed a trend that paralleled the lipophilicities of the acyl groups (Table I).

(15) Shaw, K. J. U.S. Patent 4,937,258, 1990. A synthetic study of this ring system has been recently reported: Shaw, K. J.; Vartanian, M. Synthesis of 3*H*-Pyrrolo[1,2-*c*]imidazole-3,5-(2*H*)-diones. *J. Org. Chem.* 1991, *56*, 858–861.

(16) Finkbeiner, H. The Carboxylation of Hydantoins. *J. Org. Chem.* 1965, *30*, 3414–3419.

(17) These reactions have been used to prepare similar imidazolones: Cortes, S.; Kohn, H. Selective Reductions of 3-Substituted Hydantoins to 4-Hydroxy-2-imidazolidinones and Vicinal Diamines. *J. Org. Chem.* 1983, *48*, 2246–2254.

Due to the instability of **4e**, as reflected in the half-life data in Table I, the partition coefficient for this compound could not be accurately determined. Interestingly, although there was a significant increase in the partition coefficients for **4a–d** compared to 1, the corresponding decreases in aqueous solubility were not as drastic. For example, the preference for octanol distribution for **4b** is 13-fold higher than that for 1, whereas its solubility in pH 7.4 phophate buffer is decreased by a factor of 2. Thus, the lipophilicity in this series has been significantly increased with only a moderate decrease in aqueous solubility.

The in vitro inotropic activity was measured in isolated ferret papillary muscle using a 30-min preincubation period (Table I). The inotropic activity for **4a–e** was essentially identical to that of 1. These results may be explained by the presence of esterases and amidases in the assay which could convert the acylimidazolones to 1. In addition, the non-acyl analogue **7**, which cannot be easily converted to 1, is approximately 50 times less active than its closest structural analogue **4b**. Taken together, these data suggest that **4a–e** are also inherently less active, and that the inotropic effects can be attributed to their deacylation to 1. Furthermore, if one assumes that inhibition of phosphodiesterase is a contributing mechanism for the inotropic activity, then reduced activity for an imidazolone substituted in this manner would be predicted from proposed SAR models of the cAMP phosphodiesterase receptor.[18-21] Consistent with this premise, the benzoyl analogue **4b** was found to be a significantly weaker inhibitor of cAMP phosphodiesterase when compared to 1 in vitro (i.e., **4b** IC_{50} = 157 μM, 1 IC_{50} = 37 μM).[22]

The $t_{1/2}$ values for the conversion of the acylimidazolones **4a–e** to 1 were measured at 37 °C in pH 1.5 and 7.4 buffer solutions and in canine plasma to simulate some of the conditions that the prodrugs might encounter as they passed through the GI tract and into the circulatory system. Since the small intestine is generally considered to be the predominant absorption site for nonacidic drugs, we felt that it was important for the prodrugs to have good stability at the lower pH range to insure their survival in the stomach. The pH increases from 5 to 7 between the duodenum and the end of the ileum of the small intestine and similarly, stability through this pH range was also desired. Half-life measurements determined that the benzoyl derivative **4b** was the most stable analogue in both the pH 1.5 and 7.4 buffer solutions. Interestingly, all five prodrugs converted to 1 at a slower rate at pH 1.5 than at pH 7.4, which is consistent with the expected lability of this system toward base-catalyzed hydrolysis. It was also determined that the $t_{1/2}$ values for the conversion of **4a–d** to 1 in dog plasma were all less than 1 h. Thus, the acylimidazolones appeared to have the desired in vitro profile for a prodrug: chemically stable but labile toward plasma enzymes. On the basis of a combination of preferable chemical properties (lipophilicity, solubility) and stability, the benzoyl derivative **4b** was selected as the lead prodrug for further evaluation.

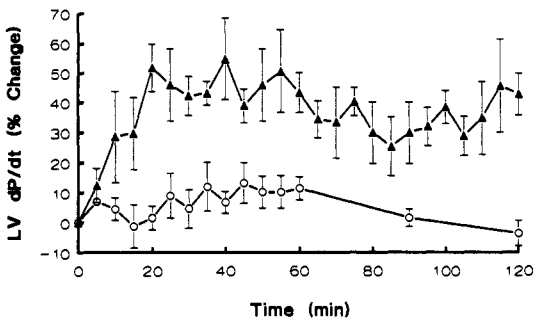


Figure 2. Effects of oral administration of compound 1 (n = 7, 3 mg/kg), and compound **4b** (n = 9, 1 mg/kg) on left ventricular dP/dt in conscious dogs: 1 (○), **4b** (▲).

The inotropic activity of **4b** in vivo was evaluated in dogs after oral and intravenous administration. Intravenous administration of **4b** indicated that the only pharmacodynamic difference between the prodrug and parent drug was a delay (10 min) in the onset of action for the prodrug (**4b**). This delay can be explained by the conversion of the relatively inactive prodrug to the active parent drug and parallels the pharmacokinetic half-life which was later verified by HPLC monitoring of plasma aliquots. After oral administration of **4b**, a dramatic increase in left ventricular (LV) dP/dt was observed when compared to 1 (Figure 2). Pharmacokinetic data, derived from HPLC analysis of both 1 and **4b** in the plasma, demonstrated that the oral bioavailability of **4b** is >75% as compared to <20% for 1. The prodrug also provides the unique selective inotropic profile exhibited by the parent drug, i.e., with a dose that produced a 50% increase in LV dP/dt, less than a 5% increase in heart rate and less than a 10% drop in blood pressure were found. In addition, **4b** produced an energy-efficient inotropic response with either no increase in LV oxygen consumption or increases in myocardial oxygen consumption that were less than the expected ratio with LV dP/dt.[23]

Esterase and amidase activities in dogs have been previously shown to correlate well with those in humans.[24] In addition, when **4b** was tested in human plasma, its half-life was found to be ca. 10 min. Taken together, these results suggest that rapid conversion of **4b** to 1 can also be expected to occur in man.

Conclusion

Acylation of acidic NH compounds is an underutilized method for the preparation of prodrugs. It has been demonstrated that simple monoacylated analogues of 1, such as the benzoyl derivative **4b** in particular, are effective prodrugs that can enhance the oral bioavailability from

(18) Erhardt, P. W.; Chou, Y.-L. A Topographical Model for the c-AMP Phosphodiesterase III Active Site. *Life Sci.* **1991**, *49*, 553–568.

(19) Erhardt, P. W.; Hagedorn, A. A., III; Sabio, M. Cardiotonic Agents. 3. A Topographical Model of the Cardiac c-AMP Phosphodiesterase Receptor. *Mol. Pharmacol.* **1988**, *33*, 1–13.

(20) Moos, M. H.; Humblett, C. C.; Sircar, I.; Rithner, C.; Weishaar, R. E.; Bristol, J. A.; McPhail, A. T. Cardiotonic Agents. 8. Selective Inhibitors of Adenosine 3′,5′-Cyclic Phosphate Phosphodiesterase III. Elaboration of a Five-Point Model for Positive Inotropic Activity. *J. Med. Chem.* **1987**, *30*, 1963–1972.

(21) Rakhit, S.; Marciniack, G.; Leclerc, G.; Schwartz, J. Computer Assisted Pharmacophore Search in a Series of Non-Steroidal Cardiotonics. *Eur. J. Med. Chem.* **1986**, *21*, 511–515.

(22) These data do not definitively answer whether the acylimidazolones **4a–e** are inactive prodrugs or whether the observed in vitro inotropic activities are a result of contributions from both 4 and their active metabolite 1. However some of the subsequent data with **4b** (i.e. short plasma half-life, delay of onset of action when administered in vivo, and similar hemodynamic profiles) are convincing evidence that the in vivo activities of this prodrug can be attributed to conversion to 1.

(23) Greenberg, S.; Touhey, B. Hemodynamic and Myocardial Energetic Effects of CK-3197, a Selective Positive Inotropic Agent. *J. Cardiovasc. Pharmacol.* **1991**, *17*, 145–153.

(24) Erhardt, P. W.; Woo, C. M.; Anderson, W. G.; Gorczynski, R. J. Ultra Short-Acting β-Adrenergic Receptor Blocking Agents. 2. (Aryloxy)propanolamines Containing Esters on the Aryl Function. *J. Med. Chem.* **1982**, *25*, 1408–1412.

<20% to >75%. Prodrug **4b** is stable in aqueous buffer solutions but is rapidly converted to 1 in the systemic circulation ($t_{1/2}$ = 10 min). The synthetic methodology that was employed to prepare the prodrugs also yielded, in certain cases, a novel heterocyclic system that is itself of further interest both chemically and biologically.[15] Availability of an oral form of 1 has allowed for the long-term toxicity testing required for its continued development. However, this testing has recently shown that **4b** exhibits significant hepatotoxicity in dogs and moderate renal toxicity in rats, dogs, and monkeys.[25] The observed toxicity appears to be inherent to 1 thus complicating decisions about the further development of both the parent inotropic agent and its prodrugs.

Experimental Section

Melting points were taken on a Fisher-Johns or a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Berlex Analytical Section, Cedar Knolls, NJ or Microlit Laboratories, Caldwell, NJ, and results were within ±0.4% of the calculated values. NMR spectra were recorded with a Varian XL-300 (300 MHz) spectrometer. Tetramethylsilane was used as the internal standard in all solvents. All NMR spectra were consistent with the assigned structures. All reactions were run under a nitrogen atmosphere.

1-Acetyl-4-ethyl-1,3-dihydro-5-[4-(2-methyl-1*H*-imidazol-1-yl)benzoyl]-2*H*-imidazol-2-one (4a). A mixture of 1 (10.0 g, 34 mmol), triethylamine (11.7 mL, 85 mmol), and acetic anhydride (160 mL) was heated at 85–90 °C for 3 h. The reaction mixture was cooled, concentrated to ca. 25 mL, and partitioned between 1 N hydrochloric acid (150 mL) and ether (100 mL). The aqueous was brought to a pH = 7 with 10% sodium bicarbonate and then extracted with dichloromethane (2 × 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford the diacetylimidazolone **5a** as a light brown solid (12.5 g): ^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3 H), 2.43 (s, 3 H), 2.60 (s, 3 H), 2.74, 2.68–2.80 (s + q, 5 H), 7.06 (d, 2 H), 7.41 (d, 2 H), 7.95 (d, 2 H).

The above solid was dissolved in a mixture of triethylamine (12.5 mL, 114 mmol) and 2-propanol (125 mL) and refluxed for 5 h. The reaction mixture was cooled and evaporated to dryness under reduced pressure. The residual solid was recrystallized from warm methanol (1 L) to afford **4a** as a pale yellow crystalline solid (4.21 g, 37%): ^{1}H NMR (DMSO-d_6) δ 1.10 (t, 3 H), 2.33, 2.28–2.39 (s + m, 5 H), 2.43 (s, 3 H), 6.95 (s, 1 H), 7.39 (s, 1 H), 7.55 (d, 2 H), 7.84 (d, 2 H), 11.40 (br s, 1 H). Anal. ($C_{18}H_{18}N_4O_3$) C, H, N.

1-Benzoyl-4-ethyl-1,3-dihydro-5-[4-(2-methyl-1*H*-imidazol-1-yl)benzoyl]-2*H*-imidazol-2-one (4b). To a stirred suspension of imidazolone 1 (9.74 g, 32.9 mmol) in methanol (500 mL) was added sodium methoxide (1.78 g, 32.9 mmol), and the mixture was refluxed for 1 h. The yellow solution was cooled, the solvent was evaporated, and the yellow solid was dried in vacuo to afford the sodium salt (10.46 g). A solution of benzoic anhydride (11.15 g, 49.3 mmol) in DMF (50 mL) was added over the course of 5 min to a stirred suspension of the sodium salt in DMF (300 mL), and the mixture was heated at 65 °C for 18 h. The reaction mixture was cooled to room temperature and filtered, the solids were washed with DMF (50 mL), and the combined filtrate was evaporated to dryness in vacuo (50 °C, 1 mm). The residue was partitioned between 1 N hydrochloric acid (200 mL) and ethyl acetate (250 mL). The aqueous was neutralized with 10% sodium bicarbonate and extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. Recrystallization of the residue from acetonitrile afforded **4b** as light yellow needles (5.96 g, 45%): ^{1}H NMR (DMSO-d_6) δ 1.13 (t, 3 H), 2.23 (s, 3 H), 2.38 (q, 2 H), 6.92 (s, 1 H), 7.34 (s, 1 H), 7.53 (m, 4 H), 7.63 (t, 1 H), 7.85 (d, 2 H), 7.91 (d, 2 H), 11.50 (br s, 1 H). Anal. ($C_{23}H_{20}N_4O_3$) C, H, N.

4-Ethyl-1,3-dihydro-5-[4-(2-methyl-1*H*-imidazol-1-yl)benzoyl]-1-(1-oxopropyl)-2*H*-imidazol-2-one (4c). To a stirred suspension of the sodium salt of 1 (14.8 g, 46.4 mmol) prepared as described above in DMF (800 mL) was added propionic anhydride (90 mL). The reaction mixture was heated at 40 °C for 2.5 h and then concentrated by distillation in vacuo (40 °C, 0.5 mm). The residue was partitioned between 1 N hydrochloric acid (300 mL) and ether (200 mL). The acidic aqueous layer was brought to a pH = 7 with 10% sodium bicarbonate and then extracted with dichloromethane (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford a brown oil. The oil was refluxed for 7 h in a mixture of triethylamine (25 mL) and 2-propanol (500 mL), cooled, and then evaporated under reduced pressure. The residue was chromatographed on silica gel with methanol/dichloromethane (4:96) as eluent, and the appropriate fractions were combined, evaporated under reduced pressure, and recrystallized from acetonitrile to afford **4c** as a pale yellow crystalline solid (3.2 g, 20%): ^{1}H NMR (DMSO-d_6) δ 0.93 (t, 3 H), 1.10 (t, 3 H), 2.32, 2.34 (s + q, 5 H), 2.89 (q, 2 H), 6.94 (s, 1 H), 7.38 (s, 1 H), 7.55 (d, 2 H), 7.84 (d, 2 H), 11.40 (br s, 1 H). Anal. ($C_{19}H_{20}N_4O_3$) C, H, N.

4-Ethyl-1,3-dihydro-5-[4-(2-methyl-1*H*-imidazol-1-yl)benzoyl]-1-(2-methyl-1-oxopropyl)-2*H*-imidazol-2-one (4d). To a stirred suspension of the sodium salt of 1 (5.0 g, 15.7 mmol) prepared as described above in DMF (100 mL) was added isobutyric anhydride (3.9 mL, 23.6 mmol). The reaction mixture was heated at 50 °C for 1 h and then concentrated by distillation in vacuo (50 °C, 1 mm). The residue was triturated with warm methanol (100 mL) and filtered. The solid was recrystallized from methanol/ether to afford **4d** as a pale yellow crystalline solid (2.35 g, 41%): ^{1}H NMR (DMSO-d_6) δ 1.00 (d, 6 H), 1.13 (t, 3 H), 2.32 (s, 3 H), 2.39 (q, 2 H), 3.77 (m, 1 H), 6.96 (d, 1 H), 7.38 (d, 1 H), 7.55 (m, 2 H), 7.81 (m, 2 H), 11.40 (br s, 1 H). Anal. ($C_{20}H_{22}N_4O_3$) C, H, N.

4-Ethyl-1,3-dihydro-5-[4-(2-methyl-1*H*-imidazol-1-yl)benzoyl]-1-(1-oxo-2-phenylethyl)-2*H*-imidazol-2-one (4e). To a stirred suspension of the sodium salt of 1 (4.2 g, 13.2 mmol) prepared as described above in DMF (100 mL) was added phenylacetic anhydride[26] (4.48 g, 19.8 mmol). The reaction mixture was heated at 40 °C for 24 h and then concentrated by distillation in vacuo (40 °C, 0.5 mm). The residue was chromatographed on silica gel with methanol/dichloromethane (4:96) as eluent to afford **4e** as a pale yellow solid (0.90 g, 16%): ^{1}H NMR (DMSO-d_6) δ 1.11 (t, 3 H), 2.30 (s, 3 H), 2.39 (q, 2 H), 4.28 (s, 2 H), 6.95 (s, 1 H), 7.12–7.21 (m, 5 H), 7.31 (s, 1 H), 7.43 (d, 2 H), 7.75 (d, 2 H), 11.42 (br s, 1 H). Anal. ($C_{24}H_{22}N_4O_3 \cdot 0.9H_2O$) C, H, N.

4-Ethyl-1,3-dihydro-1-(phenylmethyl)-2*H*-imidazol-2-one (9). To a solution of hydantoin **8** (45.0 g, 0.35 mol) in a 50% aqueous ethanol solution (240 mL) containing sodium hydroxide (14.2 g, 0.35 mol) was added benzyl bromide (42.0 mL, 0.35 mol). The solution was refluxed for 6 h, then cooled, and concentrated to ca. 100 mL under reduced pressure. The resulting solids were filtered, triturated with ether, and dried to afford the benzylhydantoin as an off-white solid (34.8 g). To a stirred solution of the benzylhydantoin in THF (1500 mL) was added over the course of 2 h, a solution of lithium aluminum hydride (6.08 g, 0.160 mol) in THF (500 mL). The addition of the lithium aluminum hydride caused the formation of a white solid that persisted throughout the course of the reduction. The reaction mixture was stirred for 48 h at room temperature, and then the excess reducing agent was destroyed by the careful addition of 5 N hydrochloric acid (105 mL) at 5 °C. The mixture was diluted with water (800 mL) to dissolve the inorganic solids and extracted with dichloromethane (3 × 800 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure, and the residue was chromatographed on silica gel with methanol/dichloromethane (1:99) as eluent to afford **9** as an off-white solid (8.4 g, 12%). Recrystallization from dichloromethane/hexane afforded an analytical sample: mp 119–121 °C; ^{1}H NMR (DMSO-d_6) δ 1.04 (t, 3 H), 2.25 (q, 2 H), 4.61 (s, 3 H), 6.08 (s, 1 H), 7.29 (m, 5 H), 9.99 (s, 1 H). Anal. ($C_{12}H_{14}N_2O \cdot 0.15H_2O$) C, H, N.

(25) Additional information pertaining to the toxicity observed for 1 and **4b** is available as supplementary material.

(26) Cabre-Castellvi, J.; Palomo-Coll, A.; Palomo-Coll, A. L. Conversion Synthesis of Carboxylic Acid Anhydrides using *N,N*-Bis[2-oxo-3-oxazolidinyl]phosphorodiamidic Chloride. *Synthesis* 1981, 616–620.

4-Ethyl-5-(4-fluorobenzoyl)-1,3-dihydro-1-(phenylmethyl)-2*H*-imidazol-2-one (10). A mixture of benzylimidazolone **9** (2.0 g, 9.8 mmol) and *p*-fluorobenzoic acid (1.5 g, 10.8 mmol) was stirred in a mixture of polyphosphoric acid (8 g) and methanesulfonic acid (8 g) while the temperature was gradually (ca. 2 h) raised to 85 °C where it was maintained for 16 h. The reaction mixture was cooled to room temperature and then poured onto ice (50 g). The gummy solid was filtered and chromatographed on silica gel with methanol/dichloromethane (1:99) as eluent to afford **10** as a white solid (0.42 g, 13%). Recrystallization from ether afforded an analytical sample: mp 150–152 °C; ^{1}H NMR (DMSO-d_6) δ 0.95 (t, 3 H), 2.00 (q, 2 H), 5.03 (s, 2 H), 7.10 (m, 2 H), 7.30 (m, 5 H), 7.61 (m, 2 H), 11.25 (br s, 1 H). Anal. ($C_{19}H_{17}FN_2O_2 \cdot 0.2H_2O$) C, H, N.

4-Ethyl-1,3-dihydro-5-[4-(2-methyl-1*H*-imidazol-1-yl)benzoyl]-1-(phenylmethyl)-2*H*-imidazol-2-one (7). A mixture of **10** (3.50 g, 10.8 mmol) and 2-methylimidazole (8.9 g, 10.8 mmol) was heated in a sealed vessel at 150 °C for 8 h. The reaction mixture was cooled, dissolved in water, and extracted with dichloromethane (2 × 75 mL). The combined organic was washed with water (50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel with methanol/dichloromethane (3:97) as eluent to afford **7** as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.13 (t, 3 H), 2.19 (q, 2 H), 2.41 (s, 3 H), 5.25 (s, 2 H), 7.06 (m, 2 H), 7.26 (m, 5 H), 7.35 (d, 2 H), 7.67 (m, 2 H), 11.80 (br s, 1 H). Anal. ($C_{23}H_{22}N_4O_2 \cdot 0.5H_2O$) C, H, N.

X-ray Crystallographic Analysis of 4b. Colorless crystals of **4b** were obtained by recrystallization from CH_3CN: $C_{23}H_{20}N_4O_3 \cdot CH_3CN$; space group $Pbn2_1$; cell constants a = 18.724 (8) Å, b = 19.974 (9) Å, c = 6.507 (2) Å, V = 2281.91 Å^3, and D_c = 1.205 g cm^{-3} (Z = 4). A computer controlled Picker four-circle goniostat equipped with a Furnas monochromator (HOG crystal) and Picker X-ray generator (Mo Kα radiation, λ = 0.71069 Å) was employed in the study, and the sample was cooled to −155 °C. A total of 1649 unique intensities were observed. Of these, 1461 were observed [$F > 3.00\sigma(F)$] and corrected for Lorentz and polarization effects. The structure was solved by a combination of direct methods (MULTAN78) and fourier techniques. All hydrogen atoms were refined isotropically and non-hydrogen atoms anisotropically in the final cycles. The function minimized was $\sum\omega(|F_o|-|F_c|^2)$ with $\omega = 1/(\sigma F)^2$ to give an unweighted residual value of 0.0327 and a weighted value of 0.0331.

Determination of Partition Coefficients. Experimental details for the determination of the partition coefficients are provided in reference 27.

Determination of Half-Lives in Buffer Solutions. Stock solutions with a concentration of 2.0 mg/mL were prepared for each sample in pH 1.5 buffer and then further diluted with pH 1.5 buffer to give a final concentration of ca. 120 μM. Solubility limitations in pH 7.4 buffer required that the concentration of each stock solution be reduced to 3–3.5 mg/250 mL. These solutions were further diluted with pH 7.4 buffer to a final concentration of ca. 10–15 μM. The above solutions were allowed to equilibrate at 37 °C, and aliquots of those solutions were removed at predetermined time intervals. The concentrations of the test compounds and **1** were determined by HPLC, using a Spectra-Physics SP-8800 ternary gradient HPLC pump with an Applied Biosystems-SF-783 variable wavelength UV detector, a Waters WISP 712 autoinjector, and an Eldex column oven to analyze the hydrolysis mixtures. Resolution of the prodrug, an internal standard, and **1** was achieved at 50 °C on a Chromegabond Alkyl Phenyl (ES Industries), 5-μm, 60 A, 250 × 4.6 mm column. The aqueous mobile phase consisted of 0.050 M NaH_2PO_4 and 0.1% (v/v) H_3PO_4 (buffer). CH_3CN was used as the organic modifier. The following linear gradient was used: buffer–CH_3CN = 85:15 for 2 min, 85:15 to 60:40 over 13 min, and 60:40 for 2 min. The buffer–CH_3CN ratio was then returned to 85:15 over 10 min and reequilibrated for 8 min between injections. A flow rate of 1.5 mL/min was maintained during the analysis. UV detection was done at 254 nm (0.05 AUFS), and an injection volume of 20 μL was used. In all cases studied, first-order kinetics for the disappearance of the test compounds were observed. The half-life is the time required for 50% conversion of the acylimidazolones to **1** and was calculated by using first-order kinetics. The results in Table I are the average of at least two separate determinations.

Determination of Half-Lives in Plasma. Stock solutions of **1**, **4a–d**, and a standard were prepared in 0.05 M NaH_2PO_4 with 0.1% H_3PO_4 to a final concentration of ca. 2 nm. A volume of 250 μL of the freshly prepared stock solutions was then diluted to 25 mL with fasted canine plasma. The sample was immersed in a 37 °C water bath during the experiment. Aliquots (1 mL) were withdrawn periodically and loaded onto a diol SPE column along with 100 μL of a 200 μM internal standard solution. Samples were eluted from the column with 1% CH_3CO_2H in CH_3OH and diluted with an equal volume of CH_3CN, and then after centrifugation the supernatent was evaporated under a nitrogen stream at 50–60 °C. Residues were redissolved in 1 mL of 0.05 M NaH_2PO_4 with 0.1% H_3PO_4 and analyzed by HPLC with a C-18 reverse-phase column using a gradient of 5%–60% CH_3CN to 0.05 M NaH_2PO_4 + 0.1% H_3PO_4 over 15 min, flow = 1.5 mL/min. The results in Table I are the average of at least two separate determinations.

Determination of Effects on Ferret Papillary Contracility. Experimental details for the determination of contractile responses in the isolated ferret papillary muscle are provided in reference 1.

Preparation and Assay of cAMP Phosphodiesterase. These studies were conducted according to the previously published method in reference 28.

Hemodynamic Measurements. Experimental details for the hemodynamic measurements in pentobarbital-anesthetized dogs are provided in reference 28.

Acknowledgment. We gratefully acknowledge some early synthetic contributions from Dr. B. Venepalli, the analytical contributions of Dr. C. A. Evans, G. Rudd, A. H. Kackensky, W. Zhong, and J. Traina, and the efforts of A. Smart, Dr. G. Hom, B. Touhey, M. Vogel, P. Bell, and W. Schutt in the pharmacological testing. We would also like to thank Dr. G. B. Phillips and Dr. M. Sullivan for their insightful discussions. The single crystal X-ray diffraction analysis of **4b** was performed by Dr. J. C. Huffman, Indiana University Molecular Structure Center.

Registry No. **1**, 101184-07-0; **1**·Na, 139199-23-8; **4a**, 116174-52-8; **4b**, 116174-51-7; **4b**·CH_3CN, 139199-24-9; **4c**, 139199-25-0; **4d**, 116174-53-9; **4e**, 116174-56-2; **5a**, 116174-42-6; **7**, 139199-26-1; **8**, 15414-82-1; **9**, 139199-27-2; **10**, 139199-28-3; **11**, 110369-25-0; **12**, 139199-29-4; **13**, 139199-30-7; acetic anhydride, 108-24-7; benzoic anhydride, 93-97-0; propionic anhydride, 123-62-6; isobutyric anhydride, 97-72-3; phenylacetic anhydride, 1555-80-2; *p*-fluorobenzoic acid, 456-22-4; 2-methylimidazole, 693-98-1.

Supplementary Material Available: Tables containing bond lengths, bond angles, fractional atomic coordinates and thermal parameters for **4b**, and information pertaining to oral and intraduodenal bioavailability, formulation, and dosage regimen studies (12 pages). Ordering information is given on any current masthead page.

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