4-Aroyl-1,3-dihydro-2*H*-imidazol-2-ones, a New Class of Cardiotonic Agents

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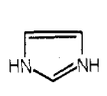
A series of 4-aroyl-1,3-dihydro-2*H*-imidazol-2-ones was synthesized and evaluated for pharmacological activity in the anesthetized dog. Most members of this series produced dose-related increases in cardiac contractile force as well as relatively minor increases in heart rate and decreases in systemic arterial blood pressure that were not blocked by propranolol. In general, 4-methoxy or 4-methylthiobenzoyl substitution afforded compounds of greatest inotropic potency. 1,3-Dihydro-4-(4-methoxybenzoyl)-5-methyl-2*H*-imidazol-one (**6**) was shown to produce a dose-related positive inotropic effect and reverse the depressant effect of pentobarbital on cardiac pump function in the dog heart–lung preparation. The cardiotonic activity of this series may have important utility in the treatment of congestive heart failure. 1,3-Dihydro-4-[4-(methylthio)benzoyl]-5-methyl-2*H*-imidazol-2-one (**17**) was chosen for human studies and is currently undergoing clinical trials.

After nearly 2 centuries the cardiac glycosides remain the basic treatment for congestive heart failure (first described by W. Withering in 1787). However, due to the life-threatening toxicity of the cardiac glycosides there exists a need for less toxic drugs. A continuing search for new cardiotonic agents in our laboratory has led to the discovery of 4-aroylimidazol-2-ones as cardioactive drugs.

Imidazole (**1**) and Ro 7-2956 (**2**) were recently reported



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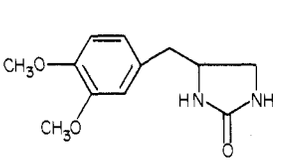

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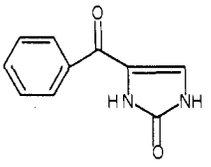

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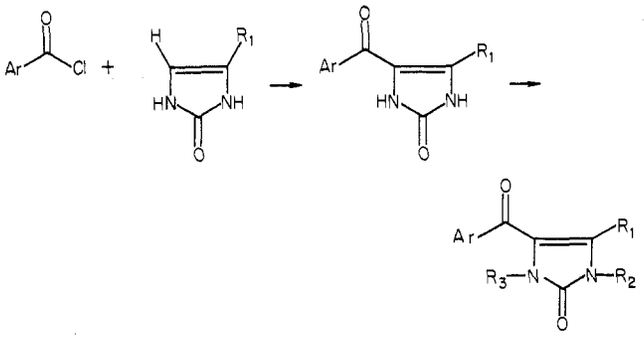
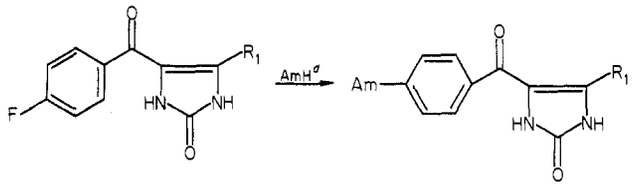
to increase myocardial contractility. Imidazole exerted a positive inotropic effect on spontaneously beating rabbit atria and isolated hearts that was not blocked by propranolol. It also produced changes in the frequency–force relationship similar to those produced by ouabain or by increasing the calcium concentration; hence, it was suggested that imidazole may act upon calcium turnover or calcium tissue levels.[1] Compound **2**, an inhibitor of cyclic nucleotide phosphodiesterases,[2] was reported to produce positive inotropic and chronotropic effects and peripheral vasodilation in dogs.[3] In isolated tissue preparations at low Ca^{2+} concentrations, compound **2** increased cardiac contractile force in a manner similar to the effect of increasing Ca^{2+} concentration. It was suggested that the compound was making more Ca^{2+} available to the contractile mechanism.

We envisioned that imidazole and **2** chelate with Ca^{2+} and in this manner deliver Ca^{2+} to active sites. Chemical changes that would increase the chelation potential thus might also increase the inotropic effect. Compounds that would appear to offer greater metal binding or chelating potential are the 4-aroylimidazol-2-ones. The parent compound **3** was first synthesized by Duschinsky and Dolan.[5] The synthesis of additional 4-aroylimidazol-2-ones is described in this paper. Pharmacological evaluation showed these compounds to indeed have strong cardiotonic activity.[6-10] The mechanism of cardiotonic activity has not been established. However, the primary compound (**17**) has been reported to be a potent inhibitor of a cAMP phosphodiesterase isozyme.[11] Whether this activity is solely responsible for the cardiotonic action is still under investigation.

Scheme I



Scheme II



[a] AmH = pyrrolidine, piperidine, *N*-methylpiperidine, morpholine, or dimethylamine.

Chemistry. The 4-aroylimidazol-2-ones were prepared by acylation of the appropriate 2(2*H*)-imidazolones[5,12,13] under Friedel–Crafts conditions according to Scheme I. The *N*-methyl compounds (**30** and **31**) were prepared by

(1) R. Knope, G. K. Moe, J. Saunders, and R. Tuttle, *J. Pharmacol. Exp. Ther.*, **185**, 29 (1973).
(2) C. Dalton, J. B. Quinn, C. R. Burkhart, and H. Sheppard, *J. Pharmacol. Exp. Ther.*, **173**, 270 (1970).
(3) M. W. Osborne, J. J. Wenger, and R. A. Moe, *J. Pharmacol. Exp. Ther.*, **1976**, 174 (1971).
(4) R. L. Kline and J. P. Buckley, *J. Pharmacol. Exp. Ther.*, **182**, 399 (1972).
(5) R. Duschinsky and L. A. Dolan, *J. Am. Chem. Soc.*, **67**, 2079 (1945).
(6) R. C. Dage, C. P. Hsieh, and N. L. Wiech, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **39**, 1105 (1980).
(7) C. P. Hsieh and R. C. Dage, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **39**, 1106 (1980).
(8) L. E. Roebel, H. C. Cheng, R. W. Lucas, R. J. Hodgeman, O. K. Reavis, and J. K. Woodward, *Pharmacologist*, **22**, 287 (1980).
(9) R. C. Dage, L. E. Roebel, C. P. Hsieh, D. L. Weiner, and J. K. Woodward, *J. Cardiovasc. Pharmacol.*, **4**, 500 (1982).
(10) L. E. Roebel, R. C. Dage, H. C. Cheng, and J. K. Woodward, *J. Cardiovasc. Pharmacol.*, in press.
(11) T. Kariya, L. J. Wille, and R. C. Dage, *J. Cardiovasc. Pharmacol.*, **4**, 509 (1982).
(12) R. Duschinsky and L. A. Dolan, *J. Am. Chem. Soc.*, **68**, 2350 (1946).
(13) The imidazolones, when not previously described, were obtained by analogy with literature procedures.

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methylation[14] with either 1 or 2 equiv of methyl iodide to give either the mono- or dimethyl compounds, respectively. Amination of the *p*-fluoro compound (**13**) with various secondary amines gave the *p*-amino compounds (**20–24**), as illustrated in Scheme II. Acylaton of the 4-aroylimidazol-2-ones with either acetic anhydride or isobutyric anhydride gave the respective *N*-acyl compounds (**32–35**). The phenolic compound (**14**) was prepared by demethylaton of the *p*-methoxy compound (**6**) with pyridine hydrochloride, whereas the ortho phenolic compound (**15**) formed spontaneously under Friedel–Crafts conditions during attempted preparation of the *o*-methoxy compound (see Experimental Section). The physical properties for all of the target compounds prepared are given in Table I.

Results and Discussion

Compounds **3–35** were screened intravenously in anesthetized dogs with a Walton–Brodie strain gauge arch sutured to the left ventricle of the heart to record contractile force and needle electrodes inserted subcutaneously to record a lead II electrocardiogram and heart rate. Additionally, blood pressure was recorded from a cannula inserted into the abdominal aorta. Dose–response curves were determined with at least three doses of each compound. The dose of each compound to increase cardiac contractile force by 30%, to increase heart rate by 15%, and to decrease blood pressure by 20% was recorded and is shown in Table I. Compound **3** produced increases in cardiac contractile force and heart rate and a decrease in blood pressure rather nonselectively, and 4-hydroxy (**14**), alkoxy (**5–9**), halogen (**10–13**), alkylthio (**16–19**), or dimethylamino (**24**) substitution of the 4-aroyl moiety markedly increased potency and inotropic selectivity.

Additionally, replacement of the 4-aroyl moiety of compounds **3** and **4** with 4-thienoyl (**25** and **26**) enhanced potency and inotropic selectivity, whereas substitution with 4-furoyl (**28** and **29**) was less effective in this regard. Among these compounds, it is apparent also that 5-methyl-substituted compounds (**4, 6, 17, 26,** and **29**) were consistently more potent inotropic agents than their normethyl analogues (**3, 5, 16, 25,** and **28**), and increasing this 5-substituent to ethyl in some cases further increased inotropic potency (compare componds **6** and **7**, **8** and **9**, **17** and **18**), although this was not always the case (**26** vs. **27**). The influence of increasing the size of the 5-alkyl substituent is apparent when comparing the positive inotropic activity of compounds **16–19**. Activity increases with size (**16** < **17** < **18**) until the substituent is *n*-propyl (**19**); then it begins to decrease. Analogues in which one or both imidazole ring N atoms are alkylated (**30** and **31**) were much less active than the unsubstituted compound (**6**). This finding indicates that a free imidazole NH is required for meaningful inotropic activity. The N-acylated analogues **32–35** retained some or all of the activity of the unsubstituted analogues (**2, 13,** and **24**) possibly due to in vivo deacetylation.

Compounds **6, 17,** and **18** were among the most potent positive inotropic compounds tested and were studied in some detail. The cardiovascular effects in anesthetized dogs of the most potent compound (**18**) are shown in Figure 1. Intravenous doses of 0.1, 0.3, and 1.0 mg/kg produced dose-related increases in cardiac contractile force lasting for 39–86 min. Additionally, it produced relatively small increases in heart rate and blood pressure. The other compounds had identical effects, although they were somewhat less potent. Compound **6** produced the same effects when given intravenously or intraduodenally to anesthetized dogs in doses of 0.3 to 10 mg/kg. These effects were not altered by a dose of propranolol that produced marked inhibition of an equiactive dose of isoproterenol, indicating that stimulation of β_1- or β_2-adrenergic receptors were not involved (Table II). Additionally, other in vivo and in vitro studies have shown that stimulation of histamine receptors (H_1, H_2) is not involved in the inotropic and hypotensive actions of compound **6** (data not shown).

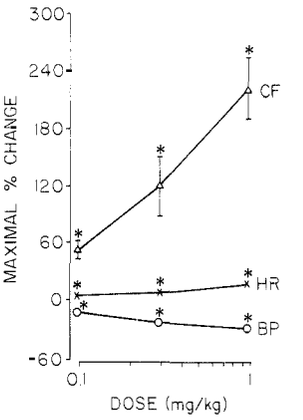


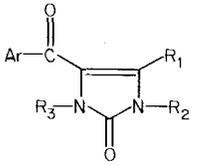
Figure 1. Effects of 1,3-dihydro-4-[4-(methylthio)benzoyl]-5-ethyl-2*H*-imidazol-2-one (**18**) on cardiac contractile force (CF), heart rate (HR), and mean systemic blood pressure (BP) in anesthetized dogs. Shown are means and standard errors of the maximal effect observed in 10 min. Each dose was given iv to five dogs. An asterisk indicates a significant effect by Student's *t* test ($p < 0.05$). Pretreatment CF, HR, and BP values for the 0.1, 0.3, and 1.0 mg/kg treatment groups were 132 ± 11, 113 ± 11, and 114 ± 6 g; 137 ± 3.4, 138 ± 7, and 145 ± 8 beats/min; 107 ± 7, 100 ± 7, and 112 ± 6 mmHg, respectively.

In order to ascertain whether **6** would improve the pump function of the heart in normal and failing hearts, it was examined in the dog heart–lung preparation with venous return and aortic blood pressure kept constant. In normal hearts, the addition of 0.3, 1, or 3 mg/kg of compound **6** to the venous blood resevoir produced significant increases in cardiac contractile force, heart rate, and cardiac output and decreases in stroke volume and left atrial pressure (Table III). Since the heart–lung preparation is not subject to nervous or hormonal influences, these effects of compound **6** resulted from a direct action on the heart. The small decrease in stroke volume observed in spite of the increase in cardiac contractile force undoubtedly resulted from the increase in heart rate, reducing diastolic filling time. The increase in cardiac output and the decrease in left atrial pressure indicated an increase in cardiac pump function. Additionally, the proportionately larger decrease in left atrial pressure than stroke volume, particularly with the 0.3 mg/kg dose of compound **6**, indicated a true cardiotonic effect of this drug.

It is well accepted that cardiotonic drugs, such as the cardiac glycosides, are more effective in failing hearts than normal hearts. In order to ascertain whether compound **6** was similar to the cardiac glycosides in this regard, we elicited heart failure in dog heart–lung preparations by adding a myocardial depressant dose of pentobarbital (20 mg/kg) to the blood reservoir. Pentobarbital significantly decreased cardiac contractile force, heart rate, cardiac output, stoke volume, and stroke work and increased left atrial pressure (Table IV). Addition of 1 mg/kg of compound **6** to the venous blood reservoir 10 min after pentobarbital reversed the depressant effects of pentobarbital. Increases in cardiac output and stroke volume, together

(14) R. A. W. Johnstone and M. E. Rose, *Tetrahedron*, **35**, 2169 (1979).

Table I. 4-Aroyl-1,3-dihydro-2*H*-imidazol-2-ones: Effect on Cardiac Contractile Force, Heart Rate, and Blood Pressure in Anesthetized Dogs



no.	Ar	R_1	R_2	R_3	yield, %	formula	mp, °C (recrystn solvent)[a]	anal.	equieffective dose,[b] mg/kg iv: contractile force, +30%	heart rate, +15%	blood pressure, −20%	no. of dogs
3	C_6H_5	H	H	H	54	$C_{10}H_8N_2O_2$	329-330 dec (A)	C, H, N	3.91	4.00	4.40	1
4	C_6H_5	CH_3	H	H	67	$C_{11}H_{10}N_2O_2$	253-255 dec (B)	C, H, N	0.23	1.55	2.55	1
5	C_6H_4-4-OCH_3	H	H	H	19	$C_{11}H_{10}N_2O_3$	315-317 dec (C)	C, H, N	0.78	1.85	3.10	1
6	C_6H_4-4-OCH_3	CH_3	H	H	26	$C_{12}H_{12}N_2O_3$	255-257 dec (C)	C, H, N	0.16	0.40	0.65	23
7	C_6H_4-4-OCH_3	C_2H_5	H	H	27	$C_{13}H_{14}N_2O_3$	232-234 dec (C)	C, H, N	0.15	0.23	0.62	1
8	C_6H_3-3,4-$(OCH_3)_2$	CH_3	H	H	32	$C_{13}H_{14}N_2O_4$	257-259 dec (B)	C, H, N	0.40	1.05	2.00	1
9	C_6H_3-3,4-$(OCH_3)_2$	C_2H_5	H	H	7	$C_{14}H_{16}N_2O_4$	223-225 dec (B)	C, H, N	0.18	>3.00	2.35	1
10	C_6H_4-4-Cl	CH_3	H	H	52	$C_{11}H_9ClN_2O_2$	291-293 dec (D)	C, H, N	0.18	4.00	0.29	1
11	C_6H_4-2-Cl	CH_3	H	H	29	$C_{11}H_9ClN_2O_2$	300-303 dec (E)	C, H, N	0.48	2.20	2.10	1
12	C_6H_3-3,4-Cl_2	CH_3	H	H	21	$C_{11}H_8Cl_2N_2O_2$	307-309 dec (F)	C, H, N	0.70	4.00	2.10	1
13	C_6H_4-4-F	CH_3	H	H	20	$C_{11}H_9FN_2O_2$	289-291 dec (E)	C, H, N	0.38	>3.00	1.03	3
14	C_6H_4-4-OH	CH_3	H	H	12	$C_{11}H_{10}N_2O_3$	>300 dec (E)	C, H, N	0.25	1.30	2.60	1
15	C_6H_4-2-OH	CH_3	H	H	41	$C_{11}H_{10}N_2O_2$	243-245 dec (E)	C, H, N	3.28	>10.00	4.50	2
16	C_6H_4-4-SCH_3	H	H	H	61	$C_{11}H_{10}N_2O_2S$	>330 dec (B)	C, H, N	0.50	1.05	pressor	1
17	C_6H_4-4-SCH_3	CH_3	H	H	51	$C_{12}H_{12}N_2O_2S$	255-258 dec (E)	C, H, N, S	0.12	1.50	0.55	5
18	C_6H_4-4-SCH_3	C_2H_5	H	H	24	$C_{13}H_{14}N_2O_2S$	223-224 dec (B)	C, H, N	0.07	0.54	0.28	5
19	C_6H_4-4-SCH_3	n-C_3H_7	H	H	23	$C_{14}H_{16}N_2O_2S$	208-210 dec (C)	C, H, N	1.13	3.00	2.30	1
20	C_6H_4-4-$N(CH_2CH_2)_2$	CH_3	H	H	26	$C_{15}H_{17}N_3O_2$	>310 dec (E)	C, H, N	>10.0	8.50	4.50	1
21	C_6H_4-4-$N(CH_2CH_2)_2CH_2$	CH_3	H	H	84	$C_{16}H_{19}N_3O_2$	260-263 dec (E)	C, H, N	>10.0	>10.0	>10.0	1
22	C_6H_4-4-$N(CH_2CH_2)_2NCH_3$	CH_3	H	H	26	$C_{16}H_{20}N_4O_2$	>305 dec (E)	C, H, N	>10.0	9.10	>10.0	1
23	C_6H_4-$N(CH_2CH_2)_2O$	CH_3	H	H	60	$C_{15}H_{17}N_3O_3$	283-286 dec (E)	C, H, N	1.20	>10.0	6.40	1
24	C_6H_4-4-$N(CH_3)_2$	CH_3	H	H	82	$C_{13}H_{15}N_3O_2$	>310 dec (E)	C, H, N	0.36	2.20	>3.00	1
25	2-C_4H_3S	H	H	H	60	$C_8H_6N_2O_2S$	338-340 dec (C)	C, H, N	0.72	>10.00	3.70	1
26	2-C_4H_3S	CH_3	H	H	16	$C_9H_8N_2O_2S$	213-215 dec (J)	C, H, N	0.28	5.40	2.50	5
27	2-C_4H_3S	C_2H_5	H	H	45	$C_{10}H_{10}N_2O_2S$	209-211 dec (C)	C, H, N	0.41	1.45	1.60	2
28	2-C_4H_3O	H	H	H	35	$C_8H_6N_2O_3$	318-320 dec (A)	C, H, N	1.84	4.30	4.20	1
29	2-C_4H_3O	CH_3	H	H	34	$C_9H_8N_2O_3$	211-213 dec (I)	C, H, N	1.05	3.30	0.72	1
30	C_6H_4-4-OCH_3	CH_3	CH_3	CH_3	39	$C_{14}H_{16}N_2O_3$	109-111 (C)	C, H, N	4.70	>10.0	2.60	1
31	C_6H_4-4-OCH_3	CH_3	CH_3(H)	H(CH_3)	28	$C_{13}H_{14}N_2O_3$	225-227 (I)	C, H, N	>10.0	>10.0	>10.00	1
32	C_6H_5	CH_3	$COCH_3$	$COCH_3$	82	$C_{15}H_{14}N_2O_4$	120-122 (B)	C, H, N	3.00	>10.0	6.50	1
33	C_6H_4-4-F	CH_3	$COCH_3$	$COCH_3$	94	$C_{15}H_{13}FN_2O_4$	102-103 (C)	C, H, N	1.00	>8.00	2.50	1
34	C_6H_4-4-$N(CH_3)_2$	CH_3	$COCH_3$	$COCH_3$	79	$C_{17}H_{19}N_3O_4$	183-184 (B)	C, H, N	0.36	>3.00	>3.00	1
35	C_6H_4-4-$N(CH_3)_2$	CH_3	$COCH(CH_3)_2$	$COCH(CH_3)_2$	70	$C_{21}H_{27}N_3O_4$	161-163 (H)	C, H, N	2.45	>10.00	>10.00	1

[a] A = MeOH/H_2O; B = EtOH; C = EtOH/H_2O; D = MeCN/H_2O; E = *i*-PrOH/H_2O; G = EtOAc/hexane; H = EtOAc; I = MeOH; J = *i*-PrOH. [b] Equieffective doses were obtained by extrapolation from a dose–response curve obtained with iv injections of at least three doses of each compound. Where more than one determination was made, value shown is the geometric mean.

Table II. Lack of Inhibition by Propranolol of the Cardiovascular Effects of 1,3-Dihydro-4-(4-methoxybenzoyl)-5-methyl-2*H*-imidazol-2-one (6)[a]

treatment group	agonist	cardiac contractile force		mean arterial BP	
		control, g	change, %	control, mmHg	change, %
control, $N = 6$	isoproterenol, 0.1 μg/kg, iv	137 ± 12	133 ± 16	96 ± 8	−27 ± 2
	compd 6, 1 mg/kg, iv	132 ± 14	127 ± 13	98 ± 8	−27 ± 4
propranolol, 0.5 mg/kg, iv, $N = 6$	isoproterenol, 0.1 μg/kg, iv	82 ± 17[b]	19 ± 5[b]	96 ± 8	−1 ± 1[b]
	compd 6, 1 mg/kg, iv	89 ± 17	144 ± 33	97 ± 8	−33 ± 4

[a] Shown are means and standard errors. [b] A significant difference from comparable control group value by Student's *t* test, $p < 0.05$.

Table III. Effect of 1,3-Dihydro-4-(4-methoxybenzoyl)-5-methyl-2*H*-imidazol-2-one (6) in the Dog Heart–Lung Preparation[a]

measurement	dose, μg/kg	*n*	control	change[b]	% change
cardiac contractile force, g	0.3	5	71.8 ± 6.8	62.0 ± 4.4[c]	88 ± 7
	1.0	8	80.1 ± 1.6	96.7 ± 6.2[c]	121 ± 7
	3.0	5	74.2 ± 4.7	128.9 ± 7.7[c]	179 ± 19
heart rate, beats/min	0.3	5	154 ± 7	22 ± 1[c]	14 ± 0.3
	1.0	8	154 ± 4	35 ± 3[c]	23 ± 1
	3.0	5	150 ± 3	41 ± 5[c]	28 ± 4
cardiac output, mL/min	0.3	5	1088 ± 31	37 ± 7[c]	3 ± 1
	1.0	8	1079 ± 34	28 ± 11[c]	3 ± 1
	3.0	5	1019 ± 74	46 ± 10[c]	4 ± 1
stroke volume, mL	0.3	5	7.1 ± 0.3	−0.7 ± 0.1[c]	−10 ± 1
	1.0	8	7.0 ± 0.3	−1.1 ± 0.1[c]	−16 ± 2
	3.0	5	6.8 ± 0.5	−1.2 ± 0.2[c]	−18 ± 3
left atrial pressure, mmHg	0.3	5	3.1 ± 0.5	−1.6 ± 0.6[c]	−49 ± 14
	1.0	8	2.8 ± 1.0	−1.2 ± 0.4[c]	−31 ± 10
	3.0	5	3.2 ± 0.7	−1.1 ± 0.7	−43 ± 23

[a] Shown are means and standard errors. [b] Measurements made 10 min after addition of 6 to the blood reservoir. [c] A significant change from control by paired Student's *t* test, $p < 0.05$. Additionally, there was a significant linear dose–response curve for cardiac contractile force and heart rate by regression analysis.

Table IV. Reversal of Pentobarbital-Induced Heart Failure by 1,3-Dihydro-4-(4-methoxybenzoyl)-5-methyl-2*H*-imidazol-2-one (6) in the Dog Heart–Lung Preparation[a]

measurement	control	pentobarbital, 20 mg/kg	pentobarbital, 20 mg/kg, 6, 1 mg/kg[b]
cardiac contractile force, g	84.2 ± 4.5	32.2 ± 6.8[c]	88.0 ± 9.4[d]
heart rate, beats/min	145 ± 5	133 ± 4[c]	151 ± 3[d]
cardiac output, mL/min	1102 ± 59	613 ± 82[c]	1053 ± 46[d]
stroke volume, mL	7.6 ± 0.4	4.6 ± 0.6[c]	7.0 ± 0.3[d]
left atrial pressure, mmHg	0.5 ± 0.4	12.1 ± 1.7[c]	2.6 ± 0.6[d]
stroke work, g-m	8.7 ± 0.6	3.0 ± 0.6[c]	7.7 ± 0.4[d]

[a] Shown are means and standard errors from five preparations. Heart failure was produced by the addition of 20 mg/mL of pentobarbital to the blood reservoir. [b] Measurements made 10 min after addition of compound 6 to the blood reservoir. [c] Significant change from control value by analysis of variance, $p < 0.05$. [d] Significant change from pentobarbital value by analysis of variance, $p < 0.05$.

with a decrease in left atrial pressure, indicated a marked increase in cardiac pump function and a reversal of the pentobarbital-induced heart failure.

The results of these studies indicate that compound **6** is a potent, positive inotropic drug that acts directly on the heart. The positive inotropic effect of compound **6** was usually accompanied by a relatively minor positive chronotropic effect and a brief hypotensive effect in anesthetized dogs. None of the cardiovascular effects of compound **6** were blocked by propranolol; hence, they do not involve β-adrenergic receptor stimulation. Compound **6** reversed the depressant effect of pentobarbital on cardiac function in the dog heart–lung preparation. Additionally, compound **6** was reported to reverse the hemodynamic characteristics of heart failure produced by propranolol in anesthetized dogs.[7] Other studies have confirmed these activities of compound **6** and extended them to compound **17**.[6-10] Further work is in progress to elucidate the mechanism of action of compound **17**. Recently, compound **17** was reported to be a potent and partially competitive inhibitor of cAMP phosphodiesterase,[11] but whether this is its mechanism of positive inotropic activity has not yet been established.

Conclusion

Based on these results, the 4-aroyl-1,3-dihydro-2*H*-imidazol-2-ones represent a new class of cardiotonic agents. In-depth studies with two (**6** and **17**) of these compounds suggest their potential utility in the treatment of congestive heart failure. Clinical trails with compound **17** (MDL 17,043) are in progress.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR and NMR spectra were obtained for all compounds and were consistent with assigned structures. IR spectra were recorded with a Perkin-Elmer 521 insrument. NMR spectra were recorded with a Varian Associates A60-A instrument with tetramethylsilane as the internal standard. Elemental analyses were within 0.4% of theoretical values when indicated by symbols of the elements.

1,3-Dihydro-4-(4-methoxybenzoyl)-5-methyl-2*H*-imidazol-2-one (6, Table I). To a stirred mixture of 19.6 g (0.2 mol) of 1,3-dihydro-4-methyl-2*H*-imidazol-2-one,[5] 53.2 g (0.4 mol) of anhydrous aluminum chloride, and 150 mL of nitrobenzene was added dropwise, over 10 min, 34.2 g (0.2 mol) of 4-methoxylbenzoyl chloride. The mixture was stirred at 60–65 °C for 6 h and then poured onto 1 kg of ice. The resulting precipitate was washed with diethyl ether and water and was recrystallized from ethanol/water to give 12 g (26%) of **6**: mp 255–257 °C; NMR (Me_2SO-d_6) δ 7.60 (d, 2, J = 10 Hz), 6.95 (d, 2, J = 10 Hz), 3.80 (s, 3), 1.90 (s, 3). The compound dissolves in 0.1 N NaOH but not in K_2CO_3 solution.

Compounds **3–5**, **7–19**, and **25–29** were prepared by this method.

1,3-Dihydro-4-(2-hydroxybenzoyl)-5-methyl-2*H*-imidazol-2-one (15, Table I). To a mixture of 46.5 g (0.35 mol) of anhydrous aluminum chloride and 17.1 g (0.175 mol) of 1,3-dihydro-4-methyl-2*H*-imidazol-2-one[5] in 100 mL of nitrobenzene was added dropwise, over 15 min, 29.8 g (0.175 mol) of *o*-methoxybenzoyl chloride. The mixture was stirred for 6 h at 60–65 °C and then poured onto 2 kg of ice. The resulting solid was collected, washed with water and ether and recrystallized from 2-propanol–water to give 15.8 g of **15**, mp 243–245 °C.

1,3-Dihydro-4-methyl-5-[4-(1-piperidinyl)benzoyl]-2*H*-imidazol-2-one (21, Table I). A suspension of 11.0 g (0.05 mol) of 1,3-dihydro-4-(4-fluorobenzoyl)-5-methyl-2*H*-imidazol-2-one (**13**) in 30 mL of piperidine was stirred at reflux temperature for 24 h. Excess piperidine was evaporated under reduced pressure, and the residue was recrystallized twice from a mixture of 2-propanol and water to give 11.9 g of **21**, mp 260–263 °C.

4-(4-Methoxybenzoyl)-1,3,5-trimethyl-2*H*-imidazol-2-one (30, Table I). In 15 mL of Me_2SO were suspended 1.90 g (0.034 mol) of KOH and 1.0 g (0.0043 mol) of compound **6**. Methyl iodide (2.44 g, 0.017 mol) was added, and the mixture was stirred at room temperature for 30 min. A solution developed, which was diluted with water and extracted with CH_2Cl_2. The organic extract was washed with water and dried over $MgSO_4$. Evaporation of solvent gave 1.11 g of crude **30**, which was recrystallized from ethanol–water to give 0.43 g (39%) of **30**, mp 109–111 °C.

1,3-Diacetyl-4-(4-fluorobenzoyl)-5-methyl-2*H*-imidazol-2-one (34, Table I). A mixture of 28.0 g (0.127 mol) of **13** and 150 mL of acetic anhydride was stirred at reflux temeprature for 4 h (after 2 h, 50 mL of the solvent was distilled off and an additional 50 mL was added). The solvent was evaporated, and the residue was crystallized from EtOAc/hexane (1:1.5) to give 36.3 g (94%) of **34**, mp 102–103 °C.

Pharmacological Methods. Dogs of either sex, weighing 9–23 kg, were anesthetized with 35 mg/kg iv of sodium pentobarbital. The lungs were ventilated artificially with a Bird Mark 7 respirator following tracheal intubation. The left femoral vein was cannulated for the injection of drugs. The left femoral artery was cannulated, and the cannula was advanced into the thoracic aorta to measure systemic blood pressure. Blood pressure was recorded with a pressure transducer (Statham P23GC). The chest was opened at the left fifth intercostal space, and the pericardium was cut to expose the heart. A calibrated Walton–Brodie strain gauge arch was sutured to the left ventricle to record cardiac contractile force. Heart rate was recorded from the EKG (lead II) with a tachograph (Grass, 7D). The dogs were allowed to stabilize for at least 30 min following surgical preparation. Mesurements of cardiac contractile force, heart rate, and blood pressure were made before and at 5- to 10-minute intervals after drug administration for 90–300 min.

Experimental compounds were given intravenously or intraduodenally by injection. Only one compound was administered to any one animal. Where animals were given different intravenous doses of the same drug, sufficient time was allowed between doses for the variables to return completely to basal levels. Equieffective doses were obtained by extrapolation from dose–response curves.

The heart–lung preparation employed was similar to that described by Somani and Bachand.[15] Mongrel dogs of either sex, weighing 11–19 kg, were used. They were anesthetized with 35 mg/kg iv of sodium pentobarbital and prepared for recording blood pressure, heart rate, and cardiac contractile force as described above, except the strain gauge arch was sutured to the right ventricle. Mean systemic blood pressure (BP) was recorded from the aortic cannula. Additionally, left atrial pressure (LAP) was measured with a pressure transducer (Statham, P23BC) attached to a cannula placed in the left atrium. Aortic blood flow was measured extracorporeally with a flow meter (Biotronex, Model BL610). Cardiac output was taken as aortic blood flow, which does not include coronary arterial inflow. Stroke volume (SV) was estimated as the quotient of cadiac output and heart rate, and stroke work was calculated by [BP (mmHg) – LAP (mmHg)]SV (mL) × 0.0136. In this preparation, the heart and lungs were vascularily isolated and perfused in situ from an extracorporeal circuit. Briefly, blood is pumped by the heart into the extracorporeal circuit via an aortic cannula; it is returned to the heart via a cannula in the superior vena cava. The extracorporeal circuit contained a blood reservoir containing 800 mL of blood. The height of blood in the reservoir above the right atrium determined venous return, and it was maintained constant. The entire extracorporeal blood volume was about 1200 mL. At the beginning of each experiment, systemic blood pressure was set between 75 and 90 mmHg by adjustment of aortic resistance; cardiac output was set by adjustment of venous return so that it was about two-thirds of that expected based on the dog's weight (100 mL/kg). Under those conditions, the column of blood in the reservoir was maintained at 18–25 cm above the right atrium. Measurements were recorded continuously on a polygraph (Grass, Model 7B). All drugs were added to the reservoir.

All experimental compounds were dissolved in normal saline or 1 N NaOH and normal saline, pH 12–13. Isoproterenol was dissolved in normal saline containing 0.01% ascorbic acid.

Data are expressed as means and standard errors. Statistical analysis of the data was performed using a Student's t test for paired or unpaired data[16] or an analysis of variance and Dunnets test.[17]

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