HCl, 81000-67-1; BOC-Chg-His(DNP)-Pro-Lac-OBzl, 109183-74-6; H-Chg-His(DNP)-Pro-Lac-OBzl·HCl, 109183-75-7; BOC-Tyr-(Bzl)-OPFp, 55878-15-4; BOC-Tyr(Bzl)-Chg-His(DNP)-Pro-Lac-OBzl, 109183-76-8; H-Tyr(Bzl)-Chg-His(DNP)-Pro-Lac-OBzl·HCl, 109183-77-9; BOC-Val-OPfp, 50903-49-6; BOC-Val-Tyr(Bzl)-Chg-His(DNP)-Pro-Lac-OBzl, 109183-78-0; H-Val-Tyr(Bzl)-Chg-His(DNP)-Pro-Lac-OBzl·HCl, 109183-79-1; BOC-Arg(NO_2)-OPFp, 57866-90-7; BOC-Arg(NO_2)-Val-Tyr(Bzl)-Chg-His(DNP), 109183-80-4; Pro-lac-OBzlH-Arg(NO_2)-Val-Tyr-(Bzl)-Chg-His(DNP)-Pro-Lac-OBzl·HCl, 109183-81-5; Z-Sar-OPFp, 80909-58-6; Z-Sar-Arg(NO_2)-Val-Tyr(Bzl)-Chg-His-Pro-Lac-OBzl, 109183-82-6; zinc lactate, 16039-53-5.

Cardiotonic Agents. 6. Synthesis and Inotropic Activity of 2,4-Dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-3*H*-pyrazol-3-ones: Ring-Contracted Analogues of Imazodan (CI-914)

Ila Sircar,*† Glenn C. Morrison,† Sandra E. Burke,‡ Richard Skeean,† and Ronald E. Weishaar‡

Departments of Chemistry and Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105. *Received January 12, 1987*

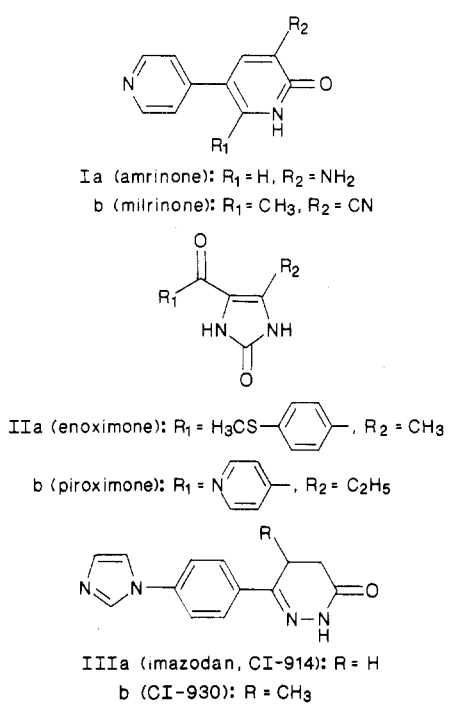
A series of 2,4-dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-3*H*-pyrazol-3-ones was synthesized and evaluated for positive inotropic activity. Only compounds with two small alkyl groups at C-4 showed significant activity. The structure–activity relationships for optimal inotropic activity are presented and compared with those of the 4,5-dihydro-3(2*H*)-pyridazinone series. The phosphodiesterase inhibitory activity is also reported and correlated with the substitution pattern at C-4 in the pyrazolone ring.

Recently several noncatecholamine, nonglycoside cardiotonic agents have been discovered that possess both inotropic and vasodilator activities.[1,2] Prototypical compounds have emerged from three different classes of potent inotropes. These are (i) 5-aryl-2(1*H*)-pyridinones, such as amrinone (Ia, Chart I)[3,4] and milrinone (Ib),[5,6] (ii) 5-aroyl-1,3-dihydro-2*H*-imidazol-2-ones, such as enoximone (IIa),[7,8] and piroximone (IIb),[9,10] and (iii) 6-aryl-4,5-dihydro-3(2*H*)-pyridazinones, namely, imazodan (CI-914, IIIa) and CI-930 (IIIb).[11,12] Although the pharmacological profiles of these newer agents appear to be similar in animal models, there exists a difference in the potency and relative balance of the inotropic and vasodilator activities.[1,2]

The positive inotropic and vascular relaxant actions of these agents are apparently due to their selective inhibitory effects on the cyclic AMP specific form of phosphodiesterase (PDE III) present in cardiac and vascular muscle.[13,14] The potent activity of 4,5-dihydro-6-[(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinones led us to investigate the corresponding five-membered analogues, namely, 2,4-dihydro-3*H*-pyrazol-3-ones.

The potential therapeutic utility of several 2,4-dihydro-5-phenyl-3*H*-pyrazol-3-ones (IV) in the treatment of hypertension, inflammation, arrhythmia, and analgesia has recently been reported.[15,16] It has also been shown that 4-unsubstituted (or monosubstituted) pyrazol-3-ones exist in several tautomeric forms (Chart II, A–D).[17,18] By contrast, 4,4-disubstituted analogues can only exist in the keto form (E). The essential features required for inotropic activity in several series of PDE inhibitors have been identified both from qualitative and quantitative structure–activity relationships.[12,19] Two key elements necessary for inotropic activity are (i) a polar group and (ii) an acidic hydrogen adjacent to the polar group (for example, CO–NH). On the basis of these observations, we reasoned that the inotropic activity in the 5-(substituted phenyl)-3*H*-pyrazol-3-one series would reside in the 4,4-disubstituted compounds that only exist in the keto form (E) To test this hypothesis, we prepared a number of 5-(substituted phenyl)-3*H*-pyrazol-3-ones having different substituents at the 4-position of the pyrazolone ring[20] and evaluated the pharmacological activity. This paper reports

Chart I

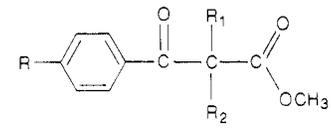


† Department of Chemistry.
‡ Department of Pharmacology.

(1) Tommaso, C. L. *Am. J. Med.* **1986**, *80* (Suppl 28), 36.
(2) Colucci, W. L.; Wright, R. P.; Braunwald, E. *N. Engl. J. Med.* **1986**, *314*, 349.
(3) Farah, A. F.; Alousi, A. A.; Schwartz, R. P. *Annu. Rev. Pharmacol. Toxocol.* **1984**, *24*, 275.
(4) Millard, R. W.; Duke, G.; Grupp, G.; Grupp, I.; Alousi, A. A.; Schwartz, A. *J. Mol. Cell. Cardiol.* **1982**, *12*, 647.
(5) Jaski, B. E.; Filer, M. A.; Wright, R. F.; Braunwald, E.; Colucci, W. S. *J. Clin. Invest.* **1985**, *75*, 643.
(6) Ureid, B. I.; Generalovich, T.; Reddy, P. S.; Spangenherg, R. B.; Follander, W. P. *Circulation* **1983**, *67*, 823.
(7) Strain, J.; Grose, R.; Maskin, C. S.; Lejemtel, T. H. *Am. Heart. J.* **1985**, *110*, 91.
(8) Shah, P. K.; Amin, D. K.; Hulse, S.; Shellock, F.; Swan, H. J. *Circulation* **1985**, *71*, 326.
(9) Roebel, L. E.; Dage, R. C.; Cheng, H. C.; Woodward, J. K. *J. Cardiovasc. Pharmacol.* **1984**, *6*, 43.

0022-2623/87/1830-1724$01.50/0

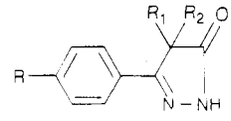
Table I. 4-(1*H*-Imidazol-1-yl)-β-oxobenzenepropanoic Acid Methyl Esters



compd	R	R_1	R_2	mp, °C	crystn solvent[a]	yield,[b] %	formula[c]
3a	Im	H	CH_3	103–104	B	41	$C_{14}H_{14}N_2O_3$
3b	Im	H	CH_2CH_3	68–69	B	29	$C_{15}H_{16}N_2O_3$
3c	Im	H	$(CH_2)_5CH_3$	163–164	B/A	75	$C_{19}H_{23}N_2O_3$·HCl
3d	Im	H	CH_2Ph	94–95	B	30	$C_{20}H_{18}N_2O_3$
4a	Im	CH_3	CH_3	91–92	B	64	$C_{15}H_{16}N_2O_3$
4b	Im	CH_3	CH_2CH_3	164–166	A/B	77	$C_{16}H_{18}N_2O_3$·HCl
4c	Im	CH_3	CH_2Ph	oil	B	32	$C_{21}H_{20}N_2O_3$
4d	Im	CH_2CH_3	CH_2CH_3	163–164	A	25	$C_{17}H_{20}N_2O_3$·HCl
4e	Im	$-(CH_2)_4-$		oil		64	$C_{17}H_{18}N_2O_3$
4f	THBIm	CH_3	CH_3	oil	B	91	$C_{19}H_{22}N_2O_3$
4g	SCH_3	CH_3	CH_3	oil		35	$C_{13}H_{19}SO_3$
4h[d]	4-Py	CH_3	CH_3	oil		62	$C_{11}H_{13}N_3O$
4i	Im	CH_2Ph	CH_2Ph	146.5–147.5	B	10	$C_{27}H_{24}N_2O_3$
4k	Im	$-(CH_2)_5-$		oil		55	$C_{18}H_{20}N_2O_3$
4j	BIm	CH_3	CH_3	oil		90	$C_{15}H_{18}N_2O_3$

[a] A = ethanol, B = isopropyl ether, C = ethyl acetate. [b] Yields are not optimized. [c] The analyses were within 0.4% of the calculated value except for **3c**. Compounds **4e–h,i,k** were purified via chromatography over silica gel and were not analyzed. Starting material for **4g** was prepared by following the literature procedure.[24] [d] 4-Py for RC_6H_4.

Table II. 2,4-Dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-3*H*-pyrazol-3-ones



compd	R	R_1	R_2	mp, °C	crystn solvent[a]	yield,[b] %	formula[c]
5	Im	H	H	306 dec	A	82	$C_{12}H_{10}N_4O$
6a	Im	H	CH_3	309 dec	A	77	$C_{13}H_{12}N_4O$
6b	Im	H	CH_2CH_3	285 dec	A/B	83	$C_{14}H_{14}N_4O$
6c	Im	H	$(CH_2)_5CH_3$	223–235	C	56	$C_{18}H_{22}N_4O$
6d	Im	H	CH_2Ph	285	A/B	72	$C_{19}H_{16}N_4O$
7a	Im	CH_3	CH_3	170–171	A/B	70	$C_{14}H_{14}N_4O$
7b	Im	CH_3	CH_2CH_3	86–88	C	71	$C_{15}H_{16}N_4O_3 \cdot {}^1/_2C_4H_8O_2$
7c	Im	CH_3	CH_2Ph	214–215	A/B	10	$C_{20}H_{18}N_4O$
7d	Im	CH_2CH_3	CH_2CH_3	162–163	B	57	$C_{16}H_{18}N_4O$
7e	Im	$-(CH_2)_4-$		225–226	A/B	83	$C_{16}H_{16}N_4O$
7f	THBIm	CH_3	CH_3	245–246	A	59	$C_{18}H_{20}N_4O$
7g	SCH_3	CH_3	CH_3	146–148	A	62	$C_{12}H_{14}N_2OS$
7h[d]	4-Py	CH_3	CH_3	306 dec	A	34	$C_{10}H_{11}N_3O$
7i	Im	CH_2Ph	CH_2Ph	>280	A	5	$C_{26}H_{22}N_4O$
7j	BIm	CH_3	CH_3	301–304	A	39	$C_{18}H_{16}N_4O$
7k	Im	$-(CH_2)_5-$		184–185	A/B	79	$C_{17}H_{18}N_4O$
7l	$SOCH_3$	CH_3	CH_3	177–179	A	80	$C_{12}H_{14}N_2O_2Sz$

[a] A = ethanol, B = isopropyl ether, C = ethyl acetate. [b] Yields are not optimized. [c] The analyses were within 0.4% of the calculated value. [d] 4-Py for RC_6H_4.

the results that confirmed the above hypothesis and discloses the syntheses and activities of a new series of inotropes, namely, 5-aryl-2,4-dihydro-4,4-dimethyl-3*H*-pyrazol-3-ones.

Chemistry

2,4-Dihydro-5-(4-substituted phenyl)-3*H*-pyrazol-3-ones (**5**, **6a–d**, **7a–k**, Table II) were obtained by treatment of the requisite β-keto esters (**2**, **3a–d**, **4a–k**, Table I) with hydrazine (Scheme I). Compound **7l** was obtained by oxidation of the corresponding sulfide **7g** with mCPBA. The yields of the pyrazolones decreased with the increase in the size of the substituents at the 4-position. The major side products were the hydrazides of the corresponding

(10) Dage, R. C.; Roebel, L. E.; Hsich, C. P.; Woodward, J. K. *J. Cardiovasc. Pharmacol.* **1984**, *6*, 35.
(11) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. *J. Med. Chem.* **1984**, *27*, 1099.
(12) Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Weishaar, R. E.; Evans, D. B. *J. Med. Chem.* **1985**, *28*, 1405.
(13) Earl, C. Q.; Linden, J.; Weglicki, W. B. *J. Cardiovasc. Pharmacol.* **1986**, *8*, 864.
(14) Weishaar, R. E.; Burrows, S. D.; Kobylarz, D. C.; Quade, M. M.; Evans, D. B. *Biochem. Pharmacol.* **1986**, *35*, 787.
(15) Nakanishi, M.; Shiraki, M. JP 49/35278, September 1974; *Chem. Abstr.* **1974**, *831*, 10068*f*.
(16) Jarreau, F. X.; Koenig, J. J. *Chem. Abstr.* **1986**, *99*, 139935*w*. (b) Ogawa, K.; Terada, T.; Honna, T. *Chem. Pharm. Bull.* **1984**, *32*, 930.
(17) Ganon, P. E.; Biovin, J. L.; Baquin, R. *J. Can. J. Chem.* **1953**, *31*, 1025.
(18) (a) Sabate-Aldury, C.; Lematre, J. *Bull. Soc. Chim. Fr.* **1969**, 4159. (b) Jacquier, R.; Petrus, C.; Petrus, F.; Verducci, J. *Bull. Soc. Chim. Fr.* **1970**, 247.
(19) Sircar, I.; Weishaar, R. E.; Kobylarz, D.; Moos, W. H.; Bristol, J. A. *J. Med. Chem.* in press.
(20) Morrison, G. U.S. Patent 4 526 982, July 2, 1985.

Chart II. Tautomers of 2,4-Dihydro-5-phenyl-3*H*-pyrazol-3-ones

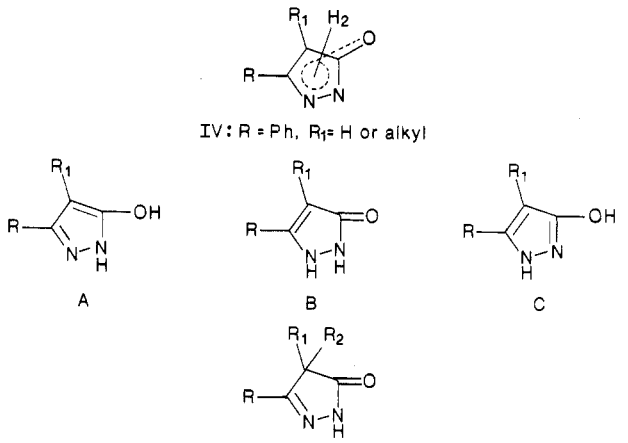


Table III. Cardiovascular Activities of 2,4-Dihydro-5-(4-substituted phenyl)-3*H*-pyrazol-3-ones

	anesthetized dog[a]		
compd	ED_{50} for contractility: mg/kg, iv	% change in HR[b]	% change in MAP[b]
5	>1	0[c]	0[c]
6a	>1	0[c]	0[c]
6b	>1	0[c]	0[c]
7a	0.18 ± 0.03	4.9 ± 3	−14 ± 2
7b	0.37	17	6
7d	>1	0[c]	0[c]
7e	1.0	3.5	−0.25
7f	0.2	10	−10.0
7g	0.35	5	−1.0
7h	0.3	11	−1.0

[a] Values are the arithmetic mean of two determinations or mean ± SEM. [b] Values are percent changes at the inotropic ED_{50}'s. [c] No measurable change at 1.0 mg/kg.

benzoic acids obtained by hydrolytic cleavage of the β-keto esters. The syntheses of keto esters (Table I) were accomplished from the corresponding acetophenones **1** with sodium hydride and dimethyl carbonate.[12] The alkylation was achieved with sodium hydride and an alkyl halide either in a stepwise fashion (method A, $R_1 \neq R_2$) or in one step (method B, $R_1 = R_2$). The structures of the pyrazolones (**5**, **6a–d**) were confirmed from microanalyses and spectral data. Absence of absorption in the carbonyl region (1550–1750 cm^{-1}) in the IR spectra (KBr) eliminated the tautomeric forms B and D. The ^1H NMR spectra ($CDCl_3$) of **5** showed one nonaromatic proton singlet at δ 5.9 for the C_4 hydrogen that also confirmed the absence of tautomers B and D. These findings are in agreement with earlier reports.[17,18] The structures of the 4,4-disubstituted pyrazolones (**7a–6**) were also confirmed from analyses and spectral data (see Experimental Section).

Biological Results and Discussion

The compounds in Table II were evaluated for inotropic activity in an acutely instrumented anesthetized dog model as described in the Experimental Section. Myocardial contractility was derived by measuring the first derivative of the increase in left ventricular pressure (dP/dt_{max}). Intravenous dose–response curves were obtained with at least four doses of each compound. The dose of each compound necessary to increase myocardial contractility by 50% is shown in Table III. Compound **5**, a prototype example of 4-unsubstituted 3*H*-pyrazol-3-one, produced a very slight increase in contractility (<20%) at doses up to 1 mg/kg. Similar results were obtained with the 4-monosubstituted 3*H*-pyrazol-3-ones (**6a–d**). Compound **7a**, in which both hydrogens in the pyrazolone ring were substituted with methyl groups, showed significant activity (ED_{50} = 0.18 ± 0.03 mg/kg) and had potency similar to that of 4,5-dihydro-3(2*H*)-pyridazinone IIIa (Table IV). Replacement of one methyl with an ethyl as in compound **7b** resulted in a slight decrease in activity, whereas the diethyl compound **7d** was nearly inactive. Connecting the two ethyl groups in a ring, as in the spiro compound **7e**, partially restored activity. These data confirm the steric requirement at C-4 allowing only a small substituent on the face of the molecule bound to the receptor, a fact that has been established in the six-membered pyridazinone series.[11,12] It is interesting to note that the rank order of potency in the six-membered 4,5-dihydro-3(2*H*)-pyridazinone series share some common features with the five-membered 3*H*-pyrazol-3-one series. 4,5-Dihydro-4,4-dimethyl-3(2*H*)-pyridazinone was more potent than the corresponding 5,5-dimethyl analogue (Chart III, Table V). These results strongly suggest the importance of an overall planar topography for potent inotropic effects in these

Table IV. Cardiovascular Profiles of 2,4-Dihydro-5-[4-(1*H*-imidazol-yl)phenyl]-4,4-dimethyl-3*H*-pyrazol-3-one (**7a**) and 4,5-Dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinone (IIIa) in Anesthetized Dogs

		% change		
compd (*n*)	dose, mg/kg	dP/dt_{max}[a]	heart rate	blood pressure
IIIa (6)	0.01	10.2 ± 1.3*	0 ± 1.2	−0.7 ± 0.4
	0.031	37.2 ± 8.0*	5.6 ± 3.4	−4.1 ± 1.0
	0.1	74.2 ± 13.3*	6.2 ± 5.8	−5.3 ± 1.6
	0.31	127.3 ± 25.0*	19.2 ± 9.1*	−13.2 ± 2.8*
	1.0	146.7 ± 25.0*	33.8 ± 17.0*	−22.4 ± 2.8*
7a (6)	0.01	6 ± 1*	0 ± 0	−0.5 ± 0
	0.031	10 ± 4*	0.2 ± 1	−4.0 ± 1*
	0.1	39 ± 7*	0.8 ± 3*	−11.0 ± 2*
	0.31	78 ± 14*	9 ± 3*	−20.0 ± 2*
	1.0	100 ± 17*	14 ± 4*	−34 ± 3*

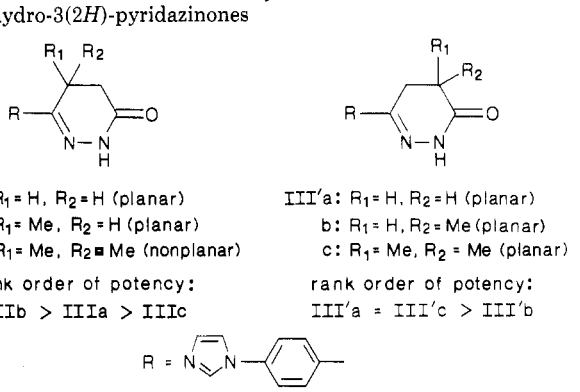
[a] (*) Significant $p < 0.05$ compared to control. *n* is the number of dogs.

Table V. Comparative Data for the Inotropic Responses of Cardiotonic Agents in Anesthetized Dogs

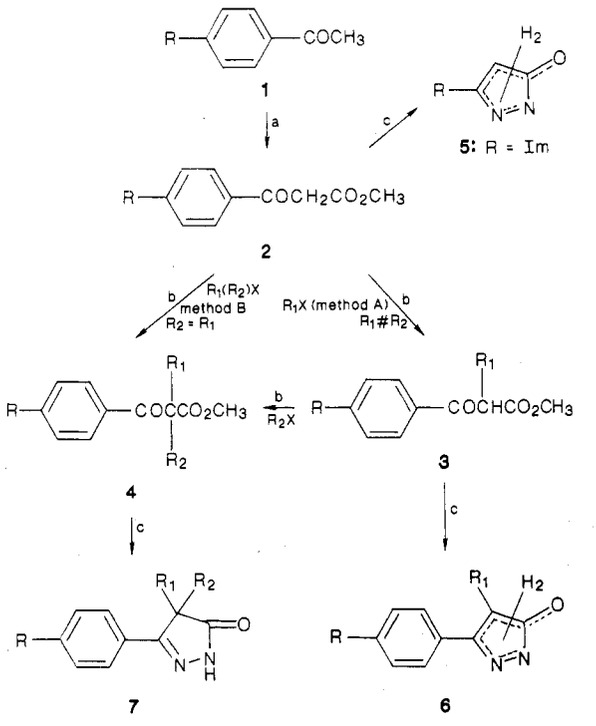
compd	dose (*n*),[a] mg/kg
IIIa (III'a)	0.045 ± 0.006 (8)
IIIb	0.013 ± 0.006 (6)
IIIc	0.2 (2)
III'b	0.5 (2)
III'c	0.05 (2)
7a	0.18 ± 0.03 (6)

[a] Values are doses producing 50% increase in dP/dt_{max} from control ± SEM when *n* is >2; otherwise values are arithmetic mean of two separate experiments.

Chart III. Rank Order of Potency of 4,5-Dihydro-3(2*H*)-pyridazinones



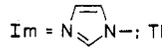
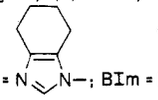
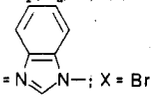
Scheme I[a]

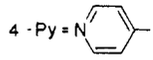


4a and **7a**: $R_1 = R_2 = CH_3$, R = Im
b: $R_1 = CH_3$, $R_2 = CH_2CH_3$, R = Im
c: $R_1 = CH_3$, $R_2 = CH_2Ph$, R = Im
d: $R_1 = R_2 = CH_2CH_3$, R = Im
e: R_1, $R_2 = (CH_2)_4$, R = Im
f: $R_1 = R_2 = CH_3$, R = THBIm
g: $R_1 = R_2 = CH_3$, $R = H_3CS$
h: $R_1 = R_2 = CH_3$, R = 4-Py
i: $R_1 = R_2 = CH_2Ph$, R = Im
j: $R_1 = R_2 = CH_3$, R = BIm
k: R_1, $R_2 = (CH_2)_5$, Im
l: $R_1 = R_2 = CH_3$, $R = H_3C\,S \rightarrow O$

3 and **6a**: R = Im, $R_1 = CH_3$
b: R = Im, $R_1 = CH_2CH_3$
c: R = Im, $R = (CH_2)_5CH_3$
d: R = Im, $R_1 = CH_2Ph$

[a] (a) NaH, $(CH_3O)_2CO$; (b) NaH, $R_1(R_2)X$; (c) N_2H_4.

Im =  ; THBIm =  ; BIm =  ; X = Br or I;

4-Py = 

series.[11] By contrast, an out-of-plane geometry has been reported in the case of milrinone, the dihedral angle between the planes formed by the pyridine and pyridone is 55.2°.[21] The 4,5,6,7-tetrahydrobenzimidazole analogue **7f** retained the potency of the parent compound **7a**, a structure–activity relationship exhibited by the related pyridazinones.[12] Compounds **7h** and **7l**, the 4-pyridyl and 4-methylsulfinyl analogues, were less potent than the corresponding imidazole **7a**. This relationship has been seen with other recently disclosed inotropes.[22] Table VI shows comparative data obtained from oral administration of **7a** and IIIa.

The inhibitory effects of several pyrazolones on isolated cyclic AMP specific phosphodiesterase (PDE III) activity was also evaluated, and IC_{50} values are reported in Table VII. The results demonstrate a correlation between the in vitro enzyme-inhibitory activity and in vivo inotropic activity and also suggest that only the 4,4-disubstituted

(21) Oelschlaeser, H.; Giebenhaim, G. *Arch. Pharm. (Weinheim, Ger.)* **1973**, *306*, 485.
(22) Sircar, I.; Duell, B. L.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1987**, *30*, 1023.

Table VI. Comparative Data for the Inotropic Responses of Cardiotonic Agents in the Conscious Dog following Oral Administration

compd	dose, mg/kg	% increase,[a] contractility
IIIa	0.31	10–20
	1.0	40 ± 6*
7a	0.31	24 ± 6*

[a] Values are maximum responses from control (mean ± SEM, n = 5, 6). Significant at $p < 0.05$ compared to control. Control dP/dt_{max} ranged from 3030 ± 104 to 2056 ± 276 mmHg/s.

Table VII. IC_{50} Values on Type III of Guinea Pig Phosphodiesterase for 2,4-Dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-3*H*-pyrazol-3-ones

compd	IC_{50},[a] μM (95% CL)	compd	IC_{50},[a] μM (95% CL)
7a	22 (16–28)	**7h**	220 (170–270)
7b	52 (38–66)	**6a**	140 (110–170)
7d	120 (88–160)	**6b**	270 (170–360)
7e	54 (43–65)	**5**	590 (230–950)
7f	3.2 (2.2–4.2)	IIIa	8.0 (4–10)

[a] IC_{50} values were determined by measuring the inhibiting effects of each agent over a concentration range of 1.0×10^{-7} to 1.0×10^{-4} M or 1.0×10^{-6} to 1.0×10^{-3} M for the less potent agents. Each value represents the mean of two to four experiments using different preparations of phosphodiesterases and were calculated from the dose–response curve.

pyrazolones possess potent and selective phosphodiesterase inhibitory activity which is primarily responsible for their inotropic action.

The PDE III inhibitory activity of five-membered pyrazolone **7a** is similar to that of the corresponding six-membered pyridazinone IIIa (IC_{50} values of 22 and 8 μM, respectively). As was previously demonstrated in the 3-(2*H*)-pyridazinone series,[19] the tetrahydrobenzimidazole analogue **7f** (IC_{50} = 3.2 μM) is the most potent compound identified in this series.

Conclusion

The 2,4-dihydro-4,4-dimethyl-3*H*-pyrazol-3-ones possess inotropic activity and exhibit a profile similar to those of the corresponding 4,5-dihydro-3(2*H*)-pyridazinones. Some of the key structural features are common between these two series and can be extended onto other series of inotropes. The lack of inotropic potency in unsubstituted or monosubstituted analogues was explained on the basis of the 5-point model hypothesis.[11]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded ($CDCl_3$ unless otherwise stated) on a Varian EM 390 and XL 200 spectrometer with Me_4Si as an internal standard. IR spectra were recorded on a Nicolet FT-IRMS-1 or FT-IR2 OSX spectrophotometer. The elemental analyses (C, H, and N) for all new compounds were within ±0.4% of theory.

General Procedures for Alkylation of 4-(1*H*-Imidazol-1-yl)-β-oxobenzenepropanoic Acid Methyl Esters (3a–d, 4a–k, Table I). 4-(1*H*-Imidazol-1-yl)-α,α-dimethyl-β-oxobenzenepropanoic Acid Methyl Ester (4a). To a stirred suspension of NaH (60% in mineral oil, 4 g, 0.1 mol) in dry DMF (30 mL) was added dropwise a solution of 4-(1*H*-imidazol-1-yl)-β-oxobenzenepropanoic acid methyl ester[12] in dry DMF (60 mL) over 0.5 h at 10–15 °C. After the addition had been completed, a solution of iodomethane (14.7 g, 0.1 mol) in DMF (20 mL) was added dropwise and stirring was continued for 20 h at room temperature. The reaction mixture was poured into 1.2 L of ice–water and the cloudy solution was allowed to stand for 1 h. The solid was filtered, washed with cold water, and air-dried, giving 8.2 g of the product. The aqueous solution was saturated with sodium chloride and extracted with ether. Ether was

evaporated to give a second crop, 1.9 g. The crude material was recrystallized as indicated in Table I.

General Procedure for Ring Closure of 4-(1*H*-Imidazol-1-yl)-β-oxobenzenepropanoic Acid Methyl Esters (5, 6a–d, 7a–k, Table II). 2,4-Dihydro-5-[4-(1*H*-imidazol-1-yl)-phenyl]-4,4-dimethyl-3*H*-pyrazol-3-one (7a). A solution of **4a**, (16.9 g, 0.06 mol) in EtOH (70 mL) containing hydrazine hydrate (4 mL, 85%) was heated at reflux for 2 h. The solution was cooled and the precipitate was filtered to give 14.4 g of the product, mp 172–173 °C. The crude material was recrystallized, if necessary, as indicated in Table II: IR (KBr) 1710 cm^{-1} (CO); ^1H NMR Me_2SO-d_6) δ 1.45 (s, 6 H, CH_3), 7.5–8.2 (m, 7 H, aromatics), 9.8 (br s, 1 H, NHCO).

Hydrochloride Salt of 7a. Ethanolic HCl was added with stirring to a hot slution of **7a** (121 g) in EtOH (1.2 L) to pH 2 and the solution was allowed to stand overnight at 23 °C. The white solid was filtered, washed with a small volume of EtOH, and air-dried to give 123.5 g of analytically pure material: mp 304–305 °C; IR (KBr) 1710 cm^{-1} (CO); ^1H NMR (Me_2SO-d_6) δ 1.45 (s, 6 H, CH_3), 7.5–8.3 (m, 6 H, aromatics), 9.8 (s, 1 H, NHCO), 12.0 (s, 1 H, aromatic).

2,4-Dihydro-5-[4-(methylsulfinyl)phenyl]-4,4-dimethyl-3*H*-pyrazol-3-one (7l). To a stirred solution of **7g** (1.17 g, 5 mmol) in CH_2Cl_2 (25 mL) was added a solution of mCPBA (85%, 1.1 g, 55 mmol) at 10 °C and stirring was continued for 0.5 h at room temperature. The solution was washed successively with saturated $NaHCO_3$ solution followed by water dried (anhydrous $MgSO_4$) and stripped to give 1 g of the desired product. The crude material was crystallized as indicated in Table II.

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

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

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

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

Isolation of Phosphodiesterases and Assay of Activity. The isolation of different forms of cardiac phosphodiesterase and their characterization was done by following the procedure of Thompson.[23] The three molecular forms of PDE (types I–III) present in guinea pig left ventricular tissue were discretely eluted from a DEAE column using a sodium acetate gradient. Cross contamination was eliminated by chromatography of pooled fractions of each peak. Following complete separation, the combined phosphodiesterase fractions were concentrated to 14% of the original volume, diluted to 65% with ethylene glycol monoethyl ether, and stored at −20 °C (no significant change in hydrolytic activity was observed with storage of up to 6 weeks).

In evaluating the inhibiting effect of the different agents examined on type I type II, and type III cardiac phosphodiesterases, the enzyme concentration in the assay was adjusted to ensure that reaction velocity was linear for 30 min at 30 °C and that hydrolysis of substrate ([^{3}H]cyclic AMP or [^{3}H]cyclic GMP) did not exceed 10–20% of the available substrate in the absence of any inhibitor. The concentration of substrate was 1.0 μM for these studies. All agents examined were dissolved in dimethyl sulfoxide (Me_2SO). The final concentration of Me_2SO in the reactions medium was 2.5%. This concentration of Me_2SO inhibited enzyme activity by approximately 10%. IC_{50} values (the concentration that produces 50% inhibition of substrate hydrolysis) were determined from concentration–response curves that ranged from 10^{-7} to 10^{-4} for the more potent inhibitors and from 10^{-5} to 10^{-3} M for the less potent inhibitors (half-log increments). Two to four such concentration–response curves were generated for each agent, typically using different enzyme preparations for each concentration–response curve.

Acknowledgment. We thank Dr. F. A. Mackellar and his associates for spectral determinations and microanalyses. We also thank R. E. Potoczak, R. McNish, D. M. Boucher, and D. C. Kobylarz-Singer for biological testing. We greatly appreciate the encouragement provided by Dr. J. A. Bristol and Dr. D. B. Evans while working in this project.

Registry No. **1** (R = Im), 10041-06-2; **1** (R = THBIm), 95644-06-7; **1** (R = XCH_3), 1778-09-2; **1** (R = 4-Py), 70581-00-9; **1** (R = BIm), 25700-10-1; **2** (R = Im), 84243-56-1; **2** (R = Im), 84243-56-1; **2** (R = SCH_3), 108818-59-3; **2** (R = 4-Py), 108818-60-6; **2** (R = BIm), 95644-07-8; **3a**, 108818-61-7; **3b**, 95644-17-0; **3c**, 108818-62-8; **3c**·HCl, 108818-63-9; **3d**, 108818-64-0; **4a**, 95644-11-4; **4b**, 108818-65-1; **4b**·HCl, 95644-18-1; **4c**, 108818-66-2; **4d**, 108818-67-3; **4d**·HCl, 108818-68-4; **4e**, 108818-69-5; **4f**, 95644-13-6; **4g**, 108818-70-8; **4h**, 108818-71-9; **4i**, 108818-72-0; **4j**, 95644-12-5; **4k**, 108818-73-1; **5**, 108818-74-2; **6a**, 108818-75-3; **6b**, 108818-76-4; **6c**, 108818-77-5; **6d**, 108818-78-6; **7a**, 95644-19-2; **7a**·HCl, 108818-79-7; **7b**, 95644-25-0; **7c**, 108818-80-0; **7d**, 108818-81-1; **7e**, 108818-82-2; **7f**, 95644-21-6; **7g**, 108818-83-3; **7h**, 108818-84-4; **7i**, 108818-85-5; **7j**, 95644-20-5; **7k**, 108818-86-6; **7l**, 108818-87-7.

(23) Thompson, W. J.; Terasaki, W. L.; Epstein, P. N.; Strada, S. *J. Adv. Cyclic Nucleotide Res.* **1979**, *10*, 69.
(24) Meeda, M.; Fukumura, T.; Kajima, M. *Chem. Pharm. Bull.* **1985**, *33*, 1301.