$(CH_2)_6COCH_2COOH$, 13283-92-6; $Me(CH_2)_{10}COCH_2COOH$, 88222-72-4; $(C_2H_5OOC)_2$, 95-92-1; $(C_4H_9OOC)_2$, 2050-60-4; $(C_5H_4OOC)_2$, 20602-86-2; $(HOOC)_2$, 144-62-7; ethyl hydrogen malonate, 1071-46-1; decanoic acid, 334-48-5; octanoyl chloride, 111-64-8; decanoyl chloride, 112-13-0; dodecanoyl chloride, 112-16-3; 4-hydroxy-6-methyl-2-pyrone, 675-10-5; hexanoyl chloride, 142-61-0; sputum elastase, 9004-06-2; 4-methoxy-6-methyl-2-pyrone, 672-89-9.

Supplementary Material Available: Physical-chemical data for compounds **2–6, 8–14, 16–19** (4 pages). Ordering information is given on any current masthead page.

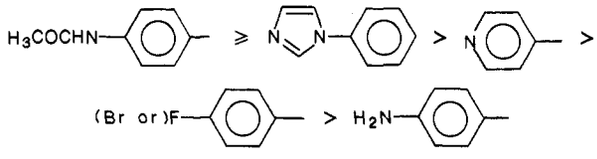
Cardiotonic Agents. 5. 1,2-Dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-6-methyl-2-oxo-3-pyridinecarbonitriles and Related Compounds. Synthesis and Inotropic Activity[1]

Ila Sircar,*† Bradley L. Duell,† James A. Bristol,† Ronald E. Weishaar,‡ and Dale B. Evans‡

Departments of Chemistry and Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105. *Received September 26, 1986*

Several 1,2-dihydro-5-(substituted phenyl)-2(1*H*)-pyridinones were synthesized and evaluated for inotropic activity. 1,2-Dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-6-methyl-2-oxo-3-pyridinecarbonitrile (**5a**) and the corresponding unsubstituted analogue **14a** were the most potent positive inotropic agents in this series. Although the 4,6-dimethyl analogue **6a** retained most of the activity of **5a**, the 4-methyl analogue **8a** was substantially less potent. The synthesis and structure–activity relationships are discussed.

Recently we have reported the positive inotropic activity of imazodan (CI-914, I), CI-930 (II), and related 4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinones.[2,3] The inotropic activities of the rigidly fused tricyclic 2,4,4a,5-tetrahydro-7-(1*H*-imidazol-1-yl)-3*H*-indeno[1,2-*c*]pyridazin-3-ones (III)[4] derived from CI-930 (II) and 6-(substituted 1*H*-imidazol-4(5)-yl)-3-(2*H*)-pyridazinones[5] were also reported. In an attempt to define the structure–activity relationships of the 4,5-dihydro-3(2*H*)-pyridazinone moiety we have investigated other series of heterocyclic systems, such as, 2,4-dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-3*H*-pyrazol-3-ones (IV)[6] and 2-[4-(1*H*-imidazol-1-yl)phenyl]-4*H*-1,3,4-oxadiazin-5-(6*H*)-ones (V)[7] (Chart I). These studies confirm the contribution of the (1*H*-imidazol-1-yl)phenyl moiety to superior inotropic activity in comparison with other more conventional aromatic substituents, such as halogen, alkyl, alkyloxy, nitro, amine, etc.[8] The rank order of potency[4] for the phenyl substituent across several series of compounds is

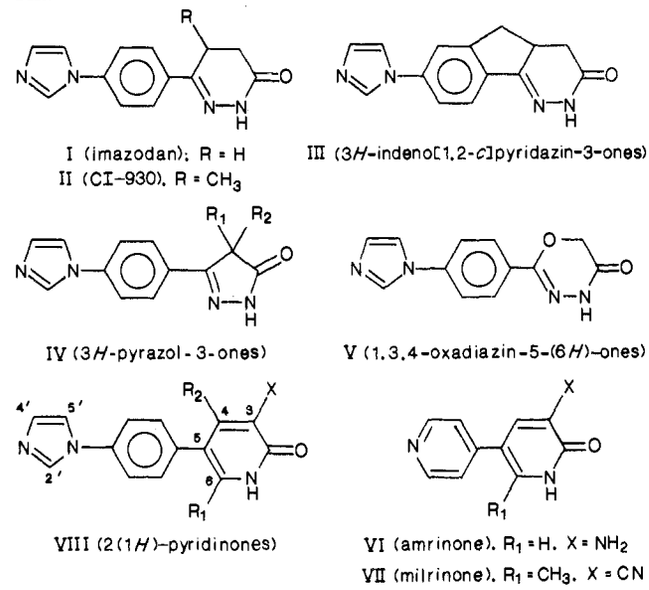


During the early stages of our investigation, amrinone (VI)[9] and milrinone (VII)[10] were reported to be promising compounds that possessed combined inotropic and vasodilator activities. The limited published data on the structure–activity relationship (SAR) of 5-substituted 2(1*H*)-pyridinones led us to investigate 5-[4-(1*H*-imidazol-1-yl)phenyl]-2(1*H*)-pyridinones (VIII, Chart I). This resulted in a series of potent inotropes,[11] the synthesis and biological activity of which is described in this paper.

Chemistry

The target compounds **5a–f** were synthesized from the requisite aldehydes **1a–g** according to Scheme I. Aldehydes **1a–g** (Table I) were prepared from 4-fluorobenzaldehyde and the requisite amines in refluxing pyridine in the presence of K_2CO_3 and Cu_2O by following the gen-

Chart I



† Department of Chemistry.
‡ Department of Pharmacology.

(1) Presented in part at the 187th National Meeting of the American Chemical Society, Miami Beach, April 1985. See *Abstracts of Paper*; American Chemical Society: Washington, DC, 1985; MEDI 40.
(2) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. *J. Med. Chem.* **1984**, *27*, 1099.
(3) Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1985**, *28*, 1405.
(4) Sircar, I.; Duell, B. L.; Cain, M. C.; Bristol, J. A.; Burke, S. E. *J. Med. Chem.* **1986**, *29*, 2142.
(5) Sircar, I.; Bobowski, G.; Bristol, J. A.; Weishaar, R. E.; Evans, D. B. *J. Med. Chem.* **1986**, *29*, 261.
(6) Morrison, G. C. U.S. Patent 4 526 982, July 2, 1985.
(7) Sircar, I.; Cain, M. C.; Topliss, J. G. U.S. Patent 4 508 718, April 2, 1985.
(8) Sircar, I. U.S. Patent 4 397 854, August 9, 1983.
(9) Farah, A. E.; Alousi, A. A. *Life Sci.* **1978**, *22*, 1139.
(10) Lesher, G. Y.; Philion, R. E. U.S. Patent 4 313 951, February 2, 1982.
(11) Bristol, J. A.; Sircar, I. U.S. Patent 4 503 061, March 5, 1985.

0022-2623/87/1830-1023$01.50/0

Scheme I

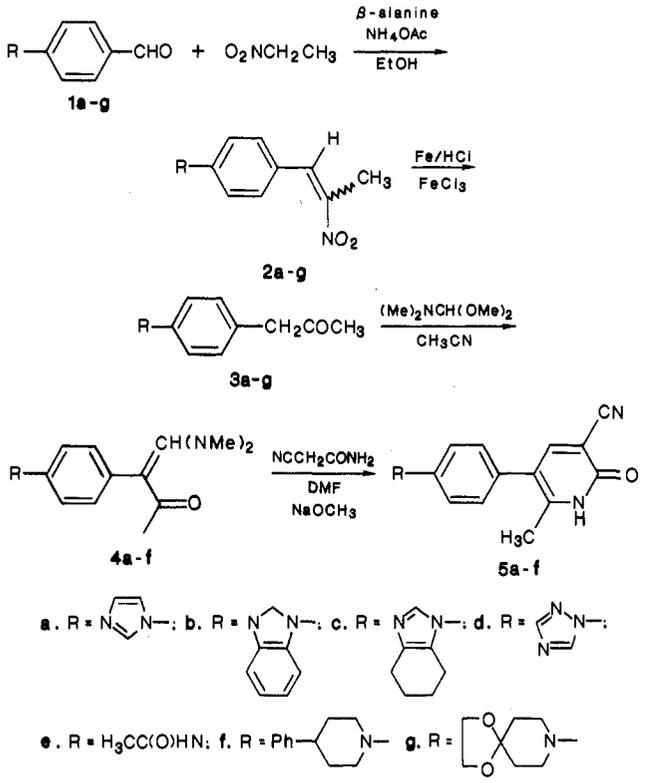
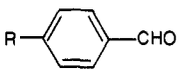
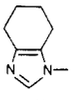
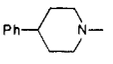
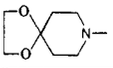


Table I. 4-Azolylbenzaldehydes

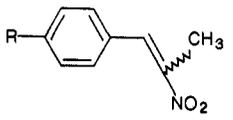


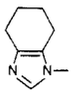
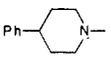
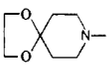
compd	R	mp, °C (recrystn solvent)	yield,[b] %	formula
1a[a]		146–147 (CH_2Cl_2)	33	$C_{10}H_8N_2O$
1b[c]		100–101	40	$C_{14}H_{10}N_2O$
1c[c]		110–111	43	$C_{14}H_{14}N_2O$
1d[c]		149–150	50	$C_9H_7N_3O$
1f		117–119 (CH_2Cl_2)	81	$C_{18}H_{19}NO$
1g		121–122 (hexane)	80	$C_{14}H_{17}NO_3$

[a] Literature[12] reports mp 149–150 °C. [b] Yields were not optimized. The analyses were within 0.4% of the calculated value. [c] Compounds were purified by chromatography over silica gel using dichloromethane as eluant. Compound 1e was available from Aldrich Chemical Co.

eral procedure of Sitkina et al.[12] Treatment of **1a–g** with nitroethane in ethanol in the presence of a catalytic amount of β-alanine gave the corresponding nitrostyrenes **2a–g** (Table II), which were mixtures of stereoisomers. The nitrostyrenes **2a–g** were subsequently converted to the key intermediate phenyl-2-propanones **3a–g** (Table III) by treatment with Fe/HCl in the presence of $FeCl_3$ catalyst.[13] Conversion of the ketones **3a–f** to the pyridinones

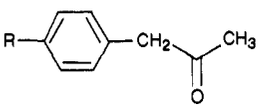
Table II. [4-(2-Nitro-1-propenyl)phenyl]azoles

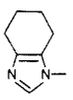
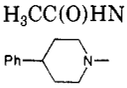
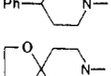


compd	R	mp, °C (recrystn solvent)	yield,[b] %	formula
2a		119–121 (1-butanol)	54	$C_{12}H_{11}N_3O_2$
2b		147–149 (EtAc)	68	$C_{16}H_{13}N_3O_2$
2c[c,d]		oil	55	$C_{16}H_{17}N_3O_2$
2d		141.5–142.5 (EtOH)	72	$C_{11}H_{10}N_4O_2$
2e[c,d]	$H_3CC(O)HN$	oil	52	$C_{11}H_{12}N_2O_3$
2f		148–149 (EtAc)	91	$C_{20}H_{22}N_2O_2$
2g		132–134 (isopropyl ether)	65	$C_{16}H_{20}N_2O_4$

[b,c] See corresponding footnotes in Table I. [d] Compound not analyzed; used as is for the next step.

Table III. (4-Substituted phenyl)-2-propanones



compd	R	mp, °C (recrystn solvent)	yield,[b] %	formula
3a		71.5–72.5	50	$C_{12}H_{12}N_2O$
3b[c,d]		oil	70	$C_{16}H_{14}N_2O$
3c		105–108	50	$C_{16}H_{18}N_2O$
3d		97–98.5	72	$C_{11}H_{11}N_3O$
3e	$H_3CC(O)HN$	118–120	68	$C_{11}H_{13}NO_2$
3f		92–93	89	$C_{20}H_{23}NO$
3g		40–46	40	$C_{16}H_{21}NO_3$

[b,c,d] See corresponding footnotes in Tables I and II.

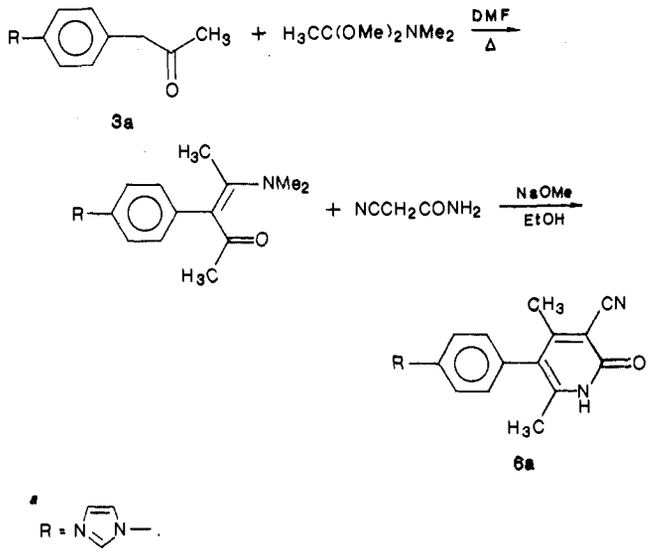
5a–f was accomplished by minor modification of the general procedure of Lesher et al.[10] Treatment of the ketones **3a–f** with *N,N*-dimethylformamide dimethyl acetal in acetonitrile provided the imino ketones **4a–f**, which were never isolated except for **4a** and **4f**. The formation of the imino ketones also proceeded smoothly at room temperature with an excess of the reagent as solvent.[14] The pyridinones **5a–f** (Table IV) were obtained by condensation of the imino ketones **4a–f** with cyanoacetamide in the presence of sodium ethoxide in DMF. Formation of **5g**

(12) Sitkina, L. M.; Simonov, A. M. *Khim. Geterotrikl. Soedin. Akad. Nauk. Latv. SSR* **1966**, 143; *Chem. Abstr.* **1966**, *65*, 13686e.

(13) Heinzelman, R. V. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 438.

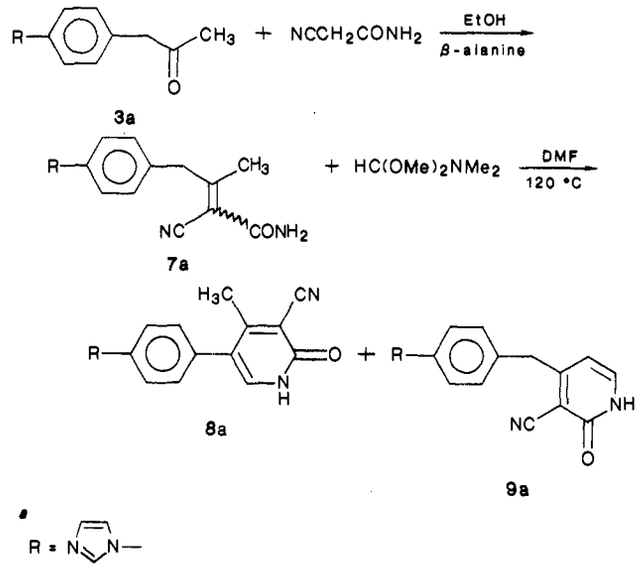
(14) Goel, O.; Krolls, U., unpublished results.

Scheme II[a]



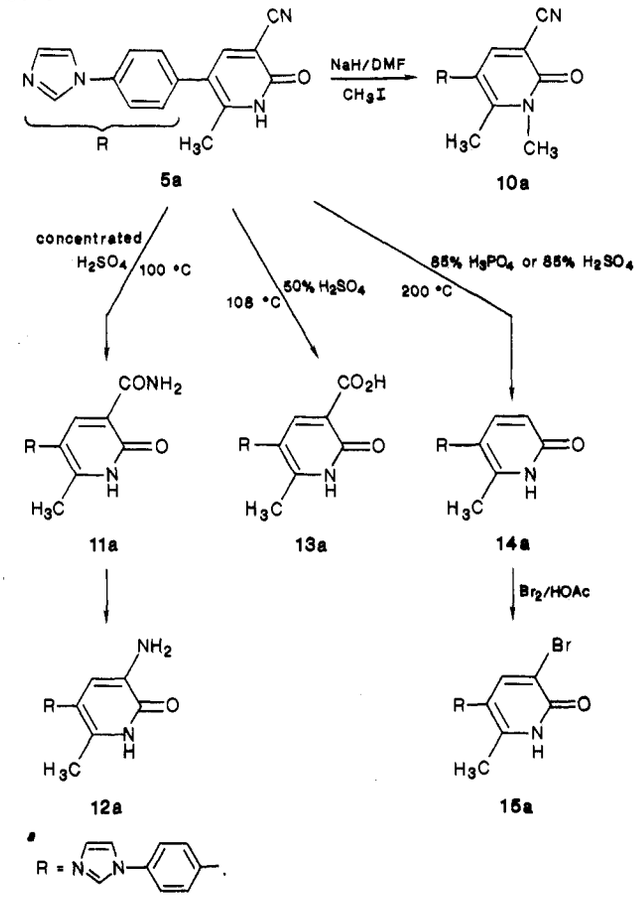
[a] R = N,N-imidazol-1-yl.

Scheme III[a]



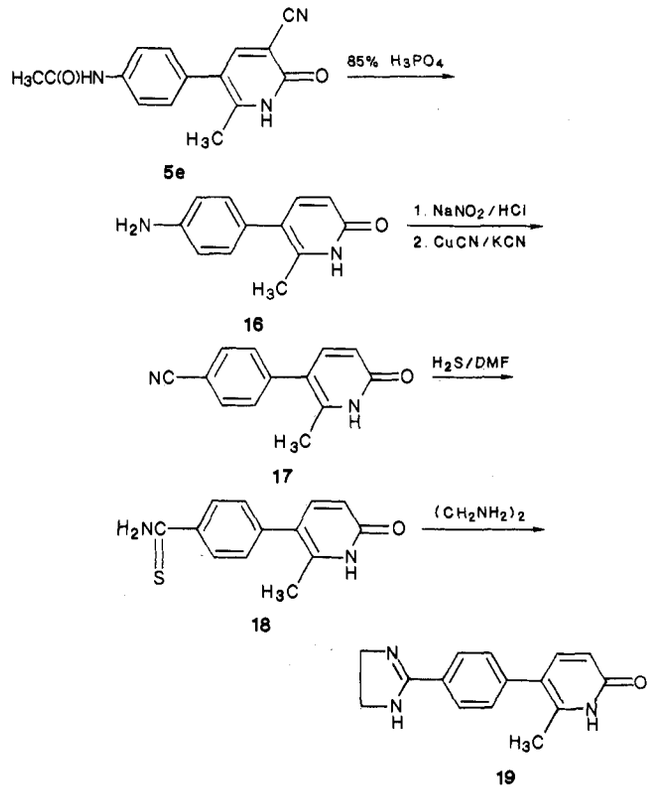
[a] R = N,N-imidazol-1-yl.

Scheme IV[a]



[a] R = N,N-imidazol-1-yl.

Scheme V

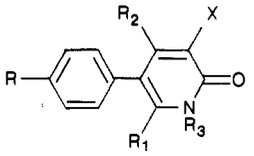


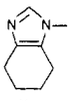
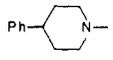
from **3g** was not accomplished. Compound **6a**, the 4,6-dimethyl analogue of **5a**, was obtained in a similar fashion from **3a** by substituting *N,N*-dimethylacetamide dimethyl acetal in place of *N,N*-dimethylformamide dimethyl acetal (Scheme II). The 4-methyl analogue **8a** was synthesized from the ketone **3a** by reversing the reaction sequence described above (Scheme III). Compound **3a** was treated with cyanoacetamide in ethanol in the presence of β-alanine to give **7a** as a mixture of stereoisomers. This was subsequently condensed with *N,N*-dimethylformamide dimethyl acetal in DMF to give a mixture of **8a** and the isomeric product **9a**,[15] which was separated by crystallization. The structures of the pyridinones **5a**, **6a**, **8a**, and **9a** were confirmed by analyses and spectral data.

Alkylation of **5a** with iodomethane in presence of sodium hydride in DMF gave the *N*-methyl analogue **10a**. Partial hydrolysis of **5a** with concentrated H_2SO_4 to the carboxamide **11a** followed by Hoffman reaction with Br_2 and NaOH save the primary amine **12a**. Hydrolysis of **5a** with 50% H_2SO_4 at 100 °C provided the carboxylic acid **13a**. Treatment of **5a** with 85% H_3PO_4 or 85% H_2SO_4 at 200 °C gave the decarboxylated product **14a**, which was subsequently brominated to provide **15a** (Scheme IV). The synthesis of 2-imidazole isomer of **5a** was outlined in Scheme V. Treatment of **5e** with 85% H_3PO_4 at 170 °C produced the pyridinone **16**. This was converted to the corresponding benzonitrile analogue **17** by diazotization

(15) Marecki, P. E.; Wemple, J. N.; Butke, G. P. *J. Heterocycl. Chem.* **1982**, *19*, 1247.

Table IV. (4-Substituted phenyl)-2(1*H*)-pyridinones



compd	R	R_1	R_2	R_3	X	mp,[a] °C (recrystn solvent)	formula	yield,[b] %
5a		CH_3	H	H	CN	305–306 (DMF) 322–323 ($MeOH/H_2O$)	$C_{16}H_{12}N_4O$ $C_{16}H_{12}N_4O{\cdot}HCl{\cdot}0.2H_2O$	30
5b		CH_3	H	H	CN	350–353 (DMF)	$C_{20}H_{14}N_4O$	30
5c		CH_3	H	H	CN	>350 (2-methoxyethanol)	$C_{20}H_{18}N_4O{\cdot}0.4CH_3O(CH_2)_2OH$	34
5d		CH_3	H	H	CN	309–310 (MeOH)	$C_{15}H_{11}N_5O{\cdot}0.1H_2O$	19
5e	$CH_3C(O)NH$	CH_3	H	H	CN	312–314 (DMF)	$C_{15}H_{13}N_3O_2$	27
5f		CH_3	H	H	CN	296–299 (EtOH)	$C_{24}H_{23}N_3O$	23
6a		CH_3	CH_3	H	CN	>340 (DMF)	$C_{17}H_{14}N_4O{\cdot}0.2DMF$	11
8a		H	CH_3	H	CN	337–340 (DMF)	$C_{16}H_{12}N_4O{\cdot}0.2DMF$	10
10a		CH_3	H	CH_3	CN	219–221 (MeOH)	$C_{17}H_{14}N_4O{\cdot}0.1H_2O$	41
11a		CH_3	H	H	$CONH_2$	313–315 (2-methoxyethanol)	$C_{16}H_{14}N_4O_2{\cdot}0.2H_2O$	31
12a[c]		CH_3	H	H	NH_2	302–304	$C_{15}H_{14}N_4O$	19
13a		CH_3	H	H	COOH	297–298 (DMF)	$C_{16}H_{13}N_3O_3$	33
14a		CH_3	H	H	H	310–313 (DMF)	$C_{15}H_{13}N_3O$	75
15a[c]		CH_3	H	H	Br	303.5–305	$C_{15}H_{12}BrN_3O$	9
16	H_2N	CH_3	H	H	CN	230–233	$C_{12}H_{12}N_2O$	54
17	NC	CH_3	H	H	H	300–301 (DMF)	$C_{13}H_{10}N_2O{\cdot}0.05DMF$	66
18	H_2NCS	CH_3	H	H	H	290–295 (DMF/H_2O)	$C_{13}H_{12}N_2OS{\cdot}0.1DMF$	90
19		CH_3	H	H	H	>300 (DMF)	$C_{15}H_{15}N_3O{\cdot}0.2H_2O$	74
20	F	CH_3	H	H	CN	312–314 (EtOH)	$C_{13}H_9FN_2O$	72
21	Br	CH_3	H	H	CN	313–314 (EtOH)	$C_{13}H_9BrN_2O$	75

[a] Melts with decomposition. [b] Yields were not optimized and refer to the last step of the scheme. The analyses were within 0.4% of the calculated value. [c] Purified by chromatography over silica gel using $CHCl_3/MeOH$ (10:1).

($NaNO_2$/HCl) and subsequent treatment with CuCN/KCN with standard reaction conditions. The nitrile was converted to the corresponding thioamide **18** by reaction with H_2S in DMF, which when heated with 1,2-ethanediamine gave the imidazoline **19**. Attempted oxidation of **19** to give the corresponding imidazole analogue gave mixtures, which could not be purified.

Biological Results

The pyridinones in Table IV were evaluated for inotropic activity intravenously in an acutely instrumented anesthetized dog model and orally in a chronically instrumented conscious dog model.[16] Brief descriptions of the methods are included in the Experimental Section. Heart rate, myocardial contractility, (derived by measuring dP/dt_{max} of left ventricular pressure), and aortic blood pressure were recorded. Dose–response curves were determined with at least four doses of each compound.

Compound **5a** produced dose-related increases in dP/dt_{max} that were associated with small increases in heart rate and small decreases in blood pressure (Table V). These responses were very similar to those of milrinone,[17] and the structure–activity relationships of this series appear to parallel those of milrinone.[18,19] The nitrile **5a** and the 3-unsubstituted analogue **14a** were the most potent compounds in this series (ED_{50} = 0.01 mg/kg). The 3-amino analogue **12a** was slightly less potent that the 3-nitrile **5a**. The presence of an acidic hydrogen in the pyridone ring is required for maximum potency (**10a**, ED_{50} > 1 mg/kg).

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Table V. Cardiovascular Profile of 5-(4-Substituted phenyl)-2(1*H*)-pyridinones in Anesthetized Dogs

		% change from control		
compd (n)[a]	dose, mg/kg	myocardial contractility (LV dp/dt)	heart rate (HR)	mean arterial blood pressure (MABP)
5a[b,c] (6)	0.001	4.5	1	−1
	0.003	18.5	3	1.7
	0.01	50.3 ± 8.5	4.5 ± 5.4	0.75 ± 2.8
	0.03	122.7 ± 5.0	14.0 ± 10	−2.2 ± 4.2
	0.1	154.0 ± 11.3	34.7 ± 2.4	−9.7 ± 4.2
6a (2)	0.01	21.0	1	0
	0.03	86.0	2	−6.0
	0.1	137.0	15	−17.5
	0.31	160.0	16	−35.0
	1.0	135.0	26	−49.0
8a (2)	0.01	2.5	−0.5	1.5
	0.03	12.0	2.0	4.7
	0.1	21.0	4.5	5.5
	0.3	54.0	7.5	9.7
	1.0	125.5	19.5	−2.5
10a (2)	0.01	8.0	1.0	2.0
	0.03	10.0	0	1.0
	0.1	16.0	3.0	2.0
	0.3	18.0	2.0	1.5
	1.0	39.0	3.0	0.5
12a (2)	0.01	24.5	−1.5	0.5
	0.03	80.5	12.0	1.0
	0.1	134.5	18.0	−5.0
	0.31	125.5	21.5	−17.5
	1.0	105.5	22.0	−27.5
14a (2)	0.01	36.0	3.0	−2.5
	0.03	85.0	9.0	−2.0
	0.1	109.0	17.0	−9.5
	0.31	121.0	26.0	−20.0
	1.0	122.0	29.0	−19.5
milrinone (6)	0.01	30.5 ± 10.0	3.0 ± 1.2	−2.0 ± 1.2
	0.03	77.5 ± 23.1	13.5 ± 1.8	−8.0 ± 3.5
	0.10	113.0 ± 29.4	27.0 ± 4.0	−13.0 ± 5.2
	0.31	142.5 ± 24.0	39.2 ± 15.3	−19.9 ± 7.0
	1.0	148.5 ± 20.3	48.5 ± 12.2	−36.9 ± 5.8

[a] n is the number of dogs. [b] Values shown are the arithmetic mean of two separate experiments except for compound **5a** and milrinone (significant at $p < 0.05$ compound to control). [c] Biological data for compounds **5b–f** could not be obtained due to poor solubility of these agents.

Compound **5a** ($ED_{50} \cong 0.01$ mg/kg) was 10 times more potent than **20** ($ED_{50} = 0.1$ mg/kg), wherein the imidazole moiety has been replaced with fluorine.

The 4,6-dimethyl compound **6a** also retained most of the activity of the parent compound whereas the corresponding 4-methyl analogue **8a** was substantially less potent (Table V). These results indicate the requirement of the 6-methyl group for improved potency, a fact that has been emphasized several times in literature.[19,20] The structural characteristics necessary for potent inotropic activity in several chemical series including phenyl-2(1*H*)-pyridones have been analyzed and discussed in greater detail in a separate paper.[20] Table VI shows comparative data obtained from oral administration of **5a** and milrinone. The mechanism of action of milrinone and related 5-phenyl-2(1*H*)-pyridinones appears to involve, at least at part, the selective inhibition of the low-K_m, cyclic AMP specific phosphodiesterase (PDE III) that is present in myocardial cells.[21-23] Consequently, selected compounds from this series have been investigated for their ability to inhibit cardiac PDE III. Compound **5a** demonstrated a potent inhibitory effect for cardiac PDE III. The inhibitory effects for PDE I and II were significantly less (Table VII).

Table VI. Effect of 5-(4-Substituted phenyl)-2(1*H*)-pyridinones on Myocardial Contractility in Conscious Dogs following Oral Administration

	% increase contractility (n),[a] dose:		
compd	0.1 mg/kg	0.31 mg/kg	1.0 mg/kg
5a	5–10 (1)	35 ± 7 (5),[b] >3 h	75–100 (1), >4
milrinone			45 ± 5 (5),[b] 3–4 h

[a] Values indicate the response observed after 34–40 min of drug administration. [b] Significant at $p < 0.05$ compared to control.

In conclusion, imidazole substitution in 5-phenyl-2-(1*H*)-pyridinone series produce compounds with potent inotropic activity. These new agents also retained potent inhibitory activity of cardiac PDE III.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The elemental analyses (C, H, and N) for all new compounds were within 0.4% of the theoretical values. All structural assignments were consistent with IR and NMR spectra. For each general synthetic procedure a representative example of the experimental details is given.

4-(4,5,6,7-Tetrahydro-1*H*-benzimidazol-1-yl)benzaldehyde (1c, Table I). General Procedure. A mixture of 76 g (0.59 mol) of 4-fluorobenzaldehyde, 90 g (0.64 mol) of K_2CO_3, and 72 g (0.59 mol) of 4,5,6,7-tetrahydro-1*H*-benzimidazole[24] in 300 mL of pyridine was heated at reflux for 18 h. Pyridine was distilled, and the reaction mixture was diluted with CH_2Cl_2 and filtered. The inorganic residue was washed thoroughly with CH_2Cl_2 and discarded. The filtrate and the washings were combined and extracted with 4 N HCl. The aqueous acidic solution was adjusted to pH 5 and cooled. The precipitate was filtered, washed with water, and air-dried. The residue was crystallized to obtain analytically pure material.

1-[4-(2-Nitro-1-propenyl)phenyl]-1*H*-imidazole (2a, Table II). General Procedure. A mixture of 292 g (1.7 mol) of **1a**, 153.7 g (1.97 mol) of nitroethane, and 15.4 g (0.17 mol) of β-alanine in 1 L of 1-butanol was heated at reflux for 9 h. The reaction mixture was cooled and filtered. The residue was washed successively with ether and water to give 169 g of yellow crystals. Upon cooling, a second crop (44.5 g) of the product was obtained from the mother liquor.

1-[4-(1*H*-Imidazol-1-yl)phenyl]-2-propanone (3a, Table III). General Procedure. A vigorously stirred mixture of 24.7 g (1 mol) of **2a**, Fe powder (94.7 g), and $FeCl_3$ (1.2 g) in methanol (50 mL)/water (170 mL) was heated at reflux and treated dropwise with 85 mL of 12 N HCl for 4 h. Upon refluxing for an additional 1 h, the reaction mixture was cooled and filtered. The filtrate was adjusted to pH 8 with 40% NH_4OH solution and extracted with EtAc. The EtAc extract was washed with water, dried ($MgSO_4$), and evaporated to give a yellow oil, which was purified by chromatography.

1,2-Dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-6-methyl-2-oxo-3-pyridinecarbonitrile (5a, Table V). General Procedure. A mixture of **3a** (12.5 g, 0.06 mol) and *N*,*N*-dimethylformamide diethyl acetal (13.4 g, 0.2 mol) in CH_3CN (1 L) was allowed to stir overnight at room temperature followed by heating at reflux for 1.5 h to complete the reaction. The solvent was distilled under vacuo and the residue was crystallized to give 4-(dimethylamino)-3-[4-(1*H*-imidazol-1-yl)phenyl]-3-buten-2-one (**4a**), mp 140–142 °C. Anal ($C_{15}H_{17}N_3O$) C, H, N.

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Table VII. IC_{50} Values of Guinea Pig Phosphodiesterase for 5-(4-Substituted phenyl)-2(1*H*)-pyridinones

	IC_{50},[a,b] μM				
	PDE I		PDE II		PDE III,
compd	cyclic AMP	cyclic GMP	cyclic AMP	cyclic GMP	cyclic AMP
5a	38.8 (34–43)	24 (15–33)	42.6 (37–49)	33.7 (27–41)	1.85 (1.68–2.03)
milrinone	310 (190–430)	340 (170–510)	220 (140–300)	200 (120–290)	2.5 (1.9–3.1)

[a] The IC_{50} values (concentration that inhibits substrate hydrolysis by 50%) were determined from concentration–response curves in which concentrations ranged from 10^{-7} to 10^{-4} M. [b] Values in parentheses represent 95% confidence limits.

To a solution of **4a** (13.2 g, 0.05 mol) in DMF (80 mL) was added 2-cyanoacetamide (4.76 g, 0.056 mol) and CH_3ONa (6.2 g, 0.11 mol) and the mixture was heated at 100 °C for 3 h. DMF was distilled under reduced pressure and the residue was suspended in a mixture of CH_3OH (60 mL) and CH_3COOH (10 mL). After cooling in ice, the rust-colored solid was filtered, washed with CH_3OH, and air-dried to afford 6.6 g of the product. This was recrystallized from DMF to obtain analytically pure material (**5a**): IR (KBr) 1665 cm^{-1} (CO), 2222 (CN), 3420 (NH); ^1H NMR (Me_2SO-d_6) δ 2.3 (s, 3 H, 6-CH_3), 7.1 (s, 1 H, 4′-H), 7.5 (d, 2 H, aromatics), 7.8 (d, 2 H, aromatics), 7.85 (s, 1 H, 5′-H), 8.15 (s, 1 H, 4-H), 8.3 (s, 1 H, 2′-H), and 12.75 (br s, 1 H, NHCO).

To a suspension of 6 g of **5a** in 50 mL of 10% aqueous CH_3OH was added concentrated HCl with stirring to pH 2. After cooling overnight at 0 °C, the solid was filtered, washed with cold CH_3OH followed by ether, and dried to provide 6.2 g of the monohydrochloride salt of **5a** as light beige powder, mp 322–326 °C.

Via this general procedure but replacing *N*,*N*-dimethylformamide dimethyl acetal with *N*,*N*-dimethylacetamide dimethyl acetal, 1,2-dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-4,6-dimethyl-2-oxo-3-pyridinecarbonitrile (**6a**, Table V, Scheme II) was obtained: IR (KBr) 1666 cm^{-1} (CO), 2225 (CN), 3435 (NH); ^1H NMR (Me_2SO-d_6) δ 1.95 (s, 3 H, 4-CH_3), 2.05 (s, 3 H, 6-CH_3), 7.0 (s, 1 H, 4′-H), 7.3 (d, 2 H, aromatics), 7.65 (d, 2 H, aromatics), 7.7 (s, 1 H, 5′-H), 8.3 (s, 1 H, 2′-H), and 13.0 (br s, 1 H, NHCO).

2-Cyano-4-[4-(1*H*-imidazol-1-yl)phenyl]-3-methyl-2-butenamide (7a, Mixture of Isomers). A mixture of **3a** (25 g, 0.13 mol), 2-cyanoacetamide (25 g, 0.3 mol), and β-alanine (5 g, 0.05 mol) in ethanol (180 mL) containing 4A molecular sieves (50 g) was heated at reflux for 22 h. The reaction mixture was filtered hot and the residue was washed with hot ethanol. The filtrate and the washings were combined and concentrated to a small volume, and the resultant oil was partitioned between water and $CHCl_3$. The aqueous layer was separated and extracted with $CHCl_3$/2-propanol (10:2; 3 × 150 mL). The combined organic extract was washed with water, dried over $MgSO_4$, and evaporated to give 27 g (80%) of the crude product, which was used in the next step without further purification. Recrystallization from CH_3OH gave analytically pure material, mp 168–171 °C dec.

1,2-Dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-4-methyl-2-oxo-3-pyridinecarbonitrile (8a). A solution of **7a** (20.3 g, 76.3 mmol) in CH_3CN (200 mL) containing *N*,*N*-dimethylformamide diethyl acetal (11.2 g, 94 mmol) was stirred at room temperature for 1 h. The reaction mixture was evaporated to dryness, DMF (120 mL) was added, and the solution was heated in an oil bath (120 °C) for 2.5 h. DMF was distilled under reduced pressure, and the residue was triturated with ethanol and filtered. ^1H NMR of this material (5.8 g) indicated a mixture of **8a** and **9a**. This was crystallized from DMF to give 2.1 g of **8a**: mp 337–340 °C dec; IR (KBr) 1670 cm^{-1} (CO), 2225 (CN), 3435 (NH); ^1H NMR (Me_2SO-d_6) δ 2.3 (s, 3 H, 4-CH_3), 7.05 (s, 1 H, 4′-H), 7.3–7.8 (m, 6 H, 4-aromatics, 6-H, and 5′-H), 8.25 (s, 1 H, 2′-H), and 12.5 (br s, 1 H, NHCO). The filtrate was evaporated to dryness and the residue upon crystallization from EtAc provided 1.5 g of the benzyl compound **9a**: mp 274–276 °C; IR (KBr) 1675 cm^{-1} (CO), 2222 (CN), 3435 (NH); ^1H NMR (Me_2SO-d_6) δ 4.0 (s, 2 H, 6-CH_2Ph), 6.2 (d, 1 H, 5-H), 7.1 (s, 1 H, 4′-H), 7.4 (d, 1 H, 4-H), 7.45 (s, 1 H, 5′-H), 7.6–7.8 (m, 4 H, aromatics), 8.2 (s, 1 H, 2′-H), and 12.5 (br s, 1 H, NHCO).

1,2-Dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-1,6-dimethyl-2-oxo-3-pyridinecarbonitrile (10a). To a slurry of NaH (120 mg, 33 mmol, 60%) in DMF (5 mL) was added a solution of **5a** (0.7 g, 2.54 mmol) in DMF (30 mL) at 23 °C over a period of 0.5 h. The resulting dark red solution was stirred for an additional 1 h to complete the reaction. Iodomethane (0.6 g, 3.8 mmol) was added and the reaction mixture was stirred for 18 h at room temperature. DMF was distilled under reduced pressure, and the residue was treated with water. The solid was collected, washed with water, dried, and recrystallized from CH_3OH to provide **10a** (0.4 g).

1,2-Dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-6-methyl-2-oxo-3-pyridinecarboxamide (11a). A solution of **5a** (5 g) in concentrated H_2SO_4 (25 mL) was heated in a steam bath for 0.5 h. The solution was cooled to room temperature and poured into ice and the solution was adjusted to pH 8 with NH_4OH. The solid was collected, washed thoroughly with water, and recrystallized from 2-methoxyethanol to give 2 g of **11a**, mp 311–315 °C dec.

3-Amino-5-[4-(1*H*-imidazol-1-yl)phenyl]-6-methyl-2-(1*H*)-pyridinone (12a). To an ice-cold solution of the above amide **11a** (1.48 g, 5 mmol) in aqueous NaOH (1.3 g in 50 mL of water) was added 0.4 mL (7.5 mmol) of bromine over 10 min with stirring. The resulting solution was heated on steam bath for 45 min, cooled to room temperature, and neutralized with 6 N HCl. The solid was collected, washed with water, air-dried, and chromatographed (SiO_2, CH_2Cl_2/CH_3OH, 9:1) to give 0.3 g of **12a**.

1,2-Dihydro-5-[4-(1*H*-imidazol-1-yl)phenyl]-5-methyl-2-oxo-3-pyridinecarboxylic Acid (13a). A solution of **5a** (2.18 g) in 15 mL of 50% H_2SO_4 was heated at 100 °C for 8 h. The solution was cooled to room temperature and poured into ice and the precipitate was collected. The solid was stirred with excess saturated $NaHCO_3$ solution and filtered. The filtrate was adjusted to pH 4 to precipitate the carboxylic acid. The acid was filtered, washed with small volume of water, and dried at 100 °C for 18 h to give 0.7 g of **13a**, mp 297–298 °C.

5-[4-(1*H*-Imidazol-1-yl)phenyl]-6-methyl-2(1*H*)-pyridinone (14a). A solution of **5a** (21.8 g) in 110 mL of 85% (w/w) H_2SO_4 was heated at 205 °C for 19 h. The dark solution was cooled to room temperature and poured into ice–water (600 mL), and the solution was adjusted to pH 8 with NH_4OH. The precipitate was collected, washed with water, air-dried, and recrystallized from DMF to give 10 g of **14a**, mp 310–314 °C.

3-Bromo-5-[4-(1*H*-imidazol-1-yl)phenyl]-6-methyl-2-(1*H*)-pyridinone (15a). To a solution of **14a** (9.9 g, 0.04 mol) in CH_3COOH (120 mL) was added dropwise a solution of Br_2 (2.2 mL, 0.04 mol) in CH_3COOH (16 mL) at 80° C over a period of 1.5 h. The reaction mixture was heated at that temperature for an additional 1 h, cooled, and filtered. The yellow residue was suspended in water (100 mL) and neutralized with 50% aqueous NH_4OH. The resulting cream solid was collected, washed with water, dried, and recrystallized from DMF and finally chromatographed (SiO_2, CH_2Cl_2/CH_3OH, 9:1) to give 1.2 g of **15a**, mp 303.5–305 °C dec.

5-(4-Aminophenyl)-6-methyl-2(1*H*)-pyridinone (16). A mixture of **5e** (14.3 g) and 85% H_3PO_4 (130 mL) was heated at reflux for 12 h, cooled, and poured over 1 L of ice–water. The solution was adjusted to pH 9 with 50% NaOH, and the precipitate was filtered and washed with copious amount of water. The solid was dried at 100 °C for 4 h under vacuum to give 10 g of **16**, mp 230–233 °C.

4-(1,6-Dihydro-2-methyl-6-oxo-3-pyridinyl)benzonitrile (17). To an ice-cold solution of **16** (30 g, 0.15 mol) in 1.2 N HCl (1100 mL) was added dropwise with stirring a solution of $NaNO_2$ (10.4 g, 0.15 mol) in water (80 mL) over a period of 5 min while the temperature was maintained around 0 °C. After stirring for 1.5 h, the solution was neutralized with Na_2CO_3 and added in portion to an ice-cold solution of CuCN (16.6 g) and KCN (31.2 g) in a mixture of water (750 mL) and toluene (380 mL). The reaction mixture was stirred at 0 °C for 2 h followed by stirring overnight at room temperature. The dark red solid was collected,

dissolved in 1 N NaOH (1.5 L), and filtered. The filtrate was neutralized with 6 N HCl, and the light yellow solid was collected, washed with water, and dried. Recrystallization from ethanol/DMF gave **17** (12 g).

4-(1,6-Dihydro-2-methyl-6-oxo-3-pyridinyl)benzenecarbothioamide (18). H_2S was bubbled into a solution of **17** (6 g, 28.6 mmol) in DMF (160 mL) for 40 min. 1,2-Ethanediamine (2.7 g, 45 mmol) was then added followed by stirring the mixture overnight at room temperature. The mixture was poured into ice–water (800 mL) and the precipitate was filtered, washed thoroughly with water, dried, and recrystallized from CH_3OH to give 5 g of **18**.

5-[4-(4,5-Dihydro-1*H*-imidazol-2-yl)phenyl]-6-methyl-2-(1*H*)-pyridinone (19). A mixture of **18** (5 g, 0.02 mol) and 1,2-ethanediamine (30 mL) was heated with stirring in an oil bath at 100 °C for 0.5 h. The mixture was cooled, poured into water (300 mL), and acidified to pH 2. The suspension was filtered, and the filtrate was adjusted to pH 10. The solid was collected, washed with water, dried, and crystallized from DMF to give **19** (2 g).

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

Left ventricular and aortic blood pressures were recorded on a strip chart recorder. Heart rate, using a biotachometer triggered from the R wave of the ECG, and the first derivative of left ventricular blood pressure (dP/dt), obtained with a differentiator amplifier coupled to the corresponding pressure amplified, 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, 0.3, 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 adminstered to any one animal. The inotropic activity of a compound was determined by measuring changes in dP/dt_{max} of left ventricular pressure.

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

Data are expressed as means ± SEM. 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.

Acknowledgment. We thank Dr. F. A. Mackellar and his associates for spectral determinations and microanalyses. We also thank Dr. S. E. Burke, R. E. Potoczak, R. Mcnish, and D. M. Boucher for biological testing and D. Kobylarz-Singer for performing phosphodiesterase studies. We greatly appreciate the technical assistance of E. Badger.

Selective Thromboxane Synthetase Inhibitors and Antihypertensive Agents. New Derivatives of 4-Hydrazino-5*H*-pyridazino[4,5-*b*]indole, 4-Hydrazinopyridazino[4,5-*a*]indole, and Related Compounds

A. Monge,*† P. Parrado,† M. Font,‡ and E. Fernández-Alvarez§

Departamento de Quimica Orgânica y Farmacéutica, Universidad de Navarra, Pamplona, Spain, Antibióticos, S. A., Madrid, Spain, and Instituto de Quimica Orgânica General del C.S.I.C., Juan de la Cierva, 3, 28006 Madrid, Spain.
Received May 27, 1986

A series of new derivatives of 4-hydrazino-5*H*-pyridazino[4,5-*b*]indole (**5**) and 4-hydrazinopyridazino[4,5-*a*]indole (**12**) have been synthesized to investigate their activities as selective thromboxane synthetase inhibitors as well as antihypertensive agents. Several of the prepared compounds were found to be selective thromboxane synthetase inhibitors, in concordance with the Gorman model.[1] The most potent were 8-(benzyloxy)-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (**3c**) and 8-methoxy-4-hydrazino-5*H*-pyridazino[4,5-*b*]indole (**5a**). This last compound did not inhibit prostacyclin formation and showed an antihypertensive activity similar to that of hydralazine. The acute toxicity in mice for **5a**·HCl is about 2.2 times less than that for hydralazine.

The action of antithrombotic drugs that act on platelet aggregation has been largely due to inhibition of platelet cyclooxygenase, the foremost example being acetylsalicylic acid (ASA).[2] A more effective approach may be the selective inhibition of thromboxane (TXA_2) synthetase.[3] TXA_2, which rapidly hydrolyzes under physiological conditions to TXB_2, is a potent vasoconstrictor and platelet aggregating agent.[4] An additional advantage would be

† Universidad de Navarra.
‡ Antibióticos, S. A.
§ Instituto de Quimica Orgânica General del C.S.I.C.

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