Synthesis and Inotropic Activity of Pyrazolo[4,3-*c*]pyridine-4-ones and Related Compounds

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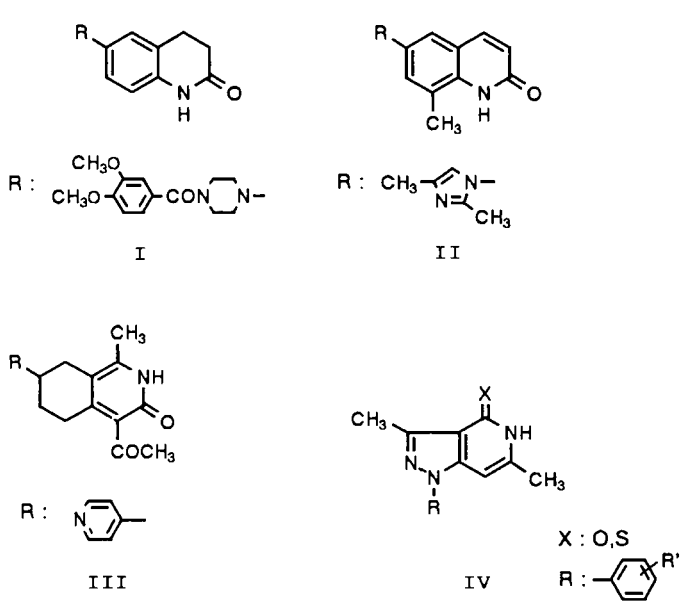
Abstract □ Two series of 3,6-dimethyl-1-phenyl-1*H*-pyrazolo[4,3-*c*]pyridine-4-ones (**5–9**) and 3,6-dimethyl-1-phenyl-1*H*-pyrazolo[4,3-*c*]pyridine-4-thiones (**11–13**) were prepared from dehydroacetic acid as starting material and evaluated for positive inotropic activity in vitro. Moreover, the activity of the synthesized compounds was compared with that of mirlinone as a reference. Among these compounds, the positive inotropic activity of **8a**, **11a**, and **12** were ~1.24, 1.77, and 1.11 times more potent, respectively, than that of mirlinone.

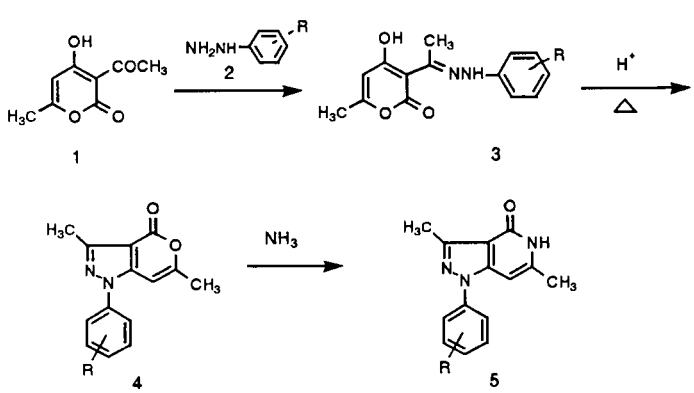
Although cardiac glycosides have major clinical utility in the treatment of congestive heart failure, their use is rather limited because of their arrythmogenic liability. The general lack of highly safe and orally effective cardiotonics has stimulated the development of new positive inotropic agents.[1] Recently, vesnarinone[2] (I) was put on market in Japan as a cardiotonic agent. It has a bicyclic lactam ring system in the quinolinone derivative and demonstrates positive inotropic action. Moreover, other quinolinone (II, UK-61260[3]) and tetrahydroisoquinolinone (III, MS-857[4]) derivatives are cardiotonic agents that have a similar ring system and are currently under clinical study (see structures). The interesting pharmacological properties of these compounds with a bicyclic lactam ring system prompted us to synthesize new bicyclic lactam compounds possessing inotropic activity. In the past, we reported a fused pyrazolo compound[5] possessing analgesic and anti-inflammatory activities. It would be interesting, from a pharmacological viewpoint, to replace the ring system adjacent to the cyclic lactam component on quinolinone or the tetrahydroisoquinolinone moiety with the pyrazolo ring system, such as pyrazolopyridine (IV). We report here the synthesis and inotropic activity of some 1*H*-pyrazolo[4,3-*c*]pyridine-4-one derivatives.



Results and Discussion

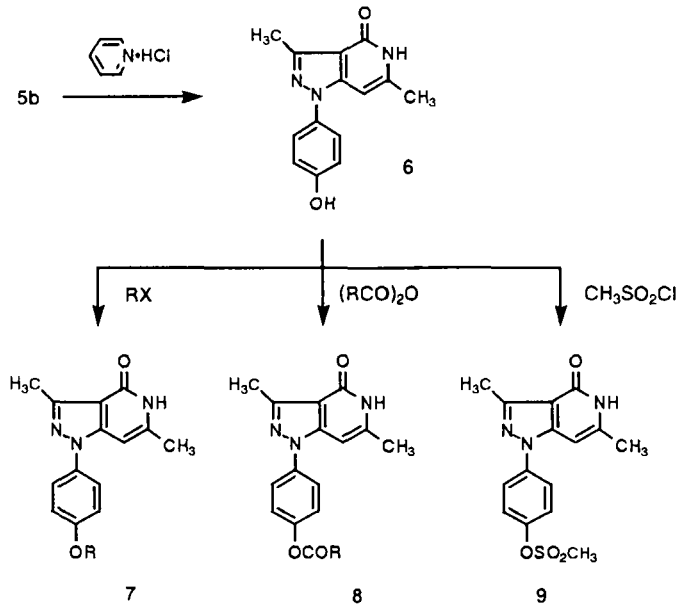
All 3,6-dimethyl-1-phenyl-1*H*-pyrazolo[4,3-*c*]pyridine-4-one derivatives (5) were prepared from dehydroacetic acid (1) as the starting material. The reaction of 1 with an appropriate phenylhydrazine derivative (2) in ethanol afforded hydrazone derivatives (3), which were converted to fused compounds (4) by dehydrating in the presence of *p*-toluenesulfonic acid. The ammonolysis of 4 with saturated ethanolic ammonia afforded lactam derivatives (5) in fair yield (Scheme I). Alkoxy (7), acyloxy (8), and methylsulfonyloxy (9) derivatives were prepared by the methods shown in Scheme II. Briefly, demethylation of methoxy derivative (**5a**) with pyridine hydrochloride afforded the hydroxy derivative (**6**). Alkylation of **6** with an appropriate alkyl halide in the presence of anhydrous potassium carbonate, acylation of **6** with an appropriate acid anhydride in pyridine, and methylsulfonylation of **6** with methylsulfonyl chloride in the presence of triethylamine afforded **7**, **8**, and **9**, respectively (Scheme II). Thiation of 4 with phosphorus pentasulfide afforded thiolactone derivatives (**10**), which were converted in the same manner as described for **5** to the thiolactam derivative (**11**). The acetoxy derivative (**13**) was obtained by demethylation of **11b** and subsequent acetylation of **12** in the same manner as described for **8** (Scheme III). The structural assignments of the synthesized compounds were based on ^{1}H NMR, IR, and mass spectral data (see *Experimental Section*). The physical and analytical data for these new compounds are listed in Table I.

As a preliminary biological test, positive inotropic activity of these compounds was determined in vitro by measuring the percent increase in contractile force of right ventricular

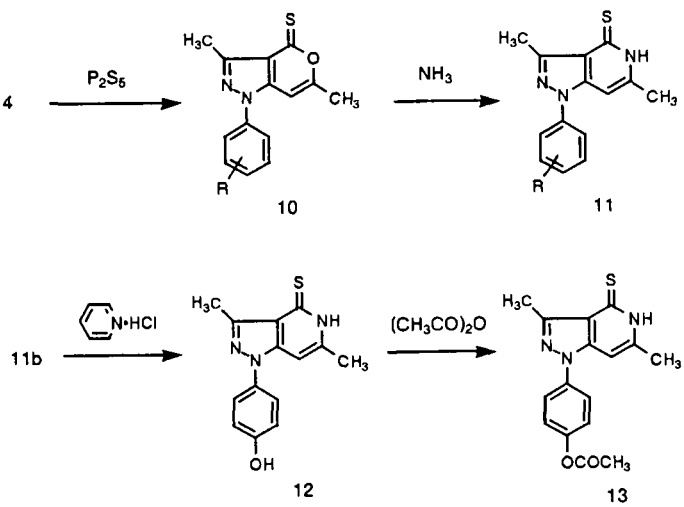


Scheme I

0022-3549/92/0600-0581$02.50/0



Scheme II



Scheme III

papillary muscles from guinea pig heart and by comparing with that of mirlinone,[6] which has previously been identified as an inotropic agent in a clinical study (Table II). Some of the pyrazolopyridine-4-one derivatives possessed moderate inotropic activity. In particular, the activity of **8a**, with an acetoxy group on the phenyl ring, was ~1.2 times that of mirlinone.[6] The introduction of a halogen atom, a carbamoylmethoxy group, and an aminoethoxy group on the phenyl ring of pyrazolopyridine compounds such as **5e**, **5f**, and **7a–7d** resulted in diminished activity. The presence of a 4-hydroxy or a 4-acetoxy group on the phenyl ring thus appears essential for the expression of potent inotropic activity in the pyridone series. For the pyrazolopyridine-4-thione derivatives, each of the three compounds possessed potent activity. In particular, 1-phenyl-1*H*-pyrazolopyridine-4-thione (**11a**) exhibited the most potent activity, being ~1.8 times more potent than mirlinone.[6] **11a** was not studied in detail because it increased heart rate, as determined in spontaneously beating right auricles isolated from guinea pig hearts in vitro.

In conclusion, the observation of more potent activity for **8a**, **11a**, and **12** appears to be related to the favorable interaction of the hydroxy, acetoxy, and thiocarbonyl groups, perhaps through hydrogen bonds, with the hydrophilic groups at the receptor surface.

Experimental Section

All mp values were recorded with a Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were obtained as follows: IR spectra, Hitachi 260-50 spectrophotometer; mass spectra, JEOL LMS-01G-2 spectrometer; and ^{1}H NMR spectra, JEOL JMN-FX 100 spectrometer (with tetramethylsilane as the internal standard). Chemical shifts of ^{1}H NMR signals are given in δ values (ppm). Elemental analysis was carried out with a Yanagimoto C H N Corder MT-2 analyzer. Dehydroacetic acid (**1**) and phenylhydrazine derivatives (**2**) were commercially available.

General Synthetic Procedure for 3—*3-(2-Phenylhydrazonoethyl)-4-hydroxy-6-methylpyrone-2-one (3a)*—A solution of phenylhydrazine (**2a**; 0.02 mol) in ethanol (10 mL) was added with stirring to a solution of dehydroacetic acid (**1**; 0.02 mol) in ethanol (50 mL). The reaction mixture was stirred at room temperature for 12 h. The precipitate was collected, and the light yellowish solid thus obtained was recrystallized from ethanol to give **3a** in 78% yield: mp, 205–207 °C; ^{1}H NMR (Me_2SO-d_6): δ 2.14 (3H, d, J = 0.73 Hz), 2.61 (3H, s), 5.91 (1H, d, J = 0.73 Hz), 6.80–7.40 (5H, m), 9.05 (1H, br s), and 15.78 (1H, br s); MS *m/e*: 258 (M^+).

Anal.—Calc. for $C_{14}H_{14}N_2O_3$: C,H,N.

General Synthetic Procedure for 4—*3,6-Dimethyl-1-(4-methoxyphenyl)-1H-pyrazolo[4,3-c]pyrane-4-one (4b)*—A mixture of **3b** (0.03 mol) and toluenesulfonic acid (0.033 mol) in toluene (300 mL) was heated under reflux for 6 h and cooled. The toluene layer was washed with water and dried over sodium sulfate. After removal of the solvent under reduced pressure, the crude white solid thus obtained was purified by silica gel column chromatography with chloroform:ethanol (10:1) as the solvent to give **4b** in 53% yield: mp, 172–173 °C; ^{1}H NMR ($CDCl_3$): δ 2.29 (3H, d, J = 0.98 Hz), 2.62 (3H, s), 3.87 (3H, s), 6.29 (1H, d, J = 0.98 Hz), 7.22 (2H, d, J = 9.2 Hz), and 7.43 (2H, d, J = 9.2 Hz); IR (KBr): 1715 cm^{-1} (lactone); MS *m/e*: 270 (M^+).

Anal.—Calc. for $C_{15}H_{14}N_2O_3$: C,H,N.

General Synthetic Procedure for 10—*3,6-Dimethyl-1-phenyl-1H-pyrazolo[4,3-c]pyrane-4-thione (10a)*—A mixture of **4a** (0.01 mol) and P_2S_5 (0.012 mol) in toluene (100 mL) was refluxed for 5 h, and the reaction mixture was filtered. The filtrate was evaporated under reduced pressure. The crude yellowish solid thus obtained was recrystallized from ethanol to give **10a** in 75% yield: mp, 154–155 °C; ^{1}H NMR (Me_2SO-d_6): δ 2.40 (3H, d, J = 0.98 Hz), 2.65 (3H, s), 7.09 (1H, d, J = 0.98 Hz), and 7.40–7.80 (5H, m); IR (KBr): 1475 and 1105 cm^{-1} (C=S); MS *m/e*: 256 (M^+).

Anal.—Calc. for $C_{14}H_{12}N_2OS$: C,H,N.

General Synthetic Procedure for 5 and 11—*3,6-Dimethyl-1-(4-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridine-4-one (5b)*—A solution of **4b** (0.006 mol) in ethanol and *N,N*-dimethylformamide (DMF; 20 mL) was saturated with ammonia under ice cooling. The mixture was heated at 100–110 °C for 10 h in a sealed tube and cooled. The precipitate was collected, and the crude white solid was recrystallized from methanol–acetone to give **5b** in 80% yield: mp, 255–257 °C; ^{1}H NMR (Me_2SO-d_6)Z:δ 2.26 (3H, d, J = 0.98 Hz), 2.48 (3H, s), 3.83 (3H, s), 6.66 (1H, d, J = 9.9 Hz), 7.11 (2H, d, J = 9.9 Hz), 7.52 (2H, d, J = 9.9 Hz), and 11.15 (1H, br s); IR (KBr): 1670 cm^{-1} (CONH); MS *m/e*: 269 (M^+).

Anal.—Calc. for $C_{15}H_{15}N_3O_2$: C,H,N.

General Synthetic Procedure for 6 and 12—*3,6-Dimethyl-1-(4-hydroxyphenyl)-1H-pyrazolo[4,3-c]pyridine-4-one (6)*—A mixture of **5b** (0.0037 mol) and pyridinium hydrochloride (0.035 mol) was heated at 200 °C for 2 h and cooled. The reaction mixture was poured into ice water. The precipitate was collected and recrystallized from ethanol to give **6** in 84% yield: mp, >300 °C; ^{1}H NMR (Me_2SO-d_6): δ 2.20 (3H, s), 2.51 (3H, s), 6.23 (1H, s), 6.92 (2H, d, J = 9.0 Hz), 7.37 (2H, d, J = 9.0 Hz), 9.80 (1H, br s), and 11.05 (1H, br s); MS *m/e*: 255 (M^+).

Anal.—Calc. for $C_{14}H_{13}N_3O_2$: C,H,N.

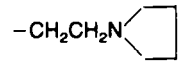
General Synthetic Procedure for 7—*3,6-Dimethyl-1-[4-(2-dimethylamino)ethoxyphenyl]-1H-pyrazolo[4,3-c]pyridine-4-one (7c)*—A mixture of **6** (0.01 mol), *N,N*-dimethylaminoethyl bromide hydrochloride (0.012 mol), and K_2CO_3 (0.012 mol) in DMF (50 mL)

Table I—Physical Data of 3–13

Compound	R	mp, °C[a]	Yield, %	Formula	Analysis, %	
					Calc.	Found
3a[b]	H	205–207 (Et)	78	$C_{14}H_{14}N_2O_3$	C 65.11 H 5.46 N 10.85	65.26 5.44 10.99
3b	4-OCH_3	145–146 (Et)	87	$C_{15}H_{16}N_2O_4$	C 62.49 H 5.59 N 9.72	62.29 5.35 9.51
3c	4-CH_3	162–163 (Et)	56	$C_{15}H_{16}N_2O_3$	C 66.16 H 5.92 N 10.29	66.54 5.98 10.16
3d	2-CH_3	129–130 (M)	61	$C_{15}H_{16}N_2O_3$	C 66.16 H 5.92 N 10.29	66.42 6.06 10.25
3e	4-Cl	198–199 (Et)	92	$C_{14}H_{13}ClN_2O_3$	C 57.45 H 4.48 N 9.57	57.82 5.57 9.59
3f	4-F	187–188 (Et:A)	93	$C_{14}H_{13}FN_2O_3$	C 60.87 H 4.74 N 10.14	60.86 4.42 9.86
3g	2,4-$(F)_2$	170–171 (Et)	62	$C_{14}H_{12}F_2N_2O_3$	C 57.15 H 4.11 N 9.52	57.46 4.21 9.57
4a[c]	H	156–157 (Et)	67	$C_{14}H_{12}N_2O_2$	C 69.99 H 5.03 N 11.66	70.20 5.00 11.60
4b	4-OCH_3	172–173 (Et)	53	$C_{15}H_{14}N_2O_3$	C 66.66 H 5.22 N 10.36	66.39 5.49 10.17
4c	4-CH_3	147–148 (Et)	43	$C_{15}H_{14}N_2O_2$	C 70.85 H 5.55 N 11.02	71.23 5.52 11.02
4d	2-CH_3	153–154 (Et:E)	58	$C_{15}H_{14}N_2O_2$	C 70.85 H 5.55 N 11.02	70.62 5.67 10.93
4e	4-Cl	226–227 (M:C)	60	$C_{14}H_{11}ClN_2O_2$	C 59.44 H 4.22 N 10.66	59.41 4.51 10.65
4f	4-F	176–177 (Et)	64	$C_{14}H_{11}FN_2O_2$	C 65.11 H 4.29 N 10.85	65.43 4.22 10.94
4g	2,4-$(F)_2$	189–190 (Et)	62	$C_{14}H_{10}F_2N_2O_2$	C 60.87 H 3.65 N 10.14	61.19 3.87 10.14
5a[d]	H	242–243 (Et)	75	$C_{14}H_{13}N_3O$	C 70.28 H 5.48 N 17.52	70.81 5.54 17.67
5b	4-OCH_3	255–257 (M:A)	80	$C_{15}H_{15}N_3O_2$	C 66.90 H 5.61 N 15.60	66.85 5.71 15.50
5c	4-CH_3	287–288 (Et)	83	$C_{15}H_{15}N_3O$	C 71.13 H 5.97 N 16.59	71.56 6.05 16.68
5d	2-CH_3	240–241 (Et)	50	$C_{15}H_{15}N_3O$	C 71.13 H 5.97 N 16.59	71.37 5.71 16.65
5e	4-Cl	301–302 (M:A)	75	$C_{14}H_{12}ClN_3O$	C 61.43 H 4.42 N 15.35	61.48 4.74 15.42
5f	4-F	287–288 (Et)	34	$C_{14}H_{12}FN_3O$	C 65.36 H 4.70 N 16.33	65.57 4.72 16.27
5g	2,4-$(F)_2$	>310 (Et)	50	$C_{14}H_{11}F_2N_3O$	C 61.09 H 4.03 N 15.27	61.36 4.09 15.50
6	—[e]	>310 (Et)	84	$C_{14}H_{13}N_3O_2$	C 65.87 H 5.13 N 16.46	65.99 4.97 16.28
7a	$-CH(CH_3)_2$	233–234 (Et)	52	$C_{17}H_{19}N_3O_2$	C 68.67 H 6.44 N 14.13	68.84 6.41 14.11
7b	$-CH_2CON(C_2H_5)_2$	150–151 (Et:E)	44	$C_{20}H_{24}N_4O_3$	C 65.20 H 6.57 N 15.21	64.95 6.60 14.99

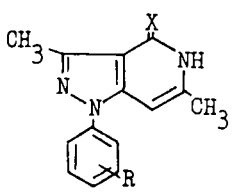
(Continued)

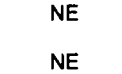
Table I—Continued

Compound	R	mp, °C[a]	Yield, %	Formula	Analysis, %	
					Calc.	Found
7c	$-CH_2CH_2N(CH_3)_2$	211–213 (Et:E)	45	$C_{18}H_{22}N_4O_2 \cdot 1/4H_2O$	C 65.34 H 6.85 N 16.93	65.49 6.72 16.95
7d		180–181 (Et:E)	58	$C_{20}H_{24}N_4O_2$	C 68.16 H 6.86 N 15.90	68.26 6.90 15.70
8a	$-CH_3$	281–282 (Et)	78	$C_{16}H_{15}N_3O_3$	C 64.64 H 5.09 N 14.13	64.87 4.98 14.19
8b	$-CH(CH_3)_2$	267–268 (Et)	67	$C_{18}H_{19}N_3O_3$	C 66.45 H 5.88 N 12.91	66.40 5.81 12.80
9	—	272–273 (M)	92	$C_{15}H_{15}N_3O_4S$	C 54.04 H 4.54 N 12.60	53.97 4.61 12.79
10a	H	154–155 (Et)	75	$C_{14}H_{12}N_2OS$	C 65.60 H 4.72 N 10.93	65.88 4.85 10.92
10b	4-OCH_3	195–196 (Et)	82	$C_{15}H_{14}N_2O_2S$	C 62.92 H 4.93 N 9.78	62.75 5.16 9.47
11a	H	252–254 (Et)	75	$C_{14}H_{13}N_3S$	C 65.85 H 5.13 N 16.46	65.64 5.19 16.55
11b	4-OCH_3	260–261 (Et)	77	$C_{15}H_{15}N_3OS \cdot 2/3H_2O$	C 60.58 H 5.53 N 14.13	60.75 5.33 14.40
12	—	295–296 (Et:A)	68	$C_{14}H_{13}N_3OS \cdot 1/2H_2O$	C 59.98 H 5.03 N 14.99	59.80 5.26 14.83
13	—	271–273 (Et)	82	$C_{16}H_{15}N_3O_2S$	C 61.32 H 4.82 N 13.41	61.07 4.88 13.42

[a] Recrystallization solvents shown in parentheses: (Et) ethanol; (M) methanol; (Et:A) ethanol:acetone; (Et:E) ethanol:ether; (M:C) methanol:chloroform; (M:A) methanol:acetone. [b] Reference 7. [c] Reference 8. [d] Reference 9. [e] —, not applicable.

Table II—Inotropic Activities



Compound	R	X	% Increase at 1 × 10^{-4} M[a]	n[b]	Relative Potency[c]
5a	H	O	4	4	0.034
5b	4-OCH_3	O	32	3	0.27
5c	4-CH_3	O	15	3	0.13
5d	2-CH_3	O	NE[d]	3	—[e]
5e	4-Cl	O	NE	3	—
5f	4-F	O	NE	3	—
6	4-OH	O	71	4	0.60
7a	4-$OCH(CH_3)_2$	O	NE	2	—
7b	4-$OCH_2CON(C_2H_5)_2$	O	NE	2	—
7c	4-$OCH_2CH_2N(CH_3)_2$	O	NE	2	—
7d	4-OCH_2CH_2N 	O	NE	2	—
8a	4-$OCOCH_3$	O	147	2	1.24
11a	H	S	131[f]	3	1.77
12	4-OH	S	139	3	1.17
13	4-$OCOCH_3$	S	82[g]	3	1.00
Mirlinone			119, 74,[f] 83[g]	3	1.00

[a] See *Experimental Section*. [b] Number of experiments. [c] Calculated as the ratio of the percent increase of potency of each compound to that of mirlinone (relative potency of mirlinone, 1.00). [d] NE, No effect. [e] —, Not determined. [f] Concentration of 3 × 10^{-5} M. [g] Concentration of 1 × 10^{-5} M.

was stirred at 70 °C for 24 h and cooled. The reaction mixture was evaporated under reduced pressure, and the residue was extracted with ethyl acetate (50 mL × 2). The organic layer was washed with water and dried over sodium sulfate. After removal of the solvent under reduced pressure, the white solid thus obtained was purified by silica gel column chromatography with chloroform:ethanol (5:1) as solvent to give **7c** in 44% yield: mp, 211–213 °C; ^{1}H NMR (Me_2SO-d_6): δ 2.20 (3H, s), 2.23 (6H, s), 2.51 (3H, s), 2.65 (2H, t, J = 5.6 Hz), 4.11 (2H, t, J = 5.6 Hz), 6.27 (1H, s), 7.08 (2H, d, J = 8.8 Hz), 7.50 (2H, d, J = 8.8 Hz), and 11.08 (1H, br s); MS *m/e*: 326 (M^+).

Anal.—Calc. for $C_{18}H_{22}N_4O_2 \cdot 1/4H_2O$: C,H,N.

General Synthetic Procedure for 8, 9, and 13—*3,6-Dimethyl-1-(4-acetyloxyphenyl)-1H-pyrazolo[4,3-c]pyridine-4-one (8a)*—A mixture of **6** (0.002 mol) and acetic anhydride (4 mL) in pyridine (6 mL) was stirred at 80 °C for 1 h and cooled. The reaction mixture was poured into ice water. The precipitate was collected and recrystallized from ethanol to give **8a** in 78% yield: mp, 281–282 °C; ^{1}H NMR (Me_2SO-d_6): δ 2.22 (3H, s), 2.32 (3H, s), 2.53 (3H, s), 6.40 (1H, s), 7.30 (2H, d, J = 9.8 Hz), 7.66 (2H, d, J = 9.8 Hz), and 11.16 (1H, br s); MS *m/e*: 297 (M^+).

Anal.—Calc. for $C_{16}H_{15}N_3O_3$: C,H,N.

3,6-Dimethyl-(4-methylsulfonyloxyphenyl)-1H-pyrazolo[4,3-c]-pyridine-4-one (9)—A solution of methylsulfonyl chloride (0.0022 mol) in DMF (2 mL) was added in a dropwise manner to a solution of **6** (0.002 mol) and triethylamine (0.5 mL) in DMF (10 mL) and stirred at room temperature for 10 h. The reaction mixture was poured into ice water. The precipitate was collected, washed with water, and recrystallized from methanol to give **9** in 92% yield: mp, 272–273 °C; ^{1}H NMR (Me_2SO-d_6): δ 2.22 (3H, s), 2.53 (3H, s), 3.45 (3H, s), 6.45 (1H, s), 7.52 (2H, d, J = 9.0 Hz), 7.75 (2H, d, J = 9.0 Hz), and 11.10 (1H, br s); MS *m/e*: 333 (M^+).

Anal.—Calc. for $C_{15}H_{15}N_3O_4S$: C,H,N.

Inotropic Activity[10]—The experiments were performed on electrically driven, right ventricular papillary muscles from guinea pig

heart. The animals (male; body weight, 550–800 g) were sacrificed and bled from the carotid arteries. The hearts of the animals were quickly excised, and the papillary muscles were dissected in aerated bathing solution (composition given below) at room temperature. Each preparation was suspended in a 30-mL glass tissue chamber to record isomeric contraction. The bathing solution was a modified Tyrode's solution containing the following (mmol/L): NaCl (119.8), KCl (5.4), $CaCl_2$ (1.8), $MgCl_2$ (1.05), NaH_2PO_4 (0.42), $NaHCO_3$ (22.6), Na_2EDTA (disodium ethylenediaminetetraacetate; 0.05), and glucose (5.0). The solution was continuously aerated with 95% O_2:5% CO_2 and maintained at 35 °C and pH 7.4. The force of contraction of the papillary muscles was measured with a force transdure (UgoBasile, 7004). Each muscle was stretched to a length at which the force of contraction would be maximal (~5 mN). The papillary muscles were electrically paced (1 Hz) by bipolar-stimulating electrodes with rectangular pulses of 5-ms duration (San-ei, 3F46). The voltage was ~20% greater than the threshold. All preparations were equilibrated in a drug-free bathing solution until complete mechanical stabilization. The test compounds were dissolved in Me_2SO, and the bathing solution also contained 2% (v/v) Me_2SO. The tissues were subsequently observed for their response to the test compounds for 10 min. Appropriate aliquots of Me_2SO were added to all control experiments.

References and Notes

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