Cardiotonic Agents. 1-Methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinones and Related Compounds. Synthesis and Activity[1]

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A series of 1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinones and related compounds were synthesized and evaluated for positive inotropic activity. Most members of this series exerted a dose-dependent increase in myocardial contractility in the dog acute heart failure model, whereas they caused only slight changes in heart rate and blood pressure. Several derivatives, especially those with cyano, acetyl, and ethyl substituents at the 4-position, were more potent than milrinone, which was used as a reference. 4-Acetyl-1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone (MS-857) is one of the most potent positive inotropic agents in this series.

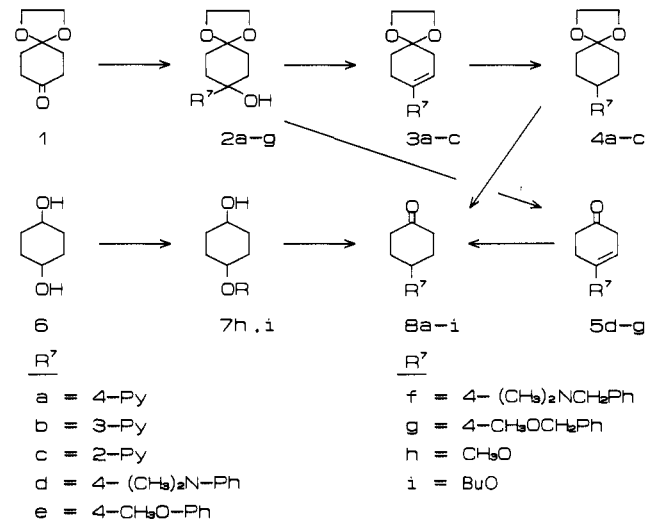
Digitalis glycosides have been the principal agents used to treat congestive heart failure for more than a century. However, their narrow therapeutic range and arrhythmogenic liability has led to increasing efforts to develop safer drugs. Sympathomimetic agents such as dopamine and dobutamine have recently been introduced for the therapy of congestive heart failure, but their use is limited by oral ineffectiveness and tachyphylaxis due to β-receptor regulation. These circumstances have led to the development of noncatecholamine and nonglycoside cardiotonic agents such as milrinone, enoximone, and imazodane[2,3] over the past decade. In this paper, we describe our work on a novel class of compounds with potent inotropic activity—5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone derivatives. Common pharmacophoric patterns among various cardiotonic agents indicate that positive inotropic action basically requires an aromatic area and an electronegative region produced by the amide system.[4] We hypothesized that introducing an aromatic substituent onto the isoquinoline ring would elevate the positive inotropic activity and found, as expected, that 5,6,7,8-tetrahydro-3(2*H*)-isoquinolinones bearing aromatic rings such as phenyl and pyridyl are very potent positive inotropic agents. 4-Acetyl-1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone (MS-857), in particular, was one of the most active compounds in this series.[5]

Chemistry

4-Cyano-1-methyl-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinones were prepared by the cyclization reaction of cyanoacetamide and 2-acetylcyclohexanone derivatives, which were derived from 4-substituted cyclohexanones by acetylation (Scheme II). The synthesis of 4-substituted cyclohexanones is illustrated in Scheme I. The action of Grignard reagents or aryllithium reagents on cyclohexane-1,4-dione monoethylene ketal (1) gave alcohols **2**. This was followed by dehydration with thionyl chloride/pyridine to obtain cyclohexenes **3**. Subsequent hydrogenation with Pd/C and deprotection with CF_3COOH, produced 4-substituted cyclohexanones **8**. This method was preferred for the 4-arylcyclohexanones. 4-Alkoxycyclohexanones were prepared by the monoalkylation of 1,4-dihydroxycyclohexane sodium salts, followed by oxidation with PCC.[6]

Several acylation methods were adapted for conversion of the 4-substituted cyclohexanones **8** to 2-acylcyclohexanones **9** (Scheme II).[7] Method A involved enolate formation with LDA and subsequent reaction with acylimidazole.[8] Alternative simple methods are the treatment

Scheme I



of cyclohexanones with NaH and ethyl acetate (method B)[9] and the acylation with carboxylic acid anhydride in the presence of $BF_3 \cdot CH_3COOH$ (method C). The other methods involve enamine formation with pyrrolidine followed by the reaction with carboxylic acid anhydride (method D).[10]

Cyclization of 4-substituted cyclohexanones with cyanoacetamide in the presence of piperidine/EtOH gave a

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(1) Presented in part at the 107th Annual Meeting of the Pharm. Soc. Japan, Kyoto, April 1987. See *Proc. Annu. Meeting Pharm. Soc. Jpn, 107th* **1987**, 429.
(2) Scriavine, A. *New Drugs Annual: Cardiovascular Drugs*; Raven Press: New York, 1985; Vol. 3, p 63 (enoximone), p 81 (imazodan), p 245 (milrinone).
(3) Erhardt, P. W. *J. Med. Chem.* **1987**, *30*, 231.
(4) Weisharr, R. E.; Cain, M. H.; Bristol, J. A. *J. Med. Chem.* **1985**, *28*, 537.
(5) (a) Ito, T.; Suzuki, T.; San-nohe, K.; Maruyama, M.; Hirayama, M.; Kitano, T. JP Kokai 229865, 1986. (b) Suzuki, T.; San-nohe, K.; Ito, T.; Kitano, T.; Maruyama, M.; Hirayama, M.; Kamiya, J.; Awaya, A. JP Kokai 291570, 1986. (c) San-nohe, K.; Otsuka, K.; Ito, T.; Maruyama, M.; Kitano, T.; Hirayama, M. JP Kokai 5963, 1987. (d) Kaiho, T.; Kajiya, S.; Otsuka, K.; Maruyama, M.; Hirayama, M. JP Kokai 57585, 1988.
(6) Beil. 8. II. 5.
(7) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; The Benjamin/Cumming Publishing Co.: Melon Park, CA, 1972; pp 734–819.
(8) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208.
(9) Čejka, J.; Ferles, M.; Chlădek, S.; Labský, J.; Zelinka, M. *Collect. Czech. Chem. Commun.* **1966**, *26*, 1429.
(10) von Strandtmann, M. P.; Cohen, M. P.; Shavel, J., Jr. *J. Org. Chem.* **1966**, *31*, 797.

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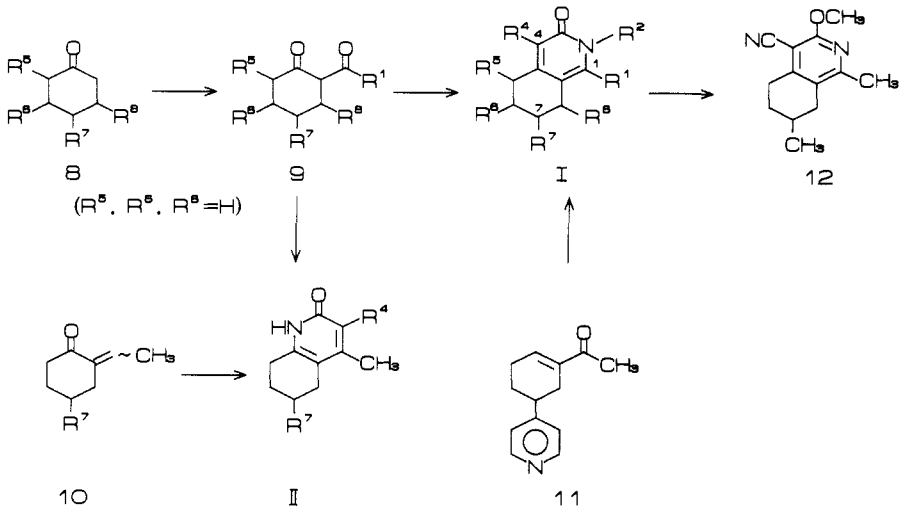
Scheme II



mixture of 4-cyano-1-methyl-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinones I and 3-cyano-4-methyl-5,6,7,8-tetrahydro-2(1*H*)-quinolinones II (approximate ratio 9:1) as evidenced by the NMR spectrum of the latter, which showed a shielded signal (singlet, 3 H) at around 2.2 ppm for the 4-methyls. This assignment was confirmed by the fact that isoquinolinone had previously been prepared from 1-acetylcyclohexene **11**.[11] 3-Cyano-4-methyl-6-(4-pyridyl)-5,6,7,8-tetrahydro-2(1*H*)-quinolinone (**51**) was also prepared as shown in Scheme II.

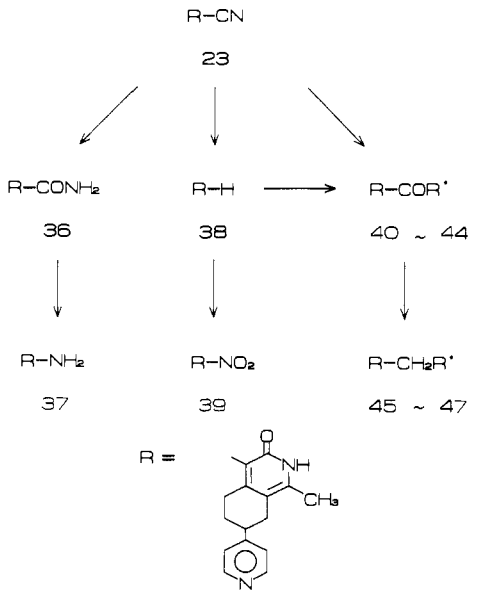
As presented in Scheme II, chlorination of **14** with phosphorus oxychloride and subsequent reaction with sodium methoxide in methanol provided the *O*-methyl analogue **12**. Alkylation with iodomethane in the presence of sodium methoxide in methanol gave the *N*-methyl analogue **15**. Variation in the position of the substituents on 2-acetylcyclohexanone enabled the preparation of 5-, 6-, and 8-methyl-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinones **30–32**. 4-Cyano-1-methyl-6-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone (**33**) was also prepared from cyclohexane-1,3-dione monoethylene ketal as shown in Scheme I.

Manipulation of the 4-cyano compound **23** was tried (Scheme III).[12] Acidic hydrolysis of nitrile **23** in 90% H_2SO_4 at 80–90 °C afforded amide **36**, which was then converted by Hoffman degradation to amine **37**. Hydrolysis of nitrile **23** in 85% H_2SO_4 at 190–200 °C gave via decarboxylation **38**. Nitration of **38** with HNO_3/H_2SO_4 afforded **39**. Formation of aldehyde **40** via Reimer–Tieman reaction of **38**, followed by the Wolff–Kishner reduction with hydrazine and KOH/ethylene glycol, provided the 4-methyl compound **45**. Nitrile **23** was converted to the 4-alkanoyl compounds **41–44** via Grignard reaction. Wolff–Kishner reaction of **41** and **42** provided the 4-alkyl compounds **46** and **47**. 4-Acetyl-1-methyl-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinones **41** could be alternatively obtained by cyclization of acetoacetamide and 2-acetylcyclohexanones **9**.[13]

Pharmacological Results and Discussion

The compounds were evaluated for positive inotropic activity in the propranolol-induced dog heart failure model,

Scheme III



as described in the Experimental Section. ED_{100} values were determined by log dose. The data are summarized in Tables I and II. The substituents at the 1-, 4-, and 7-positions on isoquinolinone were systematically modified to optimize the inotropic activity. Considerable loss of activity was observed by manipulation of the lactam moiety in this series of compounds (**12**, **15**), indicating that a tautomerizable acidic proton is required for significant positive inotropic activity. Replacing the 1-methyl substituent by hydrogen or propyl leads to a substantial reduction in potency relative to the parent compound (**28**, **29** vs **13**). An analogous modification was carried out with 4-acetyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone (**34**, **35** vs **23**). The 1-methyl appears to be the optimal-size substituent for the biological activity, and provides sufficient lipophilicity to reach the active site. This substituent effect can be attributed to a methyl-sized lipophilic pocket in the active site.[14]

The electronic effect of substituents at the 4-position appears to be relatively unimportant as evidenced by the interchangeability of the cyano and amino substituents (**23**,

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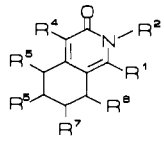
Table I. 5,6,7,8-Tetrahydro-3(2*H*)-isoquinolinones



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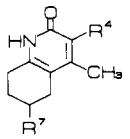
compd	R^1	R^2	R^4	R^5	R^6	R^7	R^8	mp, °C (recrystn solvent)[a]	formula[b]	yield,[c] % (prepn method)[d]	ED_{100},[e] mg/kg
13	CH_3	H	CN	H	H	H	H	278 (B)	$C_{11}H_{12}N_2O$	81 (D)	3
14	CH_3	H	CN	H	H	CH_3	H	300 dec (D)	$C_{12}H_{14}N_2O$	42 (B)	0.3
15	CH_3	CH_3	CN	H	H	CH_3	H	129–131 (A)	$C_{13}H_{16}N_2O$	*f*	(–)
16	CH_3	H	CN	H	H	Et	H	287–288 dec (A)	$C_{13}H_{16}N_2O$	49 (B)	1
17	CH_3	H	CN	H	H	*t*-Bu	H	281–282 (A)	$C_{15}H_{20}N_2O$	50 (B)	(–)
18	CH_3	H	CN	H	H	OCH_3	H	263–264 (B)	$C_{12}H_{14}N_2O_2$	17 (C)	1
19	CH_3	H	CN	H	H	O-*n*-Bu	H	204–205 (B)	$C_{15}H_{20}N_2O_2$	12 (C)	(–)
20	CH_3	H	CN	H	H	Ph	H	>300 (A)	$C_{17}H_{16}N_2O$	84 (B)	0.1
21	CH_3	H	CN	H	H	4-CH_3OPh	H	>300 (C)	$C_{16}H_{18}N_2O_2$	23 (A)	0.3
22	CH_3	H	CN	H	H	4-$(CH_3)_2$NPh	H	>300 (A)	$C_{19}H_{21}N_3O$	20 (A)	(–)
23	CH_3	H	CN	H	H	4-Py	H	298–300 dec (A)	$C_{16}H_{15}N_3O$	23 (A, D)	0.1
24	CH_3	H	CN	H	H	3-Py	H	>300 (A)	$C_{16}H_{15}N_3O$	26 (A)	0.1
25	CH_3	H	CN	H	H	2-Py	H	>300 (A)	$C_{16}H_{15}N_3O$	24 (A)	0.3
26	CH_3	H	CN	H	H	4-$(CH_3)_2NCH_2$Ph	H	269–271 dec (B)	$C_{20}H_{23}N_3O$	18 (A)	(–)
27	CH_3	H	CN	H	H	4-CH_3OCH_2Ph	H	277–279 dec (A)	$C_{19}H_{20}N_2O_2$	29 (A)	(–)
28	H	H	CN	H	H	H	H	228–230 (A)	$C_{10}H_{10}N_2O$	26[g]	(–)
29	C_3H_7	H	CN	H	H	H	H	262–265 dec (A)	$C_{13}H_{16}N_2O$	6 (C)	(–)
30	CH_3	H	CN	CH_3	H	H	H	266–267 (A)	$C_{12}H_{14}N_2O$	5 (C)	2
31	CH_3	H	CN	H	CH_3	H	H	>300 (C)	$C_{12}H_{14}N_2O$	18 (B)	1
32	CH_3	H	CN	H	H	H	CH_3	>300 (D)	$C_{12}H_{14}N_2O$	49[h]	3
33	CH_3	H	CN	H	4-Py	H	H	>300 (A)	$C_{16}H_{15}N_3O$	22 (A)	(–)
34	Et	H	$COCH_3$	H	H	4-Py	H	290 dec (A)	$C_{18}H_{20}N_2O_2$	14 (B)	0.3
35	C_4H_9	H	$COCH_3$	H	H	4-Py	H	223–224 (A)	$C_{20}H_{24}N_2O_2$	11 (B)	(–)
36	CH_3	H	$CONH_2$	H	H	4-Py	H	>300 (F)	$C_{16}H_{17}N_3O_2$	85 (23)	(–)
37	CH_3	H	NH_2	H	H	4-Py	H	>290 (C)	$C_{15}H_{17}N_3O$	62 (36)	0.2
38	CH_3	H	H	H	H	4-Py	H	>300 (E)	$C_{15}H_{16}N_2O$	88 (23)	0.3
39	CH_3	H	NO_2	H	H	4-Py	H	275–276 dec (A)	$C_{15}H_{15}N_3O_3$	23 (38)	0.1
40	CH_3	H	CHO	H	H	4-Py	H	275–278[f]	$C_{16}H_{16}N_2O_2$	9 (38)	(–)
41	CH_3	H	$COCH_3$	H	H	4-Py	H	>300 (A)	$C_{17}H_{18}N_2O_2$	71 (23)	0.1
42	CH_3	H	COEt	H	H	4-Py	H	295 dec (A)	$C_{18}H_{20}N_2O_2$	27 (23)	4
43	CH_3	H	COC_3H_7	H	H	4-Py	H	267–270 dec (A)	$C_{19}H_{22}N_2O_2$	24 (23)	(–)
44	CH_3	H	COPh	H	H	4-Py	H	160–163 (A)	$C_{22}H_{20}N_2O_2$	56 (23)	(–)
45	CH_3	H	CH_3	H	H	4-Py	H	>300 (B)	$C_{16}H_{18}N_2O$	7 (40)	2
46	CH_3	H	Et	H	H	4-Py	H	>300 (A)	$C_{17}H_{20}N_2O$	33 (41)	0.02
47	CH_3	H	Pr	H	H	4-Py	H	>300 (A)	$C_{18}H_{22}N_2O$	28 (42)	0.3
milrinone											0.1

[a] A = EtOH; B = MeOH; C = $CHCl_3$/MeOH; D = MeOH/H_2O; E = Et_2O/$CHCl_3$; F = DMF. [b] Analyses were within 0.4% of the calculated value. [c] This value shows that overall yield of acylation and cyclization (compounds **13–35**). [d] Method of acylation for compounds **13–35**. Compound number of starting material for compounds **36–47**. [e] Dose to recover the value of LV dp/dt max before the propranolol injection. Three experiments each were done unless otherwise stated. Inactive compounds were indicated with (–) and the highest does tested was 10 mg/kg. [f] See the Experimental Section. [g] **28** was prepared from 2-(aminomethylene)cyclohexanone according to Ban's procedure.[21] [h] **32** was prepared by the cyclization of 2-acetyl-3-methylcyclohexanone with cyanoacetamide.

Table II. 5,6,7,8-Tetrahydro-2(1*H*)-quinolinones



II

compd	R^4	R^7	mp, °C (recrystn solvent)[a]	formula[b]	yield,[c] %	ED_{100},[e] mg/kg
48	CN	H	291 dec (B)	$C_{11}H_{12}N_2O$	5[d]	(–)
49	CN	CH_3	280 dec (B)	$C_{12}H_{14}N_2O$	7[f]	(–)
50	CN	OCH_3	230–231 (B)	$C_{12}H_{14}N_2O_2$	3[f]	(–)
51	CN	4-Py	>300[g]	$C_{11}H_{15}N_3O$	4[f]	(–)
52	$COCH_3$	4-Py	299–300 (B)	$C_{17}H_{18}N_2O_2$	42[h]	(–)

[a,b,c,e] See corresponding footnotes in Table I. [d] **48** was prepared according to Sakurai's procedure.[22] [f] **49–51** were obtained as minor products in the cyclization reaction as shown in Scheme II. [g] Silica gel chromatography using $CHCl_3$/MeOH (10:1) as an eluent. [h] **52** was prepared from **51** via Grignard reaction.

37), which might affect the tautomerism between 5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone and 3-hydroxy-5,6,7,8-tetrahydroisoquinoline. When the acetyl substituent at the 4-position was exchanged for propionyl (**43**) and benzoyl (**44**), inotropic activity significantly decreased, indicating that bulkiness can be deleterious at the 4-position of 5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone. However, as was observed with **45**, **46**, and **47**, the activity of the 4-alkyl

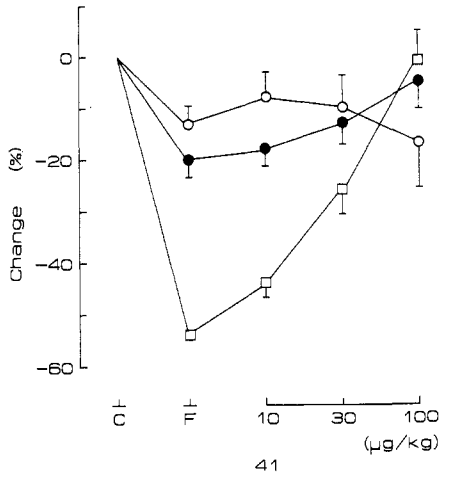


Figure 1. Effects of 41 on LV dp/dt_{max}, HR, and BP of anesthetized dogs ($n = 6$) with propranolol-induced heart failure. Each point represents the mean value, and vertical bars show SE. C: control. F: failure. $p < 0.01$ significance determined by the t test. (●) HR, (○) BP, (□) LV dp/dt_{max}.

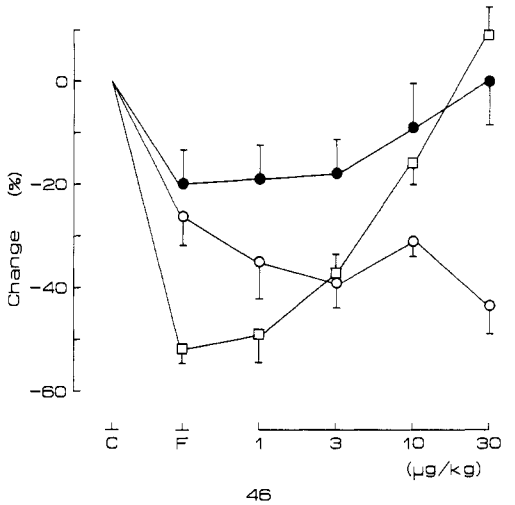


Figure 2. Effects of 46 on LV dp/dt_{max}, HR, and BP of anesthetized dogs ($n = 6$) with propranolol-induced heart failure. Values presented were the same as those in Figure 1. (●) HR, (○) BP, (□) LV dp/dt_{max}.

compounds could not be simply rationalized on the basis of their bulkiness. The 4-ethyl compound **46** displayed maximum potency, whereas the 4-methyl analogue **45** was substantially less potent.

We next explored the effect of substituents on the cyclohexene ring of 5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone. Introduction of the methyl group at the 7-position on isoquinolinone increased the inotropic activity (**14** vs. **13**). However, the 5-, 6-, and 8-methyl analogues were consistently less potent than the 7-methyl compound (**30–32** vs **14**). Replacement of the 7-methyl by the more bulky *tert*-butyl or the very flexible *n*-butoxy resulted in a reduction in potency (**17**, **19**). In contrast, introducing a 7-phenyl substituent led to an increase in potency (**20**). Because of the limited solubility of **20**, further introduction of substituents onto the aromatic ring was attempted to overcome this problem. However, all substituents tested always led to a reduction in activity (**21**, **22**, **26**, and **27**). We concluded that pyridyl substituents are the most appropriate for positive inotropic activity (**23**, **24**), as can be seen from Table I.

5,6,7,8-Tetrahydro-2(1*H*)-quinolinones, a series of minor products for the cyclization reaction, did not show positive inotropic activity (Table II).

Compounds **23**, **24**, **39**, and **41** showed high activities equivalent to those of milrinone. And compound **46** possessed the maximum positive inotropic activity in this series. Compound **41**, which has good physical properties and a low toxicity, and compound **46** were extensively evaluated. The cardiovascular profiles of **41** and **46** in anesthetized dogs are displayed in Figures 1 and 2, respectively. Intravenous administration of 10–100 μg/kg of compound **41** and 1–30 μg/kg of **46** resulted in a dose-related increase of the maximum rate of rise in the left ventricular pressure (LV dp/dt_{max}) that was accompanied by a small increase in heart rate (HR) and small decreases in blood pressure (BP). Compound **41** had a much smaller effect on BP than **46**. Several compounds from this series have been studied for their ability to inhibit PDE III, which might be the principal component for the mechanism of inotropic action.[15] Compound **41** demonstrated a selective inhibitory effect for PDE III (Table III). As oral effectiveness is essential to cardiotonic agents, compound **41** was administered orally in concious dogs and found to produce a dose-dependent increase in LV dp/dt_{max}. These results and further pharmacological studies were reported in a separate paper.[16]

Table III. IC_{50} Values (μM) for Mongrel Dog Phosphodiesterase for **41**

	IC_{50},[a-c] μM		
	PDE I (4 μM)	PDE III (4 μM)	selectivity[d]
41 (MS-857)	409 ± 38	1.5 ± 0.23	273
milrinone	198 ± 13	1.1 ± 0.11	180

[a] Drugs were dissolved in 2% DMSO (final concentration). [b] IC_{50} values (concentration that inhibits substrate hydrolysis by 50%) were determined from concentration curves range from 10^{-6} to 10^{-3} M. [c] Four experiments were done. [d] Selectivity means IC_{50} (PDE-I)/IC_{50} (PDE-III).

We concluded that 1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone derivatives represent a potent new class of positive inotropic agents. Compound **41** (MS-857), one of the most potent inotropic agents in this series, is now undergoing clinical trials.

Experimental Section

Chemistry. Melting points were obtained on a calibrated Yanagimoto hot stage apparatus and are uncorrected. ^1H NMR spectra were obtained on a JEOL JNM-MH-100 (100 MHz) instrument. Infrared spectra were recorded with a JASCO IRA-2 spectrometer using KBr pellets. Elemental analyses were within 0.4% of the theoretical values unless otherwise stated. All structural assignments were consistent with IR and NMR spectra. All organic extracts were dried over magnesium sulfate prior to evaporation.

4-Hydroxy-4-(4-pyridyl)cyclohexanone Ethylene Ketal (2a). General Procedure. To a solution of *n*-butyllithium (1.6 M in hexane, 20 mL) in dry ether (35 mL) was added a cold solution of 4-bromopyridine (5.1 g, 32 mmol) in dry ether (30 mL) dropwise at −78 °C. After stirring at the same temperature, a solution of cyclohexane-1,4-dione monoethylene ketal (1)[17] (5.0 g, 32 mmol) in dry THF (30 mL) was added over a period of 10 min. Stirring was continued for 1 h at −78 °C and then the reaction mixture was slowly warmed to −20 °C over 1 h. When the reaction mixture was poured into saturated aqueous NH_4Cl (100 mL), the layers were separated. The aqueous layer was extracted with $CHCl_3$ (100 mL × 3), and the extracts were com-

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bined with the organic layer. After drying and concentration, the residual oil was triturated with ether to provide **2a** (5.0 g, 66%), mp 165.5–167 °C.

4-(4-Pyridyl)cyclohex-3-en-1-one Ethylene Ketal (3a). Thionyl chloride (8 mL) was added to a solution of **2a** (5.0 g, 21 mmol) in pyridine (40 mL) over 10 min at −10 °C. After stirring at 0 °C for 2 h, the reaction mixture was poured onto ice (100 g) and extracted with CH_2Cl_2 (100 mL). The aqueous layer was adjusted to pH 8 with 2 N NaOH. The extracts were combined, dried, and concentrated in vacuo. The residue was dissolved in ether and filtered. Concentration of the filtrate gave **3a** (4.0 g, 88%), mp 67–70 °C.

4-(4-Pyridyl)cyclohexanone Ethylene Ketal (4a). A solution of **3a** (4.0 g, 18.4 mmol) in ethyl acetate (50 mL) containing 10% Pd/C (500 mg) was hydrogenated under atmospheric pressure at room temperature for 3 h. After filtration of the catalyst, the solution was concentrated in vacuo, giving **4a** (3.9 g, 95%), mp 85–88 °C.

4-(4-Pyridyl)cyclohexanone (8a). Water (1 mL) was added to a cold solution of **4a** (3.8 g, 17 mmol) in CF_3COOH (25 mL). The mixture was stirred at room temperature for 1.5 h and then added dropwise to saturated aqueous $NaHCO_3$ (300 mL). The resulting mixture was adjusted to pH 8 with 2 N NaOH, extracted with CH_2Cl_2 (100 mL × 4), dried, and concentrated, giving **8a** (2.9 g, 97%).

4-(3-Pyridyl)cyclohexanone (**8b**) and 4-(2-pyridyl)cyclohexanone (**8c**) were prepared by the same procedure as for **8a**.

4-Hydroxy-[4-(dimethylamino)phenyl]cyclohexanone Ethylene Ketal (2d). General Procedure. Magnesium (0.86 g) was added to a solution of 4-bromo-*N*,*N*-dimethylaniline (7.2 g, 33.6 mmol) in dry THF (35 mL). This reaction mixture was treated ultrasonically for 2 h at room temperature until the magnesium dissolved. After cooling of this solution to −30 °C, cyclohexane-1,4-dione monoethylene ketal (1) (4.68 g, 30 mmol) in dry THF (20 mL) was added dropwise. After stirring for 1 h at the same temperature, the reaction mixture was slowly warmed to room temperature and was allowed to stand at room temperature overnight. The solution was poured into saturated aqueous NH_4Cl (25 mL) and was extracted with methylene chloride. Dried extracts were concentrated, and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 3:1), which gave **2d** (5.6 g, 86%).

4-[4-(Dimethylamino)phenyl]cyclohexen-1-one (5d). General Procedure. A solution of **2d** (5.6 g, 5 mmol) in CF_3COOH (5 mL) was stirred at room temperature for 30 min and poured into saturated aqueous $NaHCO_3$ (50 mL). The chloroform extracts were dried, washed with brine, and evaporated. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 3:1), which gave **5d** (3.8 g, 88%).

4-[4-(Dimethylamino)phenyl]cyclohexanone (8d). General Procedure. A solution of **5d** (2.6 g, 4 mmol) in ethyl acetate (40 mL) containing 10% Pd/C (140 mg) was hydrogenated under atmospheric pressure at room temperature for 3 h. After filtration of the catalyst, the solution was concentrated, and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 3:1), which gave **8d** (1.1 g, 76%).

4-(4-Methoxyphenyl)cyclohexanone (**8e**), 4-[4-[(dimethylamino)methyl]phenyl]cyclohexanone (**8f**) and 4-[4-(methoxymethyl)phenyl]cyclohexanone (**8g**) were prepared by the same procedure as for **8d**.

4-Methoxycyclohexanol (7h). A mixture of 1,4-dihydroxycyclohexane (**6**) (17.5 g, 0.15 mmol), KOH (9.3 g, 0.17 mol), and water (20 mL) was refluxed until it became a clear solution. After removal of water in vacuo, iodomethane (32 g, 0.23 mol) was added and the mixture was dissolved in water (100 mL) and extracted with $CHCl_3$ (100 mL × 3). The extracts were washed, dried, evaporated, and distilled (bp 100–103 °C/15 mmHg) to obtain **7h** (10.3 g, 53%).

4-Methoxycyclohexanone (8h). A solution of **7h** (4.2 g, 34 mmol) in dry CH_2Cl_2 (30 mL) was slowly added to a suspension of PCC (pyridinium chlorochromate) (11.0 g, 62 mmol) in dry CH_2Cl_2 (60 mL). The resulting mixture was stirred at room temperature for 3 h. Florisil (20 mL) and ether (400 mL) were added to the reaction mixture, and then filtration was done with Florisil. The filtrate was concentrated and distilled (bp 86 °C/16 mmHg), giving **8h** (3.71 g, 85%).

4-*n*-Butoxycyclohexanone (**8i**) was prepared by the same procedure as for **8h**.

General Procedure for the Preparation of 2-Acetylcyclohexanones. Method A. 2-Acetyl-4-(4-pyridyl)cyclohexanone (9a, $R^1 = CH_3$). A solution of **8a** (2 g, 22.8 mmol) in dry THF (3 mL) was added to a stirred solution of freshly prepared LDA (lithium diisopropylamide) (22.8 mmol) in THF (15 mL) at −78 °C. The resulting enolate solution was stirred for 2 h. A solution of *N*-acetylimidazole (2.5 g, 22.8 mmol) in THF (10 mL) was added to the above solution. After stirring at −78 °C was continued for 1 h, the cooling bath was removed and stirring was continued for 3 h. The reaction mixture was poured into a saturated aqueous NH_4Cl (25 mL) and then extracted with CH_2Cl_2. The organic liquor was extracted with 2 N NaOH. The aqueous layer was washed with CH_2Cl_2. The aqueous layer was neutralized with 1 N HCl and extracted with CH_2Cl_2. The extracts were washed with brine, dried, and concentrated, giving **9a** (all 2-acetylcyclohexanones were purified by this method and used in the next step without further purification).

Method B. 2-Acetyl-4-methoxycyclohexanone (9h, $R^1 = CH_3$). A mixture of **8h** (1.8 g, 14 mmol) and benzene (0.5 mL) was added dropwise to a suspension of 60% sodium hydride (1.1 g, 28 mmol) in ethyl acetate (2.5 g, 28 mmol). After hydrogen evolution ceased, the reaction mixture was heated at 40 °C for 3 h. Additional stirring at room temperature was continued and excess sodium hydride was quenched with methanol. The reaction mixture was poured into water, neutralized with concentrated HCl, and extracted with ether. The extracts were purified by the same procedure used in method A.

Method C. 2-Acetyl-4-phenylcyclohexanone (9j, $R^1 = CH_3$). A mixture of 4-phenylcytclohexanone (2 g, 11.5 mmol) and acetic anhydride (2.4 g, 23 mmol) was added to 40% boron trifluoride in acetic acid (5.5 g, 17 mmol) at 0 °C. After stirring at 0 °C for 30 min and then at room temperature for 4 h, the reaction mixture was poured into aqueous NH_4Cl (40 mL). The resulting mixture was heated at 80 °C for 1 h, cooled to room temperature, and extracted with ether (50 mL × 2). The extracts were purified as in method A.

Method D. 2-Acetyl-4-(4-pyridyl)cyclohexanone (9a, $R^1 = CH_3$). A solution of pyrrolidine (2.7 g, 38 mmol) and **8a** (2.7 g, 15.4 mmol) in benzene (20 mL) was refluxed with azeotropic water entrainment through a Dean–Stark trap for 3 h. After evaporation, the residue was dissolved in dioxane (20 mL). Acetic anhydride (3.5 mL, 35 mmol) was then added. The mixture was allowed to stand at room temperature overnight, treated with water (50 mL), refluxed for 1 h, and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (50 mL) and extracted with 2 N NaOH (100 mL). The aqueous layer was washed with CH_2Cl_2, neutralized with 1 N HCl, and extracted with CH_2Cl_2. The extracts were dried and evaporated.

General Procedure for the Cyclization Reaction of Cyanoacetamide and 2-Acetylcyclohexanones. 4-Cyano-1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone (23). A mixture of **9a** (1.65 g, 7.6 mmol), cyanoacetamide (0.64 g, 7.6 mmol), and piperidine (0.1 mL) in ethanol (30 mL) was refluxed for 7 h. After cooling to room temperature, the precipitated crystals were collected, and their recrystallization from ethanol gave **23** (0.7 g): IR (KBr) 1660 cm^{-1} (CO), 2220 (CN); ^1H NMR ($CDCl_3$) δ 1.9 (m, 2 H), 2.22 (s, 3 H, 1-CH_3), 2.5 (m, 2 H), 2.9 (m, 3 H), 7.35 (dd, 2 H, J = 5 Hz, 1 Hz), 8.5 (dd, 2 H, J = 5 Hz, 1 Hz), 12.44 (s, 1 H, NH).

2-Ethylidene-4-(4-pyridyl)cyclohexanone (10a). A solution of **8a** (1.85 g, 10 mmol) in THF was added to a stirred solution of freshly prepared LDA (11 mmol) in THF (30 mL) at −78 °C. After the solution was stirred at the same temperature for 30 min, acetaldehyde (0.53 g, 12 mmol) was added. Stirring was continued at −78 °C and the reaction was quenched with CH_3COOH (0.6 g). The reaction mixture was poured into saturated aqueous NH_4Cl (50 mL) and extracted with $CHCl_3$ (50 mL × 3). Concentration of the extracts and their chromatography (SiO_2, hexane/ethyl acetate, 3:1) gave 2-(1-hydroxyethyl)-4-(4-pyridyl)-cyclohexanone (1.3 g, 59%).

A solution of 2-(1-hydroxyethyl)-4-(4-pyridyl)cyclohexanone (1.3 g, 5.9 mmol) in CF_3COOH (3 mL) was stirred at room temperature overnight. The solution was poured into saturated aqueous $NaHCO_3$ (30 mL), extracted with $CHCl_3$ (30 mL × 3),

dried, and concentrated to obtain **10a** (1.1 g, 93%), which was used in the next step without further purification.

3-Cyano-4-methyl-6-(4-pyridyl)-5,6,7,8-tetrahydro-2-(1*H*)-quinolinone (51). A mixture of **10a** (0.54 g, 2.7 mmol), ethyl cyanoacetate (0.32 g, 2.8 mmol), CH_3COOH (0.15 g, 2.6 mmol), and ammonium acetate (0.24 g, 3.1 mmol) in benzene (30 mL) was refluxed with azeotropic water entrainment through a Dean–Stark trap for 17 h. After concentration in vacuo, the residue was neutralized with aqueous $NaHCO_3$ (30 mL) and extracted with $CHCl_3$ (30 mL × 3). The extracts were dried, concentrated, and chromatographed (SiO_2, $CHCl_3$/MeOH, 10:1) to obtain **51** (0.04 g, 5.6%): NMR (Me_2SO-d_6) δ 1.8–3.2 (m, 7 H), 3.21 (s, 3 H, Me), 7.34 (d, 2 H, J = 7 Hz), 8.46 (d, 2 H, J = 7 Hz), 12.1 (br s, 1 H, NH).

4-Cyano-1,7-dimethyl-3-methoxy-5,6,7,8-tetrahydroisoquinoline (12). A suspension of **14** (1.0 g, 5 mmol) in phosphorus oxychloride (10 mL) was refluxed for 1 h. After cooling, excess phosphorus oxychloride was removed under reduced pressure. Cold water (10 mL) and saturated aqueous NH_4Cl (10 mL) were added to the residue. The solid was collected and chromatographed on silica gel ($CHCl_3$/MeOH, 20:1) to obtain 3-chloro-4-cyano-1,7-dimethyl-5,6,7,8-tetrahydroisoquinoline (0.55 g, 51%).

A mixture of 3-chloro-4-cyano-1,7-dimethyl-5,6,7,8-tetrahydroisoquinoline (0.55 g, 2.5 mmol) and sodium methoxide (0.58 g, 11 mmol) in methanol (20 mL) was refluxed for 3 days. Volatile materials were removed under reduced pressure and chromatography of the residue on silica gel ($CHCl_3$/hexane, 1:1) gave **12** (0.46 g, 86%), mp 80–82 °C.

4-Cyano-5,6,7,8-tetrahydro-1,2,7-trimethyl-3(2*H*)-isoquinolinone (15). Dimethyl sulfate (0.69 g, 5.5 mmol) was added to a solution of **14** (1.0 g, 5 mmol) and sodium methoxide (0.27 g, 5 mmol) in methanol (8 mL) at room temperature. The resulting solution was refluxed for 1 h and then 20% aqueous NaOH was added and the methanol was removed under reduced pressure. The residue was suspended in water (20 mL) and extracted with $CHCl_3$ (20 mL × 3). Extracts were dried and chromatographed on silica gel ($CHCl_3$/MeOH, 10:1), giving **15** (0.8 g, 75%).

4-Acetyl-1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3-(2*H*)-isoquinolinone (41). General Procedure. Iodomethane (3.9 g, 27 mmol) was added to magnesium turnings (0.6 g, 25 mmol) in dry ether (30 mL) under gentle refluxing. Stirring was continued until the magnesium had completely dissolved. **23** (4.0 g, 15 mmol) was then added all at once. Dry diisopropyl ether (50 mL) was slowly added. After distillation of the ether, dry THF (20 mL) was added in three portions over 1 h with vigorous stirring and refluxing. The refluxing was continued for an additional 4 h. The reaction mixture was poured into 6 N HCl (40 mL) and the resulting mixture was heated under reflux for 30 min. After cooling, diisopropyl ether and THF were removed under reduced pressure. The aqueous solution was neutralized with 10 N NaOH, extracted with $CHCl_3$ (200 mL × 2), dried, and evaporated. Recrystallization of the residue from ethanol gave **41** (1.0 g): IR (KBr) 1630 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 1.8 (m, 2 H), 2.32 (s, 3 H, 1-CH_3), 2.5 (m, 1 H), 2.62 (s, 3 H, $COCH_3$), 2.9 (m, 4 H), 7.24 (dd, 2 H, J = 5 Hz, 1 Hz), 8.6 (dd, 2 H, J = 5 Hz, 1 Hz), 11.9 (s, 1 H, NH).

42–44 were prepared by the same procedure as for **41**.

1-Methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone (38). A solution of **23** (0.5 g, 1.9 mmol) in 85% H_2SO_4 (6 mL) was heated at 190–200 °C for 5 h. After cooling to room temperature, the reaction mixture was poured into water and adjusted to pH 10 with 10 N NaOH. The precipitated crystals were collected, dissolved in $CHCl_3$, dried, and concentrated. Recrystallization of the residual crystals from ether/$CHCl_3$ gave **38** (0.4 g).

4-Carbamoyl-1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3-(2*H*)-isoquinolinone (36). A solution of **23** (3.0 g, 11 mmol) in 90% H_2SO_4 (30 mL) was heated at 80–90 °C for 1 h. The solution was cooled to room temperature and poured onto ice. The solution was then adjusted to pH 8 with 10 N NaOH. The solid was collected, washed with methanol, and recrystallized from dimethylformamide to obtain **36** (2.7 g).

4-Amino-1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3-(2*H*)-isoquinolinone (37). Bromine (0.7 g, 8.7 mmol) was added to an ice-cold solution of **36** (1.0 g, 35 mmol) in 20% aqueous NaOH (5.8 mL) over a period of 10 min with stirring. The resulting solution was heated at 100 °C for 2 h, cooled to room temperature, and neutralized with 1 N HCl. The solid was collected, washed with water, air dried, and recrystallized from $CHCl_3$/MeOH, giving **37** (0.56 g).

1-Methyl-4-nitro-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone (39). To an ice-cooled mixture of concentrated H_2SO_4 (1 mL) and 60% HNO_3 (3 mL) was added **38** (0.5 g, 2.1 mmol). The resulting solution was stirred at room temperature for 4 h and then poured onto ice. The solid was collected and dissolved in aqueous $NaHCO_3$. The solution was extracted with $CHCl_3$ (50 mL × 5), dried, and concentrated. Recrystallization of the residual solid from ethanol gave **39** (0.14 g).

4-Formyl-1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3-(2*H*)-isoquinolinone (40). Chloroform (1.2 mL) was added dropwise at 80 °C to a solution of **38** (2.4 g, 10 mmol) and KOH (4.2 g) in ethanol/H_2O (15 mL/15 mL). Additional KOH (2.4 g) and chloroform (1.2 mL) were added over 6 h at the same temperature. After cooling to room temperature, the reaction mixture was diluted with water and adjusted to pH 5 with 6 N HCl. The resulting solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with brine, dried, concentrated, and chromatographed on silica gel ($CHCl_3$/MeOH, 10:1) to obtain **40** (0.25 g).

1,4-Dimethyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone (45). General Procedure. Hydrazine monohydrate (0.5 mL) was added to a solution of **40** (0.24 g) in methanol and the resulting solution was heated at reflux for 2 h. After concentration, ethylene glycol (4 mL) and KOH (0.22 g) were added to the residue. The resulting mixture was heated at 200 °C for 3 h, cooled to room temperature, and neutralized with 1 N HCl. The solution was diluted with water (20 mL) and extracted with $CHCl_3$ (30 mL × 3). The extracts were washed with brine, dried, evaporated, and recrystallized from methanol to obtain **45** (0.16 g).

46 and **47** were prepared by the same procedure as for **45**.

4-Acetyl-1-methyl-7-(4-pyridyl)-5,6,7,8-tetrahydro-3-(2*H*)-isoquinolinone (41). A mixture of **9a** (3.5 g, 16 mmol) and diethylamine (3.8 g, 52 mmol) was stirred at room temperature. Acetoacetamide (4.8 g, 48 mmol) was then added. The resulting mixture was stirred at room temperature for 8 h and then at 55 °C for 1 day. The reaction mixture was diluted with water (40 mL) and ethyl acetate (20 mL), and the precipitated solids were collected. Recrystallization from methanol gave **41** (1.6 g).

Pharmacological Methods. Experiments with Anesthetized Dogs.[16,18] Mongrel dogs (male and female), weighing 8–12 kg, were anesthetized with sodium pentobarbital (30 mg/kg, iv) and their systemic blood pressure (BP) was recorded before administration of the test drug into the femoral vein. BP was measured with a pressure transducer, and the heart rate (HR) was counted with a cardiometer triggered by the R waves of the lead II electrocardiogram. Left ventricular pressure (LVP) was measured with a micromanometer-tipped catheter (S-Type, Mitsui Toatsu, Tokyo, Japan) introduced into the left ventricle via the right carotid artery. The rate of rise of the LVP (LV dp/dt) was derived with an electronic differentiator. All these parameters were simultaneously recorded on a polygraph. To cause heart failure, propranolol was administered as a single bolus injection of 4 mg/kg, iv, followed by infusion of 0.1 mg/kg per min, iv. This caused marked depressions of LV dp/dt_{max}, BP, and HR, which were sustained for at least 90 min. When the steady state of heart failure was achieved, at about 20 min after propranolol administration, the test compound was given in a cumulative manner. Only one dose–response curve was determined for each animal. Positive inotropic agents produced a dose-dependent increase in LV dp/dt_{max} and abolished the depressant effect of propranolol. The effective dose (ED_{100}, the approximate dose abolishing the depressant effect of propranolol) of the test compound was determined from the dose–response curves.

Preparation and Assay Isoenzyme of Canine Cardiac Phosphodiesterase (PDE). Fractionation of the three major

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isoenzymes of PDE from canine ventricular muscle was carried out essentially as described by Hidaka et al.[19] Cyclic nucleotide PDE assays were performed as described by Hidaka et al.[20] The effect of **41** and milrinone on the PDE I and III were tested at a low concentration (0.4 μM) without calmodulin and a stimulating concentration of calcium. The concentration of agents required to inhibit isoenzymes 50% (IC_{50}) is showed in Table III. The selectivity of each drug for the PDE III against PDE I was determined from the ratio of the IC_{50} for PDE I to that for PDE III.

Acknowledgment. We thank the members of the Analytical Department, Central Research Institute, Mitsui Toatsu Chemicals Inc., for the NMR and elemental analyses.

Registry No. 1, 4746-97-8; **2a**, 103319-00-2; **2b**, 103319-07-9; **2c**, 103319-04-6; **2d**, 117960-27-7; **2e**, 67019-51-6; **2f**, 117960-44-8; **2g**, 117960-45-9; **3a**, 103319-01-3; **3b**, 103319-08-0; **3c**, 103319-15-9; **4a**, 117960-46-0; **4b**, 117960-47-1; **4c**, 117960-48-2; **5d**, 117960-52-8; **5e**, 66336-47-8; **5f**, 117960-53-9; **5g**, 117960-54-0; **6**, 556-48-9; **7h**, 18068-06-9; **7i**, 66227-43-8; **8a**, 103319-02-4; **8b**, 103319-09-1; **8c**, 103319-05-7; **8d**, 117960-49-3; **8e**, 5309-16-0; **8f**, 117960-50-6; **8g**, 117960-51-7; **8h**, 13482-23-0; **8i**, 66227-44-9; **9a** (R^1 = CH_3), 103319-03-5; **9b** (R^1 = CH_3), 103319-10-4; **9c** (R^1 = CH_3), 103319-06-8; **9d** (R^1 = CH_3), 117960-55-1; **9e** (R^1 = CH_3), 117960-56-2; **9f** (R^1 = CH_3), 117960-57-3; **9g** (R^1 = CH_3), 117960-58-4; **9h** (R^1 = CH_3), 103319-11-5; **9i** (R^1 = CH_3), 117960-60-8; **9j** (R^1 = CH_3), 103319-13-7; **9** (R^1 = Me, R^5, R^6, R^8 = H, R^7 = Me), 103319-12-6; **9** (R^1 = Me, R^5, R^6, R^8 = H, R^7 = Et), 103319-12-6; **9** (R^1 = Me, R^5, R^6, R^8 = H, R^7 = *t*-Bu), 117960-59-5; **9** (R^1 = Me, R^5, R^6, R^7, R^8 = H), 874-23-7; **10a**, 117960-64-2; **12**, 117960-66-4; **13**, 17012-30-5; **14**, 103318-87-2; **15**, 117960-28-8; **16**, 103318-93-0; **17**, 117960-29-9; **18**, 103318-86-1; **19**, 117960-30-2; **20**, 103318-88-3; **21**, 117960-31-3; **22**, 117960-32-4; **23**, 103318-83-8; **24**, 103318-85-0; **25**, 103318-84-9; **26**, 117960-33-5; **27**, 117960-34-6; **28**, 53661-31-7; **29**, 117960-35-7; **30**, 103318-90-7; **31**, 103318-91-8; **32**, 103318-92-9; **33**, 117960-36-8; **34**, 115883-28-8; **35**, 115883-30-2; **36**, 117960-37-9; **37**, 117960-38-0; **38**, 107189-97-9; **39**, 107190-00-1; **40**, 115883-40-4; **41**, 107189-96-8; **42**, 115883-34-6; **43**, 117960-39-1; **44**, 115883-37-9; **45**, 115883-41-5; **46**, 115883-38-0; **47**, 115883-39-1; **48**, 16232-45-4; **49**, 117960-40-4; **50**, 117960-41-5; **51**, 117960-42-6; **52**, 117960-43-7; 4-bromopyridine, 1120-87-2; 3-bromopyridine, 626-55-1; 2-bromopyridine, 109-04-6; 4-bromo-*N*,*N*-dimethylaniline, 586-77-6; 1-bromo-4-methoxybenzene, 104-92-7; *p*-bromo-*N*,*N*-dimethylbenzylamine, 586-77-6; *p*-(methoxymethyl)bromobenzene, 1515-88-4; *N*-acetylimidazole, 2466-76-4; 2-cyanoacetamide, 107-91-5; 4-methylcyclohexanone, 589-92-4; 4-ethylcyclohexanone, 5441-51-0; 4-*tert*-butylcyclohexanone, 98-53-3; 4-phenylcyclohexanone, 4894-75-1; cyclohexanone, 108-94-1; 2-propanoylcyclohexanone, 32316-46-4; 2-methylcyclohexanone, 583-60-8; 2-acetyl-6-methylcyclohexanone, 78456-49-2; 3-methylcyclohexanone, 591-24-2; 2-acetyl-5-methylcyclohexanone, 14698-76-1; 2-acetyl-3-methylcyclohexanone, 14580-53-1; 3-(4-pyridyl)cyclohexanone, 115444-30-9; 2-acetyl-5-(4-pyridyl)cyclohexanone, 117960-61-9; 2-propanoyl-4-(4-pyridyl)cyclohexanone, 115883-26-6; 2-pentanoyl-4-(4-pyridyl)cyclohexanone, 117960-62-0; 2-(1-hydroxyethyl)-4-(4-pyridyl)cyclohexanone, 117960-63-1; ethyl cyanoacetate, 105-56-6; 3-chloro-4-cyano-1,7-dimethyl-5,6,7,8-tetrahydroisoquinoline, 117960-65-3; acetoacetamide, 5977-14-0; acetaldehyde, 75-07-0.

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Spermexatin and Spermexatol: New Synthetic Spermidine-Based Siderophore Analogues

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Syntheses of hexanediamine-based dihydroxamate (Hexamate), spermidine-based trihydroxamate (Spermexatins), and spermidine-based mixed siderophore analogues (Spermexatols) are described. Key intermediates include the *N*-hydroxysuccinimide esters of various hydroxamic acids, e.g., malonohydroxamate, succinohydroxamate, and glutarohydroxamate. These intermediates were synthesized, characterized, and incorporated as the ligating chains on spermidine. Also, mixed iron chelating compounds (Spermexatols) with both catechol and hydroxamic acid side chains were synthesized. The reagent carbobenzoxyimidazole was employed to distinguish between the primary and secondary amino groups of spermidine. The ability of these iron chelators to stimulate microbial growth is also described.

Spermidine (1,8-diamino-4-azaoctane), **1**, has been found to be an essential component of a wide variety of naturally occurring biologically active compounds.[1] Its derivatives are of considerable biological interest because of their potent antibiotic[2] and antineoplastic[3] properties. Spermidine-based microbial iron chelators (siderophores), agrobactin and parabactin, are well known and are being studied for their potential uses in the iron chelation therapy of patients suffering from Cooley's anemia[4] and anticancer treatment. These catecholates have been shown to be quite effective in deferration of mammalian cell lines.[5] Since the isolation[6] of agrobactin (**2a**), parabactin (**2b**), and the norspermidine-derived vibriobactin (**2c**), a

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[§] Recipient of a NIH Career Development Award, 1983-1988.

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0022-2623/89/1832-0357$01.50/0