Cardiotonic Agents. 4. Synthesis and Biological Evaluation of N-Substituted 2,4,4a,5-Tetrahydro-3*H*-indeno[1,2-*c*]pyridazin-3-ones: Rigid Structures Derived from CI-930 and Analogues

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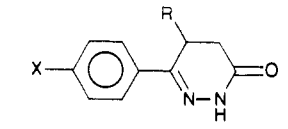
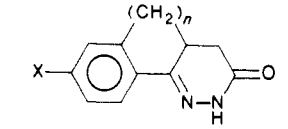
Several N-substituted 3*H*-indeno[1,2-*c*]pyridazinones (**1–23**) and a benzo[*h*]cinnolinone (**24**), which were designed as rigid structural modifications of 5-alkyl-4,5-dihydro-6-[4-N-substituted phenyl]-3(2*H*)-pyridazinones (Ib–d), were synthesized and evaluated for positive inotropic activity. Most of these tricyclic pyridazinones (**1–11, 14–15, 22–23**) demonstrated potent positive inotropic activity comparable to the corresponding phenylpyridazinones related to I.

Recently we reported the positive inotropic activity of 4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinone (Ia, CI-914)[1a,b] and related compounds from our laboratory. It has been found that the introduction of a methyl substituent at the 5-position of the 4,5-dihydropyridazinone ring (DHPZ) in CI-914 augments activity and leads to a more potent compound (Ib, CI-930). In order to extend the structure–activity relationships of these freely rotating dihydropyridazinones, we have synthesized and evaluated compounds having rigid structure (II) derived from Ib (CI-930) and analogues by bonding the 5-alkyl group to the phenyl ring. Most of these tricyclic pyridazinones possess positive inotropic activity in the same range as their acyclic analogues.

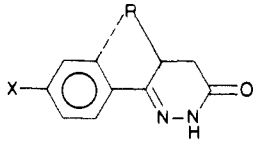
A survey of the literature revealed that several indeno[1,2-*c*]pyridazinones (IIIa–d) and benzo[*h*]cinnolinones (IIIe,f) have been prepared.[2–6] However, only the antihypertensive and antiinflammatory activities have been claimed for these compounds. In this paper we report the synthesis and inotropic activity of 7-substituted 3*H*-indeno[1,2-*c*]pyridazinones and related compounds.



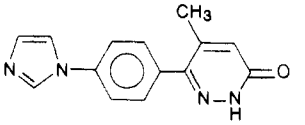
Ia: X = imidazol-1-yl, R = H (CI 914)
b: X = imidazol-1-yl, R = CH_3 (CI 930)
c: X = imidazol-1-yl, R = CH_2CH_3
d: X = H_3CCOHN, R = CH_3



IIIa: X = Cl, *n* = 1
b: X = Br, *n* = 1
c: X = F, *n* = 1
d: X = CN, *n* = 1
e: X = H, *n* = 2
f: X = OCH_3, *n* = 2



II



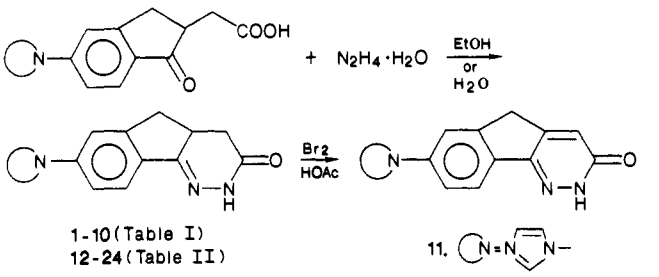
IV

X is the same as in I

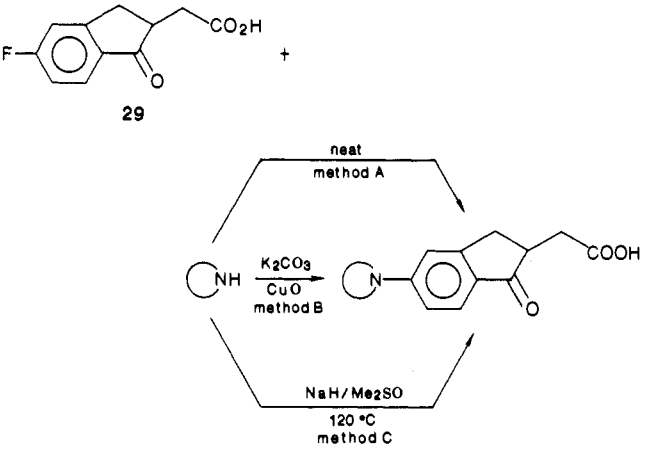
Chemistry. The syntheses of 3*H*-indeno[1,2-*c*]-pyridazin-3-ones **1–10** (Table I) and **12–24** (Tables II and III) were accomplished by treating the requisite 2,3-dihydro-1-oxo-1*H*-indene-2-acetic acids with hydrazine.[2] Bromination–dehydrobromination of 1 with bromine in acetic acid[3] gave 11 (Scheme I).

The structures of 1 and 11 were proven from elemental analyses and spectral data. The IR spectrum of 1 showed bands at 1660 (CO) and 3200 cm^{-1} (NH) vs. 1660 (CO) and

Scheme I



Scheme II



3100 cm^{-1} (NH amide) for 11. The ^1H NMR spectrum of 11 in Me_2SO-d_6 showed singlet at 12.8 ppm (NHCO) compared to 1, which showed a singlet at 9.3 ppm (NHCO). Similarly, ^{13}C NMR showed a lower field signal for the carbonyl at 161 ppm for 11 vs. 168 ppm for 1. The UV spectrum of 11 in methanol showed bands at λ 324 (ε 0.86 × 10^4) and 272 (ε 2.89 × 10^4) vs. λ 314 (ε 2.58 × 10^4), 292 (ε 1.90 × 10^4), 282 (ε 1.64 × 10^4), and 226 (ε 1.18 × 10^4) for 1.

The key intermediate 5-substituted 2,3-dihydro-1-oxo-1*H*-indene-2-acetic acids **25–28** (Table IV) were synthesized from the corresponding fluoro acid **29**[2] by nucleophilic

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(1) (a) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. E.; Weishaar, R. R. *J. Med. Chem.* **1984**, *27*, 1099. (b) Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Evans, D. E. *J. Med. Chem.* **1985**, *28*, 1405.
(2) Cignarella, G.; Loriga, M.; Pinna, G. A.; Pirisi, M. A.; Schiatti, P.; Selva, D. *Farmaco, Ed. Sci.* **1981**, *37*(2), 133.
(3) Curran, W. F.; Ross, A. *J. Med. Chem.* **1974**, *17*, 273.
(4) Yamada, T.; Nobuhara, Y.; Yamaguchi, A.; Ohki, M. *J. Med. Chem.* **1982**, *25*(8), 975.
(5) Dalton, L. K.; Elmes, B. C. *Aust. J. Chem.* **1972**, *25*(3), 625.
(6) Partyka, R. A.; Holava, H. M., Jr. *J. Med. Chem.* **1971**, *14*(3), 252.

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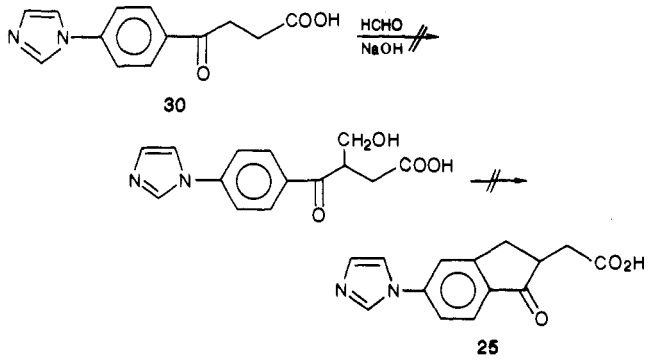
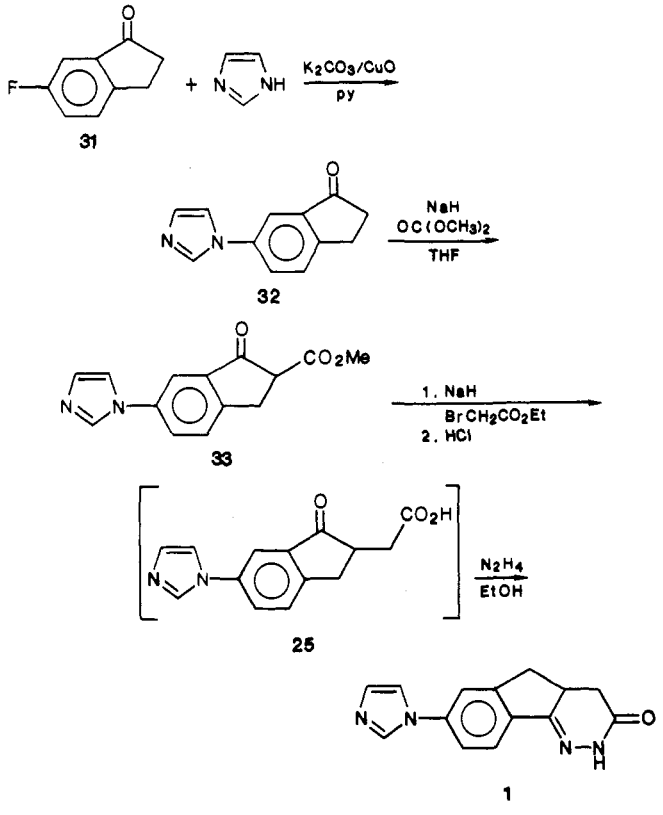
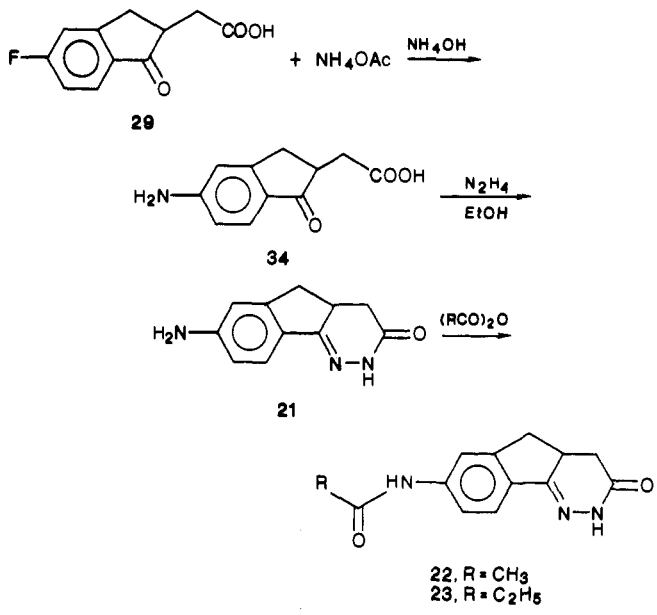
Scheme III



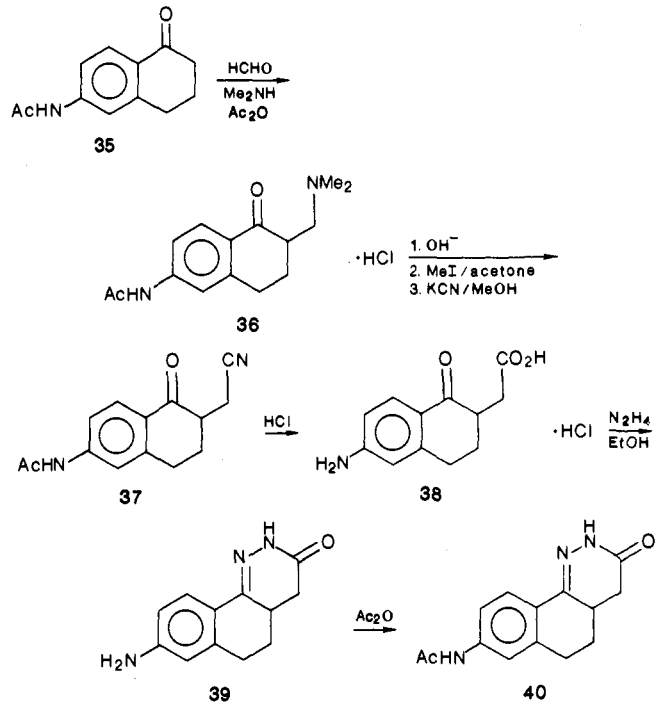
Scheme IV



Scheme V



Scheme VI



displacement of fluoride ion with the requisite amine (Scheme II).

The reaction was performed either neat (method A) or in the presence of anhydrous potassium carbonate in pyridine (method B).[7] Method C involves the use of sodium hydride as the base. An earlier attempt to prepare 2,3-dihydro-5-(1*H*-imidazol-1-yl)-1-oxo-1*H*-indene-2-acetic acid (**25**) starting from 4-(1*H*-imidazol-1-yl)-γ-oxobenzenebutanoic acid (**30**)[1] via hydroxymethylation[8] was unsuccessful (Scheme III).

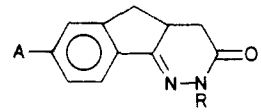
Another alternative procedure for the synthesis of **25** starting from 2,3-dihydro-6-fluoro-1*H*-inden-1-one (**31**) also gave unsatisfactory results (Scheme IV). Nucleophilic displacement of fluoride ion with imidazole gave a moderate yield of 2,3-dihydro-6-(1*H*-imidazol-1-yl)-1*H*-inden-1-one (**32**), which, upon reaction with dimethyl carbonate in the presence of sodium hydride, gave the desired β-keto ester, 2,3-dihydro-6-(1*H*-imidazol-1-yl)-1-oxo-1*H*-indene-2-carboxylic acid, methyl ester (**33**). Alkylation with ethyl bromoacetate in the presence of sodium hydride followed by hydrolysis gave the desired acid **25** in extremely poor yield, which was not fully characterized. The acid **25** was converted to the cyclized product **1** by treatment with hydrazine.

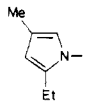
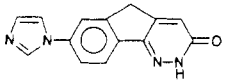
For the preparation of 5-amino-2,3-dihydro-1-oxo-1*H*-indene-2-acetic acid (**34**), **25** was treated with anhydrous ammonium acetate in a melt through which gaseous ammonia was passed continually. Acid **34** was converted to the tetrahydropyridazinone **21** by treatment with hydrazine. The amine **21** was subsequently treated with anhydrides to yield acylamino derivatives **22** and **23** (Scheme V).

The synthesis of the corresponding amino derivative in the benzo[*h*]cinnoline series is outlined in Scheme VI. 6-Acetamido-1-tetralone (**35**)[9] was converted to the requisite γ-oxo acid **38** by following the procedure of McEvoy

(7) Khan, M. A.; Polya, J. B. *J. Chem. Soc. C* **1970**, 85.
(8) Cignarella, G.; Grella, G.; Curzu, M. M. *Synthesis* **1980**, 825.
(9) Allinger, N. I.; Jones, E. S. *J. Org. Chem.* **1962**, *27*, 69.

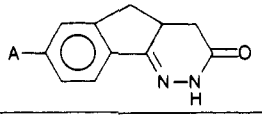
Table I. 7-(1*H*-Azol-1-yl)-2,4,4a,5-tetrahydro-3*H*-indeno[1,2-*c*]pyridazin-3-ones

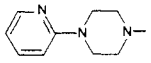
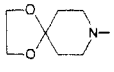
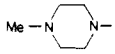


compd	A	R	mp, °C	yield,[a] %	cryst solvent	mol formula[b]
1		H	263–264 dec	19	EtOH	$C_{14}H_{12}N_4O$
2		H	302–304 dec	21	MeOH	$C_{13}H_{11}N_5O$
3		H	261–264 dec	8	EtOH	$C_{15}H_{14}N_4O$
4		H	239–241	20	EtOH	$C_{17}H_{18}N_4O$
5		H	275.5–277	52	EtOH	$C_{18}H_{18}N_4O$
6		H	272–274 dec	55	EtOH	$C_{18}H_{14}N_4O$
7		H	301–307 dec	17	$MeOC_2H_5OH$	$C_{10}H_{16}N_4O$
8		H	274–277 dec	6	MeOH	$C_{15}H_{14}N_4O_2 \cdot 0.3H_2O$
9		CH_3	208–210 dec	30	EtOH	$C_{15}H_{14}N_4O$
10		H	252–253 dec	21	2-propanol	$C_{15}H_{14}N_4O$
11			306–309	30	DMF	$C_{15}H_{14}N_4O$

[a] No attempt was made to optimize yields. Numbers represent the overall yield for last two steps. [b] All compounds were analyzed for C, H, and N within ±0.40% of the calculated values.

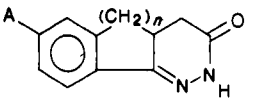
Table II. 7-Amino-2,4,4a,5-tetrahydro-3*H*-indeno[1,2-*c*]pyridazin-3-ones



compd	A	mp, °C	yield,[a] %	cryst solvent	mol formula[b]
12		286–288	29	EtOH	$C_{20}H_{21}N_5O$
13		282–284	27	EtOH	$C_{16}H_{19}N_3O$
14		252–254	14	MeOH	$C_{18}H_{21}N_3O_3$
15		246–248	22	MeOH	$C_{16}H_{19}N_3O_2$
16		256–258	23	MeOH	$C_{15}H_{17}N_3O_2$
17		244–246	11	EtOH	$C_{16}H_{20}N_4O$
18		265–268	15	EtOH	$C_{15}H_{17}N_3SO$
19	*n*-BuHN	230–234	57	EtOH	$C_{15}H_{19}N_3O$
20	$H_2N(CH_2)_3HN$	288–290	56	MeOH	$C_{14}H_{18}N_4O \cdot HCl \cdot 0.5H_2O$

[a,b] See Table I.

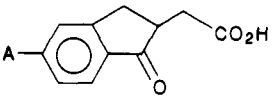
Table III. (Acylamino)- and Aminopyridazin-3-ones



compd	A	*n*	mp, °C	yield,[a] %	cryst solvent	mol formula[b]
21	H_2N	1	242 dec	41[a]	EtOH	$C_{11}H_{11}N_3O$
22	MeCONH	1	>300	80[b]	THF	$C_{13}H_{13}N_3O_2$
23	EtCOHN	1	286–289	85[b]	THF	$C_{14}H_{15}N_3O_2$
24	MeCOHN	2	288–289	23[c]	pyridine/MeOH	$C_{14}H_{13}N_3O_2$

[a] Calculated from fluorindanoneacetic acid (**29**). [b] Calculated from amine **21**. [c] Calculated from the quaternary salt.

Table IV. 5-(1*H*-Azol-1-yl)-2,3-dihydro-1-oxo-1*H*-indene-2-acetic Acids



compd	A	mp, °C	yield,[a] %	cryst solvent	mol formula[b]
25		224–226	39	MeOH	$C_{14}H_{12}N_2O_3$
26		216–218	88	DMF	$C_{13}H_{11}N_3O_3$
27		292–294 dec	63	DMF	$C_{18}H_{14}N_2O_3$
28		241–244 dec	30	$MeOCH_2CH_2OH$	$C_{20}H_{16}N_2O_3$

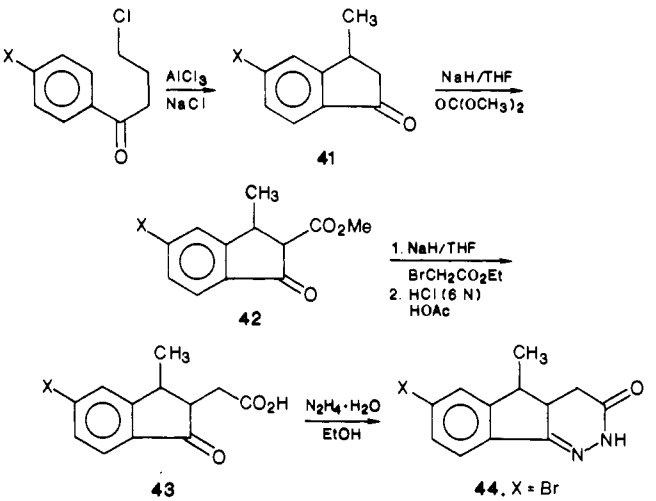
[a,b] See Table I.

and Allen.[10] The ketone **35** was converted to the Mannich product **36** by reaction of formaldehyde and *N,N*-dimethylamine in the presence of acetic anhydride. Reaction of **36** with iodomethane furnished the quaternary salt, which on exposure to aqueous or methanolic solution of potassium cyanide resulted in smooth, efficient conversion to the γ-oxo nitrile **37**. This was converted to the γ-oxo acid **38**, which when treated with hydrazine gave the desired tetrahydropyridazinone **39**. The amine **39** was converted to the acetylamino derivative **40** by treatment with acetic anhydride.

Scheme VII outlines the synthesis of 7-bromo-2,4,4a,5-tetrahydro-5-methyl-3*H*-inden[1,2-*c*]pyridazin-3-one (**44**). 1-(4-Bromophenyl)-4-chloro-1-butanone was treated with anhydrous aluminum chloride to give 5-bromo-2,3-dihydro-3-methyl-1*H*-indan-1-one (**41**).[11,12] This upon treatment with dimethyl carbonate in presence of sodium hydride gave the β-keto ester **42**.[13] Compound **42** was alkylated with ethyl bromoacetate to give the diester, which was hydrolyzed to provide the requisite acid **43**. Upon treatment with hydrazine **43** gave the desired pyridazinone **44**.

Biological Results. The positive inotropic activities of the compounds in Tables I–III were evaluated intravenously in an acutely instrumented anesthetized dog model[1b] as described briefly in the Experimental Section. The results indicate the following structure–activity relationships: First, the rigid tricyclic pyridazinones (II) retained most of the positive inotropic activity of the freely rotating pyridazinones (I). For example, **1** had potency similar (ED_{50} = 0.023 ± 0.002 mg/kg, N = 4) to Ib (ED_{50} = 0.013 ± 0.006 mg/kg, N = 8). Second, the same structure–activity relationships exist between these two series. Imidazole **1**, substituted imidazoles **2–5**, and 1,2,4-triazol **10** analogues were equipotent (ED_{50} values were in the range 0.02–0.03 mg/kg, N = 2). Substitution at the amide nitrogen with a methyl group caused significant reduction in potency (**9**, ED_{50} = 1.0 mg/kg). These findings parallel the results seen with the acyclic pyridazinones.[1b] The increases in contractility (LV dp/dt) for all of these tricyclic compounds were associated with small increases in heart rate (HR), small decreases in mean arterial blood pressure (MABP), and significant decreases in forelimb vascular resistance (FVR) (Table V). Cardiovascular activity of **1** was also evaluated in the presence of β-adrenoceptor blockade in the anesthetized dog model (nadolal, 1 mg/kg, iv). Table V shows the dose–response curve of **1** before and after β-blockade. These data indicate a direct positive inotropic action and a direct vasodilator action of **1**, which was similar to the freely rotating pyri-

Scheme VII



(10) McEvoy, F. J.; Allen, G. R., Jr. *J. Org. Chem.* **1973**, *38*(23).
(11) Olivier, M.; Marechal, E. *Bull. Soc. Chim. Fr.* **1973**, *11*, 3092.
(12) Layer, R. W.; McGregor, I. R. *J. Org. Chem.* **1956**, *21*, 1120.
(13) Corey, E. J.; Mitra, R. B.; Udo, H. *J. Am. Chem. Soc.* **1964**, *86*, 485.

Table V. Effect of 1 and 1b on Cardiovascular Function in Anesthetized Dogs

compd		dose, mg/kg	% change from control: heart rate (HR)	MABP	LV dp/dt	forelimb vasc resistance[b] (FVR)	total peripheral resistance[b] (TPR)
1	before β-blockade[a]	0.01	3 ± 2	−2 ± 1	18 ± 3	−7.5	−8.5
		0.03	4 ± 3	−7 ± 2	62 ± 11	−22.5	−22.5
		0.11	12 ± 5	−18 ± 5	106 ± 10	−34.5	−33.5
	after β-blockade[b]	0.01	0	0	11	−1.5	−12.0
		0.03	2	−3	27	−1.5	−23.0
		0.11	5	−18	57	−31.0	−39.0
1b	before β-blockade[a]	0.03	11 ± 2*	−7.5 ± 2*	76 ± 9*		
	after β-blockade[a]	0.03	7 ± 1*	−5 ± 1*	47 ± 8*		

[a] Values are mean ± SEM (n = 4–5). [b] Values are mean of two determinations. Asterisk indicates significant difference from control, $p < 0.05$. Control values were 143 ± 10 beats/min (HR), 110 ± 6 mmHg (MABP), 2388 ± 178 mmHg/s (LV dp/dt), 2.05 mmHg/mL per min (FVR), and 33.7 mmHg/per min (TPR), respectively.

dazinone **1b**. More intriguing is the fact that the acylamino derivatives **22** and **23** retained activity comparable to, or slightly greater than, that of the imidazole compound **1** (**23**, ED_{50} = 10.4 ± 1.5 μg/kg, N = 3; Id, ED_{50} = 3.1 ± 0.5 μg/kg, N = 4).

The acylamino analogue **24** in the cinnoline series could not be tested in the anesthetized dog model because of its low solubility in dilute HCl. However, data obtained from oral administration in the chronically instrumented conscious dog model[1b] indicate decreased potency compared to **22**. This unexpected drop in potency was also observed with the 5-ethyl analogue (**1c**) in the phenylpyridazinone series.[1b] Compound **11**, the aromatic analogue of **1**, retained most of the activity of **1** (data obtained from oral administration of the drug), which did not follow the same structure–activity relationship as the phenylpyridazinones. The corresponding pyridazinone in the CI-930 series (IV) is weakly active. These data suggest that a generally planar ring structure is desirable for maximum positive inotropic activity. The dihydropyridazinone Ib has a relatively planar relationship between the phenyl and the DHPZ ring in its minimum energy conformation. In contrast, the less potent pyridazinone IV is not. The aromatic tricyclic compound **11** is rigidly plannar that may contribute to the activity.[14]

Since selective inhibition of type III cardiac phosphodiesterase represents the mechanism of action of positive inotropic activity of CI-930 (Ib) and analogues, several of these tricyclic pyridazinones were evaluated for PDE III inhibitory activity. Compounds **1** and **11** possess potency similar [IC_{50} = 1.8 (**1**), 1.6 μM (**11**)] to Ib (IC_{50} = 1 μM, N = 4),[14] which also explains comparable inotropic activity of these agents.

Conclusion

The rigid analogues of CI-930 (Ib) have resulted in a series of compounds with positive inotropic activity similar to the compounds in the acyclic series. Such a modification also retained selective phosphodiesterase (PDE) inhibitory activity.

Experimental Section

Melting points are uncorrected and were taken on a Thomas-Hoover capillary melting point apparatus. IR and ^{1}H NMR spectra of all new compounds were consistent with the proposed structures. Each analytical sample was homogeneous by TLC performed on silica gel plates with methylene chloride and methanol (9:1) as eluants. Elemental analyses were within 0.4% of theoretical values unless otherwise stated.

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7-(1*H*-Azol-1-yl)-2,4,4a,5-tetrahydro-3*H*-indeno[1,2-*c*]pyridazin-3-ones of Table I Exemplified by the Preparation of 1. A mixture of 1.86 g (7.5 mmol) of **25** and 0.53 g (9 mmol) of 80% hydrazine hydrate in 25 mL of ethanol was heated at reflux for 3 h. After the mixture was cooled to room temperature, the solid was collected, washed with ethanol, and recrystallized to give **1**.

2,5-Dihydro-7-(1*H*-imidazol-1-yl)-3*H*-indeno[1,2-*c*]pyridazin-3-one (11). A solution of 0.37 mL (1.15 g, 7.2 mmol) of bromine in 15 mL of acetic acid was added dropwise over 90 min to a solution of 1.5 g (6 mmol) of **1** in 50 mL of acetic acid at 95–100 °C. Upon completion of the addition, the temperature was increased to 115 °C and the reaction mixture was heated for 4 h. After the mixture was cooled to room temperature, the solid was filteed, washed with ether, and suspended in water. The pH of the solution was adjusted to 10 with ammonium hydroxide, and the suspension was stirred for 30 min. The precipitate was filtered, washed with water, dried, and chromatographed (silica gel, eluted with 5–10% methanol in methylene chloride) to give **11**.

5-(1*H*-Azol-1-yl)-2,3-dihydro-1-oxo-1*H*-indene-2-acetic Acids of Table IV Exemplified by the Preparation of 25 and 26. 2,3-Dihydro-5-(1*H*-imidazol-1-yl)-1-oxo-1*H*-indene-2-acetic Acid (25). Method A. A mixture of 3.12 g (15 mmol) of **29** and 3.1 g (75 mmol) of imidazole was heated with stirring at 140 °C for 36 h. The reaction mixture was cooled and treated with 80 mL of water, and the solution was adjusted to pH 10 and filtered. The filtrate was acidified to pH 5 and cooled, and the precipitate was filtered and air-dried. The crude material was crystallized to give analytically pure **25**.

2,3-Dihydro-1-oxo-5-(1*H*-1,2,4-triazol-1-yl)-1*H*-indene-2-acetic Acid (26). Method B. A mixture of 6.24 g (30 mmol) of 5-fluoro-2,3-dihydro-1-oxo-1*H*-indene-2-acetic acid (**29**),[2] 2 g (30 mmol) of 1*H*-1,2,4-triazole, and 0.28 g of cupric oxide in 50 mL of pyridine was heated at reflux for 48 h. The reaction mixture was filtered, and the residue was washed thoroughly with pyridine. The filtrate and the washings were combined and evaporated under reduced pressure. The residue was dissolved in water, and the solution was adjusted to pH 10. The suspension was filtered to remove unreacted triazole, and the filtrate was acidified to pH 5 and cooled in an ice bath. The resulting solid was collected, washed with a small volume of ice-cold water, dried, and crystallized to give **26**.

2,3-Dihydro-5-[4-(hydroxymethyl)-1*H*-imidazol-1-yl]-1-oxo-1*H*-indene-2-acetic Acid. Method C. A solution of a mixture of 4 g (29.7 mmol) of 1*H*-imidazole-4-methanol hydrochloride and 6.2 g (29.7 mmol) of **29** in 50 mL of dimethyl sulfoxide was added dropwise to a slurry of 3.7 g (92.5 mmol) of sodium hydride (60% mineral oil suspension) in 25 mL of toluene with stirring. The reaction mixture was stirred at room temperature for 18 h followed by heating at 120 °C for 2 h. Dimethyl sulfoxide was distilled under reduced pressure, the residue was treated with 100 mL of water, and the solution was adjusted to pH 2. A brown gummy solid resulted that was extracted with chloroform. The aqueous solution was adjusted to pH 5 and used for cyclization.

2,4,4a,5-Tetrahydro-7-[4-(hydroxymethyl)-1*H*-imidazol-1-yl]-3*H*-indeno[1,2-*c*]pyridazin-3-one (8). Hydrazine hydrate

(1.3 g, 22 mmol) was added to an aqueous solution of the above acid, and the mixture was heated at reflux for 6 h. The reaction mixture was cooled and filtered, and the residue was suspended in water. Ammonium hydroxide was added to adjust to pH 10, and the precipitate was filtered, washed with water, and recrystallized to give **8**.

6-Fluoro-2,3-dihydro-1*H*-inden-1-one (31). 3-Chloro-1-(4-fluorophenyl)-1-propanone (20 g, 107 mmol) was added to sulfuric acid (300 mL) and heated at 140 °C for 1.25 h. The dark mixture was cooled, added to ice water (2500 mL), and then extracted with ether (3 × 1000 mL) and methylene chloride (2 × 1000 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to provide an oil. This oil was chromatographed on a column of silica gel with methylene chloride as eluant to give 8.8 g (55%) of **31**, mp 36–38 °C. Anal. (C_9H_7FO) C, H.

2,3-Dihydro-6-(1*H*-imidazol-1-yl)-1*H*-inden-1-one (32). A flask charged with 6-fluoro-2,3-dihydro-1*H*-inden-1-one (**31**; 8 g, 53.3 mmol), imidazole (3.63 g, 53.3 mmol), potassium carbonate (7.36 g), cupric oxide (300 mg), and pyridine (50 mL) was heated at reflux for 20 h. The reaction mixture was filtered, and the residue was washed successively with pyridine. The filtrate was evaporated under reduced pressure, and the residue was chromatographed on silica gel to provide 2.8 g (27%) of **32**, mp 143–145 °C. Anal. ($C_{12}H_{10}N_2O$) C, H, N.

2,3-Dihydro-6-(1*H*-imidazol-1-yl)-1-oxo-1*H*-indene-2-carboxylic Acid, Methyl Ester (33). A slurry of sodium hydride (60%, 5.45 g, 136.2 mmol) in tetrahydrofuran (50 mL) was added to a solution of **32** (9 g, 45.4 mmol) in tetrahydrofuran (290 mL). This mixture was stirred at ambient temperature for 1.5 h. Dimethyl carbonate (40.9 g, 454 mmol) was added, and the mixture was heated at reflux for 21 h. Ice water (700 mL) was added, and the unreacted starting material was extracted with ethyl acetate (200 mL). The aqueous layer was adjusted to pH 6 with glacial acetic acid, and the product was extracted with chloroform (6 × 300 mL). The combined organic extracts were evaporated, and the residue was chromatographed on silica gel to provide 5.86 g (50%) of **33**, mp 115–117 °C. Anal. ($C_{14}H_{12}N_2O_3$) C, H, N.

7-Amino-2,4,4a,5-tetrahydro-3*H*-indeno[1,2-*c*]pyridazin-3-one (21). A mixture of 5-fluoro-2,3-dihydro-1-oxo-1*H*-indene-2-acetic acid (**29**; 10 g, 50 mmol) and ammonium acetate (10 g) was heated in an oil bath at 120 °C. Over a period of 2 h an additional 30 g of ammonium acetate was added, and anhydrous ammonia was passed into the reaction mixture continually for 19 h. This mixture was cooled, and 1 N hydrochloric acid (300 mL) was added. The resultant suspension was filtered, and the filtrate was neutralized with 50% sodium hydroxide and extracted with chloroform/2-propanol (3:2, 3 × 200 mL). The combined fractions were evaporated to provide **34**. This was dissolved in ethanol (100 mL) and heated at reflux with hydrazine (55%, 10 mL) for 19 h to provide the aminopyridazinone (**21**; 1.69 g). The aqueous phase from above was also heated in the presence of excess hydrazine to provide an additional 2.32 g of **21**. The amine **21** was subsequently converted to the acylamino derivatives, **22** and **23**, by treatment with the requisite acyl anhydrides.

***N*-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl]acetamide, Monohydrochloride (36).** Dimethylamine hydrochloride (7.2 g, 88 mmol) was added to 37% aqueous formaldehyde (6.5 mL, 80 mmol) and was allowed to stand at ambient temperature for 1 h. Acetic anhydride (40 mL) was added, and the mixture was heated until a one-phase system resulted. 6-Acetamido-1-tetralone (**35**; 10 g, 49 mmol) was added, and the solution was heated at reflux for 2 h. The solvent volume was reduced to 10 mL, and acetone (50 mL) was added. The thick precipitate that formed was filtered to provide 14.7 g (97%) of **36**, mp 153–155 °C. Anal. ($C_{15}H_{20}N_2O_2 \cdot HCl \cdot 0.6H_2O$) C, H, N.

6-Amino-1,2,3,4-tetrahydro-1-oxo-2-naphthaleneacetic Acid (38). The dimethylamine hydrochloride (**36**; 9 g, 30 mmol) was added to 200 mL of 1 N sodium hydroxide and extracted with a mixture of chloroform/2-propanol (3:2, 3 × 200 mL). The combined extracts were washed with brine (200 mL) and dried over anhydrous sodium sulfate, and the solvent was evaporated to provide an oil. Acetone (100 mL) and iodomethane (12.9 g, 91 mmol) were added, and the mixture was heated at reflux for 2 h. During this period a precipitate formed that was filtered to provide 8.5 g (68%) of the quaternary salt, 6-(acetylamino)-1,2,3,4-tetrahydro-*N*,*N*,*N*-trimethyl-1-oxo-2-naphthalenemethanaminium iodide, mp 195–197 °C. Anal. ($C_{16}H_{23}IN_2O_2$) C, H, N, I.

A solution of potassium cyanide (800 g, 12 mmol) in water (3 mL) was added to the above quaternary ammonium salt (2 g, 5 mmol) in methanol/water (1:1, 100 mL) and the reaction mixture was stirred at ambient temperature for 16 h. The precipitate was filtered and washed with water to provide 1 g of nitrile **37**, which was added to 6 N hydrochloric acid (20 mL) and heated on a steam bath for 1 h. The solution was cooled to provide 700 mg of the hydrochloride salt of the amino acid **38**. This was used for the next step without further purification.

***N*-(2,3,4,4a,5,6-Hexahydro-3-oxobenzo[*h*]cinnolin-8-yl)-acetamide (40).** Hydrazine hydrate (0.2 mL) was added to the amino acid hydrochloride **38** (630 mg) in ethanol (25 mL), and the mixture was heated at reflux for 21 h. The solution was cooled to provide 320 mg of the aminopyridazinone **39**.

The above amine **39** (350 mg, 1.6 mmol) was added to DMF (12 mL) and acetic anhydride (9 mL), and the suspension was heated gently until the compound had completely dissolved. The mixture was allowed to stand at ambient temperature for 2 h, and the solvent was evaporated. The residue was triturated with methanol to provide **40**: 300 mg; mp 288–289 °C.

5-Bromo-2,3-dihydro-3-methyl-1*H*-inden-1-one (41). A mixture of anhydrous aluminum chloride (250 g) and sodium chloride (62.5 g) was heated to 130 °C. 1-(4-Bromophenyl)-4-chloro-1-butanone (50 g, 191 mmol) was added, and the mixture was heated to 180 °C for 20 min. The mixture was cooled to room temperature, 1 N hydrochloric acid (1500 mL) was added with cooling, and the solution was extracted with methylene chloride (3 × 1000 mL). The combined organic fractions were filtered over silica gel (50 g) and evaporated to provide 29.7 g (79%) of **41**, mp 55–59 °C. Anal. ($C_{10}H_9BrO$) C, H.

5-Bromo-2,3-dihydro-3-methyl-1-oxo-1*H*-indene-2-carboxylic Acid (43). To a suspension of sodium hydride (60%, 6.3 g) in tetrahydrofuran (50 mL) was added a solution of **41** (27.3 g, 121 mmol) in tetrahydrofuran (100 mL), and the suspension was allowed to stir for 30 min. Dimethyl carbonate (109.2 g) was added dropwise, and the mixture was heated at reflux for 19 h. It was poured into ice water (200 mL), sodium hydroxide (50%, 2 mL) was added, and the mineral oil was extracted with hexane (400 mL). The aqueous phase was separated, acidified (pH 2) with concentrated hydrochloric acid, and extracted with ether (3 × 500 mL). The ether extract was dried over anhydrous sodium sulfate and filtered over silica gel. The solvent was evaporated, and the residue was dissolved in isopropyl ether (100 L). Sodium hydroxide (1 N, 200 L) was added, and after cooling, the crystalline product was filtered to provide 29.1 g (79%) of the sodium salt of **42**, mp >250 °C. A portion of the above sodium salt was treated with dilute acid to provide the β-keto ester **42**, mp 47–49 °C. Anal. ($C_{12}H_{11}BrO_3$) C, H.

To a solution of the sodium salt of **42** (2 g, 6.6 mmol) in tetrahydrofuran (50 mL) was added ethyl bromoacetate (3.28 g, 20 mmol), and the mixture was heated at reflux for 3 h. The reaction mixture was poured into water (200 mL) and extracted with methylene chloride (300 mL). The organic phase was washed with brine (200 mL), filtered over silica gel (15 g), and evaporated under reduced pressure to provide an oil. This was dissolved in a mixture of 6 N hydrochloric acid (50 mL) and acetic acid (20 mL) and heated at reflux for 14 h. Upon cooling, the reaction mixture was extracted with chloroform/2-propanol (3:2, 2 × 100 mL). The combined organic fractions were washed with brine (100 mL), filtered over silica gel (15 g), and evaporated to provide an oil that was triturated with water to give 1.5 g (76%) of **43**. This material was recrystallized from isopropyl ether to yield analytically pure **43**, mp 113–115 °C. Anal. ($C_{12}H_{11}BrO_3$) C, H.

7-Bromo-2,4,4a,5-tetrahydro-5-methyl-3*H*-indeno[1,2-*c*]-pyridazin-3-one (44). Hydrazine hydrate (80%, 2 g, 50 mmol) was added to a solution of the keto acid **43** (2 g, 7 mmol) in ethanol (50 mL), and the solution was heated at reflux for 5 h. After cooling, the suspension was filtered to provide 1.1 g (56%) of **44**, mp 226–227 °C. Anal. ($C_{12}H_{11}BrN_2O$) C, H, N.

Pharmacological Methods. 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^{-1}

h^{-1}. A cannula was inserted into the femoral vein for administering test agents. A Millar catheter tip pressure transducer was inserted into the ascending aorta via the femoral artery for measuring aortic blood pressure. Another similar transducer was passed into the left ventricle via the left carotid artery for measuring left ventricular blood pressure. Needle electrodes were placed subcutaneously for recording a lead II electrocardiogram (ECG). Heart rate, using a biotachometer triggered from the R wave of the ECG, and the first derivative of left ventricular blood pressure (dP/dt), obtained with a differentiator amplifier coupled to the corresponding pressure amplifier, were also recorded. A period of 30 min was utilized to obtain control data prior to administration of test agent. Dependent 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 administrated in a volume of 0.1 mL/kg over a period of 1 min in a cumulative manner. Usually, half-log intervals were maintained between doses, with typical dosing consisting of four to six doses (for example, 0.01, 0.03, 0.1 mg/kg) in order to establish any dose–response relationships. A 10–30-min interval was used between doses for the variables to reach a steady state. Only one compound was administered to any one animal. The inotropic activity of a compound was determined by measuring changes in dP/dt_{max} of left ventricular pressure from preceding base line. Data for compounds are expressed as means ± SEM or arithmatic means of two experiments. Statistical analysis of the data was performed with use of a Student's t-test for paired or unpaired data. The probability value $p < 0.05$ was accepted as level of significance. Isoproterenol (0.3 μg/kg) was administered before and after nadolol (1.0 μg/kg) to test the degree of β-adrenoceptor blockade.

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Registry No. 1, 95967-53-6; 2, 95967-65-0; 3, 95967-58-1; 4, 103437-41-8; 5, 95967-63-8; 6, 95967-64-9; 7, 95967-62-7; 8, 95967-61-6; 9, 103422-52-2; 10, 95967-60-5; 11, 95991-83-6; 12, 95967-67-2; 13, 95967-54-7; 14, 95967-57-0; 15, 95967-56-9; 16, 95967-68-3; 17, 95967-70-7; 18, 95967-66-1; 19, 95967-71-8; 20, 95967-69-4; 21, 103422-53-3; 22, 103422-54-4; 23, 103422-55-5; 24, 103422-56-6; 25, 95967-52-5; 26, 103422-57-7; 27, 103422-58-8; 28, 103422-59-9; 29, 81198-16-5; 30, 84243-57-2; 31, 1481-32-9; 32, 103422-60-2; 33, 103422-61-3; 34, 103422-62-4; 35, 88611-67-0; 36, 103422-63-5; 37, 103422-64-6; 38, 103422-65-7; 39, 103422-66-8; 40, 103422-56-6; 41, 103422-67-9; 42, 103422-68-0; 43, 103422-69-1; 44, 103422-70-4; hydrazine, 302-01-2; imidazole, 288-32-4; 1-*H*-1,2,4-triazole, 288-88-0; 1-*H*-imidazole-4-methanol hydrochloride, 103422-88-4; 3-chloro-1-(4-fluorophenyl)-1-propanone, 347-93-3; 6-(acetylamino)-1,2,3,4-tetrahydro-*N*,*N*,*N*-trimethyl-1-oxo-2-naphthalenemethanaminium iodide, 103422-89-5; 1-(4-bromophenyl)-4-chloro-1-butanone, 4559-96-0; ethyl bromoacetate, 105-36-2; 2,3-dihydro-5-(2-methyl-1*H*-imidazol-1-yl)-1-oxo-1*H*-indene-2-acetic acid, 103422-71-5; 2,3-dihydro-5-(2-ethyl-4-methyl-1*H*-pyrrol-1-yl)-1-oxo-1*H*-indene-2-acetic acid, 103422-72-6; 2,3-dihydro-5-(4,5,6,7-tetrahydro-1*H*-benzimidazol-1-yl)-1-oxo-1*H*-indene-2-acetic acid, 103422-73-7; 2,3-dihydro-5-[4-(hydroxymethyl)-1*H*-imidazol-1-yl]-1-oxo-1*H*-indene-2-acetic acid, 103422-74-8; 2,3-dihydro-5-(4-methyl-1*H*-imidazol-1-yl)-1-oxo-1*H*-indene-2-acetic acid, 103422-75-9; 2,3-dihydro-5-(4-(pyridin-2-yl)-piperazin-1-yl)-1-oxo-1*H*-indene-2-acetic acid, 103422-76-0; 2,3-dihydro-5-piperidino-1-oxo-1*H*-indene-2-acetic acid, 103422-77-1; 2,3-dihydro-5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-1-oxo-1*H*-indene-2-acetic acid, 103422-78-2; 2,3-dihydro-5-(3-hydroxy-1-piperidinyl)-1-oxo-1*H*-indene-2-acetic acid, 103422-79-3; 2,3-dihydro-5-morpholino-1-oxo-1*H*-indene-2-acetic acid, 103422-80-6; 2,3-dihydro-5-(4-methyl-1-piperazinyl)-1-oxo-1*H*-indene-2-acetic acid, 103422-81-7; 2,3-dihydro-5-thiomorpholino-1-oxo-1*H*-indene-2-acetic acid, 103422-82-8; 2,3-dihydro-5-(butylamino)-1-oxo-1*H*-indene-2-acetic acid, 103422-83-9; 2,3-dihydro-5-(3-aminopropylamino)-1-oxo-1*H*-indene-2-acetic acid, 103422-84-0; 5-amino-2,3-dihydro-1-oxo-1*H*-indene-2-acetic acid, 103422-62-4; 5-(acetylamino)-2,3-dihydro-1-oxo-1*H*-indene-2-acetic acid, 103422-85-1; 2,3-dihydro-1-oxo-5-(propionylamino)-1*H*-indene-2-acetic acid, 103422-86-2; 6-(acetylamino)-2,3,4-trihydro-1-oxo-1*H*-naphthalene-2-acetic acid, 103422-87-3; benzimidazole, 51-17-2; 4-phenylimidazole, 670-95-1.