cavity. The left atrium was suspended in Krebs-Henseleit solution (KH) containing the following (mM): NaCl (118), KCl (4.7), $MgSO_4$ (1.2), KH_2PO_4 (1.2), $CaCl_2$ (2.5), $NaHCO_3$ (25), and glucose (11). The KH solution was maintained at 32 °C and gassed with 95% O_2, 5% CO_2 leading to a pH of 7.3–7.4. The preparation was allowed to stabilize for 1 h before starting the experiment. The effect of the compounds on electrically evoked atrial contractions (2 Hz, 2 ms, twice the threshold) was examined after cumulative addition to the organ bath. The mechanical performance was recorded isometrically.

A high-speed recording (200 mm/s) at each concentration allows calculation of relaxation time (RT). The variations in RT were expressed as percent changes from control values.

Cardiotonic Activity in the Conscious Instrumented Dog. Male beagle dogs, weighing 10–14 kg, were chronically instrumented to monitor LV dP/dt max (the first derivative of left ventricular pressure) and heart rate. Under fluothane anesthesia a Koenigsberg P_5 tip micromanometer was implanted into the left ventricle through a stab wound at the apex. Dogs were allowed to recover from surgery a minimum of 2 weeks before use in a study. Dogs were placed in a quiet room, parameters being recorded outside. To reduce the uncertainty due to solubility, drugs (and placebo) were solubilized in dimethylimidazolidinone–Tween 80–H_2O (1:2:2) and administered in 000 gelatin capsules. Drugs were administered after a control period of 90 min and parameters recorded for 22 h.

Acknowledgment. We acknowledge the outstanding technical contributions of J. Albadine-Perceveault, N. Brument, J. C. Camelin, B. Cheval, C. Dartois, I. Delimoge, J. Guibert, P. Guibet, J. Guimard, J. Jean, V. Lahouratate, M. P. Laville, M. C. Le Boulch, M. N. Legave, and M. Morvan. We thank I. Juillard for NMR studies and D. Leroux for providing computational support.

Registry No. **10**, 122280-58-4; **17** (R = Me), 122280-68-6; **22**, 122281-20-3; **23**, 122281-23-6; **24**, 122281-24-7; **25**, 19155-24-9; **26**, 137516-11-1; **27**, 137516-12-2; **28**, 137516-13-3; **29**, 122280-62-0; **30**, 137516-14-4; **31**, 122280-59-5; **32**, 137516-15-5; **33**, 122280-61-9; **34**, 122280-67-5; **35**, 122280-60-8; **36**, 100644-04-0; **37**, 122280-91-5; **38**, 122297-45-4; **39**, 137516-16-6; **40**, 103969-58-0; **41**, 120223-10-1; **42**, 137516-17-7; **43**, 137516-18-8; **44**, 137516-19-9; **45**, 122280-72-2; **46**, 122280-63-1; **47**, 122280-73-3; **48**, 122280-77-7; **49**, 122280-69-7; **50**, 122280-70-0; **51**, 137516-20-2; **52**, 122280-88-0; **53**, 122280-85-7; **54**, 122280-86-8; **55**, 122280-87-9; 2-chloropropionyl chloride, 7623-09-8; 5-(2-chloro-1-oxopropyl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one, 122281-03-2; 1-(4-aminophenyl)-2-chloropropanone, 25021-66-3; methyl 2-thiolanecarboxylate, 113990-87-7; 5′-(2-chloro-1-oxopropyl)spiro[thiolane-2,3′-[3*H*-indol]-2′(1′*H*)-one, 122281-10-1; 4-(4-aminophenyl)-4-oxobutanoic acid, 6945-94-4; ethyl 2-(methylthio)propionate, 40800-76-8; 4-(2,3-dihydro-3-methyl-3-(methylthio)-2-oxo-1*H*-indol-5-yl)-4-oxobutanoic acid, 137516-21-3; methyl α-mercaptoacetate, 2365-48-2; 5-(2-azido-1-oxopropyl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one, 122281-21-4; 5-(2-amino-1-oxopropyl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one hydrochloride, 122281-22-5; 1,3-dihydro-5-(2-hydroxy-1-oxopropyl)-3,3-dimethyl-2*H*-indol-2-one, 122297-47-6; phosphodiesterase, 9025-82-5.

Heteroatom Analogues of Bemoradan: Chemistry and Cardiotonic Activity of 1,4-Benzothiazinylpyridazinones

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A series of close analogues of the potent, long-acting cardiotonic bemoradan (**2a**) was synthesized and examined in both in vitro and in vivo test systems. Changing the oxygen heteroatom at the 1-position of the benzoxazine ring of bemoradan to sulfur gave **4a**, a more potent enzyme inhibitor and in vivo cardiotonic compound by the iv route. Intraduodenal administration of bemoradan, however, showed a superior response compared to its sulfur analogue, possibly due to oxidation of sulfur followed by a facile Pummerer rearrangement. Model studies were performed to examine the effect of the oxidation state of sulfur. Lack of a heteroatom at the 1-position, **3a** (Y-590), afforded a compound with activity and potency very similar to those of bemoradan while the 1-selena compound gave a much less potent analogue **5**. Analogues having a methyl group on the 4-nitrogen (**2b**, **3b**, and **4b**) were less potent than the desmethyl compounds, but all of these compounds have potent PDE III inhibiting activity and the ability to increase cardiac force in an anesthetized dog preparation when given iv.

Introduction

In recent years, a number of highly potent positive inotropes have been described in the literature.[1] Many of these compounds, acting through the inhibition of cyclic nucleotide phosphodiesterase III isozyme (PDE III)[2] isolated from heart muscle, consist of a pyridazinone ring attached to a substituted aromatic nucleus. In a subset of these compounds, typified by indolidan[3] (1) and bemoradan[4] (**2a**), the pyridazinone ring is attached to a benzo-fused heterocycle. The nature of this benzo-fused heterocyclic fragment of the molecule would seem to be important to the physical properties as well as the biological effects, metabolism, and distribution of the compounds. We have reported on the synthesis and biological properties of bemoradan,[5] and now report on the synthesis and biological properties of a series of compounds differing by the substitution of one atom in the 1-position of the benzoxazine ring of bemoradan (see Table I). Although

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(2) Nicholson, C. D.; Challiss, R. A. J.; Shahid, M. Differential Modulation of Tissue Function and Therapeutic Potential of Selective Inhibitors of Cyclic Nucleotide Phosphodiesterase Isoenzymes. *Trends Pharmacol. Sci.* **1991**, *12*, 19.

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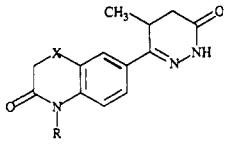
0022-2623/92/1835-0172$03.00/0

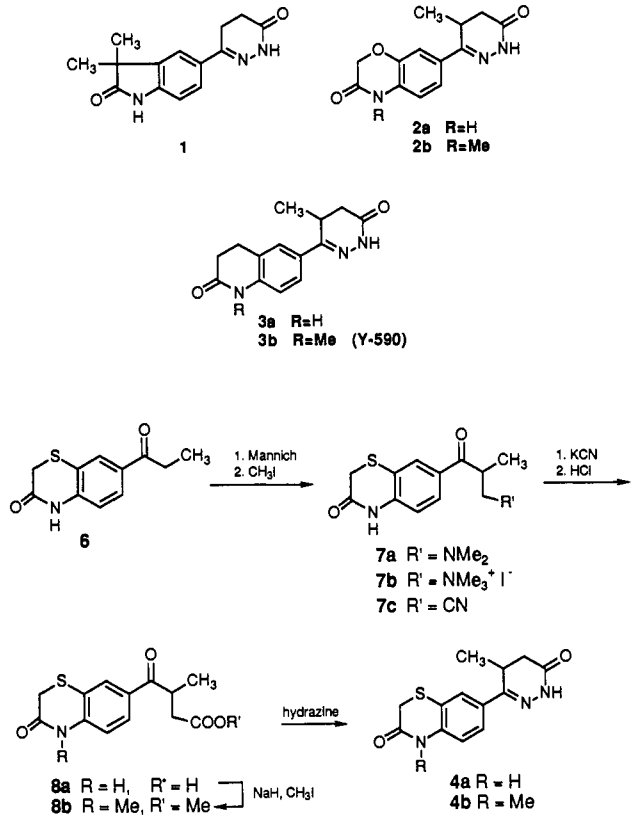
Table I. Comparison of Physical and Biological Properties of Bemoradan Analogues



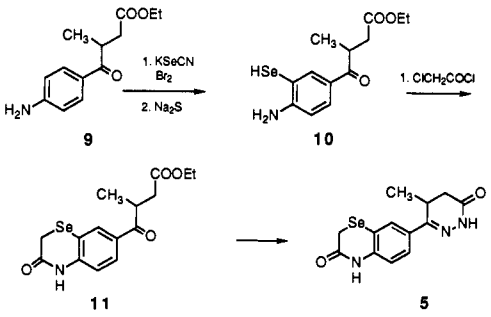
compd	X	R	mp, °C	formula	anal.	CF[a] iv ED_{50}, μg/kg	CF id ED_{50}, μg/kg	PDE[b] IC_{50}, μM
2a[c]	O	H	>300	$C_{13}H_{13}N_3O_3$	CHN	5.4	10	0.3
2b	O	Me	>300	$C_{14}H_{15}N_3O_3$	CHN	12.8	22	0.3
3a	CH_2	H	298–300	$C_{14}H_{15}N_3O_2$	CHN	5.7	10	0.3
3b[d]	CH_2	Me	>300	$C_{15}H_{17}N_3O_2$	CHN	6.0	12	0.1
4a	S	H	>300	$C_{13}H_{13}N_3O_2S$	CHN	4.0	100	0.1
4b	S	Me	193–195	$C_{14}H_{15}N_3O_2S$	CHN	31.0	nt[e]	1.0
5	Se	H	>300	$C_{13}H_{13}N_3O_2Se$	CHN	19.0	>100	2.0

[a] CF = dose causing a 50% increase in cardiac force. [b] PDE = concentration to inhibit cardiac phosphodiesterase fraction III by 50%. [c] Bemoradan. [d] Y-590. [e] nt = not tested.

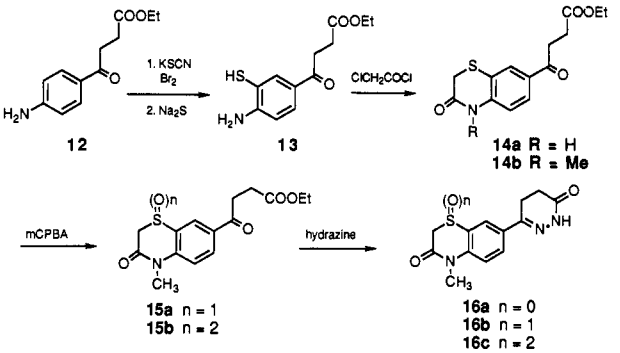
Scheme I



Scheme II



Scheme III



they are all potent inhibitors of cardiac fraction III phosphodiesterase, and act as cardiotonics in vivo, differences in cardiotonic potency with iv versus intraduodenal (id) administration of the benzothiazine analogue led us to explore the oxidation chemistry of these sulfur-containing compounds. These studies may be reflecting the metabolic fate of these compounds.

Chemistry

The synthesis of bemoradan[5] (**2a**) and its *N*-methyl homologue **2b** and the quinolinone analogues[6] **3a** and **3b** (Y-590) has been reported previously. The sulfur- and selenium-containing compounds **4a**, **4b**, and **5** were prepared by the methods described in Schemes I and II, respectively. 7-Propionyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine[7] (**6**) was elaborated to thio compound **4a** by the same five-step route first used by McEvoy and Allen[8] and subsequently used by us for the benzoxazine analogues. *N*-Methyl compound **4b** was made by methylation of acid **8a** followed by treatment with hydrazine. Ethyl 4-(4-aminophenyl)-3-methyl-4-oxobutyrate[9] (**9**) was treated with potassium selenocyanate in acetic acid and bromine. The resultant cyanate was hydrolyzed with sodium sulfide nonahydrate to give the amino selenol **10**, which was cyclized to the selenazine **11** with chloroacetyl chloride. Reaction with alcoholic hydrazine gave the desired pyridazinone **5**.

Synthesis of analogues with higher oxidation states of sulfur allowed for the exploration of the chemical and

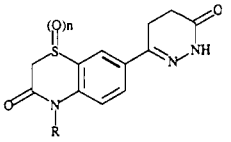
(6) U.S. Patent 4,258,185: Pyridazinone Compounds. Yoshitomi Pharmaceutical Industries, March 24, 1981.

(7) Eur. Pat. EP 272914: 6-Benzoxazinyl- and 6-Benzothiazinyl-2,3,4,5-tetrahydropyridazin-3-ones and Pharmaceutical Use. Ortho Pharmaceutical Corp. June 29, 1988. *Chem. Abstr.* **1988**, *109* (21), 190436m.

(8) McEvoy, F. J.; Allen, G. R., Jr. A General Synthesis of 3-(Substituted benzoyl)-3-Substituted Alkanoic Acids. *J. Org. Chem.* **1973**, *23*, 4044.

(9) McEvoy, F. J.; Allen, G. R., Jr. 6-(Substituted phenyl)-5-substituted-4,5-dihydro-3-(2H)-pyridazinones. Antihypertensive Agents. *J. Med. Chem.* **1974**, *17*, 281.

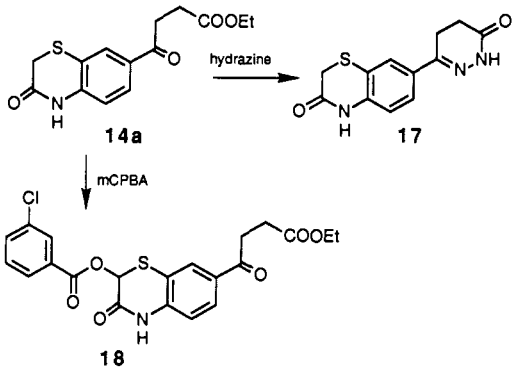
Table II. Physical and Biological Properties of Benzothiazinyl Pyridazinones



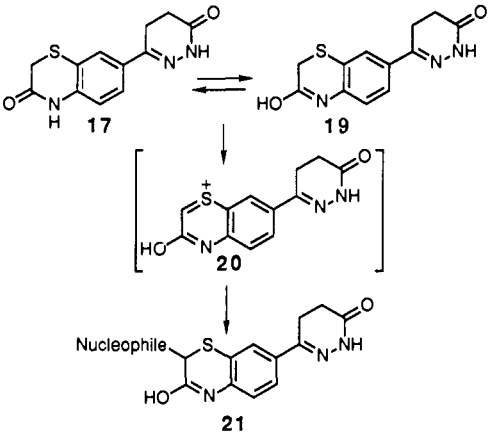
compd	R	n	mp, °C	formula	anal.	CF[a] iv (% change)	PDE,[b] IC_{50}
16a	Me	0	235–237	$C_{13}H_{13}N_3O_2S$	CHN	38	30
16b	Me	1	257–258	$C_{13}H_{13}N_3O_3S$	CHN	−3	45
16c	Me	2	295–296	$C_{13}H_{13}N_3O_4S$	CHN	20	40
17	H	0	>300	$C_{12}H_{11}N_3O_2S$	CHN	62	7

[a] Increase in cardiac force @75 μg/kg. [b] PDE = concentration to inhibit cardiac phosphodiesterase fraction III by 50%.

Scheme IV



Scheme V



biological behavior of these compounds. Introduction of sulfur in **12**[10] to give **13** and construction of the thiazine ring to give **14a**[7] was accomplished in the manner similar to that used with the selenium analogue in Scheme II. 3-Oxobenzothiazine **14a** was N-methylated with sodium hydride and iodomethane in DMF to give **14b**. Treating **14b** with hydrazine gave the pyridazinone **16a** while oxidation of **14b** with 1 equiv of MCPBA gave a stable sulfoxide **15a** and with a second equivalent provided the sulfone **15b**. Both **15a** and **15b** were independently converted to the corresponding pyridazines **16b** and **16c** with hydrazine in ethanol (Scheme III).

While we had no difficulty in preparing the N-methylated analogues, compounds having an NH group in the benzothiazine ring gave rearranged products upon oxidation. The unmethylated keto ester **14a** was easily converted to the pyridazinone **17**, but oxidation of **14a** with sodium periodate returned starting material. An alternative oxidant, MCPBA, afforded the Pummerer rearranged product **18** in 55% yield (see Scheme IV).

Discussion

The substitution of a heteroatom for a methylene group in a drug can provide profound effects on activity, potency, metabolism, and distribution.[11] The structural basis for these phenomena are both electronic, the additional electron pairs providing new binding sites on the molecule, and steric, new torsional angles and ring geometries defining a new shape for that molecule. The enhanced activity of the benzoxazinone **2a** and benzothiazinone-(**4a**) containing analogues relative to the quinolinone **3a** and lesser activity of the selenium-containing compound **5** leads us to the conclusion that smaller groups that maintain the geometry of the molecule while providing additional electron pairs for nonbonding interactions are most favorable for activity. This observation is consistent with the conclusions of Bristol[12] on the nature of the binding of PDE III inhibitors to the enzyme's active site and the experimental findings of Schnettler.[13] In addition, the *N*-methyl analogues were not as potent as the unsubstituted compounds. The iv activity of these compounds (Table I) correlates well with PDE III inhibition, indicating that these structural changes are acting at the molecular level and are associated with the mechanism of action of the drugs rather than through a physical phenomenon such as solubility or distribution.

While bemoradan (**2a**) retains its high potency and activity after id administration, the sulfur (**4a**) and selenium (**5**) analogues are 10 times less potent by this route. A model study was performed to determine if oxidation might account for this loss of potency. The sulfide (**16a**), sulfoxide (**16b**), and sulfone (**16c**) analogues of **4b** do not contain the 5′-methyl in the pyridazinone ring but do bear a methyl group at the thiazine nitrogen (Table II). There was little difference in PDE III inhibition between **16a**, **16b**, and **16c** which have IC_{50} values of 30, 45, and 40 μM, respectively. The reduced potency at the enzymic level is reflected in the poor iv activity of these compounds.

In contrast to the well-behaved oxidations of the *N*-methyl compounds, analogues with higher oxidation states of sulfur could not be synthesized in molecules with an NH moiety. The desmethyl oxobutyric acid **14a** was treated

(10) Thyes, M.; Lehmann, H. D.; Gries, J.; Konig, H.; Kretzschmar, R.; Kunze, J.; Lebkucher, R.; Lenke, D. 6-Aryl-4,5-dihydro-3-(2H)-pyridazinones. A New Class of Compounds with Platelet Aggregation Inhibiting and Hypotensive Activities. *J. Med. Chem.* **1983**, *26*, 800.

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(12) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. Cardiotonic Agents. 1. 4,5-Dihydro-6-[4-(1H-imidazol-1-yl)phenyl]-3(2H)-pyridazinones: Novel Positive Inotropic Agents for the Treatment of Congestive Heart Failure. *J. Med. Chem.* **1984**, *27*, 1099.

(13) Schnettler, R. A.; Dage, R. C.; Grisar, J. M. 4-Aroyl-1,3-dihydro-2H-imidazol-2-ones, a New Class of Cardiotonic Agents. *J. Med. Chem.* **1982**, *25*, 1477.

with hydrazine to give the sulfide **17**, which inhibits PDE fraction III with an IC_{50} of 7 μM. However, oxidation of **14a** by the addition of *m*-chloroperoxybenzoic acid gave, after workup, the Pummerer rearranged product **18**. We believe that the Pummerer rearrangement is made facile by enol–lactam tautomerism to intermediate **19**, which is driven to the aromatic benzothiazinium cation **20** due to resonance energy considerations. In vivo, intermediate **20** would be activated to attack by any number of nucleophillic species present in the gut (see Scheme V).

While replacement of the benzoxazine oxygen atom of bemoradan (**2a**) with a sulfur atom gave a more potent PDE III inhibitor and iv cardiotonic compound **4a**, the compound was not as active when given id. We have shown, in similar compounds (Table II), that oxidation of benzothiazines leads to oxygenated products which are not appreciably different in activity from the starting sulfide when the nitrogen atom of the benzothiazine ring is blocked with a methyl group. Our conclusion is that sulfoxides and sulfones themselves are not inherently an order of magnitude less potent then the corresponding sulfide.

The N-methylated compounds are, however, intrinsically less potent than their desmethyl analogues in both the oxazine and thiazine series with the *N*-Me compound being about 2–8 times less potent than the *N*-H analogue. A comparison of the iv potency of **2a** and **4a** with their methylated counterparts shows that the former cause a 50% increase in cardiac force (ED_{50}) at doses of 5.4 and 4.0 μg/kg, respectively, while **2b** and **4b** have ED_{50}'s of 12.8 and 31 μg/kg. Compound **17** increases cardiac force 62% at 75 μg/kg while **16a** can only increase force 38% at the same dose. The 5′-desmethyl compounds (**16a–c** and **17**) showed negligible changes (±5%) in heart rate and blood pressure while the more potent 5′-methyl analogues (**4a,b**) gave substantial (±20%) changes in both parameters at the ED_{50} dose.

Considering the data collected from the study of N-methylated compounds, we have no reason to believe that the sulfoxide and sulfone oxidation states would contribute to the generation of substantially less active molecules in the *N*-H series. When enol–lactam tautomerism is possible, however, a rapid Pummerer rearrangement results after sulfur oxidation. This phenomenon may well be a mechanism of inactivation of benzothiazine-containing cardiotonics given by the id or oral route.

Experimental Section

Chemical Methods. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were taken in chloroform-*d* with tetramethylsilane as the internal standard and recorded at 90 MHz on a Varian EM 390 instrument. Microanalyses were performed on a Perkin-Elmer Model 240C elemental analyzer and infrared spectra were taken on a Perkin-Elmer 1430 ratio recording spectrometer as KBr pellets. Mass spectra were obtained at 70 eV by direct insertion in a Finnigan 1015C GC/MS instrument.

6-(3,4-Dihydro-3-oxo-2*H*-1,4-benzothiazin-7-yl)-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (4a). A mixture of 37% aqueous formaldehyde (2.25 mL, 28 mmol) and dimethylamine hydrochloride (2.72 g, 33 mmol) in acetic anhydride (30 mL) was heated on a steam bath with constant swirling until a homogeneous solution resulted. Compound **6**[6] (5.0 g, 22.6 mmol) was added, and the mixture was heated at 100 °C overnight. Acetone (20 mL) was added, and heating was continued for 15 min. The solvent was removed at reduced pressure, and the residue was taken up in 1 N HCl (50 mL) and washed with ethyl acetate (50 mL). The aqueous layer was chilled and taken to pH 11 with 12 N NaOH. The cold solution was extracted with ethyl acetate (2 × 50 mL) and the organic portion dried over sodium sulfate. The solvent was removed and the residue **7a** was used in the next step.

Compound **7a** was dissolved in acetone (50 mL), and excess iodomethane (3 g, 22 mmol) was added. The mixture was heated at reflux for 3 h and cooled, and the solid was collected by filtration. The filter cake was washed with acetone (100 mL), giving 6.6 g of tan solid **7b**, which was dried and used in the next step.

Compound **7b** (6.6 g, 16 mmol) was dissolved in 20% aqueous methanol (125 mL), and excess potassium cyanide (3.8 g, 58 mmol) was added. After the mixture was stirred overnight at room temperature, the resultant off-white solid **7c** was collected by filtration and washed twice with water before being taken on to the next step.

Compound **7c** was heated to reflux in 6 N HCl (200 mL) for 30 min and then diluted with an equal volume of cold water. The resultant precipitate was collected by filtration to give 2.9 g of keto acid **8a**, which was taken on to the next step without further purification.

Compound **8a** (1.2 g, 4.1 mmol) was suspended in ethanol (50 mL), and anhydrous hydrazine (0.2 mL, 6 mmol) was added. The mixture was heated at reflux overnight and cooled, and the off-white crystals were collected by filtration and washed with cold ethanol (20 mL). The solid was dried at 1 mmHg and 100 °C, giving 0.18 g of **4a** (16%): mp >300 °C.

6-(3,4-Dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazin-7-yl)-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (4b). Compound **8a** (1.7 g, 5.8 mmol) was dissolved in DMF (50 mL), and sodium hydride (0.23 g of 60% oil dispersion, 5.8 mmol) was added portionwise. After 30 min, iodomethane (0.7 mL, 11.6 mmol) was added, and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into cold water (100 mL), and the resultant cloudy suspension was extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over sodium sulfate and evaporated at reduced pressure to give **8b** as an oil, which was used subsequently without further purification. Compound **8b** was dissolved in ethanol (50 mL) and anhydrous hydrazine (0.3 mL, 9 mmol) was added. The mixture was heated at reflux overnight and cooled, and silica gel (50 mL) was added. The solvent was removed at reduced pressure and the powder placed on a silica gel column and eluted with 1 L of 5% methanol in dichloromethane. The fractions containing product were combined and evaporated, and the residue was crystallized from ethyl acetate. The solid **4b** was dried at 1 mmHg and 70 °C, giving 0.11 g (16%): mp 193–195 °C.

6-(3,4-Dihydro-3-oxo-2*H*-1,4-benzoselenazin-7-yl)-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (5). Compound **9**[9] (4.7 g, 20 mmol) was dissolved in acetic acid (30 mL), and potassium selenocyanide (5 g, 34.7 mmol) was added. Bromine (1.1 mL, 2.2 mmol) in acetic acid (3 mL) was added dropwise under nitrogen, and the mixture was heated to 50 °C overnight. The resultant precipitate was cooled, filtered, and washed with methanol (25 mL). The filtrate was evaporated to dryness and chromatographed on 400 mL of silica gel and eluted with 2 L of 5% methanol in dichloromethane. Fractions containing the product were combined, evaporated, and recrystallized from ethyl acetate to give 1.93 g of the selenocyanate as a yellow solid. The solid was heated at reflux temperature in water containing sodium sulfide nonahydrate (3 g) for 12 h. After cooling, acetic acid was added to bring the mixture to pH 5. The resulting orange solution was extracted three times with ethyl acetate, and the combined extracts were washed with brine, dried over sodium sulfate, and evaporated to dryness, giving 0.75 g of **10** as an orange foam.

Potassium carbonate (2.5 g) was dissolved in water (100 mL) and compound **10** (1.5 g, 4.8 mmol) was added. The mixture was cooled to 5 °C, and chloroacetyl chloride (0.5 mL, 6.2 mmol) was added dropwise with vigorous stirring. After 15 min the mixture was heated at reflux for 3 h, cooled, and adjusted to pH 3 with 6 N HCl. The acidified mixture was extracted with dichloromethane (2 × 75 mL), and the organic layers were combined and dried over sodium sulfate. The solvent was removed at reduced pressure to give 1.9 g of a dark residue which was purified by column chromatography over 400 g of silica gel and eluted with 5% methanol in dichloromethane (1 L). The fractions containing product were combined, and the solvent was removed at reduced pressure to give 0.5 g (29%) of **11** as a yellow-green foam.

Compound **11** (0.5 g, 1.5 mmol) was suspended in ethanol (50 mL), and anhydrous hydrazine (0.2 mL, 6 mmol) was added. The mixture was heated at reflux overnight and then cooled, and the

white crystals were collected by filtration and washed with ethanol (10 mL) and ether (20 mL), giving a white solid which was dried at 1 mmHg and 90 °C, giving 0.15 g (30%) of **5**: mp >300 °C.

6-(3,4-Dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazin-7-yl)-2,3,4,5-tetrahydropyridazin-3-one (16a). Compound **12**[10] (30 g, 135.7 mmol) was dissolved in acetic acid (250 mL), and potassium thiocyanide (30.6 g, 315.5 mmol) was added. Bromine (8.75 mL, 17.6 mmol) in acetic acid (25 mL) was added dropwise under nitrogen. The exothermic reaction was allowed to subside, and the mixture was stirred for an additional 15 min before being poured into cold water (1 L). The precipitate was collected by filtration and washed with water (250 mL) to give 32 g (82%) of intermediate thiocyanate product as a tan powder which partially melted at 140 °C and then effervesced at 260 °C. The powder was added to a solution of sodium sulfide nonahydrate (70 g, 292 mmol) in water (200 mL) and heated to reflux under a nitrogen atmosphere. After 1 h the solution was cooled to 10 °C in an ice bath, and acetic acid was added to bring the mixture to pH 5. The resultant precipitate was collected by filtration, washed with water (50 mL), and dried to give **13** (93%) which was used in the next step.

Sodium bicarbonate (27.7 g, 0.330 mol) was dissolved in water (300 mL) and **13** (22.5 g, 0.1 mol) was added. The mixture was cooled to 5 °C and chloroacetyl chloride (9 mL, 0.11 mol) was added dropwise with vigorous stirring. After 15 min the mixture was heated at reflux for 30 min and then cooled in ice–water, and 6 N hydrochloric acid (20 mL) was added to bring the solution to pH 2. The solid product **14a** was collected by filtration and used in the next step.

Compound **14a** (6 g, 20.5 mmol) was dissolved in DMF (100 mL), and 60% sodium hydride in oil (0.82 g, 20.5 mmol) was added. After 20 min iodomethane (1.8 mL, 29 mmol) was added, and the solution was stirred at room temperature overnight. The mixture was poured into water (200 mL) and extracted with ethyl acetate (2 × 75 mL). The organic fraction was evaporated, and the residue was chromatographed on a silica gel column and eluted with ethyl acetate–dichloromethane (1:4). Compound **14b** was collected as yellow crystals, mp 72–73.5 °C, in 76% yield.

Compound **14b** (1.0 g, 3.3 mmol) was suspended in ethanol (50 mL), and anhydrous hydrazine (0.5 mL, 15.6 mmol) was added. The mixture was heated at reflux for about 3 days and cooled, and the yellow crystals were collected by filtration and washed with cold ethanol (25 mL). The solid was dried at 1 mmHg and 70 °C, giving 0.16 g of **16a** (18%): mp 235–237 °C.

6-(3,4-Dihydro-4-methyl-1,3-dioxo-2*H*-1,4-benzothiazin-7-yl)-2,3,4,5-tetrahydropyridazin-3-one (16b). Compound **14b** (1.53 g, 5.0 mmol) was dissolved in dichloromethane (40 mL), chilled in an ice bath, and treated with MCPBA (0.9 g, 5.2 mmol). After 3 h the mixture was washed with saturated sodium bicarbonate solution and dried over sodium sulfate. The solvent was removed at reduced pressure and the resultant oil was recrystallized from ether to give 1.43 g (89%) of **15a**: mp 110–113 °C. Compound **15a** (0.65 g, 2.0 mmol) was suspended in ethanol (50 mL) and anhydrous hydrazine (0.13 mL, 4 mmol) was added. The mixture was heated at reflux overnight and cooled, and the solid was collected by filtration and washed with ethanol (25 mL). The off-white solid was dried at 1 mmHg and 65 °C, giving 0.15 g (26%) of **16b**: mp 257–258 °C.

6-(3,4-Dihydro-4-methyl-1,1,3-trioxo-2*H*-1,4-benzothiazin-7-yl)-2,3,4,5-tetrahydropyridazin-3-one (16c). Compound **15a** (0.75 g, 2.3 mmol) was dissolved in dichloromethane (15 mL), and MCPBA (0.44 g, 2.5 mmol) was added at room temperature. After 3 h an additional amount of MCPBA (0.1 g) was added, and the solution was stirred overnight. The mixture was washed with saturated sodium bicarbonate solution and dried over sodium sulfate. The solvent was removed at reduced pressure, and the resultant oil **15b** was used in the next step without further purification.

Compound **15b** (0.78 g, 2.3 mmol) was suspended in ethanol (50 mL), and anhydrous hydrazine (0.15 mL, 4.7 mmol) was added. The mixture was heated at reflux overnight and cooled, and the off-white crystals were collected by filtration and washed with ethanol. The solid was dried at 1 mmHg and 65 °C, giving 0.16 g of **16c** (20%): mp 295–296 °C.

6-(3,4-Dihydro-3-oxo-2*H*-1,4-benzothiazin-7-yl)-2,3,4,5-tetrahydropyridazin-3-one (17). Compound **14a** (1.0 g, 3.4 mmol) was suspended in ethanol (50 mL), and anhydrous hydrazine (0.2 mL, 6 mmol) was added. The mixture was heated at reflux for 72 h and cooled, and the yellow crystals were collected by filtration and washed with ethanol (25 mL). The solid was dried at 1 mmHg and 70 °C, giving 0.74 g (87%) of **17**: mp >300 °C.

Ethyl 4-Oxo-4-[2-[(3-chlorobenzoyl)oxy]-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazin-7-yl]butyrate 18. Compound **14a** (10.0 g, 34 mmol) was dissolved in dichloromethane (250 mL) and chilled in an ice bath, and MCPBA (6.0 g, 35 mmol) was added. The temperature of the reaction was allowed to rise to 25 °C and was stirred for about 3 days. The mixture was diluted with an equal volume of dichloromethane and then washed with saturated sodium bicarbonate solution and dried over sodium sulfate. The solvent was removed at reduced pressure, and the resultant oil was recrystallized from ether to give 8.4 g (55%) of **18**: mp 159–160 °C.

Pharmacological Methods. The methods described in our previous paper[5] for the isolation of the cardiac PDE III isoenzyme, for the measurement of enzyme activity, and for the evaluation of compounds in an anesthetized dog model were followed.

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