Cardiac-Slowing Amidines Containing the 3-Thioindole Group. Potential Antianginal Agents

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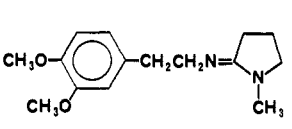
A series of 3-thioindolamidines (and 3-indolamidines) related to mixidine (1) was studied for cardiac-slowing properties, following the discovery of activity for prototype thioindole 2. Structure–activity relationships were explored, leading to many potent antitachycardic agents (**6–9**, 12, 13, 15–17, 20, 23, 24, **30**, **34**, **35**, **45**, and **47–49**). Relative to 2, cardiac-slowing activity is enhanced by substitution of the indole nitrogen with small (C_1–C_3) saturated alkyl groups (**6–9**), unsaturated alkyl groups (12, 13, and 15–17), or a methoxyethyl group (20); replacement of the *N*-methyl group with alkyl (23) or phenyl groups (24); and extension of the ethylene bridge by two methylene units (**34**). Dethio (i.e., 3-indole) analogues of 2 with alkyl substitution on the indole nitrogen (**47–49**) have greater activity as well. Several potent compounds were also found to have minimal myocardial depression (**6–9**, 13, **45**, and **47**). Secondary pharmacological testing is reported for thioindoles 2, **6**, **7**, **9**, and 28.

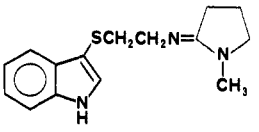
Angina pectoris is a painful symptom of ischemic heart disease, a chronic ailment associated with an imbalance between myocardial oxygen demand and supply.[1] Various factors determine myocardial oxygen demand, such as heart rate, contractility (force and velocity), and wall tension (related to ventricular volume and pressure).[1a,2] A pharmacological approach to the treatment of angina could entail influencing the key factors either to augment the oxygen supply to the heart or to diminish cardiac oxygen demand, without impairment of cardiac function. Myriad drugs have been applied to anginal therapy over the years,[1] but drug development since about 1970 has abated, perhaps because of a deficiency of predictive animal models and the lengthiness of clinical trials.[2a] Recent attention in the antianginal area has focused on calcium-entry blockers, such as verapamil and nifedipine.[3]

Some time ago, we became interested in compounds that specifically affect cardiac chronotropic responses without deleteriously altering other major cardiovascular parameters. In particular, we felt that a cardiac rate slowing agent without myocardial depressant properties would be an ideal antianginal drug. Mixidine (1), a prototype discovered in our laboratories around 1965, has received extensive chemical[4] and biological[5] study. Although mixidine (1) possesses a pharmacological profile indicative of its potential for the treatment of angina,[5a,c] its clinical usefulness was diminished by oral-absorption problems and lack of potency.

During our work on the mixidine series, we also pursued more remote analogues. Thus, a novel series of amidines containing the 3-thioindole moiety (e.g., **2**) was uncovered in which many compounds exhibit cardiac-slowing activity with minimal myocardial depression.[6] Over the course of our research, other antianginal series characterized by

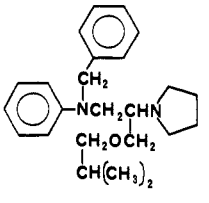


1 (mixidine, McN-1589)

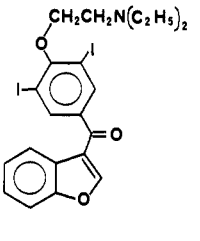


2 (McN-3415)

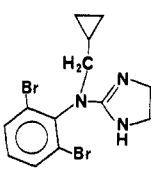
specific[7] cardiac-slowing activity have been disclosed, such as those encompassing bepridil (**3**),[8] amiodarone (**4**),[9] and



3 (bepridil)



4 (amiodarone)



5 (STH-2148)

STH-2148 (**5**).[10] In this article we report the chemistry, pharmacology, and structure–activity relationships of the 3-thioindolamidine series.

Results and Discussion

Chemistry. Synthetic routes employed in the preparation of the title compounds (Table I) are illustrated in

(1) (a) Kaverina, N. V.; Chumburidze, V. B. *Pharmacol. Ther.* **1979**, *4*, 109. (b) Ikraim, H. *Drugs* **1979**, *18*, 130. (c) For a review covering up to 1970, see: Charlier, R. "Antianginal Drugs"; Springer-Verlag, New York, 1971.

(2) (a) Francis, J. E. *Annu. Rep. Med. Chem.* **1977**, *12*, 39. (b) Sonnenblick, E. H.; Kelton, C. L. *Mod. Concepts Cardiovasc. Dis.* **1970**, *40*, 9.

(3) Rahwan, R. G.; Witiak, D. T.; Muir, W. W. *Annu. Rep. Med. Chem.* **1981**, *16*, 257.

(4) (a) Unpublished results from these laboratories. (b) See Poos, G. I. U.S. Patent 3 725 435, 1973.

(5) (a) Pruss, T. P.; Hageman, W. E.; Jacoby, H. I. *J. Pharmacol. Exp. Ther.* **1980**, *212*, 514. (b) Unpublished results from these laboratories. (c) Takeda, K.; Akera, T.; Brody, T. M. *Eur. J. Pharmacol.* **1980**, *68*, 129.

(6) McComsey, D. F., Zelesko, M. J., U.S. Patent 4 059 583 (1977).

(7) β-Blocking drugs slow heart rate, but they are not specific (e.g., β-blockers also depress myocardial contractility, which may precipitate congestive heart failure).

(8) (a) Cosnier, D.; Duchene-Marullaz, P.; Rispat, G.; Streichenberger, G. *Arch. Int. Pharmacodyn.* **1977**, *225*, 133. (b) The original structure given for bepridil (ref 8a and U.S. patent 3 962 238) is incorrect. Bepridil is correctly represented by structure **3**, which is isomeric with the original one [see Busch, N.; Simond, J.; Monteil, A.; Moleyre, J.; Mauvernay, R. Y. U.S. Patent Reissue 30 577, 1981; *WHO Chron.* **1978**, *32*(3), 15; USAN Council, *J. Am. Med. Assoc.* **1981**, *245*, 391]. (c) Bepridil has been reported to possess calcium antagonist activity, in analogy to verapamil and nifedipine [Mras, S., Sperelakis, N. *Eur. J. Pharmacol.* 1981, *71*, 13; Vogel, S.; Crampton, R.; Sperelakis, N. *J. Pharmacol. Exp. Ther.* **1979**, *210*, 378; Labrid, C.; Grosset, A.; Dureny, G.; Mironneau, J.; Duchene-Marullaz, P. *Ibid.* **1979**, *211*, 546].

(9) Charlier, D.; Deltour, G.; Baudine, A.; Chaillet, F. *Arzeim.-Forsch.* **1968**, *18* 1408. Charlier, R.; Bauthier, J.; Richard, J. *Ibid.* **1975**, *25*, 46. Charlier, R.; Bauthier, J. *Ibid.* **1973**, *23*, 1305.

(10) Stähle, H.; Daniel, H.; Kobinger, W.; Lillie, C.; Pichler, L. *J. Med. Chem.* **1980**, *23*, 1217.

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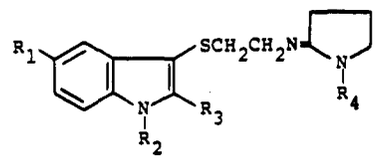
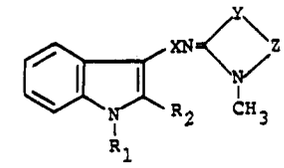
Table I. Structural Formulas





no.	R_1	R_2	R_3	R_4
2	H	H	H	CH_3
6	H	CH_3	H	CH_3
7	H	C_2H_5	H	CH_3
8	H	n-C_3H_7	H	CH_3
9	H	i-C_3H_7	H	CH_3
10	H	n-C_8H_{17}	H	CH_3
11	H	c-C_5H_9	H	CH_3
12	H	c-$C_3H_5CH_2$	H	CH_3
13	H	CH_2=$CHCH_2$	H	CH_3
14	H	CH_2=$C(CH_3)CH_2$	H	CH_3
15	H	3-butenyl	H	CH_3
16	H	2-cyclohexenyl	H	CH_3
17	H	HC≡CCH_2	H	CH_3
18	H	$C_6H_5CH_2$	H	CH_3
19	H	2-furylCH_2	H	CH_3
20	H	$CH_3OCH_2CH_2$	H	CH_3
21	H	(*E*)-cinnamyl	H	CH_3
22	H	H	H	H
23	H	H	H	CH_2=$CHCH_2$
24	H	H	H	C_6H_5
25	Cl	H	H	CH_3
26	OCH_3	H	H	CH_3
27	C_2H_5	H	H	CH_3
28	H	H	CH_3	CH_3
29	H	H	n-C_3H_7	CH_3
30	H	CH_3	CH_3	CH_3
31	H	HC≡CCH_2	CH_3	CH_3
32	Cl	H	CH_3	CH_3

no.	R_1	R_2	X	Y-Z
2	H	H	$S(CH_2)_2$	$(CH_2)_3$
33	H	H	$S(CH_2)_3$	$(CH_2)_3$
34	H	H	$S(CH_2)_4$	$(CH_2)_3$
35	C_2H_5	H	$S(CH_2)_4$	$(CH_2)_3$
36	H	H	$SCH_2CH(CH_3)$	$(CH_2)_3$
37	H	H	$S(CH_2)_2$	$(CH_2)_4$
38	H	CH_3	$S(CH_2)_2$	$(CH_2)_4$
39	H	H	$S(CH_2)_2$	$(CH_2)_5$
40	H	H	$S(CH_2)_2$	$NH(CH_2)_2$
41	H	H	$S(CH_2)_2$	$NH(CH_2)_3$
42	H	H	$S(CH_2)_4$	$NH(CH_2)_2$
43	H	CH_3	$S(CH_2)_2$	$NH(CH_2)_2$
44	H	n-C_3H_7	$S(CH_2)_2$	$NH(CH_2)_2$
45	H	H	$S(CH_2)_2$	CH_3/CH_3
46	H	H	$(CH_2)_2$	$(CH_2)_3$
47	C_2H_5	H	$(CH_2)_2$	$(CH_2)_3$
48	CH_2=$CHCH_2$	H	$(CH_2)_2$	$(CH_2)_3$
49	HC≡CCH_2	H	$(CH_2)_2$	$(CH_2)_3$
50	$C_6H_5CH_2$	H	$(CH_2)_2$	$(CH_2)_3$
51	H	H	$(CH_2)_2$	$NH(CH_2)_2$
52	H	H	$(CH_2)_4$	$(CH_2)_3$

Scheme I. Indole I was reacted with thiourea and I_2/KI, and the thiouronium intermediate product was immediately hydrolyzed with aqueous NaOH to give sodium 3-indolylthiolate II in situ.[11] The thiolate was alkylated with chloroacetonitrile to give nitrile III. If desired, N-alkylation could be conducted at this point by reaction of nitrile III with an alkyl halide and aqueous NaOH, giving alkylated nitriles IV. Reduction of III or IV with BH_3·THF[12] or $LiAlH_4/AlCl_3$ (1:1)[13] furnished amines V (Table IV). The amines were reacted with a Meerwein intermediate, such as VI, derived from *N*-methyl-2-pyrrolidinone and triethyloxonium tetrafluoroborate,[14,15] to give most of the target amidines (Table I) as fluoborate salts. The free bases were released from the fluoborate salts and purified directly or as suitable acid-addition salts.

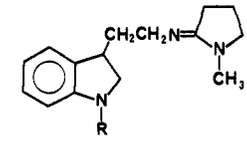
Compound **33** was prepared by reacting 3-chloropropylamine with thiolate II (X = Y = H), and the resulting amine was condensed with VI. 4-Chlorobutyronitrile was reacted with II (X = Y = H) to give the intermediate nitrile, which afforded compounds **34** and **35** according to Scheme I. Compound **36** was prepared from the reaction of VI with the amine prepared from the thiol of II (X = Y = H) and 2-methylaziridine.

Guanidine compounds **40–44** were prepared by reacting the appropriate amine with a thiouronium salt, such as VIII, derived from the appropriate cyclic thiourea and iodomethane.

Compound **46** was prepared via the reaction of tryptamine with VI; likewise, compound **51** was prepared from tryptamine and VIII. Compounds **47–50** were synthesized by reaction of compound **46** with sodamide and the appropriate alkyl halide.

Compound **52** was prepared from 4-(3-indolyl)butyric acid. Reaction of the acid with phosphorus pentachloride, followed by ammonium hydroxide, gave the butyramide, which was reduced with $LiAlH_4$ to give the amine. Reaction of the amine with VI produced amidine **52**.

The indoline analogue of **46**, compound **53**, was prepared



53, R = H
54, R = C_2H_5

by reduction of tryptamine with BH_3·THF/TFA[16] and reaction of the product diamine with VI. Indoline **54** was generated by reduction of **47** with BH_3·THF/TFA.

Pharmacology. The antianginal potential of the 3-thioindole derivatives, as well as their congeners, was generally assessed with a "triazine tachycardia test". The assay involved evaluation of cardiac-slowing activity in a

(11) Harris, R. L. N. *Tetrahedron Lett.* **1969**, 4465.
(12) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1960**, *82*, 681.
(13) Nystrom, R. F. *J. Am. Chem. Soc.* **1955**, *77*, 2544.
(14) Meerwein, H.; Borner, P.; Fuchs, O; Sasse, H. J.; Schrodt, H.; Spille, G. *Chem. Ber.* **1956**, *89*, 2060.
(15) Meerwein, H. In "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 1080.
(16) (a) Maryanoff, B. E.; McComsey, D. F. *J. Org. Chem.* **1978**, *43*, 2733. (b) Maryanoff, B. E.; McComsey, D. F.; Nortey, S. O. *J. Org. Chem.* **1981**, *46*, 355.

Table II. Chemical and Primary Pharmacological Data

compd	molec formula[a]	mp, °C (solv)[b]	D_{50} (ΔHR_{50})[c]	% ΔHR_{50}[d]	CS index (rel act.)[e]	MD[f]
2	$C_{15}H_{19}N_3S$	143.5-145.5 (I)	2.5 (-40)	20.4	8.2 (0.26)	3
6	$C_{16}H_{21}N_3S \cdot 0.5C_4H_4O_4$	186-189 (W/E)	1.2 (-30)	20.2	16.8 (0.52)	2
7	$C_{17}H_{23}N_3S \cdot C_6H_{13}NO_3S$	113.5-115.5 (I/EA)	0.8 (-39)	21.8	27.2 (0.85)	2
8	$C_{18}H_{25}N_3S \cdot C_{10}H_8O_3S$	98.5-100.5 (A)	1.7 (-60)	27.4	16.1 (0.50)	1
9	$C_{18}H_{25}N_3S$	82-84 (I)	1.0 (-31)	19.1	19.1 (0.60)	2
10	$C_{23}H_{35}N_3S \cdot C_4H_4O_4$	98-100 (I/EE)	7.3 (-32)	14.8	2.0 (0.06)	2
11	$C_{20}H_{27}N_3S \cdot C_7H_6O_2$	108.5-110 (EA/C)	2.7 (-40)	21.0	7.8 (0.24)	3
12	$C_{19}H_{25}N_3S \cdot C_4H_4O_4$	133-134 (95% E)	1.4 (-60)	25.5	18.2 (0.57)	2.5
13	$C_{18}H_{23}N_3S \cdot C_6H_{13}NO_3S$	105-107.5 (CL/EA)	1.0 (-52)	22.2	22.2 (0.69)	2
14	$C_{19}H_{25}N_3S \cdot C_6H_{13}NO_3S$	126.5-128 (CL/EA)	4.4 (-42)	20.0	4.5 (0.14)	2.5
15	$C_{19}H_{25}N_3S \cdot C_4H_4O_4$	125-127 (E)	1.1 (-33)	16.2	14.7 (0.46)	3
16	$C_{21}H_{27}N_3S \cdot C_6H_{13}NO_3S$	120-122 (M/I)	1.9 (-52)	20.8	10.9 (0.34)	3.5
17	$C_{18}H_{21}N_3S \cdot C_6H_{13}NO_3S$	114.5-115.5 (T)	1.1 (-46)	21.6	19.6 (0.61)	2.5
18[g,h]	$C_{22}H_{25}N_3S \cdot C_6H_{13}NO_3S \cdot H_2O$	133-134 (I/EE)				3
19	$C_{20}H_{23}N_3OS \cdot C_4H_4O_4$	167-168.5 (95% E)	2.6 (-42)	22.4	8.6 (0.27)	3.5
20	$C_{18}H_{25}N_3OS \cdot C_6H_{13}NO_3S$	107.5-109 (I)	1.5 (-33)	17.6	11.7 (0.37)	2.5
21	$C_{24}H_{27}N_3S \cdot C_7H_8O_3S$	132.5-135.5 (M/I)	6.1 (-58)	23.5	3.8 (0.12)	3
22	$C_{14}H_{17}N_3S \cdot C_7H_5NO_3S$	142-144 (A/W)	3.7 (-51)	23.0	6.2 (0.19)	
23	$C_{17}H_{21}N_3S \cdot C_4H_4O_4 \cdot 0.125C_2H_5OH$	115-117 (E)	0.7 (-22)	12.4	17.7 (0.55)	
24	$C_{20}H_{21}N_3S \cdot 1.25C_4H_4O_4$	122-124 (M/EA)	0.6 (-40)	19.2	32.0 (1)	2.5
25	$C_{15}H_{18}ClN_3S$	164.5-165.5 (M/I)	3.5 (-32)	16.2	4.6 (0.14)	2
26	$C_{16}H_{21}N_3OS$	154-157 (M/A)	2.3 (-39)	17.8	7.7 (0.24)	2
27	$C_{17}H_{23}N_3S$	131.5-132.5 (EA)	8.6 (-21)	15.5	1.8 (0.06)	
28	$C_{16}H_{21}N_3S$	167-168.5 (M/I)	4.5 (-34)	20.2	4.5 (0.14)	2.5
29	$C_{18}H_{25}N_3S$	173-174 (D)	7.9 (-62)	29.0	3.7 (0.11)	4
30	$C_{17}H_{23}N_3S \cdot C_4H_4O_4$	149-150 (M/EA)	0.9 (-21)	12.5	13.9 (0.43)	3.5
31	$C_{19}H_{23}N_3S \cdot C_7H_8O_3S$	152-153 (M/I)	5.5 (-20)	18.5	3.4 (0.11)	
32	$C_{16}H_{20}ClN_3S \cdot C_7H_5NO_3S$	158.5-160.5 (M/I)	2.3 (-33)	17.2	7.5 (0.23)	3
33	$C_{16}H_{21}N_3S \cdot HCl$	216.5-218.5 (M/I)	3.8 (-46)	20.4	5.4 (0.17)	3
34	$C_{17}H_{23}N_3S \cdot C_4H_4O_4$	173.5-175 (M)	2.0 (-42)	20.0	10.0 (0.31)	3
35	$C_{19}H_{27}N_3S \cdot HClO_4$	98-100.5 (M)	0.7 (-33)	16.0	22.8 (0.71)	3.5
36	$C_{16}H_{21}N_3S$	178.5-180 (EA)	2.7 (-46)	24.0	8.9 (0.28)	3.5
37	$C_{16}H_{21}N_3S \cdot C_7H_5NO_3S$	124-124.5 (E)	3.0 (-51)	22.4	7.5 (0.23)	2.5
38	$C_{17}H_{23}N_3S \cdot C_4H_4O_4$	183.5-184.5 (M/I)	2.0 (-24)	14.3	7.1 (0.22)	3
39	$C_{17}H_{23}N_3S \cdot C_4H_4O_4$	128-130 (M/E/I)	14.1 (-38)	18.5	1.3 (0.04)	
40	$C_{14}H_{18}N_4S \cdot C_4H_4O_4$	198.5, dec (M/I)	2.9 (-38)	19.9	6.9 (0.22)	2
41	$C_{15}H_{20}N_4S \cdot C_4H_4O_4$	212-213 (M)	6.4 (-38)	20.0	3.1 (0.10)	
42	$C_{16}H_{22}N_4S \cdot C_4H_4O_4$	197-198 (95% E)	12.6 (-27)	10.5	0.8 (0.03)	0
43	$C_{15}H_{20}N_4S \cdot C_4H_4O_4$	184-186 (M/I)	2.6 (-37)	19.5	7.5 (0.23)	2.5
44	$C_{17}H_{24}N_4S \cdot C_4H_4O_4$	171-173 (M/I)	2.1 (-27)	13.2	6.3 (0.20)	4
45	$C_{14}H_{19}N_3S \cdot C_6H_{13}NO_3S$	174-176.5 (M/I)	2.0 (-50)	23.0	11.5 (0.36)	2
46[h]	$C_{15}H_{19}N_3 \cdot HCl$	269-272 (M)	3.4 (-28)	16.0	4.7 (0.15)	2
47	$C_{17}H_{23}N_3 \cdot C_4H_4O_4$	162-164 (I/EE)	0.8 (-48)	20.2	25.2 (0.79)	0
48	$C_{18}H_{23}N_3 \cdot C_4H_4O_4$	139-141.5 (M/EA)	1.2 (-26)	14.7	12.2 (0.38)	
49	$C_{18}H_{21}N_3 \cdot C_4H_4O_4 \cdot 0.25H_2O$	174.5-177.5 (M/EE)	1.5 (-47)	22.3	14.9 (0.46)	3
50	$C_{22}H_{25}N_3 \cdot C_4H_4O_4 \cdot 0.2H_2O$	162-164 (M/EA)	2.6 (-52)	24.3	9.3 (0.29)	
51	$C_{14}H_{18}N_4 \cdot HI$	195.5-197.5 (M/EE)	9.7 (-47)	20.5	2.1 (0.06)	2
52	$C_{17}H_{23}N_3 \cdot C_4H_4O_4$	177-179 (M)	6.1 (-50)	19.0	3.1 (0.11)	0
53	$C_{15}H_{21}N_3 \cdot C_4H_4O_4$	180-182 (E/I)	3.5 (-27)	12.2	3.5 (0.13)	1
54[i]	$C_{17}H_{25}N_3 \cdot 2HCl \cdot 1.5H_2O$	oil	3.3 (-45)	18.4	5.6 (0.17)	2
mixidine (1)			3.3 (-34)	19.6	5.9 (0.18)	1
bepridil (3)			2.0 (-30)	14.8	7.4 (0.23)	1
amiodarone (4)			9.9 (-48)	21.4	2.2 (0.07)	2.5
propranolol			6.7 (-66)	28.5	4.2 (0.13)	3

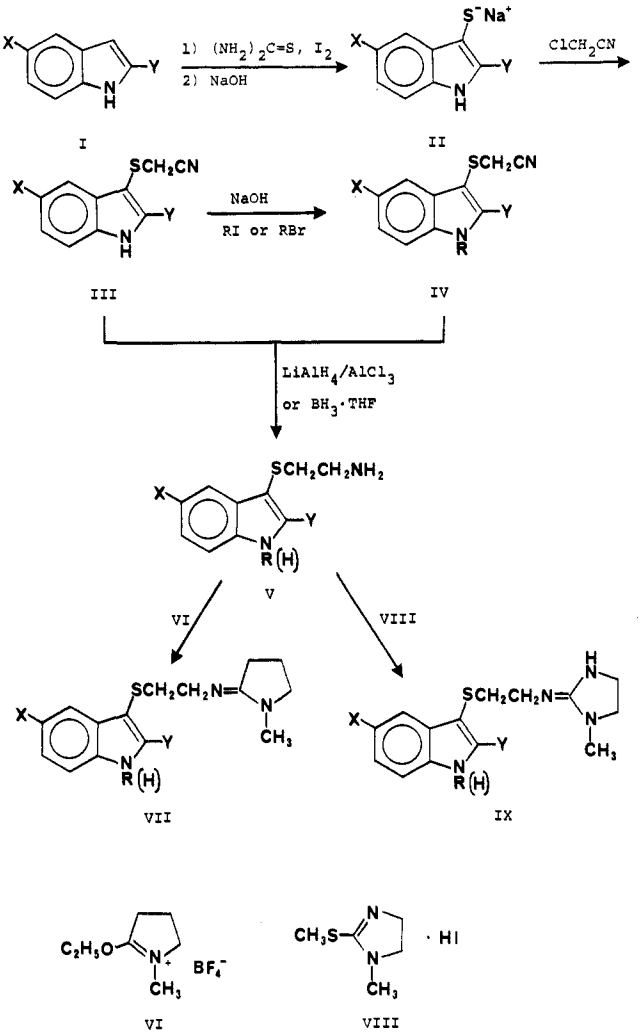
[a] All compounds analyzed within ±0.4% for C, H, and N, unless otherwise noted. For acid-addition salts: $C_4H_4O_4$ = fumaric acid; $C_6H_{13}NO_3S$ = hexamic acid; $C_7H_5NO_3S$ = saccharin; $C_7H_6O_2$ = benzoic acid; $C_7H_8O_3S$ = *p*-toluenesulfonic acid; $C_{10}H_8O_3S$ = naphthalenesulfonic acid. [b] The recrystallization solvent is given in parentheses: I = 2-propanol; M = methanol; E = ethanol; W = water; EA = ethyl acetate; A = acetone; C = cyclohexane; EE = ethyl ether; CL = chloroform; D = dichloromethane; T = tetrahydrofuran. [c] D_{50} is the dose (in milligrams per kilogram) of compound required to achieve 50% of the maximal cardiac slowing in the triazine tachycardia test (see text); ΔHR_{50} is the change in the heart rate (amount of cardiac slowing) in beats per minute realized at the D_{50} dose. [d] Half-maximal cardiac slowing represented as a percentage decrease from the initial, elevated heart rate (% $\Delta HR_{50} = \Delta HR_{50}/HR_0 \times 100$). [e] The cardiac slowing (CS) index is a measure of drug activity, especially useful for comparing compounds; it represents both potency and efficacy. The index is a composite of the percent of cardiac slowing and dose in the form of a quotient, $\%\Delta HR_{50}/D_{50}$. Relative activity, a fraction of the most active compound 24, is presented in parentheses. [f] Myocardial depression rating (see text for method): 0 = none or stimulation; 1 = barely observable; 2 = weak; 3 = moderate; 4 = severe. [g] No cardiac slowing data because of severe QRS widening. [h] C, H analysis only. [i] C, H, Cl analyses.

reflex tachycardia model, with conscious dogs (see Experimental Section).[17] A reflex tachycardia model was employed because ecause we sought an agent exhibiting specific antitachycardic activity, i.e., one that attenuates accelerated heart rate, rather than an agent exhibiting predominantly bradycardic activity.[18] The triazine test

(17) Further details of this method will be published elsewhere. It is analogous to the aminophylline-tachycardia test,[5a] which, however, involves anesthetized animals.

(18) Cf. ref 5a and 10.

Scheme I



was developed in our laboratory as a method to study antitachycardic effects in conscious animals. Cardiac-slowing activity in this test is represented (Table II) by two parameters: (1) the dose of compound in milligrams per kilogram (D_{50}) required to achieve half-maximal cardiac slowing and (2) the change in heart rate in beats per minute (ΔHR_{50}) at the half-maximal dose. The half-maximal level of cardiac slowing is represented as a percentage decrease from the initial elevated heart rate (% $\Delta HR_{50} = \Delta HR_{50}/HR_0 \times 100$) because this value, by taking the initial heart rate into account, is a more accurate determinant of the magnitude of cardiac-slowing activity. The cardiac-slowing (CS) index, which represents both efficacy and potency, was devised as a measure of drug activity, especially for comparison of compounds. The index is a composite of % ΔHR_{50} and D_{50} in the form of a quotient, % $\Delta HR_{50}/D_{50}$.

Selected analogues (**2**, **6**, **7**, **9**, and **28**) were further evaluated in three other animal models involving pharmacologically induced tachycardia: (1) aminophylline, (2) glucagon, and (3) poldine tests (Table III). The aminophylline-induced sinus tachycardia test,[5] a reflex tachycardia model in anesthetized dogs, was used to evaluate cardiac-slowing activity in support of the triazine test. The glucagon-induced sinus tachycardia test[5] was used to differentiate β-adrenergic blockade, since β blockers are not effective against this chronotropic stimulant. The test with poldine, a peripheral anticholinergic agent, was used to differentiate a cholinergic mechanism in conscious dogs. Data for these tests are supplied at three dose levels.

Table III. Secondary Pharmacological Data

compd	N^a	Am Tach[b]	Glu Tach[c]	P Tach[d]
2	4/4/4	10/22/39%	6/20/28%	9/22/33%
6	6/4/4	22/32/39	13/34/53	24/33/47
7	4/5/4	27/43/53	28/46/-	18/34/47
9	4/4/4	16/33/47	23/39/-	15/38/55
28	4/4/4	12/23/34	20/29/42	15/25/30
mixidine	6/4/6	6/25/33	-/16/28	12/24/35
bepridil	3/4/4	13/23/39	16/30/45	10/18/25
amiodarone	4/4/4	20/31/-	14/22/34	14/18/26
propranolol	4/4/4	24/32/37	3/9/-	21/32/38

[a] Number of animals, corresponding to Am Tach, Glu Tach, and P Tach, respectively. [b] Aminophylline-induced sinus tachycardia test: maximum percent decrease in heart rate at 1.0/2.5/5.0 mg/kg. [c] Glucagon-induced tachycardia: maximum percent decrease in heart rate at 1.0/2.5/5.0 mg/kg. [d] Poldine tachycardia test: maximum percent decrease in heart rate at 0.5/1.0/2.5 mg/kg.

Most of the compounds were also evaluated for myocardial depression, an undesirable side effect, by contractile-force experiments in anesthetized, ganglion-blocked dogs (Table II). The level of myocardial depression is reported by a score defined under Experimental Section.

In all of the experimental models, the compounds of interest were compared against four reference drugs: mixidine, bepridil, amiodarone, and propranolol.

Structure–Activity Relationships. For the compounds in Table II, the degree of antitachycardia activity, represented by the CS index, varies from 0.8 for **42** to 32.0 for **24**, a 40-fold range. Many of the compounds show acceptable cardiac-slowing activity (CS index ≥2), but only about one-third show very high activity (CS index ≥10): **6–9**, **12**, **13**, **15–17**, **20**, **23**, **24**, **30**, **34**, **35**, **45**, and **47–49**. The four reference compounds have comparatively low CS indexes.

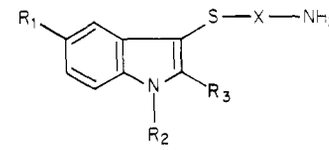
Prototype **2**, with a CS index of 8.2, showed moderate myocardial depression. Substitution of the indole nitrogen with various small (C_1 to C_3) saturated alkyl (**6–9**) groups, unsaturated alkyl groups (**12**, **13**, and **15–17**), or a methoxyethyl group (**20**) afforded enhanced CS activity. Some of these analogues had weak to insignificant (MD ≥ 2) myocardial depressant properties (**6–9** and **13**). An *N*-octyl substituent (**10**) resulted in a 4-fold loss of cardiac-slowing activity compared to **2**.

Substitution of the amidine methyl in **2** with hydrogen (**22**) caused a slight loss in activity, but substitution of a larger organic group, alkyl (**23**) and phenyl (**24**) augmented CS activity 2- and 4-fold, respectively. Phenyl derivative **24** is the most active analogue in Table II (relative activity = 1), but it shows some myocardial depression.

Substitution of methyl or *n*-propyl at the indole 2-position reduced activity (cf. **28**, **29** with **2**; **30** with **6**; **31** with **17**). Indole substitution at the 5-position also was not very useful (cf. **25–27** with **2**; **32** with **6**).

Alteration of the spacing unit between the indole and iminopyrrolidine moieties did not greatly influence CS activity. Addition of one methylene to **2** slightly increased activity (cf. **33** and **2**), and addition of two methylenes slightly increased activity (cf. **34** and **2**). Interestingly, substitution of ethyl on the indole nitrogen of **34** (viz., **35**) had a similar activity-enhancing effect as the same substitution of **2**, indicating a parallelism in the SAR. By the same token, *N*-ethyl desulfur analogue **47** displayed greatly enhanced (5-fold) CS activity compared to NH desulfur analogue **46**. The *N*-allyl and *N*-propargyl compounds further indicated a parallelism in SAR (overall cf. **2**, **7**, **13**, and **17** with **46**, **47**, **48**, and **49**, respectively). However, tetramethylene analogue **52** showed only about half the CS activity of **2**. It should be noted that **47** exhibits intense

Table IV. Intermediate Amines



R_1	R_2	R_3	X	molec formula[a]	mp, °C (solv)[b]
H	H	H	$(CH_2)_2$	$C_{10}H_{12}N_2S\cdot HCl$	226–228 (M/I)
H	H	H	$CH_2CH(CH_3)$	$C_{11}H_{14}N_2S$	110–112 (B)
H	H	H	$(CH_2)_3$	$C_{11}H_{14}N_2S$[c]	72.5–73.5 (B)
H	CH_3	H	$(CH_2)_2$	$C_{11}H_{14}N_2S\cdot C_4H_4O_4$	169, dec (M/I)
H	C_2H_5	H	$(CH_2)_2$	$C_{12}H_{16}N_2S\cdot 0.5C_4H_4O_4$	181–182 (M)
H	i-C_3H_7	H	$(CH_2)_2$	$C_{13}H_{18}N_2S\cdot C_4H_4O_4$	176.5–177.5 (M/I)
H	n-C_3H_7	H	$(CH_2)_2$	$C_{13}H_{18}N_2S\cdot 0.5C_4H_4O_4$	159.5–160.5 (M/I)
H	n-C_8H_{17}	H	$(CH_2)_2$	$C_{18}H_{28}N_2S\cdot C_4H_4O_4$[c]	152–153 (I)
H	c-C_5H_9	H	$(CH_2)_2$	$C_{15}H_{20}N_2S\cdot C_4H_4O_4$	160–161 (95% E)
H	c-$C_3H_5CH_2$	H	$(CH_2)_2$	$C_{14}H_{18}N_2S\cdot 0.5C_4H_4O_4$[c]	168–170 (I)
H	$CH_2{=}CHCH_2$	H	$(CH_2)_2$	$C_{13}H_{16}N_2S\cdot C_4H_4O_4$[c]	158–159 (M/EE)
H	$C_6H_5CH_2$	H	$(CH_2)_2$	$C_{17}H_{18}N_2S\cdot C_4H_4O_4$[c]	183–185 (M/EE)
H	2-furyl-CH_2	H	$(CH_2)_2$	$C_{15}H_{16}N_2OS\cdot C_4H_4O_4$[c]	166–167 (I)
H	$CH_3OCH_2CH_2$	H	$(CH_2)_2$	$C_{13}H_{18}N_2OS\cdot C_4H_4O_4$[c]	147–148 (I)
Cl	H	H	$(CH_2)_2$	$C_{10}H_{11}ClN_2S\cdot HCl$	251–252, dec (M)
H	H	n-C_3H_7	$(CH_2)_2$	$C_{13}H_{18}N_2S\cdot C_4H_4O_4\cdot 0.0625H_2O$	151–153 (M/I/EE)
Cl	H	CH_3	$(CH_2)_2$	$C_{11}H_{13}ClN_2S\cdot C_6H_{13}NO_3S\cdot 0.125H_2O$	167–168 (M/I)

[a] Same as for Table II. [b] Same as for Table II and also includes B = benzene. [c] C, H analysis only.

CS activity with no myocardial depression.

Enlargement of the iminopyrrolidine ring by one or two methylene groups had little effect on CS activity (cf. **2**, **37**, and **39**). Conversion from an amidine group to a guanidine (**40–44** and **51**) had an attenuating influence on activity ranging from slight to large. Seco derivative **45** displayed a 1.5-fold increase in CS activity relative to **2**.

Indoline derivatives **53** and **54** showed a small and large reduction in CS activity, respectively, relative to **46** and **47**. The indoline analogue of **2** was generated, but its instability precluded pharmacological testing.

Amine intermediates (see Table IV) generally showed little cardiac-slowing activity.

Secondary Testing. Selected analogues were evaluated in the aminophylline, glucagon, and poldine tachycardia tests, as mentioned earlier, along with four reference drugs (Table III).

In the aminophylline test, thioindole **7** showed marked activity, exceeding the reference drugs, and its congeners, at all three doses. Thioindole **9**, which gave a steep dose–response profile, ranked second in the aminophylline test at the 5-mg/kg dose.

Thioindole **7** was also the most active compound in the glucagon test; **9** again rated second. Compound **6** showed a steep dose–response profile. Bepridil was clearly the most active reference drug, and propranolol was virtually inactive.

In the poldine test, thioindole **9**, which had a steep dose–response profile, was the most active agent at 1.0 and 2.5 mg/kg. The activity levels of thioindoles **6**, **7**, and **9** greatly exceeded those of the reference drugs at the 2.5-mg/kg dosage.

Thus, the high activity of thioindole derivatives **6**, **7**, and **9** in the triazine tachycardia test is amply supported by their high activity in three other testing models. The moderate activities of thioindoles **2** and **28** in the triazine test are also reflected in these three additional screens. Overall, **6**, **7**, and **9**, which exhibit only minor depression of myocardial contractile force, are superior to mixidine, bepridil, amiodarone, and propranolol.

Mixidine and the Thioindoles. The cardiovascular profile of mixidine has been examined.[5] Mixidine attenuates elevated heart rate but does not decrease resting heart rate, mean arterial pressure, or cardiac output. The antichronotropic activity of mixidine was suggested to arise from a direct effect on the atrial sinus node and attenuation of sympathetic input to the heart.[5a]

The compounds in this paper, which are structurally analogous to mixidine, appear to possess similar antitachycardic activity. Thioindoles **2** and **7** were examined in nonanesthetized dogs and found to cause no decrease in resting heart rate, mean arterial pressure, or cardiac output.[19] Thus, **2** and **7** are specific antitachycardic agents, and **7** has a minimal myocardial depressant liability.

Conclusions

The 3-thioindolamidine series of compounds, as well as their cogeners, generally exhibit cardiac-slowing activity (Tables I and II). One-third of the derivatives (**6–9**, **12**, **13**, **15–17**, **20**, **23**, **24**, **30**, **34**, **35**, **45**, and **47–49**) show particularly marked activity in the triazine tachycardia test, exceeding the four reference drugs (mixidine, bepridil, amiodarone, and propranolol) studied. Of these very active agents, five possess extremely high activity (CS index > 20) [compound (relative activity)]: **24** (1.00), **7** (0.85), **47** (0.79), **35** (0.71), and **13** (0.69). Also, of the very active agents, several (**6–9**, **13**, **45**, and **47**) showed little myocardial depression (MD ≥ 2).

Structural changes on prototype **2** that led to enhanced activity were (1) substitution of the indole N-H with small saturated (e.g., ethyl) or unsaturated (e.g., allyl) aliphatic groups and (2) substitution of the pyrrolidine N-CH_3 with lipophilic groups (e.g., allyl and phenyl). The activity-inducing effects of the indole nitrogen substitutions carried over to systems with different spacing units, $S(CH_2)_4$ and $(CH_2)_2$, between the indole 3-position and the iminopyrrolidine group.

The series of compounds studied has led to some agents having potent antitachycardic activity with minimal myocardial depression. Since an antianginal agent working primarily by attenuating elevated heart rate should offer significant advantages over current drugs, several compounds described herein may have potential for clinical utility.

(19) Details of these experiments will be published elsewhere.

Experimental Section

General Chemical Methods. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. UV data (Cary 14 spectrophotometer), IR spectra (Perkin-Elmer 521 spectrophotometer), and ^1H NMR spectra [Varian A60 (60 MHz) or Perkin-Elmer R-32 (90 MHz) spectrometers] were recorded on all of the target compounds (Tables II and IV) and were consistent with the assigned structures. ^1H NMR spectra had $(CH_3)_4Si$ as a reference (internal standard). NMR abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartz; m, multiplet. TLC separations were conducted with Analtech, Inc., silica gel GF 250-μm plates (visualized with UV and I_2 vapor). Chemical microanalyses were determined by Atlantic Microlab, Inc., Atlanta, GA, or Scandinavia Labs, Herlev, Denmark.

Preparation of Nitriles III. A. General Procedure. Indole I[20] (0.10 mol) and thiourea (7.6 g, 0.10 mol) were dissolved in 150 mL of methanol, and 100 mL of 1 M I_2/KI solution was added with stirring. The solution was stirred for 2 h at room temperature or until all of the indole was consumed and then evaporated in vacuo to give an oily/aqueous residue. Two hundred milliliters of 1.5 N NaOH was added under an inert atmosphere to this residue, and the solution was heated at ca. 90 °C for 30 min. This solution was cooled to room temperature and extracted twice with ether. The solution was layered over with ether and chloroacetonitrile (0.10 mol) was added with stirring. The solution was stirred at room temperature under an inert atmosphere for about 2 h. The ether solution was separated and washed once with water and once with saturated NaCl solution and dried ($MgSO_4$). The solution was filtered and evaporated in vacuo to give nitrile III.

B. Example. (Indol-3-ylthio)acetonitrile. Following the above procedure, indole (23.4 g, 0.20 mol) and thiourea (15.2 g, 0.20 mol) were combined in 300 mL of methanol, and 200 mL of 1 M I_2/KI solution was added. After the NaOH hydrolysis, chloroacetonitrile (15.1 g, 0.20 mol) was added, and the reaction was stirred for 2.5 h. The reaction was extracted with a total of 400 mL of ether, and the extract was washed, dried, and filtered. This solution was evaporated in vacuo to give crystalline nitrile (36.4 g, 97%). This nitrile was recrystallized from methanol/hexane to afford white, waxy crystals (34.0 g): mp 52–54.5 °C; ^1H NMR ($CDCl_3$) δ 3.3 (s, 2 H), 7.1–7.9 (m, 5 H, aromatic), 10.2 (s, 1 H); UV (CH_3OH) λ_{max} 270 nm (ϵ 7700), 277 (7700), 287 (6560); IR (KBr) ν_{max} 2250 (C≡N) cm^{-1}. Anal. Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88. Found: C, 63.58; H, 4.30; N, 14.99.

Preparation of Nitriles IV. A. General Procedure. Nitrile III (0.10 mol) in 120 mL of tetrahydrofuran (THF) or ether was combined with 50 mL of aqueous 50% NaOH (w/v) and benzyltriethylammonium chloride (0.5 g, 2.2 mmol). The solution was cooled in an ice bath as the alkyl halide (0.11 mol) in 10 mL of THF or ether was added slowly stirring. Vigorous stirring was continued at room temperature until all of the starting nitrile was consumed. The ether layer was separated, dried ($MgSO_4$), and filtered and the filtrate was evaporated in vacuo to give N-substituted nitrile IV.

B. Example. [[1-(2-Propenyl)indol-3-yl]thio]acetonitrile. According to the above procedure, nitrile III (X = Y = H; 50.0 g, 0.265 mol) in 500 mL of ether was combined with allyl bromide (38.5 g, 0.318 mol) and stirred for 16 h. Upon workup, the reaction afforded a solid (62 g), which was recrystallized from 2-propanol/hexane to give the nitrile product (50.0 g, 83%): mp 45–47 °C; ^1H NMR ($CDCl_3$) δ 3.3 (s, 2 H), 4.7 (m, 2 H), 5.0–5.3 (m, 2 H), 5.8–6.2 (m, 1 H), 7.1–7.8 (m, 5 H, aromatic); UV (CH_3OH) λ_{max} 280 nm (ϵ 8000), 292 (6250, sh); IR (KBr) ν_{max} 2240 (C≡N) cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2S$: C, 68.38; H, 5.29. Found: C, 68.38; H, 5.26.

Preparation of Amines V. General Procedures. Method 1. Anhydrous $AlCl_3$ (10.0 g, 0.075 mol) in 150 mL of anhydrous ether was added slowly with cooling (ice bath) and stirring to $LiAlH_4$ (2.85 g, 0.075 mol) in 250 mL of anhydrous ether. To this solution was slowly added with cooling nitrile III or IV (0.075 mol) in 100 mL of anhydrous ether. The reaction solution was stirred at room temperature until no nitrile remained. Aqueous 50% NaOH (w/v) was added slowly until the pH was alkaline, and a white solid was evident. The ether solution was filtered and dried (K_2CO_3). The solution was evaporated in vacuo to give amine V.

Method 2. Nitrile III or IV (0.10 mol) was dissolved in 100 mL of dry THF, and 250 mL of 1 M BH_3·THF solution (0.25 mol) was added slowly. The solution was stirred at room temperature for 18 h. A 1 N HCl solution was added slowly until pH 1 and hydrogen evolution ceased. The solution was made alkaline with 1 N NaOH and extracted three times with ether. The ether solution was washed once with 1 N NaOH and once with saturated NaCl solution and dried (K_2CO_3). The solution was evaporated in vacuo to give amine V. Some intermediate amines were isolated, purified, and characterized (Table IV).

Preparation of Other Primary Amines. A. 3-[(2-Aminopropyl)thio]indole. Sodium thiolate II (0.035 mol) was acidified with concentrated HCl under nitrogen and extracted with ether. The ethereal solution of thiol was washed three times with water and once with saturated NaCl and dried ($MgSO_4$), all operations being done under nitrogen. The solution was filtered, and the filtrate was evaporated in vacuo to give 3-indolylthiol (4.9 g). This thiol in 30 mL of methanol was treated slowly with 2-methylaziridine (1.71 g, 0.03 mol). The reaction was stirred at room temperature for 40 min, and then the solution was evaporated in vacuo to a residue, which was dissolved in ether. The ethereal solution was extracted three times with 1 N HCl. The combined aqueous extracts were washed with ether, made alkaline with 2 N NaOH, and extracted with ether. This ethereal solution was washed twice with 1 N NaOH, once with saturated NaCl solution, and dried (K_2CO_3). The filtered solution was evaporated in vacuo to give the amine product (5.7 g). The solid was recrystallized once from ethyl acetate and then once from benzene to give analytically pure white crystals (4.3 g, 69%): mp 110.5–112.5 °C; ^1H NMR (Me_2SO-d_6) δ 1.02 (d, 3 H), 2.4–3.0 (m, 5 H), 7.0–7.8 (m, 5 H, aromatic); UV (CH_3OH) λ_{max} 272 nm (ϵ 6100), 279 (6600), 288 (5960); IR (KBr) ν_{max} 3270 and 3330 (NH) cm^{-1}. Anal. ($C_{11}H_{14}N_2S$) C, H, N (Table IV).

B. 3-[(3-Aminopropyl)thio]indole. To the aqueous NaOH solution of thiolate II (0.20 mol) was added 3-chloropropylamine hydrochloride (13.0 g, 0.10 mol), dissolved in water, dropwise with stirring under nitrogen. The solution was stirred for 3 h at room temperature and then extracted with ether. The ethereal solution was washed three times with 1 N NaOH and once with saturated NaCl solution and dried (K_2CO_3). The filtered solution was evaporated in vacuo to give the crude amine (18.5 g). The solid was recrystallized once from ethyl acetate and then once from benzene to give pure crystals (8.4 g, 41%): mp 72.5–73.5 °C; ^1H NMR (Me_2SO-d_6) δ 1.55 (m, 2 H), 2.4–2.9 (m, 4 H), 7.0–7.8 (m, 5 H, aromatic); UV (CH_3OH) λ_{max} 273 nm (ϵ 6100), 279 (6600), 287 (5800); IR (KBr) ν_{max} 3345 (NH) cm^{-1}. Anal. ($C_{11}H_{14}N_2S$) C, H, N (Table IV).

C. 3-[(4-Aminobutyl)thio]indole. 4-Chlorobutyronitrile (11.0 g, 0.106 mol) was added to the aqueous NaOH solution of thiolate II (0.10 mol), covered by ether, with stirring under nitrogen at room temperature for 18 h. The ethereal solution was washed twice with saturated NaCl solution and dried ($MgSO_4$). The filtered solution was evaporated in vacuo to give (indol-3-ylthio)butyronitrile (18.7 g). This nitrile was reduced with $LiAlH_4$ (3.5 g, 0.09 mol) and $AlCl_3$ (12.0 g, 0.09 mol) following method 1 (see above) to give the crude amine (14.5 g). The amine was dissolved in methanol, and fumaric acid (7.4 g, 0.064 mol) was added to give a salt, which separated as a solid on addition of 2-propanol. The salt was recrystallized once from methanol/2-propanol to give white crystals (12.2 g, 42%), mp 166.5–167.5 °C.

D. 3-(4-Aminobutyl)indole. To an ice-cooled suspension of 3-indolebutyric acid (20.3 g, 0.10 mol) in 100 mL of ether was added phosphorus pentachloride (22.9 g, 0.11 mol) portionwise. After stirring for 1 h, the reaction mixture was added dropwise to an ice-cooled solution of 50 mL of concentrated NH_4OH. After the mixture was stirred with cooling for 0.5 h, the ether layer was evaporated in vacuo at room temperature. The residue was treated three times with methylene chloride. The combined extracts were dried (K_2CO_3) and evaporated in vacuo to give 3-indolebutyramide (18.5 g). A portion of this amide (1.5 g, 7.5 mmol) in 35 mL of

(20) All indoles used were commercially available, except for 2-*n*-propylindole, which was prepared according to a reported method: Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

THF was added to a suspension of $LiAlH_4$ (0.84 g, 24.7 mmol) in 35 mL of THF dropwise under nitrogen. The mixture was refluxed for 6 h and then stirred at room temperature for 16 h. Water (1.4 mL) was added cautiously, followed by 1.4 mL of 3 N NaOH. The solution was filtered, and the filtrate was dried (K_2CO_3) and evaporated in vacuo to give the oily amine product (used in subsequent work without purification).

Preparation of Amidines. A. General Procedure. Boron trifluoride etherate (15.9 g, 0.112 mol) in 20 mL of anhydrous ether was added slowly with stirring to epichlorohydrin (7.76 g, 0.084 mol) in 20 mL of anhydrous ether. The solution was stirred under dry conditions at room temperature for 3 h. Under a stream of nitrogen, the ether was decanted. The solid was rinsed twice with fresh anhydrous ether and dried under a stream of nitrogen. The solid was dissolved in 20 mL of dry methylene chloride (4A molecular sieves), and the 2-pyrrolidinone (0.084 mol) in 20 mL of dry methylene chloride was added. The reaction was stirred at room temperature for 4 h. Amine (0.070 mol) in 50 mL of dry methylene chloride was added, and the solution was stirred at room temperature for 16 h. The reaction solution was washed twice with 50-mL portions of 20% NaOH, washed once with saturated NaCl solution, dried (K_2CO_3), and filtered, and the filtrate was evaporated in vacuo to give the target amidine (Tables I and II).

B. Example 1. 3-[[2-[(1-Methyl-2-pyrrolidinyliden)amino]ethyl]thio]indole (2). *N*-Methyl-2-pyrrolidinone (8.32 g, 0.084 mol) and 3-[(2-aminoethyl)thio]indole (13.44 g, 0.07 mol) were reacted according to the above procedure to give, on workup, 18.5 g of amidine 2. Recrystallization twice from 2-propanol afforded white crystals (7.4 g, 39%): mp 143.5–145.5 °C; ^1H NMR ($CDCl_3$) δ 1.7–2.5 (m, 4 H), 2.72 (s, 3 H), 2.7–3.6 (m, 6 H), 7.0–7.8 (m, 5 H, aromatic); UV (CH_3OH) λ_{max} 273 nm (ϵ 6000), 279 (6500), 287 (5900); IR (KBr) ν_{max} 1635 (C=N) cm^{-1}. Anal. ($C_{15}H_{19}N_3S$) C, H, N.

C. Example 2. *N'*-[2-(Indol-3-ylthio)ethyl]-*N*,*N*-dimethylethanimidamide (45) Cyclohexanesulfamate. Boron trifluoride etherate (11.4 g, 0.08 mol), epichlorohydrin (5.6 g, 0.6 mol), and *N*,*N*-dimethylacetamide (5.2 g, 0.06 mol) were reacted analogously to the general procedure and stirred at room temperature for 16 h. 3-[(2-Aminoethyl)thio]indole (9.6 g, 0.05 mol) was added, and the reaction was stirred for 6 h. Workup furnished the crude amidine (12.8 g), which was treated with cyclohexanesulfamic acid (8.7 g, 0.049 mol) in methanol to give a crystalline salt. Recrystallization of the salt from methanol/2-propanol gave white crystals (4.0 g, 18%): mp 174–176.5 °C; ^1H NMR (Me_2SO-d_6) δ 1.0–2.0 (m, 10 H), 2.07 (s, 3 H), 2.8–3.2 (m, s, 8 H), 3.48 (t, 2 H), 7.1–7.7 (m, 5 H, aromatic); UV (CH_3OH) λ_{max} 272 nm (ϵ 6100), 279 (6500), 287 (5900); IR (KBr) ν_{max} 1652 (C=N) cm^{-1}. Anal. ($C_{14}H_{19}N_3S \cdot C_6H_{13}NO_3S$) C, H, N.

Alkylation of Amidines. In certain cases it was convenient to obtain amidines substituted on the indole nitrogen by alkylation of 2 or 46. An example procedure follows.

1-Ethyl-*N*-(1-methyl-2-pyrroldinylidine)-1*H*-indole-3-ethanamine (47) (*E*)-Butenedioate (1:1). A solution of *N*-(1-methyl-2-pyrrolidinylidine)-1*H*-indole-3-ethanamine (46; 7.2 g, 0.03 mol) in 20 mL of dry DMF was added dropwise, with cooling, under nitrogen, to a chilled (dry ice–acetone) suspension of sodamide–liquid ammonia, prepared from sodium (0.69 g, 0.03 mol) and 100 mL of liquid ammonia containing ferric nitrate hexahydrate (0.075 g, 0.214 mmol). After stirring for 1 h at room temperature, ethyl iodide (4.6 g, 0.03 mol) in 5 mL of DMF was added dropwise. The mixture was stirred for 16 h, poured into water, and extracted with ether. The ethereal solution was dried (K_2CO_3) and evaporated in vacuo to afford the product. Treatment with fumaric acid in 2-propanol gave the fumarate salt. Three recrystallizations from 2-propanol/ether gave the pure salt (8.6 g, 75%): mp 162–164 °C; ^1H NMR (Me_2SO-d_6) δ 1.3 (t, 3 H) 1.75 (m, 2 H), 2.55 (m, 2 H), 2.97 (m, 2 H), 3.05 (s, 3 H), 3.3–3.7 (m, 4 H), 4.13 (q, 2 H), 6.51 (s, 2 H), 6.9–7.7 (m, 5 H, aromatic), 11.15 (s, 3 H); UV (CH_3OH) λ_{max} 282 nm (ϵ 6100), 286 (6100), 297 (4800, sh); IR (KBr) ν_{max} 1670 (C=O) cm^{-1}. Anal. ($C_{17}H_{23}N_3 \cdot C_4H_4O_4$) C, H, N.

Preparation of Guanidines IX. A. General Procedure. Amine V (0.10 mol) and 1-methyl-2-(methylthio)-2-imidazoline hydroiodide[21] (0.10 mol) were combined in 200 mL of 2-propanol and heated at reflux for 18 h (protected from light). The solution was evaporated in vacuo to an oil, which was partitioned between 90 mL of 2 N NaOH and 300 mL of methylene chloride. The methylene chloride solution was washed twice with 1 N NaOH, washed once with saturated NaCl solution, dried (K_2CO_3), and filtered, and the filtrate was evaporated in vacuo to give the crude guanidine IX.

B. Example. *N*-(4,5-Dihydro-1-methyl-1*H*-imidazol-2-yl)-2-[(2-propyl-1*H*-indol-3-yl)thio]ethanamine (44) (*E*)-Butenedioate (1:1). 3-[(2-Aminoethyl)thio]-2-propylindole (5.0 g, 0.0213 mol) and 1-methyl-2-(methylthio)-2-imidazoline hydriodide (5.50 g, 0.0213 mol) were combined in 40 mL of 2-propanol and reacted according to the above procedure. Workup afforded the crude guanidine (7.1 g), which was converted to a fumarate salt by addition of one equivalent of fumaric acid in methanol-/2-propanol. Two recrystallizations of the fumarate salt gave analytically pure material (6.31 g, 69%): mp 171–173 °C; ^1H NMR (Me_2SO-d_6) δ 0.92 (t, 3 H), 1.7 (m, 2 H), 2.6–3.0 (s, m, 7 H), 3.2–3.6 (m, 6 H), 6.49 (s, 2 H), 6.9–7.6 (m, 4 H, aromatic); UV (CH_3OH) λ_{max} 273 nm (ϵ 8300, sh), 278 (8700), 282 (8800), 288 (8000); IR (KBr) ν_{max} 1652 (C=O) cm^{-1}. Anal. ($C_{17}H_{24}N_4S \cdot C_4H_4O_4$) C, H, N.

Pharmacological Methods. A. Triazine Tachycardia. Dogs were anesthetized with pentobarbital sodium (30 mg/kg, iv). The left common carotid artery and left jugular vein were isolated and catheterized with catheters filled with heparinized saline (1000 USP units/mL). The catheters were drawn through the neck and exteriorized via a small incision in the back of the neck. The animal was allowed to recover and, after 18 h, U20388, a long-acting triazine vasodilator discovered by Upjohn,[22] was administered (12 mg/kg, po). Approximately 1 h later, the animal was placed in a canvas sling, and arterial pressure and ECG were monitored. Test compounds were infused iv at a rate of 0.8 (mg/kg)/min. The D_{50} value was calculated as the dose producing 50% of the maximal cardiac slowing attainable in the animal under study. A total of 30 mg/kg of the test compound was infused. The results (Table II) were derived from two to six experiments (i.e., two to six different animals), usually three to five, and are averaged.[23] The ΔHR_{50} values generally did not deviate more than ±30%; the D_{50} values did not deviate more than ±50% (usually ±20–40%).[23]

B. Contractile Force in Anesthetized, Ganglion-Blocked Dogs. Adult mongrel dogs were anesthetized with thiopental sodium (20 mg/kg, iv) and maintained with α-chloralose (60 mg/kg, iv). A femoral artery and vein were isolated and catheterized for recording of femoral arterial pressure and for intravenous injections, respectively. A cuffed, endotracheal tube was inserted to maintain a patent airway. The ECG was monitored via standard limb lead II. A midline thoractomy was performed in anesthetized dogs maintained on a positive-pressure respiratory pump. The heart was exposed and allowed to rest in a pericardial cradle. A Brodie–Walton strain gauge was sutured onto the left ventricle for recording contractile force. Mecamylamine (5 mg/kg, iv) was administered, and the extent of ganglion blockade was checked in 15 min with DMPP (10 mg/kg, iv). Test compounds were administered at doses of 1, 2.5, 5, and 10 mg/kg, successively, at 30-min intervals. The total dose that produced 25–30% depression of contractile force was estimated. Given this value, an estimate of myocardial depression was made and translated into a rating system.

Four factors were taken into account to devise the rating scale: ECG changes (specifically, QRS interval widening), lethality, degree of depression of contractile force, and the dose level of test compound. The scale is as follows: 0, no depression of myocardial contractility and/or stimulation of contractility; 0.5, depression of contractility but did not achieve 25–30% level up to an iv dose of 10 mg/kg; 1.0, less than 25–30% depression of contractility at a dose of 10 mg/kg, iv; no observable delay in ventricular conduction (QRS widening) and no lethality; 1.5, achieved 25–30%

(21) McKay, A. F.; Kreling, M. E. *J. Org. Chem.* **1957**, *22*, 1581.
(22) Zins, G. R. *J. Pharmacol. Exp. Ther.* **1965**, 150, 109.
(23) For listing of the number of animals (N) and the standard errors in D_{50} and ΔHR_{50} for each compound in the triazine test, see paragraph at the end of paper concerning Supplementary Material.

depression of contractility at 5 mg/kg, iv, but was not greater at 10 mg/kg, iv; no observable QRS widening and no lethality; 2.0, achieved 25–30% depression of contractility at 5 mg/kg, iv, and was more depressant at 10 mg/kg, iv; possible QRS widening but no lethality; 2.5, achieved 25–30% depression of contractility between 2.5 and 5 mg/kg, iv, and was more depressant at 5 and 10 mg/kg, iv (dose related); possible lethality and QRS widening; 3.0, achieved 25–30% depression of contractility at 2.5 mg/kg, iv, and was more depressant at increasing doses; QRS widening and/or lethality in some or all animals at 10 mg/kg, iv; 3.5, achieved 25–30% depression of contractility between 1 and 2.5 mg/kg, iv (dose-related depression); QRS widening and/or lethality observed at 10 mg/kg, iv, in some or all animals; 4.0, 25–35% or greater depression of contractility at 1 mg/kg, iv; QRS widening observed at 5 or 10 mg/kg, iv, and lethal in some or all animals at 5 mg/kg, iv. The values reported in Table II were established with, generally, two to four animals.

C. **Aminophylline Tachycardia.** Experiments were performed in anesthetized, vagotomized dogs according to a method described previously.[5a]

D. Glucagon Tachycardia. Experiments were performed in anesthetized, ganglion-blocked dogs according to a method described previously.[5a]

E. Poldine Tachycardia. Dogs were surgically prepared as described in the triazine tachycardia method. Poldine methyl sulfate (0.5 mg/kg, iv) was administered, and 30 min later, test compounds were administered in increasing doses at 30-min intervals.[24]

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Registry No. 2, 61020-73-3; **6** 0.5-fumarate, 61020-77-7; **7** hexamate, 83747-58-4; **8** naphthalenesulfonate, 83747-59-5; **9**, 61020-91-5; **10** fumarate, 83747-60-8; 11 benzoate, 83747-61-9; 12 fumarate, 83747-62-0; 13 hexamate, 83747-63-1; 14 hexamate, 83747-64-2; 15 fumarate, 83747-66-4; 16 hexamate, 83747-68-6; 17 hexamate, 83747-69-7; 18 hexamate, 83747-70-0; 19 fumarate, 83762-94-1; 20 hexamate, 83747-71-1; 21 tosylate, 83747-73-3; 22 saccharin, 83747-74-4; 23 fumarate, 83747-75-5; 24 fumarate, 83747-77-7; 25, 61020-83-5; 26, 61020-78-8; 27, 61020-92-6; 28, 61020-81-3; 29, 83747-78-8; 30 fumarate, 83747-79-9; 31 tosylate, 83747-81-3; 32 saccharin, 83747-83-5; 33·HCl, 83747-84-6; 34 fumarate, 83747-85-7; 35·$HClO_4$, 83747-87-9; 36, 83747-88-0; 37 saccharin, 83747-89-1; 38 fumarate, 83747-91-5; 39 fumarate, 83747-92-6; 40 fumarate, 83747-94-8; 41 fumarate, 83747-96-0; 42 fumarate, 83747-98-2; 43 fumarate, 83762-96-3; 44, 83747-99-3; 44 fumarate, 83748-00-9; 45, 61021-09-8; 45 hexamate, 83748-01-0; 46·HCl, 83748-02-1; 47, 75626-09-4; 47 fumarate, 83762-97-4; 48 fumarate, 83748-04-3; 49 fumarate, 83748-06-5; 50 fumarate, 83748-08-7; 51·HI, 83748-09-8; 52 fumarate, 83748-11-2; 53 fumarate, 83748-12-3; 54·2HCl, 83748-13-4; I (X = Y = H), 120-72-9; III (X = Y = H), 61021-51-0; IV (R = $CH_2CH{=}CH_2$; X = Y = H), 61021-45-2; VI, 41948-92-9; 3-[(2-aminoethyl)thio]indole hydrochloride, 54466-83-0; 3-[(2-aminopropyl)thio]indole, 61021-79-2; 3-[(3-aminopropyl)thio]indole, 61021-80-5; 3-[(2-aminoethyl)-thio]-1-methylindole fumarate, 61021-49-6; 3-[(2-aminoethyl)-thio]-1-ethylindole 0.5-fumarate, 61021-60-1; 3-[(2-aminoethyl)-thio]-1-isopropylindole fumarate, 83748-14-5; 3-[(2-aminoethyl)thio]-1-propylindole 0.5-fumarate, 61021-83-8; 3-[(2-aminoethyl)thio]-1-octylindole fumarate, 61021-96-3; 3-[(2-aminoethyl)thio]-1-cyclopentylindole fumarate, 61021-68-9; 3-[(2-aminoethyl)thio]-1-(cyclopropylmethyl)indole 0.5-fumarate, 61021-72-5; 1-allyl-3-[(2-aminoethyl)thio]indole fumarate, 61021-76-9; 3-[(2-aminoethyl)thio]-1-benzylindole fumarate, 61021-78-1; 3-[(2-aminoethyl)thio]-1-furfurylindole fumarate, 61021-74-7; 3-[(2-aminoethyl)thio]-1-(2-methoxyethyl)indole fumarate, 61021-70-3; 3-[(2-aminoethyl)thio]-5-chloroindole hydrochloride, 61021-65-6; 3-[(2-aminoethyl)thio]-2-propylindole fumarate, 83748-16-7; 3-[(2-aminoethyl)thio]-5-chloro-2-methylindole hexamate, 83748-18-9; chloroacetonitrile, 107-14-2; allyl bromide, 106-95-6; 3-indolylthiol, 480-94-4; 2-methylaziridine, 75-55-8; 3-chloropropylamine hydrochloride, 6276-54-6; 4-chlorobutyronitrile, 628-20-6; (indol-3-ylthio)butyronitrile, 61021-92-9; 3-[(4-aminobutyl)thio]indole fumarate, 61021-94-1; 3-indolebutyric acid, 133-32-4; 3-indolebutyramide, 6245-91-6; 3-(4-aminobutyl)indole, 669-70-5; *N*-methyl-2-pyrrolidinone, 872-50-4; 1-methyl-2-(methylthio)-2-imidazoline hydriodide, 61076-89-9; *N*,*N*-dimethylacetamide, 127-19-5; cyclohexanesulfamic acid, 100-88-9; 2,3-dihydrotryptamine, 13078-91-6; 3-[(2-aminoethyl)thio]indole, 61021-52-1.

Supplementary Material Available: Table of numbers of animals (N) and standard errors in D_{50} and ΔHR_{50} for the triazine test (2 pages). Ordering information is given on any current masthead page.

(24) The poldine test is related to the atropine-induced sinus tachycardia test;[5a] however, it does not have the potential for CNS involvement, since poldine is a peripheral agent.

Hypolipidemic Activity of Phthalimide Derivatives. 2. *N*-Phenylphthalimide and Derivatives

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A series of substituted *N*-phenylphthalimide derivatives was synthesized and examined for their ability to lower serum cholesterol and triglyceride levels in mice at 20 (mg/kg)/day, ip. Of the newly synthesized compounds, the most potent compound, *o*-(*N*-phthalimido)acetophenone, lowered serum cholesterol 57% after 16 days and lowered serum triglyceride levels 44% after 14 days. o-(*N*-Phthalimido)acetophenone was observed to be active in both normogenic (normal blood lipids levels) and hyperlipidemic mice and normogenic rats. In the latter, the reduction of serum lipids was reversible. The mode of action of this compound appeared to be multiple, including blockage of the de novo synthesis of lipids and acceleration of the excretion of lipids. The lipoprotein fractions of rat blood were reduced significantly in cholesterol, triglyceride, and neutral lipid content after 14 days treatment with o-(*N*-phthalimido)acetophenone.

A series of N-substituted phthalimides including alkyls, methyl ketones, carboxylic acids, and acetate esters has previously been shown to be potent hypolipidemic agents in rodents at 20 (mg/kg)/day, ip.[1]

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