6,7-Dihydro-5-[[(*cis*-2-hydroxy-*trans*-3-phenoxycyclopentyl)amino]methyl]-2-methylbenzo[*b*]thiophen-4(5*H*)-one: A Novel α_1-Adrenergic Receptor Antagonist and Renal Vasodilator

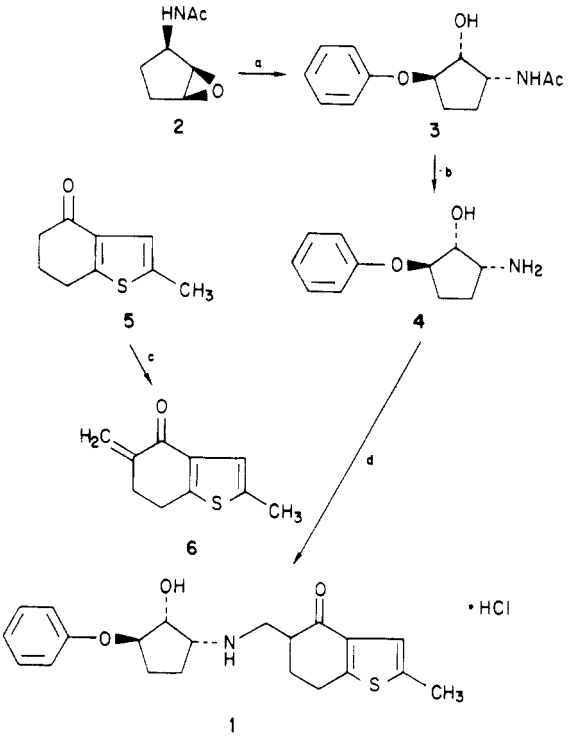
Sir:

Antihypertensive drugs that decrease total peripheral resistance can also reduce renal blood flow and urinary sodium excretion, leading to volume expansion and attenuation of the hypotensive effectiveness of the compound. In this paper, we describe a novel antihypertensive agent (**1**, MDL 19,744A), which selectively blocks α_1-adrenergic receptors and increases renal blood flow and sodium excretion in anesthetized dogs. The dose-dependent increases in renal blood flow were blocked by the dopamine receptor antagonists SCH 23390[3] and sulpiride,[4,5] suggesting that this effect was mediated by activation of renal vascular dopamine (DA_1) receptors.[6]

Initial studies on the conformational requirements for adrenergic receptors[7] and the observation that certain thiopheneamines act as α-adrenergic receptor blockers[8] led to the synthesis of **1** and its stereoisomers **7–9**. The convergent synthetic route developed for **1** is outlined in Scheme I.[9] *cis*-*N*-6-Oxabicyclo[3.1.0]hex-2-ylacetamide (**2**)[10] was treated with sodium phenoxide in DMF at 100 °C to give the desired *N*-(*cis*-2-hydroxy-*trans*-3-phenoxycyclopentyl)acetamide (**3**) (58%, mp 126–128 °C). The amide blocking group was removed from **3** with refluxing 5 N hydrochloric acid–methanol, and the amine was obtained in 81% yield (mp 90–91 °C; HCl salt mp 215–217 °C).[11]

The thiophene ketone **5**[12] was converted to the exocyclic methylene ketone **6** in 97% yield by the Gras methylenation procedure.[13] The amine **4** and the exocyclic methylene ketone **6** were readily condensed in ethanol to give **1**, isolated as a 1:1 mixture of diastereomeric hydrochloride salts (67%, mp 185–187 °C). Crystalline **1**, as the free base (crystallized from ether), was subjected to single-crystal X-ray analysis.[14] An ORTEP drawing that confirms the structure of **1** is presented in Figure 1.

Scheme I[a]



[a] Key: a = sodium phenoxide, DMF; b = 3 N HCl, CH_3OH; c = $[C_6H_5NH_2CH_3]^+CF_3CO_2^-$, $(CH_2O)_3$, THF; d = C_2H_5OH then HCl.

Stereospecific synthetic routes have been developed for the three diastereomeric amines **7a–9a**.[11] The synthesis of these compounds and the corresponding 6,7-dihydro-2-methylbenzo[*b*]thiophen-4(5*H*)-ones will be reported in subsequent papers.[11,15]

The hypotensive effects of the four stereoisomers **1**, **7b**, **8b**, and **9b** were examined in chronically cannulated spontaneously hypertensive rats (SHR's) and in anesthetized normotensive dogs. The compounds were administered orally (po) to groups of conscious SHR's at a dose of 30 mg/kg and intravenously (iv) to anesthetized dogs at doses ranging form 0.03 to 3.0 mg/kg. Maximal changes in mean arterial blood pressure were determined. In anesthetized dogs, the dose of each compound required to reduce blood pressure by 15% (ED_{15}) was also calculated. As indicated in Table I, **1** was the most potent hypotensive

(1) Present address: Research Department, Pharmaceuticals Division, Ciba-Geigy Corp., Summit, NJ 07901.

(2) Present address: Department of Chemistry, Harvard University, Cambridge, MA 02138.

(3) Goldberg, L. I.; Glock, D.; Kholi, J. D.; Barnett, A. *Hypertension (Dallas)* **1984**, *6*, I-25.

(4) Goldberg, L. I.: Musgrave, G. E.; Kohli, J. D. "Sulperide and Other Benzamides"; Spano, P. F., Trabucci, G. V., Corsini, M., Gessa, G. L., Eds.; Raven Press: New York, 1979.

(5) Goldberg, L. I. *Pharmacol. Rev.* **1972**, *24*, 1.

(6) Poste, G., Crooks, S. T., Eds. "Dopamine Receptor Agonists"; Plenum Press: New York, 1984.

(7) Watanabe, A. M.; McCarthy, J. R., in preparation.

(8) Trepanier, D. L., unpublished results.

(9) All new compounds gave satisfactory analyses for C, H, and N and were further characterized by IR, NMR, and mass spectroscopies, which were consistent with the assigned structures. The new structures reported are racemic, and only one enantiomer is shown for clarity.

(10) Vince, R.; Daluge, S. *J. Med. Chem.* **1974**, *17*, 578.

(11) McCarthy, J. R.; Wiedeman, P. E.; Schuster, A. J.; Whitten, J. P.; Huffman, J. C. *J. Org. Chem.*, in press.

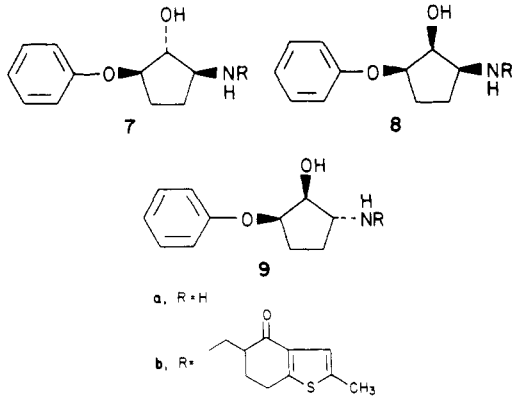
(12) Buu-Hoi, N. P.; Hoan, N.; Khoi, N. H. *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 1053.

(13) Gras, J. L. *Tetrahedron Lett.* **1978**, 2111.

(14) Crystals of **1** crystallized in the triclinic space group $P\bar{1}$ with a = 12.161 (6) Å, b = 12.469 (5) Å, c = 6.327 (2) Å, α = 87.84 (2)°, β = 95.89 (2)°, γ = 98.04 (2)° at −160 °C, D_{calcd} = 1.306 gm/cm^3, and Z = 2 molecules of $C_{21}H_{25}NO_3S$. There were 2136 data (out of 2479 unique) with $I \geq 3\sigma(I)$ collected with a Picker goniostat using graphite-monochromatized molybdenum radiation. The diffractometer, data-handling techniques, and general procedures have been described previously: Huffman, J. C.; Lewis, L. N.; Caulton, K. G. *Inorg. Chem.* **1980**, *19*, 2755. The structure was solved by direct methods and refined by full-matrix least squares. Final residuals are R = 0.050 and R_w = 0.056. Atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 1EW, England. Any request should be accompanied by the full literature citation for this paper. Complete crystallographic details are also available in microfiche form from the Chemistry Library, Indiana University, Bloomington, IN 47405. Request MSC Report 82702.

(15) Presented at the 19th National Medicinal Chemistry Symposium, University of Arizona, Tucson, AZ, June 17–21, 1984.

0022-2623/85/1828-1142$01.50/0



agent in both species, and the relative order of effectiveness for the four compounds was the same in rats and dogs regardless of the route of administration. Compound **1** was roughly equipotent to prazosin, a known selective α_1-adrenergic receptor blocker,[16] when the two were administered intravenously to anesthetized dogs (Table I) but was considerably less potent than prazosin in the SHR. In both the dog and the SHR, the other stereoisomer in which the phenoxy and amino groups are trans (**9b**) exhibited about half the hypotensive activity of **1**, whereas the two stereoisomers with a cis arrangement were either considerably less potent (**8b**) or without significant blood pressure lowering activity (**7b**). Thus, the stereochemical configuration of the three functional groups around the cyclopentyl ring is clearly important in determining the hypotensive activity of these compounds.

The interaction of the four stereoisomers with α adrenoreceptors was examined in vitro by using isolated rabbit aortic strips (α_1)[17] and radioligand receptor binding techniques (α_1 and α_2).[18] Compound **1** was studied in the field-stimulated rat vas deferens preparation for α_2 antagonism.[19] In addition, the α-adrenoreceptor antagonistic effects of **1** were investigated in vivo on the pithed rat;[20] in these tests, antagonism of the pressor effects of either phenylephrine (α_1) or M-7[21] (α_2) was determined.[22] In each of these studies, dose–response curves were established before and after the addition of increasing concentrations of each stereoisomer. pA2 and DR2 values were estimated according to the methods of Arunlakshana and Schild.[23]

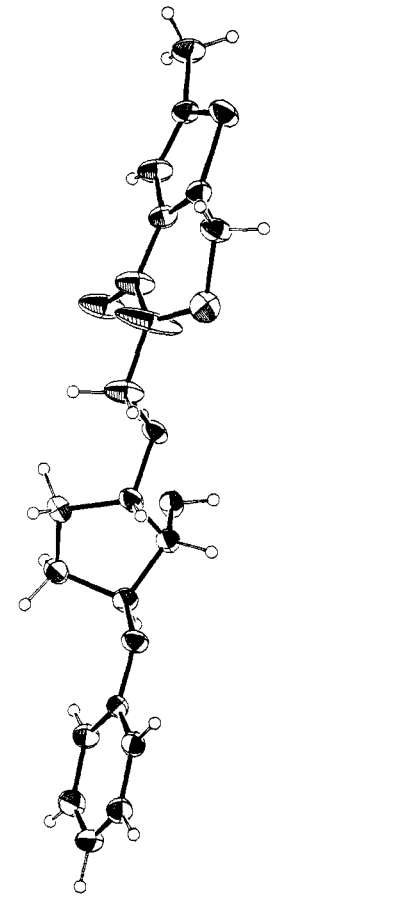


Figure 1. ORTEP drawing of **1** (as the free base).

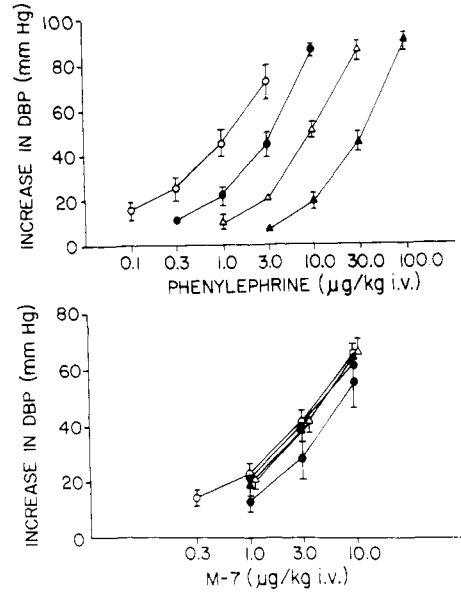


Figure 2. Effects of **1** on phenylephrine and M-7 induced increases in diastolic blood pressure (DBP) in pithed rats (n = 5) (mg/kg iv): ○, control; ●, 0.1; △, 0.3; ▲, 1.0; ●, 3.0. Animals receiving M-7 were pretreated with propranolol (1 mg/kg iv). Error bars are SEM.

As indicated in Table I, the antagonistic potencies of the four stereoisomers at α_1 adrenoreceptors corresponded with

(16) Cambridge, D.; Davey, M. J.; Massingham, R. *Br. J. Pharmacol.* **1977**, *59*, 515.

(17) Dage, R. C.; Cheng, H. C.; Woodward, J. K. *J. Cardiovasc. Pharmacol.* **1981**, *3*, 299. Modified as follows: (a) Rabbit aortic rings, 4-mm wide were cut to form strips. (b) Tyrodes solutions contained 1 μmol cocaine. (c) A tension of 2 g was maintained during equilibration and for the 30-min incubation period with antagonist. (d) Phenylephrine (kept at 1–3 °C) was added from 0.1 to 100 μM in 0.5 log unit. (e) Transducers were Gould UC-2; with results recorded by Buxco Data Analyzer.

(18) Greengrass, P.; Bremner, R. *Eur. J. Pharmacol.* **1979**, *55*, 323. U'Pritchard, D. C.; Snyder, S. H. *Life Sci.* **1979**, *24*, 79.

(19) Doxey, J. C.; Gadie, B.; Lane, A. C.; Tulloch, I. F. *Br. J. Pharmacol.* **1983**, *80*, *155*. Modified as follows: (a) Atropine (10 mM) was added to Krebs solutions. (b) The single-pulse stimulus was applied every 5 min at a frequency of 0.1 Hz, 5-ms duration, and 25–32 V. (c) Antagonists were incubated for 30 min. (d) After each stimulus, the bath was washed with Krebs solution plus blockers. Clonidine, 0.1–3200 nM, was then added in 0.5 log increments.

(20) Drew, G. M. *Eur. J. Pharmacol.* **1980**, *65*, 85. Timmermans, P. B.; Van Meel, J. C.; Van Zwieten, P. A. *J. Auton. Pharmacol.* **1980**, *1*, 53.

(21) 2-(*N*,*N*-Dimethylamino)-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene.

(22) Rats receiving M-7 were pretreated intravenously with 1 mg/kg of propranolol in order to prevent activation of β-adrenergic receptors.

(23) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.

(24) The effects of intravenous injection of isoproterenol (0.03–3 μg/kg) on heart rate in anesthetized dogs were examined before and after administration of **1** (10 mg/kg iv). Calculated pA2 = 5.05 ± 0.20.

Table I. Pharmacological Profile

compd	conscious SHR max Δ(MABP),[a] mmHg: 30 mg/kg po[b]	anesthetized dog: max Δ(MABP),[a] mmHg: 1 mg/kg iv[d]	anesthetized dog: ED_{15}, mg/kg	rabbit aorta pA2 for antag of phenylephrine (α_1)[b]	rat cerebrocortex radioligand binding: IC_{50}, nM[f]: [^{3}H]prazosin (α_1)	rat cerebrocortex radioligand binding: IC_{50}, nM[f]: [^{3}H]-*p*-aminoclonidine (α_2)
1	−70 ± 7	−47 ± 5	0.08	8.13 ± 0.10	8	800
9b	−34 ± 9	−31 ± 3	0.61	7.40 ± 0.06	45	100
8b	no change	−16 ± 3	3.30	7.28 ± 0.06	55	600
7b	no change	−8 ± 2	>10	7.04 ± 0.10	90	>1000
prazosin	−45 ± 5[c]	−30 ± 3[e]	0.10	9.00 ± 0.10	8	1000

[a] Mean arterial blood pressure. [b] Mean ± SEM; n = 4–5. [c] 1 mg/kg po. [d] Values from cumulative dose–response used to calculate ED_{15}; n = 4–5. [e] 0.3 mg/kg iv. [f] All competitive binding assays were done with five or six concentrations of each drug in triplicate. The IC_{50} values were derived from plots of the percentage inhibition of specific binding vs. the log concentration of the compounds.

Table II. Renal Effects of 1

	cumulative dose of 1,[a] mg/kg iv: 0.01	0.03	0.1	0.3	1.0
			RBF[b] (% Δ)		
control	9 ± 2[c]	17 ± 4	27 ± 6	34 ± 7	42 ± 9
after sulpiride	6 ± 2	10 ± 3*	9 ± 3*	9 ± 3**	−1 ± 3**
after SCH 23390	−2 ± 3**	−1 ± 3**	−1 ± 3**	−1 ± 3**	−6 ± 4**
			MABP[d] (% Δ)		
control	−5 ± 1	−9 ± 1	−15 ± 2	−23 ± 2	−32 ± 3
after sulpiride	−3 ± 2	−10 ± 6	−14 ± 5	−21 ± 5	−29 ± 6
after SCH 23390	−3 ± 1	−6 ± 1	−10 ± 2	−15 ± 2*	−22 ± 2*

[a] Cumulative doses administered to anesthetized dogs (n = 4–5/group) at 20-min intervals. [b] Renal blood flow. [c] Mean ± SEM. [d] Mean arterial blood pressure vs. control: *, $p < 0.05$; **, $p < 0.01$.

their respective hypotensive effects in both rats and dogs. Compound 1, the most potent blood pressure lowering agent, was also the most potent antagonist of [^{3}H]prazosin binding to α_1 receptors and blocked the vasoconstrictor effects of phenylephrine in the rabbit aorta with a pA2 of 8.13 ± 0.10. In addition, 1 possessed the greatest degree of selectivity (100-fold) for α_1 receptors in rat cerebrocortex binding studies and did not show competitive antagonism in the rat vas deferens (data not shown). This α_1 selectivity was apparent in the pithed rat preparation (Figure 2) where 1 only weakly blocked the effects of M-7. For example, a dose of 3.0 mg/kg of 1 was required to produce any shift in the dose–response curve to M-7, while doses of 0.1–1.0 mg/kg clearly shifted the response curves to phenylephrine (DR_2 = 0.07, 0.02 mg/kg).

It should also be noted that 1 is essentially inactive as a β-adrenergic blocking agent. In in vitro studies using isolated guinea pig ventricles, 1 had no effect on isoproterenol-induced increases in cyclic-AMP levels at doses of up to 3×10^{-6} M.[25] In addition, studies performed in anesthetized dogs demonstrated that 1 produced no significant effect on isoproterenol-induced increases in heart rate.[24] Thus, compound 1 is a potent blood pressure lowering agent that selectively blocks α_1-adrenergic receptors. On the basis of these findings, a number of analogues of 1 were prepared[15] and compound 1 was chosen for further development.

The effects of cumulative intravenous doses of 1 on renal blood flow, urinary sodium excretion, and glomerular filtration rate (GFR) were examined in anesthetized dogs, and the results were compared with those produced by intrarenal artery infusions of dopamine (0.03–3.0 μg/kg per min). Renal blood flow was measured on an electromagnetic flow probe positioned around the left renal artery, and urine was collected from the cannulated ureter. Urinary sodium concentration was determined by flame photometry. In a second group of dogs, the effects of 1 on blood pressure and renal blood flow were assessed after pretreatment with the selective vascular dopamine receptor blockers SCH 23390[3] (0.5 μg/kg per min iv) or sulpiride[4,5] (0.5 mg/kg iv). As indicated in Table II, 1 produced dose-related increases in renal blood flow and decreases in mean arterial blood pressure in untreated animals. GFR remained unchanged, while urinary sodium excretion was increased from a base line of 42 ± 16 to 104 ± 9 μequiv/min after a cumulative dose of 0.3 mg/kg of 1. In a similar fashion, dopamine caused a maximal increase in renal blood flow of 40 ± 6% at an infusion rate of 3 μg/kg per min and increased urinary sodium excretion from 68 ± 11 (control) to 157 ± 38 μequiv/min but had no effect on GFR; however, dopamine also had no effect on arterial pressure. The combined effects of 1 on blood pressure and renal blood flow are similar in nature to those reported with SKF 82526.[26]

Pretreatment with SCH 23390 blocked while sulpiride significantly attenuated the increases in the renal blood flow produced by 1. These results are like those previously reported with dopamine in the canine kidney[3-5] and indicate that the renal effects of 1 may be mediated by activation of vascular dopamine (DA_1) receptors.[1,4] As such, 1 possesses a unique mechanism of action that combines DA_1 receptor agonistic activity with vasodilation produced by selective α_1-adrenergic receptor blockade. It is important to note that 1 is rapidly metabolized in dogs and rats, and thus the renal effects could be attributed to a metabolite, since no increases in renal blood flow were observed when 1 was administered directly into the renal artery instead of intravenously. Also of importance is our observation that 1 does not produce emesis in dogs or monkeys when administered orally or intravenously, indicating that the compound lacks significant activity at the DA_2 receptor subtype.

Compound 1 is currently being evaluated for clinical effectiveness in the treatment of hypertension. Full details of this work will be reported in subsequent publications.

(25) Watanabe, A. M., private communication.

(26) Ackerman, D. M.; Weinstock, J.; Wiebelhaus, V. D.; Berkowitz, B. *Drug Dev. Res.* **1982**, *2*, 283.

Acknowledgment. We thank Dr. Frank Marshall for his advice and particularly for the discussions that initiated this work, Professor Victor Hruby for his interest and valuable suggestions, and Professor Giangiacomo Nathansohn (Milan, Italy) for his encouragement and enthusiasm for this project while head of the Medicinal Chemistry Department (Indianapolis Center). We also thank P. Ertel, R. Griess, M. Wenger, L. Emmert, and A. Brewer for their technical assistance.

Registry No. (±)-1, 97275-04-2; (±)-1 (free base), 97233-26-6; (±)-2, 52661-17-3; (±)-3, 95526-41-3; (±)-4, 95671-24-2; 5, 5279-03-8; 6, 95526-48-0.

James R. McCarthy,* Mark B. Zimmerman*[1]
Donald L. Trepanier, Micheal E. LeTourneau
Paul E. Wiedeman,[2] Jeffrey P. Whitten
Robert J. Broersma, Philip J. Shea
Merrell Dow Research Institute
Indianapolis Center
Indianapolis, Indiana 46268

Norbert L. Wiech
Merrell Dow Research Institute
Cincinnati Center
Cincinnati, Ohio 45255

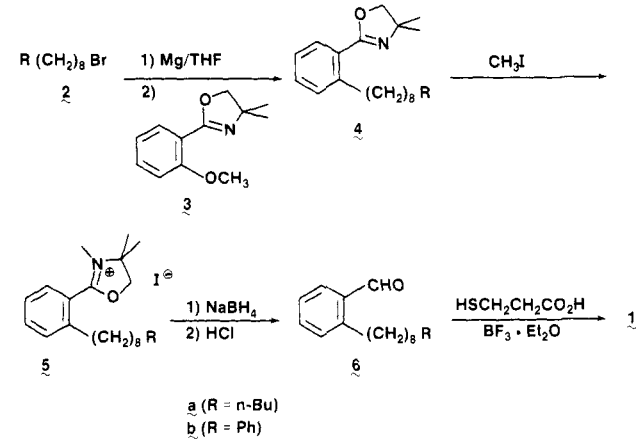
John C. Huffman
Molecular Structure Center
Department of Chemistry
Indiana University
Bloomington, Indiana 47405
Received May 28, 1985

Synthesis and Pharmacological Characterization of 5-(2-Dodecylphenyl)-4,6-dithianonanedioic Acid and 5-[2-(8-Phenyloctyl)phenyl]-4,6-dithianonanedioic Acid: Prototypes of a Novel Class of Leukotriene Antagonists

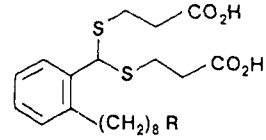
Sir:

As a result of some elegant studies in structural elucidation and chemical synthesis,[1-3] leukotrienes C_4, D_4, and E_4 are now recognized as the components of slow-reacting substance of anaphylaxis. Released upon antigenic stimulation of sensitized human and animal lung tissue,[3,4] they cause potent bronchoconstriction,[5] increased microvascular permeability,[6,7] and altered mucous production and transport.[8] Consequently, it is generally believed that these leukotrienes play a key role in the pathophysiology of allergic asthma and other immediate hypersensitivity diseases and that a leukotriene antagonist would provide novel and effective therapy for such conditions.

Scheme I



Chemical efforts in our laboratories, guided by the structures of the natural leukotrienes, have resulted in the synthesis and pharmacological characterization of 4(*R*)-hydroxy-5(*S*)-(cysteinylglycyl)-6(*Z*)-nonadecenoic acid[9,10] and its analogues[11,12] as leukotriene antagonists on airway and vascular smooth muscle. Although these compounds represent the first examples of leukotriene analogues having antagonist activity, their potency is generally modest and their duration of action in vivo is brief. In addition, some are partial agonists, possessing varying degrees of contractile activity. Further research has led to the discovery that certain 5-aryl-4,6-dithianonanedioic acids comprise a novel class of selective leukotriene antagonists having potent in vitro and in vivo activity of considerable duration, in addition to being completely devoid of agonist activity. Two prototypical members of this class, 5-(2-dodecylphenyl)-4,6-dithianonanedioic acid (**1a**, SK&F 102081) and 5-[2-(8-phenyloctyl)phenyl]-4,6-dithianonanedioic acid (**1b**, SK&F 102922) are the subjects of this paper.



1a, R = n-Bu
1b, R = Ph

Chemistry. Compounds **1a** and **1b** were readily prepared from aldehydes **6a** and **6b**, respectively, by reaction with 2.1 equiv of 3-mercaptopropionic acid (1 equiv of BF_3·Et_2O, CH_2Cl_2, 0 °C, 10 min; **1a**, mp 34–38 °C, 89%; **1b**, mp 59–60 °C, 89%).[13] The aldehydes, in turn, were

(1) Murphy, R. C.; Hammarstrom, S.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 4275.
(2) Morris, H. R.; Taylor, G. W.; Piper, P. J.; Samhoun, M. N.; Tippins, J. R. *Prostaglandins* **1980**, *19*, 185.
(3) Lewis, R. A.; Austen, K. F.; Drazen, J. M.; Clark, D. A.; Marfat, A.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3710.
(4) Dahlen, S. E.; Hansson, G.; Hedqvist, P.; Bjorck, T.; Granstrom, E.; Dahlen, B. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 1712.
(5) Dahlen, S. E.; Hedqvist, P.; Hammarstrom, S.; Samuelsson, B. *Nature (London)* **1980**, *288*, 484.
(6) Peck, M. J.; Piper, P. G.; Williams, T. J. *Prostaglandins* **1981**, *21*, 315.
(7) Woodward, D. F.; Weichman, B. M.; Gill, C. A.; Wasserman, M. A. *Prostaglandins* **1983**, *25*, 131.
(8) Marom, Z.; Shelhamer, J. H.; Bach, M. K.; Morton, D. R.; Kaliner, M. *Am. Rev. Respir. Dis.* **1982**, *126*, 449.
(9) Gleason, J. G.; Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Holden, D.; Osborn, R. R.; Zabko-Potapovich, B.; Berkowitz, B.; Wasserman, M. A. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 732.
(10) Weichman, B. M.; Wasserman, M. A.; Holden, D. A.; Osborn, R. R.; Woodward, D. F.; Ku, T. W.; Gleason, J. G. *J. Pharmacol. Exp. Ther.* **1983**, *227*, 700.
(11) Perchonock, C. D.; Uzinskas, I.; Ku, T. W.; McCarthy, M. E.; Bondinell, W. E.; Volpe, B. W.; Gleason, J. G.; Weichman, B. M.; Muccitelli, R. M.; DeVan, J. F.; Tucker, S. S.; Vickery, L. M.; Wasserman, M. A. *Prostaglandins* **1985**, *29*, 75.
(12) Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Gleason, J. G. *J. Med. Chem.*, in press.

0022-2623/85/1828-1145$01.50/0