[(6,7-Dichlorobenzo[b]thien-5-yl)oxy]acetic Acids and 1,1-Dioxides.[1] 1. A Structurally Novel Class of Diuretics with Hypotensive Activity

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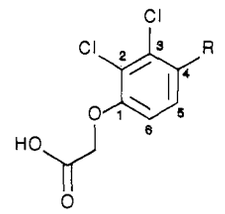
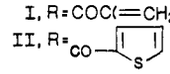
A series of [(6,7-dichlorobenzo[b]thien-5-yl)oxy]acetic acids and their corresponding 1,1-dioxides were synthesized and evaluated for diuretic activity in the acute saline loaded mice (ASLM) and hypotensive activity in the spontaneously hypertensive rat (SHR). A significant number of compounds were found to display potent activity in one or both assays, and preliminary structure-activity relationships with respect to each assay were delineated. Compound **94**, the 1,1-dioxide of [(6,7-dichloro-2-*n*-propylbenzo[b]thien-5-yl)oxy]acetic acid, was markedly active in both the ASLM and SHR by oral administration. The combined diuretic/hypotensive profile of this compound was further substantiated by its good saluretic response in water loaded conscious dogs and a moderate to good activity in renal hypertensive rats and sinoaortic-deafferented hypertensive dogs.

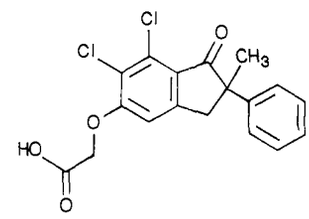
The discovery of potent, orally effective diuretics has been regarded as one of the most significant therapeutic advances in this century.[3] In the management of hypertension and congestive heart failure, these agents are among the safest and most effective in the currently available medical armamentarium. The emergence of ethacrynic acid (I) over 20 years ago[4] has stimulated a cascade of new research, which ultimately led to the discoveries of novel uricosuric diuretics, mostly with a high-ceiling profile. This list includes tienilic acid (II),[5] indacrinone (III),[6] and brocrinat (IV),[7a,b] as well as the related furobenzisoxazole derivative (V).[8] Of particular interest to us were the last three entries, which demonstrated, quite dramatically, the greatly enhanced saluretic activity brought about by ring annelations at appropriate positions, i.e., position 3 or 5 in II, or concomitantly at positions 3 and 6. In this paper we report a structurally novel class of (aryloxy)acetic acids, the alkyl-substituted [(6,7-dichlorobenzo[b]thien-5-yl)oxy]acetic acids and their 1,1-dioxides (VI), which are derived conceptually from II by a new mode of ring annelation at position 5.



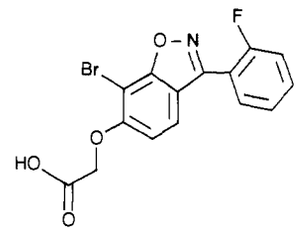
I, R = $COC(=CH_2)C_2H_5$



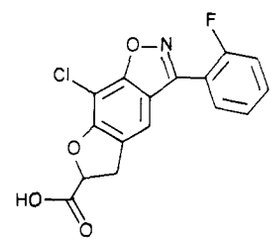
II



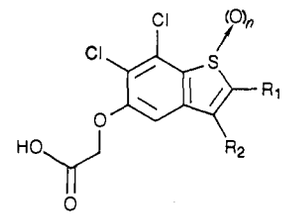
III



IV



V



VI (73-102)

Chemistry

The construction of appropriately substituted benzo[b]thiophene ring systems is outlined in Scheme I. The starting 2,3-dichloro-4-methoxythiophenol (1) was prepared via two steps by chlorosulfonation of 2,3-dichloroanisole, followed by reduction of the resulting sulfonyl chloride with zinc dust and sulfuric acid.[11] For the syntheses of benzo[b]thiophenes unsubstituted at C(2) and C(3) positions or substituted only at C(2) on the thiophene ring, compound 1 was alkylated with α-haloalkanoic acids in the presence of sodium hydride and DMF (method A) to give the substituted (phenylthio)alkanoic acids **2-10** in excellent yields. Friedel-Crafts cyclizations of the acyl chlorides generated from **2-10** at low temperature (-65 °C) afforded the corresponding ketones, which, due to their instability, were promptly reduced to the epimeric alcohols **11-19** (method B). Dehydration of alcohols could be effected readily with boron trifluoride etherate in acetic acid

(1) This paper has been presented in part; see *Abstracts of Papers*, 182nd National Meeting of the American Chemical Society: Washington, DC, August 1981; Abstr. MEDI 9.
(2) Present address: Miles Laboratories, Elkart, IN.
(3) Gifford, R. W., Jr. *JAMA J. Am. Med. Assoc.* **1976**, *235*, 1890.
(4) Cragoe, E. J., Jr., In *Diuretics, Chemistry, Pharmacology, and Medicine*; Cragoe, E. J., Jr., Ed.; Wiley-Interscience: New York, 1983; Chapter 4.
(5) Frohlich, E. D. *N. Engl. J. Med.* **1979**, *301*, 1378.
(6) Brooks, B. A.; Blair, E. M.; Finch, R.; Lent, A. F. *Br. J. Clin. Pharmacol.* **1980**, *10*, 249.
(7) (a) Shutske, G. M.; Setescak, L. L.; Allen, R. C.; Davis, L.; Effland, R. C.; Ranbom, K.; Kitzen, J. M.; Wilker, J. C.; Novick, W. J., Jr. *J. Med. Chem.* **1982**, *25*, 36. (b) Kitzen, J. M.; Schwenkler, M. A.; Bixby, P. R.; Wilson, S. J.; Shutske, G. M.; Setescak, L. L.; Allen, R. C.; Rosenblum, I. *Life Sci.* **1980**, *27*, 2549.
(8) Plattner, J. J.; Fung, A. K. L.; Parks, J. A.; Pariza, R. J.; Crowley, S. R.; Pernet, A. G.; Bunnell, P. R.; Dodge, P. W. *J. Med. Chem.* **1984**, *27*, 1016.
(9) Except in the case of **55**, which was reacted with *tert*-butyl bromoacetate to give the corresponding ester **72**.
(10) Since urine, Na^+, and Cl^- roughly paralleled each other, only Na^+ excretion is given for brevity.
(11) Tegeler, J. J.; Ong, H. H.; Profitt, J. A. *J. Heterocycl. Chem.* **1983**, *20*, 867.
(12) While **35** could be prepared satisfactorily from **23** by this method, similar attempts to cyclize **22** resulted in complex mixtures.

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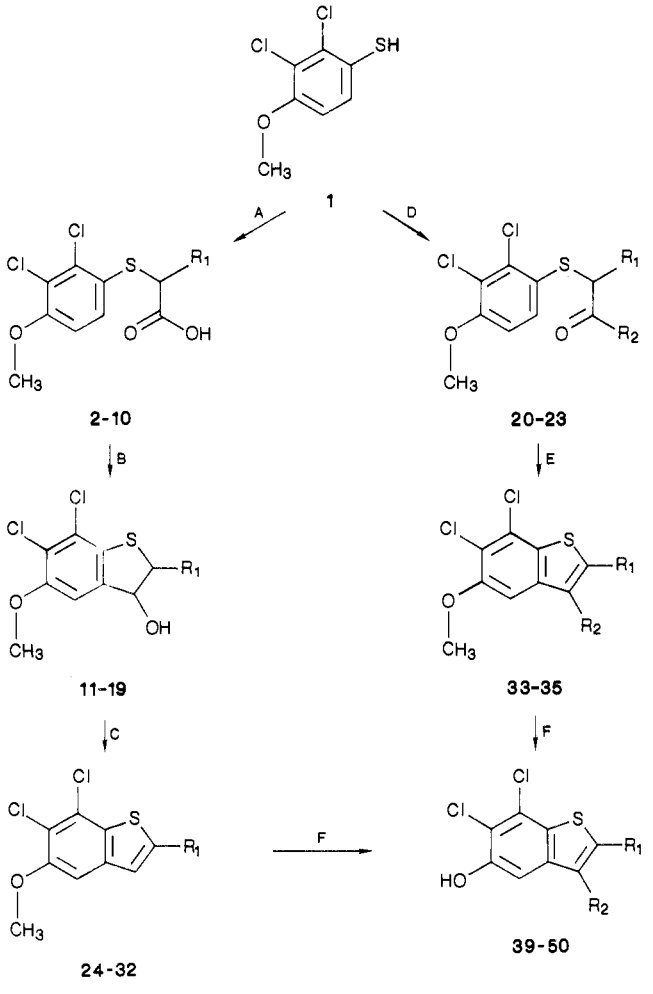
Scheme I

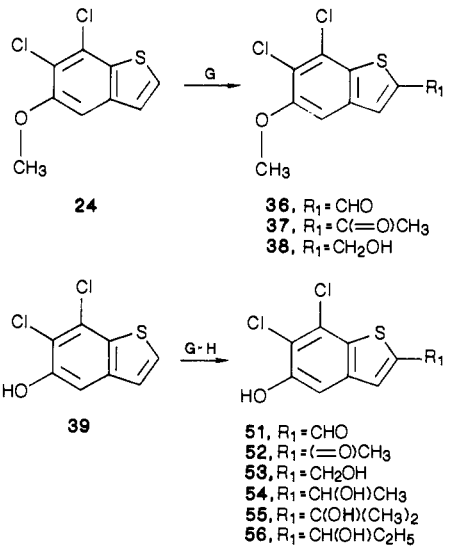


(method C) to afford the resulting benzo[*b*]thiophenes **24-32** in excellent yields.

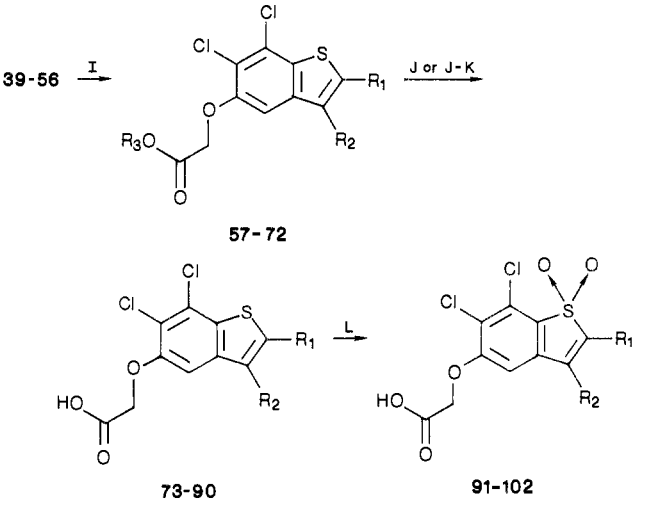
For the syntheses of 6,7-dichloro-5-methoxybenzo[*b*]-thiophenes substituted at C(2) or at both C(2) and C(3) positions, an analogous route was followed whereby the mercaptan **1** was first alkylated with appropriate α-chloro ketones in the presence of sodium hydride and DMF (method D) to give phenylthio ketones, **20-23**, followed by dehydrative cyclizations with "super" polyphosphoric acid to afford good yields of **33-35** (method E). The latter procedure worked well with most ketones except in the case of α-[(6,7-dichloro-5-methoxyphenyl)thio]cyclopentanone, **22**, which gave only tarry materials under such reaction conditions.

For the conversion of simple, 5-methoxybenzo[*b*]-thiophenes (**24-35**) to the corresponding phenolic derivatives (**39-50**), pyridine hydrochloride fusion at 170 °C or above appeared to be the method of choice (method F). However, other benzo[*b*]thiophenes carrying an acyl or a hydroxyalkyl substituent at C(2), i.e., **37**, **38**, and **53-56**, were prepared by a different approach as outlined in Scheme II. Thus, compound **39** was treated with 2 equiv of *n*-butyllithium at -20 °C to form a dianion, which, upon treatment with an appropriate electrophile such as a ketone, gave rise to 2-(hydroxyalkyl)benzo[*b*]thiophenes **54-56** in good yields (method G). For reasons not clearly understood, the same dianion failed to react with paraformaldehyde to yield the expected hydroxymethyl derivative **53**. This compound was prepared indirectly by $NaBH_4$ reduction (method H) of the 2-formyl derivative **51**, which in turn resulted from treating the lithiated **39** with a large excess of DMF. On the other hand, the lithiated derivative of **24** reacted readily with both DMF and paraformaldehyde to give **36** and **38**, respectively.

Scheme II



Scheme III



Further elaboration of the phenolic hydroxyl function into an (aryloxy)acetic acid side chain is illustrated in Scheme III. Phenols **39-56** were reacted with a slight excess of ethyl bromoacetate[9] in the presence of K_2CO_3 and DMF to give (aryloxy)acetates **57-72** in excellent yields (method I), and the esters were readily hydrolyzed to afford the targeted (aryloxy)acetic acids **73-85** and **87-90** in high purity. While this synthetic sequence (methods G–J) proved practical for the syntheses of most analogues carrying an oxygenated alkyl substituent at C(2), the preparation of **86**, a congener bearing a 2-(1-oxopropyl) radical, was best carried out by oxidizing the 2-(1-hydroxypropyl) derivative **89** with $K_2Cr_2O_7$ in glacial acetic acid (method K). Further conversion of the benzo[*b*]thienoxyacetic acids to their 1,1-dioxides (**91-102**) could be effected smoothly with *m*-chloroperoxybenzoic acid at controlled temperatures (method L).

Pharmacological Results and Discussions

All target compounds, **73-102**, were screened orally for diuretic activity in saline-loaded mice and for hypotensive activity in the spontaneous hypertensive rat. The results are summarized in Table VII.

Saline-Loaded Mice.[10] In delineating structure-activity relationships for the title compounds in this model as well as in others, it is convenient to divide them into

two groups: the [(6,7-dichlorobenzo[b]thien-5-yl)oxy]acetic acids (**73-90**) and their corresponding sulfones or 1,1-dioxides (**91-102**). The first group can then be further divided into four subgroups to include (a) targets that bear an alkyl or cycloalkyl group (or hydrogen) at C(2) but are unsubstituted at C(3) (**73-81**), (b) targets that are substituted at C(3) (**82-84**), (c) targets that carry an alkanoyl group at C(2) (**85** and **86**), and (d) targets that are substituted at C(2) with a hydroxyalkyl residue. Similar subdivisions could be made for the sulfones although most compounds synthesized in this series belong to a subgroup analogous to (a).

In comparing the diuretic activity of the 2-alkyl-substituted derivatives (**74-81**) with the unsubstituted compound **73**, it is apparent that the introduction of a lipophilic group at this position generally resulted in a moderate increase in activity. The magnitude of this effect seemed to be determined by the size as well as degree of branching of the substituent, and a convergence of optima was seen in the isopropyl analogue **77**, which displayed the best activity in this subgroup.

It is interesting to note that, contrary to the above, substitution at C(3) drastically reduced the diuretic activity; the observed values for urinary Na^+ and Cl^- excretion for compound **82-84** were all below control levels. The significance of C(2) as the locus of structural modifications for diuretic activity was further explored with alkanoyl derivatives (**85** and **86**) and with derivatives carrying a 2-(α-hydroxyalkyl) residue (**87-90**). Moderate to marked activity was observed with the latter compounds, and the most active one was more active than ethacrynic acid at the screening dose of 64 mg/kg per os. It is again worth noting that potency within this subgroup seemed to increase with the size of the substituent at C(2), and a positive contribution of branching was also suggested on the basis of relative potencies shown by isomers **89** and **90**.

With the sulfones or 1,1-dioxide targets, **91-102**, a set of similar, yet quantitatively different SAR's emerged. Not surprisingly, with the unsubstituted analogue **91** as a reference, the introduction of a methyl group at C(2) (**92**) dramatically increased the activity by a factor of greater than 10; no further enhancement of activity was seen when the 2-alkyl substituent was increased in size and degree of branching. Somewhat similar to the unoxidized benzo[b]thienyl targets, diuretic activity among the 1,1-dioxides began to fall off sharply with the *n*-butyl analogue **96**, which was again less active than its branched-chain isomer **97**. The detrimental effects of a C(3) substitution observed with **100** and **101** were somewhat expected; however, the extremely weak diuretic activity shown by **102** defies a ready explanation.

Spontaneous Hypertensive Rat. As can be readily seen from Table VII, there is apparently no close correlation between the mouse diuretic activity and the hypotensive activity (as evaluated in the spontaneous hypertensive rat) for the title compounds **73-102**. The most potent compound in this model, **74**, was only marginally active in the diuretic assay. Although one of the previously drawn conclusions that a 2-alkyl substituent generally enhanced activity was still partially true, as in the case of **74**, **77**, **78**, **93**, **94**, and **99**, the optima for SHR activity in both target groups (**73-90** and **91-102**) have now been displaced, and a rational pattern is no longer discernible. Conversely, many of the most potent compounds in the diuretic screen (i.e., **90**, **92**, and **97**) were only weakly active in the spontaneously hypertensive rat with one clear exception, **94**, which was markedly active both as a diuretic and hypotensive. Thus, it is quite plausible to assume that, within the present class of target compounds, the underlying mechanism for their hypotensive action may be unrelated to the basis for their diuretic action.

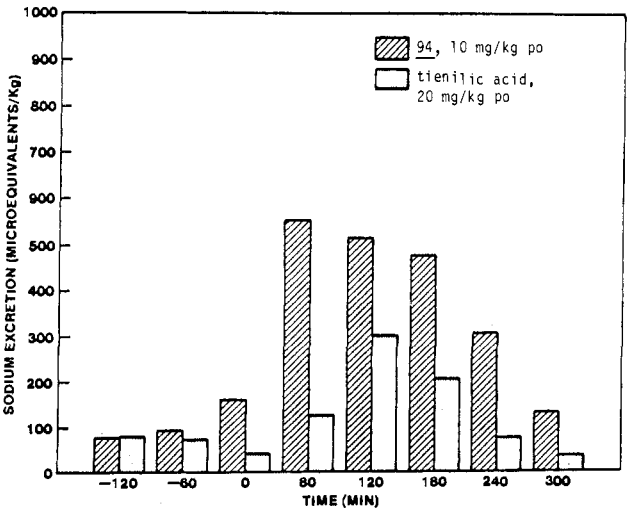


Figure 1. Effects of **94** and tienilic acid on sodium excretion in unanesthetized dogs ($N = 4$).

Activity Profile of 94. Since one of the major objectives of our program was to identify diuretic agents with hypotensive properties, compound **94** was further evaluated in a number of secondary assays.

In the water-loaded unanesthetized dog, **94** at 10 mg/kg po was significantly more potent than tienilic acid at 20 mg/kg po, with a fast onset and reasonably long duration of action (Figure 1). In the renal hypertensive rat (one kidney, one wrap; Grollman rat), compound **94** displayed good activity at 10 mg/kg po, albeit with tachyphylaxis, with its peak effect seen at 2 h postadministration (Table VIII). Further substantiation of its hypotensive profile was provided by results from the sinoaortic deafferented neurogenic dog. In this model, **94** at 10 mg/kg iv caused a significant fall of arterial pressure (ΔMAP = 33 mmHg) with minimal effects on the heart rate, contractility, and cardiac output. The target compounds were also screened for uricosuric activity in the rat, but none was found active.

In conclusion, we have synthesized a series of structurally novel [(6,7-dichlorobenzo[b]thien-5-yl)oxy]acetic acids and the corresponding 1,1-dioxides. A significant number of these compounds possess both diuretic and hypotensive activity by oral administration. The most promising member of this series, compound **94**, is currently undergoing further evaluation as a potential clinical candidate for the treatment of hypertension.

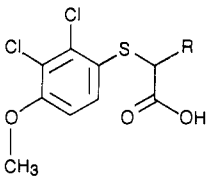
Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 547) and ^1H NMR (JEOL C60HL and Varian XL-200) spectra. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra data were determined with a Finnigan 4000 GC-MS equipped with a INCOS data system. Where analyses were indicated only by symbols of the elements, the analytical results obtained for those elements (performed by Micro-Tech Laboratories, Skokie, IL) were within 0.4% of theoretical values.

2,3-Dichloro-4-methoxythiophenol (1) was prepared by the method of Tegeler, et al. from 2,3-dichloroanisole in 90% yield, mp 81-83 °C (lit.[11] mp 81.5-83).

[(2,3-Dichloro-4-methoxyphenyl)thio]acetic Acid (2). Method A. To a stirred mixture of 99% NaH (0.82 g, 34 mmol) in 5 mL of sieve-dried DMF were added 2.0 g (9.6 mmol) of 1 and 0.81 g (8.6 mmol) of chloroacetic acid in 25 mL of the same solvent over a period of 5 min. After it was stirred for 0.5 h, the reaction mixture was quenched with 250 mL of water, followed by 20 mL

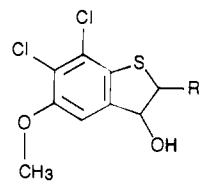
Table I. α-[(2,3-Dichloro-4-methoxyphenyl)thio]alkanoic Acids[a]



compd	R	yield,[b] %	mp, °C	recrystn solvent[c]	formula	anal.
2	H	99	155–156	A-E	$C_9H_8Cl_2O_3S$	C, H, Cl
3[d]	CH_3	78	118–120	A-H	$C_{10}H_{10}Cl_2O_3S$	C, H, S
4	C_2H_5	90	143–145	A-H	$C_{11}H_{12}Cl_2O_3S$	C, H, S
5	n-C_3H_7	85	120	E-P	$C_{12}H_{14}Cl_2O_3S$	C, H
6[e]	i-C_3H_7	80	176–178	A-P	$C_{12}H_{14}Cl_2O_3S$	C, H
7	n-C_4H_9	61	111–111.5	A-H	$C_{13}H_{16}Cl_2O_3S$	C, H
8	i-C_4H_9	47	120–121	A-P	$C_{13}H_{16}Cl_2O_3S$	C, H
9	c-C_5H_9	66	177–180	A	$C_{14}H_{16}Cl_2O_3S$	C, H
10	c-C_6H_{11}	63	144–145	E-P	$C_{15}H_{18}Cl_2O_3S$	C, H

[a] All compounds exhibited IR, ^1H NMR, and MS spectra consistent with the structures. [b] Isolated yields; no efforts were made to optimize these yields. [c] A = acetone, B = benzene, C = cyclohexane, D = dichloromethane, E = ethyl ether, F = ethyl acetate, G = ethanol, H = hexane, I = carbon tetrachloride, M = methanol, P = pentane. [d] Literature 119–120 °C; see ref 11. [e] Literature 176.5–178.5 °C; see ref 11.

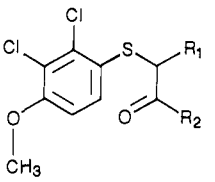
Table II. 2-Alkyl-6,7-dichloro-2,3-diydro-3-hydroxy-5-methoxybenzo[*b*]thiophenes[a]



compd	R	yield,[b] %	mp, °C	recrystn solvent[c]	formula	anal.
11	H	90	122–124	A-H	$C_9H_8Cl_2O_2S$	C, H
12	CH_3	75	78–112	P	$C_{10}H_{10}Cl_2O_2S$	C, H, S
13	C_2H_5	71	80–89	P	$C_{11}H_{12}Cl_2O_2S$	C, H, S
14	n-C_3H_7	53	119–120	D-H	$C_{12}H_{14}Cl_2O_2S$	C, H
15	i-C_3H_7	23	125–127	E-P	$C_{12}H_{14}Cl_2O_2S$	C, H
16	n-C_4H_9	50	95–96	E-P	$C_{13}H_{16}Cl_2O_2S$	C, H
17	i-C_4H_9	66	*d*	*e*	$C_{13}H_{16}Cl_2O_2S$	C, H
18	c-C_5H_9	59	129–132	E-H	$C_{14}H_{16}Cl_2O_2S$	C, H
19	c-C_8H_{11}	56	166–167	E-P	$C_{15}H_{18}Cl_2O_2S$	C, H

[a–c] See corresponding footnotes in Table I. [d] Isolated as a heavy oil. [e] Purified by column chromatography.

Table III. α-[(2,3-Dichloro-4-methoxyphenyl)thio]alkanones and α-[(2,3-Dichloro-4-methoxyphenyl)thio]cycloalkanones[a]



compd	R_1	R_2	yield,[b] %	mp, °C	recrystn solvent[c]	formula	anal.
20	H	CH_3	76	64–66	E-P	$C_{10}H_{10}Cl_2O_2S$	C, H, S
21	CH_3	CH_3	67	70–71	D-H	$C_{11}H_{12}Cl_2O_2S$	C, H
22	$-(CH_2)_3-$		67	91–93	A-H	$C_{12}H_{12}Cl_2O_2S$	C, H
23	$-(CH_2)_4-$		68	132–134	A-H	$C_{13}H_{14}Cl_2O_2S$	C, H, S

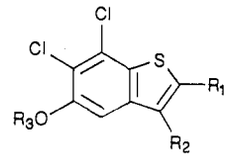
[a–c] See corresponding footnotes in Table I.

of 20% NaOH. The aqueous solution was filtered and acidified with concentrated HCl to pH 1. The precipitated solid was collected and air dried to give 2.3 g (99.5%) of **2** as a white powder. Properties of **2**, and of **3–10** prepared in a similar manner, are included in Table I.

6,7-Dichloro-2,3-dihydro-3-hydroxy-5-methoxybenzo[*b*]thiophene (11). Method B. To a suspension of **2** (1.35 g, 5 mmol) in 20 mL of CH_2Cl_2 was added 0.8 mL of $SOCl_2$ over 5 min. The reaction was refluxed for 1 h, and the excess reagent and solvent were removed under reduced pressure. Dichloromethane (15 mL) was added to the residue, and the resultant solution was added cautiously to a stirred slurry of $AlCl_3$ (0.56 g) in 3 mL of CH_2Cl_2 with a cooling bath of dry ice–acetone (−65 °C). After total addition, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 1 h. Quenching with water (50 mL), followed by extraction with ether and drying ($MgSO_4$), yielded an unstable intermediary ketone, which was reduced directly with 0.4 g of sodium borohydride in 10 mL of absolute ethanol. Working up in the usual manner yielded a grayish solid, which was recrystallized from acetone–hexane to give 1.13 g (90%) of **3** as rhombic crystals. Properties of **11**, and of **12–19**, prepared in a similar manner, are included in Table II.

6,7-Dichloro-5-methoxybenzo[*b*]thiophene (24). Method C. A mixture of **11** (0.7 g, 2.78 mmol) and 1 mL of boron trifluoride etherate in 4 mL of glacial acetic acid was heated at 120 °C for 5 min. Ice (20 g) was added, and the mixture was basified with an excess of 10% NaOH (pH 10). The off-white solid was filtered, air-dried, and recrystallized from ether–hexane to give

Table IV. 6,7-Dichloro-5-methoxybenzo[b]thiophenes and Corresponding Phenols[a]



compd	R_1	R_2	R_3	method	yield,[b] %	mp, °C	recrystn solvent[c]	formula	anal.
24	H	H	CH_3	C	98	103–104	E-H	$C_9H_6Cl_2OS$	C, H, Cl, S
25	CH_3	H	CH_3	C	71	113–114	E	$C_{10}H_8Cl_2OS$	C, H, S
26	C_2H_5	H	CH_3	C	95	73–74.5	P	$C_{11}H_{10}Cl_2OS$	C, H, Cl
27	n-C_3H_7	H	CH_3	C	74	28–29	E-H	$C_{12}H_{12}Cl_2OS$	C, H
28	i-C_3H_7	H	CH_3	C	95	*d*	*e*	$C_{12}H_{12}Cl_2OS$	C, H
29	n-C_4H_9	H	CH_3	C	49	35–36	D-H	$C_{13}H_{14}Cl_2OS$	C, H
30	i-C_4H_9	H	CH_3	C	85	40–41	E-H	$C_{13}H_{14}Cl_2OS$	C, H
31	c-C_5H_9	H	CH_3	C	75	59.5–60	D-H	$C_{14}H_{14}Cl_2OS$	C, H
32	c-C_6H_{11}	H	CH_3	C	65	60–61	E-H	$C_{15}H_{16}Cl_2OS$	C, H
33	H	CH_3	CH_3	E	86	122–124	H	$C_{10}H_8Cl_2OS$	C, H, S
34	CH_3	CH_3	CH_3	E	73	159–160	D-H	$C_{11}H_{10}Cl_2OS$	C, H
35	$-(CH_2)_4-$		CH_3	E	81	123–125	A-H	$C_{13}H_{12}Cl_2OS$	C, H, Cl
36	CHO	H	CH_3	G	61	183–184	F	$C_{10}H_6Cl_2O_2S$	C, H
37	C(=O)CH_3	H	CH_3	G	78	180–181	F	$C_{11}H_8Cl_2O_2S$	C, H
38	CH_2OH	H	CH_3	G	80	137–138	E-H	$C_{10}H_8Cl_2O_2S$	C, H
39	H	H	H	F	75	97–98	A-H	$C_8h_4Cl_2O_2S$	C, H
40	CH_3	H	H	F	72	93–95	E-P	$C_9H_6Cl_2OS$	C, H
41	C_2H_5	H	H	F	74	69–70	E-P	$C_{10}H_8Cl_2OS$	C, H, S
42	n-C_3H_7	H	H	F	60	51–53	E-P	$C_{11}H_{10}Cl_2OS$	C, H
43	i-C_3H_7	H	H	F	98	44.5–46.5	H	$C_{11}H_{10}Cl_2OS$	C, H
44	n-C_4H_9	H	H	F	69	35–36	P	$C_{12}H_{12}Cl_2OS$	C, H
45	i-C_4H_9	H	H	F	70	58–60	E-H	$C_{12}H_{12}Cl_2OS$	C, H
46	c-C_5H_9	H	H	F	78	62–63.5	E-P	$C_{13}H_{12}Cl_2OS$	C, H
47	c-C_6H_{11}	H	H	F	68	59–60	P	$C_{14}H_{14}Cl_2OS$	C, H
48	H	CH_3	H	F	72	137–139	E-H	$C_9H_6Cl_2OS$	C, H
49	CH_3	CH_3	H	F	90	143–145	A-H	$C_{10}H_8Cl_2OS$	C, H
50	$-(CH_2)_4-$		H	F	90	103–105	E-P	$C_{12}H_{10}Cl_2OS$	C, H, S
51	CHO	H	H	G	66	197–198	A-H	$C_9H_4Cl_2O_2S$	C, H
52	C(=O)CH_3	H	H	F	57	199–201	A-H	$C_{10}H_6Cl_2O_2S$	C, H
53	CH_2OH	H	H	H	74	167–169	A-H	$C_9H_6Cl_2O_2S$	C, H
54	CH(OH)CH_3	H	H	G	66	172–174	A-H	$C_{10}H_8Cl_2O_2S$	C, H
55	C(OH)$(CH_3)_2$	H	H	G	80	171–173	A-H	$C_{11}H_{10}Cl_2O_2S$	C, H
56	CH(OH)C_2H_5	H	H	G	69	145–146.5	E-H	$C_{11}H_{10}Cl_2O_2S$	C, H

[a–c] See corresponding footnotes in Table I. [d,e] See corresponding footnotes in Table II.

0.64 g (98%) of **24** as colorless prisms. Properties of **24**, and of **25–32**, prepared in a similar manner, are included in Table IV.

α-[(2,3-Dichloro-4-methoxyphenyl)thio]acetone (20). Method D. A solution of **1** (11.25 g, 50 mmol) in 100 mL of sieve-dried DMF was added over 5 min to a slurry of NaH (1.25 g, 99%) in 10 mL of the same solvent. Stirring was continued for 20 min after total addition, and to this clear solution was added 4.6 g (85%, practical grade) of chloroacetone at a rate such that the reaction temperature remained below 50 °C. The mixtue was stirred at ambient temperature for 1 h and quenched with water. Extraction with CH_2Cl_2, followed by washing (2 × 150 mL) and drying ($MgSO_4$), yielded a tan oil. Purification of the crude product was effected by column chromatography over alumina packed in ether, elution with ether gave 9.8 g (76%) of **20** as a colorless solid. Properties of **20**, and of **21–23**, prepared in a similar manner, are included in Table III.

6,7-Dichloro-5-methoxy-3-methylbenzo[*b*]thiophene (33). Method E. A dehydrating mixture of "super PPA" was prepared by mixing 45 g of polyphosphoric acid and 10 g of phosphorus pentoxide. To this rapidly stirred mixture preheated to 170 °C was added 7.5 g (28.3 mmol) of **20** in a small portion over a period of 15 min. Following total addition, the reaction mixture was stirred at 170–180 °C for an additional 30 min. The mixture was cooled, quenched with water (50 mL), and extracted exhaustively with ether. The combined ether solution was washed, dried ($MgSO_4$), and concentrated to give a tan residue. Recrystallization of the crude product from boiling hexane afforded 6.0 g (85.8%) of **33** as yellowish prisms. Properties of **33**, and of **34** and **35**,[11] prepared in a similar manner, are included in Table IV.

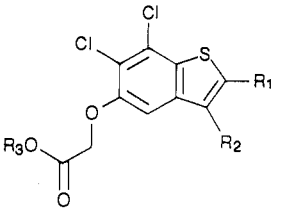
6,7-Dichloro-5-hydroxybenzo[*b*]thiophene (39). Method F. A mixture of **24** (0.56 g, 2.4 mmol) and 5 g of pyridine hydrochloride was heated under N_2 at 180 °C for 1 h. The mixture was cooled, triturated with water, and extracted with ether (3 × 150 mL). The combined ether solution was washed with water, dried ($MgSO_4$), and concentrated to give 0.42 g (74.7%) of **39** as a tan solid. Properties of **39** and of **40–50** and **52**, prepared in a similar manner, are included in Table IV.

6,7-Dichloro-2-formyl-5-methoxybenzo[*b*]thiophene (36). Method G. A solution of **24** (2.33 g, 10 mmol) in 15 mL of anhydrous THF and 5 mL of ether was cooled to −25 °C with a dry ice–acetone bath. To this, under N_2, was added 5 mL (2.6 M) of n-butyllithium at a rate that the internal temperature remained below 20 °C (15 min). After total addition, the mixture was stirred at −20 °C for 2 h before a solution of 0.9 g of DMF in 5 mL of ether was added. The cooling bath was then removed, and the mixture was allowed to warm to room temperature. The reaction was quenched by adding 200 mL of 1 N HCl, and the orange precipitate was filtered, air-dried, and recrystallized from ethyl acetate to give 1.6 g (61.3%) of **36** as fine needles. Properties of **36** are included in Table IV.

2-Acetyl-6,7-dichloro-5-methoxybenzo[*b*]thiophene (37). Method G. To a solution of **24** (5.0 g, 21 mmol) in 30 mL of anhydrous THF and 10 mL of ether was added, at −20 °C and under N_2, 11.7 mL of 2.2 M n-butyllithium in hexane while the temperature was maintained at −20 °C. After being stirred for 2 h at this temperature, the mixture was added dropwise to a vigorously stirred solution of acetic anhydride (22 mL) in 40 mL of anhydrous THF at −20 °C. Five minutes after the addition, the reaction was stopped, the solution was poured onto 200 mL of 10% HCl, and the mixture was extracted exhaustively with CH_2Cl_2 (3 × 300 mL). The combined organic solution was washed, dried ($MgSO_4$), and concentrated to give a tan solid. Recrystallization from ether–hexane afforded 2.1 g (36%) of **37** of analytical purity. Properties of **37** are included in Table IV.

6,7-Dichloro-2-formyl-5-hydroxybenzo[*b*]thiophene (51). Method G. A solution of **39** (8.7 g, 40 mmol) in 50 mL of an-

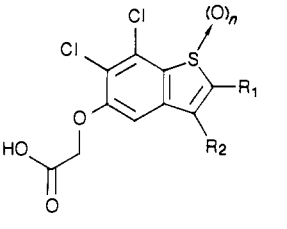
Table V [(6,7-Dichlorobenzo[*b*]thien-5-yl)oxy]acetates[a]



compd	R_1	R_2	R_3	yield,[b] %	mp, °C	recrystn solvent[c]	formula	anal.
57	H	H	C_2H_5	64	92-94	A-H	$C_{12}H_{10}Cl_2O_3S$	C, H, Cl
58	CH_3	H	C_2H_5	84	91-92	H	$C_{13}H_{12}Cl_2O_3S$	C, H
59	C_2H_5	H	C_2H_5	84	67-68	P	$C_{14}H_{14}Cl_2O_3S$	C, H, Cl
60	n-C_3H_7	H	C_2H_5	76	63-65	E-H	$C_{15}H_{16}Cl_2O_3S$	C, H
61	i-C_3H_7	H	C_2H_5	94	76-77.5	E-P	$C_{15}H_{16}Cl_2O_3S$	C, H
62	n-C_4H_9	H	C_2H_5	69	72-73	E-H	$C_{16}H_{18}Cl_2O_3S$	C, H
63	i-C_4H_9	H	C_2H_5	92	75-76	E-H	$C_{16}H_{18}Cl_2O_3S$	C, H
64	c-C_5H_9	H	C_2H_5	76	65-67	E-H	$C_{17}H_{18}Cl_2O_3S$	C, H
65	c-C_6H_{11}	H	C_2H_5	69	73-73.5	E-H	$C_{18}H_{20}Cl_2O_3S$	C, H
66	H	CH_3	C_2H_5	84	115-117	E-H	$C_{13}H_{12}Cl_2O_3S$	C, H, S
67	CH_3	CH_3	C_2H_5	85	102-104	A-H	$C_{14}H_{14}Cl_2O_3S$	C, H
68	$-(CH_2)_4-$		C_2H_5	72	157-159	A	$C_{16}H_{16}Cl_2O_3S$	C, H, S
69	CH_2OH	H	C_2H_5	89	117-118	A-H	$C_{13}H_{12}Cl_2O_4S$	C, H
70	$CH(OH)CH_3$	H	C_2H_5	87	101-103	A	$C_{14}H_{14}Cl_2O_4S$	C, H
71	$CH(OH)C_2H_5$	H	C_2H_5	69	69-70	E-H	$C_{15}H_{16}Cl_2O_4S$	C, H
72	$C(OH)(CH_3)_2$	H	$C(CH_3)_3$	81	137-138	E-H	$C_{17}H_{20}Cl_2O_4S$	C, H

[a-c] See corresponding footnotes in Table I.

Table VI. [(6,7-Dichlorobenzo[*b*]thien-5-yl)oxy]acetic Acids and 1,1-Dioxides[a]



compd	R_1	R_2	n	method	yield,[b] %	mp, °C	recrystn solvent[c]	formula	anal.
73	H	H	0	J	95	166-167	A-C	$C_{10}H_6Cl_2O_3S$	C, H, Cl, S
74	CH_3	H	0	J	85	215-216	A-H	$C_{11}H_8Cl_2O_3S$	C, H
75	C_2H_5	H	0	J	86	179-181	A-H	$C_{12}H_{10}Cl_2O_3S$	C, H
76	n-C_3H_7	H	0	J	95	165-166	A-H	$C_{13}H_{12}Cl_2O_3S$	C, H
77	i-C_3H_7	H	0	J	86	168-170	A-P	$C_{13}H_{12}Cl_2O_3S$	C, H, Cl
78	n-C_4H_9	H	0	J	80	152-153	A-H	$C_{14}H_{14}Cl_2O_3S$	C, H
79	i-C_4H_9	H	0	J	94	164-165	E-H	$C_{14}H_{14}Cl_2O_3S$	C, H
80	c-C_5H_9	H	0	J	93	173-174	A-H	$C_{15}H_{14}Cl_2O_3S$	C, H
81	c-C_6H_{11}	H	0	J	82	167-167.5	E-H	$C_{16}H_{16}Cl_2O_3S$	C, H
82	H	CH_3	0	J	88	205-206	A	$C_{11}H_8Cl_2O_3S$	C, H, Cl, S
83	CH_3	CH_3	0	J	85	218-219	A-H	$C_{12}H_{10}Cl_2O_3S$	C, H
84	$-(CH_2)_4-$		0	J	81	257-259	G	$C_{14}H_{12}Cl_2O_3S$	C, H, Cl, S
85	$C(=O)CH_3$	H	0	J	87	203-205	A-H	$C_{12}H_8Cl_2O_4S$	C, H
86	$C(=O)C_2H_5$	H	0	K	80	223-224	A-H	$C_{13}H_{10}Cl_2O_4S$	C, H
87	CH_2OH	H	0	J	81	187-188.5	A-H	$C_{11}H_8Cl_2O_4S$	C, H
88	$CH(OH)CH_3$	H	0	J	77	173-175	A-H	$C_{12}H_{10}Cl_2O_4S$	C, H
89	$CH(OH)C_2H_5$	H	0	J	86	154-155	E-H	$C_{13}H_{12}Cl_2O_4S$	C, H
90	$C(OH)(CH_3)_2$	H	0	J	93	194-196	A-P	$C_{13}H_{12}Cl_2O_4S$	C, H
91	H	H	2	L	79	227-228	A-H	$C_{10}H_6Cl_2O_5S$	C, H
92	CH_3	H	2	L	88	232-234	A-H	$C_{11}H_8Cl_2O_5S$	C, H
93	C_2H_5	H	2	L	88	232-233	A-H	$C_{12}H_{10}Cl_2O_5S$	C, H
94	n-C_3H_7	H	2	L	61	225-226	A-H	$C_{13}H_{12}cl_2O_5S$	C, H
95	i-C_3H_7	H	2	L	24	203.5-204.5	I	$C_{13}H_{12}Cl_2O_5S$	C, H
96	n-C_4H_9	H	2	L	91	246-248	A-H	$C_{14}H_{14}Cl_2O_5S$	C, H
97	i-C_4H_9	H	2	L	83	233-236	A-H	$C_{14}H_{14}Cl_2O_5S$	C, H
98	c-C_5H_9	H	2	L	55	239-240	A-H	$C_{15}H_{14}Cl_2O_5S$	C, H
99	c-C_6H_{11}	H	2	L	74	235-236	A-H	$C_{16}H_{16}Cl_2O_5S$	C, H
100	CH_3	CH_3	2	L	61	245-246	A-H	$C_{12}H_{10}Cl_2O_5S$	C, H
101	$-(CH_2)_4-$		2	L	71	264-265	G	$C_{14}H_{12}Cl_2O_5S$	C, H
102	$CH(OH)CH_3$	H	2	L	40	207-209	A-H	$C_{12}H_{10}Cl_2O_6S$	C, H

[a-c] See corresponding footnotes in Table I.

hydrous THF was blanketed with N_2 and cooled to -20 °C. To this was added dropwise a solution of n-butyllithium in hexane (42 mL, 30% excess) at a rate such that the internal temperature remained below -10 °C. After total addition, the milky suspension was stirred at 0 °C for 3 h before 14 mL of anhydrous DMF was added over a period of 20 min. The darkened mixture was then allowed to stir at ambient temperature. Quenching with 2 N HCl (400 mL), followed by extraction with ethyl acetate and drying

Table VII. Oral Diuretic and Hypotensive Activity of Title Compounds 73–102

	saline loaded mice[a]			spontaneously hypertensive rats[a]		
compd	dose,[b] mg/kg	mequiv of Na^+/kg 0–5 h	vc[c]	dose,[b] mg/kg	initial BP, mmHg	ΔBP,[e] mmHg
73	64	1.00	0.40	50	201	+2 ± 8.3
74	64	1.16	0.00	50	215	−51 ± 20.8
				10	196	−33 ± 12.7
				3	173	−37 ± 10.4
				1	177	−42 ± 18.0
75	64	2.07	0.21	25	176	−13 ± 7.8
	32	1.51		10	185	−21 ± 3.8
	16	0.74				
76	64	1.74	0.91	50	181	−1 ± 12.2
77	64	2.52	0.64	50	179	−41 ± 16.8
	32	1.64		30	195	−32 ± 5.4
	16	1.24		10	178	−14 ± 5.2
78	64	0.88	0.68	50	173	−47 ± 8.4
				30	173	−16 ± 7.3
				10	171	−17 ± 12.7
79	64	1.29	0.45	50	176	+4 ± 4.0
80	64	1.30	0.40	50	193	−31 ± 7.9
81	64	1.60	0.60	50	178	+2 ± 9.7
82	64	0.80	0.07	50	203	−12 ± 8.6
83	64	0.13	0.74	50	192	−37 ± 7.5
84	64	0.45	1.39	50	177	−12 ± 3.7
85	64	1.16	1.12	50	199	−28 ± 11.8
86	64	1.18	0.68	50	173	−1 ± 12.1
87	64	1.23	0.25	50	199	−5 ± 16.2
88	64	2.86	0.68	50	183	−7 ± 6.4
89	64	3.89	0.61	50	166	−22 ± 13.9
90	128	6.24	1.22	50	193	−25 ± 3.9
	64	4.40				
	32	2.21				
	16	0.53				
91	64	0.33	0.32	50	201	−3 ± 7.4
92	128	6.36	0.52	50	180	−25 ± 11.0
	64	4.34				
	32	2.11				
	16	1.33				
93	128	6.51	0.28	50	213	−8 ± 7.4
	64	3.35				
	32	1.84				
	16	0.66				
94	128	4.99	0.86	30	202	−64 ± 20.2
	64	3.13		3	205	−52 ± 11.5
	32	1.79				
	16	1.06				
95	128	5.32	0.35	50	192	−33 ± 8.1
	64	2.58				
	32	0.88				
96	64	2.42	0.68	50	185	−24 ± 15.9
97	64	3.24	0.45	50	176	−14 ± 5.2
98	64	1.79	0.60	50	180	−17 ± 10.7
99	64	1.25	0.60	50	202	−43 ± 4.9
				30	167	−30 ± 14.2
				3	187	−32 ± 9.4
100	64	0.92	0.74	50	165	−17 ± 8.2
101	64	0.00[d]	0.01	50	179	−8 ± 10.9
102	64	0.43	1.52	50	176	−9 ± 5.1
ethacrynic acid	64	4.14	0.30	*g*	*g*	*g*
hydrochlorothiazide	64	*g*	*g*	50	188	−26 ± 4.0
tienilic acid	64	3.31	0.10	50	200	−14 ± 25.0

[a] See the Experimental Section for testing methodology. [b] Administered orally. [c] Vehicle control (saline). The mean vehicle control value for each group of mice is given as an indication of the reliability of the results. [d] No urine was collected. [e] Peak decrease in systolic blood pressure on third day, 2 h postadministration of a compound ±SEM. [f] Fifth day, 2 h postadministration of a compound. [g] Not determined.

($MgSO_4$), afforded 7.0 g (66%) of **51** as orange prisms. Properties of **51** are included in Table IV.

6,7-Dichloro-5-hydroxy-α-methylbenzo[*b*]thiophene-2-methanol (54). Method G. To a solution of **39** (25 g, 115 mmol) in 145 mL of anhydrous THF at −25 °C was added 110 mL of 2.5 N *n*-butyllithium at a rate such that the temperature did not rise above −20 °C. Following the addition, the mixture was stirred at 0–5 °C for 4 h. A solution of 9.5 mL of freshly distilled acetaldehyde in 10 mL of THF was added (over 5 min), and the mixture was stirred for 5 min before quenching with 500 mL of ice-cold 5% HCl. The mixture was extracted with ether; the combined ether solution after washing (2 × 100 mL) and drying ($MgSO_4$) was concentrated to give 22 g (66%) of **54** as colorless crystals. Properties of **54**, and of **55** and **56**, prepared in a similar manner, are included in Table IV.

6,7-Dichloro-5-hydroxy-2-(hydroxymethyl)benzo[*b*]thiophene (53). Method H. A solution of **51** (6.0 g, 24.3 mmol) in 300 mL of 95% ethanol was treated portionwise with 1.5 g of $NaBH_4$. The mixture was stirred at room temperature for 20 min until gas evolution stopped. Water (100 mL) was added; the mixture was saturated with NaCl and extracted exhaustively with a 50:50 mixture of ethyl acetate and ether (3 × 400 mL). The combined organic solution was washed, dried ($MgSO_4$), and concentrated to give a tan residue. Recrystallization from ace-

Table VIII. Hypotensive Activity of Compound 94 in Renal Hypertensive Rats[a]

compd	no. of rats	dose, mg/kg po	initial BP, mmHg	postdrug BP, mmHg (day/h)	ΔBP, mmHg
94	4	10	166	135 (1/2)	-31
				156 (2/0)	-10
				153 (2/2)	-13
				167 (3/0)	+1
				167 (3/2)	+1
hydrochlorothiazide	3	50	168	156 (1/2)	-12
				133 (2/0)	-35
				148 (2/2)	-20
				150 (3/0)	-18
				133 (3/2)	-35

[a] Grollman model of hypertension (one kidney, one wrap).

tone–hexane afforded 4.5 g (74%) of **53** as off-white crystals. Properties of **53**, and of **38**, prepared in a similar manner, are included in Table IV.

Ethyl [(6,7-Dichlorobenzo[*b*]thien-5-yl)oxy]acetate (57). Method I. A mixture of **39** (3.6 g, 16.4 mmol), 3.0 g of ethyl bromoacetate, and 1.5 g of K_2CO_3 in 40 mL of anhydrous DMF was stirred at 70–80 °C for 16 h. The cooled mixture was diluted with ice–water (200 g), and the solid was collected by filtration. Recrystallization from acetone–hexane gave 3.2 g (64%) of **57** as yellowish needles. Properties of **57**, and of **58–72**, prepared in a similar manner, are included in Table V.

[(6,7-Dichlorobenzo[*b*]thien-5-yl)oxy]acetic Acid (73). Method J. A mixture of **57** (7.5 g, 24.6 mmol) and 15 g of 85% potassium hydroxide in 250 mL of aqueous ethanol (50:50) was heated at reflux for 1 h, during which a clear solution was formed. The excess solvents were removed under reduced pressure at 60 °C, and the residue was diluted with 100 mL of water and acidified with concentrated HCl (pH 2). The resultant slurry was stirred at room temperature for 30 min and extracted exhaustively with a 50:50 mixture of ethyl acetate and ether (3 × 250 mL). The combined organic solution was washed with water, dried ($MgSO_4$), and concentrated to give a crystalline mass. Recrystallization from acetone–hexane gave 6.5 g (95%) of **73** as off-white crystals. Properties of **73**, and of **74–85** and **87–90**, prepared in a similar manner, are included in Table VI.

[[6,7-Dichloro-2-(1-oxopropyl)benzo[*b*]thien-5-yl]oxy]acetic Acid (86). Method K. A solution of **89** (3.4 g, 10 mmol) in 50 mL of glacial acetic acid was formed by gentle warming at 45 °C. The solution was allowed to cool to 34 °C before a solution of 2.1 g of $K_2Cr_2O_7$, 8 mL of water, and 3.2 mL of concentrated H_2SO_4 was added dropwise. Occasionally, an ice bath was necessary during the addition to maintain the temperature below 35 °C. The reaction mixture was stirred for 2 h at room temperature and poured onto 200 mL of water. Extraction with ethyl acetate, followed by drying and concentration, afforded a yellowish solid, which was recrystallized from acetone–hexane to give 2.51 g (80%) of **86** as white prisms. Properties of **86** are included in Table VI.

[(6,7-Dichlorobenzo[*b*]thien-5-yl)oxy]acetic Acid 1,1-Dioxide (91). Method L. A mixture of **73** (5.5 g, 20 mmol) and 10.1 g of 85% *m*-chloroperoxybenzoic acid in 500 mL of $CHCl_3$ was warmed briefly on a steam bath and stirred at room temperature overnight. The mixture was concentrated to dryness under reduced pressure, and to this residue was added 200 mL of CH_2Cl_2. After standing at room temperature for a few hours, the crystalline material was filtered and recrystallized from acetone–hexane or ethyl acetate to give 4.9 g (79%) of **91** as rhombic crystals. Properties of **91**, and of **92–102**, prepared in a similar manner, are included in Table VI.

Acute Diuretic Evaluation in Sodium-Loaded Mice.[13] The acute sodium-loaded mouse experiments were performed with groups of male CD-1 mice weighing 18–24 g. Drugs were prepared in 1% saline and orally administered in a dosage volume of 10 mL/kg. The animals were housed in metabolic cages, each treatment group consisting of 10 animals, five per cage. Tests consisted of a vehicle control and the potential diuretic agent given at 64 mg/kg. The pooled urine samples were analyzed for sodium with a flame photometer (IL Model 343). Sodium values were expressed as the mean milliequivalents (mequiv)/kg per 5 h.

Hypotensive Activity in Spontaneously Hypertensive Rats. All compounds were screened for hypotensive activity in spontaneously hypertensive rats of the Okamoto-Aoki strain. The screening dose was 50 mg/kg po. Systolic blood pressures were determined at the following times by tail-cuff plethysmography: day 1, predose and 2 h postdose; day 3, predose and 2 h postdose; day 5, predose and 2 and 4 h postdose. Details of the method are described by Buggy et al.[14] The test compounds were suspended in distilled water with Tween 80 and administered at either 50, 30, 10, or 3 mg/kg po, unless otherwise indicated. Animals were dosed every day. Four animals were used in the preliminary screen, while four to eight animals per dose were used in the dose–response screen.

Hypotensive Activity in Renal Hypertensive Rats. Renal hypertension was produced by a modification of the method of Grollman.[15] Briefly, male Sprague–Dawley rats were anesthetized with pentobarbital sodium (50 mg/kg ip), and the right kidney was removed through a right subcoastal incision. The left kidney was exposed through an incision in the left flank. Silk sutures (size 00) were passed around both poles of the kidney and tightened to produce a visible constriction of the renal parenchyma. Animals were returned to their cages and given food and water ad libitum. After 3 weeks of stabilization, systolic blood pressures were determined as above, and rats with blood pressures >150 mmHg were selected for use in evaluating drugs.

Unanesthetized Dogs. Male mongrel dogs weighing 20–25 kg were given 20 mL/kg tap water by gavage approximately 15 h prior to drug. Water was available ad libitum overnight between this dose and the first urine collection on the morning of the test. On the morning of the test, each dog was placed in an individual metabolism cage. The bladder was emptied by catheterization and then rinsed with 20 mL of sterile distilled water. Each dog was then given 20 mL/kg tap water by gavage. One hour later, the bladder was catheterized and drained. The volume was recorded, and a small sample was retained for analysis. Each animal received 4 mL/kg tap water at this point and once each hour for the ensuing 7 h. At these time intervals, the bladder was emptied, the volume was recorded, and a sample was retained for analysis. After the third urine sample was drawn, drug was administered by gavage in the 4 mL/kg water load. Tween 80 was added to aid suspension if the compound was not readily soluble in water. Urine samples were analyzed by flame photometry for Na^+ concentrations. Calculations were made for the mean excretory rates (microequivalents/kilogram) for each interval and for each animal.

Hypotensive Activity in the Sinoaortic-Deafferented Dogs. Adult dogs of either sex were anesthetized with barbital sodium (200 mg/kg iv), thiopental sodium (15 mg/kg iv), and pentobarbital sodium (60 mg iv). A femoral vein and artery were cannulated with PE tubing for intravenous administration of drugs and to record blood pressure and heart rate, respectively.

Deafferentation was accomplished by clearing both of the carotid arteries up to the internal and external carotid artery bifurcation. The carotid sinus nerves were isolated, ligated, and sectioned, and a bilateral vagotomy was performed to produce neurogenic hypertension (mean arterial pressure >150 mmHg). Dogs were allowed to stabilize for approximately 30 min, and then a bolus intravenous injection of the test compound was administered. Heart rate, arterial pressure, left ventricular pressure, dP/dt, and cardiac output were monitored for 90 min postdose.

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Registry No. 1, 83119-51-1; 2, 83119-48-6; 3, 83119-56-6; 4, 83119-55-5; 5, 83119-84-0; 6, 83119-44-2; 7, 83119-76-0; 8, 83120-46-1; 9, 83119-46-4; 10, 83119-81-7; 11, 83118-91-6; 12, 83119-10-2; 13, 83140-66-3; 14, 83120-36-9; 15, 83119-30-6; 16, 83119-79-3; 17, 83120-49-4; 18, 83119-38-4; d19, 83119-83-9; 20, 83119-12-4; 21, 83120-23-4; 22, 83119-53-3; 23, 83119-24-8; 24, 83118-92-7; 25, 83119-11-3; 26, 83118-97-2; 27, 83120-37-0; 28, 83119-31-7; 29, 83119-80-6; 30, 83120-50-7; 31, 83119-39-5; 32, 83119-85-1; 33, 83119-13-5; 34, 83120-24-5; 35, 90340-15-1; 36, 110638-64-7; 37, 83119-86-2; 38, 110638-65-8; 39, 83118-93-8; 40, 83119-34-0; 41, 83118-98-3; 42, 83120-38-1; 43, 83119-32-8; 44, 83140-69-6; 45, 83120-51-8; 46, 83119-74-8; 47, 83120-03-0; 48, 83119-14-6; 49, 83120-25-6; 50, 90340-16-2; 51, 83119-88-4; 52, 83119-87-3; 53, 83119-90-8; 54, 83120-42-7; 55, 83119-94-2; 56, 83119-97-5; 57, 83118-96-1; 58, 83119-35-1; 59, 83118-99-4; 60, 83120-39-2; 161, 83119-33-9; 62, 83120-00-7; 63, 83120-52-9; 64, 83119-75-9; 65, 83120-04-1; 66, 83119-15-7; 67, 83140-70-9; 68, 90340-17-3; 69, 83119-91-9; 70, 83120-43-8; 71, 83119-98-6; 72, 83119-95-3; 73, 83119-00-0; 74, 83119-36-2; 75, 83119-05-5; 76, 83120-40-5; 77, 83119-37-3; 78, 83120-01-8; 79, 83120-53-0; 80, 83140-68-5; 81, 83120-05-2; 82, 83119-16-8; 83, 83120-26-7; 84, 90340-18-4; 85, 83119-93-1; 86, 83120-45-0; 87, 83119-92-0; 88, 83120-44-9; 89, 83119-99-7; 90, 83119-96-4; 91, 83119-08-8; 92, 83119-65-7; 93, 83120-15-4; 94, 83120-41-6; 95, 83119-69-1; 96, 83120-02-9; 97, 83120-54-1; 98, 83120-07-4; 99, 83120-06-3; 100, 83120-27-8; 101, 90340-19-5; 102, 110638-66-9; $ClCH(Et)CO_2H$, 4170-24-5; $ClCH(Pr\text{-}i)Co_2H$, 921-08-4; $ClCH(Bu\text{-}i)CO_2H$, 29671-29-2; chloroacetic acid, 79-11-8; 2-chloropropionic acid, 598-78-7; 2-chloropentanoic acid, 6155-96-0; 2-chlorohexanoic acid, 29671-30-5; (cyclopentyl)chloroacetic acid, 110638-67-0; (cyclohexyl)chloroacetic acid, 35468-15-6; chloroacetone, 78-95-5; 3-chloro-2-butanone, 4091-39-8; 2-chlorocyclopentanone, 694-28-0; 2-chlorocyclohexanone, 822-87-7; acetaldehyde, 75-07-0; acetone, 67-64-1; propionaldehyde, 123-38-6; ethyl bromoacetate, 105-36-2; ethyl [(2-acetyl-6,7-dichlorobenzo[*b*]thien-5-yl)oxy]acetate, 83119-89-5.

Synthesis and Antiarrhythmic Activity of Novel 3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium Salts and Related Compounds.[1] 2

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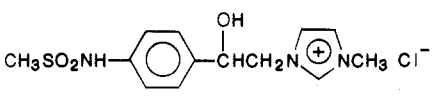
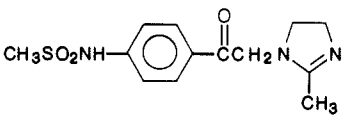
Novel analogues of the class III antiarrhythmic agent 1-[2-hydroxy-2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-3-methyl-1*H*-imidazolium chloride, 1 (CK-1649), were prepared and investigated for their class III electrophysiological activity on isolated canine cardiac Purkinje fibers and ventricular muscle tissue. Structure–activity relationships are discussed for a series of 11 compounds. One compound, *N*-[4-[1-hydroxy-2-(4,5-dihydro-2-methyl-1*H*-imidazol-1-yl)ethyl]phenyl]methanesulfonamide hydrochloride, **9**, was comparable in activity to 1 in vitro and prolonged the functional refractory period in anesthetized dogs when given intraduodenally. Unlike 1, compound **9** was ineffective at preventing ventricular tachycardia induced by programmed electrical stimulation in anesthetized dogs 24 h after an acute myocardial infarction.

Antiarrhythmic agents that selectively prolong the action potential duration (APD) and concomitantly increase the refractory period (FRP) of heart cells without significant effects on cardiac conduction are termed class III antiarrhythmic agents in the Vaughan Williams classification.[2]

In a previous paper,[3] we reported the synthesis and class III antiarrhythmic activity of a new series of 3-alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium salts. One example from this series, 1 (CK-1649), possesses potent class III electrophysiological activity in vitro. Compound 1 also showed intraduodenal activity in anesthetized mongrel dogs (10 or 30 mg/kg) and was also effective in preventing ventricular tachycardia in



1



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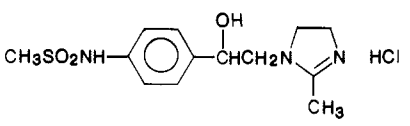

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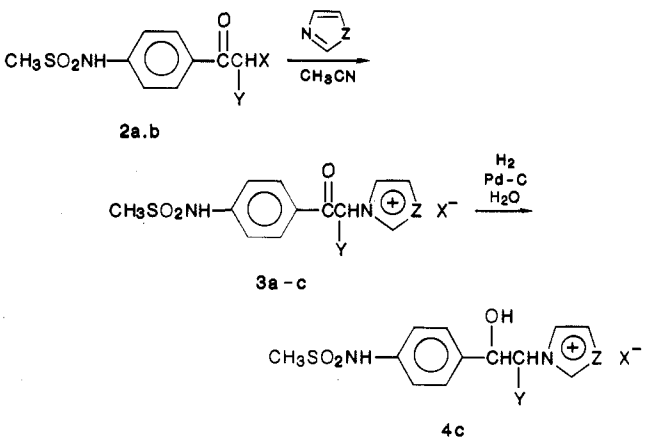
Scheme I



a: X = Cl, Y = H, Z = S
b: X = Br, Y = CH_3, Z = NCH_3
c: X = Cl, Y = CH_3, Z = NCH_3

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