solution (6 mg/kg) intraperitoneally. The carotid blood pressure was recorded with a Bell and Howell pressure transducer and the heart rate was recorded from the EKG or the pulse wave. Doses of 0.2 and 0.4 μg of isoproterenol intravenously were administered alternately at 7-min intervals. When the preparation had been shown to respond regularly, the test compound was administered 3.5 min after a 0.2-μg dose of isoproterenol. The next dose of isoproterenol 3.5 min later challenged the sensitivity of the preparation. The extent of the block produced was calculated

$$\% \text{ apparent isoproterenol} = \text{antilog } [2 - (I_2 - I_{2a})/(I_2 - I_1) \times 0.301]$$

where I_1 and I_2 are the responses to 0.2 and 0.4 μg of isoproterenol, respectively, before the dose of test compound and I_{2a} is the response to 0.4 μg of isoproterenol afterwards. By repeating the experiment with adjustment of the dose of test compound, a series of values of the above expression was obtained. From a graph of these values the dose was found by linear interpolation which reduced the sensitivity to isoproterenol to one-half. This dose is elsewhere referred to as the half-blocking dose. Both the tachycardia and diastolic hypotension responses to isoproterenol were considered separately, and in each case the dose found was called the half-blocking dose. The half-blocking doses refer only to the condition of the animal 3.5 min after dosing.

Statistics. Statistical calculations were carried out on a Wang 2200B computer using programs devised by the authors.

Acknowledgment. We wish to thank Dr. K. Bowden (University of Essex) for stimulating discussions and Miss S. E. M. Dye and Mr. C. J. Hardy for technical assistance. Compound 1 was prepared by our colleague, Mr. M. T. Briggs.

References and Notes

(1) D. Dunlop and R. G. Shanks, *Br. J. Pharmacol. Chemother.*, **32**, 201 (1968).
(2) C. J. Coulson and K. R. H. Wooldridge, *J. Chem. Soc.*, 2830 (1969).
(3) C. J. Coulson, J. Memel, B. J. Millard, and K. R. H. Wooldridge, *J. Chem. Soc.*, 1164 (1971).
(4) B. Basil, E. C. J. Coffee, D. L. Gell, D. R. Maxwell, D. J. Sheffield, and K. R. H. Wooldridge, *J. Med. Chem.*, **13**, 403 (1970).
(5) B. R. Lucchesi and H. F. Hardman, *J. Pharmacol. Exp. Ther.*, **132**, 372 (1961).
(6) M. S, Tute, *Adv. Drug Res.*, **6**, 1 (1971).
(7) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
(8) E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969).
(9) N. Bauer, K. Fajans, and S. Z. Lewin in "Physical Methods of Organic Chemistry", Vol. 1, part II, 3rd ed, A. Weissberger, Ed., Interscience, New York, N.Y., 1960, Chapter 8.
(10) K. Bowden and K. R. H. Wooldridge, *Biochem. Pharmacol.*, **22**, 1015 (1973).
(11) C. Hansch, *Acc. Chem. Res.*, **2**, 232 (1969); T. Higuchi and S. S. Davis, *J. Pharm. Sci.*, **59**, 1376 (1970).
(12) J. W. McFarland, *J. Med. Chem.*, **13**, 1192 (1970); S. H. Yalkowsky and G. L. Flynn, *J. Pharm. Sci.*, **62**, 210 (1973).
(13) K. R. H. Wooldridge, *Experientia*, **28**, 1404 (1972).
(14) B. Basil, R. Jordan, A. H. Loveless, and D. R. Maxwell, *Br. J. Pharmacol.*, **48**, 198 (1973).
(15) A. J. Coleman and W. P. Leary, *Curr. Ther. Res., Clin. Exp.*, **14**, 673 (1972); M. F. Cuthbert and K. Owuso-Ankomak, *Br. J. Pharmacol.*, **43**, 639 (1971); R. H. Briant, C. T. Dollery, T. Fenyuesi, and C. F. George, *ibid.*, **43**, 468P (1971).

Aminobenzoic Acid Diuretics. 8.[2] 3,4-Disubstituted 5-Methylsulfonylbenzoic Acids and Related Compounds

Peter W. Feit* and Ole B. Tvaermose Nielsen

Leo Pharmaceutical Products, DK-2750 Ballerup, Denmark. *Received August 22, 1975*

Various 2,4- and 3,4-disubstituted 5-methylsulfonylbenzoic acids were synthesized as methylsulfonyl analogues of previously described 5-sulfamoylbenzoic acid diuretics. The results of the diuretic screening in dogs reveal that substitution of the sulfamoyl group by the spatially and sterically similar methylsulfonyl group does not affect the diuretic pattern but leads generally to somewhat decreased potency. For the highly potent 3-benzylamino-4-phenoxy-5-methylsulfonylbenzoic acid the corresponding 5-methylthio and 5-methylsulfinyl analogs were prepared and found still to exhibit diuretic activity. Internal aldol condensation and subsequent dehydration of 3-benzylamino- and 3-*n*-butylamino-4-benzoyl-5-methylsulfonylbenzoic acid provided the corresponding inactive 4-alkylamino-6-carboxy-2,3-dihydro-3-hydroxy-3-phenylbenzo[*b*]thiophene 1,1-dioxides and 4-alkylamino-6-carboxy-3-phenylbenzo[*b*]thiophene 1,1-dioxides.

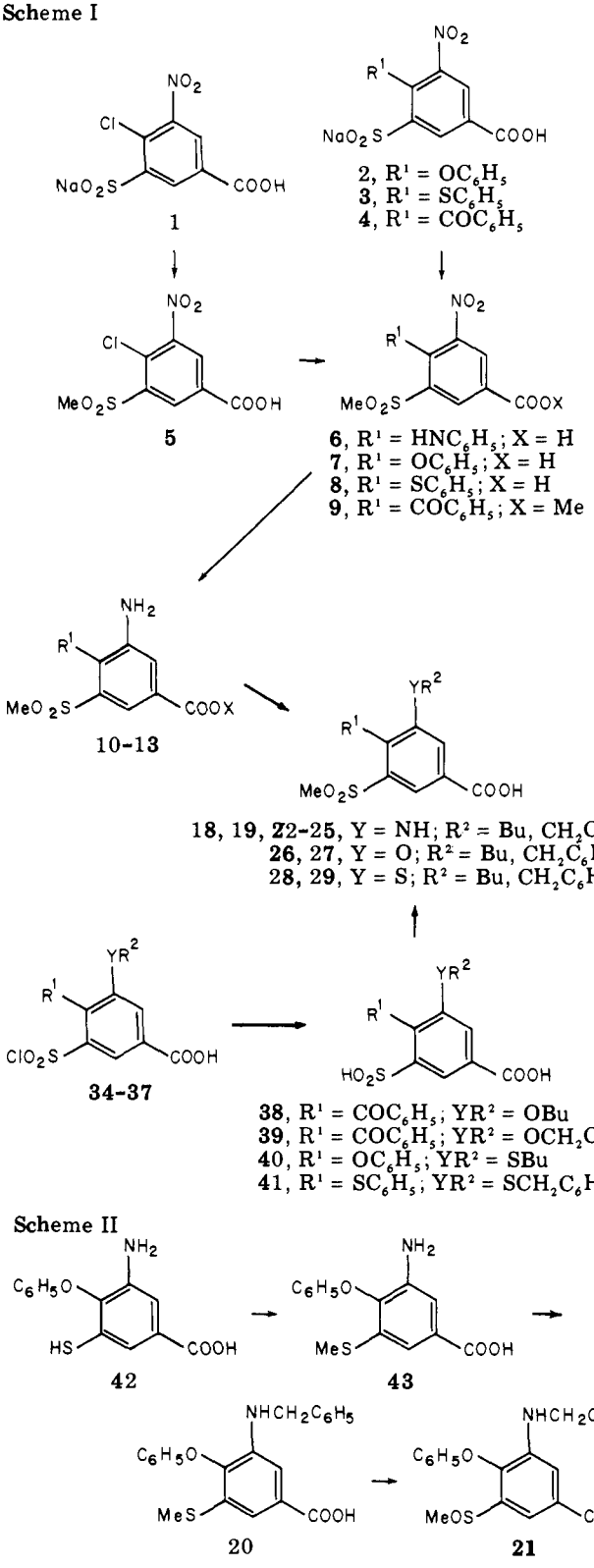
Novello et al.[1] reported that replacement of the methylsulfonyl group for either sulfamoyl group in the diuretically active 5-chloro-2,4-disulfamoylaniline and for the 7-sulfamoyl group in both 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide (chlorothiazide) and its 3,4-dihydro compound (hydrochlorothiazide) leads to weakly or inactive compounds, respectively. The present paper deals with the effect of a similar replacement in a series of 2,4- and 3,4-disubstituted 5-sulfamoylbenzoic acids selected from the recently described class of high-ceiling diuretics.[2-6]

In addition we prepared one of the corresponding 5-methylthio- and one 5-methylsulfinylbenzoic acid derivative. Furthermore, in connection with our studies on the structural requirements for high-ceiling diuretic activity, we synthesized 4-benzylamino- and 4-*n*-butylamino-6-carboxy-3-phenylbenzo[*b*]thiophene 1,1-dioxide.

Chemistry. The preparation of the 3,4-disubstituted 5-methylsulfonylbenzoic acids **18**, **19**, and **22–29** (Table I) is outlined in Scheme I. The 5-methylthio- and 5-methylsulfinylbenzoic acids **20** and **21** were provided as given in Scheme II. For details see the Experimental Section.

The N-alkylated 4-substituted methylsulfonylanthranilic acids **30–33** (Table I) were obtained by successive replacement of the halogens in the methylsulfonylbenzoic acid derivative **14** as shown in Scheme III. **14** is easily available from 2-chloro-5-chlorosulfonyl-4-fluorobenzoic acid (**44**). The 4-benzoyl-5-methylsulfonylbenzoic acid derivatives readily undergo internal aldol condensation in aqueous alkaline solution to the corresponding 6-carboxy-2,3-dihydro-3-hydroxy-3-phenylbenzo[*b*]thiophene 1,1-dioxides. This reaction was utilized for the preparation of the 4-alkylamino-6-carboxy-3-phenylbenzo[*b*]thiophene

Scheme I

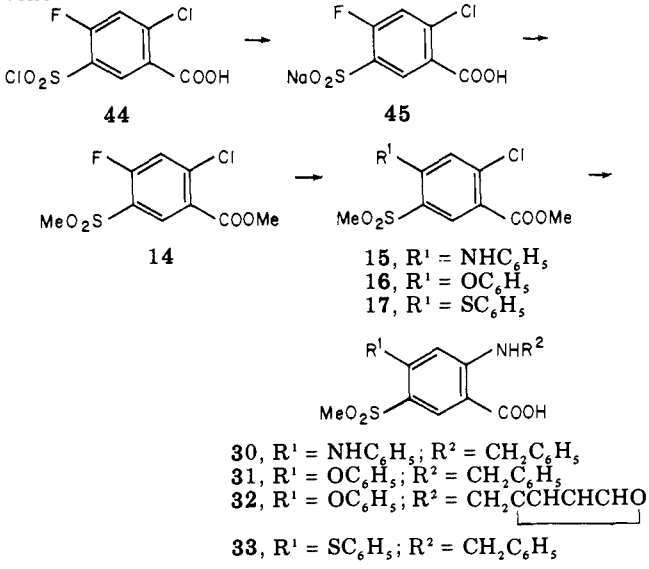


Scheme II

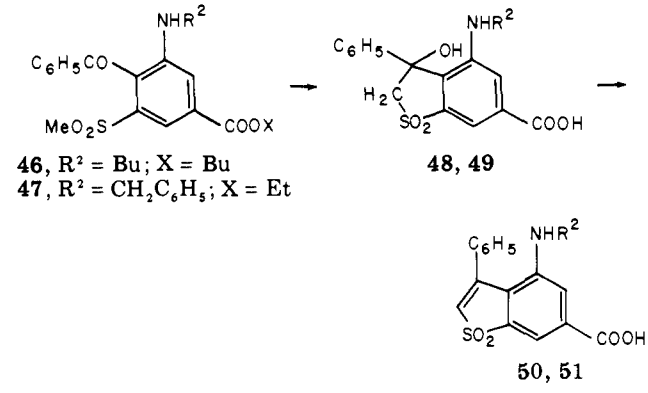
1,1-dioxides **50** and **51** as shown in Scheme IV.

Diuretic Effect and Structure-Activity Relationship. The 2,4- and 3,4-disubstituted 5-methylsulfonylbenzoic acids **18**, **19**, and **22-33** as well as the 5-methylthio- and 5-methylsulfinylbenzoic acids **20** and **21** were screened for their diuretic properties in dogs. The urinary volume and electrolyte excretion from the 3-h test period are summarized in Table I and compared with those of 3-*n*-butylamino-4-phenoxy-5-sulfamoylbenzoic acid (bumetanide) and *N*-(2-furylmethyl)-4-phenoxy-5-sulfamoylanthranilic acid. In order to avoid any internal aldol condensation the solid 3-substituted 4-benzoyl-5-methylsulfonylbenzoic acids **24-27** were administered orally.

Scheme III



Scheme IV

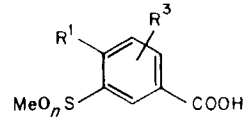


Many of the 5-methylsulfonylbenzoic acid derivatives show considerable diuretic activity. In respect to diuretic pattern, these compounds resemble the previously reported corresponding sulfamoylbenzoic acids.[2-6] However, substitution of the sulfamoyl group by the spatially and sterically similar methylsulfonyl group has led generally to decreased potency resulting for **18**, **29-31**, and **33** in inactivity at the dose tested. Substitution of the methylthio or the methylsulfinyl group for the methylsulfonyl group in the highly potent benzoic acid derivative **22** resulted in **20** and **21** with considerably less potency. Sprague and co-workers[7] have independently synthesized **19**, **22**, and 4-chloro-*N*-(2-furylmethyl)-5-methylsulfonylanthranilic acid, the latter corresponding to furosemide, and found these compounds to have diuretic activity.

It is of interest that some of the methylsulfonyl analogues of high-ceiling sulfamoylbenzoic acid diuretics show pronounced diuretic activity while the methylsulfonyl analogues of chlorothiazide and hydrochlorothiazide are reported to be inactive.[1] This could be taken as a further principal difference in the structural requirements for these two types of diuretics.[8]

The 4-alkylamino-6-carboxy-2,3-dihydro-3-hydroxy-3-phenylbenzo[*b*]thiophene 1,1-dioxides **48** and **49** as well as their respective dehydration products **50** and **51** were inactive after iv administration of 1 mg/kg. These compounds have initially been prepared due to their structural relationship to the corresponding 6-carboxy-

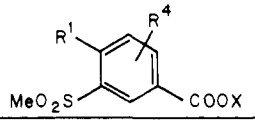
Table I. Physical Properties and Diuretic and Saluretic Activity of



No.	R^1	R^3 (NHR^2, OR^2, SR^2)	n	Method[b]	Mp, °C[c]	Recrystn solvent[d]	Yield,[e] %	Formula[f]	Treatment,[g] mg/kg	Urinary excretion[a] ml/kg/3 hr in H_2O	Urinary excretion[a] mequiv/kg/3 hr Na^+	K^+	Cl^-
						R^3 in 3 position							
18	NHC_6H_5	$NHCH_2C_6H_5$	2	J	208-209	Aq EtOH	43	$C_{21}H_{20}N_2O_4S$	0.25	As control			
19	OC_6H_5	NH-*n*-Bu	2	K	222-224	Aq EtOH	17	$C_{18}H_{22}NO_5S^h$	1	15	2.1	0.22‡	2.7
									0.1	3	0.6	0.19‡	0.4
20	OC_6H_5	$NHCH_2C_6H_5$	0	L	220-222	Aq EtOH	18	$C_{21}H_{19}NO_3S^h$	1	7	0.6	0.21‡	0.9
21	OC_6H_5	$NHCH_2C_6H_5$	1	M	200-201	Aq EtOH	41	$C_{21}H_{19}NO_4S$	1	7	0.9	0.17†	1.1
22	OC_6H_5	$NHCH_2C_6H_5$	2	J	247-248	EtOH	29	$C_{21}H_{19}NO_5S$	1	31	4.8	0.98	5.1
									0.25	21	3.0	0.99	3.5
									0.1	9	1.1	0.20‡	1.4
23	SC_6H_5	$NHCH_2C_6H_5$	2	J	196-198	Aq EtOH	26	$C_{21}H_{19}NO_4S_2^h$	1	17	2.0	0.28	2.4
									0.25	6	0.9	0.18†	1.0
24	COC_6H_5	NH-*n*-Bu	2	N	169-171	Aq EtOH	15	$C_{19}H_{21}NO_5S^i$	0.25 po	9	0.9	0.19†	1.2
25	COC_6H_5	$NHCH_2C_6H_5$	2	O	169-170	Aq EtOH	22	$C_{22}H_{19}NO_5S \cdot 0.5H_2O^i$	1 po	33	3.9	0.64	4.7
									0.1 po	12	1.2	0.28	1.7
26	COC_6H_5	O-*n*-Bu	2	P	211-212	Aq MeOH	33	$C_{19}H_{20}O_6S$	1 po	24	2.6	0.54	3.4
									0.1 po	4	0.5	0.22‡	0.8
27	COC_6H_5	$OCH_2C_6H_5$	2	P	223-224	Aq MeOH	11	$C_{22}H_{18}O_6S^h$	0.1 po	11	1.2	0.25	1.7
28	OC_6H_5	S-*n*-Bu	2	P	187-190	Aq MeOH	35	$C_{18}H_{20}O_5S_2^h$	1	21	3.0	0.64	3.2
									0.1	As control			
29	SC_6H_5	$SCH_2C_6H_5$	2	P	218-220	Aq MeOH	12	$C_{24}H_{18}O_4S_3^{h,j}$	1 po	As control			
						R^3 in 2 position							
30	NHC_6H_5	$NHCH_2C_6H_5$	2	Q	234-236	Me cellosolve	34	$C_{21}H_{20}N_2O_4S$	10	As control			
31	OC_6H_5	$NHCH_2C_6H_5$	2	Q	210-212	Aq EtOH	28	$C_{21}H_{19}NO_5S$	10	As control			
32	OC_6H_5	$NHCH_2CCHCHCHO$	2	Q	239-241	*k*	27	$C_{19}H_{17}NO_6S$	1	14	1.7	0.39	2.0
33	SC_6H_5	$NHCH_2C_6H_5$	2	Q	263-264	Me cellosolve	48	$C_{21}H_{19}NO_4S_2$	10	As control			
3-*n*-Butylamino-4-phenoxy-5-sulfamoylbenzoic acid (bumetanide)[m]									0.25	39[l] ± 12	4.0[l] ± 1.4	0.84[l] ± 0.38	5.7[l] ± 0.61
									0.1	26[l] ± 8.3	2.4[l] ± 0.4	0.44[l] ± 0.11	3.5[l] ± 0.8
									0.1 po	31[l] ± 7.6	3.3[l] ± 0.9	0.49[l] ± 0.16	4.5[l] ± 1.4
									0.01	10[l] ± 4.8	0.92[l] ± 0.42	0.27[l] ± 0.05	1.4[l] ± 0.5
N-(2-Furylmethyl)-4-phenoxy-5-sulfamoylanthranilic acid[n]									0.1	25	2.9	0.45	3.8
									0.01	8	0.6	0.27	0.8
Control										0.93[l] ± 0.35	0.10[l] ± 0.02	0.16[l] ± 0.01	0.08[l] ± 0.02

[a] The procedure is described in ref 9. In this reference the term metanilic acid has been used erroneously for 3-aminobenzoic acid throughout; when not otherwise stated, single test only. Values not significantly different from controls (one-sided 95% confidence limits) are marked with ‡. Where three or more tests were performed the average ± SD of the mean is given. [b] The letters relate to the general procedures given in the Experimental Section. [c] The yield of the analytically pure compound is given, and in most cases no attempts were made to optimalize the yields. [d] The procedure is given in the Expermental Section. [e] Several recrystallizations were usually performed, if necessary, while treating with decolorizing C. [f] The compounds were analyzed for C, H, and, if present, N and H_2O. 24-33 were additionally analyzed for S. Analytical results are within 0.4% of the theoretical values unless otherwise stated. Except when otherwise stated, the compounds were dried in air. [g] When not otherwise stated, iv injection in NaOH solution. [h] Dried in vacuo (10–14 mm) at 115 °C for several hours. [i] Dried in vacuo (10–14 mm) for 24 h in the presence of P_2O_5. [j] S: calcd, 22.34; found, 21.90. [k] Recrystallized from a mixture of EtOH (four parts) and methyl cellosolve (one part). [l] Average of four tests. [m] See ref 3. [n] See ref 4.

Table II. Physical Properties of



No.	R^1	R^4	X	Method[a]	Mp, °C[b]	Recrystn solvent[c]	Yield,[d] %	Formula[e]
					R^4 in 3 position			
5	Cl	NO_2	H	A	195–196 dec	*f*	54	$C_8H_6ClNO_6S$[g]
6	NHC_6H_5	NO_2	H	B	278–279 dec	Aq Me_2CO	82	$C_{14}H_{12}N_2O_6S$
7	OC_6H_5	NO_2	H	C	240–242 dec	MeOH	47	$C_{14}H_{11}NO_7S$
8	SC_6H_5	NO_2	H	D	291–293 dec	*f*	65	$C_{14}H_{11}NO_6S_2$
9	COC_6H_5	NO_2	Me	E	216–218[h]	Me cellosolve	32	$C_{16}H_{13}NO_7S$
10	NHC_6H_5	NH_2	H	F	238 dec	Aq EtOH	33	$C_{14}H_{14}N_2O_4S$
11	OC_6H_5	NH_2	H	F	271–272 dec	Aq Me_2CO	29	$C_{14}H_{13}NO_5S$
12	SC_6H_5	NH_2	H	F	301–302 dec	Me cellosolve	38	$C_{14}H_{13}NO_4S_2$
13	COC_6H_5	NH_2	Me	G	171–173[h]	EtOH	34	$C_{16}H_{15}NO_5S$
					R^4 in 2 position			
14	F	Cl	Me	E	134–136[h]	MeOH	16	$C_9H_8ClFO_4S$
15	NHC_6H_5	Cl	Me	H	139–141	MeOH	38	$C_{15}H_{14}ClNO_4S$
16	OC_6H_5	Cl	Me	I	139–140[h]	MeOH	53	$C_{15}H_{13}ClO_5S$
17	SC_6H_5	Cl	Me	I	144–146[h]	MeOH	52	$C_{15}H_{13}ClO_4S_2$

[a] See footnote *b* in Table I. [b] See footnote *c* in Table I. [c] See footnote *d* in Table I. [d] See footnote *e* in Table I. [e] The compounds were analyzed for C, H, and, if present, Cl and N. **9** and **13–17** were additionally analyzed for S. Analytical results are within 0.4% of the theoretical values. Except when otherwise stated, the compounds were dried in vacuo (10–14 mm) at 115° for several hours. [f] See Experimental Section. [g] Not analyzed for Cl. [h] Dried in air.

3-phenyl-1,2-benzisothiazole 1,1-dioxides.[5] However, we have recently postulated that the diuretic effect of the latter compounds is attributable to an interaction of their corresponding 4-benzoyl-5-sulfamoylbenzoic acids with the receptor enabled by a dynamic equilibrium between the benzisothiazole dioxides and the benzoyl compounds in plasma.[2,5] Consequently, the lack of activity of **48–51** is not unexpected and demonstrates the stability of the internal aldol condensation products of the diuretically active 3-alkylamino-4-benzoyl-5-methylsulfonylbenzoic acid **24** and **25**.

Experimental Section

Technical assistance was given by Mrs. Hanne Hollensen, H. Dannacher, J. Stage Johansen, T. Parbst, and W. Schlichtkrull. Analyses were performed by G. Cornali and W. Egger of these laboratories. Melting points were corrected and taken in open glass capillaries using a Hershberg apparatus. For the typical compounds NMR spectra were taken by N. Rastrup Andersen on a Varian A-60A spectrometer. Spectral features were in accordance with structures. Analytical data are indicated only by symbols of the elements; analytical results obtained for those elements were within ±0.4% of the theoretical values.

4-R^1-5-Methylsulfonyl-3- (or 2-) R^4-benzoic Acids and Methyl 4-R^1-5-Methylsulfonyl-3- (or 2-) R^4-benzoates 5–17 (Table II). Method A. A mixture of 1[6] (10 g, 34.7 mmol; H_2O of crystallization removed by drying in vacuo at 78°), MeI (50 ml), and MeOH (300 ml) was kept in an oil bath of 50° for 16 h. Excess MeI was distilled off and after cooling crude **5** precipitated by addition of H_2O (600 ml) followed by addition of 4 N HCl until pH 2. The precipitate was dissolved in hot 1 N $NaHCO_3$ (40 ml), followed by addition of saturated NaCl (10 ml). Cooling precipitated the Na salt of **5**. It was redissolved in hot H_2O and 4 N HCl added until pH 2 to precipitate **5**.

Method B. A stirred mixture of **5** (3 g, 10.7 mmol), $C_6H_5NH_2$ (3 g, 32.2 mmol), and H_2O (40 ml) was refluxed for 1.5 h. After cooling the precipitated material was collected and washed with 1 N HCl to yield **6**.

Method C. A mixture of 2[6] (8 g, 23.2 mmol; H_2O of crystallization removed by drying in vacuo at 78°), MeI (40 ml), and MeOH (300 ml) was kept in an oil bath of 50° for 16 h. Excess MeI was distilled off and after cooling **7** precipitated by addition of H_2O (500 ml).

Method D. A mixture of 3[6] (14 g, 38.7 mmol; H_2O of crystallization removed by drying in vacuo), MeI (70 ml), and MeOH (700 ml) was kept in an oil bath of 50° for 24 h. Cooling precipitated crude **8**. It was dissolved in hot 1 N $NaHCO_3$ (160 ml). Cooling precipitated the sodium salt of **8**. It was recrystallized from H_2O and redissolved in H_2O (300 ml), and **8** was liberated by addition of 4 N HCl until pH 2.

Method E. 4-Benzoyl-5-chlorosulfonyl-3-nitrobenzoic acid[5] or 44[10] was reduced with Na_2SO_3 essentially according to a procedure described in ref 6. After drying in vacuo at 115° to remove H_2O of crystallization, the obtained crude **4** or **45** was added to a solution of NaOMe (1 mmol/mmol of **4** or **45**) in MeOH (10 ml/g of **4** or **45**) followed by MeI (about 3 ml/g of **4** or **45**), and the mixture was refluxed for 20–40 h. On cooling crude **9** or **14** separated.

Method F. A hot solution of the appropriate nitrobenzoic acid in diluted NH_3 (about 12% in H_2O; 10 ml/mmol of nitrobenzoic acid) was combined with a hot aqueous solution of $FeSO_4 \cdot 7H_2O$ (7 mmol/mmol of nitrobenzoic acid in about 30 ml of H_2O). The reaction mixture was heated on a steam bath for 10–20 min and thereafter filtered hot. After cooling the crude reaction product was precipitated from the filtrate by addition of 4 N HCl until pH 2.

Method G. **9** was reduced with $Na_2S_2O_4$ according to a described procedure (see ref 5, method E) except that the heating following acidification was omitted.

Method H. A solution of **14** (2.7 g, 10 mmol) and $C_6H_5NH_2$ (5.0 ml, 55 mmol) in MeOH (25 ml) was refluxed for 18 h. After cooling and dilution with H_2O (25 ml) crude **15** separated.

Method I. **14** was allowed to react by using a described method (see ref 4, method F), except that *t*-BuOH was used as solvent instead of EtOH and that the reaction time was decreased to 3 h.

3-Amino-5-methylthio-4-phenoxybenzoic Acid (43). To a solution of 3-amino-5-mercapto-4-phenoxybenzoic acid (42,[6] 2.61 g, 10 mmol) in 1 N $NaHCO_3$ (30 ml) a solution of MeI (5.68 g, 40 mmol) in a mixture of EtOH (40 ml) and H_2O (10 ml) was added. The mixture was stirred for 5 min at room temperature, whereafter the excess MeI and EtOH were removed in vacuo. H_2O (30 ml) was added, and after filtration the filtrate was adjusted to pH 2 by addition of 4 N HCl to precipitate crude **43**. It was recrystallized from aqueous EtOH and dried in vacuo at 78° to yield **43** (68%), mp 195–196°. Anal. ($C_{14}H_{13}NO_3S$) C, H, N.

4-R^1-3-R^3-5-MeO_nS-Benzoic Acids 18–29 (Table I). Method J. The appropriate 4-R^1-3-amino-5-methylsulfonylbenzoic acid was benzylated using the process of ref 3, method 3A. The precipitated ethyl 4-R^1-3-benzylamino-5-methylsulfonylbenzoate was once recrystallized from EtOH and saponified by heating in a mixture of 1 N NaOH (4 ml/mmol of benzoate) and EtOH (6 ml/mmol of benzoate) on a steam bath for 30 min. The resulting solution was cooled, and 1 N HCl (4 ml/mmol of benzoate) was added to precipitate the crude material.

Method K. **11** was butylated adapting a method described in ref 9, method L. After the saponification process the aqueous

layer was separated and the organic layer several times washed with H_2O. The combined aqueous solutions were adjusted to pH 2.5 by addition of 4 N HCl. Precipitated crude **19** was redissolved in hot 1 N $NaHCO_3$ (3 ml/g of **19**). On cooling the Na salt of **19** precipitated. After recrystallization from H_2O (3 ml/g of Na salt) it was redissolved in H_2O (30 ml/g of Na salt), and crude **19** precipitated by addition of 4 N HCl until pH 2.5.

Method L. **43** was benzylated using the process of ref 3, method 3A. Thereafter 1 N NaOH (4 ml/mmol of methylthiobenzoic acid) was added, and the mixture was heated on a steam bath for 30 min. EtOH was removed by evaporation in vacuo, H_2O (4 ml/mmol of methylthiobenzoic acid) was added, and the mixture was extracted twice with Et_2O. The aqueous layer was adjusted to pH 3 by addition of 4 N HCl to precipitate crude **20**.

Method M. A mixture of **20** (0.45 g, 1.23 mmol), AcOH (6 ml), and H_2O_2 (30% aqueous solution, 1.5 ml) was stirred for 4 h at room temperature to precipitate crude **21**.

Method N. **13** was butylated and reesterified adapting a method described in ref 9, method L. The reaction mixture was evaporated in vacuo and the residue triturated with 1 N $NaHCO_3$. The obtained crude *n*-Bu ester of **24** was hydrolyzed by refluxing with a mixture of AcOH (4 ml/g of ester) and concentrated HCl (1 ml/g of ester) for 18 h. Cooling and dilution with H_2O precipitated an oil, which was partitioned between Et_2O and 1 N $NaHCO_3$. Acidification of the aqueous layer precipitated crude **24**.

Method O. **13** was benzylated and reesterified adapting a method described in ref 3, method 3A. The precipitated crude Et ester of **25** was hydrolyzed adapting method N. Crude **25** crystallized on cooling and dilution with H_2O.

Method P. A dry mixture of the appropriate 5-chlorosulfonylbenzoic acid **34–37**[11] (20 mmol) and Na_2SO_3 (7.56 g, 60 mmol) was, during 30–60 min, added in portions to stirred H_2O (45 ml) while keeping the temperature at 10–15° and maintaining the pH at 8 by addition of 2 N NaOH via an automatical end point titrator. After the NaOH uptake had ceased, the reaction mixture was filtered, and after cooling the crude 4-R^1-3-R^3-5-sulfinobenzoic acid precipitated by addition of concentrated HCl (20 ml). For purification **38** or **39** was redissolved in H_2O (70 ml) by addition of 1 N NaOH until pH 3.5. The solution was extracted twice with Et_2O (50 ml) and **38** (69%) or **39** (32%) precipitated from the aqueous layer by addition of concentrated HCl (20 ml). Crude **40** containing traces of the corresponding Na salt was dissolved in 80% aqueous EtOH (40 ml). After filtration and addition of 4 N HCl (80 ml), EtOH was distilled off in vacuo to precipitate **40** (82%). Crude **41** was washed with Et_2O and recrystallized from aqueous EtOH to yield **41** (57%). A mixture of the appropriate dried sulfinobenzoic acid **38–41** (2 mmol), MeI (20 ml), and MeOH (5 ml) containing MeONa (2 mmol) was refluxed for 3 h followed by evaporation in vacuo. The residue was dissolved in 1 N $NaHCO_3$ (25 ml) and the solution extracted twice with Et_2O (20 ml). Acidification of the aqueous layer with 4 N HCl until pH 2 precipitated the crude methylsulfonylbenzoic acid.

4-R^1-2-R^3-5-Methylsulfonylbenzoic Acids 30–33 (Table I). Method Q. A mixture of the appropriate methyl 4-R^1-2-chloro-5-methylsulfonylbenzoate and benzylamine or for **32** 2-furfurylamine (4 ml/g of 2-chloro derivative) was heated on a steam bath for 2.5–3 h or in the case of **30** for 22 h. The resulting solution was poured into an excess of ice-cold 4 N AcOH to precipitate the crude methyl 4-R^1-2-R^3-methylsulfonylbenzoates, which were saponified essentially according to method I.

4-*n*-Butylamino-6-carboxy-2,3-dihydro-3-hydroxy-3-phenylbenzo[*b*]thiophene 1,1-Dioxide (48). A mixture of the crude *n*-Bu ester **46** (prepared from 5.0 g, 15 mmol, of **13** as described under method N), 2 N NaOH (20 ml), and EtOH (10 ml) was refluxed for 10–15 min. After charcoaling crude **48** was precipitated by acidification with concentrated HCl. Redissolving in hot saturated $NaHCO_3$ (10 ml/g of crude **48**) and cooling precipitated the Na salt of **48**. It was dissolved in hot H_2O and **48** precipitated by acidification with 4 N HCl. Recrystallization twice from aqueous EtOH while charcoaling yielded **48** (32% based on **13**), mp 211–214°. Anal. ($C_{19}H_{21}NO_5S$) C, H, N, S.

4-Benzylamino-6-carboxy-2,3-dihydro-3-hydroxy-3-phenylbenzo[*b*]thiophene 1,1-Dioxide (49). A mixture of the crude Et ester **47** (7.4 g, 17 mmol; prepared from **13** as described under method O), 2 N NaOH (75 ml), and EtOH (30 ml) was refluxed for 30 min. **49** was obtained via the Na salt as described for the preparation of **48**. Recrystallization twice from aqueous EtOH yielded **49** (52%), mp 163–165°. Anal. ($C_{22}H_{19}NO_5S \cdot 0.5H_2O$) C, H, N, S; H_2O: calcd, 2.15; found, 2.74.

4-*n*-Butylamino-6-carboxy-3-phenylbenzo[*b*]thiophene 1,1-Dioxide (50). A mixture of **48** (1.0 g, 2.7 mmol) and concentrated H_2SO_4 (15 ml) was stirred at room temperature for 20 h. Dilution with ice–H_2O (about 50 ml) precipitated crude **50**. Recrystallization from aqueous EtOH yielded **50** (71%), mp 202–205°. Anal. ($C_{19}H_{19}NO_4S \cdot H_2O$) C, H, N, S; H_2O: calcd, 4.79; found, 5.21.

4-Benzylamino-6-carboxy-3-phenylbenzo[*b*]thiophene 1,1-Dioxide (51). **49** was dehydrated adapting the method described for the preparation of **50**. Recrystallization twice from EtOH yielded **51** (33%), mp >300°. Anal. ($C_{22}H_{17}NO_4S \cdot C_2H_5OH$) C, H, N, S.

Acknowledgment. The authors wish to express their appreciation to C. Kaergaard Nielsen and M. P. Magnussen for the diuretic screening of the compounds described in this paper.

References and Notes

(1) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 965, 970 (1960).
(2) O. B. T. Nielsen, H. Bruun, C. Bretting, and P. W. Feit, *J. Med. Chem.*, 18, 41 (1975) (paper 7).
(3) P. W. Feit, *J. Med. Chem.*, 14, 432 (1971).
(4) P. W. Feit and O. B. T. Nielsen, *J. Med. Chem.*, **15**, 79 (1972).
(5) O. B. T. Nielsen, C. K. Nielsen, and P. W. Feit, *J. Med. Chem.*, 16, 1170 (1973).
(6) P. W. Feit, O. B. T. Nielsen, and H. Bruun, *J. Med. Chem.*, 17, 572 (1974).
(7) J. M. Sprague, Merck Sharp & Dohme Research Laboratories, West Point, Pa., personal communication.
(8) P. W. Feit, O. B. T. Nielsen, and H. Bruun, *J. Med. Chem.*, **15**, 437 (1972).
(9) P. W. Feit, H. Bruun, and C. K. Nielsen, *J. Med. Chem.*, 13, 1071 (1970).
(10) K. Sturm, W. Siedel, R. Weyer, and H. Ruschig, *Chem. Ber.*, **99**, 328 (1966).
(11) The crude intermediate from the preparation of the corresponding sulfamoylbenzoic acid was used.[2,6]