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Aminobenzoic Acid Diuretics. 3.[1] 4-Substituted 5-Sulfamylanthranilic Acid Derivatives

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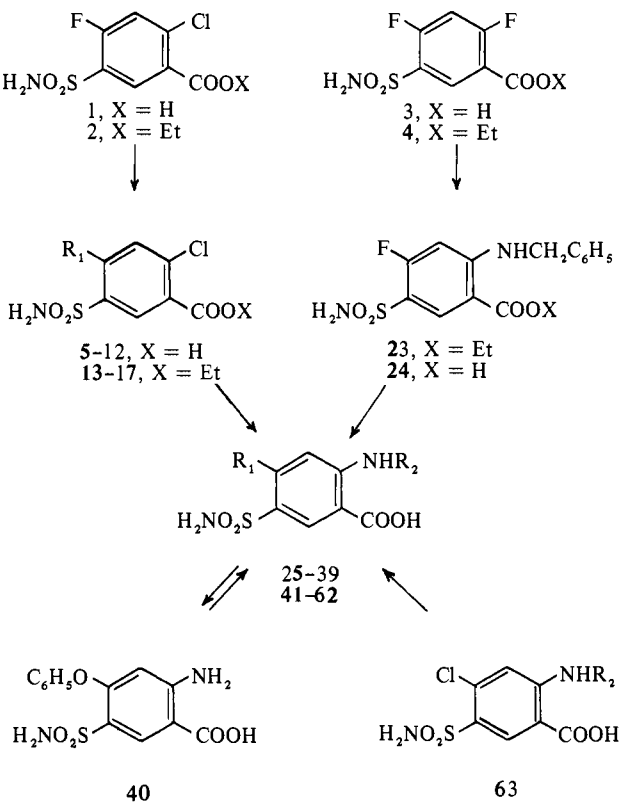
The synthesis of 37 N-alkylated 4-substituted 5-sulfamylanthranilic acids by partial and successive replacement reactions of the halogens in the 2,4-dihalogeno-5-sulfamylbenzoic acids is described. Reasons for the interest in these new anthranilic acid derivatives are discussed. Diuretic screening results for some of the compounds are summarized and compared with those of 3 selected 4-chloro-5-sulfamylanthranilic acid derivatives. The data have revealed that many of the new 4-R_1-*N*-R_2-5-sulfamylanthranilic acids are much more potent diuretics than the corresponding 4-Cl compounds. **55** (R_1 = OC_6H_5; R_2 = 2-furylmethyl) was the most potent compound having a level of activity and diuretic profile similar to that of bumetanide, recently described as a "high-ceiling" diuretic. *N*-*n*-Butyl-4-phenoxy-3-sulfamylanthranilic acid (**70**) prepared as a representative of the third isomeric aminosulfamylbenzoic acid series was devoid of diuretic activity.

In the preceding paper[1] of this series the synthesis of several 4-substituted 3-amino-5-sulfamylbenzoic acid derivatives and their diuretic properties were reported. Certain of these compounds were shown to be much more potent than the corresponding N-substituted 3-amino-4-chloro-5-sulfamylbenzoic acid diuretics.†[2] In the course of investigating the structure-activity relationship of high-ceiling diuretics we became concerned over the question of whether an analogous alteration of the 4-substituent in 4-chloro-*N*-(2-furylmethyl)-5-sulfamylanthranilic acid[3,4] (furosemide) and the related 4-chloroanthranilic acid diuretics[4] would increase their potency.

Furthermore it seemed justified to synthesize the *N*-*n*-butyl-4-phenoxy-3-sulfamylanthranilic acid (**70**) as a representative of the third possible isomeric 4-substituted aminosulfamylbenzoic acid derivatives in which the sulfonamide group still remains in the meta position to the carboxyl. Our choice of phenoxy to be the 4 substituent was prompted by the unusual potency and efficacy afforded by this substituent in both the 3-amino-5-sulfamylbenzoic acid derivatives[1] and the 5-sulfamylanthranilic acid series described in the present paper.

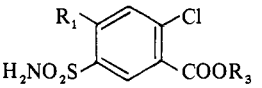
Chemistry. Different synthetic approaches (Scheme I) were used for the preparation of the 4-substituted *N*-R_2-5-sulfamylanthranilic acids[5] listed in Table III. The routes are based mainly on partial and successive replacement reactions of the halogens in various 2,4-dihalogeno-5-sulfamylbenzoic acids and are an extension of the described reactions of 2,4-dichloro- and 2-chloro-4-fluoro-5-sulfamylbenzoic acid (**1**) with different amines.[4] The most attractive route from the known 4-chloro-5-sulfamylanthranilic acid diuretics **63** was found to be only of limited application as the reactivity of the halogen atom is diminished by the aminofunction in the 2 position. It was therefore more advantageous to use 2-chloro-4-fluoro-5-sulfamylbenzoic acid (**1**) or its Et ester **2** as starting material. After reaction of the intermediate 4-R_1-2-chloro-5-sulfamylbenzoic acids (**5-12**) and esters (**13-17**) (Table I) with different amines the 4-R_1-*N*-R_2-5-sulfamyl-

Scheme I



†In ref 2 the term metanilic acid has been used erroneously for 3-aminobenzoic acid throughout.

Table I. Physical Properties of



No.	R_1	R_3	Method[a]	Mp, °C	Recrystn solvent[b]	Yield,[c] %	Formula	Analysis[d]
5	NHC_6H_5	H	A	233-233.5	Aq MeCN	26	$C_{13}H_{11}ClN_2O_4S$	C, H, Cl, N, S
6	SC_6H_5	H	B	258.5-260	MeCN	30	$C_{13}H_{10}ClNO_4S_2$	H, N, S; C,[e] Cl[f]
7	SC_6H_4, 3-Me	H	B	230-231	EtOH-H_2O	26	$C_{14}H_{12}ClNO_4S_2$	C, H,* N;* Cl,[g] S[h]
8	$SCH_2CH_2C_6H_5$	H	B	(201-202)	(Aq EtOH)	(32)	$C_{15}H_{14}ClNO_4S_2$	*i*
9	$OCH_2CH_2OCH_3$	H	C	216-218	MeCN	37	$C_{10}H_{12}ClNO_6S$	C, H, Cl, N, S
10	O-*n*-Bu	H	D	175-176	Aq EtOH	40	$C_{11}H_{14}ClNO_5S \cdot H_2O$	C, H, Cl, N, S
11	OC_6H_5	H	E	206.5-207.5	EtAc-petroleum ether[j]	35	$C_{13}H_{10}ClNO_5S$	C, H, Cl, N, S
12	OC_6H_4, 3-CF_3	H	E	242-244	Aq EtOH	23	$C_{14}H_9ClF_3NO_5S$	C, H, Cl, N, S
13	S-*n*-Bu	Et	F	99-101	Aq EtOH	33	$C_{13}H_{18}ClNO_4S_2$	C, H, Cl, N, S
14	SC_6H_4, 4-NHAc	Et	F	234-235	Methylcellosolve	72	$C_{17}H_{17}ClN_2O_5S_2$	C, H, Cl, N, S
15	OC_6H_4, 4-Cl	Et	F	142-143	Aq EtOH	63	$C_{15}H_{13}Cl_2NO_5S$	C, H, Cl, N, S
16	OC_6H_4, 2-F	Et	F	139-140	Aq EtOH	43	$C_{15}H_{13}ClFNO_5S$	C, H, Cl, N, S
17	O-β-naphthyl	Et	F	172-173	Aq EtOH	46	$C_{19}H_{16}ClNO_5S$	C, H, Cl, N, S

[a]The letters relate to the general procedure given in the Experimental Section. [b]Several recrystn were usually performed, if necessary while treating with decolorizing C. [c]The yield of the anal, pure compd is given, and in most cases no attempts were made to optimalize the yield. The compds were dried in air. [d]Where anal. are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.25% of the theoretical values or when marked with asterisk within ±0.4% of the theoretical values. [e]C: calcd 45.41; found 46.04. [f]Cl: calcd 10.31; found 9.64. [g]Cl: calcd 9.90; found 9.27. [h]S: calcd 17.91; found 17.33. [i]Not obtd anal. pure. [j]First purification by recrystn from aq EtOH.

anthranilic acids (Table III) were obtained directly or after saponification of their esters (**18-22**), summarized in Table II.

This sequence failed for the preparation of the 4-*n*-BuNH compound **25** as an aliphatic amino substituent in the 4 position markedly decreased the reactivity of the 2-Cl. **25** was therefore prepared from 2,4-difluoro-5-sulfamylanthranilic acid (**3**) through the *N*-R_2-4-fluoro-5-sulfamylanthranilic acid (**24**). The phenylsulfonyl derivative **33** was provided by H_2O_2 oxidation of the corresponding thioether **29**. The *N*-α-naphthylmethyl derivative **54** was prepared by alkylation of 4-phenoxy-5-sulfamylanthranilic acid (**40**) obtained by catalytic debenzylation of **41**.

The synthesis of *N*-*n*-butyl-4-phenoxy-3-sulfamylanthranilic acid (**70**) is summarized in Scheme II. The 2,5-dichloro-4-fluorobenzoic acid (**64**) was available by oxidation of the corresponding acetophenone. The structure of **70** is given by the synthetic route and was confirmed by nmr spectroscopy. For details and the nmr data of **70**, see the Experimental Section.

Diuretic Effect and Structure-Activity Relationships. The N-substituted 4-R_1-5-sulfamylanthranilic acids (Table III) prepared in this study were screened for their diuretic properties in dogs by a described procedure.[2] The urinary volume and electrolyte excretion following iv administration (soln in NaOH) were determined hourly. The onset of diuresis was observed within the first hour after injection and became, except for the most active compounds, almost negligible after 3 hr.

Quite early in the present work on the different 4-substituted anthranilic acid derivatives, it was found that, in

Scheme II

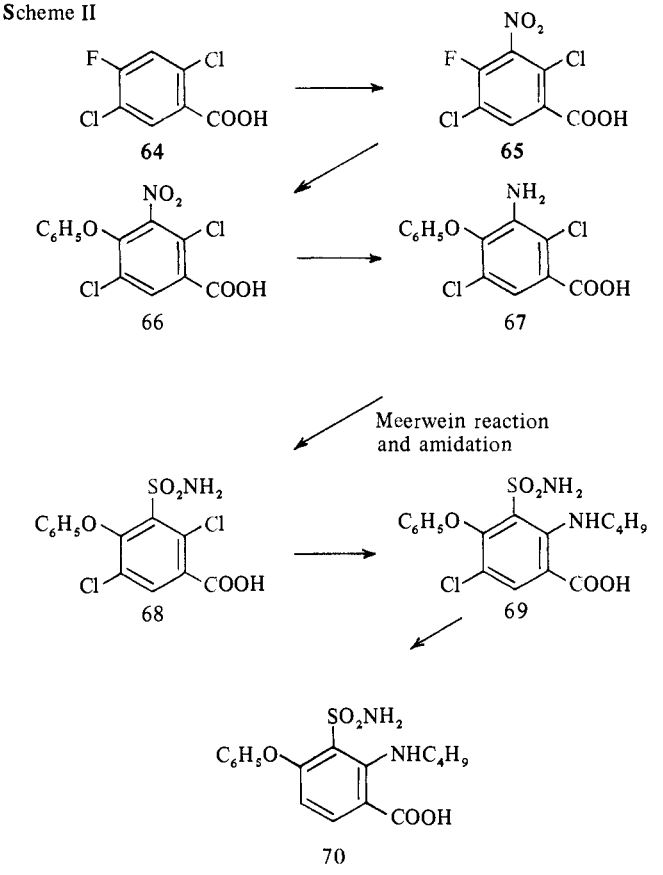
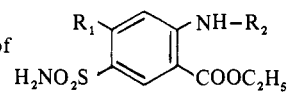


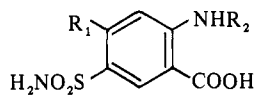
Table II. Physical Properties of



No.	R_1	R_2	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula	Analysis[d]
18	S-*n*-Bu	$CH_2C_6H_5$	G	180-182	EtOH	33	$C_{20}H_{26}N_2O_4S_2$	C, H, N, S
19	SC_6H_4, 4-NHAc	$CH_2C_6H_5$	G	237-238	Methylcellosolve	62	$C_{24}H_{25}N_3O_5S_2$	C, H, N, S
20	OC_6H_4, 4-Cl	$CH_2C_6H_5$	G	202-203	EtOH	40	$C_{22}H_{21}ClN_2O_5S$	C, H, Cl,* N, S
21	OC_6H_4, 2-F	$CH_2C_6H_5$	G	132-134	EtOH	17	$C_{22}H_{21}FN_2O_5S$	C, H, N, S
22	O-β-naphthyl	$CH_2C_6H_5$	G	189-190	EtOH[e]	30	$C_{26}H_{24}N_2O_5S$	C, H, N, S

[a-d]See corresponding footnotes in Table I. [e]First purification by recrystn from aq EtOH.

Table III. Physical Properties of



No.	R_1	R_2	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula	Analysis[d]
25	NH-*n*-Bu	$CH_2C_6H_5$	H	209–210 dec	*e*	17	$C_{18}H_{23}N_3O_4S$	C, H, N, S
26	NHC_6H_5	$CH_2C_6H_5$	I	221–222 dec	Aq methylcellosolve	14	$C_{20}H_{19}N_3O_4S$	C, H, N,* S
27	NHC_6H_5	*n*-Bu	I	197–197.5	EtOH	43	$C_{17}H_{21}N_3O_4S$	C, H, N, S
28	S-*n*-Bu	$CH_2C_6H_5$	J	236–237 dec	*e*	27	$C_{18}H_{22}N_2O_4S_2$	C, H, N, S
29	SC_6H_5	$CH_2C_6H_5$	K	245–247 dec	EtOH	31	$C_{20}H_{18}N_2O_4S_2$	C,* H, N, S
30	SC_6H_5	*n*-Bu	L	246–247 dec	Aq EtOH	9	$C_{17}H_{20}N_2O_4S_2$	C, H, S; N[f]
31	SC_6H_5	$CH_2CCHCHCHO$	M	245–246 dec	Methylcellosolve	26	$C_{18}H_{16}N_2O_5S_2$	C, H, N, S
32	SC_6H_5	$CH_2CCHNCHCHCH$	K	260–261.5 dec	Methylcellosolve	37	$C_{19}H_{17}N_3O_4S_2$	C, H, N, S*
33	$SO_2C_6H_5$	$CH_2C_6H_5$	N	290–291 dec	Methylcellosolve	29	$C_{20}H_{18}N_2O_6S_2$	C, H, N, S
34	SC_6H_4, 3-Me	$CH_2C_6H_5$	I	248–250 dec	*g*	29	$C_{21}H_{20}N_2O_4S_2$	C, H, N, S
35	SC_6H_4, 4-NHAc	$CH_2C_6H_5$	O	266–267 dec	Methylcellosolve-H_2O	14	$C_{22}H_{21}N_3O_5S_2$	C,* H, N, S
36	$SCH_2CH_2C_6H_5$	$CH_2C_6H_5$	I	234–236 dec	EtOH	17	$C_{22}H_{22}N_2O_4S_2$	C, H, N, S
37	$OCH_2CH_2OCH_3$	$CH_2C_6H_5$	K	213–214 dec	EtOH	40	$C_{17}H_{20}N_2O_6S$	C, H, N, S
38	O-*n*-Bu	$CH_2C_6H_5$	I	242–243 dec	Methylcellosolve	25	$C_{18}H_{22}N_2O_5S$	C, H, N, S
39	O-*n*-Bu	$CH_2CCHCHCHO$	P	222–222.5 dec	Aq EtOH	4[h]	$C_{16}H_{20}N_2O_6S$	C, H, N, S
40	OC_6H_5	H	Q	233–234 dec	Aq EtOH	71	$C_{13}H_{12}N_2O_5S$	C, H, N, S
41	OC_6H_5	$CH_2C_6H_5$	K	241.5–243	EtOH	26	$C_{20}H_{18}N_2O_5S$	C, H, N, S
42	OC_6H_5	$CH_2C_6H_4$, 2-Cl	I	258.5–259	EtOH	12	$C_{20}H_{17}ClN_2O_5S$	C, H, Cl, N, S
43	OC_6H_5	$CH_2C_6H_4$, 4-OMe	I	195–195.5 dec	EtOH	27	$C_{21}H_{20}N_2O_6S$	C, H, N, S
44	OC_6H_5	$CH_2C_6H_3$, 3,4-$(OMe)_2$	I	191–191.5	EtOH	30	$C_{22}H_{22}N_2O_7S$	C, H, N, S
45	OC_6H_5	$CH_2C_6H_4$, 3-Me	I	237–238 dec	EtOH	10	$C_{21}H_{20}N_2O_5S$	C, H, N, S
46	OC_6H_5	$CH_2CH_2CH_2N(CH_3)_2$	I	268–269 dec	H_2O	13	$C_{18}H_{23}N_3O_5S$	C, H, N, S
47	OC_6H_5	$CH_2CH_2CH_2OH$	I	191–192	Aq EtOH	34	$C_{16}H_{18}N_2O_6S$	C, H, N, S
48	OC_6H_5	$CH_2CH_2CH_2OCH_3$	I	189–190	Aq EtOH	43	$C_{17}H_{20}N_2O_6S$	C, H, N, S
49	OC_6H_5	$CH_2CH{=}CH_2$	R	229–230 dec	EtOH	5	$C_{16}H_{16}N_2O_5S$	C, H, N, S
50	OC_6H_5	*n*-Bu	L	217–219 dec	Aq EtOH	24	$C_{17}H_{20}N_2O_5S$	C, H, N, S
51	OC_6H_5	*i*-Bu	L	220–221 dec	EtOH	11[i]	$C_{17}H_{20}N_2O_5S$	C, H, N, S
52	OC_6H_5	*n*-Am	L	227–228 dec	EtOH	14[j]	$C_{18}H_{22}N_2O_5S$	C, H, N, S
53	OC_6H_5	$CH_2CH_2CH_2C_6H_5$	I	221–222 dec	Aq EtOH	10	$C_{22}H_{22}N_2O_5S$	C, H, N, S
54	OC_6H_5	CH_2-α-naphthyl	S	232–233 dec	*k*	23	$C_{24}H_{20}N_2O_5S$	C, H, N, S
55	OC_6H_5	$CH_2CCHCHCHO$	I	229–230 dec	EtOH	13	$C_{18}H_{16}N_2O_6S$	C, H, N, S
56	OC_6H_5	$CH_2CCHCHCHS$	I	222 dec	EtOH	8[l]	$C_{18}H_{16}N_2O_5S_2$	C, H, N, S
57	OC_6H_4, 4-Cl	$CH_2C_6H_5$	J	262–263 dec	EtOH	31	$C_{20}H_{17}ClN_2O_5S$	C, H, Cl, N, S
58	OC_6H_4, 2-F	$CH_2C_6H_5$	J	248–248.5	EtOH	39	$C_{20}H_{17}FN_2O_5S$	C, H, N, S
59	OC_6H_4, 3-OMe	$CH_2C_6H_5$	T	214.5–216	EtOH	5[m]	$C_{21}H_{20}N_2O_6S$	C, H, N, S
60	OC_6H_4, 3-CF_3	$CH_2C_6H_5$	I	226–227 dec	Aq EtOH	19	$C_{21}H_{17}F_3N_2O_5S$	C, H, N, S
61	OC_6H_4, 3-Me	$CH_2C_6H_5$	T	229.5–231 dec	EtOH	21[m]	$C_{21}H_{20}N_2O_5S$	C, H, N, S
62	O-β-naphthyl	$CH_2C_6H_5$	J	255–257 dec	EtOH	34	$C_{24}H_{20}N_2O_5S$	C, H, N, S

[a-d] See corresponding footnotes in Table I. [e] A mixt of EtOH (3 parts) and methylcellosolve (1 part) was used. [f] N: calcd 7.36; found 6.93. [g] A mixt of EtOH (3 parts) and methylcellosolve (2 parts) was used. [h] Yield over 3 steps. [i] Crude **51** (mp 216°) was obtd in 40% yield. [j] Crude **52** (mp 220°) was obtd in 55% yield. [k] A mixt of EtOH (3 parts), methylcellosolve (1 part), and H_2O (1 part) was used. [l] Crude **56** (mp 216–218°) was obtd in 35% yield. [m] Yield over 2 steps.

analogy to the diuretics of the known 4-chloro-5-sulfamylanthranilic acid derivatives, *N*-2-furylmethyl substitution has advantages over the *N*-benzyl substitution. However, for synthetic convenience and for making the results comparable, the N-benzylated anthranilic acid derivatives were prepared and tested in every case. This gave the influence of the substituent in the 4 position (R_1) and revealed that the diuretic potency in this series is somewhat more dependent on the nature of the 4 substituent than was observed for the recently reported 4-substituted 3-amino-5-sulfamylbenzoic acid derivatives. A special point of interest in this connection is that the 4-C_6H_5NH compound **26** although retaining significant activity at 1 mg/kg, was considerably less potent than the 4-C_6H_5S and 4-C_6H_5O compounds **29** and **41**, respectively. The corresponding isomers in the 3-aminobenzoic acid series equalled each other in their potency.

The urinary volume and electrolyte excretion from the 3-hr test period for those compounds resulting in a Na^+ excretion > 1.5 after iv administration of 1 mg/kg are summarized in Table IV, and compared with those of 3 selected anthranilic acid derivatives, including furosemide and 3-*n*-butylamino-4-phenoxy-5-sulfamyl benzoic acid (bumetanide). The data indicate that a departure from the Cl atom in the 4 position of the known anthranilic acid diuretics has led to a marked increase in diuretic and saluretic potency. The most interesting compound of the present series was **55** which was much more potent than furosemide both after iv and oral administration in the dog assay (Table IV). The high potency and the profile of diuretic action of **55** seems to be almost identical with that of bumetanide, recently described[1] as a "high-ceiling" diuretic.

The representative of the isomeric series, the *N*-*n*-butyl-4-phenoxy-3-sulfamylanthranilic acid (**70**) was completely devoid of activity.

Experimental Section

Analyses were performed by G. Cornali and W. Egger of these labs. Mp were cor and taken in open glass capillaries using a Hershberg apparatus. The nmr spectra were performed by N. Rastrup Andersen and obtained with a Varian Associates spectrophotometer, Model A-60-A. Anal. data are given as defined in footnote *d*, Table I; anal. results were within 0.25% or when marked with an asterisk, within 0.4% of calcd values. Technical assistance was given by Hanne G. Schmidt.

Ethyl 2-Chloro-4-fluoro-5-sulfamylbenzoate (2). 1[4] was esterified in EtOH using dry HCl as catalyst. It was recrystd from aq EtOH to yield **2** (78%), mp 135–137°. *Anal.* ($C_9H_9ClFNO_4S$) C, H, Cl, N, S.

2,4-Difluoro-5-sulfamylbenzoic Acid (3). The method described for the corresponding 2,4-dichloro compd[4] was adapted using 2,4-

Table IV. Diuretic and Saluretic Activity of Some *N*-R_2-4-R_1-5-Sulfamylanthranilic Acids in Dogs

Compd	R_1	R_2	Treatment,[b] mg/kg	Urinary excretion[d] ml/kg per 3 hr H_2O	mequiv/kg per 3 hr Na^+	K^+	Cl^-
Control[c]				2	0.2	0.13	0.13
29	SC_6H_5	$CH_2C_6H_5$	1	16	1.8	0.45	2.4
31	SC_6H_5	$CH_2CCHCHCHO$	2	40	4.3	0.95	5.9
			1	19	2.0	0.31	2.6
33	$SO_2C_6H_5$	$CH_2C_6H_5$	1	18	1.9	0.29	1.9
39	O-*n*-Bu	$CH_2CCHCHCHO$	1	21	2.7	0.32	3.2
41	OC_6H_5	$CH_2C_6H_5$	1	24	2.7	0.49	3.5
49	OC_6H_5	$CH_2CH{=}CH_2$	1	17	1.8	0.21	2.3
50	OC_6H_5	*n*-Bu	1	23	2.5	0.19	3.4
55	OC_6H_5	$CH_2CCHCHCHO$	1	43	5.0	0.8	6.4
			0.1	25	2.9	0.45	3.8
			0.01	8	0.6	0.27	0.8
			0.01 po	7	0.7	0.26	0.8
56	OC_6H_5	$CH_2CCHCHCHS$	1	39	4.1	0.72	5.6
57	OC_6H_4, 4-Cl	$CH_2C_6H_5$	1	15	1.6	0.15	2.4
58	OC_6H_4, 2-F	$CH_2C_6H_5$	1	21	2.0	0.34	3.0
61	OC_6H_4, 3-Me	$CH_2C_6H_5$	1	30	2.6	0.34	3.0
N-*n*-Butyl-4-chloro-5-sulfamylanthranilic acid[a]			10	18	1.8	0.59	2.9
			1	4	0.3	0.3	0.5
N-Benzyl-4-chloro-5-sulfamylanthranilic acid[e]			10	15	1.6	0.4	2.1
			1	5	0.4	0.21	0.7
N-(2-Furylmethyl)-4-chloro-5-sulfamylanthranilic acid (furosemide)[e]			10	33	3.7	0.8	4.8
			1	20	1.9	0.46	2.3
3-*n*-Butylamino-4-phenoxy-5-sulfamylbenzoic acid (bumetanide)[f]			0.25	39[g]	4.1[g]	0.8[g]	5.7[g]
			0.01	10[g]	1.0[g]	0.3[g]	1.4[g]

[a]The procedure is described by P. W. Feit, H. Bruun, and C. Kaergaard Nielsen, *J. Med. Chem.*, 13, 1071 (1970); when not otherwise stated single test only. [b]When not otherwise stated iv injection in NaOH soln. [c]Average of 3 tests. [d]See ref cited in footnote *a*. [e]K. Sturm, W. Siedel, R. Weyer, and H. Ruschig, *Chem. Ber.*, 99, 328 (1966). [f]P. W. Feit, *J. Med. Chem.*, 14, 432 (1971). [g]Average of 4 tests.

difluorobenzoic acid[6] as starting material. It was recrystd from aq EtOH to yield **3** (60%), mp 203.5–204.5°. *Anal.* ($C_7H_5F_2NO_4S$) C, H, N, S.

Ethyl **2,4-Difluoro-5-sulfamylbenzoate (4).** 3 was esterified as described for 1. It was recrystd from aq EtOH to yield **4** (84%), mp 133–135°. *Anal.* ($C_9H_9F_2NO_4S$) C, H, N, S.

4-R_1-2-Cl-5-Sulfamylbenzoic Acids (5–12, Table I). Method A. A stirred mixt of 1 (5.1 g), $C_6H_5NH_2$ (10 ml), and H_2O (10 ml) was refluxed for 18 hr. After cooling, satd $NaHCO_3$ (20 ml) was added, and the mixt was extd twice with Et_2O. Crude **5** was pptd from the aq layer by acidification with AcOH (10 ml).

Method B. A soln of 1 (0.01 mole), the appropriate R_1H (0.011 mole), and solid $NaHCO_3$ (5–6 g) in H_2O (25 ml) was heated on a steam bath for 5 hr (for **8** the reaction time was extended to 20 hr). The crude material was pptd from the cooled reaction mixt by acidification with concd HCl (6 ml).

Method C. 1 (2.55 g) was added to a stirred soln of $CH_3OCH_2CH_2ONa$ in $CH_3OCH_2CH_2OH$ (10 ml contg 0.7 g of Na), and the mixt was refluxed for 20 hr. After evapn *in vacuo*, H_2O (25 ml) and 4 *N* HCl (5 ml) were added, and the mixt was left at 5° for several hr. The pptd heavy oil was collected and crystd by trituration with aq MeCN to give crude **9**.

Method D. 1 (2.55 g) was added to a stirred soln of *n*-BuONa in *n*-BuOH (20 ml contg 0.7 g of Na) and the mixt was refluxed for 20 hr. After cooling, the mixt was dild with petr ether (120 ml), and the pptd Na salt of **10** was collected and washed with petr ether. After drying, it was dissolved in H_2O (20 ml) and crude **10** was liberated by acidification with concd HCl (3 ml).

Method E. A stirred mixt of **1** (2.55 g), the appropriate R_1H (10 g), and KOH (2.6 g of a product contg min 85.5%) was heated to 150–160° for 2.5–5 hr. After cooling, H_2O (10 ml) was added, and the mixt was extd several times with Et_2O. The aq layer was acidified with concd HCl (3 ml) and the pptd heavy oil crystd by trituration with hot H_2O to give crude **11** and **12**, resp.

Ethyl **4-R_1-2-Cl-5-Sulfamylbenzoates (13–17, Table I). Method F.** **2** (0.01 mole) was added to a soln of the appropriate R_1Na (prepd from R_1H (0.011–0.012 mole) and Na (0.25 g)) in abs EtOH (25 ml), and the mixt was refluxed for 18–24 hr (for **13** the reaction time was decreased to 2 hr). After evapn *in vacuo*, H_2O (about 25 ml) was added, and the pptd crude reaction product was collected, washed with H_2O, and dried.

Ethyl **4-R_1-*N*-R_2-5-Sulfamylanthranilates (18–22, Table II). Method G.** A mixt of the corresponding Et 4-R_1-2-Cl-5-sulfamylbenzoate (2.0–3.0 g) and $C_6H_5CH_2NH_2$ (6.0–9.0 ml) was stirred at 100–115° for 2–2.5 hr. The resulting soln was poured into 1 *N* AcOH (40–50 ml), and the pptd crude reaction product was collected, washed with H_2O, and dried.

Ethyl **4-Fluoro-5-sulfamyl-*N*-benzylanthranilate (23).** A mixt of **4** (1.32 g) and $C_6H_5CH_2NH_2$ (2.2 ml) was left at room temp for 3 hr. After evapn *in vacuo*, the residue was triturated with 1 *N* AcOH (10 ml), and the pptd crude **23** was collected, washed with H_2O, and dried. It was recrystd from EtOH to yield **23** (70%), mp 144–145°. *Anal.* ($C_{16}H_{17}FN_2O_4S$) C, H, N, S.

4-Fluoro-5-sulfamyl-*N*-benzylanthranilic Acid (24). A soln of **23** (1.76 g) in 1 *N* NaOH (12 ml) was heated on a steam bath for 30 min and was then filtered while hot. Crude **24** was pptd by acidification with 4 *N* HCl (4 ml). It was recrystd twice from EtOH to yield the hemihydrate of **24** (45%), mp 211–212°. *Anal.* ($C_{14}H_{13}FN_2O_4S \cdot 0.5H_2O$) C, H, N, S.

4-R_1-*N*-R_2-5-Sulfamylanthranilic Acids (25–61, Table III). Method H. A stirred mixt of **24** (1.25 g), *n*-$BuNH_2$ (5.0 ml), and H_2O (5.0 ml) was refluxed for 3 days. After evapn *in vacuo*, the residue was triturated with 4 *N* AcOH (10 ml) to give crude **25**.

Method I. A stirred mixt of the 4-R_1-2-Cl-5-sulfamylbenzoic acid and the appropriate R_2NH_2 (4 ml/g acid) was heated at 100–140° for 2–4 hr. The mixt was then poured into cold 4 *N* AcOH, and the pptd crude reaction product was collected, washed with H_2O, and dried. For **26** and **34** the reaction time was extended to 20 hr, and for **27** the mixt was refluxed for 7 days. **46** was pptd at pH 8. For **53**, **55**, and **56** the first ppt was extd with hot satd $NaHCO_3$ and filtered hot in the presence of charcoal, and crude **53**, **55**, and **56**, resp, repptd by acidification with AcOH.

Method J. The appropriate Et 4-R_1-*N*-R_2-5-sulfamylanthranilate (**18–22**) was sapond with 2 *N* NaOH (10 ml/g ester) by heating on a steam bath for 0.5–1 hr. After cooling, the crude reaction product was pptd by addn of the corresponding amt of 4 *N* HCl.

Method K. A soln of the corresponding 4-R_1-2-Cl-5-sulfamylbenzoic acid and the appropriate R_2NH_2 (4–5 ml/g acid) in methylcellosolve (4–10 ml/g acid) was heated to 130–160° for 18 hr. After evapn *in vacuo*, the residue was triturated with an excess of 1 *N* HCl (for **29**, **37**, and **41**) or 4 *N* AcOH (for **32**) to give the crude reaction product.

Method L. A stirred mixt of the corresponding 4-R_1-2-Cl-5-sulfamylbenzoic acid, the appropriate R_2NH_2 (5–7.5 ml/g acid) and H_2O (2.5 ml/g acid) was refluxed for 3–5 days. The cooled reaction mixt was then poured into a mixt of 4 *N* AcOH and 4 *N* HCl,

and the pptd crude reaction product was collected, washed with H_2O, and dried. For **50** and **51** most of the excess of amine was removed *in vacuo* before the treatment with acid.

Method M. A stirred soln of **63** (R_2 = 2-furylmethyl)[4] (3.3 g), C_6H_5SH (6.0 ml), and solid $NaHCO_3$ (10 g) in a mixt of methylcellosolve (20 ml) and H_2O (20 ml) was refluxed for 24 hr. The cooled mixt was dild with H_2O (100 ml) and adjusted to pH 4 by the addn of AcOH and HCl. The pptd crude **31** was collected, washed with H_2O, and dried.

Method N. A soln of **29** (0.5 g) and H_2O_2 (1.5 ml; 30% in H_2O) in HCOOH (5.0 ml) was stirred at room temp for 20 hr. The soln was then dild with H_2O (10 ml), and the pptd crude **33** was collected, washed with H_2O, and dried.

Method O. Method J was followed except that only 2 equiv of NaOH was used and that the reaction time was extended to 2 hr.

Method P. **3** (5.65 g) was added to a stirred soln of *n*-BuONa in *n*-BuOH (50 ml contg 0.46 g of Na) and the mixt was refluxed for 20 hr. After evapn *in vacuo*, the residue was washed with H_2O. The intermediate Et 4-*n*-BuO-2-Cl-5-sulfamylbenzoate failed to cryst and was therefore, without further purification, treated with furfurylamine following method G. The obtained crude Et ester of **39** was sapond following method J to give crude **39**.

Method Q. A soln of **41** (4.0 g) in 80% aq EtOH (100 ml) contg concd HCl (0.2 ml) was hydrogenated at room temp after addn of (10%) Pd/C (0.5 g). After 40 min the theor amt of H_2 had been absorbed and the uptake became negligible. The catalyst was removed by filtration, and the filtrate was evapd *in vacuo*. The residue was triturated with 4 *N* AcOH (10 ml), and the pptd crude **40** was collected, washed with H_2O, and dried.

Method R. A mixt of **11** (5.0 g) and CH_2=$CHCH_2NH_2$ (50 ml) was refluxed for **4** days. After evapn *in vacuo*, the residue was triturated with a mixt of 4 *N* AcOH (35 ml) and concd HCl (5 ml). The ppt was collected and washed with H_2O. It was then extd with hot satd $NaHCO_3$ (25 ml) and filtered hot in the presence of charcoal. Crude **49** was pptd from the filtrate by acidification with concd HCl (**4** ml).

Method S. A soln of **40** (1.5 g) and 1-chloromethylnaphthalene (2.0 g) in EtOH (25 ml) was refluxed for **65** hr. After evapn *in vacuo*, the oily residue was washed with H_2O and then crystd by trituration with aq EtOH. The crude Et ester of **54** was sapond following method J to give crude **54**.

Method T. **1** was treated with the appropriate R_1H following method E. The intermediate crude 4-R_1-2-Cl-5-sulfamylbenzoic acid, which failed to cryst, was treated with $C_6H_5CH_2NH_2$ following method I.

2,5-Dichloro-4-fluorobenzoic Acid (64). 2,5-Dichloro-4-fluoroacetophenone[7] (2.07 g) was at 0–5° added dropwise to a stirred soln of NaOBr (prepd from Br_2 (4.8 g) and solid NaOH (3.3 g)) in a mixt of dioxan (20 ml) and H_2O (28 ml). After addn stirring at 0–5° for 2 hr, the soln was acidified with concd HCl (6 ml), and the sepd oil was isolated. The aq layer was extd twice with Et_2O, and the combined org material was washed with H_2O, dried ($MgSO_4$), and evapd *in vacuo*. The residue was triturated with petr ether to give crude **64**. It was recrystd twice from aq EtOH to yield **64** (39%), mp 129.5–130.5°. *Anal.* ($C_7H_3Cl_2FO_2$) C, H, Cl.

2,5-Dichloro-4-fluoro-3-nitrobenzoic Acid (65). **64** (2.09 g) was added in portions to a stirred mixt of fuming HNO_3 (1.2 ml; *d* 1.50) and concd H_2SO_4 (8.0 ml). The mixt was heated on a steam bath for 1 hr and was then poured into ice. The resulting ppt was collected, washed with H_2O, and dried. Recrystn twice from aq EtOH yielded **65** (23%), mp 200.5–204°. *Anal.* ($C_7H_2Cl_2FNO_4$) C, H, Cl, N.

2,5-Dichloro-3-nitro-4-phenoxybenzoic Acid (66). A soln of **65** (2.0 g) and C_6H_5OH (0.95 g) in satd $NaHCO_3$ (20 ml) was heated on a steam bath for 2 hr. After cooling, crude **66** was pptd by acidification with concd HCl (5 ml). It was recrystd from EtOH to yield **66** (70%), mp 258–259°. *Anal.* ($C_{13}H_7Cl_2NO_5$) C, H, Cl, N.

3-Amino-2,5-dichloro-4-phenoxybenzoic Acid (67). A mixt of **66** (1.8 g), $Na_2S_2O_4$ (4.0 g), pyridine (10 ml), and H_2O (10 ml) was heated on a steam bath for 1 hr and was then evapd *in vacuo*. The residue was triturated with a mixt of AcOH (5 ml) and H_2O (25 ml) to give crude **67**. It was recrystd from aq EtOH to yield **67** (55%), mp 179–182°. *Anal.* ($C_{13}H_9Cl_2NO_3 \cdot 0.25H_2O$) C, H, Cl, N.

2,5-Dichloro-4-phenoxy-3-sulfamylbenzoic Acid (68). **67** (4.5 g) in concd HCl (10 ml) was diazotized at −5 to 0° with a soln of $NaNO_2$ (1.15 g) in H_2O (6.0 ml). The resulting diazonium mixt was, while stirring at room temp, poured into AcOH (15 ml), satd with SO_2 contg $CuCl_2 \cdot 2H_2O$ (1.0 g), and dissolved in H_2O (2.0 ml). After addnl stirring for 10 min the mixt was dild with H_2O (about 50 ml), and the pptd crude 3-chlorosulfonyl-2,5-dichloro-4-phenoxybenzoic acid was collected and washed with H_2O. It was then added in portions to concd NH_4OH (60 ml) while stirring at 10–12°, and, after addnl stirring for 2 hr, the resulting soln was concd *in vacuo* to about 25 ml. Crude **68** was pptd by acidification with concd HCl (5 ml). It was recrystd twice from aq EtOH to yield **68** (21%), mp 256–258°. *Anal.* ($C_{13}H_9Cl_2NO_3S$) C, H, Cl, N, S.

5-Chloro-4-phenoxy-3-sulfamyl-*N*-*n*-butylanthranilic Acid (69). A mixt of **68** (1.0 g) and *n*-$BuNH_2$ (10 ml) was refluxed for 20 hr and was then evapd *in vacuo*. The residue was washed with a mixt of AcOH (3 ml) and H_2O (20 ml), and the resulting oil was extd with hot satd $NaHCO_3$ (15 ml) and filtered hot in the presence of charcoal. Crude **69** was pptd by acidification with 4 *N* HCl (5 ml). It was recrystd from aq EtOH to yield **69** (21%), mp 168–169°. *Anal.* ($C_{17}H_{19}ClN_2O_5S$) C, H, Cl,* N, S.

4-Phenoxy-3-sulfamyl-*N*-*n*-butylanthranilic Acid (70). A mixt of **69** (0.6 g), AcONa (2.0 g), 1 *N* NaOH (4.5 ml), and H_2O (10 ml) was hydrogenated at room temp after addn of 10% Pd/C (0.6 g). After 2 hr the theor amt of H_2 had been absorbed and the uptake became negligible. The catalyst was removed by filtration, and crude **70** pptd from the filtrate by acidification with 4 *N* HCl (2.5 ml). It was recrystd twice from aq EtOH to yield **70** (55%): mp 144–145°; nmr [$(CD_3)_2SO$, TMS] 0.89 (t, *J* = 6 Hz, 3 H, CH_3), 1.1–1.8 (m, 4 HCH_2CH_2), 3.10 (d, *J* = 6.5 Hz, 2 H, NCH_2), 6.09 (d, *J* = 9.0 Hz, 1 H, arom H), 7.0–7.7 (m, 5 H, C_6H_5O), 7.67 (d, *J* = 9.0 Hz, 1 H, arom H). *Anal.* ($C_{17}H_{20}N_2O_5S$) C, H, N, S.

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