13 hr, after which the DMF was removed *in vacuo*. The residue was washed with abs Et_2O, dissolved in H_2O, and the soln was acidified with HCl. The product was removed by filtration, washed with H_2O, and dried. Purification was effected by recrystn.

3-Benzyloxyhydantoin (43).—A soln of 36.9 g of benzyloxyamine and 38.7 g of ethyl isocyanatoacetate in 300 ml of abs Et_2O was refluxed for 1.25 hr. The Et_2O was removed *in vacuo*, 250 ml of 3.9 *M* HCl in abs EtOH was added to the residue, and the soln was refluxed for 2 hr. About 100 ml of EtOH was evaporated under reduced pressure and the remainder of the soln was refrigerated, yielding 14.6 g of product which was sepd by filtration and purified by recrystn.

Acknowledgment.—The authors wish to acknowledge the valuable assistance of Miss Kazimiera Tomeczek and Melvin Auerbach for their contributions in the preparation of some of the compounds described in this publication.

Aminobenzoic Acid Diuretics. 1. 4-Halogeno-5-sulfamylmetanilic Acid Derivatives

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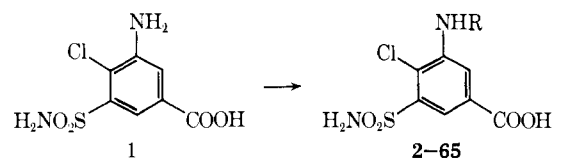
Sixty-seven N-substituted 4-halogeno-5-sulfamylmetanilic acids were prepared from the corresponding metanilic acids by different alkylation processes. The compounds were screened in dogs for their diuretic and saluretic properties and compared with 3 selected N-substituted 4-chloro-5-sulfamylanthranilic acids including furosemide, a well-established, high-ceiling diuretic. Several compounds of the new metanilic acid derivatives were found to possess activity to be comparable with that of the anthranilic acid series. However, there are differences in the influence of the N-substituent on the activity. The dose–response curves after iv and oral administration for *N*-*n*-butyl-4-chloro-5-sulfamylmetanilic acid (**45**) are presented.

Among the sulfonamide diuretics certain 4-halogeno-5-sulfamylanthranilic acid derivatives showed an outstanding characteristic of structure and diuretic effect.[1] The most interesting compound of this series is 4-chloro-*N*-(2-furylmethyl)-5-sulfamylanthranilic acid (furosemide), a well-established, nonthiazid type, high-ceiling diuretic.[2] To the best of our knowledge the corresponding metanilic acid derivatives have never been investigated. Consequently, in line with our interest in the structure–activity relationship of diuretics, we decided to determine what effect the moving of the substituted amino group from the 2 to the 3 position would have on the saluretic and diuretic effect.

Chemistry.—The N-alkylated 4-chloro-5-sulfamylmetanilic acids[3] (**2–65**) listed in Tables I and II were prepared by alkylation of 4-chloro-5-sulfamylmetanilic acid (**1**) using different alkylation processes. Details are given in the Experimental Section. Dialkylation and attack at the sulfonamide nitrogen could be avoided. The required metanilic acid **1** was available from 4-chloro-5-chlorosulfonylbenzoic acid by nitration followed by amidation to 4-chloro-3-nitro-5-sulfamylbenzoic acid and reduction of the NO_2 group. The bromo analogs (**66**, **67**, **68**) were prepared in a similar way and are listed in Table III.



1 2–65

(1) K. Sturm, W. Siedel, R. Weyer, and H. Rushig, *Chem. Ber.*, **99**, 328 (1966).

(2) See R. Muschaweck and K. Sturm, "Arzneimittel," G. Ehrhart and H. Rushig, Ed., Vol. 1, Verlag Chemie, Weinheim, Germany, 1968, chapter 16, pp 700–703.

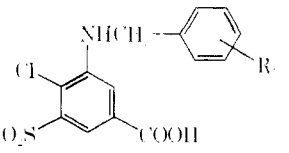
(3) P. W. Feit and H. Bruun, South African Patent 68/3145 (1968); *Chem. Abstr.*, **21**, 3141 (1969).

Diuretic Effect and Structure–Activity Relationships.—Although the metanilic acid derivatives described in this paper are related in structure to the corresponding anthranilic acid derivatives, it does not follow that these compounds should possess similar activities. The derivatives were screened in dogs for their saluretic and diuretic properties following 10 mg/kg iv (solution in NaOH). For details see the Experimental Section. The urinary volume and electrolyte excretion from the 3-hr test period for those compounds resulting in a Na^+ excretion ≥ 1.5 mequiv per kg per 3 hr are summarized in Table IV. The onset of diuresis was within 1 hr after injection and became almost negligible after 3 hr.

Compared with 3 selected anthranilic acid derivatives including furosemide the results (Table IV) indicate that in the metanilic acid series compounds could be found showing the same order of activity. The principal difference between these 2 series seems to be that *N*-2-methylfuryl substitution afforded outstanding activity[1] in the anthranilic acid series while in the metanilic acid series several N-substituted compounds approximated the corresponding *N*-2-methylfuryl compound in its activity. Generally, however, minor changes of the N-substituent had great influence on the activity. Compounds **45** and **66** carrying the *n*-Bu side chain were the most potent derivatives in the new series. Compound **45** was subjected, therefore, to further investigation. The dose–response curves after iv and oral dosage are given in Figures 1 and 2, respectively. After oral administration the onset of diuresis was still within the first hour. A prolonged effect at higher dosage levels made it necessary to extend the test period to 5 hr. It is interesting to note, that **45** is relatively inactive in the rat assay. Given orally only doses exceeding 80 mg/kg showed statistically significant diuretic action.

TABLE I

PHYSICAL PROPERTIES OF



No.	R[b]	Method[c]	Mp, °C	Recrystn solvent	Yield[d]	Formula	Analysis[e]
2	H	B,G	257–258	aq EtOH	47[f]	$C_{14}H_{13}ClN_2O_4S$	C, H, N, S
3	2-Cl	A	240–241.5	aq EtOH	31[g]	$C_{14}H_{12}Cl_2N_2O_4S$	C*, H, Cl, N, S
4	3-Cl	A	255–255.5	aq MeOH	39[f]	$C_{14}H_{12}Cl_2N_2O_4S$	C, H, N
5	4-Cl	A	274–275	aq MeOH	34[g]	$C_{14}H_{12}Cl_2N_2O_4S \cdot 0.5H_2O$	C, H, Cl, N, S*
6	2-Br	A	238–239.5	aq MeOH	37[f]	$C_{14}H_{12}BrClN_2O_4S$	C, H, N
7	3-Br	A	253–254	aq MeOH	42[g]	$C_{14}H_{12}BrClN_2O_4S$	C, H, N
8	4-Br	A	270–271.5	aq MeOH	38[g]	$C_{14}H_{12}BrClN_2O_4S$	C, H, N
9	3-CF_3	A	232–233	aq MeOH	10	$C_{15}H_{12}ClF_3N_2O_4S$	C*, H, N
10	2,3-Cl_2	A	230–230.5	aq MeOH	27	$C_{14}H_{11}Cl_3N_2O_4S \cdot 0.5H_2O$	C, H, N
11	2,4-Cl_2	A	230–231.5	aq EtOH	21[g]	$C_{14}H_{11}Cl_3N_2O_4S$	C, H, Cl, N, S
12	2,5-Cl_2	A	255–255.5	aq EtOH	37	$C_{14}H_{11}Cl_3N_2O_4S \cdot 0.5H_2O$	C, H, N
13	2,6-Cl_2	A	260–261	aq EtOH	21	$C_{14}H_{11}Cl_3N_2O_4S$	C, H, Cl, N, S
14	3,4-Cl_2	A	247.5–249	aq MeOH	48	$C_{14}H_{11}Cl_3N_2O_4S \cdot 0.5H_2O$	C, H, Cl, N, S, H_2O
15	3,5-Cl_2	A	251.5–252	aq EtOH	10	$C_{14}H_{11}Cl_3N_2O_4S$	C, H, Cl, N, S
16	2-OH	A	201–202	aq MeOH	11	$C_{14}H_{13}ClN_2O_5S \cdot 0.25H_2O$	C*, H, N, H_2O
17	3-OH	A	244–244.5	aq MeOH	20	$C_{14}H_{13}ClN_2O_5S \cdot 0.5H_2O$	C, H, N
18	4-OH	B	202–203	aq MeOH	13[h]	$C_{14}H_{13}ClN_2O_5S$	C, H, Cl, N*
19	2-Me	A	235.5–236	aq EtOH	56[g]	$C_{15}H_{15}ClN_2O_4S \cdot C_2H_5OH$	C, H, Cl, N, S
20	3-Me	A	241–241.5	aq MeOH	40[g]	$C_{15}H_{15}ClN_2O_4S$	C, H, N
21	4-Me	A	252–252.5	aq MeOH	28	$C_{15}H_{15}ClN_2O_4S$	C, H, N
22	2-OMe	A	217.5–218	aq MeOH	25[g]	$C_{15}H_{15}ClN_2O_5S \cdot 0.25H_2O$	C, H, N
23	3-OMe	A	229–229.5	aq MeOH	24	$C_{15}H_{15}ClN_2O_5S$	C, H, N
24	4-OMe	A	222–223	aq MeOH	14[g]	$C_{15}H_{15}ClN_2O_5S$	C, H, N, S
25	2,3-$(OMe)_2$	A	215.5–216	aq MeOH	14	$C_{16}H_{17}ClN_2O_6S \cdot 1.5H_2O$	C, H, N, H_2O
26	2,4-$(OMe)_2$	A	189–190	aq MeOH	16	$C_{16}H_{17}ClN_2O_6S$	C, H, N
27	3,4-$(OMe)_2$	A	215–215.5	aq MeOH	37	$C_{16}H_{17}ClN_2O_6 \cdot 0.5H_2O$	C, H, N, H_2O
28	3,4,5-$(OMe)_3$	A	224–224.5	aq MeOH	23[g]	$C_{17}H_{19}ClN_2O_7S \cdot 0.25H_2O$	C, H, N, H_2O
29	2-OH, 3-OMe	F	192–193	MeOH	49[g]	$C_{15}H_{15}ClN_2O_6S$	C, H, N
30	3-OH, 4-OMe	A	212–215.5	aq MeOH	49	$C_{15}H_{15}ClN_2O_6S$	C, H, N
31	4-OH, 3-OMe	A	212–213	aq MeOH	54	$C_{15}H_{15}ClN_2O_6S$	C, H, N
32	3,4-$(OH)_2$	A	201–202	aq MeOH	12	$C_{14}H_{13}ClN_2O_6S \cdot 0.5CH_3OH$	C, H, N
33	3,4-OCH_2O	A	246–246.5	aq MeOH	10[g]	$C_{15}H_{13}ClN_2O_6S$	C, H, N
34	3-Cl, 4-OH	A	246–246.5	aq MeOH	12	$C_{14}H_{12}Cl_2N_2O_5S$	C, H, N, Cl[i]
35	3,5-Cl_2, 4-OH	B	195–196	aq MeOH	50	$C_{14}H_{11}Cl_3N_2O_5S \cdot H_2O$	C, H, N
36	3,5-Cl_2, 2-OH	A	269.5–271.5	aq MeOH	33[g]	$C_{14}H_{11}Cl_3N_2O_5S$	C, H, Cl, N, S
37	4-*i*-Pr	B	222–223	aq EtOH	23[g]	$C_{17}H_{19}ClN_2O_4S \cdot 0.5C_2H_5OH$	C, H, Cl, N, S
38	2-NO_2	E	208–209	anhyd MeOH	7	$C_{15}H_{12}ClN_3O_8S \cdot CH_3OH$	C, H, N
39	3-NO_2	E	262–262.5	anhyd MeOH[j]	2	$C_{14}H_{12}ClN_3O_6S$	C, H, N
40	4-NO_2	E	264–266	anhyd MeOH	8	$C_{14}H_{12}ClN_3O_6S$	C, H, N
41	2-COOH	F	240 (319–321 (dec))	aq MeOH	22	$C_{15}H_{13}ClN_2O_8S \cdot 1.5H_2O$	C, H, N, H_2O
42	4-NHCOMe	A	224–224.5	aq MeOH	6	$C_{16}H_{16}ClN_3O_5S \cdot 2H_2O$	C, H, N

[a] The letters relate to the general procedure in the Experimental Section. [b] The yield of the analytically pure compd is given. All compds were purified until they failed to be diazotized and coupled with β-napthol. No attempts were made to optimate the yield. [c] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.25% of the theoretical values or, when marked with an asterisk, within ±0.40% of the theoretical values. [d] Dried *in vacuo* (10–14 mm) at 60–80° for 2–3 hr. [e] Dried *in* high *vacuo* at 80–100°. [f] C: calcd 18.28; found 17.83. [g] Recrystd using a Soxlett apparatus.

The LD_{50}'s for **45** in mice (6 days) were >1 g/kg iv, >0.5 g/kg ip, and ≧2 g/kg oral.

Experimental Section

Chemistry.[4] **4-Chloro-5-chlorosulfonyl-3-nitrobenzoic Acid.**—To a mixture of concd H_2SO_4 (450 g) and HNO_3 (225 g, d = 1.4) a warm soln of 4-chloro-5-chlorosulfonylbenzoic acid[5] (114 g) in concd H_2SO_4 (1140 g) was added during 1 hr while stirring. The temp of the reaction mixture was then raised to 80–90° and stirring continued at this temp for additional 6 hr. After cooling the mixture was poured into ice–H_2O, the ppt collected by filtration and washed with H_2O. The product was dried (80°, 14 mm) and recrystd (C_6H_6); 91 g, mp 193–194° dec. *Anal.* ($C_7H_3Cl_2NO_6S$) C, H, Cl*, N, S.

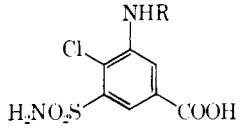
4-Bromo-5-chlorosulfonyl-3-nitrobenzoic Acid.—4-Bromo-5-chlorosulfonylbenzoic acid[5] was nitrated using the method described for the corresponding chloro compd except that the temp was raised to 100° and the heating time reduced to 3 hr: yield 83%; mp 209–210° dec. *Anal.* ($C_7H_3BrClNO_6S$) C, H, Cl*, N, S.

(4) 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. Analytical data are given as defined in footnote *c*, Table I; analytical results were within ±0.25% of calcd values, except for *elements (±0.4%). Technical assistance was given by H. Dannacher, F. Eberwein, and W. Schlichtkrull.

(5) G. B. Jackman, V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. Pharmacol.*, **14**, 679 (1962).

TABLE II

PHYSICAL PROPERTIES OF



No.	R	Method[a]	Mp, °C	Recrystn solvent	Yield[b]	Formula	Analysis[c]
43	Et	H	246.5–247	aq EtOH	25	$C_9H_{11}ClN_2O_4S \cdot H_2O$	C, H, Cl, N
44	*n*-Pr	I	233	aq EtOH	61	$C_{10}H_{13}ClN_2O_4S \cdot 0.5C_2H_5OH$	C, H, N
45	*n*-Bu	L	239–239.5	aq EtOH	63[d]	$C_{11}H_{15}ClN_2O_4S$[e]	C, H, N
46	*n*-Am	D	229–230	aq MeOH	34	$C_{12}H_{17}ClN_2O_4S$	C, H, Cl, N, S
47	*n*-C_6H_{13}	M	200–201	aq EtOH	24[d]	$C_{13}H_{19}ClN_2O_4S \cdot 0.25H_2O$	C, H, Cl, N
48	*i*-Bu	C	225–227	aq EtOH	55[d]	$C_{11}H_{15}ClN_2O_4S \cdot 0.5H_2O$	C, H, Cl, N, S
49	*i*-Am	C	209.5–211	aq EtOH	33[d]	$C_{12}H_{17}ClN_2O_4S$	C, H, Cl*, N, S
50	CH_2CHEt_2	D	199–200	aq EtOH	70[d]	$C_{13}H_{19}ClN_2O_4S$	C, H, N, S
51	CH_2CMe_3	B	245–245.5	aq EtOH	21[d]	$C_{12}H_{17}ClN_2O_4S \cdot 0.5H_2O$	C*, H, N, S
52	$CH(CH_2)_5$	D	228–229	aq MeOH	10[d]	$C_{13}H_{17}ClN_2O_4S$	C, H, Cl, N, S
53	$CH_2CH(CH_2)_5$	B	212–213	aq MeOH	27[d]	$C_{14}H_{19}ClN_2O_4S$	C, H, N
54	$CH_2CH_2CH(CH_2)_5$	D	184.5–186	aq EtOH	52[d]	$C_{15}H_{21}ClN_2O_4S$	C, H, N, S*
55	$CH_2CH_2CH(CH_2)_4$	D	196–197	aq EtOH	47[d]	$C_{14}H_{19}ClN_2O_4S$	C, H, N, S
56	$CH_2CH(CH_3)_2CH_2OH$	D	218.5–220	aq MeOH	10	$C_{12}H_{17}ClN_2O_5S \cdot CH_3OH$	C, H, N, S
57	$CH_2CH{=}CH_2$	K	223–224	H_2O	19[d]	$C_{10}H_{11}ClN_2O_4S$	C, H, Cl, N
58	$(CH_2)_3C_6H_5$	B	215.5–216	aq MeOH	5	$C_{16}H_{17}ClN_2O_4S$	C, H, N
59	CH_2-2-pyridyl	A	287–288 dec	dil $NaHCO_3$–AcOH	40[d]	$C_{13}H_{12}ClN_3O_4S$	C, H, Cl, S, N[f]
60	CH_2-4-pyridyl	A	280–281 dec	dil $NaHCO_3$–dil HCl	16	$C_{13}H_{12}ClN_3O_4S$	C*, H, N, S
61·HCl	CH_2CH_2-2-pyridyl	N_1	223–224 dec	2 *N* HCl–EtOH, 1:1	5[g]	$C_{14}H_{14}ClN_3O_4S \cdot HCl \cdot H_2O$	C, H, Cl, N
62·HCl	CH_2CH_2-4-pyridyl	N_2	253–254 dec	2 *N* HCl–EtOH, 1:1	28	$C_{14}H_{14}ClN_3O_4S \cdot HCl \cdot 0.5H_2O$	C, H, Cl, N
63	CH_2-2-quinolyl	A	232–233 dec	DMF–H_2O	14[d]	$C_{17}H_{14}ClN_3O_4S \cdot H_2O$	C, H, Cl, N, S
64	$CH_2C{=}CHCH{=}CHO$	O	197–198 dec	aq EtOH	40[d]	$C_{12}H_{11}ClN_2O_5S \cdot 0.5C_2H_5OH$	C, H, N, S
65	$CH_2CC(CH_3)C(OH)NC(OH)N$	A	320–321 dec	DMF–H_2O	18[h]	$C_{13}H_{13}ClN_4O_6S \cdot C_3H_7NO$	C, H, Cl, N, S

[a–d] See corresponding footnotes in Table I. [e] Dried in air the analytically pure **45** crystallizing with $0.5H_2O$ was obtained. [f] N: calcd 12.30; found 11.89. [g] Dried (10–14 mm) at room temp. [h] Dried (10–14) at 100° for 16 hr.

4-Chloro-3-nitro-5-sulfamylbenzoic Acid.—To well-stirred and ice-cooled aq NH_3[6] (160 ml, 25% NH_3) 4-chloro-5-chlorosulfonyl-3-nitrobenzoic acid (90 g) was added during 1 hr. The reaction mixture was stirred for additional 4 hr and allowed to reach room temp. The pptd NH_3 salt of the reaction product was collected. The crude salt was suspended in H_2O (320 ml), acidified with concd HCl to pH 1, and the mixture heated to boiling. After filtration and cooling the ppt was collected and recrystd (H_2O); 57 g, mp 235–236.5° dec. *Anal.* ($C_7H_5ClN_2O_6S$) C, H, N, S, Cl.[7]

4-Bromo-3-nitro-5-sulfamylbenzoic Acid.—4-Bromo-5-chlorosulfonyl-3-nitrobenzoic acid was treated with NH_3 using the method described for the corresponding chloro compd: yield 65%; mp 242–243°. *Anal.* ($C_7H_5BrN_2O_6S$) C, H, Br*, N, S.

4-Chloro-5-sulfamylmetanilic Acid (1).—A soln of $NaHSO_3$ (104 g) in H_2O (560 ml) was added dropwise to a boiling suspension of 4-chloro-3-nitro-5-sulfamylbenzoic acid (56 g) in H_2O (560 ml) during 1 hr. After stirring and additional refluxing for 1 hr the reaction mixture was adjusted to pH 2 by addition of 4 *N* HCl and the refluxing continued for 30 min. After cooling the ppt was collected and recrystd (H_2O): 33 g; mp 266–266.5°. *Anal.* ($C_7H_7ClN_2O_4S$) C, H, Cl, N, S.

Na Salt of 1.—Compound 1 was dissolved in the theoretical amount of boiling 2.4 *N* NaOH. After cooling the pptd salt was collected and dried (14 mm, 100°).

4-Bromo-5-sulfamylmetanilic Acid.—4-Bromo-3-nitro-5-sulfamylbenzoic acid was reduced using the method described for the corresponding chloro compd: yield 67%; mp 260–262°. *Anal.* ($C_7H_7BrN_2O_4S$) C, H, N, S.

N^3-Alkylated 4-Chloro-5-sulfamylmetanilic Acids. Method A (Table I, II).—A mixture of **1** (5 g, 0.02 mole), the appropriate aldehyde (0.02–0.022 mole), *p*-toluenesulfonic acid (0.05 g), and AcOH (130 ml) was hydrogenated at room temp after addition of PtO_2 catalyst. When the H_2 uptake became negligible the ppt was filtered off and recrystd from the appropriate solvent and the catalyst was removed by filtration. Evaporation of the AcOH filtrate and recrystn of the residue gave additional material.

Method B (Table I, II, III).—Method A was followed except that material was obtained from the AcOH filtrate.

Method C (Table II, III).—Method A was followed except that 10% Pd–C (0.3 g) was used as catalyst. In some cases additional catalyst (0.3 g) was added during the hydrogenation.

Method D (Table II).—Method C was followed except that the material was obtained from the AcOH filtrate.

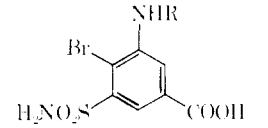
Method E (Table I).—A mixture of anhyd Na salt of 1 (8.2 g, 0.03 mole), the appropriate aldehyde (0.0315 mole), and MeOH (45 ml) was refluxed for 20 hr. After cooling the reaction mixture was filtered and to the filtrate $NaBH_4$ (1.5 g) was added in small portions while stirring. Then H_2O (70 ml) was added and the pH of the reaction mixture adjusted to 7 by addition of 4 *N* HCl.

(6) On larger scale preparation excess of liquid NH_3 was used. The NH_3 was removed totally *in vacuo* before addition of H_2O.

(7) Cl: calcd 12.63; found 13.26.

TABLE III

PHYSICAL PROPERTIES OF



No.	R	Method[a]	Mp, °C	Recrystn solvent	Yield[b]	Formula	Analysis[c]
66	*N*-Bu	L[d]	216–217	aq EtOH	26	$C_{11}H_{15}BrN_2O_4S \cdot 0.5H_2O$	C, H, N, S
67	$CH_2C_6H_5$	B[d]	250–251	aq EtOH	55	$C_{14}H_{13}BrN_2O_4S \cdot 0.25C_2H_5OH$	C, H, N, S
68	CH_2-3,4-$Cl_2C_6H_3$	B[d]	247–248	aq EtOH	41	$C_{14}H_{11}BrCl_2N_2O_4S$	C, H, N, S

[a–c] See corresponding footnotes in Table I. [d] The given procedure for the corresponding 4-chloro compd was adapted using 4-bromo-5-sulfamylmetanilic acid as starting material.

TABLE IV

DIURETIC AND SALURETIC ACTIVITY OF SOME *N*-R-4-HALOGENO-5-SULFAMYLMETANILIC ACIDS IN DOGS

Compd	R	Halogen	ml/kg per 3 hr[a] H_2O	meq/kg per 3 hr[a] Na^+	K^+	Cl^-
Control[b]			2	0.19	0.13	0.13
2	$CH_2C_6H_5$	Cl	21	2.0	0.53	2.6
14	$CH_2C_6H_3$, 3,4-Cl_2	Cl	21	2.3	0.71	2.3
18	$CH_2C_6H_4$, 4-OH	Cl	16	1.6	0.42	2.0
21	$CH_2C_6H_4$, 4-Me	Cl	17	2.0	0.95	1.9
31	$CH_2C_6H_3$, 4-OH, 3-Me	Cl	29	2.6	1.3	1.1
34	$CH_2C_6H_3$, 3-Cl, 4-OH	Cl	13	1.5	0.83	1.5
44	*n*-Pr	Cl	16	1.8	0.74	2.4
45	*n*-Bu	Cl	28	3.2	1.1	3.3
46	*n*-Am	Cl	19	2.0	0.92	3.3
48	*i*-Bu	Cl	17	1.6	0.74	2.0
49	*i*-Am	Cl	20	2.0	0.8	3.1
53	$CH_2CH(CH_2)_3$	Cl	13	1.5	0.61	1.9
59	CH_2-2-pyridyl	Cl	14	1.7	0.69	1.8
62·HCl	CH_2CH_2-4-pyridyl	Cl	19	2.0	0.52	2.9
64	CH_2C=CHCH=CHO	Cl	21	2.4	0.64	2.8
66	*n*-Bu	Br	31	3.2	0.86	4.6
67	$CH_2C_6H_5$	Br	19	1.5	0.61	2.5
N-*n*-Butyl-4-chloro-5-sulfamylanthranilic acid[c]			18	1.8	0.59	2.9
N-Benzyl-4-chloro-5-sulfamylanthranilic acid[d]			15	1.6	0.4	2.1
N-(2-Furylmethyl)-4-chloro-5-sulfamylanthranilic acid (furosemide)[d]			33	3.7	0.82	4.8

[a] Results after iv injection of 10 mg/kg in NaOH soln. When not stated otherwise single test only. [b] Average of 3 expt. [c] See Experimental Section. [d] See ref 1.

After several extractions with Et_2O the reaction product was pptd from the aq layer by addition of 4 *N* HCl until pH 3.

Method F (Table I).—A soln of anhyd Na salt of 1 (2.7 g, 0.01 mole) and of the appropriate aldehyde (0.01 mole) in MeOH (20 ml) was left at room temp for several days or, alternatively, refluxed for some hr. After cooling pptd Na salt of the Schiff Base was collected by filtration and air-dried. This compd was added in small portions to a stirred ice-cooled soln of $NaBH_4$ (0.5 g) in 2 *N* NaOH (20 ml). In some cases the temp of the reaction mixture was raised to approx 30°. Then dil HCl was added slowly until pH 3–4. The crude pptd material was collected and washed with H_2O.

Method G. *N*-Benzyl-4-chloro-5-sulfamylmetanilic Acid (2) (Table I).—A mixture of 1 (5 g) and 1 *N* NaOH (10 ml) was adjusted to pH 7.4 by addition of 2.4 *N* NaOH using an automatic end-point titrator. To the resulted soln BzCl (2.52 g) was added and the temp (30°) and pH were kept constant for 12 hr while stirring. After cooling the pptd Na salt of **2** was collected (5.3 g). The salt was dissolved in boiling H_2O (50 ml) and crude **2** (4.2 g) pptd by addition of AcOH (2 ml).

Method H. 4-Chloro-*N*-ethyl-5-sulfamylmetanilic Acid (43) (Table I).—A mixture of 1 (2.5 g), EtI (6.4 g), and anhyd EtOH was refluxed for 72 hr. After cooling the pptd **ethyl 4-chloro-*N*-ethyl-5-sulfamylmetanilate** was collected, washed with EtOH (4 ml), and recrystd (EtOH): 1.35 g; mp 159–161°. *Anal.* ($C_{11}H_{15}ClN_2O_4S$) C, H, Cl, N. The Et ester (0.9 g) was saponified by heating in 2 *N* NaOH (8 ml) at 100° for 30 min. The cooled soln was adjusted to pH 4 and the ppt collected. The solid was redissolved in 1 *N* $NaHCO_3$ (5 ml) and crude **43** pptd by adjusting the pH to 4.

Method I. 4-Chloro-*N*-*n*-propyl-5-sulfamylmetanilic Acid (44) (Table II).—A mixture of 1 (20 g), allyl bromide (12 g), and anhyd EtOH was refluxed for 18 hr. After standing in a refrigerator the pptd **ethyl 4-chloro-*N*-allyl-5-sulfamylmetanilate** was collected and recrystd (EtOH): 12.1 g; mp 154–155°. *Anal.* ($C_{12}H_{15}ClN_2O_4S$) C, H, N. Hydrogenation of this ester (1.6 g) in EtOH (10 ml) using PtO_2 catalyst (20 mg) in the usual way gave after removing of the catalyst and dilution with H_2O (10 ml) crude ethyl 4-chloro-*N*-*n*-propyl-5-sulfamylmetanilate (1.05 g): after recrystn (aq EtOH) yield 0.55 g; mp 145–146°. *Anal.* ($C_{12}H_{17}ClN_2O_4S$) C, H, N. This ester (0.5 g) was saponified by heating in 1 *N* NaOH (7 ml). After cooling AcOH was added until pH 4 and the pptd crude **44** collected.

Method K. *N*-Allyl-4-chloro-5-sulfamylmetanilic Acid (57) (Table II).—To a soln of 1 (5 g) in 1 *N* NaOH (20 ml) allyl bromide (2.42 g) was added and the reaction mixture stirred at room temp while the pH was kept at 7.4 by addition of 2.4 *N* NaOH using an automatic endpoint titrator. After the NaOH consumption had become negligible, crude **57** (1.7 g) was pptd by addn of AcOH (2 ml).

Method L. *N*-*n*-Butyl-4-chloro-5-sulfamylmetanilic Acid (45) (Table II).—A mixture of 1 (40 g), *n*-BuOH (500 ml), and concd H_2SO_4 (4 ml) was refluxed for several days using a water trap. The reaction was controlled by nmr spectroscopy of taken samples dild with *n*-BuOH. Signals of the aromatic protons were recorded only. The reaction was stopped when the proportion of the

integrals of the 2 doublets of the formed Bu ester of 1 to the integrals of the corresponding signals of the Bu ester of **45** situated at higher field was about 0.1. NaOH (2 *N*, 300 ml) was then added and saponification performed by refluxing for 30 min. After cooling the pH was adjusted to 7.5 by addition of concd HCl. After standing the pptd Na salt of **45** was collected and washed with satd NaCl soln. This salt could be recrystd (H_2O). *Anal.* ($C_{11}H_{14}ClN_2NaO_4S \cdot 3H_2O$) C, H, N, H_2O. The crude Na salt was dissolved in hot H_2O (350 ml) and after filtration crude **45** (35 g) was pptd by addn of AcOH (15 ml).

Method M. 4-Chloro-*N*-*n*-hexyl-5-sulfamylmetanilic Acid (47) (Table II).—A suspension of **I** (5 g) in *n*-$C_6H_{13}OH$ (35 ml) containing $MeSO_3H$ (0.05 ml) was refluxed using a water trap. After 2 hr additional *n*-C_6H_{13} OH (10 ml) and I_2 (0.2 g) were added and the refluxing continued for 4 days. After cooling the pptd ***n*-hexyl-4-chloro-*N*-*n*-hexyl-5-sulfamylmetanilate** (3.35 g) was collected and washed with *n*-$C_6H_{13}OH$ and pet ether. A sample was recrystd (*n*-$C_6H_{13}OH$); mp 108-110°. *Anal.* ($C_{19}H_{31}ClN_2O_4S$) C, H, N. The hexyl ester (2.1 g) was saponified by heating in 2 *N* NaOH (10 ml) on a steam bath for 45 min. After cooling and extraction with Et_2O the aq layer was adjusted to pH 7.5 by addition of 4 *N* HCl. The pptd Na salt of **47** (1.7 g) was redissolved in hot H_2O (25 ml), **47** was pptd by addition of AcOH and collected.

Method N1. 4-Chloro-*N*-(2-pyridylethyl)-5-sulfamylmetanilic Acid Hydrochloride (61·HCl) (Table II).—A mixture of 1 (5 g), 2-vinylpyridine (2.4 g), AcOH (1.2 g), and anhyd MeOH (20 ml) became a clear soln by refluxing. CuCl (0.05 g) was added and the refluxing continued for additional 2.5 days to ppt **62**. The crude **62** was collected, washed with aq EtOH, and, after drying, dissolved in 4 *N* HCl (10 ml). After standing in a refrigerator the sepd **61**·HCl was collected and washed with MeOH.

Method N2. 4-Chloro-*N*-(4-pyridylethyl)-5-sulfamylmetanilic Acid Hydrochloride (62·HCl) (Table II).—**I** (5 g), 4-vinylpyridine (2.1 g), AcOH (1.2 g), and anhyd MeOH (20 ml) were joined to form a cake (exothermic reaction). The mixture was heated on a steam bath for 3.5 hr resulting in a solution followed by spontaneous pptn of **62**. After cooling **62** was collected, washed with MeOH, and dried. The compd was dissolved in 4 *N* HCl (50 ml). After standing in a refrigerator the sepd **62**·HCl was collected.

Method O. 4-Chloro-*N*-(2-furylmethyl)-5-sulfamylmetanilic Acid (64) (Table II).—A soln of **I** (55 g) and furfural (22 g) in MeOH (370 ml) was refluxed for 24 hr. After standing for 16 hr $NaBH_4$ (13 g) was added in small portions while stirring and cooling in an ice bath. The stirring was continued for 3 hr while the reaction mixture was allowed to reach room temp. After evaporation in vac the residue was redissolved in H_2O (200 ml). Slow adjustment of the soln to pH 4 by addition of AcOH pptd **64**. After standing in a refrigerator the ppt was collected and washed with H_2O to give 14.1 g of crude **64**.

***N*-*n*-Butyl-4-chloro-5-sulfamylanthranilic Acid.**—2,4-Dichloro-5-sulfamylbenzoic acid (5 g) was treated with *n*-$BuNH_2$ (16.5 ml) according to the general method described,[1] mp 220.5–221° (aq EtOH). *Anal.* ($C_{11}H_{15}ClN_2O_4S$, H_2O) C,H,N.

Diuretic Experiments[8] (Table IV, Figures 1 and 2).—Female mongrel dogs weighing from 9 to 30 kg were used. About 16 hr before the expt the dogs were starved, but had H_2O available always. The urine was taken by catheter hourly. The Na^+, K^+, and Cl^- were determined by flame photometry and potentiometric titration, respectively. The excretion of H_2O and the electrolytes during 2 hr before dosage of the test compd served as control of the conditions.

(8) Technical assistance was supplied by Karen M. Jepsen.

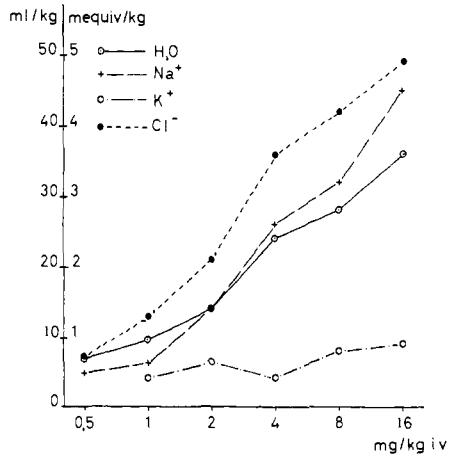


Figure 1.—Urinary volume and excretion of electrolytes during a 3-hr period after intravenous injection (soln in NaOH) of **45**. Each dose level is represented by a single dog.

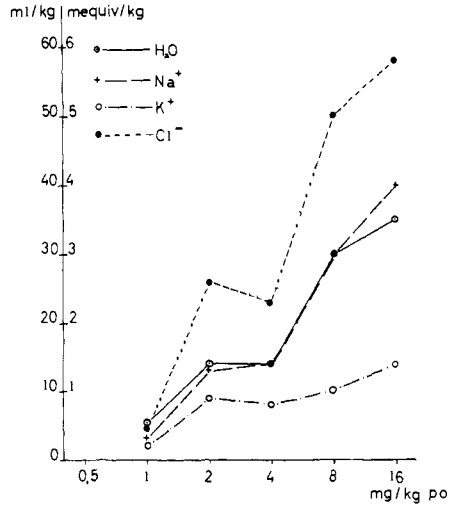


Figure 2.—Urinary volume and excretion of electrolytes during a 5-hr period after oral administration (gelatine capsules) of **45**. Each dose level is represented by a single dog.