Chem. Pharm. Bull. 27(6)1287—1298(1979)

UDC 547.583.5.04.09 : 615.254.1.011.5.015.11

Chemistry of Salicylic Acid and Anthranilic Acid. IV.[1] Synthesis of 6-Chloro-5-sulfamoyl- and 6-Chloro-3-sulfamoylanthranilic Acid Derivatives

Hiroyuki Asakawa and Mitsuo Matano

Chemical Research Laboratories, Central Research Division, Takeda Chemical Industries, Ltd.[2]

(Received August 25, 1978)

Some derivatives of 6-chloro-5-sulfamoyl- and 6-chloro-3-sulfamoylanthranilic acids, which have a chlorine atom and a sulfamoyl group *ortho* and *meta* to the carboxy group, respectively, were synthesized and the diuretic activities of the two positional isomers were compared. The presence of a chlorine atom *ortho* to the carboxy group, which enhanced the hypoglycemic activity of anthranilic acid derivatives, had no effect on the diuretic activity of sulfamoylanthranilic acid derivatives. The diuretic activity of the 6-chloro-3-sulfamoylanthranilic acid derivatives was greater than that of the 6-chloro-5-sulfamoyl ones.

Keywords——chlorine atom *ortho* to carboxy group; 6-chloro-5-sulfamoylanthranilic acids; 6-chloro-3-sulfamoylanthranilic acids; 5-chloroquinazoline-6-sulfonamide derivatives; 5-chloroquinazoline-8-sulfonamide derivatives; diuretic activity

Some 4-chloro-5-sulfamoylanthranilic acid derivatives have marked diuretic activity. Among them, furosemide (I) is a high-ceiling diuretic which has been used clinically for the treatment of edema and hypertension.[3] An isomer of I, 3-furfurylamino-4-chloro-5-sulfamoylbenzoic acid (II) and a derivative of II, bumetanide (III), also have potent diuretic activity.[4] These observations suggest that a sulfamoyl group *meta* to the carboxy group is important for diuretic activity. In the previous paper,[1] we reported that a chlorine atom *ortho* to the carboxy group of anthranilic acid or salicylic acid enhanced the hypoglycemic activity of the parent compounds. We therefore synthesized some derivatives of 6-chloro-5-sulfamoyl- and 6-chloro-3-sulfamoylanthranilic acids, which have a chlorine atom and a sulfamoyl group *ortho* and *meta* to the carboxy group, respectively, and compared their diuretic activities.

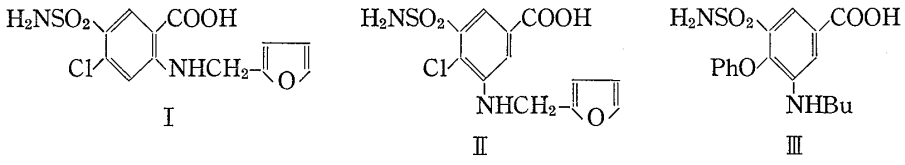
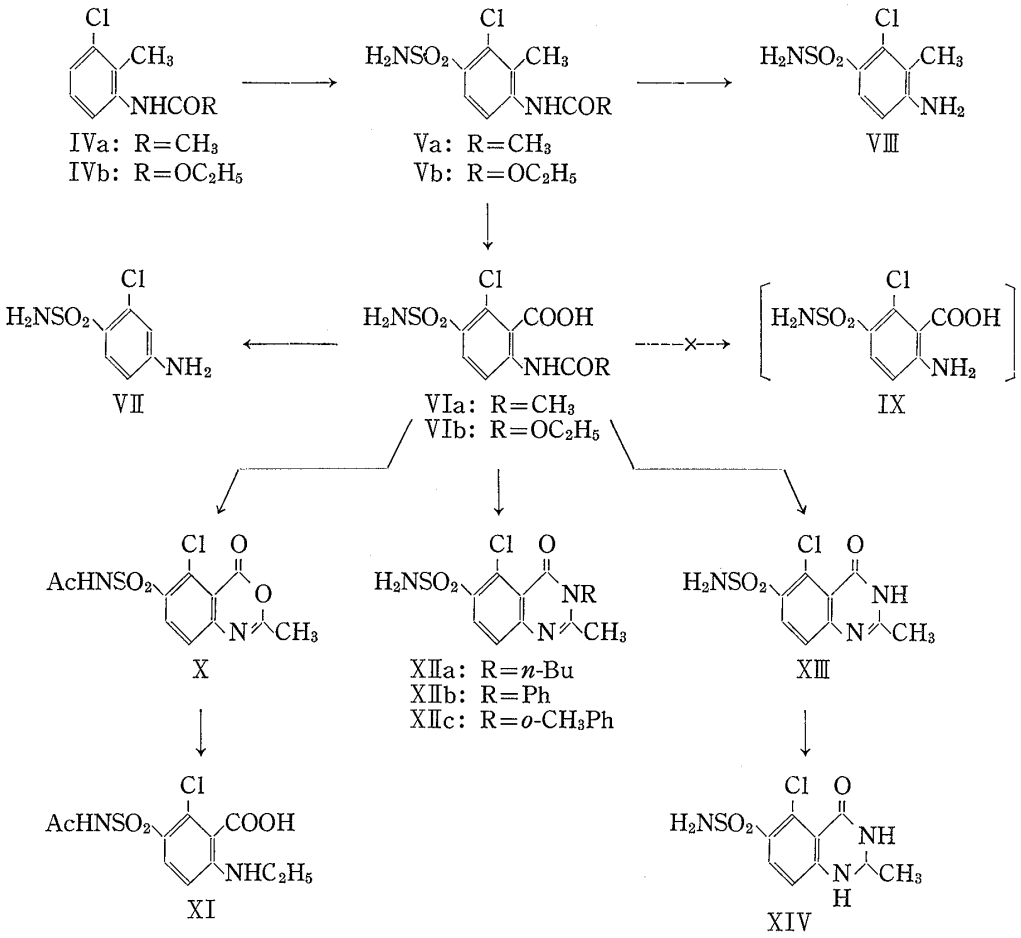


Chart 1

Chlorosulfonation of the N-acyl derivatives (IVa, IVb) of 3-chloro-2-methylaniline and subsequent treatment with aqueous ammonia afforded the sulfamoyl derivatives (Va, Vb), which were converted to the carboxylic acids (VIa, VIb) by oxidation with potassium permanganate. When VIa was treated with hydrochloric acid, hydrolysis of the acetamido

1) Part III: H. Asakawa, E. Imamiya, and Y. Hamuro, *Chem. Pharm. Bull.* (Tokyo), **27**, 1468 (1979).
2) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
3) *a*) R. Munshaweck and P. Hajdu, *Arzneim.-Forsch.*, **14**, 44 (1964); *b*) A. Heidland, K. Klutsch, and F. Suzuki, *ibid.*, **14**, 713 (1964); *c*) K. Sturm, W. Siedel, R. Weyer, and H. Ruschig, *Chem. Ber.*, **99**, 328 (1966); *d*) W. Siedel, K. Sturm, and W. Sheurich, *ibid.*, **99**, 345 (1966).
4) *a*) P.W. Feit, H. Bruun, and C.K. Nielsen, *J. Med. Chem.*, **13**, 1017 (1970); *b*) P.W. Feit, *ibid.*, **14**, 432 (1971); *c*) E.S. Ostergaad, M.P. Magnussen, Chr. K. Nielsen, E. Eilertsen, and H.H. Frey, *Arzneim.-Forsch.*, **22**, 66 (1972).

group and decarboxylation occurred simultaneously, affording 4-amino-2-chloro-benzenesulfonamide (VII), which is known in the literature.[5] The formation of VII confirmed that the sulfamoyl group had been introduced *ortho* to the chlorine atom of IVa. Hydrolysis of the acetyl or ethoxycarbonyl group of VIa or VIb in an acidic or alkaline medium, respectively, in an atempt to obtain IX did not succeed, probably due to the tendency of IX to decarboxylate. Thus, VIa and VIb could not be used as intermediates for the synthesis of N-alkyl-6-chloro-5-sulfamoylanthranilic acids.



Ph=phenyl

Chart 2

As we reported previously,[6] 2-alkylbenzoxazine is reduced to N-alkylanthranilic acid by treatment with sodium borohydride. This method was applied to VIa. Cyclization of VIa with acetic anhydride, however, afforded the acetylated benzoxazine (X), which was reduced with sodium borohydride giving the acetylated derivative, XI, of the desired compound.

Treatment of VIa with primary amine in the presence of phosphorus oxychloride and phosphorus pentachloride afforded 3-substituted-5-chloro-6-sulfamoyl-4-quinazolones (XIIa—c). Heating with urethane converted VIa to sulfamoylquinazolone (XIII), which was reduced to tetrahydroquinazolone (XIV) with sodium borohydride in the presence of aluminum chloride.

5) V. Peterow, O. Steohenson, and A.M. Wild, *J. Pharm. Pharmacol.*, **12**, 705 (1960).
6) H. Asakawa, Y. Fukushima, E. Imamiya, and Y. Kawamatsu, *Chem. Pharm. Bull.* (Tokyo), **27**, 525 (1979).

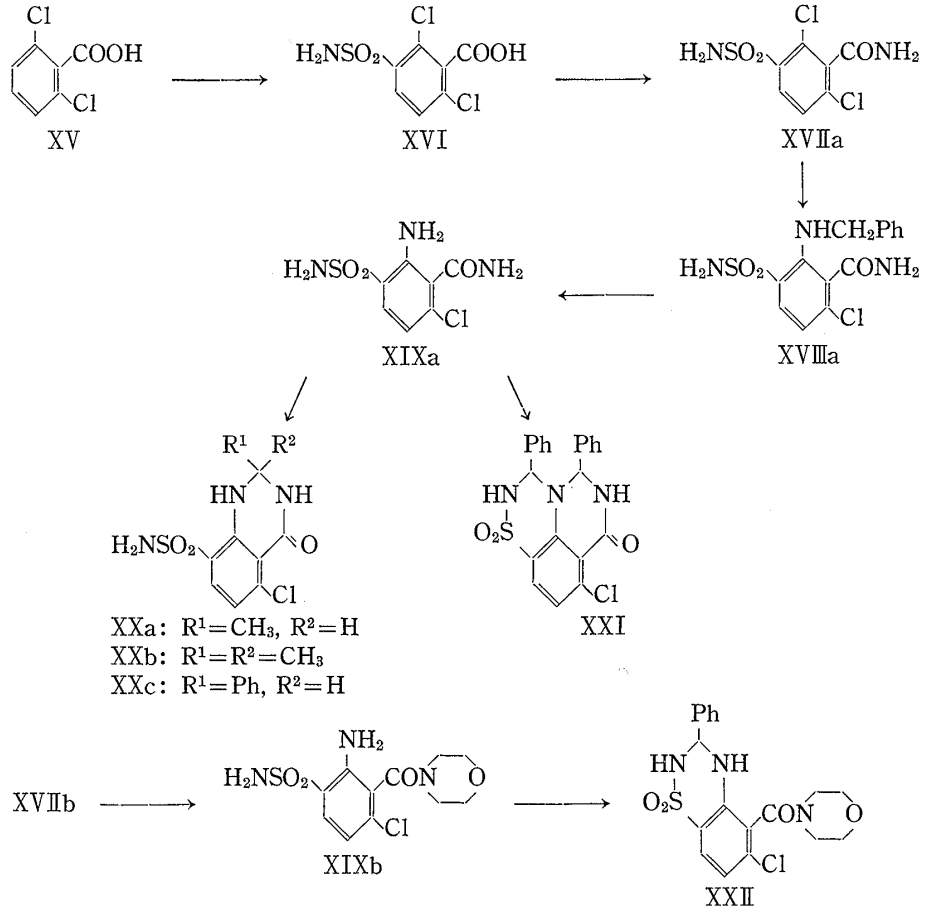
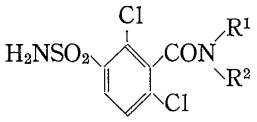


Chart 3

TABLE I. 2,6-Dichloro-3-sulfamoylbenzamide Derivatives (XVIIa—g)



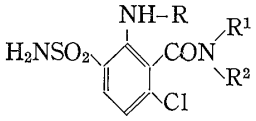
XVIIa—g

Compd. No.	R^1, R^2 N-	mp (°C)	Yield (%)	NMR (in d_6-DMSO) δ, ppm
XVIIa	H_2N	212—213	67	7.62 (1H, 5-H), 7.73 (2H, SO_2NH_2), 7.99 (1H, 4-H), 7.84, 7.18 (2H, $CONH_2$)
XVIIb	O N	221—222	100	3.13 (4H, CH_2NCH_2), 3.58 (4H, CH_2OCH_2), 7.73 (1H, 5-H), 7.72 (2H, SO_2NH_2), 8.02 (1H, 4-H)
XVIIc	CH_3 –NH	241—242	95.5	2.35 (3H, CH_3), 7.1—7.5 (4H, tolyl), 7.70 (1H, 5-H), 7.80 (2H, SO_2NH_2), 8.05 (1H, 4-H), 10.28 (1H, NH)
XVIId	$CH_3OCH_2CH_2NH$	167.5—168.5	61	3.34 (3H, CH_3O), *ca.* 4.5 (4H, CH_2OCH_2), 7.76 (2H, SO_2NH_2), 7.67 (1H, 5-H), 8.03 (1H, 4-H)
XVIIe	$PhCH_2CH_2NH$	147—149	77	3.95 (2H, $PhCH_2$), 3.54 (2H, CH_2N), 7.32 (5H, phenyl), 7.68 (1H, 5-H), 7.90 (1H, SO_2NH_2), 8.06 (1H, 4-H)
XVIIf	O CH_2NH	210—212	59	1.83 (4H, CH_2CH_2), 3.38 (2H, CH_2N), 3.5—4.2 (3H, $CHOCH_2$), 7.64 (1H, 5-H), 7.70 (2H, SO_2NH_2), 8.01 (1H, 4-H)
XVIIg	Et, Et NCH_2CH_2NH	182—182.5	49	0.99 (6H, $2\times CH_2$), 2.3—2.9 (2H, $3\times CH_2N$), 3.33 (2H, CH_2NCO), 7.64 (1H, 5-H), 8.04 (1H, 4-H)

As described above, on chlorosulfonation of 2,3-disubstituted acetanilide, the chlorosulfonyl group was introduced at the position *para* to the amino group. In order to obtain 6-chloro-3-sulfamoylanthranylic acid derivatives, in which a sulfamoyl group is located *ortho* to the amino group, the introduction of an amino group into 2,6-dichloro-3-sulfamoylbenzoic acid (XVI) was attempted by selective substitution of the chlorine atom at position 2. Chlorosulfonation of 2,6-dichlorobenzoic acid (XV) and subsequent treatment with aqueous ammonia afforded XVI in good yield (Chart 3). Substitution of the chlorine atom at position 2 in XVI with benzylamine by the usual method resulted in recovery of the starting compound, probably because of its rather weak reactivity. Therefore XVI was converted to the amide (XVIIa) by successive treatments with thionyl chloride and aqueous ammonia to enhance the reactivity of the chlorine atom. The various amides (XVIIa—g) of XVI prepared are shown in Table I. On heating XVIIa with benzylamine in dioxane, the monobenzylated derivative (XVIIIa) was obtained.

Selective substitution of the chlorine atom at position 2 in XVIIa with benzylamine was confirmed by the following reactions. Catalytic hydrogenation of XVIIIa afforded XIXa, which was subsequently converted to tetrahydroquinazolone XXa by treatment with acetaldehyde diethyl acetal in an acidic medium. Elemental analysis and spectral data of XXa showed that it was a positional isomer of 5-chloro-2-methyl-6-sulfamoyl-4-oxo-1,2,3,4-tetrahydroquinazolone (XIV) obtained from Va *via* VIa and XIII as described above. This result excluded the possibility of the alternative substitution, *i.e.*, substitution of the chlorine atom at position 6 in XVIIa. Treatment of XIXa with benzaldehyde in an alkaline medium gave XXI. The nuclear magnetic resonance (NMR) spectrum of XXI had two doublets of N–H protons at δ 8.69 and 9.00 ppm with coupling constants of 11 and 6 Hz, respectively. Spectral data and elemental analysis of XXI showed that it was a tricyclic condensation product of

Table II. 2-Amino-6-chloro-3-sulfamoylbenzamide Derivatives (XVIIIa—s)



Compd. No.	R	R¹	R²	mp (°C)	Yield (%)	NMR (in d_6-DMSO) 4-H (δ, ppm)	5-H (δ, ppm)
XVIIIa	$PhCH_2$	H	H	168—167[b]	62.3	6.89	7.68
XVIIIb	$PhCH_2$	$-(CH_2)_2O(CH_2)_2-$		196—200	76	6.97	7.76
XVIIIc	$PhCH_2$	*o*-MePh	H	211—213	67	6.87	7.76
XVIIId	$PhCH_2$	$PhCH_2CH_2$	H	87— 87.5	59	6.90	7.72
XVIIIe	*n*-Bu	H	H	159—162	86	6.87	7.51
XVIIIf	*n*-Bu	$-(CH_2)_2O(CH_2)_2-$		154—155	72	6.85	7.67
XVIIIg	*n*-Bu	*o*-MePh	H	199—200	82	6.85	7.72
XVIIIh	*n*-Bu	$PhCH_2CH_2$	H	176—177	36	7.76	7.63
XVIIIi	*n*-Bu	$Et_2N(CH_2)_2$	H	129—130	44	6.75	7.65
XVIIIj	*n*-Bu	THF[a]	H	151—152	45	6.78	7.57
XVIIIk	*n*-Bu	$MeO(CH_2)_2$	H	114—115	25	6.75	7.63
XVIIIl	$EtO(CH_2)_2$	$-(CH_2)_2O(CH_2)_2-$		185—186	78	6.90	7.69
XVIIIm	$EtO(CH_2)_2$	$PhCH_2CH_2$	H	163—164	88	6.84	7.65
XVIIIn	$EtO(CH_2)_2$	$Et_2N(CH_2)_2$	H	146—146.5	46	6.84	7.65
XVIIIo	$EtO(CH_2)_2$	THF[a]	H	161—161.5	61	6.85	7.66
XVIIIp	$EtO(CH_2)_2$	$MeO(CH_2)_2$	H	142—143	52	6.83	7.64
XVIIIq	$EtS(CH_2)_2$	H	H	98—100	36	6.85	7.65
XVIIIr	$EtS(CH_2)_2$	$-(CH_2)_2O(CH_2)_2-$		143—147	13	6.93	7.71
XVIIIs	$HOCH_2CH_2$	*o*-MePh	H	207	21	6.92	7.71

a) THF: tetrahydrofurfuryl.
b) Recrystallized from DMF–water and obtained as a solvate with 1/2 DMF.

XIXa with two mole equivalents of benzaldehyde. The production of XXI indicates that the amino group in XIXa is located *ortho* to both the carboxamide and sulfonamide groups, and provides further support for this structure of XVIIIa. Hydrolysis of XXI in a neutral or weak acidic medium liberated one mole of benzaldehyde to afford XXc, an analog of XXa.

The susceptibility of position 2 to nucleophilic attack in preference to position 6 in XVII seems to be independent of the kind of amide group sandwiched by the two chlorine atoms. Thus the morpholine analog (XVIIb) of XVIIa was similarly converted to XVIIIb, the structure of which was confirmed by converting it to the thiadiazine (XXII) *via* XIXb by catalytic hydrogenation followed by treatment with benzaldehyde in an alkaline medium. Using the method described above, 2,6-dichloro-3-sulfamoylbenzamides XVIIa—g in Table I were converted to the corresponding 2-amino-6-chloro-3-sulfamoylbenzamide derivatives XVIIIa—s in Table II. When XVIIc was heated with ethanolamine at its boiling point,

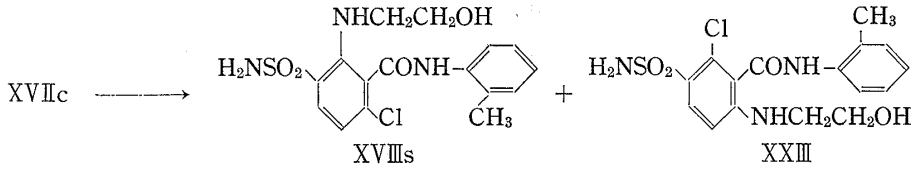


Chart 4

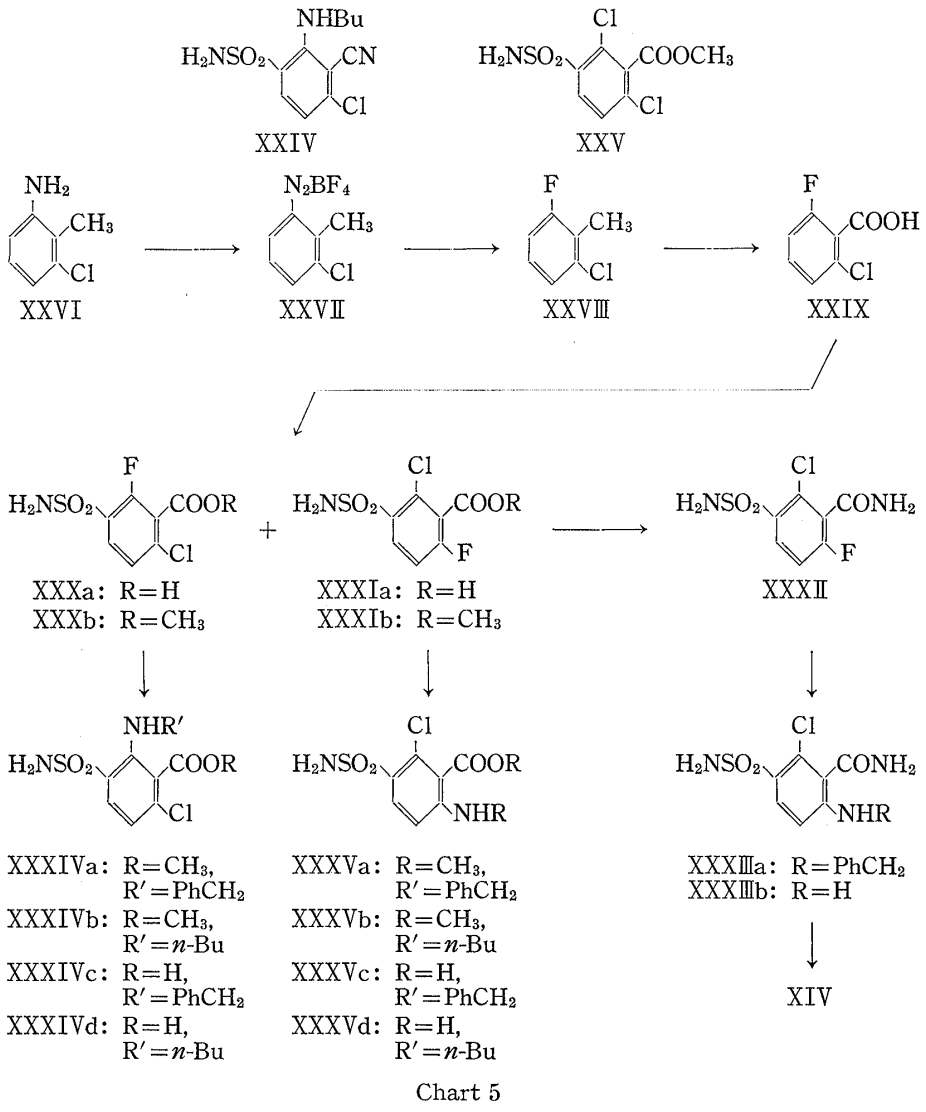


Chart 5

the isomer (XXIII) was obtained as a minor product along with the desired compound XVIIIs (Chart 4). In their NMR spectra (60 Mc), the difference of the two aromatic proton signals on the tetrasubstituted benzene ring was 0.79 ppm in the 2-aminoisomer (XVIIIs) and 1.08 ppm in the 6-aminoisomer (XXIII). Since the corresponding differences of the chemical shifts in all the compounds listed in Table II were 0.63—0.90 ppm, in fair agreement with that of XVIIIs, they were all assigned as 2-aminoisomers.

The greater reactivity of the chlorine atom at position 2 of XVIIa—g compared to that at position 6 may be attributed to the decreased steric interaction on substitution of chlorine by amine, due to the *ortho* substituents, sulfamoyl and carbamoyl groups.

To obtain the carboxylic acid derivatives of XVIII, hydrolysis of some typical compounds, XVIIIa, XVIIIe or the nitrile (XXIV), which was obtained by dehydration of XVIIIe with titanium tetrachloride in the presence of triethylamine,[7] was attempted under various conditions, but was unsuccessful. The only strategy remaining which seemed to be promising for the synthesis of free carboxylic acid derivatives was the use of compounds having a carboxylic ester group in place of the amide group in XVII. However, the ester derivative (XXV) corresponding to XVIIa would be susceptible to aminolysis during the substitution reaction of the chlorine atom with amine. To prevent this side reaction, the use of the more reactive 6-chloro-2-fluoro-3-sulfamoylbenzoic acid (XXXa) was planned.

As shown in Chart 5, 2-chloro-6-fluorobenzoic acid (XXIX) was obtained by permanganate oxidation of XXVIII, which was prepared from XXVI using the Schieman reaction.[8] Chlorosulfonation of XXIX afforded a mixture of the two isomers XXXa and XXXIa. XXXIa was isolated in pure form by crystallization of the mixture from methanol. Its structure was confirmed by converting it to XIV *via* XXXII, XXXIIIa and XXXIIIb in the usual manner. The isomer (XXXa) of XXXIa remaining in the mother liquor could not be isolated in a pure state at this stage. Esterification of the crude substance with thionyl chloride and methanol gave the methyl ester, XXXb, which was purified by recrystallization from methanol. On heating XXXb or XXXIb with benzylamine or butylamine in methanol, the desired 2-amino

Table III. Diuretic Activities of Sulfamoylanthranilic Acids and Related Compounds (30 mg/kg, *p.o.*)

Compd. No.	V	$U_{Na}V$	U_KV	Compd. No.	V	$U_{Na}V$	U_KV
XIIa	1.25	1.46**	1.37*	XVIIIm	1.18	1.00	1.08
XIIb	0.80	1.00	0.91	XVIIIn	1.27*	1.44**	1.36
XIIc	1.06	1.36**	1.28*	XVIIIo	1.23	1.06	1.23
XIII	0.77	0.94	0.79	XVIIIp	1.04	0.89	0.96
XVIIIa	1.44**	1.58**	1.23	XVIIIq	1.01	1.01	0.88
XVIIIb	1.42*	1.23	1.02	XVIIIr	1.04	0.89	0.95
XVIIIc	0.98	1.05	0.78	XVIIIs	1.01	1.01	0.88
XVIIId	0.91	1.04	1.13	XXa	1.09	1.03	1.00
XVIIIe	1.60***	1.57***	1.33***	XXc	1.09	0.85	1.06
XVIIIf	1.49**	1.44*	1.30*	XXXIIIa	1.12	1.07	1.19
XVIIIg	1.03	1.05	0.79	XXXIIIb	1.30	1.21	1.40
XVIIIh	1.46**	1.35	1.14	XXXIVc	1.13	1.10	1.12
XVIIIi	1.18	1.13	1.29	XXXIVd	1.34*	1.23*	1.40**
XVIIIj	1.37*	1.15	1.23	XXXVc	0.82	0.95	0.92
XVIIIk	1.45**	1.36	1.53*	XXXVd	1.12	1.08	1.29
XVIIIl	1.16	1.18*	1.04	H.C.[a]	1.82***	1.97***	1.62***

Significant difference: *$0.01<p<0.05$, **$0.001<p<0.01$, ***$p<0.001$.
a) H.C.: Hydrochlorothiazide (Esidrex, CIBA) was used as the reference compound (10 mg/kg, *p.o.*).

7) W. Lehnert, *Tetrahedron Lett.*, **1971**, 1501.
8) H. Wilstaedt, *Chem. Ber.*, **64**, 2688 (1931).

(XXXIVa, b) and 6-aminoisomers (XXXVa, b) were obtained, respectively. Alkaline hydrolysis of XXXIVa, b and XXXVa, b afforded XXXIVc, d and XXXVc, d, respectively.

The diuretic activities of XIIa—c, XIII, XVIIIa—s, XXa, c, XXXIIIa, b, XXXIVc, d and XXXVc, d are listed in Table III. Among the 2-amino-6-chloro-3-sulfamoylbenzamide derivatives (XVIIIa—s), XVIIIa, XVIIIe, XVIIIf and XVIIIn significantly increased both water and sodium excretion at a dose (*p.o.*) of 30 mg/kg. The 6-aminoisomers (XXXIIIa) of XVIIIa had no diuretic activity. Among the free carboxylic acid derivatives (XXXIVc, d and XXXVc, d), one of the 2-aminoisomers, XXXIVd, showed significant diuretic activity. Some derivatives of 7-chloroquinazoline-6-sulfonamide have potent diuretic activity.[9] However, 5-chloroquinazoline-6-sulfonamide derivatives (XIIa—c) and 5-chloroquinazoline-8-sulfonamide derivatives (XXa, XXc), synthesized from sulfamoylanthranilic acid derivatives, which have a chlorine atom *ortho* to the carboxy group, had no diuretic activity. These pharmacological results led to the following conclusions:

1) The presence of a chlorine atom *ortho* to the carboxy group, which enhanced the hypoglycemic activity of salicylic or anthranilic acid derivatives, has no such effect in the case of the diuretic activity of sulfamoylanthranilic acid derivatives.

2) The diuretic activity of the 6-chloro-3-sulfamoylanthranilic acid derivatives is greater than that of the 6-chloro-5-sulfamoyl derivatives.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were obtained with a Hitachi 215 spectrometer. NMR spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane (TMS) as an internal standard.

3-Chloro-2-methyl-4-sulfamoylacetanilide (Va)——A mixture of 3-chloro-2-methylacetanilide (IVa, 100 g), NaCl (30 g) and chlorosulfonic acid (400 g) was heated at 90—105° for 3 hr, then poured into ice-water (2 l) and the aqueous mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated down to remove the solvent and conc. NH_4OH (500 ml) was added to the residue. This mixture was stirred for 24 hr, then ammonia was removed under reduced pressure to afford a precipitate, which was dissolved in 1 N NaOH (100 ml). After removal of the insoluble material by filtration, 2 N HCl was added to the filtrate and its pH was adjusted to 1—2. The precipitated solid was collected by filtration and recrystallized from water to afford Va in 19.7% yield. mp 198—200°. IR ν_{max}^{Nujol} cm^{-1}: 1150, 1340 (SO_2). *Anal.* Calcd. for $C_9H_{11}ClNO_3S$: C, 41.15; H, 4.22; N, 10.56. Found: C, 40.79; H, 4.25; N, 10.38.

3-Chloro-N-ethoxycarbonyl-2-methylaniline (IVb)——Ethyl chlorocarbonate (10.8 g) was added to a solution of 3-chloro-2-methylaniline (14.2 g) in acetic acid (100 ml) with stirring and cooling. After stirring for 30 min, water (400 ml) was added to the mixture and the precipitated crystals were collected by filtration to give IVb (16.9 g, 80%). mp 97°. IR ν_{max}^{Nujol} cm^{-1}: 1685 (C=O). NMR (in $CDCl_3$) δ, ppm: 1.30 (3H, t), 2.30 (3H, s), 4.22 (2H, q), 7.00—7.74 (3H, m). *Anal.* Calcd. for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 5.56. Found: C, 56.24; H, 5.64; N, 6.65.

3-Chloro-N-ethoxycarbonyl-2-methyl-4-sulfamoylaniline (Vb)——A solution of IVb (5 g) and NaCl (1.5 g) in chlorosulfonic acid (16 ml) was allowed to stand for 3 days at room temperature. Next, the mixture was poured into ice-water and the crystals that precipitated were collected by filtration and stirred with conc. ammonium hydroxide (10 ml) for 12 hr. After the removal of ammonia under reduced pressure, conc. HCl was added to this solution. The precipitated crystals were collected by filtration and recrystallized from $CHCl_3$–MeOH to give Vb (3.3 g, 48%). mp 212—213°. NMR (in d_6-DMSO) δ, ppm: 1.27 (3H, t), 2.33 (3H, s), 4.15 (2H, q), 7.42 (2H, SO_2NH_2), 7.54 (1H, d), 7.85 (1H, d), 9.26 (1H, CONH). *Anal.* Calcd. for $C_{10}H_{13}ClN_2O_4S$: C, 41.03; H, 4.48; N, 9.57. Found: C, 41.09; H, 4.51; N, 9.56.

N-Acetyl-6-chloro-5-sulfamoylanthranilic Acid (VIa)——To a solution of $MgSO_4 \cdot 7H_2O$ (73 g) in water (560 ml), 26.2 g of Va was added at 80°. $KMnO_4$ (47 g) was added to the stirred solution portionwise during 1 hr and the reaction mixture was stirred for another 2 hr at this temperature. Purple $KMnO_4$ disappeared during this period. MnO_2 that precipitated was removed by filtration, then the filtrate was concentrated to *ca.* 300 ml and conc. HCl was added to adjust the pH to 1—2. The precipitated crystals were collected by filtration and recrystallized from water to give VIa (69%). mp 190—191°. IR ν_{max}^{Nujol} cm^{-1}: 1735 (C=O), 1335, 1180 (SO_2). NMR (in d_6-DMSO) δ, ppm: 2.06 (3H, s), 7.57 (2H, s), 7.87 (2H, q), 9.73 (1H, CONH).

9) B.V. Shetty, L.A. Campanella, T.L. Thomas, M. Fedorchuk, T.A. Davidson, L. Micheson, H. Volz, S.E. Zimmerman, E.J. Belair, and A.P. Truant, *J. Med. Chem.*, 13, 886 (1970).

Anal. Calcd. for $C_9H_9ClN_2O_5S$: C, 36.93; H, 3.10; N, 9.57; S, 10.93. Found: C, 36.93; H, 3.22; N, 9.42; S, 10.58.

6-Chloro-N-ethoxycarbonyl-5-sulfamoylanthranilic Acid (VIb)——VIb was prepared from Vb in a manner similar to that described for VIa. mp 212—213° (from THF–*n*-hexane). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1740 (COOH, NHCOOEt). NMR (in d_6-DMSO) δ, ppm: 1.26 (3H, t), 4.14 (2H, q), 7.49 (2H, SO_2NH_2), 7.88 (2H, q). *Anal.* Calcd. for $C_{10}H_{11}ClN_2O_6S$: C, 37.22; H, 3.44; N, 8.68. Found: C, 37.20; H, 3.70; N, 8.13.

Hydrolysis of VIa with Hydrochloric Acid——To a mixture of EtOH (50 ml) and conc. HCl (50 ml), 2.9 g of VIa was added and the mixture was refluxed for 5 hr, then concentrated under reduced pressure to remove the solvent. The residue was dissolved in 10% NaOH (15 ml). After removal of the insoluble matter by filtration, conc. HCl was added to the filtrate to bring the pH to 2. The precipitated solid was collected by filtration and recrystallized from water to afford needles which were identified as 4-amino-2-chlorobenzenesulfonamide. mp 177—178°.

3-Chloro-2-methyl-4-sulfamoylaniline (VIII)——a) Hydrolysis of Va with Hydrochloric Acid: A mixture of Va (5.3 g), EtOH (50 ml) and conc. HCl (50 ml) was refluxed for 1 hr and concentrated to remove EtOH. $NaHCO_3$ (10%) was added to the resulting aqueous solution and the precipitated crystals were collected and recrystallized from EtOH to afford VIII. mp 242—243°. IR ν_{max}^{Nujol} cm^{-1}: 3480, 3350, 3255 (NH_2, SO_2NH_2), 1315, 1130 (SO_2). NMR (in d_6-DMSO) δ, ppm: 2.16 (3H, s), 5.0—6.0 (2H, NH_2), 6.59 (1H, d), 6.98 (2H, SO_2NH_2), 7.54 (1H, d). *Anal.* Calcd. for $C_7H_9ClN_2O_2S$: C, 38.10; H, 4.11; N, 12.69. Found: C, 38.26; H, 4.04; N, 12.72.

b) Hydrolysis of Vb with Sodium Hydroxide: Vb (3 g) in 1 N NaOH (30 ml) was heated on a steam bath for 24 hr. After cooling, the precipitated crystals were collected and recrystallized from EtOH to afford VIII. mp 242—243°.

6-(N-Acetylsulfamoyl)-5-chloro-2-methyl-4-oxo-4H-3,1-benzoxazine (X)——A solution of VIa (4 g) in acetic anhydride (40 ml) was refluxed for 2 hr then evaporated down to remove the acetic anhydride. The residue was triturated with $(C_2H_5)_2O$ to afford 4.2 g of X. IR ν_{max}^{Nujol} cm^{-1}: 1760 (oxazine), 1690 (N-acetyl).

5-(N-Acetylsulfamoyl)-6-chloro-N-ethylanthranilic Acid (XI)——$NaBH_4$ (0.5 g) was added to a solution of X (0.5 g) in EtOH (10 ml) with stirring at 0°. After 3 hr, the mixture was concentrated to remove the solvent and the residue was dissolved in water and washed with AcOEt. The water layer was acidified to pH 2 with conc. HCl and extracted with AcOEt. The AcOEt layer was evaporated down to afford 0.15 g of XI (29%), which was recrystallized from aqueous EtOH. mp 227—229°. IR ν_{max}^{Nujol} cm^{-1}: 3320, 3110 (NH), 1720, 1700 (CH_3CONH, COOH), 1350, 1180 (SO_2). NMR (in d_6-DMSO) δ, ppm: 1.17 (3H, t), 1.97 (3H, s), 3.19 (2H, q), 7.06 (2H, SO_2NH_2). *Anal.* Calcd. for $C_{11}H_{13}ClN_2O_4S$: C, 41.19; H, 4.09; N, 8.73. Found: C, 41.22; H, 3.94; N, 8.56.

General Procedure for the Preparation of 3-Substituted-5-chloro-3,4-dihydro-2-methyl-4-oxo-6-sulfamoylquinazolines (XIIa—c)——PCl_5 (0.3 g) and $POCl_3$ (0.4 g) were added to a solution of VIa (5.0 mmol) and a primary amine (6.0 g) in toluene (30 ml). The mixture was refluxed for 8 hr and concentrated to remove the solvent. Water was added to the residue and the insoluble material was collected by filtration and washed successively with water, 10% $NaHCO_3$ and water to afford a 4-quinazolone.

a) 3-Butyl-5-chloro-3,4-dihydro-2-methyl-4-oxo-6-sulfamoylquinazoline (XIIa): XIIa was obtained in 54% yield. mp 171—174°. IR ν_{max}^{Nujol} cm^{-1}: 3330 (NH_2), 1670 (C=O), 1340, 1170 (SO_2). NMR (in d_6-DMSO) δ, ppm: 0.94 (3H, t), *ca.* 1.5 (4H, m), 2.60 (3H, s), 3.80 (2H, t), 7.55 (2H, SO_2NH_2), 7.58 (1H, d), 8.27 (1H, d). *Anal.* Calcd. for $C_{13}H_{16}ClN_3O_3S$: C, 47.34; H, 4.89; N, 12.94. Found: C, 46.85; H, 4.63; N, 12.50.

b) 5-Chloro-3,4-dihydro-2-methyl-4-oxo-3-phenyl-6-sulfamoylquinazoline (XIIb): XIIb was obtained in 57% yield. mp>300° (from DMF–EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3330, 3245 (NH_2), 1680 (C=O), 1340, 1160 (SO_2). *Anal.* Calcd. for $C_{15}H_{12}ClN_3O_3S$: C, 51.51; H, 3.46; N, 12.01. Found: C, 50.79; H, 3.48; N, 11.70.

c) 5-Chloro-3,4-dihydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-sulfamoylquinazoline (XIIc): XIIc was obtained in 78% yield. mp 285—286° (from DMF–MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3340 (NH_2), 1685 (C=O), 1350, 1165 (SO_2). NMR (in d_6-DMSO) δ, ppm: 2.06 (3H, s), 2.08 (3H, s), 7.44 (4H, s), 8.36 (1H, d), 8.64 (2H, SO_2NH_2), 8.72 (1H, d). *Anal.* Calcd. for $C_{16}H_{14}ClN_3O_3S$: C, 52.82; H, 3.88; N, 11.55. Found: C, 52.72; H, 3.91; N, 11.51.

5-Chloro-3,4-dihydro-2-methyl-4-oxo-6-sulfamoylquinazoline (XIII)——A mixture of VIa (2 g) and urethane (1.8 g) was heated at 160—180° for 5 hr. After cooling, 10% $NaHCO_3$ was added to the mixture, which was then stirred for 1 hr. The insoluble material was collected by filtration, and dissolved in 10% NaOH (8 ml). The insoluble material which formed in the alkaline medium was again removed and the filtrate was made acidic (pH 2) with 2 N HCl. The crystals that precipitated were collected to afford 0.8 g of XIII (43%). mp>300°. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O), 1360, 1175 (SO_2). NMR (in d_6-DMSO) δ, ppm: 3.38 (3H, s), 7.58 (1H, d), 7.81 (2H, SO_2NH_2), 8.26 (1H, d). *Anal.* Calcd. for $C_9H_8ClN_3O_3S$: C, 39.50; H, 2.95; N, 15.35. Found: C, 39.17; H, 3.10; N, 15.25.

5-Chloro-2-methyl-4-oxo-6-sulfamoyl-1,2,3,4-tetrahydroquinazoline (XIV)——Aluminum chloride (0.2 g) was added to a solution of XIII (0.4 g) in anhydrous diglyme (50 ml) then a solution of $NaBH_4$ (0.3 g) in diglyme (15 ml) was added dropwise. This mixture was heated at 85° for 1 hr and cooled to room tempera-

ture. Water (40 ml) and 2 N HCl were added to acidify the mixture, which was then evaporated down to remove the solvent.

The residue was triturated with water to afford XIV (0.2 g, 50%). mp 265—268°. IR ν_{max}^{Nujol} cm^{-1}: 3330, 3180 (NH_2), 1660 (C=O), 1340, 1160 (SO_2). NMR (in d_6-DMSO) δ, ppm: 1.32 (3H, d), 4.75 (1H, q), 7.10 (2H, q), 7.35 (1H, NH), 7.44 (2H, SO_2NH_2), 8.17 (1H, NH).

2,6-Dichloro-3-sulfamoylbenzoic Acid (XVI)——A solution of 2,6-dichlorobenzoic acid (33 g) in chlorosulfonic acid (150 ml) was heated at 150—160° for 2 hr. Next, the mixture was poured into ice-water (1.5 l) and the precipitated crystals were collected by filtration, yielding 42.9 g of 2,6-dichloro-3-chlorosulfonylbenzoic acid (80%). mp 169—170° (from ligroin). IR ν_{max}^{Nujol} cm^{-1}: 1720 (COOH), 1380, 1170 (SO_2). *Anal.* Calcd. for $C_7H_3Cl_3O_4S$: C, 29.04; H, 1.08; S, 11.07. Found: C, 29.34; H, 0.98; S, 10.79.

This chlorosulfonyl compound (41.7 g) was stirred in aqueous ammonia (300 ml) for 4 hr at room temperature, the mixture was concentrated to about 70 ml under reduced pressure and the resulting aqueous solution was adjusted to pH 1 with conc. HCl. The separated viscous liquid crystallized over a period of a few hours to give XVI (20 g, 43%). mp 195—197° (from water). IR ν_{max}^{Nujol} cm^{-1}: 1715 (COOH), 1340, 1150 (SO_2). *Anal.* Calcd. for $C_7H_5Cl_2NO_4S$: C, 31.13; H, 1.87; N, 5.19; S, 11.87. Found: C, 31.24; H, 1.97; N, 5.50; S, 11.72.

2,6-Dichloro-3-sulfamoylbenzoyl Chloride——A mixture of thionyl chloride (100 ml) and XVI (27 g) was refluxed for 2 hr and concentrated under reduced pressure to give 2,6-dichloro-3-sulfamoylbenzoyl chloride (28 g). IR ν_{max}^{Nujol} cm^{-1}: 1780 (COCl).

2,6-Dichloro-3-sulfamoylbenzamide (XVIIa)——A solution of 2,6-dichloro-3-sulfamoylbenzoyl chloride (5.6 g) in conc. NH_4OH (30 ml) was allowed to stand for 24 hr at room temperature. After removal of ammonia under reduced pressure, the separated oily substance gradually solidified to afford XVIIa (3.8 g, 67%).

General Procedure for the Preparation of 2,6-Dichloro-3-sulfamoylbenzamide Derivatives (XVIIb—g)——A mixture of a primary amine (30 mmol) and triethylamine (40 mmol) in THF (10 ml) was added portionwise to a solution of 2,6-dichloro-3-sulfamoylbenzoyl chloride (30 mmol) in THF (40 ml). The reaction mixture was stirred for 24 hr at room temperature then evaporated down to remove the solvent under reduced pressure. The residue was triturated with water to afford a 2,6-dichloro-3-sulfamoylbenzamide derivative. The results are listed in Table I.

General Procedure for the Preparation of 2-Substituted-amino-6-chloro-3-sulfamoylbenzamide Derivatives (XVIIIa—r)——A solution of a 2,6-dichloro-3-sulfamoylbenzamide derivative (20 mmol) and a primary amine (50 mmol) in dioxane (35 ml) was refluxed for 6 hr then concentrated under reduced pressure to remove the solvent, and 2 N HCl was added to the residue. The precipitated crystals were collected by filtration and recrystallized from a suitable solvent to afford a 6-chloro-2-substituted-amino-3-sulfamoylbenzamide derivative. The results are listed in Table II.

Reaction of XVIIc with Ethanolamine——A mixture of XVIIc (3.5 g) and ethanolamine (5 g) was heated at 180° for 1 hr then at 100—120° for 4 hr, and was then cooled to room temperature. Next, 2 N HCl and AcOEt were added to the mixture, which was stirred vigorously. The AcOEt layer was separated and concentrated under reduced pressure to remove the solvent. The residue was chromatographed on silica gel (100 g).

The first eluate with $CHCl_3$–MeOH (95:5, v/v) contained 6-chloro-2-(2-hydroxyethyl)amino-N-(2-methylphenyl)-3-sulfamoylbenzamide (XVIIIs, 0.8 g, 21%). IR ν_{max}^{Nujol} cm^{-1}: 1645 (C=O), 1320, 1145 (SO_2). NMR (in d_6-DMSO) δ, ppm: 2.28 (3H, s, CH_3), 3.3—3.7 (4H, m, N–CH_2CH_2–O), 5.10 (1H, OH), 6.01 (1H, NH), 6.92 (1H, d, aromatic 5-H), 7.1—7.3 (4H, m, tolyl), 7.43 (2H, SO_2NH_2), 7.71 (1H, d, aromatic 4-H), 10.50 (1H, CONH). *Anal.* Calcd. for $C_{16}H_{18}ClN_3O_4S$: C, 50.07; H, 4.73; N, 10.95. Found: C, 50.09; H, 4.87; N, 11.50.

The second eluate with $CHCl_3$–MeOH (95:5, v/v) contained 2-chloro-6-(2-hydroxyethyl)amino-N-(2-methylphenyl)-3-sulfamoylbenzamide (XXIII, 0.5 g, 5.4%). mp 163—164° (from AcOEt). IR ν_{max}^{Nujol} cm^{-1}: 1630 (C=O), 1325, 1160 (SO_2). NMR (in d_6-DMSO) δ, ppm: 2.32 (3H, s, CH_3), 3.25 (2H, t, CH_2O), 3.55 (2H, t, CH_2N), 4.75 (1H, OH), 5.58 (1H, NH), 6.72 (1H, d, aromatic 5-H), 7.1—7.6 (4H, m, tolyl), 7.20 (2H, SO_2NH_2), 7.80 (1H, d, aromatic 4-H), 10.13 (1H, CONH). *Anal.* Calcd. for $C_{16}H_{18}ClN_3O_4S$: C, 50.07; H, 4.73; N, 10.95. Found: C, 49.98; H, 4.59; N, 10.70.

2-Amino-6-chloro-3-sulfamoylbenzamide (XIXa)——A solution of XVIIIa (3.4 g) in MeOH (50 ml) was hydrogenated over Pd black (0.5 g) at 1 atm for 30 min. Pd black was removed by filtration and the filtrate was concentrated to remove the solvent. The residue was triturated with water to give XIXa (1.5 g, 60%). mp 159—160°. IR ν_{max}^{Nujol} cm^{-1}: 1660, 1645 ($CONH_2$), 1325, 1150 (SO_2). NMR (in d_6-DMSO) δ, ppm: 5.60 (2H, NH_2), 6.73 (1H, d, aromatic 5-H), 7.38 (2H, SO_2NH_2), 7.58 (1H, d, aromatic 4-H), 8.00, 7.64 (2H, $CONH_2$). *Anal.* Calcd. for $C_7H_8ClN_3O_3S$: C, 33.68; H, 3.23; N, 16.83. Found: C, 33.61; H, 3.07; N, 17.00.

4-(2-Amino-6-chloro-3-sulfamoylbonzoyl)morpholine (XIXb)——A solution of XVIIIb (1 g) in MeOH (20 ml) was hydrogenated over Pd black (0.3 g) at 1 atm for 1 hr. Pd black was removed by filtration and the filtrate was evaporated down to remove the solvent. The residue was dissolved in 2 N NaOH (20 ml). The solution was washed with AcOEt, acidified with 2 N HCl and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated down to remove the solvent. The residue was triturated with ether

to give XIXb (0.55 g, 70%). NMR (in d_6-DMSO) δ, ppm: 3.30, 3.50 (8H, $2\times NCH_2CH_2O$), 5.77 (2H, NH_2), 6.75 (1H, d, aromatic 5-H), 7.40 (2H, SO_2NH_2), 7.59 (1H, d, aromatic 4-H).

7-Chloro-3,4-diphenyl-6-oxo-2,3,4,5-tetrahydro-6H-1,2,4-thiadiazino[6,5,4-*i*,*j*]quinazoline-1,1-dioxide (XXI)——A mixture of XIXa (1 g), benzaldehyde (1.5 g), 10 N NaOH (0.5 g) and EtOH (50 ml) was refluxed for 10 hr then evaporated down to remove the solvent. The residue was dissolved in water and the solution was washed with ether. The aqueous layer was acidified to pH 1 with conc. HCl and the precipitated solid was collected by filtration and recrystallized from aqueous EtOH to afford XXI (0.5 g, 27%). mp 197—198°. IR ν_{max}^{Nujol} cm^{-1}: 3640, 3340 (NH), 1665 (C=O), 1325, 1150 (SO_2). NMR (in d_6-DMSO) δ, ppm: 5.21 (1H, d, J=6 Hz, 3-H), 5.99 (1H, d, J=11 Hz, 4-H), *ca.* 7.3 (5H, m, 3-phenyl), *ca.* 7.6 (5H, m, 4-phenyl), 7.75 (1H, d, 9-H), 7.01 (1H, d, 8-H), 8.69 (1H, d, J=11 Hz, 5-NH), 9.00 (1H, d, J=6 Hz, 2-NH). *Anal.* Calcd. for $C_{21}H_{16}ClN_3O_3S$: C, 59.22; H, 3.79; N, 9.87. Found: C, 58.32; H, 3.69; N, 9.62.

5-Chloro-4-oxo-2-phenyl-8-sulfamoyl-1,2,3,4-tetrahydroquinazoline (XXc)——A solution of XXI (0.5 g) in aqueous DMF was heated for 10 min at 100°. After cooling, the precipitated crystals were collected by filtration to afford XXc (0.5 g, 50%). mp 138—140°. IR ν_{max}^{Nujol} cm^{-1}: 1625 (C=O), 1330, 1150 (SO_2). NMR (in d_6-DMSO) δ, ppm: 5.84 (1H, 2-H), 6.85 (1H, d, 6-H), *ca.* 7.5 (5H, m, 2-phenyl), *ca.* 7.5 (2H, SO_2NH_2), 7.70 (1H, d, 7-H), 8.85 (1H, 3-NH). *Anal.* Calcd. for $C_{14}H_{12}ClN_3O_3S$: C, 49.78; H, 3.58; N, 12.44. Found: C, 49.53; H, 3.57; N, 12.18.

5-Chloro-2-methyl-4-oxo-8-sulfamoyl-1,2,3,4-tetrahydroquinazoline (XXa)——A mixture of XIXa (1.0 g), acetaldehyde diethyl acetal (0.5 g), conc. HCl (2 drops) and EtOH (100 ml) was refluxed for 2 hr, then evaporated down to remove the solvent.

The residue was triturated with water to afford XXa (0.9 g, 81.5%). mp 230—231° (from aqueous MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=O), 1340, 1170 (SO_2). NMR (in d_6-DMSO) δ, ppm: 2.40 (3H, d, CH_3), 4.83 (1H, q, CH), 6.55 (1H, 1-NH), 6.86 (1H, d, 6-H), 7.54 (2H, SO_2NH_2), 7.68 (1H, d, 7-H), 8.35 (1H, 3-NH). *Anal.* Calcd. for $C_9H_{10}ClN_3O_3S$: C, 39.21; H, 3.66; N, 15.24. Found: C, 39.48; H, 3.46; N, 16.35.

5-Chloro-2,2-dimethyl-4-oxo-8-sulfamoyl-1,2,3,4-tetrahydroquinazoline (XXb)——XXb (0.9 g, 77.5%) was obtained by a procedure similar to that described above using 2,2-dimethoxypropane (0.5 g) in place of acetaldehyde diethyl acetal. mp 276—278° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=O), 1320, 1170 (SO_2). NMR (in d_6-DMSO) δ, ppm: 1.51 (6H, s, dimethyl), 6.44 (1H, 1-NH), 6.85 (1H, d, 6-H), 7.64 (2H, SO_2NH_2), 7.71 (1H, d, 7-H), 8.42 (1H, 3-NH).

5-[Anhydro-N,N-(2-hydroxyethyl)carbamoyl]-6-chloro-2,3-dihydro-2-phenyl-4H-benzo-1,2,4-thiadiazine-1,1-dioxide (XXII)——A mixture of XIXb (0.4 g), benzaldehyde (0.7 g), 10 N NaOH (0.3 ml) and EtOH (25 ml) was refluxed for 4 hr then evaporated down to remove the solvent. The residue was dissolved in water and the solution was washed with ether, acidified with 2 N HCl and extracted with AcOEt. The AcOEt layer was washed with water, dried over $MgSO_4$ and evaporated down to remove the solvent. The residue was chromatographed on silica gel (50 g) and from the first eluate with $CHCl_3$–MeOH (50: 1), XXII (0.2 g, 40%) was obtained. mp 167—169° (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1620 (C=O), 1320, 1170 (SO_2). NMR (in d_6-DMSO) δ, ppm: *ca.* 3.3, 3.6 (8H, $2\times NCH_2CH_2O$), 5.93 (1H, 3-H), 6.93 (1H, 7-H), *ca.* 7.5 (5H, 2-phenyl), 7.63 (1H, 8-H), 8.07 (1H, SO_2NH_2). *Anal.* Calcd. for $C_{18}H_{18}ClN_3O_4S$: C, 53.01; H, 4.45; N, 10.30. Found: C, 52.89; H, 4.55; N, 9.88.

2-Butylamino-4-chloro-3-cyanobenzenesulfonamide (XXIV)——THF (200 ml) was added to a solution of $TiCl_4$ (13.2 g) in CCl_4 (20 ml) with stirring and cooling in an ice bath. A solution of XVIIIe (9.2 g) in THF (30 ml) was added, followed by a solution of triethylamine (14 g) in THF (20 ml) dropwise. The reaction mixture was stirred for 15 hr, then water (150 ml) was added and the aqueous mixture was extracted with ether. The ether layer was washed with water, dried over $MgSO_4$ and evaporated down to remove the solvent. The residue was triturated with petroleum ether to afford XXIV (8.1 g, quant.). mp 123° (from benzene). IR ν_{max}^{Nujol} cm^{-1}: 3390, 3280 (NH), 2210 (CN), 1345, 1250 (SO_2). NMR (in d_6-DMSO) δ, ppm: 0.92 (3H, t, CH_3), 1.50 (4H, m, C–CH_2CH_2–C), 3.60 (2H, N–CH_2), 6.50 (1H, NH), 7.00 (1H, d, 5-H), 7.78 (2H, SO_2NH_2), 7.99 (1H, d, 6-H). *Anal.* Calcd. for $C_{11}H_{14}ClN_3O_2S$: C, 45.91; H, 4.90; N, 14.60. Found: C, 45.60; H, 4.53; N, 14.35.

Methyl 2,6-Dichloro-3-sulfamoylbenzoate (XXV)——An etherial solution of diazomethane prepared from N-nitrosomethylurea (4 g) with 50% KOH (12 ml) was added to a solution of XVI (8 g) in THF (40 ml) and the mixture was allowed to stand for 30 min, then evaporated down to remove the solvent. The residue was dissolved in AcOEt. The solution was washed with 10% $NaHCO_3$, dried over $MgSO_4$ and evaporated down to remove the solvent, affording XXV (7 g, 82%). mp 117—118° (from benzene). *Anal.* Calcd. for $C_8H_7Cl_2NO_4S$: C, 33.82; H, 2.48; N, 4.93. Found: C, 34.01; H, 2.28; N, 4.98.

2-Chloro-6-fluorobenzoic Acid (XXIX)——A mixture of 2-chloro-6-fluorotoluene (XXVIII, 65.2 g), $KMnO_4$ (176 g) and water (1.8 l) was refluxed for 5 hr with stirring. After removal of the remaining starting material by steam distillation, MnO_2 was removed by filtration. The filtrate was acidified with conc. HCl and the precipitated crystals were collected by filtration, affording 53 g of XXIX (95.6%). IR ν_{max}^{Nujol} cm^{-1}: 1700 (COOH). In this example, 18.7 g of XXVIII was recovered by steam distillation.

2-Chloro-6-fluoro-3-sulfamoylbenzoic Acid (XXXIa)——A mixture of XXIX (83.2 g) and chlorosulfonic acid (440 ml) was refluxed for 2 hr, then poured into ice-water. The precipitated crystals were collected by filtration and added to conc. NH_4OH (620 ml). The mixture was stirred for 24 hr, concentrated to remove

ammonia under reduced pressure, acidified with conc. HCl and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated down to remove the solvent. The residue was crystallized from MeOH–benzene, affording XXXIa (27.7 g). mp 160—160.5°. IR ν_{max}^{Nujol} cm^{-1}: 1710 (COOH), 1340, 1170 (SO_2). *Anal.* Calcd. for $C_7H_5ClFNO_4S$: C, 33.15; H, 1.99; N, 5.52. Found: C, 32.69; H, 2.28; N, 5.82.

A mixture (30 g) of XXXa and XXXIa was obtained from the mother liquor and used for the next procedure.

Methyl 6-Chloro-2-fluoro-3-sulfamoylbenzoate (XXXb)——The above mixture (6 g) was dissolved in $SOCl_2$ (30 ml) and the solution was refluxed for 1.5 hr then evaporated down to remove $SOCl_2$. The residue was dissolved in MeOH (60 ml) and this solution was allowed to stand for 1 hr. MeOH was removed by evaporation and the residue was crystallized from aqueous MeOH then recrystallized from MeOH, affording XXXb (1.25 g). mp 106°. IR ν_{max}^{Nujol} cm^{-1}: 1740 ($COOCH_3$), 1360, 1180 (SO_2). NMR (in d_6-DMSO) δ, ppm: 3.95 (3H, s, CH_3), 7.61 (1H, 5-H), 7.84 (2H, SO_2NH_2), 8.03 (1H, 4-H). *Anal.* Calcd. for $C_8H_7ClFNO_4S$: C, 35.90; H, 2.64; N, 5.23. Found: C, 35.89; H, 2.59; N, 5.36.

Methyl 2-Chloro-6-fluoro-3-sulfamoylbenzoate (XXXIb)——A solution of XXXIa (1.0 g) in $SOCl_2$ (5 ml) was refluxed for 1.5 hr and evaporated down to remove $SOCl_2$. The residue was dissolved in MeOH (10 ml) and the solution was allowed to stand for 1 hr then evaporated to remove the solvent. The residue was crystallized from aqueous MeOH, affording XXXIb (0.4 g, 38%). mp 181—182°. IR ν_{max}^{Nujol} cm^{-1}: 1720 ($COOCH_3$), 1360, 1190 (SO_2). NMR (in d_6-DMSO) δ, ppm: 3.95 (3H, s, CH_3), 7.56 (1H, t, $J_{H-H}=J_{H-F}=9$ Hz, 5-H), 7.75 (2H, SO_2NH_2), 8.18 (1H, q, $J_{H-H}=9$ Hz, $J_{H-F}=6$ Hz, 4-H). *Anal.* Calcd. for $C_8H_7ClFNO_4S$: C, 35.90; H, 2.64; N, 5.23. Found: C, 36.02; H, 2.69; N, 5.39.

2-Chloro-6-fluoro-3-sulfamoylbenzamide (XXXII)——A solution of XXXIa (7 g) in $SOCl_2$ (27 ml) was refluxed for 1 hr then evaporated down to remove $SOCl_2$. The residue was dissolved in conc. NH_4OH (100 ml) and stirred for 24 hr. Evaporation of ammonia afforded XXXII (4.3 g, 61.5%). mp 228—230°. *Anal.* Calcd. for $C_7H_6ClFN_2O_3S$: C, 33.28; H, 2.39; N, 11.09. Found: C, 33.29; H, 2.39; N, 11.14.

6-Benzylamino-2-chloro-3-sulfamoylbenzamide (XXXIIIa)——A mixture of XXXII (3 g), benzylamine (2.5 g) and dioxane (20 ml) was refluxed for 2 hr. Water (100 ml) was added to the cooled mixture and the precipitated crystals were collected by filtration and recrystallized from aqueous dioxane, affording XXXIIIa (1.05 g, 50%). mp 238—239°. NMR (in d_6-DMSO) δ, ppm: 4.42 (2H, d, CH_2), 6.30 (1H, t, NH), 6.47 (1H, d, 5-H), 7.31 (7H, phenyl, SO_2NH_2), 7.64 (1H, d, 4-H). *Anal.* Calcd. for $C_{14}H_{14}ClN_3O_3S$: C, 49.49; H, 4.17; N, 12.37. Found: C, 49.44; H, 4.17; N, 12.31.

6-Amino-2-chloro-3-sulfamoylbenzamide (XXXIIIb)——A solution of XXXIIIa (1.0 g) in MeOH (15 ml) was hydrogenated over Pd black at 1 atm for 3 hr. Pd black was removed by filtration and the filtrate was concentrated to remove the solvent. The residue was triturated with AcOEt to afford XXXIIIb (0.65 g, 88%). mp 252.5—253°. IR ν_{max}^{Nujol} cm^{-1}: 1665, 1640 ($CONH_2$), 1355, 1180 (SO_2NH_2). NMR (in d_6-DMSO) δ, ppm: 5.70 (2H, NH_2), 6.66 (1H, d, 5-H), 7.13 (2H, SO_2NH_2), 7.46 (1H, d, 4-H), 7.96 (2H, $CONH_2$). *Anal.* Calcd. for $C_7H_8ClN_3O_3S$: C, 33.68; H, 3.23; N, 16.83. Found: C, 33.75; H, 3.03; N, 16.56.

Conversion of XXXIIIb to XIV——A mixture of XXXIIIb (0.5 g), acetaldehyde diethyl acetal (0.3 g), conc. HCl (one drop) and EtOH (50 ml) was refluxed for 2 hr then evaporated down to remove the solvent. The residue was triturated with water to afford XIV (0.4 g, 72%). This sample was identical with that obtained by the reduction of XIII with $NaBH_4$–$AlCl_3$ on the basis of mixed melting point test and spectral comparison.

N-Benzyl-6-chloro-3-sulfamoylanthranilic Acid (XXIVc)——A mixture of XXXb (0.45 g), benzylamine (0.25 g) and MeOH (10 ml) was refluxed for 5 hr then evaporated down to remove the solvent, affording XXXIVa. XXXIVa was dissolved in 1 N NaOH (10 ml) and the solution was heated at 85° for 4 hr. After cooling, 2 N HCl was added to the solution, affording XXXIVc (0.35 g, 63.6%). mp 170—173° (from aqueous MeOH). NMR (in d_6-DMSO) δ, ppm: 4.45 (2H, CH_2), 6.97 (1H, d, 5-H), 7.36 (5H, phenyl), 7.61 (2H, SO_2NH_2), 7.76 (1H, d, 4-H). *Anal.* Calcd. for $C_{14}H_{13}ClN_2O_4S$: C, 49.34; H, 3.84; N, 8.22. Found: C, 49.63; H, 3.90; N, 8.08.

N-*n*-Butyl-6-chloro-3-sulfamoylanthranilic Acid (XXXIVd)——A mixture of XXXb (0.38 g), *n*-butylamine (0.2 g) and MeOH (10 ml) was refluxed for 5 hr then evaporated down to remove the solvent, affording XXXIVb. This XXXIVb was dissolved in 1 N NaOH (10 ml) and the solution was heated at 85° for 4 hr. After cooling, the solution was acidified with 2 N HCl and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated down to remove the solvent. The residue was triturated with MeOH (1 ml), affording XXXIVd (0.2 g, 46%). mp 127—128°. NMR (in d_6-DMSO) δ, ppm: 0.8—2.0 (7H, CH_2-CH_2CH_3), 3.1—3.6 (2H, N-CH_2), 6.0 (1H, NH), 6.90 (1H, d, 5-H), 7.76 (1H, d, 4-H). *Anal.* Calcd. for $C_{11}H_{15}ClN_2O_4S$: C, 43.07; H, 4.93; N, 9.13. Found: C, 43.08; H, 4.63; N, 8.90.

N-Benzyl-6-chloro-5-sulfamoylanthranilic Acid (XXXVc)——A mixture of XXXIb (0.9 g), benzylamine (0.5 g) and MeOH (20 ml) was refluxed for 5 hr and evaporated down to remove the solvent, affording XXXVa. This XXXVa was dissolved in 1 N NaOH (15 ml) and the solution was heated at 85° for 4 hr. After cooling, 2 N HCl was added to the solution, affording XXXVc (0.2 g, 18%). mp 191—193° (from aqueous MeOH). NMR (in d_6-DMSO) δ, ppm: 4.44 (2H, CH_2), 6.58 (1H, d, 3-H), 7.19 (2H, SO_2NH_2), 7.32 (5H, phenyl), 7.68 (1H, d, 4-H). *Anal.* Calcd. for $C_{14}H_{13}ClN_2O_4S$: C, 49.34; H, 3.84; N, 8.22. Found: C, 49.52; H, 3.71; N, 8.33.

N-*n*-Butyl-6-chloro-5-sulfamoylanthranilic Acid (XXXVd)——A mixture of XXXIb (1.34 g), *n*-butylamine (1.1 g) and MeOH (20 ml) was refluxed for 2 hr then evaporated down to remove the solvent. The residue was chromatographed on silica gel (250 g). The first eluate with CH_3Cl–MeOH (95 : 5 v/v) contained methyl N-butyl-6-chloro-5-sulfamoylanthranilate (XXXVb, 0.9 g, 56%). mp 130—133°. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O), 1340, 1160 (SO_2NH_2). *Anal.* Calcd. for $C_{12}H_{17}ClN_2O_4S$: C, 44.93; H, 5.34; N, 8.73. Found: C, 44.67; H, 5.19; N, 8.48.

This XXXVb (0.6 g) was dissolved in 1 N NaOH (10 ml) and the solution was heated at 70° for 3 hr. After cooling, the soluion was acidified with 2 N HCl and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated down to remove the solvent. The residue was triturated with petroleum ether, affording XXXVd (0.3 g, 58%). mp 87° NMR (in d_6-DMSO) δ, ppm: 0.83 (3H, CH_3), *ca.* 1.4 (4H, m, C–CH_2CH_2–C), *ca.* 3.1 (2H, m, CH_2–N), *ca.* 5.9 (1H, broad, NH), 6.75 (1H, d, 4-H), 7.50 (2H, SO_2NH_2), 7.60 (2H, d, 5-H).

Assay of Diuretic Activity——The diuretic activity of test compounds was assayed according to the method described by Lipschits *et al.*[10] Groups of 5—6 male Sprague-Dawley rats aged 6—7 weeks were not given diet or water for 18 hr prior to study. One group was used as the untreated control and the rats were given 25 ml/kg *p.o.* of 0.9% NaCl. Rats in the other test groups were similarly treated with 25 ml/kg *p.o.* of 0.9% NaCl containing 30 mg/kg of test compounds suspended in a small amount of gum arabic. These rats were kept in metabolic cages (1 rat/cage) and their spontaneous urine was collected for 5 hr. The parameters used for diuretic evaluation were urine volume (V) and sodium ($U_{Na}V$) and potassium (U_KV) in the urine, which were calculated as the values per 100 g body weight per 5 hr. The relative potencies of the test compounds were expressed as the ratio of the response evoked in the test animals to that of the control ones. Data obtained were analyzed statistically using Student's t-test for the control and test groups. The probability levels for significant differences were $*0.01<p<0.05$ $**0.001<p<0.01$ and $***p<0.001$. Urinary sodium and potassium were measured with a Hitachi 205-D flame photometer.

Acknowledgement The authors wish to express their gratitude to Drs. E. Ohmura and M. Nishikawa for their valuable advice and encouragement. Thanks are also due to Dr. K. Nishikawa for the assay of diuretic activity.

10) W.L. Lipschits, Z. Hadidian, and A. Kerpscar, *J. Pharmacol. Exp. Ther.*, 79, 97 (1943).