5-Sulfamoylorthanilic Acids, a Sulfonamide Series with Salidiuretic Activity

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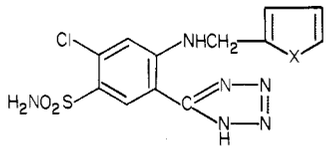
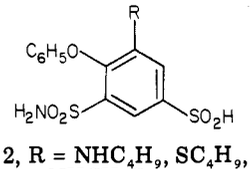
A series of 4,N-disubstituted 5-sulfamoylorthanilic acids was synthesized by nucleophilic substitution reactions starting either from 2,4-dihalogeno-5-sulfamoylbenzenesulfonic acids or, in most cases, from phenyl 2,4-dihalogeno-5-sulfamoylbenzenesulfonates. The latter method is based on the relative stability of the phenoxysulfonyl group to nucleophiles, e.g., amines, phenols, and thiols, and the possibility of smooth hydrolytic or hydrogenolytic cleavage as a final step, with formation of the SO_3H group. On evaluation of these compounds for salidiuretic activity in rats orally (po), and in dogs orally and intravenously (iv), a number of highly active substances was found; the best had a threshold dose of 0.02 mg/kg po in dogs. The results are given in tables, and the structure–activity relationships within the series are discussed. Besides the known effect of the phenoxy radical, an outstanding activating effect was shown by the butylsulfonyl and cycloalkylsulfonyl radicals and by the *N*-methylanilino radical in particular when they were located in the 4-position of the orthanilic acid molecule. The sulfanilic acid isomers corresponding to three of the most active compounds were synthesized and proved to be completely inactive in rats.

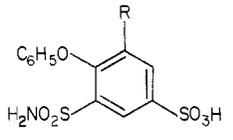
In review of the findings in the field of high-ceiling diuretics over the last 2 decades, there is evidence that one of the very common requirements for optimal and therapeutically applicable activity is an acidic moiety in the molecule. This is true for furosemide, bumetanide, and ethacrynic acid, where the carboxy group represents this center. Any structural variations that cancel the acidic character in this class of diuretic, e.g., esterification and amidation, strongly diminish or delete the activity. Other acidic groups that can replace the carboxy group without substantial loss of activity are the tetrazolyl analogues (1)



1, X = O, S



2, R = NHC_4H_9, SC_4H_9, $NHCH_2C_6H_5$

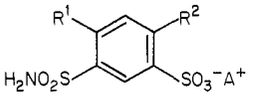


3, R = NHC_4H_9, $NHCH_2C_6H_5$, c-NC_4H_8

of furosemide[1] and the sulfo analogues (**2** and **3**) in the bumetanide series.[2] Whereas compounds **1** are active both intravenously and orally in dogs, the sulfinic acids **2** and sulfonic acids **3** are reported to be active in dogs only by the intravenous route.[2]

In this paper we report the synthesis of sulfonic acid analogues of furosemide (**4**), elaborated since 1977,[3] dividing the new compounds into groups **A–D**.

All compounds were isolated as stable sodium potassium or ammonium salts, preferably by crystallization from aqueous solution in the pH range 6.5–7.5. Generally, the



4A, R^1 = chloro
B, R^1 = phenoxy
C, R^1 = basic residue
D, R^1 = R-SO_2, R-SO, or R-S residue

water solubility of the sodium salts is considerably higher than that of the corresponding potassium salts. In each group very potent salidiuretics of the high-ceiling type were found, when tested orally in rats and dogs.

Chemistry. 4-Chloro-5-sulfamoylorthanilic Acids (7, Schemes I and II, Table I). The aim of the synthesis was primarily to form the sulfonic acid analogue of furosemide with R^2 = furfurylamino (**7a–c**). Based on the experiences in the anthranilic acid series, the relatively reactive group should be introduced into the benzene nucleus at as late a stage as possible.

The readily accessible sulfonic acid **5** (Scheme I) proved to be an unsuitable reactant. The electron-withdrawing effect of the sulfo group is too weak to ensure the smooth and selective substitution of the adjacent chlorine atom. Consequently, the fluoro compound **6e** was synthesized in eight conventional steps, starting with 4-chloro-2-fluoroaniline[7,8] (Scheme II). Excess furfurylamine at 90 °C selectively substituted the fluoro group in **6e**. The orthanilic acid formed was isolated as the fairly soluble furfurylammonium salt **7a**, which could easily be transformed to the therapeutically preferred sodium or potassium salt **7b** or **7c**. The corresponding free sulfonic acid is unstable. The compounds listed in Table I were obtained in a manner analogous to that described for **7d–c**.

4-Phenoxy-5-sulfamoylorthanilic Acids (14, Scheme III, Table II). The synthetic route for compounds of this type is illustrated for **14a** in Scheme III. The phenoxysulfonyl group, with its strong electron-withdrawing effect, allows the nucleophilic substitution of both chlorine atoms of **9** in a stepwise-directed way, as it activates the one in the para position markedly more strongly than the one in the ortho position. A byproduct of the sequences **9** → **10** was **11**, while that of **10** → **12** was **13**. Both could easily be separated by fractional crystallization. The fission of the phenoxysulfonyl group in the final step can be effected without any side reaction by refluxing **12** with aqueous NaOH or by hydrogenolysis in the presence of at least 1

(1) A. Popelak, A. Lerch, K. Stach, E. Roesch, and K. Hardebeck, German Patent 1 815 922 (1970).
(2) O. B. Tvaermose Nielsen and P. W. Feit, in "Diuretic Agents" (*ACS Symp. Ser.*, **no. 83**), E. J. Cragoe, Jr., Ed., American Chemical Society, Washington DC, 1978, p 17.
(3) K. Sturm and R. Muschaweck, U.S. Patent 4 161 533 (1979); German prior (1977).
(4) H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).
(5) P. W. Feit and O. B. Tvaermose Neilsen, *J. Med. Chem.*, **15**, 79 (1972).
(6) P. W. Feit and O. B. Tvaermose Nielsen, *J. Med. Chem.*, **19**, 402 (1976).
(7) A. Lachowicz, T. Manzonski, B. Jelonek, and W. Podolski, *Rocz. Chem.*, **43**, 507 (1969).
(8) A. W. Gay and J. H. Tobin, U.S. Patent 3 900 519 (1975).

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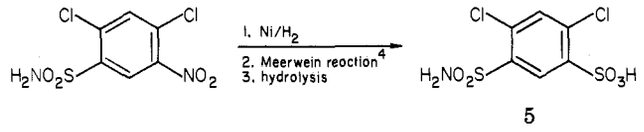
Scheme I



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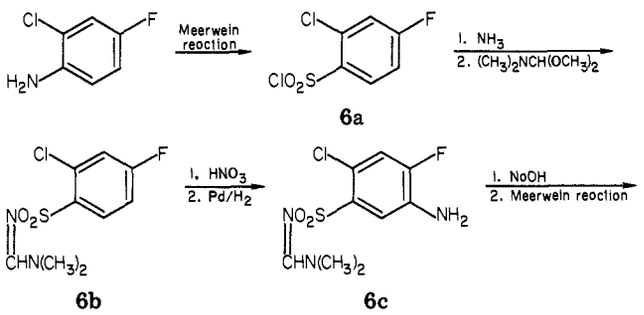
Scheme II



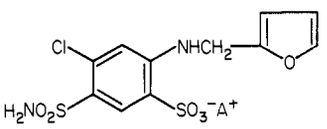
6a

6b

6c

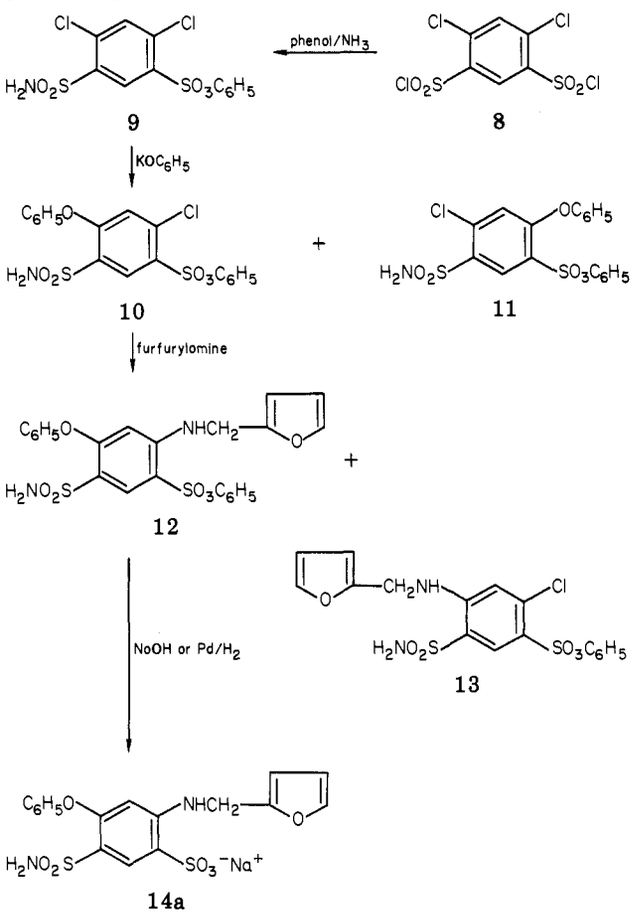
6d

6e



7a, A^+ = furfurylammonium
b, $A^+ = Na^+$
c, $A^+ = K^+$

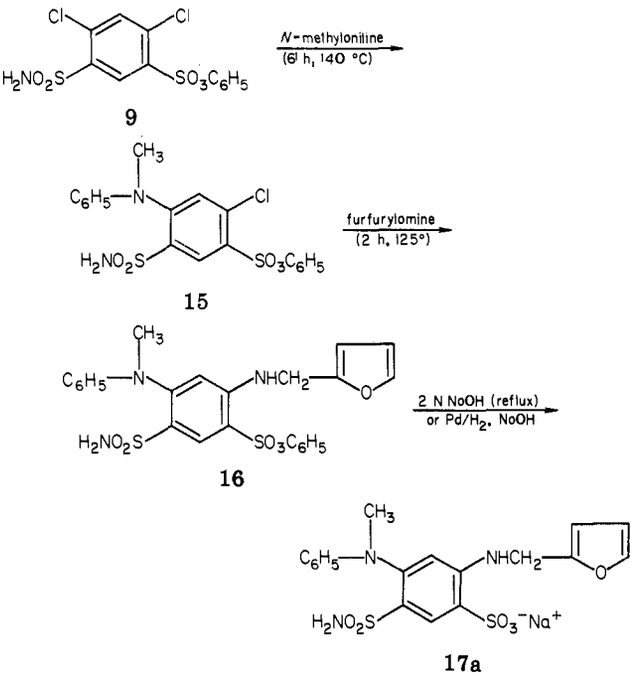
Scheme III



14a

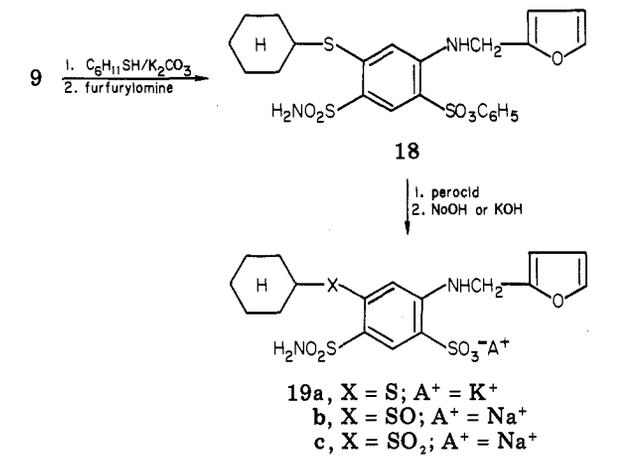
equiv of a base. If the byproduct 13 is the desired intermediate, it can be obtained in almost quantitative yield

Scheme IV



17a

Scheme V



19a, X = S; $A^+ = K^+$
b, X = SO; $A^+ = Na^+$
c, X = SO_2; $A^+ = Na^+$

by condensing 9 with furfurylamine.

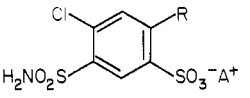
Compounds 14b–o were obtained in a similar fashion (see Table II).

4-Amino-5-sulfamoylorthanilic Acids (17, Scheme IV, Table III). The synthesis of these compounds essentially follows Scheme III, using the phenyl ester 9 as starting material. Unlike phenols (9 → 10 and 11, Scheme III), amines react by exclusively replacing the para chlorine atom in the first step. In the following step, there are no side reactions worth mentioning.

For example, Scheme IV consists of a summary of the steps involved in the synthesis of 17a, the compound possessing the greatest salidiuretic activity of this type. The other compounds (17b–r) listed in Table III were synthesized in an analogous manner.

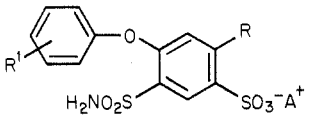
4-Thio-Substituted 5-Sulfamoylorthanilic Acids (19, Scheme V, Table IV). The compounds of this type were prepared by the method illustrated in Scheme V, using 9 as a starting material. The R = cyclohexylthio compound is shown as an example. The mercaptan reacts with 9 to selectively replace the 4-position chlorine atom, but excess mercaptan must be avoided, since under relatively mild conditions disubstitution can take place. The mercaptan can be replaced by the corresponding isothi-

Table I. Physical Properties of 7a-n



compd	R	A	method	mp, °C	recrystn solvent	formula
7a	$NHCH_2CCHCHCHO$	$H_3NCH_2CCHCHCHO$	A	178 dec	EtOH	$C_{16}H_{18}ClN_3O_7S_2$
7b	$NHCH_2CCHCHCHO$	Na	B	268 dec	H_2O	$C_{11}H_{10}ClN_2NaO_6S_2$
7c	$NHCH_2CCHCHCHO$	K	B	251 dec	H_2O	$C_{11}H_{10}ClKN_2O_6S_2$
7d	$NHCH_2CH_2CCHCHCHO$	Na	B	280 dec	EtOH	$C_{12}H_{12}ClN_2NaO_6S_2$
7e	$N(CH_3)CH_2CCHCHCHO$	Na	B	210 dec	H_2O	$C_{12}H_{12}ClN_2NaO_6S_2$
7f	$NHCH_2CHCH_2CH_2CH_2O$	Na	B	279 dec	*i*-PrOH	$C_{11}H_{14}ClN_2NaO_6S_2$
7g	$NHCH_2CCHCHCHS$	$H_3NCH_2CCHCHCHS$	A	203	H_2O	$C_{16}H_{18}ClN_3O_5S_4$
7h	$NHCH_2C_6H_5$	$H_3NCH_2C_6H_5$	A	207	H_2O	$C_{20}H_{22}ClN_3O_5S_2$
7i	$NHCH_2C_6H_3$, 3,4-OCH_2O	Na	B	238 dec	H_2O	$C_{14}H_{12}ClN_2NaO_7S_2$
7k	$NHCH_2C_6H_4$, 2-OCH_3	Na	B	240 dec	EtOH	$C_{14}H_{14}ClN_2NaO_6S_2$
7l	$N(CH_2C_6H_5)_2$	Na	B	208 dec	H_2O	$C_{20}H_{18}ClN_2NaO_5S_2$
7m	$NHCH_2CCHCHNCHCH$	Na	B	255 dec	H_2O	$C_{12}H_{11}ClN_3NaO_5S_2$
7n	$NHCH_2CH_2OC_2H_5$	Na	B	262 dec	EtOH	$C_{10}H_{14}ClN_2NaO_6S_2$

Table II. Physical Properties of 14a-o



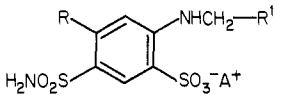
compd	R	A	R^1	method	mp, °C	recrystn solvent	formula
14a	$NHCH_2CCHCHCHO$	Na	H	E, F	242 dec	aq EtOH	$C_{17}H_{15}NaN_2O_7S_2$
14b	$NHCH_2CCHCHCHO$	K	H	E	255 dec	H_2O	$C_{17}H_{15}KN_2O_7S_2$
14c	$NHCH_2CCHCHCHO$	NH_4	H	F	190 dec	AcOEt	$C_{17}H_{19}N_3O_7S_2$
14d	$NHCH_2CCHCHCHO$	amiloride	H	*a*	250 dec	aq EtOH	$C_{23}H_{24}ClN_9O_8S_2$
14e	$NHCH_2CCHCHCHO$	$H_2N(c\text{-}C_6H_{11})_2$	H	*b*	208-210	EtOH	$C_{29}H_{39}N_3O_7S_2$
14f	$NHCH_2CCHCHCHO$	$H_3NC(CH_2OH)_3$	H	F	162-164	*i*-PrOH	$C_{21}H_{21}N_3O_{10}S_2$
14g	$NHCH_2CCHCHCHO$	K	3-CH_3	E	218 dec	H_2O	$C_{18}H_{17}KN_2O_7S_2$
14h	$NHCH_2CCHCHCHO$	K	3,4-$(CH_3)_2$	E	225 dec	H_2O	$C_{19}H_{19}KN_2O_7S_2$
14i	$NHCH_2CCHCHCHO$	K	3-Cl	E	250 dec	H_2O	$C_{17}H_{14}ClKN_2O_7S_2$
14k	$NHCH_2CCHCHCHO$	K	4-Cl	E	220 dec	H_2O	$C_{17}H_{14}ClKN_2O_7S_2$
14l	$NHCH_2CH_2CCHCHCHO$	K	H	E	230 dec	H_2O	$C_{18}H_{17}KN_2O_7S_2$
14m	$N(CH_3)CH_2CCHCHCHO$	K	H	E	183 dec	MeOH	$C_{18}H_{17}KN_2O_7S_2$
14n	$NHCH_2CCHCHCHS$	K	H	E	248 dec	H_2O	$C_{17}H_{15}KN_2O_6S_3$
14o	$NHCH_2C_6H_5$	NH_4	H	F	220 dec	AcOEt	$C_{19}H_{21}N_3O_6S_2$

[a] Precipitated by uniting equimolar aqueous solutions of 14a and amiloride hydrochloride. [b] Precipitated by uniting equimolar aqueous solutions of 14a and $HN(C_6H_{11})_2 \cdot AcOH$.

uronium salt, along with the appropriate amount of inorganic base.

Care is required in the oxidation of 18 to the corresponding sulfoxide or sulfone because of the presence of the furfurylamino group. 3-Chloroperbenzoic acid in methylene chloride at room temperature proved to be a satisfactory oxidizing agent. All of the R–X residues that were investigated survived the hydrolysis with aqueous NaOH or KOH under reflux. Phenyl ester cleavage by hydrogenation can be employed only in the case of sul-

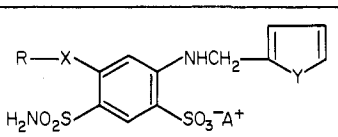
Table III. Physical Properties of 17a-r



compd	R	R^1	A	method	mp, °C	recrystn solvent	formula
17a	$N(CH_3)C_6H_5$	CCHCHCHO	Na	G, H	200 dec	H_2O	$C_{18}H_{18}N_3NaO_6S_2$
17b	$N(CH_3)C_6H_5$	CCHCHCHO	K	G	220 dec	H_2O	$C_{18}H_{18}KN_3O_6S_2$
17c	$N(CH_3)C_6H_5$	CCHCHCHO	NH_4	H	185 dec	AcOEt/*i*-Pr_2O	$C_{18}H_{22}N_4O_6S_2$
17d	$N(CH_3)C_6H_5$	CCHCHCHO	amiloride	*a*	230 dec	H_2O	$C_{24}H_{27}ClN_{10}O_7S_2$
17e	$N(C_2H_5)C_6H_5$	CCHCHCHO	Na	G	165 dec	H_2O	$C_{19}H_{20}N_3NaO_6S_2$
17f	$N(CH_3)C_6H_4$, 4-CH_3	CCHCHCHO	Na	G	205 dec	H_2O	$C_{19}H_{20}N_3NaO_6S_2$
17g	$N(CH_3)C_6H_4$, 4-Cl	CCHCHCHO	Na	G	216 dec	H_2O	$C_{18}H_{17}ClN_3NaO_6S_2$
17h	$N(CH_3)$-c-C_6H_{11}	CCHCHCHO	K	G	203 dec	H_2O	$C_{18}H_{24}KN_3O_6S_2$
17i	NHC_6H_5	CCHCHCHO	Na	G	240 dec	H_2O	$C_{17}H_{16}N_3NaO_6S_2$
17k	NHC_6H_4, 4-Cl	CCHCHCHO	Na	G	245 dec	H_2O	$C_{17}H_{15}ClN_3NaO_6S_2$
17l	NHC_6H_4, 3-CH_3	CCHCHCHO	Na	G	225 dec	H_2O	$C_{18}H_{18}N_3NaO_6S_2$
17m	$NHCH_2C_6H_5$	CCHCHCHO	K	G	228 dec	H_2O	$C_{18}H_{18}KN_3O_6S_2$
17n	$N(CH_3)C_6H_5$	CCHCHCHS	Na	G	215 dec	H_2O	$C_{18}H_{18}N_3NaO_5S_3$
17o	$N(CH_3)C_6H_5$	C_6H_5	Na	G	245 dec	H_2O	$C_{20}H_{20}N_3NaO_5S_2$
17p	NHC_6H_4, 2-Cl	CCHCHCHO	Na	G	188 dec	H_2O	$C_{17}H_{15}ClN_3NaO_6S_2$
17q	NHC_6H_4, 2-CH_3	CCHCHCHO	Na	G	>230 dec	H_2O	$C_{18}H_{18}N_3NaO_6S_2$
17r	$N(CH_3)C_6H_5$	CH_2CCHCHCHO	K	G	210 dec	H_2O	$C_{19}H_{20}KN_3O_6S_2$

[a] Precipitated by uniting equimolar aqueous solutions of 17a and amiloride hydrochloride

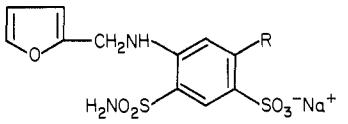
Table IV. Physical Properties of 19a-u



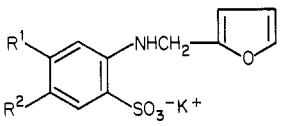
compd	X-R	Y	A	method	mp, °C	recrystn solvent	formula
19a	S-c-C_6H_{11}	O	K	I	227 dec	H_2O	$C_{17}H_{21}KN_2O_6S_3$
19b	SO-c-C_6H_{11}	O	Na	K	270 dec	H_2O	$C_{17}H_{21}N_2NaO_7S_3$
19c	SO_2-c-C_6H_{11}	O	Na	L	300 dec	H_2O	$C_{17}H_{21}N_2NaO_8S_3$
19d	SO_2-c-C_6H_{11}	S	Na	L	310 dec	H_2O	$C_{17}H_{21}N_2NaO_7S_4$
19e	SO_2-c-C_5H_9	O	Na	L	285 dec	H_2O	$C_{16}H_{19}N_2NaO_8S_3$
19f	SO_2-c-C_7H_{13}	O	Na	L	284 dec	H_2O	$C_{15}H_{23}N_2NaO_8S_3$
19g	SO_2CH_2-c-C_6H_{11}	O	Na	L	>350	H_2O	$C_{18}H_{23}N_2NaO_8S_3$
19h	SC_6H_5	O	Na	I	236 dec	H_2O	$C_{17}H_{15}N_2NaO_6S_3$
19i	SOC_6H_5	O	Na	K	235 dec	H_2O	$C_{17}H_{15}KN_2O_7S_3$
19k	$SO_2C_6H_5$	O	K	L	270 dec	H_2O	$C_{17}H_{15}KN_2O_8S_3$
19l	S-*n*-Bu	O	K	I	245 dec	H_2O	$C_{15}H_{19}KN_2O_6S_3$
19m	SO-*n*-Bu	O	Na	K	195	aq EtOH	$C_{15}H_{19}N_2NaO_7S_3$
19n	SO_2-*n*-Bu	O	Na	L	325 dec	H_2O	$C_{15}H_{19}N_2NaO_8S_3$
19o	SO_2-*s*-Bu	O	Na	L	280 dec	H_2O	$C_{15}H_{19}N_2NaO_8S_3$
19p	SO_2-*i*-Bu	O	Na	L	>300	H_2O	$C_{15}H_{19}N_2NaO_8S_3$
19q	SO_2-*t*-Bu	O	K	L	>330	H_2O	$C_{15}H_{19}KN_2O_8S_3$
19r	SO_2-c-C_6H_{11}	-CH=CH-	Na	L	296 dec	H_2O	$C_{19}H_{23}N_2NaO_7S_3$
19s	$SO_2CH_2C_6H_5$	O	K	L	145 dec	H_2O	$C_{18}H_{17}KN_2O_8S_3$
19t	SO_2-*n*-Pr	O	Na	L	320 dec	H_2O	$C_{14}H_{17}N_2NaO_8S_3$
19u	SO_2-*n*-hexyl	O	Na	L	209 dec	H_2O	$C_{17}H_{23}N_2NaO_8S_3$

fones.

In order to complete the structure–activity relationship studies, the sulfanilic acid isomers of the highly potent orthanilic acids **7b**, **14a**, and **19c** (**20a–c**) and the methyl-



20a, R = Cl
b, R = OC_6H_5
c, R = SO_2-c-C_6H_{11}



21a, R^1 = OC_6H_5; R^2 = SO_2NHCH_3
b, R^1 = OC_6H_5; R^2 = $SO_2N(CH_3)_2$
c, R^1 = $N(CH_3)C_6H_5$; R^2 = SO_2NHCH_3
d, R^1 = $N(CH_3)C_6H_5$; R^2 = $SO_2N(CH_3)_2$

and dimethylsulfamoyl analogues of **14a** and **17a** (**21a–d**) were synthesized and tested in rats orally (Tables VI and VII).

Finally, some physical data for the most interesting orthanilates, **14a** and **17a**, in comparison to furosemide are provided in Table V and Figure 1.

Pharmacology. The compounds listed in Tables I–IV were tested for diuretic and saluretic effects in rats, and some of them were also evaluated in dogs. Many of the compounds proved to be potent, orally active salidiuretics of the high-ceiling type, with an efficacy in the range of furosemide and a rapid onset of action. The results of the oral screening in rats are summarized in Tables VI and VII. The oral activity in dogs of a selected number of compounds that were found to be highly active in initial screening assays are summarized in Table VIII. The most interesting compounds of the series were the phenoxy compound **14a**, the *N*-methylanilino compound **17a**, and the cyclohexylsulfonyl compound **19c**. For compounds **14a** and **17a**, the temporal aspect of urine and Na^+ excretion after oral administration in the dog is shown in Table IX and in Figures 2–5. After oral administration of each compound at the highest of the doses, a markedly prolonged effect (for a period of 7–24 h) was evident of both urine and Na^+ excretion. Compounds **14a** and **17a** were tested for **carbonic anhydrase inhibition** (CAI) according to the method of Philpot,[12] with furosemide as reference substance; both were found to be devoid of any CAI effects.

Glomerular filtration rate (GFR) was determined for **14a** in comparison with furosemide (Table X). Whereas the GFR of furosemide slightly exceeded that of controls, the GFR of **14a** was somewhat lower than the control values. It should be noted that the SAR discussion below does not consider the influence of the orthanilic acids on GFR.

Micropuncture investigations concerning the site and mechanisms of action of **14a** in comparison with furosemide showed **14a** to be a "loop diuretic" with a main site of action in the loop of Henle, but with additional effects in the distal tubule. In comparison to furosemide, the K^+ secretion in the distal tubule after **14a** administration is moderate, resulting in a significantly diminished fractional and absolute K^+ excretion (Table X, Figures 6–8). The

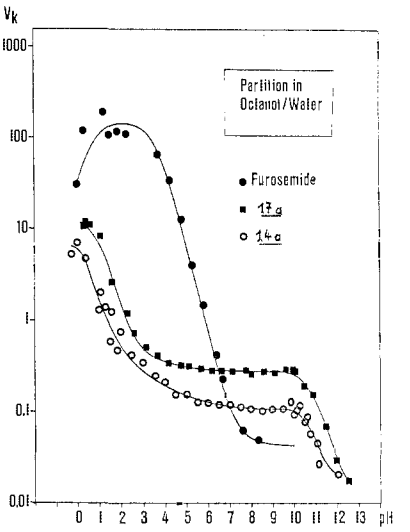


Figure 1. pH-dependent partition coefficients in octanol/water of 14a, **17a**, and furosemide.

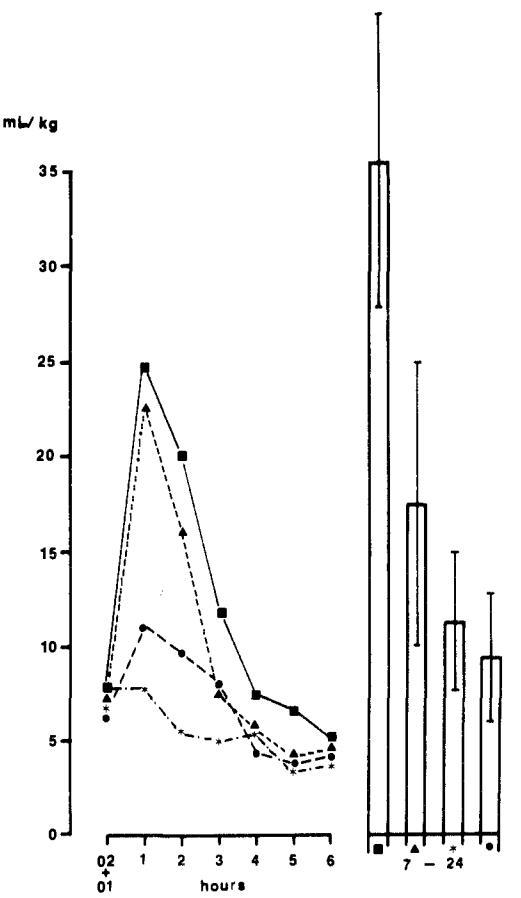


Figure 2. Urinary excretion after oral administration of **14a** in the dog: control (*-----*), 0.39 mg/kg (●---●), 1.56 mg/kg (▲---▲), 6.25 mg/kg (■—■).

method and findings are described in detail below.

Structure–Activity Relationships. Substitution of the sulfamoyl group in the *5-position* produces a strong decrease in activity. This is demonstrated by the test results of the oral administration of methylsulfamoyl and dimethylsulfamoyl analogues of **14a** and **17a** in the rat (**23–26**, Table VII).

In the 2-position, the only substituents affording any activity were furfurylamino, 2-furylethylamino, 2-thenylamino, and benzylamino. Within each series bearing the same 4-substituent, the most active compounds were al-

(9) W. L. Lipschitz, Z. Hadidan, and A. Kerpcsav, *J. Pharmacol. Exp. Ther.*, **85**, 97 (1943).
(10) K. Meng, *Naunyn-Schmiedeberg's Arch. Exp. Pharmakol. Exp. Pathol.*, **257**, 355 (1967).
(11) W. A. Ritschel, "Angewandte Biopharmazie", Wissenschaftl. Verlagsgesellschaft, Stuttgart, 1973, p 72.
(12) F. J. Philpot and J. St. L. Philpot, *Biochem. J.*, **30**, II (1936).

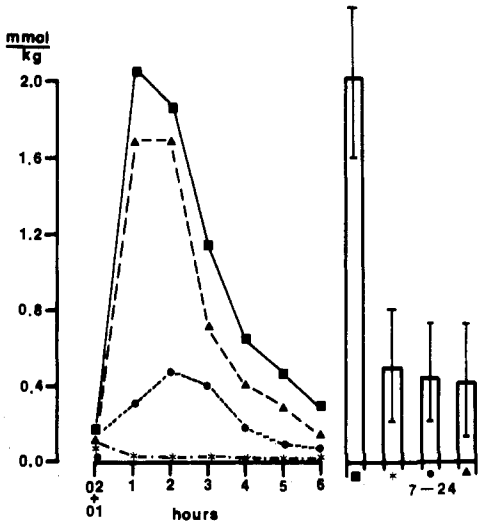


Figure 3. Sodium excretion after oral administration of 14a in the dog: control (*-----*), 0.39 mg/kg (●---●), 1.56 mg/kg (▲---▲), 6.25 mg/kg (■—■).

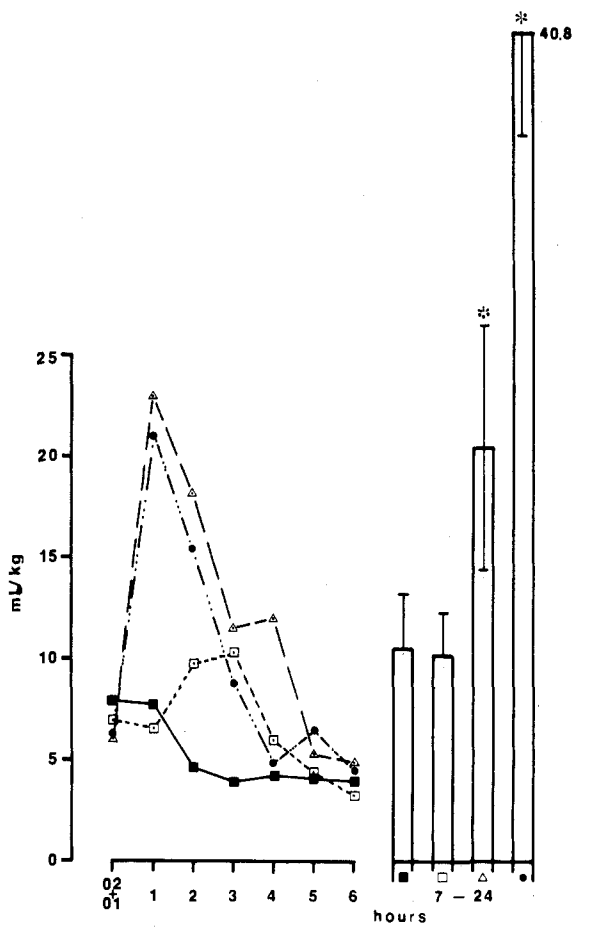


Figure 4. Urinary excretion after oral administration of 17a in the dog: control (■—■), 0.05 mg/kg (□---□), 0.39 mg/kg (△---△), 3.12 mg/kg (●·····●).

ways those with a 2-furfurylamino substituent. This observation was valid regardless of the test species used. The activity-conferring effect of the other three groups is more difficult to describe, since it varies with both the test species and the 4-substituent. It is summarized in Table XI.

The survey makes evident that the contribution of a 2-substituent to salidiuretic activity can strongly depend on the test species. This is true especially for the 2-thenylamino and 2-furylethylamino group.

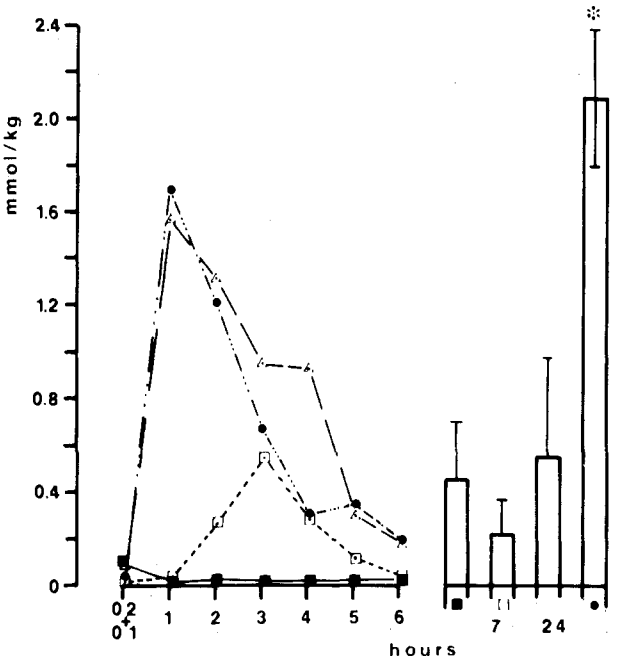


Figure 5. Sodium excretion after oral administration of 17a in the dog: control (■—■), 0.05 mg/kg (□---□), 0.39 mg/kg (△--△), 3.12 mg/kg (●·····●).

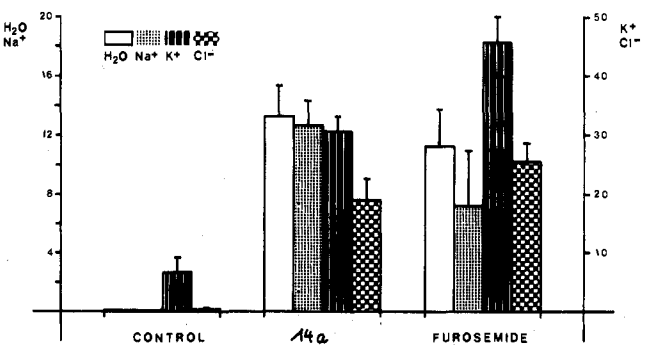


Figure 6. Effect of 14a on fractional excretion of water, Na^+, K^+, and Cl^- in comparison with furosemide.

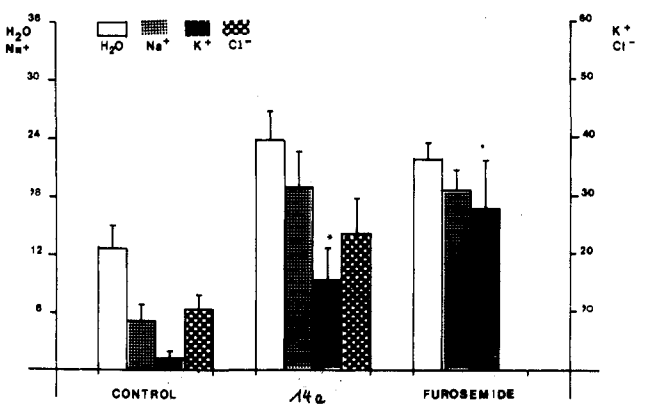
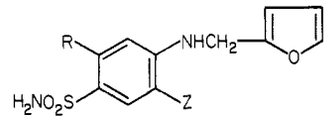


Figure 7. Effect of 14a on the fractional delivery of water, Na^+, and K^+ in the early distal tubules in comparison with furosemide.

The role of the *4-substituent* will be viewed while the 2-furfurylamino group is held constant. The potency in the oral dog assay of the 4-chloro compound **7b** was in the order of that of furosemide. In this same assay, the corresponding 4-phenoxy compound **14a** and the 4-phenylthio compound **19h** were markedly more potent than **7b**. However compound **19h** proved to be orally inactive in rats. In contrast to **19h**, the corresponding 4-phenylsulfonyl compound **19k** was highly active orally in rats but

Table V. Water Solubility, pK Values, and Partition Coefficients of 14a and 17a in Comparison with the Sodium Salt of Furosemide



compd	R	Z	solubility in water (20 °C), %	pK_1	pK_2	partition coeff (octanol/H_2O) (pH 7)
furosemide	Cl	COONa	6	3.65		0.075
14a	OC_6H_5	SO_3Na	20 (1)[a]	0.5	10.25	0.12
17a	$N(CH_3)C_6H_5$	SO_3Na	4 (1)[a]	1.0	10.47	0.28

[a] Solubility of the corresponding potassium salt.

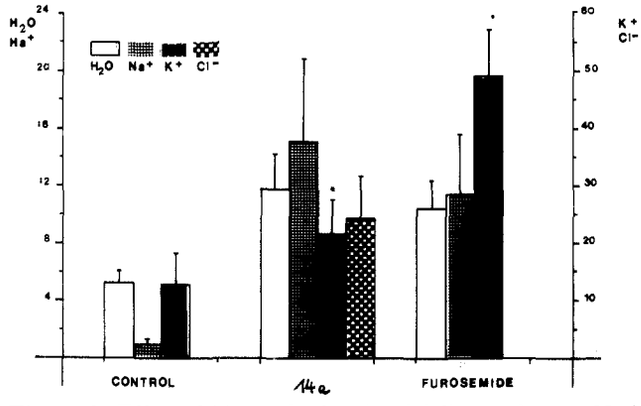


Figure 8. Effect of 14a on the fractional delivery of water, Na^+ and K^+ in the late distal tubules in comparison with furosemide.

only weakly active in dogs. Most unexpected was the strong activating effect of the *N*-methylanilino radical in the 4-position; compound **17a** exhibited threshold salidiuretic activity at a dose as low as 0.02 mg/kg po and 0.006 mg/kg iv in the dog with an efficacy comparable with that of furosemide.

In agreement with the findings of Feit et al.[5,6] in the anthranilic acid series, the activating effect of the anilino radical in the 4-position is low. The anilino compound **17i** is about 100-fold less potent than **17a** when administered orally in the dog (Table VIII). All other **17a** analogues were inactive, at least orally in the rat (Table VI).

Another unexpected result was the strong activating effect of some 4-alkylsulfonyl and 4-cycloalkylsulfonyl radicals. The highest activation was obtained with butylsulfonyl radicals and cycloalkyl(alkyl) radicals containing five to seven carbon atoms. In particular, the 4-*n*-butylsulfonyl compound (**19n**), the 4-cyclohexylsulfonyl compound (**19c**), and the cyclohexylmethylsulfonyl compound (**19g**) are highly potent salidiuretics (orally in both rats and dogs), being comparable to the *N*-methylanilino compound (**17c**). Surprisingly, the aromatic analogues of **19g**, the benzylsulfonyl compound **19s**, was inactive in the oral rat assay. None of the sulfoxide compounds of **19** tested so far possessed only salidiuretic activity in either the oral rat or oral dog assay (**19b,i,m**). However, sulfides of **19** are definitely active (**19a,h,l**), but they are weaker than the sulfones, with the exception of the phenylthio compound **19h**, which is very potent orally in the dog, as mentioned above.

Isomerization of the highly active **7b**, **14a**, and **19c** by interchanging the 2- and the 4-substituent led to the complete loss of salidiuretic activity (**20**, **21**, and **22** in Table VI). The influence of the anion on the salidiuretic activity appears to be unimportant as long as high water solubility is retained, as the comparison **14a–c,f** in Table VI indicates. The extremely low solubility of the dicyclohexylammonium salt **14e** results in the loss of salidiuretic activity (rat, po). Sufficient activity of both, the salidiuretic cation and the potassium-sparing anion, is retained in the sparingly water-soluble salts of amiloride with **14d** and **17d**.

Micropuncture Investigations Concerning the Site and Mechanism of Action of Compound 14a in Comparison with Furosemide. The clearance and micropuncture studies were performed in 32 male Wistar rats (mean body weight 258 ± 13.4 g) anesthetized with inactin, 100 mg/kg ip. The animals were fasted for 16 h before the beginning of the study but received water ad libitum. The method described by Meng[10] was used.

Fractional Excretion of Ions and Water. The effect of **14a** on urine flow (vol), glomerular filtration rate (GFR), and fractional excretion of water, Na^+, K^+, and chloride, in comparison with that of furosemide, is shown in Table X and Figure 6. The urine flow was significantly increased to 0.9094 ± 0.1415 mL/min per kilogram of body weight after **14a** administration and to 0.998 ± 0.101 after furosemide administration, the inulin U/P ratios being significantly decreased ($p < 0.05$). The fractional water excretion amounted to 13% of the filtered load with **14a** and to 10% with furosemide (Figure 6). The glomerular filtration rate was not affected. About 12.5 and 7.1% of the filtered Na^+ was excreted after **14a** and furosemide administration, respectively. The fractional chloride excretion after **14a** administration was approximately 19.1% and was distinctly lower than after furosemide administration (25.4%). The fractional K^+ excretion amounted to approximately 6.7% in the control periods and was increased to 30.4% of the filtered K^+ during **14a** infusion and to 45.5% during furosemide infusion.

Effects in the Proximal and Early Distal Tubules (Figure 7). In the proximal tubule, the reabsorption of fluid, Na^+, K^+, and chloride was not affected by **14a**. In the early distal tubule, the fractional Na^+ and water excretions were significantly increased from approximately 5 and 12.5% (control) to 18.9 and 24% following **14a** administration, respectively. The fractional K^+ excretion was also increased from 2% (control), but only to 15.4% following **14a** administration, as compared to 28.1% after furosemide administration. The early distal flow rate was significantly increased only after **14a** administration.

Effects in the Late Distal Tubules (Figure 8). Along the distal tubule, approximately 11 to 13% of the filtered fluid was reabsorbed after administration of each diuretic, but only 6% of the filtered Na^+ was reabsorbed after **14a** administration as compared to 11% after furosemide administration.

In contrast, the fractional K^+ excretion was markedly increased as compared to earlier distal values. Whereas

49.1% of filtered K^+ was excreted after furosemide administration, after **14a** administration this rate only amounts 21.5%.

Experimental Section

Melting points were determined in open glass capillaries with a Büchi (Flawil, Switzerland) apparatus and were uncorrected. The structures of all compounds described were verified by ^1H NMR spectroscopy with a Varian Associates T 60 spectrometer with Me_4Si as internal standard. The structure of the key intermediate **10** was determined by ^{13}C NMR spectroscopy in our department of Applied Physics by F. Cavagna. Suitable solvents for the TLC of sulfonic acid salts were dioxane/water/ethyl acetate/toluene (18:2:4:5) and toluene/MeOH/water/diethylamine (67:27:1:10). Partition coefficients (in octanol/Britton–Robinson buffer[11] in the range of pH 0–13) and pK values were determined in our Biochemistry Department by N. Sistovaris.

4-Chloro-2-fluoro-5-sulfamoylbenzenesulfonic Acid Dihydrate (6e). 2-Chloro-4-fluoroaniline[7,8] (146 g, 1.0 mol) was diazotized in 0.6 L of 5 N HCl, in the usual manner, by adding 72 g of $NaNO_2$ in 0.1 L of water. The diazo solution was poured in several portions into a freshly prepared mixture of 20 g of $CuCl_2 \cdot 2H_2O$ in 50 mL of H_2O and 1.0 L of HOAc, which had been saturated at room temperature with SO_2. As soon as N_2 evolution had ceased, 2 L of water was added, and the mixture was extracted with 2 L of EtOAc. After the mixture was washed with water and dried ($MgSO_4$), the organic solution was evaporated, and the residue was fractionally distilled in vacuo to give 166 g (72%) of **6a**, bp 88–90 °C. The entire quantity of **6a** was added dropwise to 1 L of liquid ammonia, the excess ammonia was allowed to evaporate at room temperature, and the residue was triturated with 0.5 L of 2 N HCl. The crystalline precipitate was filtered, and the residue was washed with water and dried to give 137 g (90%) of the corresponding sulfonamide, mp 190–192 °C. The protection of the sulfonamide group was effected by stirring with 0.4 L of DMF and 100 g of dimethylformamide dimethyl acetal for 30 min at 60 °C. Adding 2 L of water, filtering, and drying (100 °C) gave 195 g of **6b** (87%), mp 127–129 °C.

Compound **6b** (133 g, 0.5 mol) was added portionwise to a stirred mixture of 0.4 L of fuming sulfuric acid (20% SO_3) and 42 L of fuming of HNO_3 (1.0 mol) at room temperature. Nitration was completed by stirring for 2 h at 55 °C. On pouring the mixture onto ice (2 kg), the nitro compound separated in the form of yellow needles; after it was washed with water and then dried, the yield was 145 g (94%), mp 164–165 °C. Hydrogenation of the nitro group was effected in 3.0 L of tetrahydrofuran/15 mL of HOAc, with 5% Pd/C as catalyst (20 °C, 0.1 bar of H_2 pressure). After completion of the reaction (30 L of H_2 uptake), the mixture was filtered, and the filtrate was evaporated to dryness. The amorphous residue was digested with 0.4 L of EtOH until completely crystalline. After filtering and drying (100 °C), the yield was 118 g (90%) of **6c**, mp 208–210 °C.

Compound **6c** (112 g (0.4 mol) was stirred at 40 °C with a mixture of 0.6 L of 2 N NaOH and 0.3 L of MeOH until a clear solution was obtained. After the solution was left standing for 1 h at room temperature, the pH was adjusted to 5 with 5 N HCl. The sulfonamide crystallized immediately to yield, after washing with water and drying on the steam bath, 82 g (91%), mp 167–169 °C. This compound (56 g) was diazotized in a mixture of 0.2 L of 6 N HCl and 0.1 L of HOAc with 20 g of $NaNO_2$ in 0.1 L of water. The diazo solution was poured into a freshly prepared mixture of 15 g of $CuCl \cdot 2H_2O$ in 50 mL of H_2O and 0.6 L of HOAc, which had been saturated with SO_2. After the N_2 evolution had subsided, 0.5 L of water was added to separate the crystalline **6d**. After washing with water and air-drying, the yield was 48 g (62%), mp 174–176 °C. Compound **6d** (31 g, 0.1 mol) was stirred for 30 min with 1 L of water on the steam bath, and the resulting solution was clarified with decolorizing carbon and evaporated to dryness in vacuo. On standing overnight at room temperature, the oily residue completely crystallized. After pulverizing and air-drying, the yield was 30 g (92%) of **6e**, mp 128–130 °C. Anal. ($C_6H_5ClFNO_5S_2 \cdot 2H_2O$) N, S, F, Cl.

Phenyl 4-Chloro-2-fluoro-5-sulfamoylbenzenesulfonate (6f). Triethylamine (14.0 mL) was added dropwise to a solution of **6d** (31 g, 0.1 mol) and phenol (9.4 g) in 0.4 L of tetrahydrofuran, while stirring at room temperature. After the solvent had been evaporated, the residue was triturated with water, and the remaining material was recrystallized from EtOH to give 38 g (66%) of **6f**, mp 123–124 °C. Anal. ($C_{12}H_9ClFNO_5S_2$) F, S.

Furfurylammonium 4-Chloro-*N*-furfuryl-5-sulfamoylorthanilate (7a). Method A. A mixture of 33 g (0.1 mol) of **6e**, 0.1 L of dioxane, and 40 mL (0.4 mol) of furfurylamine was stirred for 1 h at 85 °C and then evaporated to dryness in vacuo. The residue was taken up in 0.3 L of water, and the filtered solution was adjusted to pH 7 with 5 N HCl and stored at 5 °C overnight. The colorless crystalline precipitate was filtered, and the residue was washed with ice–water, recrystallized from EtOH, and dried (100 °C) to give 37 g (84%) of **7a**: mp 178 °C dec; solubility in water (20 °C) 3%. Anal. ($C_{16}H_{18}ClN_3O_7S_2$) C, H, N.

Sodium 4-Chloro-*N*-furfuryl-5-sulfamoylorthanilate (7b). Method B. Compound **6e** (33 g, 0.1 mol) was treated with furfurylamine, as described above. After evaporation of the solvent, the residue was dissolved in 0.2 L of 5 N NaOH, and the solution was extracted three times with 0.2 L of EtOAc. The aqueous phase was concentrated to a volume of 0.15 L in vacuo and adjusted to pH 7 with 5 N HCl. Compound **7b** crystallized from the filtrate while standing overnight at 10 °C. After washing with a little ice–water and EtOH and drying at 100 °C, 29 g (75%) **7b** was obtained: mp 270 °C dec; solubility in water (20 °C) 15%. Anal. ($C_{11}H_{10}ClN_2NaO_6S_2$) N, S, Cl.

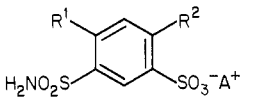
Phenyl 2,4-Dichloro-5-sulfamoylbenzenesulfonate (9). Gaseous ammonia was passed into a mixture of 516 g (1.5 mol) of 4,6-dichlorobenzene-1,3-disulfonyl chloride, 144 g (1.5 mol) of phenol, and 0.3 L of tetrahydrofuran while stirring and maintaining the temperature in the range of 5–10 °C. After approximately 2 h, the escape of ammonia signaled the end of the reaction. Precipitated NH_4Cl was removed by filtration, and the solution was evaporated in vacuo. The residue was refluxed for 10 min with 1.0 L of MeOH, and the mixture, after standing overnight at room temperature, was filtered to remove the byproduct. The filtrate, after clarification with decolorizing carbon, was added dropwise to a mixture of 0.6 L of water, 0.25 L of concentrated aqueous NH_3, and 2.0 L of EtOAc with stirring. After the layers were separated, the aqueous phase was extracted two times with 0.5 L of EtOAc, and the combined EtOAc solutions were dried over $MgSO_4$. After evaporation to dryness, the residue was triturated with 2.0 L of diisopropyl ether until completely crystallized and then filtered by suction to give 250 g of crude **9** (containing about 10% of the byproduct 4,6-dichloro-1,3-disulfamoylbenzene). This product was refluxed for 20 min with 0.6 L of isopropyl alcohol and filtered while hot. After 0.3 L of water was added to the filtrate, **9** crystallized slowly during 2 days at 10 °C. The yield, after drying at 50 °C in vacuo, was 210 g (37%), mp 145–146 °C. Anal. ($C_{12}H_9ClN_2O_4S_2$) N, Cl.

Phenyl 2-Chloro-4-phenoxy-5-sulfamoylbenzenesulfonate (10). Method C. Compound **9** (383 g, 1.0 mol) and C_6H_5OK (160 g, 1.2 mol) were refluxed with 2.5 L of 2-butanone for 6 h. After the solvent was removed in vacuo, the residue was triturated twice with 1 L of hot water, and the waxy crude product (separated by decantation) was refluxed for 10 min with 1 L of MeOH. After the solution was left standing overnight at room temperature, compound **10** was filtered (250 g, mp 170–175 °C) and recrystallized from 0.6 L of EtOH to yield 220 g (50%), mp 178–180 °C. Anal. ($C_{18}H_{14}ClNO_6S_2$) N, S, Cl.

By concentration of the MeOH mother liquor, isomer **11** was isolated and then recrystallized from EtOH, mp 176–178 °C. Anal. ($C_{18}H_{14}ClNO_6S_2$) N, Cl.

Phenyl *N*-Furfuryl-4-phenoxy-5-sulfamoylorthanilate (12). Method D. Compound **10** (440 g, 1.0 mol) and furfurylamine (0.3 L) were refluxed with 1.8 L of isopropyl alcohol for 10 h. After evaporation of the solvent in vacuo, the residue was triturated at room temperature with 10 L of 5% HOAc. The remaining semisolid material was separated by decantation and then boiled briefly with 3.0 L of MeOH, and compound **12** was allowed to crystallize for 3 h at 10 °C. The yield, after washing with 1 L of MeOH and drying at 90 °C, was 260 g (52%), mp 179–180 °C. Anal. ($C_{23}H_{20}N_2O_7S_2$) C, H, N, S.

Table VI. Diuretic and Saluretic Activity in the Rat of Compounds 7, 14, 17, 19, and 20



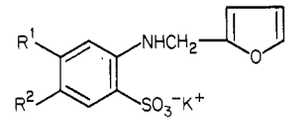
compd	R^1	R^2	A	diuretic act.,[a] *L*	saluretic act.,[b] mequiv kg^{-1} 5 h^{-1} Na^+	K^+	Cl^-
furosemide				4.9	4.8	2.6	7.2
control				1.0	0.7	0.6	0.7
7a	Cl	$NHCH_2CCHCHCHO$	$H_3NCH_2CCHCHCHO$	3.2	6.3	2.3	7.2
7b	Cl	$NHCH_2CCHCHCHO$	Na	2.8	7.1	2.3	8.3
7d	Cl	$NHCH_2CH_2CCHCHCHO$	Na	1.9	4.6	1.8	6.1
7e	Cl	$N(CH_3)CH_2CCHCHCHO$	Na	0.8	0.8	0.5	0.8
7f	Cl	$NHCH_2CHCH_2CH_2CH_2O$	Na	0.4	0.4	0.4	0.5
7g	Cl	$NHCH_2CCHCHCHS$	$H_3NCH_2CCHCHCHS$	1.0	2.7	1.7	3.3
7h	Cl	$NHCH_2C_6H_5$	$H_3NCH_2C_6H_5$	1.4	1.4	1.4	1.2
7i	Cl	$NHCH_2C_6H_3$, 3,4-OCH_2O	Na	0.4	0.4	0.3	0.3
7k	Cl	$NHCH_2C_6H_4$, 2-OCH_3	Na	0.2	0.1	0.3	0.1
7l	Cl	$N(CH_2C_6H_5)_2$	Na	0.7	0.3	0.8	0.9
7m	Cl	$NHCH_2CCHCHNCHCH$	Na	0.2	0.1	0.4	0.1
7n	Cl	$NHCH_2CH_2OC_2H_5$	Na	0.4	0.2	0.2	0.2
14a	OC_6H_5	$NHCH_2CCHCHCHO$	Na	4.1	7.0	2.1	9.6
14b	OC_6H_5	$NHCH_2CCHCHCHO$	K	1.8	5.0	1.5	7.1
14c	OC_6H_5	$NHCH_2CCHCHCHO$	NH_4	4.2	6.6	2.4	8.7
14d	OC_6H_5	$NHCH_2CCHCHCHO$	amiloride	1.9	3.7	0.3	2.7
14e	OC_6H_5	$NHCH_2CCHCHCHO$	$H_2N(c\text{-}C_6H_{11})_2$	0.9	0.7	1.0	0.8
14f	OC_6H_5	$NHCH_2CCHCHCHO$	$H_3NC(CH_2OH)_3$	4.1	5.8	2.2	7.8
14g	OC_6H_4, 3-CH_3	$NHCH_2CCHCHCHO$	K	4.4	6.7	2.2	7.9
14h	OC_6H_3, 3,4-CH_3	$NHCH_2CCHCHCHO$	K	1.3	2.2	1.4	3.7
14i	OC_6H_4, 3-Cl	$NHCH_2CCHCHCHO$	K	2.0	3.8	2.0	5.1
14k	OC_6H_4, 4-Cl	$NHCH_2CCHCHCHO$	K	2.2	5.1	2.0	6.4
14l	OC_6H_5	$NHCH_2CH_2CCHCHCHO$	K	1.2	0.6	0.7	0.9
14m	OC_6H_5	$N(CH_3)CH_2CCHCHCHO$	K	1.3	0.3	1.5	1.7
14n	OC_6H_5	$NHCH_2CCHCHCHS$	K	0.8	0.8	0.4	0.6
14o	OC_6H_5	$NHCH_2C_6H_5$	NH_4	3.0	4.9	2.2	6.9
14p	OC_6H_5	NH_2	K	1.0	0.5	1.3	0.7
17a	$N(CH_3)C_6H_5$	$NHCH_2CCHCHCHO$	Na	4.6	8.2	2.4	9.4
17b	$N(CH_3)C_6H_5$	$NHCH_2CCHCHCHO$	K	3.1	6.3	1.7	7.4
17c	$N(CH_3)C_6H_5$	$NHCH_2CCHCHCHO$	NH_4	4.8	6.8	2.1	8.3
17d	$N(CH_3)C_6H_5$	$NHCH_2CCHCHCHO$	amiloride	3.3	3.5	0.4	2.3
17e	$N(C_2H_5)C_6H_5$	$NHCH_2CCHCHCHO$	Na	0.8	0.4	1.0	0.3
17f	$N(CH_3)C_6H_4$, 4-CH_3	$NHCH_2CCHCHCHO$	Na	1.2	1.6	1.9	2.3
17g	$N(CH_3)C_6H_4$, 4-Cl	$NHCH_2CCHCHCHO$	Na	1.2	0.7	1.1	0.7
17h	$N(CH_3)$-c-C_6H_{11}	$NHCH_2CCHCHCHO$	K	0.8	0.4	1.0	0.6

Table VI (*Continued*)

compd	R^1	R^2	A	diuretic act.,[a] *L*	saluretic act.,[b] mequiv kg^{-1} 5 h^{-1} Na^+	K^+	Cl^-
17i	NHC_6H_5	$NHCH_2CCHCHCHO$	Na	0.6	0.6	0.7	1.1
17k	NHC_6H_4, 4-Cl	$NHCH_2CCHCHCHO$	Na	0.4	0.4	0.4	0.5
17l	NHC_6H_4, 3-CH_3	$NHCH_2CCHCHCHO$	Na	0.8	0.6	1.5	0.9
17m	$NHCH_2C_6H_5$	$NHCH_2CCHCHCHO$	K	1.0	0.8	0.6	1.2
17n	$N(CH_3)C_6H_5$	$NHCH_2CCHCHCHS$	Na	1.8	1.8	0.7	2.0
17o	$N(CH_3)C_6H_5$	$NHCH_2C_6H_5$	Na	2.6	3.5	1.4	4.0
17p	NHC_6H_4, 4-Cl	$NHCH_2CCHCHCHO$	Na	1.1	0.3	0.8	0.6
17q	NHC_6H_4, 2-CH_3	$NHCH_2CCHCHCHO$	Na	0.6	0.7	1.0	0.6
17r	$N(CH_3)C_6H_5$	$NHCH_2CCHCHCHO$	K	1.2	2.2	2.0	3.2
19a	S-c-C_6H_{11}	$NHCH_2CCHCHCHO$	K	0.8	1.4	0.5	1.9
19b	SO-c-C_6H_{11}	$NHCH_2CCHCHCHO$	Na	1.2	1.3	1.4	1.7
19c	SO_2-c-C_6H_{11}	$NHCH_2CCHCHCHO$	Na	2.8	8.2	2.3	9.1
19d	SO_2-c-C_6H_{11}	$NHCH_2CCHCHCHS$	Na	4.0	7.3	2.2	8.7
19e	SO_2-c-C_5H_8	$NHCH_2CCHCHCHO$	Na	4.3	8.0	2.0	9.5
19f	SO_2-c-C_7H_{13}	$NHCH_2CCHCHCHO$	Na	4.0	8.9	2.8	9.9
19g	SO_2CH_2-c-C_6H_{13}	$NHCH_2CCHCHCHO$	Na	4.6	8.8	2.7	10.7
19h	SC_6H_5	$NHCH_2CCHCHCHO$	Na	1.2	0.5	0.4	0.3
19i	SOC_6H_5	$NHCH_2CCHCHCHO$	K	0.8	0.8	1.5	1.7
19k	$SO_2C_6H_5$	$NHCH_2CCHCHCHO$	K	3.6	7.1	2.6	9.8
19l	S-*n*-Bu	$NHCH_2CCHCHCHO$	K	2.5	3.6	2.2	3.6
19m	SO-*n*-Bu	$NHCH_2CCHCHCHO$	Na	1.0	0.9	1.0	1.4
19n	SO_2-*n*-Bu	$NHCH_2CCHCHCHO$	Na	3.8	7.3	2.2	8.7
19o	SO_2-*s*-Bu	$NHCH_2CCHCHCHO$	Na	4.5	6.7	1.9	8.5
19p	SO_2-*i*-Bu	$NHCH_2CCHCHCHO$	Na	2.8	7.6	2.5	8.1
19q	SO_2-*t*-Bu	$NHCH_2CCHCHCHO$	K	2.5	3.3	1.8	4.3
19r	SO_2-c-C_6H_{11}	$NHCH_2C_6H_5$	Na	0.5	2.0	1.7	1.8
19a	$SO_2CH_2C_6H_5$	$NHCH_2CCHCHCHO$	K	1.0	0.8	0.6	0.7
19t	SO_2-*n*-Pr	$NHCH_2CCHCHCHO$	Na	2.9	1.8	1.3	2.4
19u	SO_2-*n*-hexyl	$NHCH_2CCHCHCHO$	Na	0.7	1.1	1.9	1.2
20a	$NHCH_2CCHCHCHO$	Cl	Na	0.5	0.5	0.9	1.0
20b	$NHCH_2CCHCHCHO$	OC_6H_5	K	0.8	0.8	1.0	0.8
20c	$NHCH_2CCHCHCHO$	SO_2-c-C_6H_{11}	Na	0.8	0.4	1.1	1.0

[a] Determined by a modified Lipschitz test:[9] rats that had been deprived of water 24 h prior to the experiment were divided into groups of three animals with similar weights and put into diuresis funnels. One group received 50 mg/kg of the test substance suspended in 2% starch solution, using a stomach tube; the second group received 1 g/kg of urea. Both treatments were followed by 50 mL/kg of 0.9% NaCl solution. The 5-h urine volume of the test group (in milliliters per kilogram), divided by the corresponding excretion group, results in the Lipschitz value, *L*. Diuretic activity is marked by *L* values greater than 1.0. [b] Rats that had been deprived of food 24 h prior to the experiment but had received water ad libitum were given 50 mg/kg of the test compound suspended in 2% starch solution, using a stomach tube. Without additional water loading, groups of three animals were put in diuresis funnels, and the urine excreted during the first 5 h was collected. Na^+ and K^+ were determined flame-photometrically (Eppendorf photometer), and Cl^- was determined argentometrically (Aminco-Cotlove titrator); the values were calculated in milliliters per kilogram (urine) and in milliequivalents per kilogram (ions).

Table VII. Salidiuretic Activity in the Rat of Compounds 14b, 17b, and 21a-d



compd	R^1	R^2	diuretic act.,[a] *L*	saluretic act.,[b] mequiv kg^{-1} 5 h^{-1}		
				Na^+	K^+	Cl^-
14b	OC_6H_5	SO_2NH_2	1.8	5.0	1.5	7.1
21a	OC_6H_5	SO_2NHCH_3	1.6	0.8	0.8	1.0
21b	OC_6H_5	$SO_2N(CH_3)_2$	1.2	0.3	1.1	0.7
17b	$N(CH_3)C_6H_5$	SO_2NH_2	3.1	6.3	1.7	7.4
21c	$N(CH_3)C_6H_5$	SO_2NHCH_3	1.3	1.2	1.4	1.8
21d	$N(CH_3)C_6H_5$	$SO_2N(CH_3)_2$	1.6	1.0	1.2	1.5

[a, b] See footnotes in Table VI.

Sodium *N*-Furfuryl-4-phenoxy-5-sulfamoylorthanilate (14a). Method E. Compound 12 (500 g, 1 mol) and 3.5 L of 2 N NaOH were refluxed for 6 h. The resulting solution was clarified with decolorizing carbon, neutralized with 5 N HCl, concentrated to a volume of 1.5 L, and stored at 10 °C overnight. Precipitated 14a was filtered by suction, washed with 1 L of EtOH, and dried (100 °C) to give 380 g, mp 237 °C dec, containing 5% NaCl. The latter was removed by extracting with 3 L of boiling acetone. After evaporation of the acetone, the residue crystallized on triturating with 1 L of EtOH, yielding 340 g (76%), mp 240 °C dec. Anal. ($C_{17}H_{15}N_2NaO_7S_2$) Na, S.

Ammonium *N*-Furfuryl-4-phenoxy-5-sulfamoylorthanilate (14c). Method F. Compound 12 (10 g, 20 mmol) was hydrogenated (20 °C, 0.1 bar of H_2 pressure) in a mixture of 0.1 L of tetrahydrofuran and 20 mL of 8 N aqueous ammonia in the presence of 10% Pd/C. A sudden slowing in hydrogenation occurred after the uptake of 500 mL of H_2, Pd/C was filtered out at this stage, and the solution was evaporated to dryness. The amorphous residue crystallized upon refluxing with 0.1 L of EtOAc. After the residue was dried (100 °C), the yield was 8.1 g (93%), mp 190 °C dec. Anal. ($C_{17}H_{19}N_3O_7S_2$) N, S.

Sodium *N*-Furfuryl-4-(*N*-methylanilino)-5-sulfamoylorthanilate (17a). Method G. Compound 9 (383 g, 1.0 mol) and *N*-methylaniline (0.5 L freshly distilled) were stirred for 6 h at 140 °C. After dilution with 0.5 L of MeOH at 60 °C, the reaction mixture was poured into 6 L of 1 N HCl with vigorous stirring. The amorphous precipitate was separated by decanting and recrystallized from 3.5 L of EtOH to give 240 g (53%) compound 15, mp 138–140 °C. Compound 15 (453 g, 1.0 mol) and furfurylamine (1.0 L) were stirred in a N_2 atmosphere for 2.5 h at 125 °C. After cooling (60 °C), the mixture was diluted with 1 L of MeOH and poured into 10 L of 10% HOAc while stirring. The crystalline precipitate was filtered by suction and crystallized from 10 L of MeOH to give 440 g (86%) of compound 16, mp 143 °C. Compound 16 (257 g, 0.5 mol) and 2.5 L of 2 N NaOH were refluxed for 2 h. After cooling, the faintly yellow solution was clarified with decolorizing carbon and neutralized with 5 N HCl. After the solution was left standing for 2 h at room temperature, crystalline 17a was filtered by suction, washed with water and EtOH, and dried at 100 °C to give 210 g (90%), mp 200 °C dec. Anal. ($C_{18}H_{18}N_3NaO_6S_2$) N, S, Na.

Ammonium *N*-Furfuryl-4-(*N*-methylanilino)-5-sulfamoylorthanilate (17c). Method H. In a method analogous to F, compound 16 (10.3 g, 20 mmol) was hydrogenated in tetrahydrofuran/ammonia in the presence of Pd/C. After evaporation, the amorphous residue was taken up in 50 mL of EtOAc and precipitated in crystalline form by the portionwise addition of 100 mL of diisopropyl ether. The yield was 7.8 g (91%) of compound 17c, mp 185 °C dec. Anal. ($C_{18}H_{22}N_4O_6S_2$) N, S.

Potassium 4-(Cyclohexylthio)-*N*-furfuryl-5-sulfamoylorthanilate (19a). Method I. The mixture of compound 9 (383 g, 1.0 mol), dimethylformamide (1.5 L), cyclohexyl mercaptan (116 g, 1.0 mol), and K_2CO_3 (76 g, 0.55 mol) was stirred for 1 h at 115 °C and then concentrated in vacuo to a syrupy consistency. The residue was triturated twice with 2.5 L of hot water and then recrystallized from MeOH to give 280 g (60%) of phenyl 2-chloro-4-(cyclohexylthio)-5-sulfamoylbenzenesulfonate, mp 149–150 °C. The thioether (231 g, 0.5 mol) and furfurylamine (0.5 L) were heated for 1.5 h at 90 °C in a N_2 atmosphere, with stirring. After the reaction mixture was poured into 4 L of 10% HOAc, the amorphous precipitate was separated by decantation and subsequently recrystallized from MeOH to give 230 g (88%) compound 18, mp 147–149 °C. Compound 18 (53 g, 0.1 mol) and 0.5 L of 1 N KOH were stirred for 1 h on the steam bath to give a clear solution. After the solution was neutralized with 5 N HCl and left standing overnight at room temperature, crystalline 19a was filtered out, washed with water and EtOH, and dried at 100 °C to give 40 g (83%), mp 227 °C dec. Anal. ($C_{17}H_{21}KN_2O_6S_3$) N, S, K.

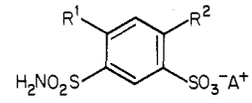
Sodium 4-(Cyclohexylsulfinyl)-*N*-furfuryl-5-sulfamoylorthanilate (19b). Method K. To a solution of compound 18 (52.3 g, 0.1 mol) in 1 L of CH_2Cl_2 at room temperature was added portionwise, with stirring, 85% 3-chloroperbenzoic acid (20.5 g, 0.1 mol). The precipitated 3-chlorobenzoic acid was filtered off after 3 h of continuous stirring. The filtrate was extracted three times with 0.1 L of 1 N $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness. Recrystallization of the residue from 90% MeOH yielded 42 g (78%) of phenyl 4-(cyclohexylsulfinyl)-*N*-furfuryl-5-sulfamoylorthanilate, mp 116–118 °C. This compound (27 g, 50 mmol) was saponified with 0.2 L of 2 N NaOH by stirring for 1 h on the steam bath. The filtrate was adjusted to pH 7 at room temperature, causing compound 19b to crystallize out. After standing for 2 h at 20 °C, it was filtered by suction, washed with water and diisopropyl ether, and dried (80 °C) to give 15.4 g (63%), mp 270 °C dec. Anal. ($C_{17}H_{21}N_2NaO_7S_3$) N, S, Na.

Sodium 4-(Cyclohexylsulfonyl)-*N*-furfuryl-5-sulfamoylorthanilate (19c). Method L. Compound 18 (52.3 g, 0.1 mol) was oxidized with 85% 3-chloroperbenzoic acid (50 g, 0.25 mol) by a procedure analogous to method K, and the resulting sulfone was recrystallized from MeOH to give 37 g (66%) of phenyl 4-(cyclohexylsulfonyl)-*N*-furfuryl-5-sulfamoylorthanilate, mp 133 °C. This sulfone (27.7 g, 50 mmol) was saponified with 0.2 L of 2 N NaOH (1 h, 95 °C). Neutralization of the resulting solution with 5 N HCl caused the precipitation of compound 19c. The yield, after washing with water and EtOH and drying at 100 °,c, was 44 g (88%), mp 300 °C dec. Anal. ($C_{17}H_{21}N_2NaO_8S_3$) N, S.

Sodium 2-Chloro-*N*-furfuryl-5-sulfamoylsulfanilate (20a). Compound 9 (38.3 g, 0.1 mol) and furfurylamine (21 mL) were refluxed in 0.2 L of tetrahydrofuran for 4 h. The reaction mixture was concentrated to half its volume and poured into 1 L of 0.5 N HCl to cause the precipitation of crystalline 13. After filtering by suction and washing with water, the moist product (mp of dried sample 154–156 °C) was saponified by refluxing for 15 h with 0.2 L of 2 N NaOH. Neutralizing with 5 N HCl at room temperature caused the precipitation of compound 21. Recrystallizing from water and drying at 100 °C yielded 23 g (59%), mp 217 °C dec. Anal. ($C_{11}H_{10}ClN_2NaO_6S_2$) N, S, Cl.

Potassium *N*-Furfuryl-2-phenoxy-5-sulfamoylsulfanilate (20b). Compound 11 (44 g, 0.1 mol) (see method C) was condensed with furfurylamine, according to method D. After recrystallization from MeOH–water, 35 g (70%) of phenyl *N*-furfuryl-2-phen-

Table VIII. Diuretic and Saluretic Activity in the Dog (Two Animals per Dose) of Furosemide and Compounds 7b,d,g,h, 14a,n,o,l, 17a,i,n,o,r, and 19a-e,h,i,k-n,r



					urinary excretion[a]					
					mL kg^{-1} 6 h^{-1}	mequiv kg^{-1} 6 h^{-1}				
compd	R^1	R^2	A	dose mg/kg, po	H_2O	Na^+	K^+	Cl^-	Na^+/K^+	$Cl^-/(Na^+ + K^+)$
furosemide				0.78	37.4	1.37	0.50	1.85	2.7	1.0
				6.25	69.0	5.54	1.26	6.27	4.4	0.9
control					28.1	0.12	0.15	0.11	0.8	0.4
7b	Cl	NHCH$_2$CCHCHCHO	Na	0.4	37.0	0.45	0.19	0.69	2.3	1.1
				1.56	42.4	2.61	0.53	3.24	4.9	1.0
				6.25	66.5	4.36	0.78	4.74	5.6	0.9
7g	Cl	NHCH$_2$CCHCHCHS	H$_3$NCH$_2$CCHCHCHS	1.56	44.5	2.33	0.55	2.76	4.2	0.95
7h	Cl	NHCH$_2$C$_6$H$_5$	H$_3$NCH$_2$C$_6$H$_5$	1.56	40.4	1.65	0.35	2.07	4.7	1.05
7d	Cl	NHCH$_2$CH$_2$CCHCHCHO	Na	1.56	29.3	0.56	0.15	0.76	3.7	1.1
14a	OC$_6$H$_5$	NHCH$_2$CCHCHCHO	Na	0.1	30.0	0.18	0.15	0.27	1.2	0.8
				0.4	36.4	1.19	0.34	1.65	3.5	1.1
				1.56	71.4	4.89	1.00	5.47	4.9	0.95
				12.5	74.3	6.49	1.17	7.13	5.5	0.95
14n	OC$_6$H$_5$	NHCH$_2$CCHCHCHS	K	1.56	58.0	3.73	1.03	4.45	3.6	0.95
				12.5	78.0	6.89	1.47	7.84	4.7	0.95
14o	OC$_6$H$_5$	NHCH$_2$C$_6$H$_5$	K	1.56	48.0	3.12	0.53	3.91	5.9	1.1
14l	OC$_6$H$_5$	NHCH$_2$CH$_2$CCHCHCHO	K	1.56	35.2	0.89	0.21	1.18	4.2	1.1
17a	N(CH$_3$)C$_6$H$_5$	NHCH$_2$CCHCHCHO	Na	0.025	33.3	0.45	0.20	0.75		
				0.1	54.3	3.08	0.72	3.99	4.3	1.1
				0.4	75.3	5.26	1.28	6.34	4.1	1.0
				1.56	69.4	5.74	1.17	6.79	4.9	1.0
17i	NHC$_6$H$_5$	NHCH$_2$CCHCHCHO	Na	1.56	32.3	0.38	0.18	0.56	2.1	1.0
				12.5	49.4	2.24	0.45	3.02	5.0	1.1
17n	NH(CH$_3$)C$_6$H$_5$	NHCH$_2$CCHCHCHS	Na	1.56	70.6	5.86	1.37	7.03	4.3	0.95
17o	N(CH$_3$)C$_6$H$_5$	NHCH$_2$C$_6$H$_5$	Na	1.56	71.7	6.59	1.51	7.34	4.4	0.9
17r	N(CH$_3$)C$_6$H$_5$	NHCH$_2$CH$_2$CCHCHCHO	K	1.56	59.9	4.70	1.08	5.81	4.3	1.0
19a	S-c-C$_6$H$_{11}$	NHCH$_2$CCHCHCHO	K	1.56	32.6	0.27	0.07	0.32	3.9	0.95
19b	SO-c-C$_6$H$_{11}$	NHCH$_2$CCHCHCHO	Na	1.56	48.4	0.59	0.33	1.27	1.8	1.4
19c	SO$_2$-c-C$_6$H$_{11}$	NHCH$_2$CCHCHCHO	Na	0.1	44.7	1.95	0.53	2.49	3.7	1.0
				0.4	59.0	3.71	0.82	4.43	4.5	1.0
				1.56	66.7	5.38	1.14	6.15	4.7	0.95
				6.25	73.5	5.50	1.16	6.83	4.7	1.0
19d	SO$_2$-c-C$_6$H$_{11}$	NHCH$_2$CCHCHCHS	Na	0.1	47.4	3.18	0.41	3.54	7.7	1.0
				1.56	66.7	5.40	1.05	6.39	5.1	1.0
19r	SO$_2$-c-C$_6$H$_{11}$	NHCH$_2$C$_6$H$_5$	Na	1.56	51.0	3.23	0.56	3.94	5.8	1.05
19e	SO$_2$-c-C$_5$H$_9$	NHCH$_2$CCHCHCHO	Na	1.56	58.0	4.24	1.02	5.26	4.2	1.0
19h	SC$_6$H$_5$	NHCH$_2$CCHCHCHO	Na	0.4	37.8	0.95	0.29	1.30	3.3	1.05
				1.56	70.1	5.64	1.01	5.99	5.6	0.9
19i	SOC$_6$H$_5$	NHCH$_2$CCHCHCHO	K	1.56	48.4	0.59	0.33	1.27	1.8	1.3
19k	SO$_2$C$_6$H$_5$	NHCH$_2$CCHCHCHO	K	1.56	35.3	0.49	0.25	1.09	2.0	1.5
				12.5	59.7	4.00	0.93	5.28	4.3	1.1
19l	S-*n*-Bu	NHCH$_2$CCHCHCHO	K	1.56	32.8	1.06	0.35	1.43	3.0	1.0
19m	SO-*n*-Bu	NHCH$_2$CCHCHCHO	Na	1.56	34.9	0.89	0.35	1.43	3.0	1.0
19n	SO$_2$-*n*-Bu	NHCH$_2$CCHCHCHO	Na	1.56	65.5	4.92	0.97	5.78	5.0	1.0

[a] The test animals were male beagles that had been trained to undergo the test procedures. Thus, the dogs were able to rest on a table for 8 h and withstand treatment with a stomach tube and catheterization without resistance. Food was withdrawn 24 h prior to the experiment, and the animals received only tap water ad libitum. On the morning of the first experimental day, the urinary bladder of the animals was emptied by means of a plastic catheter. This urine was discarded. Subsequently, the animals received 20 mL/kg of tap water by stomach tube. Following this, the dogs were catheterized hourly (up to 8 h). The volume of this urine was measured and the urine kept for subsequent analysis of the excretion parameters. At each catheterization, the dogs received 4 mL/kg of tap water orally. The urine samples of the first 2 h were used as control values. After the second catheterization, the dogs were orally dosed with the compound to be tested. The urine samples of the 1-6-h postdrug period were combined, and Na^+, K^+, and Cl^- were determined as described in Table VI, footnote *b*.

Table IX. Urinary and Sodium Excretion after Oral Administration of 14a and 17a in the Dog (Four Animals per Dose)[a]

compd	dose, mg/kg	urinary excretion, mL/kg			sodium excretion, mequiv/kg		
		1-6 h	7-24 h	1-24 h	1-6 h	7-24 h	1-24 h
14a	0.39	41.6 ± 4.9	9.3 ± 1.2	50.9 ± 3.9	1.57 ± 0.77	0.47 ± 0.46	2.04 ± 0.64
	1.56	61.1 ± 6.8	12.3 ± 2.3	78.9 ± 11.4	4.97 ± 1.22	0.48 ± 0.43	5.40 ± 1.52
	6.25	75.4 ± 8.9	38.3 ± 4.4	111.1 ± 4.4	6.52 ± 1.08	1.98 ± 0.27	8.55 ± 1.23
17a	0.05	40.5 ± 2.8	10.1 ± 2.2	50.6 ± 2.4	1.29 ± 0.52	0.22 ± 0.14	1.51 ± 0.51
	0.39	75.3 ± 6.3	20.4 ± 6.0	95.7 ± 4.0	5.26 ± 0.54	0.55 ± 0.42	5.81 ± 0.31
	3.12	61.2 ± 5.2	40.8 ± 5.1	102.0 ± 5.1	4.39 ± 0.64	2.09 ± 0.30	6.48 ± 0.57
control		28.9 ± 1.4	10.4 ± 2.8	39.3 ± 1.6	0.12 ± 0.12	0.45 ± 0.25	0.56 ± 0.22

[a] See footnote *a* in Table VI.

Table X. Effect of 14a on Urine Flow (vol), Glomerular Filtration Rate (GFR), and Inulin U/P Ratio in Comparison with Furosemide[a]

compd	vol, mL min^{-1} kg^{-1}	GFR, mL min^{-1} kg^{-1}	inulin U/P
control	0.011 ± 0.002	8.26 ± 1.13	756.27 ± 163.23
14a	0.909 ± 0.142*	6.89 ± 0.58	7.66 ± 1.19*
furosemide	0.998 ± 0.101*	8.82 ± 0.73	10.06 ± 1.25*

[a] * = $p < 0.05$.

oxy-5-sulfamoylsulfanilate, mp 132 °C, was obtained. This was saponified by refluxing for 3 h with 0.25 L of 2 N KOH. After the resulting solution was neutralized with 5 N HCl and then left standing overnight at room temperature, crystalline **20b** was filtered out, washed with ice-water, and dried at 100 °C. The yield was 21 g (45%), mp 208 °C dec. Anal. ($C_{17}H_{15}KN_2O_7S_2$) N, S.

Sodium 2-(Cyclohexylsulfonyl)-*N*-furfuryl-5-sulfamoylsulfanilate (20c). Compound **13** (44.3 g, 0.1 mol) (intermediate of **20a**), cyclohexyl mercaptan (14.0 g, 0.12 mol), and K_2CO_3 (8.3 g, 0.06 mol) were stirred for 4 h at 145 °C with 0.4 L of dimethyl sulfoxide in a N_2 atmosphere. The reaction mixture was poured into 2 L of 10% AcOH, which precipitated an amorphous crude product. This was purified by chromatography on a silica gel column, using CH_2Cl_2 as a solvent. Recrystallization of the main fraction from MeOH yielded 21.5 g (41%) of phenyl 2-(cyclohexylthio)-*N*-furfuryl-5-sulfamoylsulfanilate, mp 160–161 °C. The thioether (21 g, 40 mmol) was oxidized with 85% 3-chloroperbenzoic acid (20.5 g, 0.1 mol) in 4 L of CH_2Cl_2 by standing overnight at room temperature. The crude sulfone was isolated according to method K and purified by chromatography as described above to yield 10 g (45%), mp 199–201 °C. Saponification was effected by refluxing with 100 mL of 2 N NaOH for 1 h. The solution was neutralized at room temperature with HCl to precipitate **20c**. After the solution was washed with water and EtOH and then dried at 100 °C, the yield was 7.3 g (78%), mp 255 °C dec. Anal. ($C_{17}H_{21}N_2NaO_8S_3$) N, S.

Potassium *N*-Furfuryl-4-phenoxy-5-(methylsulfamoyl)orthanilate (21a). Compound **12** (10.0 g, 20 mmol), *N,N*-dimethylacetamide (60 mL), powdered K_2CO_3 (8.3 g, 60 mmol), and dimethyl sulfate (5.7 mL, 60 mmol) were mixed at room temperature and slowly heated to 70 °C under stirring (15 min), and stirring was continued at this temperature for 1 h. Subsequently, the reaction mixture was poured in 0.5 L of water, the amorphous precipitate was taken up in 0.3 L of EtOAc, and the dried solution ($MgSO_4$) was evaporated to dryness, yielding 12 g of a yellow oil. It was chromatographed under TLC control (toluene/EtOAc, 5:1) on a column of silica gel (Merck 60, 70–230 mesh, 300 g) with toluene/EtOAc, 40:1, as eluent. After the first fraction with R_f 0.48 (2.3 g of two difficulty separable dimethyl compounds) was discarded, the next one with a R_f of 0.33 recrystallized from EtOH, yielded 3.6 g of phenyl *N*-furfuryl-4-phenoxy-5-(methylsulfamoyl)orthanilate (NMR, mass spectra), mp 145–146 °C. This compound was hydrogenated in a mixture of tetrahydrofuran (50 mL) and 2 N NH_3 (10 mL) with pD/C as catalyst, according to method F. After evaporation of the solvent, water (30 mL) was added to the residue, the insoluble material was filtered off, and saturated aqueous KCl (5 mL) was added to the filtrate. Compound **21a** crystallized immediately at room temperature, yielding, after washing with ice-water and drying at 100 °C, 0.8 g of the dihydrate, mp 190 °C dec. Anal. ($C_{18}H_{21}KN_2O_9S_2$) N, K.

Potassium *N*-Furfuryl-4-phenoxy-5-(dimethylsulfamoyl)orthanilate (21b). Compound **10** (8.8 g, 20 mmol), K_2CO_3 (11.0 g, 80 mmol), and dimethyl sulfate (7.6 mL, 80 mmol) were allowed to react in *N,N*-dimethylacetamide (100 mL) as described above for compound **12**. The reaction mixture was poured in 0.5 L of water, and the semisolid precipitate was separated and recrystallized from isopropyl alcohol. Phenyl 2-chloro-4-phenoxy-5-(dimethylsulfamoyl)orthanilate (3.5 g), mp 168–170 °C, was obtained and treated in a next step with furfurylamine (3.5 g) by refluxing for 8 h in 50 mL of isopropyl alcohol. After evaporation of the solvent, the residue was treated with 100 mL of 10% AcOH, and the insoluble material was re-

Table XI

compd	4-substituent	2-substituent	salidiuretic act.[a] rat	salidiuretic act.[a] dog
7a	Cl	furfurylamino	+++	+++
7g	Cl	2-thenylamino	++	+++
7h	Cl	benzylamino	+	++
7d	Cl	2-furylethylamino	+++	+
14a	phenoxy	furfurylamino	+++	+++
14n	phenoxy	2-thenylamino	–	+++
14o	phenoxy	benzylamino	++	++
14l	phenoxy	2-furylethylamino	–	+
17a	*N*-methylanilino	furfurylamino	+++	+++
17n	*N*-methylanilino	2-thenylamino	+	+++
17o	*N*-methylanilino	benzylamino	++	+++
17r	*N*-methylanilino	2-furylethylamino	+	+++
19c	cyclohexylsulfonyl	furfurylamino	+++	+++
19d	cyclohexylsulfonyl	2-thenylamino	+++	+++
19r	cyclohexylsulfonyl	benzylamino	+	++

[a] Differentiated between – (inactive) and +++ (highly active), on the basis of the 50 mg/kg po rat and the 1.56 mg/kg po dog assay.

crystallized from EtOH to yield 1.8 g of phenyl *N*-furfuryl-4-phenoxy-5-(dimethylsulfamoyl)orthanilate, mp 165–166 °C. This compound was hydrogenated in the presence of Pd/C as described above for **21a**, yielding, after recrystallizing from EtOH and drying at 100 °C in vacuo, 0.6 g of **21b**, mp 201 °C dec. Anal. ($C_{19}H_{19}KN_2O_7O_2$) C, H, N.

Potassium *N*-Furfuryl-4-(*N*-methylanilino)-5-(methylsulfamoyl)orthanilate (21c) and Potassium *N*-Furfuryl-4-(*N*-methylanilino)-5-(dimethylsulfamoyl)orthanilate (21d). Compound **16** (10.3 g, 20 mmol) was allowed to react with dimethyl sulfate (5.7 mL) and the reaction mixture was fractionated by column chromatography as described in the next to the last example for compound **12**, to give 2.5 g of phenyl *N*-furfuryl-4-(*N*-methylanilino)-5-(methylsulfamoyl)orthanilate, R_f 0.26, mp 142–143 °C, and 2.4 g of phenyl *N*-furfuryl-4-(*N*-methylanilino)-5-(dimethylsulfamoyl)orthanilate, R_f 0.49, mp 173–174 °C, both identified by NMR. Hydrogenation of these compounds by means of Pd/C and precipitation of the resulting sulfonic acids in the form of the potassium salts from aqueous solution, as described for **21a** above, yielded, after drying at 100 °C, 1.5 g of **21c**, mp 180 °C dec, as a dihydrate [Anal. ($C_{19}H_{24}KN_3O_8S_2$) C, H, N] and 1.6 g **21d**, mp 168 °C dec, as a monohydrate [Anal. ($C_{20}H_{24}KN_3O_7S_2$) C, H, N].

Registry No. **6a**, 85958-57-2; **6b**, 69156-31-6; **6b** (sulfonamide), 69156-30-5; **6c**, 69202-53-5; **6c** (nitro derivative), 69156-32-7; **6c** (sulfonamide), 69156-33-8; **6d**, 69156-34-9; **6e**, 69156-35-0; **6f**, 85958-58-3; **7a**, 85958-10-7; **7b**, 69156-13-4; **7c**, 85958-11-8; **7d**, 69156-14-5; **7e**, 85958-12-9; **7f**, 85958-13-0; **7g**, 85958-14-1; **7h**, 85958-16-3; **7i**, 85958-17-4; **7k**, 85958-18-5; **7l**, 85958-19-6; **7m**, 85958-20-9; **7n**, 85958-21-0; **8**, 61791-73-9; **8** (disulfonamide), 21784-69-0; **9**, 80289-32-3; **10**, 85958-59-4; **10** (*N*,*N*-dimethyl derivative), 85958-69-6; **11**, 85958-64-1; **11** (furfurylamino derivative), 85958-65-2; **12**, 82749-80-2; **13**, 85958-63-0; **13** (cyclohexyl sulfide derivative), 85958-66-3; **13** (cyclohexyl sulfone derivative), 85958-67-4; **14a**, 69156-06-5; **14b**, 82749-82-4; **14c**, 82749-81-3; **14d**, 85958-22-1; **14e**, 85958-23-2; **14f**, 85958-24-3; **14g**, 85958-25-4; **14h**, 85958-26-5; **14i**, 85958-27-6; **14k**, 85958-28-7; **14l**, 85958-29-8; **14m**, 85958-30-1; **14n**, 85958-31-2; **14o**, 82749-86-8; **15**, 80289-33-4; **16**, 80277-29-8; **17a**, 80289-31-2; **17b**, 85958-32-3; **17c**, 82749-83-5; **17d**, 85958-34-5; **17e**, 85958-35-6; **17f**, 85958-36-7; **17g**, 85958-37-8; **17h**, 85958-38-9; **17i**, 85958-39-0; **17k**, 85414-57-9; **17l**, 85958-40-3; **17m**, 85958-41-4; **17n**, 80277-30-1; **17o**, 80277-32-3; **17p**, 85958-42-5; **17q**, 85958-43-6; **17r**, 85958-44-7; **18**, 85958-61-8; **18** (sulfoxide), 85958-62-9; **18** (sulfone), 79505-59-2; **19a**, 79505-61-6; **19b**, 85958-45-8; **19c**, 79505-60-5; **19d**, 85958-46-9; **19e**, 79505-73-0; **19f**, 79505-68-3; **19g**, 85958-47-0; **19h**, 69156-08-7; **19i**, 85958-48-1; **19k**, 79505-66-1; **19l**, 79505-69-4; **19m**, 85958-49-2; **19n**, 85414-50-2; **19o**, 85958-50-5; **19p**, 82749-84-6; **19q**, 85958-51-6; **19r**, 79505-64-9; **19s**, 85958-52-7; **19t**, 85958-53-8; **19u**, 79505-83-2; **20a**, 85958-54-9; **20b**, 85958-55-0; **20c**, 85958-56-1; **21a**, 85958-73-2; **21a** (phenyl ester), 85958-68-5; **21b**, 85414-81-9; **21b** (phenyl ester), 85958-70-9; **21c**, 85958-74-3; **21c** (phenyl ester), 85958-71-0; **21d**, 85958-75-4; **21d** (phenyl ester), 85958-72-1; $(CH_3)_2NCH(OCH_3)_2$, 4637-24-5; $C_6H_{11}SH$, 1569-69-3; 2-chloro-4-fluoroaniline, 2106-02-7; furfurylamine, 617-89-0; phenol, 108-95-2; *N*-methylaniline, 100-61-8; phenyl 2-chloro-4-(cyclohexylthio)-5-sulfamoylbenzenesulfonate, 85958-60-7.

Notes

A New Class of Nonhormonal Pregnancy-Terminating Agents. Synthesis and Contragestational Activity of 3,5-Diaryl-*s*-triazoles[1]

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A series of 3,5-diaryl-*s*-triazoles were synthesized and evaluated as postimplantation contragestational agents. The introduction of various substituents (e.g., an *o*-alkyl chain on one phenyl and a *m*-alkoxy group on the other) was found to increase the potency. Several compounds with very high pregnancy-terminating activity in both hamsters and rats were obtained. One of these, 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-*s*-triazole, DL 111 (**36**), was selected for detailed evaluation in various animal species. A synthetic scheme for the preparation of these compounds and preliminary structure–activity relationships are presented.

In a search for new nonhormonal compounds with antifertility activity, we found a new class, i.e., 2-aryltriazolo[5,1-*a*]isoindoles and the corresponding 5,6-dihydroisoquinolines, with pronounced activity in our primary screening tests as postcoital pregnancy-terminating agents. Our interest in this class was increased by the promising results obtained with selected compounds in various animal species, including monkeys and baboons.[2-8]

In an attempt to enhance potency, we synthesized some series of tricyclic analogues, in which the triazole ring was replaced by differently fused pyrazoles[9] and imidazoles.[10] As a result of this effort, the 2-aryltriazolo[5,1-*a*]isoquinoline class yielded potent compounds, but their very sustained pharmacokinetic profiles and/or their low solubility, even in oily vehicles, hindered their use in clinical studies.[11,12]

Since it was apparent that the bridge linking the benzo ring to the triazole moiety strongly affects both the potency

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