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Diuretics: Aminobenzenedisulfonamides

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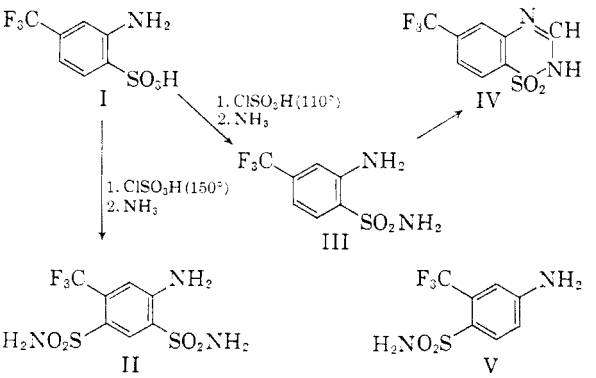
Chlorosulfonation of a number of substituted aniline derivatives followed by reaction of the resulting disulfonyl chlorides with ammonia or amines gave a series of aniline-2,4-disulfonamides possessing diuretic activity.

The diuretic activity of representative benzenedisulfonamides has been reported previously.[1,2,3] Compounds of greatest interest lie in the *meta* series, derivatives of benzene-1,3-disulfonamide. The activity is markedly influenced by further substitution in the benzene ring; halogen, amino, and acylamino groups were found to be particularly desirable. The preparation and some of the structure-activity relations of a series of aminobenzenedisulfonamides are now reported.

Anilinedisulfonyl chlorides were prepared by the reaction of *ortho*, *meta*, or *para*-substituted anilines with excess chlorosulfonic acid. Generally, the addition of sodium chloride was used to insure maximum dichlorosulfonation.[1,4] However, the use of a large excess of chlorosulfonic acid alone may suffice in certain instances.[5] A further modification[6] which permitted chlorosulfonation in the liquid phase was employed also and involved addition of thionyl chloride in place of sodium chloride. Acetanilides rather than the anilines offered no advantage as, under these conditions, the acetyl group was cleaved during the reaction. The disulfonamides were obtained by treatment of the crude disulfonyl chlorides with ammonia or appropriate amines. Compounds prepared in this manner are recorded in Table I and further examples are described in the Experimental.

Among the aniline derivatives that were chlorosulfonated only *m*-trifluoromethylaniline required special attention. The desired 5-trifluoromethylaniline-2,4-disulfonyl chloride was obtained by stepwise introduction of the two sulfonyl chloride groups. Chlorosulfonation of *m*-trifluoromethylaniline with one mole of chlorosulfonic acid in *sym*-tetrachloroethane at 125° according to the procedure of Kracker and Herrlein[7] gave a monosulfonic acid. This acid by further treatment with chlorosulfonic acid at 150° was converted to disulfonyl chloride which with ammonia gave the desired disulfonamide[8] (II) (Compound 16, Table I).



The intermediate monosulfonic acid was assigned the *para* structure, 2-trifluoromethyl-4-aminobenzenesulfonic acid, by Kracker and Herrlein. However, the monoacid obtained by us was shown to have the *ortho* structure (I) as follows. The monoacid was converted to the amide (III) by treatment with chlorosulfonic acid at 110° followed by the action of aqueous ammonia on the resulting sulfonyl chloride. This amide (III) melted at 144–146°. Caldwell and Sayi[9] prepared 2-trifluoromethyl-4-aminobenzenesulfonamide (V) by a different route and reported it to melt at 196–197°. Furthermore, our amide upon treatment with formic acid was readily converted to 6-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide (IV), which could only occur with the *ortho* amide (III).

The monochlorosulfonation of aniline and acetanilide is known to occur readily under mild conditions to yield the *para* sulfonyl chloride. However, the conditions necessary for introduction of a second sulfonyl group led only to the 2,4,6-trisulfonyl chloride, which upon conversion to the trisulfonamide afforded a compound devoid of diuretic activity. Halogen-substituted anilines proved to be especially valuable; they yielded biologically active disulfonamides and provided a

(1) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.* **79**, 2028 (1957).

(2) F. C. Novello and J. M. Sprague, 132nd Meeting of the American Chemical Society, New York, N. Y., September 8–13, 1957; abstracts, p. 32–0.

(3) J. M. Sprague, *Ann. N. Y. Acad. Sci.* **71**, 328 (1958).

(4) O. Lustig and E. Katscher, *Monatsh.*, **48**, 87 (1927).

(5) W. Logemann, P. Giraldi, and S. Galimberti, *Ann.* **623**, 157 (1959).

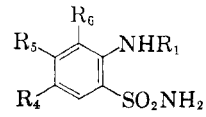
(6) We are indebted to Drs. E. F. Schoenewaldt, A. E. Erickson, and J. M. Chemerda for this modification.

(7) H. Kracker and F. Herrlein, U. S. Patent No. 2119882.

(8) After completion of this work, C. T. Holdrege, R. B. Babel, and L. C. Cheney, *J. Am. Chem. Soc.* **81**, 4807 (1959), described a preparation of 2,4-disulfamyl-5-trifluoromethylaniline by a different procedure.

(9) W. T. Caldwell and A. N. Sayi, *J. Am. Chem. Soc.* **73**, 5125 (1951).

TABLE I

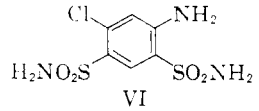


No.[a,b]	R_1	R_6	R_5	R_4	M.P.°	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	Cl	SO_2NH_2	251–252	$C_6H_8ClN_3O_4S_2$	25.22	25.48	2.82	2.81	14.71	14.68
2	H	Cl	H	SO_2NH_2	242–244	$C_6H_8ClN_3O_4S_2$	25.22	25.52	2.82	2.75	14.71	14.59
3	H	H	Br	SO_2NH_2	265–267	$C_6H_8BrN_3O_4S_2$	21.82	22.04	2.44	2.72	12.73	12.72
4	H	H	F	SO_2NH_2	227.5–228.5	$C_6H_8FN_3O_4S_2$	26.76	27.15	2.99	2.98	15.62	15.57
5	H	H	CH_3	SO_2NH_2	246–247	$C_7H_{11}N_3O_4S_2$	31.69	31.68	4.18	3.97	15.84	15.84
6	H	H	OCH_3	SO_2NH_2	252–253	$C_7H_{11}N_3O_5S_2$	29.89	30.12	3.94	4.09	14.94	14.93
7	H	H	NO_2	SO_2NH_2	260–262	$C_6H_8N_4O_6S_2$	24.32	24.53	2.72	2.71	18.91	19.11
8	CH_3	H	Cl	SO_2NH_2	248–249	$C_7H_{10}ClN_3O_4S_2$	28.05	28.09	3.36	3.35	14.02	14.00
9	H	SO_2NH_2	H	Br	252	$C_6H_8BrN_3O_4S_2$	21.83	22.28	2.44	2.81	12.73	12.64
10	H	H	SO_2NH_2	Cl	289–290	$C_6H_8ClN_3O_4S_2$	25.22	25.51	2.82	2.88	14.71	14.58
11	H	H	Cl	Cl	175–178	$C_6H_6Cl_2N_2O_2S$	29.89	29.99	2.51	2.56	11.62	11.50
12	H	H	CH_3	Cl	202–203	$C_7H_9ClN_2O_2S$	38.10	38.20	4.11	4.14	12.70	12.76
13	H	H	Cl	CH_3	191–193	$C_7H_9ClN_2O_2S$	38.10	38.32	4.11	4.13	12.70	12.70
14	H	Cl	Cl	SO_2NH_2	289	$C_6H_7Cl_2N_3O_4S_2$	22.51	22.65	2.20	2.34	3.12	3.16
15	H	I	Cl	SO_2NH_2	308–309[c]	$C_6H_7ClIN_3O_4S_2$	17.51	17.96	1.71	1.83	10.21	10.10
16	H	H	CF_3	SO_2NH_2	241–242	$C_7H_8F_3N_3O_4S_2$	26.33	26.30	2.53	2.77	13.16	13.14
17[d]	H	H	Cl	H	138.5–140.5	$C_6H_7ClN_2O_2S$	34.87	35.22	3.41	3.56	13.56	13.53
18	H	H	SO_2NH_2	H	216–217	$C_6H_9N_3O_4S_2$	28.68	29.14	3.61	3.66	16.72	16.72
19	H	SO_2NH_2	H	H	206–207	$C_6H_9N_3O_4S_2$	28.68	29.03	3.61	3.64	16.72	16.62

[a] Aqueous ethanol was employed for recrystallization. [b] Compounds 9–13 were prepared according to the general sulfonation method described in the Experimental from the following intermediates: (9) *p*-bromoaniline; (10) 5-amino-2-chlorobenzenesulfonic acid (Eastman Kodak Co.); (11) 3,4-dichloroaniline; (12) 2-amino-5-chloro-4-methylbenzenesulfonic acid (Eastman Kodak Co.); (13) 2-amino-4-chloro-5-methylbenzenesulfonic acid (Eastman Kodak Co.). [c] Corrected melting point. [d] Prepared by reduction of 5-chloro-2-sulfamylnitrobenzene according to procedure described in the Experimental for the preparation of 3-chloro-4-methylmercaptoaniline.

convenient route to other anilinedisulfonamides. Both *o*- and *m*-chloroaniline readily yielded the corresponding disulfonamides, 6-chloro-2,4-disulfamylaniline and 5-chloro-2,4-disulfamylaniline. Thus, the chlorine atom in *o*- and *m*-chloroaniline effectively blocks introduction of the third sulfonyl group. In addition, halodisulfamylanilines provided a convenient route to the isomeric disulfamylanilines which are not readily accessible by other synthetic routes. Catalytic dechlorination of both 5-chloro- and 6-chloro-2,4-disulfamylaniline using palladium-charcoal catalyst gave 2,4-disulfamylaniline. 4-Bromo-2,6-disulfamylaniline, prepared from *p*-bromoaniline, upon catalytic debromination yielded 2,6-disulfamylaniline. 2,5-Disulfamylaniline was obtained similarly from the 4-chloro derivative.

The haloaniline-2,4-disulfonamides exhibited superior activity within the series and 5-chloro-2,4-disulfamylaniline (VI) was studied more extensively. Acylation with one equivalent of an

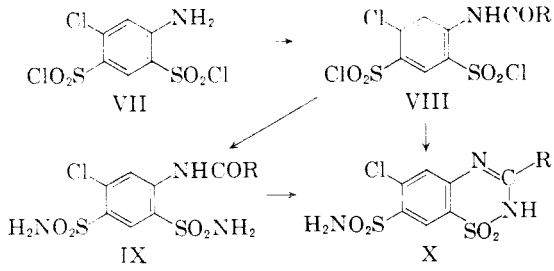


VI

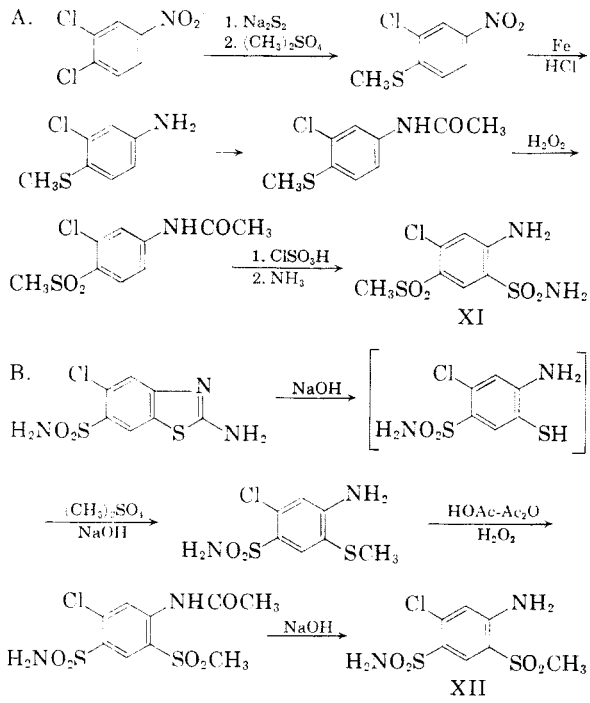
acyl chloride yielded monoacyl derivatives having the amino group acylated. In this manner a series of 5-chloro-2,4-disulfamyl-*N*-acylanilines was prepared from acetyl, chloroacetyl, butyryl, palmitoyl, benzoyl, and *o*- and *p*-chlorobenzoyl chlorides. An excess of the acylating agent resulted in acylation of both sulfamyl groups as well as the amino group to give the triacyl derivative 5-chloro-2,4-di(acylsulfamyl)-*N*-acylaniline. Acylation of the amino group was substantiated by means of a negative color test for diazotizable amine[10] and ultraviolet spectroscopy.

Acylation of the aniline-2,4-disulfonyl chloride (VII) to the *N*-acylaniline-2,4-disulfonyl chloride (VIII) followed by reaction of the acylated sulfonyl chlorides with ammonia or amines offered an attractive alternate route to the disulfamyl-*N*-acylanilines (IX). In this manner, the possibility of acylation of the sulfamyl groups would be avoided. However, treatment of the acylated disulfonyl chloride with ammonia (or secondary amines) invariably resulted in a mixture of the expected sulfamyl compound (IX) together with a benzothiadiazine-1,1-dioxide (X) resulting from cyclodehydration between the acylamino group and the adjacent sulfamyl group.[1]

(10) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).



Because of the high order of diuretic activity of 5-chloro-2,4-disulfamylaniline (VI), it was of interest to determine the effect of replacing the sulfamyl groups in turn by a methylsulfonyl group. The two isomeric methylsulfonyl analogs XI and XII were prepared as indicated in the following series of reactions.



Biologic evaluation of these compounds was determined in dogs following intravenous or oral administration by measuring sodium, chloride, and potassium excretion and urine volume.[11]

The disulfamylanilines are generally more active than monosulfamyl derivatives previously investigated. This is particularly true of compounds where the sulfamyl groups are *meta* to each other and one sulfamyl group is *ortho* to the amino group. Detailed study of 2,4-disulfamylanilines showed that additional substitution into the benzene nucleus enhances activity. Substitution into the 5-position *ortho* to the second sulfamyl group has the most favorable effect. 5-Chloro-, 5-bromo-, 5-trifluoromethyl-, and 5-nitro-2,4-disulfamylaniline are highly active by both intravenous and oral routes, whereas the 5-fluoro, 5-amino, 5-methyl, and 5-methoxy analogs are somewhat less effective.

Derivatives of 5-chloro-2,4-disulfamylaniline,[12] a representative of the highly active group, were studied further. An additional halogen in the 6-position does not improve activity. Alkylation of the aniline amino group by a methyl or an allyl group gave compounds that are active when administered intravenously, but are less active when given orally. Acylation of this amino group gave compounds of varying activity, depending upon the nature of the acyl group. Aromatic acyl derivatives are less active than the best aliphatic members. In the aliphatic acyl series, activity reaches a maximum with the butyryl and hexanoyl members. Any of a variety of substitutions into one or both sulfamyl groups generally reduces activity.[13] Complete acylation, to give 2,4-di(acylsulfamyl)-*N*-acylanilines, lowers the activity. Replacement of either sulfamyl group by a methylsulfonyl group results in structures of little activity.

EXPERIMENTAL[14,15]

The following procedure illustrates the general method for preparation of aniline-2,4-disulfonamides listed in Table I and not described elsewhere in the Experimental. The yield is typical.

5-Chloro-2,4-disulfamylaniline (No. 1, Table I) *m*-Chloroaniline (64 g., 0.5 mole) was added dropwise with stirring to 670 g. (6.0 moles) of chlorosulfonic acid in a 3-l. round bottomed 3-necked flask cooled in an ice bath. Sodium chloride (350 g., 6 moles) was added portionwise over a period of 1–2 hr. and the mixture then heated gradually in an oil bath to 150°. After 3 hr. at 150–160° the flask was cooled thoroughly in an ice bath and the contents treated with 1 l. of cold water. The product was extracted with ether and dried over sodium sulfate. After removal of ether on the steam bath, the residual 5-chloroaniline-2,4-disulfonyl chloride, which may be crystallized from benzene-hexane, m.p. 139–142°, was added to 150 ml. of cold concd. ammonium hydroxide and heated on the steam bath for 1 hr. The mixture was cooled and the product recrystallized from aqueous ethanol; yield, 44 g. (30%) of colorless needles, $\lambda_{max}^{C_2H_5OH}$ 223.5–224.5, 265–266, and 312–314 mμ, ε 41,776, 18,633, and 3874 respectively.

Acetylation of 5-chloro-2,4-disulfamylaniline by acetic anhydride and concd. sulfuric acid (trace) gave *5-chloro-2,4-di(acetylsulfamyl)acetanilide;* colorless needles from alcohol, m.p. 222–224°.

Anal. Calcd. for $C_{12}H_{14}ClN_3O_7S_2$: C, 34.99; H, 3.43; N, 10.20. Found: C, 34.91; H, 3.77; N, 10.10.

5-Chloro-2,4-disulfamyl-N-methylaniline (No. 8, Table I). *m*-Chloro-*N*-methylaniline (26.7 g., 0.15 mole) was added to 110 ml. of chlorosulfonic acid, cooled in an ice bath over 15 min., and then heated at 125–130° for 3 hr. The mixture was

(11) We are indebted to Drs. John E. Baer and Karl H. Beyer and their associates for the biological data that are summarized here.

(12) Alf Lund and Karen Størling, *Acta Pharm. Tox.* **15**, 300 (1959) have recently reported this compound to be highly active in animals and man.

(13) W. Logemann, P. N. Geraldi, and M. A. Parenti, *Nature* **182**, 1510 (1958) and ref. 5 report 5-chloro-2,4-di(methylsulfamyl)aniline to be an effective diuretic in rats.

(14) Melting points are uncorrected. Data shown in Table I are not reproduced in the Experimental.

(15) We are indebted to Mr. K. B. Streeter and his associates for analytical and spectral data.

cooled and 44 ml. of thionyl chloride[6] was added. After heating an additional hour on the steam bath, the mixture was cooled and poured onto ice. The solid was collected, washed with water, added to 100 ml. of concd. ammonium hydroxide, and heated on the steam bath for 1 hr. Recrystallization of the product from aqueous ethanol gave colorless needles; yield, 16.5 g. (37%).

2,4-Disulfamyl-5-fluoroaniline (No. 4, Table I) was prepared from *m*-fluoroaniline according to the procedure described for 5-chloro-2,4-disulfamyl-*N*-methylaniline; yield, 39% of colorless needles from aqueous alcohol.

5-Chloro-2,4-di(methylsulfamyl)aniline. 5-Chloroaniline-2,4-disulfonyl chloride (6.5 g., 0.02 mole) was added to 50 ml. of 40% aqueous methylamine and heated on the steam bath for 1–2 hr. The mixture was cooled and the product collected and recrystallized from alcohol; yield, 6.0 g. (96%) of colorless needles, m.p. 175.5–178°.

Anal. Calcd. for $C_8H_{12}ClN_3O_4S_2$: C, 30.62; H, 3.86; N, 13.39. Found: C, 30.85; H, 3.81; N, 13.34.

5-Chloro-2,4-bis(dimethylsulfamyl)aniline was prepared in a similar manner with dimethylamine (25%) in place of methylamine; yield, 54% of colorless needles from ethanol-water, m.p. 181–182°, $\lambda_{max}^{C_2H_5OH}$ 227.5, 271.5, and 314–317 mμ, ε 29,363, 19,177, and 4205 respectively.

Anal. Calcd. for $C_{10}H_{16}ClN_3O_4S_2$: C, 35.14; H, 4.61; N, 12.29. Found: C, 35.21; H, 4.89; N, 12.26.

Acetylation of 5-chloro-2,4-bis(dimethylsulfamyl)aniline by acetic anhydride and concd. sulfuric acid (trace) gave *5-chloro-2,4-bis(dimethylsulfamyl)-N-acetylaniline;* colorless needles from alcohol-water, m.p. 193–195°, $\lambda_{max}^{C_2H_5OH}$ 231–234 and 267–270 mμ, ε 26,601 and 17,098 respectively.

Anal. Calcd. for $C_{12}H_{18}ClN_3O_5S_2$: C, 37.54; H, 4.73; N, 10.95. Found: C, 37.86; H, 4.76; N, 10.90.

5-Chloro-2,4-di(pentamethylenesulfamyl)aniline. A solution of 9.7 g. (0.03 mole) of 5-chloroaniline-2,4-disulfonyl chloride in 200 ml. of benzene was added over 10 min. to 50 ml. (0.05 mole) of piperidine and heated on the steam bath for 3 hr. The solution was cooled, washed with water, dilute hydrochloric acid, water, and dried over sodium sulfate. Solvent was removed *in vacuo*. Recrystallization of the residue from ethanol gave colorless needles, m.p. 162–164°.

Anal. Calcd. for $C_{16}H_{24}ClN_3O_4S_2$: C, 45.75; H, 5.76; N, 10.00. Found: C, 46.04; H, 5.67; N, 10.00.

2-Amino-4-trifluoromethylbenzenesulfonic acid. A solution of 12.0 g. (0.10 mole) of chlorosulfonic acid in 50 ml. of *sym*-tetrachloroethane was added dropwise with stirring over 15 min. to a solution of 16.1 g. (0.10 mole) of *m*-trifluoromethylaniline in 200 ml. of *sym*-tetrachloroethane cooled in an ice bath. After heating in an oil bath at 125° for 3 hr., the mixture was cooled and the product collected and purified by reprecipitation from sodium carbonate solution; yield, 18 g. (75%) pale yellow powder, m.p. 330° dec. A sample recrystallized from water was obtained as colorless needles, m.p. 333–334° dec.

Anal. Calcd. for $C_7H_6F_3NO_3S$: N, 5.81; S. 13.29. Found: N, 5.79; S, 13.38.

*2-Sulfamyl-5-trifluoromethylaniline. 2-Amino-4-trifluoromethylbenzenesulfonic acid (24.1 g., 0.1 mole) was added portionwise with stirring to 75 ml. of chlorosulfonic acid at 0° and then the mixture was heated in an oil bath at 110–115° for 3 hr. The mixture was cooled and thionyl chloride (30 ml.) was added. After heating on the steam bath for 30 min., the solution was poured onto ice and the aqueous layer decanted. The residual solid was heated on the steam bath with 500 ml. of concd. ammonium hydroxide for 1 hr., cooled and the product (12.5 g.) collected and digested with hot toluene (500 ml.) to separate toluene insoluble 2,4-disulfamyl-5-trifluoromethylaniline (3.0 g.). Concentration of the toluene extract to 250 ml. gave 8.0 g. of 2-sulfamyl-5-trifluoromethylaniline, m.p. 144–146°.

Anal. Calcd. for $C_7H_7F_3N_2O_2S$: C, 35.00; H, 2.94; N, 11.66. Found: C, 35.30. H, 3.16; N, 11.75.

A solution of 2-sulfamyl-5-trifluoromethylaniline (4.0 g.) in 98–100% formic acid (100 ml.) was heated under reflux for 2 hr. The mixture was cooled and the product recrystallized from ethanol water. *6-Trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide* was obtained as colorless needles in 96% yield; m.p. 262–264°.

Anal. Calcd. for $C_8H_5F_3N_2O_2S$: C, 38.40; H, 2.01; N, 11.20. Found: C, 39.05; H, 2.04; N, 11.15.

2,4-Disulfamyl-5-trifluoromethylaniline (No. 16, Table I). 2-Amino-4-trifluoromethylbenzenesulfonic acid (32 g., 0.132 mole) was added portionwise with stirring to chlorosulfonic acid (100 ml.), cooled in an ice bath, over a 5–10 min. period. The solution was heated in an oil bath at 150° for 3 hr., and then cooled to room temperature. Thionyl chloride (40 ml.) was added and the mixture heated on the steam bath for 1 hr., cooled, and poured onto ice. The solid was collected and heated on the steam bath with 500 ml. of concd. ammonium hydroxide for 2 hr. The mixture was cooled and the product was collected, washed with water, and dried. To remove a trace amount of 2-sulfamyl-5-trifluoromethylaniline, the crude product was digested with 500 ml. of hot benzene, filtered, and the benzene-insoluble residue recrystallized from aqueous alcohol to give 2,4-disulfamyl-5-trifluoromethylaniline as colorless needles; yield, 15.3 g. (36%).

Dehalogenations. Catalytic dehalogenation of the halodisulfamylanilines was accomplished in 78–94% yield according to the following procedure for *2,4-disulfamylaniline.* A solution of 5.7 g. (0.02 mole) of 5-chloro-2,4-disulfamylaniline in a mixture of 100 ml. of water and 35 ml. of 5% sodium hydroxide was hydrogenated (25 min.) in the presence of 2 g. of 5% palladium-charcoal catalyst. After removal of catalyst, the solution was neutralized with concd. hydrochloric acid to give 3.9 g. of colorless needles, m.p. 230–231.5°, rep.[16] m.p. 235°.

Catalytic dehalogenation of 6-chloro-2,4-disulfamylanilline in similar manner gave the same product.

Acetylation of 2,4-disulfamylaniline by acetic anhydride and sulfuric acid (trace) gave 2,4-di(acetylsulfamyl)acetanilide, m.p. 234–235°.

Anal. Calcd. for $C_{12}H_{15}N_3O_7S_2$: C, 38.19; H, 4.01; N, 11.13. Found: C, 38.20; H, 4.17; N, 10.62.

5-Chloro-2,4-disulfamyl-N-acylanilines. A solution of 5.7 g. (0.02 mole) of 5-chloro-2,4-disulfamylaniline in 75 ml. of dioxane and 2.34 g. (0.022 mole) of butyryl chloride was heated under reflux for 20 hr. and concentrated to dryness *in vacuo*. Recrystallization of the residue from alcohol-water gave 5.2 g. (73%) of *5-chloro-2,4-disulfamyl-N-butyrylaniline,* colorless needles, m.p. 236–237°, $\lambda_{max}^{C_2H_5OH}$ 227–228.5 and 261–265 mμ, ε 38,249 and 19,843 respectively.

Anal. Calcd. for $C_{10}H_{14}ClN_3O_5S_2$: C, 33.75; H, 3.97; N, 11.81. Found: C, 33.80; H, 4.02; N, 11.81.

By this procedure the reaction with the appropriate acyl chlorides gave the following acyl derivatives.

5-Chloro-2,4-disulfamyl-N-acetylaniline, 80% yield, m.p. 240–242°, $\lambda_{max}^{C_2H_5OH}$ 226–228 and 261–263 mμ, ε 37,017 and 18,389 respectively.

Anal. Calcd. for $C_8H_{10}ClN_3O_5S_2$: C, 29.31; H, 3.08; N, 12.82. Found: C, 29.72; H, 3.21; N, 12.80.

5-Chloro-2,4-disulfamyl-N-chloroacetylaniline, 84% yield m.p. 243–244°, $\lambda_{max}^{C_2H_5OH}$ 227–228 and 260–263 mμ, ε 25,752 and 13,447 respectively.

Anal. Calcd. for $C_8H_9Cl_2N_3O_5S_2$: C, 26.53; H, 2.50; N, 11.60. Found: C, 26.84; H, 2.56; N, 11.62.

5-Chloro-2,4-disulfamyl-N-palmitoylaniline, 95% yield, m.p. 213°.

Anal. Calcd. for $C_{22}H_{38}ClN_3O_5S_2$: C, 50.41; H, 7.31; N, 8.02. Found: C, 50.67; H, 7.18; N, 7.99.

5-Chloro-2,4-disulfamyl-N-p-chlorobenzoylaniline, 76% yield, m.p. 269–270° dec.

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_5S_2$: C, 36.80; H, 2.61; N, 9.90. Found: C, 36.94; H, 2.46; N, 9.90.

5-Chloro-2,4-disulfamyl-N-o-chlorobenzoylaniline, 85% yield, m.p. 272–273° dec.

(16) P. Fischer, *Ber.* 24, 3785 (1891).

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_5S_2$: C, 36.80; H, 2.61; N, 9.90. Found: C, 36.92; H, 2.79; N, 9.94.

When excess butyryl chloride (10 ml.) was employed *5-chloro-2,4-di(butyrylsulfamyl)-N-butyrylaniline* was obtained in 63% yield, m.p. 182.5°.

Anal. Calcd. for $C_{18}H_{26}ClN_3O_7S_2$: C, 43.59; H, 5.28; N, 8.47. Found: C, 43.56; H, 5.38; N, 8.44.

5-Chloro-2,4-disulfamyl-N-benzoylaniline was obtained by the above procedure or as follows: a solution of 5.7 g. (0.02 mole) of 5-chloro-2,4-disulfamylaniline in 75 ml. of dioxane and an excess of benzoyl chloride was heated under reflux for 8 hr. Crystals began to separate within 2 hr. The mixture was cooled and the product (7.0 g., m.p. 266–267° dec.) collected and recrystallized from dimethylformamide-water; yield, 5.4 g. (69%), m.p. 275–276° dec.

Anal. Calcd. for $C_{13}H_{12}ClN_3O_5S_2$: C, 40.05; H, 3.10; N, 10.78. Found: C, 40.49; H, 3.06; N, 10.79.

5-Chloro-N-acylaniline-2,4-disulfonyl chlorides. A solution of 5 g. of 5-chloroaniline-2,4-disulfonyl chloride in 10–15 ml. of the acid anhydrides with and without benzene (10 ml.) was allowed to stand at room temperature for 1–2 hr. Brief warming of the mixture may be employed. The product separated from the reaction mixture and was recrystallized from hexane or a benzene-hexane mixture.

5-Chloro-N-acetylaniline-2,4-disulfonyl chloride, 78% yield, m.p. 137–139°.

Anal. Calcd. for $C_8H_6Cl_3NO_5S_2$: C, 26.21; H, 1.65; N, 3.82. Found: C, 26.39; H, 1.77; N, 3.79.

5-Chloro-N-butyrylaniline-2,4-disulfonyl chloride, 69% yield, m.p. 121–122°.

Anal. Calcd. for $C_{10}H_{10}Cl_3NO_5S_2$: C, 30.43; H, 2.55; N, 3.55. Found: C, 30.72; H, 2.51; N, 3.55.

5-Chloro-N-caproylaniline-2,4-disulfonyl chloride, 69% yield, m.p. 91–93°.

Anal. Calcd. for $C_{12}H_{14}Cl_3NO_5S_2$: C, 34.09; H, 3.34; N, 3.31. Found: C, 34.58; H, 3.56; N, 3.40.

3-Chloro-4-methylmercaptonitrobenzene.[17] A solution of sodium disulfide, prepared from 175 g. (0.72 mole) of sodium sulfide nonahydrate and 23.4 g. (0.73 g. atom) of sulfur dissolved in 1.3 l. of hot ethanol, was added with stirring over 20 min. to a boiling solution of 192 g. (1 mole) of 3,4-dichloronitrobenzene in 250 ml. of ethanol. A solution of 40 g. (1 mole) of sodium hydroxide in 900 ml. of 95% ethanol was then added over 10 min. and heating was continued for another 5 min. The mixture was cooled in an ice bath and diluted with 1.5 l. of ice water and 200 ml. of 20% aqueous sodium hydroxide. Dimethyl sulfate (126 g., 1 mole) was added over 15 min. and the mixture was stirred at room temperature for 45 min. The solid was collected, washed with water, and recrystallized from alcohol; yield, 150 g. (74%) of yellow needles, m.p. 85–91°; analytical sample, m.p. 92–94°.

Anal. Calcd. for $C_7H_6ClNO_2S$: C, 41.28; H, 2.97; N, 6.88. Found: C, 41.47; H, 3.17; N, 6.85.

3-Chloro-4-methylmercaptoaniline. Iron powder (56.4 g.) and concd. hydrochloric acid (236 ml.) were added in six portions over 4 hr. to a suspension of 48.8 g. (0.24 mole) of 3-chloro-4-methylmercaptonitrobenzene and 8 g. of cupric chloride in 190 ml. of water and 100 ml. of methanol, maintained at 70°. The mixture was heated at 80–85° for 1.5 hr. and transferred to a flask suitable for steam distillation. Sodium hydroxide (140 g.) was added and steam distillation carried out for 10 hr. The distillate was extracted with ether and afforded colorless needles from ether-petroleum ether; yield, 31.6 g. (73%), m.p. 73–75°.

Anal. Calcd. for C_7H_8ClNS: C, 48.41; H, 4.64; N, 8.07. Found: C, 48.65; H, 4.74; N, 8.07.

3-Chloro-4-methylmercaptoacetanilide was prepared in quantitative yield from 3-chloro-4-methylmercaptoaniline (45 g.) and acetic anhydride (150 ml.) at room temperature; colorless needles from alcohol-water, m.p. 130–132°.

Anal. Calcd. for $C_9H_{10}ClNOS$: C, 50.11; H, 4.67; N, 6.49. Found: C, 50.32; H, 4.85; N, 6.50.

3-Chloro-4-methylsulfonylacetanilide. To a suspension of 43 g. (0.2 mole) of 3-chloro-4-methylmercaptoacetanilide in 200 ml. of glacial acetic acid–acetic anhydride mixture (1:1), cooled in an ice bath, 55 g. (0.44 mole) of 30% hydrogen peroxide was added with stirring over 20 min. After 24 hr. at room temperature, excess hydrogen peroxide was destroyed by addition of manganese dioxide. The solution was filtered, concentrated to dryness *in vacuo*, and the residue recrystallized from benzene-alcohol; yield, 42 g. (85%) of colorless needles, m.p. 127–130°.

Anal. Calcd. for $C_9H_{10}ClNO_3S$: C, 43.64; H, 4.07; N, 5.66. Found: C, 43.73; H, 3.93; N, 5.62.

5-Chloro-4-methylsulfonyl-2-sulfamylaniline was prepared in 30% yield from 3-chloro-4-methylsulfonylacetanilide by the general chlorosulfonation procedure described for the preparation of 5-chloro-2,4-disulfamylaniline; colorless needles from alcohol-water, m.p. 242–244°.

Anal. Calcd. for $C_7H_9ClN_2O_4S_2$: C, 29.53; H, 3.19; N, 9.84. Found: C, 29.54; H, 3.49; N, 9.79.

2-Amino-5-chloro-6-sulfamylbenzothiazole. A solution of 24 g. (0.15 mole) of bromine in 50 ml. of acetic acid was added slowly to a stirred solution of 31 g. (0.15 mole) of 2-chlorosulfanilamide and 58.2 g. (0.6 mole) of potassium thiocyanate in a liter of 90% acetic acid maintained at 0–5°. The solution was allowed to warm to room temperature slowly and stand overnight. The yellow suspension then was heated under reflux for 2 hr. and concentrated under reduced pressure. The residue upon recrystallization from dilute alcohol yielded 20.8 g. of product, m.p. 285–287°.

Anal. Calcd. for $C_7H_6ClN_3O_2S_2$: C, 31.88; H, 2.29; N, 15.93. Found: C, 32.11; H, 2.40; N, 15.84.

5-Chloro-2-methylmercapto-4-sulfamylaniline. A solution of 7.9 g. (0.03 mole) of 2-amino-5-chloro-6-sulfamylbenzothiazole and 16.8 g. (0.3 mole) of potassium hydroxide in 35 ml. of water was heated under reflux for 6 hr. The solution was cooled and acidified. The product was collected on the filter (7.3 g., m.p. 218–223°) and methylated without further purification, as recrystallization from 90% alcohol or dimethylformamide-water always gave the *disulfide,* m.p. 298–300°.

Anal. Calcd. for $C_{12}H_{12}Cl_2N_4O_4S_4$: C, 30.31; H, 2.55; N, 11.79. Found: C, 30.77; H, 2.55; N, 11.76.

Dimethylsulfate (3.8 g., 0.03 mole) was added in three portions to a stirred solution of the crude 5-chloro-2-mercapto-4-sulfamylaniline (7.2 g., 0.03 mole) in 80 ml. of 5% sodium hydroxide maintained at 5–10°. After 1 hr., the solution was acidified and the product recrystallized from alcohol; yield, 3.2 g., m.p. 160–162°.

Anal. Calcd. for $C_7H_9ClN_2O_2S_2$: C, 33.26; H, 3.59; N, 11.09. Found: C, 33.39; H, 3.46; N, 11.06.

5-Chloro-2-methylsulfonyl-4-sulfamylaniline. One gram (0.9 ml., 0.03 mole) of 30% hydrogen peroxide was added slowly to a suspension of 5-chloro-2-methylmercapto-4-sulfamylaniline (3.0 g., 0.0125 mole) in a mixture of 30 ml. of acetic acid and 25 ml. of acetic anhydride maintained at 0–5°. The solution was allowed to stand at room temperature overnight. Solvent was removed on the steam bath *in vacuo* and the residue poured into water. The product was recrystallized from alcohol-water to give 1.1 g. of *5-chloro-2-methylsulfonyl-4-sulfamylacetanilide,* m.p. 283–285°.

Anal. Calcd. for $C_9H_{11}ClN_2O_5S_2$: C, 33.08; H, 3.39; N, 8.57. Found: C, 33.11; H, 3.38; N, 8.59.

A solution of 2 g. (0.006 mole) of the above acetanilide in 20 ml. of 5% sodium hydroxide was heated on the steam bath for 2 hr. and acidified; yield, 1.4 g., m.p. 229–231°. Recrystallization from water did not change the melting point.

Anal. Calcd. for $C_7H_9ClN_2O_4S_2$: C, 29.52; H, 3.19; N, 9.84. Found: C, 29.69; H, 3.39; N, 9.87.

5,6-Dichloro-2,4-disulfamylaniline (No. 14, Table I). A solution of 25.7 g. (0.09 mole) of 5-chloro-2,4-disulfamylaniline in a mixture of 100 ml. of water, 200 ml. of glacial acetic acid, and 150 ml. of concd. hydrochloric acid was

(17) Based on the procedure for *p*-nitrothiophenol. C. C. Price and G. W. Stacy, *J. Am. Chem. Soc.,* **68,** 498 (1946).

treated with 9 ml. of 30% hydrogen peroxide at 75–80° and allowed to cool to room temperature (2 hr.). The mixture was cooled and the crystalline precipitate collected, washed with water, and recrystallized from alcohol-water; yield, 12 g. (42%) of colorless needles.

5-Chloro-2,4-disulfamyl-6-iodoaniline[18] (No. 15, Table I). A solution of iodine monochloride (21.1 g., 0.13 mole) in concd. hydrochloric acid (50 ml.) was added dropwise over 30 min. to a solution of 5-chloro-2,4-disulfamylaniline (25.3 g., 0.089 mole) in concd. hydrochloric acid (350 ml.) maintained at 98°. After stirring at 98° for 24 hr., the mixture was cooled to 5° and the product collected on a sintered glass funnel, washed with water, and dried; yield, 27 g. (82%), m.p. 308–309° dec. (corr.). An analytical sample prepared by recrystallization from ethanol-water showed no change in melting point.

(18) We are indebted to Dr. E. J. Cragoe for this preparation.

WEST POINT, PA.

[CONTRIBUTION FROM THE MERCK SHARP AND DOHME RESEARCH LABORATORIES DIVISION OF MERCK AND COMPANY, INC.]

Diuretics: 1,2,4-Benzothiadiazine-1,1-dioxides

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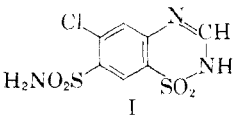
Ring closure of aniline-2,4-disulfonamides with acylating agents, aldehydes, or urea to give sulfamylbenzothiadiazine-1,1-dioxide derivatives is described. Sulfamylbenzothiadiazine-1,1-dioxides promote excretion of sodium chloride in animals and man and constitute a novel class of orally effective diuretic agents. Several aspects of the chemistry of this class of compounds are reported in detail.

6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide[1] (I) is an orally effective diuretic and is



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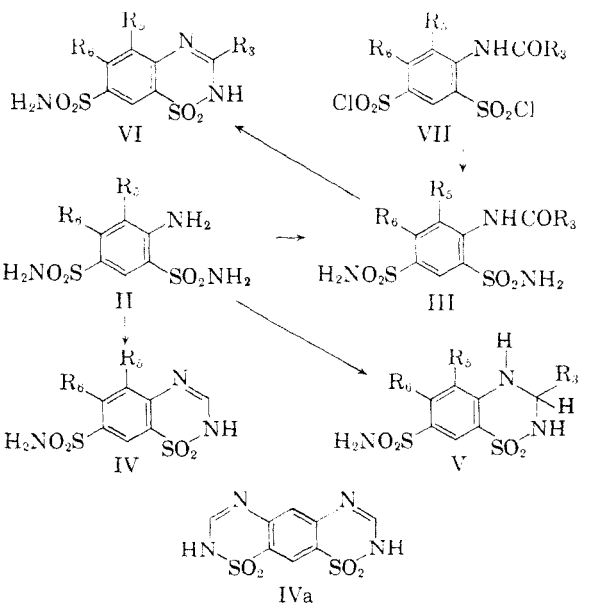
being employed currently in therapy for conditions associated with fluid and electrolyte retention such as congestive heart failure and hypertension. Preliminary communications have reported some of the chemistry and biological properties of this compound and some closely related derivatives.[2,3,4] The present paper reports on these more fully and describes the extension of this series of compounds.

1,2,4-Benzothiadiazine-1,1-dioxides as a class have been known since 1902[5–9] and a number of derivatives have been prepared from the appropriately substituted orthanilamide by the general procedures involving ring closure of the orthanilamide by reaction with acylating agents, aldehydes or urea. However, no compound of this class has been reported where a sulfamyl group is present. The only biologic property previously noted for any 1,2,4-benzothiadiazine-1,1-dioxide is the sweet taste of 3-oxodihydro-1,2,4-benzothiadiazine-1,1-dioxide.[6,7,9]

In our studies, compounds of greatest interest have the general structures IV, V and VI where a sulfamyl group occupies the 7 position. Benzothiadiazine-1,1-dioxides of types IV and VI and related isomers having the sulfamyl group in the 5 or 6 position as well as representative reference compounds lacking a sulfamyl group are recorded in Table I.



(1) The generic name of chlorothiazide has been given to this compound and Diuril is the trademark of Merck and Co., Inc., for chlorothiazide.

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(3) F. C. Novello and J. M. Sprague, 132nd Meeting of the American Chemical Society, New York, N. Y., September 8–13, 1957; abstracts, pp. 32-40.

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