their infrared spectra were identical. *Anal.* Calcd. for $C_{14}H_{16}O_4N_4$: C, 55.28; H, 5.29; N, 18.39. Found: C, 55.05; H, 5.17; N, 18.36.

Anhydrocycloheximide (VI).—Cycloheximide (1 g.) was dissolved in 6 *N* hydrochloric acid (15 ml.) and the solution maintained at 80–90° for about 5 minutes. The crystalline solid which separated out on cooling was filtered and recrystallized from aqueous methanol. The product separated out as glistening colorless rectangular plates, m.p. 133–135° (reported[2] m.p. for anhydrocycloheximide 134–135°). *Anal.* Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.92; H, 8.17; N, 5.48.

Anhydrocycloheximide Acid (VII).—Anhydrocycloheximide (0.5 g.) was refluxed with 6 *N* hydrochloric acid for 1 hour. The mixture was cooled and extracted with ether. The acid VII was obtained as a colorless glassy solid and hence it was characterized as the following salts. A solution of the acid in ether was treated with benzylamine in ether until there was no more precipitate. The benzylamine salt was crystallized from acetone–ethyl acetate. It separated out as colorless rectangular prisms, m.p. 153–154°. *Anal.* Calcd. for $C_{29}H_{40}O_5N_2$: C, 70.13; H, 8.12; N, 5.64. Found: C, 70.57; H, 7.98; N, 5.66.

The above benzylamine salt was dissolved in water and passed through Amberlite IR-C50 which is converted into the barium form. The effluent and the wash were concentrated to dryness and the product crystallized from aqueous methanol. The barium salt separated out as colorless glistening plates which decomposed at 275–280° (ϵ 9000 at 241 mμ). *Anal.* Calcd. for $C_{15}H_{20}O_5Ba$: C, 43.15; H, 4.82; Ba, 32.88. Found: C, 43.58; H, 4.83; Ba, 32.79.

Acknowledgment.—The author is grateful to Dr. R. L. Wagner for analyses and to Dr. F. A. Hochstein for many helpful suggestions.

MAYWOOD, N. J.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Synthesis of Potential Diuretic Agents. I. Derivatives of 7-Sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide

BY W. J. CLOSE, LEO R. SWETT, LEONARD E. BRADY, JAMES H. SHORT AND MAYNETTE VERNSTEN

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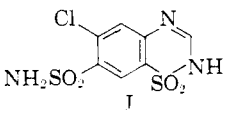
The synthesis of several new 7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides from substituted 4-amino-1,3-benzenedisulfonamides is described. Ring closure was effected with formaldehyde as well as with higher aldehydes and halogenated aldehydes.

The need for better diuretic and hypotensive agents is attested by the extensive research effort which is being expended in these areas. Although a great variety of drugs is now available to the physician, most of these substances have severe limitations that impair their usefulness.

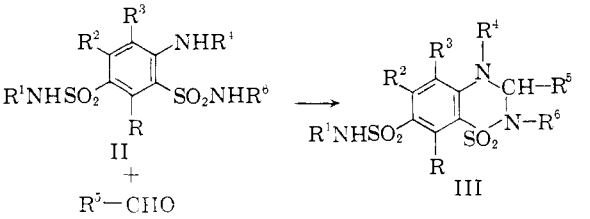
Recently, derivatives of 1,2,4-benzothiadiazine 1,1-dioxide have been shown in experimental animals to be carbonic anhydrase inhibitors, and to produce marked diuresis.[1-4] One member of this class (chlorothiazide, I) has achieved wide clinical acceptance as a diuretic and hypotensive agent.



I

In a systematic study of compounds related to chlorothiazide, we discovered that some dihydro compounds in the same series are considerably more effective in experimental animals than the aromatic substances.[5,6] This report describes the synthesis of compounds belonging to this class.

7-Sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides (III) were prepared by condensation of substituted 4-amino-1,3-benzenedisulfonamides (II) with aldehydes, usually in aqueous solution.[7] The intermediate disulfonamides were generally prepared in the classical manner through chlorosulfonation followed by treatment with ammonia.



II + R^5—CHO → III

Most of the compounds prepared were derived from 4 - amino - 6 - chloro - 1,3 - benzenedisulfonamide, but compounds containing fluoro, bromo, methyl, trifluoromethyl, methoxy and nitro groups were also made. Simple aliphatic and halogenated aliphatic aldehydes were used in the cyclization. The products are high-melting solids which tend to decompose at elevated temperatures. They are insoluble in water and acid, but soluble in caustic solutions, from which they can be recovered unchanged by acidification. Boiling with alkali readily opens the thiadiazine ring with the formation of the original disulfonamide.

Special consideration was given to the preparation of N-alkylated products. Chlorosulfonation of methylaniline was used to prepare 4-methylamino-1,3-benzenedisulfonamide, from which a 4-methyl derivative (III, $R^4 = CH_3$) was obtained. A compound in which both sulfonamide nitrogens carry a methyl substituent (III, $R^1 = R^6 = CH_3$; $R^2 =$

(1) F. C. Novello and J. M. Sprague, THIS JOURNAL, **79**, 2028 (1957).

(2) R. F. Pitts, F. Krück, R. Lozano, D. W. Taylor, O. P. A. Heidenreich and R. H. Kessler, *J. Pharmacol. Exptl. Therap.*, **123**, 89 (1958).

(3) K. H. Beyer, *Ann. New York Acad. Sci.*, **71**, 363 (1958).

(4) J. M. Sprague, *ibid.*, **71**, 328 (1958).

(5) Since this work was begun, we have learned that other groups have independently carried out investigations on similar compound. Compare G. de Stevens, L. H. Werner, A. Halamandaris and S. Ricca, Jr., *Experientia*, **14**, 463 (1958); W. Kobinger and F. Lund, *Ugeskrift Laeger*, **120**, 1583 (1958); C. T. Holdredge, R. B. Babel and L. C. Cheney, Abst. 135th National Meeting Am. Chem. Soc., p. 19N (1959); and L. H. Werner, A. Halamandaris, S. Ricca, Jr., L. Dorfman, and G. de Stevens, *ibid.*, p. 27N (1959); J. E. Baer, H. F. Russo, and K. H. Beyer, *Proc. Soc. Exptl. Biol. Med.*, **100**, 442 (1959).

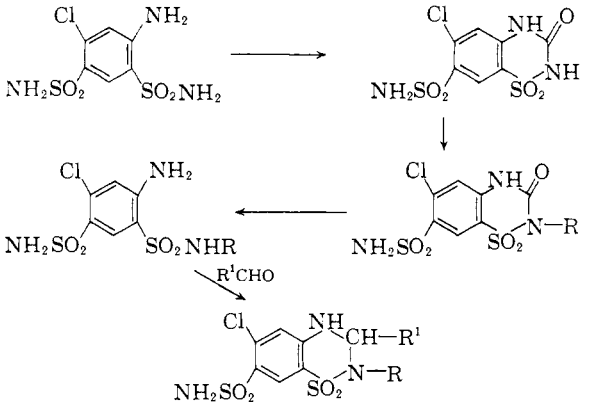
(6) Preliminary pharmacological data on the compounds described in this report were presented by M. E. Goldberg and K. Hwang, *Federation Proc.*, **18**, 396 (1959).

(7) J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).

Cl) was made by ring closure of 5-chloro-2,4-bis-(methylsulfamyl)-aniline.

Preparation of 2-alkyldihydrobenzothiadiazines (III, R^6 = alkyl) presents more of a problem. We have found that a fair yield of a 2-methyl derivative could be obtained by direct alkylation of 6-chloro - 7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine 1,1-dioxide, but alkylation with larger groups was unsatisfactory. A more general method is given in Scheme A. This involves cyclization with urea to the 3-keto derivative, which could be alkylated readily in high yield, followed by hydrolysis and re-cyclization with appropriate aldehydes.

SCHEME A



Experimental[8]

Preparation of Disulfonyl Chlorides.—These intermediates were prepared by chlorosulfonation with chlorosulfonic acid in large excess, occasionally with the use of sodium chloride.[9] Many of the products were not purified but were used directly in subsequent steps without characterization. The preparations of the disulfonyl chlorides which were characterized are given below, and serve to illustrate the general procedures involved.

4-Amino-6-chloro-1,3-benzenedisulfonyl Chloride.—A two-liter flask was equipped with a stirrer, dropping funnel, gas inlet tube and gas outlet tube. A slow stream of nitrogen was introduced during the course of the reaction, and the exit gases were led through a hydrogen chloride trap.

Chlorosulfonic acid (1300 cc.) was placed in the flask and 100 g. of *m*-chloroaniline was added dropwise with stirring and cooling. The reaction mixture was then heated at 115–125° for two hours. The cooled solution was added dropwise to a stirred ice–water mixture. The solid product was separated by filtration, washed with water, and dried at room temperature. The yield was 140–155 g. (55–61%), m.p. 135–143°. Recrystallization from chloroform brought the m.p. to 144–145°.

Anal. Calcd. for $C_6H_4Cl_3NO_4S_2$: C, 22.2; H, 1.2; N, 4.3. Found: C, 22.3; H, 1.0; N, 4.2.

4-Amino-6-methyl-1,3-benzenedisulfonyl chloride was prepared in 42% yield following the procedure given above. The product melted at 155° after recrystallization from chloroform.

Anal. Calcd. for $C_7H_7Cl_2NO_4S_2$: C, 27.6; H, 2.3; N, 4.6. Found: C, 27.8; H, 2.4; N, 4.5.

4-Amino-6-methoxy-1,3-benzenedisulfonyl Chloride.—The usual procedure gave this substance in 51% yield, m.p. 144–146° dec.

Anal. Calcd. for $C_7H_7Cl_2NO_5S_2$: C, 26.3; H, 2.2; S, 20.0 Found: C, 26.5; H, 2.3; S, 20.1.

(8) We wish to thank Mr. Elmer Shelberg and his staff for all microanalytical data; Mr. William Washburn and his associates for infrared spectra; Messrs. M. Freifelder and George Stone for the catalytic hydrogenation; and Messrs. John Nelson and Carl Nordeen for technical assistance in many of the preparations.

(9) O. Lustig and E. Katscher, *Monatsh.*, **48**, 87 (1927); J. Pollack, R. Pollack and E. Riesz, *ibid.*, **58**, 118 (1931).

Methyl 2-Amino-3,5-bis-(chlorosulfonyl)-phenyl sulfone was prepared in 24% yield from methyl *o*-acetaminophenyl sulfone by a procedure similar to that described above. The m.p. was 206–207°.

Anal. Calcd. for $C_7H_7Cl_2NO_6S_3$: C, 22.8; H, 1.9; N, 3.8. Found: C, 22.8; H, 2.0; N, 3.9.

4-Methylamino-1,3-benzenedisulfonyl Chloride.—Chlorosulfonic acid (233 g.) was cooled below 10° and stirred during the slow addition of 11 g. of methylaniline. The reaction mixture was heated at 115–123° for four hours and then allowed to stand at room temperature overnight. The dark semi-solid which formed when the reaction mixture was poured into ice-water was extracted with hot chloroform. Cooling of the chloroform solution yielded 10 g. (33%) of product, m.p. 109–110°.

Anal. Calcd. for $C_7H_7Cl_2NO_4S_2$: C, 27.6; H, 2.3; Cl, 23.3. Found: C, 27.8; H, 2.6; Cl, 23.1.

Preparation and Alkylation of 3-Ketodihydrobenzothiadiazines.—The following compounds were involved as intermediates in the synthesis of 2-substituted dihydrobenzothiadiazines.

6-Chloro-3-keto-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide.—Ten grams of 4-amino-6-chloro-1,3-benzenedisulfonamide and 4.2 g. of urea were ground intimately together and heated to 180° in an oil-bath. The temperature was maintained for one hour after liquefaction of the solid substances. The solid was taken up in hot water and filtered. The filtrate was allowed to stand overnight at room temperature, during which time 1.2 g. of crude starting material precipitated. This was separated by filtration. The filtrate was made strongly acidic with hydrochloric acid. The product which separated was filtered and washed with water. The yield was 9.6 g. (88%), m.p. 318–320° dec.

Anal. Calcd. for $C_7H_6ClN_3O_5S_2$: C, 27.0; H, 1.9; N, 13.5. Found: C, 27.1; H, 2.2; N, 13.6.

6-Chloro-3-keto-2-methyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide.—Ten grams of the ketodihydrobenzothiadiazine described above was dissolved in 25 cc. of dimethylformamide. Sodium hydride (0.77 g.) was added and the reaction mixture was stirred at 70° for 15 minutes. Methyl iodide (4.6 g.) was added dropwise to the heated solution, which was maintained at 70° for an additional hour. The cooled solution was poured into 800 cc. of water and allowed to stand overnight in the refrigerator. Filtration gave 9.0 g. (87%), m.p. 295° dec.

Anal. Calcd. for $C_8H_8ClN_3O_5S_2$: C, 29.5; H, 2.5; N, 12.9. Found: C, 29.6; H, 2.8; N, 12.7.

6-Chloro-2-ethyl-3-keto-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide.—A procedure similar to that described above was carried out with ethyl iodide in place of methyl iodide. The yield of product was 10.2 g. (95%), m.p. 277–278° dec.

Anal. Calcd. for $C_9H_{10}ClN_3O_5S_2$: C, 31.8; H, 3.0; N, 12.4. Found: C, 32.0; H, 3.2; N, 12.6.

6-Chloro-2-isopropyl-3-keto-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide.—The usual procedure was used with isopropyl iodide in place of methyl iodide. The product was obtained in 41% yield, m.p. 227–228° dec.

Anal. Calcd. for $C_{10}H_{12}ClN_3O_5S_2$: C, 33.9; H, 3.4; N, 11.9. Found: C, 34.1; H, 3.4; N, 12.0.

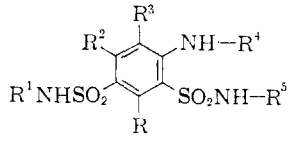
Preparation of Disulfonamides.—These intermediates are listed in Table I. The compounds having no substituents on the sulfamyl groups were prepared by reaction of the sulfonyl chlorides with concentrated ammonium hydroxide or liquid ammonia. In general, the latter reagent gave better yields. The preparation of 4-amino-6-chloro-1,3-benzenedisulfonamide is given to illustrate this method.

The remainder of the sulfonamides were prepared in other ways. These preparations are described below.

4-Amino-6-chloro-1,3-benzenedisulfonamide (No. 2).—4-Amino-6-chloro-1,3-benzenedisulfonyl chloride (453 g.) was added in portions to 2000 cc. of liquid ammonia, with stirring. The clear solution was allowed to stand until the ammonia had evaporated. Recrystallization from water yielded 327 g. (82%), m.p. 259–260°.[1]

4-Amino-5-bromo-6-chloro-1,3-benzenedisulfonamide (No. 11).—A suspension of 11.4 g. of 4-amino-6-chloro-1,3-benzenedisulfonamide in 200 cc. of acetic acid was warmed to 80°. A solution of 6.4 g. of bromine in 10 cc. of acetic acid was added dropwise with stirring. Stirring at 80° was con-

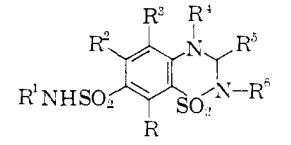
TABLE I



Cpd.	R	R^1	R^2	R^3	R^4	R^5	M.p., °C.	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
1	H	H	F	H	H	H	227–228	$C_6H_8FN_3O_4S_2$	26.8	3.0	15.6	26.6	3.2	15.7
2	H	H	Cl	H	H	H	259–260[a]	$C_6H_8ClN_3O_4S_2$	25.1	2.8	14.7	25.4	3.0	14.7
3	H	H	CH_3	H	H	H	251	$C_7H_{11}N_3O_4S_2$	31.7	4.2	15.8	31.6	4.2	15.7
4	H	H	CF_3	H	H	H	246–247	$C_7H_8F_3N_3O_4S_2$	26.3	2.5	13.2	26.5	2.6	13.1
5	H	H	CH_3O	H	H	H	246–248	$C_7H_{11}N_3O_5S_2$	29.9	3.9		30.0	4.1	
6	H	H	H	F	H	H	246–247	$C_6H_8FN_3O_4S_2$	26.8	3.0	15.6	27.0	3.1	15.4
7	H	H	H	SO_2CH_3	H	H	300–302	$C_7H_{11}N_3O_6S_3$	25.5	3.4	12.8	25.7	3.5	12.7
8	H	H	H	H	CH_3	H	249–250	$C_7H_{11}N_3O_4S_2$	31.7	4.2	15.8	31.9	4.3	15.8
9	Cl	H	H	CH_3	H	H	272–273	$C_7H_{10}ClN_3O_4S_2$	28.0	3.4	14.0	28.3	3.6	13.9
10	CH_3	H	H	CH_3	H	H	231–232	$C_8H_{13}N_3O_4S_2$	34.4	4.7	15.0	35.1	4.8	14.8
11	H	H	Cl	Br	H	H	295–297 d.	$C_6H_7BrClN_3O_4S_2$	19.8	1.9	11.5	20.1	2.3	11.4
12	H	H	Cl	NO_2	H	H	297 d.	$C_6H_7ClN_4O_6S_2$	21.8	2.1		22.2	2.3	
13	H	H	Cl	H	H	CH_3	168–170	$C_7H_{10}ClN_3O_4S_2$	28.0	3.4	14.0	28.2	3.6	13.9
14	H	H	Cl	H	H	C_2H_5	145–148	$C_8H_{12}ClN_3O_4S_2$	30.6	3.9		30.5	3.9	
15	H	H	Cl	H	H	i-C_3H_7	155–157	$C_9H_{14}ClN_3O_4S_2$	33.0	4.3	12.8	33.3	4.5	12.9
16	H	CH_3	Cl	H	H	CH_3	178–181	$C_8H_{12}ClN_3O_4S_2$	30.6	3.9	13.4	31.0	4.0	13.1

[a] Novello and Sprague, ref. 1, report 251–252°.

TABLE II



Cpd.	R	R	R^2	R^3	R^4	R^5	R^6	M.p., °C.[a]	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
17	H	H	H	H	H	H	H	219–220	$C_7H_9N_3O_4S_2$	32.1	3.5	16.0	32.0	3.7	15.8
18	H	H	F	H	H	H	H	229–230	$C_7H_8FN_3O_4S_2$	29.9	2.9	14.9	29.6	3.0	15.0
19	H	H	Cl	H	H	H	H	270–272[b]	$C_7H_8ClN_3O_4S_2$	28.2	2.7	14.1	28.3	2.8	14.3
20	H	H	CH_3	H	H	H	H	258–258.5	$C_8H_{11}N_3O_4S_2$	34.7	4.0	15.2	34.8	4.1	15.4
21	H	H	CF_3	H	H	H	H	272–273[c]	$C_8H_8F_3NO_4S_2$	29.0	2.4	12.7	29.3	2.7	12.6
22	H	H	CH_3O	H	H	H	H	248–249	$C_8H_{11}N_3O_5S_2$	32.8	3.8	21.8	32.6	4.0	22.0
23	H	H	H	F	H	H	H	210–211	$C_7H_8FN_3O_4S_2$	29.9	2.9	14.9	30.0	3.1	14.9
24	H	H	H	SO_2CH_3	H	H	H	271–273	$C_8H_{11}N_3O_6S_3$	28.2	3.3	12.3	28.2	3.1	12.2
25	H	H	H	H	CH_3	H	H	245–246	$C_8H_{11}N_3O_4S_2$	34.7	4.0	15.2	34.7	4.1	15.2
26	Cl	H	H	CH_3	H	H	H	300–303	$C_8H_{10}ClN_3O_4S_2$	30.8	3.2	13.5	31.2	3.6	13.5
27	CH_3	H	H	CH_3	H	H	H	279	$C_9H_{13}N_3O_4S_2$	37.1	4.5	14.4	37.2	4.4	14.6
28	H	H	Cl	Br	H	H	H	299–300	$C_7H_7BrClN_3O_4S_2$	22.3	1.9	11.2	22.4	1.9	10.9
29	H	H	Cl	NO_2	H	H	H	297	$C_7H_7ClN_4O_6S_2$	24.5	2.1	16.3	24.9	2.4	16.3
30	H	H	Cl	H	H	CH_3	H	249–250	$C_8H_{10}ClN_3O_4S_2$	30.8	3.2	13.5	30.6	3.4	13.4
31	H	H	Cl	H	H	C_2H_5	H	266–267	$C_9H_{12}ClN_3O_4S_2$	33.2	3.7	12.9	33.3	3.8	13.0
32	H	H	Cl	H	H	i-C_3H_7	H	286–290	$C_{10}H_{14}ClN_3O_4S_2$	35.3	4.2	12.4	35.2	4.4	12.4
33	H	H	Cl	H	H	Cyclo-C_3H_5	H	255–257	$C_{10}H_{12}ClN_3O_4S_2$	35.6	3.6	12.4	35.7	3.9	12.6
34	H	H	Cl	H	H	CH_2Cl	H	235–236	$C_8H_9Cl_2N_3O_4S_2$	27.8	2.6	12.1	27.5	2.6	12.1
35	H	H	Cl	H	H	CCl_3	H	300–303	$C_8H_7Cl_4N_3O_4S_2$	23.2	1.7	10.1	23.5	1.8	10.3
36	H	H	Cl	H	H	C_2F_5	H	297–298	$C_9H_7ClF_5N_3O_4S_2$	26.0	1.7	10.1	26.5[d]	1.9	10.0
37	H	H	Cl	H	H	H	CH_3	248	$C_8H_{10}ClN_3O_4S_2$	30.8	3.2	13.5	30.8	3.4	13.3
38	H	H	Cl	H	H	H	C_2H_5	114–116	$C_9H_{12}ClN_3O_4S_2$	33.2	3.7	12.9	33.3	3.9	13.1
39	H	H	Cl	H	H	H	i-C_3H_7	195–197	$C_{10}H_{14}ClN_3O_4S_2$	35.3	4.2	12.4	35.1	4.1	12.4
40	H	CH_3	Cl	H	H	H	CH_3	202–205	$C_9H_{12}ClN_3O_4S_2$	33.2	3.7	12.9	33.5	4.0	12.7
41	H	H	Cl	H	H	CH_2Cl	CH_3	225	$C_9H_{11}Cl_2N_3O_4S_2$	30.0	3.1	11.7	30.3	3.2	11.8

[a] All m.p.'s with decomposition. [b] de Stevens, *et al.*, ref. 5, report m.p. 273–275°. [c] Kobinger and Lund, ref. 5, report m.p. 272–273°, but do not otherwise characterize their product. [d] Calcd.: F, 22.9. Found: F, 22.6.

tinued for three hours, after which the reaction mixture was poured into 500 cc. of water. The product was filtered and washed with water. Seven grams (48%), m.p. 295–297° dec., was obtained. Recrystallization from alcohol–water did not alter the melting point.

4-Amino-6-chloro-5-nitro-1,3-benzenedisulfonamide (No. 12).—A solution of 16.5 g. of 4-amino-6-chloro-1,3-benzenedisulfonamide in 65 cc. of concentrated sulfuric acid was cooled to 0°. A mixture of 4.2 cc. of concentrated nitric acid and 4.5 cc. of concentrated sulfuric acid was added dropwise with stirring, while maintaining the temperature below 5°. The reaction mixture was allowed to stand without additional cooling for one hour, after which it was poured onto ice and filtered. The product, after recrystallization from alcohol–water, amounted to 4.5 g. (24%) of yellow needles, m.p. 297° dec.

5-Chloro-2,4-bis-(methylsulfamyl)-aniline (No. 16).—4-Amino-6-chloro-1,3-benzenedisulfonyl chloride (25 g.) was added portionwise to 100 cc. of stirred 30% methylamine. The mixture was refluxed briefly, cooled, and filtered. The

crude product (22.4 g., 92%) melted at 160–176°. Recrystallization from methanol brought the m.p. to 178–181°.

4-Amino-2-chloro-5-(methylsulfamyl)-benzenesulfonamide (No. 13).—6-Chloro-3-keto-2-methyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (9 g.) was dissolved in 90 cc. of 20% sodium hydroxide solution and refluxed overnight. The solution was filtered, cooled, and acidified with hydrochloric acid. The precipitate was filtered and washed with water to yield 7.8 g. (94%) of product, m.p. 168–170°.

4-Amino-2-chloro-5-(ethylsulfamyl)-benzenesulfonamide (No. 14) was obtained in a manner similar to that described above. The yield was 71%, m.p. 145–148°.

4-Amino-2-chloro-5-(isopropylsulfamyl)-benzenesulfonamide (no. 15) was obtained in a similar manner. The yield was 92%, m.p. 155–157°.

Preparation of 7-Sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxides.—All of these products are given in Table II. With the exception of a few compounds (*vide infra*) they were prepared by the condensation of aldehydes with the disulfonamides, usually in aqueous solution. Occasionally a non-aqueous solvent (acetone or dimethylformamide) gave better results. The yields were good (70–97%) in nearly all cases, but no attempt was made to find optimum conditions for all preparations. Several typical preparations are described in detail below.

Compound 17 was prepared by catalytic dehalogenation. Compound 37 was prepared by alkylation, as well as by cyclization. These experiments are described.

6-Chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (No. 19).—A suspension of 287 g. of 4-amino-6-chloro-1,3-benzenedisulfonamide in five liters of water was brought to reflux. To this was added a solution of 95 cc. of formalin and 60 g. of ammonium chloride in 100 cc. of water. Refluxing was continued for 90 minutes. The reaction mixture was cooled and filtered. The yield was 283 g. (95%), m.p. 268–271° dec. Recrystallization from water brought the m.p. to 270–272° dec.

6-Chloro-3-ethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (No. 31).—A solution of 5.7 g. of 4-amino-6-chloro-1,3-benzenedisulfonamide and 5.8 g. of propionaldehyde in 75 cc. of acetone was refluxed for two hours. Removal of the acetone and treatment of the residue with chloroform precipitated 6.3 g. (96%) of crude product, m.p. 258–260° dec. Recrystallization from alcohol–water brought the m.p. to 266–267° dec.

6-Chloro-3-(chloromethyl)-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (No. 34).—A solution of 7.9 g. of 45% aqueous chloroacetaldehyde and 1.2 g. of ammonium chloride in 10 cc. of water was added to 5.7 g. of 4-amino-6-chloro-1,3-benzenedisulfonamide in 25 cc. of dimethylformamide. The reaction mixture was heated for 30 minutes on the steam-bath, cooled, and poured into water. Filtration gave 6.0 g., (87%) m.p. 226–228° dec. The product was purified by dissolving in dimethylformamide and reprecipitating with water. The pure material decomposed at 235–236°.

6-Chloro-2-methyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (No. 37). A. By Cyclization with Formalin.—A solution of 3.0 g. of 4-amino-2-chloro-5-(methylsulfamyl)-benzenesulfonamide in 70 cc. of boiling water was prepared in a round-bottom flask fitted with a reflux condenser. The solution was refluxed while 1.5 g. of formalin was added through the condenser. Refluxing was continued for 90 minutes. After standing overnight, the solution deposited 2.8 g. (90%) of product which was recrystallized from water. The analytical sample melted at 248° dec.

B. By Alkylation of 6-Chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide.—Sodium hydride (0.48 g.) was added, with stirring, to a solution of 5.96 g. of 6-chloro-7 sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide in 30 cc. of dimethylformamide. The mixture was stirred at 70° for 30 minutes, after which 2.84 g. of methyl iodide in 3 cc. of dimethylformamide was added dropwise. Stirring was continued for one hour at 70°.

The reaction mixture was poured into 800 cc. of water. The supernatant liquid was decanted from the gummy precipitate and allowed to stand overnight. The product (2.4 g., m.p. 237–240° dec.) crystallized from the aqueous solution. Recrystallization from water brought the m.p. to 242–243° dec. Although the higher m.p. obtained in the alternate method of preparation was not achieved here, a melting point of the mixture was not depressed. Identity was confirmed by infrared spectra and elemental analyses.

Anal. Calcd. for $C_9H_{10}ClN_3O_4S_2$: C, 30.8; H, 3.2; N, 13.5. Found: C, 31.2; H, 3.5; N, 13.5.

7-Sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (No. 17).—6-Chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (6 g.) was dissolved in 100 cc. of water containing 3.2 g. of sodium hydroxide. The material was hydrogenated under two atmospheres of pressure with 1.2 g. of 5% palladium-on-carbon as a catalyst. When the uptake was complete (less than 1 hr.) the catalyst was removed by filtration. Acidification precipitated 4.2 g. (80%), m.p. 218° dec.

The material was found to cling tenaciously to water of crystallization. Recrystallization from water and prolonged drying under vacuum gave an analytical sample melting at 219–220° dec.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Synthesis of Potential Diuretic Agents. II. Dichloro Derivatives of 1,2,4-Benzothiadiazine 1,1-Dioxide[1]

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The following were allowed to react with chlorosulfonic acid, and the resulting sulfonyl chlorides converted to the corresponding sulfonamides: 2,3-dichloro-, 2,5-dichloro-, 3.4-dichloro- and 3,5-dichloroaniline. Except for 2,5-dichloroaniline, which did not sulfonate in the position *ortho* to the amino group, the sulfonamides were cyclized with formic acid, and also with formaldehyde, to obtain substituted 1,2,4-benzothiadiazine 1,1-dioxides. Further, 2-aminobenzenesulfonamide and 2-amino-4-chlorobenzenesulfonamide were prepared by a known procedure not involving the use of chlorosulfonic acid. These, also, were cyclized with formic acid and formaldehyde. The diuretic potency of the compounds described was compared with chlorothiazide and dihydrochlorothiazide.

In our continuing investigation of potential diuretic agents related to chlorothiazide and dihydrochlorothiazide, we have turned our attention to dichlorobenzothiadiazines. The latter seemed a logical group to investigate since the necessary isomeric dichloroanilines are readily available.

The chlorosulfonation of 2,3-dichloroaniline (I), followed by treatment with ammonia, gave the desired 4 - amino - 5,6 - dichloro - 1,3 - benzenedisulfonamide (II). Refluxing II with 98% formic acid gave 5,6-dichloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (III). With formalin II gave rise to the dihydro derivative IV.

The chlorosulfonation of 2,5-dichloroaniline,

(1) For paper I in this series see W. J. Close, *et al.*, THIS JOURNAL, **82**, 1132 (1960).