7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (No. 13). The ester (XII) (7.4 g.) was dissolved in 90 cc. of methanol and treated with a solution of 2.0 g. of biguanide in 10 cc. of methanol. The reaction mixture was stirred 24 hr. at room temperature. The product (1.9 g.; 23%) m.p. 247–248° was separated by filtration.

NORTH CHICAGO, ILL.

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

Synthesis of Potential Diuretic Agents. IV. Bromo Derivatives of 1,2,4-Benzothiadiazine 1,1-Dioxide

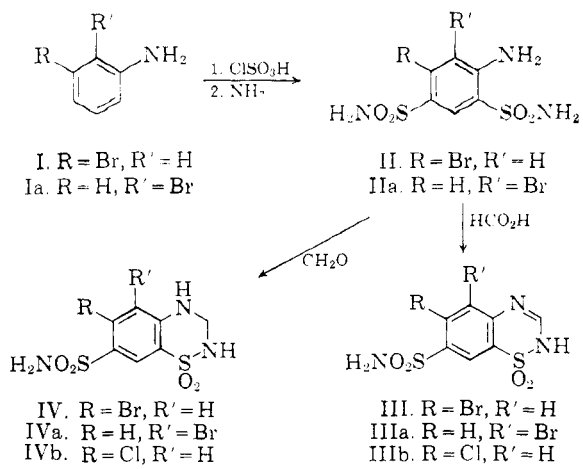
JAMES H. SHORT AND LEO R. SWETT

Received February 6, 1961

Chlorosulfonation of *o*-bromoaniline and *m*-bromoaniline, followed by ammonolysis, gave, respectively, 4-amino-5-bromo-1,3-benzenedisulfonamide and 4-amino-6-bromo-1,3-benzenedisulfonamide. The latter was condensed with urea, methylated, and hydrolyzed to obtain 4-amino-2-bromo-5-methylsulfamylbenzenesulfonamide. These three sulfonamides were condensed with formic acid and various aldehydes to give derivatives of 1,2,4-benzothiadiazine 1,1-dioxide.

Previous papers[1–3] in this series have described efforts to correlate diuretic potency of derivatives of 1,2,4-benzothiadiazine 1,1-dioxide with variations in structure, using chlorothiazide[4] (IIIb) and hydrochlorothiazide (IVb, Oretic®) as reference standards. We have found that a sulfamyl group in the 7-position is absolutely essential for significant activity; that compounds with a double bond in the heterocyclic ring are less active than the dihydro analogs; that certain substituents in the 3-position increase activity; that a 2-methyl group increases activity; and that, on the benzene ring, substituents other than 6-chloro tend to reduce activity.

Although variations of the 6-chloro function generally caused a marked reduction in activity, it still seemed worthwhile to prepare the bromo analogs of chlorothiazide and hydrochlorothiazide. This was accomplished by the same sequence of reactions used for chloro derivatives. Chlorosulfonation of *m*-bromoaniline (I) gave a disulfonyl chloride which, when treated with ammonia, led to 4-amino-6-bromo-1,3-benzenedisulfonamide (II). Cyclization of the latter with formic acid gave 6-bromo-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (III). With formaldehyde, the product was 6-bromo-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (IV). The latter substance showed a slight, but significant, increase in diuretic potency when compared with Oretic.® Therefore, we decided to investigate further bromo-substituted benzothiadiazines.



I. R = Br, R′ = H
Ia. R = H, R′ = Br

II. R = Br, R′ = H
IIa. R = H, R′ = Br

IV. R = Br, R′ = H
IVa. R = H, R′ = Br
IVb. R = Cl, R′ = H

III. R = Br, R′ = H
IIIa. R = H, R′ = Br
IIIb. R = Cl, R′ = H

Chlorosulfonation of *o*-bromoaniline (Ia) followed by ammonolysis, gave a disulfonamide, presumed to be 4-amino-5-bromo-1,3-benzenedisulfonamide (IIa). Debromination of this material gave an aminobenzenedisulfonamide identical in all respects to the 4-amino-1,3-benzenedisulfonamide obtained by debromination of the disulfonamide from *m*-bromoaniline.

Reaction of IIa with formic acid gave the expected 5-bromo-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (IIIa). It is interesting to note that IIa was cyclized with formic acid much more slowly than was the isomeric sulfonamide II. Cyclization of IIa with formaldehyde gave rise to 5-bromo - 3,4 - dihydro - 7 - sulfamyl - 2H - 1,2,4-benzothiadiazine 1,1-dioxide (IVa).

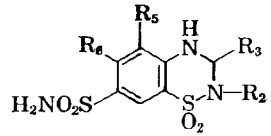
As the 5-bromobenzothiadiazines (IIIa, IVa) were much less active as diuretic agents than the corresponding 6-bromo isomers (III, IV), further work was restricted to the 6-bromo series.

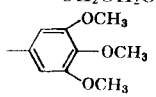
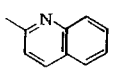
Condensation of II with various aldehydes and acetals gave rise to a series of 3-substituted 6-bromo - 3,4 - dihydro - 7 - sulfamyl - 2H - 1,2,4-benzothiadiazine 1,1-dioxides, and these compounds are described in Table I.

In general, we found that these benzothiadiazines were best obtained from the sulfonamide and only one equivalent of the aldehyde. In several cases, we

(1) W. J. Close, L. R. Swett, L. E. Brady, J. H. Short, and M. Vernsten, *J. Am. Chem. Soc.*, **82**, 1132 (1960).
(2) J. H. Short and U. Biermacher, *J. Am. Chem. Soc.*, **82**, 1135 (1960).
(3) W. J. Close, L. R. Swett, and C. W. Nordeen, *J. Org. Chem.*, **26**, 3423 (1961).
(4) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2028 (1957).

TABLE I

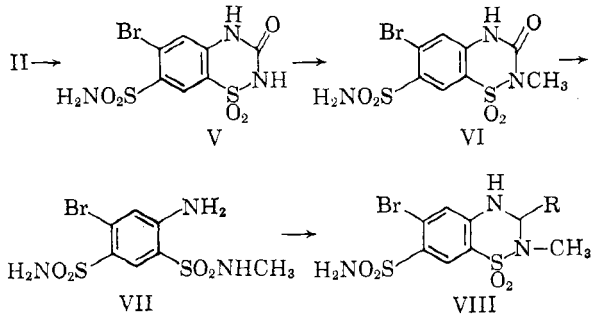


No.	R_2	R_3	R_5	R_6	M.P.	Method[a]	Molecular Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	H	Br	297–298[b]	A	$C_7H_5BrN_3O_4S_2$	24.55	24.78	2.36	2.60	12.28	12.38
2	H	H	Br	H	236–237	A	$C_7H_5BrN_3O_4S_2$	24.55	24.59	2.36	2.56	12.28	12.05
3	H	CH_3	H	Br	253–254	A	$C_8H_7BrN_3O_4S_2$	26.97	27.13	2.83	2.99	22.44	22.18
4	H	CH_2OH	H	Br	223	A[c]	$C_8H_7BrN_3O_5S_2$	25.81	25.86	2.71	2.45	11.29	11.45
5	H	CH_2Cl	H	Br	237	A,C[d]	$C_8H_7BrClN_3O_4S_2$	24.59	24.72 24.64	2.33	2.68 2.71	10.73	10.87
6	H	CH_2Br	H	Br	228	C[d]	$C_8H_7Br_2N_3O_4S_2$[e]	22.08	22.38	2.09	2.25	9.66	9.56
7	H	$CHCl_2$	H	Br	243–244	C[d]	$C_8H_6BrCl_2N_3O_4S_2$	22.60	22.94	1.90	1.96	9.89	9.98
8	H		H	Br	251–253	B	$C_9H_9BrN_3O_5S_2$	28.13	28.20	2.63	2.83	10.93	10.80
9	H	$CH_2CH_2OCH_3$[g]	H	Br	250–252	A	$C_{10}H_{14}BrN_3O_5S_2$	30.01	30.29	3.53	3.54	10.50	10.59
10	H	$CH_2CH_2C_6H_5$	H	Br	218–219	C[f,h]	$C_{15}H_{16}BrN_3O_4S_2$	40.36	40.34	3.61	3.89	9.41	9.20
11	H		H	Br	251–252	B[i]	$C_{16}H_{18}BrN_3O_7S_2$	37.80	37.60	3.57	3.61	8.27	8.16
12	H		H	Br	207–209	B	$C_{11}H_{14}BrN_3O_5S_2$	32.05	31.97	3.43	3.75	10.19	10.10
13	H		H	Br	295–297	B	$C_{12}H_{11}BrN_4O_4S_2$	34.38	34.58	2.65	2.86	13.36	13.26
14	H		H	Br	237–240	B	$C_{13}H_{13}BrN_4O_4S_2$	36.03	35.80	3.02	3.02	12.93	12.68
15	H		H	Br	323–325	B	$C_{16}H_{13}BrN_4O_4S$	40.94	40.79	2.79	3.30	11.94	12.37
16	CH_3	H	H	Br	248	A	$C_8H_{10}BrN_3O_4S_2$	26.97	27.24	2.82	2.85	11.79	11.75
17	CH_3	COOH	H	Br	160–162	A[j]	$C_9H_{10}BrN_3O_6S_2 \cdot H_2O$	25.84	25.68	2.89	3.15	10.04	9.95
18	CH_3	$COOCH_3$	H	Br	224–228	[k]	$C_{10}H_{12}BrN_3O_6S_2$	28.98	29.02	2.90	2.97	10.14	10.18

[a] Yields in most cases were above 75%. [b] F. C. Novello *et al.*, *J. Org. Chem.*, **25**, 970 (1960), report m.p. 287–288°. [c] A five-fold excess of aldehyde was used. [d] The acetal was used. [e] Br: Calcd.: 36.73. Found: 36.69. [f] The aldehyde was used. [g] Infrared analysis indicated that considerable uncyclized anil was present. [h] Procedure C was modified. No acid was added, and the reflux period was overnight. The crude product was recrystallized from methanol-2-propanol. [i] Recrystallized from methanol. [j] Two-fold excess of glyoxylic acid was used. [k] For method of preparation see experimental section.

found that the use of an excess of the aldehyde gave less pure products. However, with glycolaldehyde, the desired substance, 6-bromo-3,4-dihydro-3-hydroxymethyl - 7 - sulfamyl - 2H - 1,2,4 - benzothiadiazine 1,1-dioxide, was obtained only when a large excess of the aldehyde was used.

As diuretic potency of hydrochlorothiazide was increased by introduction of a 2-methyl substituent, we thought it desirable, therefore, to determine if the 2-methyl group also increases activity in the 6-bromo series.



By the series of reactions previously described[1] for the 6-chloro analog, 4-amino-6-bromo-1,3-benzenedisulfonamide (II) was condensed with urea to give 6 - bromo - 3 - (4H) - oxo - 7 - sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (V). Reaction of V with methyl iodide in the presence of sodium hydride led to 6-bromo-2-methyl-3(4H)-oxo - 7 - sulfamyl - 2H - 1,2,4 - benzothiadiazine 1,1-dioxide (VI), which was hydrolyzed to the desired 4-amino-2-bromo-5-methylsulfamylbenzenesulfonamide (VII). Two crystal modifications of VII, melting at 96–98° and 142–144°, were obtained. Novello[5a] and co-workers have observed two melting points for 4-amino-2-chloro-5-methylsulfamylbenzenesulfonamide, the chloro analog of VII.

Condensation of VII with formaldehyde gave 6-bromo - 3,4 - dihydro - 2 - methyl - 7 - sulfamyl-2H - 1,2,4 - benzothiadiazine 1,1 - dioxide (VIII, R = H). Glyoxylic acid and VII gave rise to 6-bromo - 3 - carboxy - 3,4 - dihydro - 2 - methyl - 7-sulfamyl - 2H - 1,2,4 - benzothiadiazine 1,1-dioxide (VIII, R = COOH), and diazomethane converted the latter to its methyl ester (VIII, R = $COOCH_3$).

The pharmacology of these compounds will be reported in detail elsewhere.

EXPERIMENTAL[6]

4-Amino-6-bromo-1,3-benzenedisulfonamide (II). A solution of 375 g. (2.18 moles) of *m*-bromoaniline in 2.0 l. of chlorosulfonic acid was stirred and heated at 120–125° for 4 hr. After standing overnight at room temperature, the solution was poured onto about 15 kg. of cracked ice. The white solid which precipitated was collected on a filter and then added in small portions to about 3.0 l. of 28% ammonia water. The resulting solution was filtered to clarify it, and heated on the steam bath to drive off ammonia. On chilling, 234 g. of white solid was obtained. Acidification of the filtrate with acetic acid gave an additional 54 g. of the product. The total yield was 288 g. (40%) of material melting at 260–270°. A portion was dissolved in ammonia water, treated with charcoal, heated to boiling and chilled. Fine, white needles precipitated, m.p. 276°. The recorded[5b] melting point is 265–267°.

4-Amino-5-bromo-1,3-benzenedisulfonamide (IIa). A solution of 86 g. (0.5 mole) of *o*-bromoaniline in 400 ml. of chlorosulfonic acid was heated at 120° overnight and worked up as above. The crude material was recrystallized twice from water, once with the aid of charcoal, to give 35 g. (21%) of white solid, m.p. 259–259.5°.

Anal. Calcd. for $C_6H_8BrN_3O_4S_2$: C, 21.83; H, 2.44; S, 19.42. Found: C, 21.90; H, 2.44; S, 19.37.

6-Bromo-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (III). A solution of 16.5 g. (0.05 mole) of 4-amino-6-bromo-1,3-benzenedisulfonamide in 400 ml. of 98% formic acid was heated under reflux for 2 hr. The solution was poured into 1.0 l. of water and chilled. The white powder obtained weighed 11.5 g. (69%), m.p. 355°. The recorded melting point is 347–349.[5a]

5-Bromo-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (IIIa). A solution of 3.3 g. (0.01 mole) of 4-amino-5-bromo-1,3-benzenedisulfonamide in 25 ml. of 98% formic acid was heated under reflux for 48 hr. After chilling, 2.8 g. (82%) of fine, white needles were collected, m.p. 287–289°.

Anal. Calcd. for $C_7H_6BrN_3O_4S_2$: C, 24.71; H, 1.78; N, 12.35. Found: C, 24.87; H, 2.00; N, 12.06.

6-Bromo-3,4-dihydro-3-substituted 7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxides (Table I). *Procedure A.* A solution of 4-amino-6-bromo-1,3-benzenedisulfonamide in water (100 ml. of water for each gram of sulfonamide) containing an equivalent quantity of aldehyde was heated under reflux for 2 hr. After chilling, the precipitated product was collected. The crude products, when necessary, could be purified by recrystallization from an appropriate solvent, or by dissolving in ammonia water and then precipitating with acetic acid.

Procedure B. A solution of the sulfonamide and an equivalent amount of aldehyde in dimethylformamide (4 ml. of dimethylformamide for each gram of sulfonamide) was heated on the steam bath for 2 hr. The solution was poured into ten times its volume of water, chilled, and the product collected.

Procedure C. Dry hydrogen chloride or hydrogen bromide (when bromoacetal was used) was bubbled into 1,2-dimethoxyethane (8 ml. for each gram of sulfonamide) for several minutes. Then the sulfonamide and an equivalent amount of an acetal or an aldehyde was added and heated on the steam bath for 2 hr. The solvent was removed under vacuum. The residual oil was dissolved in 25 ml. of 2-propanol, diluted with 25 ml. of water, chilled, and the product collected.

Debromination of 4-amino-6-bromo-1,3-benzenedisulfonamide.[7] A solution of 3.3 g. (0.01 mole) of 4-amino-6-bromo-1,3-benzenedisulfonamide in 50 ml. of water containing 6 ml. of 5*N* sodium hydroxide (0.03 mole) was hydrogenated at 2 atm. over 0.5 g. of 5% palladium on charcoal. The theoretical amount of hydrogen was taken up in 10 min. The catalyst was removed, and the filtrate acidified with hydrochloric acid. After filtering and washing with water, 1.95 g. (78%) of 4-amino-1,3-benzenedisulfonamide was obtained, m.p. 234–236°. The recorded melting point is 235°.[8]

Debromination of 4-amino-5-bromo-1,3-benzenedisulfonamide. Debromination of 3.3 g. (0.01 mole) of 4-amino-5-

(5) (a) F. C. Novello, S. L. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960); (b) 965.

(6) We wish to thank Mr. Elmer Shelberg and his staff of the Microanalytical Laboratory, Abbott Laboratories, for all microanalytical data.

(7) The catalytic debrominations were carried out by Mr. Morris Freifelder and Mr. George Stone.

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

bromo-1,3-benzenedisulfonamide was carried out as described for the 6-bromo isomer. The yield was 1.94 g. (78%) of material, m.p. 234–236°, identical in every way to the 4-amino-1,3-benzenedisulfonamide described above.

6-Bromo-3(4)-oxo-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (V). An intimate mixture of 25 g. (0.076 mole) of 4-amino-6-bromo-1,3-benzenedisulfonamide and 9.1 g. (0.152 mole) of urea was heated at 185° for 1 hr. The reaction mass was taken up in 100 ml. of water, filtered, and the filtrate acidified to obtain 20.7 g. (76.5%) of material melting at 315–317°. The recorded m.p. is 323–324°.[5a]

4-Amino-2-bromo-5-methylsulfamylbenzenesulfonamide (VII). To 47 g. (0.13 mole) of 6-bromo-3(4H)-oxo-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide in 150 ml. of dimethylformamide was added portionwise 6.0 g. (0.13 mole) of sodium hydride (53% suspension in mineral oil, Metal Hydrides, Inc.). The reaction was stirred at 70° for 1 hr. and then 20 g. (0.14 mole) of methyl iodide in 20 ml. of dimethylformamide was added dropwise. Stirring at 70° was continued for 3 hr.; then the reaction mixture was poured into 2.5 l. of water and chilled overnight. The product was collected on a filter and it was washed with both cold water and with ether. The yield of 6-bromo-2-methyl-3(4*H*)-oxo-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide was 38.3 g., and it melted at 289–290°

Without further purification, the material was dissolved in 400 ml. of 20% sodium hydroxide solution and the resulting solution was refluxed overnight. The cooled solution was acidified with 6*N* hydrochloric acid. The material which precipitated was recrystallized from water to obtain 19 g. (46% overall from V) of white solid, m.p. 142–144°. In some runs material melting at 96–98° was obtained.

Anal. Calcd. for $C_7H_{10}BrN_3O_4S_2$: C, 24.42; H, 2.92; N, 12.20. Found: C, 24.60; H, 3.09; N, 12.27.

6-Bromo-3-carbomethoxy-3,4-dihydro-2-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide[9] (VIII, R = CO_2CH_3). To a solution of 2.1 g. (0.005 mole) of 6-bromo-3-carboxy-3,4-dihydro-2-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (Table I, compound 17) in 100 ml. of methanol was added 40 ml. of ether containing 0.005 mole of diazomethane. After 5 min. the solution tested neutral to litmus. The solvent was removed and water was added to the residue causing a solid to form. The crude product was dissolved in 40 ml. of methanol, concentrated to 10–15 ml., and chilled to give 1.6 g. (78%) of product, see Table I, compound 18.

NORTH CHICAGO, ILL.

(9) Prepared by Dr. W. J. Close.

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

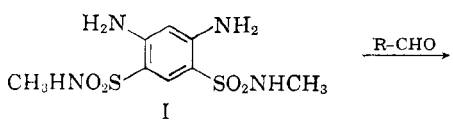
Synthesis of Potential Diuretic Agents. V. Derivatives of a New Tricyclic System, Benzo[1,2-e,5,4-e']bis[2-methyl-3,4-dihydro-1,2,4-thiadiazine 1,1-Dioxide]

LEO R. SWETT, MORRIS FREIFELDER, AND GEORGE R. STONE

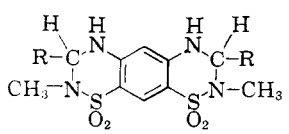
Received February 6, 1961

A novel and practical synthesis of 4,6-diamino-N^1,N^3-dimethyl-1,3-benzenedisulfonamide is described. Ring closure of this substance with aldehydes makes possible the formation of a new tricyclic system.

In the preparation of compounds related to dihydrobenzothiadiazines as diuretic agents, it was desirable to obtain quantities of 4,6-diamino-N^1,-N^3-dimethyl-1,3-benzenedisulfonamide (I) to serve as an intermediate in the preparation of a new tricyclic system,[1,2] benzo[1,2-e,5,4-e']bis[2-methyl-3,4-dihydro-1,2,4,-thiadiazine 1,1-dioxide] (II).



I



IIa. R = H
IIb. R = CH_2Cl
IIc. R = COOH

(1) Preparation of the unsaturated analog, benzo-[1,2-e,5,4-e']bis[1,2,4-thiadiazine 1,1-dioxide], has been reported by F. C. Novello, S. C. Bell, E. L. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960).

(2) Since the completion of our work, F. J. Lund and W. Kobinger, *Acta Pharmacol. Toxicol.*, **16**, 297 (1960), have described two compounds related to this type, but no synthetic details were presented.

The most obvious method of preparing I would be the chlorosulfonation of *m*-phenylenediamine or its diacyl derivative, followed by treatment of the disulfonyl chloride with methylamine. The chlorosulfonation has been described.[3,4] The yields reported were very poor and in our experience proved quite unsatisfactory. This report describes a practical synthesis of I and the condensation of the intermediate with several aldehydes.

The electron attracting effect of the sulfonamide groups suggested that the halogen atom in 4-amino-6-chloro-N^1,N^3-dimethyl-1,3-benzenedisulfonamide (VII) could be replaced directly with ammonia. Preliminary experiments with a model substance, 4-amino-6-chloro-1,3-benzenedisulfonamide (III), were disappointing. However, since urea is known to be a good source of ammonia, we next turned our attention to reactions involving this substance.

Fusion of urea with III at atmospheric pressure gave 6-chloro-3-oxo-7-sulfamyl-3,4-dihydro-1,2,4-

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

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