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

Synthesis of Potential Diuretic Agents. III. Derivatives of 6-Chloro-3,4-dihydro-2-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-Dioxide[1]

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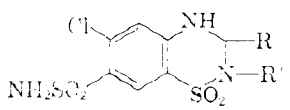
The synthesis of 2-methylated compounds of the hydrochlorothiazide class is given. These substances were prepared by the reaction of aldehydes with 4-amino-2-chloro-5-(methylsulfamyl)benzenesulfonamide. Alternative routes to this key intermediate were studied in detail. Several new hydrochlorothiazide-like compounds containing acid, amide, and ester functions at the 3- position are described.

The independent discovery of hydrochlorothiazide (I)[2] in our[3,4] as well as other[5-8] laboratories has stimulated much synthetic effort in the 3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide series. Attempts have been made to find substances which are more potent, have less effect upon potassium stores, and exhibit a qualitatively superior action.

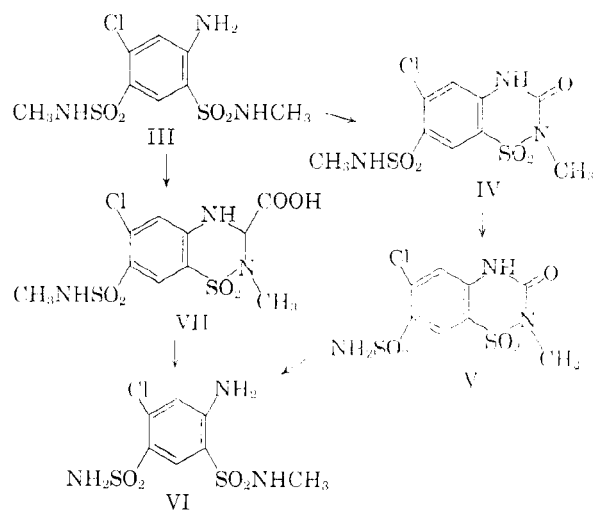


I. R = R' = H
II. R = CH_2Cl; R' = CH_3

One of the earlier compounds (II)[9] prepared by us[4] was found to have outstanding activity in laboratory animals, and this was later confirmed in clinical studies.[10] We attributed the higher order of activity seen with II to the presence of the 2-methyl group. In pursuing this concept, we prepared a number of other derivatives of this type. Twelve pairs of compounds were compared pharmacologically; in each of these pairs the *N*-methyl homolog was more potent than its unmethylated congener.[11,12]

This paper reports the synthesis and properties of these 2-methylated substances. In addition, related 2-unsubstituted and 2-higher alkyl derivatives not described before are discussed.

The 2-methylated compounds were usually prepared by condensation of an aldehyde with 4-amino-2-chloro-5-(methylsulfamyl)benzenesulfonamide (VI). A satisfactory method for securing this key intermediate was given in our first publication.[4] Two other routes which offer some advantages over the original preparation, have now been developed. These syntheses are based upon the selective replacement (with NH_2) of only one of the two CH_3NH-groups present in 5-chloro-2,4-bis-(methylsulfamyl)aniline (III).



In the first reaction scheme, this objective is accomplished by forming an oxo bridge between one methylsulfamyl group and the adjacent amino

(1) Paper No. II in this series; J. H. Short and U. Biermacher, *J. Am. Chem. Soc.*, **82**, 1135 (1960). A summary of the present work was presented before the Medicinal Chemistry Symposium at Kingston, R. I., June 21, 1960.

(2) Abbott Laboratories' registered trade name for hydrochlorothiazide is Oretic.

(3) M. E. Goldberg and K. Hwang, *Federation Proc.*, **18**, 396 (1959).

(4) W. J. Close, L. R. Swett, L. E. Brady, J. H. Short, and M. Vernsten, *J. Am. Chem. Soc.*, **82**, 1132 (1960).

(5) G. deStevens, L. H. Werner, A. Halamandaris, and S. Ricca, Jr., *Experientia*, **14**, 463 (1958).

(6) L. H. Werner, A. Halamandaris, S. Ricca, Jr., L. Dorfman, and G. deStevens, *J. Am. Chem. Soc.*, **82**, 1161 (1960).

(7) J. E. Baer, H. F. Russo, and K. H. Beyer, *Proc. Soc. Expll. Biol. Med.*, **100**, 442 (1959).

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

(9) The generic name for II is methyclothiazide; Abbott Laboratories' registered trade name is Enduron.

(10) R. V. Ford, *Current Therap. Res.*, **2**, 422, 430 (1960).

(11) K. Hwang, H. K. Iwamoto, L. Coen, and H. E. Johnson, *Federation Proc.*, **19**, 363 (1960).

(12) This is in marked contrast to the experience of Novello and co-workers, ref. 8, who reported that substitution in the 2- position decreases activity. F. J. Lund and W. Kobinger, *Acta Pharmacol. Toxicol.*, **16**, 297 (1960), have also concluded that 2-substitution has an inactivating influence.

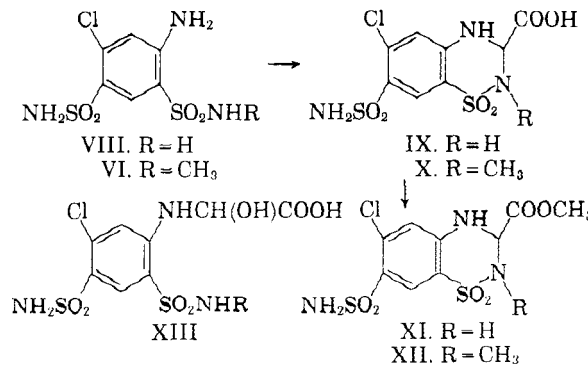
substituent.[13] The stability of the keto-heterocyclic ring permits the use of chlorosulfonic acid as a means of deaminating the exocyclic methylsulfamyl group. This treatment, followed by ammonia, leads to V, and hydrolytic ring-opening gives VI.

The formation of a 3-ketobenzothiadiazine ring to protect a methylsulfamyl group against attack by chlorosulfonic acid suffers from one disadvantage: a vigorous hydrolysis is necessary to regenerate the open-ring compound. It occurred to us that other dihydrobenzothiadiazines might be more easily cleaved. Indeed, a suitably substituted heterocyclic ring might remain intact long enough to permit the desired demethylamination with chlorosulfonic acid, but then succumb to cleavage by the reagent itself—thereby eliminating the hydrolysis step altogether.

Preliminary experiments with 3-alkyldihydrobenzothiadiazines were not promising. The parent compound, 6 - chloro - 3,4 - dihydro - 2 - methyl-7 - (methylsulfamyl) - 2H - 1,2,4 - benzothiadiazine 1,1-dioxide, also was not suitable. This latter substance gave an unexpected result: 4-chloro-6-methylamino - 1,3 - benzenedisulfonamide was obtained as the only isolable product of its reaction with chlorosulfonic acid.

A suitable solution was found in the 3-carboxy derivative (VII), obtainable in excellent yield from III and glyoxylic acid. When this substance was refluxed for fifteen minutes in chlorosulfonic acid and the resulting product was treated with ammonia, compound VI was obtained directly in 70% yield.[14] Thus, a simple, convenient, and economical route to VI becomes available.

The reaction with glyoxylic acid described above was of interest to us in another connection: one of the chief objectives of the present study was the synthesis and evaluation of hydrochlorothiazide derivatives containing 3-carboxylic acid, amide, and ester functions. Such substances have not been described previously. Condensation of the sulfonamide VIII with sodium glyoxylate in water occasionally gave excellent yields of IX, but the reaction was unpredictable. A more convenient reagent is methyl dimethoxyacetate, which is converted to glyoxylic acid in boiling water. Good yields were obtained uniformly with this reagent.



The 2-methyl analog (X) was obtained in a similar way from VI.

The acids (IX and X) were obtained as hydrates which could be freed from water only by prolonged heating *in vacuo*. Indeed, we have been unable to remove water of crystallization completely from X without decomposition. Since the elements of water were present in the products, an open-chain structure such as represented by XIII had to be considered.[15] This structure can be ruled out on the basis of the following argument: Both the hydrated and dehydrated forms of IX yield the same ester (XI) when treated with an equivalent of diazomethane. An excess of diazomethane converts IX to XII; this same ester is produced from X (hydrate) with diazomethane. The structure of XII has been confirmed by NMR spectra.

It is curious that no product corresponding to methylation of the 7-sulfamyl group was isolated in the reaction of IX and X with diazomethane, even though an excess of reagent was sometimes available for reaction. Furthermore, alkylation of IX with methyl iodide in basic solution leads to XII, again with no substitution of the 7-sulfamyl group. The preferred position of alkylation in hydrochlorothiazide itself is also the 2- position.[6]

The tendency toward methylation of the 2- position in preference to the 7-sulfamyl group presumably reflects the rather substantial difference in the dissociability of protons located on the endocyclic and exocyclic —SO_2NH— groups (Table I). 2-Unsubstituted compounds titrate as dibasic acids. We attribute the lower pK'_α values, which vary widely with the electronegativity of the 3-substituents, to the 2-H atom. The higher values, which are reasonably constant at 10.0–10.3, represent the less dissociable hydrogen atom of the 7-sulfamyl group.

2-Substituted compounds behave as monobasic acids, with uniform pK'_α values of 9.3–9.5, attributable to the 7-sulfamyl group. The shift from *ca.* 10.1 to *ca.* 9.4 is in the direction expected in going

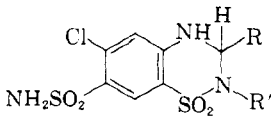
(13) This can be accomplished in nearly quantitative yield with phosgene; however, fusion with urea fails. It has been our experience that *ortho*-amino-*N*-methylbenzenesulfonamides are resistant to attack by urea, in contrast to unsubstituted sulfonamides. F. C. Novello, U. S. Pat. 2,886,566, reports the preparation of 2-alkyl-3,4-dihydro-3-oxo-2H-1,2,4-benzothiadiazine 1,1-dioxides by the urea process. One example was offered: the reaction of 2-amino-4-chloro-*N*-methylbenzenesulfonamide with urea. We have recovered only starting material in attempting this conversion.

(14) A similar transformation was reported recently by Novello and co-workers, ref. 8, who obtained compound VI from 6-chloro-2-methyl-7-(methylsulfamyl)-1,2,4-benzothiadiazine 1,1-dioxide by treatment with chlorosulfonic acid followed by ammonia.

(15) We have never encountered this type of compound in our research on benzothiadiazines, and to our knowledge it has not been reported by others. M. Sherlock, J. G. Topliss, and N. Sperber, *Abst. 136th Meeting Amer. Chem. Soc.*, 14-O (1959), reported that open-chain anils were obtained occasionally in their series.

TABLE I[a]

PROTON DISSOCIATION IN BENZOTHIADIAZINES



R	R′	pK'_α 7-SO_2NH_2	pK'_α 2-H	pK'_α 3-COOH
H	H	10.05	8.6	
H	CH_3	9.45		
CH_3	H	10.2	8.6	
CH_3	CH_3	9.4		
CH_2Cl	H	10.0	7.6	
CH_2Cl	CH_3	9.4		
$CHCl_2$	H	10.15	6.75	
$CHCl_2$	CH_3	9.5		
COOH	H	10.3	9.0	2.5
COOH	CH_3	9.5		2.5
$COOCH_3$	H	10.0	7.05	
$COOCH_3$	CH_3	9.3[b]		

[a] The pK'_α values reported here were determined by titrations in two concentrations of acetone in water, followed by extrapolation to zero acetone concentration. We are greatly indebted to Mr. Ross Robinson and Miss Gwen Prior for these determinations. [b] This substance has an additional pK'_α value of 10.3 (see text).

from dibasic to monobasic acids, and indicates some interaction between the ionized centers in the dibasic structures.

Substances containing free carboxyl groups, of course, show an additional low pK'_α value corresponding to this relatively strong acidic center.

Compound XII behaves anomalously, having in addition to a pK'_α value of 9.3, attributable to the 7-sulfamyl group, a second value of 10.3. We are currently investigating the behavior of this substance in an effort to explain this datum.

Compounds XI and XII could also be prepared in good yield by esterification with methanolic hydrogen chloride. Higher esters were prepared in an analogous manner. The esters were used as starting points for the synthesis of various amides, most of which were prepared by standard procedures.

In a few instances, higher alkyl groups (ethyl and propyl) were introduced in the 2-position. These substances were prepared in a manner analogous to the preparation of the 2-methyl derivatives.

All of the hydrochlorothiazide derivatives prepared in this study are brought together in Table II.

EXPERIMENTAL[16]

Preparation of intermediates. All aldehydes used in the formation of the benzothiadiazines were obtained from commercial sources or synthesized by known procedures. The synthesis of other intermediates is given below.

6-Chloro-2-methyl-7-(methylsulfamyl)-3(4H)-oxo-2H-1,2,4-benzothiadiazine 1,1-dioxide (IV). Three grams of phosgene was dissolved in 50 cc. of 1,2-dimethoxyethane. Compound III[4] (6.3 g.) was added. The solution was stirred for 1 hr. at room temperature, after which it was concentrated to near dryness, diluted with water, and filtered. The yield was 6.3 g. (92%), m.p. 272–273°.

Anal. Calcd. for $C_9H_{10}ClN_3O_5S_2$: C, 31.8; H, 3.0; N, 12.4. Found: C, 31.9; H, 3.2; N, 12.3.

6-Chloro-2-methyl-3(4H)-oxo-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (V). The keto derivative (IV) (3.4 g.) was heated at 110° for 1 hr. in 6.5 cc. of chlorosulfonic acid. The cooled reaction mixture was treated with 1.45 cc. of thionyl chloride and kept at room temperature for 1 hr. The sulfonyl chloride separated as a solid when the reaction mixture was quenched in ice-water. This solid was converted to the sulfonamide with 25 cc. of liquid ammonia. After evaporation of the ammonia, addition of water, and acidification with hydrochloric acid, there was obtained 2.9 g. (90%), m.p. 298–300° dec., identical with material prepared earlier.[4]

3-Carboxy-6-chloro-3,4-dihydro-2-methyl-7-(methylsulfamyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (VII) was prepared in 90% yield from III by using the procedure for compound IX, described under *preparation of acids*. The product was obtained as a hydrate, m.p. 161–164° (gas).

Anal. Calcd. for $C_{10}H_{12}ClN_3O_6S_2 \cdot H_2O$: C, 31.0; H, 3.6; N, 10.8. Found: C, 31.0; H, 3.6; N, 11.0.

4-Amino-2-chloro-5-(methylsulfamyl)benzenesulfonamide (VI). (a) *From compound* V. This hydrolysis has been described.[4] Originally we reported a m.p. of 168–170°. This represents a less stable crystalline form; in most subsequent preparations we have obtained material melting at 190–192°. These crystalline modifications have been observed by others.[8]

(b) *From compound* VII. The carboxylic acid hydrate (1.94 g.) was refluxed for 15 min. with 6.6 cc. of chlorosulfonic acid. The cooled reaction mixture was poured onto ice. The solid which precipitated was separated by filtration and added to 25 cc. of liquid ammonia. The residue after evaporation of the ammonia was treated with water and acidified. The yield was 1.05 g. (70%), m.p. 189–190°.

(c) *Attempted preparation from 6-chloro-3,4-dihydro-2-methyl-7-(methylsulfamyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide.* This intermediate (9.8 g.) was treated as described under (b) above. Only 2.4 g. of water-insoluble material was obtained, which after two recrystallizations from water melted at 251–252°. The substance was postulated to be 4-chloro-6-methylamino-1,3-benzenedisulfonamide on the basis of analytical results and its melting point.[17]

Anal. Calcd. for $C_7H_{10}ClN_3O_4S_2$: C, 28.0; H, 3.4; N, 14.0. Found: C, 28.0; H, 3.5; N, 14.1.

The structure was confirmed by catalytic dehalogenation to 4-methylamino-1,3-benzenedisulfonamide, m.p. 257–258°. When the dehalogenated product was mixed with authentic material[4] melting at 250°, the m.p. was 256–258°.

4-Amino-2-chloro-5-(n-propylsulfamyl)benzenesulfonamide 6-Chloro-3,4-dihydro-3-oxo-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide was alkylated with *n*-propyl iodide. The procedure described for alkylation with methyl iodide[4] was used. The crude product, m.p. 255–256°, was hydrolyzed[4] directly with 20% sodium hydroxide. The product melted at 117–119°.

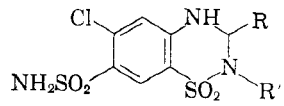
Anal. Calcd. for $C_9H_{14}ClN_3O_4S_2$: C, 33.0; H, 4.3; N, 12.8. Found: C, 33.0; H, 4.4; N, 12.7.

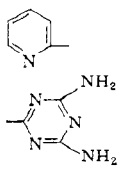
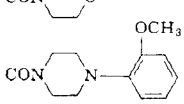
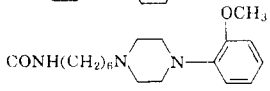
4-Amino-2-chloro-5-(ethylsulfamyl)benzenesulfonamide has been described.[4]

(16) Analytical data presented in Table II are not included in the descriptions given below. We are indebted to Mr. Elmer Shelberg and his staff for all microanalytical data; to Mr. M. Freifelder and Mr. George Stone for the catalytic hydrogenation; and to Dr. Richard Mattoon and Miss Anna Slawinska for crystallographic studies and NMR analyses.

(17) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, 25, 965 (1960), report m.p. 248–249°.

TABLE II



Cpd.	R	R′	M.P.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	CH_3	CH_3	250–251[b]	$C_9H_{12}ClN_3O_4S_2$	33.2	32.9	3.7	3.7	12.9	12.8
2	C_2H_5	CH_3	229–231	$C_{10}H_{14}ClN_3O_4S_2$	35.3	35.3	4.1	4.2	12.4	12.4
3	i-C_3H_7	CH_3	237–238	$C_{11}H_{16}ClN_3O_4S_2$	37.3	37.4	4.6	4.6	11.9	12.1
4	Cyclo-C_3H_5	CH_3	243–244	$C_{11}H_{14}ClN_3O_4S_2$	37.5	37.6	4.0	4.0	11.9	11.8
5	$C_6H_5CH_2$	CH_3	257–258	$C_{15}H_{16}ClN_3O_4S_2$	44.8	45.1	4.0	4.0	10.5	10.3
6	CH_2Br	CH_3	193–195	$C_9H_{11}BrClN_3O_4S_2$	26.7	27.0	2.7	2.9	10.4	10.5
7	$CHCl_2$	CH_3	247–248	$C_9H_{10}Cl_3N_3O_4S_2$	27.4	27.6	2.6	2.7	10.6	10.6
8	CF_3	H	313–314	$C_8H_7ClF_3N_3O_4S_2$	26.2	26.3	1.9	2.2	11.5	11.5
9	CF_3	CH_3	231–233	$C_9H_9ClF_3N_3O_4S_2$	28.5	28.8	2.4	2.7	11.1	11.2
10	C_2F_5	CH_3	241–242	$C_{10}H_9ClF_5N_3O_4S_2$	27.9	28.1	2.1	2.3		
11	CH_2OH	CH_3	190–192	$C_9H_{12}ClN_3O_5S_2$	31.6	31.4	3.5	4.1	12.3	12.1
12		CH_3	230–231	$C_{13}H_{13}ClN_4O_4S_2$	40.2	40.3	3.4	3.5	14.4	14.6
13		CH_3	247–248	$C_{11}H_{13}ClN_8O_4S_2$	31.4	31.2	3.1	3.3	26.6	26.3
IX	COOH	H	177–181	$C_8H_5ClN_2O_6S_2$	28.1	28.2	2.4	2.6	12.3	12.3
X	COOH	CH_3	158–160	$C_9H_{10}ClN_3O_6S_2 \cdot H_2O$	28.9	29.1	3.2	3.4	11.2	11.2
14	COOH	C_2H_5	186–188	$C_{10}H_{12}ClN_3O_6S_2 \cdot H_2O$	31.0	31.0	3.6	3.9	10.8	11.1
15	COOH	n-C_3H_7	212–214	$C_{11}H_{14}ClN_3O_6S_2$	34.4	34.2	3.7	3.7	10.9	10.8
XI	$COOCH_3$	H	234–236	$C_9H_{10}ClN_3O_6S_2$	30.4	30.4	2.8	3.0	11.8	11.7
XII	$COOCH_3$	CH_3	229–231	$C_{10}H_{12}ClN_3O_6S_2$	32.5	32.4	3.3	3.4	11.4	11.2
16	$COOCH_3$	C_2H_5	222–224	$C_{11}H_{14}ClN_3O_6S_2$	34.4	34.3	3.7	3.8	10.9	11.0
17	$COOCH_3$	n-C_3H_7	263–265	$C_{12}H_{16}ClN_3O_6S_2$	36.2	36.0	4.1	4.1	10.6	10.4
18	$COOC_2H_5$	CH_3	208–209	$C_{11}H_{14}ClN_3O_6S_2$	34.4	34.5	3.7	3.8	10.9	10.9
19	$COOC_4H_9(n)$	H	214–215	$C_{12}H_{16}ClN_3O_6S_2$	36.2	36.2	4.1	4.0	10.6	10.6
20	$COOC_4H_9(n)$	CH_3	222–224	$C_{13}H_{18}ClN_3O_6S_2$	37.9	38.1	4.4	4.7	10.2	10.4
21	$CONH_2$	H	266–267	$C_8H_8ClN_4O_5S_2$	28.2	28.4	2.6	2.7	16.5	16.4
22	$CONH_2$	CH_3	245–247	$C_9H_{11}ClN_4O_5S_2$	30.5	30.4	3.1	3.6	15.8	15.8
23	$CONH_2$	C_2H_5	257–258	$C_{10}H_{13}ClN_4O_5S_2$	32.6	32.2	3.6	3.7	15.2	15.1
24	$CONH_2$	n-C_3H_7	270–271	$C_{11}H_{15}ClN_4O_5S_2$	34.5	34.5	3.9	4.1	14.6	14.7
25	$CONHCH_3$	CH_3	270–271	$C_{10}H_{13}ClN_4O_5S_2$	32.6	32.6	3.6	3.7	15.2	15.3
26	$CON(CH_3)_2$	CH_3	265–267	$C_{11}H_{15}ClN_4O_5S_2$	34.5	34.6	3.9	4.2	14.6	14.4
27	$CONHC_3H_5$(cyclo)	CH_3	276	$C_{12}H_{15}ClN_4O_5S_2$	36.5	36.4	3.8	3.9	14.2	14.2
28	$CONHCH_2C_6H_5$	CH_3	254–255	$C_{16}H_{17}ClN_4O_5S_2$	43.2	43.2	3.8	3.9	12.6	12.4
29	$CONHCH_2CH_2N(C_2H_5)_2$	CH_3	195–196	$C_{15}H_{24}ClN_5O_5S_2 \cdot H_2O$	38.2	38.3	5.6	5.4	14.8	14.7
30		CH_3	234–235	$C_{13}H_{17}ClN_4O_6S_2 \cdot H_2O$	35.3	35.2	4.3	4.3	12.7	12.7
31[c]		CH_3	165–166	$C_{20}H_{24}ClN_5O_6S_2$	45.3	45.1	4.6	4.9	13.2	13.1
32[d]		CH_3	187–188	$C_{26}H_{37}ClN_6O_6S_2$	49.6	49.4	5.9	6.1	13.4	13.3

[a] All compounds, except the esters, melted with decomposition. Most of the esters, when pure, did not appear to decompose upon melting. [b] L. H. Werner and co-workers, ref. 6, report m.p. 274–276°.

[c] The amine from which this amide was derived has been described by V. Prelog and Z. Blazek, *Collection Czechoslov. Chem. Commun.*, **6**, 211 (1934); *Chem. Abstr.*, **28**, 5824 (1934). [d] The amine from which this amide was derived will be described in a forthcoming publication by Dr. J. H. Short and co-workers.

Preparation of acids. Details are given below for the preparation of the acids IX and X. Acids containing higher alkyl groups at the 2-position (cpds. 14,15) were prepared in an analogous manner. Yields were good (> 68%) in all cases.

3-Carboxy-6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (IX). An aqueous solution of glyoxylic acid was prepared by refluxing 20 g. of methyl dimethoxyacetate in 300 cc. of water for 3 hr. Methanol was removed by distillation, and 28.6 g. of 4-amino-6-chloro-1,3-benzenedisulfonamide was added. Refluxing was continued for 3 hr. After standing in the cold room overnight, the mixture was filtered. The solid weighed 30.7 g. (80% based on a dihydrate), m.p. 119–125° (gas). Recrystallization from water gave material melting at 121–125° (gas) which proved to be a dihydrate.

Anal. Calcd. for $C_8H_5ClN_2O_6S_2 \cdot 2H_2O$: C, 25.4; H, 3.2; N, 11.1. Found: C, 25.4; H, 3.2; N, 11.1.

When the hydrate was heated *in vacuo* for 22 hr. at 100°,

the m.p. rose to 177–181° dec. Analysis indicated that water of crystallization had been lost (Table II). The product reverted to the dihydrate when recrystallized from water.

3-Carboxy-6-chloro-3,4-dihydro-2-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (X). Methyl dimethoxyacetate (73 g.) was refluxed in 135 cc. of water for 2.5 hr. Methanol was removed by distillation; water was added to maintain a constant volume during this process. The hot solution was added to 108 g. of 4-amino-2-chloro-5-(methylsulfamyl)benzenesulfonamide in 1500 cc. of boiling water. Refluxing was continued for 45 min. Upon standing overnight the solution yielded 110 g. (82% based on a monohydrate) of product which melted at 158–160° (gas). Dehydration of the acid hydrate could not be accomplished without decomposition.

Neutralization of an ammonia solution of the acid with hydrochloric acid to *p*H 8–9 precipitated the *ammonium salt*, m.p. 238–240° dec. The salt is easily soluble in strong ammonia solutions, but is sparingly soluble in water. *Anal.* Calcd. for $C_9H_{13}ClN_4O_6S_2$: C, 29.0; H, 3.5; N, 15.0. Found: C, 29.0; H, 3.7; N, 15.6.

Preparation of esters. Details are given below for the preparation of the important methyl esters XI and XII. Higher esters (cpds. 18, 19, 20) were prepared by standard procedures from the corresponding acids. Those compounds with higher alkyl groups in the 2-position (cpds. 16, 17) were prepared in a manner analogous to the preparation of XII, Procedure (a).

6-Chloro-3,4-dihydro-3-methoxycarbonyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (XI). The dehydrated acid IX (1.71 g.) was dissolved in 10 cc. of methanol and treated with 1 equivalent of diazomethane in ether solution. Concentration and addition of water gave 1.58 g. (88%), m.p. 222–227° dec. Recrystallization from methanol brought the m.p. to 234–236°. The same product was obtained from the acid hydrate by diazomethane or *via* Procedure (a) below. The ester was unusually sensitive to hydrolysis; it could not be recrystallized from water or extracted with cold sodium bicarbonate solution without extensive decomposition.

6-Chloro-3,4-dihydro-3-methoxycarbonyl-2-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (XII). (a) *From X via methanol.* Fifty grams of hydrated acid, 15 cc. of 2,2-dimethoxypropane,[18] and 3 cc. of concd. hydrochloric acid were dissolved in 170 cc. of methanol. The reaction mixture was heated at 50° for 20 hr. Two additional 15-cc. portions of 2,2-dimethoxypropane were added at hourly intervals. The solvents were removed *in vacuo*; the residue was taken up in methanol, treated with Darco, filtered, and diluted with an equal volume of water. Upon standing, the solution yielded 40 g. (81%), m.p. 217–218°.

The ester exists in at least three crystalline modifications: α, m.p. 205–208°, obtained from water as thin hexagonal plates or thin needles with parallel extinction under the polarizing microscope; β, m.p. 224–226°, obtained from methanol as thin plates with oblique extinction; and γ, m.p. 229–231°, occasionally obtained from water as long, thin plates with oblique extinction. The three forms listed all give satisfactory elemental analyses, are interconvertible by recrystallization, but have different x-ray patterns. Recrystallization from methanol-water mixtures usually precipitates material melting in the range 215–225°. The x-ray pattern indicates that this is a pure β-form, but individual crystals observed under the microscope melt sharply at different temperatures within the 215-225° range.

NMR spectra were obtained on the α- and γ-forms in deuterated acetone. The spectra were essentially identical and consistent with the assigned structure.

(b) *From IX or X via diazomethane.* Treatment of either acid IX or X with an excess of diazomethane in methanol produced XII. The products could not be distinguished from that obtained in procedure (a) above.

Preparation of amides. The amides (cpds. 21–32) which appear in Table II were prepared by aminolysis of the methyl esters. Illustrative procedures are given below.

3-Carbamoyl-6-chloro-3,4-dihydro-2-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (No. 22). The ester XII (2.9 g.) was added to 100 cc. of liquid ammonia. The ammonia was allowed to evaporate. The residue was treated with water. The solid obtained (2.3 g.; 83%) melted at 245–247° dec.

6-Chloro-3-(cyclopropylcarbamoyl)-3,4-dihydro-2-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (No. 27). The ester XII (4 g.) was dissolved in 50 cc. of methanol and treated with 10 cc. of cyclopropylamine. The solution was refluxed for 1 hr., during which time the product precipitated. Filtration gave 3.6 g. (85%), m.p. 276° dec.

6-Chloro-3-(diethylaminoethylcarbamoyl)-3,4-dihydro-2-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (No. 29). The ester XII (3.7 g.) and 5 cc. of diethylaminoethylamine were refluxed for 2 hr. in 70 cc. of methanol. About two thirds of the solvent was removed and 3 cc. of water was added. Upon standing overnight the solution yielded 2.8 g. (60%) of product as a monohydrate melting at 195–196° dec.

Preparation of other benzothiadiazine 1,1-dioxides. Most of the remaining compounds listed in Table II were prepared as described earlier.[4] Those prepared in a substantially different manner are given below.

3-Bromomethyl-6-chloro-3,4-dihydro-2-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (No. 6). A saturated solution of anhydrous hydrogen bromide in 75 cc. of bis(2-methoxyethyl) ether was prepared. Four grams of bromoacetaldehyde diethyl acetal and 6 g. of compound VI were added. The solution was heated at 100° for 1 hr. before concentrating to near dryness *in vacuo*. The residue was taken up in 25 cc. of isopropyl alcohol, treated with Darco, filtered, and diluted with 10 cc. of water. Standing produced 3.1 g. (38%) of precipitate, m.p. 188–190° dec. An analytical sample, m.p. 193–195° dec., was prepared from methanol-water.

6-Chloro-3-dichloromethyl-3,4-dihydro-2-methyl-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (No. 7). Anhydrous hydrogen chloride was bubbled into 2600 cc. of 1,2-dimethoxyethane for 30 min. A solution of 124 g. of dichloroacetaldehyde in 400 cc. of the same solvent was added, followed by 300 g. of the sulfonamide (VI). The reaction mixture was refluxed for 2 hr. Most of the solvent was removed by distillation, and methanol was added to the residue. The product which precipitated amounted to 249 g., m.p. 243–245° dec. An additional 44 g., m.p. 242–244° dec., was obtained from the filtrate for a total yield of 74%. Recrystallization from a mixture of methanol, dimethylformamide and water brought the m.p. to 247–248°.

6-Chloro-3,4-dihydro-2-methyl-3-(pentafluoroethyl)-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (No. 10). A solution of 4.16 g. of 6-chloro-3,4-dihydro-3-(pentafluoroethyl)-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide[4] in 8 cc. of dimethylformamide was added to 0.24 g. of sodium hydride (0.43 g. of 56% dispersion) in 2 cc. of dimethylformamide, with stirring. Methyl iodide (1.42 g.) was added. The mixture was kept at 80° for 1 hr. Water (5 cc.) was added and the solution was filtered. The filtrate was diluted with 50 cc. of hot water and allowed to stand. The solid that separated amounted to 3.37 g. (78%), m.p. 241–242° dec.

6-Chloro-3,4-dihydro-2-methyl-7-sulfamyl-3-(trifluoromethyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (No. 9) was prepared as described for compound No. 10 by the alkylation of the corresponding 3-(trifluoromethyl) compound (No. 8).

6-Chloro-3-(4,6-diamino-2-triazinyl)-3,4-dihydro-2-methyl-

(18) N. B. Lorette and J. H. Brown, Jr., *J. Org. Chem.*, **24**, 261 (1959).

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

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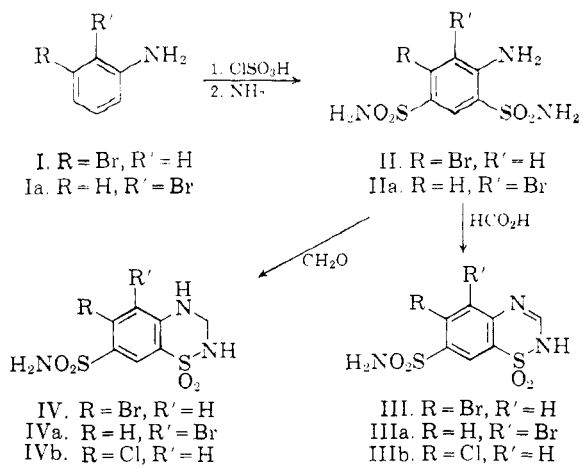
Chlorosulfonation of *o*-bromoaniline and *m*-bromoaniline, followed by ammonolysis, gave, respectively, 4-amino-5-bromo-1,3-benzenedisulfonamide and 4-amino-6-bromo-1,3-benzenedisulfonamide. The latter was condensed with urea, methylated, and hydrolyzed to obtain 4-amino-2-bromo-5-methylsulfamylbenzenesulfonamide. 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

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(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).