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.

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(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]

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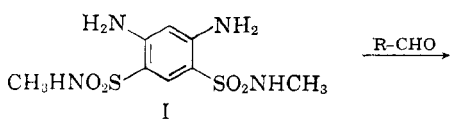
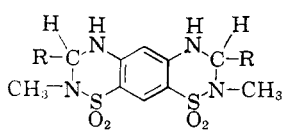
A novel and practical synthesis of 4,6-diamino-N^1,N^3-dimethyl-1,3-benzenedisulfonamide is described. Ring closure of this substance with aldehydes makes possible the formation of a new tricyclic system.

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.

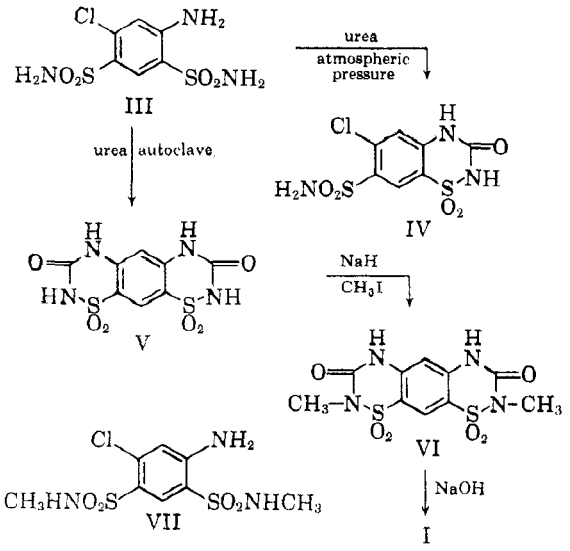
The most obvious method of preparing I would be the chlorosulfonation of *m*-phenylenediamine or its diacyl derivative, followed by treatment of the disulfonyl chloride with methylamine. The chlorosulfonation has been described.[3,4] The yields reported were very poor and in our experience proved quite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

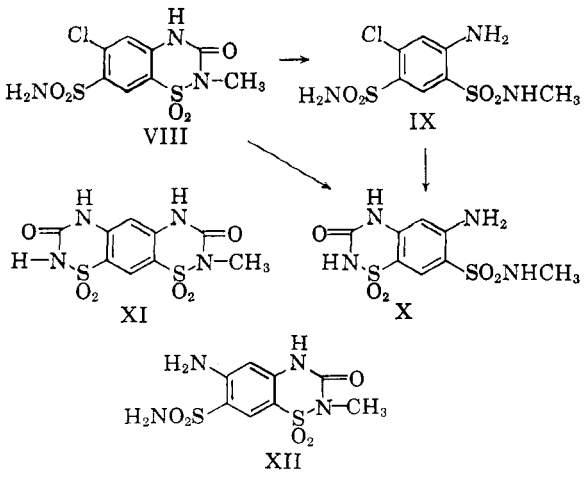
(3) O. Lustig and E. Katscher, *Monatsh.*, **48**, 87 (1927).

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



benzothiadiazine 1,1-dioxide[5] (IV). When the ratio of urea to amide became greater than fifteen to one, we were able to isolate, other than the main product (IV), a compound that contained no chlorine which was later proved to be V. To avoid the loss of ammonia the fusion was carried out in a closed vessel. This afforded the described V in excellent yield. Compound V alkylated with ease to give VI, which in turn produced I through hydrolytic cleavage.

It is noteworthy that the unmethylated substance (V) is resistant to hydrolysis This was expected, however, since we had previously learned that the 3-oxothiadiazine ring in IV is stable to acid or alkaline hydrolysis.



Further studies were carried out to delineate more fully the nature of the reaction with urea. On the basis of work described above, fusion of urea with VIII would be expected to yield XI. When this reaction was carried out, no product corresponding to XI was isolated. Elemental analyses, infrared spectra, and the presence of a free amino group pointed to either X or XII. It is difficult to distinguish between these two possibilities by physical means; however, the strong chemical evidence cited below supports our contention that X is the main product of the reaction.

The product is impervious to alkali or acid, as are IV and V, which are known to contain the 3-oxo-3,4-dihydro-1,2,4-thiadiazine 1,1-dioxide ring present in X. It has been demonstrated that the introduction of a methyl group in the 2-position of IV,[4] and in the 2,2′-positions of V makes them susceptible to these reagents. When the fusion time between urea and VIII was reduced to eight hours, we were able to isolate as much as 25% of IX. It appears, then, that the first step of the reaction between VIII and urea is the cleavage of the heterocyclic ring to form a free methylsulfamyl group. Furthermore, urea is incapable of effecting cyclization when the sulfamyl group is substituted, so that once the heterocyclic ring in VIII is opened, it cannot be recyclized. This latter point was demonstrated by attempting, unsuccessfully, to cyclize 2-amino-4-chloro-N^1-methylbenzenesulfonamide. This failure is unfortunate, for it rules out the possibility of obtaining VI directly from VII by reaction with urea.

The route III → V → VI → I → II was used to prepare several representative examples (IIa,b,c) of the title substance. The compounds were ineffective diuretic agents.

EXPERIMENTAL[6]

Benzo[1,2-e,5,4-e′]bis[3-oxo-3,4-dihydro-1,2,4-thiadiazine 1,1-dioxide] (V). A finely ground mixture of 4-amino-6-chloro-1,3-benzenedisulfonamide (236 g., 0.83 mole) and urea (247 g., 4.12 moles) was charged into a 3-l. Hastelloy bomb containing a glass liner. The mixture was heated at 180° for 26 hr. without shaking. Upon cooling, the solid melt was dissolved in 3 l. of water, treated with Darco, and filtered. The filtrate was made strongly acid with concentrated hydrochloric acid and allowed to stand at 4° overnight. The crude product which was filtered and washed with water was recrystallized from dimethylformamide and water. This afforded 208 g. of product as a monohydrate decomposing at 370°. (Yield 75%.)

Anal. Calcd. for $C_8H_6N_4O_6S_2 \cdot H_2O$: C, 28.56; H, 2.39; N, 16.66. Found: C, 28.67; H, 2.39; N, 16.58.

Benzo[1,2e,5,4-e′]bis[2-methyl-3-oxo-3,4-dihydro-1,2,4-thiadiazine 1,1-dioxide] (VI). A solution of benzo[1,2-e,5,4-e′] bis[3-oxo-3,4-dihydro-1,2,4-thiadiazine 1,1-dioxide] (25 g., 0.079 mole) in 100 ml. of dimethylformamide was added dropwise to a stirred suspension of sodium hydride (6.8 g. of a 56% oil dispersion, 0.158 mole) in 80 ml. of dimethylformamide. The suspension was stirred for 1 hr. at 70°, and then a solution of 22.5 g. (0.158 mole) of methyl iodide in 25 ml. of dimethylformamide was added dropwise. After an hour interval, enough methyl iodide was added to effect solution (25–30 g.). Stirring and heating were continued for another

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

(6) We wish to thank Dr. Warren J. Close for helpful consultation; Mr. Elmer Shelberg and his staff for the microanalyses; and Mr. William Washburn and his associates for infrared spectra.

hour when 200 ml. of water was added and the mixture allowed to cool. The precipitate was filtered and washed with water. The product weighed 25 g. (92%) and decomposed at 350–353°. A small sample was recrystallized from dimethylformamide, methanol, and water to decompose at 350–353°.

Anal. Calcd. for $C_{10}H_{10}N_4O_6S_2$: C, 34.67; H, 2.91; N, 16.17. Found: C, 34.64; H, 3.06; N, 15.99.

4,6-Diamino-N^1,N^3-dimethyl-1,3-benzenedisulfonamide (I) Ninety grams (0.26 mole) of benzo[1,2-e,5,4-e′)bis[2-methyl-3-oxo-3,4-dihydro-1,2,4-thiadiazine 1,1 dioxide] was dissolved in 900 ml. of 20% sodium hydroxide solution. The solution was refluxed overnight and filtered. With cooling and stirring, the filtrate was made acidic with 6*N* hydrochloric acid. The precipitate was filtered and the filter cake washed well with water. The crude product was recrystallized from dimethylformamide and water to yield 53 g. (70%) melting at 274–276°.

Anal. Calcd. for $C_8H_{14}N_4O_4S_2$: C, 32.64; H, 4.79; N, 19.03. Found: C, 32.81; H, 4.86; N, 18.89.

Benzo[1,2-e,5,4-e′]bis[2-methyl-3,4-dihydro-1,2,4-thiadiazine 1,1-dioxide] (IIa). Three grams (0.01 mole) of 4,6-diamino-N^1,N^3-dimethyl-1,3-benzenedisulfonamide was dissolved in a boiling solution of 150 ml. of water and 10 ml. of dimethylformamide. At reflux temperature, 8 ml. of 37% formaldehyde solution was added down the condenser. Within 15 min. a precipitate started to form. The mixture was refluxed an additional 30 min. and allowed to cool to room temperature. Filtration gave 3.1 g. of crude product decomposing at 323–325°. Recrystallization from dimethylformamide, methanol and water gave 2.2 g., decomposing at 318–319°. (Yield 70%.)

Anal. Calcd. for $C_{10}H_{14}N_4O_4S_2$: C, 37.72; H, 4.43; N, 17.59. Found: C, 37.77; H, 4.54; N, 17.81.

Benzo[1,2-e,5,4-e′]bis[3-chloromethyl-2-methyl-3,4-dihydro-1,2,4-thiadiazine 1,1-dioxide] (IIb). 4,6-Diamino-N^1,N^3-dimethyl-1,3-benzene-disulfonamide (5.3 g., 0.0175 mole) was dissolved in 50 ml. of dimethylformamide and 150 ml. of water. To this was added a 40% solution of chloroacetaldehyde (9.8 g., 0.05 mole). The solution was refluxed 90 min., and 50 ml. of water was added. Upon standing overnight, the solution deposited 5.5 g. (79%) of crude product. Recrystallization from dimethylformamide and water gave 4.8 g. melting at 202–203°.

Anal. Calcd. for $C_{12}H_{16}Cl_2N_4O_5S_2$: C, 34.70; H, 3.88; N, 13.49. Found: C, 34.77; H, 4.12; N, 13.74.

Benzo[1,2-e,5,4-e′]bis[3-carboxy-2-methyl-3,4-dihydro-1,2,4-thiadiazine 1,1-dioxide] (IIc). A solution of methyl dimethoxyacetate (26.8 g., 0.2 mole) in 150 ml. of water was refluxed 2 hr. The alcohol was removed by distillation at atmospheric pressure, while keeping the volume constant by the addition of water. This solution was added to 4,6-diamino-N^1,N^3-dimethyl-1,3-benzenedisulfonamide (10 g., 0.034 mole) and the mixture refluxed 45 min. Solution occurs in approximately 5 min. Upon standing at 4° for several days the solution deposited 1.5 g. (11%) of product which decomposes at 254–256°.

Anal. Calcd. for $C_{12}H_{14}N_4O_8S_2$: C, 35.46; H, 3.47; N, 13.78. Found: C, 35.20; H, 3.45; N, 13.95.

6-amino-7-(methylsulfamyl)-3-oxo-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (X). *From* VIII. An intimate mixture of 6-chloro-2-methyl-3-oxo-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (12.1 g., 0.0375 mole) and urea (20.0 g., 0.333 mole) was charged into an autoclave and heated at 180° for 24 hr. The resultant sticky mass was treated with approximately 200 ml. of water and allowed to stand until solution occurred. The solution was treated with Darco, filtered, and heated under vacuum to remove excess ammonia. Upon cooling, a small amount of cyanuric acid precipitated and was removed by filtration. The filtrate was made strongly acid with hydrochloric acid and allowed to stand overnight at 4°. The precipitate was recrystallized from water to give 3.2 g. (28%) of product melting at 285–286°.

Anal. Calcd. for $C_8H_{10}N_4O_5S_2$: C, 31.36; H, 3.29; N, 18.29. Found: C, 31.67; H, 3.31; N, 18.51.

From IX. Following the procedure outlined above, a mixture of 4-amino-2-chloro-5-(methylsulfamyl)benzenesulfonamide (29.95 g., 0.1 mole) and urea (60.0 g., 1.0 mole) gave 18.95 g. (62%) of product melting at 283–285°. The melting point was not depressed upon mixing with the product obtained in the previous experiment.

Anal. Calcd. for $C_8H_{10}N_4O_5S_2$: C, 31.36; H, 3.29; N, 18.29. Found: C, 31.42; H, 2.72; N, 18.29.

Fusion of urea with 3-chloro-6-(methylsulfamyl)aniline. Under similar conditions the fusion was carried out with 3-chloro-6-(methylsulfamyl)aniline (8.0 g.) and urea (24.0 g.). Work-up afforded 7.3 g. of starting material.

Attempted hydrolysis of V. Twenty-five grams of V was refluxed 18 hr. in 250 ml. of 20% NaOH solution. The solution was filtered and the filtrate made acidic with 6 *N* hydrochloric acid. The precipitate weighed 23.2 g. and decomposed at 370°. The melting point was not depressed when mixed with the starting material. The desired product, 4,6-diamino-1,3-benzenedisulfonamide, has been reported[3] to melt at 187°.

Isolation of IX *from the fusion of urea with* VIII *for shorter periods.* The fusion was performed as described, using VIII (17.0 g., 0.054 mole) and urea (32.5 g., 0.54 mole); however, the heating was stopped at the end of 8 hr. Water, 150 ml., was added to the mixture and the insoluble material was separated by filtration. This insoluble substance was taken up in dilute sodium hydroxide solution, treated with Darco, and filtered. The filtrate was acidified with dilute hydrochloric acid to give 4.1 g. (25.3%) of product melting at 196°. The melting point was not depressed when mixed with an authentic sample of IX.

Acidification of the original filtrate gave X.

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