

## The Synthesis of 1,2,4-Benzothiadiazepine 1,1-Dioxides

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Previously (1) we have reported on the synthesis of 2*H*-1,2,3-benzothiadiazepine 1,1-dioxides, 11*H*-11,11a-dihydrobenzimidazo[1,2-*b*][1,2]benzothiazole 5,5-dioxides and 6*H*-dibenzo[*c,g*][1,2,5]thiadiazocine 5,5-dioxides from 2-benzoylbenzenesulfonyl chlorides. We wish to report now on the synthesis of 1,2,4-benzothiadiazepine 1,1-dioxides (III), a previously unreported heterocyclic system (2), starting with 4-chloro-2-benzoylbenzenesulfonyl chloride (I). Reaction of I with benzamidine hydrochloride, guanidine carbonate, or 2-methyl-2-thiopseudourea sulfate in acetone-water solution under alkaline conditions gave the corresponding 2-benzoyl-4-chlorobenzesulfonylamidines (II) in good yields. The latter compounds were heated under reflux in xylene solution in the presence of a small amount of *p*-toluene-

sulfonic acid as catalyst, using a Dean-Stark water separator, to effect ring closure. The compounds prepared are listed in Table I.

7-Chloro-3,5-diphenyl-1,2,4-benzothiadiazepine 1,1-dioxide (IIIa) significantly showed no NH absorption in its infrared spectrum. The nmr spectrum showed only aromatic protons. The mass spectrum showed a parent *m/e* of 380.

The nmr spectrum of 3-amino-7-chloro-5-phenyl-1,2,4-benzothiadiazepine 1,1-dioxide (IIIb) consisted of a broad band centered at  $\delta$  8.2, attributable to aromatic amine protons, in addition to aromatic proton absorption.

7-Chloro-3-methylmercapto-5-phenyl-1,2,4-benzothiadiazepine 1,1-dioxide (IIIc) showed no NH absorption in its infrared spectrum. The nmr spectrum consisted of only a singlet at  $\delta$  2.45, attributable to the protons of the CH<sub>3</sub> group, in addition to aromatic protons.

The methylthio group in the 3-position of 7-chloro-3-methylthio-5-phenylbenzothiadiazepine 1,1-dioxide (IIIc) was found to undergo nucleophilic displacement with secondary amines. Thus, it reacted readily with diethylamine and 1-methylpiperazine to give the corresponding 3-substituted 1,2,4-benzothiadiazepine 1,1-dioxides (IV) (cf. Table I).

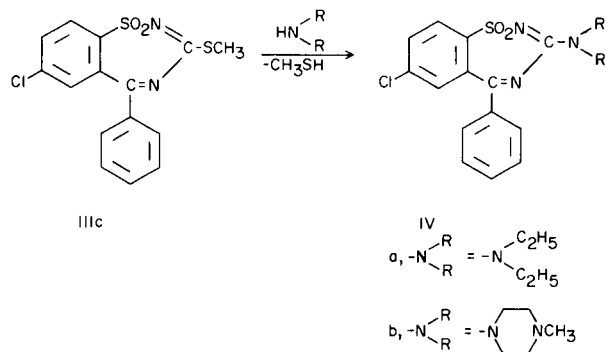
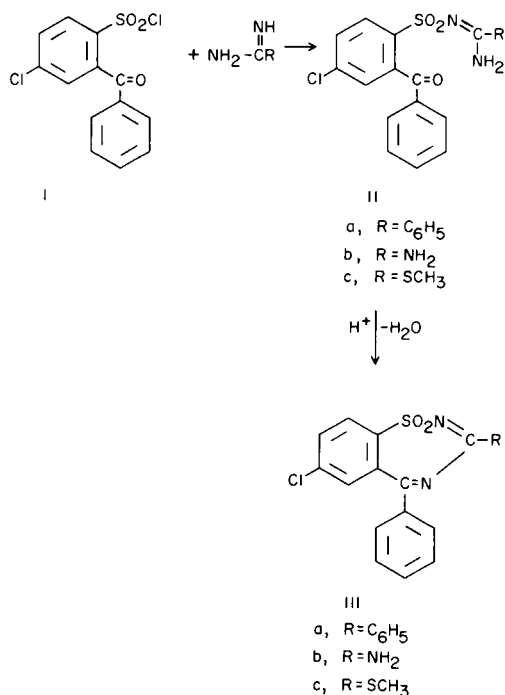
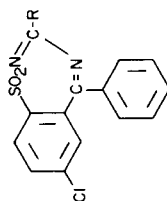


TABLE I

## 7-Chloro-5-phenyl-1,2,4-benzothiadiazepine 1,1-dioxides



R	Procedure	Yield %	M.P. °C	Formula	C	H	Calcd., % Cl	N	S	C	H	Found, % Cl	N	S	λ max, (ethanol) (ε), mμ
C <sub>6</sub> H <sub>5</sub>	A (a)	71 (b)	220-221	C <sub>20</sub> H <sub>13</sub> ClN <sub>3</sub> O <sub>2</sub> S	63.07	3.44	9.31	7.36	8.42	63.00	3.84	9.39	7.03	8.22	251 (16,150) 285 (21,350) 304 (20,150)
NH <sub>2</sub>	A (c,d)	67	269-270	C <sub>14</sub> H <sub>10</sub> ClN <sub>3</sub> O <sub>2</sub> S	52.59	3.15	11.09	13.14	10.03	52.29	2.83	11.02	13.02	9.97	226 (24,650) 269 (11,850) 290 (sh) (10,450)
SCH <sub>3</sub>	A	77	203-205	C <sub>15</sub> H <sub>11</sub> ClN <sub>3</sub> O <sub>2</sub> S <sub>2</sub>	51.35	3.16	10.10	7.99	18.28	51.57	3.47	10.33	8.16	18.08	222 (23,000) 251 (15,100) 278 (sh) (12,700) 303 (13,350)
N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	B	70	211-212	C <sub>18</sub> H <sub>18</sub> ClN <sub>3</sub> O <sub>2</sub> S	57.52	4.83	9.43	11.18	8.53	57.84	4.76	9.37	11.08	8.43	257 (17,900) 290 (sh) (11,800) 345 (sh) ( 1,700)
	B (e)	49 (f)	202-203	C <sub>19</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>2</sub> S	56.64	4.75	8.80	13.91	7.96	56.32	4.97	8.81	13.75	7.94	257 (18,500) 289 (13,100) 335 (sh) (2,600)

(a) The reflux time was 70 hours. At the end of this time, the reaction mixture, on cooling, precipitated 4.80 g. of starting material. (b) The yield is based on the amount of starting material consumed in the reaction, taking into account recovered starting material. (c) The reflux time was 120 hours. The reaction mixture was then allowed to cool to room temperature and the product removed by filtration. (d) Recrystallized from ethanol. (e) Fifteen ml. of 1-methylpiperazine was used in place of diethylamine. Dioxane was not used. The reaction mixture was heated at 50° for 17 hours. To the residue after removal of the excess 1-methylpiperazine was added water and the product was obtained by filtration. (f) Recrystallized from 2-propanol.

## EXPERIMENTAL (3) (4)

## 2-Benzoyl-4-chlorobenzenesulfonylbenzamidine (IIa).

To a stirred solution of 8.0 g. (0.2 mole) of sodium hydroxide, 50 ml. of water and 100 ml. of acetone was added 15.60 g. (0.1 mole) of 2-benzoyl-4-chlorobenzenesulfonyl chloride (1) in 100 ml. of acetone. The mixture was stirred at room temperature for two and one-half hours, diluted with 1 liter of water, filtered, and the precipitate washed with water. There was obtained 33.15 g. (83%) of material melting at 218-220°. Recrystallization from 2-butanone gave colorless prisms melting at 221-222°;  $\lambda$  max (ethanol), 250  $m\mu$  ( $\epsilon$ , 32,700);  $\nu$  max (nujol mull), 3420, 3310, 1680, 1620, 1515, 1275  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{20}H_{15}ClN_2O_3S$ : C, 60.22; H, 3.79; Cl, 8.89; N, 7.03; S, 8.04. Found: C, 60.29; H, 3.84; Cl, 8.96; N, 6.70; S, 8.10.

## 2-Benzoyl-4-chlorobenzenesulfonylguanidine (IIb).

To a stirred solution of 6 g. of guanidine carbonate and 6 g. of sodium hydroxide in 36 ml. of water and 20 ml. of acetone was added over a period of fifteen minutes a solution of 16.6 g. (0.053 mole) of 2-benzoyl-4-chlorobenzenesulfonyl chloride (1) in 100 ml. of acetone, keeping the solution below 10°. The thick mixture was diluted with water (200 ml.) and filtered. After recrystallization from a large volume (800 ml.) of ethanol, there was obtained 8.70 g. (49%) of colorless prisms melting at 240-244.5°. Additional recrystallization raised the melting point to 245-246°.  $\lambda$  max (ethanol), 246  $m\mu$  ( $\epsilon$ , 20,675).  $\nu$  max (nujol mull), 3430, 3320, 1670, 1535, 1280, 1160, 1145, 825, 710  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{14}H_{12}ClN_3O_3S$ : C, 49.78; H, 3.58; Cl, 10.50; N, 12.44; S, 9.49. Found: C, 49.82; H, 3.73; Cl, 10.52; N, 12.01; S, 9.37.

## S-Methyl-2-benzoyl-4-chlorobenzenesulfonylthiopseudourea (IIc).

To a stirred solution of 6.91 g. (0.05 mole) of potassium carbonate in 10 ml. of water and 20 ml. of acetone cooled below 5° was added 2.78 g. (0.01 mole) of 2-methyl-2-thiopseudourea sulfate. To the resulting solution was added a solution of 6.31 g. (0.02 mole) of 2-benzoyl-4-chlorobenzenesulfonyl chloride (1) in 20 ml. of acetone and then 70 ml. of water. Stirring was continued at room temperature for four and one-half hours. An additional 150 ml. of water was added and the mixture filtered. The yellow solid was recrystallized from ethanol, weight, 6.15 g. (84%), m.p. 160-162°. An additional recrystallization gave yellow prisms

melting at 160.5-162.5°;  $\lambda$  max (ethanol), 248  $m\mu$  ( $\epsilon$ , 26,650);  $\nu$  max (nujol mull), 3410, 3310, 1660, 1615, 1350, 1305, 1295, 1285, 1260, 1150, 1125, 760, 710  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{15}H_{13}ClN_2O_3S_2$ : C, 48.84; H, 3.55; Cl, 9.61; N, 7.60; S, 17.38. Found: C, 48.98; H, 3.85; Cl, 9.75; N, 7.58; S, 17.63.

## 7-Chloro-3-methylthio-5-phenyl-1,2,4-benzothiadiazepine 1,1-dioxide (IIIc).

## Procedure A.

A stirred mixture of 35.28 g. (0.096 mole) of S-methyl-2-benzoyl-4-chlorobenzenesulfonylthiopseudourea and 1.0 g. of p-toluenesulfonic acid in 800 ml. of xylene was heated under reflux using a Dean-Stark trap until the theoretical amount of water separated (42 hours). The solution was concentrated under reduced pressure and the residue was recrystallized from ethyl acetate.

## 7-Chloro-3-diethylamino-5-phenyl-1,2,4-benzothiadiazepine 1,1-dioxide (IVa).

## Procedure B.

A solution of 3.51 g. (0.01 mole) of 7-chloro-3-methylthio-5-phenylbenzo 1,2,4-thiadiazepine 1,1-dioxide and 40 ml. of diethylamine in 75 ml. of dioxane was heated under reflux for 17 hours. The excess amine and the dioxane were removed by distillation under reduced pressure. The residue was recrystallized from ethyl acetate.

## REFERENCES

- (1) John B. Wright, *J. Heterocyclic Chem.*, **5**, 453 (1968).
- (2) 2,5-dihydro-1,2,4-benzothiadiazepine 1,1-dioxide has been reported by G. Cignarella and U. Teotino, *J. Am. Chem. Soc.* **82**, 1594 (1960).
- (3) All melting points are corrected.
- (4) Microanalyses were performed by Mr. N. Knight and his associates and NMR data were obtained by Dr. G. Slomp, Mr. F. MacKellar and Mr. J. Zieserl, Jr., of our Physical and Analytical Chemistry Department. The author is indebted also to Mr. P. Meulman for the infrared data, to Miss B. Zimmer for the ultraviolet data and to Mr. A. Lallinger for excellent technical assistance.

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