

## The Synthesis and Properties of 1,4,5-Benzothiadiazocine Derivatives

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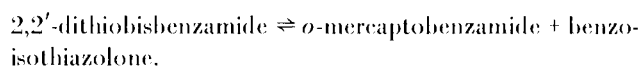
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Due to our interest in the little explored chemistry of the eight-membered nitrogen-containing rings as potential new pharmacological compounds, we attempted to prepare the new class of heterocycles, 1,4,5-benzoxadiazocine-3,6-dione by intramolecular cyclization of *N'*-chloroacetyl-salicylhydrazide; no phenol alkylation occurred and the reaction gave only a phenyloxadiazine (1). Because thiols and their salts are considerably more nucleophilic than phenols and phenoxides, the investigation was continued using *o*-mercaptobenzohydrazide instead of salicylhydrazide. There is little literature related to seven or eight membered ring closures by Aryl-SH alkylation by means of an alkyl halide (2,3,4). The ring closure of the parent compound 1,4-benzothiazepine-3,5-dione was achieved by intramolecular dehydration of a carboxamide and a carboxyl group (5).

The precursor *N'*-chloroacetyl-2-mercaptobenzohydrazide (I) was obtained by stirring a mixture of chloroacetyl chloride and *o*-mercaptobenzohydrazide in dioxane (nitrogen atmosphere) at room temperature. When the reaction was carried out at reflux temperature, the yield was lower than at room temperature and also 2,2'-dithiobis-*N'*-chloroacetylbenzohydrazide (II) was produced. Compound I was unstable to recrystallization and no analytical sample was available; therefore, the nature of I was confirmed by means of benzylation of the free SH group. The resulting product was identical by mixed m.p. and ir with III, obtained from 2-benzylthiobenzohydrazide. Likewise the disulfide II was identified when it was also obtained by an unequivocal synthesis (see Scheme I).

First attempts at ring closure were carried out by warming I with one equivalent of sodium hydroxide in DMF solution, but this method failed to yield identifiable products. However, simple warming at 130° in DMF solution resulted in approximately 55% of the benzothiadiazocine IV with a little resin formation. Under high dilution conditions the yield was not improved.

Treatment of disulfide II with potassium carbonate in acetone solution at room temperature gave about 44% of IV suggesting that II has a dismutation similar to that described by McClelland (6) for the 2,2'-dithiobisbenzamide:



Unexpectedly the reduction of the S-S bond of II with sodium hydrosulfite in aqueous alkaline solution resulted in the formation of the oxadiazinone V and not in I or IV. This oxadiazinone is an unstable product which could

SCHEME I

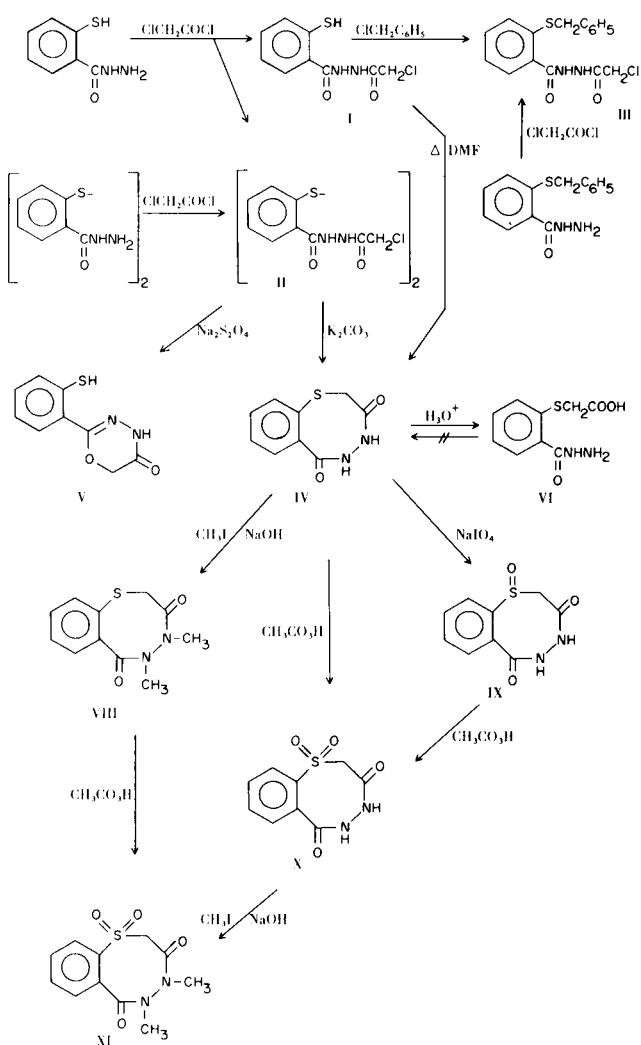


TABLE I

NMR Chemical Shifts (a) and Coupling Constants (b)

Compound	Solvent	-CO-CH <sub>2</sub> -	-CONHNHCO-	-N-CH <sub>3</sub>	-SH	Aromatic H
1	DMSO	4.1; 2H; s	10.5; 1H; s 11.0; 1H; s		5.2; 1H; s	7.6; 4H; m
2	DMSO	4.5; 4H; s	10.7; 2H; s 11.0; 2H; s			7.7; 8H; m
4	DMSO	AB {3.4; 1H; d 4.2; 1H; d J gem: 9.3	9.65; 1H; s 10.00; 1H; s			7.5; 4H; m
8	CDCl <sub>3</sub>	AB {3.5; 1H; d 4.0; 1H; d J gem: 9.3		2.85; 3H; s 3.4; 3H; s		7.4; 4H; m
9	DMSO	AB {2.9; 1H; d 5.1; 1H; d J gem: 13.3	9.5; 1H; s 9.8; 1H; s			7.6; 4H; m
10	DMSO	AB {4.2; 1H; d 5.0; 1H; d J gem: 13.3	9.6; 1H; s 19.0; 1H; s			7.8; 4H; m
11	CDCl <sub>3</sub>	AB {4.3; 1H; d 4.7; 1H; d J gem: 12.0		2.85; 3H; s 3.40; 3H; s		7.8; 4H; m

(a) In parts per million ( $\delta$ ) from internal TMS. (b) J, the observed coupling constant, in cps. (c) Multiplicity: s, singlet; d, doublet; m, multiplet.

only be identified by elemental analysis and spectroscopy.

Attempts to obtain IV from the sulfide VI by azeotropic distillation with or without acid catalysis, DCC or heating in high-boiling solvents failed and starting material was recovered.

The structure of IV was established by analysis (including S), molecular weight (Rast), ir, nmr and its chemical properties. Mild acid hydrolysis yielded the sulfide VI and alkaline hydrolysis gave VII thus confirming ring closure by SH alkylation. Potentiometric titration of IV showed two acidic hydrogens;  $pK_1$ : 10.10 and  $pK_2$ : 11.05, but by treatment with methyl iodide in alkaline solution no monomethylation was possible. Decrease of concentrations of reactants only lowered the yield of the dimethyl derivative VIII.

The ring remains stable to oxidation; the treatment of IV with sodium periodate gave a sulfoxide (IX) and with peracetic acid the sulfone X was obtained.

The ir spectra are in good agreement with the assigned structure (7) (see Experimental); nmr spectra especially, demonstrated the variations of the CH<sub>2</sub> shift in the series (see Table I). This group shows a singlet in all non-cyclic derivatives. Deuteration on the sulfone X exchanged three active protons and turned the CH<sub>2</sub> doublet into a singlet (1H). When X was potentiometrically titrated, it showed only two  $pK$  values,  $pK_1$ : 8.43 and  $pK_2$ : 10.43; the methylation of it gave the 4,5-dimethyl derivative XI.

The structure of XI was further established by oxidation of VIII with peracetic acid which afforded an identical compound.

#### EXPERIMENTAL

Melting points were taken on a Buchi apparatus and are uncorrected. Ir spectra were determined as potassium bromide pellets with a Beckman 20 A instrument. Nmr spectra were determined with a 60-Mc Perkin Elmer R-12 Spectrometer using TMS as an internal standard. The potentiometric titrations with 0.1N sodium hydroxide were carried out in aqueous solution with a Beckman Zeromatic II potentiometer. Molecular weights were determined by the Rast method (in camphor).

##### *N*'-Chloroacetyl-*o*-mercaptobenzhydrazide (I).

To a solution of 1.68 g. (0.01 mole) of *o*-mercaptobenzhydrazide (8) in 10 ml. of dry dioxane was added dropwise with stirring under a nitrogen atmosphere, 1.13 g. (0.01 mole) of chloroacetyl chloride. Stirring was continued for 4 hours at room temperature and then the pale yellow precipitate was filtered, washed with dioxane and dried *in vacuo*, giving 1.8 g. (73%) of I, m.p. 164-165°, ir 3300 and 3070 (NH), 2600 (SH), 1650 and 1630 (C=O), 790 cm<sup>-1</sup> (Cl). The compound is unstable to recrystallization. Consequently, elemental analysis was carried out on the benzyl derivative (III).

##### *N*'-Chloroacetyl-2-benzylthiobenzhydrazide (III).

###### A. From I.

To a suspension of I (1.0 g., 0.004 mole) in 2 ml. of ethanol with 0.5 ml. of benzyl chloride under a nitrogen atmosphere, was

added dropwise 1.7 ml. of 10% sodium hydroxide solution. The mixture was allowed to stand for 2 hours, the white solid which separated was collected, washed with water, dried and crystallized from ethyl acetate giving 0.8 g. (60%) of III, m.p. 143-144°; ir 3030 and 3200 (NH), 1630 and 1500  $\text{cm}^{-1}$  (C=O), 740  $\text{cm}^{-1}$  (C-S-C).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}$ : C, 57.39; H, 4.48; N, 8.37; Cl, 10.61. Found: C, 57.38; H, 4.51; N, 8.41; Cl, 10.50.

#### B. From 2-benzylthiobenzohydrazide.

To a stirred suspension of 2.58 g. (0.01 mole) of 2-benzylthiobenzohydrazide (9) in 10 ml. of dry dioxane was added dropwise 1.13 g. (0.01 mole) of chloroacetyl chloride. An exothermic reaction took place and stirring was continued at room temperature for 3 hours. By partial evaporation of the solvent *in vacuo*, the crude product crystallized. Recrystallization from ethyl acetate gave 2.8 g. (84%) of III as white solid, m.p. 143-144°. The compound was identical to a sample obtained by method A by mixed m.p. and ir spectrum.

#### 2,2'-Dithiobis-*N*'-chloroacetylbenzhydrazide (II).

To a solution of 3.34 g. (0.01 mole) of 2,2'-dimercaptobisbenzohydrazide (8) in 20 ml. of dry dioxane was added dropwise with stirring 2.26 g. (0.02 mole) of chloroacetyl chloride. Stirring was continued 4 hours at room temperature and then the insoluble product was collected and washed with dioxane. Recrystallization from DMF-water gave 3.0 g. (60%) of colorless crystals; m.p. 243-244°; ir 3300 and 3070 (NH); 1680 and 1620 (C=O); 790  $\text{cm}^{-1}$  (Cl).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_4\text{S}_2$ : C, 44.35; H, 3.28; N, 11.49. Found: C, 44.42; H, 3.31; N, 11.48.

#### 2-Carboxymethylenethiobenzhydrazide (VI).

To a solution of 2.26 g. (0.01 mole) of *o*-carboxymethoxyphenylthioacetic acid (10) in 5 ml. of dry ethanol was added dropwise 0.5 ml. (0.01 mole) of 99% hydrazine hydrate and the mixture was heated to 80° in a water bath for 2.5 hours. The solvent was evaporated *in vacuo* and the residue neutralized with hydrochloric acid to pH 5. Upon standing at 0° for a few minutes, the crude product crystallized. Recrystallization from methanol gave 1.5 g. (65%) of colorless crystals of VI, m.p. 171-173°; ir 3190 (NH), 1690 and 1630 (C=O), 740  $\text{cm}^{-1}$  (C-S-C).

*Anal.* Calcd. for  $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_3\text{S}$ : C, 47.78; H, 4.42; N, 12.38; S, 14.15. Found: C, 47.80; H, 4.48; N, 12.44; S, 14.20.

#### 3,4,5,6-Tetrahydro-2*H*-1,4,5-benzothiadiazocine-3,6-dione (IV).

##### A. From I.

A solution of 2.44 g. (0.02 mole) of I in 150 ml. of dry DMF under a nitrogen atmosphere, was heated at 130° in an oil bath for 5 hours. The solvent was evaporated *in vacuo* to give an oil which was dissolved in a minimum amount of acetone with 10% of water. After standing overnight at 0° 0.5 g. of IV, white solid m.p. 262-264° dec., had crystallized. Further evaporation of the mother liquor to dryness and crystallization of the residue from ethanol-water afforded 0.8 g. of a second crop, m.p. 251-254° dec. After recrystallization from methanol gave 1.15 g. (total yield 55%) of pure product m.p. 265-266° dec.; ir 3200 and 3090 (NH), 1670 (C=O), 760  $\text{cm}^{-1}$  (C-S-C).

*Anal.* Calcd. for  $\text{C}_9\text{H}_8\text{N}_2\text{O}_2\text{S}$ : C, 51.92; H, 3.84; N, 13.46; S, 15.38. Found: C, 52.00; H, 3.91; N, 13.38; S, 15.29. Molecular weight, 199.

##### B. From II.

A mixture of 2.44 g. (0.005 mole) of II, 2.76 g. of anhydrous potassium carbonate and 100 ml. of acetone in a stoppered flask was stirred for 48 hours at room temperature and then filtered. The solvent was evaporated to dryness and crystallization of the residue from methanol gave 0.92 g. (44%) of IV, identical in m.p., mixed m.p. and ir spectra to a sample obtained according to method A.

#### 5,6-Dihydro-2-*o*-mercaptophenyl-4*H*-1,3,4-oxadiazin-5-one (V).

To a solution of 5.0 g. of sodium hydrosulfite and 6.66 g. of anhydrous sodium carbonate in 50 ml. of water was added 4.87 g. (0.01 mole) of II. The mixture was stirred 20 minutes at room temperature and then heated on a steam bath for 60 minutes. The solution was filtered, cooled and acidified with hydrochloric acid to pH 5.6 precipitating the crude product. Crystallization from ethanol gave 1.8 g. (43%) of yellow crystals, m.p. 221-223°; ir 3230 and 3040 (NH), 2600 (SH), 1630 and 1590 (C=O), 1110  $\text{cm}^{-1}$  (C-O-C).

*Anal.* Calcd. for  $\text{C}_9\text{H}_8\text{N}_2\text{O}_2\text{S}$ : C, 51.92; H, 3.84; N, 13.46; S, 15.38. Found: C, 51.99; H, 3.90; N, 13.37; S, 15.29. Molecular weight, 212.

#### Acid Hydrolysis of IV.

A solution of 0.1 g. of IV in 20 ml. of hydrochloric acid was refluxed for 2 hours. Cooling and filtering gave 0.11 g. (87%) of white needles, m.p. 197-198°, identified as the hydrochloride of VI and identical to an authentic sample by mixed m.p. and ir spectra.

#### Alkaline Hydrolysis of IV.

A solution of 0.3 g. of IV in 10 ml. of 10% sodium hydroxide was refluxed for 6 hours and then cooled and extracted with benzene. The aqueous layer was neutralized with 10% hydrochloric acid and evaporated *in vacuo* to dryness. The solid residue was crystallized from acetic acid giving 0.15 g. (50%) of *o*-carboxyphenylthioacetic acid (VII), m.p. 212-213°, identical with an authentic sample in mixed m.p. and ir spectra.

#### 1,4,5-Benzothiadiazocine-3,6-dione 1-Oxide (IX).

To a stirred solution of 2.08 g. (0.01 mole) of IV in 100 ml. of methanol was added a solution of 2.1 g. (0.01 mole) of sodium periodate in 20 ml. of water. The mixture was stirred for 12 hours at room temperature. The precipitated sodium iodate was removed by filtration, and the filtrate was concentrated to a small volume. On cooling, 1.5 g. (67%) of crystals was obtained. Recrystallization from methanol-ether gave IX as colorless needles, m.p. 198-200° dec.; ir 3230 and 3100 (NH), 1720 and 1630 (C=O), 1070 and 1040 (S=O), 740  $\text{cm}^{-1}$  (C-S-C).

*Anal.* Calcd. for  $\text{C}_9\text{H}_8\text{N}_2\text{O}_3\text{S}$ : C, 48.21; H, 3.57; N, 12.50; S, 14.28. Found: C, 48.27; H, 3.61; N, 12.45; S, 14.22.

#### 1,4,5-Benzothiadiazocine-3,6-dione 1,1-Dioxide (X).

To a solution of 2.08 g. of IV in 25 ml. of glacial acetic acid was added 10 ml. of 30% hydrogen peroxide and the mixture was allowed to stand at room temperature for 36 hours. The crude sulfone X crystallized and was washed with water. Recrystallization from water gave 1.8 g. (75%) of white flakes, m.p. 247-248°; ir 3240 and 3020 (NH), 1720 and 1680 (C=O), 1340 (SO<sub>2</sub>), 770  $\text{cm}^{-1}$  (C-S-C).

*Anal.* Calcd. for  $\text{C}_9\text{H}_8\text{N}_2\text{O}_4\text{S}$ : C, 45.00; H, 3.33; N, 11.66; S, 13.33. Found: C, 44.97; H, 3.39; N, 11.65; S, 13.28.

## 4,5-Dimethyl-1,4,5-benzothiadiazocine-3,6-dione (VIII).

A stirred suspension of 2.08 g. (0.01 mole) of IV in 40 ml. of acetone was dissolved by adding a solution of 0.8 g. (0.02 mole) of sodium hydroxide in 10 ml. of water; 2.4 ml. (0.038 mole) of methyl iodide was then added and the mixture was stirred for 3 hours at room temperature. Filtering gave VIII as a white crystalline product. After recrystallization from ethanol 1.6 g. (67%) of VIII was obtained, m.p. 162-163°;  $\nu$  1690 and 1600 (C=O), 770  $\text{cm}^{-1}$  (C-S-C).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ : C, 55.93; H, 5.08; N, 11.86; S, 13.55. Found: C, 55.87; H, 4.97; N, 11.91; S, 13.45.

## 4,5-Dimethyl-1,4,5-benzothiadiazocine-3,6-dione 1,1-Dioxide (XI).

## A. From VIII.

To a solution of 2.36 g. (0.01 mole) of VIII in 25 ml. of acetic acid, was added 10 ml. of 30% hydrogen peroxide and the mixture was allowed to stand at room temperature for 15 days. Partial evaporation of solvent *in vacuo* determined the separation of a white crystalline product. Recrystallization from methanol gave 2.1 g. (81%) of XI, m.p. 209-210°;  $\nu$  1700 (C=O), 1380 ( $\text{SO}_2$ ), 760  $\text{cm}^{-1}$  (C-S-C).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_4\text{S}$ : C, 49.25; H, 4.47; N, 10.44; S, 11.94. Found: C, 49.20; H, 4.50; N, 10.49; S, 11.98.

## B. From X.

A stirred suspension of 2.4 g. (0.01 mole) of X in 40 ml. of acetone was dissolved by adding a solution of 1.2 g. (0.03 mole) of sodium hydroxide in 10 ml. of water; 3.6 ml. (0.057 mole) of methyl iodide was then added and the mixture was stirred for 2 hours and filtered. The acetone was evaporated and the residual aqueous solution extracted with chloroform. The chloroform

solution was dried and evaporated *in vacuo*, the residue was crystallized from methanol giving 0.6 g. (22%) of XI, identified by mixed m.p. and ir spectrum.

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