On the Synthesis of 3,4-Dihydro-2*H*-1,2-benzothiazine 1,1-Dioxides

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The 3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxides were prepared by reduction of the corresponding 1,2-benzothiazin-2-ones with diborane. The latter were obtained by the action of primary amines on 4,5-dimethoxy-2-carbomethoxymethylbenzenesulfonyl chloride followed by basic hydrolysis and cyclization of the formed 4,5-dimethoxy-2-carbomethoxymethylbenezenesulfonamides.

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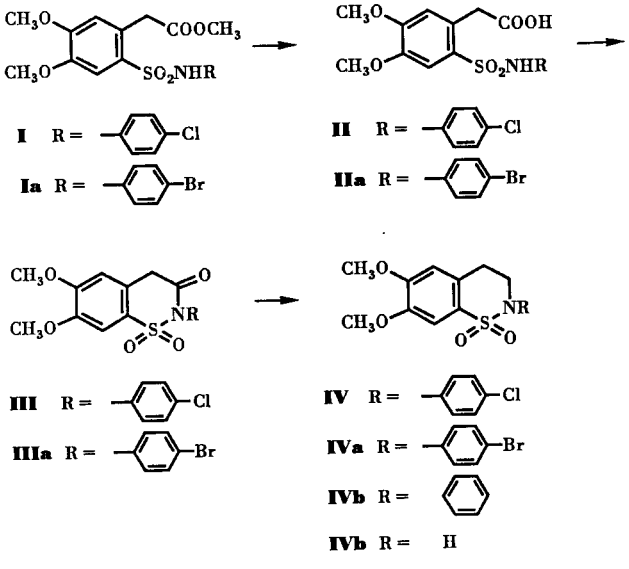
The benzothiazinone nucleus has had widespread synthetic application since some of its compounds have interesting pharmacological properties [1,2].

The general method for the synthesis of *N*-substituted 6,7-dimethoxy-1,2-benzothiazin-(4*H*)-3-one 1,1-dioxides is the cyclization of 2-carboxymethylbenzenesulfonamide in anhydrous benzene with phosphorus pentachloride at room temperature [3].



The reaction of *N*-substituted 6,7-dimethoxy-1,2-benzothiazin-(4*H*)-3-one 1,1-dioxides with lithium aluminum hydride for the formation of 3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxides **IV** was unsuccessful. However diborane is a mild reducing agent for the conversion of amide into the corresponding amines [4], therefore benzothiazinone with diborane in tetrahydrofuran solution produced *N*-substituted 6,7-dimethoxy-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxides **IV-IVc** in good yields.

EXPERIMENTAL

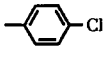
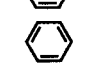
Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 29B spectrophotometer with polystyrene as the reference peak. The C, H, N, elemental analyses were performed in the Laboratory of Organic Chemistry, University of Salonika, Greece.

General Procedure for the Synthesis of the *N*-Substituted Sulfonamides.

Three mmoles of 4,5-dimethoxy-2-carbomethoxymethylbenzenesulfonyl chloride were dissolved in 25 ml of anhydrous benzene and to the solution was added 6 mmoles of the aromatic amine. The reaction mixture was refluxed for 2 hours. After this time the solvent was removed and ice water was added to produce the corresponding sulfonamides in 90-95% yield. The sulfonamides showed strong absorption in the ir spectra at 1740 cm^{-1} ($COOCH_3$).

Table I

3,4-Dihydro-2*H*-1,2-benzothiazine 1,1-Dioxides

Compound	NR	Mp °C	Formula	Yield %	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
IV		171-172	$C_{16}H_{16}ClNO_4S$	84	54.31	4.52	3.96	54.41	4.55	3.69
IVa		163-165	$C_{16}H_{16}BrNO_4S$	82	48.24	4.02	3.51	48.31	4.11	3.58
IVb		174-175	$C_{16}H_{17}NO_4S$	87	60.20	5.37	4.40	60.10	5.72	4.30
IVc	H	166-167	$C_{10}H_{13}NO_4S$	83	49.38	5.35	5.77	49.35	5.50	5.60

Recrystallization solvents: **IV, IVa, IVb** (methanol-chloroform), **IVc** (methanol).

N-p-Chlorophenyl-4,5-dimethoxy-2-carbomethoxymethylbenzenesulfonamide (**I**).

This compound was crystallized from methanol, mp 158-160°.

Anal. Calcd. for $C_{17}H_{18}ClNO_6S$: C, 51.06; H, 4.50; N, 3.50. Found: C, 51.26; H, 4.60; N, 3.39.

N-p-Bromophenyl-4,5-dimethoxy-2-carbomethoxymethylbenzenesulfonamide (**Ia**).

This compound was crystallized from methanol, mp 152-154°.

Anal. Calcd. for $C_{17}H_{18}BrNO_6S$: C, 45.84; H, 4.05; N, 3.15. Found: C, 45.50; H, 4.20; N, 3.12.

Procedure for the Hydrolysis of the *N*-Substituted Sulfonamide Esters.

To a solution of 50% methanol containing 1 g of potassium hydroxide, 1 g of the esters **I** or **Ia** was added and the mixture was refluxed for 2 hours. The solution was poured into ice water and acidified with concentrated hydrochloric acid. The precipitate was collected by filtration to give acids **II** or **IIa** in quantitative yield; ir: ν max 1710 cm^{-1} (COOH).

N-p-Chlorophenyl-4,5-dimethoxy-2-carboxymethylbenzenesulfonamide (**II**).

This compound was crystallized from methanol, mp 191-192°.

Anal. Calcd. for $C_{16}H_{16}ClNO_6S$: C, 49.80; H, 4.15; N, 3.63. Found: C, 49.55; 4.30; N, 3.47.

N-p-Bromophenyl-4,5-dimethoxy-2-carboxymethylbenzenesulfonamide (**IIa**).

This compound was crystallized from methanol, mp 193-194°.

Anal. Calcd. for $C_{16}H_{16}BrNO_6S$: C, 44.65; H, 3.72; N, 3.25. Found: C, 44.46; H, 3.64; N, 3.20.

6,7-Dimethoxy-2*H*-1,2-benzothiazin-(4*H*)-3-one 1,1-Dioxide.

To a solution of **II** or **IIa** (1 g) in 15 ml of anhydrous benzene and phosphorus pentachloride (2 g) was added and the mixture was allowed to stand for 2 hours at room temperature. The solvent was evaporated and ice water was added. The resulting precipitate was collected by filtration, washed several times with water and dried to produced benzothiazines **III** or **IIIa** in 85-90% yield; ir: ν max 1700-1710 cm^{-1} (CO).

N-p-Chlorophenyl-6,7-dimethoxy-1,2-benzothiazin-3-one 1,1-Dioxide (**III**).

This compound was crystallized from methanol-chloroform, mp 204-205°.

Anal. Calcd. for $C_{16}H_{14}ClNO_5S$: C, 52.24; H, 3.81; N, 3.81. Found: C, 51.96; H, 3.54; N, 3.74.

N-p-Bromophenyl-6,7-dimethoxy-1,2-benzothiazin-3-one 1,1-Dioxide (**IIIa**).

This compound was crystallized from methanol-chloroform, mp 207-208°.

Anal. Calcd. for $C_{16}H_{14}BrNO_5S$: C, 46.74; H, 3.39; N, 3.39. Found: C, 46.42; H, 3.32; N, 3.33.

General Procedures for the Synthesis of 3,4-Dihydro-2*H*-1,2-benzothiazine 1,1-dioxides.

To a solution 30 ml of 1*M* borane in tetrahydrofuran in a 200 ml flask was added 0.5 g of *N*-substituted or *N*-unsubstituted benzothiazinone [3]. The solution was then refluxed for 10 hours. The flask was permitted to cool to room temperature. The solvent was removed under reduced pressure at room temperature. Water was added slowly to the residue, which was then extracted several times with chloroform. The solvent was removed *in vacuo* after washing with water and drying over sodium sulfate and recrystallized from the appropriate solvent. The prepared compounds did not show carbonyl absorption and are reported in Table I.

REFERENCES AND NOTES

[1] P. Catsoulacos and Ch. Camoutsis, *J. Heterocyclic Chem.*, **16**, 1503 (1979).

[2] J. G. Lombardino and D. E. Kuhle, *Adv. Heterocyclic Chem.*, **28**, 73 (1981).

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[4] H. C. Brown and P. Heim, *J. Am. Chem. Soc.*, **86**, 3566 (1964).