Thiazo Compounds. Derivatives of 4,5-Dihydro-7,8-dimethoxybenzothiazepin-3-one 1,1-Dioxides

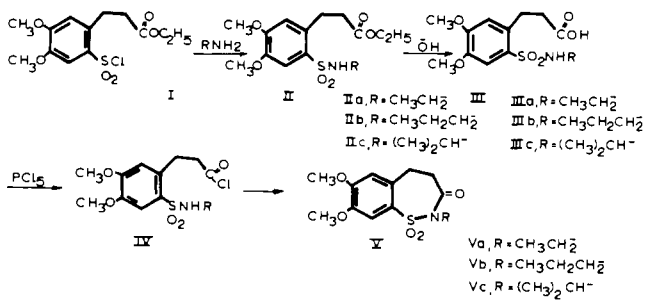
Panayotis Catsoulacos* and Charalabos Camoutsis
Department of Chemistry, Nuclear Research Center "Demokritos" Aghia Paraskevi Attikis, Athens, Greece

N-Substituted 4,5-dihydro-7,8-dimethoxy-1,2-benzothiazepin-3-one 1,1-dioxides (V) were prepared by cyclization of the 2-chlorocarboxyethyl-4,5-dimethoxybenzenesulfonamides. The latter were obtained by the action of phosphorus pentachloride on the 2-carboxyethyl-4,5-dimethoxybenzenesulfonamides (III) which in turn have been synthesized from 2-carboethoxyethyl-4,5-dimethoxybenzene sulfochloride (I) and aliphatic amines.

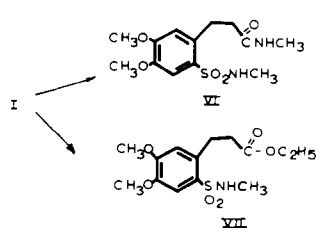
In a previous paper we reported that the treatment of 4,5-dimethoxy-2-carboxymethylbenzenesulfonamides with phosphorus pentachloride in anhydrous benzene gave N-substituted 6,7-dimethoxy-1,2-benzothiazin(4*H*)-3-one 1,1-dioxides (*3*).

This work has been extended to the synthesis of benzothiazinones since related structure compounds indicated interesting pharmacological results (*1, 2, 5–7*).

The substituted sulfonamides were prepared by the action of aliphatic amines on 2-carboethoxyethyl-4,5-dimethoxybenzene sulfochloride (*4*) in anhydrous benzene. Basic hydrolysis of the ester III gave in good yield the corresponding acids. The latter were converted to the acid chlorides with phosphorus pentachloride. When acid chlorides IV were heated in xylene then benzothiazepinones V were obtained in up to 60% yield.

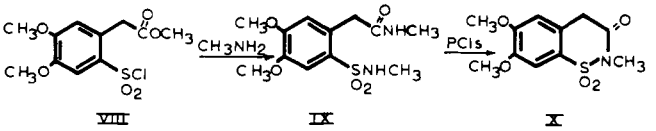


Reaction of 2-carboethoxyethyl-4,5-dimethoxybenzene sulfochloride in dioxane with excess aqueous methylamine at room temperature resulted in a product VI readily isolated. The structure of the sulfonamide VI was confirmed by its analytical and spectral data, 3200 (SO_2NHCH_3), 3440 ($CONHCH_3$), and 1655 cm^{-1} (C=O).



When the above sulfochloride was treated with 2 equiv of methylamine then sulfonamide ester VII was obtained. The structure of the latter was apparent from elemental analysis and infrared spectrum (ν_{max} 3300 (NH) and 1720 cm^{-1} (C=O)).

In an analogous way, the 2-carbomethoxymethyl-4,5-dimethoxybenzene sulfochloride VIII was treated with excess methylamine to give sulfonamideamide IX which then was cyclized to the *N*-methyl-6,7-dimethoxy-1,2-benzothiazin(4*H*)-3-one 1,1-dioxide, X, with phosphorus pentachloride.



Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 521 in solid phase potassium bromide. NMR spectra were determined with a Varian Associates A-60 instrument using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Department, "Demokritos".

General Procedure for the Preparation of the N-Substituted Sulfonamides (II). To a flask containing 3 mmol of I (*4*) in 20 mL of anhydrous benzene, 6 mmol of propylamine or isopropylamine was added and the reaction mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure and ice water was added to yield the corresponding sulfonamides. Elemental analysis (C, H, N) in agreement with theoretical values was obtained and submitted for review.

4,5-Dimethoxy-2-carboethoxyethylbenzenepropylsulfonamide (IIb). This compound, mp 92–93 °C, was crystallized from methanol, 94% yield: ν_{max} 3280 (NH), 1730 (CO), 1320 and 1140 cm^{-1} (SO_2).

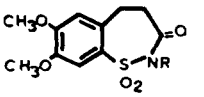
4,5-Dimethoxy-2-carboethoxyethylbenzeneisopropylsulfonamide (IIc). This compound mp 124–125 °C was crystallized from methanol, 83% yield: ν_{max} 3270 (NH), 1720 (CO), 1300 and 1120 cm^{-1} (SO_2).

4,5-Dimethoxy-2-carboethoxyethylbenzeneethylsulfonamide (IIa). In a 100-mL three-necked flask fitted with stirrer and two addition funnels 3.365 g of sulfochloride in 25 mL of dioxane was placed. With stirring, a solution of 3.2 g of sodium hydroxide in 10 mL of water and a solution of 8.15 g of ethylamine hydrochloride in 30 mL of water were added dropwise. After the addition, the mixture was heated under reflux for 30 min. Then it was poured into ice water and the precipitate was collected by filtration to give compound IIa, 2.14 g (62%), mp 86–87 °C (methanol): ν_{max} 3310 (NH), 1720 (CO), 1315 and 1130 cm^{-1} (SO_2).

4,5-Dimethoxy-2-methylamidoethylbenzenemethylsulfonamide (VI). To a flask containing 2.8 g of sulfochloride I an excess of 40% solution of methylamine (15 mL) was added. The mixture was agitated at room temperature for 2 h. The excess of amine was evaporated under reduced pressure and cold water was added to the residue. The precipitate was collected by filtration to give compound VI, 1.6 g, mp 114–116 °C (ether–ethyl acetate): ν_{max} 3440 ($CONHCH_3$), 3200 ($NHSO_2$), and 1655 cm^{-1} (CO).

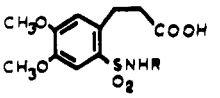
4,5-Dimethoxy-2-carboethoxyethylbenzenemethylsulfonamide (VII). To a solution of 10 mL of dioxane containing 10 mmol (3.365 g) of sulfochloride I, 20 mmol of methylamine 40% was added and the mixture was refluxed for 1 h. The solution was poured into ice water. The resulting precipitate was

Table I. 2-Carboxyethyl-4,5-dimethoxybenzenesulfonamides



No.	R	Mp, °C	Yield, %	Solvent for recryst	Formula
IIIa	C_2H_5	156–157	80	CH_3OH	$C_{13}H_{19}NO_6S$
IIIb	$CH_3CH_2CH_2$	150–151	86	CH_3OH	$C_{14}H_{21}NO_6S$
IIIc	$(CH_3)CH$	162–163	78	CH_3OH	$C_{14}H_{21}NO_6S$

Table II. N-Substituted 4,5-Dihydro-7,8-dimethoxy-1,2-benzothiazepin-3-one 1,1-Dioxide



No.	R	Mp, °C	Yield, %	Formula	IR bands (cm^{-1})
Va	C_2H_5	135–137	96	$C_{13}H_{17}NO_5S$	1690 (CO), 1325, 1135 (SO_2)
Vb	$CH_3CH_2CH_2$	118–119	63	$C_{14}H_{19}NO_5S$	1695 (CO), 1330, 1140 (SO_2)
Vc	$(CH_3)_2CH$	119–120	60	$C_{14}H_{19}NO_5S$	1680 (CO), 1340, 1140 (SO_2)

Table III. NMR of N-Substituted 4,5-Dihydro-7,8-dimethoxy-1,2-benzothiazepin-3-one 1,1-Dioxide

No.	C_9–H τ	C_6–H τ	CH_3O τ	CH_2CH_2 τ
Va	2.47 s	3.15 s	5.97 s	6.53 m, 6.1 (CH_2CH_3), 8.82 (t, CH_2CH_3)
Vb	2.47 s	3.17 s	5.97 s	6.53 m, 6.15 (m, $CH_2CH_2CH_3$), 8.40 (m, $CH_2CH_2CH_3$), and 9.16 (t, $CH_2CH_2CH_3$)
Vc	2.48 s	3.20 s	5.98 s	6.60 m, 5.12 [m, $CH(CH_3)$], 8.55 and 8.67 ($2CH_3$)

collected by filtration to yield compound VII (2.9 g), mp 114–116 °C (methanol).

4,5-Dimethoxy-2-methylamidomethylbenzenemethylsulfonamide (IX). To a flask containing 15.4 g of sulfochloride VIII (*3*) an excess 40% solution of methylamine was added. The mixture was agitated at room temperature for 2 h. Then the excess of amine was evaporated under reduced pressure and cold water was added to the residue. The precipitate was collected by filtration to give compound IX (13.2 g), mp 177–179 °C (CH_3OH–$CHCl_3$): ν_{max} 3380 (NHCO), 3100 (SO_2NH), 1650 (CO), 1310 and 1150 cm^{-1} (SO_2).

N-Methyl-6,7-dimethoxy-1,2-benzothiazin(4H)-3-one 1,1-Dioxide (X). IX (10 g) was added to 100 mL of anhydrous benzene phosphorus pentachloride (25 g), and the mixture was allowed to stand for 3 h at room temperature. The solvent was then evaporated on a steam bath and cold water was added. The resulting precipitate was collected by filtration, washed several times with water, and dried to yield X (8.85 g), mp 183–184 °C (CH_3OH): ν_{max} 1700 (CO), 1320 and 1150 cm^{-1} (SO_2).

General Procedure for the Hydrolysis of the N-Substituted Sulfonamide Esters. To a solution of 50% aqueous methanol containing 1 g of potassium hydroxide, 1 g of ester II was added, and the mixture was refluxed for 3 h. The solution was poured into ice water and acidified with concentrated hydrochloric acid. The resulting precipitate was collected by filtration to yield compounds III. All of the acid sulfonamides obtained showed strong absorption at 3200–3290 (NH) and 1700–1715 cm^{-1} (CO). The compounds prepared are summarized in Table I.

All of the compounds gave elemental analyses (C, H, N) within ±0.45 of the calculated values.

Procedure for the Preparation of N-Substituted 4,5-Dihydro-7,8-dimethoxy-1,2-benzothiazepin-3-one 1,1-Dioxide. 4,5-Dimethoxy-2-carboxyethylbenzenesulfonamide III (1 g) was added to 30–40 mL of anhydrous benzene phosphorus pentachloride (2.5 g), and the mixture was agitated for 5 h at room temperature. The resulting precipitate was filtered, washed with anhydrous benzene, and dried over phosphorus pentoxide.

Five-hundred milligrams of the above prepared acid chloride was added to 10 mL of anhydrous xylene and heated for 20 h. Then the solvent was evaporated and the residue crystallized from methanol. The compounds prepared are summarized in Table II.

All of the compounds gave elemental analyses (C, H, N) within ±0.45 of the calculated values.

Literature Cited

(1) Bertani, M., Dare, P., Radaelli, R., Sianesi, E., *Chem. Ber.*, **103**, 1992 (1970).
(2) Catsoulacos, P., *Chim. Chron.*, **3**, 129 (1974).
(3) Catsoulacos, P., *J. Heterocycl. Chem.*, **8**, 947 (1971).
(4) Catsoulacos, P., Camoutsis, Ch., *J. Heterocycl. Chem.*, in press.
(5) Lombardino, J. G., Wiseman, E. H., *J. Med. Chem.*, **14**, 973 (1971).
(6) Magistrelli, M. J., Massarani, E., Radaelli, R., Sianesi, E., *J. Med. Chem.*, **16**, 1133 (1973).
(7) Massarani, E., Setricar, I., Sianesi, E., German Patent, 2 022 694 (1970).

Received for review July 7, 1976. Accepted January 15, 1977.