Synthesis of Some *N*-Substituted 4,5-Dihydro-7,8-dimethoxybenzothiazepin-3-one 1,1-Dioxides

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Reaction of ethyl 3,4-dimethoxyphenylpropionate with chlorosulfonic acid yielded 2-carboethoxyethyl-3,4-dimethoxybenzene sulfochloride, which was converted to 2-carboethoxyethyl-3,4-dimethoxybenzenesulfonamides by the action of ammonia or substituted aromatic amines. Alkaline hydrolysis of these sulfonamide esters furnished the corresponding acids. The reaction of acids with phosphorus pentachloride resulted in the key intermediates, the chlorocarboxyethyl-3,4-dimethoxybenzenesulfonamides. The latter was cyclized to *N*-substituted 4,5-dihydro-7,8-dimethoxybenzothiazepine-3-one 1,1-dioxide. Reactions of benzothiazepinone ring and ir and nmr spectra are described.

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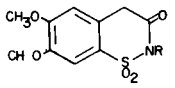
In earlier work in this laboratory it was found that the treatment of various 4,5-dimethoxy-2-carboxymethylbenzenesulfonamides with phosphorus pentachloride in anhydrous benzene gave *N*-substituted-6,7-dimethoxy-1,2-benzothiazin-4*H*(3)one dioxides (**1**) (1-3).



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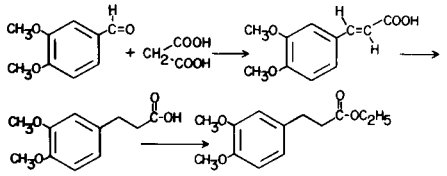
In recent publications compounds of these structures have shown interesting pharmacological properties (4-8).

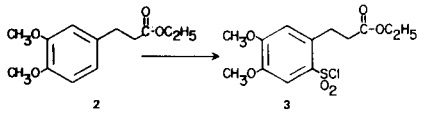
In our current research program we were interested in thiazo compounds of type **1** and particularly in 1,2-benzothiazepin-3-one 1,1-dioxide in order to examine their anti-inflammatory and central nervous system activity.

A survey of the literature revealed that there are no convenient methods to prepare this type of compound, because of the difficult availability of the required starting material, 2-carboethoxyethylbenzenesulfonyl chloride or the experimental conditions of known methods are inconvenient. In view of its similarity to 2-carboethoxymethylbenzenesulfonyl chloride, our attention was directed to the possibility of chlorosulfonation of the 3,4-dimethoxyphenylpropionic ester, since the position *para* to one of the methoxy groups is activated.

The dimethoxyphenylpropionic ester was obtained by the reduction of 3,4-dimethoxycinnanic acid (9) which was prepared by the Knoevenagel reaction of 3,4-dimethoxybenzaldehyde with malonic acid (10) following esterification.



However, direct chlorosulfonation of the latter at low temperature afforded 4,5-dimethoxy-2-carboethoxyethylbenzenesulfonyl chloride (3) in 50% yield.



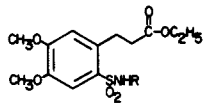
2 **3**

The structure of compound **3** was apparent from elemental analysis, ir spectrum [ν max: 1730 (C=O) and 1355, 1160 cm^{-1} due to the symmetric and antisymmetric vibrations of the two SO bonds] and nmr (τ 2.38 and 2.9 two aromatic protons, a quartet at τ 5.8 for $CO\boldsymbol{CH_2}CH_3$, two multiplets centered at τ 6.5 and 7.2 correspond to CH_2CH_2 and a triplet at τ 8.52 for $COCH_2\boldsymbol{CH_3}$).

For the preparation of 2-carboethoxyethyl-3,4-dimethoxybenzenesulfonamide (**4a**), two synthetic routes were utilized. In the first of these, the sulfochloride (**3**) was fused with ammonium carbonate and gave the expected compound in low yield. In the second, treatment of the sulfochloride with ammonia in purified dioxane, resulted

Table I

2-Carboethoxyethyl-4,5-dimethoxybenzenesulfonamides



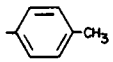
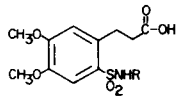
Compound No.	R	Yield %	M.p. °C	Recrystallization Solvent	Formula	Analyses % Calcd. C	H	N	Found C	H	N
4a	H	75	148-149	Methanol	$C_{13}H_{19}NO_6S$	49.21	5.99	4.43	48.84	6.40	4.21
4b		96	122-123	Methanol	$C_{19}H_{23}NO_6S$	58.01	5.85	3.56	58.26	6.07	3.40
4c		98	106-107	Methanol	$C_{20}H_{25}NO_6S$	58.96	6.14	3.44	58.79	6.42	3.36
4d		85	126-127	Methanol	$C_{19}H_{22}ClNO_6S$	53.33	5.14	3.27	53.53	5.55	3.11
4e		95	118-120	Methanol	$C_{19}H_{22}BrNO_6S$	48.30	4.65	2.95	48.19	4.75	2.87
4f		92	195-196	Chloroform-methanol	$C_{18}H_{22}N_2O_6S$	54.82	5.58	7.10	54.40	6.00	6.86

Table II

2-Carboxyethyl-4,5-dimethoxybenzenesulfonamides



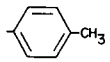
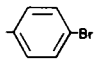
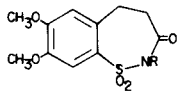
Compound No.	R	Yield %	M.p. °C	Recrystallization Solvent	Formula	Analyses % Calcd. C	H	N	Found C	H	N
5a	H	54	204-205	Methanol	$C_{11}H_{15}NO_6S$	45.67	5.18	4.84	45.92	5.23	4.76
5b		90	163-165	$CH_3COOC_2H_5$	$C_{17}H_{19}NO_6S$	55.89	5.20	3.83	55.85	5.06	3.79
5c		97	154-155	Methanol	$C_{18}H_{21}NO_6S$	56.99	5.54	3.69	56.48	5.30	3.58
5d		95	186-187	Methanol	$C_{17}H_{18}ClNO_6S$	51.06	4.55	3.54	51.39	4.60	3.32
5e		94	175	$CH_3COOC_2H_5$	$C_{17}H_{18}BrNO_6S$	45.94	4.05	3.15	45.92	4.50	3.06
5f		87	255-256	Chloroform	$C_{16}H_{18}N_2O_6S$	52.45	4.91	7.65	52.55	5.19	7.47

Table III

N-Substituted 4,5-Dihydro-7,8-dimethoxy-1,2-benzothiazepin-3-one 1,1 Dioxides



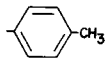
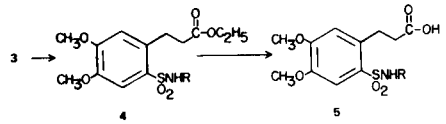
Compound No.	R	Yield %	M.p. °C	Recrystallization Solvent	Formula	Analyses % Calcd. C	H	N	Found C	H	N
7a	H	68	205-206	Methanol	$C_{11}H_{13}NO_5S$	48.70	4.79	5.16	48.63	4.85	5.20
7b		77	183-184	$CH_3COOC_2H_5$	$C_{17}H_{17}NO_5S$	58.79	4.89	4.03	58.73	5.20	3.94
7c		70	188-189	Chloroform-methanol	$C_{18}H_{19}NO_5S$	59.83	5.26	3.87	59.49	5.66	3.65
7d		65	152-153	Chloroform-methanol	$C_{17}H_{16}ClNO_5S$	53.47	4.19	3.67	52.99	4.03	3.58
7e		55	161-162	Methanol	$C_{17}H_{16}BrNO_5S$	47.88	3.75	3.28	48.21	4.20	3.20
7f		62	183-184	Chloroform-methanol	$C_{16}H_{16}N_2O_5S$	55.17	4.59	8.04	54.86	4.54	7.82

Table IV

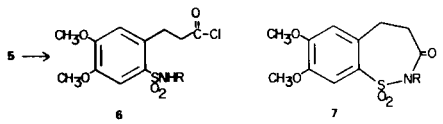
Compound No.	NH Stretching vibrations (cm^{-1})	C=O Stretching vibrations (cm^{-1})	S-O Stretching vibrations (cm^{-1})
4a	3340, 3250	1705	1325, 1140
4b	3230	1715	1340, 1160
4c	3280	1710	1335, 1135
4d	3240	1720	1320, 1130
4e	3240	1725	1320, 1135
4f	----	1730	1355, 1125
5a	3380, 3250	1740	1300, 1125
5b	3290	1715	1340, 1145
5c	3290, 3140	1730	1350, 1130
5d	3300, 3130	1700	1315, 1145
5e	3290, 3120	1690	1305, 1130
5f	---	1675	1340, 1180
7a	3230	1700	1330, 1145
7b	----	1710	1350, 1130
7c	----	1710	1350, 1120
7d	----	1700	1350, 1130
7e	----	1700	1350, 1130
7f	----	1720	1345, 1130

The ir spectra of acid chlorides showed strong absorption at 1800 cm^{-1} (C=O).



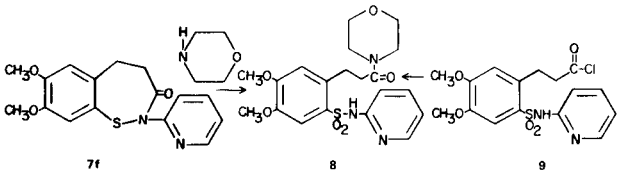
in sulfonamide (**4a**), which was obtained in 75% yield.

The substituted sulfonamides were prepared by the action of aromatic amines on 2-carboethoxyethyl-3,4-dimethoxybenzenesulfochloride in anhydrous benzene. Hydrolysis of **4** with base formed the corresponding sulfonamido-acids (**5**). The latter were transformed to chlorocarboxyethyl-3,4-dimethoxybenzenesulfonamides by the action of phosphorus pentachloride in anhydrous benzene. When **6** in anhydrous xylene was heated under reflux, the benzothiazepinones (**7**) were obtained in good yields.



Treatment of **7** with sodium hydroxide produced the sodium salt of the corresponding acid (**5**), which upon acidification gave the free acid.

When compound **7f** was treated with morpholine, 4,5-dimethoxy-2-morpholinocarboxamidoethylbenzene-*N*-(2-pyridyl)sulfonamide was obtained. The structure of **8** was confirmed by its independent synthesis from 4,5-dimethoxychlorocarboxyethylbenzene-*N*-(2-pyridyl)sulfonamide and morpholine.



Compound **7f** was tested in vitro for antiinflammatory activity (12) using the Tomlinson, *et al.*, (11) method.

EXPERIMENTAL

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 of hexadeuterodimethylsufloxide as a solvent and tetramethylsilane as the internal standard. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Department of N.R.C. "DEMOCRITOS".

4,5-Dimethoxy-2-carboethoxyethylbenzenesulfonyl Chloride (**3**).

Twenty two g. of ester **2** were placed in a three-necked flask fitted with a mechanical stirrer, condenser and addition funnel, both protected from moisture. Chlorosulfonic acid (25 ml.) was added dropwise over a period of 40 minutes, while the mixture was stirred at -5° to 0°. The reaction was completed at room temperature in one hour. It was then poured into ice-water and immediately extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure to yield a residue which on recrystallization from ethyl acetate-*n*-hexane gave compound **3** in 50% yield, m.p. 54-55°; ir: ν max 1730 cm^{-1} ($COOC_2H_5$).

Anal. Calcd. for $C_{13}H_{17}ClSO_6$: C, 46.36; H, 5.05. Found: C, 46.43; H, 5.10.

General Method for the Preparation of the *N*-Substituted Sulfonamides (**4**).

Table V

Nmr of 4,5-Dimethoxy-2-carboethoxyethylbenzenesulfonamides

Compound No.	C_6-H	C_3-H	CH_2CH_3	CH_3O	CH_2CH_2	CH_2CH_3
4a	2.38 s	3.05 s	5.87 q	6.00,6.05 s	6.60,7.2 m	8.75 t
4b	2.53 s	3.08 s	5.73 q	6.05,6.17 s	6.60,7.2 m	8.77 t
4c	2.55 s	3.10 s	5.80 q	6.05,6.18 s	6.65,7.25 m	8.77 t
4d	2.55 s	3.08 s	5.83 q	6.03,6.15 s	6.6, 7.25 m	8.75 t
4e	2.55 s	3.10 s	5.80 q	6.04,6.15 s	6.63,7.25 m	8.76 t
4f	2.20 s	3.10 s	6.02 q	5.98,6.03 s	6.65,7.35 m	8.95 t

Table VI

Nmr of *N*-Substituted
4,5-Dihydro-7,8-dimethoxy-1,2-benzothiazepin-3-one 1,1-Dioxide

Compound No.	C_9-H	C_6-H	CH_3O	CH_2CH_2
7a	2.7 s	2.93 s	6.13 s	6.83 m
7b	2.77 s	2.88 s	6.14,6.23 s	6.53 s
7c	2.85 s	3.0 s	6.12,6.22 s	6.55 s
7d	2.77 s	2.85 s	6.10,6.20 s	6.53 s
7e	2.77 s	2.85 s	6.12,6.22 s	6.53 s
7f	2.73 s	2.88 s	6.13,6.20 s	6.53 s

Three mmoles of **3** were dissolved in 20 ml. of anhydrous benzene and to this solution was added 6 mmoles of aromatic amine. The reaction mixture was refluxed for 3 hours. After this time the solvent was removed under reduced pressure and ice-water was added to produce the corresponding sulfonamides. The compounds prepared are reported in Table I.

4,5-Dimethoxy-2-carboethoxyethylbenzenesulfonamide (**4a**).

Three g. of **3** were dissolved in 25 ml. of purified dioxane and the solution was saturated with ammonia. The mixture was allowed to stand at room temperature for 3 hours. Water was added and the precipitate collected by filtration to give compound **4** in 75% yield.

Procedure for the Hydrolysis of the *N*-Substituted Sulfonamide Esters (**5**).

To a solution of 50% aqueous methanol containing 2 g. of potassium hydroxide, 2 g. of ester **4** were added and the mixture was refluxed for 3 hours. The solution was poured into ice-water and acidified with concentrated hydrochloric acid. (To obtain compound **5f**, the solution was acidified with acetic acid.) The resulting precipitate was collected by filtration to yield substances **5**. The compounds prepared are reported in Table II.

General Procedure for the Preparation of *N*-Substituted 4,5-Dihydro-7,8-dimethoxy-1,2-benzothiazepin-3-one 1,1-Dioxides (**7**).

To a solution of **5** (2 g.) in 100 ml. of anhydrous benzene, phosphorus pentachloride (4 g.) was added and the mixture was allowed to stand for 5 hours at room temperature (for compound **5a** the mixture was agitated at room temperature for 100 hours), and the resulting precipitate was filtered, washed with anhydrous benzene and dried over phosphorus pentoxide.

One g. of the above prepared acid chloride was added to 20 ml. of anhydrous xylene and heated under reflux for 20 hours. Then the solvent was evaporated and the residue crystallized from the appropriate solvent. (Compound **7f** was isolated after treatment with aqueous ammonia.) The dihydrobenzothiazepinones obtained are reported in Table III.

Procedure for the Hydrolysis of the *N*-Substituted Dihydrobenzothiazepinones.

To a solution of 50% methanol (30 ml.) containing 0.1 g. of potassium hydroxide, 0.1 g. of **7b** or **7d** was added and the mixture was stirred at room temperature for 4 hours. The solution was poured into ice-water and acidified with dilute hydrochloric acid. The resulting precipitate was collected by filtration to yield compound **5b** or **5d** quantitatively, identical by comparison of their melting points and infrared spectra to authentic compounds.

4,5-Dimethoxy-2-morpholinocarboxamidoethylbenzene-*N*-(2-pyridyl)sulfonamide (**8**).

Method A.

A solution of 780 mg. of dihydrobenzothiazepinone (**7f**) in 10 ml. of anhydrous toluene and 5 ml. of morpholine was refluxed for 20 hours. The solvent with the excess of amine was evaporated under reduced pressure and the residue was recrystallized from chloroform-ethanol to give **8** (800 mg.), m.p. 182-183°; ir: ν max 1630 cm^{-1} (C=O).

Anal. Calcd. for $C_{20}H_{25}N_3O_6S$: C, 55.20; H, 5.75; N, 9.65. Found: C, 55.74; H, 5.82; N, 9.49.

Method B. From 4,5-Dimethoxychlorocarboxyethylbenzene-*N*-(2-pyridine)sulfonamide.

To a flask containing 800 mg. of acid chloride, an excess of morpholine (5 ml.) was added and the reaction mixture was heated on a steam bath for one hour. The amine was evaporated and water was added to yield a clear solution which was extracted with chloroform. The organic layer was washed with water and dried over magnesium sulfate. Removal of the solvent produced a semisolid that was crystallized twice from chloroform-methanol to yield **8**, identical by comparison of melting point and infrared spectrum to the compound prepared by Method A.

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(12) The results are summarized: concentration, 10^{-4}M; percent inhibition, 5-12%.