Synthesis of Some *N*-Substituted 6,7-Dimethoxy-1,2-benzothiazin(4*H*)-3-one 1,1-Dioxides

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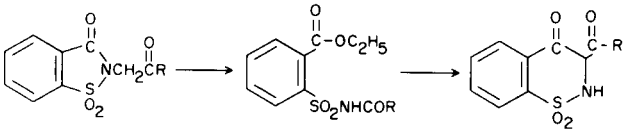
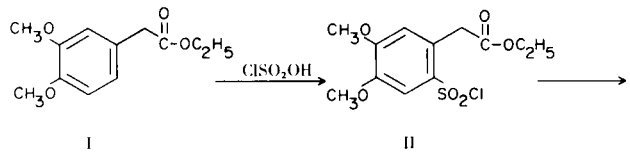
Substituted 1,2-benzothiazin-3-ones have been prepared by cyclization of 4,5-dimethoxy-2-carboethoxymethybenzenesulfonamides. The latter were obtained by the action of ammonia and primary and secondary amines on 4,5-dimethoxy-2-carboethoxymethylbenzenesulfonyl chloride which in turn was obtained from ethyl 3,4-dimethoxyphenylacetate and chlorosulfonic acid.

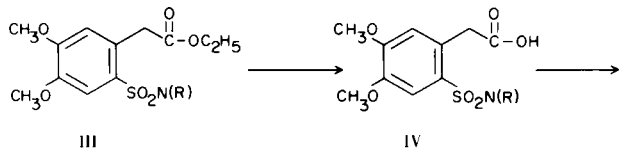
It has been recently demonstrated that substituted 1,2-benzothiazin-4-one 1,1-dioxide derivatives are of pharmacological interest (1-2). These compounds can be prepared from *N*-acetonylsaccharin by ethanolysis of the carboxamide linkage, followed by a Dieckmann cyclization (3-4).



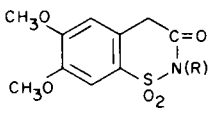
In the course of our work on thia-azo compounds (5-7) we have attempted the synthesis of some sulfonamides to be studied as diuretics as well as some substituted 1,2-benzothiazin-3-ones for pharmacological purposes.



I II



III IV



V

Since the position *para* to one of the methoxy groups in ethyl 3,4-dimethoxyphenylacetate (I) is activated, direct chlorosulfonation at low temperature afforded 4,5-dimethoxy-2-carboethoxymethylbenzenesulfonyl chloride (II).

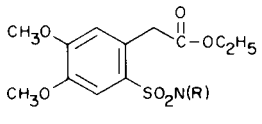
We found that II reacts readily with primary and secondary amines to give excellent yields of the corresponding sulfonamides. Compound IIIa was obtained by fusing II together with ammonium carbonate at about 210°. Basic hydrolysis of the esters III gave a yield of up to 80% of the corresponding acids IV. In the case of 4,5-dimethoxy-2-carboethoxymethylbenzenesulfonamide (IIIa) after hydrolysis, we isolated 6,7-dimethoxy-1,2-benzothiazin(4*H*)-3-one dioxide (Va). Compounds IVa, IVb and IVc were cyclized at a temperature above their melting point or by heating in anhydrous benzene with phosphorus pentachloride.

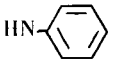
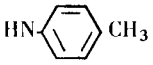
Both nuclear magnetic resonance and the infrared spectra supported their structure.

In particular, the infrared spectra demonstrated the following results:

Ref. No.	S-O stretching vibration cm^{-1}		NH stretching vibration cm^{-1}	
IIIa	1140	1320	3440	3300
IIIb	1140	1325	----	----
IIIc	1140	1310	----	----
IIId	1125	1310	----	3260
IIIe	1150	1335	----	3260
IIIf	1150	1340	----	3290
IVa	1125	1335	----	3280
IVb	1150	1350	----	3320
IVc	1150	1340	----	3340
Va	1155	1330	----	----
Vb	1140	1335	----	----
Vc	1150	1340	----	----
Vd	1150	1340	----	----

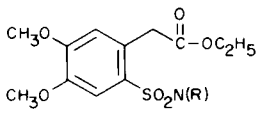
TABLE I

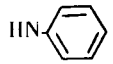


Compound	N(R)	M.p. °C	Formula	Yield %	Calcd. % C	H	N	Found % C	H	N
IIIa	NH_2	151-152	$C_{12}H_{17}NO_6S$	72	47.52	5.61	4.62	48.16	5.53	4.61
IIIb		100-101	$C_{17}H_{25}NO_6S$	95	54.98	6.73	3.77	55.34	6.80	3.77
IIIc		105-106	$C_{16}H_{23}NO_7S$	92	51.47	6.16	3.75	51.76	6.32	3.64
IIId	$HNCH(CH_3)_2$	100-101	$C_{15}H_{23}NO_6S$	90	52.17	6.66	4.05	52.51	6.94	4.09
IIIe		170-172	$C_{18}H_{21}NO_6S$	93	56.99	5.54	3.69	57.06	5.57	3.64
IIIf		120-121	$C_{19}H_{23}NO_6S$	96	58.01	5.85	3.56	58.40	5.95	3.60

Recrystallization solvents: IIIa, IIIb, IIIc, IIIf (methanol), IIId (Hexane-ethylacetate), IIIe (methanol-chloroform).

TABLE II



Compound	N(R)	M.p. °C	Formula	Yield %	Calcd. % C	H	N	Found % C	H	N
IVa	$HNCH(CH_3)_2$	155-157	$C_{13}H_{19}NO_6S$	79	49.21	5.99	4.41	49.50	6.0	4.40
IVb		190-192	$C_{16}H_{17}NO_6S$	92	54.70	4.84	3.98	55.10	4.87	4.01
IVc		195-197	$C_{17}H_{19}NO_6S$	88	55.89	5.47	4.03	56.09	5.36	3.85

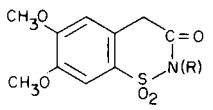
Both the frequency of the OH of COOH (2700-2300 cm^{-1}) and that of the NH of IV disappeared after cyclization to the benzothiazinone V.

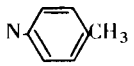
The nmr spectrum of compound II had signals at τ 2.6 and 3.23 which corresponded to the two aromatic protons, and the two methoxy groups appeared at 6.1 as a singlet. The singlet at τ 5.96 must be due to the chain methylene group and the quartet at 5.87 (J = 7 Hz) to the methylene of the ester, with the methyl at 8.75 (triplet).

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 as a solvent and tetramethylsilane as the internal standard. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Division, DEMOCRITOS.

TABLE III



Compound	N(R)	M.p. °C	Formula	Yield %	Calcd. % C	H	N	Found % C	H	N
Va	NH	198-200	$C_{10}H_{11}NO_5S$	48	46.69	4.28	5.44	47.0	4.08	5.25
Vb	$NCH(CH_3)_2$	156-157	$C_{13}H_{17}NO_5S$	74	52.17	5.68	4.68	52.48	5.78	4.62
Vc		225-228	$C_{16}H_{15}NO_5S$	89	57.65	4.50	4.20	57.38	4.44	4.03
Vd		204-206	$C_{17}H_{17}NO_5S$	83	58.78	4.89	4.03	58.51	5.0	3.89

Recrystallization solvents: IVa (Hexane-Ethylacetate), IVb (methanol-chloroform), IVc (methanol), V (methanol-ethylacetate), Vb (methanol), Vc, Vd (methanol-chloroform).

4,5-Dimethoxy-2-carboethoxymethylbenzenesulfonyl Chloride (II).

Twenty g. of ester I were placed in a three-necked flask fitted with a mechanical stirrer, condenser and addition funnel, both protected from moisture. Chlorosulfonic acid (22 ml.) were 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 washed with water, dried over sodium sulfate and evaporated under reduced pressure to yield a residue which on recrystallization from ether-hexane gave compound II in 40% yield, m.p. 82-83°; ν max 1730 cm^{-1} ($COOC_2H_5$).

Anal. Calcd. for $C_{12}H_{15}ClO_6S$: C, 44.65; H, 4.65. Found: C, 44.90; H, 4.90.

General Procedures for the Preparation of the *N*-Substituted Sulfonamides (III).

To a flask containing 3 mmoles of II, an excess of aliphatic amine (5 ml.) was added (for aromatic amines we used 6 mmoles in 10 ml. of anhydrous benzene) and the reaction mixture was refluxed for 2-3 hours. The excess amine or the solvent was evaporated under reduced pressure and ice-water was added to yield the corresponding sulfonamides. The compounds prepared are reported in Table I. All of the sulfonamides obtained showed strong absorption at 1725-1735 cm^{-1} ($COOC_2H_5$).

4,5-Dimethoxy-2-carboethoxymethylbenzenesulfonamide (IIIa).

Compound II (4 g.) was mixed with 15 g. of well pulverised ammonium carbonate. The mixture was immersed in an oil bath at 200-210° for 20 minutes. The reaction mixture was allowed to reach room temperature and then water was added with agitation. The solid was collected by filtration, washed several times with water and crystallized from methanol to yield compound IIIa; ν max 1720 cm^{-1} ($COOC_2H_5$).

The nmr spectrum in addition to the common peaks (at τ 2.6 and 3.4 (aromatic protons), 8.75 (CH_3 triplet), 6.15 (OCH_3 singlet), the methylene of the chain and the methylene of the ester come together as a multiplet centered at 5.9) shows at τ 4.6 the two protons of the amino group.

Procedures for the Hydrolysis of the *N*-Substituted Sulfonamide Esters III.

To a solution of 50% methanol containing 2 g. of potassium hydroxide, 1 g. of ester III was added and the mixture was refluxed for 2-3 hours. The solution was poured into ice-water and acidified with concentrated hydrochloric acid. The resulting precipitate was collected by filtration to yield compounds IVb and IVc. (Compound IVa was obtained by extraction with chloroform). (Table II). The sulfonamides obtained showed strong absorption at 1700-1710 cm^{-1} (COOH).

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

Following the above procedures for the hydrolysis of 4,5-dimethoxy-2-carboethoxymethylbenzenesulfonamide, after acidification we have obtained the benzothiazinone (Va); ν max 1705 cm^{-1} (C=O).

Procedures for the Preparation of *N*-Substituted 6,7-Dimethoxy-1,2-benzothiazin-(4*H*)-3-one 1,1-Dioxide.

Method A.

One g. of IV was placed in a flask and was immersed in an oil bath in about 210° for 10 minutes. The resulting compound was allowed to reach room temperature and was recrystallized from the appropriate solvent. The compounds thus prepared are reported in Table III.

The thiazinones obtained showed absorption at 1700-1710 cm^{-1} (C=O).

Nmr spectrum of Vb showed at τ 2.8 and 3.3 (2 aromatic protons), 5.2 (-CH<) 6.2 (singlet, CH_2, 2 OCH_3), 8.48 and 8.6 (CH_3-C-CH_3).

Method B.

To a solution of IV (0.5 g.) in 5 ml. of anhydrous benzene phosphorus pentachloride (1.2 g.) was added and the mixture was allowed to stand for 90 minutes 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 give V in 85±5% yield, which were identical by infrared to the benzothiazinones prepared by method A.

REFERENCES

(1) A. Kraajeveld and A. M. Akkerman, S. African Patent 646,150 (1965).

(2) A. Kraajeveld and A. M. Akkerman, U. S. Patent 3,284,450 (1966).

(3) K. Abe, S. Yamamoto and K. Matsui, *J. Pharm. Soc. (Japan)*, 76, 1058 (1956).

(4) H. Zinnes, R. A. Comes, F. R. Zuleski, A. N. Caro and J. Shavel, *J. Org. Chem.*, 30, 2241, (1965).

(5) P. Catsoulacos, *J. Heterocyclic Chem.*, 4, 645 (1967).

(6) P. Catsoulacos, *ibid.*, 7, 409 (1970).

(7) P. Catsoulacos, *Chim. Ther.*, 6, 401, (1970).