Derivatives of 2-Sulfonamido-4,5-dimethoxyphenylacetic Acid and of 2-Carboxamido(2-chloroethyl)methylbenzenesulfonamides

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Series of variously sustituted amides of 2-sulfonamido-4,5-dimethoxyphenylacetic acid have been prepared. The reaction of diethylamine, piperidine, morpholine and bis(2-chloroethyl)amine with carbomethoxymethyl-3,4-dimethoxybenzenesulfonyl chloride produced the corresponding sulfonamido derivatives. Acid hydrolysis of the latter and action of thionyl chloride gave the chlorocarboxymethylbenzenesulfonamides. The acid chlorides of the sulfonamides were transformed to the 2-carboxamido-bis(2-chloroethyl)methylbenzenesulfonamides with bis(2-chloroethyl)amine. These agents were tested in L-1210 and P-388 leukemias and were found not to possess antitumor activity in these two transplantable tumor lines.

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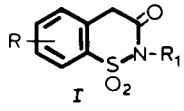
Recent experiments (1-6) have indicated that 1,2-benzothiazin-3(4*H*)one 1,1-dioxide derivatives are effective in the central nervous system of animals, and also, they have shown antiinflammatory activity.

Having in mind these pharmacological observations and because of our interest in thia-azo compounds (7-10), it was decided to prepare compounds with structure similar to benzothiazinone (I) but varying in that the heterocyclic ring is open between $CON(R)_2$ and in that they maintain the amide and sulfonamide groups in the nucleus.

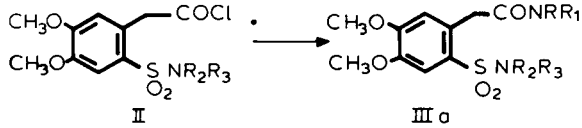


I

Several of these derivatives were conveniently synthesized and divided to the following groups:

1. *N*-Substituted 4,5-Dimethoxy-2-*N*-substituted Carboxamidomethylbenzenesulfonamides.

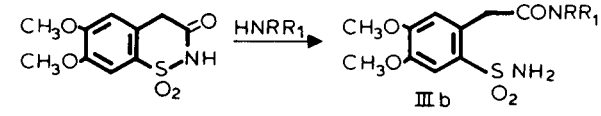
The *N*-substituted-4,5-dimethoxy-2-chlorocarboxymethylbenzenesulfonamides (II) (10) were found to react readily with aliphatic amines giving the corresponding amides-sulfonamides IIIa (Table I).



II IIIa

2. 4,5-Dimethoxy-2-*N*-substituted Carboxamidomethylbenzenesulfonamides.

For the synthesis of this type of compounds IIIb (Table II), we used dimethoxy-2*H*-1,2-benzothiazin-3-(4*H*)one 1,1-dioxide (4) as the starting material and secondary aliphatic amines. This due to the reason that the 4,5-dimethoxy-2-chlorocarboxymethylbenzenesulfonamide cannot be isolated, because readily cyclization occurs forming the corresponding 1,2-benzothiazin-3-(4*H*)one 1,1-dioxide (4).



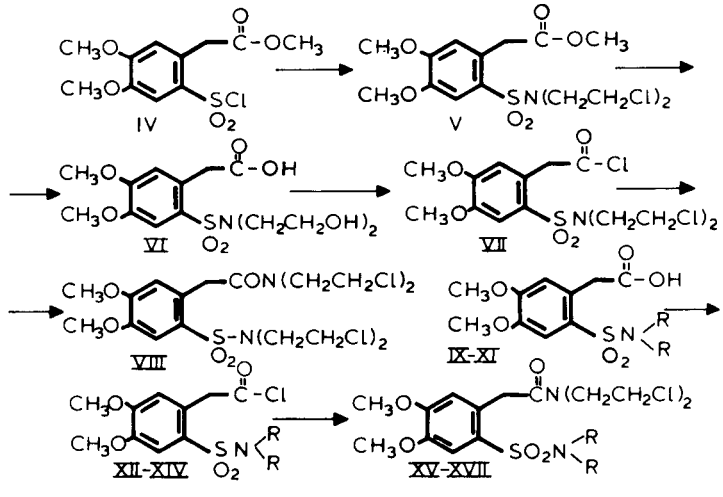
IIIb

Alkylating agents of the nitrogen mustard class are well known chemotherapeutic agents for the treatment of malignant diseases.

In continuation of our studies on the synthesis of nitrogen mustard derivatives (11-14), some aromatic sulfonamides containing bis(2-chloroethyl)amine molecule have been prepared.

The well known biological activity of sulfonamides and the antitumor activity of certain alkylating sulfonamides (15) prompted us to prepare compounds in which the active group was connected to the main molecule by the stable bond $-SO_2N$ and on the other hand in the same molecule a second active of bis(2-chloroethyl)amine with a less stable bond was added (-CON<).

The source for the synthesis of such derivatives is the carbomethoxymethyl-3,4-dimethoxybenzenesulfonyl chloride (10), which could be a useful reagent for the attachment of the bis(2-chloroethyl)amine.



IV V VI VII VIII IX-XI XII-XIV XV-XVII

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IX , XII , XV RRN = $(C_2H_5)_2N$

X , XIII , XVI = 

XI , XIV , XVII = 

Reaction of bis(2-chloroethyl)amine, piperidine, morpholine and diethylamine with carbomethoxymethyl-3,4-dimethoxybenzenesulfonyl chloride IV produced the 4,5-dimethoxy-2-carbomethoxymethylbenzenesulfonamides.

The ester group of compound V was removed by acid hydrolysis to give compound VI in good yield. The hydrolysis of the ester was probably accompanied by hydrolysis of the halide groups. [The infrared spectrum showed OH absorption at 3540 cm^{-1} (OH)]. The latter was converted to VII with thionyl chloride as was affected for the formation of the acid chlorides (XII-XIV) (10).

Treatment of the acid chlorides VII and XII-XIV with bis(2-chloroethyl)amine produces 2-carboxamido-bis(2-chloroethyl)methylbenzenesulfonamides VIII and XV-XVII.

Biological Results and Discussion.

Compounds XV, XVI and XVII were tested in doses

Table I

N-Substituted 4,5-Dimethoxy-2-*N*-substituted Carboxamidomethylbenzenesulfonamides

Compound No.	NR_2R_3	NRR_1	Formula	Yield %	M.p. °C	Recrystallization Solvent	Calcd. % / Found % C	H	N
$IIIa_1$	$N(C_2H_5)_2$	$(NC_2H_5)_2$	$C_{18}H_{30}N_2O_5S$	61	84-86	$CH_3COOC_2H_5$	55.95 56.20	7.77 7.60	7.25 6.97
$IIIa_2$	$N(C_2H_5)_2$		$C_{19}H_{30}N_2O_5S$	80	115-117	"	57.28 57.48	7.53 7.63	7.03 6.94
$IIIa_3$	$N(C_2H_5)_2$		$C_{18}H_{28}N_2O_6S$	42	132-133	"	54.00 54.02	7.00 7.10	7.00 6.90
$IIIa_4$		$N(C_2H_5)_2$	$C_{19}H_{30}N_2O_5S$	62	99-101	"	57.28 57.38	7.53 7.45	7.03 7.10
$IIIa_5$			$C_{20}H_{30}N_2O_5S$	83	144-145	"	58.53 58.53	7.31 7.09	6.82 7.13
$IIIa_6$			$C_{19}H_{28}N_2O_6S$	45	158-159	"	55.33 55.46	6.79 6.53	6.79 6.56
$IIIa_7$		$N(C_2H_5)_2$	$C_{18}H_{28}N_2O_6S$	76	144-145	"	54.00 54.50	7.00 7.35	7.00 7.11
$IIIa_8$			$C_{19}H_{28}N_2O_6S$	57	147-148	"	55.34 55.46	6.79 6.53	6.79 6.56
$IIIa_9$			$C_{18}H_{26}N_2O_6S$	66	170-172	"	52.17 52.60	6.28 6.34	6.76 6.87

All the compounds reported showed strong absorption at 1640-1660 cm^{-1} (CO) and at 1135-1140 cm^{-1} (S-O sym), 1310-1335 cm^{-1} (S-O antisym).

Table II

N-Substituted 4,5-Dimethoxy-2-carboxamidomethylbenzenesulfonamides

Compound No.	NRR_1	Formula	Yield %	M.p. °C	Recrystallization Solvent	Calcd. % / Found % C	H	N
$IIIb_1$	$N(C_2H_5)_2$	$C_{14}H_{22}N_2O_5S$	85	132-133	$CH_3COOC_2H_5$	50.91 51.30	6.66 6.84	8.48 8.35
$IIIb_2$		$C_{15}H_{22}N_2O_5S$	86	140-141	CH_3OH	52.63 52.24	6.43 6.17	8.18 7.95
$IIIb_3$		$C_{14}H_{20}N_2O_6S$	40	158-160	CH_3OH	48.83 48.58	5.81 5.39	8.14 7.99

The compounds reported showed strong absorption at 3410-3450 cm^{-1} and 3160-3180 cm^{-1} (NH_2), 1680 cm^{-1} (CO) and at 1130-1150 cm^{-1} (S-O sym) and 1330-1350 cm^{-1} (S-O antisym).

10-25 mg./kg. i.p. on a daily × 8 schedule and in doses of 20-40 mg./kg. i.p. on a day 1,5 and 9 schedule in L-1210 leukemia without any demonstration of activity. Additionally, in P-388 leukemia these agents were tested in doses of 5-40 mg./kg. i.p. on a daily × 8 schedule with no activity.

L-1210 leukemia was maintained in our laboratory by weekly i.p. passage of 10^5 L-1210 cells in DMA/2 mice. P-388 leukemia was maintained by weekly i.p. passage of 10^6 P-388 cells into DBA/2 mice. C57BL/6 × DBA/2 female mice averaging 22.7 grams each were used for the test animals in both cases. L-1210 cells (10^5) or 10^6 P-388 cells were inoculated i.p. into each test animal; life span was recorded. For all experiments groups of eight mice uniform as to sex and age were kept in an air conditioned, light controlled environment.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus, and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 521 in potassium bromide. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Department, "Demokritos", N.R.C.

N-Substituted 4,5-Dimethoxy-2-*N*-substituted Carboxamidomethylbenzenesulfonamides (IIIa).

To a flask containing 0.5 g. of *N*-substituted 4,5-dimethoxy-2-chlorocarboxymethylbenzenesulfonamide (II) (4,10) an excess of aliphatic amine (5 ml.) was added and the reaction mixture was heated under reflux for one hour. The excess of amine was evaporated under reduced pressure and ice-water was added and the precipitate collected by filtration to give the corresponding amides (see Table I).

4,5-Dimethoxy 2-Substituted Carboxamidomethylbenzenesulfonamides (IIIb).

To a solution of 6,7-dimethoxy-2*H*-1,2-benzothiazin-3-(4*H*)one (4) 1 g. in 25 ml. of anhydrous benzene, 10 ml. of aliphatic amine was added and the mixture was heated under reflux for 20 hours. Then the solvent and the excess of amine was evaporated and the residue crystallized from the appropriate solvent (see Table II).

4,5-Dimethoxy-2-carbomethoxymethylbenzene-bis(2-chloroethyl)sulfonamide (V).

To a solution of 0.01 mole (3.085 g.) (7) of IV in 50 ml. of anhydrous benzene 0.02 mole (2.84 g.) of bis(2-chloroethyl)amine was added. The mixture was heated under reflux for 3 hours. The solvent was evaporated under reduced pressure and the residue was obtained in crystalline form by addition of ice-water. Crystallization from ethyl acetate gave an 84% yield of compound V, m.p. 103-104°; ir: ν max 1730 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{21}Cl_2NO_6S$: C, 43.47; H, 5.07; N, 3.38. Found: C, 43.10; H, 5.30; N, 3.35.

4,5-Dimethoxy-2-carboxamido-bis(2-chloroethyl)methylbenzene-bis(2'-chloroethyl)sulfonamide (VIII).

The prepared ester V (3 g.) was heated under reflux in 90 ml. of concentrated hydrochloric acid for 3 hours. The solution was cooled, cold water was added and the resulting precipitate was collected by filtration to yield compound VI in 83% yield.

To a solution of VI (3 g.) in 50 ml. of chloroform or anhydrous benzene, 20 ml. of freshly distilled thionyl chloride was added dropwise with stirring at 0-5°. The solution was stirred at the same temperature for one hour and then it was allowed to stand at −3° for 24 hours. After this time the solvent and the excess of thionyl chloride was removed under reduced pressure and the residue without further purification was used for the synthesis of compound VIII.

To a solution of the above prepared compound VII (0.02 mole) in 300 ml. of anhydrous benzene 0.04 mole of bis(2-chloroethyl)amine was added and the mixture was heated under reflux for one hour. The solvent was evaporated under reduced pressure and cold water was added. This mixture was extracted with chloroform. The chloroform layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent and crystallization from a mixture of *n*-hexane-ethyl acetate yielded compound VIII in 85% yield, m.p. 76-78°; ir: ν max 1640 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{26}Cl_4N_2O_5$: C, 41.22; H, 4.96; N, 5.34. Found: C, 41.63; H, 5.26; N, 5.49.

General Procedure for the Preparation of 4,5-Dimethoxy-2-carboxamido-bis(2-chloroethyl)methylbenzene *N*-Substituted Sulfonamides (XV-XVII).

To a solution of chlorocarboxymethylbenzenesulfonamide (XII-XIV) (10) (5 mmoles in 30 ml. of anhydrous benzene) 10 mmoles of dichlorodiethylamine was added. The mixture was heated under reflux for one hour. The solvent was evaporated under reduced pressure and the residue was redissolved in chloroform. The chloroform layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent and crystallization from a mixture of ethyl acetate-ether gave compounds XV-XVII in 85-90% yield.

4,5-Dimethoxy-2-carboxamido-bis(2-chloroethyl)methylbenzenediethylaminosulfonamide (XV).

This compound had m.p. 97-98°; ir: ν max 1654 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{28}Cl_2N_2O_5S$: C, 47.47; H, 6.15; N, 6.15. Found: C, 47.43; H, 6.08; N, 6.18.

4,5-Dimethoxy-2-carboxamido-bis(2-chloroethyl)methylbenzenepiperidinosulfonamide (XVI).

This compound had m.p. 105-106°; ir: ν max 1655 cm^{-1} (C=O).

Anal Calcd. for $C_{19}H_{28}Cl_2N_2O_5S$: C, 48.82; H, 6.00; N, 6.00. Found: C, 48.89; H, 5.99; N, 5.97.

4,5-Dimethoxy-2-carboxamido-bis(2-chloroethyl)methylbenzenemorpholinosulfonamide (XVII).

This compound had m.p. 130-131°; ir: ν max 1655 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{26}Cl_2N_2O_6S$: C, 46.05; H, 5.54; N, 5.97. Found: C, 46.17; H, 5.77; N, 5.90.

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