Derivatives of 2-Sulfonamido-4,5-dimethoxyphenylacetic Acid and their Oxazolines and Aminoesters

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Series of variously substituted aminoesters and oxazolines of 2-sulfonamido-4,5-dimethoxyphenylacetic acid have been prepared and some of them screened for biological activity.

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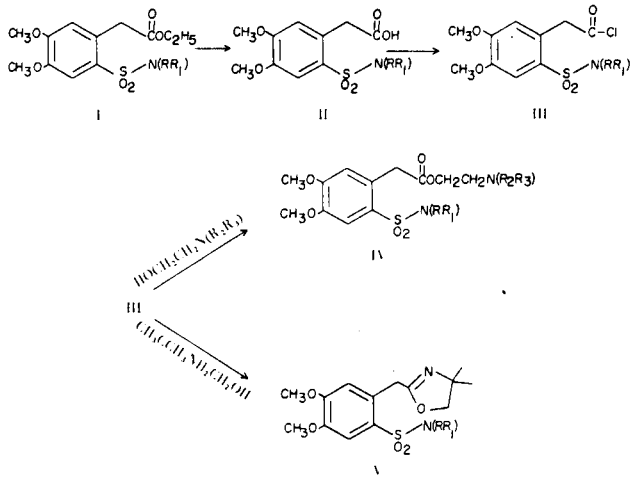
In the course of our work on thia-azo heterocyclic compounds (2-4) and the recent pharmacological properties of 1,2-benzothiazin-(4*H*)-3-one 1,1-dioxide derivatives (5-9) prompted us to study compounds with similar structure.

Since many carboxylic acid esters of aminoalcohols have local anesthetic and other pharmacological activity, we were interested in studying 4,5-dimethoxy-2-carboxymethylbenzenesulfonamide esters of aminoalcohols. When acid (7) (II) was treated with thionyl chloride in anhydrous chloroform, the corresponding acid chloride (III) was obtained, which was then converted into the aminoester (IV). Extension of the above reaction using as aminoalcohol 2-amino-2-methylpropanol, we obtained oxazolines (V) in good yield.



Compounds IVa-IVc (aminoesters) and Va-Vc (oxazolines) were tested as their hydrochloric salts for local anesthetic activity in the guinea pig cornea. Substances Va-Vc showed appreciable activity as a surface anesthetic at a 2% (w/v) concentration possessing an average activity of 40 minutes duration.

In the corneal reflux aminoesters IVb, IVg and IVf at a 2% (w/v) concentration showed an average duration of activity of 15 minutes.

Oxazolines Va-Vc were screened as their hydrochloride salts for antifungal activity against *Aspergillus midulans*, *Ustilago maydis*, *Fusarium moniliforme* and *Sal Seleocotium rolfsii*. None of these exhibited activity at concentrations up to 20 ppm.

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 Associated 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, N. R. C. "Demokritos".

N-Substituted 4,5-Dimethoxy-2-carboethoxymethylbenzenesulfonamides (I).

To a solution of 4,5-dimethoxy-2-carboethoxymethylbenzenesulfonamide (7) (0.01 mole) in 30 ml. of anhydrous benzene was added aliphatic amine (0.02 mole). The mixture was heated under reflux for 2 hours. Then the solvent was evaporated under reduced pressure and to the residue was added water.

The precipitate was collected by filtration, washed with water and recrystallized from the appropriate solvent (see Table I).

N-Substituted 4,5-Dimethoxy-2-carboxymethylbenzenesulfonamides (II).

These acids were prepared according to the reported method (7) (see Table II).

N-Substituted 4,5-Dimethoxy-2-chlorocarboxymethylbenzenesulfonamides (III).

One g. of *N*-substituted 4,5-dimethoxy-2-carboxymethylbenzenesulfonamide in 20 ml. of dry chloroform was added dropwise with stirring to 4 ml. of freshly distilled thionyl chloride at 0-2°. After stirring at the same temperature for one hour the mixture was allowed to stand at 0° overnight. Then the solvent and the excess of thionyl chloride were distilled under reduced pressure. The residue was crystallized with ethyl acetate and collected by filtration. Without further purification the acid-chlorides were used for the synthesis of aminoesters and oxazolines.

The acid-chlorides prepared are reported below:

N-Diethylamino-4,5-dimethoxy-2-chlorocarboxymethylbenzenesulfonamide.

This compound had m.p. 94-96°; ν max 1800 cm^{-1} (CO).

N-Piperidino-4,5-dimethoxy-2-chlorocarboxymethylbenzenesulfonamide.

This compound had m.p. 130-131°; ν max 1800 cm^{-1} (CO).

N-Morpholino-4,5-dimethoxy-2-chlorocarboxymethylbenzenesulfonamide.

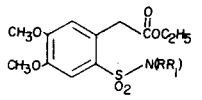
This compound had m.p. 155-156°; ν max 1800 cm^{-1} (CO).

Dialkylaminoethylesters of 4,5-Dimethoxy-2-sulfonamidophenylacetic Acid (IV).

To a solution of 4,5-dimethoxy-2-chlorocarboxymethylbenzenesulfonamide (0.01 mole) in 25 ml. of anhydrous benzene was

Table I

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

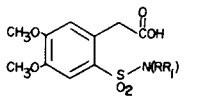


Compound No.	$N\langle^{R}_{R_1}$	Formula	Recrystallization Solvent	Yield %	M.p. °C	Analysis Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Ia	NH_2	$C_{12}H_{17}NO_6S$	Methanol	85	151-152	47.52	48.10	5.61	5.53	4.62	4.61
Ib	$N(C_2H_5)_2$	$C_{16}H_{25}NO_6S$	Ethyl acetate-Hexane	95	67-68	53.48	52.99	6.96	6.99	3.90	3.84
Ic		$C_{17}H_{25}NO_6S$	Methanol	95	101 (Lit. (7) 100-101)						
Id		$C_{16}H_{23}NO_7S$	Methanol	97	104-106 (Lit. (7) 105-106)						

The sulfonamides obtained showed strong absorption at 1725-1735 cm^{-1} ($COOC_2H_5$) and at 1125-1150 cm^{-1} (S-O sym), 1320-1375 cm^{-1} (S-O antisym).

Table II

N-Substituted-4,5-dimethoxy-2-carboxymethylbenzenesulfonamides

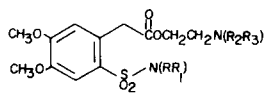


Compound No.	$N\langle^{R}_{R_1}$	Formula	Recrystallization Solvent	Yield %	M.p. °C	Analysis Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
IIa	$N(C_2H_5)_2$	$C_{14}H_{21}NO_6S$	Methanol	91	127-128	50.75	51.25	6.34	6.58	4.23	4.19
IIb		$C_{15}H_{21}NO_6S$	Methanol	95	192	52.47	52.90	6.12	6.33	4.08	4.16
IIc		$C_{14}H_{19}NO_7S$	Methanol	95	209-210	48.69	48.45	5.50	5.20	4.15	4.30

The compounds reported showed strong absorption at 1710 cm^{-1} (CO) and at 1130-1140 cm^{-1} (S-O sym), 1310-1320 cm^{-1} (S-O antisym).

Table III

Dialkylaminoethylesters of 4,5-Dimethoxy-2-sulfonamidophenylacetic Acid



Compound No.	$N<^{R_2}_{R_1}$	$N<^{R}_{R_1}$	Formula	Yield %	M.p. °C	Recrystallization Solvent	Analysis Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
IVa		$N(CH_3)_2$	$C_{19}H_{30}N_2O_6S$	77	104	Ethyl Acetate-*n*-Hexane	55.07	55.36	7.24	7.38	6.76	6.51
IVb		$N(C_2H_5)_2$	$C_{21}H_{34}N_2O_6S$	60	107-108	Ethyl Acetate-*n*-Hexane	57.01	57.18	7.69	7.49	6.33	6.25
IVc			$C_{21}H_{32}N_2O_6S$	70	98-99	Ethyl Acetate	57.27	57.23	7.27	6.99	6.36	6.44
IVd			$C_{22}H_{34}N_2O_6S$	74	125-126	Ethyl Acetate	58.15	58.24	7.48	7.79	6.16	5.95
IVe			$C_{21}H_{32}N_2O_7S$	60	112	Methanol	55.26	54.98	7.01	6.95	6.14	6.01
IVf		$N(CH_3)_2$	$C_{18}H_{28}N_2O_7S$	58	92-93	Ethyl Acetate	51.92	51.86	6.73	6.86	6.73	6.51
IVg		$N(CH_2H_5)_2$	$C_{20}H_{32}N_2O_7S$	71	77-78	Ethyl Acetate-*n*-Hexane	54.05	53.96	7.20	6.92	6.30	5.94
IVh			$C_{20}H_{30}N_2O_7S$	72	98-99	Ethyl Acetate-*n*-Hexane	54.29	53.91	6.78	6.85	6.33	5.98
IVi			$C_{21}H_{32}N_2O_7S$	55	119-121	Ethyl Acetate	55.26	55.45	7.01	6.85	6.14	6.32
IVk			$C_{20}H_{30}N_2O_8S$	84	108-111	Ethyl Acetate	52.40	52.90	6.55	6.90	6.11	6.11

The reported compounds showed strong absorption at 1725-1735 cm^{-1} (CO), 1315-1330 cm^{-1} (S-O antisym), 1130-1140 cm^{-1} (S-O sym).

Table IV

2-(2-Sulfonamido-4,5-dimethoxybenzyl)-4,4-dimethyl-2-oxazolines

Compound No.	$N<^{R}_{R_1}$	Formula	Yield %	M.p. °C	Recrystallization Solvent	Analysis Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
XIa	$N(C_2H_5)_2$	$C_{18}H_{28}N_2O_5S$	55	113-114	Methanol	56.25	55.90	7.29	6.90	7.29	7.53
XIb		$C_{19}H_{28}N_2O_5S$	70	128	Methanol	57.57	57.55	7.07	6.87	7.07	7.08
XIc		$C_{18}H_{26}N_2O_6S$	57	161	Methanol	54.27	53.99	6.54	6.41	7.03	6.87

The reported compounds showed absorption at 1660-1665 cm^{-1} (C=N), 1310-1340 cm^{-1} (S-O antisym), 1130-1150 cm^{-1} (S-O sym).

added 0.02 mole of aminoalcohol. The mixture was heated under reflux for 2-3 hours. After this time the solvent was evaporated under reduced pressure and to the residue was added water and extracted several times with chloroform. The chloroform solution was washed with water, dried over magnesium sulfate and the solvent evacuated. The residue crystallized from the appropriate solvent (see Table III).

2-(2-Sulfonamido-4,5-dimethoxybenzyl)-4,4-dimethyl-2-oxazolines (V).

To a solution of 0.02 mole of 2-amino-2-methylpropanol in 15 ml. of anhydrous dichloromethane was added dropwise at 0°, 0.01 mole of *N*-substituted 4,5-dimethoxy-2-chlorocarbomethylbenzenesulfonamide dissolved in anhydrous dichloromethane. After the addition, the solution was agitated at room temperature for 3 hours. Filtration of the reaction mixture and the filtrate was evaporated. To this residue was added dropwise with stirring 2 ml. of freshly distilled thionyl chloride. The solution was added in 10 ml. of anhydrous ether and the hydrochloric salt of the compound was precipitated. The precipitate after neutralization with cold solution of potassium hydroxide (20%) was extracted with ethyl acetate. The organic solution was dried and the solvent removed to leave an oil which was crystallized from methanol (see Table IV).

REFERENCES AND NOTES

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