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SYNTHESIS OF ANISIC ACID–AND ANISOLE--SULFONYLAMINO ACID DERIVATIVES

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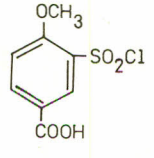
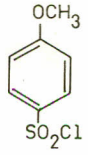
Synthesis of some 2-methoxy-5-carboxybenzene sulfonylamino acids and 4-methoxybenzene sulfonylamino acids and some of their corresponding methyl esters, hydrazides and dipeptide derivatives (Table 1, Compounds 2-21 and Table 2, Compounds 22-43) are described. Compounds (16-19 and 36-39) were found to be active against a number of microorganisms.

Aromatic sulfonylamino acid derivatives have been reported as hypoglycaemic agents [1–5]. In continuation of our work [6–15], the synthesis of some 2-methoxy-5-carboxybenzene sulfonylamino acids and 4-methoxybenzene sulfonylamino acids, their methyl esters, hydrazides and some dipeptides (Table 1, Compounds 2–21 and Table 2, Compounds 22–43) are reported in this paper.

The sulfonyl chlorides (1-a and 1-b) of anisic acid and anisole were prepared by their direct chlorosulfonation. The reaction of (1-a or 1-b) with the appropriate amino acid in ether in the presence of sodium hydroxide gave 2-methoxy-5-carboxybenzene sulfonylamino acids (Table 1, Compounds 2–10) and 4-methoxybenzene sulfonylamino acids (Table 2, Compounds 22–31) respectively.



(I-a)

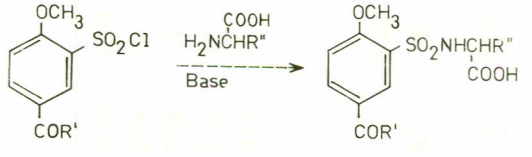


(I-b)

Complete acid hydrolysis of (Compound 2 or 22) at 100° for 24 hr using 6N-HCl, gave glycine.

The IR spectra of 2-methoxy-5-carboxybenzene sulfonylamino acids (Compounds 2–10) in KBr showed characteristic bands at: 1130, 1180, 1360 (SO_2), 3390, 3420 (NH and SO_2NH), 1735, 1140 (Ar-COOH), 1540, 2920, 2960 (Ar-OCH_3), 1310, 1360 (R-COOH), 1080, 1030, 910, 840, 800 and 780 cm^{-1} (1,2,5-Trisubstituted benzene), and other bands due to amino acid moieties.

The IR spectra of 4-methoxybenzene sulfonylamino acids (Compounds 22–31) in KBr showed characteristic bands at: 1150, 1180, 1360 (SO_2), 3300, 3210, (NH and SO_2NH), 1450, 1340, 2920, 2960 (Ar-OCH_3), 1080, 1030, 960, 860 and 720 cm^{-1} (1, 4-Disubstituted benzene), and other bands due to amino acid moieties.



Synthesis of 2-methoxy-5-carboxybenzene sulfonyl-Gly-Gly (Compound 11) and 4-methoxybenzene sulfonyl-Gly-Gly (Compound 40) was carried out by the reaction of (1-a or 1-b) with Gly-Gly using sodium bicarbonate-dioxan medium. The IR spectra of compounds (11 and 40) in KBr showed characteristic bands at: 1150, 1180, 1360 (SO_2), 3300, 3210 (NH and SO_2NH), 1680, 1540, 1320 (amide I, II and III), 2940, 2960 (Ar-OCH_3), 1690, 1310 and 1360 cm^{-1} (COOH) and other bands due to the benzene and amino acid moieties, thereby confirming their structures,

The methyl esters (Table 1, Compounds 12–15 and Table 2, Compounds 32–35) were prepared by treating the corresponding amino acid derivatives (Compounds 2–11 and 22–31) with methanol and pure thionyl chloride at 0° to – 10°. The methyl ester ($COOCH_3$) residue exhibited its characteristic IR absorption bands at : 1120, 1240 and 1735 cm^{-1} thereby supporting their structures.

Hydrazinolysis of the methyl esters (Table 1,) Compounds 12–15 and Table 2, Compounds 22–25) in metha-

Table 1: N(2-Methoxy-5-carboxybenzenesulfonyl) amino acid and dipeptide derivatives (2-21). 

Compound No.	R	R	Yield %	P.M. 0	R_f	E (cm)	Molecular formula	Elemental analyses, % Calculated C	H	N	Found C	H	N
2	-Gly	OH	77	222-224	0.91	14	$C_{10}H_{11}NO_7S$	41.52	3.80	4.84	41.62	3.95	4.99
3	-DL-Ala	OH	71	224-226	0.66	13	$C_{11}H_{13}NO_7S$	43.56	4.29	4.62	43.86	4.50	4.65
4	β-Ala	OH	73	234-236	0.86	9.5	$C_{11}H_{13}NO_7S$	43.56	4.29	4.62	43.88	4.59	4.63
5	-L-Val	OH	63	244-246	0.84	18	$C_{13}H_{17}NO_7S$	47.12	5.13	4.22	47.38	5.20	4.30
6	-L-Leu	OH	66	204-206	0.73	13.4	$C_{14}H_{19}NO_7S$	48.69	5.50	4.05	48.75	5.70	4.23
7	-DL-Ser	OH	50	239-240	0.68	9	$C_{11}H_{12}NO_8S$	41.37	4.07	4.38	41.51	4.21	4.39
8	-L-Tyr	OH	69	215-217	0.90	16	$C_{17}H_{17}NO_8S$	51.64	4.30	3.54	51.98	4.55	3.76
9	-L-Asp	OH	61	250-252	0.52	7	$C_{12}H_{13}NO_9S$	41.49	3.74	4.03	41.62	3.89	4.33
10	-DL-Glu	OH	56	258-260	0.49	14	$C_{13}H_{15}NO_9S$	43.21	4.15	3.87	43.40	4.22	3.95
11	-Gly-Gly	OH	65	266-268	0.76	11	$C_{12}H_{14}N_2O_8S$	41.61	4.04	8.02	41.72	4.13	8.19
12	-Gly-OMe	$-OCH_3$	90	132-134	0.92	Zero	$C_{12}H_{15}NO_7S$	45.43	4.73	4.41	45.60	4.80	4.45
13	-β-Ala-OMe	$-OCH_3$	89	90-92	0.93	Zero	$C_{13}H_{15}NO_7S$	47.13	5.13	4.22	47.25	5.22	4.40
14	-L-Leu-OMe	$-OCH_3$	80	123-125	0.95	Zero	$C_{16}H_{23}NO_7S$	51.47	6.16	3.75	51.88	6.24	3.88
15	-L-Tyr-OMe	$-OCH_3$	82	188-190	0.80	Zero	$C_{19}H_{21}NO_8S$	53.90	4.96	3.31	53.98	5.10	3.50
16	-Gly-N_2H_3	$-N_2H_3$	79	170-172	0.59	Zero	$C_{10}H_{15}N5O_5S$	37.85	4.73	22.08	38.01	4.74	22.18
17	-β-Ala-N_2H_3	$-N_2H_3$	72	126-128	0.80	Zero	$C_{12}H_{17}N_5O_5S$	39.88	5.15	21.13	39.89	5.25	21.35
18	-L-Leu-N_2H_3	$-N_2H_3$	80	205-207	0.56	Zero	$C_{14}H_{23}N_5O_5S$	45.04	6.16	18.76	45.20	6.22	18.84
19	-L-Tyr-N_2H_3	$-N_2H_3$	82	243-245	0.75	Zero	$C_{17}H_{21}N_5O_6S$	48.22	4.96	16.54	48.35	5.03	16.68
20	-Gly-Gly-OMe	-Gly-OMe	53	190-192	0.64	Zero	$C_{16}H_{21}N_3O_9S$	44.54	4.87	9.74	44.56	4.89	9.82
21	-β-Ala-L-Tyr-OMe	-L-Tyr-OMe	54	250-252	0.52	Zero	$C_{31}H_{35}N_3O_{11}S$	56.62	5.32	6.39	56.67	5.49	6.50

$[\alpha]_D^{20}$ (C = 0.8 DMF) For compounds (5) = -12.5; (6) = -19; (8) = -21.5; (9) = -10; (14) = -24.5; (15) = -28; (18) = -9.5; (19) = -13; (21) = -16.5.

Table 2 : 4-Methoxybenzenesulfonylamino acid and dipeptide derivatives (22-43)

Compound No.	R	Yield %	M.P. °C	R_f	E (cm)	Molecular formula	Elemental analyses, % Calculated C	H	N	Pound C	H	N
22	-Gly	74	124-126	0.71	8	$C_9H_{11}NO_5S$	44.08	4.48	5.71	44.29	4.66	5.75
23	-Dl-Ala	65	129-131	0.83	18	$C_{10}H_{13}NO_5S$	46.33	5.01	5.40	46.40	5.22	5.47
24	-β-Ala	58	138-140	0.82	13	$C_{10}H_{13}NO_5S$	46.33	5.01	5.40	26.45	5.32	5.58
25	-L-Val	52	146-148	0.40	15	$C_{12}H_{17}NO_5S$	50.17	5.92	4.87	50.26	5.99	4.98
26	-L-Leu	60	152-154	0.36	16.5	$C_{13}H_{19}NO_5S$	51.82	6.31	4.65	51.95	6.52	4.80
27	-DL-Ser	55	199-201	0.40	12.5	$C_{10}H_{13}NO_6S$	43.63	4.72	5.09	43.85	4.89	5.20
28	-DL-Phe	68	134-136	0.53	9	$C_{16}H_{17}NO_5S$	57.31	5.07	4.17	57.43	5.12	4.28
29	-L-Tyr	49	232-234	0.77	19	$C_{16}H_{17}NO_6S$	54.70	4.84	3.98	54.90	4.98	4.01
30	-L-Asp	63	245-247	0.56	11	$C_{11}H_{13}NO_7S$	43.56	4.29	4.62	43.68	4.40	4.70
31	-DL-Glu	44	165-167	0.72	7	$C_{12}H_{15}NO_6S$	45.42	4.73	4.41	45.59	4.82	4.47
32	-Gly-OMe	81	80-82	0.44	Zero	$C_{10}H_{13}NO_5S$	46.33	5.02	5.40	46.50	5.12	5.60
33	-DL-Ser-OMe	87	68-70	0.27	Zero	$C_{11}H_{15}NO_6S$	45.67	5.19	4.84	45.75	5.23	4.93
34	-DL-Ala-OMe	84	52-54	0.52	Zero	$C_{11}H_{19}NO_5S$	48.35	5.49	5.12	48.39	5.66	5.30
35	-DL-Phe-OMe	80	116-118	0.63	Zero	$C_{17}H_{19}NO_5S$	58.45	5.44	4.01	58.52	5.64	4.28
36	-Gly-N_2H_3	85	128-130	0.65	Zero	$C_9H_{13}N_3O_4S$	41.69	5.01	16.21	41.80	5.23	16.36
37	-DL-Ser-N_2H_3	87	160-162	0.37	Zero	$C_{10}H_{15}N_3O_5S$	41.52	5.19	14.53	41.60	5.31	14.69
38	-DL-Ala-N_2H_3	81	151-153	0.41	Zero	$C_{10}H_{15}N_3O_4S$	43.95	5.49	15.38	44.12	5.69	15.50
39	-DL-Phe-N_2H_3	80	144-146	0.61	Zero	$C_{16}H_{19}N_3O_4S$	55.01	5.44	12.03	55.25	5.61	12.21
40	-Gly-Gly	66	238-240	0.60	12	$C_{11}H_{14}N_2O_6S$	43.70	4.63	9.27	43.72	4.80	9.39
41	-Gly-Gly-OMe	61	145-147	0.98	Zero	$C_{12}H_{16}N_2O_6S$	45.56	5.06	8.86	45.72	5.29	8.98
42	-DL-Ala-L-Tyr-OMe	55	170-172	0.65	Zero	$C_{20}H_{24}N_2O_7S$	55.04	5.50	6.42	55.22	5.69	6.58
43	-Gly-Gly-N_2H_3	67	214-216	0.70	Zero	$C_{11}H_{16}N_4O_5S$	41.77	5.06	17.72	41.85	5.21	17.90

$[\alpha]_D^{20}$ (C = 0.8 0.5 DMF) For compounds (25) = -14.5, (26) = -19.5; (29) = -23; (30) = -11.5; (42) = -27.

nol gave the corresponding hydrazides (cf. Table 1, Compounds 16–19, and Table 2, Compounds 36–39).

Coupling of 4-methoxybenzene sulfonlyamino acid or 2-methoxy-5-carboxybenzene sulfonylamino acid with amino acid methyl ester hydrochlorides in dioxan-DMF-Et_3N mixture using the dicyclohexyl-carbodiimide method afforded the dipeptide methyl esters (Table 1, Compounds 20–21 and Table 2, Compounds 40–43). Most of the dipeptides were obtained in crystalline form in 55–63 % yield and all gave chromatographically homogeneous spots. The dipeptide methyl esters (Compounds 20–21 and 40–43) gave blue copper (II) complexes, λmax 650–680 nm, characteristic for normal dipeptides.

IR spectrum of Compound 40 in KBr shows the characteristic bands at: 3100, 3230 (NH and CONH), 1360, 1140 (SO_2NH), 1650, 1560, 1280, 2920 2960 (OCH_3), 1120, 1240 and 1730 cm^{-1} ($COOCH_3$), thereby confirming its structure.

Complete acid hydrolysis of the dipeptides (Table 1, Compound 21 and Table 2, Compound 42) gave a ninhydrin positive spots of alanine and tyrosine thereby supporting the structure of these dipeptides.

Hydrazinolysis of the dipeptide methyl ester (41) in ethanol afforded the dipeptide hydrazide (43) in 67 % yield.

Structures of all new derivatives 2–43 were confirmed by chromatographic studies, elemental analysis, spot reactions and the IR spectra.

The antimicrobial activity of the compounds thus synthesized were tested using the hole plate and filter paper disc methods [16–19]. The rusults were compared with the activity of the parent ortho-anisic acid and anisole. The hydrazides (Table 1, Compounds 16–19 and Table 2, Compounds 36–39 and 43) were found active against *Bacillus subtilis, Bacillus mycoids, Bacillus cereus, Escherichia coli, Salmonella typhosa* and inactive against *Penicillum chrysogenum.* The remaining amino acid derivatives were biologically inactive against the tested micro-organisms, perhaps due to low solubility of these derivatives in most of the common solvents. The biological activity of their corresponding salts are under investigation. The pharmacoligcal activities of anisole-4-sulfonylamino aicd hydrazides and anisic acid-sulfonylamino acid hydrazides showed properties due to which these compounds may be used in the field of analgesic, antipyretic and sulfonamide active derivatives.

EXPERIMENTAL

Paper chromatography was done on Whatman No.1 paper, using *n*-butanol-pyridine-acetic acid-water (15 : 10 : 3:12) as eluant. Paper electrophoresis was carried out on Whatman No. 1 paper by the method of vertical high voltage electrophoresis using pyridine-acetate buffer (pH 5.6), at 1000 V, for 2 hr. Benzidine, ninhydrin, silver nitrate and hydroxamate reactions were used for development [20]. All melting points are uncorrected.

2-Methoxy-5-carboxybenzenesulfonyl Chloride (1-a). The title compound was prepared starting from anisic acid and chlorosulfonic acid using the procedure described by Buchi [21]. Yield 71 %, m.p. 174–176°. Analysis: (Found: C, 38.33; H, 2.66 $C_8H_7O_5SCL$; Calc. : C, 38.32; H, 2.79%).

4-Methoxybenzenesulfonyl Chloride (1-b); The title compound was prepared starting from anisole and chlorosulfonic acid using the procedure described by Buch [21]. Yield 54 %, m.p. 41-42°.

General Procedure for Synthesis of 2-Methoxy-5-carboxybenzene sulfonylamino Acids (Table 1, Compounds 2–10) and 4-methoxy Benezenesulfonylamino Acids (Table 2, Compounds 22–31). Amino acid (0.02 mole) was dissolved in water (20 ml) and 2N-sodium hydroxide (30 ml) was added. The mixture was cooled to 0° and a solution of 2-methoxy-5-carboxybenzenesulfonyl chloride (1-a) (5.26 g, 0.02 mole) or 4-methoxybenzenesulfonyl chloride (1-b) (4.54 g, 0.22 mole) in ether (30 ml) was added dropwise during 30 min. The reaction mixture was maintained at zero until complete addition and then was shaken for additional 3 hr at 20°. The solution was cooled at 0° and acidified with 6N-HCl to Congo red (pH 5). Upon standing overnight at 5°, the crystalline product was filtered off and recrystallized from water, methanol, ethanol or their mixtures. All compounds were obtained in crystalline form and found to be chromatographically homogeneous when developed with benzidine, and gave ninhydrin negative reaction (cf. Table 1, Compounds 2–10 and Table 2, Compounds 22–31).

2-Methoxy-5-carboxybenzenesulfonyl-Gly-Gly (compound 11) and 4-Methoxybenezenesulfonyl-Gly-Gly (Compound 40). Glycylglycine (2.64 g, 0.02 mole) was added to 20% sodium bicarbonate (20 ml) and the mixture cooled to 0°. A solution of Compound 1-a or 1-b, (0.025 mole) in dioxane (20 ml) was added in portions during 30 min to the precooled mixture. The reaction mixture was stirred for 3 hr at room temperature. The solvent was evaporated *in vacuo* and the residual material dissolved in water. The solution was extracted with chloroform (50 ml) and the aqueous layer was cooled at 0° and acidified with 2N-HCl to (pH 4). The crude products were filtered off and purified by recrystallization from water. The products were chromatographically homogeneous when developed with

benzidine (cf. Table 1, Compound 11 and Table 2, Compound 40).

General Procedure for Synthesis of 2-Methoxy-5-carbomethoxybenzenesulfonylamino Acid Methyl Esters (Table 1, Compounds 12-15) and 4-Methoxybenzenesulfonylamino Acid Methyl Esters (Table 2, Compounds 32–35). The amino acid derivative (0.1 mole of Compounds 2–9 or 22–31) was dissolved in abs. methanol (600 ml), cooled to -10^{o} and pure thionyl chloride (50 ml, 0.44 mole) added dropwise. The temperature of the reaction mixture was kept at -5^{o} durng the process of addition. Stirring was continued for another 3 hr at 20^{o}. The reaction mixture was left for 48 hr at room temperature and the solvent evaporated *in vacuo*. Methanol was added and reevaporated several times. The crude methyl esters were recrystallized from methanol-ether. They were chromatographically homogeneous when developed with benzidine and hydroxamate reactions.

General Procedure for Synthesis of 2-Methoxy-5-carboxyhydrazide benzenesulfoylamino Acid Hydrazides (Table 1, Compounds 16–19) and 4-Methoxybenzenesulfonylamino Acid Hydrazides (Table 2, Compounds 36–39). The methyl ester derivative (0.01 mole of Compounds 12–15 or 32–35) was dissolved in abs. ethanol (20 ml) and hydrazine hydrate (85%, 2.5 ml, 2.05 mole) added. The reaction mixture was stirred for 2 hr and left for 24 hr at 20^{o}. The crystalline products were filtered, washed with ethanol, water and ether and recrystallized (cf. Table 1, Compounds 16–19 and Table 2, Compounds 36–39).

General Procedure for Synthesis of Dipeptide Methyl Esters (Table 1, Compounds 20–21 and Table 2, Compounds 41–42). The amino acid methyl ester hydrochloride (0.012 mole) and 2-methoxy-5-carboxybenzenesulfonylamino acid (0.01 mole) or 4-methoxybenzenesulfonylamino acid (0.01 mole) were dissolved in a mixture of dimethylformamide (50 ml) and dioxane (30 ml) containing triethylamine (2.8 ml). The mixture was cooled to 0^{o} and dicyclohexylcarbodiimide (2.3 g, 0.01 mole) added and the mixture stirred 3–4 hr at 0^{o} and left for 24 hr at room temperature. The precipitated dicyclohexylurea was filtered off and the filtrate evaporated *in vacuo*. The residue was recrystallized from methanol or ethanol. The dipetides were obtained as white crystalline products and were chromatographically homogeneous when developed with benzidine and hydroxamate reactions (cf. Table 1, Compounds 20–21 and Table 2, Compounds 41–42).

4-Methoxy-benzenesulfonyl-Gly-Gly-N_2H_3 (43). 4-Methoxybenezenesulfonyl-Gly-Gly-OMe (0.01 mole) was dissolved in ethanol (80 ml) and hydrazine hydrate (85%, 2.5 ml, 2.05 mole) added. The reaction mixture was treated as described for preparation of Compounds (36–39). The hydrazide 43 was recrystallized from ethanol and chromatographically homogeneous material obtained (cf. Table 2, Compounds 43).

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