Synthesis of xanthotoxin-4-sulfonylamino acid, di- and tripeptide derivatives

A. M. EL-NAGGAR, M. H. A. ELGAMAL, B. A. H. EL-TAWIL, and A. M. ABD EL-SALAM

Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt, ARE

Received 8 October 1975

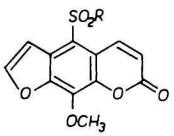
Accepted for publication 28 May 1976

The synthesis of some xanthotoxin-4-sulfonylamino acids has been achieved by the reaction of xanthotoxin-4-sulfonyl chloride with the appropriate amino acid in dioxan—triethylamine medium. Glycine chloride derivatives on coupling with different amino acids or with Gly-Gly-OMe furnish the desired di- and tripeptide derivatives, respectively.

Синтез некоторых ксантотоксин-4-сульфониламинокислот был получен реакцией ксантотоксин-4-сульфонилхлорида с соответствующей аминокислотой в среде триэтиламин—диоксан. Производные глицинхлорида связанные с различными аминокислотами или с Гли-Гли-ОМе дают требуемые производные ди- или трипептида.

Previously xanthotoxin and some furocoumarins were found to have different pharmacological activities [1, 2]. Recently, we have reported the synthesis of some coumarin and furocoumarinamino acids which were expected to possess some biological activities [3, 4]. However, the effect of variations in the coumarin, amino acid, di- and tripeptide moieties on the biological and pharmacological activities has not yet been studied.

The present investigation involved a synthesis of some xanthotoxin-4-sulfonylamino acids, di- and tripeptides *II—XXIII* (Scheme 1; Tables 1 and 2).



Scheme 1

Experimental

All melting points are uncorrected. All thin-layer chromatograms (R_F value) were made on Silica Gel G using benzene—ethyl acetate (1 : 1) as solvent system and iodine—potassium iodide solution as detection reagent. Benzidine, ninhydrin, and hydroxamate reactions were used for development (spot reactions) [5].

The u.v. spectra were measured with a Unicam SP 8000 Ultraviolet Spectrophotometer. The i.r. spectra were measured with a Unicam SP 1200 in KBr. $[\alpha]_D^{20}$ were taken in Zeiss polarimeter 1 dm tube (*c* 0.6).

Xanthotoxin-4-sulfonyl chloride (*I*) was prepared from 9-methoxypsoralene and chlorosulfonic acid using the procedure described in [6].

Xanthotoxin-4-sulfonylamino acid derivatives (II—XIV)

I (6.3 g; 0.02 mole) was dissolved in dioxan (200 ml) and added in portions to a solution of amino acid (0.024 mole) in dioxan (200 ml) containing triethylamine (20 ml). The reaction mixture was stirred at room temperature and then briefly refluxed till completion as monitored by TLC. The precipitated triethylammonium chloride was filtered off and benzene—ether mixture 1 : 1 (500 ml) added. The solution was washed with water, 10% $NaHCO_3$, water and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave crystalline materials. The products were recrystallized from methanol, ethanol, acetone or their mixtures. The products were chromatographically homogeneous when developed with benzidine, iodine solution and gave negative ninhydrin reaction. Characterization of the products is given in Table 1.

N^2,N^6-Di(xanthotoxin-4-sulfonyl)-L-Lys (XV) and N^2,N^5-di(xanthotoxin-4-sulfonyl)-L-Orn (XVI)

I (6.3 g; 0.02 mole) was dissolved in dioxan (150 ml) and added dropwise to a solution of L-lysine (1.8 g; 0.01 mole) or L-ornithine (1.67 g) in dioxan (100 ml) containing triethylamine (12 ml). The remaining procedure was followed as described for synthesis of *II—XIV*. The products were recrystallized from methanol and gave negative ninhydrin reaction. Characterization of the products is given in Table 1.

Xanthotoxin-4-sulfonylglycine acid chloride

II (3.5 g; 0.01 mole) was dissolved in dry benzene (100 ml) and phosphorus pentachloride (1.7 g) added in portions. The reaction mixture was stirred at room temperature and refluxed for 2 hrs at 60°C. Evaporation of the solvent *in vacuo* gave the acid chloride which was recrystallized from benzene—petroleum ether. Yield 3.2 g (70%), m.p. 140—142°C. The product was chromatographically homogeneous, R_F 0.83.

Xanthotoxin-4-sulfonyldi- and tripeptides (XVII—XXIII)

Xanthotoxin-4-sulfonylglycine acid chloride (3.71 g; 0.01 mole) was dissolved in dioxan (100 ml) and added dropwise to a solution of amino acid (0.01 mole) or its methyl ester hydrochloride (0.012 mole) in dioxan (100 ml) containing triethylamine (4 ml). The reaction mixture was stirred at room temperature and briefly refluxed till completion as monitored by TLC. The remaining procedure was conducted as described for synthesis of *II—XIV*. The products were recrystallized from methanol, ethanol or chloroform. All the products were chromatographically pure since *XVII—XXII* gave a positive blue biuret reaction and *XXIII* a violet one. Characterization of the products is given in Table 2.

Table 1

Characterization of xanthotoxin-4-sulfonylamino acid derivatives (*II—XVI*)

No.	R	Formula	*M*	Calculated/found			Yield %	M. p. °C	R_F	Solvent	$[\alpha]_D^{20}$
				% C	% H	% N					
II	-Gly	$C_{14}H_{11}O_8NS$	353.20	47.59 47.61	3.11 3.42	3.96 3.94	66	164—166	0.40	—	—
III	-L-Ala	$C_{15}H_{13}O_8NS$	367.23	49.04 49.08	3.50 4.00	3.80 3.86	59	171—172	0.68	Chloroform	+ 59.5
IV	-L-Val	$C_{17}H_{17}O_8NS$	395.28	51.64 52.20	4.30 4.26	3.50 3.80	78	210—212	0.41	Chloroform	+138.2
V	-L-Leu	$C_{18}H_{19}O_8NS$	499.30	52.81 52.81	4.64 4.60	3.42 3.34	60	171—172	0.55	Chloroform	+ 87.1
VI	-L-Ser	$C_{15}H_{13}O_9NS$	383.22	49.03 49.13	3.80 3.49	3.90 3.95	55	182—184	0.61	Chloroform	+ 42.5
VII	-D,L-Ser	$C_{15}H_{13}O_9NS$	383.22	49.03 49.15	3.80 3.59	3.90 3.92	54	169—170	0.62	—	—
VIII	-D-Phe	$C_{21}H_{17}O_8NS$	443.32	56.80 56.85	3.80 4.03	3.16 2.99	63	186—188	0.58	Chloroform	+ 44.1
IX	-L-Tyr	$C_{21}H_{17}O_9NS$	459.31	54.80 54.87	3.90 4.10	3.04 3.17	54	177—179	0.61	Chloroform	− 51.1

Table 1 (Continued)

No.	R	Formula	*M*	Calculated/found			Yield %	M.p. °C	R_F	Solvent	$[\alpha]_D^{20}$
				% C	% H	% N					
X	-L-Met	$C_{17}H_{17}O_8NS_2$	427.34	47.77 47.97	3.98 4.23	3.27 3.44	74	215—217	0.52	Chloroform	+123.3
XI	-L-Thr	$C_{16}H_{15}O_9NS$	397.24	48.36 48.81	3.77 4.78	3.52 3.52	76	161—162	0.56	Chloroform	−165.4
XII	-L-Pro	$C_{17}H_{11}O_8NS$	389.23	52.40 52.73	2.80 3.12	3.50 3.71	59	265—266	0.53	Dimethylformamide	+110
XIII	-L-Glu	$C_{17}H_{15}O_{10}NS$	425.24	48.00 47.96	3.52 3.45	3.29 3.81	54	153—155	0.70	Chloroform	+ 64.1
XIV	-L-Cyst	$C_{15}H_{13}O_8NS_2$	399.29	49.00 49.41	3.50 3.55	3.80 4.32	69	162—164	0.69	Chloroform	− 48.5
XV	-L-Lys	$C_{30}H_{26}O_{14}N_2S_2$	702.47	51.20 51.33	3.70 4.50	3.99 3.68	61	251—253	0.72	Dimethylformamide	+ 65.5
XVI	-L-Orn	$C_{29}H_{24}O_{14}N_2S_2$	688.45	50.58 50.81	3.48 3.21	4.06 4.41	72	159—160	0.66	Chloroform	−178.3

Table 2

Characterization of xanthotoxin-4-sulfonyldi- and tripeptides (*XVII—XXIII*)

No.	R	Formula	*M*	Calculated/found % C	% H	% N	Yield %	M.p. °C	R_F	Solvent	$[\alpha]_D^{20}$
XVII	Gly-Gly-OMe	$C_{17}H_{16}O_9N_2S$	424.26	48.20 48.25	3.12 3.42	6.76 6.89	78	190—192	0.87	—	—
XVIII	Gly-L-Val-OMe	$C_{20}H_{22}O_9N_2S$	466.30	51.50 51.23	4.70 5.12	6.08 6.13	57	166—168	0.75	Chloroform	+125.1
XIX	Gly-Gly	$C_{16}H_{14}O_9N_2S$	410.25	46.82 46.92	3.90 3.99	6.82 7.12	68	210—212	0.71	—	—
XX	Gly-L-Leu	$C_{20}H_{22}O_9N_2S$	466.30	51.54 51.64	4.72 4.95	6.08 6.18	52	177—180	0.86	Chloroform	+115.37
XXI	Gly-L-Ser	$C_{17}H_{16}O_{10}N_2S$	440.26	46.36 46.66	3.63 3.52	6.36 6.29	65	170—172	0.84	Dimethylformamide	+ 95.5
XXII	Gly-L-Orn	$C_{19}H_{21}O_9N_3S$	467.42	48.90 48.99	4.50 4.60	9.01 9.11	56	182—184	0.85	Chloroform	+140.2
XXIII	Gly-Gly-Gly-OMe	$C_{19}H_{19}O_{10}N_3S$	481.39	47.90 48.10	3.90 4.12	8.73 8.78	72	158—160	0.88	—	—

Results and discussion

Condensation of 9-methoxypsoralene-4-sulfonyl chloride *I* with the appropriate amino acid (1 : 1.2 mole) in dioxan—triethylamine afforded the desired xanthotoxin-4-sulfonylamino acid derivatives *II—XVI* (Table 1). The time required for completion of the reaction (1/2—3 hrs) was monitored by TLC. Synthesis of the Ser, Tyr, Thr, and Trp derivatives did not require the prior protection of the side chain groups and no side reactions were observed. Preparation of N^2,N^6-di(xanthotoxin-4-sulfonyl)-L-Lys (*XV*) and the corresponding ornithine derivatives *XVI* required 2 moles of *I* per mole of lysine and ornithine, respectively. Most of the products (*II—XVI*) were easily isolated, purified, recrystallized, and obtained in 54—80% yield.

The i.r. spectrum of *II* showed the characteristic bands at 3260, 1370, and 1170 (SO_2NH); 3440 (NH); 2850 (COOH); 2940 (OCH_3); 1750, 1650, 1450 (α-pyrone); 1305, 1150 (SO_2) cm^{-1} thereby confirming the structure of *II*. The i.r. spectra of all other compounds (*III—XVI*) showed analogous bands confirming their structures.

The u.v. spectra of *II—XVI* in ethanol showed the expected absorption maxima of furocoumarin residue at λ_{max} (log ε) 225 (4.32), 252 (4.16), 265 (4.14), and 310 nm (3.98).

Synthesis of xanthotoxin-4-sulfonyldipeptides (*XVII—XXII*; Table 2) was performed starting from *II*. When *II* was treated with phosphorus pentachloride in benzene, the corresponding acid chloride was obtained. *XVII—XXII* were readily prepared by the reaction of xanthotoxin-4-sulfonyl-Gly-COCl with the appropriate amino acid (or the corresponding methyl ester hydrochloride) in dioxan—triethylamine medium. Synthesis of xanthotoxin-4-sulfonyl-Gly-Gly-OMe (*XVII*) was performed using two ways. Coupling reaction of *I* with Gly-Gly-OMe [7] gave identical product with that obtained from the reaction of xanthotoxin-4-sulfonyl-Gly-COCl with Gly-OMe. The two products gave the same m.p., R_F, analysis, however the first procedure gave 80% yield. Condensation of xanthotoxin-4-sulfonyl-Gly-COCl with Gly-Gly-OMe gave *XXIII* in 72% yield.

The i.r. spectrum of *XVII* showed the characteristic bands at 3390 (NH); 3280, 1370, and 1170 (SO_2NH); 1665, 1530, and 1280 (amide *I, II, III*); 1740, 1650, and 1560 (α-pyrone); 1445, 1360 ($COOCH_3$); 2960 (OCH_3); 1960 (>C=O) and 1310, 1160 (SO_2) cm^{-1} thereby confirming the structure of *XVII*.

Xanthotoxin-4-sulfonyl-L-Ser (*VI*) and xanthotoxin-4-sulfonyl-Gly-L-Ser (*XXI*) were found to be active against *Escherichia coli, Sarcina lutea, Candida albicans, Bacillus subtilis, Micrococcus pyogenes,* and *Staphylococcus aureus.* However, all the remaining derivatives were inactive against all the microorganisms tested. Other pharmacological studies are still under investigation.

References

1. Soine, T. O., *J. Pharm. Sci.* ***53***, 231 (1964).
2. Brokke, M. M., *Psoralene and Radiant Energy. Proceeding of Symposium; J. Inrest. Dermet.* ***32***, 2 (1959).
3. El-Naggar, A. M., Elgamal, M. H. A., El-Tawil, B. A. H., and Ahmed, F. S. M., *Indian J. Chem.* ***13***, 415 (1975).
4. El-Naggar, A. M., Elgamal, M. H. A., El-Tawil, B. A., H., and Ahmed, F. S. M., *Acta Chim. Acad. Sci. Hung.* ***77***, 54 (1976).
5. El-Naggar, A. M., Salem, E. M. S., and Zaher, M. R., *Indian J. Chem.* ***12***, 1161 (1974).
6. Brokke, M. M. and Christensen, B. E., *J. Org. Chem.* ***24***, 523 (1959).
7. Islam, A. M., El-Naggar, A. M., and Abd El-Salam, A. M., *Egypt J. Chem.* ***18***, 430 (1975).