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SYNTHESIS OF XANTHOTOXIN AND THIOXANTHOTOXIN SULPHONAMIDES WITH EXPECTED BIOLOGICAL ACTIVITIES

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A variety of xanthotoxin sulphonamides were prepared via reaction-4-sulphonyl chloride with amines. The preparation of thioxanthotoxin-4-sulphonyl chlorides and its reactions with amines was described.

Key words: Xanthotoxin, Thioxanthotoxin.

INTRODUCTION

Current literature showed that the furocoumarins of *Ammi majus* L. plant, a common annual herbaceous plant belongs to the family Umbelliferae [1] grows freely in the drained areas of the Delta Nile region, exhibit mollucicidal activity [2] and coumarin derivatives having methyl, hydroxyl and methoxyl groups were found to exhibit significant anthelemintic activity [3]. Also, coumarin derivatives have found to be physiologically active in animals as well as in man [4], specially as photosensitizers.

Sulphonamides have received a great deal of interest due to their antibacterial activity [5]. Sulphonamide itself was widely used in medicine against *Cocci* infections, *Streptococci, Gonococci* and *Pneumococci* but it has been largely replaced by various derivatives are less toxic or more potent for particular.

EXPERIMENTAL

All melting points were uncorrected. i.r. spectra were performed on a Unicam Sp 1200 apparatus (in KBr). The u.v. measurements were taken in methanol on Carl Zeiss Spectrophotometery type PMQ II. All compounds were analysed for C,H and N(± 0.5 % limit).

Preparation of xanthotoxin-4-sulphonamides (II-IX). A mixture of I (0.005 mole), the amino derivative (0.005 mole) and few drops of pyridine in 30 ml of dry acetone, was refluxed for 2 hours. The reaction mixture was concentrated and 20 ml. of dilute hydrochloric acid (1:1) was added. The solid formed was separated, washed with water, dried and crystallised from the proper solvent. I.R. spectra showed bands at 3440 cm^{-1} (NH) and 1705, 1660 cm^{-1} (lactone carbonyl).

Monochloro-sulphacetamido-xanthotoxin (XII). Xanthotoxin-4-sulphonamide (X,1g.) was dissolved in acetone, then, 0.5 ml. of monochloroacetyl chloride was added dropwise to the mixture and refluxed for 2 hours, the reaction mixture was left overnight, the deposited material was crystallised from ethanol.

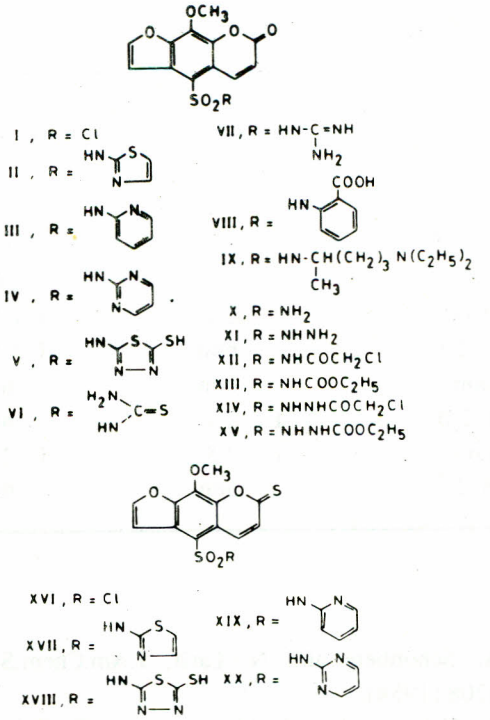
Xanthotoxin-4-sulphonamido-ethyl acetate (XIII). Xanthotoxin-4-sulphonamide (X, 0.5 g) was dissolved in dry acetone (50 ml.), then 0.3 g. ethyl bromoacetate was added dropwise , the reaction mixture was refluxed for 0.5 hr., cooled, the deposited material was crystallised from ethanol.

Xanthotoxin-4-sulphonohydrazo-mono-chloro acetamide (XIV). Xanthotoxin-4-sulphonohydrazide (XI, 0.5 g) was dissolved in dry acetone, then mono-chloro-acetyl chloride (0.5 g) was added dropwise in the presence of pyridine as catalyst, refluxed for 0.5 hr. The reaction mixture cooled and the deposited material was filtered off and crystallised from *n*-hexane.

Xanthotoxin-4-sulphonohydrazide ethyl acetate derivative (XV). Xanthotoxin-4-sulphonohydrazide (XI, 0.5 g) in dry acetone was added to 0.5 g. of ethyl bromo acetate and 1 g. anhydrous potassium carbonate. The reaction mixture was refluxed for 0.5 hr. After cooling, the deposited material was filtered off and crystallised from methanol.

Preparation of thioxanthotoxin-4-sulphonyl chloride (XVI). 10 g. Thioxanthotoxin (10 g.) was allowed to react with 50 ml. chlorosulphonic acid at -5°. The reaction mixture was stirred for 3 hours, then poured onto ice, the deposited material was filtered off, washed with water and crystallised from petroleum ether (40-60°) to give crystalline product, m.p. 163-165°.

Preparation of thioxanthotoxin-4-sulphonamides (XVII-XX). A mixture of (XVI, 0.01 mole) and the amino derivative (0.01 mole) was refluxed in dry acetone (30 ml.) for 0.5-4 hours. The reaction mixture was concentrated, cooled, the deposited material was filtered off, crystallised from *n*-hexane.



RESULTS AND DISCUSSION

The present work describes the preparation of newer xanthotoxin and thioxanthotoxin sulphonamides derivatives for biological screening as antibacterial agents. The sulphonamide moiety was chosen so as to be biologic active, such as 2-aminothiazole [7], 2-aminopyridine, 2-aminopyrimidine, 2-amino-1,3,4-thiadiazole-5-thiol [8], thiourea, guanidine, 2-amino-benzoic acid and 2-amino-5-diethylaminopentane.

Xanthotoxin-4-sulphonyl chloride (i) [9] has been prepared and allowed to react with the previously mentioned amino derivatives to give the corresponding xanthotoxin-4-sulphonamides (II-IX). Also xanthotoxin-4-sulphonamide (X) and xanthotoxin-4-sulphonohydrazide (XI) [10] were allowed to react with monochloroacetyl chloride and bromoethyl acetate to afford the corresponding derivatives (XII-XV).

Thioxanthotoxin-4-sulphonyl chloride (XVI) was prepared by the action of chlorosulphonic acid on thioxanthotoxin, which have been previously prepared. To resulting product was allowed to react with some strong biologically active amino compounds to give thioxanthotoxin-4-sulphonamide derivatives (XVII-XX).

The structures of the prepared compounds were confirmed by their analytical and spectral data. The i.r. u.v. spectra of the products in full agreement with the assigned structures and exhibit the expected characteristic absorption bands. The physical data of the prepared compounds are given in Table 1.

The effect of xanthotoxin and thioxanthotoxin sulphonamide derivatives was examined on *Bacillus subtilis, Escherichia coli, Aerobacter aerogenes, Micobacterium*

Table 1. Physical data of various compounds prepared.

Compd.	m.p.°	Yield %	Mol.formula	Analysis (%)					
				Calc.			Found		
II	272°	65	$C_{15}H_{10}N_2O_6S_2$	47.61	2.64	7.40	47.54	2.70	7.25
III	220°	70	$C_{17}H_{12}N_2O_6S$	54.80	3.22	7.52	54.78	3.20	7.61
IV	177°	70	$C_{16}H_{11}N_3O_6S$	51.47	2.95	11.26	51.5L	2.89	11.15
V	192°	65	$C_{14}H_9N_3O_6S3$	40.08	2.18	10.20	40.47	2.12	10.08
VI	162°	80	$C_{13}H_{10}N_2O_6S_2$	44.07	2.82	7.92	44.19	2.86	7.81
VII	182°	80	$C_{13}H_{11}N_3O_6S$	46.20	3.26	12.46	46.39	3.15	12.20
VIII	195°	60	$C_{19}H_{13}NO_8S$	54.90	3.13	3.37	54.68	3.10	3.40
IX	218°	90	$C_{20}H_{27}N2O_6S$	56.75	6.37	6.62	56.49	6.29	6.71
XII	256°	75	$C_{14}H_{10}NO_7CIS$	45.22	2.69	3.77	45.70	2.62	3.96
XIII	130°	70	$C_{15}H_{13}NO_4S$	50.39	3.93	3.67	50.27	3.87	3.59
XIV	248°	70	$C_{14}H_{11}N_2O_7CIS$	43.35	3.09	7.22	43.12	3.12	7.31
XV	176°	70	$C_{15}H_{14}N_2O_9S$	48.36	4.28	7.05	48.42	4.19	7.12
XVI	165°	65	$C_{12}H_7O_5CIS_2$	43.57	2.12		43.41	2.10	
XVII	207°	50	$C_{15}H_{10}N_2O_5S_3$	45.58	2.59	7.10	54.93	2.53	7.16
XVIII	197°	50	$C_{14}H_9N_3O_5S_4$	39.34	2.11	9.84	39.52	2.17	9.78
XIX	256°	60	$C_{17}H_{12}N_2O_5S_2$	52.57	2.10	7.22	52.81	2.98	7.18
XX	130	60	$C_{16}H_{11}N_3O_5S_2$	49.36	2.83	10.79	48.92	2.75	10.72

Table 2. Effect of antimicrobial substances on the tested organisms.

Sample No.	*B.subtilis*	*E.coli*	*A.aerogenes*	*Myco.pheli*	*Sacch.cerevisieae*	*Micro.flavus*
II	I 1.5	non	non	non	non	I 1.2
III	non	non	non	S 1.3	non	non
IV	non	S 1.2	non	S 2.3	non	non
V	I 2.4	non	non	I 2.5	non	I 2.6
VI	I 2.0	non	non	non	I 2.2	I 1.5
VII	I 2.4	I 1.7	non	I 2.3	non	I 1.8
IX	non	non	non	non	non	non
XVII	I 2.0	non	non	I 2.0	I 2.1	non
XVIII	I 2.5	non	non	non	I 2.5	I 2.0
XIX	non	non	non	S 2.2	non	non

I = Inhibition effect; S = Stimulation effect
The activity measured as width of zones (mm).

pheli, Micrococcus flavus and *Saccharomyces cerevisieae* using the paper disc plate method of Lao *et al.* [11].

The obtained results indicated that all xanthotoxin-4-sulphonamide derivatives had no effect on *Aerobacter aerogenes* micro-organism, but show a different considerable activities against the other various gram positive and gram negative bacteria.

The more active derivatives were xanthotoxin and thioxanthotoxin-4-sulphon-5-amido-2-mercapto-1-3,4-thiadiazole which were found to have a considerable inhibition activities against *Bacillus subtilis, Micobacterium pheli* and *micrococcus flavus,* respectively. This indicates that the introduction of a sulphon-5-amido-2-mercapto-1,3,4-thiadiazole group in the molecule of xanthotoxin and thioxanthotoxin sulphonamides renders it highly active against the tested micro-organisms. The obtained results are give in Table 2.

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