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SYNTHESIS OF SOME FUROCOUMARIN DERIVATIVES AND THEIR ANTI-MICROBIAL ACTIVITIES

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Treatment of xanthotoxol (I) with some primary and secondary amines in the presence of formaline solution 40% afforded the Mannich bases (IIa-f). Chlorosulphonation of compound (I) using chlorosulphonic acid led to the formation of xanthotoxol-4- sulphonyl chloride (III), which allowed to react with some primary and secondary amines to give the corresponding sulphonamide derivatives (IVa-f, V, VIa-c). The condensation of the sulphonamide derivatives (V and VIa-c) with some aromatic aldehydes led to the formation of the corresponding Schiff's bases (VIIa-d, VIIIa-d and Xa-d).

Key words: Xanthotoxol-Sulphonamides-Mannich and Schiff's bases.

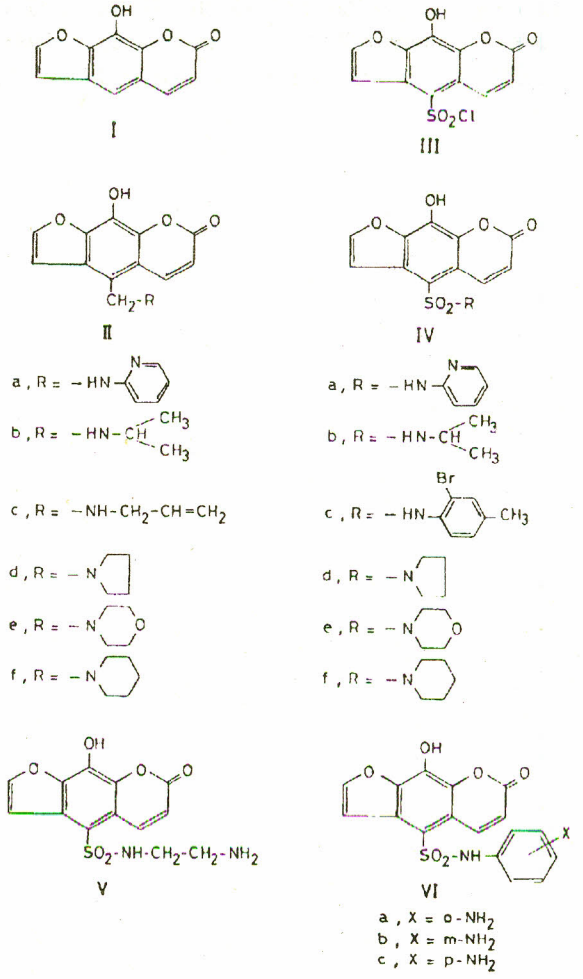
Introduction

It has been reported that xanthotoxol possesses some biological activities like nervous system depressant [1], antiserotonin smooth muscle [2]and some esters and ethers have predictable skin photosensitizing agent [3]. Also the biological activity of Mannich bases [4], like antiamoebic and anti-inflammatory agents have been reported. The remarkable bacteriostatic action of the sulphonamides [5,6] and the biological activity of the Schiff's bases [7,8] led us to synthesize some new Mannich base, sulphonamide and Schiff's base derivatives with expected biological activity.

Results and Disccussion

Mannich reaction of xanthotoxol (I) using primary or secondary amines i.e., 2-aminopyridine, isopropylamine, allyl amine, pyrrolidine, morpholine and piperidine gave the corresponding Mannich bases (IIa-f). The structures were confirmed by correct chemical analyses. All the compounds gave green colour reaction with aqueous ferric chloride solution. the infrared spectrum of compound (IId) shows characteristic bands at 1730 cm^{-1} (C=O, δ-lactone), at 3500 cm^{-1} (OH), at 1290 cm^{-1} (C-N) and at 3200 cm^{-1} (NH). The ^1H NMR spectrum of compound IId in $CDCl_3 + D_2O$, shows signals at δ = 7.1 and 7.9 ppm as doublet (J=3 Hz) for the 2 protons of furanoid moiety, at δ = 6.2 and 8.2 ppm, as doublet (J = 10 Hz) for the 2 protons of the pyranoid moiety, at δ = 2.1 ppm as singlet 2H for the CH -N- and at δ = 1.65 and 3.2 ppm as multiplet 8H for the pyrrolidine moiety (Scheme 1).

The chlorosulphonation of compound (I) using chlorosulphonic acid at 0° led to the formation of 9-hydroxypsoralen-4-sulphonyl chloride (III) [9], which allowed to react with primary and secondary amines i.e., 2-aminopyridine, isopropylamine, 2-bromo-4-methylaniline, pyrrolidine, morpholine and piperidine to give the corresponding sulphonamide derivative (IVa-f). The structures were confirmed by correct chemical analyses. The infrared spectrum of compound IVd shows bands at 3500 cm^{-1} (OH), 3150 cm^{-1}



Scheme 1.

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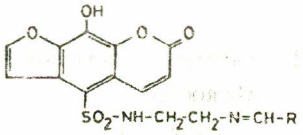
(NH), 1350 cm^{-1} and 1160 cm^{-1} (SO_2-N) and at 1750 cm^{-1} for δ-lactone (Scheme 1).

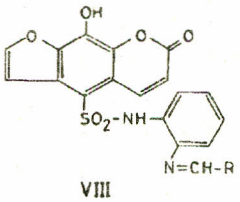
The ^1H NMR spectrum of compound IVd in $CDCl_3 + D_2O$ revealed signals at δ =7.14 and 7.85 ppm as doublet (J= 3Hz) 2H for the furanoid moiety, at δ =6,48 and 8.26 ppm as doublet (J= 10Hz) 2H for the pyranoid moiety, at δ =1.65 and 3.2 ppm for the pyrrolidine moiety (m,8H).

On the other hand the reaction of compound (III) with ethylenediamine, *o*,*m*,or *p*-phenylenediamine in an equi-molecular mass and in the presence of triethylamine as a catalyst led to the formation of sulphonamide derivatives (V and VIa-c), respectively. The free amino group in these sulphonamide derivatives was allowed to react with some aromatic aldehydes to give the Schiff's bases derivatives (VIIa-d, VIIIA-d, IXA-d and Xa-d), respectively (Scheme 1,2).

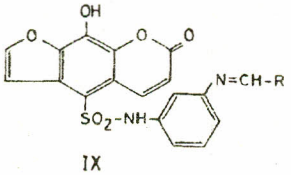
The infrared of compound V shows bands at 3500 cm^{-1} (OH), 3300 cm^{-1} (NH), 3200cm^{-1}, 3250 cm^{-1} (NH), 1740 cm^{-1} (δ-lactone), and 1375 and 1160 cm^{-1} (SO_2-N), The infrared of compound (VIIa) shows bands at 3400 cm^{-1} (OH), 3100 cm^{-1} (NH), 1740 cm^{-1} (δ-lactone), 1370 and 1150 cm^{-1} (SO-N), and at 1570 cm^{-1} (-C=N-).



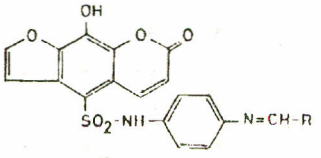
VII



VIII



IX



X

VII , VIII , IX and X a , R = C_6H_5
b , R = C_6H_4-OCH_3-p
c , R = C_6H_4-Cl-p
d , R = C_6H_4-$N(CH_3)_2$-p

Scheme 2.

The ^1H NMR spectrum of compound IXb in $CDCl_3$ = D_2O revealed signals at δ =7.2 and 8.0 ppm as doublet (J=3 Hz), for 2 protons of the furanoid moiety, at δ =6.5 and 8.3 ppm as doublet (J=10 Hz) for the 2 protons of the pyranoid moiety, at δ =8.5 ppm singlet 1 proton for the imino group, δ=3.8ppm 3 portions singlet for the OCH_3, and at δ =7.1-7.4ppm (m, 8 H of the 2 phenylene moieties).

Experimental

M.P.'s are uncorrected. The infrared spectra (KBr) were recorded on Unicam SP 1000 infrared spectrophotometer. The

TABLE 1. PHYSICAL AND ANALYTICAL DATA OF THE COMPOUNDS.

Compd. No.	M.P. °C	Yield %	Molicular formula	Analysis Calc/Found% C	H	N
IIa	295	75	$C_{17}H_{12}O_4N_2$	66.23	3.90	9.09
				65.92	3.40	8.78
b	310	83	$C_{15}H_{15}O_4N$	65.93	5.49	5.13
				65.49	5.28	5.02
c	280	80	$C_{15}H_{13}O_4N$	66.40	4.80	5.17
				66.75	4.40	4.92
d	150	82	$C_{16}H_{15}O_4N$	67.37	5.26	4.91
				67.74	5.37	4.67
e	200	85	$C_{16}H_{15}O_5N$	63.79	4.98	4.65
				63.53	4.80	4.34
f	165	80	$C_{17}H_{17}O_4N$	67.92	5.60	4.68
				68.23	5.69	4.32
IVa	190	70	$C_{16}H_{10}O_6N_2S$	53.63	2.79	7.82
				53.50	2.70	7.65
b	245	65	$C_{14}H_{13}O_6NS$	52.01	4.02	4.33
				52.36	4.50	4.20
c	227	65	$C_{18}H_{12}BrNS$	48.01	2.67	3.11
				48.45	2.53	3.60
d	180	80	$C_{15}H_{13}O_6NS$	53.7	3.88	4.18
				53.99	4.27	4.35
e	210	75	$C_{15}H_{13}O_7NS$	51.28	3.70	3.99
				50.93	3.80	3.49
f	255	70	$C_{16}H_{15}O_6NS$	55.01	4.30	4.01
				54.70	4.50	4.46
V	270	85	$C_{13}H_{12}O_6N_2S$	48.15	3.70	8.64
				47.83	3.68	8.70
VIa	210	60	$C_{17}H_{12}O_6N_2S$	54.84	3.22	7.53
				54.39	3.67	7.82
b	230	65	$C_{17}H_{12}O_6N_2S$	54.84	3.22	7.53
				54.71	2.95	7.42
c	225	60	$C_{17}H_{12}O_6N_2S$	54.84	3.22	7.53
				54.65	2.89	7.09
VIIa	305	70	$C_{20}H_{16}O_6N_2S$	58.25	3.88	6.80
				58.69	3.62	6.39
b	296	75	$C_{21}H_{18}O_7N_2S$	57.01	4.07	6.33
				56.84	4.32	6.57
c	280	68	$C_{20}H_{15}ClO_6N_3S$	53.75	3.36	6.27
				53.91	3.42	6.72
d	269	80	$C_{22}H_{21}O_6N_3S$	58.02	4.62	9.23
				58.34	4.75	9.43

(Table 1, Contd.)

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VIIIa	217	60	$C_{24}H_{17}O_6N_2S$	62.61	3.48	6.08
				62.75	3.43	6.25
b	235	65	$C_{25}H_{18}O_7N_2S$	61.22	3.67	5.71
				61.79	3.45	5.92
c	240	60	$C_{24}H_{15}ClO_6N_2S$	58.24	3.03	5.66
				58.53	3.42	5.34
d	237	70	$C_{26}H_{21}O_6N_3S$	62.03	4.17	8.35
				62.41	4.50	8.43
IXa	235	68	$C_{24}H_{16}O_6N_2S$	62.61	3.48	8.35
				62.75	3.54	6.35
b	250	60	$C_{25}H_{18}O_7N_2S$	61.22	3.67	5.71
				61.66	3.42	5.36
c	225	70	$C_{24}H_{15}ClO_6N_2S$	58.24	3.03	5.66
				58.64	3.52	5.99
d	224	75	$C_{26}H_{21}O_6N_3S$	62.03	4.17	8.35
				62.42	4.23	8.24
Xa	236	65	$C_{24}H_{16}O_6N_2S$	62.61	3.48	6.08
				62.93	3.72	6.54
b	227	60	$C_{25}H_{18}O_7N_2S$	61.22	3.67	5.71
				61.52	3.43	5.64
c	228	68	$C_{24}H_{15}ClO_6N_2S$	58.24	3.03	5.66
				58.45	3.41	5.97
d	226	70	$C_{26}H_{21}O_6N_3S$	62.03	4.17	8.35
				62.50	4.43	8.25

^{1}HNMR spectra were run on Ieol FX 90q spectrometer using $CDCl_3$ and TMS as internal solvent.

General procedure for the preparation of Mannich bases (IIa-f). Xanthotoxol (I) (0.01 mole) in ethanol 20 ml and an ethanolic solution of the amine (0.02 mole) and (0.01 mole) of 40% formaldehyde solution were refluxed together for 1 hr. After cooling the precipitate formed was filtered off, washed with water, then recrystallized from ethyl alcohol.

Preparation of sulphonamide derivatives (IVa-f): Genral procedure. Xanthotoxol-5-sulphonyl chloride (III) (0.01 mole) in ethanol 30 ml and the appropriate amine (0.02 mole) were refluxed together for 4—8 hr. The formed product after cooling was filtered off, washed with water and then recrystsllized from ethyl alcohol.

Preparation of sulphonamide derivatives (V and VIa-c): General procedure. Xanthotoxol-5-sulphonyl chloride (III) (0.01 mole) in 30 ml absolute ethanol and that appropriate amine (0.01 mole) and few drops of triethylamine, were refulxed together for 4-5 hr. The solid formed after cooling was filtered off, washed with water and then recrystalllized from alcohol.

Preparation of Schiff's bases (VII, VIII, IX and X): General procedure. A mixture of equimolecular quantities of the compounds (V and/or VIa-c) and the appropriate aromatic aldehyde in ethanol and few drops of acetic acid was refluxed for 2 hr. The reaction mixture was concentrated to its 1/3 volume, and formed precipitate was filtered off, washed with water and then recrystallized from ethanol.

Biological activity test. The activity of the compounds were tested by the disk diffusion method [10]. Whattman No.1 filter paper disks were sterilized by autoclaving for 1 hr. at 140°. The sterile disks were impregnated with the different new compounds (100 µg/disk). Agar plated were surface inoculated uniformly from fresh broth culture of *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Proteus mirabilis, Serratia marcescens, Staphylococcus aureus, Bacillus cereus and Candida albicans.* The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated 24 hr at 28°.

The sensitivity of micro-organisms to the compounds is identified in the following manners:

+++ = Highly sensitive (inhibition zone 12 mm).
++ = Fairly sensitive (inhibition zone 9-12mm).
+ = Slightly sensitive (inhibition zone 6-9 mm).
- = Not sensitive.

The code number of the micro-organisms tested: (1). *Escherichia coli.* (2). *Pseudomonas aeruginosa.* (3).*Klebsiella pneu-monia.* (4). *Proteus mirabilis.* (5). *Serratia marcescens.* (6). *Staphylococcus aureus.* (7). *Bacillus cereus.* (8). *Candida albicans.*

TABLE 2. THE PREPARED COMPOUNDS AGAINST MICROORGANISMS.

Compound	Micro-organisms							
No.	1	2	3	4	5	6	7	8
IIa	+	-	+	-	-	-	+	-
IIb	+	++	+	+++	+	-	+	+
IIc	+	+	+	+	-	-	+	-
IId	+	+	+	+	-	-	+	-
IIe	+	++	+	-	+	+	-	+
IIf	+	++	+	+	+	+	-	-
IIIb	+	+	+	-	-	-	+	+
IVa	+	+	+	-	+	-	+	++
IVb	+	+	+	+	+	+	+++	-
IVc	+	+	+	+	+	+	+	+
IVe	+	++	+	-	+	+	-	+
IVf	+	+	+	+	+	+	-	+
V	+	-	+	+	+	+	-	-
VIIa	+	+	+	++	++	+	++	-
VIIb	+	+	+	-	-	-	+	-
VIIc	+	+	+	+	+	+	+	-
VIId	+	-	+	-	-	-	+	+
VIII	+	+	+	+	+	++	-	+
VIIIa	+	++	+	+	+	-	+	+
VIIIb	+	+	+	+	+	++	-	+

(Table 2 , Contd.)

(Table 2, Cont.)

VIIIc	+	+	+	+	+	-	+	-
VIIId	+	+	++	++	++	++	++	+
IX	+	+	+	-	+	+	-	-
IXa	+	++	+	+	+	+	+	-
IXb	+	++	+	+	+	-	+	-
IXc	+	+	+	+	+	-	+	+
IXd	+	+	+	+	+	+	+	+
X	+	+	+	+	+	+	-	+
Xa	+	+	+	+	+	+	+	-
Xb	+	+	+	+	+	-	+	-
Xc	+	+	+	+	+	-	+	-
Xd	+	+	+	+	+	+	+	+

The results of the biological activity are shown in Table 2.

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