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SYNTHESIS OF XANTHOTOXIN DERIVATIVES

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ABSTRACT

A number of xanthotoxin–5–sulpho–derivatives 2a–c, 3a–c and 4a–e have been prepared by reaction of xanthotoxin–5–sulphonyl chloride (1) with amino–compounds or phenolic–compounds. The action of hydrazine derivatives on (1) have also been investigated. The interaction of hydrazine derivatives on xanthotoxin–5–sulphonamides 1, 2a and 4a has been discussed.

INTRODUCTION

The incorporation of sulphonamide moiety into xanthotoxin molecule appeared to be of expected biological activity since both xanthotoxin and sulphonamide derivatives are well known for their chemotherapeutic profile (1–4). The present investigation deals with synthesis of some xanthotoxin derivatives involving sulphonyl group, through reaction of xanthotoxin–5–sulphonyl chloride with amines or phenolic compounds. Investigation of α–pyrone ring cleavage of xanthotoxin ring by hydrazine derivatives is studied.

EXPERIMENTAL

N–substitutedxanthotoxin–5–sulphonamides 2a–c and 4a–e.

A mixture of 1 (0.01 mol), the amino–compound (0.01 mol) and pyridine (1 ml) in acetone (50 ml) was heated under reflux for 5 hr. The solution was concentrated, triturated with diluted HCl and filtered off. The product was washed with water and crystallized from the proper solvent to give the title compounds (Table I)

Xanthotoxin–5–sulphonic acid asters 3a–c.

A solution of 1 (0.01 mol) and the phenolic–compound (0.01 mol) in acetone (50 ml) was heated under reflux for 8 hr. After concentration

and cooling, the product was filtered off and crystallized from the proper solvent. (Table I).

Methylation of 4a and 4b: Formation of 5a and 5b.

The sulphonamide 4a or 4b (0.01 mol) was dissolved in 2 ml of 0.01 M NaOH solution diluted with 10 ml water, cooled and then 2 ml dimethylsulphate was added dropwise with stirring. The stirring was continued overnight. The product was filtered off, washed with water and crystallized (Table I).

Reaction of 1 with hydrazine hydrate: Formation of 6a.

To a solution of hydrazine hydrate (0.01 mol) and pyridine (1 ml) in ethanol (50 ml) 0.01 mol of 1 was added. The mixture was stirred for one hour and kept overnight at room temperature. The product filtered off and crystallized (Table I).

Synthesis of the hydrazide (7).

A mixture of 1 (0.01 mol) and hydrazine hydrate (0.05 mol) in ethanol (50 ml) was refluxed for 15 hr. after cooling and concentration, the product was filtered off and crystallized to give 7. (Table I).

Synthesis of the hydrazones (8a) and (8b.)

Equimolar amounts of 2a and hyrazine hydrate or phenyl hydrazine in ethanol was refluxed for 3 hr. The reaction mixture was allowed to cool. The solid that separated was filtered off, dried and recrystallized from the proper solvent. (Table I).

Synthesis of the hydrazide (9)

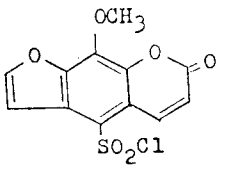
A mixture of 2a (0.01 mol) and hydrazine hydrate (0.05 mol) in ethanol (50 ml) was boiled under reflux for 30 hr. After concentration and cooling the solid product which separated was crystallized. (Table I).

Synthesis of the hydrazide (10)

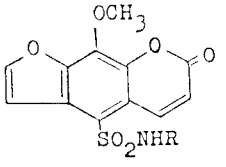
A mixture of 4a (0.01 mol) and hydrazine hydrate (0.05 mol) in ethanol (40 ml) was refluxed for 35 hr. The separated product was filtered off, washed with ethanol and recrystallized to give 10. (Table I).

Reaction of 1 with phenylhydrazine or isonicotinic hydrazide: Formation of 6a or 11.

Equimolar amounts of 1 and the hydrazine derivative in ethanol was boiled under reflux for 4 hr. After concentration and cooling, the product was filtered off and crystallized from the proper solvent (Table I).



(1)



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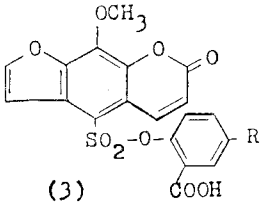


(3)

2a, R = 4-$CH_3COC_6H_4$

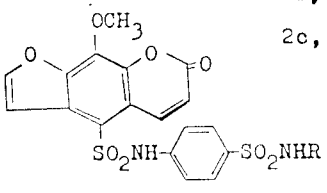
2b, R = 3-OH-4-$COOHC_6H_3$

2c, R = CH_2-$COOC_2H_5$

3a, R = H

3b, R = Br

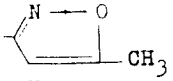
3c, R = Cl



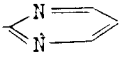
(4)

4a, R =

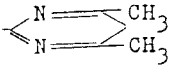
4b, R =



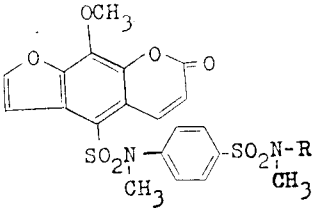
4c, R =



4d, R =

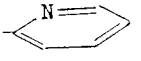


4e, R = -CNH-NH_2

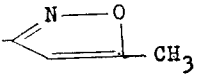


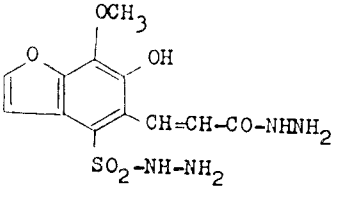
(5)

5a, R =

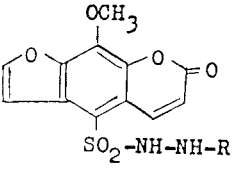


5b, R =





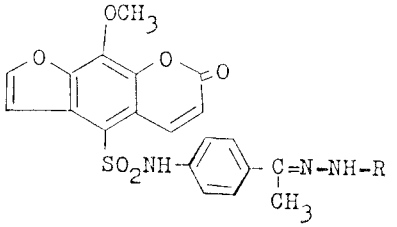
(7)



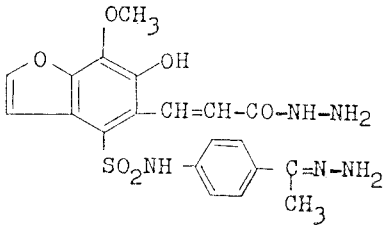
(6)

6a, R = H

6b, R = C_6H_5



(8) 8a, R = H
8b, R = C_6H_5



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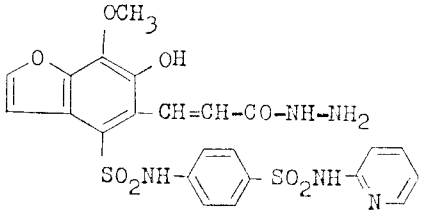

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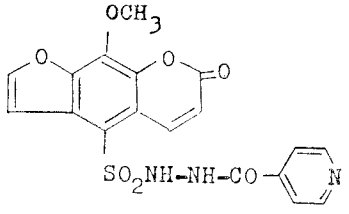

(11)

THE BIOLOGICAL DATA

The biological screening tests were performed according to the cup–plat method(5). The results obtained are summarized in Table (II). The micro–organisms used were: 1) *Bacillus subtilis*, 2) *Escherichia coli*, 3) *Candida albicans, and* 4) *Aspergillus niger*..

The sensitivity of micro–organisms to the tested compounds was identified in the following manner:

+++ = Highly sensitive (inhibition zone 15 mm).
++ = Fairly sensitive (inhibition zone 10 mm).
+ = Slightly sensitive (inhibition zone 5 mm).
— = Not sensitive.

DISCUSSION

Condensation of xanthotoxin–5–sulphonyl chloride 1 with amino–compounds namely 4–aminoacetophenone, 4–aminosalicylic acid or ethylester of glycin in presence of pyridine as base catalyst gives xanthotoxin–5–sulphonamide derivatives 2a–c.

Xanthotoxin–5–sulphonic acid esters 3a–c were formed by reaction of 1 with salicylic acid, 5–bromosalicylic acid or 5–chlorosalicylic acid.

Sulpha-drugs are famous for their bacteriological activity (3,4) and it was found to prepare xanthotoxin-derivatives involving sulpha-drug moiety in the hope of producing a series of compounds with diff-ferent activities. Thus reaction of 1 with sulphapyridine, sulpha-methexazole, sulpha-diazine, sulpha-demidine or sulpha-guanidine gives the compounds 4a–e. Action of dimethylsulphate on 4a, b gives the methylated derivatives 5a, b.

Table (I).

No.	Formula	M.p. °C	Cryst. solv.	Yield
2a	$C_{20}H_{15}NO_7S$	208	EtOH	60 %
2b	$C_{19}H_{13}NO_9S$	210	EtOH	40 %
2c	$C_{16}H_{15}NO_8S$	198	MeOH	35 %
3a	$C_{19}H_{12}O_9S$	145	MeOH	75 %
3b	$C_{19}H_{11}BrO_9S$	175	EtOH	70 %
3c	$C_{19}H_{11}ClO_9S$	142	MeOH	75 %
4a	$C_{23}H_{17}N_3O_9S_2$	271	EtOH	70 %
4b	$C_{22}H_{17}N_3O_9S_2$	215	EtOH	76 %
4c	$C_{22}H_{16}N_4O_8S_2$	150	EtOH	77 %
4d	$C_{24}H_{20}N_4O_8S_2$	207	EtOH	80 %
4e	$C_{19}H_{16}N_4O_8S_2$	191	MeOH	81 %
5a	$C_{25}H_{21}N_3O_8S_2$	255	EtOH	85 %
5b	$C_{24}H_{21}N_3O_9S_2$	150	EtOH	75 %
6a	$C_{12}H_{10}N_2O_6S$	170	EtOH	80 %
6b	$C_{18}H_{14}N_2O_6S$	160	MeOH	82 %
7	$C_{12}H_{14}N_4O_6S$	195	EtOH	40 %
8a	$C_{20}H_{17}N_3O_6S$	205	EtOH	60 %
8b	$C_{26}H_{22}N_3O_6S$	250	MeOH	65 %
9	$C_{20}H_{21}N_5O_6S$	207	MeOH	45 %
10	$C_{23}H_{21}N_5O_8S$	198	EtOH	40 %
11	$C_{18}H_{13}N_3O_7S$	260	MeOH	65 %

Elemental analysis for C, H and N were obtained for all compounds (± 0.4 %).

The reaction of 1 with equimolar amount of hydrazine hydrate gives the sulphonohydrazide 6a. On the other hand 1 reacts with excess amount of hydrazine hydrate to give 7.

The compound 2a reacts with hydrazine hydrate in two manners, 2a reacts with equimolar amount of hydrazine hydrate to give the hydrazone 8a. When alcoholic solution of 2a is boiled with excess hydrazine hydrate α-pyrone ring fission takes place with the formation of the hydrazide 9. The reaction of hydrazine hydrate with 4a proceeds with α-pyrone ring cleavage yielding 10. In support for the structure assignment of 7, 9 or 10 are, $FeCl_3$ gives violet colour due to the (OH) group, elemental analysis and spectral data. Phenylhydrazine reacts with 1 to give 6b whether equimolar or excess amount of phenylhydrazine are used. (ie. no α-pyrone ring fission takes place) Phenylhyd-

razine reacts with 2a in equimolar ratio yielding 8b. The same product is obtained if exsess phenylhydrazine used. 1 reacts similarly with isonicotinic hydrazide yielding 11.

The infrared spectra of 2a–c, 4a–c, and 5a, b show absorption bands at 3300 cm^{-1} (N–H), 1330, 1150 cm^{-1} (SO_2NH), 1680, 1600 cm^{-1} (CO–O lactone) and a number of bands in 1600–1500 cm^{-1} region (C = C aromatic and furan). While the ir spectra of 5a, b are devoid the band at 3300 cm^{-1} (N–H). IR spectra of 3a–c show bands at 1270 cm^{-1} (SO_2–O), 1700, 1600 (CO–O lactone) and a number of bands in the region 1600–1500 cm^{-1} (C = C) aromatic and furan). IR spectrum of 6a shows bands at 3390, 3300, 3130 cm^{-1} ($NH-NH_2$)

BIOLOGICAL ACTIVITY DATA

Some of the prepared compounds were tested against one strain of Gram–positive, one strain of Gram–negative bacteria, yeast and fungus. From the data in Table (II), it is clear that, compound 4d possesses high activity against Gram–positive bacteria, where 3a, 4a 4a and 4b possess moderate activity against Gram–negative bacteria. All the compounds possess slight activity against bacteria, yiest and fungus.

Table (II). The preliminary screening of biological activity of the compounds.

No.	1	2	3	4
2a	+	+	+	+
2b	++	+	+	+
2c	++	+	+	—
3a	+	++	+	+
3c	+	+	+	+
4a	+	++	+	+
4b	++	++	+	++
4c	++	+	+	—
4d	+	+	+	+++
4e	+	+	—	+

1– *Bacillus subtilis*
2– *Escherichia coli*
3– *Candida albicans*
4– *Aspergillus niger*
+++ = Highly active
++ = Fairly active
+ = Slightly active
— = Not sensitive

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