SYNTHESIS AND BIOLOGICAL STUDY OF A NOVEL COUMARIN DERIVATIVES

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Abstract

7-Hydroxy- 4- methyl coumarin (II) was obtained from the reaction of resorcinol (I) with ethyl acetoacetate then this compound was fused with 2- hydroxynaphthaldehyde to give compound (III) .

On treatment of compound (III) through Mannich reaction with glycine and formaldehyde, it yields the final product (IV).

Both compounds (III) and (IV) were characterized by physical and spectral methods; they were also screened for their antibacterial activity.

Key words: 7- Hydroxy - 4- methyl coumarin; Resorcinol; 2-Hydroxynaphthaldehyde; Glycine; Antibacterial

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Introduction

Coumarin constitutes one of the major classes of naturally occurring compounds. Coumrain derivatives have been reported for antimicrobial [1,2] antioxidant[3-5] anticancer[6,7] and antiviral activity[8]. These compounds are also represents the core structure of several molecules of pharmaceutical importance.

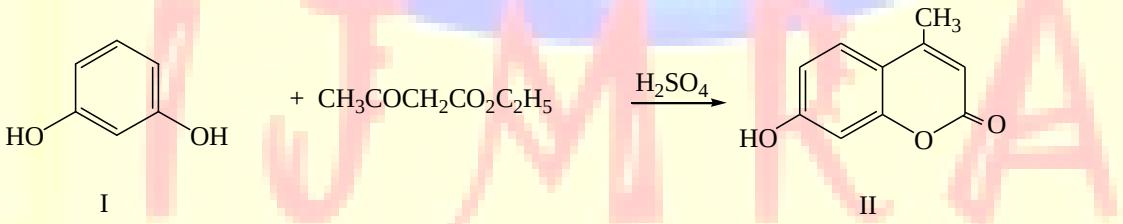
Based on the above observation we found it's worthwhile to prepare newer coumrain derivatives for their antimicrobial activity.

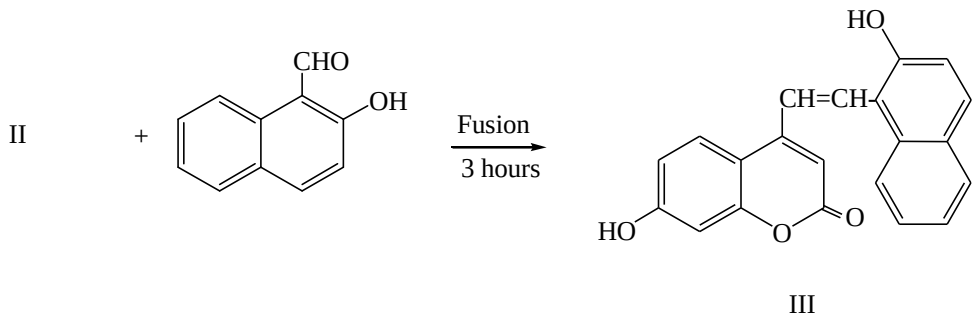
In this work we report a simple and effective method for the synthesis of coumrain derivative.

In the first step 7-hydroxy-4- methyl coumrain (II) was prepared through Pechaman condensation of resorcinol (I) with ethylacetoacetate in presence of concentrated sulphuric acid [9].

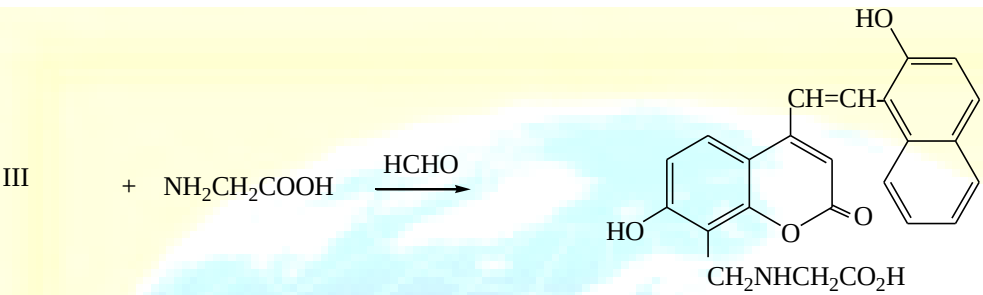
Compound (II) was fused with 2- hydroxynaphthaldehyde, which was prepared according to standard procedure [10] and gave 7-hydroxy-4-[(1-ethylidene-2-hydroxy)naphthyl]-2H-chromen-2-one (III).

This compound then underwent Mannich reaction by treating with glycine and formaldehyde to give the final product [(7-hydroxy-2-oxo-4-ethylidene-2-hydroxynaphthyl)chromen-8-methylamino]acetic acid (IV) (Scheme)





III



IV

Scheme

The structural assignments of compounds (III and IV) were established by IR, ^{1}HNMR and elemental analysis as shown on table 1 and 2.

Compounds III and IV were also tested for antibacterial activity and both compounds exhibited comparable activity as that of the standard drug (Ampicillin), the results are given in table 3.

Experimental

Melting points were measured on Stuart melting point apparatus and are uncorrected.

The microanalysis, IR spectra and ^{1}HNMR spectra were done at the Faculty of Science, Ain Shams University, Egypt.

Preparation of compound (II)

Resorcinol (3 gm, 0.02 mol) was dissolved in ethylacetoacetate (4 mL, 0.02 mol) and the mixture was cooled under 15^{o}C, while the solution was cool, concentrated sulphuric acid (30 mL) was added drop- wise over a period of half an hour, and the reaction mixture was brought to

room temperature. Ice – cold water was then added with stirring, the precipitate formed was filtered and crystallized from ethanol. The purity of the compound was checked by TLC. The melting point of the compound was in agreement with the literature value (185^{o}C) m.p. 184-186; 90 % yield.

Preparation of compound (III)

Equimolars from compound (II) and 2-hydroxynaphthaldehyde were fused together in presence of catalytic amount of piperidine for about 3 hrs at 120-130^{o}C. After the reaction has finished the mixture was cooled, treated with ethanol and poured onto ice-water, the formed precipitate was filtered and recrystallized from toluene, m.p. 286-289^{o}C; 70 % yield.

Preparation of compound (IV)

A warm solution of compound (III) (1.65 gm, 0.005 mol) in ethanol (15 mL) was treated with a solution of glycine (0.38 gm, 0.005 mol) in water (15 mL) and formalin (0.45 mol). The reaction mixture was held at 80-90^{o}C for 6 hrs. The resulting precipitate was filtered and recrystallized from ethanol, m.p. 260^{o}C; 64 % yield.

Antimicrobial studies [11]

Compounds III and IV were screened for their activity against gram positive bacteria B .Subtilis and gram negative bacteria E. Coli, standard drug (Ampicillin) was used at a concentration of (100 µg/100 mL) for comparison. The biological activities of these compounds have been evaluated by filter paper disc method after dissolving in DMF. The inhibition zones of microbial growth were measured in millimeter at the end of an incubation period of 24 hrs at 28^{o}C. DMF alone showed no inhibition zone.

It is apparent from the data listed in table 3 that both compounds III and IV showed antibacterial activity comparable of Ampicillin reference drug used.

Results and Discussion

The scheme outlined above showed the steps carried out for preparation of compounds II, III and IV.

Table 1 showed the physical data and table 2 showed the spectral data of compounds III and IV

Table 1: Physical data and compounds III and IV

Compound No.	Mol. formula	M .P .^{0}C	Yield %	Micro analysis		
				C	H	N
III	$C_{21}H_{14}O_4$	286 – 9	70	76.36 (75.98)	4.24 (4.73)	……..
VI	$C_{24}H_{19}NO_6$	260	64	69.06 (69.65)	4.55 (4.01)	3.35 (3.58)

Table 2: Spectral data of compounds III and IV

Compound No	IR υ cm^{-1}	^{1}HNMR δ ppm
III	1160(C-O-C); 1600(C=C); 1720(C=0); 3400(OH)	3.8(CH olefin); 6.8-7(m,ArH); 8.4(d,=CH-Ar); 9.8(s,OH)
IV	1162(C-O-C); 1623(C=C); 1724(C=0); 2987(CH); 3430(OH)	3.6(CH olefin); 3.9(s,CH_2-Ar); 4.1(s, CH_2-N); 5.7(s,NH); 6.9-7.3(m,ArH); 8.3(d, =CH- Ar); 9.0(s,COOH); 9.7(s,OH)

Table 3: Biological activity of compound III and IV

Compound No	Zone of inhibition (mm)	
	B .Subtilis	E. Coli
III	21	22
IV	26	20

Std (100 µg / 100mL)	24	22
Solvent Control (DMF)	……..	……...

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References

1- Mulwad V. V and Shirodkhar J . M., Indian Journal of Heterocyclic Chemistry, 11, 192(2002)

2- Ukhov S. V. Konshin, M. E. and Odegova, T. F., Pharm. Chem J. 35, 364(2001)

3- Manohar K., Manjunath G. and Ravira J. K., Indian Journal Heterocyclic Chemistry, 13, 201 (2004)

4- Trapkov V.A., Parfenov E. A., Smiruov L. D., Pharm. Chem. J. 30, 445 (1996)

5- Vukovic N., Sukdolak S., Solujic and Niciforovic N., Arch. Pharm. Res., 33, 5(2010)

6- RajeshwarRao V., Srimouth K. and Vijayakumar P., Indian Journal of Heterocyclic Chemistry 14, 141(2004)

7- Emmanuel-Giota A. A., Fylaktakidou, K. C., Hadjipavlou Litina D. J. Litinas K. E. .and Nicolaides D. N. J. Heterocyclic Chem. 38, 717 (2001)

8- Nofal Z. M., El-Zahar M. I. and Abd El-Karim S. S. Journal of Antimicrobial Chemotherapy, 5, 483 (2005)

9- Srinivasan K. K., Neelima Y., Alex J. Sreejith G., Ciraj A. M. and Rao J. V., Indian .J. Pharm. Sci., 69, 323(2007)

10- Russell A. and Lockhart L. B., Organic Synthesis Coll .Vol. 3, 463(1955); Vol. 22, 63(1942)

11- Murray P. R., Baron E. J., Pfaller M. A., Tenover F. C. and Yolken R. H., Manual of Clinical Microbiology 6th Ed. 1995.