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SYNTHESIS AND REACTIONS OF 3-ACETYL AND 3-CINNAMOYL COUMARINS

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3-Cinnamoyl and 3-(5'-aryl-2', 4'-pentadienoyl) - coumarin derivatives (II) have been prepared. The reaction of compounds (II) with hydrazines, aromatic hydrocarbons under Friedel-Craft conditions, Grignard reagents and active methylene compounds under Michael conditions have been investigated. Also the condensation of compound (Ia) with cyclohexanone, ethyl methyl ketone, diethyl malonate, hydrazines and aromatic amines have been studied. Most of the prepared compounds were subjected to *in vitro* testing against two gram-positive and two gram-negative bacteria.

Key words: Reaction of 3-acetyl, Reaction of 3-cinnamoyl coumarins.

Introduction

A considerable number of naturally occuring coumarins such as murralongin[1], osthol and 2,3-auraptin [2,3] were found to have strong antimicrobial and anticancer activities. Also it was reported that coumarin derivatives are known to have antifungal and antibacterial properties [4-6]. On the other hand, 3-haloacetamido [7,8] and 3-(N, N-disubstituted carboxamido) [9] coumarins were proved to possess amoebicid activity and anaesthetic property, respectively.

Recently, it was discovered that coumarin dyes are widely used in dye laser to achieve tunable blue-green light, and are also employed in other important applications of industrial and biological interest, e.g. in enzyme determination, photobiological energy transfer processes, fluorescent probe technique and fluorescence whiteners in detergent product [10-14].

Previously mentioned facts had encouraged us to synthesize and study the reactions of some novel coumarins. Also, it was thought judicious to investigate the antibacterial activity *in vitro* of most of the synthesized compounds.

Thus condensation of coumarins [15,16] (I) with *p*-chlorobenzaldehyde, 2-naphthaldehyde, *p*-hydroxybenzaldehyde, *p*-N, N-dimethylaminobenzaldehyde or benzaldehyde in boiling butanol and in the presence of a few drops of piperidine yielded the corresponding 3-cinnamoyl coumarin derivatives (II a-f). Also the condensation of cinnamaldehyde or *p*-N, N-dimethylaminocinnamaldehyde with (Ia) gave the corresponding 3-(5'-aryl-2',4'-pentadienoyl)-coumarin derivatives (II g,h).

3-(β-2'-Naphtyl-acryloyl)-coumarin (II b) underwent condensation with hydrazine hydrate or phenylhydrazine in boiling ethanol to give the corresponding hydrazone or phenylhydrazone (III a,b).

On the other hand the condensation of 3-(*p*-chlorocinnamoyl)-coumarin (IIa) with *p*-toludine gave expected amine (III c).

Alkylation of (II a) or (II b) with aromatic compounds such as benzene, chlorobenzene and *o*-xylene under Friedel-Craft conditions yielded 3-(β, β-diaryl-propanoyl)-coumarins (IV a-e). It has been stated that, this reaction takes place by the addition of the aromatic substrate to the cinnamoyl double bond. [17,18]

We investigate the behaviour of (II a) or (II b) towards Grignard reagents. The decomposition of Grignard complexes gave 2,2,4-trimethyl (or triphenyl)-3[β-methyl(or phenyl)-β-aryl propanoyl]-chromans (V a-c) [19-21] by the incorporation of four moles of Grignard reagent.

Compounds (II a) and (II b) were found to undergo several smooth condensation reactions with different active methylene compounds. Thus condensation of (II b) with ethyl cyanoacetate or ethyl acetoacetate in presence of sodium ethoxide at 170-180° yielded 3-(β-naphthyl- β-carboethoxy cyanomethyl-propanoyl)-coumarin (VI) and 3-(5'-naphthyl-3'-oxo-4'-carboethoxycyclohex-1-enyl)-coumarin (VII), respectively.

However, the Michael condensation of (IIa) with diethyl malonate gave 3-(3'-carboethoxy-2'-oxo-4'-*p*-chlorophenyl-2', 3'-dihydro-4'-H-pyranyl)-coumarin (VIII).

As a point of interest in this investigation, the condensation of compound (Ia) with cyclohexanone or ethylmethyl ketone in boiling ethanol and in the presence of few drops of piperidine as catalyst yielded 3-(cyclohexylideneacetyl)- and 3-(β-ethyl-β-methylacryloyl)-coumarins (IX) and (X), respectively. Also (I a) reacted with hydrazine hydrate, phenylhydrazine, aniline or *p*-toludine and gave the corresponding 3-(1'-hydrazoethyl), 3-(1'-phenyl-hydrazoethyl)-, 3-(1'-anilinoethyl) or 3-(1'-*p*-toludino ethyl)-coumarins (XI a-d), respectively.

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When compound (Ia) was treated with diethyl malonate in presence of sodium ethoxide, 4,5-dihydrobenzo-α-pyrano-6-carboethoxy-1,3-cyclohexandione (XII) was obtained in a good yield.

Antibacterial activity. Applying the agar plate diffusion technique[22] most of the newly synthesized compounds were screened *in vitro* for antibacterial activity against *Bacillus* subtilis, *Bacillus cereus, Esch. coli* and *Pseudomonas solanarium*. In this method a standard 5 mm diameter sterilised filter paper disc impregnated with the compound (1 mg/ml of acetone) was placed on an agar plate seeded with the test organism. The plates were incubated for 24 hrs at 37° The zone of inhibition of bacterial growth around the disc was observed. The screening results given in Table 3 indicate that coumarin derivatives containing *p*-chlorophenyl moiety exhibited reasonable antibacterial activities against one or the other type of bacteria. 3-[5'-(*p*-N,N-Dimethylaminophenyl)-2,4-pentadienoyl]-coumarin (II h), showed the highest inhibitory effect against all the test organisms and this may be due to the extended conjugation present in that compound.

Experimental

General procedure. Melting points: uncorrected. IR-spectra (KBr): Unicam SP1200. ^{1}H-NMR-spectra: Perkin-Elmer 90 MHz, TMS as internal reference (chemical shift in δ scale) and $CDCl_3$ as a solvent. 3-Acetyl coumarin (Ia) was prepared according to the literature methods. [15,16].

3-Acetyl-7-hydroxy coumarin (I b). A mixture of 2,4-dihydroxybenzaldehyde (0.01 mole), ethyl acetoacetate and few drops of piperidine in *n*-propanol (50 ml) was refluxed for 3hr. The reaction mixture was concentrated, dil. HCl was added (100 ml) and the solid separated was crystallized from a proper solvent (Tables 1, 2).

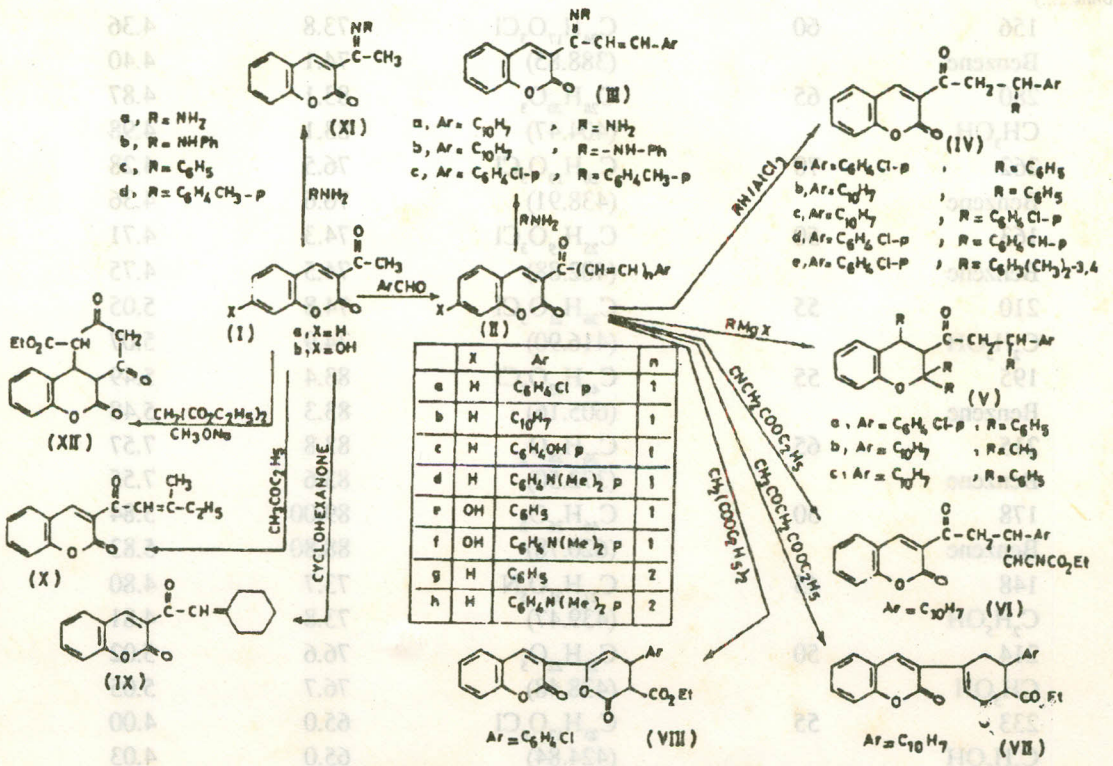
3-Cinnamoyl or 3-(5-aryl-2,4-pentadienoyl)-coumarins (II a-h). A solution of (Ia) or (Ib) (0.01 mole), the appropriate aromatic aldehyde (0.015 mole) and piperidine (1 ml) in butanol was refluxed for 3 hrs. Cooled and the solid separated was crystallized from the suitable solvent (Tables 1, 2).

Reaction of 3-(β-2-naphthyl-acryloyl)-or 3-(p-chlorocinnamoyl)-coumarins (IIa) or (IIb) with hydrazines or aromatic amines: Formation of (III a-c). To a solution of (IIa) or (IIb) (0.01 mole) in 50 ml ethanol, the appropriate hydrazine or amine (0.01mole) was added and the reaction mixture was refluxed for 2hrs. The mixture was concentrated and the precipitate was recrystallized from the proper solvent.

3-(β,β-Diaryl-propanoyl)-coumarins (IV a-c). To a cold, stirred mixture of anhyd. aluminium chloride (0.04 mole) and dry aromatic substrate (150 ml) such as benzene, chlorobenzene or *o*-xylene was added dropwise a solution of

TABLE 1. SPECTRAL DATA OF THE PREPARED COMPOUNDS.

Comp.	IR (cm^{-1}); ^{1}H-NMR (ppm)
IIa	IR: 1730(CO of coumarin), 1685 (CO of cinnamoyl) and 1610 (C=C) ^{1}H - NMR: 7.52–8.0 (*m*, 11] H; aromatic and olefinic protons).
IIb	IR: 1735 (CO of coumarin), 1670 (CO of cinnamoly) and 1605 (C=C) ^{1}H-NMR: 7.45–8.20 (*m*, 14 H; aromatic and olefinic protons).
IIc	IR: 3380 broad (OH), 1735 (CO of coumarin), 1680 (CO of cinnamoyl) and 1610 (C=C)
IId	IR: 1730 (CO of coumarin), 1675 (CO of cinnamoyl) 1600 (C=C). ^{1}H-NMR: 7.60–8.22 (*m*, 9H; aromatic and olefinic protons) and 5.62–6.30 (*m*, 4H; $CH=CH_2$.).
IIIa	IR: 3330(NH), 1725 (CO of coumarin), 1640 (C=N)and1615 (C=C). ^{1}H-NMR: 7.69–8.32 (*m*, 14H; aromatic and olefinic protons) and 2.70 (S, 2H; NH_2).
IVa	IR: 1690 (CO of coumarin) and 1645 (CO of $COCH_2$.). ^{1}H-NMR: 7.60–8.41 (*m*, 14H; aromatic and olefinic protons), 3.22 (t, 1H; CH, J = 6 Hz) and 2.43 (d, 2H, CH_2, J = 6 Hz).
IVd	IR: 1685 (CO of coumarin) and 1650 (CO of $COCH_2$). ^{1}H-NMR: 7.72–8.39 (*m*, 13H, aromatic protons and olifinic protons), 3.61 (t, 1H; CH, J = 5.8 Hz), 2.65 (d, 2H; CH_2, J =5.8 Hz), and 2.30 (s, 3H, CH_3).
Va	IR: 1710 (CO) ^{1}H-NMR: 7.62–8.31 (*m*, 28H; aromatic protons), 3.80 (t, 1H; CH-CH2, J = 6.3 Hz), 2.91 (d, 1H; Hb J = 9 Hz), 2.73 (d, 2H; CO CH J = 6.3 Hz), and 1.88 (d, 1H; Ha, J = 9 Hz).
VI	IR: 2250 (C ≡ N), 1675 (CO of coumarin) and 1645 (CO of $COCH_2$).
VII	IR: 1735 (CO of ester) and 1680 (CO of δ-lactone). ^{1}H-NMR: 7.40–8.22 (*m*, 13H; aromatic and olefinic protons), 4.10 (q, 2H; CH_2-CH_3, J = 7 Hz), 3.52 (t, 3H, CH_2.CH_3, J = 7.3 Hz), 2.83 (d, 1H; α CH of cyclohexanone), 2.14 (*m*, 1H; β-CH of cyclohexanone), 1.91 (d, 2H, γ-CH_2 of cyclohexanone).
VIII	IR: 1740 (CO of ester) and 1680 (CO of δ-lactone). ^{1}H-NMR: 7.42–8.32 (*m*, 10H; aromatic and olefinic H), 4.16 (q, 2H; CH_2-CH_3, J=7.0 Hz), 3.5 (t, 3H; CH_2-CH_3, J=7.0 Hz), 2.9 (d, 1H; Ha), and 2.17 (d, 1H; Hb).
IX	IR: 1720 (CO of coumarin) and 1670 (CO of α, β-unsatu rated ketone). ^{1}H-NMR: 7.40 – 8.30 (*m*,5 H; a romatic and olefinic H), 1.80–2.70 (*m*, 10H; cyclohexanone protons).
X	IR: 1725 (CO of coumarin) and 1675 (CO of α, β-unsatu rated ketone). ^{1}H-NMR: 7.42–8.32 (*m*, 5H; aromatic and olefinic H), 5.8 (s, 1H; CH=), 2.3(q, 2H; CH_2–CH_3, J=7.5 Hz), 2.00 (s, 3H; CH_3C=) and 1.10 (t, 3H, CH_2–CH_3, J=7.5 Hz).
XI	IR: 1730 (CO of coumarin) and 1630 (C=N). ^{1}H-NMR: 7.40–8.30 (*m*, 5H; aromatic and olefinic H) and 2.30 (s, 3H; CH_3).
XII	IR: 1735 (CO of ester), 1720 (CO of coumarin) and 1690 (CO of ketone).



	X	Ar	n
a	H	C_6H_4Cl p	1
b	H	$C_{10}H_7$	1
c	H	C_6H_4OH p	1
d	H	$C_6H_4N(Me)_2$ p	1
e	OH	C_6H_5	1
f	OH	$C_6H_4N(Me)_2$ p	1
g	H	C_6H_5	2
h	H	$C_6H_4N(Me)_2$ p	2

TABLE 2. PHYSICAL DATA OF COMPOUNDS I-XII.

Compd.	m.p. °C solvent	Yield (%)	Mol. formula	Found / Calc. C	 H	 N
Ib	231	85	$C_{11}H_8O_4$	64.6	3.77	
	CH_3OH		(204.18)	64.7	3.95	
IIa	126	65	$C_{18}H_{11}O_3Cl$	69.0	3.52	
	C_2H_5OH		(310.74)	69.6	3.57	
IIb	168-70	70	$C_{22}H_{14}O_3$	80.8	4.30	
	Propanol		(326.35)	81.0	4.32	
IIc	251	65	$C_{18}H_{12}O_4$	73.8	4.02	
	C_2H_5OH		(292.29)	74.0	4.13	
IId	217	60	$C_{20}H_{17}O_3N$	74.8	5.31	4.3
	Propanol		(319.36)	75.2	5.37	4.4
IIe	115	55	$C_{18}H_{12}O_4$	73.8	4.11	
	Dioxane		(292.29)	74.0	4.14	
IIf	255	70	$C_{20}H_{17}O_4N$	71.3	5.05	4.2
	Propanol		(335.36)	71.6	5.10	4.2
IIg	184	70	$C_{20}H_{14}O_3$	79.4	4.58	
	C_2H_5OH		(302.33)	79.5	4.66	
IIh	220	45	$C_{22}H_{19}O_3N$	76.5	5.51	4.0
	Dioxane		(345.40)	76.5	5.54	4.1
IIIa	202	70	$C_{22}H_{16}O_2N_2$	77.8	4.70	8.0
	CH_3OH		(340.38)	77.6	4.73	8.2
IIIb	195	75	$C_{28}H_{20}O_2N_2$	80.7	4.71	6.5
	Propanal		(416.48)	80.8	4.84	6.7
IIIc	140	65	$C_{22}H_{18}O_2NCl$	74.9	5.50	3.4
	Benzene		(399.88)	75.1	4.53	3.5

(Contd.....)

(Table 2, Contd.....)

IVc	156	60	$C_{24}H_{17}O_3Cl$	73.8	4.36	
	Benzene		(388.85)	74.1	4.40	
IVb	280	65	$C_{28}H_{20}O_3$	83.1	4.87	
	CH_3OH		(404.47)	83.1	4.98	
IVc	262	70	$C_{28}H_{19}O_3Cl$	76.5	4.28	
	Benzene		(438.91)	76.6	4.36	
IVd	163	50	$C_{25}H_{19}O_3Cl$	74.3	4.71	
	Benzene		(402.88)	74.5	4.75	
IVe	210	55	$C_{26}H_{21}O_3Cl$	74.8	5.05	
	C_2H_5OH		(416.90)	74.9	5.07	
Va	195	55	$C_{42}H_{33}O_2Cl$	83.4	5.49	
	Benzene		(605.16)	83.3	5.48	
Vb	215	65	$C_{26}H_{28}O_2$	83.8	7.57	
	Benzene		(372.50)	83.6	7.55	
Vc	178	50	$C_{46}H_{36}O_2$	89.00	5.84	
	Benzene		(620.78)	88.80	5.83	
VI	148	45	$C_{27}H_{21}O_5N$	73.7	4.80	3.2
	C_2H_5OH		(439.47)	73.8	4.81	3.2
VII	214	50	$C_{28}H_{22}O_5$	76.6	5.02	
	CH_3OH		(438.48)	76.7	5.05	
VIII	233	55	$C_{23}H_{17}O_6Cl$	65.0	4.00	
	C_2H_5OH		(424.84)	65.0	4.03	
IX	230	80	$C_{17}H_{16}O_2$	76.1	5.82	
	C_2H_5OH		(268.31)	76.1	6.01	
X	260	75	$C_{15}H_{14}O_3$	74.3	5.81	
	C_2H_5OH		(242.27)	74.4	5.82	
XIa	95	70	$C_{11}H_{10}O_2N_2$	65.3	4.95	13.7
	Propanol		(202.21)	65.3	4.98	13.9
XIb	185	75	$C_{17}H_{14}O_2N_2$	73.3	5.05	10.0
	C_2H_5OH		(278.31)	73.4	5.07	10.1
XIc	102	65	$C_{17}H_{13}O_2N$	77.4	4.79	5.3
	C_2H_5OH		(263.29)	77.6	4.97	5.3
XId	104	65	$C_{18}H_{15}O_2N$	77.9	5.28	4.9
	C_2H_5OH		(277.32)	77.9	5.45	5.1
XII	285	45	$C_{16}H_{14}O_6$	63.4	4.53	
	CH_3OH		(302.28)	63.6	4.67	

(IIa) or (IIb) (0.01 mole) in 50 ml of the same aromatic substrate, stirring was continued further 12 hrs at room temperature, the complex decomposed with dil-HCl and the excess aromatic substrate evaporated. The product thus obtained was crystallized from the suitable solvent (Tables 1 and 2).

2,2,4-Trimethyl (or triphenyl)-3 [β-methyl (or phenyl)-β-aryl-propanoyl]-chromans (V a-c). To the Grignard solution prepared from magnesium (0.04 mole) and methyl iodide or bromobenzene (0.04 mole) in 100 ml of anhyd. ether was added a suspension of (IIa) or (IIb) (0.01 mole) in dry ether (50 ml). The reaction mixture was heated under reflux for 2hrs., decomposed with sat. aq. ammonium chloride solution and the aqueous layer was extracted with ether which was evaporated. The residue was washed with 150 ml light petroleum (40/60°) and crystallized from the proper solvent.

3-(β-Naphthyl-β-carboethoxy cyanomethyl propanoyl)-coumarin (VI), 3-(5-naphtyl-3-oxo-4-carboethoxy cyclohex-1-enyl)-coumarin (VII) and 3-(3-carboethoxy-2-oxo4-p.chlorophenyl-2-,3-dihydro-4 H-6-pyranyl)-coumarin (VIII). The appropriate active methylene compound (0.01 mole) was heated with (IIa) or (IIb) at 170-180° in presence of sodium ethoxide for 2hrs, cooled and washed with dil-HCl. The solid separated was crystallized from the suitable solvent.

TABLE 3. ANTIBACTERIAL ACTIVITY OF THE PREPARED COUMARINS.

Comp.	*B.subtilis*	*B.cereus*	*Esch.coli*	*P.solamarium*
IIa	++	++	–	+
IIb	–	–	+	–
IIc	+	+	–	–
IIg	++	++	++	+
IIh	+++	++	++	++
IIIa	–	–	–	+
IIIc	++	++	+	+
IVa	+	+	–	–
IVb	+	+	–	–
IVc	–	–	+	–
Va	+	-	–	–
Vb	–	–	–	–
VI	–	–	–	–
VII	–	–	–	–
X	+	-	+	–
XIa	–	–	–	–
XIb	–	–	–	–

Zone of inhibition: + = 5.7 mm, ++ = 8.14 mm, +++ = 15.2 mm, – = No inhibition.

3-(Cyclohexylideneacetyl)-coumarin (IX) and 3-(β–ethyl-β-methyl acryloyl)-coumarin (X). A mixture of (Ia) (0.01 mole), cyclohexanone or ethyl methyl ketone (10 ml) and piperidine (1 ml) was heated at 170-180° for 2hrs, cooled, acidified with dil HCl and the separated solid was crystallized from a proper solvent (Tables 1 and 2).

3-(1-Hydrazoethyl), 3-(1-phenylhydrazoethyl), 3-(1-anilinoethyl) or 3-(1-*p*-toluidino ethyl)-coumarins (XI a-d). A mixture of the appropriate hydrazine or aromatic amine (0.01 mole), (Ia) (0.01 mole) in 20 ml ethanol was refluxed for 4hrs., cooled and the solid separated was crystallized from a suitable solvent (Tables 1 and 2).

4,5-Dihydrobenzo-α-pyrano-6-carboethoxy-1,3-cyclohexandione (XII). A mixture of (Ia) (0.01 mole), sodium ethoxide (0.025 mole) and diethyl malonate (0.01 mole) was heated at 170-180° for 6 hrs. The excess reagents were removed and the residue was stirred with 20 ml conc. HCl, washed with water and recrystallized from a proper solvent.

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