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Synthesis of Some Coumarin Derivatives and their Antimicrobial Activity

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Abstract □ When 3-acetyl coumarin derivatives are treated with bromine, 3-(w-bromoacetyl) coumarin derivatives are obtained. The reaction of 3-(w-bromoacetyl) coumarin derivatives with thiourea or with amines for two hours leads to the formation of 2-Amino-4-(3-coumarinyl) thiazole or 3-(w-aminoacetyl) coumarin derivatives, respectively. While 3-(w-bromoacetyl) coumarin derivatives react with amines for 5-8 hours to yield imino derivatives of 3-(w-aminoacetyl) coumarin. The antimicrobial activity of **Ia-b, IIa-c, IVc-f, IVh** and **Vc,f,h,k,m,** and **q** was studied.

Keywords □ 3-(w-bromoacetyl) coumarins, 2-amino 4(3-coumarinyl) thiazoles, 3-(w-aminoacetyl) coumarins, antimicrobial activity.

3-Acetylamino coumarin derivatives show antibacterial activity[1,2] which increases with size of the acyl group,[3] the larger the acyl group the greater becomes the antibacterial action.[3] The derivatives of aminocoumarin are effective against several bacterial strains.[4-8]

This paper deals with the synthesis of several 2-amino-4-(3-coumarinyl)thiazoles, 3-(w-aminoacetyl) coumarins and the imino derivatives of 3-(w-aminoacetyl) coumarins and the results of their antibacterial activity.

Chemistry

When 6-bromo-3-acetylcoumarin (**Ia**), 6, 8-dibromo-3-acetylcoumarin (**Ib**) or 8-methoxy-3-acetylcoumarin (**Ic**) is treated with bromine in chloroform, the corresponding 3-(w-bromoacetyl) coumarin derivatives (**IIa-c**) are obtained.

The infra-red spectra of **IIb** and **IIc** reveal the presence of two C = O groups (Table I).

The ^{1}H NMR spectrum of **IIb** ($CDCl_3$/DMSO) shows signals at δ 3.5 (2H, $COCH_2$,S), δ 7.4 and 8.2 (2H, aromatic, two S) and δ 8.9 (1H, pyrone H-4, S). 2-Amino-4-(3-coumarinyl) thiazole (**IIa-c**) are formed by reacting 3-(w-bromoacetyl) coumarin derivatives (**IIa-c**) with thiourea in ethanol.

The infra-red spectra of **IIIa-c** show the presence of C = O group of α-pyrone (Table I). The ^{1}H NMR spectrum of **IIIa** ($CDCl_3$/DMSO) reveals signals at δ 3(2H, NH_2 broad S), δ 6.25(1H, thiazole H-5, S), δ 7.15-7.65(3H, aromatic, m) and δ 8.35 (1H, pyrone H-4, S). The reaction of 3-(w-bromoacetyl) coumarin derivatives (**IIa-c**) with amines in ethanol-chloroform mixture for two hours leads to the formation of 3-(w-aminoacetyl) coumarin derivatives (**IVa-i**).

The infra-red spectra of **IVb,e** and **h** reveal the presence of a C = O of the α-pyrone and NH group (Table I). The ^{1}H NMR. spectrum of **IVh** (DMSO) reveals signals at δ 2.2 (3H, CH_3, S), at δ 3.9 (3H, OCH_3, S) and at δ 4.56 (2H, $COCH_2$, S), at δ 6.54 and 6.95 (2H each, 4 aromatic of p-toluidine, d), at δ 7.2-7.6(3H, pyrone H-5, H-6 and H-7, m), at δ 8.6 (1H, pyrone H-4, S).

When 3-(w-bromoacetyl) coumarin derivatives (**IIa-c**) react with amines for 5-8 hours in ethanol-chloroform mixture, the imino derivatives of 3-(w-amino acetyl) coumarin (**Va-r**) are obtained. The infra-red spectra of **Vc,h,i,k,m,o** and **p** show strong characteristic absorptions for C = O of α-pyrone and NH group (Table I). The ^{1}H NMR spectrum of **Vh** ($CDCl_3$) reveals signals at δ 2.6 (2H, CH_2, S), δ 4.2(1H, NH, broad S), δ 7.0-7.85 (11H, aromatic protons, m), δ 8.6(1H, pyrone H-4, S). The ^{1}H NMR spectrum of **Vq** ($CDCl_3$/DMSO) shows signals at δ 2.2 (3H, CH_3, S), δ 2-4(3H, CH_3,

Table I. Infrared spectral data for Compounds II, III, IV and V (cm^{-1})

Cmp. No.	—C=O pyrone	—C=O	NH cm^{-1}	Aromatic Absorption, cm^{-1}	—C=N cm^{-1}	C-cl cm^{-1}	C-Br cm^{-1}	OCH_3 cm^{-1}	NH_2 cm^{-1}
IIb	1750	1700	—	1450,1480,1555	—	—	650,695	—	
c				and 1600			710		
IIc	1750	1700	—	1445,1470,1600	—	—	670	—	
IIIa	1730	—	—	1485,1540,1605	1640	—	650	—	3200
IIIb	1730	—	—	1450,1470,1540	1625	—	630,670	—	3400
IIIc	1730	—	—	1485,1540,1580	1625	—	—	1275	3380
IVb	1740	1625	3390	1420,1510,1550	—	—	710	1230	
IVe	1730	1620	3300	1455,1520,1525	—	—	705,730	—	
IVh	1745	1630	3400	1470,1520,	—	—	—	1265	
				1575,1600					
Vc	1735	—	3100-3380	1460,1505	1630	—	720	—	
				1520,1555					
Vh	1740	—	3120-3400	1450,1490	1615	—	690,720	—	
				1500			770		
Vi	1740	—	3100-3380	1455,1505,1600	1630	—	695,765	—	
Vk	1740	—	3090-3340	1450,1505	1605	—	700,730	—	
				1520,1550					
Vm	1750	—	3120-3390	1465,1485	1615	—	700,725	1260	
				1505,1520					
Vo	1740	—	3100-3380	1450,1500	1640	825	725.770	—	
				1570,1580					
Vp	1740	—	3200-3400	1500,1550	1640	—	650,710	—	
				1580	—	—	730,770		

S), δ 2.9(2H, CH_2, S), δ 4.0(3H, OCH_3, S), δ 4.3 (1H, NH, broad S), δ 6.6-7.5 (11H, aromatic protons, m), δ 8.7(1H, pyrone H-4, S).

Table IV shows the effect of compounds, **Ia-b**, **IIa-c**, **IVc-f**, **IVh** and **Vc,f,h,k,m** and **q** on the microorganisms tested. It is of interest to note that whereas 6-bromo-3-acetyl coumarin (**Ia**) possesses pronounced activity against gram-ve bacteria (*E. coli*), introduction of a second bromine atom in the aromatic ring as in 6,8-dibromo-3-acetyl coumarin (**Ib**) diminished the activity considerably.

Introduction of a bromine atom in the side chain as in 6-bromo-3-(w-bromoacetyl) coumarin (**IIa**) maintained its potency, while 6,8-dibromo-3-(w-bromoacetyl)coumarin (**IIb**) increased its activity to moderate.

Displacement of the bromine atom in the side chain by p-anisidine, p-bromoaniline or p-toluidine as in **IVc**, **IVd**, **IVe**, and **IVf** either diminished the activity or completely abolished the activity. On the other hand, displacement of the bromine atom in the side chain of 8-methoxy-3-(w-bromoacetyl) coumarin as in **IVh** leads to pronounced activity.

Condensation with amines *i.e.* p-toluidine, p-anisidine or p-bromoaniline to form the imines abolished the activity as in **Vc**, **Vf** and **Vm**. Moderate activity was observed in the imino compounds of the dibromo **Vk** and methoxy **Vq**. The moderate activity of **Vh** may be due to the introduction of two bromine atoms in the p-position of the amine moieties.

EXPERIMENTAL

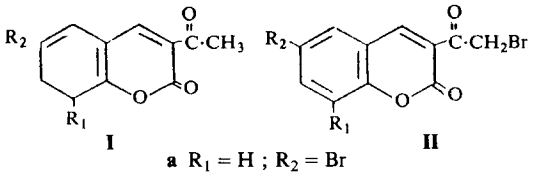
All m.p.s are not corrected. The IR spectra were recorded in (KBr) on a Beckmann spectrophotometer Model Acculab T. M6. The NMR spectra were carried out on a varian EM 360-60 MH_z or EM 390-90 MH_z Spectrometer.

Table II. w-bromoacetyl-(IIa-c), 2-amino 4(3-coumarinyl)thiazoles (IIIa-c) and W (aminoacetyl) Coumarin derivatives (IVa-i)

Comp. No.	M.P. C°	Yield	Formula	Elemental analysis %											
				Calcd						Found					
				C	H	N	Cl	Br	S	C	H	N	Cl	Br	S
IIa	204	75	$C_{11}H_6O_3Br_2$	38.15	1.73	—	—	46.24	—	38.5	2.0	—	—	46.4	—
IIb	185	75	$C_{11}H_5O_3Br_3$	31.05	1.17	—	—	56.47	—	30.8	1.2	—	—	56.7	—
IIc	160	70	$C_{12}H_9O_4Br$	48.48	3.03	—	—	26.93	—	48.2	3.2	—	—	26.6	—
IIIa	200	60	$C_{12}H_7O_2N_2BrS$	44.58	2.16	8.66	—	24.76	9.90	44.6	2.0	8.8	—	25.0	10.0
IIIb	300	70	$C_{12}H_6O_2N_2Br_2S$	35.82	1.49	6.96	—	39.80	7.96	36.0	1.5	7.0	—	40.0	8.0
IIIc	260	50	$C_{13}H_{10}O_3N_2S$	56.93	3.64	10.21	—	—	11.67	57.0	3.5	10.1	—	—	11.8
IVa	170	70	$C_{18}H_{14}O_4NBr$	55.67	3.60	3.60	—	20.61	—	55.2	3.4	3.8	—	20.7	
IVb	240	65	$C_{18}H_{14}O_4NBr$	55.67	3.60	3.60	—	20.61	—	56.0	3.3	4.0	—	20.7	—
IVc	170	70	$C_{18}H_{14}O_4NBr$	55.67	3.60	3.60	—	20.61	—	55.7	3.3	3.9	—	20.8	—
IVd	185	65	$C_{17}H_{11}O_3NBr_2$	46.68	2.51	3.20	—	36.61	—	46.7	2.8	3.0	—	37.0	—
IVe	195	60	$C_{18}H_{13}O_3NBr_2$	47.89	2.88	3.10	—	35.47	—	48.0	3.0	3.4	—	35.6	—
IVf	245	65	$C_{18}H_{13}O_4NBr_2$	46.25	2.78	2.99	—	34.26	—	46.6	3.0	3.2	—	34.0	—
IVg	230	65	$C_{18}H_{15}O_3N$	73.72	5.11	4.77	—	—	—	73.4	5.0	4.5	—	—	—
IVh	250	70	$C_{19}H_{17}O_4N$	70.58	5.2	4.33	—	—	—	70.3	5.1	4.1	—	—	—
IVi	188	65	$C_{18}H_{14}O_4NCl$	62.97	4.08	4.08	10.20	—	—	63.2	3.9	4.0	9.9	—	—

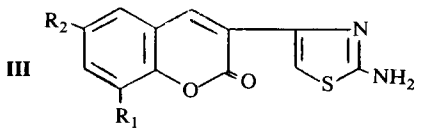
Table III. Imino derivatives of w-(aminoacetyl) Coumarins (IVa-r)

Comp. No.	M.P. C°	Yield %	Formula	Elemental analysis %									
				Calcd					Found				
				C	H	N	Cl	Br	C	H	N	Cl	Br
Va	219-221	70	$C_{23}H_{17}O_2N_2Br$	63.74	3.92	6.46	—	18.47	64.0	4.0	6.7	—	18.1
Vb	206-207	65	$C_{25}H_{21}O_2N_2Br$	65.07	4.55	6.07	—	17.35	65.4	4.6	5.8	—	17.5
Vc	240	60	$C_{25}H_{21}O_2N_2Br$	65.07	4.55	6.07	—	17.35	65.0	4.4	6.2	—	17.0
Vd	255	60	$C_{25}H_{21}O_4N_2Br$	60.85	4.25	5.67	—	16.22	60.5	4.9	5.7	—	16.0
Ve	240	70	$C_{25}H_{21}O_4N_2Br$	60.85	4.25	5.67	—	16.22	61.0	4.6	5.3	—	16.5
Vf	230	65	$C_{25}H_{21}O_4N_2Br$	60.85	4.25	5.67	—	16.22	60.9	3.9	6.0	—	16.0
Vg	260	70	$C_{23}H_{15}O_2N_2BrCl_2$	55.08	2.99	5.58	13.97	15.96	55.4	3.0	6.0	14.2	16.0
Vh	170	60	$C_{23}H_{15}O_2N_2Br_3$	46.70	2.53	4.73	—	40.60	46.3	2.8	5.0	—	41.0
Vi	245	70	$C_{23}H_{16}O_2N_2Br_2$	53.90	3.12	5.46	—	31.25	53.5	3.2	5.6	—	31.0
Vj	235	60	$C_{25}H_{20}O_2N_2Br_2$	55.55	3.70	5.18	—	29.62	56.0	3.4	5.3	—	30.0
Vk	233	70	$C_{25}H_{20}O_2N_2Br_2$	55.55	3.70	5.18	—	29.62	55.4	3.7	5.0	—	29.9
Vl	237	65	$C_{25}H_{20}O_4N_2Br_2$	52.44	3.49	4.89	—	27.97	52.4	3.9	5.0	—	28.0
Vm	235	70	$C_{25}H_{20}O_4N_2Br_2$	52.44	3.49	4.89	—	27.97	52.1	3.2	4.8	—	27.8
Vn	270	65	$C_{23}H_{14}O_2N_2Br_2Cl_2$	47.59	2.41	4.82	12.06	27.58	48.0	2.6	4.9	12.1	27.5
Vo	222	70	$C_{23}H_{14}O_2N_2Br_2Cl_2$	47.59	2.41	4.82	12.06	27.58	48.0	2.5	5.0	11.9	27.8
Vp	195	70	$C_{23}H_{14}O_2N_2Br_4$	41.19	2.08	4.17	—	47.76	40.8	1.9	4.0	—	47.6
Vq	263	70	$C_{26}H_{24}O_3N_2$	75.72	5.82	6.79	—	—	75.9	5.7	7.0	—	—
Vr	205	70	$C_{24}H_{18}O_3N_2Br_2$	53.13	3.32	5.16	—	29.52	53.5	3.5	5.6	—	29.8



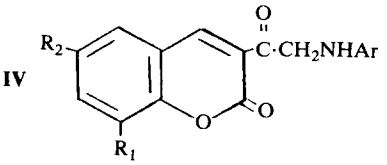
I II

a $R_1 = H$; $R_2 = Br$
b $R_1 = R_2 = Br$
c $R_1 = OCH_3$; $R_2 = H$



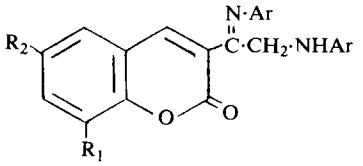
III

a $R_1 = H$; $R_2 = Br$
b $R_1 = R_2 = Br$
c $R_1 = OCH_3$; $R_2 = H$



IV

a $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4OCH_3$-O
b $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4OCH_3$-m
c $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4OCH_3$-P
d $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4Br$-P
e $R_1 = R_2 = Br$; $Ar = C_6H_4CH_3$-P
f $R_1 = R_2 = Br$; $Ar = C_6H_4OCH_3$-P
g $R_1 = OCH_3$; $R_2 = H$; $Ar = C_6H_5$
h $R_1 = OCH_3$; $R_2 = H$; $Ar = C_6H_4CH_3$-P
i $R_1 = OCH_3$; $R_2 = H$; $Ar = C_6H_4cl$-P



a $R_1 = H$; $R_2 = Br$; $Ar = C_6H_5$
b $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4CH_3$-m
c $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4CH_3$-P
d $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4OCH_3$-O
e $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4OCH_3$-m
f $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4OCH_3$-P
g $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4cl$-P
h $R_1 = H$; $R_2 = Br$; $Ar = C_6H_4Br$-P
i $R_1 = R_2 = Br$; $Ar = C_6H_5$
j $R_1 = R_2 = Br$; $Ar = C_6H_4CH_3$-m
k $R_1 = R_2 = Br$; $Ar = C_6H_4CH_3$-P
l $R_1 = R_2 = Br$; $Ar = C_6H_4OCH_3$-O
m $R_1 = R_2 = Br$; $Ar = C_6H_4OCH_3$-P
n $R_1 = R_2 = Br$; $Ar = C_6H_4cl$-m
o $R_1 = R_2 = Br$; $Ar = C_6H_4cl$-P
p $R_1 = R_2 = Br$; $Ar = C_6H_4Br$-P
q $R_1 = OCH_3$; $R_2 = H$; $Ar = C_6H_4CH_3$-P
r $R_1 = OCH_3$; $R_2 = H$; $Ar = C_6H_4Br$-P

Table IV. Antibacterial activity

Compound	gram + bacteria *B. cereus*	gram − ve bacteria *E. coli*
Ia	− ve	+ + + ve
Ib	− ve	+ ve
IIa	+ ve	+ + + ve
IIb	+ ve	+ + ve
IIc	+ ve	+ + ve
IVc	+ ve	+ ve
IVd	+ + ve	+ ve
IVe	− ve	− ve
IVf	− ve	− ve
IVh	+ ve	+ + + ve
Vc	− ve	− ve
Vf	− ve	− ve
Vh	+ ve	+ + ve
Vk	− ve	+ + ve
Vm	− ve	− ve
Vq	− ve	+ + ve

Preparation of 3-(w-Bromoacetyl) coumarin derivatives (IIa-c)

To a solution of 0.2 mol of **Ia-c** in 200 m*l* of chloroform is added 0.5 mol of bromine in 25 m*l* of chloroform while shaking for half an hour. The reaction mixture is heated for fifteen minutes on a water-bath to expel most of the hydrogen bromide, cooled and filtered. The solid separated is washed with ether giving pure product which is crystallized from acetic acid to give **IIa-c**. All compounds give no colour reaction with aqueous ferric chloride solution (Table II).

Preparation of 2-Amino-4-(3-coumarinyl)thiazoles (IIIa-c)

When a suspension of 0.008 mol of **IIa-c** in 15 m*l* of hot ethanol is treated with 0.02 mol of thiourea, a smooth exothermic reaction takes place giving a clear solution that soon deposites crystals. The deposit is removed, washed with ethanol and then boiled with water containing sodium acetate. The bright yellow needles obtained were crystallized from butanol to give **IIIa-c** (Table II).

Preparation of 3-(w-aminoacetyl)coumarin derivatives (IVa-h)

A solution of 0.03 mol of **IIa-c** and 0.05 mol of the appropriate amine in 30 m*l* of ethanol-chloro-

form mixture is refluxed for two hours, cooled and the solid separated is crystallized from ethanol or ethanol-chloroform mixture to give **IVa-h**. All compounds give no colour reaction with aqueous ferric chloride solution (Table II).

Preparation of imino derivatives of 3-(w-amino-acetyl) coumarin(Va-r)

A solution of 0.03 mol of **IIa-c** and 0.1 mol of the appropriate amine in 30 m*l* of ethanol chloroform mixture is refluxed for 5-8 hours. The reaction mixture is concentrated to about 5 m*l* under reduced pressure then left to cool. The solid obtained is crystallized from ethanol or ethanol-chloroform mixture to give **Va-r**. All compounds give no colour reaction with aqueous ferric-chloride solution (Table III).

Antimicrobial Activity

The antimicrobial activity was tested in vitro against the microorganisms *E. coli* (gram–ve bacteria) and *B. cereus* (gram + ve bacteria) at 10 μg/m*l* concentration on the nutrient broth and nutrient agar media following the Kirby-Bauer filter paper disc method.[9] The compounds under investigation were insoluble in water, therefore they were dissolved in acetone and filtered through bacterial membrane filter (0.45 μm). The diameters of the inhibition zones were measured per applied disc after 24 hours incubation at 37 °C. A control disc with acetone was also performed. The results were recorded by measuring the inhibition zones (in millimeters) caused by various compounds on the tested microorganisms.

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