Synthesis of -3-(2-Benzimidazolyl)-Coumarines of Anticipated Biological Activity.

A. HAMMAD, ALI S. EL-SAYED*, INAS E. ISLAM AND N. SHAFIK
National Research Centre, Dokki, Cairo, Egypt.
**Faclty of Science, Al-Azhar University, Cairo, Egypt.*

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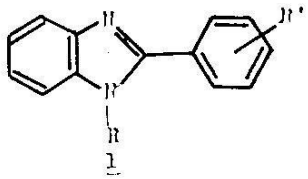
Summary: 3-(2'-benzimidazolyl)-coumarines (5a-c) were synthesised through cyclocondensation of different o- hydroxyaldehydes with benzimidazole-2-acetonitrile (2). The reaction mechanism and the different spectral data were discussed as well as the biological results were evaluated.

Introduction

Details of the analgesic activity of numerous compounds having the general formula 1 have been reported [1]. A large number of them are highly active in mice, some being many times more potent than moprhine. Etonitazene (1; R = H and R' = p-OEt) is a potent analgesic with 50 times activity of morphine [2]. The studies revealed also that 2-methyl and 5-nitromethylbenzimidazole are active analgesic [3,4].



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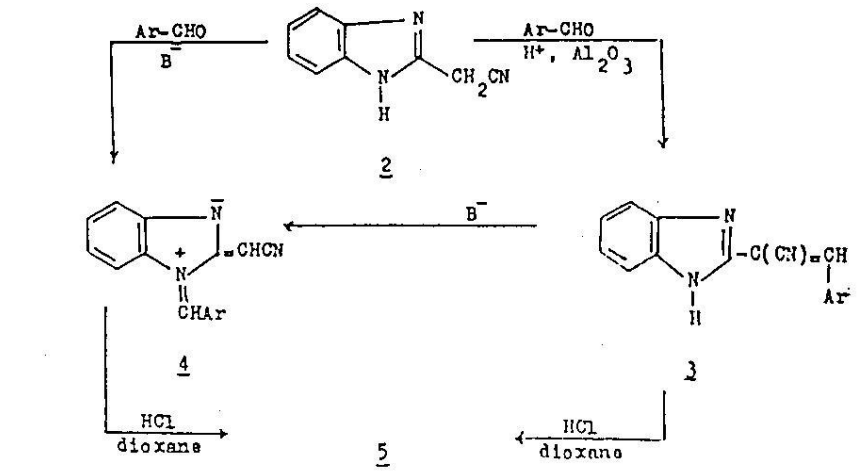
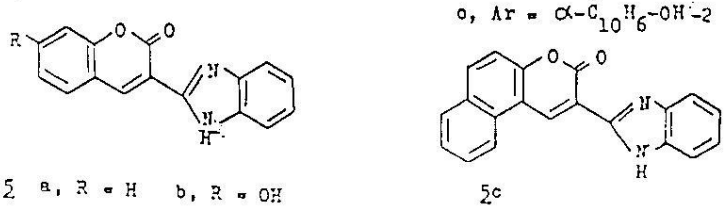
Beside the above facts, it was known that coumarine derivatives have anticoagulent effect and are used as bactericidals [5,6]. These facts



where:

3, 4 a, Ar = C_6H_4-OH o- b, Ar = C_6H_3-$(OH)_2$ 2,4

o, Ar = α-$C_{10}H_6$-OH-2



5 a, R = H b, R = OH 5c

(Scheme 1)

prompted us to synthesis some coumarine derivatives containing the benzimidazolyl group which are of biological interest [7].

We report here on the reaction of 2-cyanomethylbenzimidazole **2** with 2-hydroxybenzaldehydo, 2,4-dihydroxybenzaldehyde and 2-hydroxy-1-naphthaldehyde. It has been found that **2** reacted with the mentioned aldehydes in acidic media or in the presence of Al_2O_3 (without solvent, see experimental) to give the corresponding 2-(2'-benzimidazolyl)-,1-arylacrylnitriles **3a-c**, whereas in presence of piperidine gave the azomethine derivatives **4a-c** (cf. Scheme 1).

The structure of acrylonitriles derivatives **3a-c** was proved by studying their infrared spectra. They showed bands at 3400, 3200 and 2220 cm^{-1} regions (cf. Table 2), whereas, 1-arylmethylenebenzimidazole-2-cyanomethine-imidazole **4a-c** lack the stretching vibration due to the imino group which appears in the spectra of **3a-c**. The ^{1}H-NMR of (**4a-c**)

Table-1: List of Prepared Compounds*

Comp. No.	m.p. °C	Molecular form. Molecular Wt.	Analysis C	H	Calcd./Found% N
3a	245-7	$C_{16}H_{11}N_3O$	73.56	4.21	16.09
		(261)	73.46	4.20	16.07
3b	287-9	$C_{16}H_{11}N_3O_2$	69.31	3.97	15.16
		(277)	69.10	3.80	14.95
3c	263-5	$C_{20}H_{13}N_3O$	77.17	4.18	13.50
		(311)	76.66	4.28	12.98
4a	238	$C_{16}H_{11}N_3O$	73.56	4.21	16.09
		(261)	73.89	3.98	16.33
4b	257-9	$C_{16}H_{11}N_3O_2$	69.31	3.97	15.16
		(277)	69.42	3.52	14.87
4c	256-8	$C_{20}H_{13}N_3O$	77.17	4.18	15.50
		(311)	76.90	4.20	14.92
5a	298-9	$C_{16}H_{10}N_2O_2$	73.28	3.81	10.68
		(262)	73.09	4.12	10.09
5b	300	$C_{16}H_{10}N_2O_3$	69.06	3.59	10.07
		(278)	69.30	3.40	3.93
5c	292-5	$C_{20}H_{12}N_2O_2$	76.92	3.80	8.97
		(312)	76.80	4.00	8.67
6a	<300	$C_{16}H_{11}N_3O$	73.56	4.21	16.09
		(261)	73.82	4.32	15.98

*Compounds 3a-c, 5a-c and 6a are yellow in colour, whereas 4a-c are orange products.

Table-2: Infrared Spectra of the Products (KBr disc)

Comp.	νC=C	νC=N	νC=O cm^{-1}	νC=N	νN-H	νOH
3a	1580	1620	--	2220	26-3200	3400
b	1560	1615	--	2220	2600-3180	3410
c	1580	1615	--	2220	2600-3200	3450
4a	1540	1615,1620	--	2220	--	3350
b	1530	1620,1625	--	2180	--	3360
c	1540	1615,1620	--	2220	--	3410
5a	1520	1620	1695	--	2600-3180	--
b	1520	1620	1695	--	2600-3180	--
c	1520	1620	1698	--	2600-3060	--
6a	1515	1630,1625	--	--	2600-3050 3105	--

revealed the azomethine linkage at $\delta = 8.45$ ppm and 7.2 ppm and 7.72 ppm ring proton respectively due to the desheilding effect of the azomethine linkage. The ^{1}H-NMR of the **3a-c**, shows a ring changeable N-H (imidazoyl) at δ 8.78 beside a singlet at δ - 6.88 ppm. for protons assignable for ring protons. The ^{1}H-NMR of the **4** or **3** shows a broad singlet at δ 9.95 ppm and δ 9.98 respectively.

When compounds **3a-c** or **4a-c** were refluxed in dioxan in presence of HCl, 3-(2-benzimidazolyl)-coumarin-2-ones **5a-c** were obtained. In case of **3a** in the above reaction another compounds **6a** was separated. The compound **6a** could be prepared through the reaction of salicylaldehyde with 2-cyanomethylbenzimidazole in presence of acetic acid/AcO_2NH_4, like the reaction of ethylcyano-acetate with *o*-hydroxybenzaldehyde [8,9].

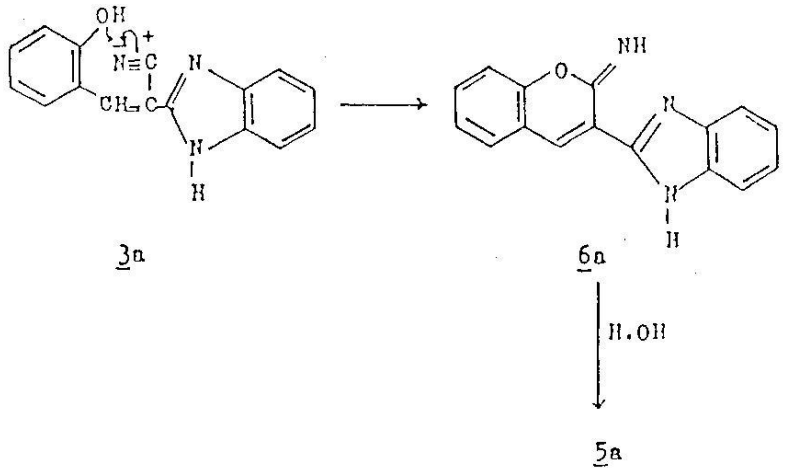
When **6a** was boiled in a mixture of HCl/dioxane **5a** was separated. So, cyclization of the hydroxyacrylonitrile derivatives **3a-c** in acidic media occured, presumably due to the enhanced hydrogen transfered from the hydroxyl group to the nitrile group followed by hydrolysis of the imino group.

The infrared spectra of the coumarin-2-one derivatives **5a-c** showed bands characteristic to coumarinones and benzimidazolyl moiety (cf. Table 2). The mass spectrum of the product **5a** gave M^+ m/z = 262 which gave correct molecular weight. The ^{1}H-NMR of (**5a-c**) shows signlets attributed to H-4 at $\delta = 7.20$, 7.35, 7.63 ppm respectively, beside other signals due to the aromatic protons [10].

The infrared spectrum of **6a** lacked the carbonyl and the nitrile bands which appeared in the spectra of 5a-c respectively and showed band due to the imino group at 3105 cm^{-1} region, besides the band of the benzimidazolyl moiety which appeared in 3050-2600 cm^{-1} region. The mass spectrum of **6a** gave M^+ m/z = 261; which gave another support for its structure.

Antimicrobial Activity

The newly synthesized compounds had been screened for their antimicrobial activity against 13 fungi and 2 kinds of bacteria (cf. Table 3). Czapek agar cup method was used for cultivating the fungal test organism, while nutrient agar cup method was used for bacteria. Solutions were prepared with concentrations ranges from 25-100 mg/l in acetone. The results obtained showed that most of these compouds have activity towards the tested fungi, while few of them have an effect on bacteria.



3a 6a 5a

Table-3: Antimicrobial Activity of the Prepared Compounds as Minimum Inhibitory Zones (mg/ml) in Acetone.

Microorganism	3a	4a	5a	3b	4b	5b	3c	5c
1. Alternaria tenius	100	100	100	25	25	100	100	25
2. Aspergillus flavus	--	--	100	25	25	--	100	50
3. Aspergillus niger	--	100	100	25	25	--	100	25
4. Aspergillus ochraccus	--	100	100	25	50	100	100	25
5. Aspergillus terreus	--	100	100	25	25	--	100	25
6. Cephalosporium naydis	100	50	100	25	25	25	100	25
7. Curvularia sp.	100	50	100	25	25	100	100	50
8. Fusarium oxysporum	100	50	25	25	25	25	25	50
9. Fusarium solani	--	50	25	25	25	25	25	50
10. Penicillium crysogenum	--	50	100	50	25	25	50	50
11. Rhizopus nigricans	--	50	100	50	50	25	50	100
12. Trichoderma viride	100	100	100	100	25	25	50	100
16. Rhizoctonia solani	100	50	100	25	25	100	25	100
Bacteria								
14. Pseudomonas aeroginosa		50	--	--	--	50	--	--
15. E.coli	--	--	--	--	--	25	--	100

These results are rather interesting, since the fungi are responsible to cause some diseases which affect crops in Egypt.

The Fungicidal Activity

The benzimidazolyls **3a-c, 4a** and **4b** have different activity towards fungi, whiel **4, 3b** are very effective for all fungi used. Compounds **3c** and **4a** have moderate effect. On the other hand, compound **3a** has very little effect. In this view, it seems that the presence of dihydroxy group together with benzimidazole moiety in **3b** and **4b** load to this high fungicidal activity. Furthermore, the benzimidazoyl coumarin-2-ones **5a-c** are effective for fungi but the superior compound of these is **5c** which has the naphthyl moiety.

Antibacterial Activity

The compounds that have bacterial activity are **5b, 4a** and **5c.** This activity differs according to the structure of the compounds used. For example, compound **4a** has activity twoards *pseudomonas aeroginosa*, while **5c** has activity towards *E.Coli* and **5b** is very effective for the two kinds of bacteria used. This is presumably due to the presence of hydroxyl group together with coumarine and benzimidazole moieties in this compounds.

Experimental

All meling points were uncorrected. IR spectra were carried out using KBr discs on a Py Unicam SP/1000 spectrophotometer. Analytical data were performed at Nationl Research Centre, Dokki, Cairo, Egypt. The mass spectra were determined with MAT 311 and MAT CH7A mass spectromter. ^{1}H-NMR was performed on PYE unicam SP- 1000.

Preparation of 2-(2'-benzimidazolyl)-1-arylarylonitriles 3a- c

Method A

A solution of the aldehyde (0.01 mole) in ethanol was treated with 2-cyanomethylbenzimidazole **2** (0.01 mol) in presence of few drops of HCl. The reaction mixture was stirred for 1/2 hour. The solid separated was collected and crystallised from methanol. The compounds **3a-c** are listed in Table 1.

Method B

A mixture of the aldehyde (0.01 mol), Al_2O_3 (0.02 mol and 2 (0.01 mol) in a round bottom flask was heated on boiling water bath for 1/2 hour. The yellow product was extracted with ethanol, filtered, and crystallised from methanol to give **3a-c.**

Preparation of 1-(Aryl)-methylenebenzimidazole-2-cyanomethine-iminimidazole 4a-c

A solution of **2** (0.01 mol) in ethanol (25 ml) and piperidine (0.2 ml) was treated with the aldehyde (0.01 mol). The reaction mixture was stirred for 1/2 hour. The solid separated was collected and crystallised from methanol (cf. Table 1).

Preparation of 3-(2-benzimidazolyl)-coumarin-2-ones 5a-c

A solution of **3a-c** or **4a-c** (0.01 mol) in dioxane (20 ml) in presence of concentrated hydrochloric acid (5 ml) was refluxed for 3 hr. The solid separated after cooling and addition of water was collected, recrystallised from methanol to give **5a-c** (cf. Table). In case of **4a** two products were separated **5a** and **6a.**

Preparation of 6a

A mixture of salicylaldehyde (0.01 mol) and 1 (0.01 mol) in acetic acid (20 ml) and NH_4COOCH_3 (0.03 mol) was boiled for 3 hrs. The solid separated was collected and washed with water several times, crystallised from methanol to give a product which was found to be **6a** (m.p. and mixed m.p.). When **6a** was boiled in a mixture HCl/dioxane **5a** was separated.

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