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REACTIONS OF BENZOPYRAN-2-ONE-3-CARBONYL DERIVATIVES WITH NUCLEOPHILIC REAGENTS

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Several benzopyran-2-one-3-carboxamides have been prepared by the condensation of coumarin 3-carbonyl chloride (I) with various nucleophilic reagents. The reaction of 3- carboethoxy coumarin with *o*-phenylene diamine and *o*-aminophenol gave 3-(benzimidazoyl) and 3-(benzoxazolyl) coumarins (XIa) and (XIc) respectively. The reaction of ω-bromo-3-acetyl coumarin with 3-cyano-4,6-dimethylpyridine-2- thiol in the presence of K_2CO_3 gave 3-[(3- amino-4,6-dimethyl-1-thio-7-azainden-2-yl) carbonyl] coumarin (XIV).

Key words: Benzopyran-2-one-3-carboxamides, Nucleophilic reagents.

Introduction

Several pharmacologically active compounds containing the coumarin nucleus are available [1]. Coumarins show quite diverse biological activity in addition to their anticoagulant properties and have value as vasodilators, anthelminitics and diuretics. Hymecromone is a systematic insecticide, which is especially effective against the colorado beetle [2,3].

In view of these and in continuation of our work [4-8], it was considered worth while to prepare compounds having the coumarin moiety and to other heterocyclic moieties.

Experimental

All melting points are uncorrected, elemental analyses were carried out in the microanalytical laboratories of the Faculty of Science, Cairo University. The IR spectra were measured on Shimadzu IR 440 spectrophotometer using KBr technique. The ^{1}H-NMR spectra were measured on Varian EM-360 60 MHz , Department of Chemistry, Faculty of Science, Al-Azhar University. High field (400 MHz) ^{1}H-NMR spectra were recorded using the high field NMR service Burker WM 400, mass spectra was recorded on Varian MAT 711 spectrometer, 70 eV direct in let at Institute for Organic Chemistry, Berlin (West Germany).

Condensation of coumarin-3-carbonyl chloride with nucleophilic reagents. To a solution of the heterocyclic and aromatic amino compounds or 3-hydroxy coumarin derivatives or 3- cyano-4,6-dimethyl pyridine-2-thiol (0.01 mole) in dry pyridine (20 ml), coumarin-3-carbonyl chloride (I), (0.01 mole) was added portion wise for about 30 mins. The reaction mixture was stirred for a further 2 hrs at room temperature, then decomposed with ice-cold dilute HCl. The obtained solid was recrystallized from the appropriate solvent to give (II, VIa-c) VII, VIII, Xa and Xb) (Table 1). In the case of (Xb), 1-hydrazino-4-benzyl phthalazine (IXb) [prepared by the stirring of 1-chloro-4- benzylphthalazine (Xa) (0.02 mole) with an excess of hydrazine hydrate (0.06 mole) in ether at room temperature for about 1 hr.] was used (Scheme 3).

Formation of the acetyl derivative (III). A mixture of (II) (0.01 mole) and acetic anhydride (10 ml) containing fused NaOAc (0.1 gm) was heated under reflux for 1 hr. Cooling and decomposition onto ice, gave a solid which was collected and recrystallized from ethanol to give (III) (Table 1).

Formation of the acid chloride (IV). A mixture of (III) (0.01 mole) and thionyl chloride (10 ml) in dry benzene (100 ml) was heated under reflux for 2 hrs. The excess of $SOCl_2$ was distilled under vacum and the solid obtained was collected and recrystallized from benzene to afford the acid chloride (IV) (Table 1).

Synthesis of 3-[(4-hydroxy-3-acetyl-2-oxo-2H-1-benzopyran-7- yl) iminocarbonyl] coumarin (V). A mixture of (IV) (0.01 mole) and ethyl sodioacetoacetate [prepared from Na in xylene and ethyl acetoacetate (0.01 mole)] was heated under reflux for 18 hrs in ether on a water bath. The resultant solid was filtered off, washed with ether and dissolved in H_2O. The solution was neutralised with dilute cold H_2SO_4. The solid was recrystallized from CH_3COOH to afford (V).

Condensation of 3-carboethoxy coumarin with o- phenylenediamines and o-aminophenol. 3-carboethoxy coumarin (I, R = OEt), (0.01 mole) in xylene (50 ml) and the respective *o*- phenylene diamine, 3,4-diaminotoluene or *o*-aminophenol (0.01 mole) were heated under reflux for 10 hrs. The collected solid was recrystallized from the appropriate solvent to give (XIa-c), (Table 1).

Bromination of (XIa-c). A solution of (XIa-c) (0.001 mole) in boiling acetic acid (30 ml) was treated portion wise with excess of a bromine solution (0.004 mole Br_2 in 20 ml of CH_3COOH). The reaction mixture was heated under reflux for 1 hr. The obtained solid on recrystallization gave the corre-

sponding bromoderivative (XId, e and XII).

Preparation of 3-[(3-amino-4,6-dimethyl-1-thio-7-azainden-2- yl carbonyl] coumarin (XIV). A mixture of ω-bromo-3-acetyl coumarin (XIII) (0.01 mole) and 3-cyano-4, 6-dimethylpyridine-2- thiol were heated under reflux for about 2 hrs in absolute ethanol containing anhydrous K_2CO_3 (2g). The solution was diluted with H_2O and the obtained solid was collected and recrystallized to give compound (XIV), (Table 1).

TABLE 1.

Compound	Solvent of recryst.	m.p. (°C)	Yield (%)	Formula M. wt.	Analysis Required/found C	H	N
II	ACOH	280	75	$C_{17}H_{11}NO_6$	62.77	3.38	4.31
				325	62.50	3.10	4.10
III	EtOH	330	80	$C_{19}H_{13}NO_7$	62.10	3.54	3.81
				367	61.80	3.39	3.60
IV	Benzene	205	83	$C_{19}H_{12}ClNO_6$	61.04	3.21	3.75
				385.5	61.98	3.10	3.50
V	ACOH	275	69	$C_{21}H_{13}NO_7$	64.45	3.32	3.58
				391	64.20	3.10	3.40
VIa	ACOH	304	75	$C_{19}H_{11}NO_5$	68.50	3.30	4.20
				333	68.20	3.10	4.00
b	ACOH	224	69	$C_{19}H_{10}O_6$	68.26	2.99	- -
				334	68.10	2.81	- -
c	ACOH	275	80	$C_{19}H_9BrO_6$	55.20	2.18	- -
				413	55.00	2.10	- -
VII	EtOH	175	69	$C_{15}H_7N_5O_3$	59.01	2.30	22.95
				305	58.89	2.00	22.50
VIII	EtOH	265	75	$C_{18}H_{12}N_2O_3S$	64.28	3.57	8.33
				336	64.10	3.40	8.10
Xa	ACOH	280	63	$C_{22}H_{12}N_2O_3S$	68.75	3.16	7.29
				384	68.65	3.12	7.19
Xb	MeOH	223	60	$C_{25}H_{18}N_4O_3$	71.09	4.26	13.27
				422	70.89	3.90	13.00
XIa	ACOH	245	70	$C_{16}H_{10}N_2O_2$	73.28	3.81	10.69
				262	73.10	3.60	10.50
b	ACOH	218	75	$C_{17}H_{12}N_2O_2$	73.91	4.35	10.14
				276	73.80	4.10	9.80
c	ACOH	288	69	$C_{16}H_9NO_3$	73.00	3.42	5.32
				263	72.80	3.20	5.10
d	DMF	270	85	$C_{16}H_9BrN_2O_3$	65.50	2.65	23.23
				340	65.35	2.40	23.10
e	DMF	318	80	$C_{17}H_{11}BrN_2O_2$	57.60	3.11	22.32
				354	57.40	3.00	22.20
XII	DMF	303	80	$C_{16}H_{13}BrN_2O_3$	53.33	3.61	21.94
				360	53.20	3.50	21.70
XIV	DMF	>350	68	$C_{19}H_{14}NO_3S$	67.86	4.17	4.17
				281	67.50	3.90	3.80

Results and Discussion

The condensation of coumarin-3-carbonyl chloride (I), with *p*-amino salicylic acid gave coumarin-3N-[(-3'-hydroxy-4'- carboxyl)phenyl] carboxamide (II), the IR spectrum for (II) showed υ CO at 1700, COOH and OH with intramolecular hydrogen bond at (3250-3500) cm^{-1}, the ^{1}H-NMR spectrum (60 MHz, DMSO-D_6) exhibited seven aromatic and N-H protons as a multiplet signal at δ 7-8.1, the olefinic proton at δ 9.0 and the carboxyl phenolic proton at δ 10.7 ppm. Acetylation of compound (II) with Ac_2O/NaOAc gave the corresponding acetyl derivative (III) (Scheme 1). The ^{1}H.NMR spectrum for (III) showed the acetyl protons at δ 2.3, aromatic and N-H protons at 7.4-8.2, olefinic proton and the carboxyl proton at 9.1 and 10.1 ppm respectively. Treatment of (III) with $SOCl_2$/benzene gave the corresponding acid chloride (IV), IR spectrum of compound (IV) exhibited no absorption bands for the OH region. This acid chloride (IV) when reacted with ethyl sodio acetoacetate in dry ether according to the literature [9] gave 3-[(4-hydroxy-3-acetyl-2-oxo-2H-1-benzopyran-7-yl) iminocarbonyl] coumarin (V) (Scheme 1). IR of (V) showed υ OH and NH as a broad band at 3210 cm^{-1}.

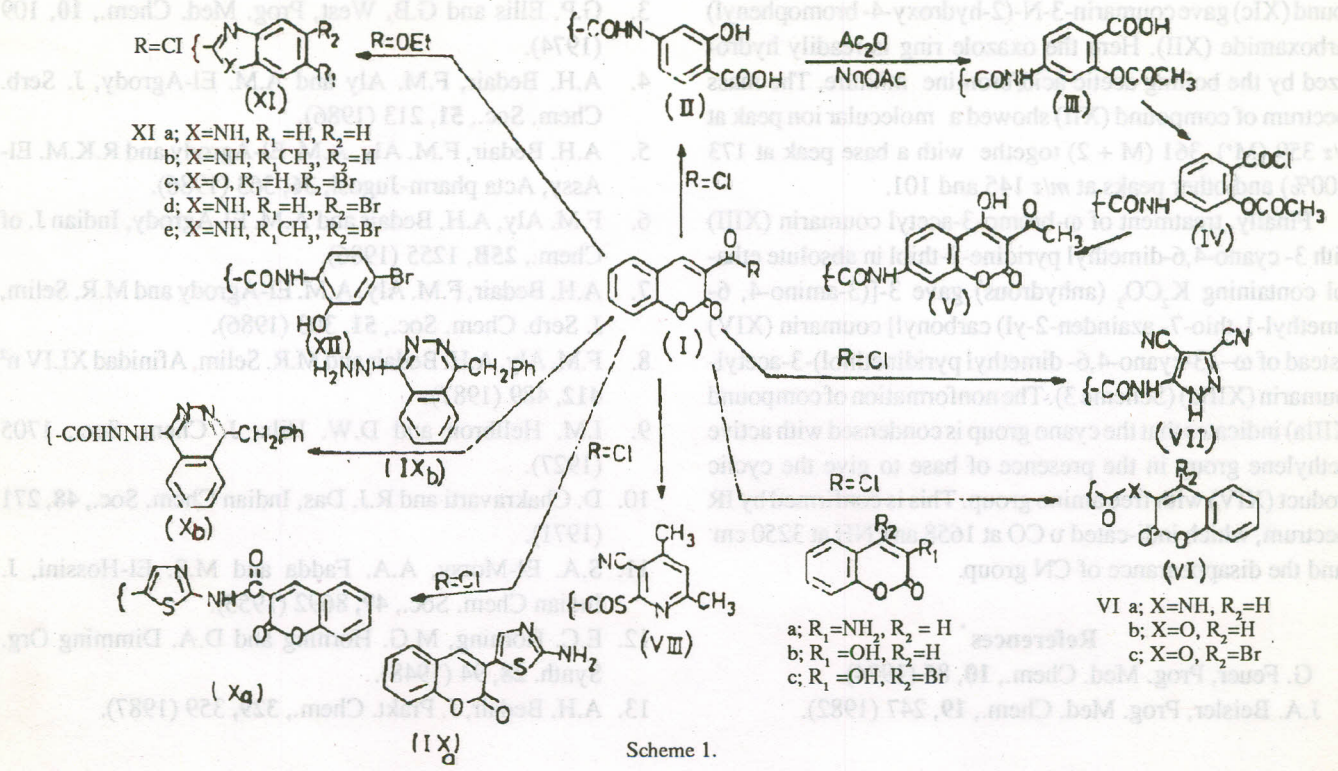
Condensation of compound (I), with 3-aminocoumarin [10] in dry pyridine afforded the corresponding carboxamide (VIa). IR spectrum for compound (VIa) showed υ CO and NH at 1729-1700 and 3192 respectively.

Interaction of coumarin-3-carbonyl chloride (I) with 3-hydroxy coumarin and 4-bromo-3-hydroxy coumarin [10] produced the corresponding ester (VIb and c). IR spectrum for compound (VIb) showed υCO at 1766-1716 cm^{-1}. Compounds (VIb and c) did not give colour reactions with alcoholic/$FeCl_3$. Mass spectrum of compound (VIb) showed a molecular ion peak at *m/z* 334 (M^+) together with a base peak at *m/z* 290 and fragmentations at *m/z* 234, 145, 101 and 89.

Reaction of coumarin-3-carbonyl chloride (I) with 3,4-dicyano-5-amino pyrazole gave coumarin-3-N-(3,4-dicyano pyrazol-5- yl) carboxamide (VII). The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) for compound (VII) showed the aromatic and NH protons signals at δ 8.96 ppm. Mass spectral data for (VII) gave a molecular ion peak at *m/z* 305 (100%) along with other peaks at 249, 190, 173, 118 and 89.

Condensation of compound (I) with 3-cyano-4-,6-dimethylpyridine-2-thiol gave 3-[(3-cyano-4,5-dimethylpyridine-2- thiocarbonyl coumarin (VIII). The IR spectrum for compound (VIII) showed υCH aliphatic absorption at 2875, CN at 2210, CO at 1668 and C-C and C-N at 1583 - 1488 cm^{-1}.

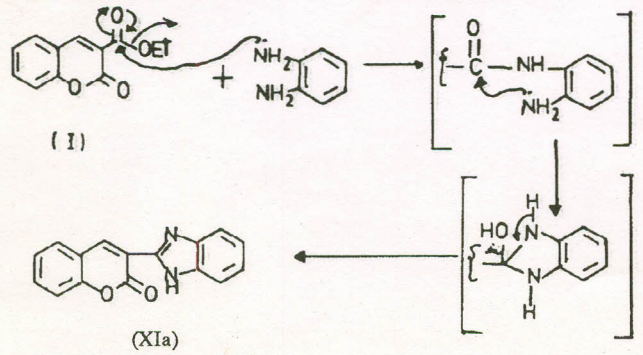
Treatment of coumarin-3-carbonyl chloride (I), with the amino heterocyclic compounds (IXa and b) gave the corresponding carboxamides (Xa and b) respectively (Scheme 1). The IR spectrum for (Xa and b) showed the disappearance of



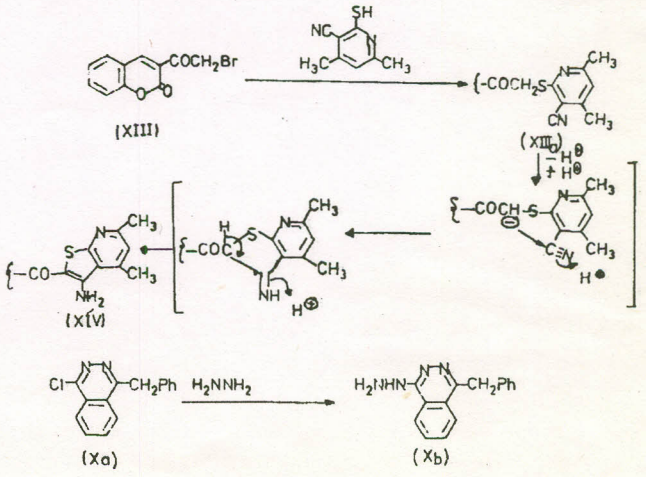
Scheme 1.

υ NH_2 at 3420 cm^{-1} (in original starting amino compounds). The ^{1}H-NMR spectrum for compound (Xb) showed the following signals at δ 4.5 (4H, multiplet, NH-NH and CH_3, the hydrazino protons signal are obscured by the addition of D_2O),(7.2-8.6) (13H, m, Ar-H's) and at 8.65 [1H,S,-CH=(a)].

The interaction of 3-carboethoxy coumarin with o-phenylene diamine, 3,4-diaminotoluene and *o*-aminophenol in boiling xylene for several hrs gave the corresponding 3-(benzimidazol-2-yl), 3- (6-methylbenzimidazol-2-yl) coumarin and 3-[benzoxazol-2-yl] coumarin (XIa-c) respectively as shown (Scheme 1). The formation of such compounds was explained through the cyclization of the corresponding coumarin-3-arylcarboxamides [13], which are initially formed (Scheme 2). The structure assignment for these products (XIa and b) was confirmed by the IR spectra which showed υ CO at 1708 and NH at 3346 cm^{-1}. The ^{1}H-NMR spectrum for compound (XIb) showed signals for the N-H group at δ 2.13; Ar-CH_3 at 2.49, olefinic C-H at 9.5 The aromatic protons for the benzimidazol and benzopyranone moieties were at δ 7.13(1H, d, HX), 7.39 (1H, t, HB), 7.43(1H, d, HA). The other aromatic protons were in the form of two sets of multiplets at δ 7.63 and 7.72 ppm. Also the mass spectrum for compound (XIb) showed the molecular ion peak at *m/z* 276 (M^+) (100%) as a base peak while other prominent fragments were at *m/z* 248, 220 and 219. Bromination of compounds (XIa and b) with an excess of bromine in acetic acid gave the correspon-ding bromo derivatives (XId & e). However bromination of com-



Scheme 2



Scheme 3.

pound (XIc) gave coumarin-3-N-(2-hydroxy-4- bromophenyl) carboxamide (XII). Here the oxazole ring is readily hydrolyzed by the boiling acetic acid/bromine mixture. The mass spectrum of compound (XII) showed a molecular ion peak at *m/z* 359 (M^+), 361 (M + 2) togethe with a base peak at 173 (100%) and other peaks at *m/z* 145 and 101.

Finally, treatment of ω-bromo-3-acetyl coumarin (XIII) with 3- cyano-4,6-dimethyl pyridine-2-thiol in absolute ethanol containing K_2CO_3 (anhydrous) gave 3-[(3-amino-4, 6-dimethyl-1-thio-7- azainden-2-yl) carbonyl] coumarin (XIV) instead of ω– (3-cyano-4,6- dimethyl pyridinethiol)-3-acetylcoumarin (XIIIa) (Scheme 3). The nonformation of compound (XIIIa) indicates that the cyano group is condensed with active methylene group in the presence of base to give the cyclic product (XIV) with free amino group. This is confirmed by IR spectrum, which indi-cated υ CO at 1658 and NH at 3250 cm^{-1} and the disappearance of CN group.

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