Reactions of 4-Hydroxycoumarin and 4-Hydroxyfurocoumarins with α,β-Unsaturated Nitriles. Mass Spectrometry of the New γ-Pyrano-α-pyran Derivatives

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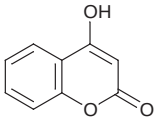
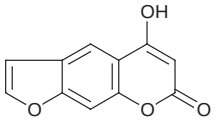
Reactions of 4-hydroxycoumarin and 4-hydroxyfurocoumarins with αβ-unsaturated nitriles provide routes to a range of novel pyranocoumarins and furopyranocoumarins, respectively.

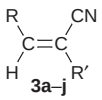
4-Hydroxycoumarin **1** comprises the structural nucleus of many natural products, drugs and pesticides.[1–3] It is the key intermediate for various widely used oral anticoagulants and rodenticides,[7] which are principally prepared by the Michael-condensation reaction of **1** with appropriate α,β-unsaturated carbonyl compounds.[9] A literature survey, however, revealed that the reaction of both 4-hydroxycoumarin **1** and compounds incorporating a similar structural unit, *viz*. 4-hydroxybergapten **2a** and 4-hydroxyisopimpinellin **2b** with α, β-unsaturated nitriles, has hitherto been not investigated. Therefore, it appeared of interest to study the reaction of **1**, **2a** and **2b** with the nitrile synthons **3a**–**j** in the search for new *N*- and *O*-heterocycles of promise as new biocides.



1



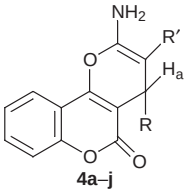
2a R = H
b R = OMe



3a–j

	R	R′		R	R′
a	Ph	CN	**f**	$C_6H_4NO_2$-*p*	CO_2Et
b	Ph	CO_2Et	**g**	C_6H_4OH-*o*	CN
c	C_6H_4OMe-*p*	CN	**h**	C_6H_4OH-*p*	CN
d	$C_6H_4NO_2$-*m*	CN	**i**	2-furyl	CN
e	$C_6H_4NO_2$-*p*	CN	**j**	2-thienyl	CN

Reaction of 4-hydroxycoumarin **1** with α,β-unsaturated nitriles **3a**–**j** proceeds in absolute ethanol to give 1 : 1 adducts for which structures **4a**–**j** were assigned. The reactions were markedly accelerated when a base was introduced in the medium. The pyranocoumarin structures of compound **4** were based upon the following grounds: (a) elemental analyses and molecular weight determination (MS) , (b) IR spectra and (c) NMR spectra (in DMSO).

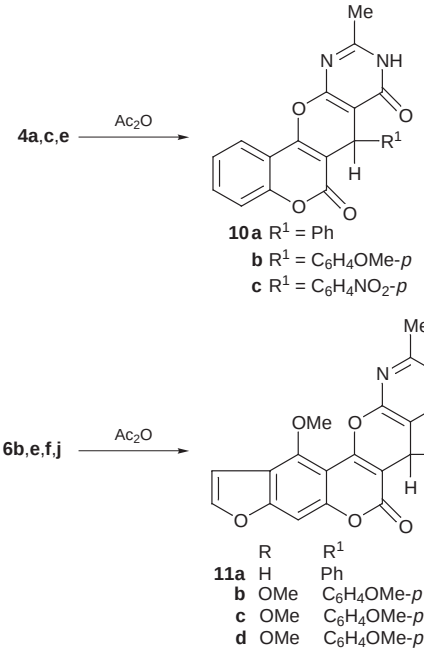


4a–j

R and R′ as in **3**

Under similar conditions, compounds **2a** and **2b** reacted with the cyanomethylene reagents **3a**–**j** to afford the respective pyranofurocoumarins **6a**–**r**. Structures **6** were based upon the following evidence: (a) correct elemental analyses and molecular weight determination (MS) were observed for the new products as well as (b) IR spectra in which the strong OH band present at 3350 in the spectrum of **2a** and at 3320 cm^{-1} in the spectrum of **2b**, was absent in the IR spectra of **6a**–**r**.

The behaviour of compounds **4** and **6** towards acetylation was also studied. Thus, refluxing of **4a**,**c**,**e** in acetic anhydride yielded colourless crystalline products for which structures **10a**–**c** (Scheme 1) were assigned, respectively for the following reasons: (a) correct elemental analyses and molecular weight determinations (MS) were obtained for all products, (b) ^{13}C NMR spectra (in DMSO), (c) ^{1}H NMR spectra and (d) the strong CN-absorption band present in the IR spectrum of **4a** (KBr) at 2200 cm^{-1}, was absent in the spectrum of **10a**. However, the spectrum of **10a** showed two strong bands at 1720 cm^{-1} (C=O, lactone) and at 1660 cm^{-1} (C=O, lactam).



10a R^1 = Ph
b R^1 = C_6H_4OMe-*p*
c R^1 = $C_6H_4NO_2$-*p*

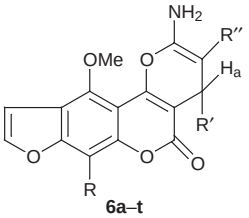
	R	R^1	R^2
11a	H	Ph	COMe
b	OMe	C_6H_4OMe-*p*	COMe
c	OMe	C_6H_4OMe-*p*	COMe
d	OMe	C_6H_4OMe-*p*	H

Scheme 1

In the same sense, boiling of compounds **6b**,**e**,**f**,**j** with acetic anhydride afforded products which were assigned the new heterocyclic ring structure **11** (Scheme 1). Thus, the ^{13}C NMR spectrum of 9,13-dimethoxy-5,7-dioxo-3-methyl-6-(*p*-nitrophenyl)-4*H*-pyrimidino[5′,4′ : 2,3]pyrano-7*H*-furo[3,2-*g*][1]-benzopyran **11d** (in DMSO), for example, showed two downfield signals at δ 172.09 (C=O,

* To receive any correspondence.

pyrimidinone) and δ161.79 (C=O, lactone) as well as four up-field signals at δ 21.09 (−N=C*C*H$_3$), 34.59 (*C*HAr), 61.11 (C$_8$-OCH$_3$) and 62.57 (C$_5$-OCH$_3$). Remeasurement of the spectrum using the DEPT technique showed that the HC carbons of the furan ring appear at δ 146.14 (C-2′) and 103.18 (C-3′) while HC-carbons of the aryl moiety appear at δ 130.02, 105.03, 146.38 and 123.23. The ^{1}H NMR spectrum of **11d** (in DMSO) showed singlets at δ 2.35 (3H, –N=CCH$_3$), 4.00 (3H, OCH$_3$), 4.10 (3H, OCH$_3$), 5.00 (CHAr) and 12.75 (NH, D$_2$O exchangeable). It also showed doublet signals at δ 8.15 (1H, furan HC-2′, J_{HH} = 2.5 Hz) and 7.30 (furan HC-3′, J_{HH} = 2.5 Hz). Signals due to protons of the AB-system of the aryl moiety appeared as two doublets (each with J_{HH} = 9 Hz) at 7.60 and 8.10. The IR spectrum of **11d** (in KBr cm^{-1}) showed strong absorption bands at 3440 (NH), 1730 (C=O, lactone), 1670 (C=O, lactam), 1600–1480 (C=C, furan and aromatic) and at 1240 (C–O, stretching).



6a–t

	R	R′	R″		R	R′	R″
6a	H	Ph	CN	**k**	H	$C_6H_4NO_2$-*p*	CO_2Et
b	OMe	C_6H_4OMe-*p*	COMe	**l**	OMe	$C_6H_4NO_2$-*p*	CO_2Et
c	H	Ph	CO_2Et	**m**	H	C_6H_4OH-*p*	CN
d	OMe	Ph	CO_2Et	**n**	OMe	C_6H_4OH-*p*	CN
e	H	C_6H_4OMe-*p*	CN	**o**	H	C_6H_4OH-*o*	CN
f	OMe	C_6H_4OMe-*p*	CN	**p**	OMe	C_6H_4OH-*o*	CN
g	H	$C_6H_4NO_2$-*m*	CN	**q**	H	C_4H_3O	CN
h	OMe	$C_6H_4NO_2$-*m*	CN	**r**	OMe	C_4H_3O	CN
i	H	$C_6H_4NO_2$-*p*	CN	**s**	H	C_4H_3S	CN
j	OMe	$C_6H_4NO_2$-*p*	CN	**t**	OMe	C_4H_3S	CN

Scheme 2

Structure elucidation of compounds **10a**,**c** and **11d** was based mainly on a high field ^{1}H and ^{13}C NMR spectroscopy and on comparison with data of other related molecules.[13–15] The assignment of the NMR signals was achieved by ^{1}H and ^{13}C NMR (DEPT) measurements. Fragmentation patterns of compounds **4** and **6** under electron bombardment (EIMS) were studied in some detail.

Experimental

All melting points were determined on an Electrothermal melting point apparatus and are uncorrected. The IR spectra were carried out in KBr on a Perkin Elmer infrared spectrometer (Grating). Microanalyses were carried out at the Microanalytical Laboratory of Cairo University. The ^{1}H NMR spectra were measured with a JEOL GLM 270 MHz spectrometer (superconducting magnet) in $CDCl_3$ or DMSO-d_6 and the chemical shifts were recorded in δ relative to TMS as an internal reference. The mass spectra were run at 70 eV with a Schimadzu GC/MS QP 1000 EX and Finnigan SSQ GC/MS spectrometers using the electron ionization (EI) technique.

Preparation of Compounds **4a**–**j** *and* **6a**–**t**.— *General Procedure.* A mixture of the starting material (**1**, **2a** or **2b**) (1 mmol) and the α,β-unsaturated nitrile **3** (1.2 mmol) in absolute ethanol (25 ml) was refluxed for 6–8 h, TLC monitored and left to cool at ambient temperature. The precipitated material was collected by filtration and recrystallized from the appropriate solvent to give adducts (**4** and/or **6**) as coloured crystals.

Reaction of Compounds **4** *and/or* **6** *with Acetic Anhydride.— General Procedure.* 1 mmol of compound **4** and/or **6** was refluxed in 15 ml acetic anhydride for 9–12 h (TLC controlled). The precipitates formed (compounds **10a**–**c** and **11d**) were filtered off from the hot reaction mixture and washed with ethanol several times, followed by crystallization from DMF–water. For compounds **11a**,**b**,**c**, no precipitate was formed. Therefore, the reaction mixture was poured onto ice-cold water to obtain a white precipitate which was filtered off, washed with water, dried and recrystallized from acetone—light petroleum.

Techniques used: ^{1}H NMR, IR, EI-MS

Tables: 5 (Characterizing data)

Charts: 2 (Mass fragmentation pathways)

References: 25

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