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Chromones **1** react with diamine **2** to give various products depending on the nature of the position 3 substituent in the heterocycle.

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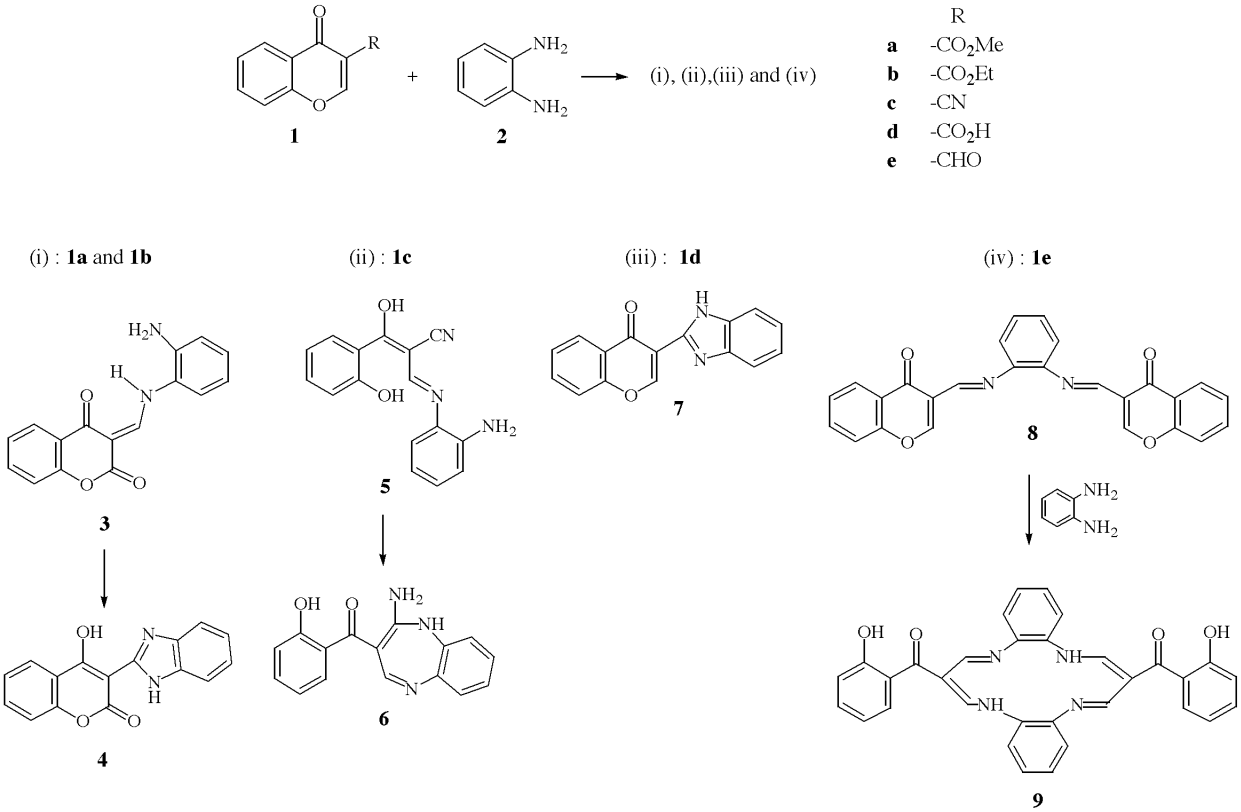
Chromones are one of the most widely distributed classes of natural compounds occurring in the plant kingdom [1,2]. Many natural and synthetic derivatives perform a variety of biological activities [3], including anti-inflammatory [4] and immune-stimulatory [5] activity. Since their reactivity towards nucleophiles provides a useful route to the preparation of a variety of rearranged products and new heterocyclic systems, their versatility as reactive intermediates is well documented in literature. For example, the addition of hydrazines, hydroxylamine and amidines resulted in the formation of *o*-hydroxyphenyl pyrazoles, isoxazoles and pyrimidines respectively by an identical mechanistic pathway [1,6]. Despite this susceptibility to C-2 attack and the resulting easy opening of the heterocyclic ring, we attempted to reduce the C-C double bond in chromones in order to produce chromanones. This is in line with previous studies in which benzimidazolines generated *in situ* from 1,2-phenylendiamine and arylaldehyde [7] were successfully used as chemoselective reducing agents of exo- [8] or endo-cyclic [9] C-C double bonds. These attempts failed, however, probably because these systems do not incorporate a styrenic double bond, while complex sequences of conjugative additions were observed with the starting 1,2-diamine alone [10]. Depending on the functional groups connected to the heterocyclic framework, a variety of different products were found to be formed as a

Scheme 1



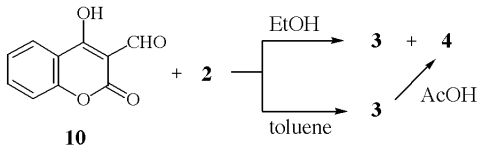
result of direct reaction between chromones **1** and diamine **2** [11] and the results of this investigations are described here.

The different reaction paths observed for the various substrates **1** are summarized in Scheme 1: (i) with esters **1a** and **1b**, coumarin derivatives **3** and **4** are obtained; (ii) with the 3-cyano derivative **1c**, *via* **5**, benzodiazepine **6** is formed; (iii) from the 3-carboxylic substrate **1d**, benzimidazole derivative **7** is obtained; (iv) using the 3-formyl derivative **1e**, the intermediate **8** is isolated together with the tetraaza[14]annulene **9** as a further diamine attack product.

Structures **7** and **9** were assigned by comparison with authentic samples [10,12]. Structures **4** and **6**, however, were assigned on the basis of elemental analyses and spectral data. In the ^{1}H-NMR spectrum of compound **4**, only the aromatic hydrogens of the coumarin and benzimidazole moieties are observed, and the IR shows the coumarin C=O stretching band (1715 cm^{-1}) and the enolic OH (3412 cm^{-1}).

Proof of structure **4** assignment was obtained by independent synthesis (see Experimental) starting directly from 3-formyl-4-hydroxycoumarin **10** and 1,2-phenylenediamine **2** (Scheme 2) and comparison of the spectra.

Scheme 2



The IR spectra of **6** shows a conjugated aromatic C=O band (1663 cm^{-1}) and OH and NH_2 bands in the region between 3175 and 3441 cm^{-1}. In the ^{1}H-NMR spectrum, in addition to the aromatic hydrogens, a singlet at δ 8.87 belonging to the olefinic hydrogen of the benzodiazepine moiety is observed. Heterocorrelated 2D NMR experiments allowed for the assignment of the *ortho*-hydrogen of the benzoyl group to the resonance at δ 7.85. The 2D NOESY spectrum shows clear evidence of dipolar interaction between these two hydrogens thus showing their close proximity (Scheme 1, path ii) and thereby proving that the chromone ring underwent ring-opening during the reaction.

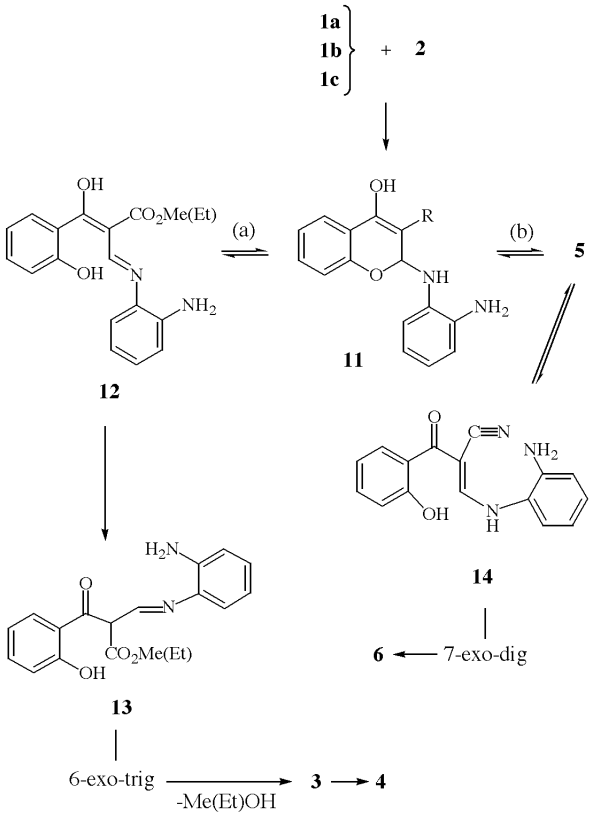
Indeed, further indirect evidence of the structure **6** can arise from its transformation into the benzimidazole **7** [12] by treatment with AcOH, according to an analogous reaction for annulene **9** [10,12], confirming the presence of a free *o*-hydroxy-ketone.

Derivatives **4** [13] and **6** may assume various tautomeric configurations; however, the results showed that the observed forms for these compounds, either in solid or solution phase, are those described in Scheme 1.

Structures **3** and **5** were assigned using analytical and spectral data. Significant NOE enhancement (5%) between azomethine hydrogen and *ortho*-proton of the adjacent aminophenyl group, $\nu_{C=O}$ =1725 cm^{-1} and δ_{CH} = 8.97, according to previous results [14], support unambiguously the *E*-configuration for the structure **3**.

Compounds **4** and **6** are formed by the initial attack of the diamine on the electrophile site C2 of the corresponding chromones **1**. Subsequently, according to previous results [15], the chroman-4-one **11** is formed and evolves differently depending on the R substituent (Scheme 3).

Scheme 3



In path a (R = -COOMe or -COOEt), after a preliminary rearrangement into **13** [16] followed by favoured 6-exo-trig cyclisation [17] of the phenolic OH with the carbonyl of the initial ester group, the Schiff base **3** is obtained, from the tautomeric imine **12**. The latter can either be isolated from anhydrous toluene in which it is completely insoluble, or refluxed in ethanol or treated with AcOH to yield benzimidazole derivative **4** by oxidative cyclisation.

When R=CN (path b), imine **5** is isolated, this can partially isomerize into the enamine ketone **14** and undergo a rapid ring closure, through a 7-exo-dig

cyclisation [17], to give **6**. As proof of this, the isolated key-intermediates **3** and **5** were individually reacted to generate compounds **4** and **6** respectively.

Compound **7** (Scheme 1, path iii) is formed according to the classic reaction between diamine and carboxylic acids. Annulene **9** (Scheme 1, path iv) derives from the preliminary attack of the diamine **2** on the aldehydic carbon to form **8**. This step goes through a macrocyclic ring closure and subsequent chromone ring opening by diamine attack on the C-2 position of **8**. As confirmation of this, the isolated chromone **8** reacted with the diamine **2** to give the tetraaza derivative **9**.

EXPERIMENTAL

Melting points were determined using Reichert-Kofler hot stage apparatus and are uncorrected. IR spectra were performed using a Nicolet FT-IR Impact 400D spectrometer and microanalyses using a Carlo Erba 1102 element analyser. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker ARX 300 spectrometer, in the solvent indicated. Chemical shifts (δ) refer to TMS, which was used as an internal reference. Column chromatography was performed on Merck silica gel 70-270 mesh. The starting materials **1** were prepared according to literature methods [18].

General Procedure for the Reaction of Chromones **2** with 1,2-Phenylenediamine **2**.

1,2-Phenylenediamine **2** (5 mmol) was added to an absolute EtOH solution (60 ml) of chromones **1** (5 mmol) at room temperature in the same solvent. The resulting yellow reaction mixture was refluxed under continuous stirring until a yellow precipitate appeared. After cooling at room temperature this solid was filtered and purified by washing or by crystallisation from the solvent indicated. Yield (%), melting point (°C), microanalytical data, and selected spectroscopic data for the new compounds are as follows.

3-[(2-Amino-phenylamino)-methylene]-chroman-2,4-dione (**3**).

(i) Chromones **1a** and **1b** gave in good yield (73%): enamine **3**, as yellow crystals from toluene, mp 220 °C. IR (Nujol): ν_{max}(cm^{-1}) = 3412, 3352 and 1725. ^{1}H NMR ($CDCl_3$): δ = 8.97 (1H, d, *J* = 10 Hz, NH), 8.77 (1H, d, *J* = 10 Hz, CHazomethine), 8.00-6.67 (8H, m), 3.95 (2H, br, NH_2). ^{13}C NMR ($CDCl_3$): δ = 179.98, 161.10, 156.48, 154.31, 141.42, 137.32, 134.94, 128.51, 125.55, 124.41, 122.50, 120.09, 118.61, 118.07, 117.36, 99.03.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found C, 68.38; H, 4.17; N, 9.94.

3-(1*H*-Benzoimidazol-2-yl)-4-hydroxy-chroman-2-one (**4**).

Hydroxycoumarin **4**, was obtained as almost colourless crystals from MeOH, mp 290 °C. IR (nujol): ν_{max}(cm^{-1}) = 3415 and 1715. ^{1}H NMR($CDCl_3$): δ = 14.08 (br, OH), 12.19 (br, NH), 7.7 - 7.2 (m, 8H).

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found C, 68.89; H, 3.50; N, 10.10.

2-[(2-Amino-phenylimino)-methyl]-3-hydroxy-3-(2-hydroxy-phenyl)-acrylonitrile (**5**).

(ii) Chromone **1c** gave Schiff base **5** in 81% yield as yellow crystals from mother liquor (EtOH), mp 205 °C. IR (Nujol): ν_{max}(cm^{-1}) = 3250, 3190, 2204, 1625. ^{1}H and ^{13}C NMR spectra can't be recorded for compound **5** because it is insoluble in the more usual deuterated solvents at room temperature and with heating it evolves to **6**.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found C, 68.62; H, 4.55; N, 14.99.

(2-Amino-1*H*-benzo[*b*][1,4]diazepin-3-yl)-(2-hydroxy-phenyl)-methanone (**6**).

Benzodiazepine **6** was obtained as an orange powder from EtOH, mp 217 °C. IR (nujol): ν_{max}(cm^{-1}) = 3442, 3330, 1663, 1602. ^{1}H NMR (DMSO-d_6): δ = 10.4 (1H, br, OH), 9.34 (1H, br, NH), 8.87 (1H, s, CH azomethine), 8.05-7.4 (m, 4H), 6.97-6.55 (m, 4H), 5.1 (2H, br, NH_2). ^{13}C NMR (DMSO-d_6): δ = 178.98, 169.10, 159.45, 158.01, 147.52, 142.72, 138.52, 131.37, 130.39, 130.21, 127.10, 122.99, 121.89, 121.90, 119.87, 100.45.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found C, 68.71; H, 4.59; N, 15.01.

(iii) Chromone **1d** gave the known benzimidazole **7** (63%), mp 270 °C (lit. [10,12] mp 268 °C).

(iv) Chromone **1e** gave the known dihydrotetraaza[14]-annulene **9** mp 210 °C; (lit. [10,12] mp 205 °C). By working as above, but with chromone/1,2-phenylenediamine 2:1 ratio, bis-chromone **8** (65%) mp 195 °C has been obtained [19].

Reaction of 3-formyl-4-hydroxycoumarin **10** with 1,2-phenylenediamine **2**.

To absolute EtOH solution (30 ml) of 0.9 g (4,7 mmol) of 3-formyl-4-hydroxycoumarin **10**, prepared according to literature procedure [20], a stoichiometric amount of 1,2-phenylenediamine **2** in the same solvent (20 ml) was added. Then, the reaction mixture was heated and maintained under reflux until a yellow solid appears. Ather cooling this solid is collected for filtration and recrystallised to give compound **4** (1.09 g; 83%) and traces of **3**.

The same reaction in dry toluene gives almost quantitatively only **3**, which, after treatment with glacial AcOH, evolves quantitatively to **4**.

Reaction of **5** or **6** with AcOH.

Benzodiazepine **6** (0.7 g) or the open-chain isomer **5** are refluxed under constant stirring in glacial AcOH (10 ml). Afther 1 hour, the mixture is then cooled and diluted with cold water (30 ml). A colourless solid was precipitated, isolated by suction, washed with water, dried and recrystallised from chloroform to give quantitatively the known benzimidazole **7** [10,12].

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