Structure of reaction products of 3-cyanochromones with ethylenediamine

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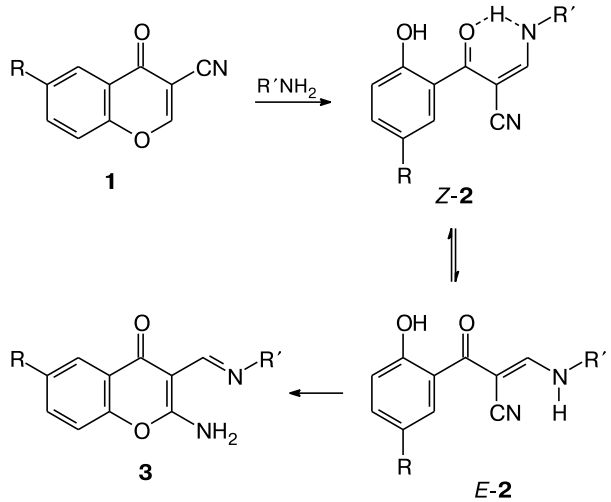
A reaction of 3-cyanochromones with ethylenediamine in ethanol afforded *N*,*N*´-ethylene-bis(2-amino-3-iminomethylchromones), which depending on the time of reflux in acetic acid give 2-amino-3-formylchromones or products of their dimerization, 2-(chromon-3-yl)-5*H*-chromeno[2,3-*d*]pyrimidin-5-ones.

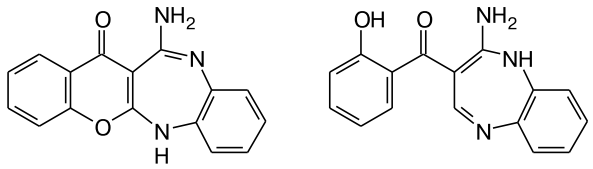
Key words: 3-cyanochromones, ethylenediamine, recyclization, 2-amino-3-formylchromones, 2-amino-3-iminomethylchromones, 2-(chromon-3-yl)-5*H*-chromeno[2,3-*d*]-pyrimidin-5-ones.

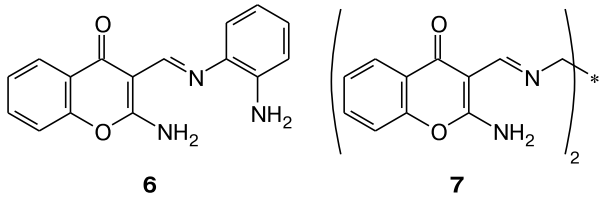
It is known that introduction of a nitrile group into chromones at position 3 significantly changes reactivity of the pyrone ring with respect to nucleophilic agents and provides wide synthetic possibilities of this very important oxygen-containing heterocyclic system.[1] Recently,[2] we have shown that the reaction of 3-cyanochromones **1** with primary aromatic and aliphatic amines begins from the attack on the unsubstituted atom C(2) and is accompanied by the pyrone ring opening, that leads to the formation of a mixture of *Z*- and *E*-3-aryl/alkylamino-2-(2-hydroxyaroyl)acrylonitriles **2**, which readily and irreversibly cyclize to 2-amino-3-(aryl/alkyliminomethyl)chromones **3** (Scheme 1).

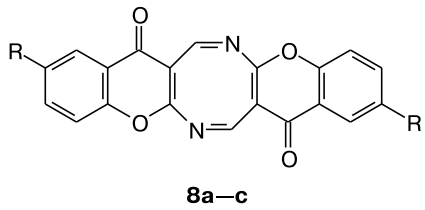
Scheme 1



From these data, it followed that the product of the reaction of **1** with *o*-phenylenediamine should have the structure of 2-amino-3-(2-aminophenyliminomethyl)-chromone **6**, rather than the benzodiazepine structures **4** or **5** as was indicated in the literature,[3,4] which was confirmed by us based on the spectroscopic data.[5] Taking into account the results obtained,[2,5] it could have been expected that the reaction of 3-cyanochromone **1** with more nucleophilic ethylenediamine would lead to bis-imine **7**.







R = H (**a**), Me (**b**), Et (**c**)

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Analysis of published reports showed that this reaction has been already studied, however, the 1,5-diazocine structure **8** was assigned to the products obtained based on the spectral data and the fact that they hydrolyze to 2-amino-3-formylchromones upon reflux in acetic acid.[6] The present study was undertaken in order to clear the arisen contradiction with respect to the structure of the products of reaction of 3-cyanochromones **1** with ethylenediamine.

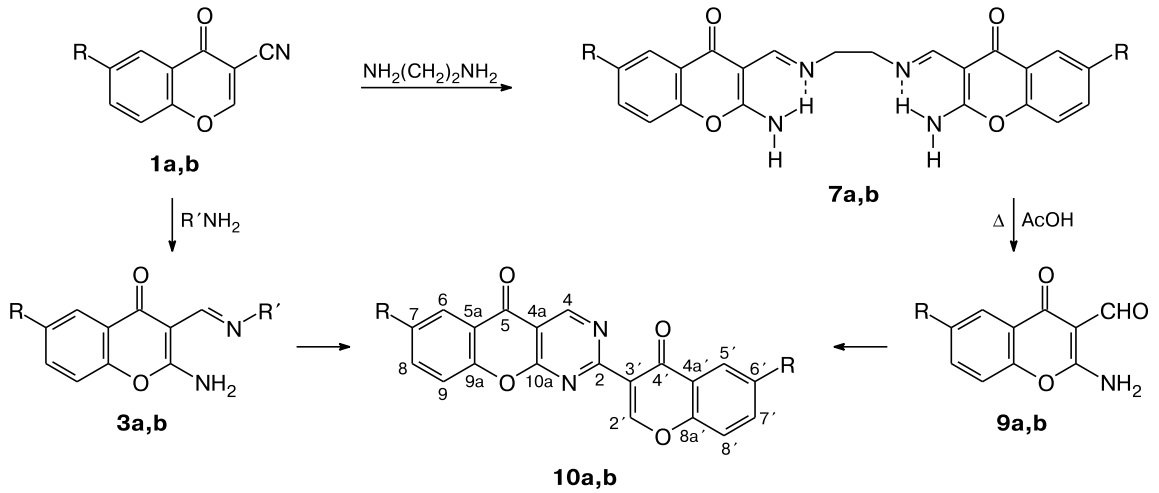
Results and Discussion

Heating 3-cyanochromones **1a,b** (1 equiv.) with ethylenediamine (0.5 equiv.) in ethanol for 10 min gives 84—86% yields of products, whose structure was inferred from the elemental analysis data and ^{1}H NMR spectroscopic data and found as *N*,*N*′-ethylene-bis(2-amino-3-iminomethylchromones) **7a,b**. Thus, the ^{1}H NMR spectra of these compounds in DMSO-d_6, in addition to the signals for the aromatic protons, exhibit singlets for the CH_2 and CH=N groups at δ 3.8 and 8.7, respectively, while the protons of the NH_2 group, which are nonequivalent due to the intramolecular hydrogen bonds (IMHB), are found as somewhat broadened singlets at δ 8.8 and 10.8 These results are in good agreement with the data for 2-amino-3-iminomethylchromones **3** described by us in the preceding work[2] and allow us to reject the diazocine structure **8** suggested earlier[6] for the products of the reaction under consideration in favor of bis-imines **7**. The work[6] also reported that diazocines **8a,b** (in fact, bis-imines **7a,b**) on reflux in acetic acid for 0.5 h hydrolyze to 2-amino-3-formylchromones **9a,b**. We found that if this reaction is carried out over longer time, the initially formed chromones **9a,b** undergo selfcondensation to chromeno-[2,3-*d*]pyrimidin-5-ones **10a,b**. According to the ^{1}H NMR spectroscopic data, after reflux of compound **7a** in ethanol for 3.5 h the reaction mixture contained **9a—10a** (3 : 2), while the full transformation **7a,b** → **10a,b** required 10—12 h. In addition, it turned out that other 2-amino-3-iminomethylchromones **3** can be also involved into the selfcondensation reaction. For instance, reflux of compound **3a** with R′ = Pr^i and 2-HOC_6H_4 in acetic acid gives dimer **10a** in 28 and 60% yields, respectively (Scheme 2).

Earlier, dimers **10a,b** have been obtained on reflux of 3-cyanochromones **1a,b** with ammonium acetate in acetic acid,[3] the equimolar mixture of chromones **1a,b** and **9a,b** in acetic acid,[3] chromone **9a** in toluene in the presence of *p*-toluenesulfonic acid,[7] as well as from 2-amino-3-(*p*-tolyliminomethyl)chromones **3a,b** (R′ = 4-MeC_6H_4) in boiling DMF (see Ref. 8). The mechanism of formation of compounds **10** either was not discussed at all[7], or was considered as 1,2-addition of the NH_2 group of chromone **9** at the CN group of chromone **1** with subsequent intramolecular cyclization involving arising amidine functional group and CHO group.[3] The case of chromones **3a,b** (R′ = 4-MeC_6H_4)[8] assumed a possibility of partial reverse transformation of **3** to **1** with further 1,2-addition at the CN group and cyclization involving the CH=NC_6H_4Me-4 fragment similarly to chromone **9**.[3]

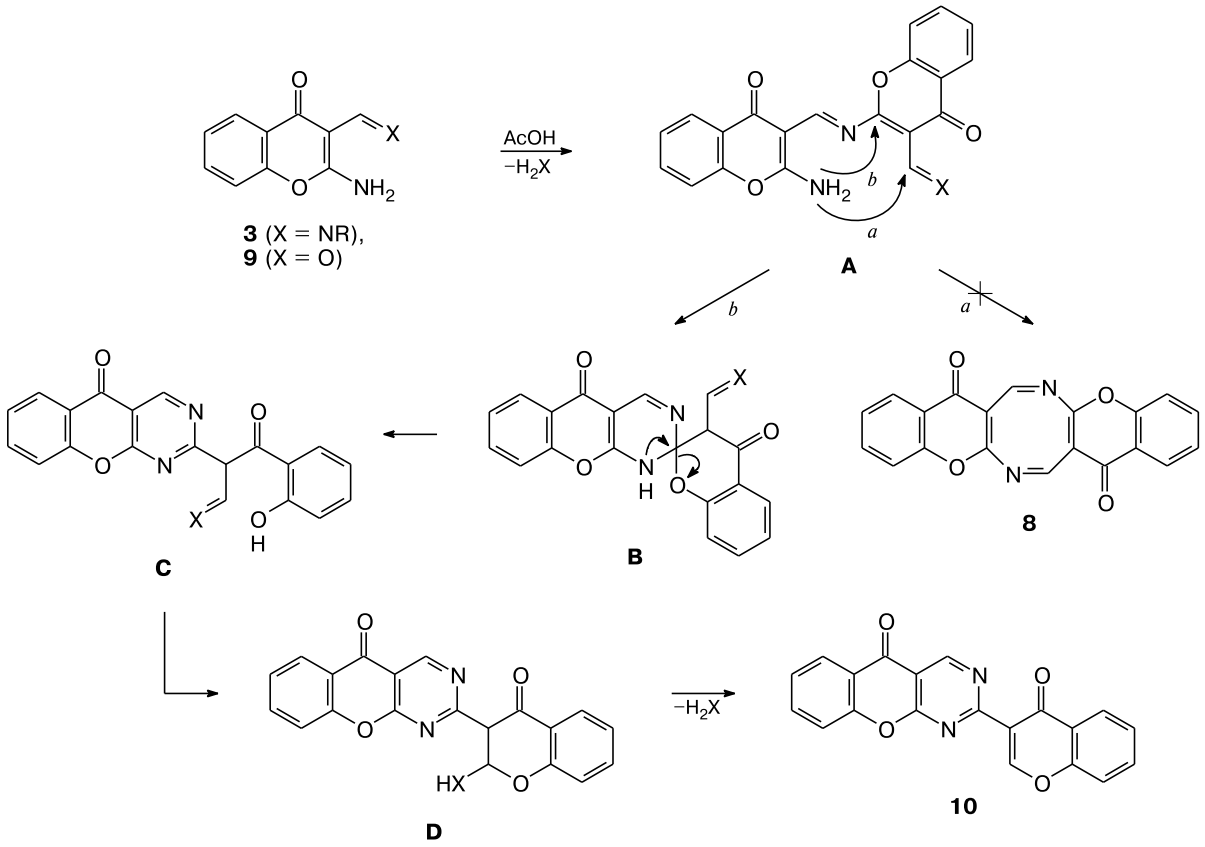
Taking into account the fact that the results in works[3,9] on the study of 3-cyanochromones **1**, which assumed a possibility of nucleophilic 1,2-addition at the cyano group, later were not confirmed,[5,10—12] we suggest that chromeno[2,3-*d*]pyrimidin-5-ones **10** are formed without involvement of **1** and are the products of selfcondensation of 2-amino-3-formylchromones **9** or their imines **3**; the latter give the reaction either due to their imino-enamine form, or are initially hydrolyzed to compounds **9**, which in

Scheme 2



R = H (**a**), Me (**b**); R′ = Pr^i, 2-HOC_6H_4, 4-MeC_6H_4

Scheme 3



turn give **10**. A plausible mechanism of this reaction is given in Scheme 3 and includes in the first step (1,2 A_N—E between the NH_2 group of one molecule and the CH=X group of another molecule) formation of the intermediate **A**, whose further intramolecular cyclization can proceed through the 1,2 A_N—E (*a*) or 1,4 A_N—E (*b*) pathways. Judging from our data, the first direction leading to diazocine **8** is not realized, while the second gives the spirointermediate **B**, which further recyclize to chromenopyrimidine **10** through the intermediates **C** and **D**.

The structure of dimers **10a,b** was confirmed by the ^1H and ^{13}C NMR spectroscopic data, the full assignment of all the signals, which has not been made earlier, was performed based on analysis of the ^1H—^{13}C HSQC and HMBC 2D-experiments using **10a** as an example. The most informative were the cross-peaks in the 2D HMBC spectrum in DMSO-d_6: H(2′)/C(3′), H(2′)/C(8a′), H(2′)/C(2), H(2′)/C(4′), H(4)/C(4a), H(4)/C(2), H(4)/C(10a) and H(4)/C(5). A specific feature of the ^1H NMR spectra of compounds **10** consists in the double set of signals for the aromatic protons, which are very close in chemical shifts and partially overlap, as a result in the case of **10a**, doublets of doublets for the protons H(6) and H(5′) are found at δ 8.21 as a triplet of doublets with J = 7.9 and 1.7 Hz. The signals for the protons H(2′) and H(4) are the most downfield and are observed at δ 9.1 and 9.6, respectively.

In conclusion, the reaction of 3-cyanochromones **1** with ethylenediamine leads to the formation of bis-imines **7** rather than 1,5-diazocines **8**, as it has been indicated earlier.[6] The imines on reflux in acetic acid through the step of formation of 2-amino-3-formylchromones **9** are transformed to chromenopyrimidines **10**. The acid and base catalyzed selfcondensation of compounds **3** and **9** to dimers **10** is a characteristic property of 2-amino-3-formylchromones and their imines. Therefore, the data in the work,[13] in which the structure of 1,5-diazocine **8c** was assigned to the product of selfcondensation of 3-cyano-6-ethylchromone in the presence of piperidine, are doubtful and need to be verified.

Experimental

IR spectra were recorded on a Perkin—Elmer Spectrum BX-II spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 and Bruker Avance II spectrometers in DMSO-d_6 (400 and 100 MHz, respectively) with Me_4Si as an internal standard. Solvents were purified ac-

cording to the standard procedures. Chromones **1a**,**b** and **3a** (R′ = Pr^i) have been described earlier.[2,3]

2-Amino-3-(2-hydroxyphenyliminomethyl)chromone (3a) (R′ = 2-HOC$_6$H$_4$). A solution of chromone **9a** (200 mg, 1.06 mmol) and *o*-aminophenol (120 mg, 1.1 mmol) in dry toluene (5 mL) was refluxed for 5 h, cooled, a precipitate formed was filtered off, washed with toluene, and dried. The yield was 260 mg (88%), yellow lamellar crystals, m.p. 225—227 °C. Found (%): C, 68.71; H, 4.18; N, 10.08. $C_{16}H_{12}N_2O_3$. Calculated (%): C, 68.56; H, 4.32; N, 9.99. IR, ν/cm^{-1}: 3266, 3147, 1655, 1614, 1555, 1494, 1462. ^{1}H NMR, δ: 6.84 (td, 1 H, H(5′), *J* = 7.5 Hz, *J* = 1.4 Hz); 6.89 (dd, 1 H, H(3′), *J* = 8.0 Hz, *J* = 1.4 Hz); 7.03 (ddd, 1 H, H(4′), *J* = 8.0 Hz, *J* = 7.3 Hz, *J* = 1.6 Hz); 7.09 (dd, 1 H, H(6′), *J* = 7.8 Hz, *J* = 1.6 Hz); 7.41—7.46 (m, 2 H, H(6), H(8)); 7.71 (ddd, 1 H, H(7), *J* = 8.5 Hz, *J* = 7.2 Hz, *J* = 1.7 Hz); 8.05 (dd, 1 H, H(5), *J* = 7.8 Hz, *J* = 1.7 Hz); 9.00 (s, 1 H, =CH); 9.20 (br.s, 1 H, OH); 9.29 (br.s, 1 H, NH); 10.84 (br.s, 1 H, NH).

2-Amino-3-{2-[(2-aminochromon-3-yl)methylidene]aminoethyl}iminomethylchromone (7a) was obtained according to the procedure described earlier.[6] The yield was 84%, m.p. 225—227 °C (*cf.* Ref. 6: m.p. 210 °C for **8a**). Found (%): C, 65.73; H, 4.53; N, 14.00. $C_{22}H_{18}N_4O_4$. Calculated (%): C, 65.66; H, 4.51; N, 13.92. ^{1}H NMR, δ: 3.81 (s, 2 H, CH$_2$); 7.35 (dd, 1 H, H(8), *J* = 8.2 Hz, *J* = 1.0 Hz); 7.36 (ddd, 1 H, H(6), *J* = 8.2 Hz, *J* = 7.2 Hz, *J* = 1.0 Hz); 7.65 (ddd, 1 H, H(7), *J* = 8.2 Hz, *J* = 7.2 Hz, *J* = 1.7 Hz); 7.97 (dd, 1 H, H(5), *J* = 8.2 Hz, *J* = 1.7 Hz); 8.69 (s, 1 H, CH=N); 8.82 (s, 1 H, NH); 10.88 (s, 1 H, NH).

2-Amino-6-methyl-3-{2-[(2-amino-6-methylchromon-3-yl)-methylidene]aminoethyl}iminomethylchromone (7b) was obtained according to the procedure described earlier.[6] The yield was 86%, m.p. 233—235 °C (*cf.* Ref. 6: m.p. 215 °C for **8b**). Found (%): C, 66.63; H, 5.16; N, 13.12. $C_{24}H_{22}N_4O_4$. Calculated (%): C, 66.97; H, 5.15; N, 13.02. ^{1}H NMR, δ: 2.37 (s, 3 H, Me); 3.80 (s, 2 H, CH$_2$); 7.25 (d, 1 H, H(8), *J* = 8.3 Hz); 7.46 (dd, 1 H, H(7), *J* = 8.3 Hz, *J* = 1.8 Hz); 7.75 (s, 1 H, H(5)); 8.67 (s, 1 H, CH=N); 8.78 (s, 1 H, NH); 10.83 (s, 1 H, NH).

2-(Chromon-3-yl)-5*H*-chromeno[2,3-*d*]pyrimidin-5-one (10a). A solution of chromone **3a** (R′ = 2-HOC$_6$H$_4$) (200 mg, 0.71 mmol) in glacial acetic acid (5 mL) was refluxed for 3 h, partially concentrated, followed by addition of water (5 mL). A precipitate formed on cooling was filtered off, washed with dilute acetic acid, and dried. The yield was 73 mg (60%), a yellow powder, m.p. 254—256 °C (*cf.* Ref. 7: m.p. 254 °C). ^{1}H NMR, δ: 7.59 (ddd, 1 H, H(6′), *J* = 7.9 Hz, *J* = 7.2 Hz, *J* = 1.0 Hz); 7.60 (ddd, 1 H, H(7), *J* = 7.9 Hz, *J* = 7.2 Hz, *J* = 1.0 Hz); 7.78 (dd, 1 H, H(8′), *J* = 8.5 Hz, *J* = 1.0 Hz); 7.81 (dd, 1 H, H(9), *J* = 8.5 Hz, *J* = 1.0 Hz); 7.90 (ddd, 1 H, H(7′), *J* = 8.5 Hz, *J* = 7.2 Hz, *J* = 1.7 Hz); 7.98 (ddd, 1 H, H(8), *J* = 8.5 Hz, *J* = 7.2 Hz, *J* = 1.7 Hz); 8.20 (dd, 1 H, H(5′), *J* = 7.9 Hz, *J* = 1.7 Hz); 8.22 (dd, 1 H, H(6), *J* = 7.9 Hz, *J* = 1.7 Hz); 9.14 (s, 1 H, H(2′)); 9.57 (s, 1 H, H(4)). ^{13}C NMR, δ: 112.6 (C(4a)), 118.6 (C(9)), 118.7 (C(8′)), 121.6 (C(3′)), 122.5 (C(4a′)), 124.5 (C(5a)), 125.5 (C(5′)), 125.6 (C(6′)), 126.0 (C(6)), 126.3 (C(7)), 134.6 (C(7′)), 136.5 (C(8)), 155.0 (C(8a′)), 155.3 (C(9a)), 158.5 (C(4)), 160.9 (C(2′)), 164.2 (C(2)), 165.2 (C(10a)), 173.0 (C(4′)), 175.7 (C(5)).

Dimer **10a** was also obtained from **7a** (40% yield) and **3a** (R′ = Pr^i) (28% yield) under similar conditions except that reflux in acetic acid continued for 10—12 h.

7-Methyl-2-(6-methylchromon-3-yl)-5*H*-chromeno[2,3-*d*]-pyrimidin-5-one (10b). A solution of bis-imine **7b** (200 mg, 0.5 mmol) in glacial acetic acid (3.5 mL) was refluxed for 12 h, cooled, crystals formed were filtered off, washed with acetic acid, ethanol, and dried. The yield was 53 mg (31%), yellow fine crystal, m.p. 303—304 °C (*cf.* Ref. 3: m.p. 297 °C). ^{1}H NMR, δ: 2.48 (s, 6 H, 2 Me); 7.68 (d, 1 H, H(8′), *J* = 8.6 Hz); 7.72 (d, 1 H, H(9), *J* = 8.6 Hz); 7.72 (dd, 1 H, H(7′), *J* = 8.6 Hz, *J* = 2.3 Hz); 7.80 (dd, 1 H, H(8); *J* = 8.6 Hz, *J* = 2.3 Hz); 7.98 (d, 1 H, H(5′), *J* = 2.3 Hz); 8.02 (d, 1 H, H(6), *J* = 2.3 Hz); 9.09 (s, 1 H, H(2′)); 9.56 (s, 1 H, H(4)).

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