Chemistry of Heterocyclic Compounds, Vol. 46, No. 1, 2010

TRANSFORMATIONS OF COUMARINS ACCOMPANIED BY INTERMEDIATE OPENING AND RECYCLIZATION OF THE LACTONE RING 3.* STUDY OF THE REACTIONS OF 3-ETHOXY-CARBONYLCOUMARINS WITH CYANOACETYL-HYDRAZINES BY NMR SPECTROSCOPY

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The reaction of 3-ethoxycarbonylcoumarin with derivatives of cyanoacetylhydrazine directly in the sample tube of the NMR spectrometer was investigated by ^{1}H NMR spectroscopy. The structure of the components of the reaction mixtures was established, and their relative concentrations at the various stages of the reaction were estimated. The sequence of processes occurring in the reactions was analyzed. Both the general characteristics and the differences in the course of the reaction with cyanoacetylhydrazine or its N-isopropylidene derivative as second component were established.

Keywords: cyanoacetylhydrazine derivatives, 3-ethoxycarbonylcoumarin, coumarin lactone ring opening and recyclization, Michael reaction, ^{1}H NMR spectroscopy.

In a continuation of earlier researches in which the reaction of 3-ethoxycarbonylcoumarin **1** with cyanoacetylhydrazines **2** was studied by mass spectrometry [2, 3] we have investigated the reaction by ^{1}H NMR spectroscopy directly in the tube used to record the spectra. As second component of the reaction we used both cyanoacetylhydrazine **2a** itself and its isopropylidene derivative **2b**. The reaction was conducted in 1 ml of methanol-d_4 with the components **1** + **2a** and **1** + **2b** in an equimolar ratio.

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* For Communication 2 see [1].

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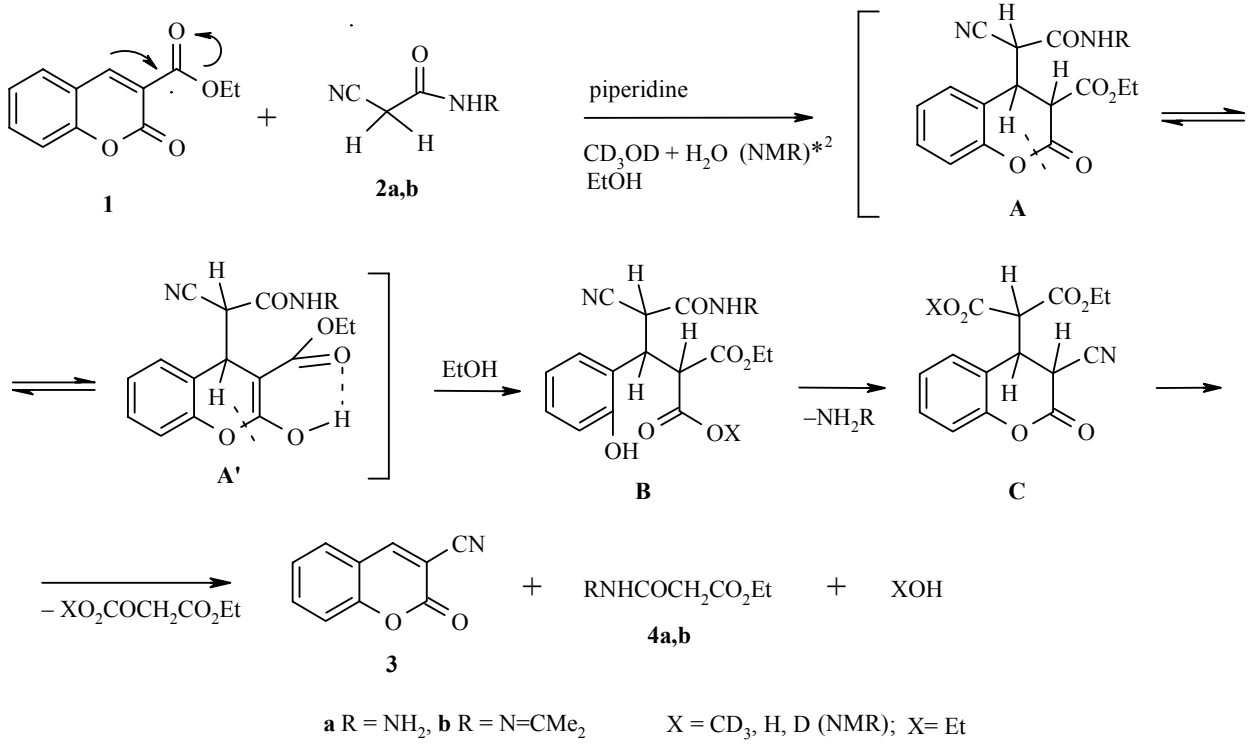
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 44-60, January, 2010. Original article submitted October 5, 2007. Revision submitted December 4, 2009.

The characteristics of the obtained ^{1}H NMR spectra are presented in Tables 1 and 2. For reliable identification of the components of the reaction mass the ^{1}H NMR spectra of the individual initial compounds **1** and **2a**,**b** (solvent methanol-d_4 and DMSO-d_6) and of compounds that could serve as model structures for the reaction products (adducts **5** and **6**, see below) were analyzed. It should be noted that, to judge from the ^{1}H NMR spectra, compounds **2a**,**b** exist in solutions in the form of a mixture of amide conformers (Table 1). When the ^{1}H NMR spectra of solutions of compounds **1** + **2** in methanol-d_4* are recorded fairly rapid deutero-exchange occurs with the formation of CHD and CD_2 fragments, leading both to an appreciable decrease in the intensity of the singlet for the methylene protons in the spectra and to the appearance of a triplet signal corresponding to the CHD fragment. (There is a small change in the value of the chemical shift on account of isotopic substitution, $\Delta\delta = \delta CH_2 - \delta CHD \sim 0.01$-$0.02$ ppm, Table 1).

Earlier, during a mass spectrometric investigation [2] of the structure of the components of the reaction mixtures remaining after the isolation of 3-cyanocoumarin **3** from the analogous reaction of **1** + **2**, conducted under laboratory conditions in alcohol in the presence of a catalytic amount of piperidine, a scheme was put forward for the first stage of the reaction of 3-ethoxycarbonylcoumarin **1** with derivatives of cyanoacetyl-hydrazines **2a**,**b** leading to the formation of 3-cyanocoumarin. According to this scheme, the hydrazine **2** adds

Scheme 1



a R = NH_2, **b** R = N=CMe_2 X = CD_3, H, D (NMR); X= Et

* The H_2O in methanol-d_4 is partly or wholly deuterated.

*[2] During the mass-spectrometric investigation the reaction mixtures (**1**) + (**2**) in alcohol were analyzed, and to study the reaction of **1** + **2** by ^{1}H NMR spectroscopy methanol-d_4, which always contains small amounts of H_2O, HDO, and D_2O, was used as solvent. In methanol-d_4 the methylene protons of compounds **2a**,**b** and **4a**,**b** are easily exchanged for D (see the text), as a result of which in all the structures examined during investigation by NMR the methine protons (except H-4) and also the protons at the NH group are actually substituted by D.

TABLE 1. The ^{1}H NMR Spectra of Compounds **1-3** and **7**

Compound	Chemical shifts, δ, ppm (*J*, Hz)*								
	Coumarin fragment						Cyanoacetylhydrazide fragment		
	H-4 (s)	H-5 (d)	H-6 (m)	H-7 (m	H-8 (d)	3-Z*[2]	CH_2	CH_3	NH
1	8.72	7.91 (^3J = 7.6)	7.40	7.73	7.42 (^3J = 8.4)	1.31 (t, ^3J = 7.2, CH_3); 4.30 (q, ^3J = 7.2, CH_2)	—	—	—
3	8.96	7.82 (^3J = 7.6)	7.47	7.81	7.52 (^3J = 8.8)	—	—	—	—
2b*[3]	—	—	—	—	—	—	4.01 (s) 3.76 (s)	1.84, 1.90 (s) 1.85, 1.93 (s)	10.59 (br. s) 10.30 (br. s)
1 + 2a*[3]	8.70	7.80 (^3J = 7.6)	7.42	7.74	7.38 (^3J = 8.4)	1.41 (t, ^3J = 7.2, CH_3); 4.40 (q, ^3J = 7.2, CH_2)	3.55 (s, CH_2), 3.54 (t, $^2J_{HD}$ = 2.8, CHD)	—	—
1+2b*[3]	8.70	7.80 (^3J = 7.6)	7.42	7.74	7.39 (^3J = 8.4)	1.42 (t, ^3J = 7.2, CH_3); 4.41 (q, ^3J = 7.2, CH_2)	3.92 (s, CH_2), 3.90 (t, $^2J_{HD}$ = 2.8, CHD) 3.73 (s, CH_2), 3.72 (t, $^2J_{HD}$ = 2.8, CHD) 3.98 (s, CH_2), 3.96 (t, $^2J_{HD}$ =2.8, CHD)	— 1.91, 2.00 1.99, 2.06	— — —
	8.72	7.91 (^3J = 7.6)	7.40	7.73	7.42 (^3J = 8.4)	1.31 (t, ^3J = 7.2, CH_3); 4.30 (q, ^3J = 7.2, CH_2)	4.00 (s, CH_2) 3.76 (s, CH_2)	1.84, 1.89 1.85, 1.93	10.60 10.30
7a	8.80	7.99 (^3J = 7.7)	7.44	7.73	7.48 (^3J = 8.0)	4.92 (br. s, NH_2); 9.59 (br. s, NH)	—	—	—
7b	8.98	8.05 (^3J = 7.6)	7.42	7.78	7.48 (^3J = 8.2)	1.96, 2.04 (s, CH_3); 11.20 (br. s, NH)	—	—	—

* The ^{1}H NMR spectra were recorded in DMSO-d_6 (compounds **1**, **2b**, **3**, and **7a**,**b**) and MeOH-d_4 [compounds **1** +**2a** and **1** + **2b**) solutions. 3-Cyanocoumarin **3** is not soluble in methanol-d_4.

*[2] **1** Z = CO_2Et, **7a** Z = $CONHNH_2$, **7b** Z = $CONHNCMe_2$.

*[3] In methanol-d_4 and DMSO-d_6 solutions compounds **2a**,**b** are represented by a mixture of amide conformers; the chemical shifts of the protons of the predominant form are shown in the first line, and then the minor form; the relative contents of the amide isomers are 65 and 35% for **2b** (DMSO-d_6); 80 and 20% for **1** + **2a** (methanol-d_4); 55 and 45% for **1** + **2b** (methanol-d_4); 65 and 35% for **1** + **2b** (DMSO-d_6). Solutions **1** + **2a** and **1** + **2b** do not contain the catalyst (piperidine); the structure of the minor products is described in the text. In methanol-d_4 solution the methylene protons in **2a**,**b** are exchanged for D, as a result of which the protons are represented in the spectra both as singlets (the CH_2 fragment) and as triplets (the CHD fragment).

initially at position 4 of the coumarin ring (structure **A**). The pyran ring is then opened with the addition of a molecule of the alcohol (structure **B**). Successive elimination of a hydrazine molecule and closure of the pyran ring (structure **C**) and elimination of malonic ester lead finally to the formation of the cyanocoumarin **3**. The malonic ester in turn reacts readily with the previously released hydrazine, leading to the appearance of the monohydrazide of malonic ester **4** in the reaction mixture. The hydrazines eliminated in the recyclization process also enter into reaction with the initial 3-ethoxycarbonylcoumarin **1**; the reaction takes place both at the ethoxycarbonyl group with the formation of the corresponding hydrazide of coumarin-3-carboxylic acid and by addition of the hydrazines at position 4 of the lactone ring [2].

During investigation of the reaction by ^{1}H NMR spectroscopy the spectrum of a freshly prepared solution of compounds **1** and **2a** in methanol-d_4 without the addition of the catalyst (piperidine) was analyzed. Together with the signals of the initial compounds **1** and **2a** (Table 1) the recorded spectrum contains: clearly defined low-intensity signals (≤1%) of the cyanocoumarin **3** (a singlet for the H-4 proton at 8.69 ppm); low-intensity signals for the ethyl protons of the EtOCO fragment, belonging to the monohydrazide of malonic ester **4a** (δ, ppm: 1.29 t, 4.20 q); a low-intensity multiplet (~1%) for the aromatic protons in the region of 6.80-7.20 ppm. In the ^{1}H NMR spectrum of the investigated solution recorded 20 min later an increase in the concentration of the reaction products to ~5% (in relation to the initial **1**) was observed. Thus, it follows from the experiment that the cyanocoumarin **3** is formed even in the absence of the catalyst. An analogous experiment was conducted for compounds **1** + **2b** (in methanol-d_4), and this also showed a minor amount of cyanocoumarin. Moreover, the reaction of compounds **1** + **2b** without the catalyst (piperidine) and with the components in an equimolar ratio was also conducted in DMSO-d_6, and the ^{1}H NMR spectrum also contained clearly defined signals for newly formed compounds (concentration ~1%): cyanocoumarin **3** [8.96 (s, H-4) and 7.82 ppm (d, H-5)]* and an intermediate reaction product of type **A** (enolic form **A'**), characterized by the signals: 1.19 [s, N=C(CH_3)$_2$); 1.17 (t, ^3J = 7.2 Hz), 4.10 (bq) ($CO_2C_2H_5$); 3.47 (s, H-4'), 4.79 (s, H-4); 7.08-7.25 (m, CH arom.); 8.55 (NHC=O); 10.10 ppm (2-OH). The formation of the cyanocoumarin in this case can be explained only by the fact that the DMSO-d_6 used in the experiment contained a certain amount of water, which promotes the Michael reaction. Here the pyran ring of the coumarin ring (structure **B**) opens as a result of hydrolysis (and not alcoholysis as during the reaction in ethanol), leading subsequently to the formation of the cyanocoumarin **3**. Therefore, when the reaction of compounds **1** + **2** is conducted in methanol-d_4 (which also contains water) opening of the pyran ring of the coumarin ring can be expected both as a result of methanolysis and as a result of hydrolysis (as occurred in the case of DMSO-d_6 as solvent). According to data from the mass spectra of the reaction mixture of compounds **1** + **2a**, in methanol ring opening takes place mainly as a result of methanolysis [2].

During further investigation of the Michael reaction a catalytic amount of piperidine was added to the freshly prepared solutions of compounds **1** + **2a** and **1** + **2b** (in methanol-d_4), after which ^{1}H NMR spectrum No. 1 was recorded immediately. (Preparation of the solution and production of spectrum No. 1 took 20 min.) The ^{1}H NMR spectra were then recorded every 10 min: spectrum No. 2 after 30 min from the beginning of the reaction, No. 3 after 40 min, No. 4 after 50 min; then after 1h 20 min (spectrum No. 5), after 3 h (spectrum No. 6), and after 6 h (spectrum No. 7). The last two spectra were recorded 1 and 2 days after the beginning of the experiment.

In ^{1}H NMR spectra No. 1 for the two reactions (**1** + **2a** and **1** + **2b**) strong signals for cyanocoumarin **3** and particularly a singlet for the H-4 proton at 8.69 ppm are recorded clearly in addition to the signals of compounds **1** and **2**. At the same time there are signals for the monohydrazides of malonic ester **4a**,**b**: The signals of the $CO_2C_2H_5$ fragment at 1.28 (t, ^3J = 7.2) and 4.20 ppm (q, ^3J = 7.2 Hz) are characteristic of the

* The low-intensity signals of the other aromatic protons of compound **3** are masked by the signals of the analogous protons of the initial compound **1**.

hydrazide **4a**; compound **4b**, which exists in solution in the form of a mixture of the isomeric forms with relative contents of 2:1, is characterized by the singlet signals of the $N=C(CH_3)_2$ fragment at 1.99, 2.00, 2.06, and 2.07 and signals for the protons of the $CO_2C_2H_5$ group at 1.27, 1.30 (t, ^3J = 7.2) and 4.18, 4.21 (q, ^3J = 7.2 Hz). From analysis of the relative concentrations of the main components given in Table 2 it is seen that components **3** and **4a**,**b** are already present in significant amounts at the beginning of the reaction (spectrum No. 1): 15% of **3** and 16.5% of **4a** for the **1** + **2a** reaction and 30% of **3** and 39% of **4b** for **1** + **2b***. The first stage of the Michael reaction is quite fast. The intermediate products **A**, **B**, and **C** are short-lived and are practically undetectable in the case of the reaction of compounds **1** + **2b** (~1%); for the reaction of **1** + **2a** the total concentration of these compounds amounts to ~4.5%.*[2] A high rate of transformation of the intermediate structures **A** → **B** → **C** into the final reaction product **3** was also observed during mass-spectrometric investigation of the reaction [2].

As soon as the cyanocoumarin **3** was formed in the solution the second stage of the reaction, in which compound **3** reacts with the initial cyanohydrazines **2a**,**b**, began. Addition of **2a**,**b** takes place at position 4 of the coumarin ring (as also in the case of compound **1**) with the formation of the intermediate dihydropyran adduct **D**, which is transformed fairly quickly into a tricyclic structure of the **E** ⇌ **E'** type. In the ^{1}H NMR spectra the **E** (**E'**) structures are characterized by a multiplet for the aromatic protons in the region of 7.0-7.4 ppm; for structures **D** it is shifted upfield to 6.70-6.95 ppm. The signals of the methine protons H-4 are observed at 4.6-4.9 ppm; on account of deuteroexchange the signals of the H-3 and H-4' protons are observed in the spectrum in the form of strongly broadened and weak signals in the region of 3.40-3.65 ppm.

The respective adducts **5** (see the experimental section) and **6***[3] [1], in the ^{1}H NMR spectra of which the signals of the aromatic protons are represented by multiplets at 6.70-7.10 for **5** and 7.00-7.40 ppm for **6**, were used as model compounds for the reaction products **D** and **E**.

In addition, the reaction of the cyanocoumarin **3** with the monohydrazides of malonic ester **4a**,**b** takes place in parallel, leading to the formation of the dihydropyran adducts **G**, which are easily transformed into the tricyclic compounds **H** (**H'**). Like compounds **D** and **E**, in the ^{1}H NMR spectra compounds **G** and **H** are characterized by multiplets for the aromatic protons in the regions of 6.70-7.00 and 7.00-7.40 ppm respectively and also by the presence of signals for the protons of the ester groups $CO_2CH_2CH_3$: (like **C**) 0.85-1.10 (t, ^3J = 7.2, CH_3), 3.70-3.90 (m, CH_2) for **G**; 1.02–1.18 (t, ^3J = 7.2 Hz, CH_3), ~ 4.05 ppm (narrow m, CH_2) for **H**. The complicated form of the signals for the methylene protons of the ester groups results from the presence of asymmetric carbon atoms in the molecule, and in the dihydropyran structures **C**, **G** the multiplet for the protons of the CH_2 group of the ester groups (δ 3.70-3.90) is largely extended, whereas for the tricyclic structures **H** the methylene protons form a narrow sharp multiplet centered at ~4.05 ppm. An overall estimate of the relative content of the dihydropyran compounds with two CN groups **D** and of the tricyclic structures **E** was made on the basis of the integral intensity of the signals for the aromatic protons in the region of 6.70-7.40 ppm, from which the integral intensity of the aromatic protons corresponding to the structures of the dihydro adducts of types **A**, **C**, and **G** and the tricyclic structure **H** was deducted. The last two values were calculated from the integral area of the multiplets for the methylene protons of the $CO_2CH_2CH_3$ fragment at 3.70-3.90 and 4.05 ppm respectively.

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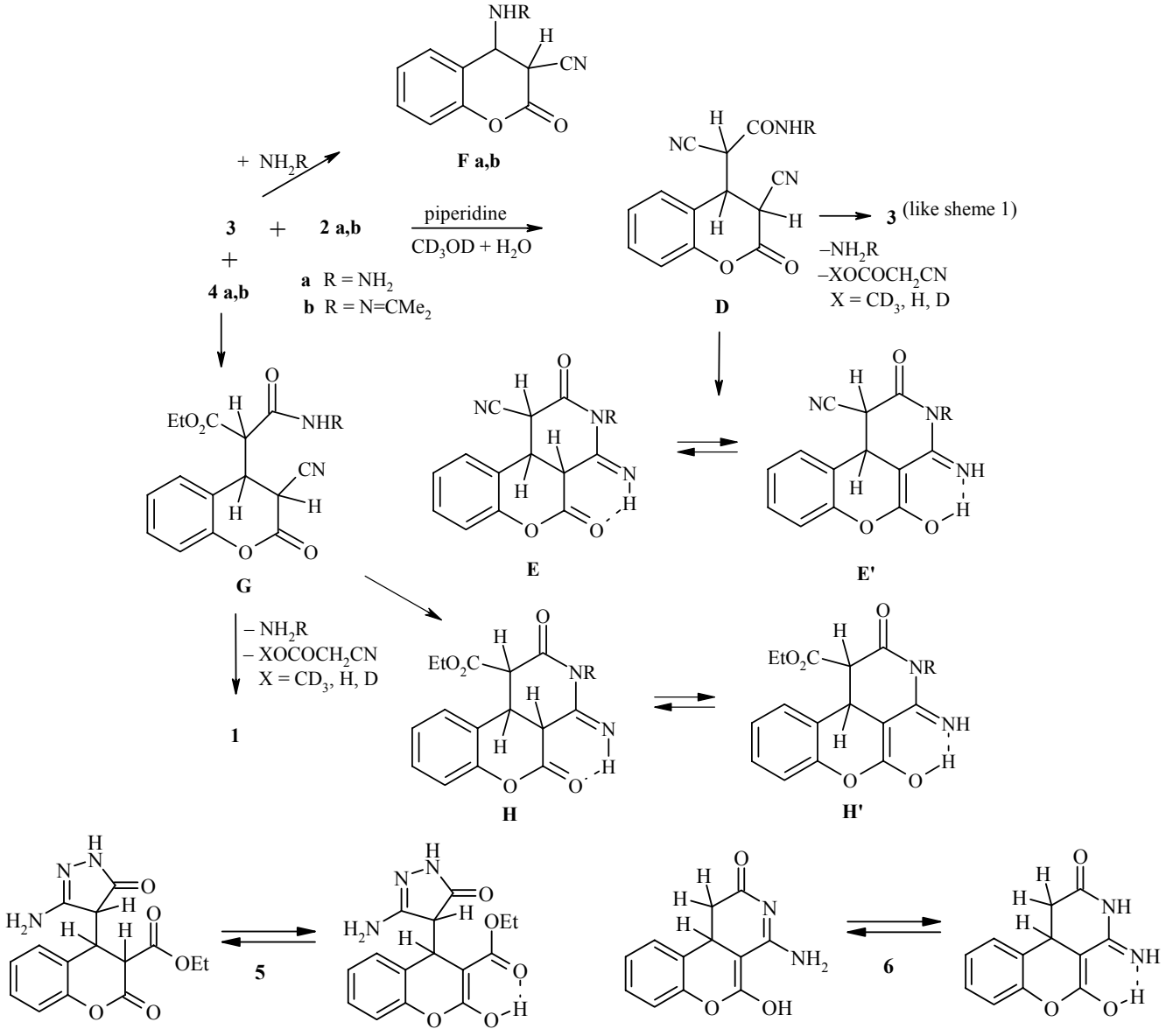
* Here and subsequently the relative concentrations of the main reaction components, determined without regard to the concentration of compounds **2a**,**b**, are presented and compared (see Table 2, notes).

*[2] The relative concentrations of compounds **A**, **B**, and **C** were determined on the basis of comparison of the intensities of the signals of the ester groups and the multiplets of the aromatic protons with the analogous signals of the initial compound **1**. For forms **A**, **B**, and **C**: 0.85-1.10 (bt, $C\underline{H}_3CH_2O$), 3.70-3.90 (m, $CH_3C\underline{H}_2O$), 6.70-7.00 ppm (m, CH arom.).

*[3] ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 2.40, 3.09 (1H each, dd, $^2J_{HA,HB}$ = 15.7, $^3J_{CHA,CH}$ = 13.6, $^3J_{CHB,CH}$ = 4.6, CH_2); 4.00 (1H, dd, $^3J_{CHA,CH}$ = 13.6, $^3J_{CHB,CH}$ = 4.6, H-10b); 7.00-7.40 (4H, m, H arom.); 8.00 (2H, bs, 2NH); 10.2 (1H, s, OH).

In the investigated solutions of compounds **1** + **2** the reaction of compounds **1** and **3** with the hydrazines NH_2R released during the reaction can take place in parallel. Addition of the hydrazines takes place at position 4 of the coumarin ring with the formation of dihydropyran structures of types **Fa**,**b** (**3** +NH_2R) and **La**,**b** (**1** + NH_2R). For structure **La** further cyclization with the elimination of ethyl alcohol, leading to the tricyclic compound **M**, is possible, and this is impossible in the case of structure **Lb**.



As in the case of the previously discussed dihydropyran structures the signals for the aromatic protons of structures **F** and **L** in the ^1H NMR spectra must be the multiplets in the region of ~6.70-7.00 ppm. This makes it difficult to determine the contribution from the reactions of **1** + NH_2R and **3** + NH_2R to the general course of the reaction of compounds **1** and **3** with various products in the investigated mixtures. However, since the relative content of the monohydrazides of malonic esters **4a**,**b** in the investigated reactions is comparable with or even exceeds the relative amount of the cyanocoumarin **3** (Table 2) it can be supposed that the greater

TABLE 2. The Relative Contents of the Main Components of the Reaction Mixtures* **1** + **2a** and **1** + **2b** (solvent methanol-d_4, catalyst piperidine)

Spectrum No.	Reaction time	**1 + 2a**, %					**1 + 2b**[*2], %				
		1	**3**	**4a**	**D + E(E') + F + I(I')**	**H(H') +K(K')**	**1**	**3**	**4b**	**D + E(E') + F**	**H(H') +K(K')**
1[*3]	20min[*4]	38[*4]	8.5	9.5	2	2	17	28	32	8	<1
1'	20 min	58	15	16.5	3	3	22	30	39	6	<1
2	30 min	44	20	21	6	5	21	25	38	11	2
3	40 min	33	22	24	9	8	20	20	37	15	5
4	50 min	21	23	27	13	12	18	15	35	20	8
5	1 h 20 min	16	20	30	15	15	15	9	31	25	14
6	3 h	12	13	35	19	18	10	4	25	29	22
7	6 h	6	8[*5]	41	21	21	6	~0	20	30	29

* The total content of the minor components in the mixture does not exceed 5%.

*[2] Spectra Nos. 5-7 of the reaction of **1** + **2b** contain the signals of ethanol, the amount of which increases from 2% (spectrum No. 5) to 10% (spectrum No. 7). (δ CH_3 1.20 ppm, t; ^3J = 7.2 Hz, δ CH_2 3.60 ppm, q, ^3J = 7.2 Hz).

*[3] Freshly prepared solution. (It took 20 min to prepare the solution and record spectra Nos. 1 and 1'.)

*[4]The relative concentrations of the components are given with allowance for component **2** (**2a** 37%, **2b** 12%). Since it is difficult to estimate the concentration of compound **2** more reliably on account of the rapid D-substitution of the CH_2 protons and the strong overlap of the singlet signals for the methyl protons of the isopropylidene fragment ($NCMe_2$), subsequent estimates of the relative concentrations of the components of the mixture (spectra Nos. 2-7) were made without allowance for the concentration of compound **2**. As a result of this for convenience of comparison the values for the freshly prepared solution (spectrum No. 1') are also given without allowance for compound **2**.

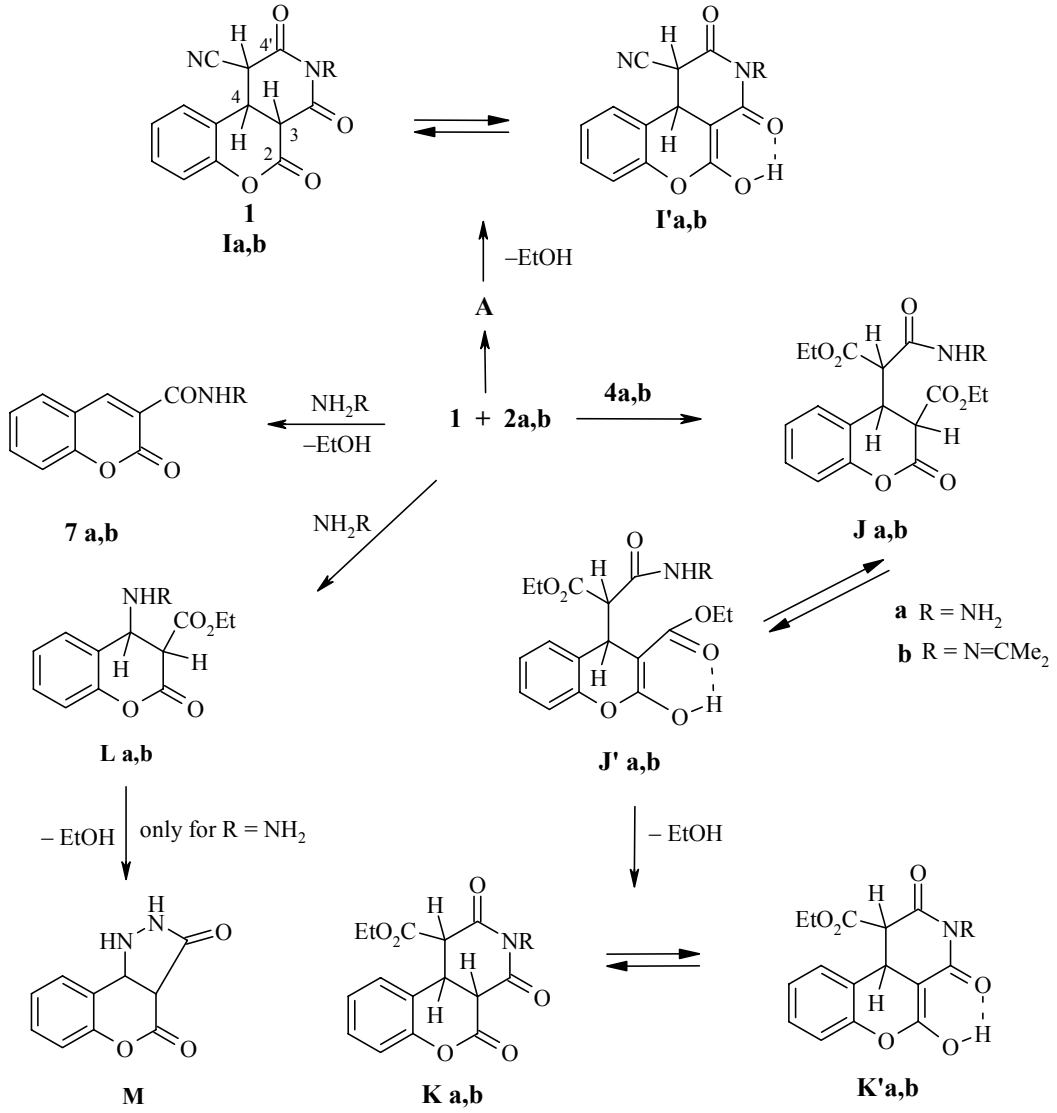
*[5] A precipitate of cyanocoumarin **3** appeared in the tube.

part of the hydrazines NH_2R released in the course of the reaction forms the hydrazides **4a**,**b**, and only a small amount participates in the reactions of **1** + NH_2R and **3** + NH_2R. In an article devoted to the mass-spectrometric investigation of the reaction it was also noted that the monohydrazides of malonic ester are some of the main components of the reaction mixtures [2].

In the reactions of compounds **1** + **2a**,**b** a new coumarin derivative is formed in parallel with the processes described above. Thus, in the ^{1}H NMR spectra of both reactions, recorded 30 min after the beginning of the reaction (Table 2, spectrum No. 2), there are low-intensity signals (~1-2%) of a new coumarin derivative: 8.78 (1H, s); 8.20 (1H, d, ^3J = 7.7 Hz) in the reaction of **1** + **2a** and 8.86 (1H, s), 8.19 ppm (1H, d, ^3J = 7.7 Hz) in the reaction of **1** + **2b**. Since, according to the data from mass-spectrometric investigation [2], a coumarin derivative formed during the reaction of compound **1** with the hydrazine derivatives H_2N–R released during the reaction (compound **7**) was detected among the reaction products it was natural to attribute such signals to coumarin derivatives.

It is also possible that the initial 3-ethoxycarbonylcoumarin **1** reacts with the monohydrazides of malonic ester **4a**,**b** during the second stage of the reaction, while the dihydropyran adducts **Ja**,**b** are formed initially and can be transformed into the tricyclic compounds **Ka**,**b** by the elimination of ethanol.

Scheme 3



It is also impossible to rule out the possibility that the tricyclic compounds of type **1a**,**b** are formed from the intermediate adduct **A** with the elimination of ethanol provided that the intermediate **A** has sufficient life time [2]. However, as already mentioned above, in the case of the reaction of compounds **1** + **2b** structure **A** is short-lived; the total content of the adducts **A**, **B**, and **C** does not exceed 1%, and the appearance of compounds with a tricyclic structure of type **Ib** is consequently unlikely. For the reaction of compounds **1** + **2a**, where the total concentration of the reaction products **A** + **B** + **C** amounts to ~4.5%, the formation of the tricyclic structure **Ia** is somewhat more likely. While summarizing all the foregoing it must be emphasized that the formation of tricyclic structures of types **K**, **I**, and **M** must necessarily take place with the release of a molecule of ethanol. The ethanol may participate, albeit partially, in the opening of the pyran ring in the coumarin ring (structure **B**).

It was interesting to analyze the sequence of the processes occurring in reactions **1** + **2** and to reveal both the general relationships of the reactions for **1** + **2a** and **1** + **2b** and the differences between them. Table 2 gives the relative contents of the main components of the reactions of **1** + **2a** and **1** + **2b** determined for each of seven successively recorded ^{1}H NMR spectra corresponding to a specific reaction time. As already mentioned above, it follows from analysis of the data of spectrum No. 1, recorded immediately after preparation of the solution (reaction time 20 min), that the cyanocoumarin **3** is formed very quickly in both reactions. Moreover, to judge from the same spectrum No. 1 the concentrations of compounds **3** and **4** compared with the concentration of the initial **1** are significantly higher in the case of the reaction of **1** + **2b** (22% of **1**, 30% of **3**, 39% of **4b**) than for the reaction of **1** + **2a** (58% of **1**, 15% of **3**, 16.5% of **4a**), i.e., the Michael reaction (at the first stage) takes place appreciably more readily in the case of the isopropylidene derivative of cyanoacetyl-hydrazine **2**.

From the estimated values presented in Table 2 it then follows that the main components of both reaction mixtures after 40 min (spectra Nos. 1-3) are compounds **1**, **3**, and **4**. However, the course of the reactions differs. The reaction of **1** + **2a** is characterized by a gradual decrease in the concentration of the initial coumarin **1** and an approximately equal increase in the concentration both of the cyanocoumarin **3** and of the monohydrazide of malonic ester **4a**; in spectrum No. 4 (50 min after the beginning of the reaction) the relative concentration of the main components amounts to 21% for **1**, 23% for **3**, and 27% for **4a**. During this reaction there is a gradual almost identical increase in the relative total content of the bi- and tricyclic products containing only CN groups (structures **D** + **E**(**E'**) + **I**(**I'**)) and of the tricyclic structures containing the CO_2Et fragment (**H**(**H'**) and **K**(**K'**)) from 3% (spectrum No. 1) to 12-13%* (spectrum No. 4). Such a situation presupposes the simultaneous occurrence of several secondary reactions: Reaction of compounds **3** and **2a** leading to the formation of structures **D** + **E**(**E'**); reaction of compounds **3** and **4a** with the formation of structures **H**(**H'**); reaction of compounds **1** and **4a** leading to the formation of structures **K**(**K'**). The last reaction must take place with the elimination of alcohol, but its signals were not detected in the spectra of the reaction mass. This makes it possible to suppose that the contribution from structures **K**(**K'**) is small and that the formed ethanol is immediately involved in the reaction of **1** + **2a**.

In the case of the reaction of **1** + **2b** the situation is different. From analysis of spectra Nos. 1-4 it follows that the relative content of the cyanocoumarin **3** is highest (30%) at the beginning of the reaction. After 50 min from the beginning of the reaction the content of this substance has decreased by half (to 15%). In parallel, in the analyzed solution there is a significant increase in the concentration of the compounds containing only CN groups: the dihydro derivatives **D** and **F** and the tricyclic structures **E**, the total content of which after 50 min has increased from 6 to 20%. During this time the concentration of the monohydrazide of malonic ester **4b** decreases by only 4%. Thus, during the second stage of the reaction of **1** + **2b** the cyanocoumarin **3** mostly reacts with the initial **2b** and with the hydrazine released during the reaction. This is why the contribution from the tricyclic structures of type **H**(**H'**), which can be formed during the reaction of compounds **3** and **4a**, is fairly small.

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* The total content of the intermediate structures with one or two CO_2Et fragments (**A**(**A'**) + **B** + **C** + **G** + **J** + **L**) in spectrum No. 1 amounts to 4.5%. In the course of the reaction their concentration decreases to 3%.

In parallel, during this same second stage of the reaction there is a similar small gradual decrease in the content of compounds **1** and **4b**. It is natural to assume that the initial compound **1** reacts with the hydrazide **4b**, resulting in the formation of dihydro compounds containing CO_2Et fragments (structures **J**(**J'**)); then during the elimination of a molecule of ethanol the tricyclic structures **K**(**K'**) containing a CO_2Et group are formed. In fact, according to the data in Table 2, in the solution of **1** + **2b** a gradual increase in the concentration of the tricyclic compounds **K**(**K'**) from 2 to 8% is observed in spectra Nos. 2-4. The total content of the dihydropyran compounds with a CO_2Et fragment does not exceed 1-2%. The presence of ethanol was not recorded in the analyzed spectra in the first 50 min of the reaction, and this is probably due to the fact that its small amount, formed as a result of the reaction **1** + **4b** → **J**(**J'**) → **K**(**K'**), is immediately involved in the chain of transformations that occur in the reaction mixture.

Thus, it follows from the experimental data that in the first stage of the investigated reaction of compounds **1** + **2** the cyanocoumarin **3** is formed significantly more rapidly in the case where N-isopropylidenecyanoacetylhydrazine **2b** is used in the reaction. The second stage of the reaction, which includes reaction of the cyanocoumarin **3** with compounds **2a** and **4a** for the reaction of **1** + **2a**, takes place in parallel with the initial reaction. In the case of the reaction of **1** + **2b** the formed cyanocoumarin **3** begins to react actively with the **2b** practically removing it from the reaction and thereby blocking the path of the initial process **1** + **2b**.

During the further progress of both reactions (from 1 h 20 min to 6 h) the ^{1}H NMR spectra record a gradual decrease in the concentrations of the initial 3-ethoxycarbonylcoumarin **1** and of the product from the reaction of the cyanocoumarin **3** and a parallel increase in the content of the dihydropyran derivatives and tricyclic structures. The content of the monohydrazide of malonic ester **4** is significant in both reactions, but whereas the content of this compound is always increasing (from 16.5 to 41%) during the reaction of **1** + **2a** in the case of the reaction of **1** + **2b** its concentration decreases gradually from 39 to 20%.

It is interesting to compare data on the relative concentrations of the components of the investigated reactions 6 h after the beginning of the reactions (spectrum No. 7, Table 2). For the reaction of compounds **1** + **2b** the content of the initial compound **1** amounts to ~6%, the cyanocoumarin is practically absent, and the main components are the monohydrazides of malonic ester (20%) and the various dihydropyran and tricyclic derivatives; the total content of the derivatives with two CN fragments amounts to 30%, the total content of the tricyclic structures with CN and CO_2Et fragments or with two CO_2Et groups amounts to 29%, and the total amount of the dihydropyran derivatives with CN and CO_2Et fragments or with two CO_2Et groups is not greater than 5%. Thus, in the solution of the reaction of compounds **1** + **2b** at the given moment of time the initially formed cyanocoumarin **3** had already reacted almost completely, being converted into the dihydropyran derivatives, which were then transformed into the tricyclic structures; processes due to reaction of the initial 3-ethoxycarbonylcoumarin **1** with the monohydrazides of malonic ester then occur in the solution, leading to the dihydropyran derivative **J**. During the elimination of ethanol **J** is converted into the tricyclic compound **K**. The spectrum contains the signals of ethanol (Table 2); the relative content of ethanol at the this time increases to 10%.

In the analogous spectrum for the reaction of compounds **1** + **2a** (spectrum No. 7) the situation is similar, but there is a difference in that although the spectrum contains the signals of cyanocoumarin **3** (~8%) a deposit characterized, after removal and dissolution in DMSO-d_6, as the individual cyanocoumarin **3** is observed in the tube. Thus, in the course of this reaction, in contrast to the reaction of compounds **1** + **2b**, the cyanocoumarin that forms does not enter fully into further transformations. The content of the monohydrazide of malonic ester is very large (41%), and the total amount of dihydropyran and tricyclic derivatives with two CN groups (21%) is close to the total amount of analogous compounds containing CN and CO_2Et groups or two CO_2Et groups (21% of the tricyclic structures and 3% of the dihydropyran structures). The spectrum does not contain the signals of ethanol.

All that was said above about the features of the reactions of **1** + **2a**,**b** is clearly illustrated by the graphs for the dependence of the relative concentrations of the reaction components on the duration of the reaction (data from Table 2, Fig. 1 for the reaction of **1** + **2a**, Fig. 2 for **1** + **2b**).

It should be noted that the formation of the initial 3-ethoxycarbonylcoumarin **1** from cyanocoumarin during the given reaction is also possible [1]; here hydrazine and derivatives of cyanoacetic acid of the CN–CD_2–CO_2X' type (X' = H, D, CD_3) will be eliminated (from structure **G**). It is also impossible to rule out the secondary formation of cyanocoumarin from compound **D**. However, in the spectra recorded 6 h after the beginning of the reaction the content of the initial compound **1** was small for both reactions, and as already reported above the presence of cyanocoumarin was not detected in the reaction with the hydrazide **2b**. From this it can be concluded that the paths for the repeated formation of compounds **1** and **3** are not determining for these reactions.

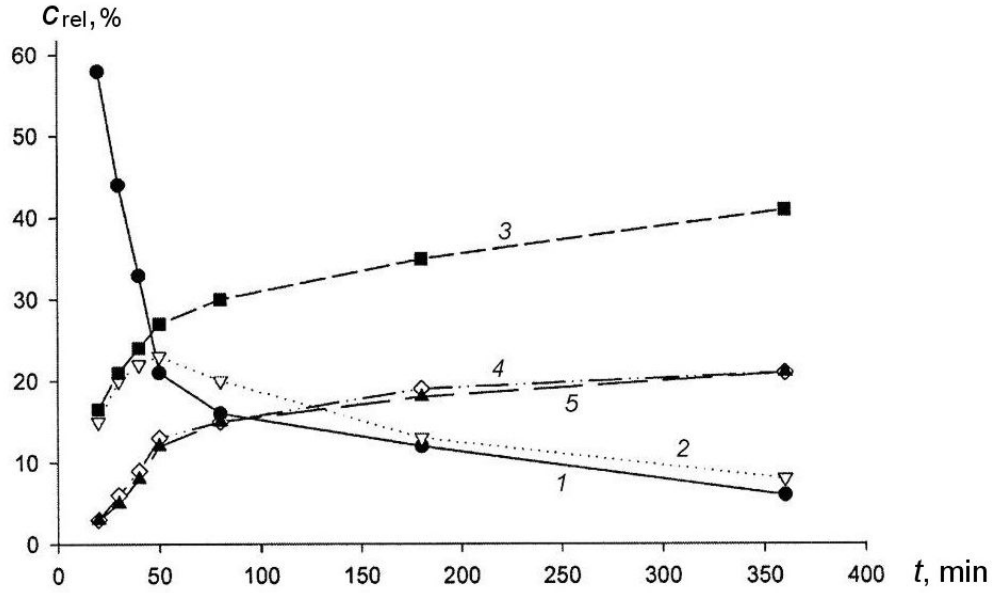

Fig. 1. The dependence of the relative concentrations of the reaction components **1** + **2a** on the duration of the reaction: *1* – 3-Ethoxycarbonylcoumarin **1**; *2* – cyanocoumarin **3**; *3* – malonic ester **4a**; *4* – **D** + **E(E')** + **F** + **I(I')**; *5* – **H(H')** + **K(K')**.

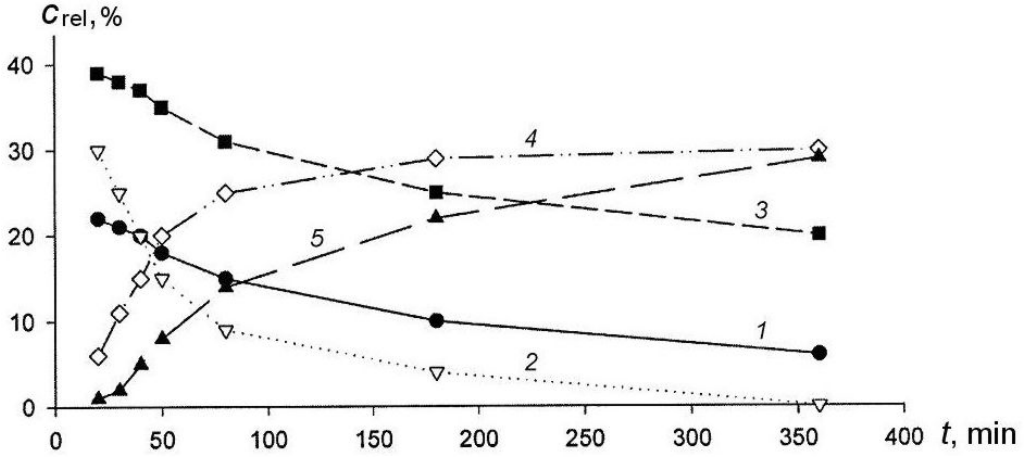

Fig. 2. The dependence of the relative concentrations of the reaction components **1** + **2b** on the duration of the reaction: *1* – 3-Ethoxycarbonylcoumarin **1**; *2* – cyanocoumarin **3**; *3* – malonic ester **4b**; *4* – **D** + **E(E')** + **F**; *5* – **H(H')** + **K(K')**.

In the spectra recorded 24 h after the beginning of the reaction a substantial increase is observed in the area of the multiplet signals of the aromatic protons in the regions of 6.60-6.90 and 7.00-7.40 ppm for the reaction of **1** + **2a** and 7.00-7.40 ppm for **1** + **2b**, and there is smoothing in the form of the multiplets. This is apparently due to the fact that in both solutions the dimerization and trimerization processes and then the polymerization of the formed compounds, in which both the dihydropyran derivatives and the tricyclic structures can participate, are greatly increased.

Thus, by ^{1}H NMR investigation of the Michael reaction for 3-ethoxycarbonylcoumarin **1** with the derivatives of cyanoacetylhydrazine **2a**,**b**, realized directly in the tube for recording the spectra, it was possible to follow the whole course of the transformations in the initial compounds and the products formed from them. Both the general relationships and the differences between these reactions were established in parallel.

In conclusion it is necessary to dwell on comparison of the data obtained during investigation of the products of the Michael reaction by mass spectrometry [2] and ^{1}H NMR spectroscopy. It is significant that the subjects studied by these methods differed both in the conditions of production and in the conditions of observation and could not therefore be completely identical in composition. The dynamics of the successive transformations was observed by ^{1}H NMR spectroscopy in the reaction mixture without isolation of any individual components in the process, and the reaction was realized directly in the tube used to record the spectra. In the case of mass spectrometry the products of the reaction carried out under laboratory conditions and stopped after separation of the precipitate were investigated. Here both the precipitated 3-cyanocoumarin and the reaction mixture remaining after separation of the 3-cyanocoumarin and removal of the solvent were analyzed.

Nevertheless, the overwhelming majority of the reaction products could be identified by both methods. At the same time a series of the products from subsequent transformation of the 3-cyanocoumarin could only be recorded by ^{1}H NMR spectroscopy; this was probably due to the removal of the 3-cyanocoumarin **3** from the reaction mixture that was studied by mass spectrometry.

It is important to note that it was possible to prove the structure of the tricyclic products formed in the reactions of **1** + **2a**,**b** unambiguously by ^{1}H NMR spectroscopy. It was shown that these structures only contain the condensed six-membered rings and that condensation is consequently realized only with the participation of the amide nitrogen atom. The other possible variant of cyclization in the case of compound **2a** with participation of the terminal NH_2 group and the formation of a diazepine ring is not realized. At the time it was not possible to make a choice between these structures on the basis of the data from mass spectrometry due to the fact that both structures have identical mass for the molecular ion and a similar type of fragmentation.

Another interesting fact is that the products from dehydrogenation of the tricyclic structures, recorded in the mass spectra, were absent from the reaction mixtures. As mentioned earlier [2], this indicates that the appearance of these compounds is due either to the ease of aromatization of the tricycles when the samples are heated under the conditions for recording the mass spectra or to aromatization as a result of oxidation processes during prolonged storage of the evaporated reaction mixtures.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Unity+400 spectrometer (400 MHz) with TMS as internal standard. The mass spectra were obtained on a Finnigan SSQ-710 chromato-mass spectrometer with direct injection of the sample into the ion source. The energy of the ionizing electrons was 70 eV, and the temperature of the ion source was 150°C. The IR spectra were obtained in vaseline oil on a Perkin-Elmer 457 instrument.

4-(3-Amino-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-3-ethoxycarbonyl-3,4-dihydrocoumarin (5). To a mixture of 3-ethoxycarbonylcoumarin (**1**) (0.5 g, 2.3 mmol) and 3-amino-5-oxo-4,5-dihydropyrazole (0.20 g, 2.4 mmol) in methanol (20 ml), two drops of piperidine were added. The mixture was stirred at ~20°C

for 24 h, and the obtained solution was evaporated under vacuum at a temperature no higher than 30°C. The residue was treated with water, and the precipitate was filtered off. We obtained 0.6 g (69%) of a light-yellow finely crystalline substance, which caked at 117-120°C and did not then melt up to 300°C (ethanol). IR spectrum, ν, cm^{-1}: 2720 (N-H); 1710, 1680-1650 (C=O, C=N). 1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.13 (3H, t, ^3J = 7.2, C<u>H</u>$_3$CH$_2$); 3.56 (1 H, d, $^3J_{4,4'}$ = 2.1, H-4'); 4.07 (2H, q, ^3J = 7.2, CH$_3$C<u>H</u>$_2$); 4.71 (1H, d, $^3J_{4,4'}$ = 2.1, H-4); 6.60–7.00 (4H, m, CH arom.), 10.36 (1H, s, OH enol); 11.40 (3H, bs, NH_2 + NH) (enolic form). ^{1}H NMR spectrum (acetone-d_6), δ, ppm (*J*, Hz): 1.18 (3H, t, ^3J = 7.2, C<u>H</u>$_3$CH$_2$); 3.31 (1H, s, H-3); 3.76 (1H, d, $^3J_{4,4'}$ = 2.2, H-4'); 4.13 (2H, q, ^3J = 7.2, CH$_3$C<u>H</u>$_2$); 4.87 (1H, d, $^3J_{4,4'}$ = 2.2, H-4); 6.70–7.10 (4H, m, CH arom.); 9.52 (1H, very broad signal, NH); the protons of the NH_2 group are quickly exchanged with the water of the solvent and form a general very broad signal at 3.00 ppm (the keto form). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 317 $[M]^+$ (100). Found, %: C 56.64; H 4.92; N 13.18. $C_{15}H_{15}N_3O_5$. Calculated, %: C 56.78; H 4.76; N 13.24.

The synthesis of compounds **7a**,**b** was described in [1].

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