# Synthesis of 3-aminomethyl-4-hydroxycoumarins and their retro-Mannich reaction in dimethyl sulfoxide

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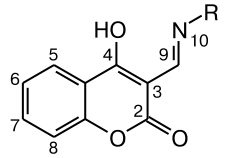
Hydrogenation of 3-formyl-4-hydroxycoumarin aliphatic imines leads to 3-aminomethyl-4-hydroxycoumarins, which undergo a retro-Mannich reaction in dimethyl sulfoxide containing even traces of water.

**Key words:** 4-hydroxycoumarin derivatives, imines, enamines, hydrogenation, aminomethylcoumarins, retro-Mannich reaction, dicoumarol.

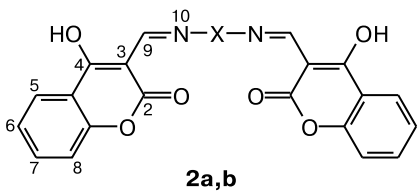
4-Hydroxycoumarins substituted at position 3 are of significant interest because of their high biological activity.[1—3] Among them are many known biologically active agents possessing antiinflammatory, antituberculosis, or anticoagulation properties (dicoumarol, sincoumar, phenprocoumon, warfarin). A number of 3-substituted 4-hydroxycoumarins are used in agriculture as deraticides.

The aminomethyl fragment is also an efficient pharmacophore. In order to synthesize new coumarin derivatives promising for the evaluation of their pharmacological properties, we carried out the reduction reaction of aromatic and aliphatic imines of 3-formyl-4-hydroxycoumarin. The analysis performed using the PASS Online program[4] showed the high levels of predicted biological activity for the reduction products, the coumarin alkyl(aryl)aminomethyl derivatives, no less than to 30 biological targets. During identification of obtained 3-aminomethylcoumarins, we studied their hydrolytic transformations in dimethyl sulfoxide.

The structures of imines **1a—d** and **2a**,**b**, which were subjected to reduction, are given below.



**1a—d**



**2a,b**

**1:** R = Bu (**a**), Bn (**b**), $CH_2CH_2OH$ (**c**), 4-$MeC_6H_4$ (**d**)
**2:** X = 1,2-$C_6H_4$ (**a**), $CH_2CH_2$ (**b**)

Initially, for the reduction of imines **1a—d** and **2a**,**b** we applied the reagents commonly used in the reduction of a C=N bond: sodium borohydride, sodium cyanoborohydride, and triethylsilane. However, the use of these reducing agents did not lead to the preparation of the target aminomethyl derivatives. In particular, the reaction of compound **1a** with sodium borohydride gives an unseparable mixture of products, in which only traces of the expected aminomethyl derivative were found by thin-layer chromatography. A similar result was obtained upon attempted reduction of imine **2a** with sodium cyanoborohydride in acetic acid. When triethylsilane in trifluoroacetic acid was used for the reduction of compound **2d**, the starting imine was recovered.

The failure of the reducing agents mentioned above can be possibly explained by the increased tendency of 3-formyl-4-hydroxycoumarin imines to tautomeric transformations. Earlier, we found that both in crystals and in solutions these imines virtually completely exist as a mixture of *E*- and *Z*-isomers of the ketoenamine tautomeric form (Scheme 1).[5—7]

As it turned out, the reduction of compounds **1** and **2** can be accomplished under hydrogenation conditions of the C=C double bond. The hydrogenation was carried out with gaseous hydrogen in the presence of heterogeneous catalysts, Raney nickel and palladium on charcoal (Pd/C, 10% of Pd), at temperatures from 20 to 60 °C and hydrogen pressure from 2 to 10 atm.

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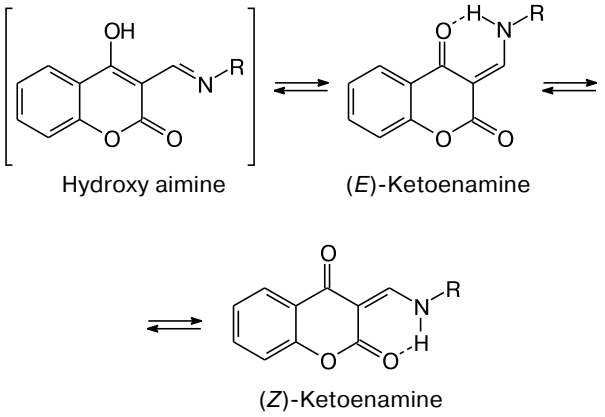
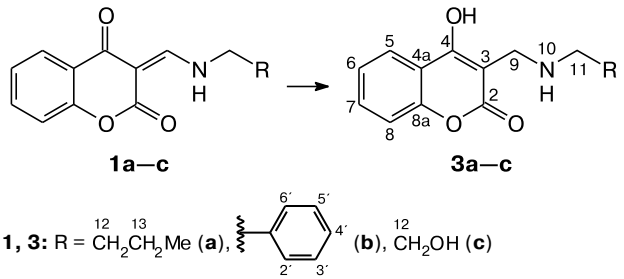
**Scheme 1**



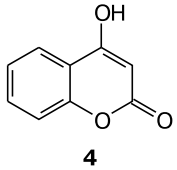

The hydrogenation of ketoenamines **1a—c** derived from aliphatic and aliphatic aryl amines in the presence of Raney nickel (Scheme 2) proceeds smoothly and the yields of the target products **3a—c** reach 76—91%. The $^1$H NMR spectra of the hydrogenation products **3a—c** exhibit singlets for the protons C(9)$H_2$ in the region from δ 3.97 to 4.07 as characteristic signals. The chemical shift values for the carbon atoms in the $^{13}$C NMR spectra of compounds **3a—c** also confirm the structure suggested for the hydrogenation products. For example, if for the predominant in solution ($CDCl_3$) *E*-isomer of ketoenamine **1b** the chemical shifts for the carbon atoms C(2), C(4), C(3), C(9) are δ 163.7, 181.2, 97.1, 154.7, for amine **3b** ($CDCl_3$—DMSO-$d_6$) their values are δ 174.3, 164.2, 87.6, 49.2, respectively. It should be noted that the chemical shift for carbon atom C(4) in 4-hydroxycoumarin ($CDCl_3$—DMSO-$d_6$) is δ 160.5, whereas for atom C(2) it is at δ 163.9.

**Scheme 2**



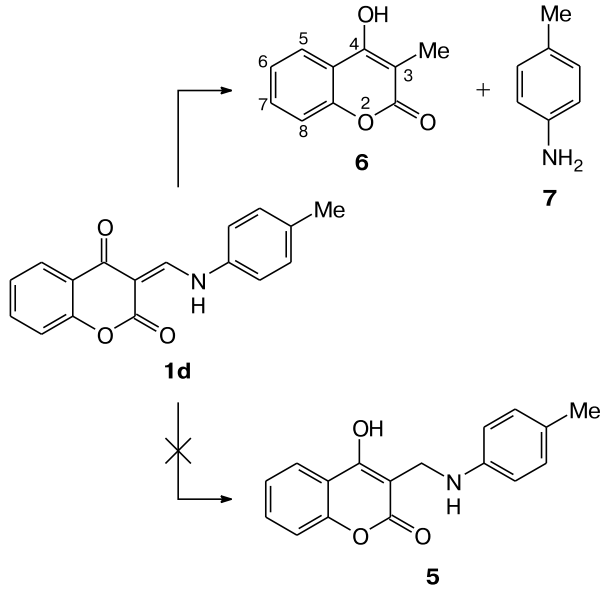

**Reagents and conditions:** Raney Ni, $H_2$ (2 atm.), MeOH, 20 °C.

To confirm a possibility of the preparation of compounds **3a—c** by the hydrogenation reaction of the corresponding imines, we obtained compound **3a** by the Mannich condensation of 4-hydroxycoumarin **4** with *n*-butylamine and formaldehyde.[8,9] A comparison of melting points and $^1$H NMR spectra showed that the products obtained by two alternative pathways are identical. At the same time, the yield of compound **3a** in the Mannich reaction was considerably lower (58%) than in the hydrogenation of ketoenamine **1a** (91%), that leads, apart from anything else, to certain difficulties in the isolation of the target product in the pure form.




At the same time, the hydrogenation of ketoenamines **1d** and **2a** derived from aromatic amines is more complicated. The $^1$H NMR spectroscopic ($CDCl_3$—DMSO-$d_6$) and mass spectrometric data showed that the hydrogenation of 3-((4-methylphenylamino)methylidene)-2*H*-chromene-2,4(*3H*)-dione (**1d**) using palladium on charcoal (hydrogen pressure of 10 atm., 60 °C) did not lead to the expected hydrogenation product **5**. The reaction mixture obtained by hydrogenation of ketoenamine **1d** contains 4-hydroxy-3-methylcoumarin **6** and *p*-toluidine **7**, that indicates that the hydrogenolysis of the carbon—nitrogen bond takes place in the course of the reaction (Scheme 3). Besides, the products of hydrogenation of the benzene ring of *p*-toluidine were identified in the reaction mixture. Hydrogenation of **1d** on Raney nickel under milder conditions (hydrogen pressure of 2 atm., 20 °C) is also accompanied by hydrogenolysis, however, no products of hydrogenation of *p*-toluidine were found in this case.

**Scheme 3**

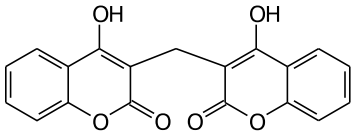



**Reagents and conditions:** Pd/C, $H_2$ (10 atm.), MeOH, 60 °C.

Similar results were obtained in the hydrogenation of compound **2a** using Raney nickel and palladium on charcoal (hydrogen pressure of 2 or 10 atm., temperature of 20 or 60 °C) and compound **2b** on Raney nickel (hydrogen pressure of 2 atm., 20 °C). The $^1$H NMR spectra and mass spectra of the reaction mixture obtained by hydrogenation

of compounds **2a** and **2b** showed that it contains signals of 4-hydroxy-3-methylcoumarin **6** and *o*-phenylenediamine or 1,2-diaminoethane, respectively. The formation of 4-hydroxy-3-methylcoumarin **6** in the course of hydrogenation of imines of 3-formyl-4-hydroxycoumarin and compound **2a** is not a surprise, since there are literature[10] examples of the carbon—nitrogen bond cleavage during hydrogenation of aminomethylarenes.

During synthesis and studies of hydrogenation products of ketoenamines **1a—c**, we noticed their hydrolytic instability. It turned out that the $^1$H NMR spectra of compounds **3a—c** recorded in DMSO-$d_6$ containing even insignificant amount of water clearly exhibit signals of the products of their hydrolysis, first of all, of dicoumarol **8** and the corresponding amines.* We studied in greater details hydrolytic transformations of aminomethyl compound **3b**. It was found that when compound **3b** was allowed to stand in solution in DMSO-$d_6$ at room temperature for several days, a new strong singlet appears in the spectrum at δ 4.02, as well as signals of dicoumarol **8** ($\delta_{CH_2}$ 3.65) and benzylamine ($\delta_{CH_2}$ 3.61) (Fig. 1).



**8**

To confirm the presence of compound **8** in the products of transformation of **3b** in DMSO-$d_6$, dicoumarol **8** was synthesized by an alternative method: by the reaction of 4-hydroxycoumarin with formaldehyde. The following signals in the NMR spectra (DMSO-$d_6$) are characteristic of dicoumarol **8**: a singlet for the $CH_2$ group at δ 3.65 and the signal for the carbon atom of the methylene group at δ 19.79.**

Among the products of the hydrolytic transformation of aminomethyl derivatives **3**, other compounds were also found. In particular, we assign the signal at δ 4.02 with the hetero spin-spin coupling constant $^1J_{C,H}$ = 148.2 Hz to the protons of the methylene group of 4-hydroxy-3-hydroxymethylcoumarin **9**. Besides, a weak singlet is observed in the $^1$H NMR spectrum at δ 5.25, which corresponds to proton H(3) of 4-hydroxycoumarin **4**. This was confirmed by the $^1$H NMR spectrum of a mixed probe with the authentic sample of 4-hydroxycoumarin **4**. Another weak broad signal is observed at δ 6.83, which can be assigned to the protons of the methylene group of 3-methylidene-2*H*-chromene-2,4(3*H*)-dione (quinone-methide, **10**).

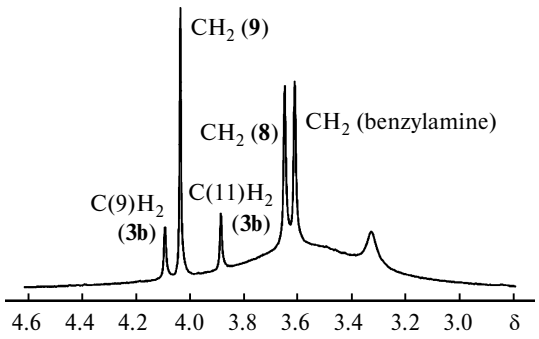
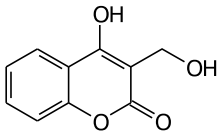
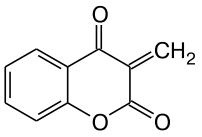



**Fig. 1.** Signals of dicoumarol **8**, 4-hydroxy-3-hydroxymethylcoumarin (**9**), and benzylamine in the $^1$H NMR spectrum (DMSO-$d_6$) of compound **3b**.

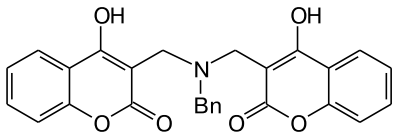


**9**



**10**

The LC/MS of compound **3b** in DMSO containing water added on purpose makes it possible using ion-detection method to identify the following compounds: benzylaminomethylcoumarin **3b** (*m/z* 282), dicoumarol **8** (*m/z* 337), free benzylamine (*m/z* 108), and 4-hydroxy-3-(hydroxymethyl)coumarin **9** (*m/z* 193). A peak with *m/z* 456 should be also noted, which can be assigned to the tertiary amine **11**, the condensation product of secondary amine **3b** with compound **9**. Thus, it can be suggested that the transformation of compound **3b** to dicoumarol **8** proceeds through the formation of 4-hydroxy-3-(hydroxymethyl)coumarin **9**, which gives rise to both quinone-methide **10** and 4-hydroxycoumarin **4** (Scheme 4).



**11**

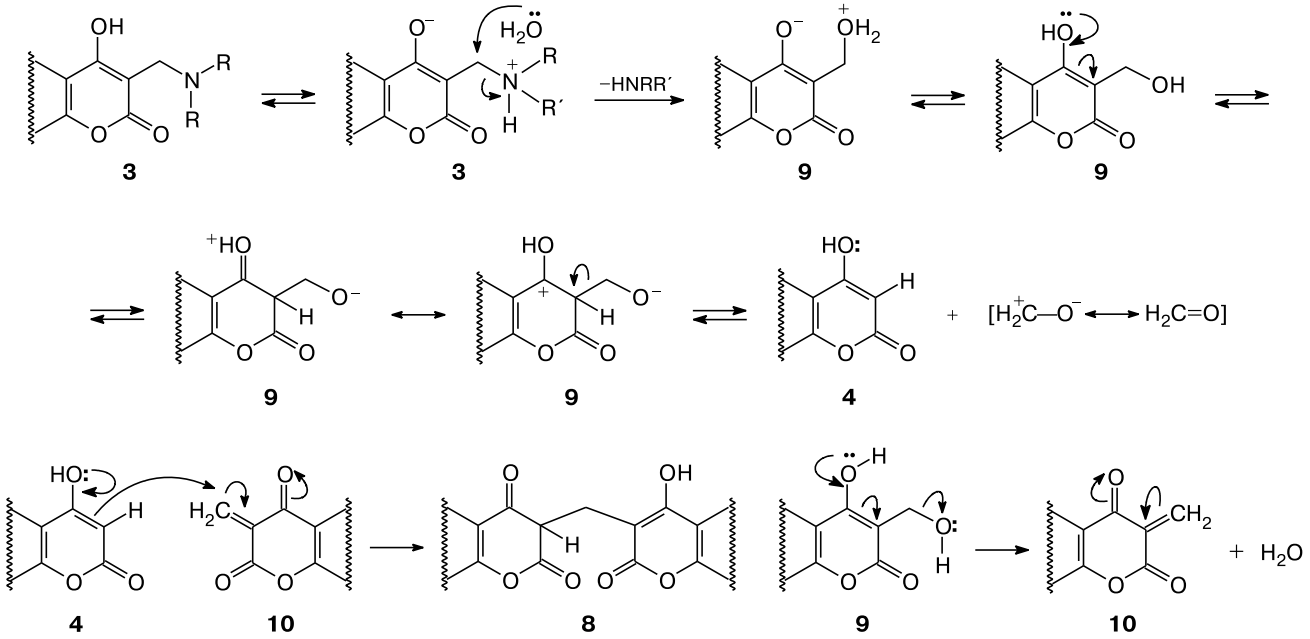
We found that the addition of water to the solutions of compounds **3a** and **3c** in DMSO or methanol even at low temperatures also leads to a noticeable increase in the amount of dicoumarol **8**. The data obtained allows us to suggest the following scheme of the hydrolytic transformation of aminomethyl derivatives **3a—c** under conditions studied (see Scheme 4).

The scheme is based on the retro-Mannich reaction. This scheme differs from the explanation suggested earlier for the hydrolytic transformations of 4-hydroxy-3-piperidinomethylcoumarin upon its heating in a dilute hydrochloric acid,[8] according to which piperidine and quinone-methide **10** are formed in the first step (Scheme 5). The latter undergoes the retro-aldol condensation to give

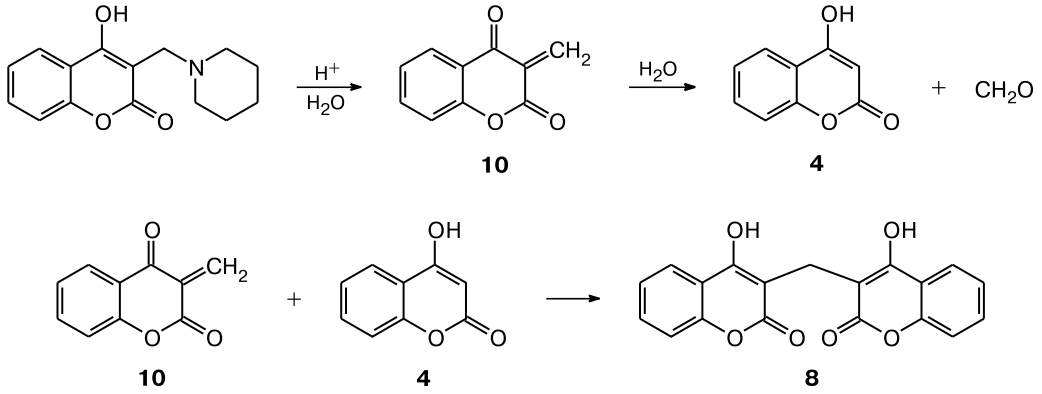
* $^1$H NMR spectra were recorded in DMSO-$d_6$ (99.6%, from Deutero GmbH).

** Synthesis of dicoumarol was described earlier in the work,[11] the reported chemical shift values for carbon atoms in the $^{13}$C NMR spectrum agree with those obtained in this work.

**Scheme 4**



**Scheme 5**



4-hydroxycoumarin **4**, which is involved in the Michael addition to quinone-methide **10** with the formation of dicoumarol **8**. It should be noted that the intermediate quinone-methide **10** was not isolated,[8] but a similar condensation product of 4-hydroxycoumarin **4** and salicylaldehyde was characterized earlier.[12]

In conclusion, in the present work hydrogenation of imines of 3-formyl-4-hydroxycoumarin was used to synthesize the corresponding 4-hydroxycoumarin 3-aminomethyl derivatives. Such an approach to the preparation of aminomethyl derivatives can be useful for the development of organic synthesis methodology, including that for the preparation of compounds with an aminomethyl group, the synthesis of which by the Mannich reaction is complicated or impossible.[13] An ability of 4-hydroxycoumarin 3-aminomethyl derivatives to undergo a retro-Mannich reaction in dimethyl sulfoxide containing even insignificant amount of water was also studied.

## Experimental

$^1$H and $^{13}$C NMR spectra were recorded on Bruker WP-200-SY (200 MHz), Varian Unity+ 400 (400 MHz), and Bruker AM 300 spectrometers (300 MHz) in $CDCl_3$ (99.8%, from Deutero GmbH), DMSO-$d_6$ (99.6%, from Deutero GmbH), and their mixtures. The signals of residual protons of the solvent were used as a reference ($CDCl_3$, $\delta_H$ 7.27; DMSO-$d_6$ and a mixture of $CDCl_3$—DMSO-$d_6$, $\delta_H$ 2.5, $\delta_C$ 39.5). Mass spectra (EI, 70 eV) was obtained on a Kratos MS-30 (United Kingdom), temperature of the source of ions was 200 °C, direct injection of the sample. LC/MS were performed on a PE SCIEX API 165 spec-

trometer (ELSD and UV 254 nm detectors). Elemental analysis was performed on a Euro Vector Instruments analyzer and the Euro EA Software (Elemental Analyzer).

Reaction progress and individuality of compounds obtained were monitored by TLC on Silufol UV-254, ARMSORB plates.

3-Formyl-4-hydroxycoumarin and bisimines **2a**,**b** were obtained according to the published procedure.[5] Imines **1b**,**d** were obtained according to the described procedure.[6,7]

Before use, Raney nickel was several times washed with anhydrous methanol and dried *in vacuo* at 100 °C, then added to anhydrous methanol. The thus prepared catalyst was active for 10 days.[14]

**3-{[(*n*-Butyl)amino]methylidene}-2*H*-chromene-2,4(3*H*)-dione (1a).** *n*-Butylamine (0.05 mL, 0.5 mmol) was added to a solution of 3-formyl-4-hydroxycoumarin (100 mg, 0.5 mmol) in ethanol (5 mL). The mixture obtained was refluxed for 2 h. The reaction mixture was cooled to room temperature to obtain compound **2a**. The yield was 73.5 mg (60%), m.p. 128—130 °C (ethanol) (*cf.* Ref. 15: m.p. 131—132 °C (chloroform—hexane)). $^1$H NMR (200 MHz, $CDCl_3$), δ: 11.91 (br.s, 0.7 H, NH (*E*-isomer)); 10.27 (br.s, 0.3 H, NH (*Z*-isomer)); 8.55 (d, 0.3 H, H(9) (*Z*-isomer), $^3J$ = 14.6 Hz); 8.39 (d, 0.7 H, H(9) (*E*-isomer), $^3J$ = 13.7 Hz); 8.06 (d, 1 H, H(5), $^3J$ = 7.9 Hz); 7.57 (m, 1 H, H(7)); 7.27 (m, 2 H, H(6), H(8)); 3.56 (m, 2 H, NHC$\underline{H}_2$); 1.61 (m, 4 H, NHCH$_2$C$\underline{H}_2$C$\underline{H}_2$Me); 0.99 (m, 3 H, $CH_3$).

**3-{[(2-Hydroxyethyl)amino]methylidene}-2*H*-chromene-2,4-(3*H*)-dione (1c).** 2-Aminoethanol (0.032 mL, 0.5 mmol) was added to a solution of 3-formyl-4-hydroxycoumarin (100 mg, 0.5 mmol) in anhydrous toluene (5 mL). The reaction mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature to obtain compound **1c**. The yield was 107 mg (92%), m.p. 176—178 °C (dioxane—*n*-hexane). The $^1$H NMR spectrum corresponds to that described in the literature.[15] $^1$H NMR (200 MHz, $CDCl_3$), δ: 11.65 (br.s, 0.6 H, NH (*E*-isomer)); 10.36 (br.s, 0.4 H, NH (*Z*-isomer)); 8.47 (m, 1 H, H(9)); 7.93 (d, 1 H, H(5), $^3J$ = 7.9 Hz); 7.68—7.25 (m, 3 H, H(6), H(7), H(8)); 5.03 (br.s, 1 H, OH); 3.63 (br.s, 4 H, $CH_2CH_2$).

**Hydrogenation of imines 1 and 2 under hydrogen atmosphere (general procedure).** A suspension of the corresponding ketoenamine (0.86 mmol) and Raney nickel (or palladium on charcoal) (about 50 mg) in anhydrous methanol (40 mL) was stirred for 6 h under hydrogen (2 atm). After the starting ketoenamine disappeared (TLC data, Silufol UV-254 plates, eluent light petroleum—ethyl acetate, 1 : 1), the catalyst was filtered off, the solvent was evaporated. A precipitate obtained was washed with ethyl acetate, the product was dried *in vacuo*.[14]

**3-[(Butylamino)methyl]-4-hydroxy-2*H*-chromen-2-one (3a).** The yield was 193 mg (91%), m.p. 132 °C (decomp.) (*cf.* Ref. 8: m.p. 133 °C (decomp.)). $^1$H NMR (200 MHz, $CDCl_3$—DMSO-$d_6$), δ: 7.83 (d, 1 H, H(5), $^3J$ = 7.9 Hz); 7.35—7.47 (m, 1 H, H(7)); 7.08—7.20 (m, 2 H, H(6), H(8)); 3.90 (s, 2 H, C(9)H$_2$); 2.83 (t, 2 H, C(11)H$_2$, $^3J$ = 7.4 Hz); 1.51—1.69 (m, 2 H, C(12)H$_2$); 1.19—1.43 (m, 2 H, C(13)H$_2$); 0.88 (m, 3 H, $CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$—DMSO-$d_6$), δ: 174.5 (C(2)); 164.7 (C(4)); 154.4 (C(8a)); 131.0 (C(7)); 124.2 (C(5)); 122.6 (C(6)); 116.0 (C(8)); 115.9 (C(4a)); 88.1 (C(3)); 46.0 (C(9)H$_2$); 43.4 (C(11)H$_2$); 27.8 (C(12)H$_2$); 19.8 (C(13)H$_2$); 13.9 ($CH_3$). Found (%): C, 61.64; H, 7.00; N, 4.99. $C_{14}H_{17}NO_3$. Calculated (%): C, 61.70; H, 6.90; N, 5.14.

**3-[(Benzylamino)methyl]-4-hydroxy-2*H*-chromen-2-one (3b).** The yield was 188 mg (78%), m.p. 157 °C (decomp.) (*cf.* Ref. 8: m.p. 159 °C (decomp.)). $^1$H NMR (200 MHz, DMSO-$d_6$), δ: 7.82 (d, 1 H, H(5), $^3J$ = 7.9 Hz); 7.33—7.62 (m, 6 H, H(7), H(2′), H(3′), H(4′), H(5′), H(6′)); 7.09—7.23 (m, 2 H, H(6), H(8)); 4.09 (br.s, 2 H, C(9)H$_2$); 3.87 (br.s, 2 H, C(11)H$_2$). $^{13}$C NMR (50 MHz, $CDCl_3$—DMSO-$d_6$), δ: 174.3 (C(2)); 164.2 (C(4)); 154.0 (C(8a)); 132.4 (C(1′)); 130.8 (C(7)); 130.1 (C(3′), C(5′)); 128.8 (C(4′)); 128.7 (C(2′), C(6′)); 124.5 (C(5)); 121.3 (C(6)); 116.0 (C(8)); 115.5 (C(4a)); 87.6 (C(3)); 49.2 (C(9)H$_2$); 42.8 (C(11)H$_2$). MS (EI, 70 eV), *m/z* ($I_{rel}$ (%)): 174 [M − $-C_7H_9N]^+$ (4), 162 [M − $C_8H_9N]^+$ (8), 121 [M − $C_8H_9N$ − $-C_2HO]^+$ (34), 106 [M − $C_{10}H_7O_3]^+$ (57), 91 $[C_7H_7]^+$ (100).

**4-Hydroxy-3-{[(2-hydroxyethyl)amino]methyl}-2*H*-chromen-2-one (3c).** The yield was 153 mg (76%), m.p. 175—176 °C (decomp.) (*cf.* Ref. 8: m.p. 177 °C (decomp.)). $^1$H NMR (200 MHz, DMSO-$d_6$), δ: 7.81 (d, 1 H, H(5), $^3J$ = 7.9 Hz); 7.38—7.50 (m, 1 H, H(7)); 7.09—7.22 (m, 2 H, H(6), H(8)); 5.19 (br.s, 1 H, CH$_2$O$\underline{H}$); 3.94 (s, 2 H, C(9)H$_2$); 3.63 (m, 2 H, C(12)H$_2$); 2.92 (m, 2 H, C(11)H$_2$). $^{13}$C NMR (50 MHz, $CDCl_3$—DMSO-$d_6$), δ: 174.3 (C(2)); 164.3 (C(4)); 154.0 (C(8a)); 130.7 (C(7)); 124.4 (C(5)); 122.3 (C(6)); 116.0 (C(8)); 115.4 (C(4a)); 87.5 (C(3)); 56.4 (C(12)H$_2$); 47.7 (C(9)H$_2$); 43.2 (C(11)H$_2$).

**Hydrogenation of imine 1d.** According to the $^1$H NMR spectroscopic (400 MHz, $CDCl_3$—DMSO-$d_6$) and mass spectrometric data, the mixture of hydrogenation products of imine **1d** contains 4-hydroxy-3-methylcoumarin **6**,[16] *p*-toluidine, and products of hydrogenation of *p*-toluidine benzene ring.

**Hydrogenation of ketoenamine 2a.** According to the $^1$H NMR spectroscopic (400 MHz, $CDCl_3$—DMSO-$d_6$) and mass spectrometric data, the mixture of hydrogenation products of ketoenamine **2a** contains 4-hydroxy-3-methylcoumarin **6** (see Ref. 16) and *o*-phenylenediamine.

**Hydrogenation of ketoenamine 2b.** According to the $^1$H NMR spectroscopic (400 MHz, $CDCl_3$—DMSO-$d_6$) and mass spectrometric data, the reaction mixture obtained contains 4-hydroxy-3-methylcoumarin **6** (see Ref. 16) and 1,2-diaminoethane.

**Synthesis of compound 3a by Mannich condensation.** A 40% aqueous solution of formalin (0.41 mL, 0.006 mol calculated on formaldehyde $CH_2O$) was added to a solution of *n*-butylamine (0.6 mL, 0.006 mol) in anhydrous ethanol (10 mL), followed by the addition of a solution of 4-hydroxycoumarin **4** (1 g, 0.006 mmol) in anhydrous ethanol at room temperature. The crystallization of the product was completed after cooling of the mixture to 5 °C and standing at this temperature for 1 h. A precipitate of compound **3a** was filtered off, washed with diethyl ether, and dried. The yield was 2.6 g (58%), m.p. 129—130 °C (EtOH, with decomp.).

**Dicoumarol 8.** A 40% aqueous solution of formalin (0.41 mL, 0.006 mol calculated on formaldehyde $CH_2O$) was added to a solution of 4-hydroxycoumarin **4** (2 g, 0.012 mol) in 50% aqueous ethanol. After 1 h of stirring, a precipitate of dicoumarol **8** was filtered, washed on the filter with water and ethanol, and dried. The yield was 1.9 g (94%), m.p. 287—288 °C (*cf.* Ref. 17: m.p. 288—289 °C). $^1$H NMR (200 MHz, $CDCl_3$), δ: 8.01 (d, 2 H, H(5), $^3J$ = 7.9 Hz); 7.54—7.66 (m, 2 H, H(7)); 7.30—7.44 (m, 4 H, H(6), H(8)); 3.87 (s, 2 H, $CH_2$). $^{13}$C NMR (50 MHz, $CDCl_3$—DMSO-$d_6$), δ: 168.0 (C(2)); 163.7 (C(4)); 151.7 (C(8a)); 132.1 (C(7)); 124.3 (C(6)); 123.4 (C(5)); 121.3 (C(4a)); 116.1 (C(8)); 102.3 (C(3)); 19.3 ($CH_2$). The $^1$H and $^{13}$C NMR spectra correspond to those described in the work.[11] MS (EI, 70 eV), *m/z* ($I_{rel}$ (%)): 336 $[M]^+$ (78), 215 [M − $C_7H_5O_2]^+$ (34), 187 [M − − $C_7H_5O_2$ − CO]$^+$ (15), 174 [M − $C_9H_6O_3]^+$ (94), 162 [M −

$-C_{10}H_6O_3]^+$ (70), 121 $[M-C_{12}H_7O_4]^+$ (94), 120 $[M-C_{12}H_8O_4]^+$ (100), 92 $[M-C_{13}H_8O_5]^+$ (70).

**Reduction of ketoenamine 1a with sodium borohydride.** Sodium borohydride (0.86 mmol) was added to a solution of ketoenamine **1a** (0.86 mmol) in methanol in several portions. After the reaction reached completion (TLC monitoring, Silufol UV-254 plates, eluent *n*-hexane—ethyl acetate, 3 : 2), the reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried with freshly calcined magnesium sulfate, the drying agent was filtered off, the solvent was evaporated on a rotary evaporator to obtain an oily mixture of products, which was difficult to separate. Thin-layer chromatography showed the presence of only traces of desired aminomethyl derivative **3a**.

**Reduction of ketoenamine 1a with triethylsilane.** Triethylsilane (1 mL, 0.74 mmol) was added to a solution of ketoenamine **1a** (103 mg, 0.37 mmol) in trifluoroacetic acid (4.5 mL). The solution was refluxed for 5 h and allowed to stand at room temperature for 16 h. The solvent was evaporated on a rotary evaporator. A precipitate obtained was washed with ethanol and dried to recover the starting ketoenamine **1a**.

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