Synthesis of 4-Aminocoumarin Derivatives with *N*-Substitutents Containing Hydroxy or Amino Groups

Ivo C. Ivanov[a], Violina T. Angelova[a], Nikolay Vassilev[b], Ioannis Tiritiris[c], and Boyan Iliev[d]

[a] Faculty of Pharmacy, Medical University of Sofia, Dunav 2, BG-1000 Sofia, Bulgaria
[b] Institute of Organic Chemistry with Centre of Phytochemistry, Acad. G. Bonchev St. 9, BG-1113 Sofia, Bulgaria
[c] University of Applied Sciences, Beethovenstr. 1, D-73631 Aalen, Germany
[d] Ionic Liquids Technologies GmbH, Salzstrasse 184, D-74076 Heilbronn, Germany

Reprint requests to Prof. Dr. Ivo C. Ivanov. Fax: +359 2 9879874. E-mail: ivanov43@gmail.com

Z. Naturforsch. **2013**, *68b*, 1031 – 1040 / DOI: 10.5560/ZNB.2013-3102
Received March 21, 2013

Dedicated to Professor Willi Kantlehner on the occasion of his 70th birthday

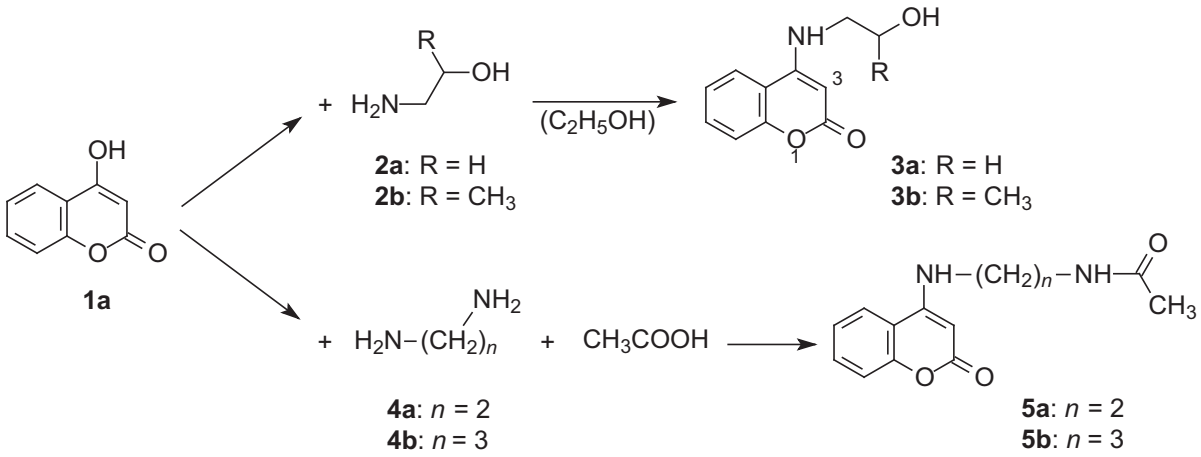
Reactions of 4-hydroxycoumarin (**1a**) and 4-chlorocoumarin-3-carbaldehyde (**1b**) with amino alcohols or alkylene diamines led to the formation of the corresponding *N*-substituted 4-aminocoumarins **3**, **5** and **6**. However, 4-hydroxycoumarin-3-carbaldehyde (**8**) reacted with 2-aminoethanol and ethylenediamine to give *N*-substituted 3-(aminomethylene)-chromane-2,4-diones **9a**, **b**. The structure and the *E*-configuration of compound **6** were proven by X-ray crystal structure analysis. Products **9a**, **b** displayed signals of both *E*- and *Z*-isomers in their NMR spectra. All novel products have been characterized by means of spectral (IR, NMR, MS) data and elemental analyses.

Key words: Hydroxycoumarins, Aminocoumarins, Aminoalcohols, Alkanediamines, Crystal Structure

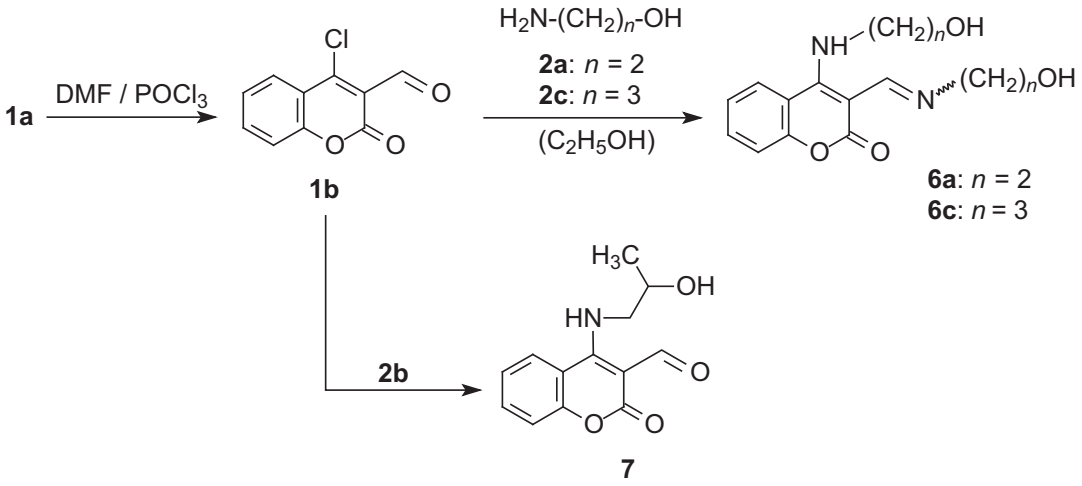
Introduction

N-Substituted 4-aminocoumarins and their derivatives attract more and more attention because of their biological activity, *e. g.* estrogenic [1], antioxidant [2], anticancer [3], antimicrobial [4], antimycobacterial [5] or neurotropic [6] activity. On the other hand, the thermodynamic stability of the conjugated bicyclic coumarin system and, being an enamine [7], the enhanced electron density at C-3 through the positive resonance effect of the amino group, promote the reactivity toward electrophilic replacements [8]. It is known from the literature that this position favors the Vilsmeier-Haack formylation [9, 10] and the Mannich aminomethylation [11, 12] among other reactions. These properties characterize 4-aminocoumarins as typical enaminocarbonyl compounds and as representatives of polyfunctional enamines.

According to the literature, the synthesis of 4-aminocoumarins involves a two-step procedure starting from 4-hydroxycoumarins through 4-chlorocoumarins after which the latter are reacted with amines [13 – 16] (Scheme 1). On amination of 4-halocoumarins, however, formation of side products is often observed since the amine attacks the α-pyrone ring, hydrogen halogenide is eliminated, and the ring-opened 3-(2-hydroxyphenyl)propynoic amides and related compounds are isolated [4]. Alternatively, direct replacement of the hydroxy by an amino group is more convenient, *e. g.* by treatment of 4-hydroxycoumarins with high-boiling primary, secondary or aromatic amines [6, 13, 17]. High-boiling solvents such as ethoxyethanol were also used as reaction medium [1]. When ammonia or low molecular weight amines were applied, the reaction had to be carried out in glacial acetic acid, in order to prevent the opening of the lactone ring [18, 19]. As reported earlier [20], microwave irradiation drastically shortened the reaction time, lowered amine wastes, and favored higher yields of *N*-substituted 4-aminocoumarins without the need of any solvent.



Scheme 1. Reaction of 4-hydroxycoumarin (**1a**) with aminoalcohols **2a**, **b** and diaminoalkanes **4a**, **b**.



Scheme 2. Reaction of 4-chlorocoumarin-3-carbaldehyde (**1b**) with aminoalcohols **2a**–**c**.

Another very useful source for obtaining *N*-substituted 4-aminocoumarins is 4-chlorocoumarin-3-carbaldehyde (**1b**), first synthesized by Moorty *et al.* [21] by Vilsmeier-Haack formylation of 4-hydroxycoumarin (**1a**, Scheme 2). This method has been improved several times by subsequent authors [1, 22–24]. Steinführer *et al.* [22] reported that the raw product 4-chloro-3-coumarincarbaldehyde (**1b**) contained up to 20% of 4-chlorocoumarin as an undesired side product which can be removed by Soxhlet extraction [1, 24]. The chloroaldehyde **1b** was further subjected to amination with a variety of amino compounds. With secondary amines it gave *N,N*-disubstituted 4-aminocoumarin-3-carbaldehydes [21, 25]. When *p*-methylbenzylamine was used the coumarin **1b** reacted with two equivalents of the amine affording simultaneously *N*-substitution of the 4-amino group and a Schiff base on the 3-formyl group [26]. Ultrasound promoted reaction of **1b** with substituted anilines led to the formation of chromeno[4,3-*b*]quinolin-6-ones [27]. By employing *o*-arylene diamines and 2-aminophenol some novel *N*-substituted 4-aminocoumarin-3-carbaldehydes were successfully synthesized [24].

In continuation of our efforts [19, 20, 23] to study the reactions of 4-hydroxy- and 4-chlorocoumarin

derivatives with amino compounds we tried to determine the preparative scope of these approaches using amino compounds which possess hydroxy or amino groups as a second function (aminoalkanols, diaminoalkanes). The results of these studies are reported here.

Results and Discussion

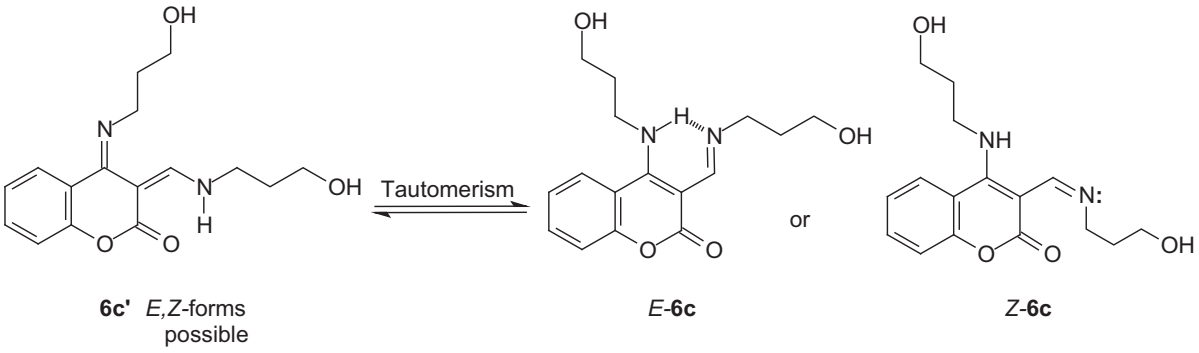
The direct synthesis of 4-(monoalkylamino)coumarins from primary amines was developed [19] on the basis of the reaction of 4-hydroxycoumarin with ammonium acetate in acetic acid as reported by Joshi *et al.* [18]. In this study, experiments were carried out for the synthesis of *N*-mono(hydroxyalkylamino) derivatives (Scheme 1), in analogy to the synthesis of the *N*-monoalkylamino coumarins reported earlier [19, 20]. Similar compounds have been synthesized before, *e. g.* **3a**, due to their potential biological activity [15], but starting from 4-chlorocoumarin and without any spectral characterization. We accomplished the amination by dropwise addition of a large excess (10 : 1 to 5 : 1) of the aminoalcohol **2a**, **b** to a solution of 4-hydroxycoumarin (**1a**) in anhydrous ethanol and prolonged reflux (5 – 10 h). The products **3a**, **b** of this reaction are presented in Table 1. Our efforts in obtaining these *N*-monosubstituted derivatives in acetic acid failed, and we found that ethanol as a solvent provides the best reaction conditions.

On the contrary, attempts to react **1a** with diaminoalkanes **4a**, **b** in boiling ethanol were not

Table 1. Characterization of compounds **3a**, **b**, **5a**, **b**, **6a**, **c**, **7**, and **9a**, **b**.

Product	Educts (react. cond.)	Yield[a] (%)	M. p. (°C) (solvent)	Mol. formula (mol. weight)	Calcd./found (%) C	H	N
3a	**1a** + **2a** (4 h/reflux)	40	173 – 174[b] (dioxane)	$C_{11}H_{11}NO_3$ (205.21)	64.38 64.23	5.40 5.47	6.83 6.77
3b	**1a** + **2b** (28 h/reflux)	35	181 – 183 (dioxane)	$C_{12}H_{13}NO_3$ (219.24)	65.74 65.39	5.98 6.12	6.39 6.46
5a	**1a** + **4a** (2 h/reflux)	68	261 – 263 (ethanol)	$C_{13}H_{14}N_2O_3$ (246.10)	63.40 63.42	5.73 5.77	11.38 11.41
5b	**1a** + **4b** (3.5 h/reflux)	53	206 – 208 (ethanol)	$C_{14}H_{16}N_2O_3$ (260.29)	64.60 64.07	6.20 6.39	10.76 11.16
6a	**1b** + **2a** (15 min/r. t.)	45	180 – 181 (ethanol)	$C_{14}H_{16}N_2O_4$ (276.29)	60.86 60.74	5.84 5.84	10.14 10.12
6c	**1b** + **2c** (15 min/r. t.)	53	126 – 127 (ethanol)	$C_{16}H_{20}N_2O_4$ (304.34)	63.14 61.94	6.62 6.01	9.20 8.80
7	**1b** + **2b** (4 h/reflux)	33	135 – 137 (ethanol)	$C_{13}H_{13}NO_4$ (247.25)	63.15 62.76	5.30 4.99	5.67 5.86
9a	**8** + **2a** (4 h/reflux)	48	180 – 182 (2-propanol)	$C_{12}H_{11}NO_4$ (233.22)	61.80 61.60	4.75 4.77	6.01 5.96
9b	**8** + **4a** (2 h/reflux)	53	201 – 202 (ethanol)	$C_{14}H_{14}N_2O_4$ (274.27)	61.31 61.00	5.14 5.16	10.21 10.09

[a] Yields of TLC products; [b] ref. [19]: m. p. 172.5 – 174° C (methanol).



6c' *E,Z*-forms possible — *E*-**6c** — *Z*-**6c**

Scheme 3. Tautomerism of compounds **6a**, **c** and stable *E*-geometric isomer of **6c** according to its crystallographic structure (Fig. 1); the tautomeric form **6c'** should be neglected.

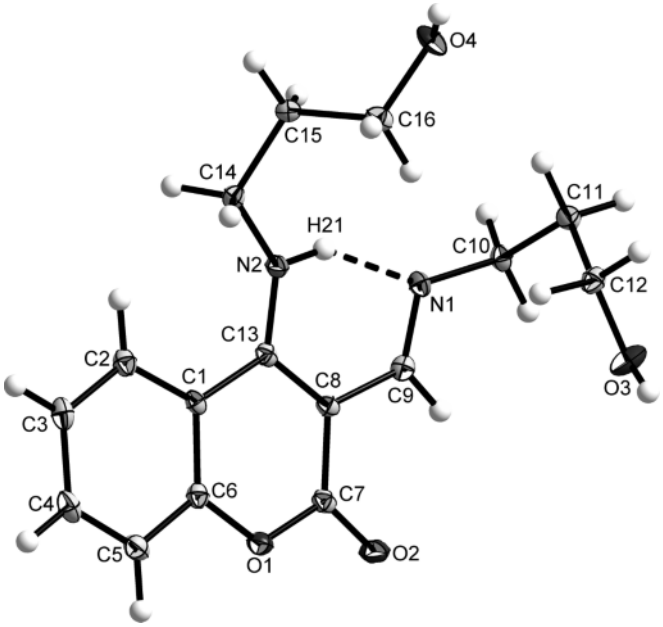


Fig. 1. ORTEP representation of the molecular structure of **6c** in the solid state with displacement ellipsoids at the 50 % probability level (*cf.* Table 2); an intramolecular hydrogen bond between N-1 and N-2 stabilizes the *E*-form.

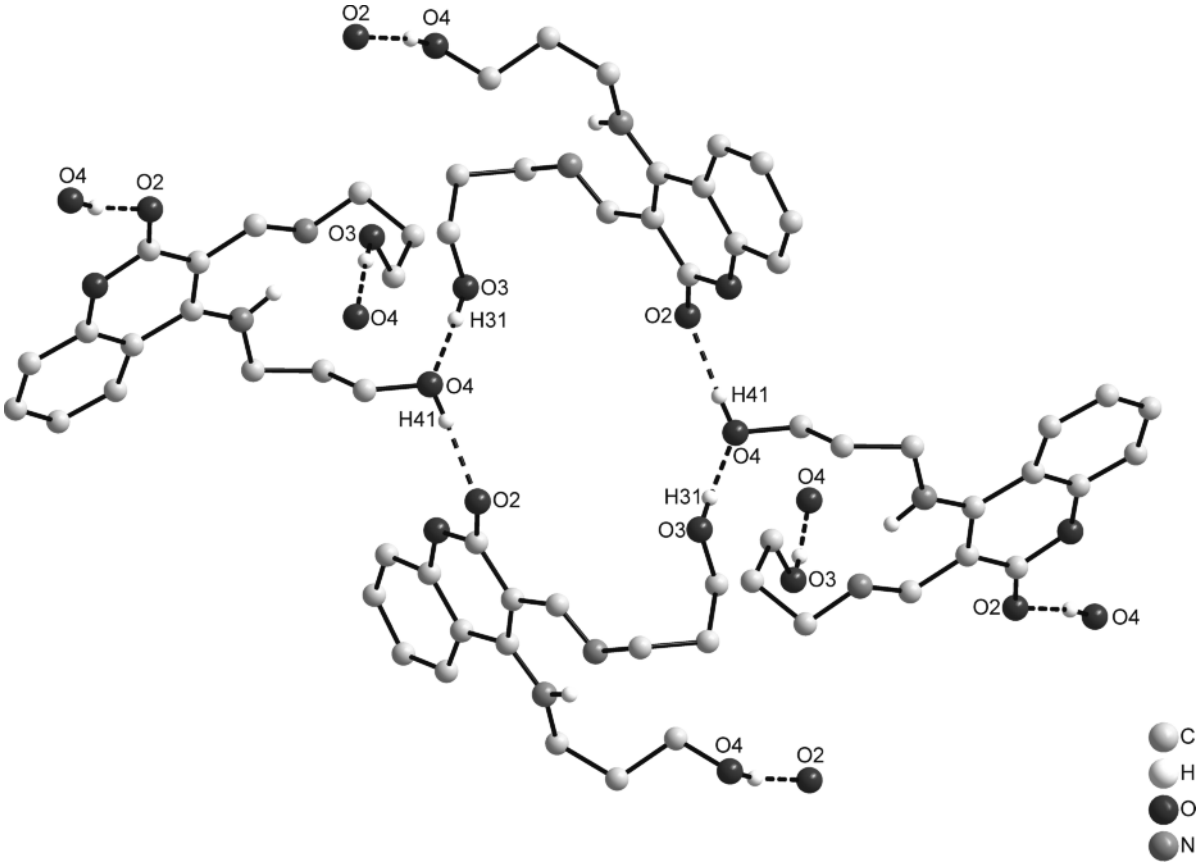


Fig. 2. O–H···O hydrogen bonds (dashed lines) in the crystal structure of **6c**.

Table 2. Crystal structure data for **6c**.

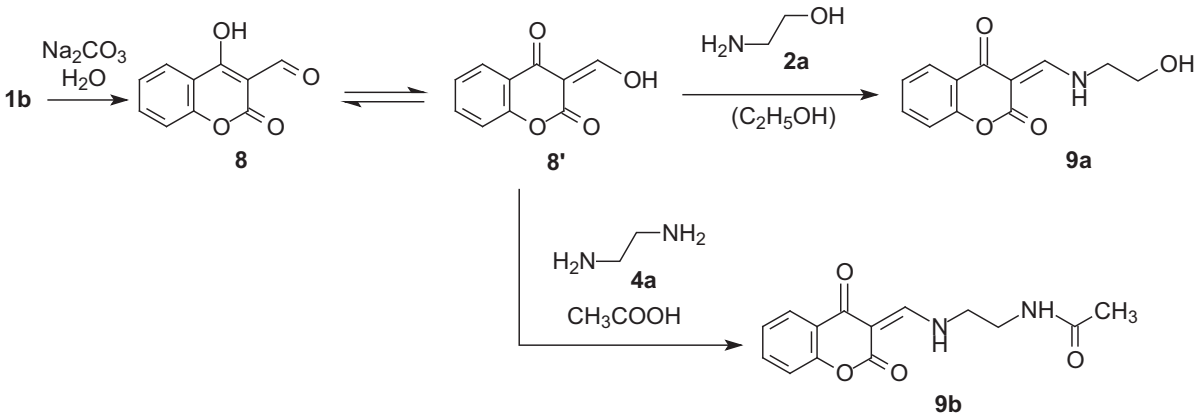
Formula	$C_{16}H_{20}N_2O_4$
M_r	304.34
Crystal size, mm^3	$0.28 \times 0.21 \times 0.14$
Temperature, K	100(2)
Crystal system	monoclinic
Space group	$P2_1/n$ (no. 14)
a, Å	9.3590 (6)
b, Å	8.2745 (5)
c, Å	19.2583 (9)
β, deg	98.377 (2)
V, Å^3	1475.47 (15)
Z	4
$D_{calcd.}$, g cm^{-3}	1.37
μ(MoK_α), mm^{-1}	0.1
F(000), e	648
θ range, deg	2.14 – 30.51
hkl range	$-12/+13, \pm 11, \pm 27$
Refl. measured / unique	16293 / 4492
R_{int}/R_σ	0.0396 / 0.0483
Parameters refined	215
$R(F)/wR(F^2)$ for 3183 refl. with $I > 2\sigma(I)$	0.0453 / 0.0998
$R(F)/wR(F^2)$ (all reflections)	0.0753 / 0.1134
GoF (F^2)	1.020
$\Delta\rho_{fin}$ (max / min), e Å^{-3}	0.41 / −0.29

successful, *i. e.* no definite product could be isolated. In a preliminary experiment [28], compound **5a** (Scheme 1) was synthesized in a similar way from 4-hydroxycoumarin (**1a**) and a great excess (20 : 1) of ethylene diamine (**4a**) in boiling glacial acetic acid. Starting with **1a** and 1,3-diaminopropane (**4b**), the corresponding homolog **5b** was obtained in moderate yield (Table 1). A simultaneous and unavoidable selective N'-acetylation of the second amino group took place in both cases.

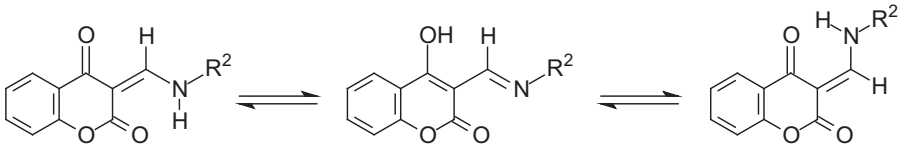
Two structural features of **6a**, **c** could not be unambiguously resolved only on the basis of their ^{1}H NMR and ^{13}C NMR spectra: (I) the predominant tautomeric form and (II) the true geometry (*E* or *Z*) of the molecule (Scheme 3). These problems were solved by means of X-ray crystallographic analysis of **6c**. Selected crystal structure data are summarized in Table 2. As it can be seen from Fig. 1, the intramolecular hydrogen bond [d(N1···H21) = 1.84 Å; d(N1···N2) = 2.6478(2) Å; ∠(N2–H21···N1) = 147.0°] additionally stabilizes the energetically preferred *E*-form in the solid state. Furthermore O–H···O hydrogen bonds between terminal hydroxy groups of neighboring molecules and also between the hydroxy group and the carbonyl oxygen atom have been detected [d(H41···O2) = 1.85 Å; d(O4···O2) = 2.6869(2) Å; ∠(O4–H41···O2) = 171.0° and d(H31···O4) = 1.86 Å; d(O3···O4) = 2.7196(2) Å; ∠(O3–H31···O4) = 175.7°] (Fig. 2).

We assume that the configuration of the *N*-hydroxyethyl compound **6a**, in analogy to **6c**, adopts the same *E*-geometry form. This is evidenced by comparison of their IR and NMR spectra. The existence of the tautomeric form **6c′** with all its possible geometric (*E, Z*) variants (Scheme 3) could not be confirmed by either spectral or crystallographic analyses.

In two of our experiments we proved the suitability of the readily available [29, 30] 4-hydroxycoumarin-3-carbaldehyde (**8**) for replacing the hydroxy by an amino group (Scheme 4). Thus, the 4-hydroxycoumarin-3-carbaldehyde (**8**) was allowed to react with 2-aminoethanol (**2a**) and 1,2-diaminoethane (**4a**). The reaction with the amine **2a** succeeded in boil-



Scheme 4. Reaction of 4-hydroxycoumarin-3-carbaldehyde (**8**) with 2-aminoethanol (**2a**) and ethylenediamine (**4a**).



***Z*-9a,b** **9a,b** ***E*-9a,b**

Scheme 5. Plausible *E,Z*-interconversion of **9a**, **b** (*cf.* Scheme 4).

ing ethanol to give **9a**, whereas the latter diamine (**4a**) reacted smoothly in glacial acetic acid to afford the *N*-monoacetylated product **9b**. Unfortunately, in both cases the newly substituted amino group turned out to be adjacent to the aldehyde carbon atom thus building the corresponding enamine bases **9a**, **b**. Evidently, in the tautomeric equilibrium **8** ⇆ **8′** (Scheme 4) the 3-hydroxymethylene group in the chromane-2,4-dione tautomer (**8′**) is the more reactive function. This behavior has also been confirmed by other authors [30, 31].

When we used 4-hydroxycoumarin-3-carbaldehyde (**8**) instead of 4-chlorocoumarin-3-carbaldehyde (**1b**), we obtained *N*-substituted 3-aminomethylenechromane-2,4-diones **9a**, **b** (Scheme 4). As described by Ollinger *et al.* [30], the nucleophilic addition-elimination took place at the most reactive 3-formyl group. The structures of **9a**, **b** were suggested on the basis of literature data for analogous compounds [30, 31] and confirmed by means of their spectral (IR, NMR) properties and elemental analyses (Table 1). The products **9a**, **b** are mixtures of (*E,Z*)-isomers which have to be interconvertible through the imine-enamine tautomerism (Scheme 5).

In the ^{1}H NMR spectrum of the products **9a/9b**, characteristic doublets for the methine protons of both geometrical isomers (Schemes 4 and 5) at $\delta = 8.41/8.34$ (*E*-isomers) and $8.53/8.43$ (*Z*-isomers) ppm are observed beside the expected signals of methylene and aromatic protons. The ratio between the integrals of both signals is approximately 2 : 1, and this corresponds to the proportion of the two isomers. Since the spatial environment of the NH group of the two isomers is different, two signals for NH at $\delta = 10.30$ and 11.62 (for **9a**) and at $\delta = 10.33$ and 11.55 (for **9b**) are observed. The conclusion drawn from these data is that one of the two isomers is energetically more stable and thus predominant. The determination of the configuration of the predominant isomer is a difficult task because, generally, it cannot be decided which of the two is the energetically less favorable because hydrogen bonds in both forms are almost identical. Comparing the signals of the NH's of analogous morpholine derivatives in similar conjugated systems, Uray *et al.* [32] have concluded that, when the *N*-proton forms a hydrogen bond with the lactone carbonyl (when the configuration is *Z*), its signal is located between $\delta = 10$ and 11 ppm, and when the keto oxygen is hydrogen-bound (*E*-isomer), the signal is shifted to $\delta = 11 - 12$ ppm. If we apply this conclusion to the spectrum of **9a**, it follows that the signal at $\delta = 10.30$ ppm belongs to the *Z*-isomer, and the one at $\delta = 11.62$ to the *E*-isomer, *i. e.* the E/Z ratio is approximately 2 : 1. Ollinger *et al.* [30] analyzed the signals of the methine protons in this type of compounds, assuming that the signal of the *E*-isomer appeared at about $\delta = 8.35$ ppm whereas the *Z*-isomer resonated at $\delta = 8.55$ ppm. Our data show signals at $\delta = 8.41$ and 8.53 ppm with an integral ratio of 2.5 : 1. Therefore, the greater stability of the *E*-isomer (*E*-**9a**) has been confirmed by all criteria established by both research teams.

It is noteworthy that in all our experiments where diaminoalkanes were used in the reaction with the hydroxycoumarins **1a** or **8**, the procedure was successful in boiling glacial acetic acid, and a regiospecific *N′*-monoacetylation took place to afford the products **5a**, **b** and **9b**.

Experimental Section

The IR spectra were recorded in nujol on a Shimadzu 8001 FTIR spectrometer. All NMR experiments were measured on Bruker DRX 250 MHz and Bruker Avance II+ 600 MHz NMR spectrometers at 25 °C. Chemical shifts on the δ scale are given in ppm. The precise assignment of the ^{1}H and ^{13}C NMR spectra was accomplished by measurement of 2D homonuclear correlation (COSY), DEPT-135 and 2D inverse detected heteronuclear (C–H) correlations (HMQC and HMBC). Elemental analyses were performed by the Microanalytical Laboratory, Institute of Organic Chemistry, University of Stuttgart (Head Dr. Joachim

Opitz). TLC: silica gel 60 F_{254} Merck pre-coated aluminum sheets, eluted by chloroform-acetone-methanol 6 : 4 : 1 (vol. parts); visualization of spots was done by treatment with I_2 (vapor) and under UV irradiation ($\lambda = 254$ nm).

*4-[(2-Hydroxyethyl)amino]-2H-chromen-2-one (**3a**)* [15]

To a solution of 0.81 g (5 mmol) of 4-hydroxycoumarin (**1a**) in 10 mL of anhydr. ethanol, 1.53 g (25 mmol) of 2-aminoethanol (**2a**) was added under stirring. The mixture was heated at reflux for 4 h. On cooling, the resulting precipitate of **3a** was filtered and washed with 2-propanol (2 × 10 mL) and dried at 90 – 100 °C to give product **3a** as almost colorless crystals with m. p. 172 – 173 °C in 40 % yield (ref. [15]: m. p. 172.5 – 174 °C). – IR (nujol): ν (cm^{-1}) = 3283 (NH/OH), 1659 (C=O, lactone), 1606 (C=C), 1142 (C-O-C, lactone). – ^{1}H NMR (600 MHz, [D_6]DMSO): $\delta = 3.32$ (q, $J = 5.8$ Hz, 2H, CH_2N), 3.62 (q, $J = 5.8$ Hz, 2H, CH_2O), 4.86 (t, $J = 5.7$ Hz, 1H, OH), 5.18 (s, 1H, 3-H), 7.30 (dd, $J = 8.2$ Hz, $J = 1.1$ Hz, $1H_{arom.}$, 8-H), 7.32 (ddd, $J = 8.2$ Hz, $J = 7.6$ Hz, $J = 1.0$ Hz, $1H_{arom.}$, 6-H), 7.59 (ddd, $J = 8.2$ Hz, $J = 7.6$ Hz, $J = 1.1$ Hz, $1H_{arom.}$, 7-H), 7.64 (t, $J = 5.3$ Hz, 1H, NH), 8.06 (dd, $J = 8.0$ Hz, $J = 1.0$ Hz, $1H_{arom.}$, 5-H). – ^{13}C NMR (150.9 MHz, [D_6]DMSO): $\delta = 45.1$ (NCH_2), 58.4 (CH_2O), 81.3 (C-3), 114.5 (C-4a), 117.0 (C-8), 122.5 (C-5), 123.3 (C-6), 131.9 (C-7), 153.1 (C-4), 153.4 (C-8a), 161.6 (C-2). – EI-MS (70 eV): m/z (%) = 205 (100) $[M]^+$, 174 (76), 162 (64), 146 (30), 133 (25), 118 (12), 107 (11), 91 (9), 89 (13).

*4-[(2-Hydroxypropyl)amino]-2H-chromen-2-one (**3b**)*

To a solution of 0.81 g (5 mmol) 4-hydroxycoumarin (**1a**) in 10 mL of anhydr. ethanol, 1.88 g (25 mmol) of 1-amino-2-propanol (**2b**) was added under stirring, and the mixture was heated at reflux for 28 h. The resulting precipitate was filtered and washed with 2-propanol (2 × 10 mL). The solid was filtered and dried at 90 – 100 °C to afford almost colorless crystals of **3b** with m. p. 181 – 183 °C in 35 % yield. – IR (KBr): ν (cm^{-1}) = 3399 (OH), 3360 (NH), 1645 (C=O), 1610 (C=C), 1101 (C-O-C). – ^{1}H NMR ([D_6]DMSO, 600 MHz): $\delta = 1.12$ (d, 3H, $J = 6.2$ Hz, CH_3), 3.17 (m, 2H, CH_2), 3.93 (m, 1H, CH-O), 4.90 (bs, 1H, OH), 5.20 (s, 1H, 3-H), 7.30 (dd, $J = 8.2$ Hz, $J = 1.1$ Hz, $1H_{arom.}$, 8-H), 7.32 (ddd, $J = 8.2$ Hz, $J = 7.6$ Hz, $J = 1.2$ Hz, $1H_{arom.}$, 6-H), 7.58 (ddd, $J = 8.1$ Hz, $J = 7.6$ Hz, $J = 1.1$ Hz, $1H_{arom.}$, 7-H), 7.64 (t, $J = 5.6$ Hz, 1H, NH), 8.07 (d, $J = 8.1$, $J = 1.2$ Hz, $1H_{arom.}$, 5-H). – ^{13}C NMR (150.9 MHz, [D_6]DMSO): $\delta = 21.3$ (CH_3), 50.1 (NCH_2), 63.7 (CH-O), 81.4 (C-3), 114.5 (C-4a), 117.0 (C-8), 122.5 (C-5), 123.3 (C-6), 131.9 (C-7), 153.1 (C-4), 153.4 (C-8a), 161.6 (C-2).

*N-{2-[(2-Oxo-2H-chromen-4-yl)amino]ethyl}acetamide (**5a**)* [28]

To 1.62 g (10 mmol) of 4-hydroxycoumarin (**1a**) in 30 mL (0.53 mol) of glacial acetic acid, 12.0 g (0.2 mol) of ethylene diamine (**4a**) was added under stirring. The mixture was heated at reflux for 2 h and then poured under stirring into 75 mL of cold water. The resulting precipitate of **5a** was filtered and washed with hot water (2 × 10 mL). The solid was stirred with ether (20 mL) for 10 min, filtered, washed with small amounts of ether and dried at 90 – 100 °C to yield 1.85 g (75 %) of **5a** as almost colorless crystals with m. p. 261 – 262 °C. After recrystallization from ethanol: colorless needles, m. p. 262 – 263 °C (updated spectral data, *cf.* [28]). – FT-IR (nujol): ν (cm^{-1}) = 3333 (NH), 3271 (NH), 1684 (C=O), 1653 (C=O), 1609, 1557, 1327, 1262, 1223, 1196, 1150, 1080, 1040, 938, 797, 764, 752, 722, 695. – ^{1}H NMR (600 MHz, [D_6]DMSO): $\delta = 1.83$ (s, 3H, $COCH_3$), 3.29 – 3.30 (m, 4H, NCH_2CH_2N), 5.22 (s, 1H, 3-H), 7.31 (d, $J = 7.9$ Hz, $1H_{arom.}$, 8-H), 7.33 (t, $J = 7.7$ Hz, $1H_{arom.}$, 6-H), 7.59 (t, $J = 7.4$ Hz, $1H_{arom.}$, 7-H), 7.77 (br. t, 1H, 4-NH), 7.96 (d, $J = 7.7$ Hz, $1H_{arom.}$, 5-H), 8.12 (br. t, 1H, NHCO). – ^{13}C NMR (150.9 MHz, [D_6]DMSO): $\delta = 22.7$ (CH_3), 37.0 (NCH_2), 42.3 (CH_2N), 81.4 (C-3), 114.4 (C-4a), 117.0 (C-8), 122.3 (C-5), 123.4 (C-6), 132.0 (C-7), 153.1 (C-8a or C-4), 153.2 (C-4 or C-8a), 161.6 (C-2), 170.2 (NHCO). – EI-MS (70 eV): m/z(%) = 246 (51) $[M]^+$, 188 (9), 187 (67), 186 (26), 175 (18), 174 (100), 162 (46), 159 (28), 146 (24), 145 (10), 118 (12), 107 (14), 91 (10), 89 (14), 73 (11), 43 (19), 30 (22). – HRMS: m/z = 246.1006 (calcd. 246.10044 for $C_{13}H_{14}N_2O_3$, $[M]^+$).

*N-{3-[(2-Oxo-2H-chromen-4-yl)amino]propyl}acetamide (**5b**)*

To 1.62 g (10 mmol) of 4-hydroxycoumarin (**1a**) in 30 mL (0.53 mol) of glacial acetic acid, 14.8 g (0.2 mol) of 1,3-propanediamine (**4b**) was added under stirring, and the mixture was heated at reflux for 3.5 h and then poured into 75 mL of cold water under stirring. The resulting precipitate was filtered, washed with hot water (2 × 10 mL) and filtered. The solid was treated with ether (20 mL) for 10 min under stirring, filtered, washed with small amounts of ether and dried at 90 – 100 °C to yield 53 % of **5b** as almost colorless crystals with m. p. 206 – 208 °C. – IR (KBr): ν (cm^{-1}) = 3297 (NH), 3263 (NH), 1698 (C=O), 1653 (C=O). – ^{1}H NMR (600 MHz, [D_6]DMSO): $\delta = 1.76$ (pentet, $J = 6.9$ Hz, 2H, CH_2), 1.83 (s, 3H, $COCH_3$), 3.14 (q, $J = 6.4$ Hz, 2H, CH_2N), 3.26 (q, $J = 6.5$ Hz, 2H, NCH_2), 5.17 (s, 1H, 3-H), 7.32 (d, $J = 8.2$ Hz, $1H_{arom.}$, 8-H), 7.33 (t, $J = 7.7$ Hz, $1H_{arom.}$, 6-H), 7.60 (t, $J = 7.7$ Hz, $1H_{arom.}$, 7-H), 7.67 (br. t, $J = 5.1$ Hz, 1H, 4-NH), 7.98 (br. t, $J = 5.1$ Hz, 1H, NHCO), 8.04 (d, $J = 7.9$ Hz, $1H_{arom.}$, 5-H). – ^{13}C NMR (150.9 MHz, [D_6]DMSO): $\delta = 22.7$ (CH_3, acetyl),

27.6 (CH_2), 36.4 (CH_2N), 40.1 (CH_2N), 81.4 (C-3), 114.5 (C-4a), 117.1 (C-8), 122.4 (C-5), 123.0 (C-6), 132.0 (C-7), 153.2 (C-8a or C-4), 153.2 (C-4 or C-8a), 161.8 (C-2), 169.6 (NHCO).

*4-[(2-Hydroxyethyl)amino]-3-{(E)-[(2-hydroxyethyl)imino]methyl}-2H-chromen-2-one (**6a**)*

To a stirred solution of 1.04 g (5 mmol) of 4-chlorocoumarin-3-carbaldehyde (**1b**) [22, 23, 33] in 5 mL of anhydr. ethanol, 0.92 g (0.015 mol) of 2-aminoethanol (**2a**) was added dropwise. The reaction mixture was vigorously stirred for 15 min at room temperature. The resulting pale-yellow precipitate was filtered and washed with dioxane (2 × 10 mL), recrystallized from ethanol and air-dried to give colorless crystals of **6a** with m. p. 180 – 181 °C in 45 % yield. – IR (KBr): ν (cm^{-1}) = 3361 (NH), 3272 (OH), 1646 (C=O), 1616 (C=O). – ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 3.56 (t, J = 5.4 Hz, 2H, OCH_2), 3.63 (t, J = 5.5 Hz, 2H, OCH_2), 3.69 (t, J = 5.2 Hz, 2H, NCH_2), 3.94 (q, J = 4.8 Hz, 2H, NCH_2), 4.69 (s, 1H, OH), 5.20 (s, 1H, OH), 7.33 (t, J = 7.2 Hz, $1H_{arom.}$, 6-H), 7.34 (d, J = 8.0 Hz, $1H_{arom.}$, 8-H), 7.65 (t, J = 7.7 Hz, $1H_{arom.}$, 7-H), 8.21 (d, J = 8.0 Hz, $1H_{arom.}$, 5-H); 8.60 (s, 1H, CH=N), 13.05 (s, 1H, NH). – ^{13}C NMR ([D_6]DMSO, 62.9 MHz): δ = 49.7 (CH_2NH), 60.2 (NCH_2), 61.5 (CH_2O), 62.4 (CH_2O), 91.4 (C-3), 114.7 (C-4a), 117.6 (C-8), 123.6 (C-6), 127.4 (C-5), 133.0 (C-7), 153.6 (C-8a), 156.2 (C-4), 161.2 (C-2), 161.6 (CH=N).

*4-[(3-Hydroxypropyl)amino]-3-{(E)-[(3-hydroxypropyl)imino]methyl}-2H-chromen-2-one (**6c**)*

To a stirred solution of 1.04 g (5 mmol) of 4-chlorocoumarin-3-carbaldehyde (**1b**) in 5 mL of anhydr. ethanol, 1.13 g (0.015 mol) 3-amino-1-propanol (**2c**) was added dropwise. The reaction mixture was vigorously stirred for 15 min at room temperature. The resulting pale-yellow precipitate was filtered and washed with dioxane (2 × 10 mL), recrystallized from ethanol and air-dried to give colorless crystals of **6c** in 53 % yield, m. p. 126 – 127 °C. – IR (KBr): ν (cm^{-1}) = 3348 (NH), 3233 (OH) 1645 (C=O), 1612 (C=O). – ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 1.75 (pentet, J = 6.6 Hz, 2H, CH_2), 1.85 (pentet, J = 6.3 Hz, 2H, CH_2), 3.49 (q, J = 4.8 Hz, 2H, OCH_2), 3.57 (m, 4H, 2 × CH_2), 3.96 (dt, J = 4.8 Hz, J = 6.8 Hz, 2H, NCH_2), 4.48 (t, J = 5.0 Hz, 1H, OH), 4.65 (t, J = 4.9 Hz, 1H, OH), 7.31 – 7.42 (m, $2H_{arom.}$, 6-H, 8-H), 7.66 (ddd, J = 1.4 Hz, J = 7.1 Hz, J = 8.4 Hz, $1H_{arom.}$, 7-H), 8.24 (dd, J = 1.4 Hz, J = 8.4 Hz, $1H_{arom.}$, 5-H), 8.64 (s, 1H, CH=N), 12.76 (s, 1H, NH). – ^{13}C NMR ([D_6]DMSO, 62.9 MHz): δ = 33.0 (CH_2), 34.3 (CH_2), 43.9 (CH_2N), 56.7 (NCH_2), 57.5 (CH_2O), 58.4 (CH_2O), 91.1 (C-3), 114.7 (C-4a), 117.6 (C-8), 123.6 (C-6), 127.4 (C-5), 133.0 (C-7), 153.6 (CH=N), 156.1 (C-8a), 160.8 (C-2), 161.5 (C-4). A sample of **6c** was additionally recrystallized twice from ethanol to afford single crystals suitable for X-ray analysis.

*4-[(2-Hydroxypropyl)amino]-2-oxo-2H-chromene-3-carbaldehyde (**7**)*

To a stirred solution of 1.04 g (5 mmol) of 4-chlorocoumarin-3-carbaldehyde (**1b**) in 5 mL of anhydr. ethanol, 1.13 g (0.015 mol) of 1-amino-2-propanol **2b** was added dropwise. The reaction mixture was then stirred for 4 h at reflux. After cooling, the resulting precipitate was filtered, washed with dioxane (2 × 10 mL) and recrystallized from ethanol to give colorless crystals of **7** with m. p. 135 – 137 °C in 33 % yield. – IR (KBr): ν (cm^{-1}) = 3388 (O/NH), 1700 (C=O), 1620 (C=O). – ^{1}H NMR (600 MHz, [D_6]DMSO): δ = 1.18 (d, J = 5.9 Hz, 3H, CH_3CO), 3.77 (m, 1H from CH_2, diastereotopic) and 3.96 (m, 1H from CH_2, diastereotopic), 3.92 (m, 1H, CH-O), 5.32 (d, J = 3.1 Hz, 1H, OH), 7.37 (m, $2H_{arom.}$, 6-H, 8-H), 7.74 (t, J = 7.5 Hz, $1H_{arom.}$, 7-H), 8.24 (d, J = 8.0 Hz, $1H_{arom.}$, 5-H), 9.93 (s, CH=O), 11.96 (s, NH). – ^{13}C NMR (150.9 MHz, [D_6]DMSO): δ = 21.0 (CH_3), 54.1 (CH_2O), 64.7 (CH), 95.6 (C-3), 113.7 (C-4a), 117.9 (C-8), 124.0 (C-6), 128.8 (C-5), 134.8 (C-7), 154.6 (C-4), 159.0 (C-8a), 161.9 (C-2), 190.0 (CH=O).

*(E,Z)-3-[(2-Hydroxyethyl)aminomethylene]-chromane-2,4-dione (**9a**)*

To a stirred solution of 0.95 g (5 mmol) of 4-hydroxycoumarin-3-carbaldehyde (**8**), prepared according to ref. [30], in 10 mL of anhydr. ethanol, 3 mL (50 mmol) of 2-aminoethanol (**2a**) was added under stirring. The mixture was refluxed for 4 h, allowed to cool to r. t., and the solvent was removed *in vacuo*. From the yellow oily residue a colorless solid crystallized, which was filtered, washed with ethanol and recrystallized from 2-propanol. Yield 540 mg (48 %) of **9a**, colorless crystals with m. p. 180 – 182 °C. – IR (nujol): ν (cm^{-1}) = 3395 (OH), 3142 (NH), 1703 (C=O), 1651 (C=O, lactone), 1597 (C=C), 1111 (C-O-C, lactone). – ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 3.62 (s, 4H, 2 × CH_2), 5.03 (br. m, 1H, OH), 7.26 – 7.34 (m, $2H_{arom.}$, 6-H and 8-H), 7.65 (m_c, $1H_{arom.}$, 7-H), 7.93 (dd, J = 7.0 Hz, J = 1.5 Hz, $1H_{arom.}$, 5-H), 8.42 (d, J = 14.7 Hz, 2/3H, =CH–, *E*-isomer), 8.53 (d, J = 15.5 Hz, 1/3H, =CH–, *Z*-isomer), 10.35 (br. d, 1/3H, NH, *Z*-isomer), 11.66 (br. d, 2/3H, NH, *E*-isomer). – ^{13}C NMR (63 MHz, [D_6]DMSO), *E*-isomer: δ = 52.6 (NCH_2), 59.5 (OCH_2), 95.6 (C-3), 116.9 (C-8), 120.3 (C-4a), 123.9 (C-6), 125.2 (C-5), 134.2 (C-7), 154.2 (C-8a), 161.3 (C-2), 162.8 (3-CH=), 179.3 (C-4). The signals of the *Z*-isomer are of very low intensity because of poor solubility.

*(E,Z)-N-{2-[(2,4-Dioxo-2H-chroman-3-ylidene)methylamino]ethyl}acetamide (**9b**)*

To a solution of 4.5 mL (67 mmol) of ethylenediamine **4a** in 10 mL of glacial acetic acid, 0.7 g (3.66 mmol) of 4-hydroxycoumarin-3-carbaldehyde (**8**) was added under stirring. The mixture was refluxed for 2 h, cooled and poured under stirring into 75 mL of cold water. The product was extracted with 3 × 20 mL of ethyl acetate, and the solvent was removed *in vacuo* to afford 0.46 g (53 %) of **9b** as orange crystals. Recrystallization from ethanol yielded beige crystals of **9b** with m. p. 201 – 202 °C. – IR (nujol): ν (cm^{-1}) = 3304 (NH), 3098 (NH, amide), 1695 (C=O), 1651 (C=O, lactone), 1628 (C=O, amide), 1566 (C=C), 1113 (C-O, lactone). – ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 1.80 (s, 3H, CH_3CO), 3.5 (m, 2H, N-CH_2), 3.62 (m, 2H, N-CH_2), 7.27 – 7.34 (m, 2H$_{arom.}$), 7.66 (m, 1H$_{arom.}$), 7.91 – 7.95 (m, 1H$_{arom.}$), 8.08 (s, NH, amide), 8.34 (d, J = 14 Hz, 2/3H, =CH–, *E*-isomer), 8.43 (d, J = 14 Hz, 1/3H, =CH–, *Z*-isomer), 10.33 (br. s, 1/3H, NH, *Z*-isomer), 11.55 (br. s, 2/3H, NH, *E*-isomer).

X-Ray structure determination

A suitable single crystal (from ethanol) coated with perfluorinated oil was mounted on the tip of a glass fiber. X-Ray diffraction data were collected on a Bruker Kappa APEX II Duo diffractometer, using graphite-monochromatized MoK_α radiation (λ = 0.71073 Å). Unit cell parameters were obtained by indexing of the peaks in the first 10 frames and refined by employing the whole data set. All frames were integrated and corrected for Lorentz and polarization effects. The structure was solved by Direct Method using SHELXS-97 [34, 35]. All non-hydrogen atoms were located and refined anisotropically by full-matrix least-squares using SHELXL-97 [36, 37]. The carbon-bonded hydrogen atoms were placed in idealized positions. The nitrogen- and oxygen-bonded hydrogen atom were found in difference Fourier maps and were allowed to refine freely with isotropic displacement parameters. The results of the crystal structure analysis are presented in the Table 2. For the preparation of the structural images the program DIAMOND [38] was used.

CCDC 923050 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgement

Acknowledgements are due to our former students Stoyan Tikvarski, Jivko Georgiev and Stefan Kadiyski for their technical assistance. We like to thank Dr. Wolfgang Frey (Institut für Organische Chemie, Universität Stuttgart) for the measurement of the X-ray data. The financial support by the National Research Fund of Bulgaria for the purchase of the Bruker Avance II+ 600 NMR spectrometer as part of the Promotion of the Research Potential through Unique Scientific Equipment Program (project UNA-17/2005), and for upgrading the existing NMR spectrometers (project DRNF-02/13(2009)) is also gratefully acknowledged.

[1] Y. Jacquot, I. Laïos, A. Cleeren, D. Nonclercq, L. Bermont, B. Refouvelet, K. Boubekeur, A. Xicluna, G. Leclercq, G. Laurent, *Bioorg. Med. Chem.* **2007**, *15*, 2269 – 2282.
[2] A. S. Al-Ayed, *Molecules* **2011**, *16*, 10292 – 10302.
[3] Y. Dong, K. Nakagawa-Goto, C.-Y. Lai, S. L. Morris-Natschke, K. F. Bastow, K.-H. Lee, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 546 – 549.
[4] O. H. Hishmat, A. M. Gohar, M. E. Wassef, M. R. Shalash, I. Ismail, *Pharm. Acta Helv.* **1977**, *52*, 252 – 255.
[5] V. Virsdoia, M. S. Shaikh, A. Manvar, B. Desai, A. Parecha, R. Loriya, K. Dholariya, G. Patel, V. Vora, K. Upadhyay, K. Denish, A. Shah, E. C. Coutinho, *Chem. Biol. Drug Des.* **2010**, *76*, 412 – 424.
[6] V. L. Savel'ev, N. T. Pryanishnikova, O. S. Artamonova, I. V. Fedina, V. A. Zagorevskii, *Pharm. Chem. J.* **1975**, *9*(6), 360 – 362; *Khim.-Farm. Zh.* **1975**, *9*, No. (6), 10 – 12 (in Russian).
[7] A. G. Cook, *Enamines. Synthesis, Structure and Reactions*, Marcel Dekker, New York **1969**, pp 396 – 401.
[8] B. Stamboliyska, V. Janevska, B. Shivachev, R. P. Nikolova, G. Stojkovic, B. Mikhova, E. Popovski, *Arkivoc* **2010**, *x*, 62 – 76.
[9] D. Heber, *Arch. Pharm. (Weinheim)* **1987**, *320*, 577 – 581.
[10] I. C. Ivanov, S. K. Karagiosov, M. F. Simeonov, *Liebigs Ann. Chem.* **1992**, 203 – 208.
[11] I. C. Ivanov, S. K. Karagiosov, *Synthesis* **1995**, 633 – 634.
[12] S. Neetha, D. N. Joshipura, M. A. Sridhar, J. S. Prasad, A. Shah, *X-Ray Structure Analysis Online* **2011**, *27*, 1 – 2.
[13] V. A. Zagorevskii, V. L. Savel'ev, N. V. Dudykina, *J. Org. Chem. USSR* (Engl. Transl.) **1968**, *4*, 1970 – 1977.
[14] V. A. Zagorevskii, V. L. Savel'ev, L. M. Meshcheryakova, *Khim. Geterotsikl. Soed.* **1970**, *6*, 1019 – 1023; *Chem. Abstr.* **1971**, *74*, 76269c.
[15] M. S. Newman, C. Y. Perry, *J. Org. Chem.* **1963**, *28*, 116 – 120.

[16] M. A. Kirpichenok, S. K. Gorozhankin, I. I. Grandberg, *Chem. Heterocycl. Comp.* **1990**, *26*, 693 – 697.
[17] K. Tabaković, I. Tabaković, N. Ajdini, O. Leci, *Synthesis* **1987**, 308 – 310.
[18] S. D. Joshi, V. D. Sakhardande, S. Seshadri, *Indian J. Chem. Sect. B* **1984**, *23*, 206 – 208.
[19] I. C. Ivanov, S. K. Karagiosov, I. Manolov, *Arch. Pharm. (Weinheim)* **1991**, *324*, 61 – 62.
[20] E. V. Stoyanov, I. C. Ivanov, *Molecules* **2004**, *9*, 627 – 631.
[21] S. R. Moorty, V. Sundaramurthy, N. V. Subba Rao, *Indian J. Chem.* **1973**, *11*, 854 – 856.
[22] T. Steinführer, A. Hantschmann, M. Pietsch, M. Weißenfels, *Liebigs Ann. Chem.* **1992**, 23 – 28.
[23] D. Heber, I. C. Ivanov, S. K. Karagiosov, *J. Heterocycl. Chem.* **1995**, *32*, 505 – 509.
[24] A. Sabatié, D. Végh, A. Loupy, L. Floch, *Arkivoc* **2001**, *vi*, 122 – 128.
[25] B. I. Iliev, I. C. Ivanov, *Molecules* **2001**, *6*, M218.
[26] D. Rambabu, G. R. Krishna, C. M. Reddy, M. Pal, *Acta Crystallogr.* **2010**, *E66*, o2870.
[27] J. V. Prasad, J. S. Reddy, N. R. Kumar, K. A. Solomon, G. Gopikrishna, *J. Chem. Sci.* **2011**, *123*, 673 – 679.
[28] S. K. Karagiosov, I. C. Ivanov, B. I. Iliev, *Molecules* **1999**, *4*, M126.
[29] S. Klutchko, J. Shavel, Jr., M. Von Strandtmann, *J. Org. Chem.* **1974**, *39*, 2436 – 2437.
[30] P. Ollinger, O. S. Wolfbeis, H. Junek, Darstellung, *Monatsh. Chem.* **1975**, *106*, 963 – 971.
[31] F. Risitano, G. Grassi, F. Foti, *J. Heterocycl. Chem.* **2001**, *38*, 1083 – 1086.
[32] G. Uray, O. S. Wolfbeis, H. Junek, *J. Mol. Struct.* **1979**, *54*, 77 – 88.
[33] V. V. Mulwad, A. S. Hegde, *Indian J. Chem.* **2009**, *48B*, 1558 – 1564.
[34] G. M. Sheldrick, SHELXS-97, Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany), **1997**.
[35] G. M. Sheldrick, *Acta Crystallogr.* **1990**, *A46*, 467 – 473.
[36] G. M. Sheldrick, SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen (Germany), **1997**.
[37] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112 – 122.
[38] K. Brandenburg, DIAMOND (version 2.1d), Crystal and Molecular Structure Visualization, Crystal Impact – K. Brandenburg & H. Putz GbR, Bonn (Germany) **2000**.