2070 *Russian Chemical Bulletin, International Edition, Vol. 51, No. 11, pp. 2070—2073, November, 2002*

Synthesis, acid-base and spectral properties of 3-(benzoimidazol-2-yl)-2-phenylimino-2*H*-chromenes

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3-(Benzoimidazol-2-yl)-2-phenylimino-2*H*-chromenes were synthesized. The protolytic equilibrium constants in 50% ethanol were determined. The correlations of the pK_a values for the compounds in the ground and excited states and the PM3-calculated heats of formation with the σ^+ constants of substituents were established. The nitrogen atom of the benzoimidazole fragment is the center of protonation in the studied compounds.

Key words: iminochromenes, protolytic equilibria, protonation, hydrolysis.

In investigations of the reactivity of 3-(benzoimidazol-2-yl)-2-imino-2*H*-chromenes **1** (Scheme 1) we established that only 2-amino-3-(benzoimidazol-2-yl)benzopyrylium cations **6** or, in a more acidic medium, dications **7** rather than the initial compounds undergo hydrolysis in water-organic media.[1,2] The methylation of the imino group remains its basicity virtually unchanged, while the stability of 2-methylamino-1-benzopyrilium cation **8** toward hydrolysis increases by ~10 times compared to that of cation **6**. Based on these results, we decided to search for iminochromenes stable toward hydrolysis among their *N*-substituted derivatives. With this purpose, a series of derivatives of 3-(benzoimidazol-2-yl)-2-phenylimino-2*H*-chromene **3** was synthesized in this work. The main physicochemical and spectral parameters of the obtained compounds are presented in Table 1.

Experimental

Compounds **1** [1] and **3** [3] were synthesized using known procedures. Electronic absorption spectra were measured using a Hitachi-3210 spectrophotometer at 20 °C. IR spectra were measured on a Specord M-80 spectrophotometer in pellets with KBr. ^{1}H NMR spectra were recorded on a Bruker AMX-400

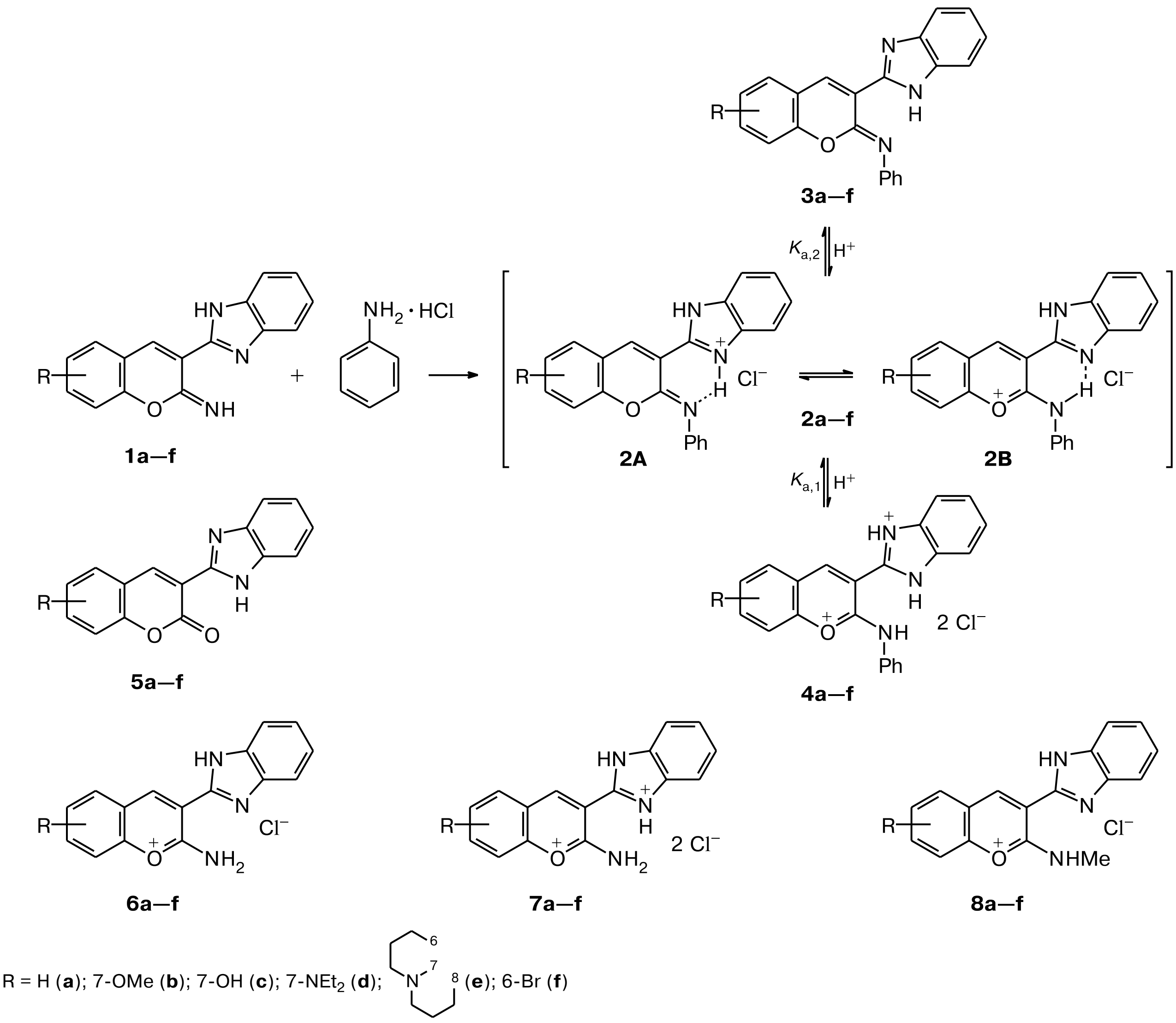
Table 1. Physicochemical and spectral characteristics of *N*-phenyl-2-imino-2*H*-chromenes **3a—f**

Compound	Yield (%)	M.p./°C	EAS		IR, ν/cm^{-1} (C=NPh)	^{1}H NMR, δ (*J*/Hz)
			ν^{abs}_{max}/cm^{-1}	ε/L mol^{-1} cm^{-1}		
3a	65	202	27320	16600	1642	8.77 (s, 1 H, H(4)); 7.67—7.07 (m, 13 H, H arom.); 12.45 (s, 1 H, NH)
3b	60	212	25460	24500	1642	8.59 (s, 1 H, H(4)); 7.75—6.60 (m, 12 H, H arom.); 12.38 (s, 1 H, NH); 3.80 (s, 3 H, Me)
3c	55	314	25380	25200	1645	8.68 (s, 1 H, H(4)); 7.58—6.48 (m, 12 H, H arom.); 12.40 (s, 1 H, NH); 10.05 (s, 1 H, OH)
3d	62	191	22400	44900	1642	8.62 (s, 1 H, H(4)); 7.56—6.18 (m, 12 H, H arom.); 12.35 (s, 1 H, NH); 3.40 (q, 4 H, 2 CH_2, $J \approx 7$); 1.20 (t, 6 H, 2 Me, $J \approx 7$)
3e	59	207	21500	41300	1635	8.51 (s, 1 H, H(4)); 7.56—6.94 (m, 10 H, H arom.); 3.15—1.85 (m, 12 H, 6 CH_2); 12.35 (s, 1 H, NH)
3f	55	234	25860	19000	1642	8.74 (s, 1 H, H(4)); 7.89—7.02 (m, 12 H, H arom.); 12.50 (s, 1 H, NH)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 1915—1918, November, 2002.

1066-5285/02/5111-2070 $27.00 © 2002 Plenum Publishing Corporation

Scheme 1



R = H (**a**); 7-OMe (**b**); 7-OH (**c**); 7-NEt$_2$ (**d**); (**e**); 6-Br (**f**)

instrument in DMSO-d$_6$ using Me$_4$Si as the internal standard. The ^{1}H NMR spectra of all compounds studied in this work and earlier studied 3-(benzoimidazol-2-yl)coumarins[4,5] exhibit a single signal from the H(4) proton (δ 8.5—8.8), a multiplet from the aromatic protons (δ 6.2—7.9), and a signal from the NH proton of benzoimidazole (δ 12.4—12.5). The vibrations of the C=NPh group are manifested in the IR spectra in an interval of 1635—1642 cm^{-1}.

Protolytic equilibrium constants (K_a) in an aqueous-ethanol medium* were determined by the spectrophotometric method at 20 °C using buffer solutions based on hydrochloric, acetic, and malonic acids, ammonium chloride, borax, sodium hydroxide, and sodium chloride (supporting electrolyte) at a constant ionic strength of 0.05 mol L^{-1}. The pH values of solutions were measured using procedures described previously in detail[1] in a cell with glass and silver-silver chloride auxiliary electrodes. The cell was standardized by buffer solutions based on hydrochloric, salicylic, acetic, and 5,5-diethylbarbituric acids, sodium hydroxide, and sodium chloride by the compensation scheme using an R-363-2 potentiometer and a pH-121 pH-meter.

The rate constants of hydrolysis (k) of monocation **2a** and dication **4a** at 20 °C in an aqueous-alcohol medium were determined from the results of measurements of the apparent hydrolysis constants (k_{app}) at different acidity values in the region where these species prevailed. The k_{app} values were calculated using the modified Guggenheim method.[6]

The quantum-chemical calculations at the PM3 level[7] were performed using the MOPAC-97 program including the COSMO unit,[8] which allows the simulation of the polar influence of the solvent.

Results and Discussion

The electronic absorption spectra of *N*-phenyl-2-imino-2*H*-chromenes **3** are characterized by an insignifi-

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* Hereafter the content of ethanol in an aqueous-ethanol medium is 50 vol.%.

cant hypsochromic shift of the absorption bands compared to those of iminochromenes **1**,[1] which have no substituents at the N atom of the imino group ($\leq$500 cm^{-1}), and a ~1.5-fold decrease in the molar absorption coefficient. On going from aprotic to protic media for 2-imino-7-hydroxy-2*H*-chromenes, we have previously detected the appearance of the second tautomeric form.[1] In the case of *N*-phenyl-7-hydroxy derivative **3c** in aqueous-alcohol solutions, a similar tautomerism is not observed, which can be related to a decrease in the basicity of the imino group in this derivative compared to that in chromene **1c**.

Analysis of the K_a values in an aqueous-ethanol medium (Table 2) showed that the presence of the Ph substituent in the imino group substantially decreases the basicity of iminochromenes **3** (p$K_{a,2}$ 3—5, while for unsubstituted analogs **1** p$K_{a,2}$ is 5—8). The obtained p$K_{a,2}$ values are close to pK_a of the benzoimidazole fragment in 3-(benzoimidazol-2-yl)coumarins **5** (pK_a 3—5).[1] This suggests that the benzoimidazole fragment rather than the imino group is the protonation center in *N*-phenyliminochromenes.

The quantum-chemical PM3 calculations of heats of formation (ΔH_f) for alternative cationic forms **2A** and **2B** (see Scheme 1) showed somewhat higher (by ~3 kcal mol^{-1}) stability of cation **2A** for all compounds studied (Table 3). The theoretical simulation of the polar effect of the solvent revealed that an increase in the dielectric constant of the medium increased the difference in the calculated heats of formation ($\delta\Delta H_f$) for cations **2Aa** and **2Ba** to 6 kcal mol^{-1} (Table 4). This suggests that iminochromenes **3a—f** in an acidic medium exist in the form with the protonated benzoimidazole fragment.

We established a good linear correlation between the p$K_{a,2}$ values and the σ^+ constants of substituents R (r = 0.995, s = 0.026, ρ = 0.58). The reaction constant ρ turned out to be close to that for the protonation of the benzoimidazole fragment in 3-(benzoimidazol-2-yl)coumarins (ρ = 0.51) and differed substantially from the ρ value for the protonation of the imino group in the series of 3-(benzoimidazol-2-yl)-2-imino-2*H*-chromene derivatives (ρ = 0.93).[2] This confirmed our assumption about the protonation in an acidic medium of the benzoimidazole fragment instead of the *N*-phenylimino group.

Table 2. The pK_a values and characteristics of long-wave absorption bands (ν/cm^{-1}, ε/L mol^{-1} cm^{-1}) in the electronic absorption spectra (aqueous-ethanol solution, 20 °C) of dications **4a—f** and monocations **2a—f**

R	4			2			pK_a*
	p$K_{a,1}$	ν	ε	p$K_{a,2}$	ν	ε	
a	(−2.0)	—	—	3.50±0.02	25620	12100	4.76
b	−1.6±0.1	25040	27000	3.81±0.01	24380	23650	6.08
c	(−1.4)	—	—	3.95±0.01	24280	25850	6.26
d	−0.57±0.03	20620	29000	4.70±0.01	20260	57400	9.19
e	−0.15±0.03	19780	49900	5.09±0.01	19420	56500	9.46
f	(−2.3)	—	—	3.19±0.02	25260	12600	—

Note. The p$K_{a,1}$ values for compounds **4a,c,f** (presented in parentheses) were estimated using the found satisfactory correlation between p$K_{a,1}$ and p$K_{a,2}$. pK_a* are the pK_a values of *N*-phenyl-2-imino-2*H*-chromenes in the electron-excited state.

Table 3. Calculated heats of formation (ΔH_f) for compounds **3a—f** and alternative cationic forms **2A** and **2B** and their difference ($\delta\Delta H_f$) (by the data of quantum-chemical calculation by the PM3 method)

R	ΔH_f/kcal mol^{-1}			$\delta\Delta H_f$	
	2A	**2B**	**3**	for **3** and **2A**	for **3** and **2B**
a	231.10	234.47	97.52	133.58	136.95
b	185.98	188.80	53.29	132.69	135.51
c	191.30	194.46	58.91	132.39	135.55
d	214.25	216.69	84.50	139.75	132.19
e	210.29	212.72	81.45	128.84	131.27
f	241.24	245.36	105.33	135.91	140.03

Table 4. Calculated heats of formation (ΔH_f) for cations **2Aa** and **2Ba** and their difference ($\delta\Delta H_f$) in media with different dielectric constants (ε)

ε (medium)	ΔH_f/kcal mol^{-1}		$\delta\Delta H_f$
	2Aa	**2Ba**	
1 (vacuum)	231.10	234.47	3.37
10 (dichloroethane)	188.29	194.03	5.74
25 (ethanol)	183.53	189.53	6.00
55 (ethanol—water)	181.64	187.81	6.17
79 (water)	181.18	187.35	6.17

The $\delta\Delta H_f$ values for neutral form **3** and cations **2A** and **2B** also correlate linearly to the σ^+ constants of substituents R (r = 0.971, s = 0.22, ρ = 2.02 (for **3** and **2A**); r = 0.961, s = 0.30, ρ = 2.33 (for **3** and **2B**)).

The pK_a values of *N*-phenyl-2-imino-2*H*-chromenes in the electron-excited state (pK_a*) were estimated using the Forster method[9] (see Table 2). The plots of pK_a* *vs.* σ^+ constants of substituents in the studied series of compounds in comparison with similar plots for iminochromenes **1** (protonation at the imino group) and coumarins **5** (protonation at the imidazole cycle) are presented in Fig. 1.[10] Their comparison shows that the character of the electronic influence of the substituents on the basicity of compounds **3** in the excited state is similar to that for coumarins **5** (curves with saturation). This fact also indicates the protonation of the imidazole cycle in the compounds under study.

The study of hydrolysis of compound **3a** showed that the uncharged form **3** does not virtually undergo hydroly-

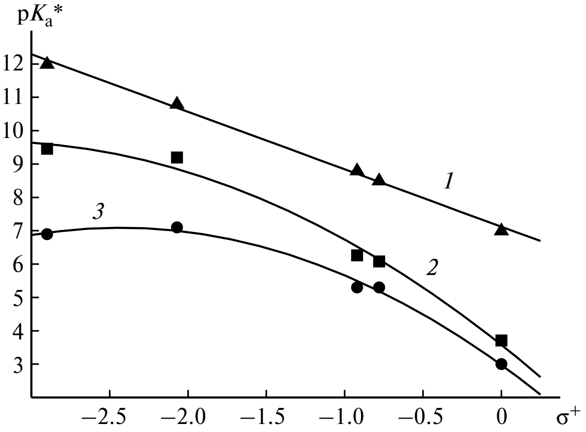

Fig. 1. Plots of pK_a for compounds in the electron-excited state (pK_a*) of iminochromenes **1** (*1*), *N*-phenyl-2-imino-2*H*-chromenes **3** (*2*), and coumarins **5** (*3*) *vs.* σ^+ constants of substituents.

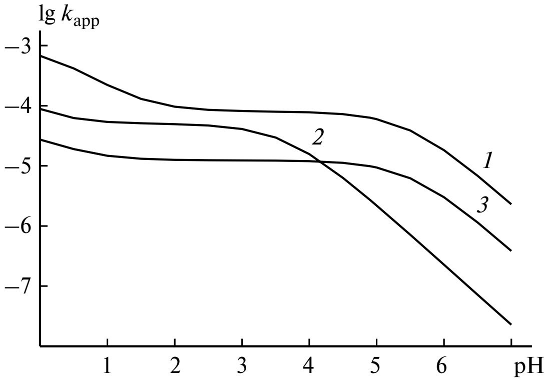

Fig. 2. Plots of the apparent rate constants of hydrolysis (k_{app}) of compounds **1a** (*1*), **3a** (*2*), and **8a** (*3*) *vs.* pH of the medium.

sis, like that in 2-imino-2*H*-chromenes **1**, and the hydrolysis rate constants of both the corresponding monocations ($k = 5 \cdot 10^{-5}$ s^{-1} (**2a**) and $8 \cdot 10^{-5}$ s^{-1} (**6a**)) and dications ($k = 1.3 \cdot 10^{-3}$ s^{-1} (**4a**) and $1.0 \cdot 10^{-3}$ s^{-1} (**7a**)) are very close. Therefore, the presence of the aromatic substituent at the amino group of cations **2** and **4** does not increase their stability in comparison with unsubstituted cations **6** and **7**. Thus, due to the low basicity, *N*-phenyl-2-imino-2*H*-chromenes are stable in a wider pH interval than iminochromenes **1**. Compounds **3** are not hydrolyzed on boiling in aqueous-ethanol solutions, whereas short-time boiling in dilute acetic acid (1 : 1) results in their hydrolysis to form the corresponding coumarins in ~100% yield. The plots of the hydrolysis rates of compound **1a** and its *N*-methyl- and *N*-phenyl-substituted derivatives *vs.* acidity of their aqueous-alcohol solutions (Fig. 2) show that the introduction of the aryl group allows the extension of the stability interval to the acidic region by 2—2.5 pH units for compounds of the considered class.

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Received July 14, 2001;
in revised form March 5, 2002