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SYNTHESIS, SPECTRAL-LUMINESCENCE, AND ACID-BASE PROPERTIES OF 3-FLUORO-7-DIALKYLAMINOCOUMARINS

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The corresponding 3-fluoro-substituted coumarins were obtained by reactions of 7-diethylaminocoumarin, 2,3,6,7-tetrahydro-1H,5H-quinolizino[9,9a,1-gh]coumarin, and 2,3,6,7-tetrahydro-9-methyl-1H,5H-quinolizino[9,9a,1-gh]coumarin with XeF_2 , $FClO_3$, or N-fluoropyridinium tetrafluoroborate. A strong mesomeric effect of the fluorine atom on the 7-amino group was established as a result of a study of the absorption and fluorescence spectra and the acid-base properties of the synthesized compounds.

We have previously reported [1] methods for the synthesis of various 3-chloro-, 3-bromo-, and 3-iodo-7aminocoumarins. It was found that 3-halo-7-aminocoumarins are rather interesting substances: the 3-iodo derivatives are useful synthones in photochemical reactions [2-4] and nucleophilic substitution reactions [5]; 3-chloro-7aminocoumarins have intense fluorescence and show promise as laser dyes [1, 6].

In this connection we felt it would be particularly interesting to study 3-fluoro-7-aminocoumarins, for which one might expect high fluorescence quantum yields and increased photostability. In addition, it was desirable to ascertain what effect the fluorine atom — a highly electronegative element that has simultaneously a strong +M effect [7] — has on the acid-base characteristics of 7-aminocoumarins.

The most promising method for the synthesis of 3-fluoro-7-aminocoumarins was the direct introduction of a fluorine atom into the 3 position.

For this we studied the reaction of coumarins I-IV with various fluorinating reagents: XeF_2 , FCIO₃, VF₅, and N-fluoropyridinium tetrafluoroborate. One might have expected that the high tendency of 7-aminocoumarins to undergo one-electron oxidation [8] in conjunction with the oxidative properties of the series of listed reagents would lead to the realization of processes that take place with electron transfer and make it possible to accomplish regioselective substitution at the C₍₃₎ atom [9].



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Com- pound	Empirical formula	mp, °C	R _j *	$\frac{ \text{IR spe} }{v, cm}$	c=c	Con- ver- sion,	Yield, % **
V VI VII	$\begin{array}{c} C_{13}H_{14}FNO_2\\ C_{14}H_{16}FNO_2\\ C_{15}H_{14}FNO_2 \end{array}$	106 101 147 dec.	0,25 0,19 0,13	1735 1720 1730	1635 1625 1615	30 40 25	27 15 22
VIII IX X	$\begin{array}{c} C_{16}H_{16}FNO_2\\ C_{14}H_{16}FNO_2\\ C_{14}H_{15}F_2NO_2 \end{array}$	183 87 113	0,12 0,12 0,27	1710 1715 1720	1620 1620 1610	20 40 40	20 19 6

TABLE 1. Physicochemical Characteristics of Coumarins V-X

*The R_f values were measured on Silufol plates in benzene. **For the reactions with XeF_2 .

TABLE 2. PMR Spectra of Coumarins V-X in CDCl₃

	Chemical shifts, δ , ppm (SSCC, Hz)						
Com- pound					NGU		NCH2CH2CH2-C74
pound	4-R (9-R)	5-H (8-H)	6-H	8 H	NCH ₂	NCH ₂ CH ₂ R	NCH ₂ CH ₂ CH ₂ -C _{12b}
v	7,24 (d. $J=9,0$)	7,28 (d, J = 9,0)	6.72 (dd, $J = -0.025$)	$ \begin{array}{c} 6,60 & (d) \\ J=2,5) \end{array} $	$\begin{vmatrix} 3,40 \\ (q J = 7,0) \end{vmatrix}$	1,20 (t, J=7,0)	
VI	2,34 (d, J=2,8)	7,39 (d., J = 9,0)	6,85 (dd $J = 90.25$)	$\begin{array}{c} 6,67 \ (d, J=2,5) \end{array}$	3.41 (q, $J=7,0$)	1.21 (t, J=7,0)	
VII	7,23 (d, $J = 9,0$)	6,90 s		-	3,28 (t, $J = 6,3$); 3,31	2,12 m	2,83 (t, $J = 6,3$) 2,93 (t, $J = 6,3$)
VIII	2,45 (br s)	6,99 s		-	(t, J=6,3) 3,25 (t, J=6,3)	1,98m	2,79 (t, $J=6,3$) 2,87 (t, $J=6,3$)
IX*	2,32 (d $J = 1,3$)	7,14 (d, J=14,0)	_	$\begin{array}{c} 6,70 \ (d, J=8,0) \end{array}$	3,37 (q. d, $J = 7,0;$ J = 1,3)	1,19 (t J = 7,0)	
Х	2,31 (d, J=3,0)	7,13 (d, $J = 14,0$)		6,78 (d, J=8,0)	$\begin{array}{c} 3,38\\ (q. d. J = 7,0;\\ J = 1,3) \end{array}$	$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	

*The signal of the 3-H atom is found at 6.08 ppm (d, J = 1.3 Hz).

The reactions were carried out in a dry atmosphere (N_2) in the cold in solution in acetonitrile, methylene chloride, or carbon tetrachloride. It was established that the use of XeF₂ and FClO₃ is the most effective method. Intense colorization of the reaction mixture, which attests to the formation of ion radicals [10], was observed when these reagents were added to solutions of the starting 7-aminocoumarins. Despite the mild conditions, the fluorination reactions were not selective even in the initial stages and were accompanied by significant resinification. Nevertheless, we were able to isolate 3-fluorocoumarins V-VIII (Table 1) from the reaction mixtures. To increase the regioselectivity of the reactions we tested various catalysts, viz., Lewis acids, tertiary amines, KF, etc., and also varied the reagent ratios. We found that catalysis is ineffective and that it is best to carry out the reactions with significant dilution in acetonitrile with cooling and slow addition of the fluorinating agent; the yields of V-VIII in this case ranged from 15% to 30%.

In the case of coumarin II we made a detailed study of the composition of the reaction mixture. In addition to the desired 3-fluorocoumarin V we isolated yet another monofluoro derivative, viz., 6-fluorocoumarin IX, which was obtained in somewhat higher yield than V. The primary fluorination by xenon difluoride in the ortho position relative to the amino group is also known for other aromatic amines [11]. Polyfluorination products, viz., coumarin X and, in trace amounts according to PMR data, 3,6,8-trifluoro-4-methyl-7-diethylaminocoumarin (XI), are also formed during the reaction. Another side product is 4-methyl-7-ethylaminocoumarin (XII) [6], the yield of which reaches 30%.

The fluorination of coumarins I-IV with N-fluoropyridinium tetrafluoroborate gives a similar set of products but with lower yields of the 3-fluorocoumarins. The primary products of the reaction of I and II with VF_5 are the corresponding N-deethylated derivatives, while coumarins III and IV do not react with VF_5 .

An increase in the regioselectivity of ion-radical and electrophilic substitution reactions in 7-aminocoumarins in the presence of $ZnCl_2$ was noted in [6, 9]. In the series of reactions under consideration the addition of catalytic

amounts of zinc chloride to the reaction media led to a decrease in the percentage of the N-de-ethylation product, but, simultaneously with this, the ratio of the mono- and polyfluorination products increased to favor the latter.

The structures of V-VIII follow from the PMR spectra, in which signals of 3-H (10-H) protons, which usually appear at 5.5-6.0 ppm [12], are absent. The locations and structures of the signals of the remaining aromatic protons are similar to those for other 3-halo-substituted 7-aminocoumarins [1]. Constants of spin-spin coupling of the fluorine atom with the protons of the CH₃ group (${}^{4}J_{F,H} \approx 3$ Hz) can be observed in the spectra of VI and X. The ${}^{3}J_{F,H}$ vicinal spin-spin coupling constants (SSCC) in the spectra of coumarins V, VII, IX, and X have the usual values for fluorinated aromatic derivatives (9-14 Hz). Long-range ${}^{6}J_{6-F,4-CH_3}$ and ${}^{5}J_{6-F,NCH_2}$ SSCC are also observed in the spectra of coumarins IX and X (Table 2).

In the case of coumarins VII-X we also studied the mass spectra, in which we observed an intense molecular-ion peak (relative intensity 75-100%). The subsequent scheme of fragmentation of VII-X under electron-impact conditions is typical for most 7-aminocoumarins [13] and includes realization of the $[M - CH_3]^+$, $[M - CH_3 - C_2H_5]^+$, $[M - CH_3 - C_2H_5 - NCH_3]^+$, $[M - CH_3 - C_2H_5 - NCH_3 - C_0]^+$, and $[M - CH_3 - C_2H_5 - NCH_3 - CO]^+$ processes for the 7-diethylamino derivatives and contraction of the hydrogenated six-membered rings of the $[M - C_2H_4]^+$, $[M - C_2H_4 - C_2H_4]^+$ type for the quinolizine derivatives.

The formation of 3-fluorocoumarins V-VIII is evidently the result of the occurrence of ion-radical reactions in which the investigated fluorinating reagents act as one-electron oxidizing agents. Thus, for example, in the case of XeF_2 the mechanism of the process may include a step involving the generation of cation radicals Ia-IVa (1) and a step involving their fluorination (3) on reaction with an XeF particle [14] with subsequent elimination of a proton:



The development of side compounds IX-XI in the case of coumarin II is quite typical for the reactions of XeF_2 , which are usually unselective and may be accompanied by the formation of oxidation products [14].

The electronic spectra of 3-fluoro derivatives V-VIII recorded in ethanol or acetonitrile (see Table 3) contain a long-wave absorption band at 370-400 nm and an emission band at 460-505 nm. A comparison of the UV spectra of V-VIII and other 3-halo-7-aminocoumarins [1] indicates an appreciable difference in the spectral characteristics of the 3-fluoro derivatives, for which the long-wave maximum is shifted to the short-wave region ($\Delta \lambda_{max}^{ab} \approx 15$ nm). In this respect 3-fluoro-7-aminocoumarins are most similar to the starting I-IV [15], and, consequently, in the series of other halogens the fluorine atom participates most effectively in p, π conjugation, hindering charge transfer from the 7-amino group to the pyrone ring in the ground state [16]. On the other hand, the emission maxima of the investigated 3-fluoro derivatives virtually coincide with the fluorescence maxima of the corresponding 3-chlorocoumarins [1]. The fluorescence quantum yields of V-VIII have high values (0.7-0.9), which makes it possible to regard these compounds as effective luminophores.

The introduction of a fluorine atom into the 6 position in IX and X is accompanied by a rather pronounced shift of the absorption bands (of the emission band for coumarin X) to the short-wave region as compared with coumarins V-VIII. A similar effect is observed for 6- and 8-chloro-substituted 7-aminocoumarins [1] and may be associated with a decrease in the capacity of the 7-dialkylamino group for charge transfer as a consequence of steric or electronic perturbation.

We also studied the acid-base properties of coumarins V-X in aqueous ethanol solutions (1:1). We found (Table 4) that the pK_a values of the conjugate acids of V-VIII in a series of related 3-halo-7-aminocoumarins are maximal and exceed even the pK_a values of unsubstituted coumarins I-IV [15]. The character of the observed spectral changes makes it possible to assert that primary protonation involves the nitrogen atom in the 7 position [15]. The increased basicities of 3-fluorocoumarins is evidently a consequence of the strong +M effect of the fluorine atom, which at rather long distances exceeds the -I effect of this substituent. The pK_a^* values of the examined compounds, calculated by the Forster method, are also presented in Table 4. The low negative pK_a^* values of coumarins V-X are also characteristic for other 7-aminocoumarin dyes and are due to marked charge separation during excitation of these molecules [16].

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Com-	Solvent		Fluorescence	
pound		Absorption, λ_{max} nm (log ε)	λ _{max} , nm	quantum yield ($arphi_{\mathrm{f}}$)
V VI	C2H5OH CH3CN C2H5OH	246 (4,14); 258 (4,20); 310 (3,59); 382 (4,37) 247 (4,07); 259 (4,11); 324 (3,72); 377 (4,36) 248 (4,24); 280 (3,42); 308 (3,62); 322 (3,74); 376	485 470 476	0,59 0,79 0,75
	CH₃CN	(4,34) 244 (4,31); 254 (4,30); 280 (3,73); 306 (3,82); 320 (3,93): 370 (4,45)	460	0,80
VII	C ₂ H ₅ OH	(3,76); (259) (3,72); 312 (3,34); 330 (3,44); 392 (4,00)	505	0,72
	CH ₃ CN	252 (3,87); 265 (3,86); 316 (3,37); 330 (3,45); 396 (4,17)	495	0,58
VIII	C ₂ H ₅ OH	257 (4,02); 262 (4,02); 290 (3,51); 317 (3,93); 403 (4,33)	495	0,83
IX X	CH ₃ CN C ₂ H ₅ OH CH ₃ CN C ₂ H ₅ OH CH ₃ CN	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	480 450 440 480 470	$ \begin{vmatrix} 0.70 \\ < 0.10 \\ < 0.10 \\ < 0.10 \\ < 0.10 \\ < 0.10 \end{vmatrix} $
	r			1

TABLE 3. Spectral-Luminescence Properties of Coumarins V-X

TABLE 4. Acid-Base Properties ofCoumarins V-X in Aqueous EthanolSolutions (1:1)

Com pound	Absorp $\frac{\lambda_{max}}{neutral}$ mole-	tion, nm cat- ion	pK_a	р <i>К_а*</i>			
V VI VII VIII IX X	393 384 405 416 375 370	306 306 316 324 308 303	1,99 2,06 0,31 0,11 2,05 2,22	$-13,63 \\ -12,28 \\ -14,46 \\ -14,44 \\ -10,36 \\ -10,45$			

Measurement of the pK_a values for coumarins IX and X showed that the introduction of a fluorine atom into the 6 position also leads to an additional increase in the basicity. Thus the short-wave shift of the absorption and emission maxima observed in the electronic spectra for coumarins IX and X should be associated precisely with the steric hindrance that is created by the o-fluoro atom and leads to partial rotation of the diethylamino group about the $C_{(7)}$ —N axis. In this case IX and X upon excitation should be inclined to transition to the nonfluorescing TICT state [17]. The weak fluorescence of these coumarins is an indirect confirmation of this.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Perkin-Elmer 577 spectrometer. The UV and fluorescence spectra were obtained with a Hitachi EPS-3T spectrophotometer with a G-3 luminescence adapter. The fluorescence was excited by irradiation at the long-wave absorption band of the corresponding coumarin. The relative fluorescence quantum yields were determined with respect to 3-aminophthalimide [18]. The NMR spectra of solutions in $CDCl_3$ were obtained with a Bruker WM-250 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were obtained with a Varian MAT-311A spectrometer at an ionizing voltage of 70 eV.

The pK_a values were determined by the method in [19] in 50% alcohol solutions with an \pm V-74 universal pH meter with glass and calomel electrodes (the error in the determination was \pm 0.04).

The reaction products were isolated with columns (40 by 2.5 cm) packed with Silpearl sorbent in benzene and benzene—hexane systems. The purity of the substances was monitored by TLC on Silufol plates with development by UV light and iodine. The conversion was determined from the residual unchanged coumarin after chromatography of the reaction mixture.

The results of elementary analysis of the synthesized compounds for C, H, and N were in agreement with the calculated values.

General Method for Obtaining Coumarins V-X. A solution of 3.5 mmole of XeF_2 (or 4 mmole of $FClO_3$) in 50 ml of acetonitrile (dichloroethane) was added dropwise with stirring and cooling to 0°C to a solution of 3.5 mmole of starting coumarins I-IV in 200-300 ml of acetonitrile, and the mixture was stirred for 0.5 h. It was then evaporated; and the residue was separated by chromatography. The isolated products were crystallized from hexane—acetone.

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