# SYNTHESIS, SPECTRAL-LUMINESCENCE, AND ACID-BASE PROPERTIES OF 3-HALO-7-AMINOCOUMARINS

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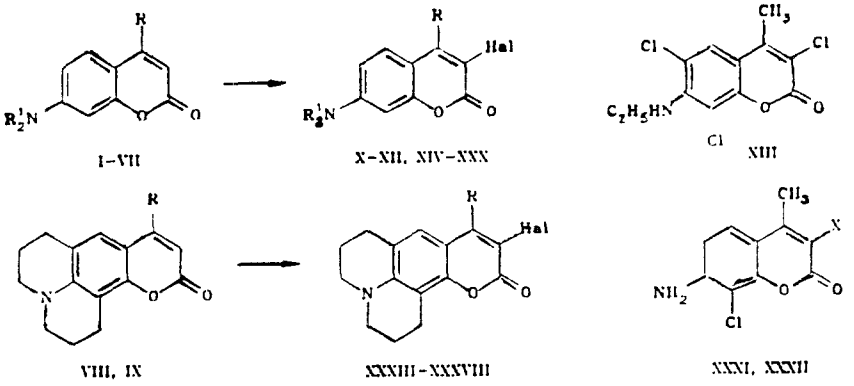
*The reactions of substituted coumarins with a variety of halogenating agents, leading to the formation of the corresponding 3-chloro-, 3-bromo-, and 3-iodo-7-aminocoumarins, have been studied. It has also been shown, based on the results of studies of the spectral-luminescence and acid–base characteristics of these 3-halo-7-aminocoumarins, that their basicity increases as the electron-donating nature of the substituent in the 4-position increases, and is also greater, as expected, for 3-iodo- and 3-chloro derivatives than for 3-bromo derivatives.*

We have previously reported several representatives of the class of 3-halo-7-aminocumarins, such as 3-chloro-, 3-bromo-, and 3-iodo-4-methyl-7-diethylaminocoumarin [1], which were prepared by treatment of 4-methyl-7-diethylaminocoumarin (I) with copper halides or with iodine, respectively. Our interest in these compounds arises from the fact that 3-iodo-4-methyl-7-diethylaminocoumarin is a convenient synthon in photochemical substitution reactions [2-4], and that 3-chloro-4-methyl-7-diethylaminocoumarin exhibits intense fluorescence and is thus a promising potential laser dye [1]. We were also interested in the specific nature and characteristics of the spectral-luminescence properties of other 3-halo derivatives, such as the degree of correlation, if any, between the quenching effect of a heavy atom (Cl, Br, and I) and dye structure [5].




I, VII, VIII, X—XII, XXVIII—XXX, XXXIII—XXXV R=$CH_3$; II, XIV—XVI R=H; III, XVII, XVIII R=$NHCH_2C_6H_5$; IV, XIX—XXI R=$N(CH_2CH_2)_2O$; V, IX, XXII—XXIV, XXXVI—XXXVIII R=Cl; VI, XXV—XXVII R=$CH(COCH_3)_2$; I—VI, X—XII, XIV—XXVII $R^1$=$C_2H_5$; VII, XXVIII—XXX $R^1$=H; X, XIV, XVII, XIX, XXII, XXV, XXVIII, XXXIII, XXXVI Hal=Cl; XI, XV, XVIII, XX, XXIII, XXVI, XXIX, XXXIV, XXXVII Hal=Br; XII, XVI, XXI, XXIV, XXVII, XXX, XXXV, XXXVIII Hal=I, XXXI X=H; XXXII X=Cl

In the present paper we have carried out the directed synthesis of 3-halo derivatives of a series of 7-aminocoumarins II-IX with a variety of substituents in the 4- and 7-positions. In order to develop an optimum procedure or conditions (for halogenation), we examined the activity of coumarins II-IX with several halogenating agents [halogens, N-chloro- and N-bromosuccinimide, copper(II) chloride and bromide, and chlor- and bromanil] in different solvents, for example acetonitrile, 1,4-dioxane, nitromethane, pyridine, methylene chloride, carbon tetrachloride, acetic acid, and 50% sulfuric acid. In some examples

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TABLE 1. Physical Chemical Characteristics of Compounds X-XXXVIII

| Compound | Empirical formula | $T_{mp}$, °C | $R_f$* | IR spectra ν, $cm^{-1}$ | | Yield, % |
|---|---|---|---|---|---|---|
| | | | | C=O | C=C | |
| X** | $C_{14}H_{16}ClNO_2$ | 108 | 0,24 | 1715 | 1615 | 92 |
| XI** | $C_{14}H_{16}BrNO_2$ | 93 | 0,20 | 1710 | 1610 | 96 |
| XII** | $C_{14}H_{16}INO_2$ | 114 | 0,20 | 1700 | 1610 | 95 |
| XIII | $C_{12}H_{10}Cl_3NO_2$ | 136 | 0,68 | 1735 | 1630 | 60 |
| XIV | $C_{13}H_{14}ClNO_2$ | 121 | 0,44 | 1700 | 1615 | 70 |
| XV | $C_{13}H_{14}BrNO_2$ | 137 | 0,32 | 1695 | 1620 | 90 |
| XVI | $C_{13}H_{14}INO_2$ | 157 | 0,43 | 1740 | 1625 | 90 |
| XVII | $C_{20}H_{21}ClN_2O_2$ | 163 | 0,06 | 1670 | 1620 | 93 |
| XVIII | $C_{20}H_{21}BrN_2O_2$ | 138 (dec.) | 0,06 | 1670 | 1620 | 80 |
| XIX | $C_{17}H_{21}ClN_2O_3$ | 150 | 0,08 | 1710 | 1615 | 95 |
| XX | $C_{17}H_{21}BrN_2O_3$ | 139 (dec.) | 0,10 | 1700 | 1610 | 82 |
| XXI | $C_{17}H_{21}IN_2O_3$ | 145 (dec.) | 0,12 | 1700 | 1610 | 70 |
| XXII | $C_{13}H_{13}Cl_2NO_2$ | 101 | 0,51 | 1720 | 1615 | 75 |
| XXIII | $C_{13}H_{13}BrClNO_2$ | 88 | 0,49 | 1725 | 1625 | 94 |
| XXIV | $C_{13}H_{13}ClINO_2$ | 130 | 0,51 | 1715 | 1610 | 90 |
| XXV | $C_{18}H_{20}ClNO_4$ | 143 | 0,32 | 1735 | 1615 | 78 |
| XXVI | $C_{18}H_{20}BrNO_4$ | 148 | 0,32 | 1730 | 1615 | 80 |
| XXVII | $C_{18}H_{20}INO_4$ | 170 | 0,35 | 1710 | 1615 | 76 |
| XXVIII | $C_{10}H_8ClNO_2$ | 268 | 0,08 | 1700 | 1620 | 68 |
| XXIX | $C_{10}H_8BrNO_2$ | 206 (dec.) | 0,12 | 1700 | 1620 | 92 |
| XXX | $C_{10}H_8INO_2$ | 210 (dec.) | 0,08 | 1725 | 1610 | 43 |
| XXXI | $C_{10}H_8ClNO_2$ | 208 | 0,07 | 1700 | 1620 | 35 |
| XXXII | $C_{10}H_7Cl_2NO_2$ | 222 | 0,16 | 1720 | 1615 | 28 |
| XXXIII | $C_{16}H_{16}ClNO_2$ | 178 | 0,24 | 1710 | 1615 | 85 |
| XXXIV | $C_{16}H_{16}BrNO_2$ | 155 (dec.) | 0,24 | 1700 | 1610 | 88 |
| XXXV | $C_{16}H_{16}INO_2$ | 182 | 0,24 | 1690 | 1615 | 82 |
| XXXVI | $C_{15}H_{13}Cl_2NO_2$ | 179 | 0,23 | 1715 | 1610 | 75 |
| XXXVII | $C_{15}H_{13}BrClNO_2$ | 159 (dec.) | 0,24 | 1700 | 1610 | 92 |
| XXXVIII | $C_{15}H_{13}ClINO_2$ | 214 | 0,25 | 1695 | 1610 | 85 |

*Benzene–acetone, 40:1.

**Melting point and IR spectral data were consistent with the literature [1].

additives were also used, namely zinc chloride, tertiary amines, and hydrogen peroxide. The most convenient and effective reagents for the selective introduction of a chlorine atom in the 3-position in 7-aminocoumarins were found to be N-chlorosuccinimide and $CuCl_2$. For instance, coumarins X, XIV, XVII, XIX, and XXXVI were obtained in 70-95% yields (Table 1) upon reaction (of the appropriate coumarin) with a small excess (1.5 equiv) of N-chlorosuccinimide in acetonitrile.

Coumarins V, VI, and VIII could be converted most conveniently to their 3-monochlorosubstituted derivatives by refluxing in acetonitrile in the presence of $CuCl_2$. 3-Chloro-4-methyl-7-aminocoumarin (XXVIII) could not be prepared by either of these methods, however. The principal products of the chlorination of compound VII under these conditions were the 8-monochloro derivative (XXXI) and the 3,8-dichlorosubstituted derivative XXXII. The formation of the 3,8-dihalogenation product was also observed, based on PMR spectral data, upon chlorination of cumarin II. Nevertheless, we were able to prepare compound XXVIII upon treatment of coumarin VII with copper(II) chloride in nitromethane solvent in the presence of $ZnCl_2$. The activating effect of zinc chloride has been noted previously in the case of electrophilic substitution reactions of a series of 7-aminocoumarins [1, 6]. Substantially poorer results were obtained with the other chlorinating agents for the synthesis of 3-chlorocoumarin derivatives: chloranil did not react with coumarins I-IX, while chlorination with elemental chlorine was accompanied by the formation of polychlorination products (for example, compound XIII) and N-deethylation.

In contrast to the chlorination results, bromination of coumarins I-IX was found to occur completely, selectively, and rapidly with all of the brominating agents examined, with the exception of bromanil. The most convenient or efficient choice from a preparative standpoint involves the use of an equimolar amount of N-bromosuccinimide in acetonitrile.

Introduction of an iodine atom in the 3(10)-position in coumarins I, II, IV-VI, VIII, and IX was achieved by reaction of these compounds with excess iodine indioxane in the presence of pyridine. Iodination of coumarin VII under these conditions did not occur, but the corresponding iodo derivative was obtained upon reaction with iodine in nitromethane solvent in the presence of $ZnCl_2$ and pyridine. 3-Iodo-4-(N-benzylamino)-7-diethylaminocoumarin could not be isolated due to its extreme instability. In an attempt to achieve an independent synthesis of this compound from coumarin XXIV and benzylamine [7]

TABLE 2. PMR Spectra of Halocoumarins XIV-XXXII in $CDCl_3$.

| Compound | δ, ppm (SSCC, J Hz) | | | | | |
|---|---|---|---|---|---|---|
| | 5-H (d, J=9,0) | 6-H, d.d | 8-H (d, J=2,5) | N—$CH_2$ (q, J=7,0) | $NCH_2CH_3$ (t, J=7,0) | other protons |
| XIV | 7,20 | 6,58 | 6,47 | 3,40 | 1,20 | 7,68 (1H, s, 4-H) |
| XV | 7,20 | 6,59 | 6,47 | 3,40 | 1,20 | 7,88 (1H, s, 4-H) |
| XVI | 7,20 | 6,63 | 6,52 | 3,41 | 1,21 | 8,12 (1H, s, 4-H) |
| XVII | 7,58 | 6,60 | 6,54 | 3,38 | 1,20 | 4,90 (2H, d, J=6,0, $CH_2$); 5,50 (1H, br.s, NH); 7,30 ... 7,46 (5H, m, $C_6H_5$) |
| XVIII | 7,57 | 6,52 | 6,48 | 3,39 | 1,19 | 4,90 (2H, d, J=6,0, $CH_2$); 5,50 (1H, br.s, NH); 7,30 ... 7,44 (5H, m, $C_6H_5$) |
| XIX | 7,50 | 6,65 | 6,52 | 3,41 | 1,20 | 3,52 (4H, t, J=4,5, $2CH_2$); 3,88 (4H, t, J=4,5, $2CH_2$) |
| XX | 7,52 | 6,57 | 6,46 | 3,40 | 1,20 | 3,52 (4H, t, J=4,5, $2CH_2$); 3,90 (4H, t, J=4,5, $2CH_2$) |
| XXI | 7,56 | 6,55 | 6,46 | 3,38 | 1,20 | 3,50 (4H, t, J=4,5, $2CH_2$); 3,91 (4H, t, J=4,5, $2CH_2$) |
| XXII | 7,61 | 6,68 | 6,50 | 3,43 | 1,23 | — |
| XXIII | 7,60 | 6,64 | 6,48 | 3,43 | 1,21 | — |
| XXIV | 7,61 | 6,60 | 6,46 | 3,43 | 1,21 | — |
| XXV | 7,17 | 6,65 | 6,59 | 3,44 | 1,23 | 1,94 (6H, s, $2CH_3$) |
| XXVI | 7,19 | 6,62 | 6,57 | 3,43 | 1,22 | 1,93 (6H, s, $2CH_3$) |
| XXVII | 7,20 | 6,57 | 6,54 | 3,40 | 1,22 | 1,90 (6H, s, $2CH_3$) |
| XXVIII | 7,50 | 6,62 | 6,58 | — | — | 2,51 (3H, s, $CH_3$); 4,20 (2H, s, $NH_2$) |
| XXIX | 7,42 | 6,59 | 6,55 | — | — | 2,55 (3H, s, $CH_3$); 4,20 (2H, s, $NH_2$) |
| XXX | 7,39 | 6,51 | 6,49 | — | — | 2,56 (3H, s, $CH_3$); 4,20 (2H, s, $NH_2$) |
| XXXI | 7,30 | 6,68* | — | — | — | 2,36 (3H, s, $CH_3$); 4,50 (2H, s, $NH_2$); 6,06 (1H, s, 3-H) |
| XXXII | 7,02 | 6,33* | — | — | — | 2,00 (3H, s, $CH_3$); 6,00 (2H, s, $NH_2$) |

*Doublet, J = 9.0 Hz.

TABLE 3. PMR Specta of Halocoumarins XXXIII-XXXVIII in $CDCl_3$

| Compound | δ, ppm (SSCC, J Hz) | | | | | |
|---|---|---|---|---|---|---|
| | 8-H, s | N—$CH_2$, m | $CH_2$—$C_{(7a)}$ (t, J=6,0) | $CH_2$—$C_{(12b)}$ (t, J=6,0) | $NCH_2CH_2$, m | $CH_3$, s |
| XXXIII | 7,02 | 3,29 | 2,81 | 2,88 | 2,02 | 2,46 |
| XXXIV | 7,00 | 3,25 | 2,77 | 2,86 | 1,97 | 2,47 |
| XXXV | 7,03 | 3,24 | 2,77 | 2,86 | 1,95 | 2,54 |
| XXXVI | 7,18 | 3,29 | 2,80 | 2,86 | 2,02 | — |
| XXXVII | 7,20 | 3,30 | 2,80 | 2,87 | 1,98 | — |
| XXXVIII | 7,21 | 3,28 | 2,77 | 2,88 | 1,97 | — |

the 3-iodo derivative was detected in the reaction mixture in only trace amounts, with the principal product being the result of dehalogenation, namely 4-N-benzylaminocoumarin III.

Retention of the coumarin structure in compounds X-XXXVIII was confirmed by the presence in their IR spectra of the lactone carbonyl absorption band in the region 1670-1740 $cm^{-1}$, as well as by the presence of C=C bond absorption in the 1610-1630 $cm^{-1}$ range. The C–Cl, C–Br, and C–I bond stretching vibrations appear in the 500-750 $cm^{-1}$ region (Table 1).

The aromatic protons (5-H, 6-H, and 8-H) in the PMR spectra of coumarins XIV-XXX and XXXII-XXXVIII are observed in their normal frequency interval and with characteristic SSCC values [8, 9] (Tables 2 and 3). The presence of a halogen atom in the 3-position (or in the 10-position in the case of the julolidine derivatives XXXIII-XXXVIII) is inferred from the absence of 3-H proton (10-H) signals, which are generally at 5-6 ppm [8]. Similarly, the PMR spectrum of compound XXXI leads us to conclude that substitution has occurred in the 8-position of the coumarin structure. In the PMR spectrum of compound XXXII the only downfield signals observed are doublets for 5-H and 6-H, while in the case of coumarin XIII the only downfield signal is a singlet for the 5-H proton. The absence of methine proton signals in the spectra of the halogen-substituted derivatives XXV-XXVII in $CDCl_3$ solution can be explained apparently in terms of dynamic prototropic tautomerization processes, which has been noted previously for other 4-methyl bifunctional 7-aminocoumarin-substituted derivatives [9].

TABLE 4. Spectral Luminescence Properties of Halocoumarins XIII-XXXVIII

| Compound | Solvent | Absorption $\lambda_{max}$, nm (log ε) | Fluorescence λ, nm | | $\varphi_f$* |
|---|---|---|---|---|---|
| | | | exc | max | |
| XIII | $C_2H_5OH$ | 246 (4,19), 316 (3,95), 360 (4,34) | 360 | 457 | 0,30 |
| | $CH_3CN$ | 246 (4,18), 316 (3,89), 357 (4,35) | 360 | 445 | 0,64 |
| XIV | $C_2H_5OH$ | 256 (4,10), 310 (3,40), 325 (3,51), 398 (4,41) | 400 | 485 | 0,69 |
| | $CH_3CN$ | 255 (4,08), 310 (3,42), 325 (3,52), 393 (4,36) | 400 | 475 | 0,72 |
| XV | $C_2H_5OH$ | 255 (4,20), 310 (3,52), 324 (3,59), 400 (4,50) | 400 | 482 | 0,50 |
| | $CH_3CN$ | 255 (4,15), 310 (3,54), 325 (3,62), 395 (4,47) | 400 | 474 | 0,50 |
| XVI | $C_2H_5OH$ | 256 (4,30), 310 (3,85), 325 (3,63), 400 (4,60) | — | — | — |
| XVII | $C_2H_5OH$ | 255 (4,27), 290 (4,34), 365 (4,38) | 365 | 450 | 0,32 |
| | $CH_3CN$ | 253 (4,24), 288 (4,25), 366 (4,45) | 365 | 450 | 0,10 |
| XVIII | $C_2H_5OH$ | 254 (4,28), 290 (4,34), 365 (4,50) | 365 | 450 | 0,23 |
| | $CH_3CN$ | 253 (4,29), 288 (4,31), 356 (4,47), 365 (4,50) | 365 | 450 | 0,10 |
| XIX | $C_2H_5OH$ | 260 (4,21), 316 (4,05), 384 (4,41) | 380 | 476 | 0,22 |
| | $CH_3CN$ | 260 (4,23), 316 (4,12), 380 (4,47) | 380 | 466 | 0,10 |
| XX | $C_2H_5OH$ | 255 (4,19), 316 (4,05), 340 (4,13), 386 (4,49) | 400 | 480 | 0,10 |
| | $CH_3CN$ | 255 (4,15), 318 (4,02), 340 (4,10), 383 (4,43) | 400 | 475 | 0,10 |
| XXI | $C_2H_5OH$ | 255 (4,31), 318 (3,98), 391 (4,50) | — | — | — |
| XXII | $C_2H_5OH$ | 253 (4,23), 288 (3,49), 309 (3,43), 322 (3,45), 402 (4,41) | 400 | 490 | 0,10 |
| | $CH_3CN$ | 254 (4,19), 288 (3,15), 309 (3,15), 322 (4,41), 400 (4,41) | 400 | 474 | 0,10 |
| XXIII | $C_2H_5OH$ | 254 (4,25), 310 (3,49), 321 (3,49), 405 (4,46) | 400 | 490 | <0,10 |
| | $CH_3CN$ | 255 (4,35), 310 (3,68), 400 (4,54) | 400 | 450 | <0,10 |
| XXIV | $C_2H_5OH$ | 258 (4,29), 310 (3,48), 322 (3,46), 406 (4,54) | — | — | — |
| XXV | $C_2H_5OH$ | 260 (4,39), 280 (4,21), 405 (4,38) | 400 | 490 | 0,41 |
| | $CH_3CN$ | 259 (4,31), 280 (4,11), 400 (4,31) | 400 | 480 | 0,85 |
| XXVI | $C_2H_5OH$ | 260 (4,40), 288 (4,19), 326 (3,69), 408 (4,49) | 400 | 490 | 0,24 |
| | $CH_3CN$ | 248 (4,23), 286 (4,13), 402 (4,47) | 400 | 485 | 0,46 |
| XXVII | $C_2H_5OH$ | 263 (4,33), 280 (4,13), 408 (4,49) | — | — | — |
| XXVIII | $C_2H_5OH$ | 241 (4,22), 302 (3,58), 368 (4,34) | 365 | 457 | 0,61 |
| | $CH_3CN$ | 237 (4,12), 302 (3,60), 355 (4,28) | 365 | 440 | 0,50 |
| XXIX | $C_2H_5OH$ | 242 (4,17), 304 (3,57), 370 (4,34) | 370 | 460 | 0,56 |
| | $CH_3CN$ | 239 (4,20), 357 (4,40) | 370 | 440 | <0,10 |
| XXX | $C_2H_5OH$ | 310 (3,99), 380 (4,26) | — | — | — |
| XXXI | $C_2H_5OH$ | 234 (4,20), 355 (4,29) | 360 | 440 | 0,75 |
| | $CH_3CN$ | 230 (4,13), 346 (4,25) | 360 | 430 | 0,75 |
| XXXII | $C_2H_5OH$ | 236 (4,12), 278 (3,52), 364 (4,25) | 355 | 450 | 0,55 |
| | $CH_3CN$ | 240 (4,07), 274 (3,57), 351 (4,31) | 355 | 435 | 0,45 |
| XXXIII | $C_2H_5OH$ | 260 (4,08), 290 (3,63), 404 (4,37) | 400 | 495 | 0,95 |
| | $CH_3CN$ | 255 (4,04), 290 (3,38), 400 (4,38) | 400 | 480 | 0,96 |
| XXXIV | $C_2H_5OH$ | 260 (3,67), 290 (3,37), 404 (3,95) | 400 | 485 | 0,65 |
| | $CH_3CN$ | 257 (4,10), 292 (3,66), 320 (3,54), 404 (4,44) | 400 | 470 | <0,10 |
| XXXV | $C_2H_5OH$ | 219 (4,52), 264 (3,99), 294 (3,62), 406 (4,38) | — | — | — |
| XXXVI | $C_2H_5OH$ | 263 (4,10), 296 (3,79), 424 (4,43) | 410 | 500 | <0,10 |
| | $CH_3CN$ | 261 (4,16), 296 (3,83), 420 (4,48) | 400 | 470 | <0,10 |
| XXXVII | $C_2H_5OH$ | 253 (4,17), 296 (3,77), 420 (4,47) | 400 | 500 | <0,10 |
| | $CH_3CN$ | 251 (4,02), 296 (3,61), 310 (3,43), 416 (4,34) | 400 | 475 | <0,10 |
| XXXVIII | $C_2H_5OH$ | 266 (4,05), 294 (3,73), 423 (4,47) | — | — | — |

*$\varphi_f$, relative fluorescence quantum yield.

The electronic spectra of the halogen derivatives X-XXXVIII in ethanol of acetonitrile solution exhibit, as expected, a group of absorption bands in the regions 230-260, 280-310, and 355-425 nm (cf. Tables 4 and 5 and [1]); the long-wavelength band is shifted bathochromically about 10-25 nm relative to their unsubstituted coumarin precursors I-IX. The absorption spectra of 7-aminocoumarins XIV-XXXVIII are not very sensitive to the nature of the halogen atom in the 3(10)-position; in the transition series chlorine to bromine to iodine the tendency toward bathochromic displacement of the long-wavelength absorption maximum is rather insubstantial ($\Delta\lambda$ = 0-5 nm).

The fluorescence spectra of the 3-chloro- and 3-bromocoumarins are more sensitive to the effect of the halogen atom; their emission bands are shifted bathofluorically by 10-45 nm relative to their coumarin precursors I-IX (Tables 4 and 5). Also, an increase in the fluorescence quenching effect of the heavy atom is readily observed in the substituent series Cl → Br → I [10]; as a consequence, the 3-iodo derivatives XVI, XXI, XXIV, XXV, and XXXVIII exhibit practically no fluorescence. Comparison of the fluorescence quantum yields for coumarins I-IX and their corresponding 3-chloro derivatives reveals that for coumarins I, II, and 4-alkyl substituted derivatives VI-VIII introduction of a chlorine atom in the 3-position is accompanied

TABLE 5. Spectral Luminescence Properties of Coumarins X and XI in Different Solvents

| Compound | Solvent | Absorption | | Fluorescence | | | $\Phi_f$ |
|---|---|---|---|---|---|---|---|
| | | $\lambda_{max}$, nm (log ε) | $\Delta\nu_{1/2}\cdot10^{-3}$, $cm^{-1}$ | $\lambda_{exc}$, nm | $\lambda_{max}$, nm | $\Delta\nu_{1/2}\cdot10^{-3}$, $cm^{-1}$ | |
| X | $C_6H_{14}$ | 381 (4,45) | 3,33 | 370 | 427 | 3,21 | 0,49 |
| | $C_2H_5OH$ | 388 (4,36) | 3,66 | 380 | 476 | 3,08 | 0,81 |
| | $CH_3COOC_2H_5$ | 384 (4,37) | 3,75 | 380 | 448 | 3,16 | 0,53 |
| | 1,4-Dioxane | 374 (4,38) | 3,76 | 380 | 443 | 3,24 | 0,85 |
| | $C_6H_6$ | 385 (4,15) | 3,69 | 370 | 438 | 3,14 | 0,71 |
| | $CH_3COCH_3$ | 383 (4,46) | 3,81 | 370 | 457 | 3,00 | 0,37 |
| | $CH_3CN$ | 385 (4,40) | 3,65 | 380 | 466 | 3,15 | 0,74 |
| | $CH_2Cl_2$ | 393 (4,39) | 3,73 | 380 | 452 | 3,02 | 0,87 |
| | DMFA | 389 (4,44) | 3,79 | 370 | 465 | 3,03 | 0,48 |
| | DMSO | 392 (4,45) | 3,67 | 370 | 470 | 3,00 | 0,43 |
| XI | $C_6H_{14}$ | 383 (4,42) | 3,64 | 380 | 430 | 3,36 | 0,60 |
| | $C_2H_5OH$ | 390 (4,47) | 3,88 | 390 | 478 | 3,18 | 0,51 |
| | $CH_3COOC_2H_5$ | 386 (4,50) | 3,81 | 380 | 450 | 3,22 | 0,32 |
| | 1,4-Dioxane | 385 (4,44) | 3,84 | 380 | 445 | 3,26 | 0,91 |
| | $C_6H_6$ | 389 (4,42) | 3,80 | 380 | 419 | 3,09 | 0,69 |
| | $CH_3COCH_3$ | 384 (4,49) | 3,94 | 380 | 460 | 3,12 | 0,22 |
| | $CH_3CN$ | 386 (4,53) | 3,90 | 390 | 469 | 3,17 | 0,18 |
| | $CH_2Cl_2$ | 395 (4,45) | 3,76 | 380 | 454 | 3,01 | 0,53 |
| | DMFA | 390 (4,48) | 4,17 | 380 | 465 | 3,19 | 0,17 |
| | DMSO | 394 (4,49) | 4,11 | 380 | 468 | 3,38 | 0,12 |

by enhancement of their luminescence properties. At the same time, however, in the case of coumarins III-V and IX, which have a +M (mesomeric, or +R, resonance) substituent in the 4-position (such as Cl, $NR^1R^2$), fluorescence quenching is observed. We hypothesize that the factor responsible for this dichotomy is increased charge transfer along the conjugation chain 4-R → C(4)=C(3) which, in turn, disturbs the conjugative interaction in the system 7-$NR_2$ → C(2)=O that is responsible for the fluorescence effect in 7-aminocoumarins [11].

The substituent in the 4(9)-position exerts an essential and significant effect on the absorption and luminescence spectra of these compounds. As the electron-donating ability of the substituent in this position is reduced in the series $NHCH_2C_6H_5$ → $N(CH_2CH_2)_2O$ → $CH_3$ → H → Cl → $CH(COCH_3)_2$ [12], their absorption and emission bands undergo bathochromic and bathofluoric shifts, respectively.

Using compounds X and XI as examples, we have examined the absorption and luminescence spectra of these compounds in ten different organic solvents (Table 5). In nonpolar solvents (hexane, 1,4-dioxane, benzene, etc.) their absorption and emission bands exhibit pronounced vibrational fine structure, which is gradually erased as the medium polarity is enhanced, and finally disappears completely in solvents which are more polar than ethyl acetate.

Our investigation of the spectral properties of coumarins X and XI also supports the validity of the approach correlating both the positions of the absorption ($\nu_{max}^{ab}$) and fluorescence ($\nu_{max}^{em}$) maxima and their spectral line width ($\Delta\nu_{1/2}$) with the solvent polarity function $\pi^*$ [13], which is based on the use of the solvatochromic equation [13-15]. As the solvent polarity is increased, bathochromic and bathofluoric shifts of their absorption and fluorescence maxima, respectively, are observed; there is a near linear relationship between $\nu_{max}^{ab}$ and $\nu_{max}^{em}$ and the function $\pi^*$. We have summarized below the correlation equations (1)-(4) which characterize these dependence functions for the entire series of solvents examined, with the exception of ethanol, in which a large deviation can be attributed to hydrogen bond formation [13].

$$\nu_{max}^{ab}(X) = 27{,}41 - 1{,}56\pi^*\ (\cdot 10^3\ cm^{-1}),\ r = 0{,}97,\ n = 9; \quad (1)$$

$$\nu_{max}^{ab}(XI) = 27{,}19 - 1{,}39\pi^*\ (\cdot 10^3\ cm^{-1}),\ r = 0{,}98,\ n = 9; \quad (2)$$

$$\nu_{max}^{em}(X) = 24{,}15 - 2{,}93\pi^*\ (\cdot 10^3\ cm^{-1}),\ r = 0{,}96,\ n = 9; \quad (3)$$

$$\nu_{max}^{em}(XI) = 23{,}94 - 2{,}67\pi^*\ (\cdot 10^3\ cm^{-1}),\ r = 0{,}93,\ n = 9; \quad (4)$$

$$\nu_{max}^{ab}(X) = 27{,}41 - 1{,}38^*\pi - 0{,}60\alpha - 0{,}21\beta\ (\cdot 10^3\ cm^{-1}),\ r = 0{,}98,\ n = 10; \quad (5)$$

TABLE 6. Acid–Base Properties of Halocoumarins X-XII, XIV-XVI, XIX-XXVII, and XXXIII-XXXVIII in 50% Aqueous Ethanol

| Compound | $\lambda_{max}^{abs}$, nm | | $pK_a$ | $pK_a^*$ |
|---|---|---|---|---|
| | neutral molecule | cation | | |
| X | 400 | 315 | 1,53 | −12,81 |
| XI | 400 | 318 | 1,52 | −12,18 |
| XII | 404 | 323 | 1,51 | −11,97 |
| XIV | 405 | 317 | 1,45 | −13,10 |
| XV | 408 | 333 | 1,32 | −13,87 |
| XVI | 410 | 322 | 1,48 | −12,64 |
| XIX | 386 | 346 | 1,35 | −11,47 |
| XX | 393 | 346 | 1,33 | −12,15 |
| XXI | 397 | 352 | 1,83 | −11,87 |
| XXII | 417 | 312 | 0,66 | −16,46 |
| XXIII | 413 | 336 | 0,62 | −14,57 |
| XXIV | 415 | 341 | 0,63 | −13,07 |
| XXV | 412 | 315 | 1,02 | −14,92 |
| XXVI | 418 | 317 | 1,00 | −14,69 |
| XXVII | 420 | 329 | 0,96 | −14,23 |
| XXXIII | 414 | 312 | −0,03 | −14,81 |
| XXXIV | 417 | 324 | −0,15 | −14,87 |
| XXXV | 419 | 330 | −0,18 | −13,94 |
| XXXVI | 433 | 329 | −0,94 | −16,57 |
| XXXVII | 435 | 333 | −0,89 | −15,96 |
| XXXVIII | 435 | 338 | −0,45 | −15,57 |

$$\nu_{max}^{ab}(XI) = 27{,}19 - 1{,}18\pi^* - 0{,}52\alpha - 0{,}29\beta\ (\cdot 10^3\ cm^{-1}),\ r = 0{,}99,\ n = 10; \quad (6)$$

$$\nu_{max}^{em}(X) = 24{,}15 - 2{,}19\pi^* - 0{,}14\alpha - 0{,}11\beta\ (\cdot 10^3\ cm^{-1}),\ r = 0{,}99,\ n = 10; \quad (7)$$

$$\nu_{max}^{em}(XI) = 23{,}94 - 2{,}07\pi^* - 0{,}15\alpha - 0{,}10\beta\ (\cdot 10^3\ cm^{-1}),\ r = 0{,}98,\ n = 10. \quad (8)$$

The more general linear regression equations (5)-(8), taking into account specific solvation as well, due to hydrogen bond formation (the parameters $\alpha$ and $\beta$ [14]), also verify the great sensitivity of these spectral maxima to solvent polarity $\pi^*$, and are characterized by high correlation coefficients (r). Also noteworthy for coumarins X and XI are the increase in Stokes shift ($\nu_{max}^{em} - \nu_{max}^{ab}$) with increasing solvent polarity and the tendency toward absorption band broadening and emission band narrowing in the same transition (Table 5). This latter trend can be ascribed to the greater polarity of the excited state compared to the ground state and has been considered in detail in the literature [13].

At the same time, however, there is no discernible or unilateral relationship between solvent polarity and the fluorescence quantum yields for coumarins X and XI, which vary over quite a broad range ($\varphi_f$ from 0.2 to 0.9) for both compounds (Table 5).

In order to evaluate the electronic effect of the halogen atoms we have determined the $pK_a$ values for the conjugate acids of compounds X-XII, XIV, XVI, XIX-XXVII, and XXXIII-XXXVIII in aqueous ethanol solutions (1:1) (Table 6). The results indicate that the basicity of these compounds overall varies very little as the halogen atom in the 3(10)-position is altered; the range of variation is less than 0.5 $pK_a$ units. Nevertheless, the 3-chloro-7-aminocoumarin derivatives in practically all cases are slightly more basic than their corresponding 3-bromo analogs. This trend, in our opinion, can be explained in terms of the relatively strong +M (+R) effect of the Cl atom, which at a sufficient distance can, in many cases, compensate for or balance the high –I effect of this halogen atom. In contrast, a Br atom is substantially inferior to Cl in terms of its electron-donating properties, but it still exerts a relatively strong –I effect compared to an I atom, such that Br is the strongest acceptor substituent in this series. As support for our conclusion we cite the $\sigma_R^0$ and $\sigma_I$ substituent constants developed by Taft in the naphthalene series [16], which are equal to –0.20, –0.16, and –0.12; and 0.47, 0.45, and 0.39, respectively, for Cl, Br, and I. Analogous principles are followed in onium compounds [17].

Our analysis of the $pK_a$ values of these compounds indicates that the basicity of coumarin derivatives depends quite strongly on the nature of the substituent in the 4-position, increasing in the series Cl < $CH(COCH_3)$ < H < $CH_3$ by approximately an order of magnitude (Table 6). The position of the morpholino group in this substituent series is ambiguous. Fixing the nitrogen atom in a six-membered ring in coumarins XXXIII-XXXVIII leads to a sharp decrease in basicity, by almost

TABLE 7. $^{13}C$-NMR Spectra of Coumarins I, X-XII in $CDCl_3$

| Compound | ppm (SSSC, J, Hz) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $C_{(2)}$, s | $C_{(3)}$, m | $C_{(4)}$, m | $C_{(4a)}$, m | $C_{(5)}$ (d, $J$=160,0) | $C_{(6)}$ (d.d $J$=160,0, $J$=5,8) | $C_{(7)}$, m | $C_{(8)}$ (d.d, $J$=160,0, $J$=5,4) | $C_{(8a)}$ (d.d, $J$=6,0, $J$=9,3) | 4-$CH_3$ (k, $J$=129,0) | 7-$NCH_2$ (t, k, $J$=135,6, $J$=4,3) | 7-N—$CH_2CH_3$ (k, $J$=126,7) |
| I | 161,4 | 108,2* | 152,1 | 109,2 | 125,4 | 109,0 | 150,4 | 97,8 | 156,1** | 18,4 | 44,7 | 12,6 |
| X | 158,1 | 113,9 | 148,4 | 108,6 | 125,8 | 109,0 | 150,5 | 97,2 | 153,9 | 15,8 | 44,7 | 12,4 |
| XI | 158,0 | 105,5 | 151,5 | 108,7 | 123,5 | 109,0 | 150,6 | 97,1 | 154,3 | 19,0 | 44,7 | 12,4 |
| XII | 158,5 | 83,5*** | 156,6 | 108,7 | 126,2 | 108,8 | 150,8 | 96,7 | 154,9 | 24,8 | 44,7 | 12,4 |

*Doublet, 171.8 ppm.

**Multiplet.

***Quartet, 6.5 ppm.

1-2 orders of magnitude. The reason for this effect seems to be the unfavorable tetrahedral configuration which the nitrogen atom in julolidine derivatives must assume upon protonation incompounds XXXIII-XXXVIII.

Using the Ferster method [5], we have estimated the basicity of coumarins X-XII, XIV-XVI, XIX-XXVII, and XXXIII-XXXVIII in their singlet excited states. Their $pK_a^*$ values show a sharp reduction in basicity (up to 16 orders of magnitude) upon molecular excitation, which is consistent with earlier literature data [9, 12]. The $pK_a^*$ values for these coumarins, depending on the change in the halogen atom in the 3(10)-position, vary over the range 0.7-3.4, while the normal basicity decreases in the series I > Br > Cl, i.e., in accord with the inductive effect of halogen atoms. This observation provides evidence for significant rearrangement of π-electron density in 7-aminocoumarins in the excited state, which appears to be a charge transfer state [11]. The characteristic effects of substituents in the 4(9)-position on the basicity of these coumarin derivatives in the excited state are retained in almost the same order as in the ground state. The magnitude of the effects, however, is considerably greater in the excited state; the transition from an acetylacetonyl group to a methyl group is marked by an increase in $pK_a^*$ value of 3-4 orders of magnitude.

In order to obtain a more complete understanding of the effect of a halogen atom in the 3-position on the distribution of π-electron density in 7-aminocoumarins we have also studied the $^{13}C$-NMR spectra of compounds X-XII in $CDCl_3$ solution (Table 7). Signal assignments were made based on chemical shift calculations using an additivity scheme [18], and also taking into account characteristic $J_{^{13}C,H}$ SSCC values [8]. From the data in Table 7 it is apparent that the effect of a halogen atom in these molecules X-XII is limited primarily to the 3- and 4-positions. The degree of electronic interaction of Cl and Br atoms with the coumarin system is very similar, but differs significantly from the degree of interaction of an I atom. This observation reflects or confirms the appreciable +M (+R) effect of Cl and Br atoms, which in the neutral (7-aminocoumarin) molecules is not extended to or felt by the benzene fragment due to the strong opposing +M (+R) effect of the 7-dialkylamino group. Another position may be operative as a result of protonation at the N-atom, which converts the 7-amino group to a strong electron acceptor; as a consequence, the larger +M (+R) effect of Cl relative to Br may be responsible for the increased basicity of 3-chloro-7-aminocoumarins compared to their analogous 3-bromo derivatives (Table 6).

## EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer 577 spectrophotometer using KBr pellets, UV spectra and fluorescence spectra on a Hitachi EPS-3T spectrophotometer equipped with a G-3 luminescence accessory. Relative fluorescence quantum yields were determined based on 3-aminophthalimide [19]. NMR spectra were obtained on a Bruker WM-250 spectrometer using $CDCl_3$ solutions versus HMDS as internal standard.

$pK_a$ values were determined according to a literature procedure [20] in 50% alcohol solutions using an ÉV-74 universal ion (pH) meter with glass and calomel electrodes (with an experimental error of +0.04).

Regression analysis was performed using an ES-1206 computer and a standard program.

Reaction products were separated by column chromatography (15 × 3.5 cm) on Silpearl sorbent with benzene and benzene–acetone (40:1) as eluting systems. Product purity was monitored by TLC on Silufol plates, which were visualized under UV light and with iodine.

The results of elemental analysis for all the newly synthesized compounds agreed with calculations.

**General Procedure for the Preparation of Coumarins X, XIV, XVII, XIX, XXXI, XXXII, XXXVI (XI, XV, XVIII, XX, XXVI, XXIX, XXXIV, XXXVII).** To a solution of 2.0 mmoles coumarin starting material I-IX in 50-100 ml acetonitrile was added with stirring a solution of 3.0 (2.0) mmoles N-chlorosuccinimide (N-bromosuccinimide) in acetonitrile in a dropwise manner; the mixture was stirred for 30 min to 1 h (5-10 min). The reaction mixture was evaporated and the residue was separated by chromatography; the isolated products were recrystallized from a mixture of hexane–acetone.

**General Procedure for the Preparation of Coumarins XXII, XXV, XXXIII.** A solution of 2.0 mmoles coumarin V, VI, VIII was refluxed in acetonitrile in the presence of 2.5 mmoles anhydrous copper(II) chloride for 30 min; the reaction mixture was filtered, evaporated, and the residue separated by chromatography. The isolated products were crystallized from hexane–acetone mixture.

**General Procedure for the Preparation of Coumarins XII, XVI, XXI, XXIV, XXVII, XXV, and XXXVIII.** To a solution containing 9.0-24.0 mmoles iodine in a mixture of 50-100 ml dioxane and 2.5-5.0 ml pyridine was added a solution of 3.0 mmoles coumarin starting material I, II, IV-VI, VIII, and IX in 20 ml dioxane; the mixture was stirred for 5-10 h. The reaction mixture was then diluted twofold with a saturated solution of sodium thiosulfate, extracted

with ethyl acetate (3 × 100 ml), and the combined organic layers evaporated; the residue was separated by chromatography and the isolated products recrystallized from a hexane–acetone mixture.

**3,6,8-Trichloro-4-methyl-7-ethylaminocoumarin (XIII).** Chlorine (in 2- to 3-fold excess) was bubbled through a solution of 1.00 g coumarin I in 40 ml $CCl_4$ . The reaction mixture was evaporated and the residue separated by chromatography with benzene eluent. Yield 0.87 g of compound XIII. PMR spectrum ($CDCl_3$): 1.28 (3H, t, J = 7.0, $NCH_2CH_3$), 2.50 (3H, s, $CH_3$), 3.66 (2H, q, J = 7.0, $NCH_2CH_3$), 7.45 ppm (1H, s, 5-H).

**3-Chloro-4-methyl-7-aminocoumarin (XXVIII).** Coumarin (1.00 g, 5.7 mmoles) VII and 1.55 g (11.4 mmoles) $ZnCl_2$ were stirred together in 30 ml nitromethane for 10 min at 50-60°C, and 3.00 g (22.2 mmoles) $CuCl_2$ was then added and the mixture stirred an additional 30 min. The reaction mixture was profiltered, evaporated, and the residue separated by chromatography using benzene–acetone (15:1) as the eluting system. Yield 0.82 g of compound XXVIII.

**3-Iodo-4-methyl-7-aminocoumarin (XXX).** A mixture of 1.00 g (5.7 mmoles) coumarin VII, 1.55 g (11.4 mmoles) $ZnCl_2$, and 2.20 g (8.7 mmoles) iodine in 50 ml nitromethane and 10 ml pyridine was stirred together for 6 h. The reaction mixture was profiltered and treated with saturated sodium thiosulfate solution (3 × 50 ml); the solution was then evaporated and the residue separated by chromatography using 20:1 benzene–acetone. Yield 0.74 g of compound XXX.

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