SYNTHESIS OF 4-ALKYL FUNCTIONALLY SUBSTITUTED 7-DIALKYLAMINOCOUMARINS

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7-Dialkylaminocoumarins that, depending on the reaction conditions, contain an alkyl substituent with one or two functional groups in the 4 position, were obtained in the reaction of 4-chloro-7-diethylamino-, 4-chloro-7-N-morpholino-, and 2,3,6,7-tetrahydro-9-chloro-1H,5H-quinolizino[9,9a,1-gh]coumarin with sodium derivatives of acetylacetone and acetoacetic, malonic, and cyanoacetic esters. The spectral-luminescence characteristics of the synthesized compounds were studied.

It has been previously shown [1] that it is possible to use 4-chloro-7-dialkylaminocoumarins [2] in the synthesis of 4,7-diaminocoumarins – new effective luminophores. In the present publication we have studied the reactions of 4-chloro-7-dialkylaminocoumarins with C-nucleophiles, which lead to difficult-to-obtain functionally substituted 7-aminocoumarins.

As the subjects of our investigation we selected 4-chloro-7-diethylaminocoumarin (I), 4-chloro-7-N-morpholinocoumarin (II), and 2,3,6,7-tetrahydro-9-chloro-1H,5H-quinolizino-[9,9a,1-gh]coumarin (III). We studied the reaction of coumarins I-III with carbanions of typical CH acids: acetylacetone and acetoacetic, malonic, and cyanoacetic esters. The interest in reactions of this type was due to several reasons. First, the regiospecificity of the primary nucleophilic attack, which could take place at the $C_{(4)}$ or $C_{(2)}$ atom, and the carbanion could act as a C- or O-nucleophile, was previously unclear; the formation of products of acidic cleavage of the methylene component also could not be excluded in this case. Second, we were interested in the possibility of obtaining 7-aminocoumarins that contain (in the 4 position) a CH-acid fragment, which holds promise for the synthesis of cyclocondensed derivatives. In addition, compounds of this sort are potentially capable of chelate formation and, consequently, their chromophoric and fluorophoric properties are of interest [3].

We initially accomplished the reactions of coumarins I-III with excess amounts of sodium derivatives of the selected carbonyl compounds by refluxing in the same methylene component as the medium for 5-7 h. The completion of the reactions was established by means of TLC at the instant of complete disappearance of the starting 4-chlorocoumarin. As a result, we obtained monofunctionally substituted coumarins IV-IX in 35-45% yields, as well as bifunctionally substituted coumarins X-XVII, the yields of which reached 22-30%. Thus, cleavage of the initially formed X-XVII via a mechanism of the acidic type [4] takes place simultaneously during the reaction.

TABLE 1. Characteristics of IV-XVII

Compound	Empirical formula	mp, °C	IR spectrum, $\nu_{C=O}$, cm^{-1}	Yield %	Compound	Empirical formula	mp, °C	IR spectrum, $\nu_{C=O}$, cm^{-1}	Yield, %
IV	$C_{16}H_{19}NO_3$	110	1720, 1730	60	XII	$C_{19}H_{23}NO_5$	92	1720	62
					XIII	$C_{18}H_{20}N_2O_4$	104	1720, 1730	60
V	$C_{17}H_{21}NO_4$	82	1720	55					
VI	$C_{15}H_{16}N_2O_2$	176	1700	45	XIV	$C_{19}H_{21}NO_6$	120	1720	60
VII	$C_{18}H_{19}NO_3$	187	1715	57	XV	$C_{20}H_{21}NO_4$	182	1720	65
VIII	$C_{19}H_{21}NO_4$	130	1710	52	XVI	$C_{21}H_{23}NO_5$	108	1715	58
IX	$C_{17}H_{16}N_2O_2$	199	1715	48	XVII	$C_{20}H_{20}N_2O_4$	140	1700, 1730	52
X	$C_{18}H_{21}NO_4$	131	1720	75					
XI	$C_{20}H_{25}NO_6$	72	1730	65					

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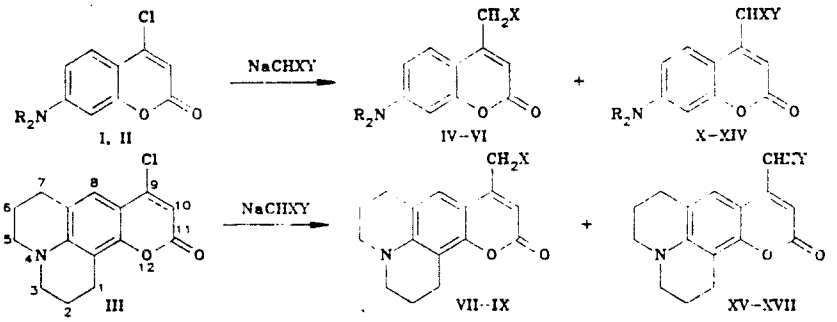
When we increased the reflux time of the reaction mixture to 8-10 h, the yields of IV-IX could be raised to 45-60% (Table 1).



I, IV—VI, X—XIII R=C_2H_5; II, XIV R—R=$(CH_2)_2O(CH_2)_2$-; IV, VII, X, XII, XIV—XVI X=$COCH_3$; V, VIII, XI X=$CO_2C_2H_5$; VI, IX, XIII, XVII X=CN; X, XV Y=$COCH_3$; XI—XIV, XVI, XVII Y=$CO_2C_2H_5$

Coumarins X-XVII are evidently formed via an addition–cleavage mechanism (or a tetragonal mechanism [5]) with primary attack by the carbanion at the $C_{(4)}$ atom of the 4-chlorocoumarin. The selective obtaining of products of substitution at the $C_{(4)}$ atom is evidently determined by the strong nucleofugal properties of the chlorine anion, which makes the substitution irreversible. On the other hand, in the case of attack by the nucleophile at the $C_{(2)}$ atom in the initial stages the process is reversible.

In order to selectively obtain bifunctionally substituted 7-aminocoumarins X-XVII, we studied the reaction of coumarins I-III with selected CH acids in other solvents (DMSO, DMF, THF, dioxane, etc.), and also in the presence of various bases (NaH, tert-BuOK, NEt3, etc.). Refluxing coumarins I-III with a twofold excess of the corresponding sodium derivative in solution in 1,4-dioxane for 5-6 h proved to be the optimum method for the synthesis of X-XVII. In this case, the preparative yields of coumarins X-XVII reach 52-75% (Table 1). Thus, when one varies the reaction conditions, the specific obtaining of mono- or bifunctionally substituted (at the 4-methyl group) 7-dialkylaminocoumarins is possible.

The structures of IV-XVII were established from PMR spectral data (Tables 2 and 3). In the case of coumarins IV-VI and X-XIV, the signals of the aromatic 3-H, 5-H, 6-H, and 8-H protons, which are identified unambiguously over the 5.8-7.5 ppm range from the form of splitting in the spectrum [6], are satisfactorily distinguishable. Singlet signals of the aromatic 8-H and 10-H protons of coumarins VII-IX and XV-XVII are also located in the same range. It should be noted that the chemical shifts (CS) of the 3-H protons of coumarins IV-VI and X-XIV and the analogous 10-H protons in the case of coumarins VII-IX and XV-XVII are most sensitive to the effect of the 4-alkyl substituent ($\Delta \sim 0.4$ ppm). An analysis of the CS of these protons makes it possible to construct the following order of the deshielding effect of the groups that enter into the alkyl functional substituent: CN > $CO_2C_2H_5$ > $COCH_3$. The signals of the protons located at the $C_{(\alpha)}$ atoms bonded at the 4(9) position of the coumarin ring show up in the form of singlets at 3.6-4.9 ppm for IV-IX, XI, XII, and XVII.

In the spectra of coumarins X, XII, and XIV-XVI, which contain two electron-acceptor groups at the $C_{(\alpha)}$ atom, one of which is an acetyl group, a signal of a methylidyne $C_{(\alpha)}$–H proton does not show up either at 3-4 ppm or at weak field, where it might have been found if an intermolecular hydrogen bond (IMHB) were present. The reason for this is evidently keto-enol tautomerism, the rate of which is comparable to the rate of NMR relaxation [7]. The potential ability of coumarins X, XII, and XIV-XVI to exist in the enol form is confirmed by the formation of brightly colored chelates when these compounds are treated with a methanol solution of $FeCl_3$. Compounds IV-IX, XI, XII, and XVII do not give a reaction of this sort. The assignment of the signals of the protons of the N-alkyl substituents in coumarins X-XVII was made on the basis of [6].

In the IR spectra of 4-alkyl functionally substituted 7-dialkylaminocoumarins IV-XVII carbonyl absorption shows up at 1700-1730 cm^{-1} (Table 1), which corresponds to the usual values for other 7-aminocoumarins [8]. Vibrations of the C=C bonds of the aromatic fragment show up at 1590-1630 cm^{-1}, usually in the form of two bands.

A band of long-wave absorption at 370-410 nm is present in the UV spectra of coumarins IV-XVII in ethanol and acetonitrile (Table 4). The fastening of the 7-dialkylamino group into six-membered rings in VII-IX and XV-XVII leads to a bathochromic shift of the long absorption band by 10-20 nm as compared with the corresponding 7-diethylamino analogs. On the other hand, the presence of a lesser electron-donor 7-N-morpholino group leads to a hypsochromic shift of the long-wave band by 23 nm in the case of XIV as compared with coumarin XII. Coumarin XV (λ_{max} 410 nm) has the longest-wave absorption, while XIV has the shortest-wave absorption (λ_{max} 367 nm).

TABLE 2. PMR Spectra of Coumarins IV-VI and X-XIV (in $CDCl_3$)

Compound	Chemical shifts, δ, ppm (SSSC, J, Hz)						
	8-H, s	5-H, d (J=9,0)	6-H, dd (J=9,0; J=2,7)	8-H, d (J=2,7)	7-NCH_2, q (J=7,0)	7-NCH_2CH_2R, t (J=7,0)	Other protons
IV	6,00	7,28	6,59	6,52	3,40	1,19	2,22 (3H, s, CH_3); 3,72 (2H, s, $C_{(4)}$—CH_2)
V	6,04	7,38	6,65	6,55	3,40	1,20	1,24 (3H, t, J=7,0, CH_2CH_3); 4,18 (2H, q, J=7,0, CH_2CH_3); 3,67 (2H, s, $C_{(4)}$—CH_2)
VI	6,22	7,26	6,62	6,51	3,38	1,18	3,75 (2H, s, $C_{(4)}$—CH_2)
X	6,00	7,18	6,65	6,60	3,42	1,21	1,97 (6H, s, $2CH_3$)
XI	6,11	7,32	6,59	6,50	3,40	1,20	1,27 (6H, t, J=7,0, $2CH_2CH_3$); 4,22 (4H, q, J=7,0, $2CH_2CH_3$); 4,84 (1H, s, $C_{(4)}$—CH)
XII	5,90	7,12	6,65	6,60	3,40	1,20	1,12 (3H, t, J=7,0, CH_2CH_3); 1,90 (3H, s, CH_3); 4,14 (2H, q, J=7,0, CH_2CH_3)
XIII	6,25	7,51	6,61	6,50	3,38	1,16	1,20 (3H, t, J=7,0, CH_2CH_3); 4,25 (2H, q, J=7,0, CH_2CH_3); 4,88 (1H, s, $C_{(4)}$—CH)
XIV	6,07	7,22	6,40	6,00	3,30t*	3,90*	1,12 (3H, t, J=7,0, CH_2CH_3); 1,90 (3H, s, CH_3); 4,13 (2H, q, J=7,0, CH_2CH_3)

*J = 4.7 Hz.

TABLE 3. PMR Spectra of Coumarins VII-IX and XV-XVII (in $CDCl_3$)

Compound	Chemical shifts, δ, ppm (SSCC, J, Hz)				
	10-H, s	8-H, s	4-NCH_2, q (J=6,2)	4-NCH_2CH_2R, m	Other protons
VII	5,99	6,87	3,26	2,03	2,22 (3H, s, CH_3); 2,76 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(12b)}$); 2,90 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(7a)}$); 3,72 (2H, s, $C_{(4)}$—CH_2)
VIII	5,98	6,95	3,24	1,97	1,24 (3H, t, J=7,0, CH_2CH_3); 2,75 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(12b)}$); 2,88 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(7a)}$); 3,62 (2H, s, $C_{(4)}$—CH_2); 4,17 (2H, q, J=7,0, CH_2CH_3)
IX	6,11	6,78	3,22	1,96	2,70 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(12b)}$); 2,80 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(7a)}$); 3,68 (2H, s, $C_{(4)}$—CH_2)
XV	5,91	6,72	3,28	1,95	1,94 (6H, s, $2CH_3$); 2,72 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(12b)}$); 2,90 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(7a)}$)
XVI	5,85	6,72	3,26	1,98	1,12 (3H, t, J=7,0, CH_2CH_3); 1,90 (3H, s, CH_3); 2,72 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(12b)}$); 2,90 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(7a)}$); 4,18 (2H, q, J=7,0, CH_2CH_3)
XVII	6,21	7,00	3,29	2,00	1,28 (3H, t, J=7,0, CH_2CH_3); 2,77 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(12b)}$); 2,88 (2H, t, J=6,0, *cyclo*-CH_2—$C_{(7a)}$); 4,28 (2H, q, J=7,0, CH_2CH_3); 4,75 (1H, s, $C_{(4)}$—CH)

TABLE 4. Spectral–Luminescence Characteristics of Coumarins IV-XVII

Compound	Solvent	Absorption, λ_{max}, nm (log ε)	Luminescence		
			λ_{exc}, nm	λ_{max}, nm	φ_f
IV	C_2H_5OH	250 (4,28), 308 (3,38), 320 (3,47), 385 (4,28)	380	470	0,35
	CH_3CN	248 (4,22), 308 (3,63), 320 (3,66), 379 (4,41)	380	455	0,44
V	C_2H_5OH	250 (4,20), 308 (3,53), 319 (3,59), 385 (4,38)	380	465	0,31
	CH_3CN	244 (4,18), 308 (3,56), 319 (3,66), 378 (4,37)	380	455	0,44
VI	C_2H_5OH	252 (4,21), 308 (3,63), 385 (4,42)	385	470	0,17
	CH_3CN	254 (4,08), 310 (3,51), 381 (4,39)	385	460	0,33
VII	C_2H_5OH	253 (4,08), 290 (3,65), 401 (4,33)	400	490	0,79
	CH_3CN	251 (4,08), 290 (3,59), 394 (4,35)	400	475	0,74
VIII	C_2H_5OH	252 (4,07), 290 (3,63), 314 (3,48), 403 (4,34)	395	484	0,82
	CH_3CN	250 (4,18), 290 (3,77), 314 (3,72), 386 (4,40)	395	470	0,74
IX	C_2H_5OH	253 (3,99), 268 (3,91), 298 (3,62), 404 (4,32)	395	490	0,79
	CH_3CN	251 (4,06), 268 (3,93), 292 (3,64), 398 (4,35)	395	480	0,75
X	C_2H_5OH	256 (4,28), 284 (4,10), 394 (4,38)	390	472	0,18
	CH_3CN	254 (4,28), 284 (4,14), 386 (4,42)	390	460	0,43
XI	C_2H_5OH	252 (4,19), 321 (4,37), 391 (4,33)	380	480	0,47
	CH_3CN	258 (4,15), 321 (3,55), 386 (4,34)	380	470	0,64
XII	C_2H_5OH	253 (4,39), 322 (3,61), 390 (4,39)	390	475	0,61
	CH_3CN	251 (4,36), 322 (3,65), 385 (4,37)	390	460	0,51
XIII	C_2H_5OH	254 (4,36), 310 (3,84), 374 (4,61)	375	466	<0,10
	CH_3CN	252 (4,12), 312 (3,60), 386 (4,29)	375	475	<0,10
XIV	C_2H_5OH	248 (4,37), 367 (4,29)	370	480	0,98
	CH_3CN	246 (4,37), 352 (4,32)	370	470	0,73
XV	C_2H_5OH	268 (4,18), 292 (4,08), 410 (4,28)	400	490	0,18
	CH_3CN	266 (4,09), 402 (4,24)	400	475	0,10
XVI	C_2H_5OH	256 (4,39), 404 (4,48)	400	495	0,83
	CH_3CN	252 (4,31), 400 (4,37)	400	485	0,76
XVII	C_2H_5OH	255 (4,10), 320 (3,67), 382 (4,45)	390	505	<0,10
	CH_3CN	257 (3,99), 298 (3,58), 410 (4,31)	390	490	<0,10

All of the synthesized compounds fluoresce over the 460-500 nm range (Table 4). The emission bands in the case of coumarins VII-IX and XV-XVII are also shifted by ~20 nm to the longer-wave region as compared with the corresponding 7-diethylamino derivatives IV-VI and X-XIII. The fluorescence quantum yields for coumarins VII-IX, XV, and XVI are generally higher (φ_f 0.7-0.8) than for noncyclic analogs IV-VI and X-XII (φ_f 0.2-0.6). One's attention is drawn to the sharp decrease in the fluorescence for cyanoacetic ester derivatives XIII and XVII, as well as coumarin XV ($\varphi_f \leq 0.1$). In contrast to the absorption band, the emission band for coumarin XIV experiences a small bathofluoric shift (Δ ~ 5-10 nm) as compared with 7-diethylamino analog XII. Compound XIV has intense fluorescence in ethanol (φ_f ~ 1.0).

EXPERIMENTAL

The IR spectra were recorded with a Perkin–Elmer 577 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Bruker WM spectrometer (250 MHz) with hexamethyldisiloxane (HMDS) as the internal standard.

The reaction products were isolated by chromatography with a column (30 × 2 cm) packed with Silpearl UV-254 silica gel in hexane–acetone systems. The purity of the substances was monitored by means of TLC on Silufol UV-254 plates (development with UV light or in iodine vapors).

General Method for Obtaining 4-Alkyl Functionally Substituted 7-Dialkylaminocoumarins IV-XVII. A 0.23 g (10 mmoles) sample of sodium was dissolved in 30 ml of the methylene component (acetylacetone or malonic, acetoacetic, and cyanoacetic esters) or in a mixture consisting of 50 mmoles of the methylene component and 30 ml of absolute dioxane. A 5.0 mmole sample of the corresponding 4-chlorocoumarin was added to the resulting solution, and the reaction mixture was heated at 100-120°C (when the reaction was carried out directly in the methylene component) or refluxed (solution in dioxane) for 4-8 h until the starting 4-chlorocoumarin vanished (monitoring by TLC). The solvent was evaporated in vacuo, and the residue was treated with 30 ml of 3% acetic acid. The acidic mixture was extracted with methylene chloride (three 30-ml portions), and the extract was evaporated in vacuo. The residue was chromatographed with collection of the fractions that luminesce under UV light. The R_f values of IV-XVII on Silpearl UV-254 silica gel in a hexane–acetone system (1:1) ranged from 0.20 to 0.50.

LITERATURE CITED

1. M. A. Kirpichënok, S. K. Gorozhankin, and I. I. Grandberg, *Khim. Geterotsikl. Soedin.*, No. 6, 830 (1990).
2. M. A. Kirpichënok, S. K. Gorozhankin, and I. I. Grandberg, *Khim. Geterotsikl. Soedin.*, No. 6, 836 (1990).
3. H.-G. Lohr and F. Vogtle, *Acc. Chem. Res.*, **18**, 65 (1985).
4. K. Byuler and D. Pearson, *Organic Syntheses* [Russian translation], Part 2, Mir, Moscow (1973), p. 264.
5. Z. Rappoport and P. Peled, *J. Am. Chem. Soc.*, **101**, 2682 (1979).
6. M. A. Kirpichënok, I. I. Grandberg, L. K. Denisov, and L. M. Mel'nikova, *Izv. Timiryazev. Sel'skokhoz. Akad.*, No. 3, 172 (1985).
7. H. Günther, *Introduction to a Course in NMR Spectroscopy* [Russian translation], Mir, Moscow (1984).
8. I. I. Grandberg, L. K. Denisov, and O. A. Popova, *Khim. Geterotsikl. Soedin.*, No. 2, 147 (1987).

PREPARATIVE SYNTHESIS OF BENZO[b]THIO-(SELENO,TELLURO)PHENE DERIVATIVES*

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A preparative synthesis of aminomethyl derivatives of benzo[b]thio(seleno,telluro)phenes and their hydrohalides by the reaction of sulfur, selenium, and tellurium halides with 1-phenylpropynamines was developed.

As we previously reported, benzo[b]selenophene derivatives were obtained in good yields under conditions of two-phase selenohalogenation of phenylacetylene derivatives [2]. The introduction of a methyleneamino group into phenylacetylene could facilitate the reaction and make it possible to expand the limits of applicability of the method. With this end in mind, we studied the reactions of 1-phenylamino derivatives Ia-e of 1-propyne with selenium and tellurium tetrahalides and sulfur dichloride. The starting amines were obtained from phenylacetylene, paraformaldehyde, and the corresponding amine under the catalytic action of cuprous chloride [3, 4]. It is known that the use of two-phase seleno- or tellurohalogenation [5] markedly increases the yields of products, shortens the reaction time, and makes these reactions preparatively advantageous for the synthesis of benzo[b]seleno(telluro)phene derivatives IIa-m (see scheme on page 1108).

Benzo[b]thiophene derivatives IIn-q are formed in good yields in the reaction of amine derivatives Ia-e with sulfur dichloride in an organic medium (see scheme on page 1108).

It was established that the order of addition of the reagents does not affect the way in which the reaction proceeds – the only reaction products are benzo[b]thio(seleno,telluro)phene derivatives (see Table 1). In contrast to starting amines Ia-e, the IR spectra of IIa-q do not contain bands of stretching vibrations at 2100-2250 cm^{-1} (C≡C) but do contain bands of stretching vibrations at 1590-1640 and 1260-1580 cm^{-1}, which characterize the stretching vibrations of the C=C group and the benzo[b]thio(seleno,telluro)phene system [6], respectively, and bands of stretching vibrations of the C–A (A = Se, Te) and C–Hal bonds (see Table 1). In the PMR spectra the protons of the methylene group show up in the form of a doublet at 4.32-4.96 ppm (J = 4.0-6.0 Hz), in contrast to the position of the same group in starting amines Ia-e (3.35-3.58 ppm, singlet).

*Communication 12 from the series "Electrophilic reactions of halides of group VI elements." See [1] for Communication 11.

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