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SYNTHESIS OF 4-CHLORO-7-DIALKYLAMINOCOUMARINS

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UDC 547.587.51.07'564.4'476.1.04: 543.422

A series of 4-chloro-7-dialkylaminocoumarins has been synthesized by heating m-diethylaminophenol, m-N-piperidinophenol, m-N-morpholinophenol, and 8-hydroxyjulolidine, respectively, with malonic acids in the presence of excess phosphorus oxychloride. The feasibility of preparing other 4-substituted 7-aminocoumarins from these 4-chloro derivatives has been demonstrated using as an example the reactions of 4-chloro-7-diethylaminocoumarins with sodium ethoxide, hydrazine, and dibutylamine. The spectral and luminescence characteristics of these newly synthesized compounds have been investigated.

Traditional methods for the synthesis of 4-substituted 7-aminocoumarins are generally based on the classical Pechman condensation of m-aminophenols with β-ketoacetic acid esters, or on modifications of this reaction [1]. The synthesis of each individual new 7-aminocoumarin derivative depends, therefore, on the availability of the corresponding carbonyl compound and on the selection of optimal reaction conditions.

An approach which seems to us to be just as promising would involve the use of reactive compounds already incorporating the aminocoumarin fragment. As part of our goal of searching for possible synthons in this regard, we have developed a method for the synthesis of 4-chloro-7-dialkylaminocoumarins.

4-Chloro-7-dialkylaminocoumarins I-VII were prepared by heating equivalent amounts of m-dialkylaminophenols with malonic acid or an appropriate alkylmalonic acid in the presence of excess phosphorus oxychloride (see scheme below).

The intermediates in this reaction are 4-hydroxy-7-dialkylaminocoumarins, which react with excess $POCl_3$ to give the final 4-chloro derivatives I-VII. This fact was confirmed by the reaction of m-diethylaminophenol with malonic acid; 4-hydroxy-7-diethylaminocoumarin [2] was isolated and identified from the reaction mixture, and upon further treatment with $POCl_3$ gave coumarin I.

The yields of compounds I-VII were in the 15-40% range (Table 1). In the case of the synthesis of coumarins I, V, and VII side products in the form of compounds VIII-X were also isolated from the reaction mixtures; these were formed in 10-15% yield as a result of condensation of the intermediate 4-hydroxycoumarins with a second molecule of malonic acid.

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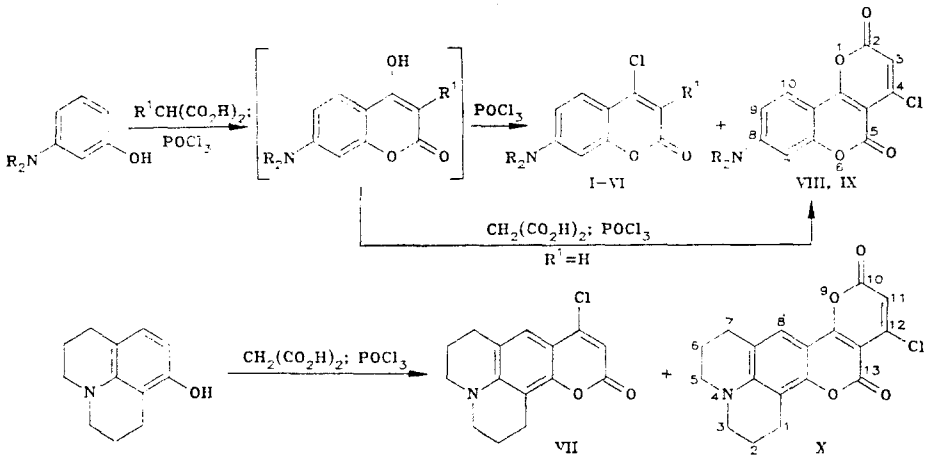
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 830-835, June, 1990. Original article submitted May 18, 1988.



I—IV, VIII $R=C_2H_5$; V, IX $R_2=-(CH_2)_5-$; VI $R_2=-(CH_2)_2O(CH_2)_2-$; I, V, VI $R^1=H$; II $R^1=C_2H_5$; III $R^1=$ cyclohexyl IV $R^1=CH_2C_6H_5$

Isolation of coumarins I-X does not present serious difficulties, but does require strict pH control during the neutralization process of the reaction mixture (see Experimental). In order to optimize this method for the synthesis of 4-chloro-7-dialkylaminocoumarins we used compound I as an example to study the effects of reagent ratio, reaction temperature, and a series of additives on the yield of product. It was found that excess (greater than 2 equiv.) malonic acid led to the formation of compound VIII predominantly, while an excess of diethylaminophenol did not change the yield of compound I, but did make it more difficult to isolate. Carrying out the reaction in $POCl_3$–PCl_5, $POCl_3$–$SOCl_2$, and $POCl_3$–$(COCl)_2$ systems did not increase the yield of coumarin I, and neither did it help to use milder reaction conditions (for example, heating to 70-90°C). As can be seen from Table 1, the yields of coumarins II-IV remain relatively low with the other alkylmalonic acids as well. The lower yield of compound VI can be attributed to opening of the morpholine ring upon action by $POCl_3$ during the course of the reaction [3].

In the PMR spectra of compounds I-VI (Table 1) the signals for the 5-H, 6-H, and 8-H aromatic protons appear slightly more downfield relative to, for instance, 4-alkyl-7-aminocoumarins [4]. The 3-H proton signal in compounds I, V, and VI undergoes an even more significant downfield shift. Signal assignments for the protons in the julolidine fragment in coumarin VII were made based on analogy with known data for the 4-methylsubstituted derivative [5]. In the spectrum of coumarin III the signal for the methine proton in the cyclohexyl substituent is observed at δ 3.12 ppm in the form of a triplet of triplets (J_1 = 10.8; J_2 = 2.0 Hz); this is indicative of an equatorial orientation for the coumarin substituent. The chemical shifts for the protons in the two β-methylene groups differ substantially ($\Delta\sim$ 0.3 ppm), which is probably associated most of all with restricted or hindered rotation about the $C_{(3)}$–$C_{(\alpha)}$ bond in compound III. The signals for the β-CH_2 protons should appear further downfield, since they are deshielded by the lactone carbonyl group [6]. The PMR spectra of compounds I and VIII, V and IX, and VII and X (Table 1) exhibit pairwise similar appearances, such as practically superimposable structures for the aromatic proton signals. The chemical shift (CS) values differ most markedly for the 5-H protons in coumarins I, V, and VII relative to the analogous protons in compounds VIII-X, which are shifted upfield by 0.4-0.5 ppm.

The carbonyl absorption bands in the IR spectra of coumarins I-VII apper in the 1690-1730 cm^{-1} region, which is normal for 7-aminocoumarins [1]. The vibrations for the aromatic fragments in these molecules give rise, as expected, to two intense bands at 1580 and 1610 cm^{-1}. Compounds VIII-X exhibit two carbonyl absorption bands in their IR spectra, 1700-1720 and 1730-1740 cm^{-1}, respectively.

The UV spectra of coumrins I-VII in ethanol or acetonitrile solution (Table 2) exhibit long-wavelength absorption bands at 370-400 nm; the position of the band depends to a larger degree on the nature of the 7-dialkylamino group than on the alkyl substituent in the 3-position. The longest-wavelength band is found for coumarin VII (λ_{max} 410 nm), the shortest-wavelength band for coumarin VI (λ_{max} 370 nm). Increasing the length of the conjugation chain in compounds VIII-X leads to a bathochromic shift of the absorption band to 430-445 nm. Compounds I-V display practically no luminescence (Table 2), in contrast to 3-chloro-4-methyl-7-diethylaminocoumarin [4], for example. 4-Chlorocoumarins VI and VII do luminescence slightly more intensely ($\varphi_j \sim 0.2$), as do the pyranocoumarins VIII-IX ($\varphi_j \sim 0.2$-0.3).

In order to evaluate the potential of using coumarins I-VII for the synthesis of other 4-substituted 7-dialkylaminocoumarins, we examined a series of reactions of compound I with nucleophilic reagents. Thus, for example, heating coumarin I with sodium ethoxide in ethanol resulted in the isolation of coumarin I in 45% yield, while refluxing coumarin I with excess dibutylamine gave the 4-dibutylamino-substituted derivative XII in excellent yield.

TABLE 1. Characteristics of Compounds I-XIII

Compound	Molecular formula	mp, °C	IR spectrum, $\nu_{C=O}$, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)							Yield, %
				3-H, s	5-H	6-H, dd	8-H, d	NCH_2	NCH_2CH_2	other protons	
I	$C_{13}H_{14}ClNO_2$	94	1692	6,19	7,59 d (9,1)	6,63 (9,1; 2,6)	6,48 (2,6)	3,42 q (7,0)	1,21 t (7,0)	—	40
II	$C_{15}H_{18}ClNO_2$	71	1699	—	7,60 d (9,1)	6,63 (9,1; 2,6)	6,48 (2,6)	3,39 q (7,0)	1,20 t (7,0)	1,15 (3H, t, 7,0, CH_3); 2,71 (2H, q, 7,0, CH_2)	34
III	$C_{19}H_{24}ClNO_2$	127	1700	—	7,60 d (9,1)	6,62 (9,1; 2,5)	6,42 (2,5)	3,39 q (7,0)	1,17 t (7,0)	1,29 ... 1,90 (8H, m, $4CH_2$); 2,13 (2H, m CH_2); 3,12 (1H, tt, 10,8, 2,0, CH)	38
IV	$C_{20}H_{20}ClNO_2$	89	1691	—	7,61 d (9,1)	6,64 (9,1; 2,5)	6,50 (2,5)	3,38 q (7,0)	1,20 t (7,0)	4,08 (2H, s, CH_2); 7,15 ... 7,40 (5H, m, C_6H_5)	42
V	$C_{14}H_{14}ClNO_2$	75	1730	6,22	7,60 d (9,0)	6,82 (9,0; 2,6)	6,65 (2,6)	3,47 q (7,0)	1,70 m	1,70 (2H, m, $NCH_2CH_2CH_2$)	27
VI	$C_{13}H_{12}ClNO_3$	225	1722	6,25	7,91 d (9,2)	6,93 (9,2; 2,6)	6,86 (2,6)	3,33 t (4,7)	3,92 t (4,7)	—	15
VII	$C_{15}H_{14}ClNO_2$	159	1695	6,10	7,18 s	—	—	3,29 q (6,2)	1,95 q (6,2)	2,77 (2H, t, J=7,0, $C_{(8)}$—CH_2CH_2); 2,85 (2H, t, J=6,2, $C_{(6)}$—CH_2CH_2)	25
XI	$C_{15}H_{19}NO_3$	84	1700	5,38	7,57 d (9,0)	6,54 (9,0; 2,6)	6,43 (2,6)	3,37 q (7,0)	1,17 q (7,0)	1,46 (3H, t, 7,0, OCH_2CH_3); 4,12 (2H, q, J=7,0, OCH_2)	45
XII	$C_{21}H_{32}N_2O_2$	Oil	1695	5,38	7,41 d (9,0)	6,52 (9,0; 2,6)	6,46 (2,6)	3,37 q (7,0)	1,20 t (7,0)	0,93 (6H, t, J=7,0 2δ-CH_3); 1,30 (4H, q, J=7,0, 2γ-CH_2); 1,61 (4H, q, J=7,0, 2β-CH_2); 3,29 (4H, t, J=7,0, 2α-CH_2)	63
XIII	$C_{13}H_{17}N_3O_2$	212	1700	5,72	7,29 d (9,0)	6,20 (9,0; 2,5)	6,18 (2,5)	3,29 q (7,0)	1,09 t (7,0)	4,00 (3H, m, $NHNH_2$)	17
VIII*	$C_{16}H_{14}ClNO_4$	189	1720	6,24						—	
IX**	$C_{17}H_{14}ClNO_4$	228	1710, 1740	6,29						1.70 (2H, m, $NCH_2CH_2CH_2$)	14
X***	$C_{18}H_{14}ClNO_4$	247	1700							2,79 (2H, t, J=6,3, $C_{(14b)}$—CH_2); 2,83 (2H, t, J=6,3, $C_{(7a)}$-CH_2)	11

*PMR spectrum, δ: 7.80 (10-H, d, J = 9.1 Hz); 6.67 (9-H, d.d, J = 2.6, J = 9.1 Hz); 6.24 (7-H, d, J = 2.6 Hz); 3.47 (8-NCH_2, q, J = 7.0 Hz); 1.25 ppm (8-NCH_2CH_2R, t, J = 7.0 Hz).

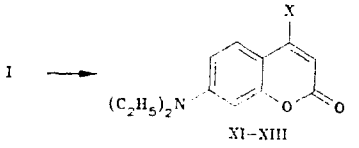
**PMR spectrum, δ: 7.82 (10-H, d, J = 9.1 Hz); 6.89 (9-H, d.d, J = 9.1, J = 2.6 Hz); 6.62 (7-H, d, J = 2.6 Hz); 3.44 (8-NCH_2, m); 1.70 ppm (8-NCH_2CH_2R, m).

***PMR spectrum, δ: 6.21 (11-H, s); 7.45 (8-H, s); 3.46 (4-NCH_2, q, J = 6.3 Hz); 2.00 ppm (4-NCH_2CH_2R, q, J = 6.3 Hz).

TABLE 2. Spectral-Luminescence Characteristics of Compounds I-XIII

Compound	Solvent	Absorption, λ_{max}, nm (log ε)	Luminescence		
			λ_{exc}, nm	λ_{max}, nm	φ^*_f
I	C_2H_5OH	248 (4,23), 286 (3,41), 308 (3,41), 390 (4,42)	390	470	<0,10
	CH_3CN	248 (4,20), 252 (4,15), 285 (3,33), 318 (3,49), 386 (4,42)	390	460	<0,10
II	C_2H_5OH	250 (4,26), 259 (4,21), 284 (3,39), 310 (3,53), 320 (3,60), 386 (4,45)	380	474	<0,10
	CH_3CN	249 (4,23), 259 (4,16), 284 (3,35), 320 (3,65), 380 (4,44)	380	474	<0,10
III	C_2H_5OH	251 (4,31), 258 (4,27), 284 (3,57), 308 (3,60), 319 (3,66), 386 (4,50)	380	465	<0,10
	CH_3CN	250 (4,23), 258 (4,20), 284 (3,51), 320 (3,66), 382 (4,46)	380	440	<0,10
IV	C_2H_5OH	254 (4,26), 284 (3,49), 308 (3,45), 320 (3,49), 392 (4,46)	390	475	<0,10
	CH_3CN	250 (4,22), 256 (420), 284 (3,49), 308 (3,49), 320 (3,56), 387 (4,46)	380	460	<0,10
V	C_2H_5OH	250 (4,20), 320 (3,55), 385 (4,35)	390	480	<0,10
	CH_3CN	249 (4,18), 319 (3,63), 380 (4,37)	390	467	<0,10
VI	C_2H_5OH	212 (4,54), 246 (4,13), 370 (4,32)	370	474	0,17
	CH_3CN	212 (4,49), 244 (4,14), 366 (4,36)	360	465	<0,10
VII	C_2H_5OH	255 (4,10), 263 (4,07), 292 (3,36), 410 (4,42)	410	490	0,23
	CH_3CN	254 (4,02), 260 (3,97), 293 (3,53), 404 (4,59)	410	480	0,10
VIII	C_2H_5OH	240 (4,34), 247 (4,35), 308 (3,75), 326 (3,88), 430 (4,73)	430	520	0,22
VIII	CH_3CN	236 (4,32), 245 (4,32), 308 (3,80), 324 (3,92), 428 (4,73)	430	490	0,22
IX	C_2H_5OH	244 (4,33), 322 (3,85), 428 (4,64)	410	510	0,23
	CH_3CN	240 (4,26), 322 (3,83), 425 (4,59)	410	496	0,26
X	C_2H_5OH	247 (4,21), 296 (3,73), 370 (3,78), 446 (4,66)	410	510	<0,10
	CH_3CN	253 (4,05), 258 (4,00), 340 (3,79), 445 (4,61)	410	505	<0,10
XI	C_2H_5OH	247 (4,37), 307 (3,86), 357 (4,52)	350	426	0,49
	CH_3CN	242 (4,48), 307 (3,96), 353 (4,51)	350	417	0,70
XII	C_2H_5OH	252 (4,23), 297 (4,27), 358 (4,50)	350	440	0,15
	CH_3CN	250 (4,14), 298 (4,17), 356 (4,43)	350	440	0,10
XIII	C_2H_5OH	218 (4,45), 293 (4,26), 327 (4,25), 359 (3,92)	330	410	0,58
	CH_3CN	216 (4,28), 245 (3,93), 293 (4,02), 320 (4,08), 354 (4,37)	330	412	0,10

*φ_f is the quantum yield.



XI–XIII

XI X=OC_2H_5; XII X=$N(C_4H_9\text{-}p)_2$; XIII X=$NHNH_2$

The reaction of coumarin I with hydrazine hydrate is even more effective. 4-Hydrazinocoumarin XIII was obtained in 65% yield upon brief mixing of the reagents in DMF solution at room temperature, along with 7-diethylaminocoumarin XIV as a side product [7]; this can be explained in terms of the reductive ability of hydrazine. The rapid reaction of coumarin I with hydrazine hydrate can be rationalized, apparently, in terms of the "supernucleophilic" properties of hydrazine (α-effect [8]), since use of DMF as the solvent in the case of reaction with dibutylamine did not lead to rate acceleration for that reaction.

In the PMR spectra of coumarins XI-XIII the greatest change is observed in the position of the 3-H proton signal, which is very sensitive to the electronic effect of the group in the 4-position. For the substituent series Cl → H → $NHNH_2$ → OC_2H_5 ~ $N(C_4H_9)_2$ in the transition from coumarin I to coumarin XI this signal is shifted upfield by a total of 0.8 ppm (Table 1).

The electronic spectra of compounds XI-XIII in ethanol and acetonitrile solution exhibit long-wavelength absorption bands at 350-360 nm and emission bands in the 410-440 nm region (Table 2). Coumarins XI and XIII display relatively intense luminescence (φ_f 0.5-0.7).

In conclusion, therefore, the 4-chlorosubstituted coumarin derivatives I-VII may be regarded as convenient intermediates for the direct synthesis of other 4-substituted 7-aminocoumarins.

EXPERIMENTAL

IR spectra were recorded on a Jasco IR-S spectrophotometer, UV spectra and luminescence spectra on a Hitachi EPS-3T spectrophotometer with a G-3 luminescence adapter. Relative fluorescence quantum yields were determined using a standard procedure [9] with quinine bisulfate. PMR spectra were obtained on a Bruker WM spectrometer (250 MHz) using $CDCl_3$ solutions (versus HMDS as internal standard).

Reaction products were isolated by column chromatography (30 × 2.0 cm) on Silufol UV-254 silica gel using hexane–acetone eluent system. Reaction course and reagent purity were monitored by TLC using Silufol UV-254 plates.

The physical characteristics of coumarins I-XIII are summarized in Tables 1 and 2. The results of elemental analysis for all the newly synthesized compounds agreed with calculations.

General Procedure for 4-Chloro-7-dialkylaminocoumarins I-VII and Pyranocoumarins VIII-X. To a mixture of 30 mmoles m-dialkylaminophenol and 30 mmoles of the appropriate malonic acid was added dropwsie 150 mmoles of phosphorus oxychloride and the mixture was heated at 90-100°C for 3 h. Upon completion of the reaction 20 ml water was added to the mixture and the aqueous phase was then neutralized with 20% NaOH solution to pH 8. The aqueous organic mixture was extracted with methylene chloride (4 × 50 ml), the extract was evaporated, and the residue was separated chromatographically. Coumarins I-VII were isolated by evaporation from the fraction with R_f 0.5-0.7 (hexane–acetone, 1:1). Compounds VIII-X were isolated from the R_f 0.2-0.3 fraction (hexane–acetone, 1:1). Analytical samples of chromatographically pure products I-X were obtained by recrystallization from hexane–acetone.

3-Ethoxy-7-diethylamino-2H-benzopyran-2-one (XI). Metallic sodium (0.46 g, 20 mmoles) was dissolved in 20 ml absolute ethanol and a solution of 1.25 g (5 mmoles) coumarin I in 10 ml ethanol was then added to the resulting (ethoxide) solution. The mixture was refluxed in a flask for 2 h to complete disappearance of the coumarin starting material (TLC control). The reaction mixture was then evaporated under vacuum and the residue was chromatographed using hexane–acetone, 5:1, eluent system. The R_f 0.15 fraction was collected. Yield 0.62 g (45%) of compound XI with mp 84°C (from hexane–acetone).

4-n-Dibutylamino-7-diethylamino-2H-benzopyran-2-one (XII). A solution of 1.25 g (5.0 mmoles) coumarin I in 40 ml dibutylamine was refluxed in a flask for 5 h. The reaction mixture was evaporated under vacuum and the residue was chromatographed. Coumarin XII was isolated (in the form of an oil) in 1.08 g (63%) yield from the R_f 0.30 fraction (hexane–acetone, 4:1).

4-Hydrazino-7-diethylamino-2H-benzopyran-2-one (XIII) and 7-Diethylamino-2H-benzopyran-2-one (XIV). A solution of 1.25 g (5 mmoles) coumarin I and 0.50 g (10 mmoles) hydrazine hydrate in 20 ml DMF was stirred for 0.5 h at room temperature. The solvent DMF was evaporated under vacuum and the residue was chromatographed using hexane–acetone, 2:1, eluent system. The R_f 0.22 fraction gave 0.81 g (65%) compound XIII, mp 212°C (from acetone).

The R_f 0.43 fraction gave 0.29 g (27%) coumarin XIV, mp 90°C (from hexane–acetone mixture). According to [7], mp 90°C. PMR spectrum: 7.55 (1H, d, J = 9.3 Hz, 4-H); 7.23 (1H, d, J = 9.0 Hz, 5-H); 6.56 (1H, d.d, J_1 = 9.0, J_2 = 2.9 Hz, 6-H); 6.33 (1H, d, J = 2.9 Hz, 8-H); 5.80 (1H, d, J = 9.3 Hz, 3-H); 3.35 (4H, q, J = 7.0 Hz, $2CH_2$), and 1.13 ppm (6H, t, J = 7.0 Hz, $2CH_3$).

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