REACTIONS OF 4-CHLORO-7-DIALKYLAMINO- AND 3-ALKYL-4-CHLORO-7-DIALKYLAMINOCOUMARINS WITH PRIMARY AND SECONDARY ALKYLAMINES

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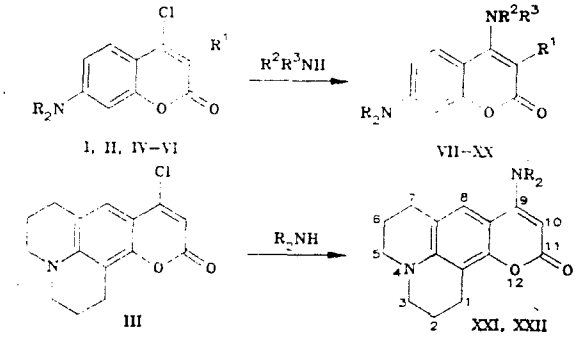
Reaction of series of 4-chloro-7-dialkylaminocoumarins and 3-alkyl-4-chloro-7-dialkylaminocoumarins with primary and secondary amines, namely tert-butylamine, benzylamine, cyclohexylamine, monoethanolamine, diethylamine, piperidine, and morpholine, has yielded novel substituted 4,7-diaminocoumarins. The PMR spectra of these newly synthesized compounds are discussed.

We have previously [1] described a method for the preparation of 4-chloro-7-dialkylaminocoumarins I-III and 3-alkyl-4-chloro-7-dialkylaminocoumarins IV-VI and have demonstrated the feasibility of using these compounds for the synthesis of other 7-aminocoumarins. As part of a more extensive evaluation of the synthetic potential of 4-chlorocoumarins we have in the present paper undertaken a more detailed study of the reactions of compounds I-VI with primary and secondary amines (tert-butylamine, benzylamine, cyclohexylamine, monoethanolamine, diethylamine, piperidine, and morpholine), and have prepared in this manner a series of new 4,7-diaminocoumarins VII-XXII, which appear to be promising luminophores.

The reactions of 4-chloro-7-dialkylaminocoumarins I-VI with amines occur upon heating the reagents for 5-10 h in the absence of solvent or in DMF solution at 100-150°C. The yields of the resulting 4,7-diaminocoumarins VII-XXII are in the 50-70% range (Table 1). The relatively high reaction temperature is needed for complete reaction to occur. For this reason the use of DMF is advantageous only for low-boiling amines [$(C_2H_5)_2NH$, $(CH_3)_3CNH_2$] and does not lead to increased yields in the other cases. In most of the reactions a significant excess (>50 equiv.) of amine relative to 4-chlorocoumarin derivative was used.



I, IV—XVII, XXI $R=C_2H_5$; II, XIX, XX, XXII $R_2=(CH_2)_2O(CH_2)_2$; I, II, VII—XIII, XIX, XX $R^1=H$; IV, XIV $R^1=C_2H_5$; V, XV, XVI $R^1=CH_2C_6H_5$; VI, XVII, XVIII $R^1=$ = cyclohexyl VII—X, XV, XVII $R^2=H$; XI, XX $R^2=C_2H_5$; XII $R^2R^3=(CH_2)_5$; XIII, XIV, XVI, XVIII, XIX $R^2R^3=(CH_2)_2O(CH_2)_2$; VII $R^3=t$-C_4H_9; VIII, XV $R^3=CH_2C_6H_5$; IX, XVII $R^3=$cyclohexyl X, XI $R^3=CH_2CH_2OH$

These reactions may be classified apparently as nucleophilic substitution reactions at an sp^2-carbon atom, occurring via either an addition–elimination or tetrahedral mechanism [2]. Nucleophilic attack at the carbonyl group may compete with this process, and would be expected to give chlorocoumarinic acid amide derivatives. The formation of 4,7-diaminocoumarins VII-XXII, therefore, can be explained to a first approximation in terms of the strong nucleofugacity of the chlorine anion; after elimination of the latter the process becomes irreversible. In contrast, reaction at the carbonyl group would be expected to be reversible in the initial stages (addition, ring opening).

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TABLE 1. Characteristics of Compounds VII-XXI

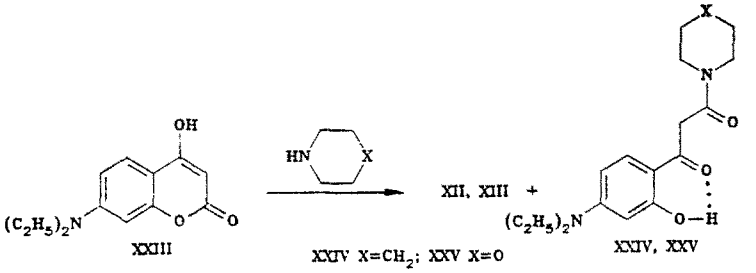
Compound	Molecular formula	mp, °C	IR spectrum, $\nu_{C=O}$, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)							Yield, %
				3-H, s	5-H, d	6-H, dd	8-H, d	7-NCH_2	7-NCH_2CH_2R	other protons	
VII	$C_{17}H_{24}N_2O_2$	186,5	1672	5,32	7,17 (9,0)	6,55 (9,0; 2,7)	6,46 (2,7)	3,36 q (7,0)	1,15 t (7,0)	1,45 (9H, s, $C(CH_3)_3$; 4,91 (1H, s, NH)	48
VIII	$C_{20}H_{22}N_2O_2$	212	1660	5,19	7,35 (9,0)	6,61 (9,0; 2,6)	6,49 (2,6)	3,38 q (7,0)	1,18 t (7,0)	4,42 (2H, d, J=5,1, CH_2); 5,40 (1H, m, NH); 7,38 (5H, s, C_6H_5)	65
IX	$C_{19}H_{26}N_2O_2$	197	1655	5,12	7,22 (9,0)	6,57 (9,0; 2,7)	6,48 (2,7)	3,37 q (7,0)	1,18t (7,0)	1,3...2,1 (10H, m, $-(CH_2)_5-$); 3,36 (1H, m, CH); 4,88 (1H, s, NH)	71
X	$C_{15}H_{20}N_2O_2$	208	1657	5,10	7,41 (9,0)	6,54 (9,0; 2,6)	6,43 (2,6)	3,35q (7,0)	1,15 t (7,0)	2,60 (1H, s, OH); 3,32 (2H, m, NCH_2); 3,93 (2H, m, OCH_2); 5,87 (1H, s, NH)	47
XI	$C_{17}H_{24}N_2O_2$	65	1691	5,37	7,43 (9,0)	6,58 (9,0; 2,5)	6,50 (2,5)	3,36q (7,0)	1,18 t (7,0)	1,22 (6H, t, J=7,0, 4-$N(CH_2CH_3)_2$); 3,40 (4H, q, J=7,0 $N(CH_2CH_3)_2$)	49
XII	$C_{18}H_{24}N_2O_2$	118,5	1682	5,39	7,35 (9,0)	6,52 (9,0; 2,5)	6,43 (2,5)	3,38q (7,0)	1,18 t (7,0)	1,70 (6H, m, $(CH_2)_3$); 3,16 (4H, m, $N(CH_2)_2$)	53
XIII	$C_{17}H_{22}N_2O_3$	134	1700	5,43	7,39 (9,0)	6,57 (9,0; 2,5)	6,48 (2,5)	3,39q (7,0)	1,20 t (7,0)	3,22 (4H, t, J=4,6, $N(CH_2)_2$); 3,88 (4H, t, J=4,6, $O(CH_2)_2$)	55
XIV	$C_{16}H_{26}N_2O_3$	139	1698	—	7,60 (9,0)	6,63 (9,0; 2,5)	6,55 (2,5)	3,44q (7,0)	1,22 t (7,0)	1,21 (3H, t, J=7,0, CH_3); 2,70 (2H, q, J=7,0, CH_2); 3,32 (4H, m, $N(CH_2)_2$); 3,95 (4H, m, $O(CH_2)_2$)	58
XV	$C_{27}H_{28}N_2O_2$	156,5	1655	—	7,48 (9,0)	6,62 (9,0; 2,5)	6,54 (2,5)	3,38q (7,0)	1,17 t (7,0)	3,91 (2H, s, CH_2); 4,38 (2H, d J=5,0, NH—CH_2); 4,49 (1H, m, H); 7,0...7,4 (10H, m, $2C_6H_5$)	63
XVI	$C_{24}H_{28}N_2O_3$	150	1699	—	7,60 (9,0)	6,65 (9,0; 2,6)	6,62 (2,6)	3,47q (7,0)	1,21 t (7,0)	4,11 (2H, s, $CH_2C_6H_5$); 3,20 (4H, m, $N(CH_2)_2$; 3,80 (4H, m, $O(CH_2)_2$); 7,25 (5H, m, C_6H_5)	72
XVII	$C_{25}H_{36}N_2O_2$	193	1654	—	7,37 (9,1)	6,52 (9,1; 2,7)	6,41 (2,7)	3,36 q (7,0)	1,15t (7,0)	1,20...2,25 (18H, m, $9CH_2$); 2,20 (2H, m, CH_2); 2,55 (1H, tt, J=10,8; 2,1, CH—$C_{(3)}$); 3,35 (1H, m, CH-NH); 4,89 (1H, s, NH)	69
XVIII	$C_{23}H_{32}N_2O_3$	204	1700	—	7,62 (9,1)	6,58 (9,1; 2,6)	6,46 (2,6)	3,37 q (7,0)	1,15t (7,0)	1,20...1,85 (8H, m, $4CH_2$); 2,20 (2H, m, CH_2); 2,85 (1H, tt, J=10,8; 2,1, CH—$C_{(3)}$); 3,19 (4H, t, J=4,6, $N(CH_2)_2$); 3,85 (4H, t, J=4,6, $O(CH_2)_2$)	54
XIX	$C_{17}H_{20}N_2O_4$	158	1695	5,55	7,43 (9,0)	6,80 (9,0; 2,6)	6,72 (2,6)	3,21m	3,88 m	3,27 (4H, m, $N(CH_2)_2$); 3,90 (4H, m, $O(CH_2)_2$)	65
XX	$C_{19}H_{21}N_2O_2$	165	1663	5,44	7,49 (9,1)	6,74 (9,1; 2,7)	6,68 (2,7)	3,20 t (5,6)	3,85 t (5,6)	1,22 (6H, t, J=7,0, 4-$N(CH_2CH_3)_2$); 3,40 (4H, q, J=7,0, 4-$N(CH_2CH_3)_2$)	53
XXI*	$C_{16}H_{21}N_2O_2$	140	1695							1,17 (6H, t, J=7,0, 9-$N(CH_2CH_3)_2$); 2,75 (2H, t, J=6,1, $CH_2—C_{(12b)}$); 2,85 (2H, t, J=6,1, $CH_2—C_{(7a)}$); 3,41 (4H, q, J=7,0, 9-$N(CH_2CH_3)_2$	65
XXII**	$C_{19}H_{22}N_2O_3$	164	1692							2,72 (2H, t, J=6,2, $CH_2—C_{(12b)}$; 2,85 (2H, t, J=6,2, $CH_2—C_{(7a)}$); 3,18 (4H, m, $N(CH_2)_2$); 3,87 (4H, m, $O(CH_2)_2$)	67

*PMR spectrum, δ: 5.39 (10-H, s); 7.03 (8-H, s); 3.20 (4-NCH_2, q, J = 6.1 Hz); 1.93 ppm (4-NCH_2CH_2R, m).

**PMR spectrum, δ: 5.42 (10-H, s); 6.95 (8-H, s); 3.20 (4-NCH_2, q, J = 6.2 Hz); 1.91 ppm (4-NCH_2CH_2R, q, J = 6.2 Hz).

The above hypothesis is supported by our observations concerning the reaction of 4-hydroxy-7-diethylaminocoumarin XXIII [3] with piperidine and morpholine, which were carried out by prolonged heating with excess amine. In this case, in addition to coumarins XII and XIII (in 30-35% yields), amides XXIV and XXV were also isolated from the reaction mixture in comparable amounts (see Experimental). The reduced propensity of the hydroxyl group relative to chlorine anion with respect to elimination thus leads to a leveling of the reactivity at the two reaction sites $C_{(4)}$ and $C_{(2)}$.

Another factor which is responsible for preferential or predominant attack of the N-nucleophile at the 4-position in chlorocoumarins I-VI is the greater shielding of the $C_{(2)}$ reactive site compared to the $C_{(4)}$ atom. This latter fact is apparent if one takes into account that nucleophilic attack takes place preferentially at a small angle (~60°) relative to the plane of the σ-skeleton in the multiple bond, in the direction of the sp^2-carbon atom and from the side of the least amount of overlap with the π-bond [4].



Based on their PMR spectral data, compounds XXIV and XXV exist in their chelate forms, as evidenced the weak field CS of the phenolic protons (δ ~ 12.5 ppm), which are engaged in intramolecular hydrogen bonding (IMHB) with the proximate carbonyl group; this is also confirmed by the IR spectra of amides XXIV and XXV, in which the carbonyl absorption band is shifted toward lower frequency (~1650 cm^{-1}).

In the IR spectra of 4,7-diaminocoumarins VII-XXII their carbonyl absorption bands appear in the 1655-1700 cm^{-1} range (Table 1). The aromatic C=C bond vibrations give rise to two intense bands at normal frequencies of 1580 and 1610 cm^{-1}.

The PMR spectra of compounds VII-XXII provide the most information (see Table 1). In the case of coumarins VII-XXII, XIX, and XX, which have substituents only in the 4- and 7-positions, the 3-H, 5-H, 6-H, and 8-H aromatic proton signals are well resolved; each of these proton signals can be easily identified in the 6.4-7.6 ppm region based on the splitting pattern in the spectrum [5]. The 3-H proton signal in these compounds displays a substantial upfield shift compared to, for example, the signal in 7-diethylaminocoumarin (5.80 ppm [6]), appearing in the form of a singlet at 5.1-5.4 ppm. The presence of an alkyl substituent in the 3-position in coumarins XIV-XVIII does not produce dramatic changes in the CS of the 5-H, 6-H, and 8-H protons. The signal for the 10-H proton in compounds XXI and XXII* is displaced toward higher field (~7.0 ppm) due to the effect of the julolidine fragment [5].

The NH proton signal for coumarins VII-IX, XV, and XVII is observed in the 4.5-4.9 ppm region, but is shifted significantly downfield in the case of coumarin X (5.87 ppm), possibly due to the influence of IMHB formation.

Signal assignments for the alkyl substituent protons in coumarins VII-XXII are somewhat more difficult to make. In the case of the cyclohexylamino-derivatives IX and XVII the methine proton signal for the CH–N fragment is masked by the quartet due to the methylene protons in the 7-diethylamino group at 3.4 ppm. The chemical shifts for the remaining cyclohexane protons occur in the 2.0-3.0 ppm range, in the form of three multiplets at 2.0, 2.3, and 2.5 ppm. The signal for the methine proton in the 3-cyclohexyl-substituted coumarins XVII and XVIII consists of a triplet of triplets at 2.6-2.9 ppm (J_1 = 10.8, J_2 = 2.1 Hz), indicative of an equatorial orientation of the coumarinyl fragment [7]. In the 3,4-disubstituted 7-aminocoumarin derivatives XIV-XVI the methylene proton signals for the 3-alkyl groups do not display any asymmetry associated with nonequivalent chemical environments, while in compounds XVII and XVIII the protons for the two β-methylene groups differ from one another by more than 0.4 ppm, apparently due to hindered or restricted rotation about the $C_{(3)}$–C(α) bond. We assign the more downfield signal (2.2 ppm) in this case to the β-CH_2 protons, which are close to the exocyclic oxygen atom and thus under the deshielding influence of the carbonyl group [7].

In the PMR spectra of the 4-morpholino derivatives XIII, XIV, XVI, XVIII, XIX, and XXII the protons for the morpholino group are observed in the form of two characteristic groups of triplets or distorted triplet signals at 3.2-3.3 and 3.8-4.0 ppm. The signal assignments for the julolidine fragment in coumarins XXI and XXII were made based on the results of a previous study [5]. In the case of the symmetrically substituted 4,7-bis(dialkylamino)coumarin derivatives XI and XIX the

*For atom numeration sequence, cf. Scheme.

CS values for the 4- and 7-dialkylamino groups do not overlap exactly (see Table 1). Comparison of the PMR spectra of compounds XI-XIII, XIX, and XX reveals, however, that under almost equivalent or identical conditions the signals for 4-dialkylamino groups are found further downfield than those for 7-dialkylamino groups (compare, for example, compounds XIII and XX). For this reason, in the case of coumarins XI and XIX, the more upfield groups of signals are assigned to the substituent in the 7-position. In addition, based on comparison of the spectra of coumarins XI-XIII, XIX, and XX we conclude that the interactive effect of a substituent in the 7-position on the substituent in the 4-position is greater than the reverse effect. This relatively unexpected conclusion is supported by the observation that the CS for the aromatic 3-H, 6-H, and 8-H protons in compounds XI-XIII, XIX, and XX and others are more sensitive to the effect of a substituent attached to the $C_{(7)}$ atom than one attached to $C_{(4)}$. At the same time, in the series of 7-diethylaminocoumarins XI-XIII the signals for the 3-H, 6-H, and 8-H protons are shifted in the spectra by no more than 0.10 ppm. The transition to coumarins XIX and XX is accompanied, however, by shift changes up to 0.18 ppm for the 3-H proton and up to 0.30 ppm for the 6-H and 8-H protons.

The electronic spectra of coumarins VII-XXII exhibit long-wavelength absorption bands in the 350-380 nm region. Most of these newly synthesized compounds also display intense luminescence in the 400-460 nm range. Data concerning this and other properties of 4,7-diaminocoumarins VII-XXI will be the subject of a separate publication.

EXPERIMENTAL

IR spectra were recorded on a Jasco IR-S spectrophotometer, PMR spectra on a Bruker WM (250 MHz) spectrometer for $CDCl_3$ solutions (versus HMDS as internal standard).

The reaction products were isolated by column chromatography (30 × 2.0 cm) on Silpearl UV-254 silica gel using hexane–acetone eluent systems. The newly synthesized compounds were also recrystallized from a mixture of hexane and acetone. Reagent purity was assessed by TLC on Silufol UV-254 plates (which were visualized in UV light or with iodine). The physical and spectral characteristics of coumarins VII-XXII are summarized in Table 1. The results of C, H, and N elemental analysis for the newly synthesized compounds agreed with calculations.

General Method for the Preparation of 4,7-Diaminocoumarins VII-XXII. A solution of 5.0 mmoles coumarin I-VI in 30 ml of the appropriate amine or in a solution of 30 ml amine in 30 ml DMF was refluxed in a round-bottomed flask equipped with a condenser for 2-5 h, to complete disappearance of the 4-chlorocoumarin starting material (TLC control). The reaction mixture was evaporated under vacuum and the residue was chromatographed, collecting the fraction which luminesced under UV light. The R_f values for compounds VII-XXII on Silpearl silica gel with hexane–acetone, 1:1 as eluent were 0.10-0.50.

(2'-Hydroxy-4'-diethylaminobenzoyl)acetic Acid Piperidide (XXIV, $C_{18}H_{26}N_2O_3$). The reaction mixture obtained upon heating 1.17 g (5.0 mmoles) coumarin XXIII in 40 ml piperidine was subjected to chromatographic resolution in 2:1 hexane–acetone, and the R_f 0.30 fraction was collected, yielding 0.53 g (35%) of coumarin XII, while the R_f 0.25 fraction gave 0.51 g (32%) of compound XXIV, mp 82°C. IR spectrum (KBr): 3500 (OH), 1650 (C=O), 1630, 1600 cm^{-1} (C=C). PMR spectrum (in $CDCl_3$): 12.55 (1H, s, OH); 7.60 (1H, d, J = 9.0 Hz, 6'-H); 6.10 (1H, d.d, J_1 = 9.0, J_2 = 2.5 Hz, 5'-H); 5.93 (1H, d, J = 2.5 Hz, 3'-H); 3.97 (2H, s, CH_2CO); 3.36 and 3.50 (each 2H, m, two NCH_2); 3.30 [4H, q, J = 7.0 Hz, $N(CH_2CH_3)_2$]; 1.47 (6H, m, two $-(CH_2)_3-$); 1.10 ppm [6H, t, J = 7.0 Hz,$N(CH_2CH_3)_2$].

(2'-Hydroxy-4-diethylaminobenzoyl)acetic Acid Morpholide (XXV, $C_{17}H_{24}N_2O_4$). The reaction mixture obtained upon heating 1.17 g (5.0 mmoles) coumarin XXIII and 35 ml morpholine was subjected to chromatographic separation using 2:1 hexane–acetone; the R_f 0.29 fraction yielded 0.47 g (31%) coumarin XIII, while the R_f 0.23 fraction gave 0.60 g (37%) of compound XXV, mp 98°C. IR spectrum (KBr): 3500 (OH), 1650 (C=C), 1630, 1600 cm^{-1} (C=C). PMR spectrum (in CDCl3): 12.52 (1H, s, OH); 7.68 (1H, d, J = 9.0 Hz, 6'-H); 6.21 (1H, d.d, J_1 = 9.0, J_2 = 2.5 Hz, 5'-H); 6.06 (1H, d, J = 2.5 Hz, 3'-H); 3.95 (2H, s, CH_2CO); 3.57 and 3.64 (each 2H, m, two NCH_2); 3.39 [4H, q, J = 7.0 Hz, $N(CH_2CH_3)_2$]; 1.19 ppm [6H, t, J = 7.0 Hz, $N(CH_2CH_3)_2$].

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