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REACTIONS OF 3-IODO-7-DIALKYLAMINOCOUMARINS WITH SECONDARY AMINES

M. A. Kirpichënok, L. Yu. Fomina, and I. I. Grandberg

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The reaction of 3-iodo-7-diethylaminocoumarin and 2,3,6,7-tetrahydro-10-iodo-1H,5H-quinolizino[9,9a,1-gh]coumarin with secondary amines (diethylamine, piperidine, morpholine, imidazole, and benzimidazole) leads to 4,7-diaminocoumarins. The corresponding 3-iodo-4-chloro-7-dialkylaminocoumarins under similar conditions give 3-iodo-4,7-diaminocoumarins. 4-Aminomethyl derivatives of coumarins are formed in the reactions of 3-iodo-4-methyl-7-diethylaminocoumarin and 2,3,6,7-tetrahydro-9-methyl-10-iodo-1H,5H-quinolizino[9,9a,1-gh]coumarin with these secondary amines.

The controversy regarding the transformation pathways of 3-halocoumarins [1-3], as well as other closely related compounds such as 3-nitro-4-halocoumarins [4], in reactions with nucleophiles currently continues in the literature. It is known [1] that the reaction of 3-halocoumarins with strong nucleophilic reagents, including amines, can lead, depending on the substituent in the 4 position, to the usual products of nucleophilic substitution or may be accompanied by contraction of the pyrone ring, which leads to benzofuran derivatives [2]. It is also known that the reaction of 3-bromo-4-methylcoumarin with secondary amines is accompanied by the elimination of a hydrogen halide and leads to the corresponding aminomethyl derivatives in addition to products of nucleophilic substitution at the sp^2 carbon atom [5].

To ascertain the specific character of analogous reactions in the 3-halo-7-aminocoumarin series [6] in the present research we studied the reaction of I-VI with a number of secondary amines, viz., diethylamine, piperidine, morpholine, imidazole, and benzimidazole.

The most efficient reactions were observed when I-VI were heated with excess amine in solution in DMF and DMSO or without a solvent. As a result, we found that the starting coumarins can be divided into three types with respect to nucleophilic reagents.

On heating for 4-6 h at 80-120°C in an excess ($\geq$10 equivalents) of the amine, I and II gave amino-substituted derivatives VII-XII in 60-80% yields (Table 1) (see scheme on next page).

Under similar conditions dihalo derivatives III and IV gave 3-iodo-4,7-diaminocoumarins XIII-XVI in high yields (see Table 1). Compounds XIII-XVI are rather unstable substances that are sensitive to the action of light and decompose appreciably during chromatographic separation on silica gel to give dehalogenation products VIII-X and XII.

In contrast to I-IV, coumarins V and VI were converted to 4-aminomethyl derivatives XVII-XXIII, the yields of which reached 60-70%, in reactions with the amines. A more detailed analysis of the compositions of the reaction

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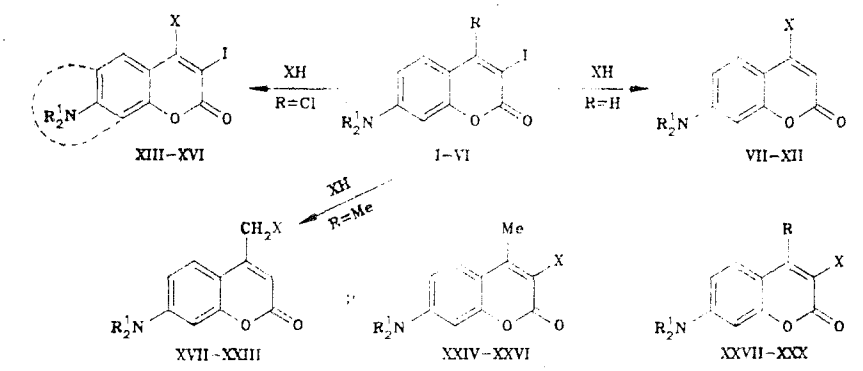
TABLE 1. Physicochemical Characteristics of Coumarins VII-XXVI

Compound*	Empirical formula	mp, °C	R_f**	IR spectrum, $\nu_{C=O}$, cm^{-1}	Yield, %
VII	$C_{17}H_{24}N_2O_2$	119	0,30	1682	66
VIII	$C_{17}H_{22}N_2O_3$	134	0,20	1700	75
IX	$C_{16}H_{17}N_3O_2$	132	0,22	1700	65
X	$C_{20}H_{19}N_3O_2$	134	0,27	1720	71
XI	$C_{19}H_{22}N_2O_3$	164	0,21	1692	78
XII	$C_{18}H_{17}N_3O_2$	160	0,19	1710	63
XIII	$C_{17}H_{21}IN_2O_3$	145 dec.	0,17	1700	50
XIV	$C_{16}H_{16}IN_3O_2$	184	0,21	1710	57
XV	$C_{20}H_{18}IN_3O_2$	203	0,29	1720	62
XVI	$C_{18}H_{16}IN_3O_2$	234	0,23	1710	48
XVII	$C_{18}H_{26}N_2O_2$	dec.	0,36	1710	63
XVIII	$C_{19}H_{26}N_2O_2$	76	0,34	1710	58
XIX	$C_{18}H_{24}N_2O_3$	97	0,34	1715	65
XX	$C_{17}H_{19}N_3O_2$	184	0,05	1700	67
XXI	$C_{21}H_{21}N_3O_2$	202	0,16	1710	70
XXII	$C_{20}H_{24}N_2O_3$	171	0,34	1710	64
XXIII	$C_{19}H_{19}N_3O_2$	224	0,02	1700	68
XXIV	$C_{19}H_{26}N_2O_2$	95	0,86	1710	17
XXV	$C_{18}H_{24}N_2O_3$	132	0,49	1715	20
XXVI	$C_{20}H_{24}N_2O_3$	151	0,37	1710	15

*The physicochemical characteristics of VII, VIII, and XI were in agreement with the data in [7], while the characteristics of XIII were in agreement with the data in [6].

**The R_f values were measured on Silufol UV-254 plates in a hexane—acetone (2:1) system.



I, II, XXVII R=H; III, IV R=Cl; V, VI, XXVIII—XXX R=CH_3; I, III, V, VII—X, XIII—XV, XVII—XXI, XXIV, XXV, XXVIII—XXX R^1=C_2H_5; II, IV, VI, XI, XII, XVI, XXII, XXIII, XXVI, XXVII R^1=—$(CH_2)_3$—C·orthoVII, XVII X=$N(C_2H_5)_2$; VIII, XI, XIII, XIX, XXII, XXV, XXVI X= morpholino; IX, XII, XIV, XVI, XX, XXIII X=N-imidazolyl X, XV, XXI X=N-benzimidazolyl;XVIII, XXIV X= piperidinoXXVII—XXIX X=H; XXX X=NH_2

mixtures carried out in the case of the reactions of coumarin V with piperidine and coumarins V and VI with morpholine also indicates the formation of small amounts (≲20%) of side products, to which the structure of 3-amino derivatives XXIV-XXVI was assigned. Only trace amounts of side compounds were detected in the reactions of coumarins V and VI with diethylamine, imidazole, or benzimidazole.

The structures of coumarins IX, X, XII, and XIV-XXVI were confirmed by the necessary physicochemical methods (Tables 1-5) and, for the previously described [6, 7] VII, VIII, XI, and XIII, also by comparison with samples obtained by an independent method from the corresponding 4-chloro-7-aminocoumarins [8]. In our study of the properties of coumarins VII-XXVI we also used the known coumarins XXVII-XXX [9] as models for comparison.

TABLE 2. PMR Spectra of Coumarins IX, X, XIV, XV, XVII-XXI, XXIV, and XXV in $CDCl_3$

Compound	Chemical shifts, ppm (SSCC, J, Hz)						
	3-H	6-H (d J=9,0)	6-H d.d J=9,0; 2,6)	8-H (d J=2,6)	7-NCH_2 (q J=7,0)	7-NCH_2CH_3 (t J=7,0)	other protons
IX	5,95 s	7,30	6,59	6,56	3,44	1,21	7,27, 7,33 and 7,83 (1H each, br. m, 4′-H, 5′-H, 2′-H)
X	6,17 s	7,12	6,54	6,62	3,44	1,23	7,42 (3H, m, 4′-H, 5′-H, 6′-H); 7,93 (1H, d d, J=6,5; 2,2, 7′-H); 8,27 (1H, s, 2′-H)
XIV	—	6,78	6,51	6,56	3,43	1,21	7,19, 7,35, 7,75 (1H each, m, 4′-H, 5′-H and 2′-H)
XV	—	6,68	6,41	6,61	3,40	1,19	7,38 (3H, m, 4′-H, 5′-H and 6′-H); 7,94 (1H, d,d, J=6,5; 2,2, 7′-H); 8,10 (1H, s, 2′-H)
XVII	6,13 (t, $^4J_{3\text{-H, CH}_2}$= =1,1)	7,70	6,63	6,46	3,43	1,20	1,03 (6H, t, J=7,0, $N(CH_2\mathbf{CH_3})_2$); 2,55 (4H, q, J=7,0, $N(\mathbf{CH_2}CH_3)_2$); 3,62 (2H, br.m, 4-CH_2)
XVIII	6,18 (t, $^4J_{3\text{-H, CH}_2}$= =1,1)	7,66	6,58	6,50	3,40	1,20	1,47 (2H, m, γ-*cyclo*-CH_2); 1,62 (4H, m, 2β-*cyclo*-CH_2); 2,50 (4H, m, 2α-*cyclo*-CH_2); 3,56 (2H, br.m, 4-CH_2)
XIX	6,19 br.s	7,65	6,59	6,49	3,41	1,20	2,49 (4H, m, *cyclo*-$N(CH_2)_2$); 3,61 (2H, 1H each, 4-CH_2); 3,78 (4H, m, *cyclo*-$O(CH_2)_2$)
XX	5,58 s	7,30	6,59	6,50	3,41	1,20	5,20 (2H, s, 4-CH_2); 7,00, 7,20 and 7,96 (1H each, br.m 4′-H, 5′-H and 2′-H)
XXI	5,44 s	7,37	6,60	6,52	3,42	1,21	5,44 (2H, s, 4-CH_2); 7,30 (3H, m, 4′-H, 5′-H and 6′-H); 7,85 (1H, m, 7′-H); 8,00 (1H, s, 2′-H)
XXIV	—	7,45	6,74	6,60	3,40	1,18	1,60 (6H, m, *cyclo*-$(CH_2)_3$); 3,10 (4H, br. m, *cyclo*-$N(CH_2)_2$)
XXV	—	7,42	6,73	6,59	3,41	1,20	2,46 (3H, s, CH_3); 3,08 (4H, br.m, *cyclo*-$N(CH_2)_2$); 3,80 (4H, t, J=4,6, *cyclo*-$O(CH_2)_2$)

TABLE 3. PMR Spectra of Coumarins XII, XVI, XXII, XXIII, XXVI, and XXVII in $CDCl_3$

Compound	Chemical shifts, ppm (SSCC, J, Hz)						
	8-H, s	10-H	$N—CH_2$ (J=6,2)	$CH_2—C_{(12b)}$ (t, J=6,2)	$CH_2—C_{(7a)}$ (t, J=6,2)	NCH_2CH_2 (J=6,2)	other protons
XII	6,82	5,92s	3,30 t (J=6,0)	2,90	2,69	1,96 m	7,20, 7,28 and 7,84 (1H each, br m, 4′-H, 5′-H and 2′-H)
XVI	6,30	—	3,29 q)	2,89	2,62	1,93 q	7,06, 7,30 and 7,60 (1H each, br m, 4′-H, 5′-H and 2′-H)
XXII	7,21	6,19 s	3,27 q)	2,90	2,78	2,98 q	2,65 (4H, br. m, $N(CH_2CH_2)_2O$); 3,65 (2H, br. m, 9-CH_2); 3,81 (2H, br. m, $N(CH_2CH_2)_2O$)
XXIII	6,90	5,52 s	3,29 q	2,89	2,75	1,95 q	5,20 (2H, s, 9-CH_2); 7,00, 7,20 and 7,90 (1H each, br m, 4′-H, 5′-H and 2′-H)
XXVI	7,03	—	3,24 q	2,90	2,82	1,92 q	2,51 (3H, s, CH_2); 3,20 (4H, br m, $N(CH_2CH_2)_2O$); 3,85 (4H, m, $N(CH_2CH_2)_2O$)
XXVII	6,80	5,95 d (J=9,0)	3,22 q	2,84	2,71	1,92 q	7,41 (1H, d, J=9,0; 9-H)

TABLE 4. ^{13}C NMR Spectra of Coumarins VIII, IX, XIV, XVIII, XIX, XXIV, XXVIII, and XXX in $CDCl_3$

Compound	Chemical shifts, δ, ppm (SSCC, $J_{^{13}C-^{1}H}$, Hz)											
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(4a)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(8a)}$	7-NCH_2	7-NCH_2CH_3	other carbon atoms
VIII	163,2 (d, J=5,0)	92,3 (d, J=166,4)	161,7s	104,0 m	125,5 (d, J=159,7)	107,8 (dd, J=159,9; J=5,8)	150,0 m	97,7 (dd, J=159,9; J=5,3)	156,4 (dd, J=9,7; J=5,1)	44,4 (t, J=135,4)	12,3 (q, J=126,6)	51,3 (t, J=136,8); 66,3 (t, J=143,8)
IX	161,5 (d, J=72,9)	102,5 (d, J=172,5)	148,3 m	103,7 m	125,2 (d, J=161,2)	109,2 (dd, J=161,1; J=5,7)	151,5m	97,9 (dd, J=161,1; J=5,5)	157,0 (dd, J=9,7; J=5,2)	44,9 (t, J=135,9)	12,4 (q, J=126,9)	119,6 (d J=196,0); 130,7 (d, J=192,0); 136,8 (d, J=214,7)
XIV	159,5 s	80,3 s	153,7 m	108,3m	126,1 (d, J=162,8)	110,6 (dd, J=126,6; J=5,4)	153,1 m,	97,6 (dd, J=161,5; J=3,8)	156,7 (dd, J=10,0; J=5,2)	45,5 (t, J=136,4)	12,7 (q, J=127,0)	120,5 (d, J=195,7); 130,8 (d, J=193,2); 137,4 (d, J=213,0)
XVIII	162,5 (d, J=4,7)	108,3 (d) J=170,0)	153,2 m	108,1 m	125,9 (d, J=160,4)	108,3 (dd, J=159,6; J=5,5)	150,4m	97,5 (dd, J=159,6; J=5,2)	156,3 (dd, J=10,0; J=5,1)	44,7 (t, J=135,4)	12,5 (q, J=126,4)	24,2 (t, J=130,0); 26,0 (t, J=128,1); 55,0 (t, J=132,2); 59,9 (t, J=132,2)
XIX	162,3 s	108,7 (d, J=170,6)	152,0 m	108,1 (m)	125,9 (d, J=160,3)	108,4 (dd, J=159,6; J=5,9)	150,6 m	97,7 (dd, J=159,9; J=5,5)	156,5 (dd, J=9,8; J=5,3)	44,8 (t, J=135,9)	12,5 (q, J=126,4)	53,9 (t, J=132,3); 59,6 (t, J=125,2); 67,0 (t, J=142,7)
XXIV	160,0 s.	130,7 m	147,4 m	109,8 m	126,2 (d, J=160,1)	108,5 (dd, J=159,5; J=5,8)	149,4 m	97,5 (dd, J=159,5; J=5,5)	154,2 (dd, J=9,7; J=6,2)	44,7 (t, J=135,0)	12,5 (q J=126,5)	13,0 (q, J=128,5); 24,2 (t, J=130,5); 26,9 (t, J=128,2); 51,1 (t, J=134,0)
XXVIII*	161,4	108,2	152,1	109,2	125,4	109,0	150,4	97,8	156,1	44,7	12,6	18,4
XXX	160,0 s	124,9 m	122,6 m	110,5 m	123,5 (d, J=158,0)	109,2 (dd, J=158,5; J=5,9)	147,8 m	98,3 (dd, J=159,1; J=5,7)	151,0 (dd, J=9,7; J=5,6)	44,6 (t, J=144,9)	12,6 (q J=126,4)	11,8 (q, J=127,5)

*According to the data in [10].

TABLE 5. ^{13}C NMR Spectra of Coumarins XII, XXIII, XXVII, and XXIX in $CDCl_3$

Compound	Chemical shifts, δ, ppm (SSCC, $J_{^{13}C-^{1}H}$, Hz)															
	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$	$C_{(11)}$	$C_{(7a)}$	$C_{(8a)}$	$C_{(12a)}$	$C_{(12b)}$	$C_{(12c)}$	other carbon atoms
XII	20,2 (J = 130,0)	20,3 (J = 130,6)	49,4 (t, J = 136,8)	49,8 (t, J = 137,9)	21,1 (t, J = 130,2)	27,5 (t, J = 129,4)	120,9 (d.t, J = 158.9 J = 3,8)	148,3 m	101,7 (d, J = 172,2)	161,7 (d J = 172,2)	118,8 (q, J = 5,5)	103,3 (d J = 5,3)	151,8 (d, J = 9,3)	106,9 (q, J = 5,7)	146,8 m	119,7 (d, J = 194,1); 130,3 (d, J = 191,4); 136,8 (d, J = 212,2)
XXIII	20,4 (t, J = 129,9)	20,5 (t, J = 130,0)	49,5 (t, J = 137,3)	50,0 (t, J = 138,0)	21,4 (t, J = 134,6)	27,8 (t, J = 130,5)	120,1 (d, J = 155,4)	149,9 m	106,3 (d, J = 169,9)	161,9 (d J = 3,0)	118,5 m	107,1 m	151,3 m	105,8 m	146,3 m	47,1 (t J = 136,1); 120,0 (d, J = 195,2); 130,5 (d, J = 192,0); 136,8 (d. J = 213,5)
XXVII	19,9 (t, J = 130,7)	20,2 (tt, J = 129,7; J = 3,7)	49,2 (t J = 137,3)	49,6 (t, J = 137,6)	21,1 (tt, J = 129,8; J = 3,9)	27,1 (t. d. t, J = 129,0; J = 4,7; J = 4,4)	124,7 (d q, J = 157,6; J = 3,9)	143,7 (dd, J = 160,3; J = 5,9)	167,3 (d, J = 171,4)	162,2 (dd, J = 11,0; J = 4,5)	118,0 (q, J = 4,4)	107,8 (d, J = 7,7)	151,3 m	106,0 m	145,6 m	—
XXIX*	20,2	20,3	49,2	49,6	21,3	27,4	121,4	150,8	107,8	162,2	117,6	108,6	152,7	106,4	145,4	—

*According to the data in [10].

In the PMR spectra of 7-diethylaminocoumarins IX, X, XIV, XV, XVII-XXI, XXIV, and XXV (see Table 2) the signals of the 5-H, 6-H, and 8-H aromatic protons of the aminocoumarin fragment are observed at 6.4-7.7 ppm in the form of doublets (5-H and 8-H) or a doublet of doublets (6-H) with characteristic spin-spin coupling constants (SSCC) [10]. While both the chemical shifts of the 6-H and 8-H protons are confined within rather narrow limits, the position of the signals of the 5-H protons changes substantially, depending on the substituents attached to the $C_{(3)}$ and $C_{(4)}$ atoms. The weakest-field chemical shift of the 5-H protons is observed for 4-alkyl-substituted derivatives XVII-XXI, as well as for coumarins XXIV and XXV. It might be assumed that the shift to strong field of the signals of the indicated proton on passing to IX and X and particularly to 3-iodo derivatives XIV and XV is due to the shielding effect of the heteroaromatic substituent in the 4 position, which is inclined relative to the plane of the coumarin fragment. It should be expected that for 3-iodocoumarins XIV and XV this angle of inclination will be maximal as a consequence of the additional steric hindrance created by the iodine atom, and, consequently, the shielding effect of the heteroaromatic substituent will increase [11]. Let us also note that the shielding effect of a heteroaromatic substituent on the proton in the peri position is well known for α-substituted naphthalenes [12]. Evidence in favor of the proposed interpretation is also provided by the absence of a shielding effect for the 5-H proton in coumarin XIII as compared with coumarin VIII, in which the substituent in the 4 position is not aromatic. Similar regularities are observed in the PMR spectra of julolidine derivatives XII and XVI for the signals of the 8-H protons (see Table 3).

The shielding effect of the heteroaromatic substituent in coumarins XX, XXI, and XXIII is appreciably smaller but nevertheless appreciable, which is confirmed by the strong-field shift of the signals of the 5-H atoms (8-H for the quinolizine derivatives) as compared with coumarins XVIII, XIX, and XXII. Signals of 3-H protons in the spectra of coumarins IX, X, and XVII-XXI, as well as of analogous protons (10-H) for XII, XVII, and XXIII, are observed at 5.4-6.2 ppm, usually in the form of somewhat broadened singlets. Splitting of the indicated signal to a triplet as a result of the manifestation of an allyl SSCC ($^4J_{H,H}$ = 1.1 Hz) can be observed in the spectra of coumarins XVII and XVIII, which confirms the presence of a methylene grouping in XVII-XXIII. In comparing the signals of the 3-H (10-H) protons in the spectra of coumarins VII-XII and XVII-XXII (see also [7]) the specific character of the effect of the N-imidazole and N-benzimidazole fragments is manifested most graphically; in the case of direct bonding to the $C_{(4)}$ [$C_{(9)}$] atom these fragments shift the indicated signals to weak field, while in the presence of a methylene link they have the opposite effect due to entry of the 3-H (10-H) protons into the cone of the magnetic anisotropy of the heteroaromatic substituent [11].

A characteristic peculiarity of the PMR spectra of aminomethyl derivatives XVII-XIX and XXI is the broadened structure of the signals of the protons of the 4-dialkylaminomethyl fragment, which attests to the conformational lability of the indicated amino group. It is also interesting that appreciable broadening of the signals of the protons of the 7-diethylamino group, as well as of the 6-H and 8-H protons, is observed in the PMR spectra of 3-aminocoumarins XXIV and XXV. This fact is, in our opinion, associated with a decrease in the effectiveness of conjugation of the 7-amino group with the heteroaromatic system as a consequence of an "electronic counteraction" on the part of the 3-dialkylamino group, which leads to weakening of the $C_{(7)}$—N bond and an increase in the rotational mobility of the substituent in the 7 position. In the case of coumarin XXVI, in which the $N_{(5)}$ atom is fastened securely by six-membered rings, on the other hand, the mobility of the morpholino group increases, as evidenced by the broadening of the signals of the protons of the 9-CH_3 and 10-$N(CH_2)_2$ groups.

Some difficulty is encountered in assigning the triplet signals of the protons of the 7a-CH_2 and 12b-CH_2 groups in coumarins XII, XVI, XXII, and XXIII. This problem was solved for model coumarin XXVII by means of double resonance. In the PMR spectrum of XXVII recorded at 300 MHz one observes a fine (doublet) structure of the triplet at 2.71 ppm, which can be ascribed to manifestation of the SSCC $^4J_{8\text{-H},7a\text{-}CH_2}$ = 0.7 Hz. In fact, suppression of the signal of the 8-H proton led to disappearance of the doublet structure of the signal of the 7a-CH_2 group. We also investigated the ^{13}C NMR spectra of coumarins VIII, IX, XII, XIV, XVIII, XIX, XXIII, and XXIV (see Tables 4 and 5). For comparison, data from the ^{13}C NMR spectra of coumarins XXVII-XXX are presented in the tables. It was found that the ^{13}C chemical shifts of the carbon atoms of the coumarin skeleton in aminomethyl derivatives XIX and XXIII and methyl-substituted analogs XXVIII and XXIX virtually coincide. Thus the effect of a nitrogen-containing substituent separated by a methylene link on the coumarin fragment is insignificant. On the other hand, the amino group directly bonded to the coumarin system in VIII, IX, and XII has a rather strong effect on the signals of the $C_{(3)}$ and $C_{(4)}$ atoms, but this effect is small in the benzene fragment. In coumarin XIV the presence of an iodine atom leads to a marked strong-field shift of the signal of the $C_{(3)}$ atom and to a small weak-field shift for the $C_{(4)}$ atom as compared with the shifts for coumarin IX; however, an appreciable electronic effect on the $C_{(5)}$ atom is not observed.

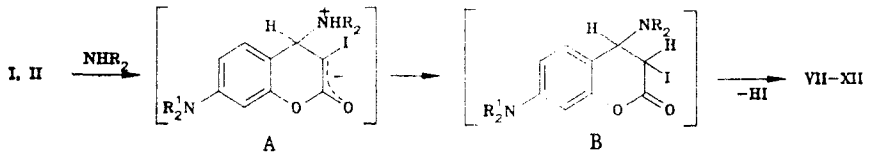
The ^{13}C NMR data for XXIV confirm retention of the coumarin structure, as evidenced by the close values of the chemical shifts of most of the aromatic carbon atoms in XXIV and XXVIII. However, as compared with coumarin XXVIII, the signal of the $C_{(3)}$ atom experiences a strong shift to weak field, while the chemical shift of the $C_{(4)}$ atom changes only slightly (see Table 4). This effect can be explained by steric reasons or by cross conjugation between the

piperidino and carbonyl groups, as a result of which electron density is transferred from the $N_{(3)}$ atom to the exocyclic oxygen atom without substantial electronic changes in the $C_{(4)}$ atom. To clarify the indicated anomaly by the method in [13] we specially synthesized 3-amino-4-methyl-7-diethylaminocoumarin (XXX) and studied the ^{13}C NMR spectrum of this compound (see Table 4). As compared with coumarin XXVIII, the change in the chemical shifts of the $C_{(3)}$ and $C_{(4)}$ atoms in the spectrum of XXX is close to that expected from the increments of the NH_2 group [10]. Thus precisely steric hindrance, which leads to disruption of the p,π conjugation of the piperidino substituent with the pyrone ring should be acknowledged as being the reason for the observed deviations for coumarin XXIV.

In studying the ^{13}C NMR spectra of coumarins XII, XXIII, XXVII, and XXIX the assignment of the ^{13}C signals for the $C_{(1)}$···$C_{(3)}$ and $C_{(5)}$···$C_{(7)}$ atoms in the saturated rings is most difficult. This problem was solved in the case of coumarin XXVII by means of ^{13}C—{^1H} double heteronuclear selective resonance. The SSCC $^3J_{^{13}C,^1H}$ = 4.7 Hz vanished in the multiplet centered at 27.1 ppm in the proton-undecoupled ^{13}C NMR spectrum when the signal of the aromatic 8-H proton was irradiated. The same signal changed in the case of irradiation of the protons at 2.71 ppm and was assigned to the $C_{(7)}$ atom. The protons observed at 3.22 ppm are associated with carbon atoms, the ^{13}C NMR signals of which appear at 49.2 and 49.6 ppm, while the protons observed at 2.84 ppm are associated with the ^{13}C atoms recorded at 19.9 ppm. Finally, irradiation of the multiplet of β-methylene protons at 1.92 ppm leads to a response in the ^{13}C signals at 20.2 and 21.2 ppm. On the basis of these data we also made assignments of the signals for the remaining quinolizine derivatives (see Table 5).

Within the framework of this publication we did not set out to study the mechanism of the observed reactions; however, some assumptions can be made on the basis of the data obtained.

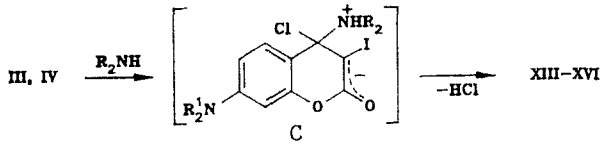
The formation of coumarins VII-XII from 3-iodo derivatives I and II is evidently the result of primary nucleophilic addition to the $C_{(4)}$ [$C_{(9)}$] atom and can be formally represented as proceeding through intermediates **A** and **B**:



This sort of scheme was classified by Kauffman and coworkers [14] as an addition—anomalous elimination (AEa) mechanism and includes inter- or intramolecular proton transfer to the $C_{(3)}$ atom. Let us also note that deprotonation of the onium group need not necessarily take place in the second step, and thus, instead of intermediate **B**, its protonated form may be realized. In our opinion, substitution at the $C_{(4)}$ atom in this case demonstrates the specific character of 3-halocoumarins [1] in contrast to, for example, the reactions of other α-halo-α,β-unsaturated carbonyl compounds with nucleophiles, which lead to a different spectrum of products [15, 16]. The most interesting fact in the reactions under consideration is evidently proton transfer to the $C_{(3)}$ reaction center, which, in principle, indicates the possibility of the addition of other electrophilic particles, which opens up a pathway to the synthesis of 3,4-disubstituted coumarins.

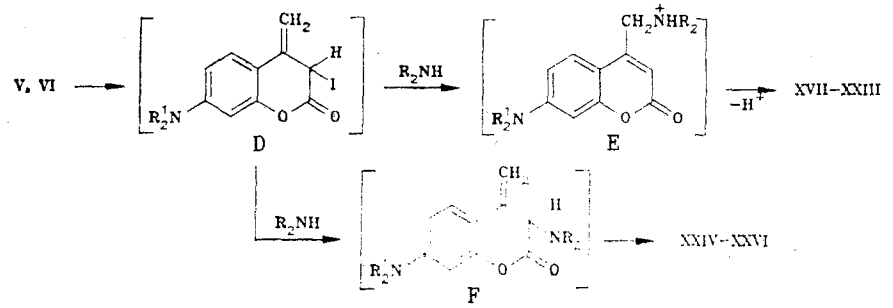
For a qualitative evaluation of the relative reactivities of other 3-halo-7-aminocoumarins we compared the behavior of 3-fluoro-, 3-chloro-, 3-bromo-, and 3-iodo-7-diethylaminocoumarins in the case of their reaction with morpholine. We found that precisely 3-iodo derivative I is the most reactive compound in the examined series and that the effectiveness of the process decreases in the order I > Br > Cl > F. Thus the rate-determining step in the reaction may be cleavage of the $C_{(3)}$—Hal bond during elimination.

In the case of 3-iodo-4-chlorocoumarins III and IV substitution of the chlorine atom apparently takes place via an addition—elimination mechanism or a tetrahedral mechanism [17], for example, through intermediate **C**:



One should, however, bear in mind, that reactions of this type (S_N *vin*) are extremely diverse with respect to their kinetic schemes [18] and may be accompanied by catalysis on the part of the nucleophilic reagent [19]. The difference between this variant and the variant examined above is associated with the absence of the indispensable necessity of proton migration to the $C_{(3)}$ atom, and thus we have the simplest example of nucleophilic substitution reactions at an sp^2 carbon atom [18].

The most interesting case is evidently the reaction of 3-iodo derivatives V and VI with amines. A possible mechanism for this transformation includes a proton-transfer step (allylic rearrangement) and S_N2' attack of the resulting intermediate **D** with the subsequent elimination of a proton from cation **E**:



The simultaneous formation of 3-amino derivatives XXIV-XXVI, which was also observed by Zagorevskii and coworkers [1] in the case of 3-bromo-4-methylcoumarin, can be explained by direct nucleophilic substitution at the $C_{(3)}$ reaction center in intermediate **D** accompanied by protonation [20]. The primary formation of 4-aminomethyl derivatives is most likely associated with the steric hindrance that arises during nucleophilic attack at the $C_{(3)}$ atom. A study of the relative reactivities of 3-halo derivatives in the case of 3-fluoro-, 3-chloro-, 3-bromo-, and 3-iodo-4-methyl-7-diethylaminocoumarins [6] in the reaction with morpholine, just as in the case of 3-halo-7-diethylaminocoumarins, provides evidence for a decrease in the rate of the process in the order I > Br > Cl > Fl.

Thus precisely 3-iodo derivatives of 7-aminocoumarins are the most convenient intermediates for obtaining new dyes of this class.

EXPERIMENTAL

The IR spectra were recorded with a Perkin—Elmer 577 spectrometer. The ^1H and ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded with Bruker WM-250 and Bruker AM-300 spectrometers with hexamethyldisiloxane (HMDS) as the internal standard.

The reaction products were isolated by chromatography with a column (30 by 2.0 cm) packed with Silpearl UV-254 silica gel in hexane—acetone systems. The purity of the substances was monitored by TLC on Silufol UV-254 plates with development in UV light or in iodine vapors.

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

General Method for Obtaining Coumarins IX, X, XII, XIV, and XV-XXVI. A mixture of 5 mmole of coumarins I-VI and 100 mmole of the corresponding amine in 20-40 ml of freshly distilled DMF or DMSO or without a solvent (in the case of liquid amines) was heated with stirring for 4-6 h at 80-120°C until starting coumarins I-VI disappeared (monitoring by TLC), after which the mixture was evaporated in vacuo, and the residue was chromatographed with collection of the fractions that luminesce in UV light. The chromatographically pure products were recrystallized from hexane—acetone.

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

N. A. Gordeeva, M. A. Kirpichënok, N. S. Patalakha, V. M. Khutoretskii, and I. I. Grandberg

UDC 547.587.51

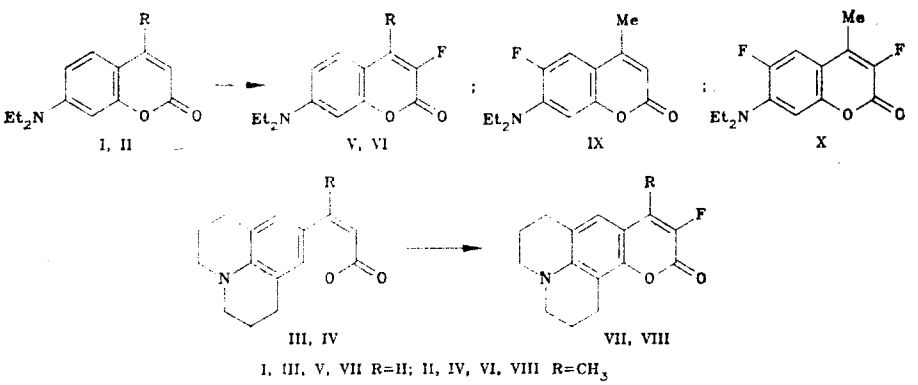
The corresponding 3-fluoro-substituted coumarins were obtained by reactions of 7-diethylaminocoumarin, 2,3,6,7-tetrahydro-1H,5H-quinolizino[9,9a,1-gh]coumarin, and 2,3,6,7-tetrahydro-9-methyl-1H,5H-quinolizino[9,9a,1-gh]coumarin with XeF_2, $FClO_3$, or N-fluoropyridinium tetrafluoroborate. A strong 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-7-aminocoumarins. 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-7-aminocoumarins 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, $FClO_3$, VF_5, 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].



K. A. Timiryazev Moscow Agricultural Academy, Moscow 127550. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 619-624, May, 1991. Original article submitted January 25, 1990.

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