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NEW DERIVATIVES OF COUMARIN: 2-(N-R-IMINO)-2H-1-BENZOPYRANS

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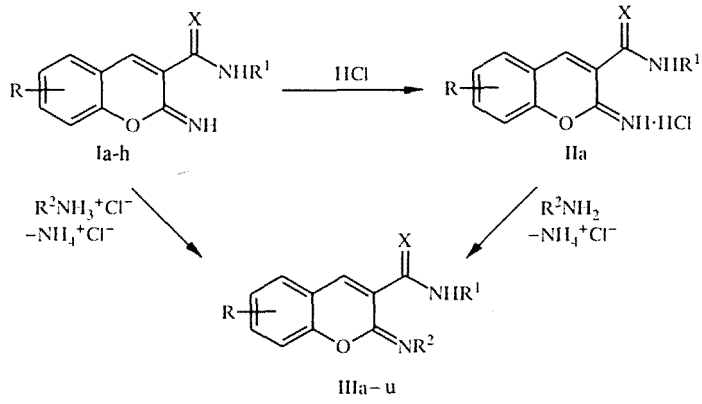
Methods of synthesizing previously unknown derivatives of coumarin — 2-(N-R-imino)-2H-1-benzopyrans, where R = Alk, Ar — are proposed. Possibilities of alternative synthetic schemes are discussed, and hypotheses concerning probable mechanisms of the reactions are formulated.

2-Imino-2H-1-benzopyrans (2-iminocoumarins) with substituents at the 3 position are a well-known class of compounds. Their synthesis is accomplished mainly by condensing o-hydroxybenzaldehydes with methylene-active nitriles under Knoevenagel reaction conditions [1-3]. Thus far, however, only a small number of papers dealing with the reactivity of 2-iminocoumarins have been published [4, 5]. This is apparently due to the fact that as a rule, 2-iminocoumarins are fairly labile compounds that readily hydrolyze to the corresponding coumarins [6, 7].

To determine new synthetic capabilities of 2-iminocoumarins, this paper investigates the interaction of 2-iminocoumarin-3-carboxamides (thiocarboxamides) with primary amines (Scheme 1).

The initial 2-iminocoumarins Ia-h were obtained by condensing salicylaldehydes with amides of cyanoacetic acid and cyanothioacetamide in accordance with known methods [8, 9]. The presence in these structures of the "iminolactone" ring, which may be regarded as a cyclic iminoester, led us to the assumption that for these compounds, transformations are possible that resemble the reactions of iminoesters with N-nucleophiles [10]. However, direct interaction of 2-iminocoumarin-3-carboxamide (Ia) with amines in alcohols did not produce satisfactory results. By using instead of iminocoumarin Ia its hydrochloride IIa, we obtained 2-(N-R-imino) coumarins IIa-d,p (method A) in high yields.

Scheme 1



Ia-f, h R^1 = H; a-g X = O; a R = H, b R = 6-OMe, c R = 7-NEt_2, d R = 7-OH, e R = 6-Br, f R = 5,6-benzo; g R = H, R^1 = Me; h R = H, X = S; IIa R, R^1 = H, X = O; IIIa-q, t, u R^1 = H; a-s X = O; a R = H, R^2 = Ph; b R = H, R^2 = 4-MeC_6H_4; c R = H, R^2 = 3-MeC_6H_4; d R = H, R^2 = 2-MeC_6H_4; e R = 6-OMe, R^2 = Ph, f R = 7-NEt_2, R^2 = Ph; g R = 7-OH, R^2 = Ph; h R = 6-Br, R^2 = Ph; i R = 5,6-benzo R^2 = Ph; j R = H, R^2 = Me; k R = 6-OMe, R^2 = Me; *l* R = 7-NEt_2, R^2 = Me; m R = 7-OH, R^2 = Me; n R = 6-Br, R^2 = Me; o R = 5,6-benzo, R^2 = Me; p R = H, R^2 = $CH_2C_6H_5$; q R = H, R^2 = C_6H_{13}; r R = H, R^1 = Me, R^2 = Ph; s R = H, R^1 = Me, R^2 = Me; t R = H, R^2 = Ph, X = S; u R = H, R^2 = Me, X = S

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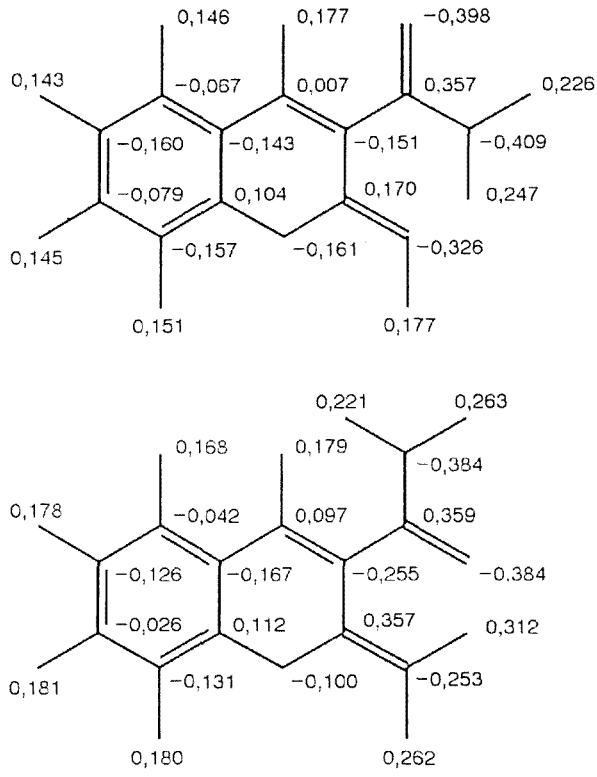
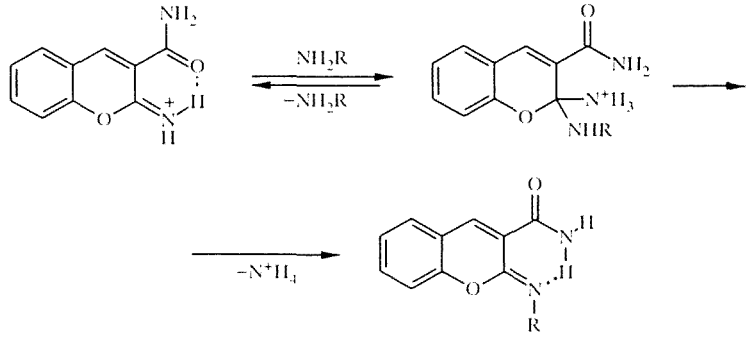


Fig. 1. Charges on atoms of the most stable conformation isomers Ia and IIa, calculated by the AM1 method (a complete optimization of the geometry was carried out using the method of molecular mechanics MMX [13]).

The mechanism of this reaction is obviously analogous to that of acid hydrolysis of 2-iminocoumarins [11] (Scheme 2).

Scheme 2



Formation of salt IIa leads to a significant increase in electrophilicity of the carbon atom of the imino group, and this atom then easily adds an amine molecule. According to quantum-chemical calculations carried out using the AM1 method [12], protonation of compound Ia is associated with a significant decrease in electron density on the carbon atom in the 2 position of iminocoumarin (see Fig. 1).

The intermediate formed is stabilized by the splitting off of the ammonium salt with the formation of N-substituted 2-iminocoumarin.

TABLE 1. Characteristics of Synthesized Compounds IIIa-u

Compound	Empirical formula	M.p., °C	IR spectra, ν, cm^{-1}	EAS λ (nm) $\varepsilon \cdot 10^{-3}$ (mole/liter cm^{-1})	Method of preparation	Yield, %
IIIa	$C_{16}H_{12}N_2O_2$	236	3254, 3118 (NH), 1703 (C=O), 1650 (C=N)	248 (19,1), 364 (6,7)	A, B C	95, 96, 89
IIIb	$C_{17}H_{14}N_2O_2$	235...236	3252, 3110 (NH), 1702 (C=O), 1650 (C=N)	249 (19,1), 370 (6,4)	A, B C	94, 94, 91
IIIc	$C_{17}H_{14}N_2O_2$	216...217	3252, 3116 (NH), 1702 (C=O), 1652 (C=N)	248 (18,3), 363 (6,4)	A, B, C	97, 93, 88
IIId	$C_{17}H_{14}N_2O_2$	203...205	3243, 3113 (NH), 1700 (C=O), 1654 (C=N)	248 (17,8), 358 (6,2)	A, B, C	95, 94, 92
IIIe	$C_{17}H_{14}N_2O_3$	202...203	3261, 3104 (NH), 1702 (C=O), 1640 (C=N)	250 (25,5), 283 (15,0), 390 (6,5)	B, C	90, 91
IIIf	$C_{20}H_{21}N_3O_2$	204...206	3244, 3127 (NH), 1678 (C=O), 1652 (C=N)	253 (17,9), 329 (5,0), 419 (29,7)	B	73
IIIg	$C_{16}H_{12}N_2O_3$	263...265	3210 уш, (NH + OH), 1694 (C=O), 1650 (C=N)	273 (15,7), 324 (8,0), 388 (14,2)	B	78
IIIh	$C_{16}H_{11}BrN_2O_2$	215	3274, 3129 (NH), 1705 (C=O), 1655 (C=N)	265 (26,9), 401 (6,5)	B	82
IIIi	$C_{20}H_{14}N_2O_2$	255...257	3263, 3111 (NH), 1697 (C=O), 1637 (C=N)	220 (38,7), 246 (28,7), 262 (26,6), 304 (10,1), 394 (9,8)	B	77
IIIj	$C_{11}H_{10}N_2O_2$	210...212	3246, 3132 (NH), 1690 (C=O), 1655 (C=N)	231 (18,4), 245 (14,9), 253 (13,8), 299 (7,0), 312 (6,5), 359 (6,4)	B	95
IIIk	$C_{12}H_{12}N_2O_3$	200...201	3255, 3126 (NH), 1691 (C=O), 1651 (C=N)	204 (22,9), 247 (13,2), 298 (8,7), 378 (6,1)	B	91
IIIl	$C_{15}H_{19}N_3O_2$	195...197	3242, 3124 (NH), 1669 (C=O), 1652 (C=N)	206 (27,2), 247 (13,2), 299 (2,7), 400 (32,4)	B	83
IIIm	$C_{11}H_{10}N_2O_3$	267...268	3269 уш (NH + OH), 1690 (C=O), 1660 (C=N)	205 (28,7), 224 (17,0), 260 (7,9), 310 (6,4), 356 (15,2)	B	80
IIIn	$C_{11}H_9BrN_2O_2$	227...228	3270, 3140 (NH), 1700 (C=O), 1658 (C=N)	206 (23,6), 243 (28,6), 293 (7,4), 306 (5,7), 356 (15,2)	B	86
IIIo	$C_{15}H_{12}N_2O_2$	229...231	3263, 3142 (NH), 1679 (C=O), 1633 (C=N)	236 (42,9), 243 (42,5), 259 (19,2), 332 (8,5), 390 (10,6)	B	82
IIIp	$C_{17}H_{14}N_2O_2$	148...149	3278, 3149 (NH), 1689 (C=O), 1644 (C=N)	227 (24,2), 239 (19,4), 247 (16,7), 291 (7,9), 304 (7,3), 347 (7,4)	A, B	91, 94
IIIq	$C_{16}H_{20}N_2O_2$	101...103	3252, 3133 (NH), 1686 (C=O), 1651 (C=N)	232 (23,1), 245 (18,3), 254 (16,6), 299 (8,1), 313 (7,5), 360 (7,5)	B	97
IIIr	$C_{17}H_{14}N_2O_2$	146	3175 (NH), 1676 (C=O), 1638 (C=N)	247 (19,4), 361 (7,2)	B	89
IIIs	$C_{12}H_{12}N_2O_2$	130...131	3202 (NH), 1672 (C=O), 1650 (C=N)	226 (19,7), 239 (15,3), 247 (14,1), 290 (9,5), 302 (8,5)	B	80
IIIt	$C_{16}H_{12}N_2OS$	238...239	3218, 3034 (NH), 1646 (C=N)	260 (22,1), 280 (21,0), 359 (6,5)	B	85
IIIu	$C_{11}H_{10}N_2OS$	185...187	3224 (NH), 1650 (C=N)	249 (23,5), 295 (10,2), 307 (10,1), 359 (6,3), 389 (6,6)	B	79

We note that the salts of 2-iminocoumarins are assigned the structure of 2-aminobenzo[b]pyrilium salts [14]. However, quantum-chemical calculations show that the cation of IIa has the structure of a carbonium ion, and the oxygen atom has only a slight positive charge. This result is consistent with the observed reactivity of salts of 2-iminocoumarins.

2-(N-R-imino)coumarins IIIa-u were also obtained by reacting iminocoumarins Ia-h with hydrochlorides of primary amines (method B, Scheme 1). Method B is distinguished by the simplicity of the synthesis and high yields. Thus, prolonged boiling for 15 to 30 min of the initial reactants in alcohol (2-propanol, ethanol) leads to the formation of the target products. Equilibrium in this case is probably established between the basic and salt forms of 2-iminocoumarin and amine, resulting in their mutual activation.

TABLE 2. PMR Spectra of 2-(N-R-imino)coumarins IIIa-u

Compound	Chemical shift, δ, ppm, spin–spin coupling constant (J, Hz)			
	NH	4-H III, s	H_{arom}	other protons
IIIa	9,27 (1H, s) 7,92(1H, s)	8,49	7,76(1H, d, 5-H); 7,52 (1H, t, 7-H); 7,42...7,07 (8H,m)	
IIIb	9,33(1H, s) 7,90(1H, s)	8,47	7,76(1H, d, 5-H); 7,52 (1H, t, 7-H); 7,26...7,11 (6H,m)	2,30 (3H, s, CH_3)
IIIc	9,30 (1H, d; 3,3) 7,94 (1H, d; 3,3)	8,49	7,79 (1H, d.d, 5-H; 5,75; 1); 7,54 (1H, d.t, 7-H; 6,5; 6,25; 1); 7,32...6,94 (6H,m)	2,31 (3H, s, CH_3)
IIId	9,33 (1H, d; 3,3) 7,93 (1H, d; 3,3)	8,51	7,78 (1H, d, 5-H); 7,50 (1H, t, 7-H); 7,26...7,0 (6H,m)	2,14 (3H,s, CH_3)
IIIe	9,34 (1H, d; 3,34) 7,93 (1H, d; 3,68)	8,47	7,40...7,02 (8H,m)	3,76 (3H, s, 6-OCH_3)
IIIf	9,35 (1H, d; 4,35) 7,66 (1H, d; 4,35)	8,35	7,48 (1H, d, 5-H; 6,75); 7,39...7,04 (5H,m); 6,61 (1H,d.d, 6-H; 6,75; 1,5); 6,15 (1H,d, 8-H; 1,5)	3,37 (4H,q, 7-N($\underline{CH_2}CH_3)_2$); 1,05 (6H,t, 7-N($CH_2\underline{CH_3}$)$_2$)
IIIg	9,27 (1H, d; 4,78) 7,77 (1H, d; 4,78)	8,44	7,60 (1H, d, 5-H); 7,40...7,135 (5H,m); 6,70 (1H,d.d, 6-H); 6,42 (1H, d, 8-H)	
IIIh	9,20 (1H, s) 7,96 (1H, s)	8,46	8,05 (1H,d, 5-H; 2,57); 7,65 (1H, d.d, 7-H; 8,82; 2,57); 7,42...7,05 (6H,m)	
IIIi	9,38 (1H, s) 8,01 (1H, s)	8,30	8,15...7,16 (11H,m)	
IIIj	9,48 (1H, s) 7,76 (1H, s)	8,28	7,70 (1H, d.d, 5-H; 5,85; 1,2); 7,52 (1H, d.t, 7-H; 5,85; 5,85; 1,2); 7,285 (1H, d, 8-H; 5,85); 7,23 (1H, t.d, 6-H; 5,85; 5,85; 0,9)	3,14 (3H, s, =N—CH_3)
IIIk	9,56 (1H,d) 7,76 (1H,d)	8,27	7,30 (1H, d, 5-H); 7,23 (1H, d, 8-H); 7,10 (1H,d.d, 7-H)	3,13 (3H, s, =N—CH_3); 3,76 (3H, s, 6-OCH_3)
IIIl	9,53 (1H, s) 7,46 (1H, s)	8,12	7,415 (1H, d, 5-H); 6,56 (1H, d, 6-H); 6,43 (1H,s, 8-H)	3,12 (3H, s, =NCH_3); 3,41 (4H, q, 7-N($\underline{CH_2}CH_3)_2$); 1,11 (6H, t 7-N($CH_2\underline{CH_3}$)$_2$)
IIIm	9,48 (1H, d) 7,60 (1H, d)	8,20	7,51 (1H,d, 5-H; 8,6) 6,67 (1H,d.d, 6-H; 8,6; 2,2) 6,58 (1H,d, 8-H; 2,2)	10,61 (1H, br, 7-OH); 3,11 (3H,s, =N—CH_3)
IIIn	9,41 (1H, d) 7,81 (1H, d)	8,25	7,965 (1H,d, 5-H); 7,66 (1H,d.d, 7-H); 7,325 (1H,d, 8-H)	3,14 (3H,s, =N—CH_3)
IIIo	9,63 (1H, s) 7,87 (1H, s)	9,04	8,89...7,37 (7H,m)	3,18 (3H,s, =N—CH_3)
IIIp	9,58 (1H, d) 7,82 (1H, d)	8,37	7,72 (1H, d.d, 5-H); 7,56 (1H,d.t, 7-H); 7,42...7,22 (7H,m)	4,71 (2H,s, —$\underline{CH_2}$Ph)
IIIq	9,63 (1H, d 3,3) 7,79 (1H, d, 3,3)	8,30	7,69 (1H, d.d, 5-H; 5,85; 1,2); 7,52 (1H, s.t, 7-H; 5,85; 5,85; 1,2); 7,27...7,19 (2H,m, 6-H, 8-H)	3,47 (2H,q, $\underline{CH_2}CH_2(CH_2)_3CH_3$; 1,59 (2H,q, $CH_2\underline{CH_2}(CH_2)_3CH_3$; 1,31 (6H, s, $CH_2CH_2(\underline{CH_2})_3CH_3$; 0,25 (3H, s, $CH_2CH_2(CH_2)_3\underline{CH_3}$
IIIr	9,81 (1H, q)	8,50	7,79 (1H, d.d, 5-H; 5,8; 1); 7,56...7,08 (8H, m	2,87 (3H, d, —$NHCH_3$; 4,78)
IIIs	10,04 (1H, d; 4,8)	8,29	7,72 (1H,d, 5-H; 5,7); 7,525 (1H, t, 7-H; 6,0; 6,0); 7,29...7,20 (2H, m, 7-H, 8-H)	3,15 (3H, s, =N—CH_3); 2,805 (3H,d, —$NHCH_3$; 4,78)
IIIt	11,10 (1H,s) 10,44 (1H, s)	8,82	7,83 (1H, d.d, 5-H; 6,25; 1,65); 7,55...7,13 (8H,m)	
IIIu	11,65 (1H, s) 10,34 (1H, s)	8,79	7,78 (1H,d.d, 5-H); 7,575 (1H,d.t, 7-H); 7,32...7,26 (2H,m, 7-H, 8-H)	3,16 (3H,s, =N—CH_3)

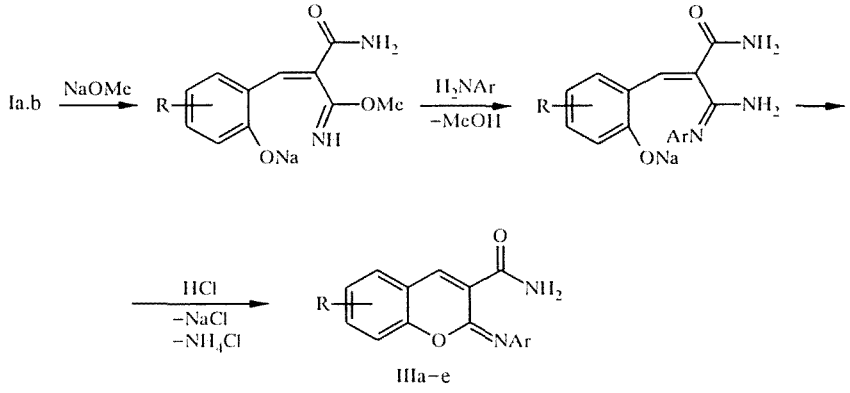
TABLE 3. Mass Spectra of Compound IIIa,b,j

Compound	m/z (I_{rel}, %)*
IIIa	264 (100), 221 (14), 220 (82), 172 (7), 161 (40), 145 (73), 132 (16), 118 (14), 89 (17)
IIIb	278 (100), 262 (6), 234 (56), 220 (18), 172 (5), 161 (47), 145 (61), 130 (18), 118 (19), 91 (23), 89 (23)
IIIк	202 (94), 185 (39), 173 (8), 157 (24), 145 (77), 130 (100), 118 (14), 102 (22), 89 (30)

*Listed are peaks with $I_{rel} \geq 5\%$.

Formation of 2-(N-R-imino)coumarins also takes place in the presence of sodium methoxide (method C, Scheme 3).

Scheme 3



IIIa–e

Satisfactory results were obtained by using method C only with aromatic amines. In this case, the action of sodium methoxide evidently involves the opening of the "iminolactone" ring with the formation of the iminoester of the arylidenemalonamic acid, which then reacts with the amine. Compounds IIIa-e were isolated by acidifying the solution.

The PMR spectra of compounds IIIa-u (Table 2) in the 7.86-9.04 ppm range show a singlet signal of the proton in the 4 position of iminocoumarin. The signals of the protons of the iminocoumarin benzene ring of compounds IIIj-n,q,r,u, which contain an alkylimino group in the 2 position, are manifested in the spectra, depending on the presence of substituents, in the form of systems ABCD or ABX. Aromatic protons of compounds IIIa-i,r,t, in the 2 position of which the arylimino group is located, are observed in the 7.02-7.52-ppm range in the form of a complex multiplet.

For the N-substituted amides IIIr,s, the signal of the amide proton is located in the 9.81-ppm and 10.04-ppm range. The signals of the protons of the amide group of the remaining compounds are manifested in the form of two doublets or broadened singlets, the chemical shifts of these protons being substantially different ($\Delta\delta$ = 0.66-2.07 ppm). This attests to the nonequivalence of the amide protons and indicates that a fairly stable hydrogen bond exists in these structures.

Formation of intramolecular hydrogen bonds is also confirmed by data of IR spectroscopy (Table 1). For compounds IIIa-u, the absorption band due to vibrations of the NH group is shifted to the low-frequency region and is located in the range 3202-3274 cm^{-1}. Among other characteristic bands confirming the structure of 2-(N-R-imino)coumarins, we should mention $\nu_{C=O}$, manifested at 1669-1705 cm^{-1}, as well as a strong band corresponding to $\nu_{C=N}$, located in the range 1633-1660 cm^{-1}.

The electronic absorption spectra of 2-alkylimino derivatives IIIj-q,s,u have bands characteristic of 2-iminocoumarin-3-carboxamides with a distinct vibronic structure (Table 1). For the 2-arylimino derivatives IIIa-i,r,t, a bathochromic shift of the long-wavelength spectral band and an intensification of absorption in the 235-245 nm range are observed. These changes are due to the conjugation of the coumarin and aryl chromophores.

The mass spectra of compounds IIIa,b,j are characterized by the presence of a strong peak corresponding to a molecular ion (IIIa,b – 100%, IIIj – 94%) and have the same type of fragmentation of the molecular ion (Table 3).

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded with a Specord M80 instrument in KBr pellets. The EAS were measured with a Specord M40 instrument in 2-propanol. The mass spectra were obtained with a Finnigan MAT 4615 B instrument, with 70-eV ionization energy and ballistic heating of the sample. The PMR spectra were recorded with a Bruker WP-200 instrument in DMSO-d_6, with TMS as internal standard.

The data of elemental analysis for C, H, N of compounds IIIa-u correspond to the calculated data.

2-Iminocoumarin-3-carboxamide hydrochloride (IIa), $C_{10}H_9ClN_2O_2$). A fast stream of dry gaseous HCl was passed with vigorous stirring through a solution of 9.4 g (0.05 mole) of 2-iminocoumarin-3-carboxamide (Ia) in 200 ml of dry dioxane at 50-60°C. The precipitate was filtered off and dried over KOH in a vacuum desiccator. Yield, 96% mp 223-225°C.

General method of preparation of 2-N-R-iminocoumarins IIIa-u. A. A solution of 1.1 g (5 mmole) of 2-iminocoumarin-3-carboxamide hydrochloride IIa and 5 mmole of the corresponding amine in 20 ml of absolute ethanol is boiled for 15-20 min. The precipitate is filtered off and dried.

B. Equimolar amounts of 2-iminocoumarin Ia-h and amine hydrochloride (5 mmole) in 20-40 ml of 2-propanol or ethanol are boiled for 20-30 min. The process involves precipitation of NH_4Cl. The reaction mixture is diluted with 100 to 150 ml of water. The precipitate is filtered off and dried.

C. To an equimolar amount of 2-iminocoumarin and arylamine (0.01 mole) is added a solution of sodium methoxide [prepared from 0.23 g (0.01 mole) of metallic sodium and 15 ml of absolute methanol] and the mixture is boiled for 15 to 20 min. After cooling, the reaction mixture is acidified to pH 6 with HCl solution. The precipitate is filtered off and dried.

The physicochemical characteristics of 2-(N-R-imino)coumarins IIIa-u are listed in Tables 1-3.

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