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STUDY OF ACYLATION REACTIONS IN 3-AMINOCARBOSTYRIL DERIVATIVES

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Acylation of 3-amino-1(2H)-isoquinolinone may proceed at three points – at the oxygen atom of the carbonyl group, at the nitrogen atom of the 3-amino group, and at the carbon atom in position 4 of the isoquinolinone fragment. Factors influencing the results of the reactions have been determined, and conditions have been found for the synthesis of three types of products – 4-(acyl)-3-(R-amino)-1(2H)-isoquinolinones, N-(1-oxo-1,2-dihydro-3-isoquinolinyl)-R-amides, and esters of 3-(R-amino)-1-isoquinolinol.

Keywords: 1-aminocarbostyril, 3-amino-1-isoquinolinol, enamine, isoquinoline, acylation.

Systematic study of the properties of 3-amino-1(2H)-isoquinolinone (3-aminoisocarbostyril) derivatives was begun in the middle of the last century and in recent years obtained a new stimulus with the discovery among them of substances with a high level of biological activity [1]. The simplest 3-aminoisocarbostyrils have been studied less than the condensed derivatives. Data on their chemical properties are limited to several examples of acylation [2-5], condensation [6-8], and Michael addition of olefins [8].

3-Aminoisocarbostyrils, in which all four nucleophilic centers in the molecule (oxygen atoms, N(2), N-3, and C(4)) are available for attack by electrophilic reagents, are a special group of compounds, which is caused by the possibility of forming reaction products varying in structure. Results are presented in this paper on a study of the acylation reactions of 3-amino-1(2H)-isoquinolinone (**1**) and its derivatives substituted at the 3-amino group.

We have established that boiling 3-aminoisocarbostyril **1** in dioxane with acetic anhydride or benzoyl chlorides leads to the formation of N-(1-oxo-1,2-dihydro-3-isoquinolinyl)acetamide (**2a**) and N-(1-oxo-1,2-dihydro-3-isoquinolinyl)benzamides **2b**,**c** in high yields (71-89%). 3-(Alkylamino)-1(2H)-isoquinolinones **3a,b** under the same conditions are converted into the C-acyl derivatives 4-(4-ethoxybenzoyl)-3-[(R-methyl)amino]-1(2H)-isoquinolinones **4a**,**b**. Retention of the N(2)H proton signal in the ^{1}H NMR spectra at δ >11.0 ppm (Table 1) indicates the formation of substitution products at the enamine fragment of the molecule of compounds **1** and **3a**,**b** and not at the lactam. The criterion for assigning the structure of products **2a-c** and **4a**,**b** to N-acyl or C-acyl derivatives is the presence or absence of the H-4 proton signal in the range 5.0-7.0 ppm nonexchangeable with D_2O. Additional confirmation of the structure of compounds **4a**,**b** may be served by the characteristic

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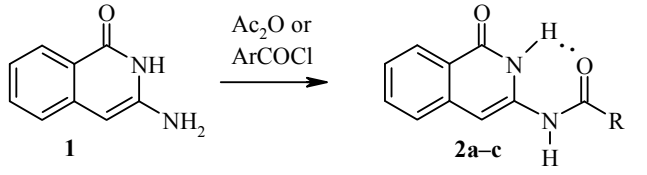
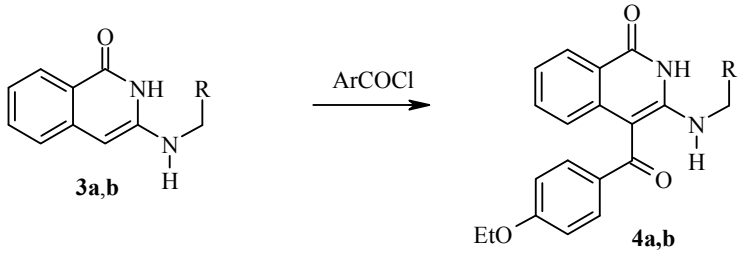
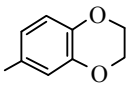
special feature of the ^{1}H NMR spectra of 3-[(R-methyl)amino]-1(2H)-isoquinolinones [9] as derivatives of secondary alkylamines. This is the presence of a spin-spin interaction between the protons of the 3-NH group and the methylene group, which is displayed as a the broadening of the 3-NH signal and splitting of the signal of the CH_2 group into a doublet with coupling constant 6.0 Hz (Table 1).

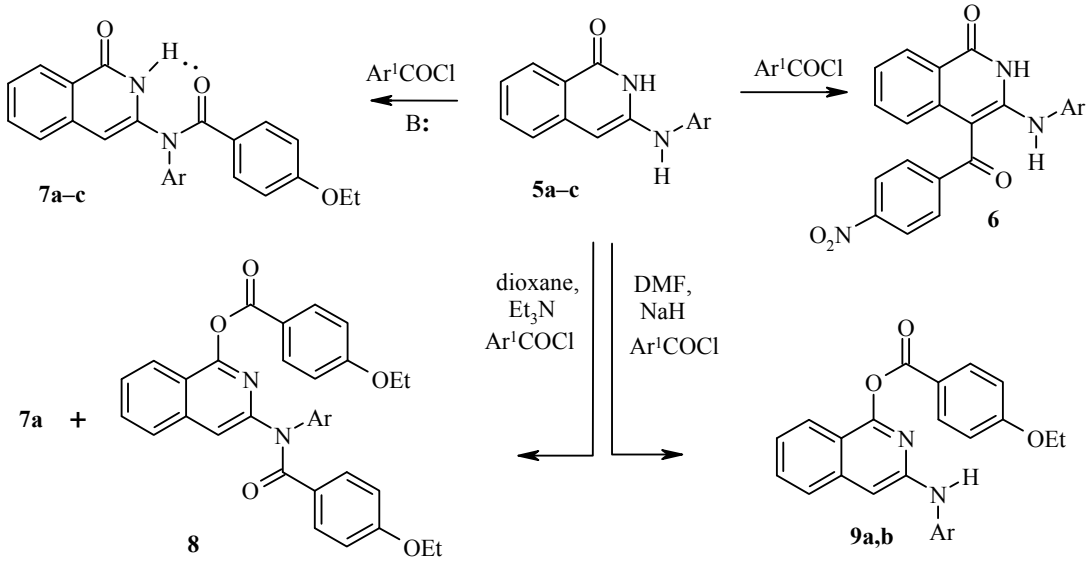
Previously [10-12], when studying electrophilic substitution reactions in a series of condensed derivatives of 3-aminoisocarbostyril (analogs of 2-alkyl-3-(alkylamino)-1(2H)-isoquinolinone), it was established that the products of the acylation reaction depended on the conditions, especially on the basicity of the medium. We found that in the case of the acylation of compounds **3a**,**b** the use of a basic catalyst (heating in dioxane in the presence of Et_3N, maintaining in DMF at room temperature in the presence of NaH) leads only to a reduction in the yield of products of type **4** (to 55 and 20% respectively).



a R = Me, **b** R = 4-$EtOC_6H_4$, **c** R = 4-$O_2NC_6H_4$



a R =  , **b** R = 



5, **7**, **9 a** Ar = 4-$MeOC_6H_4$, **b** Ar = 4-$O_2NC_6H_4$; **5**, **7 c** Ar = 4-FC_6H_4;
6, **8** Ar = 4-$MeOC_6H_4$; Ar^1 = 4-$EtOC_6H_4$; 4-$O_2NC_6H_4$

TABLE 1. ^{1}H NMR Spectra Characteristics of Acyl Derivatives of 3-Amino-1(2H)-isoquinolinone

Compound	Chemical shifts (DMSO-d_6)*, δ, ppm (*J*, Hz)				
	N(2)H (1H)	3-NH (1H)	ArH	H-4 (1H, s)	Other signals
1	2	3	4	5	6
2a	11.33 (s)	10.45 (s)	8.08 (1H, d, ^3J = 8.0, H-8); 7.63 (1H, t, ^3J = 8.0, H-6); 7.55 (1H, d, ^3J = 8.0, H-5); 7.32 (1H, t, ^3J = 8.0, H-7)	6.35	2.09 (3H, s, CH_3)
2b	11.19 (br. s)	10.34 (br. s)	8.11 (1H, d, ^3J = 8.0, H-8); 7.95 (2H, d, ^3J = 8.5, H-2',6'); 7.63 (1H, t, ^3J = 8.0, H-6); 7.58 (1H, d, ^3J = 8.0, H-5); 7.35 (1H, t, ^3J = 8.0, H-7); 7.08 (2H, d, ^3J = 8.5, H-3',5')	6.89	4.13 (2H, q, ^3J = 7.0, OCH_2); 1.36 (3H, t, ^3J = 7.0, $CH_2C\underline{H}_3$)
2c	11.20 (br. s)	10.71 (br. s)	8.43 (2H, d, ^3J = 8.5, H-3',5'); 8.20 (2H, d, ^3J = 8.5, H-2',6'); 8.14 (1H, d, ^3J = 8.0, H-8); 7.65 (2H, m, H-5,6); 7.42 (1H, t, ^3J = 8.0, H-7)	6.93	—
4a	11.38 (br. s)	9.65 (br. m)	7.99 (1H, d, ^3J = 8.0, H-8); 7.60 (1H, s, H-5'); 7.40 (2H, d, ^3J = 8.5, H-2",6"); 7.19 (1H, t, ^3J = 8.0, H-6); 7.06 (1H, t, ^3J = 8.0, H-7); 6.88 (2H, d, ^3J = 8.5, H-3",5"); 6.80 (1H, d, ^3J = 8.0, H-5); 6.40 (1H, d, ^3J = 3.0, H-4'); 6.33 (1H, d, ^3J = 3.0, H-3')	—	4.74 (2H, d, ^3J = 6.0, NCH_2); 4.05 (2H, q, ^3J = 7.0, OCH_2); 1.32 (3H, t, ^3J = 7.0, $CH_2C\underline{H}_3$)
4b	11.28 (br. s)	9.78 (br. m)	7.99 (1H, d, ^3J = 8.0, H-8); 7.41 (2H, d, ^3J = 8.5, H-2",6"); 7.20 (1H, t, ^3J = 8.0, H-6); 7.06 (1H, t, ^3J = 8.0, H-7); 6.90 (2H, d, ^3J = 8.5, H-3",5"); 6.83-6.77 (4H, m, H-5,5',7',8')	—	4.59 (2H, d, ^3J = 6.0, NCH_2); 4.21 (4H, s, O–$(CH_2)_2$–O); 4.07 (2H, q, ^3J = 7.0, $OC\underline{H}_2CH_3$); 1.34 (3H, t, ^3J = 7.0, $CH_2C\underline{H}_3$)
6	11.17 (br. s)	9.84 (s)	8.14 (2H, d, ^3J = 8.5, H-3",5"); 8.09 (1H, d, ^3J = 8.0, H-8); 7.77 (2H, d, ^3J = 8.5, H-2",6"); 7.40 (2H, m, H-5,7); 7.24 (1H, t, ^3J = 8.0, H-6); 6.99 (2H, d, ^3J = 8.5, H-2',6'); 6.84 (2H, d, ^3J = 8.5, H-3',5')	—	3.73 (3H, s, OCH_3)
7a	11.87 (s)	—	8.15 (1H, d, ^3J = 7.8, H-8); 7.58 (1H, t, ^3J =7.8, H-6); 7.45 (3H, m, H-5,2",6"); 7.40 (1H, t, ^3J = 7.8, H-7); 7.21 (2H, d, ^3J = 8.5, H-2',6'); 6.82 (2H, d, ^3J = 8.5, H-3',5'); 6.74 (2H, d, ^3J = 8.0, H-3",5")	6.29	3.98 (2H, q, ^3J = 7.0, OCH_2); 3.74 (3H, s, OCH_3); 1.34 (3H, t, ^3J = 7.0, $CH_2C\underline{H}_3$)
7b	12.11 (s)	—	8.23 (2H, d, ^3J = 8.0, H-3',5'); 8.17 (1H, d, ^3J = 8.0, H-8); 7.68 (1H, t, ^3J =8.0, H-6); 7.58 (3H, m, H-5,2',6'); 7.48 (3H, m, H-7,2",6"); 6.90 (2H, d, ^3J = 8.0, H-3",5")	6.61	4.01 (2H, q, ^3J = 7.0, OCH_2); 1.28 (3H, t, ^3J = 7.0, $CH_2C\underline{H}_3$)
7c	11.98 (s)	—	8.13 (1H, d, ^3J = 7.8, H-8); 7.66 (1H, t, ^3J = 7.8, H-6); 7.55 (1H, d, ^3J = 7.8, H-5); 7.47 (3H, m, H-7,2",6"); 7.38 (2H, m, H-2',6'); 7.20 (2H, m, H-3',5'); 6.85 (2H, d, ^3J = 8.0, H-3",5")	6.53	3.99 (2H, q, ^3J = 7.0, OCH_2); 1.28 (3H, t, ^3J = 7.0, $CH_2C\underline{H}_3$)
8*[2]	—	—	8.15 (2H, d, ^3J = 9.0, H-2'",6'"); 8.01 (1H, d, ^3J = 8.0, H-8); 7.93 (1H, d, ^3J = 8.0, H-5); 7.82 (1H, t, ^3J = 8.0, H-6); 7.66 (1H, t, ^3J = 8.0, H-7); 7.42 (2H, d, ^3J = 8.5, H-2",6"); 7.16 (4H, m, H-2',6',3'",5'"); 6.91 (2H, d, ^3J = 8.5, H-3",5"); 6.79 (2H, d, ^3J = 8.5, H-3',5')	7.78	4.19 (2H, q, ^3J = 7.0, 4'"-OCH_2); 4.01 (2H, q, ^3J = 7.0, 4"-OCH_2); 3.74 (3H, s, OCH_3); 1.39 (3H, t, ^3J = 7.0, 4'"-$OCH_2C\underline{H}_3$); 1.28 (3H, t, ^3J = 7.0, 4"-$OCH_2C\underline{H}_3$)
9a	—	8.69 (s)	8.16 (2H, d, ^3J = 8.5, H-2",6"); 7.69 (1H, d, ^3J = 8.0, H-8); 7.61 (1H, d, ^3J = 8.0, H-5); 7.50 (1H, t, ^3J = 8.0, H-6); 7.34 (2H, d, ^3J = 8.5, H-2',6'); 7.17 (1H, t, ^3J = 8.0, H-7); 7.07 (2H, d, ^3J = 8.5, H-3",5"); 6.83 (2H, d, ^3J = 8.5, H-3',5')	6.93	4.17 (2H, q, ^3J = 7.0, OCH_2); 3.75 (3H, s, OCH_3); 1.44 (3H, t, ^3J = 7.0, $CH_2C\underline{H}_3$)

TABLE 1 (continued)

1	2	3	4	5	6
9b	—	10.16 (s)	8.22 (2H, d, ^3J = 8.5, H-3',5'); 8.16 (2H, d, ^3J = 8.5, H-2",6"); 7.96 (1H, d, ^3J = 8.0, H-8); 7.90 (1H, d, ^3J = 8.0, H-5); 7.74 (1H, t, ^3J = 8.0, H-6); 7.69 (2H, d, ^3J = 8.5, H-2',6'); 7.48 (1H, t, ^3J = 8.0, H-7); 7.18 (2H, d, ^3J = 8.5, H-3",5")	7.42	4.18 (2H, q, ^3J = 7.0, OCH_2); 1.40 (3H, t, ^3J = 7.0, $CH_2\underline{CH_3}$)
11a	11.78 (br. s)	—	8.15 (1H, d, ^3J = 8.0, H-8); 7.65 (1H, d, ^3J = 8.0, H-5); 7.62 (1H, t, ^3J = 8.0, H-6); 7.45 (1H, t, ^3J = 8.0, H-7)	6.15 (br.)	3.67 (3H, s, NCH_3); 2.23 (3H, s, 3'-CH_3); 2.12 (3H, s, 5'-CH_3); 1.90 (3H, br. s, $COCH_3$)
11b	11.88 (br. s)	—	8.26 (1H, d, ^3J = 8.0, H-8); 7.79 (1H, t, ^3J = 8.0, H-6); 7.72 (1H, d, ^3J = 8.0, H-5); 7.61 (1H, t, ^3J = 8.0, H-7); 7.43 (1H, d, ^3J = 5.0, H-5'); 7.38 (1H, d, ^3J = 5.0, H-4')	6.91	2.23 (3H, s, CH_3)
12a	—	9.95 (s)	8.34 (1H, d, ^3J = 4.0, H-6'); 8.21 (2H, d, ^3J = 9.0, H-2",6"); 7.91 (1H, d, ^3J = 8.0, H-8); 7.84 (1H, d, ^3J = 8.0, H-5); 7.70 (1H, t, ^3J = 8.0, H-6); 7.66 (1H, t, ^3J = 7.0, H-4'); 7.41 (1H, t, ^3J = 8.0, H-7); 7.20 (3H, m, H-3',3",5"); 6.90 (1H, t, J = 6.0, H-5')	8.59	4.20 (2H, q, ^3J = 7.0, OCH_2); 1.41 (3H, t, ^3J = 7.0, $CH_2\underline{CH_3}$)
12b	—	10.32 (s)	9.11 (1H, s, H-2'); 8.37 (1H, d, ^3J = 8.0, H-4'); 8.34 (1H, d, ^3J = 5.0, H-6'); 8.23 (2H, d, ^3J = 8.5, H-2",6"); 7.97 (1H, d, ^3J = 8.0, H-8); 7.93 (1H, d, ^3J = 8.0, H-5); 7.83 (1H, m, H-5'); 7.76 (1H, t, ^3J = 8.0, H-6); 7.48 (1H, t, ^3J = 8.0, H-7); 7.20 (2H, d, ^3J = 8.5, H-3",5")	7.36	4.21 (2H, q, ^3J = 7.0, OCH_2); 1.41 (3H, t, ^3J = 7.0, $CH_2\underline{CH_3}$)
13a	10.53 (s)	9.18 (s)	8.02 (1H, d, ^3J = 7.8, H-8); 7.50 (2H, d, ^3J = 8.5, H-2",6"); 7.30 (1H, t, ^3J = 7.8, H-7); 7.12 (1H, t, ^3J = 7.8, H-6); 6.94 (3H, m, H-5,3",5")	—	4.08 (2H, q, ^3J = 7.0, OCH_2); 3.58 (3H, s, NCH_3); 1.95 (3H, s, 3'-CH_3); 1.89 (3H, s, 5'-CH_3); 1.35 (3H, t, ^3J = 7.0, $CH_2\underline{CH_3}$)
13b	10.62 (br. s)	9.88 (br. s)	8.03 (1H, d, ^3J = 7.8, H-8); 7.55–7.49 (4H, m, H-2",3",5",6"); 7.30 (1H, t, ^3J = 7.8, H-7); 7.14 (1H, t, ^3J = 7.8, H-6); 6.87 (1H, m, H-5)	—	3.62 (3H, s, NCH_3); 2.00 (3H, s, 3'-CH_3); 1.92 (3H, s, 5'-CH_3)
13c	13.77 (s)	10.61 (s)	8.34 (1H, d, ^3J = 4.8, H-6'); 8.13 (1H, d, ^3J = 8.0, H-8); 7.75 (1H, t, ^3J = 7.7, H-4'); 7.63 (2H, d, ^3J = 8.5, H-2",6"); 7.40 (1H, t, ^3J = 8.0, H-7); 7.25 (1H, t, ^3J = 8.0, H-6); 7.10 (1H, d, ^3J = 8.0, H-5); 7.05 (2H, m, H-3',5'); 6.92 (2H, d, ^3J = 8.5, H-3",5")	—	4.06 (2H, q, ^3J = 7.0, OCH_2); 1.31 (3H, t, ^3J = 7.0, $CH_2\underline{CH_3}$)
14a	13.61 (s)	—	8.39 (1H, d, ^3J = 7.8, H-8); 8.14 (1H, d, ^3J = 5.0, H-5'); 7.70 (1H, t, ^3J = 7.8, H-7); 7.65 (1H, d, ^3J = 5.0, H-4'); 7.58 (2H, d, ^3J = 8.5, H-2",6"); 7.51 (1H, t, ^3J = 7.8, H-6); 7.31 (2H, d, ^3J = 8.5, H-3",5"); 6.95 (1H, d, ^3J = 7.8, H-5)	—	4.21 (2H, q, ^3J = 7.0, OCH_2); 1.49 (3H, t, ^3J = 7.0, $CH_2\underline{CH_3}$)
14b	13.78 (s)	—	8.73 (2H, d, ^3J = 8.0, H-3",5"); 8.41 (1H, d, ^3J = 7.8, H-8); 8.12 (1H, d, ^3J = 5.0, H-5'); 7.99 (2H, d, ^3J = 8.0, H-2",6"); 7.81 (1H, d, ^3J = 5.0, H-4'); 7.77 (1H, t, ^3J = 7.8, H-7); 7.60 (1H, t, ^3J = 7.8, H-6); 6.83 (1H, d, ^3J = 7.8, H-5)	—	—
14c	13.65 (s)	—	8.77 (2H, d, ^3J = 8.0, H-3",5"); 8.48 (1H, t, ^3J = 7.7, H-4'); 8.42 (1H, d, ^3J = 8.0, H-3'); 8.39 (1H, d, ^3J = 7.0, H-6'); 8.29 (1H, d, ^3J = 8.0, H-8); 8.00 (2H, d, ^3J = 8.0, H-2",6"); 7.78 (1H, t, ^3J = 7.7, H-5'); 7.70 (1H, t, ^3J = 8.0, H-7); 7.59 (1H, t, ^3J = 8.0, H-6); 6.68 (1H, d, ^3J = 8.0, H-5)	—	—

* The ^{1}H NMR spectra of compounds **7a**, **9a**, **14a** were recorded in a DMSO-d_6–CCl_4, 1:1 mixture.
*2 ^{1}H NMR spectra of compound **8** in the mixture (**7a** + **8**, 1:1).

3-(Arylamino)-1(2H)-isoquinolinones **5**, like alkylamino derivatives **3a**,**b**, on heating in dioxane with isonicotinoyl chloride are also converted into the products of C-alkylation, 4-acyl-3-anilino-1(2H)-isoquinolinones, in high yield (61-85%) [5]. It turned out that on using the less reactive acid chlorides of benzoic acids the reaction proceeds in a more complex manner. In all cases, irrespective of the nature of the substituent in the benzene ring of the 3-arylamino group of compounds **5a-c**, on heating in dioxane with aroyl chlorides complex mixtures of reaction products are formed. In the case of the reaction of 3-(4-methoxy-anilino)isocarbostyril (**5a**) with 4-nitrobenzoyl chloride we successfully isolated one of the main components of the mixture in a pure state, *viz.* 3-(4-methoxyanilino)-4-(nitrobenzoyl)-1(2H)-isoquinolinone (**6**). The structure of compound **6** was established on the basis of the data of its ^{1}H NMR spectrum, in which the signal of the H-4 proton was absent and the signals of N(2)H and 3-NH were retained (Table 1).

On acylating compounds **5a-c** with aroyl chlorides in dioxane in the presence of Et_3N or in pyridine the result of the reaction depends on the structure of the acid chloride and the duration of heating the reaction mixture. Interaction with 4-nitrobenzoyl chloride under these conditions leads to a complex mixture of reaction products. The main component of these mixtures is evidently hydrolytically unstable and in the process of its separation and purification by crystallization is converted into the initial 3-aminoisocarbostyril of type **5**. When using 4-ethoxybenzoyl chloride on extended heating (7 h) of compounds **5a-c** with an excess of acid chloride N-aryl-4-ethoxy-N-(1-oxo-1,2-dihydro-3-isoquinolinyl)benzamides **7a-c** were obtained in 44-56% yield. In their ^{1}H NMR spectra only one signal exchangeable with D_2O was present, *viz.* the H-2 proton in the 11.8-12.1 ppm region, and the resonance of the H-4 methine proton was observed at 6.3-6.6 ppm. On restricting the time of heating (3 h) of the reaction mixture of 3-aminoisocarbostyril **5a** with 4-ethoxybenzoyl chloride the intercation product was a 1:1 mixture of N-acyl derivative **7a** and the diacyl derivative 3-[(4-methyoxyphenyl)(4-ethoxy-benzoyl)amino]-1-isoquinolinyl 4-ethoxybenzoate (**8**). The structure of compound **8** was established on the basis of data of mass spectroscopy (peak with *m/z* 563 corresponds to $[M+1]^+$ of the diacylation product) and of the spectral data of the products of acylation of 3-aminoisocarbostyrils **5** in the presence of NaH. Attempts to separate the mixture by chromatographic methods proved to be unsuccessful, and on recrystallization from alcoholic solvents (2-propanol, ethanol) only N-arylbenzamide **7a** was obtained.

It was shown previously [13-15], in the examples of 3-aminoisocarbostyril derivatives condensed on face *c,* that in the presence of strong bases products of electrophilic substitution at the lactam fragment of the molecule may be formed. It is evident that in the case of compounds of type **5,** having no substituent at the N(2) atom, such a variant of the conversion may also be possible. 3-Aminoisocarbostyrils **5a**,**b** interact with 4-ethoxybenzoyl chloride in DMF in the presence of NaH at room temperature and are converted into monoacyl derivatives in 54-68% yield. In the ^{1}H NMR spectra of the reaction products one proton signal exchangeable with D_2O was present in the 8.6-10.2 ppm range and a singlet of the H-4 methine proton at 6.9-7.4 ppm which may correspond, both to the N-3 or N(2)–acyl derivative, and also to the O-acyl derivative. In addition, in difference to the ^{1}H NMR spectra of compounds **4a**,**b**, **6**, and **7a-c**, the resonance of the H-8 proton of these products is observed not at lower, as might be expected on introducing an electron-withdrawing substituent into the molecule, but at higher field (at 7.7 and 7.9 ppm) in comparison with those for the initial compounds **5a** (8.0 ppm) and **5b** (8.11 ppm [5]). There is also a significant difference in the IR spectra. The band for the stretching vibrations of the carbonyl groups of **4a**,**b**, **6**, and **7a-c** is observed in the 1650-1676 cm^{-1} region, and of the unknown products in the 1712-1738 cm^{-1} region characteristic of esters. On the basis of these data we proposed that on acylation of 3-aminoisocarbostyrils **5a**,**b** in the presence of NaH 3-anilino-1-isoquinolinyl 4-ethoxybenzoates **9a**,**b** are formed.

Final confirmation of this hypothesis was obtained on studying the NOESY, HMQC, and HMBC ^{13}C NMR spectra of compounds **7a** and **9a** (Fig. 1, *a,b*). The most significant difference in the ^{13}C NMR spectra of these compounds is in the values of the chemical shifts of the C(1) atom. For **9a** this is observed in a region not characteristic for the carbons of carbonyl groups (155.1 ppm), and for **7a** at 163.0 ppm. The presence of a correlation between the NH group proton (8.69 ppm) in the HMBC spectrum of compound **9a** and the carbon

atoms in the *ortho* position of the benzene ring of the 3-arylamino group C-2', C-6' (121.9 ppm), and also the spatial proximity of the NH protons and H-4, H-2', and H-6' (in the NOESY spectrum), shows unequivocally the formation of an acyl derivative at the lactam fragment of the molecule, and in conjunction with the data of IR and ^{1}H NMR spectra, to the formation of an O-acyl derivative.

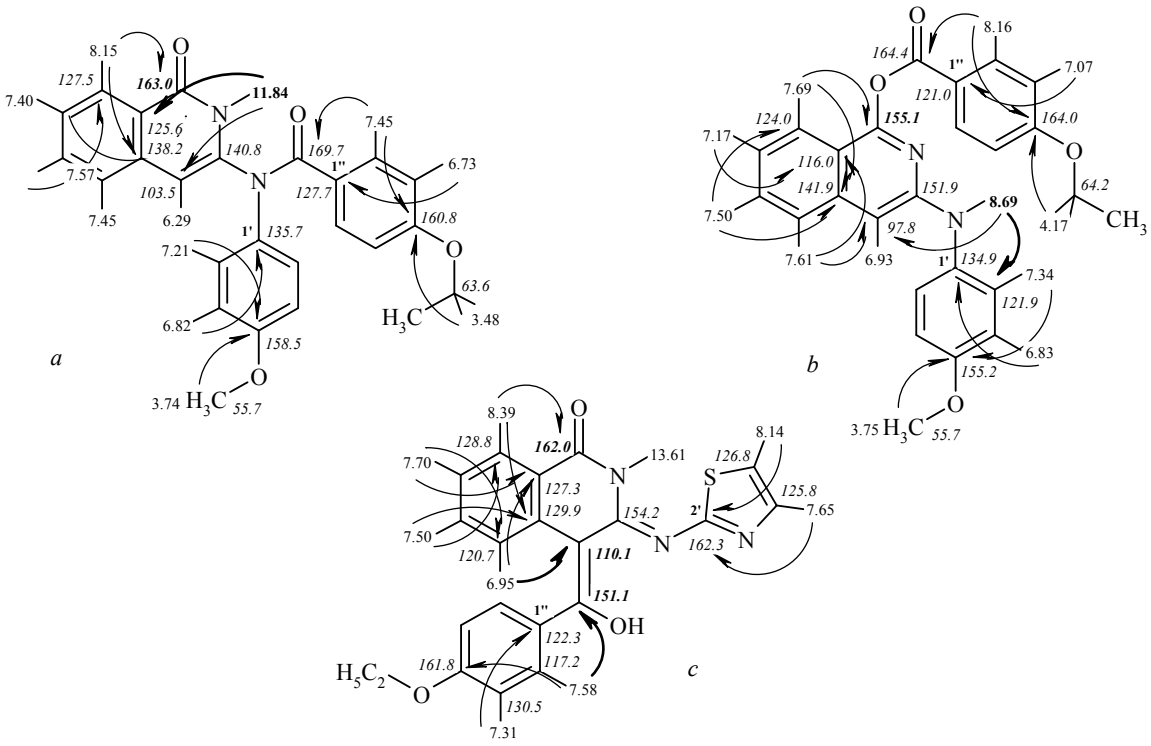
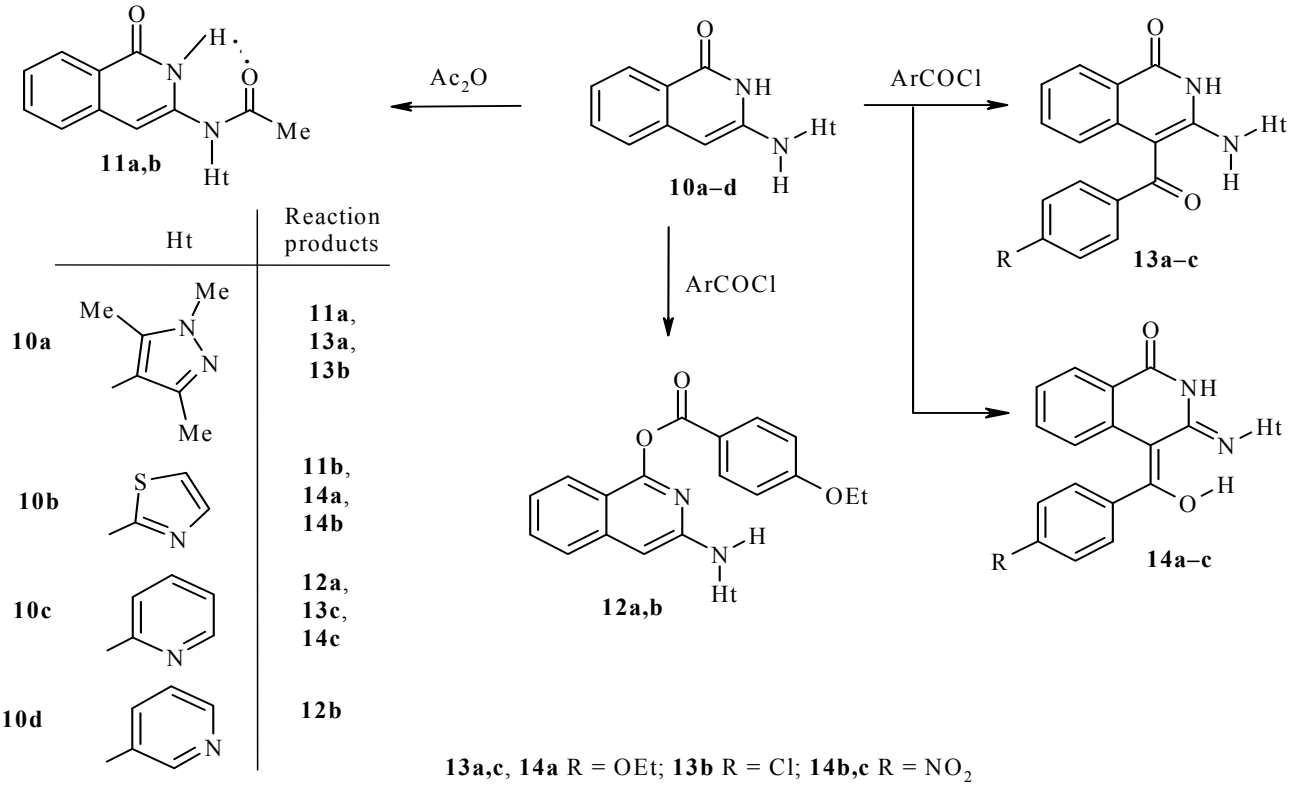


Fig. 1. Structurally significant correlations in the HMBC of compounds **7a** (*a*), **9a** (*b*), and **14a** (*c*).

The acylation of compound **5a** with 4-nitrobenzoyl chloride in the presence of NaH is accompanied by the formation of a large quantity of side products. On attempting to isolate an acyl derivative in a pure state the initial compound **5a** was obtained, probably as a result of the low hydrolytic stability of 1-isoquinolinyl benzoates of type **9**. The latter evidently explains the dependence of the result of acylation in the system dioxane–Et_3N on the time of heating the reaction mixture. On more extended heating the yield of the N-acylation product of type **7** increases as a result of hydrolysis of the initially formed diacyl derivative of type **8**.

We then studied further the acylation of (3-hetarylamino)-1(2H)-isoquinolinones **10a-d**. Heating 3-aminoisocarbostyril derivatives **1**, **3**, **5,** and **10** in acetic anhydride leads to the formation of complex mixtures of products and only in the case of **10a**,**b** did we successfully isolate N-(hetaryl)-N-(1-oxo-1,2-dihydro-3-isoquinolinyl)acetamides **11a**,**b** in good yield in a pure state (52 and 61%). However we did not successfully obtain acylation products of compounds **10a-d** with benzoic acid chlorides in the absence of a basic catalyst.

In the presence of bases acyl derivatives are formed in high yield (63-84%), but their structure depends both on the strength of the base, the extent of heating and also on the structure of the acid chloride and heterocyclic substituent in the 3-amino group of the initial 3-aminoisocarbostyril **10**. Thus on brief heating (30 min) of compound **10d** with 4-ethoxybenzoyl chloride in pyridine 3-(3-pyridylamino)-1-isoquinolinyl 4-ethoxybenzoate (**12b**) was obtained. The reaction of compound **10c** in DMF in the presence of NaH at room temperature leads to an analogous result – the O-acyl derivative **12a**. Extended (7-8 h) heating of 3-amino-isocarbostyrils **10a-c** with aroyl chlorides in dioxane with Et_3N or in pyridine leads to the C-acylation product 4-aroyl-3-(hetarylamino)-1(2H)-isoquinolinones **13a-c** and 4-[(*Z*)-aroyl(hydroxy)methylidene]-3-(hetarylimino)-1(2H)-isoquinolinones **14a-c**.



The spectral criteria determined above for compounds **2**, **4**, **6-9** (Tables 1, 2) were used to assign the structure of the acyl derivatives of 3-(hetarylamino)isocarbostyrils **11-14**. In the NMR spectra the value of the chemical shift of the NH group proton and of the C-1 atom, the presence or absence of the H-4 signal, and in the IR spectrum the frequency of the stretching vibrations of the carbonyl group were used. However the NMR spectra of the products of acylation by aroyl chlorides of 3-(1,3-thiazol-2-ylamino)-1(2H)-isoquinolinone (**10b**) and by 4-nitrobenzoyl chloride of 3-(2-pyridylamino)-1(2H)-isoquinolinone (**10c**), corresponding in all criteria for C-acyl derivatives, have certain special features. Thus in their ^{1}H NMR spectra, as a result of rapid exchange, the signal of the 3-NH group proton was absent, but the resonance of the H-5 proton was observed in a more high field region (d, 6.5-6.9 ppm) in comparison with its position in the spectra of the initial 3-(hetaryl-amino)isocarbostyrils **10b**,**c** [9]. The latter may be explained by the shielding of the H-5 proton by the benzene ring of the aroyl substituent fixed perpendicularly to the plane of the isoquinoline fragment. In the ^{13}C NMR spectra signals were absent for carbon atoms in the region $\delta > 165$ ppm, while for aromatic ketones, as are C-acyl-substituted 3-aminoisocarbostyrils, the presence of a carbonyl group signal at $\delta > 190$ ppm (192.2-193.3 ppm for **4a**, **13a- c**) is characteristic. The latter fact in our opinion indicated the formation of the enolic form of ketones as in structure **14a-c**. With the aim of a precise assignment of carbon atom signals in the ^{13}C NMR spectra of these compounds a two-dimensional spectrum was recorded for the acyl derivative **14a** (HMBC method). On the basis of the observed heteronuclear ^{1}H-^{13}C correlations (Fig. 1, *c*) the chemical shift of the carbon atom of the benzoyl fragment linked to the C-4 atom of the isoquinoline ring (151.1 ppm) was determined to be in a region not characteristic for the resonance of carbonyl group carbon atoms, which confirms the correctness of our proposal on the formation of the enolic form of the ketone. The formation of enols **14** is evidently the result of an increase in the mobility of the proton at the nitrogen atom of the 3-amino group with an increase of the acceptor properties of the heterocyclic residue and the substituent in the benzene

ring of the aroyl fragment. Comparison of the UV spectra of 3-aminoisocarbostyrils **13** and **14** enables the differences in structure of the chromophore of compounds **14** to be noted. In the spectra of the enols the absorption bands at 322 (for **14c**) and 362 nm (for **14a**) are displaced bathochromically relative to the band at 290-296 nm (compound **13**). We explain this by the increase in the system of conjugated bonds in **14a,c** due to the more effective implication in conjugation of the carbonyl group at atom C-1 with the heterocyclic fragment (2-pyridyl or 2-thiazolyl) at the 3-imino group.

The result of the acylation of derivatives of 3-aminocarbostyrils is determined by the reaction conditions, and by the structure of the substituent at the 3-amino group, and of the acylating reagent. In the presence of a strong base (NaH) O-acyl derivatives are formed preferentially. A reduction in the basicity of the medium assists substitution at the enamine fragment of the molecule and leads to N-acyl and/or C-acyl substituted isocarbostyril depending on the structure of the substituent at the 3-amino group. In the absence of a basic catalyst the direction of substitution is determined by the structure of the acylating reagent. The more reactive acid chlorides attack position 4 of the isoquinoline, and the less reactive acylating reagents attack the nitrogen atom of the 3-amino group.

TABLE 2. Data of IR Spectra of Acyl Derivatives of 3-Amino-1(2H)-isoquinolinone

Compound	ν, cm^{-1}
2a	3216 (NH), 3185 (NH), 3064, 3020, 1669 (C=O), 1600, 1497, 1348, 1287, 1144, 819, 750
2b	3272 (NH), 3182 (NH), 2980, 1661 (C=O), 1608, 1287, 1256 (C–O), 1183, 1046, 814
2c	3277 (NH), 3188 (NH), 3120, 1667 (C=O), 1611, 1597, 1521 (NO_2), 1351 (NO_2), 853, 816, 752, 710
4a	3142 (NH), 2980, 1676 (br., C=O), 1622, 1603, 1315, 1259 (C–O), 1175, 1158, 917, 775
4b	3143 (NH), 2986, 1673 (br., C=O), 1606, 1510, 1315, 1295 (C–O), 1245 (C–O), 1069, 778
6	3154 (NH), 3042, 1661 (C=O), 1614, 1564, 1513 (NO_2), 1315 (NO_2), 1253 (C–O), 825, 783, 763
7a*	3057 (NH), 2983, 2840, 1667 (C=O), 1652 (C=O), 1641, 1607, 1510, 1305, 1253 (C–O), 1174, 1045, 840, 758, 626
7b	3081 (NH), 2980, 2840, 1650 (C=O), 1606, 1510 (NO_2), 1339 (NO_2), 1295, 1256 (C–O), 1175, 848, 758, 660
7c	3045 (NH), 2980, 2868, 1667 (C=O), 1648 (br.), 1606, 1505, 1317, 1303, 1253 (C–O), 1174, 1043, 845, 758
9a	3217 (NH), 3040, 2977, 1738 (C=O), 1632, 1595, 1535, 1512, 1248 (C–O), 1170, 1151, 1077 (C–O), 1034, 760
9b	3344 (NH), 2980, 1712 (C=O), 1639, 1603, 1589 (NO_2), 1326 (NO_2), 1250 (C–O), 1077, 847, 750
11a	3204 (NH), 1656 (C=O), 1625, 1555, 1494, 1379, 1278, 792, 747
11b	3283 (NH), 3115, 2796, 1690 (C=O), 1661 (C=O), 1499, 1443, 1371, 1301, 1287, 755
12a	3356 (NH), 3047, 2936, 1720 (C=O), 1603, 1589, 1527, 1480, 1452, 1253 (C–O), 1071 (C–O), 764, 752
12b	3289 (NH), 3064, 2600, 1731 (C=O), 1639, 1605, 1555, 1474, 1449, 1253 (br., C–O), 1169 (C–O), 1085, 833, 792, 760, 694
13a	3193 (NH), 2975, 1656 (br., C=O), 1606, 1564, 1292, 1253 (C–O), 1178, 1040, 783
13b	3182 (NH), 3092, 1659 (br., C=O), 1608, 1566, 1312, 1292, 1085, 783, 769
13c	3000 (br., NH), 2986, 1690 (C=O), 1687 (C=O), 1628, 1605, 1583, 1477, 1438, 1315, 1298, 1262 (C–O), 1150, 1035, 926, 786, 769
14a	3417 (br., OH), 3126 (NH), 3020, 2527 (br., SH), 1692 (br., C=O), 1611, 1589, 1564, 1438, 1320, 1292 (C–O), 1246, 1146, 1046, 764
14b	3412 (br., OH), 3126 (NH), 3031, 2583 (br., SH), 1695 (C=O), 1611, 1586, 1524 (NO_2), 1348 (NO_2), 1320, 1292 (C–O), 1147, 836, 764
14c	3143 (br., NH, OH), 3064, 2740, 1695 (C=O), 1614, 1583, 1516 (NO_2), 1351 (NO_2), 1326, 1292 (C–O), 1130, 870, 775

TABLE 3. Physicochemical Characteristics of the Synthesized Compounds

Compound*	Empirical formula	Found, % / Calculated, %			mp, °C*[2]	Yield, %
		C	H	N		
2a	$C_{11}H_{10}N_2O_2$	65.29 / 65.34	4.91 / 4.98	13.87 / 13.85	260-263 (dec)	71
2b	$C_{18}H_{16}N_2O_3$	70.08 / 70.12	5.18 / 5.23	9.11 / 9.09	257-260	82
2c	$C_{16}H_{11}N_3O_4$	62.11 / 62.14	3.55 / 3.58	13.60 / 13.59	> 300	89
4a	$C_{23}H_{20}N_2O_4$	71.09 / 71.12	5.15 / 5.19	7.20 / 7.21	260-262	76
4b	$C_{27}H_{24}N_2O_5$	71.00 / 71.04	5.36 / 5.30	6.17 / 6.14	238-239	48
5a	$C_{16}H_{14}N_2O_2$	72.17 / 72.16	5.25 / 5.30	10.50 / 10.52	199-201	83
5c	$C_{15}H_{11}FN_2O$	70.82 / 70.86	4.30 / 4.36	11.01 / 11.02	224-225	77
6	$C_{23}H_{17}N_3O_5$	66.45 / 66.50	4.08 / 4.12	10.14 / 10.12	> 300	67
7a	$C_{25}H_{22}N_2O_4$	72.40 / 72.45	5.31 / 5.35	6.78 / 6.76	162-164	44
7b	$C_{24}H_{19}FN_2O_3$	71.59 / 71.63	4.74 / 4.76	6.96 / 6.96	207-209	56
7c	$C_{24}H_{19}N_3O_5$	67.08 / 67.13	4.42 / 4.46	9.81 / 9.79	167-168	42
9a	$C_{25}H_{22}N_2O_4$	72.42 / 72.45	5.30 / 5.35	6.78 / 6.76	184-185	68
9b	$C_{24}H_{19}N_3O_5$	67.09 / 67.13	4.43 / 4.46	9.78 / 9.79	174-175	54
11a	$C_{17}H_{18}N_4O_2$	65.76 / 65.79	5.83 / 5.85	18.08 / 18.05	201-202	52
11b	$C_{14}H_{11}N_3O_5S$	58.91 / 58.93	3.85 / 3.89	14.74 / 14.73	220-223 (dec)	61
12a	$C_{23}H_{19}N_3O_3$	71.64 / 71.67	4.93 / 4.97	10.93 / 10.90	171-172	63
12b	$C_{23}H_{19}N_3O_3$	71.62 / 71.67	4.94 / 4.97	10.92 / 10.90	227-228	66
13a	$C_{24}H_{24}N_4O_3$	69.18 / 69.21	5.76 / 5.81	13.47 / 13.45	228-229	69
13b	$C_{22}H_{19}ClN_4O_2$	64.91 / 64.94	4.68 / 4.71	13.79 / 13.77	267-268	74
13c	$C_{23}H_{19}N_3O_3$	71.63 / 71.67	4.92 / 4.97	10.92 / 10.90	202-203	71
14a	$C_{21}H_{14}N_4O_4$	65.22 / 65.28	3.63 / 3.65	14.50 / 14.50	290-293 (dec)	80
14b	$C_{21}H_{17}N_3O_3S$	64.38 / 64.43	4.35 / 4.38	10.75 / 10.73	> 300	82
14c	$C_{19}H_{12}N_4O_4S$	58.15 / 58.16	3.05 / 3.08	14.30 / 14.28	> 300	84

* Compound **11b**. Found, %: S 11.26. Calculated, %: S 11.24. Compound **14b**. Found, %: S 8.22. Calculated, %: S 8.19. Compound **14c**. Found, %: S 8.16. Calculated, %: S 8.17. Compound **13b**. Found, %: Cl 8.70. Calculated, %: Cl 8.71.

*[2] Solvents for crystallization: EtOH (compounds **2a-c**, **4a**,**b, 7c**, **12a**, **14c**) and 2-propanol (compounds **5a,c**, **6**, **7a**,**b**, **9a**,**b**, **11a**,**b**, **12d**, **13a-c**, **14a**,**b**)

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer Spectrum BX instrument in KBr disks. The UV spectra were recorded on a UV-vis Lambda 20 Spectrometer in methanol. The ^1H and ^{13}C NMR spectra of the

synthesized products and experiments on HMQC and HMBC heteronuclear correlations were carried out on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively). In all cases the solvent was DMSO-d_6, internal standard was TMS. Melting points were determined on a Boetius type heating apparatus and were not corrected. A check on the purity of the obtained compounds was effected by TLC on Silufol UV-254 plates and by a mass spectrometric method with HPLC on an Agilent 1100 Series instrument with an Agilent LC/MSD SL selective detector (samples were introduced in a TFA matrix, ionization by EI). Physicochemical characteristics of the synthesized compounds are given in Table 3.

3-Amino-1(2H)-isoquinolinone (**1**) was obtained by the procedure of [16], 3-(alkylamino)-1(2H)-isoquinolinones **3a,b** by [9], 3-(arylamino)-1(2H)-isoquinolinones **5b**,**d** by [5], and 3-(hetarylamino)-1(2H)-isoquinolinones **10a-d** by [9].

N-(1-Oxo-1,2-dihydro-3-isoquinolinyl)acetamide (2a). Ac_2O (0.7 ml, 7 mmol) was added to a solution of 3-amino-1(2H)-isoquinolinone (**1**) (0.8 g, 5 mmol) in dioxane (80 ml) and the mixture boiled for 4 h. The solid precipitated on cooling was filtered off, and washed with diethyl ether.

N-(1-Oxo-1,2-dihydro-3-isoquinolinyl)benzamides 2b,**c** were obtained by the procedure for synthesizing product **2a**, using an excess (7.5 mmol) of 4-ethoxy- or 4-nitrobenzoyl chloride.

4-(4-Ethoxybenzoyl)-3-[(R-methyl)amino]-1(2H)-isoquinolinones 4a,**b.** 4-Ethoxybenzoyl chloride (1.38 g, 7.5 mmol) and Et_3N (1.15 ml) were added to a suspension of 3-(alkylamino)-1(2H)-isoquinolinone **3a** or **3b** (5 mmol) in dioxane (50 ml) and the mixture boiled for 3 h. The mixture was cooled, the solvent evaporated in vacuum and water (100 ml) poured onto the residue. The solid substance was filtered off, washed with water, and with alcohol.

Compound 4a. ^{13}C NMR spectrum, δ, ppm: 192.3 (4-C=O); 162.8 (C-1); 161.6 (C-4"); 152.0 (C-3); 151.3 (C-2'); 143.1 (C-5'); 139.3 (C-4a); 134.6 (C-1"); 131.6 (C-6); 131.3 (C-2",6"); 127.4 (C-8); 126.3 (C-5); 122.5 (C-7); 120.3 (C-8a); 114.3 (C-3",5"); 110.9 (C-4'); 108.1 (C-3'); 96.3 (C-4); 63.8 (OCH_2); 39.3 (NCH_2); 15.2 ($CH_2\underline{C}H_3$).

3-(Arylamino)-1(2H)-isoquinolinones 5a,**e** were obtained by the procedure for the synthesis of 3-arylaminoisocarbostyrils **5b**,**d** [5].

Compound 5a. IR spectrum, ν, cm^{-1}: 3378 (NH), 3247 (NH), 2885, 1673 (C=O), 1634, 1608, 1510, 1239 (C–O), 1029, 831, 778. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.64 (1H, s, N(2)H); 7.95 (1H, d, ^3J = 8.0, H-8); 7.58 (1H, s, 3-NH); 7.43 (1H, t, ^3J = 8.0, H-6); 7.27 (1H, d, ^3J = 8.0, H-5); 7.16 (1H, d, ^3J = 9.0, H-2',6'); 7.09 (1H, t, ^3J = 8.0, H-7); 6.93 (2H, d, ^3J = 9.0, H-3',5'); 5. 68 (1H, s, H-4); 3.74 (3H, s, OCH_3).

Compound 5c. IR spectrum, ν, cm^{-1}: 3300 (br, NH), 2980, 1667 (C=O), 1648, 1611, 1513, 1337, 1217, 811, 741. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.68 (1H, br. s, N(2)H); 7.99 (1H, d, ^3J = 8.0, H-8); 7.89 (1H, s, 3-NH); 7.47 (1H, t, ^3J = 8.0, H-6); 7.34 (1H, d, ^3J = 8.0, H-5); 7.13-7.22 (5H, m, 7,2',6',3',5'); 5.87 (1H, s, H-4).

3-(4-Methoxyanilino)-4-(4-nitrobenzoyl)-1(2H)-isoquinolinone (6). 4-Nitrobenzoyl chloride (1.39 g, 7.5 mmol) was added to a suspension of 3-(4-methoxyanilino)-1(2H)-isoquinolinone (**5a**) (1.33 g, 5 mmol) in dioxane (50 ml) and the mixture boiled for 10 h. The mixture was cooled and the solvent evaporated in vacuum. 2-Propanol (30 ml) was added to the residue, the mixture heated to boiling, and the insoluble solid filtered off.

N-Aryl-4-ethoxy-N-(1-oxo-1,2-dihydro-3-isoquinolinyl)benzamides 7a-c. A. 4-Ethoxybenzoyl chloride (1.38 g, 7.5 mmol) and Et_3N (1.15 ml) were added to a suspension of 3-(4-methoxyanilino)-1(2H)-isoquinolinone (**5a**) (1.33 g, 5 mmol) in dioxane (50 ml). The mixture was boiled for 3 h, cooled, the solvent evaporated in vacuum, and water (100 ml) was added to the residue. The aqueous solution was decanted and an oily residue was obtained, which was a mixture of 4-ethoxy-N-(4-methoxyphenyl)-N-(1-oxo-1,2-dihydro-3-isoquinolinyl)benzamide (**7a**) and 3- (4-ethoxybenzoyl)-[(4-methoxyphenyl)amino]-1-isoquinolinyl 4-ethoxybenzoate (**8**) (1:1). The oil was dissolved in 2-propanol and boiled for 1-2 min. After cooling, the precipitated solid product **7a** was filtered off. Yield was 0.83 g (40%). UV spectrum, λ_{max}, nm (ε·10^{-3}): 280 (16.28). ^{13}C NMR spectrum, δ, ppm: 169.7 (3-N–C=O); 163.0 (C-1); 160.8 (C-4"); 158.5 (C-4'); 140.8 (C-3); 138.2 (C-4a); 135.7 (C-1'); 132.7 (C-6); 131.2 (C-2",6"); 129.0 (C-2',6'); 127.7 (C-1"); 127.5 (C-8); 126.8 (C-5); 126.6 (C-7); 125.6 (C-8a); 114.8 (C-3',5'); 113.9 (C-3",5"); 103.5 (C-4); 63.6 (OCH_2); 55.7 (OCH_3); 15.2 ($CH_2\underline{C}H_3$).

B. Analogous to procedure A, using compound **5a** (1.33 g, 5 mmol) or 3-(4-nitroanilino)-1(2H)-isoquinolinone (**5b**) (1.40 g, 5 mmol). The mixture was boiled for 3 h, cooled, the solvent evaporated in vacuum, and water (100 ml) added to the residue. The solid substance was filtered off, washed with water, and with alcohol, and products **7a**,**b** obtained.

C. 4-Ethoxybenzoyl chloride (1.38 g, 7.5 mmol) was added to a solution of 3-(4-fluoroanilino)-1(2H)-isoquinolinone (**5c**) (1.27 g, 5 mmol) in pyridine (30 ml) and the mixture boiled for 7 h. The mixture was cooled, the solvent evaporated in vacuum, and water (100 ml) added to the residue. The solid substance was filtered off, washed with water, and with alcohol and product **7c** was obtained.

3-Anilino-1-isoquinolinyl 4-Ethoxybenzoates 9a,**b.** Sodium hydride (2.4 g) was added to a solution of 3-arylamino-1(2H)-isoquinolinone **5a**,**c** (5 mmol) in DMF (20 ml). After 20 min 4-ethoxybenzoyl chloride (1.38 g, 7.5 mmol) was added, the mixture stirred at room temperature for 10 h, and the solvent evaporated in vacuum. Water (50 ml) was added to the residue, and when using compound **5a** the solid substance (product **9a**) was filtered off. When using compound **5c** the aqueous solution was decanted from the oily residue, which was then dissolved with heating in 2-propanol. On cooling product **9b** was obtained from the solution.

Compound 9a. UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 286 (16.41). ^{13}C NMR spectrum, δ, ppm: 164.4 (–OC=O); 164.0 (C-4'); 155.2 (C-4"); 155.1 (C-1); 151.9 (C-3); 141.9 (C-4a); 134.9 (C-1'); 132.8 (C-2",6"); 131.3 (C-6); 125.6 (C-5); 124.0 (C-8); 123.6 (C-7); 121.9 (C-2',6'); 121.0 (C-1"); 116.0 (C-8a); 115.2 (C-3",5"); 114.6 (C-3',5'); 97.8 (C-4); 64.2 (OCH_2); 55.7 (OCH_3); 15.1 ($CH_2\underline{C}H_3$).

N-(Hetaryl)-N-(1-oxo-1,2-dihydro-3-isoquinolinyl)acetamides 11a,b. 3-[(Hetaryl)amino]-1(2H)-isoquinolinone **10a** or **10b** (5 mmol) was dissolved in Ac_2O (20 ml) and the solution boiled for 1-2 h. The excess of Ac_2O was evaporated in vacuum and water (50 ml) was added. The solid substance was filtered off, washed with water, and with alcohol.

3-(2-Pyridylamino)-1-isoquinolinyl 4-Ethoxybenzoate (12a) was obtained by the procedure for the synthesis of compound **9a** using 3-(2-pyridylamino)-1(2H)-isoquinolinone **10c**. UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 316 (25.77).

3-(3-Pyridylamino)-1-isoquinolinyl 4-Ethoxybenzoate (12b) was obtained by the procedure for the synthesis of product **7c** (method C), using 3-(3-pyridylamino)-1-(2H)-isoquinolinone (**10d**). The reaction mixture was heated for 30 min.

4-Aroyl-3-[(1,3,5-trimethyl-1H-pyrazol-4-yl)amino]-1(2H)-isoquinolinones 13a,b were obtained by the procedure for synthesizing products **7a**,**b** (method B), using 3-[(1,3,5-trimethyl-1H-pyrazol-4-yl)amino]-1(2H)-isoquinolinone (**10a**).

Compound 13a. UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 290 (22.70), 378 (12.68). ^{13}C NMR spectrum, δ, ppm: 192.9 (4-C=O); 162.2 (C-1); 162.0 (C-4"); 149.5 (C-3); 143.0, 139.0, 137.3, 133.6, 132.5, 131.3 (C-2",6"); 127.3, 124.8, 123.0, 120.4, 114.6 (C-3",5"); 114.3, 93.8 (C-4); 63.9 (OCH_2); 36.6 (1'-CH_3); 15.0 ($OCH_2\underline{C}H_3$); 11.3 (3'-CH_3); 9.2 (5'-CH_3).

Compound 13b. UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 296 (25.75), 380 (22.87). ^{13}C NMR spectrum, δ, ppm: 192.2 (4-C=O); 162.2 (C-1); 151.5 (C-3); 142.8, 140.5, 138.5, 137.3, 136.6, 132.5, 130.9 (C-2",6"); 129.1 (C-3",5"); 125.2, 123.3, 120.7, 113.8, 93.5 (C-4); 36.7 (1'-CH_3); 11.2 (3'-CH_3); 9.3 (5'-CH_3).

4-(4-Ethoxybenzoyl)-3-(2-pyridylamino)-1(2H)-isoquinolinone (13c) and 4-[(*Z*)-aroyl(hydroxy)-methylidene]-3-(hetarylamino)-1(2H)-isoquinolinones 14a-c were obtained by the procedure for the synthesis of product **7c** (method C), using 3-(hetarylamino)-1(2H)-isoquinolinones **10c** or **10b**.

Compound 13c. UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 292 (14.50), 378 (10.54). ^{13}C NMR spectrum, δ, ppm: 193.3 (4-C=O); 162.5 (C-1); 161.2 (C-4"); 154.5 (C-3); 146.7, 145.0, 139.7, 138.0, 132.9, 132.6, 132.0 (C-2",6"); 127.4, 125.5, 124.3, 121.5, 118.3, 114.6 (C-3",5"); 114.0, 97.3 (C-4); 63.9 (OCH_2); 15.0 ($OCH_2\underline{C}H_3$).

Compound 14a. UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 362 (20.64), 378 (15.50). ^{13}C NMR spectrum, δ, ppm: 162.3 (C-2'); 161.9 (C-1); 161.8 (C-4"); 154.2 (C-3); 151.1 (=COH); 133.5 (C-6); 130.7 (C-7); 130.5 (C-3",5");

129.9 (C-4a); 128.8 (C-8); 127.3 (C-8a); 126.8 (C-5'); 125.8 (C-4'); 122.3 (C-1"); 120.7 (C-5); 117.2 (C-2",6"); 110.1 (C-4); 64.0 (OCH_2); 14.9 (CH_3).

Compound 14b. ^{13}C NMR spectrum, δ, ppm: 162.1 (C-1,2'); 154.9 (C-3); 150.4 (=COH); 148.9 (C-4"); 136.8, 134.6, 131.6, 131.0 (C-3",5"); 129.2, 129.1, 127.2, 127.1 (C-2",6"); 127.0, 126.7, 121.0, 110.2 (C-4).

Compound 14c. UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-1}$): 322 (13.21), 408 (11.20). ^{13}C NMR spectrum, δ, ppm: 162.1 (C-1); 154.1 (C-3); 150.4 (=COH); 148.5, 148.4, 141.8, 136.7, 134.4, 133.6, 132.0 (C-3",5"); 131.8, 129.2, 129.1, 128.0, 127.8, 127.3 (C-2",6"); 126.0, 121.7, 113.2 (C-4).

REFERENCES

1. V. A. Kovtunenko, L. M. Potikha, and R. M. Gutsul, *Zh. Org. Farm. Khim.*, **7**, No. 1, 17 (2009).
2. H. Natsugari, H. Shira, and T. Doi, EP Patent 566069; *Chem. Abstr.*, **120**, 134310 (1994).
3. S. Kimoto, M. Okamoto, T. Kawabata, and S. Ohta, *Yakugaku Zasshi*, **94**, 55 (1974); *Chem. Abstr.*, **81**, 37521 (1974).
4. S. Kimoto, M. Okamoto, and S. Ohta, *Yakugaku Zasshi*, **91**, 1279 (1971); *Chem. Abstr.*, **76**, 85662 (1972).
5. T. T. Kucherenko, R. Gutsul, V. M. Kisel, and V. A. Kovtunenko, *Tetrahedron*, **60**, 211 (2004).
6. S. Ohta, S. Kimoto, and M. Okamoto, *Yakugaku Zasshi*, **92**, 1479 (1972); *Ref. Zh. Khim.*, **19**, Zh280 (1973).
7. S. Ohta, S. Kimoto, and M. Okamoto, *Yakugaku Zasshi*, **92**, 1473 (1972); *Chem. Abstr.*, **78**, 97517 (1973).
8. L. W. Deady, N. H. Quazi, and H. Nurul, *J. Heterocycl. Chem.*, **31**, 793 (1994).
9. L. M. Potikha, R. M. Gutsul, V. A. Kovtunenko, and A. A. Tolmachev, *Khim. Geterotsikl. Soedin.*, 575 (2010).
10. K. Nagarajan, V. Ranga Rao, and R. K. Shah, *Indian J. Chem.*, **8**, 663 (1970).
11. K. Nagarajan, V. Ranga Rao, R. K. Shah, S. J. Shenoy, H. Fritz, W. J. Richter, and D. Muller, *Helv. Chim. Acta*, **71**, 77 (1988).
12. M. Bollini, S. E. Asis, and A. M. Bruno, *Synthesis*, 237 (2006).
13. J. P. Paolini, F. P. Palopoli, and L. J. Lendvay, *J. Heterocycl. Chem.*, **24**, 549 (1987).
14. G. Winters, N. Di Molla, M. Berti, and V. Arioli, *Farmaco*, **34**, 507 (1979).
15. W. A. Bolhofer, E. J. Cragoe, and J. M. Hoffman, Jr., US Pat. 4133885; *Chem. Abstr.*, **90**, 137793 (1979).
16. S. Goya, A. Takadate, T. Tanaka, Y. Tsuruda, and H. Ogata, *Yakugaku Zasshi*, **100**, 819 (1980); *Chem. Abstr.*, **94**, 47098 (1981).