SYNTHESIS AND PROPERTIES OF 2-SUBSTITUTED 1-ARYL-4-OXO-1,4-DIHYDROPYRIDO[2,3-d]PYRIMIDINES

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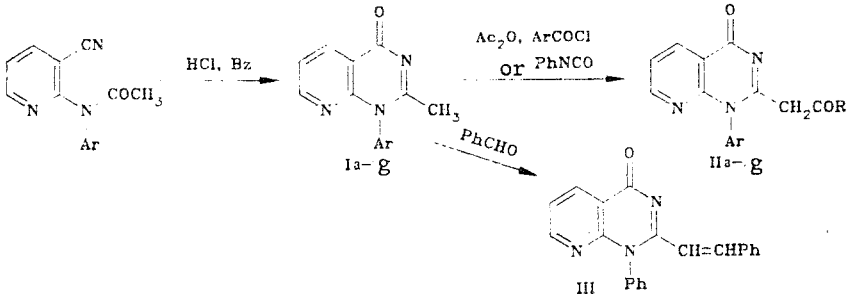
UDC 547.859.2'822.7

Cyclization of 2-(N-acetyl-N-arylamino)nicotinonitriles in the presence of dry HCl gave 1-aryl-2-methyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines. It was shown that they are acylated by acetic anhydride, aroyl chlorides, and phenyl isocyanate at the methyl group and that with benzaldehyde they give styryl derivatives. It was determined by UV, IR, and NMR spectra that 2-acetonyl, 2-phenacyl, and 2-(N-phenylcarbamoylmethyl) derivatives of 1-aryl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines exist in enaminocarbonyl and imino enol forms with strong chelate-type intramolecular hydrogen bonding.

In [1] it was shown that 1-aryl-2,7-dimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines are acetylated at the methyl group in the 2 position. For further investigation of the reactivity of the methyl group in such compounds and also for a study of the structure of the acylation products, new 1-aryl-2-methyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (Ia-g, Table 1) were synthesized by cyclization of 2-(N-acetylarylamino)nicotinonitriles in the presence of hydrogen chloride in benzene; the structure of compounds Ia-g was confirmed by IR and PMR spectra.

As a result of the investigations that were carried out, it was found that compounds Ia and Ib were acylated during heating with acetic anhydride with formation of acetonyl derivatives IIa and IIb. The reaction of compounds Ia, Ib, and If with benzoyl chloride in pyridine or with 4-bromobenzoyl chloride indioxane in the presence of triethylamine gave the corresponding phenacyl derivatives (IIc-f). During boiling with phenyl isocyanate in benzene, compound Ia gave 1-phenyl-2-(N-phenylcarbamoylmethyl)-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine (IIg). Boiling of a solution of compound Ia and benzaldehyde in isopropanol was accompanied by the formation of 2-styryl-1-phenyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine (III).



I a Ar = C_6H_5; b Ar = 4-$CH_3C_6H_4$; c Ar = 3-$CH_3C_6H_4$; d Ar = 4-$CH_3OC_6H_4$; e Ar = 2-$CH_3OC_6H_4$; f Ar = 2,4-$(CH_3)_2C_6H_3$; g Ar = 2-ClC_6H_4; II a Ar = C_6H_5, R = CH_3; b Ar = 4-$CH_3C_6H_4$, R = CH_3; c Ar = R = C_6H_5; d Ar = 4-$CH_3C_6H_4$, R = C_6H_5; e Ar = 2,4-$(CH_3)_2C_6H_3$, R = C_6H_5; f Ar = C_6H_5, R = 4-BrC_6H_4; g Ar = C_6H_5, R = C_6H_5NH

The ease of occurrence of these reactions indicates significant CH acidity of the methyl group in the 2 position of compounds I, which agrees with the calculations that we carried out by the linear-combination-of-atomic-orbitals molecular-orbital (LCAO MO) method in the Hueckel approximation, showing the presence of a negative charge on the carbon atom of the CH_3 group of compound Ia (the residual electron density was —0.075) and the positively charged hydrogen atom (+0.103).

Perm Pharmaceutical Institute, Perm 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1397-1401, October, 1991. Original article submitted April 4, 1990; revision submitted September 27, 1990.

0009-3122/91/2710-1125$12.50

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	mp, °C	R_f**	PMR spectrum, δ, ppm					Yield, %
				CH_3, s	=CH, s	H of arom, m	H of pyridine, m***	H of chelate ring, s	
Ia	$C_{14}H_{11}N_3O$	218...220	0,25	2,21	—	7,50...7 64	—	—	65,0
Ib	$C_{15}H_{13}N_3O$	250...252	0,76	2,20; 2,36	—	6.98...7,36	8.30...8,45	—	33,3
Ic	$C_{15}H_{13}N_3O$	194...196	0,56	—	—	—	—	—	66,7
Id	$C_{15}H_{13}N_3O_2$	255...257	0,67	2,20; 3,83	—	7,00...7,47	8,53...8,67	—	62,7
Ie	$C_{15}H_{13}N_3O_2$	148...150	0,52	—	—	—	—	—	45,5
If	$C_{16}H_{15}N_3O$	204...206	0,70	1,86; 2,16; 2,36	—	6,97...7,53	8,50...8,63	—	71,4
Ig	$C_{14}H_{10}ClN_3O$	255...257	0,72	2,23	—	7,30...7,67	8,43...8,77	—	30,0
IIa	$C_{16}H_{13}N_3O_2$	235...237 [2]	0,68	1,99	4,48	7,23...7,67	8,30...8,54	14,28	46,2
IIb	$C_{17}H_{15}N_3O_2$	224...226	0,70	1,90; 2,40	4,40	6,94...7,40	8,25...8,40	14,03	51,7
IIc	$C_{21}H_{15}N_3O_2$	305...307	0,71	—	5,06	7,21...7,84	8,39...8,58	13,28	55,6
IId	$C_{22}H_{17}N_3O_2$	274...276	0,82	2,33	4,94	7,03...7,50	8,12...8,32	14,30	53,1
IIe	$C_{23}H_{19}N_3O_2$	250...252	0,74	2,00; 2,38	5,06	7,11...7,44	8,26...8,60	14,56	43,1
IIf	$C_{21}H_{14}BrN_3O_2$	276...278	0,72	—	5,03	7,13...7,73	8,30...8,56	14,43	46,4
IIg	$C_{21}H_{16}N_4O_2$	291...293	0,73	—	4,10	7,05...7,64	8,21...8,52 (9,50 1H, NH, s)	13,43	44,8
III	$C_{21}H_{15}N_3O$	255...257	0,34	—	6,36d, 8,03d	7,21...7,53	8,38...8,62	—	66,5

*UV spectrum, λ_{max}, nm (log ε): Ia 310 (4.21); IIa 315 (4.55), 340 (4.34); IIg 317 (4.20).

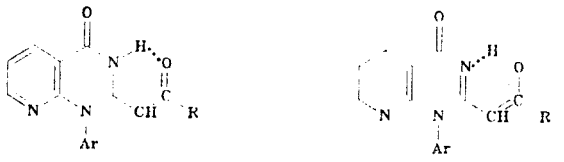
**Internal standard of thin-layer chromatography.

***For compound Ia: 8.43 (1H, C_5-H, d); 8.53 (1H, C_7-H, d); 8.63 ppm (1H, C_6-H, q); $J_{5,6}$ = 1.91, $J_{6,7}$ = 2.23 Hz.

TABLE 2. Carbon-13 NMR Spectra of Compounds Ia, IIa and IIc [in dimethyl-D_6 sulfoxide (DMSO-D_6)]

Compound	Chemical shift, δ, ppm					
	$C_{(2)}$	$C_{(4)}$	=CH	C=O	CH_3	Ar
Ia	162,84	168,30	—	—	24,47	153,39; 152,18; 137,88; 136,43; 129,16; 129,18; 128,74; 121,95; 113,83
IIa	154,00	158,72	83,36	194,71	29,62	153,03; 152,48; 136,67; 136,07; 130,00; 129,22; 129,00; 119,65; 112,44
IIc	154,73	158,73	80,39	186,84	—	154,06; 152,43; 139,22; 136,19; 131,41; 130,13; 129,47; 129,29; 128,50; 126,25; 119,96; 112,80

The PMR spectra of compounds IIa-f confirmed their structure, and the presence of peaks at 4.10-5.06 ppm in them due to the ethylene proton and at 13.28-14.56 ppm due to the chelate-ring proton suggested that the compounds exist in the form of the two tautomers **A** and **B**:



A B

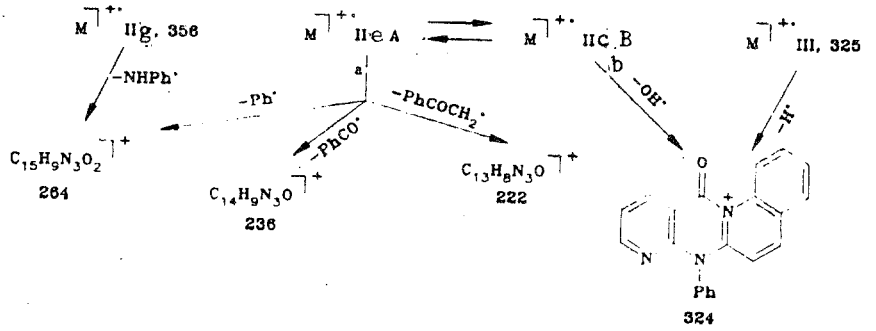
A study of the PMR spectra of compounds IIa and IIc at temperatures from —38 to 48°C showed that with increasing temperature the peaks at 4.48-5.06 and 13.28-14.28 ppm broadened until complete disappearance in the case of compound IIc, which was probably due to an increase of the rate of proton exchange in that case; no other changes were observed.

The absence of peaks of CH_2-group protons in the PMR spectra of compounds IIa-f and the absence of bands of free OH or NH groups in the IR spectra showed that these compounds contained no nonchelate tautomers having acetonyl or phenacyl groups. In this case, there was probably fast [1,5]-sigmatropic **A** ⇄ **B** tautomerism [3], for which, in accordance with symmetry requirements [4], an intramolecular proton-transfer mechanism is permitted. Such a type of tautomerism is widely encountered in organic chemistry and has been studied using various models, including α-azaheteryl ketones, by NMR methods [5, 6].

The ^{13}C NMR spectra of compounds IIa and IIc (Table 2) contained peaks of an ethylene carbon atom at 83.36 and 80.39 ppm, a CO-group carbon atom at 194.71 and 186.83 ppm of acetonylidene or phenacylidene fragments which were close to those of enamino ketones having chelate-type intramolecular hydrogen bonds [7]. A comparison of $\delta_{C(2)}$ of compounds Ia, IIa, and IIc showed that the latter ones exhibited a strong-field shift of approximately 9 ppm. On the basis of this comparison, and also from the data of [7], according to which δ_C for C—N is always approximately in a field 10 ppm stronger than for C=N, we can conclude that compounds IIa and IIc probably existed predominantly in form **A** in the DMSO-D_6 solution of ionization of these compounds also did not occur. Such a conclusion agrees with the data concerning the structure of 3-acetonyl-2-oxo-1,2-dihydroquinoxaline, existing in $CDCl_3$ and DMSO 100% in the enaminocarbonyl form with a strong intramolecular hydrogen bond [5], and with calculations by the Hueckel MO method, according to which form **A** is, on the average, 38 kcal/mole more energetically advantageous than form **B**.

A bathochromic shift and the appearance of an additional long-wave band in the UV spectra of compounds IIa and IIg in comparison with those of compound Ia indicated an increase of the conjugate chain length in these substances. Tautomeric forms **B** should absorb in a longer-wave region because in them the chain is conjugated more than in forms **A**. This is confirmed by calculations by the LCAO MO method in the Hueckel approximation for compound IIa showing that the energy of the boundary electron transition of tautomeric form **B** is less than that of form **A**. On the basis of what has been said above, we assume that the maximum in the spectrum of compound IIa at 315 nm belongs to form **A** and that the one at 340 nm belongs to form **B**. Such an assumption agrees with the data of the UV spectrum of phenylcarbamoylmethyl derivative IIg, in which, because of the weak enolizability of the carbonyl group, the predominant form is form **A**, and the long-wave maximum is virtually absent.

Scheme



We studied the mass spectra of compounds IIa, IIc, IIg, and III, the molecular ions of which correspond to their molecular weights.

TABLE 3. Mass Spectra of Compounds IIb, IIc, IIg, and III

Compound	m/z (I_{rel}, %) *
IIb	293 (37), 278 (36), 250 (100), 249 (36), 236 (13), 210 (7), 182 (10)
IIc	341 (100), 340 (19), 324 (20), 323 (7); 322 (23), 312 (9), 264 (37), 236 (83), 222 (8), 196 (18), 168 (37), 156 (32), 128 (8)
IIg	356 (18), 264 (100), 236 (84), 222 (42), 196 (26), 168 (43), 140 (22), 128 (16), 115 (10)
III	325 (66), 324 (82), 322 (7), 296 (9), 248 (12), 237 (80), 196 (89), 168 (100), 140 (34), 128 (9), 115 (18), 103 (9), 93 (17), 84 (28), 77 (84), 64 (18), 51 (50)

*Peaks of ions with intensity >5% are presented.

The molecular ion M^+ of acetonyl derivative IIa decomposed in three directions, namely $[M - CH_3]^+$, $M - COCH_3]^+$, and $[M - CH_2COCH_3]^+$, with α-decomposition occurring predominantly. Fragmentation of the M^+ molecular ion of phenacyl derivative IIc occurred more complexly. In the mass spectrum of this compound, there were not only ions 264 $[M - Ph]^+$, 236 $[M - COPh]^+$, and 222 $[M - CH_2COPh]^+$ (see the scheme, route **a**, and Table 3), but also ion 324 $[M - OH^+]$ (route **b**), which is characteristic of the enol tautomeric form (cf. the decomposition of acetoacetic ester [8]). Another proof of this is the decomposition of the molecular ion M^+ of 2-styryl-1-phenyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine (III), having structural similarity with the enol tautomeric form of compound IIc. During electron impact, M^+ of compound III eliminated H· and was converted to stable aromatic ion 324 (82%), identical to $[M - OH]^+$ of phenacyl derivative IIc.

The decomposition of the enaminocarbonyl tautomeric form of IIc probably occurred by route **a**. This was confirmed by fragmentation of M^+ of compound IIg, existing predominantly in form **A**, which eliminated an aniline radical, being converted to ion 264 $[M - NHPh]^+$. Both the enol and enaminocarbonyl tautomeric forms of compound IIc probably existed in the gas phase, whereas the latter form was more stable in the case of the acetonyl derivative.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in white mineral oil, and the UV spectra were recorded on an SF-16 instrument in ethanol ($c = 1 \cdot 10^{-5}$ M). The PMR spectra were obtained on Bruker WP-80, RYa-2310, and RS-60 (60 MHz) spectrometers for compounds Ib-g, IIe, and IIf in $CDCl_3$ and for compounds Ia, IIa-c, IIg, and III in DMSO-D_6. The ^{13}C NMR spectra were recorded on a Bruker WP-80 instrument (20 and 13 MHz) with complete decoupling from protons in DMSO-D_6, and the internal standard was hexamethyldisiloxane (HMDS). The mass spectra were obtained on Kratos MS-20 and MX-1303 instruments with direct sample injection into the ion source with ionizing voltage 70 eV. Thin-layer chromatography was carried out on Silufol UV-254 plates in a 1:1 butanol—benzene solvent system for compounds Ia-g and in ethyl acetate for IIa-g and III.

1-Aryl-2-methyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (Ia-g). Dry hydrogen chloride was passed into a solution of 10 mmoles of 2-(N-acetyl-N-arylamino)nicotinonitrile in 20 ml of anhydrous benzene for 1 h, the resulting precipitate was filtered, and the product was worked up with a sodium acetate solution and crystallized from ethanol. IR spectrum: 1635-1645 cm^{-1} (CO).

1-Aryl-2-acetonyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (IIa) and (IIb). A solution of 10 mmoles of compound Ia or Ib in 20 ml of acetic anhydride was boiled for 6 h, the solution was poured into water, and the resulting precipitate was crystallized from ethanol. IR spectrum of compound Ia: 1610 and 1665 cm^{-1} (CO).

1-Aryl-2-phenacyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (IIc-e). A solution of 10 mmoles of compound Ia, Ib, or If and 2.5 ml (20 mmoles) of benzoyl chloride in 20 ml of pyridine was boiled for 5 h, the solution was poured into water, and the resulting precipitate was filtered, worked up with a sodium bicarbonate solution, and crystallized from a 1:1 ethanol—dimethylformamide (DMFA) mixture. IR spectrum of compound IId: 1595 and 1670 cm^{-1} (CO).

1-Phenyl-2-(4-bromophenacyl)-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine (IIf). A solution of 2.4 g (10 mmoles) of compound Ia, 2.2 g (10 mmoles) of 4-bromobenzoyl chloride, and 2 ml of triethylamine in 20 ml of dry dioxane was heated at 100°C for 2 h, cooled, and diluted with a soda solution, and the resulting precipitate was filtered, dried, and crystallized from butanol.

1-Phenyl-2-(N-phenylcarbamoylmethyl)-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine (IIg). A solution of 2.4 g (10 mmoles) of compound Ia and 1.2 g (10 mmoles) of phenyl isocyanate in 20 ml of dry benzene was boiled for 6 h. The solvent was driven off, and the residue was crystallized from ethanol.

1-Phenyl-2-styryl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine (III). A solution of 2.3 g (10 mmoles) of compound Ia in 40 ml of isopropanol containing 0.1 ml of piperidine and 2 ml (20 mmoles) of benzaldehyde was boiled for 10 h and cooled, and the resulting precipitate was filtered and crystallized from DMFA.

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