SYNTHESIS AND PROPERTIES OF 1-ARYL-1,4-DIHYDRO-2,7-DIMETHYL-4-OXOPYRIDO[2,3-d]PYRIMIDINE-6-CARBOXYLIC ACIDS AND THEIR DERIVATIVES

A. B. Deyanov, M. Yu. Gavrilov, and M. E. Konshin

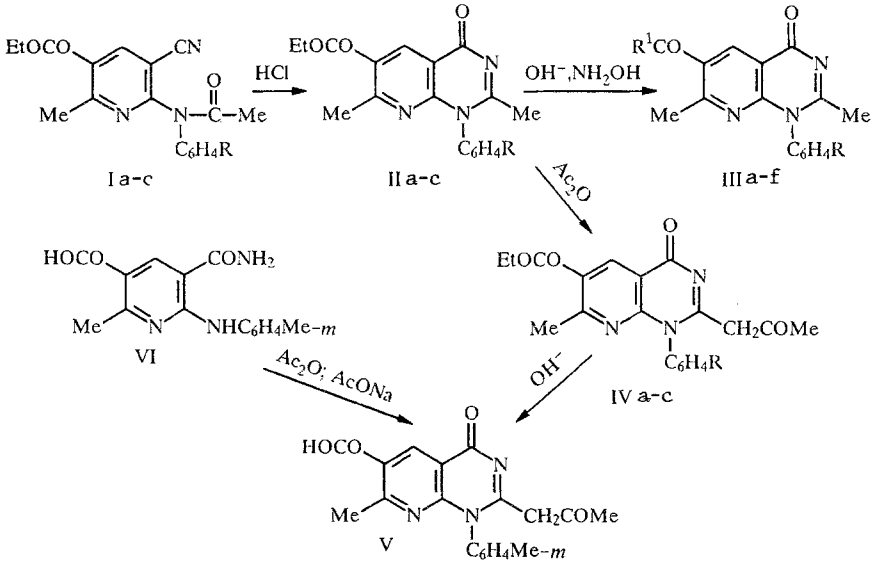
Acetylation of 2-arylamino-5-carbethoxy-6-methylnicotinonitriles gave N-acetyl-2-arylamino-5-carbethoxy-6-methylnicotinonitriles, which, under the influence of hydrogen chloride, are cyclized to 1-aryl-1,4-dihydro-6-carbethoxy-2,7-dimethyl-4-oxopyrido[2,3-d]pyrimidines. The latter can be converted to the corresponding carboxylic and hydroxamic acids, as well as to acetylation products 1-aryl-2-acetonyl-1,4-dihydro-6-carbethoxy-7-methyl-4-oxopyrido[2,3-d]pyrimidines.

In one of our preceding communications [1] it was shown that 2-substituted 1-aryl-1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines are formed in the cyclization of N-acyl-2-arylamino-6-methylnicotinonitriles.

For a further study of this method we investigated the cyclization of N-acetyl-2-arylamino-5-carbethoxy-6-methylnicotinonitriles Ia-c.

Compounds Ia-c are obtained in good yields when the corresponding 2-arylaminonicotinonitrile derivatives are refluxed with excess acetic anhydride.

It was established that N-acetyl-2-arylamino-5-carbethoxy-6-methylnicotinonitriles Ia-c, under the influence of dry hydrogen chloride in benzene (or in ethanol), are cyclized to 1-aryl-1,4-dihydro-6-carbethoxy-2,7-dimethyl-4-oxopyrido[2,3-d]pyrimidines IIa-c, the structures of which were confirmed by IR and PMR spectral data.



I, II, IVa R=H, b R=3'-Me, c R=4'-Me; III aR=H, R^1=OH, b R=3'-Me, R^1=OH, cR=4'-Me, R^1=OH, dR=H, R^1=NHOH, e R=3'-Me, R^1=NHOH, f R=4'-Me, R^1=NHOH

Perm Pharmaceutical Institute, Perm 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 535-539, April, 1992. Original article submitted May 30, 1990.

0009-3122/92/2804-0449$12.50

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp,* °C	R_f	Yield %	Compound	Empirical formula	mp,* °C	R_f	Yield, %
Ia	$C_{18}H_{17}N_3O_3$	90...92	0,43	93	IIIe	$C_{17}H_{16}N_4O_3$	265...266	0,58	54
Ib	$C_{19}H_{19}N_3O_3$	108...109	0,47	68	IIIf	$C_{17}H_{16}N_4O_3$	279...280	0,51	43
Ic	$C_{19}H_{19}N_3O_3$	75...77	0,40	82	IVa	$C_{20}H_{19}N_3O_4$	242...243	0,60	52
IIa	$C_{18}H_{17}N_3O_3$	212...214	0,32	79	IVb	$C_{21}H_{21}N_3O_4$	203...204	0,81	41
IIb	$C_{19}H_{19}N_3O_3$	217...218	0,37	67	IVc	$C_{21}H_{21}N_3O_4$	205...206	0,72	65
IIc	$C_{19}H_{19}N_3O_3$	230...231	0,35	85	V	$C_{19}H_{17}N_3O_4$	265...266	0,32	46**
IIIa	$C_{16}H_{13}N_3O_3$	263...264	0,82	75	VI	$C_{15}H_{15}N_3O_3$	269...270	0,57	87
IIIb	$C_{17}H_{15}N_3O_3$	258...259	0,75	87	VII	$C_{23}H_{19}N_3O_3$	113...115	0,64	53
IIIc	$C_{17}H_{15}N_3O_3$	271...272	0,79	88	VIII	$C_{23}H_{19}N_3O_3$	255...257	0,41	59
IIId	$C_{16}H_{14}N_4O_3$	260...261	0,61	42					

*UV spectra, λ_{max} (log ε), nm: IIa 314 (3.68); IIc 315 (3.70); IIIa 313 (3.97); IVa 320 inflection (4.15), 345 (4.33); IVc 325 (4.01), 348 (4.08); V 315 (4.15), 333 inflection (4.08).

**Obtained by method A.

TABLE 2. PMR Spectra of I-VIII

Compound	Chemical shifts, δ, ppm*						
	$C_{(4)}(C_{(5)})$, 1H, s	$CH_3-C_{(}(C_{(7)})$, 3H, s	C_6H_5, m	$CH_3-C_{(2)}$, 3H, s	$COOC_2H_5$	OH, 1H, s	Other protons
Ia-c	8,48...8,55	2,42...2,55	7,02...7,25	—	1,25...1,32 t; 4,18...4,22 q	—	1,98...2,12 s (3H, CO—CH_3)
IIa-c	8,50...8,62	2,42...2,55	7,22...7,42	2,05...2,12	1,28...1,32 t; 4,18...4,2: q	—	—
IIIa-c	8,48...8,58	2,48...2,62	7,32...7,52	2,18...2,28	—	10,32...11,05	—
IIId-f	8,38...8,42	2,48...2,85	7,00...7,22	2,32...2,42	—	10,05...10,18	7,62...8,22 s (1H, NH)
IVa-c	8,38...8,58	2,45...2,55	7,22...7,40	1,92...2,05	1,25...1,32 t 4,32...4,38 q	—	13,82...14,05 s (1H, NH); 4,35...4,38 s (2H, CH_2)
V	8,60	2,42	7,25	2,00	—	10,90	4,35 s (2H, CH_2); 14,22 s (1H, NH)
VI	8,38	2,45	7,15	2,22	—	11,12	8,62 s (1H, NH); 7,48 br.s (2H, NH_2)
VII	8,50	2,52	7,12	—	1,25 t; 4,25 q	—	—
VIII	8,65	2,42	7,22	—	1,28 t; 4,25 q	—	—

*Signals of the CH_3 group of substituent R are observed at 2.18-2.42 ppm.

TABLE 3. Mass Spectra of IIa, c, IVb, and V

Compound	m/z (rel.intensity, %)
IIa	341(11, $M-H_2O^{+\cdot}$), 323(96, $M^{+\cdot}$), 295(47), 280(98), 277(37), 251(100), 249(16), 236(9), 234(39), 223(48), 210(16), 208(63), 182(24), 154(36)
IIc	355(15, $M-H_2O^{+\cdot}$), 337(73, $M^{+\cdot}$), 309(68), 394(56), 391(19), 265(100), 250(7), 248(36), 238(34), 233(36), 224(18), 222(48), 196(18), 188(13)
IVb	379(64), 364(30), 336(100), 333(12), 351(5), 322(6), 308(25), 294(11), 268(6), 250(5), 224(12), 198(6), 154(42)
V	351(41), 336(39), 333(11), 308(100), 337(31), 294(12), 250(5), 224(8), 198(18), 154(64)

The ester group of pyrido[2,3-d]pyrimidines IIa-c is readily saponified by alcoholic alkali; the corresponding acids IIIa-c are formed. Hydroxamic acids IIId-f are obtained when IIa-c are heated with hydroxylamine. The pyrimidine ring is not destroyed in either case.

There are two methyl groups that are potentially capable of manifesting CH-acidic properties in pyrido[2,3-d]pyrimidines IIa-c. In [1] it was shown that the methyl group attached to the $C_{(2)}$ group has higher reactivity in such compounds. In the case of IIa-c the activity of the methyl group attached to the $C_{(7)}$ group should be increased due to the effect of the adjacent carbethoxy group. However, it follows from several examples of the acetylation of IIa-c that 1-aryl-2-acetonyl-6-carbethoxy-7-methyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines IVa-c are formed as a result (Table 1). The individuality of IVa-c was established by TLC.

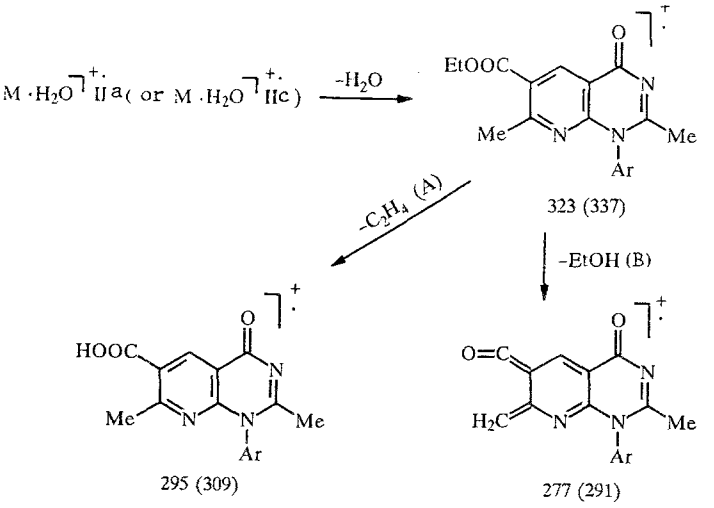
6-Carbethoxy-7-methyl-1,2-diphenyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine (VIII) was obtained by cyclization of N-benzoyl-2-anilino-5-carbethoxy-6-methylnicotinonitrile (VII) to prove the inertness of the methyl group attached to the $C_{(7)}$ atom in acetylation. It was found that VIII is not acetylated either on refluxing in Ac_2O or in a mixture of Ac_2O with AcONa.

Evidence for acetylation at the methyl group attached to the $C_{(2)}$ atom is also provided by the results of a comparison of the PMR spectra of IIa, IVa, V, and VIII, which have signals at 2.55-2.82 ppm that make it possible to assign them to the methyl group attached to the $C_{(7)}$ atom (Table 2).

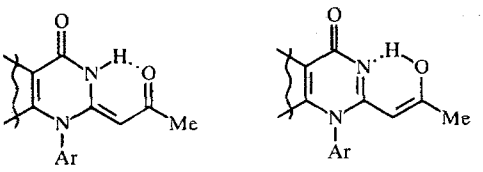
Ester IVb is hydrolyzed on heating with sodium hydroxide in ethanol to acid V, which was also obtained by refluxing 2-arylamino-5-carboxy-6-methylnicotinonitrile in excess Ac_2O in the presence of AcONa.

An analysis of the mass spectra of IIa, c, IVb, and V (Table 3) leads to the conclusion that IIa, c evidently exist, in part, in a hydrated form, since they have ions at 341 $[M \cdot H_2O]^{+\cdot}$ and 355 $[M \cdot H_2O]^{+\cdot}$, respectively. The latter split out a molecule of H_2O and are converted to ions at 323 ($M^{+\cdot}$, IIa) and 337 ($M^{+\cdot}$, IIc), which then undergo fragmentation via two pathways, either with the liberation of ethylene (pathway A) and the formation of ions at 295 $[M(IIa) - C_2H_4]^{+\cdot}$ and 309 $[M(IIc) - C_2H_4]^{+\cdot}$ or with splitting out of ethanol (pathway B) and the development of ions at 277 $[M(IIa) - EtOH]^{+\cdot}$ and 291 $[M(IIc) - EtOH]^{+\cdot}$; the ions at 295 and 309 either undergo decarboxylation or split out a CH_3 group.

Compounds IVb and V upon electron impact give molecular ions with mass numbers 379 and 351, respectively. The principal fragmentation of these ions involves splitting out of an acetonyl residue and the formation of ions at 364 and 336 $[M - CH_3]^+$, 336 and 308 $[M - CH_3CO]^+$, and 322 and 294 $[M - CH_3COCH_2]^+$. The primary process is α cleavage accompanied by separation of an acetyl residue, which is associated with the stability of the ions at 308 and 336 due to stabilization of the charge through its distribution over the heterocyclic system. Evidence for this is also provided by the loss by the ion at 336 (100%) of a molecule of ethylene rather than acetonitrile, which is characteristic for 2-methylpyrimidines.



A multiplet centered at 4.35 ppm, which is made up of the quartet of two protons of the CH_2 group of the ester residue and the singlet at 4.38 ppm of the ethylene proton of tautomeric forms A and B, is observed in the PMR spectra of acetonyl derivatives IVa-c. In the PMR spectra of the acetonyl derivatives containing a carboxy group there is only a singlet of an ethylene proton at 4.35 ppm. Singlets at 13.8-14.2 ppm, which are due to the protons of the chelate ring of tautomers A and B, are present in the spectra of all IVa-c and V.



A B

The UV spectra of IIa, c, IIIa, IVa, c, and V are similar to the spectra of the corresponding 2-methyl and 2-acetonyl derivatives of 1,4-dihydro-4-oxopyrido[2,3-d]pyrimidines that do not contain a carbethoxy group [2]; in the spectra of acid V the band at 315 nm has a higher intensity, while in the spectra of esters IVa, c the bands at 345 and 348 have higher intensities. It follows from the assignment of these bands to, respectively, the enamino carbonyl and imino enol forms [2] that the first form predominates in compounds with a free carboxy group.

EXPERIMENTAL

The UV spectra of solutions of the compounds in EtOH (10^{-5} mole/liter) were recorded with an SF-16 spectrophotometer. The IR spectra of suspensions in mineral oil were obtained with a UR-20 spectrometer. The PMR spectra of solutions in d_6-DMSO were recorded with an RYa-2310 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing voltage of 70 eV. Thin-layer chromatography was carried out on Silufol UV-254 plates.

The results of elementary analysis of I-VIII for C, H, and N were in agreement with the calculated values.

N-Acetyl-2-arylamino-6-methyl-5-carbethoxynicotinonitriles (Ia-c). A solution of 0.01 mole of 2-arylamino-6-methyl-5-carbethoxynicotinonitrile was refluxed with 10 ml of acetic anhydride for 5-6 h, after which it was poured into water. The aqueous mixture was neutralized with 10% NaOH solution, and the liberated oil was washed several times with water and crystallized from benzene—hexane. IR spectrum: 1660-1680 (CO, $NCOCH_3$), 1700-1720 (CO, $COOC_2H_5$), 2230-2250 cm^{-1} (CN).

1-Aryl-6-carbethoxy-2,7-dimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (IIa-c). Dry HCl gas was passed for 1-2 h through a solution of 0.01 mole of Ia-c in 50 ml of anhydrous benzene, after which the resulting precipitate was removed by filtration, treated successively with 10% sodium acetate solution and water (50-100 ml each), and crystallized from aqueous ethanol. IR spectrum: 1660-1680 (CO, C_4), 1700-1715 cm^{-1} (CO, $COOC_2H_5$).

1-Aryl-2,7-dimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine-6-carboxylic Acids (IIIa-c). A 0.01-mole sample of IIa-c was heated on a water bath for 4 h with 25 ml of a 20% solution of NaOH in ethanol, after which the mixture was poured into water. The aqueous mixture was neutralized with 50% acetic acid solution, and the resulting precipitate was removed by filtration, washed with water, and crystallized from DMF—H_2O. IR spectrum: 1660-1680 (CO, C_4), 1700-1720 (CO, COOH), 3530-3550 cm^{-1} (OH in CCl_4).

1-Aryl-2,7-dimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine-6-carboxylic Acid N-Hydroxyamides (IIId-f). A solution of 1.95 g (0.03 mole) of hydroxylamine hydrochloride and 5.61 g (0.1 mole) of KOH in 50 ml of dioxane was added to a solution of 0.01 mole of IIa-c in 20 ml of dioxane, and the mixture was refluxed for 10 min and allowed to stand at room temperature for 15 h. It was then poured into 100 ml of water, and the aqueous mixture was acidified slightly with 10% HCl solution. The precipitate was removed by filtration and crystallized from DMF—H_2O. IR spectrum: 1620-1640 (CO, CONHOH), 1660-1680 (CO, C_4), 3290-3310 (NH), 3560-3580 cm^{-1} (OH in CCl_4).

1-Aryl-2-acetonyl-7-methyl-6-carbethoxy-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (IVa-c). A 0.01-mole sample of IIa-c was refluxed in 10 ml of acetic anhydride for 4-5 h, after which the mixture was poured into 50 ml of water. The aqueous mixture was neutralized with 20% NaOH solution, and the resulting precipitate was dissolved in 50% acetic acid, and the solution was refluxed with activated charcoal, filtered, and treated with ammonium hydroxide. The precipitate was removed by filtration and crystallized from aqueous dioxane. IR spectrum: 1640-1660 (CO of the acetonyl radical), 1680-1690 (CO, C_4), 1700-1720 cm^{-1} (CO, $COOC_2H_5$).

2-(3′-Methylphenylamino)-5-carboxy-6-methylnicotinic Acid Amide (VI). A solution of 0.01 mole of 2-(3′-methylphenylamino)-5-carbethoxy-6-methylnicotinonitrile and 2.8 g (0.05 mole) of KOH in 20 ml of ethanol was refluxed for 8 min, after which it was allowed to stand for 20 h at room temperature and then poured into 100 ml of water. The aqueous mixture was neutralized with 50% acetic acid, and the precipitate was removed by filtration and crystallized from DMF—H_2O.

IR spectrum: 3560 (OH in CCl_4); 3200-3210 and 3410-3420 (NH_2 in $CONH_2$); 3340-3350 (NH); 1640-1650 (CO, $CONH_2$); 1665-1675 cm^{-1} (CO, COOH).

1-(3′-Methylphenyl)-2-acetonyl-7-methyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine-6-carboxylic Acid (V). A. A 0.01-mole sample of IVb was refluxed in 25 ml of a 20% alcohol solution of NaOH for 4 h, after which the mixture was poured into 50 ml of water. The aqueous mixture was neutralized with 50% acetic acid, and the precipitate was crystallized from DMSO.

B. A mixture of 0.01 mole of VI and 0.01 mole of anhydrous sodium acetate was refluxed in 10 ml of acetic anhydride for 10 h, after which it was poured into 50 ml of water. The aqueous mixture was neutralized with 20% $NaHCO_3$ solution, and the precipitate was removed by filtration, dried, and crystallized from DMSO. IR spectrum: 1610-1620 (CO of the acetonyl radical), 1630-1640 (CO, C_4), 1690-1700 cm^{-1} (CO, COOH). No melting-point depression was observed for a mixture of this product with the substance obtained in the preceding experiment. The yield was 0.87 g (24%).

N-Benzoyl-2-anilino-5-carbethoxy-6-methylnicotinonitrile (VII). A solution of 2.81 g (0.01 mole) of 2-anilino-5-carbethoxy-6-methylnicotinonitrile was refluxed in a mixture of 5 ml of benzoyl chloride and 5 ml of pyridine for 5.5 h, after which the mixture was poured into water. The aqueous mixture was neutralized with 10% NaOH solution, and the liberated oil was treated with water and crystallized from hexane. IR spectrum: 1660-1680 (CO, NCOPh), 1710-1720 (CO, $COOC_2H_5$), 2230-2240 cm^{-1} (CN).

1,2-Diphenyl-6-carbethoxy-7-methyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine (VIII). Dry HCl gas was passed for 1 h through a solution of 3.85 g (0.01 mole) of VII in 50 ml of anhydrous benzene, and the resulting precipitate was removed by filtration, treated successively with 10% sodium acetate solution and water (50-100 ml each), and crystallized from aqueous ethanol. IR spectrum: 1660-1670 (CO, C_4), 1710-1715 cm^{-1} (CO, COOEt).

LITERATURE CITED

1. N. I. Shramm and M. E. Konshin, *Khim. Geterotsikl. Soedin.*, No. 1, 114 (1985).
2. L. M. Demina, M. Yu. Gavrilov, M. I. Vakhrin, and M. E. Konshin, *Khim. Geterotsikl. Soedin.*, No. 10, 1397 (1991).