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SYNTHESIS OF DERIVATIVES OF 4,6-DIOXO-1,4,6,7,8,9-HEXAHYDRO-PYRIMIDO[4,5-*b*][1,6]NAPHTHYRIDINES

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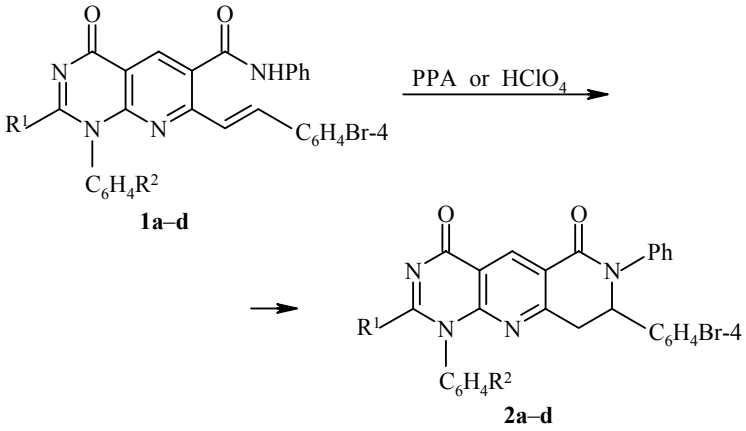
It has been shown that 1-aryl-8-(4-bromophenyl)-4,6-dioxo-2H(phenyl)-7-phenyl-1,4,6,7,8,9-hexahydropyrimido[4,5-b][1,6]naphthyridines are formed on heating anilides of 1-aryl-7-(4-bromostyryl)-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine-6-carboxylic acids in PPA.

Keywords: 4,6-dioxo-1,4,6,7,8,9-hexahydropyrimido[4,5-*b*][1,6]naphthyridines, anilides of 4-oxo-1,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic acids, cyclization.

In the preceding paper [1] we showed that derivatives of 1,6-naphthyridine were formed when 5-cyano-6-oxo-2-styrylnicotinamides were heated in PPA. It was of interest to extend this reaction to arylamides of 1-aryl-4-oxo-7-styryl-1,4-dihydro[2,3-*d*]pyrimidine-6-carboxylic acids with the objective of preparing the poorly studied [2] derivatives of pyrimido[4,5-*b*][1,6]naphthyridine.



1, 2 **a** R^1 = H, R^2 = 2-Me, **b** R^1 = Ph, R^2 = H, **c** R^1 = Ph, R^2 = 2-Me, **d** R^1 = Ph, R^2 = 4-Me

The starting materials, anilides of 1-aryl-7-(4-bromostyryl)-4-oxo-1,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic acids **1a-d** (Table 1), were obtained by heating the anilides of 2-substituted 1-aryl-7-methyl-4-oxo-1,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic acids with a one and a half fold excess of *para*-bromobenzaldehyde in xylene in the presence of a catalytic amount of piperidine. The compounds obtained were crystalline with a yellow tinge, soluble in 2-propanol, dioxane, and acetic acid. The IR spectra of these

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TABLE 1. Characteristics of the Substances Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Hal		
1a	$C_{29}H_{21}BrN_4O_2$	65.03 / 64.81	4.10 / 3.94	10.22 / 10.43	14.95 / 14.87	257-259	51
1b	$C_{34}H_{23}BrN_4O_2$	68.26 / 68.12	4.05 / 3.87	9.09 / 9.35	13.40 / 13.33	221-224	35
1c	$C_{35}H_{25}BrN_4O_2$	68.39 / 68.52	4.40 / 4.11	8.91 / 9.13	13.10 / 13.02	233-237	44
1d	$C_{35}H_{25}BrN_4O_2$	68.74 / 68.52	4.27 / 4.11	9.06 / 9.13	12.95 / 13.02	286-287	30
2a	$C_{29}H_{21}BrN_4O_2$	64.93 / 64.81	4.18 / 3.94	10.48 / 10.43	15.00 / 14.87	>300	44
2b	$C_{34}H_{23}BrN_4O_2$	67.98 / 68.12	4.11 / 3.87	9.29 / 9.35	13.14 / 13.33	291-293	41
2c	$C_{35}H_{25}BrN_4O_2$	68.67 / 68.52	4.26 / 4.11	9.05 / 9.13	12.92 / 13.02	260-262	39
2d	$C_{35}H_{25}BrN_4O_2$	68.75 / 68.52	4.39 / 4.11	8.84 / 9.13	12.97 / 13.02	248-251	48

compounds contained stretching bands of $C_{(4)}$=O at 1645-1665 and of amide group at 1600-1620 (C=O) and 3220-3260 cm^{-1} (N–H). In contrast to the spectra of the starting anilide, the ^{1}H NMR spectra of the compounds **1a-d** did not contain signals of the methyl group at 2.63-2.70 ppm while integrated intensity of the aromatic proton multiplet was increased because of the protons of the styryl group.

In the mass spectrum of compound **1b** a molecular ion* peak was observed at 599 and the 4-bromostyryl radical was eliminated in further fragmentation.

Intramolecular cyclization with participation of the *ortho*-position of the phenyl of the styryl unit and the heterocyclic nitrogen atom of pyridine (by analogy with the fragmentation of the anilide of 2-(4-bromostyryl)-5-cyano-6(1H)-oxonicotinic acid [3]) was not under mass spectrometric conditions, probably because the positive charge on the molecular ion was localized on the pyrimidine ring and not on the nitrogen atom of pyridine.

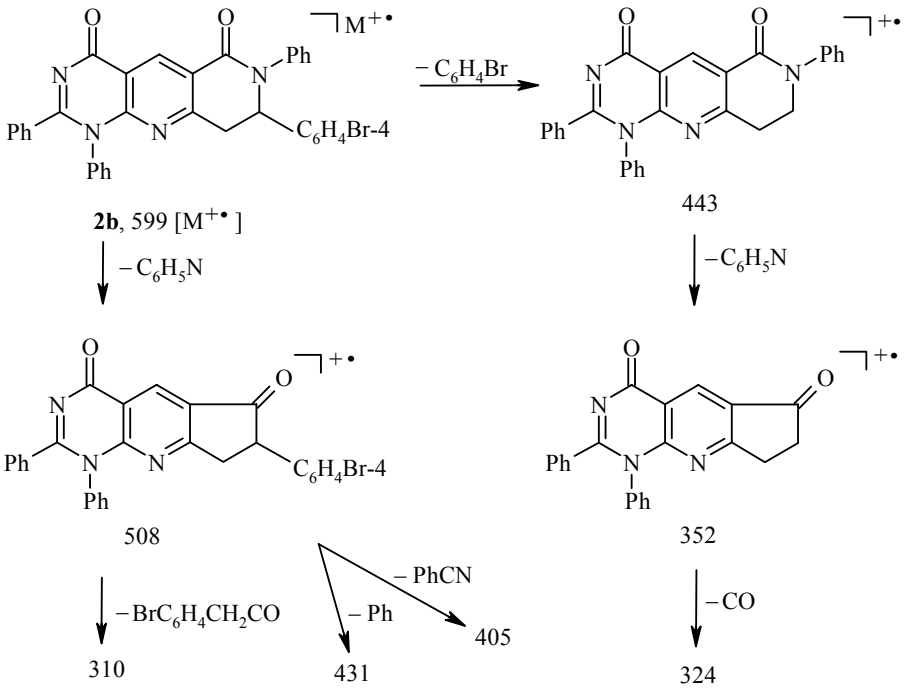
Investigation showed that compounds **1a-d** dissolved in PPA and heated at 145°C for 3 h cyclized to derivatives of pyrimido[4,5-*b*][1,6]naththyridine **2a-d.**

It was shown with compound **2c** as an example, that an analogous reaction occurred when the initial anilide **1c** was heated in a mixture of glacial acetic acid and perchloric acid at 100°C for 1.5 h. The IR spectra of these compounds showed two carbonyl stretches: $C_{(4)}$=O at 1640-1660 and $C_{(6)}$=O at 1630-1640 cm^{-1}. In the ^{1}H NMR spectra of compounds **2a-d**, in comparison with the starting anilide **1**, the signal of the amide protons is extinguished and signals of two protons H-9 as a doublet centred at 3.35-3.95 and of a single proton H-8 as a triplet centered at 5.42-5.65 ppm appeared (Scheme 1).

The mass spectrum of compound **2b**, which has a molecular ion peak at 599 (13%), was the first of these heterocyclic systems studied. The molecular ion underwent further decomposition in two directions: with loss of bromophenyl and formation of the 443 ion or with elimination of phenylnitrene and formation of the 508 ion. The 443 ion also eliminated phenylnitrene on account of the piperidine ring to give the 352 ion. The 508 ion underwent either retrodiene decomposition with elimination of benzonitrile and conversion to the 405 ion, or elimination of $BrC_6H_4CH_2CO$ or Ph· to give the ions 310 and 431 respectively.

* Here and below the value of *m/z* is given for ion peaks.

Scheme 1



EXPERIMENTAL

IR spectra of nujol mulls were recorded with a UR-20 machine. ^{1}H NMR spectra of DMSO-d_6 solutions with HMDS as internal standard were recorded with a PS-60 (60 MHz) spectrometer. Mass spectra were recorded with an MX-1303 (70 eV) machine with insertion of samples into the ion source and ^{200}Hg as standard.

Anilides of 1-Aryl-7-(4-bromostyryl)-4-oxo-1,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic Acids 1a-d. A solution of 0.01 mol of the corresponding anilide of 1-aryl-7-methyl-4-oxo-1,4-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid [4] and *para*-bromobenzaldehyde (2.78 g, 0.015 mol) was boiled for 7.5 h in a mixture of xylenes with a catalytic amount piperidine. The excess of *para*-bromobenzaldehyde, the xylenes, and piperidine were removed by steam distillation. The precipitate was filtered off, dried and crystallized from aqueous solutions of dioxane (compound **1a**), ethanol (**1b,c**) or DMF (**1d**). ^{1}H NMR spectrum, δ, ppm: 8.45-8.57 (1H, s, H-5), 7.27-7.57 (m, aromatic protons), 9.46-10.48 (1H, s, NH). IR spectrum, ν, cm^{-1}: 1645-1665 ($C_{(4)}$=O), 1600-1620 (C=O in CONHPh), 3220-3260 (NH in CONHPh). Mass spectrum of **1b,** *m/z* (I_{rel}, %): 599 $[M]^+$ (6), 417 (27), 326 (98), 298 (18), 249 (21), 223 (99), 197 (100), 195 (21), 181 (88), 169 (85), 154 (37), 139 (82), 117 (57).

1-Aryl-8-(4-bromophenyl)-4,6-dioxo-2H(phenyl)-7-phenyl-1,4-6,7,8,9-hexahydropyrimido[4,5-*b*]-[1,6]naphthyridines (2a-d). A. A solution of the corresponding compound **1a-d** (0.01 mol) in PPA (20 ml) was heated at 145°C for 3 h. The mixture was poured into water (100 ml) and neutralized with 20% sodium hydrogen carbonate solution. The precipitate was filtered off, dried and crystallized from ethanol. ^{1}H NMR spectrum, δ, ppm: 8.55-8.82 (1H, s, H-5), 7.38-7.62 (m, aromatic protons), 5.42-5.65 (1H, t, H-8), 3.35-3.95 (2H, d, H-9). IR spectrum, ν, cm^{-1}: 1640-1660 ($C_{(4)}$=O), 1630-1640 ($C_{(6)}$=O). Mass spectrum of **2b,** *m/z* (I_{rel}, %): 599 $[M]^+$ (13), 508 (22), 443 (32), 431 (15), 405 (83), 352 (37), 324 (100), 310 (82), 290 (65), 281 (66), 259 (35), 252 (37), 209 (50), 198 (70).

B. Compound **1c** (6.13 g, 0.01 mol) was added to a freshly prepared solution of perchloric acid in glacial acetic acid (50 ml) containing a small amount of acetic anhydride (10-12% perchloric acid) and the mixture was heated for 1.5 h (~100°C), poured into water (150 ml), and neutralized with 20% sodium hydroxide solution. The precipitate was filtered off, dried, and crystallized. A mixed melting point test with a sample of compound **2c** made by method A did not give a depression of the melting point.

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