Efficient methods for the synthesis of pyrido[2,3-*d*]pyrimidin-5-ones from 4-amino-5-acetylpyrimidines

A. V. Komkov, B. I. Ugrak, V. S. Bogdanov, and V. A. Dorokhov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Scienses, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328

New methods for annelation of a pyridine ring to a pyrimidine ring were suggested. Substituted 8*H*-pyrido[2,3-*d*]pyrimidin-5-ones (**8a—f**) were synthesized by the interaction of 2,6-disubstituted 4-amino-5-acetylpyrimidines (**1—4**) with formamide or acetamide acetals followed by cyclization under the action of sodium methoxide in methanol. 2,4-Disubstituted 7-phenyl-8*H*-pyrido[2,3-*d*]pyrimidin-5-ones (**11a—c**) were prepared by the reaction of 2,6-disubstituted 5-acetyl-4-benzoylaminopyrimidines (**10a—c**) with MeONa in boiling BuOH.

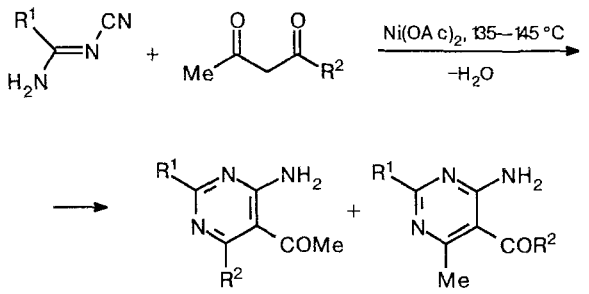
Key words: 4-amino-5-acetylpyrimidines, 4-benzoylamino-5-acetylpyrimidines, dimethylformamide dimethylacetal, dimethylacetamide dimethylacetal, pyrido-[2,3-*d*]pyrimidin-5-ones.

Pyrido[2,3-*d*]pyrimidine derivatives possess a broad spectrum of biological activity, and two compounds of the pyrido[2,3-*d*]pyrimidin-5-one series (pypemidic and pyromidic acids) are used in practical medicine as efficient antibacterial agents (see Review 1). In the present paper we propose novel methods for the synthesis of pyrido[2,3-*d*]pyrimidin-5-ones from pyrimidines containing vicinal amino and acetyl groups. Recently[2] we developed a convenient method for preparing 4-amino-5-acetyl-2-methyl(or phenyl)-6-methylpyrimidines (**1**, **2**) by the reaction of *N*-cyanoacetamidine or *N*-cyanobenzamidine with acetylacetone in the presence of $Ni(OAc)_2$. To advance this study we have shown that if the unsymmetrical β-diketone, benzoylacetone, is taken for the reaction, mixtures of isomeric pyrimidines, *viz.* **3** and **5** or **4** and **6**, respectively, are formed. The desired pyrimidines **3** and **4**, that are similar in their structure to compounds **1** and **2**, are the prevailing products (according to the ^1H NMR spectra, the **3** to **5** or **4** to **6** ratio is 8 : 1; Scheme 1).

Pyrimidines **3** and **5** can be readily isolated in the individual state from their mixture, and, therefore, compound **3**, like compounds **1** and **2**, is an available starting reagent for the purpose in hand , *i.e.*, building the pyrido[2,3-*d*]pyrimidine system. On the other hand, it is difficult to free pyrimidine **4** from an admixture of compound **6**; however, it turned out that this admixture does not hamper the use of **4** for purposes analogous to that of compounds **1—3**.

The structures of pyrimidines **3** and **5** were confirmed by IR, ^1H and ^{13}C NMR spectroscopy, and mass spectrometry (see Experimental). The unambiguous decision between structures **3** and **5** was based on the

Scheme 1



1—4 **5, 6**

$R^1 = R^2 = Me$ (**1**); $R^1 = Ph$, $R^2 = Me$ (**2**);
$R^1 = Me$, $R^2 = Ph$ (**3**, **5**); $R^1 = R^2 = Ph$ (**4**, **6**)

^{13}C NMR spectra. The C atom of the carbonyl group of compound **3** is responsible for a quartet at 203.10 ppm, and the Me group of the acetyl fragment accounts for a quartet at 31.63 ppm, whereas the spectrum of pyrimidine **5** exhibits a triplet with a chemical shift of 197.22 ppm due to the CO group and no signal in the region ~30 ppm. Pyrimidines **4** and **6** could be identified by comparing the ^1H NMR spectrum of their mixture with the spectra of compounds **3** and **5**.

Pyrimidines **1—4** react with DMF and dimethylacetamide (DMAA) dimethylacetals to give amidines (**7a—f**), whose structures were confirmed by ^1H NMR spectra (Table 1). It was found that compounds **7a—f** readily undergo cyclization when boiled with MeONa in MeOH to give pyrido[2,3-*d*]pyrimidin-5-ones (**8a—f**)

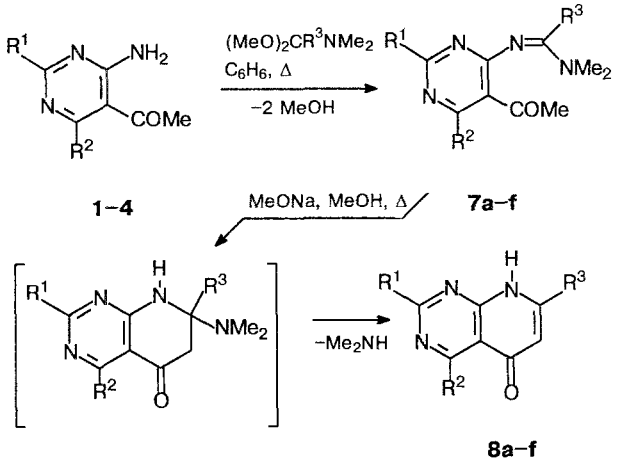
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 8, pp. 1469—1474, August, 1994.

1066-5285/94/4308-1392 $12.50

Table 1. Melting points and ^{1}H NMR spectra of amidines **7** and pyrimidines **10**

Compound	M.p./°C	^{1}H NMR ($CDCl_3$), δ
7a	98—99 (hexane, cooled to 10 °C)	2.34 (s, 3 H, Me), 2.54 (s, 3 H, Me), 2.57 (s, 3 H, Me), 3.06 (s, 3 H) and 3.14 (s, 3 H) (NMe_2), 8.61 (s, 1 H, CH=)
7b	Oil	2.00 (s, 3 H, Me), 2.28 (s, 3 H, Me), 2.42 (s, 3 H, Me), 2.49 (s, 3 H, Me), 2.99 (s, 6 H, NMe_2)
7s	119—120 (hexane)	2.47 (s, 3 H, Me), 2.63 (s, 3 H, Me), 3.11 (s, 3 H) and 3.20 (s, 3 H) (NMe_2), 7.38—7.57 (m, 3 H, Ph), 8.37—8.50 (m, 2 H, Ph), 8.86 (s, 1 H, CH=)
7d	Oil	2.24 (s, 3 H, Me), 2.47 (s, 3 H, Me), 2.56 (s, 3 H, Me), 3.12 (s, 6 H, NMe_2), 7.39—7.55 (m, 3 H, Ph), 8.33—8.47 (m, 2 H, Ph)
7e	171—172 (hexane—C_6H_6, 4 : 1)	2.37 (s, 3 H, Me), 2.64 (s, 3 H, Me), 3.06 (s, 3 H) and 3.14 (s, 3 H) (NMe_2), 7.35—7.48 (m, 3 H, Ph), 7.55—7.66 (m, 2 H, Ph), 8.66 (s, 1 H, CH=)
10a	169—170	2.58 (s, 3 H, Me), 2.63 (s, 3 H, Me), 2.65 (s, 3 H, Me), 7.51 (m, 2 H, Ph), 7.61 (m, 1 H, Ph), 7.95 (m, 2 H, Ph), 9.25 (br.s, 1 H, NH)
10b	167—168	2.64 (s, 3 H, Me), 2.75 (s, 3 H, Me), 7.44—7.70 (m, 6 H, Ph), 7.98 (m, 2 H, Ph), 8.47 (m, 2 H, Ph), 9.48 (br.s, 1 H, NH)
10c	201—202	2.02 (s, 3 H, Me), 2.82 (s, 3 H, Me), 7.44—7.70 (m, 8 H, Ph), 8.00 (m, 2 H, Ph), 10.51 (br.s, 1 H, NH)

Scheme 2

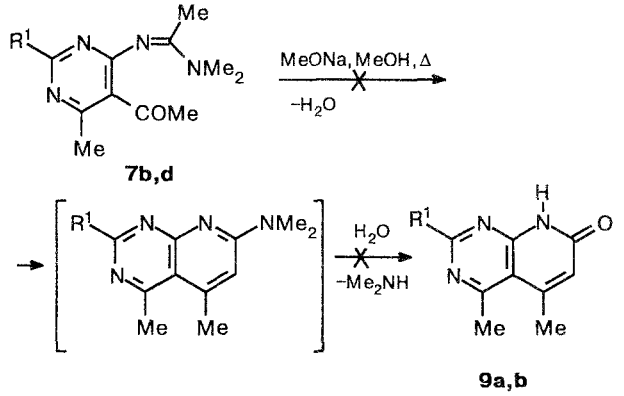


$R^1 = R^2 = Me$ (**1**); $R^1 = Ph$, $R^2 = Me$ (**2**);
$R^1 = Me$, $R^2 = Ph$ (**3**); $R^1 = R^2 = Ph$ (**4**);
$R^1 = R^2 = Me$, $R^3 = H$ (**7a, 8a**); $R^1 = R^2 = R^3 = Me$ (**7b, 8b**);
$R^1 = Ph$, $R^2 = Me$, $R^3 = H$ (**7c, 8c**);
$R^1 = Ph$, $R^2 = R^3 = Me$ (**7d, 8d**);
$R^1 = Me$, $R^2 = Ph$, $R^3 = H$ (**7e, 8e**);
$R^1 = R^2 = Ph$, $R^3 = H$ (**7f, 8f**)

(Scheme 2). (When **7f** is prepared from pyrimidine **4**, the compound **6** present in the latter as an admixture also forms the corresponding amidine with the DMF acetal. However, this amidine is not involved in the subsequent cyclization and does not hamper the isolation of the sparingly soluble pyridopyrimidine **8f**.) This process is likely to occur through a nucleophilic attack by Me of the acetyl group at the C atom of the amidine fragment followed by elimination of dimethylamine. Compounds **8a—f** are formed in a 52—94 % yield based on the starting **1—4**.

The structures of the pyridopyrimidinones synthesized were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry (Tables 2, 3, and 4). For the cyclization of amidines **7b,d** prepared from DMAA dimethylacetal, we had to take into account the possibility of an alternative reaction pathway that would have given pyrido[2,3-*d*]pyrimidin-7-ones (**9a,b**) (Scheme 3), which are isomeric to compounds **8b,d**. For example, it is known that 4-amino-5-ethoxycarbonylpyrimidines react with DMAA diethylacetal to give the corresponding amidines, which undergo cyclization in the presence of a sodium alkoxide to yield 7-dimethylamino-5-oxypyrido[2,3-*d*]pyrimidines,[3,4] *i.e.*, the closure of the pyridine ring results from the attack of the methyl group of the amidine fragment at the C atom of the COOEt group and abstraction of ethanol.

Scheme 3



R^1 = Me (**7b, 9a**), Ph (**7d, 9b**)

Table 2. Yields, melting points, elemental analysis data, and IR and mass spectra of pyrido[2,3-*d*]pyrimidin-5-ones **8** and **11**

Compound	Yield (%)	M.p./°C (Solvent)	Found / Calculated (%) C	H	N	Molecular Formula	IR spectrum (KBr, ν/cm^{-1})	Mass spectrum *m/z* (I_{rel}(%))
8a	77	259—261 (acetonitrile)	61.91 / 61.70	5.14 / 5.18	23.92 / 23.99	$C_9H_9N_3O$	3300—2700 (NH, CH), 1640 (CO), 1590, 1560, 1505	175 [M]$^+$ (100), 147 [M−CO]$^+$ (60), 134 [M−MeCN]$^+$ (21)
8b	73	275—277 (ethanol)	63.40 / 63.48	5.94 / 5.86	21.95 / 22.21	$C_{10}H_{11}N_3O$	3300—2600 (NH, CH), 1665 (CO), 1630, 1600, 1550 1500	189 [M]$^+$ (100), 161 [M−CO]$^+$ (44), 160 [M−CO−H]$^+$ (50)
8c	94	291—293 (dec.) (ethanol)	70.68 / 70.87	4.50 / 4.67	18.01 / 17.71	$C_{14}H_{11}N_3O$	3300—2600 (NH, CH), 1660 (CO), 1620, 1605, 1585 1565, 1540, 1510	237 [M]$^+$ (100), 209 [M−CO]$^+$ (27),
8d	52	319—321 (dec.) (ethanol)	71.98 / 71.70	4.94 / 5.21	16.93 / 16.72	$C_{15}H_{13}N_3O$	3300—2600 (NH, CH), 1645 (CO), 1595, 1580, 1565 1535	251 [M]$^+$ (100), 223 [M−CO]$^+$ (30), 222 [M−CO−H]$^+$ (35)
8e	89	315—317 (dec.) (ethanol)	71.00 / 70.87	4.71 / 4.67	17.85 / 17.71	$C_{14}H_{11}N_3O$	3200—2500 (NH, CH), 1660 (CO), 1620, 1595, 1565 1540, 1500	237 [M]$^+$ (48), 236 [M−H]$^+$ (100)
8f	78	365—367 (dec.) (ethanol)	76.06 / 76.24	4.35 / 4.38	14.23 / 14.04	$C_{19}H_{13}N_3O$	3200—2700 (NH, CH), 1652 (CO), 1618, 1598, 1580 1530, 1505	299 [M]$^+$ (41), 298 [M−H]$^+$ (100)
11a	69	277—278 (acetonitrile)	71.47 / 71.70	5.41 / 5.21	16.75 / 16.72	$C_{15}H_{13}N_3O$	3280—2900 (NH, CH), 1630 (CO), 1585, 1550	251 [M]$^+$ (100), 223 [M−CO]$^+$ (40)
11b	64	242—243 (acetonitrile)	76.82 / 76.66	4.83 / 4.83	13.60 / 13.41	$C_{20}H_{15}N_3O$	3260—3040 (NH, CH), 1625 (CO), 1585, 1560	313 [M]$^+$ (100), 285 [M−CO]$^+$ (32)
11c	73	219—220 (acetonitrile)	76.29 / 76.66	4.80 / 4.83	13.52 / 13.41	$C_{20}H_{15}N_3O$	3300—2900 (NH, CH), 1620 (CO), 1600, 1580, 1540	313 [M]$^+$ (50), 312 [M−H]$^+$ (100)

Table 3. ^{1}H NMR spectra of pyrido[2,3-*d*]pyrimidin-5-ones **8** and **11**

Compound	Solvent	δ (*J*/Hz)
8a	$CDCl_3$	2.70 (s, 3 H, 2-Me), 3.06 (s, 3 H, 4-Me), 6.34 (d.d, 1 H, H(6), $J_{H,H}$ = 7.5, $J_{H,NH}$ = 1.5), 7.55 (d.d, 1 H, H(7), $J_{H,H}$ = 7.5, $J_{H,NH}$ = 6.0), 8.75 (br.s, 1 H, NH)
8b	$CDCl_3$	2.36 (s, 3 H, 7-Me), 2.68 (s, 3 H, 2-Me), 3.04 (s, 3 H, 4-Me), 6.14 (s, 1 H, H(6)), 8.30 (br.s, 1 H, NH)
8c	$CDCl_3$	3.16 (s, 3 H, 4-Me), 6.35 (d.d, 1 H, H(6), $J_{H,H}$ = 8.0, $J_{H,NH}$ = 2.0), 7.45—7.62 (m, 4 H, H(7) и Ph), 8.45—8.58 (m, 2 H, Ph), 8.64 (br.s, 1 H, NH)
8d	$CDCl_3$	2.39 (s, 3 H, 7-Me), 3.14 (s, 3 H, 4-Me), 6.17 (s, 1 H, H(6)), 7.45—7.60 (m, 3 H, Ph), 8.33 (br.s, 1 H, NH), 8.45—8.57 (m, 2 H, Ph)
	CF_3COOD	2.51 (s, 3 H, 7-Me), 3.25 (s, 4-Me, is partly deuterated), 6.75 (s, 1 H, H(6)), 7.44 (m, 2 H, Ph), 7.60 (m, 1 H, Ph), 8.00 (m, 2 H, Ph)
8e	$CDCl_3$	2.78 (s, 3 H, 2-Me), 6.29 (d.d, 1 H, H(6), $J_{H,H}$ = 8.0, $J_{H,NH}$ = 1.5), 7.40—7.70 (m, 6 H, H(7) и Ph), 8.64 (br.s, 1 H, NH)
8f	DMSO-d_6	6.11 (d, 1 H, H(6), $J_{H,H}$ = 7.5), 7.32—7.75 (m, 8 H, Ph), 7.33 (d, 1 H, H(7), $J_{H,H}$ = 7.5), 8.38—8.58 (m, 2 H, Ph)
11a	$CDCl_3$	2.61 (s, 3 H, 2-Me), 3.08 (s, 3 H, 4-Me), 6.61 (s, 1 H, H(6)), 7.45—7.63 (m, 3 H, Ph), 7.63—7.75 (m, 2 H, Ph), 9.81 (br.s, 1 H, NH)
11b	$CDCl_3$	3.17 (s, 3 H, 4-Me), 6.61 (d, 1 H, H(6), $J_{H,NH}$ = 1.8), 7.42—7.60 (m, 6 H, Ph), 7.70 (m, 2 H, Ph), 8.50 (m, 2 H, Ph), 9.12 (br.s, 1 H, NH)
11c	$CDCl_3$	2.67 (s, 3 H, 2-Me), 6.56 (s, 1 H, H(6)), 7.35—7.74 (m, 10 H, Ph), 9.34 (br.s, 1 H, NH)

Table 4. ^{13}C NMR spectra of pyrido[2,3-*d*]pyrimidin-5-ones **8** and **11** in DMSO-d_6 δ ($J_{C,H}$/Hz)

Compound	C(2)	C(4)	C(4a)	C(5)	C(6)	C(7)	C(8a)	Me	Ph
8a	167.32 (q, ^2J = = 7.0)	170.49 (q, ^2J = = 6.5)	113.20 (q, ^3J = = 2.6)	178.63 (d, ^3J = = 8.8)	113.99 (d.d, ^1J = 167.10, ^2J = 2.5)	139.62 (d.d, ^1J = 179.04, ^2J = 3.9)	155.82 (d, ^3J = 8.9)	25.57 (2-Me) 25.16 (4-Me)	—
8b	166.79 (q, ^2J = = 6.6)	169.71 (q, ^2J = = 6.8)	111.51	177.93 s	112.70 (d.q, ^1J = 165.0, ^3J = 4.3)	149.49 (q.d, ^2J = 6.2, ^3J = 3.4)	155.71 s	25.05 (2-Me) 24.27 (4-Me) 18.47 (7-Me)	—
8c	162.17	170.67	113.66	178.16	113.96	139.02	155.83	25.05 (4-Me)	128.04, 128.18 130.94, 136.23
8d	162.11	170.27	112.49	177.88	113.10	149.99	156.10	18.69 (7-Me) 24.97 (4-Me)	128.04, 128.29 130.98, 136.36
11a	167.31	170.08	112.11	179.30	112.15	149.86	156.45	24.81 (4-Me) 25.37 (2-Me)	127.36, 128.64 130.52, 132.68
11b*	164.42	172.63	113.62	179.88	113.36	149.36	156.72	25.84 (4-Me)	126.66, 128.62 129.14, 129.54 131.21, 131.57 133.40, 136.87

* The spectrum was recorded in $CHCl_3$.

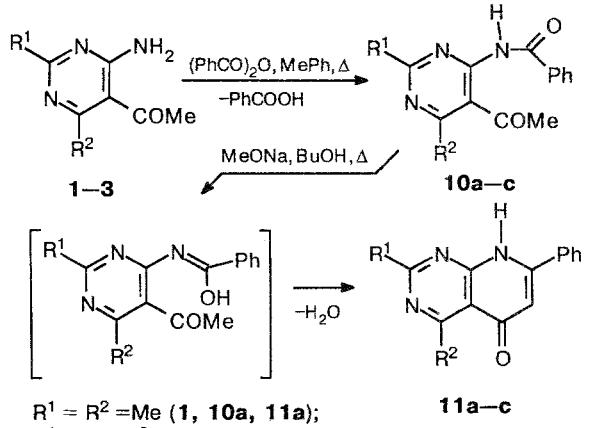
However, comparison of the ^1H and ^{13}C NMR spectra of the cyclization products derived from **7b,d** with the spectra of pyridopyrimidinones **8a,c** (see Tables 3,4) makes it possible to rule out the type **9** structures for these compounds. In addition, the spectroscopic data and the melting point of compound **8d** substantially differ from those of pyridopyrimidinone **9b** described previously in the literature[5] (the signals for the methyl groups and for H(6) in the ^1H NMR spectrum of **8d** in CF_3COOD are recorded at 2.51, 3.25, and 6.75 ppm, respectively, whereas in the spectrum of **9b** the corresponding signals are at 2.45, 2.70, and 6.50 ppm; m.p. of **8d** is 319—321 °C, while m.p. of **9b** is 265—270 °C). It should be noted that in the ^1H NMR spectra (in $CDCl_3$) of compounds **8a—d**, the signal for the protons of the 4-Me group located at the *peri*-position with respect to the carbonyl group is exhibited in a relatively low field (3.04—3.16 ppm), which is due to the deshielding effect of the CO group.

Pyridopyrimidines **8a—f** are crystalline solids slightly soluble in most organic solvents and only sparingly soluble in dimethylsulfoxide. However, they are readily soluble in aqueous alkaline solutions.

Pyrimidines **1—3** smoothly react with benzoic anhydride when boiled in toluene to give the corresponding benzoyl derivatives (**10a—c**) (Scheme 4), which undergo cyclization in boiling butanol under the action of MeONa to give pyrido[2,3-*d*]pyrimidin-5-ones (**11a—c**) (the yields of the cyclization step are 64—73 %). At lower temperatures, for example, in boiling methanol, cyclization occurs slowly, and in this case, the competing process, debenzoylation of pyrimidines **10a—c**, becomes prevailing, which does not enable compounds **11a—c** to be prepared in good yields.

The intermediate benzoylamides **10a—c** were characterized by ^1H NMR spectra (see Table 1). The intramolecular cyclization of compounds **10a—c** is likely to involve (*cf.* Scheme 2) a nucleophilic attack of the acetyl-group Me at the C atom of the enolized benzamide fragment with elimination of water (see Scheme 4). It is significant that pyrimidines **1** and **2** acetylated at the NH_2 group do not undergo cyclization to yield pyridopyrimidines **8b,d** under these conditions, probably, owing to the lower tendency of the acetamide group to enolize. Previously we observed a similar type of cyclization for 5-acetyl-4-benzoylamino-6-methylthio-2-phenylpyrimidine;[6] this confirms the efficiency of the approach offered for building the pyrido[2,3-*d*]pyrimidine system.

Scheme 4



The pyridopyrimidines **11a—c** synthesized are much more readily soluble in chloroform and ethanol than their analogs **8a—f**. Their structures were confirmed by IR spectroscopy, ^1H and ^{13}C NMR spectroscopy, and mass spectrometry (see Tables 2, 3, and 4).

In general, according to the schemes presented in this paper, one can prepare 6-unsubstituted pyrido-[2,3-*d*]pyrimidin-5-ones having substituents in positions 2, 4, and 7 as well as those having no substituents in position 7.

Previously[6] we synthesized derivatives of pyrido[2,3-*d*]pyrimidin-5-one from 4-RNH-5-acetylpyrimidines and DMF dimethylacetal, however, in that case, the annelation of the pyridine ring involved condensation of the acetal at the methyl group of the 5-acetyl fragment. A similar scheme has been used in a number of patents[7,8] that describe preparation of 6-formylpyrido[2,3-*d*]-pyrimidin-5-ones from 2-substituted 4-ethylamino-5-acetylpyrimidines, DMF, and $POCl_3$ (or PCl_3). A widely used method for the synthesis of pyrido[2,3-*d*]pyrimidin-5-ones is the Gould—Jacobs reaction consisting of condensation of 6-aminopyrimidines with diethyl ethoxymethylenemalonate followed by thermal cyclization.[1,9] However, this route is efficient only if there are electron-donating substituents in positions 2 or 4 of the pyrimidine ring. Base-catalyzed condensation of 4-amino-5-ethoxycarbonylpyrimidines with CH acids is often used too.[10,11] However, this method does not always allow one to obtain good results either. For example, the reaction with acetophenone affords 7-phenylpyrido[2,3-*d*]pyrimidin-5-one in a low yield (11 %).[10]

In conclusion, it should be noted that, in contrast to the methods reported in the literature, which rely on the final formation on the 5—6,[3,4,10,11] 7—8,[6—8] and 4a—5 [9] bonds of pyrido[2,3-*d*]pyrimidin-5-ones, our synthetic schemes involve a unique type of annelation of the pyridine ring to a pyrimidine ring consisting of the formation of the C(6)—C(7) bond.

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 spectrometer and ^{13}C NMR spectra were run on a Bruker AM-300 spectrometer. IR spectra were obtained on UR-20 (in CH_2Cl_2) and Perkin-Elmer 577 (KBr pellets) instruments. Mass spectra were obtained on a Varian MAT-311A mass spectrometer (EI, 70 eV). Pyrimidines **1** and **2** were prepared according to the known procedure.[2]

4-Amino-5-acetyl-2-methyl-4-phenylpyrimidine (3) and 4-amino-5-benzoyl-2,6-dimethylpyrimidine (5). A mixture of *N*-cyanoacetamidine (2.00 g, 24 mmol), benzoylacetone (7.78 g, 48 mmol), and $Ni(OAc)_2$ (4.26 g, 24 mmol) was heated at 135—145 °C for 6 h. The reaction mixture was cooled to ~20 °C, then 50 mL of $CHCl_3$ was added, the precipitate was filtered off, the filtrate was concentrated, the residue was dissolved in $CHCl_3$, and the resulting solution was filtered through a SiO_2 layer ($CHCl_3$ as the eluent). The solvent was evaporated and the residue was recrystallized from benzene to give 1.61 g (29 %) of pyrimidine **3**. The filtrate was concentrated, and the residue was chromatographed on a column with SiO_2 (elution was successively carried out with C_6H_6, a C_6H_6—$CHCl_3$ mixture (1 : 1), and $CHCl_3$). 0.67 g of pyrimidine **3** (overall yield 42 %) and 0.26 g (5 %) of pyrimidine **5** were successively isolated.

Pyrimidine **3**, m.p. 219—220 °C (from benzene). Found (%): C, 68.68; H, 5.83; N, 18.21. $C_{13}H_{13}N_3O$. Calculated (%): C, 68.70; H, 5.77; N, 18.49. IR (CH_2Cl_2), ν/cm^{-1}: 3505 (NH), 3380 (NH), 1660 (CO), 1595, 1550. ^1H NMR ($CDCl_3$) δ: 1.84 (s, 3 H, MeCO), 2.57 (s, 3 H, Me), 6.75 (br.s, 2 H, NH_2), 7.41—7.60 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 25.97 (q, Me, $^1J_{C,H}$ = 127.9 Hz), 31.63 (q, MeCO, $^1J_{C,H}$ = 128.8 Hz), 111.17 (C(5)), 128.83, 129.29, 130.38, 139.82 (Ph), 161.92 (C(6)), 167.62 (C(4)), 168.42 (q, C(2), $^2J_{C,H}$ = 6.6 Hz), 203.10 (q, CO, $^2J_{C,H}$ = 5.7 Hz). MS, *m/z* (I_{rel}(%)): 227 $[M]^+$ (68), 226 $[M-H]^+$ (100), 212 $[M-Me]^+$ (86).

Pyrimidine **5**, m.p. 174—175 °C (from hexane—benzene, 1 : 1). Found (%): C, 69.09; H, 5.84; N, 18.07. $C_{13}H_{13}N_3O$. Calculated (%): C, 68.70; H, 5.77; N, 18.49. IR (CH_2Cl_2) ν/cm^{-1}: 3515 and 3410 (NH_2), 1650 (CO), 1600, 1560. ^1H NMR ($CDCl_3$) δ: 2.08 (s, 3 H, Me), 2.53 (s, 3 H, Me), 5.83 (br.s, 2 H, NH_2), 7.48 (m, 2 H, Ph), 7.61 (m, 1 H, Ph), 7.76 (m, 2 H, Ph). ^{13}C NMR ($CDCl_3$) δ: 24.01 (q, Me, $^1J_{C,H}$ = 128.3 Hz), 25.36 (q, Me, $^1J_{C,H}$ = 127.6 Hz), 111.04 (C(5)), 128.71, 128.78, 133.37, 138.49, (Ph), 161.60 (C(4)), 164.71 (q, C(6), $^2J_{C,H}$ = 6.0 Hz), 167.73 (q, C(2)), $^2J_{C,H}$ = 6.0 Hz), 197.22 (t, CO, $^2J_{C,H}$ = 8.0). MS, *m/z* (I_{rel}(%)): 227 $[M]^+$ (85), 226 $[M-H]^+$ (100), 150 $[M-Ph]^+$ (69).

4-Amino-5-acetyl-2,6-diphenylpyrimidine (4) and 4-amino-5-benzoyl-6-methyl-2-phenylpyrimidine (6). A mixture of *N*-cyanobenzamidine (0.50 g, 3.4 mmol), benzoylacetone (1.10 g, 6.8 mmol), and $Ni(OAc)_2$ (0.60 g, 3.4 mmol) was heated at 135—145 °C for 6 h. The reaction mixture was cooled to ~20 °C, then 20 mL of $CHCl_3$ was added, the precipitate was filtered off, the filtrate was concentrated, and the residue was chromatographed on a column with SiO_2 (elution was carried out with a C_6H_6—$CHCl_3$ (1 : 1) mixture, and then with $CHCl_3$) to give 0.45 g (46 %) of pyrimidine **4** with an admixture of pyrimidine **6** (the **4** to **6** ratio was 8.5 : 1 according to the ^1H NMR spectrum) as an oil, which was directly used in the subsequent synthesis. The ^1H NMR spectrum of pyrimidine **4** ($CDCl_3$), δ: 1.90 (s, 3 H, MeCO), 7.62 (br.s, 2 H, NH_2), 7.35—7.65 (m, 6 H, Ph), 7.70 (m, 2 H, Ph), 8.50 (m, 2 H, Ph). The ^1H NMR spectrum of pyrimidine **6** ($CDCl_3$), δ: 2.18 (s, 3 H, Me), 5.85 (br.s, 2 H, NH_2), 7.80 (m, 2 H, Ph), 8.42 (m, 2 H, Ph), the signals for other protons were overlapped with the signals of the prevailing pyrimidine **4**.

2-Methyl(or phenyl)-4-methyl(or phenyl)-7-unsubstituted(or methyl)-8*H*-pyrido[2,3-*d*]pyrimidin-5-ones (8a—e) (General procedure). A mixture of 4-amino-5-acetylpyrimidine **1—3** (2 mmol) and DMF dimethylacetal or DMAA dimethylacetal (3 mmol) in benzene (6 mL) was boiled for 2—3 h. The solvent was evaporated *in vacuo* to give amidines **7a—e** (the ^1H NMR spectra are given in Table 1). MeONa (2 mmol) in MeOH (8 mL) was added to compounds **7a—e** and the mixture was boiled for 2 h. The solvent was evaporated *in vacuo* and the residue was dissolved in H_2O (10 mL) and acidified with AcOH. The precipitate was filtered off, washed with water, and dried to afford pyridopyrimidinones **8a—e** (compounds **8b,d** were washed, in addition, with 5 mL of $CHCl_3$). To carry out elemental analysis, compounds **8a—e** were recrystallized from ethanol or acetonitrile and dried *in vacuo* at 80 °C. Yields, melting points, elemental analysis data,

and IR and mass spectra of pyridopyrimidinones **8a—e** are summarized in Table 2, and their ^1H and ^{13}C NMR spectra are given in Tables 3 and 4.

2,4-Diphenyl-8H-pyrido[2,3-*d*]pyrimidin-5-one (8f) was prepared similarly to compounds **8a—e** by reacting pyrimidine **4** (0.29 g, 1 mmol) with an admixture of 10.5 % of pyrimidine **6** with DMF dimethylacetal (0.20 mL, 1.5 mmol) followed by treatment with MeONa (1 mmol) in MeOH (4 mL). Pyridopyrimidinone **8f** was isolated as described in the previous procedure and washed with 10 mL of $CHCl_3$ (to purify it from the product of condensation of compound **6** with DMF acetal). Yield 0.21 g (see Tables 2—4).

5-Acetyl-4-benzoylamino-2-methyl(or phenyl)-6-methyl(or phenyl)pyrimidines (10a—c). A mixture of pyrimidine **1—3** (1 mmol) and benzoic anhydride (2 mmol) in toluene (5 mL) was boiled for 16 h and cooled to ~20 °C. Hexane (15 mL) was added and the precipitate was filtered off to give pyrimidines **10b,c** in 65 and 76 % yields, respectively. Pyrimidine **10a** was prepared in 87 % yield after removal of the solvent from the reaction mixture and separation of the residue on a column with SiO_2 (elution was carried out with C_6H_6 and then with $CHCl_3$). Melting points and the ^1H NMR spectra of pyrimidines **10a—c** are given in Table 1. IR spectrum of compound **10c** (CH_2Cl_2), ν/cm^{-1}: 3400 (NH), 1710 (CO), 1665 (CO), 1580, 1530, 1500. (IR spectra of **10a,b** are similar to that of **10c**)

2-Methyl(or phenyl)-4-methyl(or phenyl)-7-phenyl-8H-pyrido[2,3-*d*]pyrimidin-5-ones (11a—c) (General procedure). A solution of pyrimidine **10a—c** (1 mmol) in butanol (8 mL) heated to boiling was added to MeONa (1 mmol), and the reaction mixture was boiled for 10 min, cooled to ~20 °C, and acidified with AcOH. The solvent was evaporated *in vacuo* and the residue was dissolved in $CHCl_3$ and chromatographed on a column with SiO_2 (elution was carried out with a benzene—$CHCl_3$ mixture, 3 : 1 and then with $CHCl_3$). to give pyridopyrimidines **11a—c**. Their yields, melting points, elemental analysis data, and spectroscopic characteristics are listed in Tables 2—4. IR spectrum of pyridopyrimidinone **11c** (CH_2Cl_2), ν/cm^{-1}: 3398 (NH), 1642 (CO), 1580, 1540, 1500.

A portion of the work was supported of Russian Foundation for Basic Research (grant № 94-03-08964).

References

1. A. Sh. Oganisyan, A. S. Noravyan, and S. A. Vartanyan, *Usp. Khim.*, 1987, **56**, 2001 [*Russ. Chem. Rev.*, 1987, **56** (Engl. Transl.)].
2. V. A. Dorokhov, M. F. Gordeev, A. V. Komkov, and V. S. Bogdanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 145 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 130 (Engl. Transl.)].
3. USSR Pat 554675, Byul. Izobret., 1977, №35, 209.
4. V. G. Granik, N. B. Marchenko, and R. G. Glushkov, *Khim. Geterotsikl. Soedin.*, 1978, 1549 [*Chem. Heterocycl. Compd.*, 1978 (Engl. Transl.)].
5. T. Sakamoto, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.*, 1982, **30**, 2410.
6. V. A. Dorokhov, A. V. Komkov, E. M. Shashkova, V. S. Bogdanov, and M. N. Bochkareva, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1932 [*Russ. Chem. Bull.*, 1993, **42**, 1848 (Engl. Transl.)].
7. Japan Kokai Tokkyo Koho 77151196, *Chem. Abstrs.*, 1978, **88**, 136668.
8. Japan Kokai Tokkyo Koho 7981299, *Chem. Abstrs.*, 1980, **92**, 94418.
9. S. Nishigaku, K. Ogiwara, K. Senda, S. Fukazawa, K. Aida, Y. Machida, and Yoneda, *Chem. Pharm. Bull.*, 1970, **18**, 1385.
10. H. Brederek, F. Effenberger, E. Henseleit, E. H. Schweizer, *Chem. Ber.*, 1963, **96**, 1868.
11. Span. Pat. ES 498856, *Chem. Abstrs.*, 1982, **97**, 55829.

Received February 14, 1994