SOME ASPECTS OF REACTION OF 6-AMINOURACIL AND 6-AMINO-2-THIOURACIL WITH α,β-UNSATURATED KETONES

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A number of 5,7-diaryl-5,8-dihydropyrido[2,3-*d*]pyrimidines and 5,7-diarylpyrido[2,3-*d*]-pyrimidines were obtained by the reaction of 6-aminouracil derivatives with α,β-unsaturated ketones. Basic catalysts decrease yields of the dihydro derivatives whereas acids increase it. In the reactions of ketones containing the dimethylamino group, elimination of the aryl substituent from position 5 of the pyridopyrimidine system was observed. Some aspects of oxidation of 5,8-dihydropyrido[2,3-*d*]pyrimidines and synthesis of pyrido[2,3-*d*]pyrimidines were also investigated.

Keywords: Nitrogen heterocycles; Pyrido[2,3-*d*]pyrimidines; Pyrimidines; Oxidation; NMR spectroscopy; Cyclizations; α,β-Unsaturated ketones; Heteroannulations.

It is well known that many pyrido[2,3-*d*]pyrimidine derivatives possess interesting physiological properties. They have been proved to posses antibacterial[1], antiviral[2], diuretic[3] and other activities[4]. As a result, compounds of this class present a considerable interest for research. One of the facile synthetic pathways to such compounds is reaction of 6-aminouracil and its derivatives with β-ketoesters[5,6], β-diketones[7–10] or α,β-unsaturated carbonyl compounds[11–14]. The reactions of 6-aminouracil with α,β-unsaturated carbonyl compounds are the most general-purpose methods because they allow to obtain both pyrido[2,3-*d*]pyrimidines and their dihydro derivatives with different substituents in positions 5 and 7 of the heterocyclic system. Alternative pathways are not suitable for synthesis of the dihydro derivatives and pyrido[2,3-*d*]pyrimidines containing various substituents.

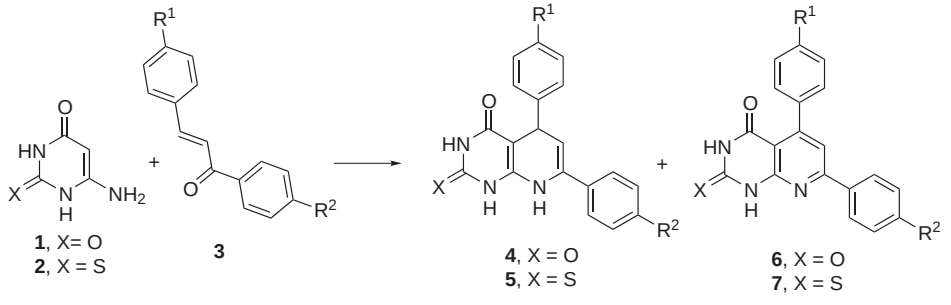
As it was previously reported[11], refluxing of 2-thio-6-aminouracil **2** in DMF with a series of chalcones leads to 5,7-diaryl-2-thioxopyrido[2,3-*d*]-pyrimidin-4-ones. Synthesis of their 5,8-dihydro derivatives was carried out

in argon atmosphere. The structures of compounds synthesized were confirmed by ^{1}H and ^{13}C NMR spectroscopy. In support of the positions of aryl substituents, a series of NOE experiments was made.

In the framework of the present investigation, the influence of reaction conditions and electronic nature of substituents on the composition of reaction products was studied. Elaboration of a facile synthetic procedure for 5,7-diaryl-5,8-dihydropyrido[2,3-*d*]pyrimidines and their oxidation were also goals of the research.

The starting materials were prepared by the following literature procedures. Thus, 6-aminouracil derivatives **1** and **2** were obtained by treatment of ethyl cyanoacetate with urea or thiourea in the presence of sodium ethoxide[15]. α,β-Unsaturated ketones **3a**–**3h** and **8a**, **8b** were prepared by a known method[16] from corresponding aldehydes and acetophenones.

The reactions of amino derivatives **1**, **2** with chalcones **3a**–**3h** were performed by refluxing in DMF in the presence of basic or acidic catalysts and also by heating in glacial acetic acid (Scheme 1). After a short open-air heating (10–20 min) of amines **1**, **2** with ketones **3a**–**3h** in DMF, only the starting compounds could be isolated from the reaction mixture. A prolonged reflux (2 h and more) led to pyrido[2,3-*d*]pyrimidines **6a**, **6b**, **7a**, **7c**–**7h** (compounds **6b**, **7a**, **7c**–**7e** were isolated in a mixture with 5,8-dihydropyrido[2,3-*d*]pyrimidines **4b**, **5a**, **5c**–**5e**). A further increase of the heating time to 6–10 h and passing air through the reaction mixture did not lead to any change of both the yield and the ratio of pyridopyrimidines **6b**, **7a**, **7c**–**7e** and their dihydro derivatives **4b**, **5a**, **5c**–**5e** in the reaction products.



3–7	R^1	R^2	3–7	R^1	R^2
a	H	H	**e**	Me_2N	Cl
b	Cl	Me	**f**	NO_2	Cl
c	H	Cl	**g**	F	H
d	MeO	Cl	**h**	CO_2Me	H

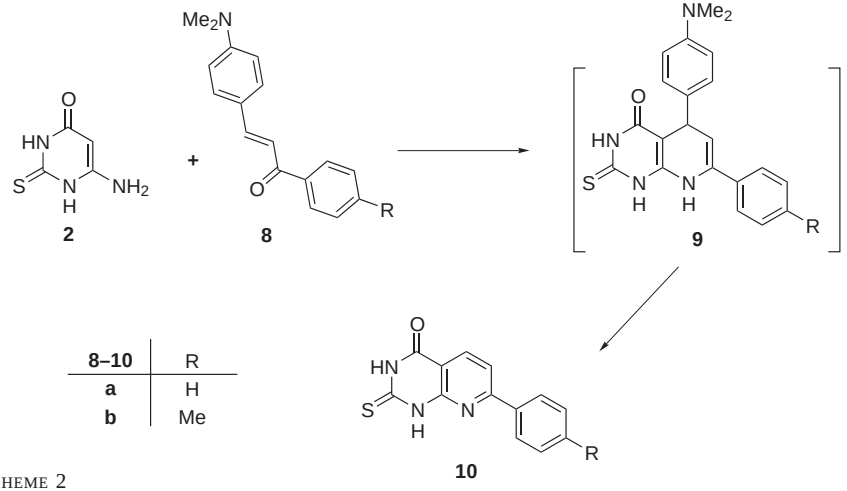
SCHEME 1

The treatment of amino derivatives **1**, **2** with ketones **3a**, **3f**–**3h** in the presence of triethylamine or potassium hydroxide yielded sufficiently pure corresponding pyrido[2,3-*d*]pyrimidines **6a**, **7a**, **7f**–**7h**, whereas the reaction of **1**, **2** with chalcones **3c**–**3e** under the same conditions led to the formation of mixtures of **5c**–**5e** and **7c**–**7e**, which could be hardly separated.

An addition of several drops of acetic acid to DMF increased content of the dihydro derivatives in the resulting mixture. Refluxing aminouracils **1**, **2** and chalcones **3b**–**3e** in glacial acetic acid led to the formation of 5,8-dihydropyrimidines **4b**, **5c**–**5e**. However, in the case of chalcones **3a**, **3f**–**3h** under the same conditions, only pyridopyrimidines **6a**, **7a**, **7f**–**7h** were isolated.

The results obtained in this way show that the ratio of 5,7-diarylpyrido-[2,3-*d*]pyrimidines to their dihydro derivatives in the product mixture depends on reaction conditions: basic catalysts decrease the yields of the dihydro derivatives, whereas acid catalysts increase them. This is possibly closely related to protonation and deprotonation of the dihydro derivatives, which are reflected in their ability to aromatize. On the other hand, a dependence of the product composition on the electronic nature of substituents in the heterocycle was observed. Introduction of electron-withdrawing substituents into position 5 increases the content of pyrido- [2,3-*d*]pyrimidines, whereas electron-donating groups have an opposite effect.

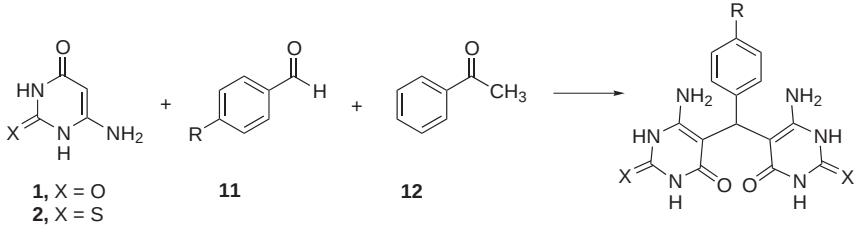
In the presence of strong electron donor groups, elimination of the aryl substituent from position 5 of the pyridopyrimidine moiety could be observed. Thus, in the reaction of **2** with chalcones **8a**, **8b** in acetic acid only compounds **10a**, **10b** were isolated (Scheme 2). Similar processes have been



SCHEME 2

described in literature[17] just in the case of heterocycles with electron-rich eliminated aryl substituents.

To find an alternative synthesis of pyrido[2,3-*d*]pyrimidine derivatives, the three-component reaction of amines **1**, **2** with synthetic precursors of chalcones was attempted. It was found that the one-pot heating of aldehydes **11a**–**11c** and acetophenone **12** with amino derivatives **1**, **2**, both in DMF and in acetic acid, led to the formation of 6,6′-diamino-5,5′-(arylmethylene)bispyrimidines **13a**, **14b**, **14c** (Scheme 3). In this case, the reaction proceeded without participation of acetophenone which was determined in the reaction mixtures by HPLC.



1, X = O
2, X = S

11

12

11, 13, 14	R
a	Me
b	Cl
c	F

13, X = O
14, X = S

+ **12**

SCHEME 3

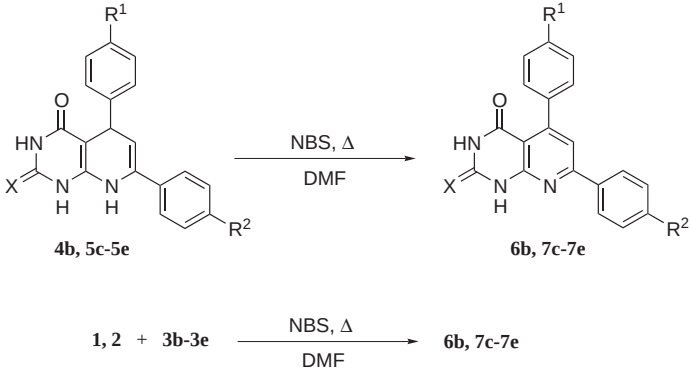
One of the goals of the investigation was to study oxidation of 5,8-dihydro derivatives **4b**, **5c**–**5e** to the corresponding pyrido[2,3-*d*]pyrimidines. As it was earlier mentioned, passing air through the reaction mixture was not an effective oxidation method of 5,8-dihydropyrido[2,3-*d*]pyrimidines. Common methods of heteroaromatization, such as treatment **4b**, **5c**–**5e** with sodium nitrite or with bromine in acetic acid led to pyrido-[2,3-*d*]pyrimidines **6b**, **7c**–**7e**, but the products contained considerable amounts of starting compounds.

The use of *N*-bromosuccinimide (NBS) turned out to be a preparative method for the oxidation of 5,8-dihydropyrido[2,3-*d*]pyrimidines. Reflux of equimolar amounts of compounds **4b**, **5c**–**5e** and NBS in dry DMF for 3 h led to sufficiently pure pyrido[2,3-*d*]pyrimidines **6b**, **7c**–**7e** (Scheme 4).

The results obtained allowed to elaborate a simple method for synthesis of 5,7-diarylpyrido[2,3-*d*]pyrimidines by the reaction of amino derivatives **1**, **2** with chalcones in DMF in the presence of equimolar amounts of NBS. Using this method, compounds **6b**, **7c**–**7e** were obtained.

The composition of compounds **4b**, **5c**–**5e**, **6a**, **6b**, **7a**, **7c**–**7h**, **10a**, **10b**, **13a** and **14b**, **14c** was confirmed by elemental analysis and their structures

were proved by ^{1}H NMR and ^{13}C NMR spectral data (see Experimental). The ^{1}H NMR spectra of 5,8-dihydropyrido[2,3-*d*]pyrimidines **4b**, **5c**–**5e** show signals of functional groups and aryl substituents, a doublet of methine protons (ca. 4 ppm, $^3J \approx 5$ Hz), a doublet of ethylene proton (ca. 5 ppm, $^3J \approx 5$ Hz), a broad singlet of NH group of pyridine ring near 8 ppm, signals of pyrimidine amino groups at 11.5 and 12.0 ppm. The ^{1}H NMR spectra of compounds **6a**, **6b** and **7a**, **7c**–**7h** show signals of terminal groups, singlet of pyridine proton at ca. 8 ppm and broad signals of amino groups, which are low-field-shifted (ca. 1 ppm) relative to compounds **4b**, **5c**–**5e**. In the ^{1}H NMR spectra of **10a**, **10b**, besides signals of aromatic protons and pyrimidine NH groups, two doublets at 7.9 and 8.3 ppm (^3J = 8.2 Hz) are present. A singlet of methine proton in Michael adducts **13a** and **14a**, **14b** is located at ca. 5.3 ppm. ^{13}C NMR spectroscopic data are not in contradiction with the proposed structures **4b**, **5c**–**5e**, **6a**, **6b**, **7a**, **7c**–**7h**, **10a**, **10b**.



SCHEME 4

Thus, a number of 5,7-diarylpyrido[2,3-*d*]pyrimidines and their 5,8-dihydro derivatives were synthesized by the reaction of 6-aminouracil (**1**) and 2-thio-6-aminouracil (**2**) with chalcones. The obtained experimental data showed an influence of the catalyst type on the composition of reaction products: basic catalysts decreased yields of the dihydro derivatives whereas acids increased them. Synthetic procedures for 5,8-dihydropyrido[2,3-*d*]-pyrimidines by refluxing of α,β-unsaturated ketones with 6-aminouracil derivatives in glacial acetic acid were developed. The synthesis of pyrido-[2,3-*d*]pyrimidines by the treatment of the same starting compounds in dry DMF with NBS was also proposed. In the case of chalcones containing dimethylamino group, elimination of aryl substituent from position 5 of the pyridopyrimidine ring system was observed. An attempted three-component reaction of aromatic aldehydes and acetophenones with

6-aminouracil derivatives led to 6,6′-diamino-5,5′-(arylmethylene)bis-2-(thioxopyrimidin-4-one)s or 6,6′-diamino-5,5′-(arylmethylene)bis(pyrimidine-2,4-dione)s instead of pyrido[2,3-*d*]pyrimidines.

EXPERIMENTAL

Starting aromatic aldehydes, acetophenones, ethyl cyanoacetate, urea and thiourea are commercially available. All reactions were monitored by TLC on Silufol UV-254 plates using ethyl acetate–chloroform (1:1). Melting points were determined with a Kofler apparatus. IR spectra (in cm^{-1}) were measured on Specord 75-IR in KBr pellets. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 200 MHz (50 MHz for ^{13}C) on a Varian Mercury VX-200 spectrometer and analyzed with ADVASP(tm) Analyzer program (Umatek International Inc.). Chemical shifts are reported in ppm (δ-scale), coupling constants (*J*) in Hz, internal standard was $Si(CH_3)_4$. Melting points and spectral characteristics for compounds **3a**–**3h**, **8a**, **8b** are corresponding to the literature data[16,18–23]. Elemental analysis for C, H, N, S and halogens was made at the Department of Analytical Chemistry of the Institute.

5-(4-Chlorophenyl)-7-(4-methylphenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4-dione (**4b**), 5,7-Diaryl-2-thioxo-5,8-dihydropyrido[2,3-*d*]pyrimidin-4-ones (**5c**–**5e**) and 7-Aryl-2-thioxopyrido[2,3-*d*]pyrimidin-4-ones (**10a**, **10b**). General Procedure (Method *A*)

A solution of 6-aminouracil derivative (**1**, **2**; 0.01 mol) and appropriate chalcone (0.01 mol) in glacial acetic acid (10 ml) was refluxed for 3 h. Then the reaction mixture was cooled down and poured onto crushed ice. The precipitate formed was filtered off and crystallized from ethanol.

5-(4-Chlorophenyl)-7-(4-methylphenyl)-5,8-dihydropyrimido[2,3-d]pyrimidine-2,4-dione (**4b**). Yield 78%. M.p. >300 °C. For $C_{20}H_{16}ClN_3O_2$ (365.8) calculated: 65.67% C, 4.41% H, 9.69% Cl, 11.49% N; found: 65.62% C, 4.47% H, 9.70% Cl, 11.51% N. IR: 3409, 3229, 2843, 2303, 1709, 1662, 1622, 1602, 1542, 1476, 1436, 1396, 1336, 1089, 1016. ^1H NMR: 2.32 s, 3 H (CH_3); 4.54 d, ^3J = 5.1, 1 H (H-5); 5.21 d, ^3J = 5.1, 1 H (H-6); 7.05–7.40 m, 8 H (Ar); 8.10 bs, 1 H (NH-8); 11.58 bs, 1 H (NH-1); 12.00 bs, 1 H (NH-3). ^{13}C NMR: 20.9 (CH_3); 36.9 (C-5); 85.0 (C-4a); 103.1 (C-6); 138.6 (C-7); 146.5 (C-8a); 150.0 (C-2); 163.2 (C-4); 126.3, 128.8, 129.0, 130.5 (CH_{Ar}); 131.1, 131.3, 137.6, 140.3 (C_{Ar}).

7-(4-Chlorophenyl)-5-phenyl-2-thioxo-5,8-dihydropyrido[2,3-d]pyrimidine-4-one (**5c**). Yield 58%. M.p. >300 °C. For $C_{19}H_{14}ClN_3OS$ (367.8) calculated: 62.04% C, 3.84% H, 9.64% Cl, 11.42% N, 8.72% S; found: 62.00% C, 3.89% H, 9.67% Cl, 11.40% N, 8.70% S. IR: 3420, 3235, 2843, 2310, 1720, 1635, 1600, 1480, 1442, 1402, 1329, 1070, 1025. ^1H NMR: 4.55 d, ^3J = 5.1, 1 H (H-5); 5.36 d, ^3J = 5.1, 1 H (H-6); 7.26–7.47 m, 9 H (Ar); 8.17 bs, 1 H (NH-8); 11.60 bs, 1 H (NH-1); 11.98 bs, 1 H (NH-3). ^{13}C NMR: 37.1 (C-5); 90.6 (C-4a); 103.6 (C-6); 140.0 (C-7); 146.6 (C-8a); 150.0 (C-4); 163.4 (C-2); 125.8, 127.8, 128.7, 128.8, 129.1 (CH_{Ar}); 132.4, 133.6, 142.2 (C_{Ar}).

7-(4-Chlorophenyl)-5-(4-methoxyphenyl)-2-thioxo-5,8-dihydropyrido[2,3-d]pyrimidin-4-one (**5d**). Yield 52%. M.p. >300 °C. For $C_{20}H_{16}ClN_3O_2S$ (397.9) calculated: 60.37% C, 4.05% H, 8.91% Cl, 10.56% N, 8.06% S; found: 60.30% C, 4.10% H, 8.90% Cl, 10.50% N, 8.08% S. IR: 3416, 3336, 2849, 2303, 1708, 1658, 1642, 1542, 1509, 1482, 1429, 1402, 1209, 1129, 1002. ^1H NMR: 3.67 s, 3 H (OCH_3); 4.48 d, ^3J = 5.5, 1 H (H-5); 5.33 d, ^3J = 5.5, 1 H (H-6); 6.82–7.48 m, 8 H (Ar); 8.13 bs, 1 H (NH-8); 11.60 bs, 1 H (NH-1); 12.01 bs, 1 H (NH-3).

^{13}C NMR: 36.8 (C-5); 55.7 (OCH_3); 90.7 (C-4a); 105.5 (C-6); 134.1 (C-7); 146.2 (C-8a); 158.5 (C-4); 161.2 (C-2); 114.4, 127.0, 129.2, 129.5 (CH_{Ar}); 132.3, 133.9, 139.2, 140.3 (C_{Ar}).

7-(4-Chlorophenyl)-5-[4-(dimethylamino)phenyl]-2-thioxo-5,8-dihydropyrido[2,3-d]pyrimidin-4-one (**5e**). Yield 67%. M.p. >300 °C. For $C_{21}H_{19}ClN_4OS$ (410.9) calculated: 61.38% C, 4.66% H, 8.63% Cl, 13.63% N, 7.80% S; found: 61.42% C, 4.62% H, 8.61% Cl, 13.68% N, 7.81% S. IR: 3489, 3215, 2843, 2315, 1706, 1660, 1618, 1600, 1531, 1420, 1391, 1222, 1013. ^{1}H NMR: 2.81 s, 6 H ($N(CH_3)_2$); 4.41 d, ^3J = 5.2, 1 H (H-5); 5.32 d, ^3J = 5.2, 1 H (H-6); 6.60–7.48 m, 8 H (Ar); 8.10 bs, 1 H (NH-8); 11.34 bs, 1 H (NH-1); 11.98 bs, 1 H (NH-3). ^{13}C NMR: 37.2 (C-5); 40.5 ($N(CH_3)_2$); 90.2 (C-4a); 105.1 (C-6); 134.0 (C-7); 145.9 (C-8a); 158.9 (C-4); 165.4 (C-2); 114.3, 124.6, 126.5, 127.4 (CH_{Ar}); 132.5, 140.3, 143.0, 147.5 (C_{Ar}).

7-Phenyl-2-thioxopyrido[2,3-d]pyrimidin-4-one (**10a**). Yield 74%. M.p. >300 °C. For $C_{13}H_9N_3OS$ (255.3) calculated: 61.16% C, 3.55% H, 16.46% N, 12.56% S; found: 61.21% C, 3.50% H, 16.48% N, 12.52% S. IR: 3395, 3160, 3050, 2891, 2791, 2309, 1699, 1679, 1612, 1601, 1575, 1500, 1372, 1239, 1177, 1125. ^{1}H NMR: 7.53–8.16 m, 4 H (Ar); 7.87 d, ^3J = 8.2, 1 H (H-6); 8.28 d, ^3J = 8.2, 1 H (5-H); 12.56 bs, 1 H (NH-1); 13.08 bs, 1 H (NH-3). ^{13}C NMR: 112.6 (C-4a); 121.7 (C-6); 137.1 (C-5); 154.8 (C-8a); 158.9 (C-4); 161.2 (C-7); 171.5 (C-2); 129.5, 130.0, 133.4 (CH_{Ar}); 140.1 (C_{Ar}).

7-(4-Methylphenyl)-2-thioxopyrido[2,3-d]pyrimidin-4-one (**10b**). Yield 68%. M.p. >300 °C. For $C_{14}H_{11}N_3OS$ (269.3) calculated: 62.43% C, 4.12% H, 15.60% N, 11.91% S; found: 62.49% C, 4.18% H, 15.58% N, 11.89% S. IR: 3389, 3176, 3050, 2883, 2796, 2316, 1695, 1682, 1615, 1600, 1555, 1502, 1415, 1368, 1242, 1168, 1115, 1068. ^{1}H NMR: 2.36 s, 3 H (CH_3); 7.34–8.06 m, 5 H (Ar); 7.92 d, ^3J = 8.2, 1 H (H-6); 8.33 d, ^3J = 8.2, 1 H (H-5); 12.57 bs, 1 H (NH-1); 13.12 bs, 1 H (NH-3). ^{13}C NMR: 22.1 (CH_3); 112.8 (C-4a); 121.9 (C-6); 137.0 (C-5); 154.5 (C-8a); 158.8 (C-4); 161.4 (C-7); 171.4 (C-2); 126.4, 128.5 (CH_{Ar}); 129.0, 137.9 (C_{Ar}).

5,7-Diphenylpyrido[2,3-*d*]pyrimidine-2,4-dione (**6a**) and
5,7-Diaryl-2-thioxopyrido[2,3-*d*]pyrimidin-4-one (**7a**, **7f**–**7h**).
General Procedure (Method *B*)

A solution of 6-aminouracil derivative (**1**, **2**; 0.01 mol), appropriate chalcone (0.01 mol) and triethylamine (0.01 mol) in dry DMF (5 ml) was refluxed for 3 h. Then the reaction mixture was cooled down and diluted with methanol. The precipitate formed was filtered off and crystallized from ethanol.

5-(4-Chlorophenyl)-7-(4-methylphenyl)pyrido[2,3-*d*]pyrimidine-2,4-dione (**6b**) and
5,7-Diaryl-2-thioxopyrido[2,3-*d*]pyrimidin-4-one (**7a**, **7c**–**7h**).
General Procedure (Method *C*)

A solution of 6-aminouracil derivative (**1**, **2**; 0.01 mol), appropriate chalcone (0.01 mol) and NBS (0.01 mol) in of dry DMF (5 ml) was refluxed for 3 h. Then the reaction mixture was cooled down and diluted with methanol. The precipitate formed was filtered off and crystallized from ethanol.

5,7-Diphenylpyrido[2,3-d]pyrimidine-2,4-dione (**6a**). Yield 75%. M.p. 275 °C. For $C_{19}H_{13}N_3O_2$ (315.3) calculated: 72.37% C, 4.16% H, 13.33% N; found: 72.40% C, 4.10% H, 13.34% N. IR: 3363, 3189, 3036, 2843, 2309, 1702, 1682, 1600, 1550, 1490, 1444, 1400, 1370, 1288, 1150, 1009. ^{1}H NMR: 7.40–8.16 m, 10 H (Ar); 7.48 s, 1 H (H-6); 12.10 bs, 1 H (NH-1); 12.88 bs, 1 H (NH-3). ^{13}C NMR: 106.1 (C-4a); 118.2 (C-6); 150.5 (C-8a); 153.7 (C-2); 154.1 (C-5); 159.1 (C-7); 161.6 (C-4); 127.7, 127.8, 128.2, 128.8 (CH_{Ar}); 129.1, 130.8, 137.0, 139.1 (C_{Ar}).

5-(4-Chlorophenyl)-7-(4-methylphenyl)pyrido[2,3-d]pyrimidine-2,4-dione (**6b**). Yield 69%. M.p. >300 °C. For $C_{20}H_{14}ClN_3O_2$ (363.8) calculated: 66.03% C, 3.88% H, 9.75% Cl, 11.55% N; found: 66.13% C, 3.85% H, 9.72% Cl, 11.54% N. IR: 3416, 3016, 3043, 2850, 2309, 1715, 1695, 1655, 1599, 1575, 1548, 1488, 1408, 1362, 1262, 1188, 1088, 1015. ^{1}H NMR: 2.37 s, 3 H (CH_3); 7.08–8.22 m, 8 H (Ar); 7.59 s, 1 H (H-6); 12.12 bs, 1 H (NH-1); 12.94 bs, 1 H (NH-3). ^{13}C NMR: 21.0 (CH_3); 106.0 (C-4a); 119.3 (C-6); 150.8 (C-8a); 153.6 (C-2); 154.8 (C-5); 156.3 (C-7); 161.7 (C-4); 123.2, 127.2, 128.6, 132.8 (CH_{Ar}); 133.4, 136.6, 137.8, 145.3 (C_{Ar}).

5,7-Diphenyl-2-thioxopyrido[2,3-d]pyrimidin-4-one (**7a**). Yield 60%. M.p. >300 °C. For $C_{19}H_{13}N_3OS$ (331.4) calculated: 68.86% C, 3.95% H, 12.68% N, 9.68% S; found: 68.80% C, 3.99% H, 12.69% N, 9.64% S. IR: 3397, 3170, 3043, 2855, 2329, 1708, 1688, 1648, 1600, 1548, 1488, 1402, 1368, 1255, 1168, 1122, 1062, 1028. ^{1}H NMR: 7.41–8.20 m, 10 H (Ar); 7.63 s, 1 H (H-6); 12.29 bs, 1 H (NH-1); 13.05 bs, 1 H (NH-3). ^{13}C NMR: 106.2 (C-4a); 118.6 (C-6); 150.7 (C-8a); 153.6 (C-5); 158.7 (C-4); 162.3 (C-7); 175.2 (C-2); 123.1, 126.1, 126.6, 128.7 (CH_{Ar}); 128.5, 129.0, 141.7, 146.0 (C_{Ar}).

7-(4-Chlorophenyl)-5-phenyl-2-thioxopyrido[2,3-d]pyrimidin-4-one (**7c**). Yield 66%. Melting point and spectral data correspond to literature data[11].

7-(4-Chlorophenyl)-5-(4-methoxyphenyl)-2-thioxopyrido[2,3-d]pyrimidin-4-one (**7d**). Yield 52%. M.p. >300 °C. For $C_{20}H_{14}ClN_3O_2S$ (395.9) calculated: 60.68% C, 3.56% H, 8.96% Cl, 10.61% N, 8.10% S; found: 60.72% C, 3.52% H, 8.97% Cl, 10.58% N, 8.12% S. IR: 3376, 3229, 3069, 2829, 2323, 1715, 1708, 1682, 1601, 1548, 1515, 1455, 1402, 1362, 1242, 1182, 1168, 1082, 1022, 1008. ^{1}H NMR: 3.81 s, 3 H (OCH_3); 6.97–8.25 m, 8 H (Ar); 7.58 s, 1 H (H-6); 12.33 bs, 1 H (NH-1); 13.02 bs, 1 H (NH-3). ^{13}C NMR: 55.2 (OCH_3); 106.4 (C-4a); 118.2 (C-6); 151.7 (C-8a); 153.8 (C-5); 158.4 (C-4); 162.0 (C-7); 175.2 (C-2); 117.9, 129.5, 130.0, 133.4 (CH_{Ar}); 134.7, 138.7, 144.9, 158.2 (C_{Ar}).

7-(4-Chlorophenyl)-5-[4-(dimethylamino)phenyl]-2-thioxopyrido[2,3-d]pyrimidin-4-one (**7e**). Yield 65%. M.p. >300 °C. For $C_{21}H_{17}ClN_4OS$ (408.9) calculated: 61.68% C, 4.19% H, 8.67% Cl, 13.70% N, 7.84% S; found: 61.72% C, 4.15% H, 8.65% Cl, 13.72% N, 7.80% S. IR: 3389, 3129, 3043, 2843, 2316, 1703, 1695, 1642, 1600, 1542, 1495, 1408, 1362, 1248, 1188, 1122, 1095, 1015. ^{1}H NMR: 2.96 s, 6 H ($N(CH_3)_2$); 6.72–8.27 m, 8 H (Ar); 7.61 s, 1 H (H-6); 12.27 bs, 1 H (NH-1); 12.93 bs, 1 H (NH-3). ^{13}C NMR: 40.6 ($N(CH_3)_2$); 105.8 (C-4a); 118.1 (C-6); 151.4 (C-8a); 153.0 (C-5); 158.1 (C-4); 162.1 (C-7); 175.2 (C-2); 112.1, 130.0, 130.1, 132.4 (CH_{Ar}); 133.4, 138.8 146.3, 146.7 (C_{Ar}).

7-(4-Chlorophenyl)-5-(4-nitrophenyl)-2-thioxopyrido[2,3-d]pyrimidin-4-one (**7f**). Yield 40%. M.p. >300 °C. For $C_{19}H_{11}ClN_4O_3S$ (410.8) calculated: 55.55% C, 2.70% H, 8.63% Cl, 13.64% N, 7.80% S; found: 55.49% C, 2.76% H, 8.62% Cl, 13.66% N, 7.82% S. IR: 3376, 3169, 3070, 2489, 2309, 1708, 1682, 1642, 1600, 1555, 1515, 1402, 1348, 1242, 1175, 1088, 1008. ^{1}H NMR: 7.61–8.27 m, 8 H (Ar); 7.74 s, 1 H (H-6); 12.44 bs, 1 H (NH-1); 13.16 bs, 1 H (NH-3). ^{13}C NMR: 106.3 (C-4a); 118.0 (C-6); 153.4 (C-8a); 153.6 (C-5); 158.2 (C-4); 162.2 (C-7); 175.3 (C-2); 126.9, 129.5, 129.9, 133.2 (CH_{Ar}); 134.4, 138.8, 146.3, 150.5 (C_{Ar}).

5-(4-Fluorophenyl)-7-phenyl-2-thioxopyrido[2,3-d]pyrimidin-4-one (**7g**). Yield 58%. M.p. >300 °C. For $C_{19}H_{12}FN_3OS$ (349.4) calculated: 65.32% C, 3.46% H, 12.03% N, 9.18% S; found: 65.28% C, 3.50% H, 12.05% N, 9.14% S. IR: 3403, 3156, 3056, 2849, 2936, 1702, 1675, 1648, 1599, 1548, 1468, 1408, 1362, 1235, 1182, 1135. ^{1}H NMR: 7.22–8.20 m, 9 H (ArH); 7.63 s, 1 H (H-6); 12.37 bs, 1 H (NH-1); 13.01 bs, 1 H (NH-3). ^{13}C NMR: 107.2 (C-4a); 118.4 (C-6); 153.2 (C-8a); 153.5 (C-5); 158.2 (C-4); 162.6 (C-7); 175.2 (C-2); 119.3, 126.4, 128.7, 129.0, 134.6 (CH_{Ar}); 141.7, 144.3, 158.5 (C_{Ar}).

5-[4-Methoxycarbonyl)phenyl]-7-phenyl-2-thioxopyrido[2,3-d]pyrimidin-4-one (**7h**). Yield 52%. M.p. >300 °C. For $C_{21}H_{15}N_3O_3S$ (389.4) calculated: 64.77% C, 3.88% H, 10.79% N, 8.23% S; found: 64.82% C, 3.82% H, 10.83% N, 8.24% S. IR: 3416, 3209, 3050, 2843, 2316, 1705, 1680, 1650, 1599, 1550, 1475, 1408, 1368, 1282, 1175, 1135, 1102, 1028. ^{1}H NMR: 3.88 s, 3 H ($COOCH_3$); 7.50–8.24 m, 9 H (Ar); 7.67 s, 1 H (H-6); 12.39 bs, 1 H (NH-1); 13.10 bs, 1 H (NH-2). ^{13}C NMR: 51.8 ($COCH_3$); 106.5 (C-4a); 118.2 (C-6); 153.7 (C-8a); 153.9 (C-5); 158.2 (C-4); 162.1 (C-7); 166.3 ($COOCH_3$); 175.3 (C-2); 126.4, 128.6 128.7, 129.0, 132.1 (CH_{Ar}); 135.0, 141.7, 148.8 (C_{Ar}).

5-(4-Chlorophenyl)-7-(4-methylphenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4-dione (**6b**) and 5,7-Diaryl-2-thioxo-5,8-dihydropyrido[2,3-*d*]pyrimidin-4-ones (**7c**–**7e**) by Oxidation. General Procedure

A solution of 5,8-dihydropyrido[2,3-*d*]pyrimidine derivative (**4b**, **5c**–**5e**; 0.005 mol) and NBS (0.005 mol) in dry DMF (3 ml) was refluxed for 2 h. Then the reaction mixture was cooled down and diluted with methanol. The precipitate formed was filtered off and crystallized from ethanol to give products identical with compounds prepared by methods given above. The yields are given in Table I.

Reaction of 6-Aminouracil Derivatives with Aromatic Aldehydes and Acetophenone. General Procedure

A solution of 6-aminouracil derivative (**1**, **2**; 0.01 mol), appropriate aromatic aldehyde (0.01 mol) and acetophenone (0.01 mol) in glacial acetic acid (10 ml) (method *A*) or in dry DMF (5 ml) (method *B*) was refluxed for 3 h. Then the reaction mixture was cooled down and poured on crushed ice (method *A*) or diluted with methanol (method *B*). The precipitate formed was filtered off and crystallized from ethanol.

6,6′-Diamino-5,5′-[(4-methylphenyl)methylene]bispyrimidine-2,4-dione (**13a**). Yield 38%. M.p. >300 °C. For $C_{16}H_{16}N_6O_4$ (356.3) calculated: 53.93% C, 4.53% H, 23.58% N; found: 53.99% C, 4.49% H, 23.60% N. IR: 3363, 3156, 2776, 2325, 1708, 1662, 1622, 1598, 1515, 1448, 1402, 1282, 1168, 1088, 1022. ^{1}H NMR: 1.89 s, 3 H (CH_3); 5.25 s, 1 H (CH); 6.67 bs, 4 H (NH_2-5,5′); 6.80–7.10 m, 4 H (Ar); 11.23 bs, 1 H (NH-1); 11.87 bs, 1 H (NH-3). ^{13}C NMR: 22.4 (CH_3); 30.1 (CH); 126.4 (C-5,5′); 154.5 (C-2); 160.1 (C-4); 163.3 (C-6,6′); 125.6, 132.6 (CH_{Ar}); 133.5, 145.2 (C_{Ar}).

6,6′-Diamino-2,2′-dithioxo-5,5′-[(4-chlorophenyl)methylene]bispyrimidin-4-ones (**14b**). Yield 42%. M.p. >300 °C. For $C_{15}H_{13}ClN_6O_2S_2$ (408.9) calculated: 44.06% C, 3.20% H, 8.67% Cl, 20.55% N, 15.68% S; found: 44.10% C, 3.15% H, 8.68% Cl, 20.57% N, 15.66% S. IR: 3336, 3156, 2849, 2304, 1705, 1665, 1640, 1599, 1535, 1435, 1242, 1202, 1175, 1008. ^{1}H NMR: 5.30 s, 1 H (CH); 6.74 bs, 4 H (NH_2-5,5′); 6.90–7.30 m, 4 H (Ar); 11.79 bs, 1 H (NH-1); 12.02 bs, 1 H (NH-3). ^{13}C NMR: 32.3 (CH); 131.2 (C-5,5′); 158.1 (C-4); 163.8 (C-6,6′); 179.1 (C-2); 128.4, 129.3 (CH_{Ar}); 132.8, 148.5 (C_{Ar}).

6,6′-Diamino-2,2′-dithioxo-5,5′-[(4-fluorophenyl)methylene]bispyrimidin-4-ones (**14c**). Yield 45%. M.p. >300 °C. For $C_{15}H_{13}FN_6O_2S_2$ (392.4) calculated: 45.91% C, 3.34% H, 21.42% N, 16.34% S; found: 45.86% C, 3.38% H, 21.44% N, 16.36% S. IR: 3370, 3145, 2766, 2315, 1701, 1665, 1609, 1595, 1432, 1400, 1177, 1065, 1002. ^{1}H NMR: 5.26 s, 1 H (CH); 6.69 bs, 4 H (NH_2-5,5′); 6.90–7.20 m, 4 H (Ar); 10.29 bs, 1 H (NH-1); 12.50 bs, 1 H (NH-3). ^{13}C NMR: 31.4 (CH); 131.3 (C-5,5′); 157.9 (C-4); 163.9 (C-6,6′); 179.0 (C-2); 121.2, 130.0 (CH_{Ar}); 146.7, 155.5 (C_{Ar}).

TABLE I
Synthesis of pyrido[2,3-*d*]pyrimidines

Starting materials		Reaction products		
Chalcones	Amine	Compound	Method[a]	Yield, %
3b	**1**	**4b**	A	78
3c	**2**	**5c**	A	58
3d	**2**	**5d**	A	52
3e	**2**	**5e**	A	67
3a	**1**	**6a**	A	75
3b	**1**	**6b**	C	69
3a	**2**	**7a**	B/C	60[b]
3c	**2**	**7c**	C	66
3d	**2**	**7d**	C	52
3e	**2**	**7e**	C	65
3f	**2**	**7f**	B/C	40[b]
3g	**2**	**7g**	B/C	58[b]
3h	**2**	**7h**	B/C	52[b]
8a	**2**	**10a**	A	74
8b	**2**	**10b**	A	68
Aldehydes				
11a	**1**	**13a**	A/B	38[c]
11b	**2**	**14b**	A/B	42[c]
11c	**2**	**14c**	A/B	45[c]
5,8-Dihydropyrido[2,3-*d*]pyrimidines				
4b	–	**6b**	B	63
5c	–	**7c**	B	62
5d	–	**7d**	B	60
5e	–	**7e**	B	65

[a] *A*, reflux in glacial acetic acid; *B*, reflux in DMF with NEt_3; *C*, reflux in DMF with NBS. [b] Method *C*. [c] Method *B*.

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