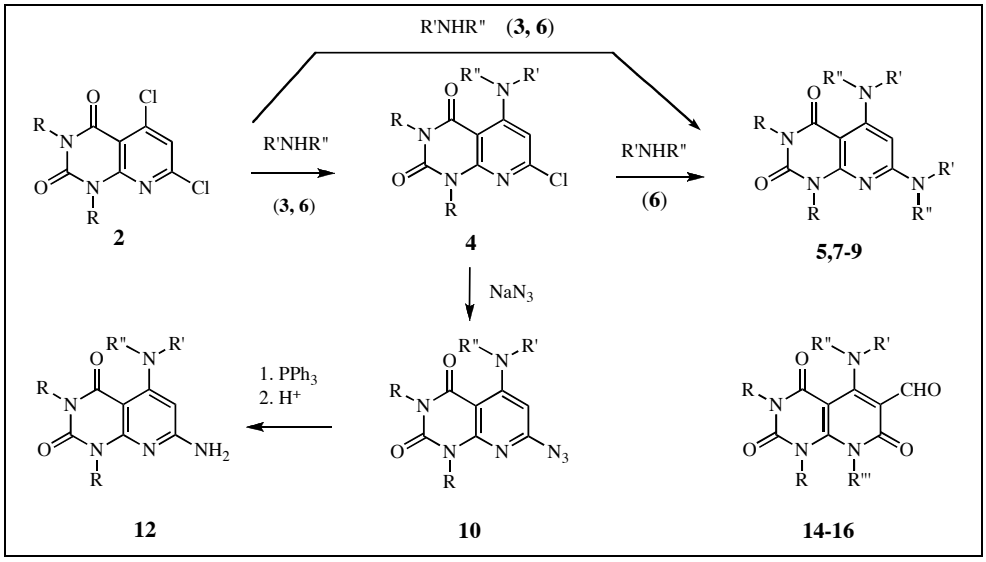
Synthesis of 5-Mono- and 5,7-Diamino-pyrido[2,3-*d*]-pyrimidinediones with Potential Biological Activity by Regioselective Amination [1]

Dang Van Tinh[a] and Wolfgang Stadlbauer* [b]

[a]University of Medicine and Pharmacy at Hochiminh City
41 Dinh Tien Hoang Str., Dist. 1, Ho Chi Minh City (Viet Nam)
[b] Institute of Chemistry, Organic Synthesis Group, Karl-Franzens University of Graz,
Heinrichstrasse 28, A-8010 Graz (Austria)
wolfgang.stadlbauer@uni-graz.at
Received October 2, 2007



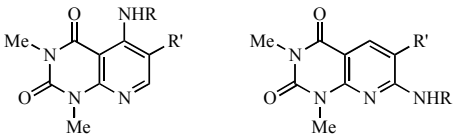
5-Alkyl-/arylamino- and 5,7-dialkyl/arylamino-pyrido[2,3-*d*]pyrimidine-2,4-diones (**4,5, 7-9**) were prepared from the corresponding 5,7-dichloro-pyrido[2,3-*d*]pyrimidine-2,4-diones **2** with aliphatic and aromatic amines **3** and **6** in a regioselective reaction. The 7-monoazides **10**, obtained by azidation of 5-amino-7-chloro derivatives **4**, were converted to iminophosphoranes by reaction with triphenyl-phosphane *via* Staudinger reaction. Hydrolysis with aqueous acetic acid produced in one step 7-unsubstituted-amino-pyrido[2,3-*d*]pyrimidine-2,4-diones **12**. In a similar amination reaction, 5-chloropyrido[2,3-*d*]pyrimidine-2,4,7-triones **13** were aminated and formylated to 5-alkyl/arylamino-6-formyl derivatives **14**-**16** in a combined one-step-reaction with bulky arylamines or alkylamines in the presence of dimethylformamide.

J. Heterocyclic Chem., **45**, 821 (2008).

INTRODUCTION

Pyrido[2,3-*d*]pyrimidinediones form a class of fused heterocyclic compounds which reveal interesting pharmacological and biological properties generated from the two biological interesting structural elements, the uracil and the pyridine part, present in a number of biological active products. Thus, they have been used as effective antitumor agents, as antibacterial, anticonvulsant or enzyme inhibitor agents [2]. Amino-substituted pyrido-[2,3-*d*]pyrimidinediones with structures **A** and **B** have been recently investigated [3]. They were found to bind to adenosine A_1 and A_{2A} receptor in micromolar concentration and the structure-activity relationship for pyrido[2,3-*d*]pyrimidinediones as ligands of adenosine receptors has been studied.

Scheme 1



(R' : H, CN, $CO_2C_2H_5$)

These findings prompted us to study the synthesis of 5-amino- and 5,7-diamino-pyrido[2,3-*d*]pyrimidinediones having similar structural elements as the above mentioned structures **A** and **B**. The synthetic routes described in ref. [3] involve either a 2-step reaction *via* a Vilsmeier formylation and ring closure with acetonitrile derivatives, or cyclization of dimethyluracil with ethoxymethylene-

malonate, followed by a chlorination step. We started according to our earlier studies on pyrido[2,3-*d*]pyrimidinediones from substituted uracils and malonate [4b] to obtain in one step 5-hydroxy-pyrido[2,3-*d*]pyrimidine-2,4,7-triones **1**, which should give in a chlorination step the starting material for amination. The dichloro-pyridine part of the pyrido[2,3-*d*]pyrimidinedione structure **2** should have similar properties as observed in well investigated amination reactions of dichloroquinolines [5]; in this reaction with several amines, 2,4-diamino-quinolines, 2-amino-4-chloroquinolines or 4-amino-2-chloroquinolines were obtained. Kinetic studies indicate that the chloro atom in position 4 of 2,4-dichloro-quinolines is about two times more reactive towards nucleophiles [6] and predominantly an addition-elimination mechanism is observed [7].

In this contribution the transformation of such amination reactions to the pyrido[2,3-*d*]pyrimidinedione heterocyclic sytstem is described. Furthermore, a synthetic sequence *via* a 2-step reaction of azides to amines is developed, similar as described earlier in the quinoline series [8].

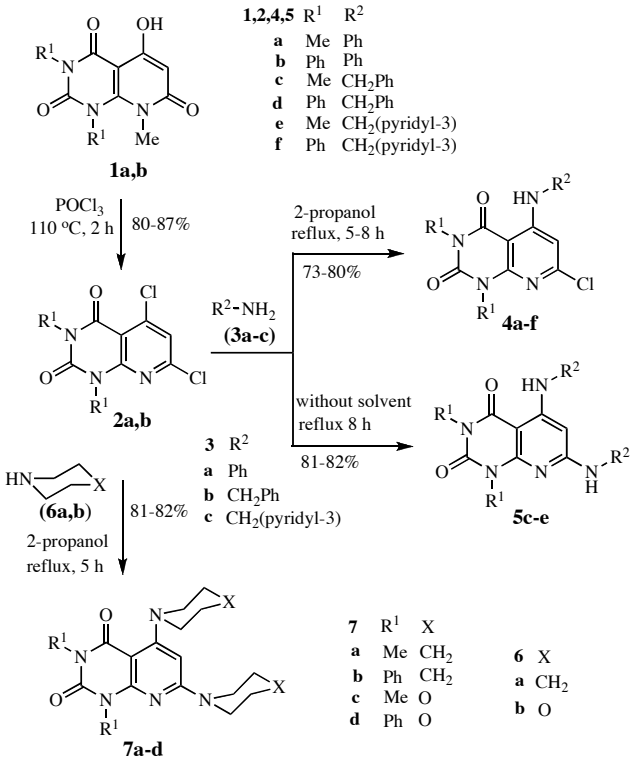
RESULTS AND DISCUSSION

5,7-Dichloro-pyrido[2,3-*d*]pyrimidine-2,4-diones **2a,b**, which were used as starting materials for regioselective amination reactions, were obtained from 5-hydroxy-8-methyl-pyrido[2,3-*d*]pyrimidine-2,4,7-triones **1a,b** [4b]. During the chlorination reaction, not only the oxygen atom in position 5 was substituted by a chloro atom, but also the methyl group in position 8 was cleaved already at rather mild reaction conditions to form the tautomeric 7-hydroxy intermediate. This hydroxy group was then in turn converted to the 7-chloro group. The methyl groups of **1a** at position 1 and 3 remained unchanged. Such a demethylation cleavage is also known from the 4-hydroxypyridone series [9].

When dichloro compounds **2a,b** were heated with aniline (**3a**) under reflux in 2-propanol as the solvent, in excellent yields as the only products the mono-amination derivatives, 7-chloro-5-phenylamino-pyrido[2,3-*d*]pyrimidinediones **4a,b** were isolated. Comparison of ^{1}H nmr data of dichloro compound **2** and anilino compound **4** indicates the appearence of an amine signal in **4** at δ 10.85-10.90 ppm caused by the formation of the -NH-group. To exclude a 7-anilino structure, spectra of **4a,b** were compared with those of 5-phenylaminopyrido-[2,3-*d*]pyrimidinetriones, obtained from its 5-tosyloxy derivative with aniline [4b]. Both ^{1}H NMR spectra showed the proton signal of the aniline-NH at δ 10.10-10.90 ppm, which is a proof for substitution at the position 5 and not at 7. Also ^{13}C nmr data confirm the structure of **4**.

The reaction of 5,7-dichloro-pyrido[2,3-*d*]pyrimidinediones **2a,b** with benzylamine (**3b**) or 3-picolylamine (**3c**) in refluxing 2-propanol as the solvent gave similar results as obtained with aniline: again 5-mono-amination products such as 5-benzylamino-7-chloro- and 7-chloro-5-(3-picolylamino)-pyrido[2,3-*d*]pyrimidinedione **4c-f** were obtained. ^{1}H nmr data showed a shift to lower δ-values: the NH signals appeared in **4c-f** between δ 9.55 and 9.70 ppm.

Scheme 1



When the reaction of dichloro compounds **2a,b** with amines **3b,c** was carried out using the amine as the solvent, a substitution of the both chloro atoms in **2** was observed and 5,7-dibenzylamino- or 5,7-di-(3-picolyl-amino)-pyrido[2,3-*d*]pyrimidinediones **5c-e** were obtained in excellent yields. The ^{1}H nmr data of **5** indicated the appearence of an additional signal of the NH at C-7 at δ 4.50-5.20 ppm (besides the signal of the NH at C-5 at δ 9.10-9.40 ppm). These different values of the NH signals could be explained by a shift of the NH in position 5 by hydrogen bonding with the 4-oxo group, whereas the NH in position 7 without any neighbour groups did not show a shift. So it was possible due to the different reactivity of the chloro atoms in position 5 and 7 to get in a simple way mono- or diaminated products **4** and **5**.

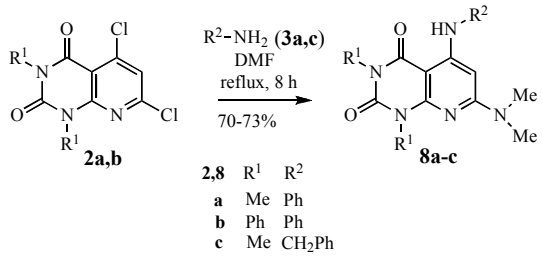
The reaction of 5,7-dichloro compounds **2a,b** with secondary alkyl amines such as piperidine (**6a**) or

morpholine (**6b**) gave - in contrast to primary alkylamines **3b,c** - already in 2-propanol under reflux conditions a substitution of both chloro atoms leading to 5,7-dipiperidino- and 5,7-dimorpholino-pyrido[2,3-*d*]pyrimidinediones **7a-d**. It was not possible when using lower reaction temperatures to obtain a mono-aminated derivative.

The reaction of 5,7-dichloro compounds **2a,b** with aniline (**3a**) both in refluxing 2-propanol or at higher reaction temperatures using refluxing aniline as the solvent, gave only a substitution of the chloro atom at the position 5. When dimethylformamide as a high boiling solvent was applied to raise the reactivity and to force a di-substitution, a substitution of the both chloro atoms was observed. Surprisingly, the second chloro atom at position 7 was not replaced by aniline, but structure elucidation revealed the presence of a dimethylamino group. The formation of 7-dimethylamino-5-phenylamino-pyrido[2,3-*d*]pyrimidinediones **8a,b** can only be explained by decomposition of dimethylformamide used as the solvent and substitution of the 7-chloro substituent by the resulting dimethylamine. ^{1}H nmr data of **8** indicate the appearence of the already known phenylamine NH signal in at δ 10.50-10.60 ppm formed by the substitution of the 5-chloro atom, and an additional dimethylamine signal at δ 2.75-3.07. The reaction of the 5,7-dichloro compound **2a** with benzylamine (**3b**) in dimethylformamide gave in good yields 5-benzylamino-7-dimethylamino-pyrido[2,3-*d*]pyrimidine-2,4-dione (**8c**), similar as observed with aniline.

The meanwhile obtained results show a significant difference in the reactivity of the chloro atoms at position 5 and 7 which allowed us to obtain in one-pot reactions either mono- or diaminated pyrido[2,3-*d*]pyrimidinediones **4**, **5**, **7** and **8**.

Scheme 3

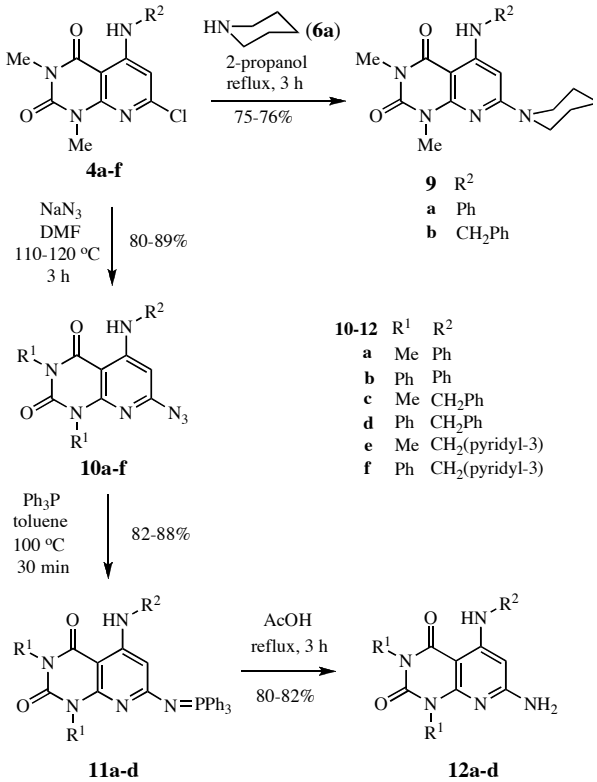


To get other mixed diamines, a sequential amination reaction was applied, in the first step with less reactive amines or by mild reaction conditions, which gave only 5-amino products **4**. In the second step, with more reactive amines such as piperidine (**6a**) the reaction at C-7 took place, and with 2-propanol as the solvent we obtained in good yields the mixed amines, 7-piperidino-pyrido[2,3-*d*]-pyrimidinediones **9a,b**, having at position 5 either a phenylamino- or a benzylamino group. At these reaction conditions no displacement of the primary introduced amine at position 5 was observed.

Whereas N-substituted amines **4, 5, 7**-**9** are amenable in good yields by direct amination, the introduction of an unsubstituted amino group showed some difficulties. Direct amination with ammonia produced a mixture of decomposition products, and debenzylation of **4c,d** destroyed the 7-chloro group. So another pathway *via* the introduction of the azido group followed by a Staudinger and an Aza-Wittig reaction, which was applied in our lab several times (*e.g.* ref. [8,4a]), was started. When dichloro-pyrido[2,3-*d*]pyrimidinediones **2a,b** were heated with sodium azide in dry dimethylformamide at room temperature for 2 hours, in good yields azides of pyrido[2,3-*d*]pyrimidinediones were isolated; however, these compounds were rather unstable. The characteristic azido infrared signals could be detected, but further purification or exact structural assignment failed. Attempts to convert the azides to iminophosphoranes as more stable intermediates by reaction with triphenylphosphane *via* a Staudinger reaction produced a mixture of compounds, which could not be purified sufficiently for structure elucidation and further reactions.

In contrast to the unstable azides described above, 7-azido-pyrido[2,3-*d*]pyrimidinediones were prepared easily from the corresponding 5-amino-substituted-7-

Scheme 4



chloro-compounds **4**. Reaction of 7-chloro-5-amino-substituted compounds **4a-f** with sodium azide in dimethylformamide gave 7-azido-5-amino-substituted compounds **10a-f** in good yields and already in a pure form.

Heterocyclic azides having a ring-nitrogen in ortho-position are known to exist either in the openchain azido-form or in the cyclized tautomeric tetrazolo form [10]. In contrast to the findings in the quinoline series [8], the 7-monoazides **10** showed strong azide signals in the infrared spectra which reveals that the equilibrium is shifted in 7-azido-pyrido[2,3-*d*]pyrimidinediones **10** to the azide form.

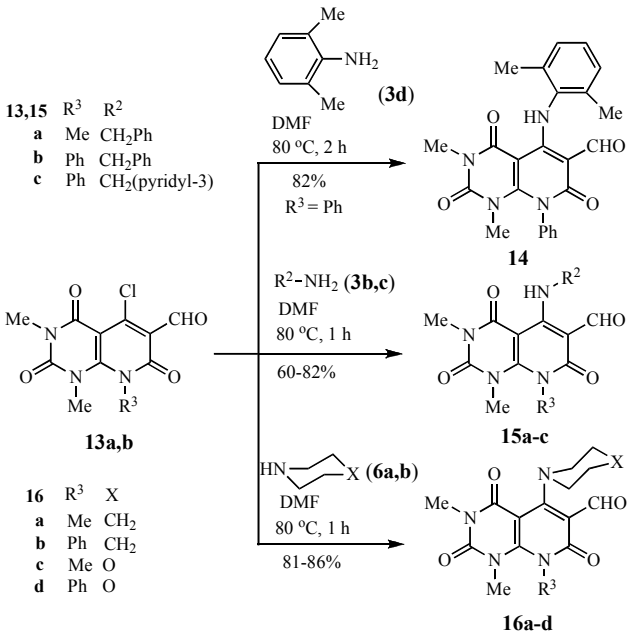
To perform a chemical structural assignment and for the synthetic aim, the 7-monoazido-pyrido[2,3-*d*]pyrimidinediones **10a-d** were converted to iminophosphoranes **11a-d** by reaction with triphenylphosphane *via* a Staudinger reaction. Hydrolysis with aqueous acetic acid produced in one step 7-amino-pyrido[2,3-*d*]pyrimidinediones **12a-d**. The ^{1}H nmr spectra of 7-amino compounds **12a-d** showed the NH_2 protons at δ 4.50-6.70 ppm; the 5-NH signals were observed as expected between 9.10-11.40 ppm, depending on the nature of the amino substituent.

The investigated amino-pyridopyrimidinediones of type **A** and **B** [3] (Scheme 1) bear in many cases an electron withdrawing group in position 6, such as an ester or cyano substituent, which was observed to change Adenosine A_{2A} receptor affinity. So we intended to introduce a formyl group as a versatile substituent at position 6 in a reaction similar to the Vilsmeier formylation using dimethylformamide as formylation agent. From our earlier studies [4b] we knew that amination of 5-chloro-6-formyl-pyrido[2,3-*d*]pyrimidinetriones **13** resulted in a subsequent cyclization of the 5-arylamino substituent with the 6-formyl group to give benzo[*b*]-pyrido[4,5-*h*]1,6-naphthyridinetrione derivatives.

To stop the reaction at the amination step, **13b** was reacted with 2,6-dimethylaniline, which is unable to cyclize in *ortho*-position. This amination reaction gave in excellent yields 6-formyl-1,3-dimethyl-5-(2,6-dimethyl-phenylamino)-8-phenyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (**14**). ^{1}H nmr data of **14** showed the NH signal at δ 11.88 ppm. A differential scanning calorimetry (DSC) plot of **14** revealed that no cyclization of the 2,6-dimethylanilino substituent with the formyl group took place; the diagram contained only the melting point of the amine **14**. Amination of chloro compounds **13a-c** in position 5 with benzylamine and 3-picolylamine (**3b,c**) as aliphatic primary amines could be carried out under mild conditions to afford in good yields 5-alkylamino derivatives **15a-c**. No further reaction with the formyl group was observed. With morpholine and piperidine (**6a,b**) 5-alkylamino derivatives **16a-d** were formed in excellent yields.

In conclusion, we have developed a regioselective amination on 5,7-dichloro-pyrido[2,3-*d*]pyrimidinediones **2**. Due to the different reactivity of the chloro atoms in position 5 and 7, a regioselective mono-amination at position 5 and a subsequent amination reaction with different, however more reactive amines at position 7 was achieved. Unsubstituted amino groups could be introduced at position 7 *via* azidation followed by Staudinger and Aza-Wittig reaction. As additional substituent the formyl group was introduced at position 5 by a Vilsmeier type reaction.

Scheme 5



EXPERIMENTAL

Melting points were obtained on a Gallenkamp Melting Point Aparatus, Mod. MFB 595 in open capillary tubes. ^{1}H and ^{13}C nmr spectra were recorded on a Bruker AMX 360 instrument (360 or 90 MHz) or on a Bruker Avance DRX 500 instrument (500 or 125 MHz). Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ-units. The solvent was $CDCl_3$ unless otherwise stated. Infrared spectra were taken on a Mattson Galaxy Series FTIR 7020 instrument with potassium bromide discs. Elemental analyses were performed on a Fisons EA 1108 C,H,N-automatic analyzer and are within ± 0.4 of the theoretical percentages. Mass spectra were obtained from a HP 1100 LC/MSD mass spectral instrument (positive or negative APCI ion source, 50–200 V, nitrogen). Calorimetric data were obtained on a Rheometric Scientific DSC-Plus instrument with the software Orchestrator V6.5.8. between 25 - 700 °C, a heating rate of 2-10 °C/min, and 1.5-3 mg compound in sealed aluminium crucibles (11 bar).

All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silicagel F-254 (Merck) plates using uv light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

5,7-Dichloro-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2a). A mixture of 5-hydroxypyrido[2,3-*d*]pyrimidine **1a** [4b] (2.37 g, 10 mmol) in phosphoryl chloride (20 mL) was heated under reflux for 2-3 hours. Then the excess solvent was removed by distillation, the residue poured into ice/water (200 mL) and brought to pH = 6-7 with 2 *N* aq. sodium hydroxide. The obtained precipitate was filtered by suction, washed with water and dried. The yield was 1.80 g (80%), colorless prisms, mp 247-250 °C (dimethylformamide); ir: 3085 w, 1715 s, 1670 s cm^{-1}; ^1H nmr: δ 3.46 and 3.70 (2 s, 2x3 H, 2 NMe), 7.25 (s, 1 H, 6-H). *Anal.* Calcd. for $C_9H_7Cl_2N_3O_2$ (260.08): C, 41.56; H, 2.71; N, 16.16. Found: C, 41.41; H, 2.55; N, 16.08.

5,7-Dichloro-1,3-diphenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2b). This compound was obtained from 5-hydroxypyrido[2,3-*d*]pyrimidine **1b** [3b] (3.13 g, 10 mmol) as described for **2a**; the yield was 3.16 g (82%), colorless prisms, mp 286-288 °C (dimethylformamide/ethanol); ir: 3080 w, 1715 s, 1670 s cm^{-1}; ^1H nmr: δ 7.25 (s, 1 H, 6-H), 7.28-7.35 (m, 4 H, ArH), 7.45-7.55 (m, 6 H, ArH). *Anal.* Calcd. for $C_{19}H_{11}Cl_2N_3O_2$ (384.22): C, 59.40; H, 2.89; N, 10.94. Found: C, 59.07; H, 2.84; N, 10.89.

7-Chloro-1,3-dimethyl-5-phenylaminopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4a). A mixture of 5,7-dichloropyrido[2,3-*d*]pyrimidine **2a** (2.60 g, 10 mmol) and aniline (**3a**) (4.70 g, 50 mmol) in 2-propanol (20 mL) was heated under reflux for 8 hours with intensive stirring. After cooling, the solvent was evaporated under reduced pressure, and the residue was digested with water (20 mL). The formed precipitate was collected by suction, washed with water and dried. The yield was 2.53 g (80%), colorless prisms, mp 197-199 °C (dimethylformamide/ethanol); ir: 3220 w, 1710 s, 1650 s cm^{-1}; ^1H nmr: δ 3.45 and 3.65 (2 s, 2x3 H, 2 NMe), 6.60 (s, 1 H, 6-H), 7.25-7.30 (m, 3 H, ArH), 7.42-7.48 (m, 2 H, ArH), 10.90 (s, 1 H, NH). *Anal.* Calcd. for $C_{15}H_{13}ClN_4O_2$ (316.75): C, 56.88; H, 4.14; N, 17.69. Found: C, 57.13; H, 4.02; N, 17.53.

7-Chloro-1,3-diphenyl-5-phenylaminopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4b). This compound was obtained from 5,7-dichloropyrido[2,3-*d*]pyrimidine **2b** (3.84 g, 10 mmol) and aniline (**3a**) (4.70 g, 50 mmol) in 2-propanol (20 mL) as described for **4a**; the yield was 3.43 g (78%), colorless prisms, mp 228-231 °C (ethanol); ir: 3220 w, 1715 s, 1660 s cm^{-1}; ^1H nmr: δ 6.68 (s, 1 H, 6-H), 7.20-7.55 (m, 15 H, ArH), 10.85 (s, 1 H, NH). *Anal.* Calcd. for $C_{25}H_{17}ClN_4O_2$ (440.89): C, 68.11; H, 3.89; N, 12.71. Found: C, 67.89; H, 3.82; N, 12.79.

5-Benzylamino-7-chloro-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4c). A mixture of 5,7-dichloropyrido[2,3-*d*]pyrimidine **2a** (2.60 g, 10 mmol) and benzylamine (**3b**) (3.20 g, 30 mmol) in 2-propanol (20 mL) was heated under reflux for 5 hours with intensive stirring. After cooling, the formed precipitate was collected by suction, washed with 2-propanol and dried. The yield was 2.60 g (78%), colorless prisms, mp 165 °C (dimethylformamide/ethanol); ir: 3280 w, 1710 s, 1655 s cm^{-1}; ^1H nmr: δ 3.43 and 3.65 (2 s, 2x3 H, 2 NMe), 4.46 (d, J = 5 Hz, 2 H, CH_2), 6.35 (s, 1 H, 6-H), 7.32-7.38 (m, 5 H, ArH), 9.65 (t, J = 4.5 Hz, 1 H, NH); ^{13}C nmr: δ 27.9 and 30.1 (2 Me), 46.9 (CH_2), 76.7, 77.0 and 77.4 (PhC), 99.9 (C-6).127.1, 127.9 and 129.5 (C-4a, C-5 and C-8a), 136.3 (C-7), 156.9 and 163.9 (C-2 and C-4). *Anal.* Calcd. for $C_{16}H_{15}ClN_4O_2$ (330.78): C, 58.10; H, 4.57; N, 16.94. Found: C, 58.20; H, 4.43; N, 16.94.

5-Benzylamino-7-chloro-1,3-diphenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4d). This compound was obtained from 5,7-dichloropyrido[2,3-*d*]pyrimidine **2b** (3.84 g, 10 mmol) and benzylamine (**3b**) (3.20 g, 30 mmol) in 2-propanol (20 mL) as described for **4c**; the yield was 3.41 g (75%), colorless prisms, mp 190 °C (ethanol); ir: 3260 w, 1720 s, 1660 s cm^{-1}; ^1H nmr: δ 4.42 (d, J = 5 Hz, 2 H, CH_2), 6.38 (s, 1 H, 6-H), 7.28-7.55 (m, 15 H, ArH), 9.50 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{26}H_{19}ClN_4O_2$ (454.92): C, 68.65; H, 4.21; N, 12.32. Found: C, 68.48; H, 4.13; N, 12.35.

7-Chloro-1,3-dimethyl-5-[(pyridin-3-ylmethyl)amino]-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4e). A mixture of 5,7-dichloropyrido[2,3-*d*]pyrimidine **2a** (2.60 g, 10 mmol) and 3-picolylamine (**3c**) (3.24 g, 30 mmol) in 2-propanol (20 mL) was heated under reflux for 5 hours with intensive stirring. After cooling, the formed precipitate was collected by suction, washed with 2-propanol and dried. The yield was 2.40 g (73%), colorless prisms, mp 178-180 °C (ethanol); ir: 3280 w, 1720 s, 1650 s cm^{-1}; ^1H nmr: δ 3.40 and 3.63 (2 s, 2x3 H, 2 NMe), 4.48 (d, J = 5 Hz, 2 H, CH_2), 6.29 (s, 1 H, 6-H), 7.29 (t, J = 7 Hz, 1 H, 5'-H of pyridyl), 7.63 (d, J = 8 Hz, 1 H, 6'-H of pyridyl), 8.58 (d, J = 8 Hz, 1 H, 4'-H of pyridyl), 8.60 (s, 1 H, 2'-H of pyridyl), 9.70 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{15}H_{14}ClN_5O_2$ (331.76): C, 54.31; H, 4.25; N, 21.11. Found: C, 54.46; H, 4.13; N, 21.21.

7-Chloro-1,3-diphenyl-5-[(pyridin-3-ylmethyl)amino]-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4f). This compound was obtained from 5,7-dichloropyrido[2,3-*d*]pyrimidine **2b** (3.84 g, 10 mmol) and 3-picolylamine (**3c**) (3.24 g, 30 mmol) in 2-propanol (20 mL) as described for **4e**; the yield was 3.60 g (79%), colorless prisms, mp 220-222 °C (ethanol); ir: 3270 w, 1710 s, 1640 s cm^{-1}; ^1H nmr: δ 4.44 (d, J = 5 Hz, 2 H, CH_2), 6.35 (s, 1 H, 6-H), 7.26-7.52 (m, 11 H, ArH and 5'-H of pyridyl), 7.63 (d, J = 8 Hz, 1 H, 6'-H of pyridyl), 8.57 (d, J = 8 Hz, 1 H, 4'-H of pyridyl), 8.62 (s, 1 H, 2'-H of pyridyl), 9.55 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{25}H_{18}ClN_5O_2$ (455.91): C, 65.86; H, 3.98; N, 15.36. Found: C, 65.82; H, 3.87; N, 15.18.

5,7-Dibenzylamino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5c). A mixture of 5,7-dichloropyrido[2,3-*d*]-pyrimidine **2a** (2.60 g, 10 mmol) and benzylamine (**3b**) (20 mL, 190 mmol) was heated under reflux for 8 hours. The solvent was evaporated under reduced pressure, and the residue was digested with water (20 mL), then brought to pH = 6 with hydrochloric acid and extracted with chloroform (3x50 mL). The combined organic solvent was dried over anhydrous calcium chloride and taken to dryness *i.vac*. The residue was digested with ethanol and the formed precipitate was collected by suction, washed with ethanol and dried. The yield was 3.30 g (81%), colorless prisms, mp 165 °C (ethanol); ir: 3300 w, 3280 w, 1680 s, 1640 s cm^{-1}; ^1H nmr: δ 3.38 and 3.55 (2 s, 2x3 H, 2 NMe), 4.33 and 4.43 (2 d, J = 5 Hz, 2x2 H, 2 CH_2), 5.13 (t, J = 4.5 Hz, 1 H, 7-NH), 5.23 (s, 1 H, 6-H), 7.28-7.30 (m, 10 H, ArH), 9.32 (t, J = 4.5 Hz, 1 H, 5-NH). *Anal.* Calcd. for $C_{23}H_{23}N_5O_2$ (401.47): C, 68.81; H, 5.77; N, 17.44. Found: C, 68.52; H, 5.81; N, 17.44.

5,7-Dibenzylamino-1,3-diphenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5d). This compound was obtained from 5,7-dichloropyrido[2,3-*d*]pyrimidine **2b** (3.84 g, 10 mmol) and benzylamine (**3b**) (20 mL, 190 mmol) as described for **5c**; the yield was 4.36 g (82%), colorless prisms, mp 233-235 °C (dimethylformamide/ethanol); ir: 3430 w, 3330 w, 1710 s, 1645, 1610 s cm^{-1}; ^1H nmr: δ 4.13 and 4.30 (2 d, J = 5 Hz, 2x2 H, 2 CH_2), 4.49 (t, J = 4.5 Hz, 1 H, 7-NH), 5.21 (s, 1 H, 6-H), 7.05-7.50 (m, 20 H, ArH), 9.18 (t, J = 4.5 Hz, 1 H, 5-NH). *Anal.* Calcd. for $C_{33}H_{27}N_5O_2$ (525.62): C, 75.41; H, 5.18; N, 13.32. Found: C, 74.73; H, 5.14; N, 13.24.

1,3-Dimethyl-5,7-bis[(pyridin-3-ylmethyl)amino]pyrido-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5e). A mixture of 5,7-dichloropyrido[2,3-*d*]pyrimidine **2a** (2.60 g, 10 mmol) and 3-picolylamine (**3c**) (20 mL, 190 mmol) was heated under reflux for 8 hours. The solvent was evaporated under reduced pressure, and the residue was digested with water (50 mL), the formed precipitate was collected by suction, washed with ethanol and dried. The yield was 3.30 g (82%), colorless prisms, mp 194-196 °C (ethanol); ir: 3290 w, 1670 s, 1645 s cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.19 and 3.38 (2 s, 2x3 H, 2 NMe), 4.44 and 4.47 (2 d, J = 6 Hz, 4 H, 2 CH_2), 5.41 (s, 1 H, 7-NH), 7.30 (m, J = 7 Hz, 2 H, 2x 5'-H of pyridyl), 7.67 (t, J = 8 Hz, 3 H, 6-H and 2x 6'-H of pyridyl), 8.41 (dd, J = 2 and 8 Hz, 2 H, 2x 4'-H of pyridyl), 8.50 and 8.54 (2 s, 2x1 H, 2x 2'-H of pyridyl), 9.14 (s, 1 H, 5-NH). *Anal.* Calcd. for $C_{21}H_{21}N_7O_2$ (403.45): C, 62.52; H, 5.25; N, 24.30. Found: C, 62.61; H, 5.31; N, 24.55.

1,3-Dimethyl-5,7-dipiperidin-1-ylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7a). A mixture of 5,7-dichloropyrido[2,3-*d*]-pyrimidine **2a** (2.60 g, 10 mmol) and piperidine (**6a**) (4.25 g, 50 mmol) in 2-propanol (20 mL) was heated under reflux for 5 hours with intensive stirring. After cooling, the formed precipitate was collected by suction, washed with 2-propanol and dried. The yield was 3.02 g (84%) colorless prisms, mp 180 °C (ethanol); ir: 2930 w, 1695 s, 1650 s cm^{-1}; ^1H nmr: δ 1.60 and 1.77 (2 m, 2x6 H, 2x 3,4,5-piperidinyl-CH_2), 3.04 and 3.60 (2 m, 2x4 H, 2x 2,6-piperidinyl-CH_2), 3.39 and 3.58 (2 s, 2x3 H, 2 NMe), 5.78 (s, 1 H, 6-H). *Anal.* Calcd. for $C_{19}H_{27}N_5O_2$ (357.46): C, 63.84; H, 7.61; N, 19.59. Found: C, 63.78; H, 7.74; N, 19.64.

1,3-Diphenyl-5,7-dipiperidin-1-ylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7b). This compound was obtained from 5,7-dichloropyrido[2,3-*d*]pyrimidine **2b** (3.84 g, 10 mmol) and piperidine (**6a**) (4.25 g, 50 mmol) in 2-propanol (20 mL) as described for **7a**; the yield was 4.01 g (85%), colorless prisms, mp 259-261 °C (dimethylformamide/ethanol); ir: 2930 w, 2845 w, 1720 s, 1660 s cm^{-1}; ^1H nmr: δ 1.45, 1.58 and 1.78 (3 m, 3x4 H, 2x 3,4,5-piperidinyl-CH_2), 3.10 and 3.25 (2 m, 2x4 H, 2x 2,6-piperidinyl-CH_2), 5.88 (s, 1 H, 6-H), 7.29-7.45 (m, 10 H, ArH). *Anal.* Calcd. for $C_{29}H_{31}N_5O_2$ (481.60): C, 72.33; H, 6.49; N, 14.54. Found: C, 72.11; H, 6.52; N, 14.56.

1,3-Dimethyl-5,7-dimorpholin-4-ylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7c). A mixture of 5,7-dichloropyrido-[2,3-*d*]pyrimidine **2a** (2.60 g, 10 mmol) and morpholine (**6b**) (4.35 g, 50 mmol) in 2-propanol (20 mL) was heated under reflux for 5 hours with intensive stirring. After cooling, the formed precipitate was collected by suction, washed with 2-propanol and dried. The yield was 3.21 g (88%), colorless prisms, mp 233-235 °C (ethanol); ir: 2960 w, 1680 s, 1645 s cm^{-1}; ^1H nmr: δ 3.12 (t, J = 4.5 Hz, 4 H, 2x 3,5-morpholinyl-CH_2), 3.40 and 3.59 (2 s, 2x3 H, 2 NMe), 3.62 (t, J = 4.5 Hz, 4 H, 3,5-morpholinyl-CH_2), 3.78 and 3.91 (2 t, J = 4.5 Hz, 2x4 H, 2x 2,6-morpholinyl-CH_2), 5.76 (s, 1 H, 6-H). *Anal.* Calcd. for $C_{17}H_{23}N_5O_4$ (361.40): C, 56,50; H, 6.41; N, 19.38. Found: C, 56.35; H, 6.40; N, 19.27.

5,7-Dimorpholin-4-yl-1,3-diphenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7d). This compound was obtained from 5,7-dichloropyrido[2,3-*d*]pyrimidine **2b** (3.84 g, 10 mmol) and morpholine (**6b**) (4.35 g, 50 mmol) in 2-propanol (20 mL) as described for **7c**; the yield was 4.02 g (83%), colorless prisms, mp 291-294 °C (ethanol); ir: 2960 w, 2850 w, 1715 s, 1665 s cm^{-1}; ^1H nmr: δ 3.18 and 3.30 (2 t, J = 4.5 Hz, 2x4 H, 2x 3,5-morpholinyl-CH_2), 3.60 and 3.88 (2 t, J = 4.5 Hz, 2x4 H, 2x 2,6-morpholinyl-CH_2), 5.75 (s, 1 H, 6-H), 7.26-7.49 (m, 10 H, ArH). *Anal.* Calcd. for $C_{27}H_{27}N_5O_4$ (485.55): C, 66.79; H, 5.61; N, 14.42. Found: C, 66.37; H, 5.51; N, 14.35.

7-Dimethylamino-1,3-dimethyl-5-phenylaminopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8a). A mixture of 5,7-dichloro-pyrido[2,3-*d*]pyrimidine **2a** (2.60 g, 10 mmol) and aniline (**3a**) (4.70 g, 50 mmol) in dimethylformamide (20 mL) was heated under reflux for 8 hours with intensive stirring. After cooling, the solution was evaporated under reduced pressure, and the residue digested with water (50 mL). The formed precipitate was collected by suction, washed with water and dried. The yield was 2.28 g (70%), colorless prisms, mp 182-184 °C (dimethylformamide); ir: 1690 s, 1645 s cm^{-1}; ^1H nmr: δ 3.07 (s, 6 H, NMe_2), 3.42 and 3.62 (2 s, 2x3 H, NMe), 5.85 (s, 1 H, 6-H), 7.18-7.40 (m, 5 H, ArH), 10.62 (s, 1 H, NH) MS: m/z (%) 326 (8), 325 (41), 317 (37), 316 (100). *Anal.* Calcd. for $C_{17}H_{19}N_5O_2$ (325.37): C, 62.76; H, 5.89; N, 21.52. Found: C, 62.72; H, 5.79; N, 21.54.

7-Dimethylamino-1,3-diphenyl-5-phenylaminopyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (8b). This compound was obtained from 5,7-dichloropyrido[2,3-*d*]pyrimidine **2b** (3.84 g, 10 mmol) and aniline (**1a**) (4.70 g, 50 mmol) in dimethylformamide (20 mL) as described for **8a**; the yield was 3.28 g (73%), colorless prisms, mp 260-262 °C (dimethylformamide/ethanol); ir: 1710 s, 1645 s, 1610 s cm^{-1}; ^1H nmr: δ 2.75 (s, 6 H, NMe_2), 5.88 (s, 1 H, 6-H), 7.13-7.50 (m, 15 H, ArH), 10.50 (s, 1 H, NH). *Anal.* Calcd. for $C_{27}H_{23}N_5O_2$ (449.52): C, 72.14; H, 5.16; N, 15.58. Found: C, 71.73; H, 5.01; N, 15.46.

5-Benzylamino-7-dimethylamino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (8c). A mixture of 5,7-dichloropyrido[2,3-*d*]pyrimidine **2a** (2.60 g, 10 mmol) and benzylamine (**3b**) (3.20 g, 30 mmol) in dimethylformamide (20 mL) was heated under reflux for 8 hours with intensive stirring. After cooling, the solution was evaporated under reduced pressure, and the residue was digested with water (50 mL). The formed precipitate was collected by suction, washed with water and dried. The yield was 2.44 g (72%) colorless prisms, mp 185-187 °C (ethanol); ir: 3280 w, 1695 s, 1650 s cm^{-1}; ^1H nmr: δ 3.04 (s, 6 H, NMe_2), 3.40 and 3.58 (2 s, 2x3 H, 2 NMe), 4.42 (d, J = 5 Hz, 2 H, CH_2), 5.21 (s, 1 H, 6-H), 7.30-7.35 (m, 5 H, ArH), 9.25 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{18}H_{21}N_5O_2$ (339.40): C, 63.70; H, 6.24; N, 20.63. Found: C, 63.37; H, 6.25; N, 20.69.

1,3-Dimethyl-5-phenylamino-7-piperidin-1-ylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (9a). A mixture of 7-chloro-pyrido[2,3-*d*]pyrimidine **4a** (3.31 g, 10 mmol) and piperidine (**6a**) (1.70 g, 20 mmol) in 2-propanol (20 mL) was heated under reflux for 3 hours. The solvent was removed under reduced pressure, and the residue was digested with ethanol (20 mL), the formed precipitate was collected by suction, washed with ethanol and dried. The yield was 2.74 g (75%), colorless prisms, mp 145 °C (ethanol); ir: 2935 w, 2835 w, 1690 s, 1650, 1610 s cm^{-1}; ^1H nmr: δ 1.58 (m, 6 H, 3,4,5-piperidinyl-CH_2), 3.42 (s, 3 H, NMe), 3.52 (m, 4 H, 2,6-piperidinyl-CH_2), 3.60 (s, 3 H, NMe), 5.98 (s, 1 H, 6-H), 7.15-7.45 (m, 5 H, ArH), 10.63 (s, 1 H, NH). *Anal.* Calcd. for $C_{20}H_{23}N_5O_2$ (365.44): C, 65.74; H, 6.34; N, 19.16. Found: C, 65.33; H, 6.17; N, 18.99.

5-Benzylamino-1,3-dimethyl-7-piperidin-1-ylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (9b). This compound was obtained from 7-chloropyrido[2,3-*d*]pyrimidine **4c** (3.30 g, 10 mmol) and piperidine (**6a**) (1.70 g, 20 mmol) in 2-propanol (20 mL) as described for **9a**; the yield was 2.96 g (78%), colorless prisms, mp 173 °C (ethanol); ir: 2940 w, 2860 w, 1690 s, 1660, 1610 s cm^{-1}; ^1H nmr: δ 1.55 (m, 6 H, 2x 3,4,5-piperidinyl-CH_2),

3.40 (s, 3 H, NMe), 3.50 (m, 4 H, 2,6-piperidinyl-CH_2), 3.56 (s, 3 H, NMe), 4.38 (d, J = 4.5 Hz, 2 H, CH_2), 5.38 (s, 1 H, 6-H), 7.25-7.35 (m, 5 H, ArH), 9.24 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{21}H_{25}N_5O_2$ (379.47): C, 66.47; H, 6.64; N, 18.46. Found: C, 66.75; H, 6.69; N, 18.60.

General Procedure for the Preparation of 5-Amino-substituted 7-Azido-pyrido[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-diones 10. A suspension of the appropriate 7-chloro-pyrido-[2,3-*d*]pyrimidine **4** (10 mmol) and sodium azide (2.00 g, 30 mmol) in dry dimethylformamide (30 mL) was stirred at 110-120 °C for 3 hours. Then the reaction mixture was poured into ice/water (300 mL), the precipitate filtered, washed with water and dried to obtain colorless prisms. Further data: see Table 1

Table 1

Chemical Yields and Mp for Compounds **10-12.**

	Yield	Mp (°C)	Recryst. Solvent
10a	2.58 g (80%)	180-182	ethanol
10b	4.00 g (89%)	192-194	ethanol
10c	2.70 g (81%)	173-175	ethanol
10d	3.82 g (83%)	185	ethanol
10e	2.65 g (82%)	186	ethanol
10f	3.74 g (81%)	189-191	ethanol
11a	4.74 g (85%)	234-236	ethanol
11b	6.02 g (88%)	303-305	ethanol
11c	4.85 g (85%)	238-230	ethanol
11d	5.70 g (82%)	299-301	dimethylformamide
12a	2.38 g (80%)	238-240	ethanol
12b	3.45 g (82%)	270	ethanol
12c	2.55 g (82%)	213-215	ethanol
12c	3.52 g (81%)	300-302	DMF/ethanol

7-Azido-1,3-dimethyl-5-phenylaminopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10a). From **4a** (3.16 g, 10 mmol); ir: 3220 w, 2140 s, 2110 s, 1710 s, 1650 s, 1610 m cm^{-1}; ^1H nmr: δ 3.45 and 3.65 (2 s, 2x3 H, 2 NMe), 6.12 (s, 1 H, 6-H), 7.21-7.30 (m, 3 H, ArH), 7.39-7.45 (m, 2 H, ArH), 10.90 (s, 1 H, NH). *Anal.* Calcd. for $C_{15}H_{13}N_7O_2$ (323.32): C, 55.72; H, 4.05; N, 30.33. Found: C, 55.81; H, 3.94; N, 30.60.

7-Azido-1,3-diphenyl-5-phenylaminopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10b). From **4b** (4.50 g, 10 mmol); ir: 3260 w, 2130 s, 1715 s, 1650 s, 1610 cm^{-1}; ^1H nmr: δ 6.15 (s, 1 H, 6-H), 7.18-7.55 (m, 15 H, ArH), 10.82 (s, 1 H, NH). *Anal.* Calcd. for $C_{25}H_{17}N_7O_2$ (447.46): C, 67.11; H, 3.83; N, 21.91. Found: C, 67.07; H, 3.78; N, 21.53.

7-Azido-5-benzylamino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10c). From **4c** (3.30 g, 10 mmol); ir: 3280 w, 2140 s, 2120 s, 1690 s, 1655 s cm^{-1}; ^1H nmr: δ 3.41 and 3.63 (2 s, 2x3 H, 2 NMe), 4.42 (d, J = 5 Hz, 2 H, CH_2), 5.75 (s, 1 H, 6-H), 7.28-7.35 (m, 5 H, ArH), 9.62 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{16}H_{15}N_7O_2$ (337.34): C, 56.97; H, 4.48; N, 29.06. Found: C, 56.86; H, 4.43; N, 28.49.

7-Azido-5-benzylamino-1,3-diphenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10d). From **4d** (4.55 g, 10 mmol); ir: 3280 w, 2130 s, 1715 s, 1655 s, 1600 m cm^{-1}; ^1H nmr: δ 4.35 (d, J = 5 Hz, 2 H, CH_2), 5.78 (s, 1 H, 6-H), 7.25-7.55 (m, 15 H, ArH), 9.44 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{26}H_{19}N_7O_2$ (461.49): C, 67.67; H, 4.15; N, 21.25. Found: C, 67.70; H, 4.01; N, 20.97.

7-Azido-1,3-dimethyl-5-[(pyridin-3-ylmethyl)amino]pyrido-[2,3-d]pyrimidine-2,4(1H,3H)-dione (10e). From **4e** (3.31 g, 10 mmol); ir: 3280 w, 2160 s, 1700 s, 1650 s cm^{-1}; ^1H nmr: δ 3.42 and 3.63 (2 s, 2x3 H, 2 NMe), 4.45 (d, J = 5 Hz, 2 H, CH_2), 5.73 (s, 1 H, 6-H), 7.30 (t, J = 7 Hz, 1 H, 5'-H of pyridyl), 7.63 (d, J = 8 Hz, 1 H, 6'-H of pyridyl), 8.55 (d, J = 8 Hz, 1 H, 4'-H of pyridyl), 8.60 (s, 1 H, 2'-H of pyridyl), 9.65 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{15}H_{14}N_8O_2$ (338.33): C, 53.25; H, 4.17; N, 33.12. Found: C, 53.37; H, 3.98; N, 33.18.

7-Azido-1,3-diphenyl-5-[(pyridin-3-ylmethyl)amino]-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10f). From **4f** (4.56 g, 10 mmol); ir: 3330 m, 2140 s, 1705 s, 1640 s cm^{-1}; ^1H nmr: δ 4.34 (d, J = 5 Hz, 2 H, CH_2), 5.75 (s, 1 H, 6-H), 7.25-7.50 (m, 11 H, ArH & 5'-H of pyridyl), 7.60 (d, J = 8 Hz, 1 H, 6'-H of pyridyl), 8.52 (d, J = 8 Hz, 1 H, 4'-H of pyridyl), 8.55 (s, 1 H, 2'-H of pyridyl), 9.50 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{25}H_{18}N_8O_2$ (462.47): C, 64.93; H, 3.92; N, 24.23. Found: C, 65.06; H, 3.78; N, 23.90.

General Procedure for the Preparation of 5-Aminosubstituted 7-[(Triphenylphosphoranylidene)amino]pyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-diones 11. To a solution of triphenyl-phosphane (3.15 g, 12 mmol) in dry toluene (30 mL) was added the appropriate 7-azidopyrido[2,3-*d*]pyrimidine **10** (10 mmol) at room temperature; a slightly exothermic reaction started, and the starting material dissolved, followed immediately by precipitation of the product. After stirring for 30 minutes, the temperature was gradually raised to 80-100 °C for 30 minutes. The reaction mixture was cooled to room temperature and allowed to stand overnight, then filtered by suction and washed with cyclohexane to obtain colorless prisms. Further data see Table 1.

1,3-Dimethyl-5-phenylamino-7-[(triphenylphosphoranylidene)amino]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11a). From **10a** (3.23 g, 10 mmol); ir: 1700 s, 1640 s cm^{-1}; ^1H nmr: δ 2.78 and 3.36 (2 s, 2x3 H, 2 NMe), 6.40 (s, 1 H, 6-H), 7.10-7.75 (m, 20 H, ArH), 10.51 (s, 1 H, NH). *Anal.* Calcd. for $C_{33}H_{28}N_5O_2P$ (557.60): C, 71.09; H, 5.06; N, 12.56. Found: C, 71.11; H, 5.01; N, 12.64.

1,3-Diphenyl-5-phenylamino-7-[(triphenylphosphoranylidene)amino]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11b). From **10b** (4.47 g, 10 mmol); ir: 1700 s, 1655 s cm^{-1}; ^1H nmr: δ 6.52 (s, 1 H, 6-H), 6.80-7.52 (m, 30 H, ArH), 10.50 (s, 1 H, NH). *Anal.* Calcd. for $C_{43}H_{32}N_5O_2P$ (681.74): C, 75.76; H, 4.73; N, 10.27. Found: C, 75.56; H, 4.54; N, 10.18.

5-Benzylamino-1,3-dimethyl-7-[(triphenylphosphoranylidene)amino]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11c). From **10c** (3.37 g, 10 mmol); ir: 3330 w, 1680 s, 1645 s cm^{-1}; ^1H nmr: δ 2.73 and 3.32 (2 s, 2x3 H, 2 NMe), 4.43 (d, J = 5 Hz, 2 H, CH_2), 5.90 (s, 1 H, 6-H), 7.28-7.75 (m, 20 H, ArH), 9.03 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{34}H_{30}N_5O_2P$ (571.62): C, 71.44; H, 5.29; N, 12.25. Found: C, 71.61; H, 5.27; N, 12.09.

5-Benzylamino-1,3-diphenyl-7-[(triphenylphosphoranylidene)amino]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11d). From **10d** (4.61 g, 10 mmol); ir: 1730 s, 1642 m cm^{-1}; ^1H nmr: δ 4.42 (d, J = 5 Hz, 2 H, CH_2), 6.07 (s, 1 H, 6-H), 6.80-7.50 (m, 30 H, ArH), 8.95 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{44}H_{34}N_5O_2P$ (695.77): C, 75.96; H, 4.93; N, 10.07. Found: C, 75.44; H, 4.99; N, 10.20.

General Procedure for the Preparation 5-Aminosubstituted 7-Amino-pyrido[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-diones 12. A mixture of the appropriate phosphazene **11** (10 mmol), glacial acetic acid (40 mL) and water (10 mL) was refluxed for 3 hours. After cooling, to the reaction mixture was added water (50 mL), then the precipitate was filtered by suction and washed with water. Further data: see Table 1.

7-Amino-1,3-dimethyl-5-phenylaminopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (12a). From **11a** (5.57 g, 10 mmol); ir: 3440 m, 3340 m, 3230 w, 1690 s, 1635 s cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.25 and 3.47 (2 s, 2x3 H, 2 NMe), 5.90 (s, 1 H, 6-H), 6.66 (s, 2 H, 7-NH_2), 7.18-7.33 (m, 3 H, ArH), 7.40-7.50 (m, 2 H, ArH), 10.64 (s, 1 H, 5-NH). *Anal.* Calcd. for $C_{15}H_{15}N_5O_2$ (297.32): C, 60.60; H, 5.09; N, 23.55. Found: C, 60.43; H, 5.12; N, 23.78.

7-Amino-1,3-diphenyl-5-phenylaminopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (12b). From **11b** (6.82 g, 10 mmol); ir: 3470 m, 3340 m, 1710 s, 1615 s cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.48 (s, 2 H, 7-NH_2), 5.80 (s, 1 H, 6-H), 7.20-7.50 (m, 15 H, ArH), 10.60 (s, 1 H, 5-NH). *Anal.* Calcd. for $C_{25}H_{19}N_5O_2$ (421.46): C, 71.25; H, 4.54; N, 16.62. Found: C, 70.97; H, 4.42; N, 16.40.

7-Amino-5-benzylamino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (12c). From **11c** (5.71 g, 10 mmol); ir: 3480 w, 3430 w, 3340 m, 3230 w, 1670 s, 1645 s, 1620 s cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.21 and 3.43 (2 s, 2x3 H, NMe), 4.39 (d, J = 5 Hz, 2 H, CH_2), 5.40 (s, 1 H, 6-H), 6.53 (s, 2 H, 7-NH_2), 7.32-7.38 (m, 5 H, ArH), 9.15 (t, J = 4.5 Hz, 1 H, 5-NH). *Anal.* Calcd. for $C_{16}H_{17}N_5O_2$ (311.35): C, 61.72; H, 5.50; N, 22.49. Found: C, 61.02; H, 5.39; N, 22.28.

7-Amino-5-benzylamino-1,3-diphenyl-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (12d). From **11d** (6.96 g, 10 mmol); ir: 3500 w, 3390 m, 3300 w, 1700 s, 1640, 1600 s cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.40 (d, J = 5 Hz, 2 H, CH_2), 5.44 (s, 1 H, 6-H), 6.32 (s, 2 H, 7-NH_2), 7.32-7.52 (m, 15 H, ArH), 9.05 (t, J = 4.5 Hz, 1 H, 5-NH). *Anal.* Calcd. for $C_{26}H_{21}N_5O_2$ (435.49): C, 71.71; H, 4.86; N, 16.08. Found: C, 71.41; H, 4.82; N, 16.07.

General Procedure for the Preparation of 5-Aminosubstituted 2,4,7-Trioxo-8-phenyl-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbaldehydes 14-16. A mixture of the appropriate 5-chloropyrido[2,3-*d*]pyrimidine-trione **13** [4b] (10 mmol) and amine **3** (12 mmol) in dimethyl-formamide (15 mL) was stirred fro 1-2 hours at 70-80 °C. The solvent was removed *in vacuo*, and the residual product triturated with water (100 mL). The resulting precipitate was filtered and washed with water to give yellow prisms. Further data: see Table 2.

Table 2

Chemical Yields and Mp for Compounds **14-16.**

	Yield	Mp (°C)	Recryst. Solvent
14	3.53 g (82%)	232-234	ethanol
15a	2.83 g (80%)	205-207	ethanol
15b	3.41 g (82%)	214-216	DMF/ ethanol
15c	2.50 g (60%)	233-235	ethanol
16a	2.87 g (86%)	167-169	ethanol
16b	3.39 g (86%)	265-267	dimethylformamide
16c	2.70 g (81%)	194-196	ethanol
16d	3.37 g (85%)	273-275	dimethylformamide

5-(2,6-Dimethylphenylamino)-1,3-dimethyl-2,4,7-trioxo-8-phenyl-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbaldehyde (14). From **13b** (3.45 g, 10 mmol) and 2,6-dimethylaniline (**13d**) (1.45 g, 12 mmol); ir: 1720 s, 1670 s, 1610 s cm^{-1}; ^1H nmr: δ 2.16 (s, 6 H, 2 Me), 2.90 and 3.47 (2 s, 2x3 H, 2 NMe), 7.09 (s, 3 H, ArH), 7.30-7.50 (m, 5 H, ArH), 9.63 (s, 1 H, CH=O), 11.88 (s, 1 H, NH). *Anal.* Calcd. for $C_{24}H_{22}N_4O_4$ (430.47): C, 66.97; H, 5.15; N, 13.02. Found: C, 66.82; H, 5.12; N, 13.04.

5-Benzylamino-1,3,8-trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbaldehyde (15a). From **13a** (2.83 g, 10 mmol) and benzylamine (**3b**) (1.28 g, 12 mmol); ir: 3080 w, 1715 s, 1665 s, 1640 s cm^{-1}; ^1H nmr: δ 3.35, 3.50 and 3.55 (3 s, 3x3 H, 3 NMe), 4.22 (d, J = 5 Hz, 2 H, benzyl-CH_2), 7.25-7.32 (m, 5 H, ArH), 10.10 (s, 1 H, CH=O), 10.58 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{18}H_{18}N_4O_4$ (354.37): C, 61.01; H, 5.12; N, 15.81. Found: C, 60.80; H, 4.95; N, 15.79.

5-Benzylamino-1,3dimethyl-2,4,7-trioxo-8-phenyl-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbaldehyde (15b). From **13b** (3.45 g, 10 mmol) and benzylamine (**3b**) (1.28 g, 12 mmol); ir: 3150 w, 3080 w, 1710 s, 1670 s, 1655 m cm^{-1}; ^1H nmr: δ 2.85 and 3.35 (2 s, 2x3 H, 2 NMe), 4.44 (d, J = 5 Hz, 2 H, benzyl-CH_2), 7.30-7.50 (m, 10 H, ArH), 10.10 (s, 1 H, CH=O), 10.80 (t, J = 4.5 Hz, 1 H, NH). *Anal.* Calcd. for $C_{23}H_{20}N_4O_4$ (416.44): C, 66.34; H, 4.84; N, 13.45. Found: C, 66.13; H, 4.73; N, 13.43.

1,3-Dimethyl-2,4,7-trioxo-8-phenyl-5-[(pyridin-3-ylmethyl)-amino]-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbaldehyde (15c). From **13b** (3.45 g, 10 mmol) and 3-picolylamine (**3c**) (1.29 g, 12 mmol); ir: 1720 s, 1670 s, 1650 s cm^{-1}; ^1H nmr: δ 2.87 and 3.40 (2 s, 2x3 H, 2 NMe), 4.50 (d, J = 5 Hz, 2 H, CH_2), 7.25-7.35 (m, 3 H, ArH and 5'-H of pyridyl), 7.48-7.52 (m, 3 H, ArH), 7.70 (d, J = 8 Hz, 2 H, 4'-H and 6'-H of pyridyl), 8.62 (s, 1 H, 2'-H of pyridyl), 10.10 (s, CH=O). *Anal.* Calcd. for $C_{22}H_{19}N_5O_4$ (417.43): C, 63.30; H, 4.59; N, 16.78. Found: C, 62.94; H, 4.58; N, 16.45.

1,3,8-Trimethyl-2,4,7-trioxo-5-piperidin-1-yl-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbaldehyde (16a). From **13a** (2.83 g, 10 mmol) and piperidine (**6a**) (1.02 g, 12 mmol); ir: 3400 w, 2940 w, 2850 w, 1710 s, 1670 s, 1640 s cm^{-1}; ^1H nmr: δ 1.67 (m, 6 H 3,4,5-piperidinyl-CH_2), 3.30 (m, 4 H, 2,6-piperidinyl-CH_2), 3.32, 3.48 and 3.50 (3 s, 3x3 H, 3 NMe), 9.83 (s, 1 H, CH=O). *Anal.* Calcd. for $C_{16}H_{20}N_4O_4$ (332.36): C, 57.82; H, 6.07; N, 16.86. Found: C, 57.43; H, 5.99; N, 16.67.

1,3-Dimethyl-2,4,7-trioxo-8-phenyl-5-piperidin-1-yl-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbaldehyde (16b). From **13b** (3.45 g, 10 mmol) and piperidine (**6a**) (1.02 g, 12 mmol); ir: 3060 w, 2930 w, 2850 w, 1720 s, 1680 s, 1655 s cm^{-1}; ^1H nmr: δ 1.75 (m, 6 H, 3,4,5-piperidinyl-CH_2), 2.85 and 3.39 (2 s, 2x 3 H, 2 NMe), 3.51 (m, 4 H, 2,6-piperidinyl-CH_2), 7.25-7.50 (m, 5 H, ArH), 9.80 (s, 1 H, CH=O). *Anal.* Calcd. for $C_{21}H_{22}N_4O_4$ (394.43): C, 63.95; H, 5.62; N, 14.20. Found: C, 63.73; H, 5.57; N, 14.27.

1,3,8-Trimethyl-5-morpholin-4-yl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbaldehyde (16c). From **13a** (2.83 g, 10 mmol) and morpholine (**6b**) (1.03 g, 12 mmol); ir: 2970 w, 1710 s, 1675 s, 1650 s, 1635 s cm^{-1}; ^1H nmr: δ 3.33 (t, J = 4.5 Hz, 4 H, 3,5-morpholinyl-CH_2), 3.51, 3.52 and 3.53 (3 s, 3x3 H, 3 NMe), 3.92 (t, J = 4.5 Hz, 4 H, 2,6-morpholinyl-CH_2), 9.92 (s, 1 H, CH=O). *Anal.* Calcd. for $C_{15}H_{18}N_4O_5$ (334.33): C, 53.89; H, 5.43; N, 16.76. Found: C, 53.72; H, 5.57; N, 16.75.

1,3-Dimethyl-5-morpholin-4-yl-2,4,7-trioxo-8-phenyl-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbaldehyde (16d). From **13b** (3.45 g, 10 mmol) and morpholine (**6b**) (1.03 g, 12 mmol); ir: 3060 w, 2980 w, 2850 w, 1720 s, 1675 s, 1650 s cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.62 and 3.20 (2 s, 2x3 H, NMe), 3.47 (t, J = 4.5 Hz, 4 H, 3,5-morpholinyl-CH_2), 3.82 (t, J = 4.5 Hz, 4 H, 2,6-morpholinyl-CH_2), 7.52 (m, 5 H, ArH), 9.61 (s, 1 H, CH=O).

Anal. Calcd. for $C_{20}H_{20}N_4O_5$ (396.41): C, 60.60; H, 5.09; N, 14.13. Found: C, 60.21; H, 5.06; N, 14.24.

Acknowledgement. This work was supported by an ASEA-Uninet scholarship (D.V.T).

REFERENCES

[1] Organic Azides in Heterocyclic Synthesis, part 34. part 33: Dang, H. V.; Knobloch, B.; Habib, N. S.; Kappe, T.; Stadlbauer, W.; *J. Heterocyclic Chem*. **2005**, *42*, 85.

[2a] Suzuki, N. *Chem. Pharm Bull*. **1980**, *28*, 761; [b] Grivsky, E. M.; Lee, S.; Sigel, C.W.; Duch, D. S.; Nichols, C. A. *J. Med. Chem*., **1980**, *23*, 327.

[3a] Bulicz, J.; D. Bertarelli, C. G.; Baumert, D.; Fülle, F.; Müller, C. E.; Heber, D. *Bioorg. Med. Chem.,* **2006**, *14*, 2837; [b] Heber, D.; Heers C.; Ravens U. *Pharmazie* **1993**, *48*, 537.

[4a] Dang, V. T.; Stadlbauer, W. *Molecules* **1996**, *1*, 201; [b] Khattab, A.; Dang, V. T.; Stadlbauer, W. *J. Prakt. Chem. - Chem. Ztg*. **1996**, *338*, 151.

[5a] Dunning, L.; Jaroch, S.; Kochanny, M. J.; Lee, W.; Lian, X.; Liang, M.; Lu, S.-F.; Onuffer, J.; Phillips, G.; Wei, G.-P.; Ye, B. *PCT Int. Appl., WO* 2004002960, A1 20040108 (2004); *Chem. Abstr*. **2004**, *140*, 93938; [b] Ukrainets, I. V.; Taran, S. G.; Gorokhova, O. V.; Marusenko, N. A.; Kovalenko, S. N.; Turov, A. V.; Filimonova, N. I.; Ivkov, S. M. *Khim. Get. Soedin*. **1995**; 195; [c] Patel, H. V.; Vyas, K. A.; Fernandes, P. S. *Ind. J. Chem*. **1990**, *29b***,** 836; [d] Di Braccio, M.; Roma, G.; Balbi, A.; Sottofattori, E.; Carazzone, M. *Farmaco*, *Ed. Sci*. **1989**, *44*, 865; [e] Van der Plas, H. C.; Wozniak, M. *J. Heterocycl. Chem*. **1986**, *23* 573; [f] Fournier, C.; Decombe, J. *C. R. Acad. Sci.Paris, Ser. C* **1967**, *265*, 1169; [g] Curd, F. H. S.; Raison, C. G.; Rose, F. L. *J. Chem. Soc*. **1947**, 899; [h] Dziewonski, K.; Dymek, W. *Bull. Int. Acad. Pol. Sci. A,* **1936**, 413; [i] Ephraim, J. *Ber. Dtsch. Chem. Ges*. **1893**, *26*, 2230.

[6a] Albert, A., *Chemie der Heterocyclen,* Verlag Chemie, Weinheim, 1962; [b] Lettau, H. *Chemie der Heterocylen*, S. Hirzel-Verlag, Leipzig, 1981; [c] Belli, M. L.; Illuminati, G.; Marino, G. *Tetrahedron* **1963**, *19*, 345; [d] Belli, M. L.; Fatutta, S.; Forchiassin, M.; Illuminati, G.; Linda, P.; Marino, G.; Zinato, E. *Ric. Sci., Rend. Sez. A*. **1963**, *3*, 530.

[7] Newkome, G. R.; Paudler, W. W. *Contemporary Heterocyclic Chemistry,* J. Wiley and Sons, Inc., New York, 1982.

[8] Steinschifter, W.; Stadlbauer, W. *J. Prakt. Chem. - Chem. Ztg*. **1994**, *336*, 311.

[9a] Knops, H. J.; Born, L. *Tetrahedron Lett*., **1983**, *24*, 2973; [b] Kappe, T.; Ajili, S.; Stadlbauer, W. *J. Heterocycl. Chem*. **1988**, *25*, 463.

[10] Sasaki, T.; Kanematsu, K.; Murata, M. *Tetrahedron* **1972**, *28*, 2383.