Synthesis of 6-Amino-2-aryl-1,2-dihydro-3*H*-pyrido[2,3-*d*]pyrimidin-4-one Derivatives

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This paper reports the synthesis of new pyrido[2,3-*d*]pyrimidin-4-one derivatives as diuretic agents. Starting with 1,2-dihydro-5-nitro-2-oxo-3-pyridinecarboxylic acid **1**, ethyl 2-ethoxy-5-nitro-3-pyridincarboxylate **4** was obtained. Compound **4** reacts with ammonia, methylamine or *S*-methylpseudothiourea to give the respective 2-amino-5-nitro-3-pyridinecarboxamide derivatives **5** and **6** or 2-methylthio-6-nitro-3*H*-pyrido[2,3-*d*]pyrimidin-4-one **8**. Treating carboxamide **5** with arylaldehydes and zinc dichloride, new 2-aryl-1,2-dihydro-6-nitro-3*H*-pyrido[2,3-*d*]pyrimidin-4-ones **9** were synthetised. These compounds reduced with iron(II) hydroxide gave 6-amino-2-aryl-1,2-dihydro-3*H*-pyrido[2,3-*d*]pyrimidin-4-ones **10** as expected.

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In the past years we were interested in searching for new pyrido[2,3-*d*]pyrimidines as diuretics [2-6]. Our studies as well as other related ones [7-12] dealt with new substituents on the pyrimidine ring which gave new diuretic compounds. However, Parish and co-workers [11] suggested a qualitative correlation between diuretic activity and basicity of the ring fused to pyrimidine. To estimate this relation we proposed the synthesis of 2-aryl-1,2-dihydro-3*H*-pyrido[2,3-*d*]pyrimidin-4-one derivatives with several substituents on pyridine ring. This paper begins a series of 6-substituted 2-aryl-1,2-dihydro-3*H*-pyrido[2,3-*d*]-pyrimidin-4-one derivatives with the objective of finding quantitative structure-diuretic activity relationships.

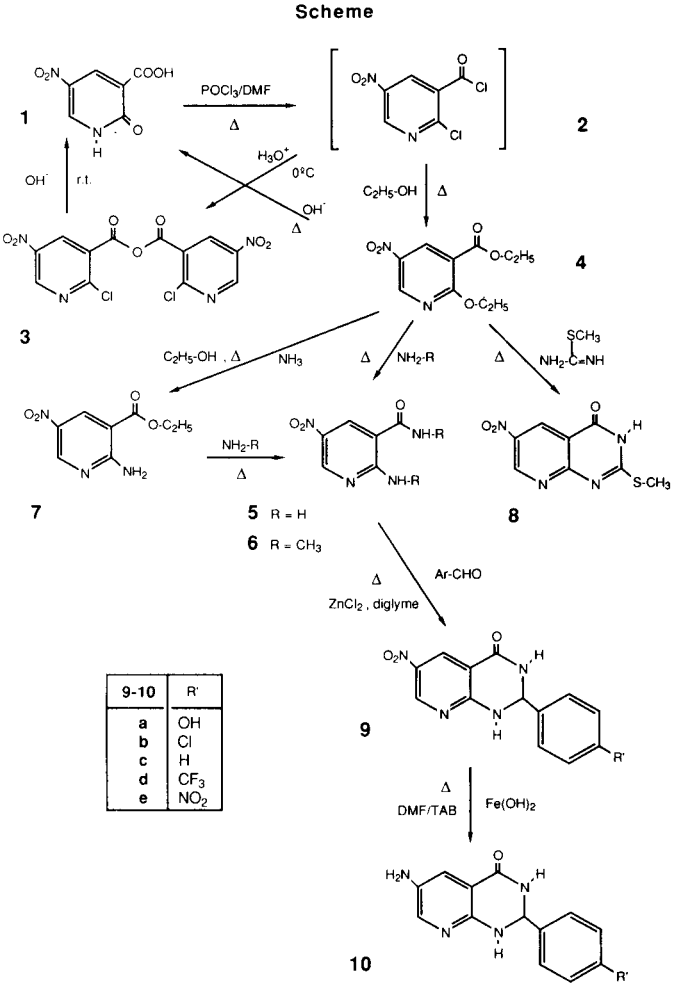
1,2-Dihydro-3*H*-pyrido[2,3-*d*]pyrimidin-4-one derivatives are generally obtained by condensation of 2-amino-3-pyridincarboxamides with the respective aldehydes [13]. Surprisingly only a very small number of 5-substituted 2-amino-3-pyridinecarboxylic acid derivatives have been reported in the literature [14,15]. Most papers report condensations between cyanoacetic acid derivatives and 1,3-dicarbonyl compounds or related, to give 4 or 6 monosubstituted or disubstituted 3-pyridinecarboxylic acid derivatives [16]. Here we study the synthesis of 2-amino-5-nitro-3-pyridinecarboxamide **5** as starting material of 6-nitro and 6-aminopyrido[2,3-*d*]pyrimidin-4-one derivatives.

1,2-Dihydro-5-nitro-2-oxo-3-pyridinecarboxylic acid **1** was obtained in a 75% yield by a modification of the Carboni nitration method [17] of 1,2-dihydro-2-oxo-3-pyridinecarboxylic acid. Compound **1** was previously reported by condensation of nitromalonic aldehyde and cyanoacetamide [18].

The reaction of **1** with phosphorus oxychloride, phosphorus pentachloride or mixtures of them in several proportions and temperatures was fruitless in changing the 2-hydroxy group into a 2-chloro group. Nevertheless when **1** was treated with phosphorus oxychloride/DMF at reflux, **2** was obtained. Compound **2** was not directly analyzed, however its treatment with water at 0° gave 2-chloro-5-nitro-3-pyridinecarboxylic acid anhydride **3** in 65% yield. Hydrolysis of **3** in boiling water, toluene/water or chloroform/water as well as in diluted sodium hydroxide at room temperature, always gave **1**.

Crude product **2** reacted with boiling ethanol to give ethyl 2-ethoxy-5-nitro-3-pyridinecarboxylate **4** in 70% yield. However in other less conjugated 2-halopyridines,

Scheme



an alcoholate is necessary in order to convert a 2-halo group into a 2-alkoxyl group [19,20].

Due to strong conjugation of the 2-ethoxy group with N^1, 3-carboxy and 5-nitro, ethyl carboxylate **4** was a good starting material for small 2-amino derivatives such as **5**. The reaction of **4** with ammonia/methanol at 100° gave 2-amino-5-nitro-3-pyridinecarboxamide **5** in 85% yield. On the other hand **4** reacted regioselectively with ammonia/-ethanol to give ethyl 2-amino-5-nitro-3-pyridinecarboxylate **7** in a 40% yield at room temperature or in a 76% yield at 150°. Compound **7** was previously reported [14] by condensation of ethyl amidinoacetate and nitromalonic aldehyde.

Similarly, treatment of **4** diluted methylamine gave *N*-methyl-2-methylamino-5-nitro-3-pyridinecarboxamide **6** in about 50% yield. Compound **6** was also prepared (20%) by reacting **7** with methylamine at 150°. This class of substitution was not detected in the reaction of methylamine with ethyl 2-amino-3-pyridinecarboxylate [11].

When a bulky *S*-methylpseudothiourea reacted with **4**, 2-methylthio-5-nitro-3*H*-pyrido[2,3-*d*]pyrimidin-4-one **8** was obtained in poor yield. On the other hand compound **4** was stable to acid hydrolysis but it reacted with sodium hydroxide to give the hydroxy acid **1**.

In spite of possessing strong conjugation of the amino group in **5**, this compound condensed with arylaldehydes under acid catalysis at 120° to give 2-aryl-1,2-dihydro-6-nitro-3*H*-pyrido[2,3-*d*]pyrimidin-4-ones **9** in about 60% yield. However, it is interesting to point out that the reaction was very slow when carried out at a temperature less than 120° and on the other hand above 120° 2-aryl-6-nitro-3*H*-pyrido[2,3-*d*]pyrimidin-4-ones were also obtained.

Aminopyridines are generally obtained by reduction of the respective nitropyridines; the reducing agents used most frequently are ferrous hydroxide [14], iron in acid solution [21], stannous chloride [22], hydrogen/Raney Ni [23] or Pd-C [24].

We found that the first reagent was better for obtaining 6-amino-2-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-4-ones **10**. Treating **9a-9c** with freshly prepared iron(II) hydroxide in water/dimethylformamide at reflux gave **10a-10c** in 45-70% yield. In the reduction of **9d**, the yield of **10d** was improved by addition of interphase catalyst tetrabuthylammonium bromide (TAB).

Preliminary diuretic testing indicated **10d** as active with an oral dose of 3 mg/Kg on male Wistar rats.

EXPERIMENTAL

Melting points were determined in a Mettler FP82 + FP80 apparatus and are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorus pentoxide at 3-4 mm Hg, 2-3 hours at about 60-70°). Infrared spectra were recorded on a Perkin-Elmer 681 apparatus, using potassium bromide tablets for solid products and sodium chloride plates for liquid products; the frequencies are expressed in cm^{-1}. The ^{1}H-nmr spectra were obtained on a Bruker AC-200E (200 MHz) instrument, with tetramethylsilane as the internal reference, at a concentration of about 0.1 g/ml and with dimethyl sulfoxide-d_6 the as solvent; the chemical shifts are reported in ppm relative to tetramethylsilane (δ units), and the abreviations (s, m, t) are the usual. The mass spectra were recorded on a Hewlett-Packard 5988-A instrument at 70 eV.

Thin-layer chromatography (tlc) was carried out in silica gel (DSF-5, Cammaga 0.3 mm thickness) with benzene:dioxane:acetic acid (90:25:4) as the solvent and the plates were scanned under ultraviolet light λ = 254 and 366 nm. Column chromatography was carried out on silica gel 60 Merck (70-230 mesh ASTM) with indicated solvents.

Solvents were usually removed under vacuum or in a rotavapory evaporator when stated.

1,2-Dihydro-5-nitro-2-oxo-3-pyridinecarboxylic Acid **1**.

Method A.

Nitric acid (7.0 g of density 1.4 g/cc) was added dropwise to a stirred solution of 1,2-dihydro-2-oxo-3-pyridinecarboxylic acid (10.0 g, 71.0 mmoles) in concentrated sulfuric acid (100.0 g), at a temperature less than 40°. The mixture was stirred for 2 hours at 60° and then cooled in an ice-bath with 300 g of ice added in small portions. The yellow solid material was collected by filtration and recrystallized from ethanol to give 8.87 g (76%) of **1**, mp 243-245° (from ethanol, reported [18], from water 265-266°); ir: 3300-2500 (broad, COOH), 1720 (CO), 1350 (NO_2); ^{1}H-nmr: 8.72 (d, 1H, H-4), 9.01 (d, 1H, H-6), 12.34 (bs, 2H, COOH and OH), J_{46} = 3 Hz.

Anal. Calcd. for $C_6H_4N_2O_5$: C, 39.14; H, 2.18; N, 15.21. Found: C, 39.19; H, 2.30; N, 15.30.

Method B.

Compound **3** (or **4**) (2 mmoles), was added to a solution of potassium hydroxide and methanol (10 ml, 1*M*), and the mixture was stirred at room temperature for 24 hours. Methanol was removed under vacuum. The residual solution was diluted with water (5 ml) and acidified with hydrochloric acid to *p*H 2. The yellow solid material was collected by filtration and recrystallized as indicated above, yield 0.14 g (76%).

Method C.

Compound **4** (2 mmoles) was added to a solution of potassium hydroxide (10 ml, 1*M*) and methanol, and the mixture was stirred at 60° for 24 hours. Methanol was removed under vacuum. The residual solution was diluted with water (5 ml) and acidified with hydrochloric acid to *p*H 2. The yellow solid material was collected by filtration and recrystallized as indicated above, yield 0.12 g (65%).

Bis(2-chloro-5-nitro-3-pyridinecarboxylic) Anhydride **3**.

A suspension of 2.0 g (10.9 mmoles) of **1**, 0.5 ml of DMF and 4.5 ml of phosphorus oxychloride in 45 ml of monochlorobenzene was boiled for two hours with stirring. The mixture was protected from humidity with a calcium chloride tube. The solvents were removed in vacuum, and the residual material was treated twice with xylene. The solvent was removed once again in vacuum. Monochlorobenzene (40 ml) was added to residual crude oil **2** and

the mixture was stirred in an ice-bath. Subsequently, water (40 ml) was added in drops and the suspension was stirred at room temperature for 3 hours. The solid material was collected by filtration and recrystallized (0.5 g). The organic layer of the filtrate was separated and the aqueous layer was extracted with monochlorobenzene (2 x 40 ml). The re-collected organic extracts were dried (sodium sulfate) and the solvent was removed in vacuum. The resulting residue was recrystallized (0.77 g), total yield 1.27 g (65%), mp >300° (ethyl acetate); ir: 1800, 1745 (COOCO), 1350 (NO_2); ^{1}H-nmr: 8.82-8.94 (m, 2H, H-4, H-4'), 9.29-9.41 (m, 2H, H-6, H-6').

Anal. Calcd. for $C_{12}H_4N_4O_7Cl_2$: C, 37.21; H, 1.03; N, 14.47. Found: C, 37.24; H, 0.98; N, 14.35.

Ethyl 2-Ethoxy-5-nitro-3-pyridinecarboxylate **4**.

A stirred mixture of 10.0 g (54.0 mmoles) of **1**, 2 ml of DMF and 20 ml of phosphorus oxychloride in 200 ml of monochlorobenzene was boiled for two hours. The solvents were removed in vacuum, and the residual material was treated twice with xylene. The solvent was removed once again in vacuum. The residual crude oil **2** was boiled with 150 ml of absolute ethanol for two hours. The solvent was removed in vacuum. The residual material was dissolved in 300 ml of chloroform and treated with 200 ml of water. Potassium carbonate was then added in small portions to reach *p*H = 8. The organic layer was washed with 200 ml of water and dried in anhydrous sodium sulfate. The solvent was removed in vacuum and the solid residue was recrystallized, mp 55-56° (isooctane) yield 9.0 g (70%); ir: 1730 (CO), 1340 (NO_2); ^{1}H-nmr: 1.20-1.50 (m, 6H, CH_3), 4.32 (q, 2H, CH_2), 4.53 (q, 2H, CH_2), 8.73 (d, 1H, H-4), 9.21 (d, 1H, H-6), $J_{4,6}$ = 2 Hz.

Anal. Calcd. for $C_{10}H_{11}N_2O_5$: C, 50.00; H, 5.00; N, 11.67. Found: C, 49.21; H, 5.18; N, 11.76.

2-Amino-5-nitro-3-pyridinecarboxamide **5**.

Ethyl 2-ethoxy-5-nitro-3-pyridinecarboxylate **4** (10.0 g, 41.7 mmoles) and 200 ml of methanol previously saturated with anhydrous ammonia were heated in an autoclave at 80° for 1 hour and then at 100° (≈150 psi) for 3 hours more. The solvent was removed under vacuum and the solid residue was washed with water and recrystallized to give 6.4 g (85%) of **5**, mp >300° (DMF); ir: 3450-3100 (several bands, NH_2), 1650 (CO), 1325 (NO_2); ^{1}H-nmr: 7.68 (s, 1H, NH), 8.10-8.70 (bs, 3H, NH, $CONH_2$), 8.84 (d, 1H, H-4), 9.00 (d, 1H, H-6), $J_{4,6}$ = 2 Hz.

Anal. Calcd. for $C_6H_6N_4O_3$: C, 39.56; H, 3.30; N, 30.77. Found: C, 39.45; H, 3.47; N, 30.94.

N-Methyl-2-methylamino-5-nitro-3-pyridinecarboxamide **6**.

A mixture of **4** (10 g, 41.7 mmoles) and 300 ml of 40% aqueous methylamine was stirred in an autoclave at 90° for 5 hours. Subsequently, the solid material which crystallized on cooling was collected by filtration and recrystallized to give 4.4 g (50%) of **6**, mp 244-246° (2-propanol); ir: 3400, 3320 (NH), 1650 (CO), 1340 (NO_2); ^{1}H-nmr: 2.79 (d, 3H, NCH_3), 3.04 (d, 3H, NCH_3), 8.69 (d, 1H, H-4), 8.75-9.00 (bs, 1H, NH), 9.05 (d, 1H, H-6), 9.25-9.40 (bs, 1H, NH), $J_{4,6}$ = 2 Hz.

Anal. Calcd. for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.76; N, 26.67. Found: C, 45.71; H, 4.76; N, 26.62.

Compound **6** was also obtained from **7** in a similar manner to that described above for **4**, but at 150° for 8 hours, yield 20%.

Ethyl 2-Amino-5-nitro-3-pyridinecarboxylate **7**.

Ethyl 2-ethoxy-5-nitro-3-pyridinecarboxylate **4** (7 g, 29.16 mmoles) and 100 ml of ethanol previously saturated with anhydrous ammonia were heated in an autoclave at 100° (*ca* 100 psi) for 8 hours and then at 150° (*ca* 200 psi) for an additional 14 hours. Upon cooling, a solid **7** was collected and recrystallized, mp 193-194° (with 2-propanol, reported [14] 196° with acetic acid), yield 4.6 g (76%); ir: 3400, 3280 (NH_2), 1700 (CO), 1340 (NO_2); ^{1}H-nmr: 1.35 (t, 3H, CH_3), 4.34 (q, 2H, CH_2), 8.00-8.30 (bs, 1H, NH), 8.50-8.70 (m, 2H, NH, H-4), 9.00 (d, 1H, H-6), $J_{4,6}$ = 2 Hz.

Anal. Calcd. for $C_8H_9N_3O_4$: C, 45.50; H, 4.26; N, 19.90. Found: C, 45.39; H, 4.25; N, 20.07.

2-Methylthio-6-nitro-3*H*-pyrido[2,3-*d*]pyrimidin-4-one **8**.

Solid *S*-methylpseudothiourea as the hydroiodide (0.92 g, 4.20 mmoles) was added at room temperature to a stirred solution of **4** (1.0 g, 4.17 mmoles) and triethylamine (0.92 g, 4.20 mmoles) in 10 ml of dimethylformamide (DMF). The mixture was heated at 80° for 2 hours and then at reflux for 3 hours. The solution was cooled in an ice bath, water (70 ml) was added, and the mixture was stirred for 1 hour. The solid material was collected and recrystallized to give 0.2 g (21%) of **8**, mp 238-239° (ethanol/DMF); ir: 1700 (CO), 1350 (NO_2); ^{1}H-nmr: 2.63 (s, 3H, SCH_3), 8.90 (d, 1H, H-5), 9.52 (d, 1H, H-7), 13.40 (s, 1H, NH), $J_{5,7}$ = 2 Hz.

Anal. Calcd. for $C_8H_6N_4O_3S$: C, 40.33; H, 2.52; N, 23.52. Found: C, 40.61; H, 2.82; N, 23.21.

2-Aryl-1,2-dihydro-6-nitro-3*H*-pyrido[2,3-*d*]pyrimidin-4-ones **9**.

A stirred mixture of **5** (1.0 g, 5.5 mmoles), zinc chloride (0.1 g) and the respective arylaldehyde (11 mmoles) in diglyme (10 ml) was heated at 120° for 7 hours. When the solution cooled, a solid appeared. It was collected by filtration, triturated in ethyl ether and recrystallized as indicated.

1,2-Dihydro-2-(4-hydroxyphenyl)-6-nitro-3*H*-pyrido[2,3-*d*]pyrimidin-4-one **9a**.

From 4-hydroxybenzaldehyde **9a** had mp 248-250° (ethanol/2-propanol), yield 1.07 g (68%); ir: 3500-3050 (several bands, OH, NH), 1690 (CO), 1350 (NO_2); ^{1}H-nmr: 5.97 (s, 1H, H-2), 6.78 (d, 2H, H-3', H-5'), 7.23 (d, 2H, H-2', H-6'), 8.48 (d, 1H, H-5), 8.88 (s, 1H, NH), 9.00 (d, 1H, H-7), 9.46 (s, 1H, NH), 9.63 (s, 1H, OH), $J_{5,7}$ = 2 Hz, $J_{2',3'}$ = 8 Hz.

Anal. Calcd. for $C_{13}H_{10}N_4O_4$: C, 54.55; H, 3.50; N, 19.58. Found: C, 54.77; H, 3.64; N, 19.31.

1,2-Dihydro-2-(4-chlorophenyl)-6-nitro-3*H*-pyrido[2,3-*d*]pyrimidin-4-one **9b**.

From 4-chlorobenzaldehyde, **9b** had mp 261-263° (ethanol/2-propanol), yield 1.02 g (61%); ir: 3190 (NH), 1680 (CO), 1350 (NO_2); ^{1}H-nmr: 6.11 (s, 1H, H-2), 7.41-7.55 (m, 4H, H-2', H-3', H-5', H-6'), 8.49 (d, 1H, H-5), 8.96-9.10 (m, 2H, H-7, NH), 9.57 (s, 1H, NH), $J_{5,7}$ = 2 Hz.

Anal. Calcd. for $C_{13}H_9N_4O_3Cl$: C, 51.24; H, 2.96; N, 18.39. Found: C, 51.54; H, 3.02; N, 18.53.

1,2-Dihydro-6-nitro-2-phenyl-3*H*-pyrido[2,3-*d*]pyrimidin-4-one **9c**.

From benzaldehyde, **9c** had mp 255-257° (2-propanol), yield 0.99 g (67%); ir: 3190 (NH), 1690 (CO), 1350 (NO_2); ^{1}H-nmr: 6.07 (s, 1H, H-2), 7.35-7.49 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 8.50 (d, 1H, H-5), 8.95-9.10 (m, 2H, H-7, NH), 9.58 (s, 1H, NH), $J_{5,7}$ = 2 Hz.

Anal. Calcd. for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.70; N, 20.74. Found: C, 57.78; H, 3.79; N, 20.62.

1,2-Dihydro-6-nitro-2-(4-trifluoromethylphenyl)-3*H*-pyrido[2,3-*d*]-pyrimidin-4-one **9d**.

From 4-trifluoromethylbenzaldehyde, **9d** had mp 231-233° (ethanol/water), yield 0.80 g (43%); ir: 3200 (NH), 1680 (CO), 1330 (NO_2); ^{1}H-nmr: 6.21 (s, 1H, H-2), 7.67 (d, 2H, H-2', H-6'), 7.81 (d, 2H, H-3', H-5'), 8.50 (d, 1H, H-5), 9.03 (s, 1H, NH), 9.10 (d, 1H, H-7), 9.63 (s, 1H, NH), $J_{5,7}$ = 2 Hz, $J_{2',3'}$ = 8 Hz.

Anal. Calcd. for $C_{14}H_9N_4O_3F_3$: C, 49.70; H, 2.66; N, 16.57. Found: C, 50.18; H, 2.75; N, 16.41.

1,2-Dihydro-6-nitro-2-(4-nitrophenyl)-3*H*-pyrido[2,3-*d*]pyrimidin-4-one (**9e**).

From 4-nitrobenzaldehyde, **9e** had mp 231-233° (ethanol/2-propanol), yield 0.85 g (49%); ir: 3200 (NH), 1690 (CO), 1350 (NO_2); ^{1}H-nmr: 6.27 (s, 1H, H-2), 7.73 (d, 2H, H-2', H-6'), 8.30 (d, 2H, H-3', H-5'), 8.51 (d, 1H, H-5), 9.05 (d, 1H, H-7), 9.18 (s, 1H, NH), 9.70 (s, 1H, NH), $J_{5,7}$ = 2 Hz, $J_{2',3'}$ = 8 Hz.

Anal. Calcd. for $C_{13}H_9N_5O_5$: C, 49.52; H, 2.85; N, 22.22. Found: C, 49.73; H, 2.87; N, 22.29.

6-Amino-2-aryl-1,2-dihydro-3*H*-pyrido[2,3-*d*]pyrimidin-4-ones **10**.

Compounds **10** were obtained by the following methods.

Method 1.

The respective compound **9** (3.50 mmoles) in 25 ml of DMF was added dropwise to a stirred suspension of 35 mmoles of freshly precipitated ferrous hydroxide (from ferrous sulphate heptahydrate, 9.72 g, and barium hydroxide octahydrate, 11.01 g, in water, 75 ml) at room temperature. Subsequently, the mixture was boiled for 1 hour and then filtered. The filtrate and washings were evaporated in vacuum and the residue was triturated with 150 ml of water and saturated with sodium carbonate. The insoluble material was collected by filtration and recrystallized as indicated.

6-Amino-1,2-dihydro-2-(4-hydroxyphenyl)-3*H*-pyrido[2,3-*d*]pyrimidin-4-one (**10a**).

From **9a**, **10a** had mp >300° (methanol), yield 0.62 g (70%); ir: 3400-3100 (several bands, OH, NH_2, NH), 1670 (CO); ^{1}H-nmr: 4.71 (s, 2H, NH_2), 5.59 (s, 1H, H-2), 6.72 (d, 2H, H-3', H-5'), 6.83 (s, 1H, NH), 7.20-7.26 (m, 3H, H-2', H-6', H-5), 7.65 (d, 1H, H-7), 8.27 (s, 1H, NH), 9.47 (s, 1H, OH), $J_{5,7}$ = 2 Hz, $J_{2',3'}$ = 8 Hz.

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.04; H, 4.69; N, 21.88. Found: C, 59.64; H, 4.76; N, 21.54.

6-Amino-2-(4-chlorophenyl)-1,2-dihydro-3*H*-pyrido[2,3-*d*]pyrimidin-4-one **10b**.

From **9b**, **10b** had mp >300° (ethyl acetate), yield 0.44 g (46%); ir: 3400, 3330, 3220 (NH_2, NH), 1670 (CO); ^{1}H-nmr: 4.76 (s, 2H, NH_2), 5.69 (s, 1H, H-2), 7.08 (s, 1H, NH), 7.27 (d, 1H, H-5), 7.45 (s, 4H, H-2', H-3', H-5', H-6'), 7.67 (d, 1H, H-7), 8.47 (s, 1H, NH), $J_{5,7}$ = 2 Hz.

Anal. Calcd. for $C_{13}H_{11}N_4OCl$: C, 56.84; H, 4.01; N, 20.40. Found: C, 56.53; H, 4.02; N, 20.05.

6-Amino-1,2-dihydro-2-phenyl-3*H*-pyrido[2,3-*d*]pyrimidin-4-one **10c**.

From **9c**, **10c** had mp 195-197° (ethanol/water), yield 0.43 g (52%); ir: 3400, 3330, 3220 (NH_2, NH), 1660 (CO); ^{1}H-nmr: 4.72 (s, 2H, NH_2), 5.68 (s, 1H, H-2), 7.03-7.42 (m, 7H, NH, H-2', H-3', H-4', H-5', H-6', H-5), 7.66 (d, 1H, H-7), 8.44 (s, 1H, NH), $J_{5,7}$ = 2 Hz.

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 65.00; H, 5.00; N, 23.33. Found: C, 64.74; H, 5.31; N, 23.15.

Method 2.

The method is illustrated for the preparation of **10d**.

6-Amino-1,2-dihydro-2-(4-trifluoromethylphenyl)-3*H*-pyrido[2,3-*d*]-pyrimidin-4-one **10d**.

Compound **9d** (1 g, 3.07 mmoles) and tetrabutylammonium bromide (0.5 g) in 20 ml of DMF was added, dropwise to a stirred suspension of 30.7 mmoles of freshly precipitated ferrous hydroxide (from ferrous sulphate heptahydrate, 8.53 g, and barium hydroxide octahydrate, 9.67 g, in water, 125 ml), at room temperature. Subsequently, the mixture was boiled for 1 hour and then filtered. The filtrate and washings were evaporated in vacuum. The residue was eluted by column chromatography with chloroform/ethanol 8:2 and recrystallized, (water) mp >300° yield 0.73 g (70%); ir: 3400, 3220 (NH_2, NH), 1660 (CO); ^{1}H-nmr: 4.76 (s, 2H, NH_2), 5.78 (s, 1H, H-2), 7.19 (s, 1H, NH), 7.28 (d, 1H, H-5), 7.64-7.78 (m, 5H, H-2', H-3', H-5', H-6', H-7), 8.57 (s, 1H, NH), $J_{5,7}$ = 3 Hz.

Anal. Calcd. for $C_{14}H_{11}N_4OF_3$: C, 54.55; H, 3.57; N, 18.18. Found: C, 54.69; H, 3.49; N, 18.13.

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