

NEW SYNTHESIS OF PYRIDO[2,3-*d*]PYRIMIDINES. I.
 REACTION OF 6-ALKOXY-5-CYANO-3,4-DIHYDRO-2-PYRIDONES
 WITH GUANIDINE AND CYANAMIDE

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Abstract - The first step of a new synthesis of pyrido[2,3-*d*]pyrimidines, the substitution of the enolic alkoxy group of 6-alkoxy-5-cyano-3,4-dihydro-2-pyridones (**2**) by guanidine and cyanamide is described. By this procedure a series of 2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8H)-ones (**6**) and 6-cyanamino-5-cyano-3,4-dihydro-2-pyridones (**3**) have been synthesized. Products **3** have been isolated in this work for the first time, and tautomeric equilibrium with the cyanimino form has been detected in every case.

Pyrido[2,3-*d*]pyrimidines have been normally obtained by two general ways: a) formation of the pyridine ring by cyclization of suitable substituents of a pyrimidine¹, and b) formation of the pyrimidine ring by cyclization of suitable substituents of a pyridine².

In the last years our group has been studying a new synthesis of pyrido[2,3-*d*]pyrimidines following a 'b' type methodology as depicted in scheme 1. In this way, any α , β -unsaturated ester can be converted, in a maximum of four synthetic steps, into heterocycles having a large variety of substituents in carbons C-2, C-4, C-5 and C-6.

Our synthesis begins with the preparation of 6-alkoxy-5-cyano-3,4-dihydro-2-pyridones (**2**) by a Michael reaction between propanedinitrile and an α , β -unsaturated ester in an alcoholic solvent. Table 1 shows the products **2** which have been obtained in this work, inclusive of some others previously reported by our group^{3,4} for comparison purposes. Yields are generally better with methanol than with ethanol, due to the lower thermic level of the reaction that is carried out at reflux.

The reaction of **2** with some amines has been described in a previous paper⁵. In particular the reaction with hydrazine and phenylhydrazine at low temperature leads to the hydrazino substituted pyridone.

Now we wish to report the results obtained in the reaction of **2** with guanidine and cyanamide as nucleophiles.

Scheme 1

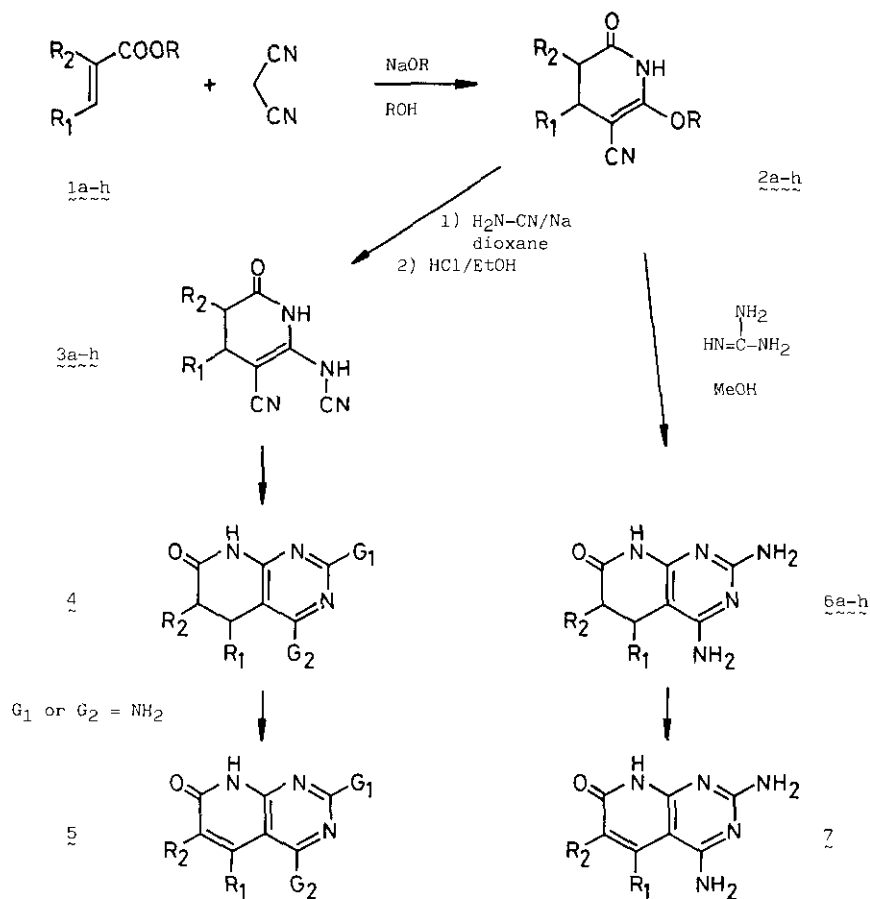


Table 1

	R ₁	R ₂	Yields (%)			
			R=Me	2	3	6
a	CH ₃	H	50	60	90	97
b	H	CH ₃	49	--	74	87
c	---(CH ₂) ₄ ---		57	--	74	80
d	CH(OCH ₃) ₂	H	72*	60	80	90
e	C ₆ H ₅	H	85	80	95	89
f	2-furyl	H	87	75	63	82
g	2-thienyl	H	90	70	91	88
h	C ₆ H ₅	C ₆ H ₅	88	--	94	75

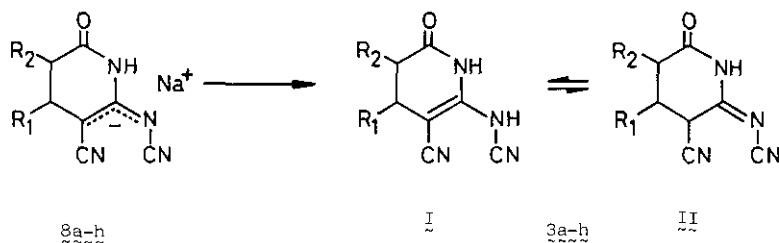
*Previously reported by our group^{3,4}

Reaction of $\underline{2a-h}$ ($R=CH_3$) with guanidine in methanol at reflux provides 2,4-diamino-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-ones ($\underline{6a-h}$) in good yields (Table 1).

Substitution of the methoxyl group of $\underline{2a-h}$ ($R=CH_3$) by cyanamide carried out in dioxane at reflux, in the presence of a stoichiometric amount of sodium, affords $\underline{8a-h}$ in quantitative yield for all the studied members of the family. Systems like $\underline{8}$ have usually been the starting material for the synthesis of pyrimidines^{6,7} and we ourselves actually synthesized⁵ the corresponding 2-amino-5,6-dihydro-4-methoxypyrido[2,3-d]pyrimidin-7(8H)-one by addition of methanol to $\underline{8d}$.

Treatment of sodium salts $\underline{8a-h}$ with the stoichiometric quantity of hydrogen chloride in either methanol or ethanol has allowed the isolation of $\underline{3a-h}$ (Table 1).

Scheme 2



The ir spectra of the whole family in the solid state exhibit two C=O bands (1760-1700 cm^{-1}), two stretching N-H bands (3220-3100 cm^{-1}) due to the cis associated amide and four C≡N bands more or less resolved (2260-2150 cm^{-1}). As elemental analyses are correct for every product, the multiplicity of bands confirms the tautomeric equilibrium expected, which is clearly detected in some cases (for example $\underline{3a}$) by ¹H-nmr thanks to the lucky chemical shift of the malonic proton of \underline{II} which appears as a 0.5 protons doublet ($\delta = 4.7$, $J = 11Hz$) which collapses to a singlet upon irradiation at 2.64 ppm, and the aminic proton of \underline{I} as a 0.5 protons broad signal ($\delta = 4.91$).

Potentiometric titration of $\underline{3a}$ presents a unique inflexion point allowing the calculation of the pK_a as 8.5 that would correspond to the more acidic tautomer, assuming a fast enough interconversion rate.

Products $\underline{3}$ are of great interest because of their special 1,3-dicarbonitrile substructure which is completely unknown in the literature. On the other hand, $\underline{3}$ is one of the most complex α,ω -dicyano substituted systems ever employed in the synthesis of fused pyrimidines and we will study the addition of acids and bases onto it in order to compare the results with those that have been predicted^{8,9}.

EXPERIMENTAL

The ir spectra were obtained on a Perkin Elmer 683 spectrophotometer. The ^1H -nmr spectra were recorded on a Varian XL 200/F-19 and a Perkin Elmer R-24 spectrophotometers with TMS as an internal standard in the solvents as indicated. Mass spectra were obtained on a Hitachi-Perkin Elmer RM 50 and Hewlett-Packard 5930 A mass spectrometers. Melting points were determined on a Büchi-Tottoli apparatus, and are uncorrected.

5-Cyano-3,4-dihydro-6-methoxy-2-pyridones 2a-h. (General procedure¹⁰). To a solution of sodium in anhydrous methanol, the specified quantity of propanedinitrile was added and the mixture left to cool down. The corresponding α,β -unsaturated ester was added slowly and the mixture refluxed for the specified time. The solvent was distilled in vacuo and the residue dissolved in the minimum quantity of water. Careful neutralization to pH=7 allowed the precipitation of a solid which was filtered and washed with cold water. The precipitate was dissolved in chloroform and the solution was dried with anhydrous magnesium sulphate. Distillation of the solvent in vacuo yielded the corresponding pyridones. Proportion of reagents is shown in each case (ester:propanedinitrile:sodium, methanol (l/mol of ester), reaction time (h)).

5-Cyano-3,4-dihydro-6-methoxy-4-methyl-2-pyridone (2a); yield: 50%, (1:1.19:1.43, 1.8, 1.5); mp 146-147°C (from benzene); ir (KBr): 3180, 3095 (NH), 2195 (CN), 1685 (CO), 1635 cm^{-1} ; ^1H -nmr (CDCl_3): δ 8.65 (br s, 1H, NH), 4.05 (s, 3H, CH_3O), 2.90-2.15 (m, 3H, CH and CH_2), 1.17 ppm (d, J 6 Hz, 3H, CH_3); ms: 166 (M^+ , 32), 151 (100). Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{N}_2\text{O}_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.01; H, 6.09; N, 16.56.

5-Cyano-3,4-dihydro-6-methoxy-3-methyl-2-pyridone (2b); yield: 49%¹¹, (1:1.19:1.43, 1.8, 1.5); mp 146-147°C (lit.³ mp 146-147°C).

4-Cyano-4a,5,6,7,8,8a-hexahydro-3-methoxyisoquinolin-1(2H)-one (2c); yield: 57%, (1:1.25:1.25, 1.4, 2); mp 158-159°C (from a 1:5 mixture of hexane:benzene); ir (KBr): 3200, 3100 (NH), 2200 (CN), 1685 (CO), 1640 cm^{-1} ; ^1H -nmr (CDCl_3): δ 8.6 (br s, 1H, NH), 4.0 (s, 3H, CH_3O), 2.75-2.50 (m, 2H, CH), 1.50-1.30 ppm (m, 8H, CH_2); ms: 206 (M^+ , 61), 164 (100). Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.16; H, 6.89; N, 13.36.

5-Cyano-4-dimethoxymethyl-3,4-dihydro-6-methoxy-2-pyridone (2d); yield: 72%, (1:1:1.7, 1.0, 2.5); mp 98-99°C (lit.¹² mp 98-99°C).

5-Cyano-3,4-dihydro-6-methoxy-4-phenyl-2-pyridone (2e); yield: 85%, (1:1.1:1.25, 1.6, 5); mp 143-144°C (from a 1:5 mixture of hexane:benzene); ir (KBr): 3200, 3120 (NH), 2200 (CN), 1695 (CO), 1640 cm^{-1} ; ^1H -nmr (CDCl_3): δ 8.82 (br s, 1H, NH), 7.13 (s, 5H, H arom), 4.0 (s, 3H, CH_3O), 3.8 (t, J 6 Hz, 1H, CH), 2.80 and 2.73 ppm (ABX system, J_{gem} 16 Hz, 2H, CH_2); ms: 228 (M^+ , 80), 115 (100). Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.24; H, 5.28; N, 12.06.

5-Cyano-4-(2-furyl)-3,4-dihydro-6-methoxy-2-pyridone (2f); yield: 87%, (1:1.3:1.9, 2.2, 5); mp 116-117°C (from diethyl ether); ir (KBr): 3200, 3110 (NH), 2200 (CN), 1695 (CO), 1640 cm^{-1} ; ^1H -nmr (CDCl_3): δ 8.7 (br s, 1H, NH), 7.2 (m, 1H, furan ring), 6.2-6.0 (m, 2H, furan ring), 4.0 (s, 3H, CH_3O), 3.8 (t, J 5 Hz, 1H, CH), 2.8 ppm (d, 2H, CH_2); ms: 218 (M^+ , 51), 122 (100). Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.54; H, 4.58; N, 12.98.

5-Cyano-3,4-dihydro-6-methoxy-4-(2-thienyl)-2-pyridone (2g); yield: 90%, (1:1.25:1.25, 2.3, 5); mp 135-136°C (from 1:5 mixture of hexane:benzene); ir (KBr): 3200, 3100 (NH), 2200 (CN), 1700 (CO), 1635 cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3): δ 9.0 (br s, 1H, NH), 7.75 (m, 1H, thiophene ring), 6.9 (m, 2H, thiophene ring), 4.25 (s, 3H, CH_3O), 4.25 (m, 1H, CH), 2.9 ppm (m, 2H, CH_2); ms: 234 (M^+ , 85), 191 (100). Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: C, 56.41; H, 4.30; N, 11.96; S, 13.66. Found: C, 56.48; H, 4.29; N, 11.75; S, 13.90.

5-Cyano-3,4-dihydro-6-methoxy-3,4-diphenyl-2-pyridone (2h); yield: 88%, (1:1.3:1.9, 4.5, 5); mp 174-175°C (from a 1:5 mixture of hexane:benzene); ir (KBr): 3220, 3170 (NH), 2200 (CN), 1710 (CO), 1630 cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3): δ 8.4 (br s, 1H, NH), 7.2 (s, 10H, H arom), 4.05 (s, 3H, CH_3O), 3.9 ppm (s, 2H, CH); ms: 304 (M^+ , 12), 118 (100). Anal. Calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.98; H, 5.30; N, 9.58.

2,4-Diamino-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-ones 6a-h. (General procedure). To a solution of sodium (0.011 g-atoms) in anhydrous methanol (30 ml), 5.5 mmol of guanidine carbonate were added and the mixture was refluxed for 15 min. The mixture was filtered and 5 mmol of the desired 5-cyano-3,4-dihydro-6-methoxy-2-pyridone (2) were added to the filtrate. The solution was refluxed for 20 h. The desired product was obtained as a precipitate from the mixture by filtration and washed with methanol and diethyl ether. Recrystallization from ethanol gave the following pyrido[2,3-d]pyrimidines 6:

2,4-Diamino-5,6-dihydro-5-methylpyrido[2,3-d]pyrimidin-7(8H)-one (6a); yield: 97%; mp 287-288°C; ir (KBr): 3460, 3340, 3230, 3120 (NH), 1670 cm^{-1} (CO); ms: 193 (M^+ , 38), 178 (100). Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{N}_5\text{O}$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.38; H, 6.01; N, 36.05.

2,4-Diamino-5,6-dihydro-6-methylpyrido[2,3-d]pyrimidin-7(8H)-one (6b); yield: 87%; mp >300°C; ir (KBr): 3460, 3410, 3380, 3340, 3220, 3090 (NH), 1695 cm^{-1} (CO); ms: 193 (M^+ , 100). Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{N}_5\text{O}$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.60; H, 5.92; N, 36.10.

2,4-Diamino-4b,5,6,7,8,8a-hexahydropyrimido[4,5-c]isoquinolin-9(10H)-one (6c); yield: 80%; mp >300°C; ir (KBr): 3495, 3470, 3390, 3200, 3090 (NH), 1670 cm^{-1} (CO); ms: 233 (M^+ , 80), 191 (100). Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{N}_5\text{O}$: C, 56.64; H, 6.48; N, 30.02. Found: C, 56.66; H, 6.70; N, 29.69.

2,4-Diamino-5-dimethoxymethyl-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-one (6d); yield: 90%¹³; mp 290°C (dec.) (lit.⁵ mp 290°C (dec.)).

2,4-Diamino-5,6-dihydro-5-phenylpyrido[2,3-d]pyrimidin-7(8H)-one (6e); yield: 89%; mp 303-304°C (dec.); ir (KBr): 3500, 3490, 3320, 3180 (NH), 1690 cm^{-1} (CO); ms: 255 (M^+ , 100). Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}$: C, 61.12; H, 5.13; N, 27.43. Found: C, 61.03; H, 5.14; N, 27.43.

2,4-Diamino-5-(2-furyl)-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-one (6f); yield: 82%; mp 302-303°C; ir (KBr): 3495, 3320, 3220, 3110 (NH), 1680 cm^{-1} (CO); ms: 245 (M^+ , 100). Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_5\text{O}_2$: C, 53.87; H, 4.52; N, 28.56. Found: C, 54.16; H, 4.64; N, 28.93.

2,4-Diamino-5,6-dihydro-5-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8H)-one (6g); yield: 88%; mp >300°C; ir (KBr): 3540, 3460, 3330, 3220, 3110 (NH), 1680 cm^{-1} (CO); ms: 261 (M^+ , 100). Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_5\text{OS}$: C, 50.57; H, 4.24; N, 26.81; S, 12.25. Found: C, 50.41; H, 4.23; N, 26.52; S, 12.09.

2,4-Diamino-5,6-dihydro-5,6-diphenylpyrido[2,3-d]pyrimidin-7(8H)-one (6h); yield: 75%; mp >300°C (lit.¹⁴ mp 313-314°C).

6-Cyanamino-5-cyano-3,4-dihydro-2-pyridones 3a-h. (General procedure). A mixture of 60 ml freshly distilled dioxane, 8.8 mmol of cyanamide, 0.0088 g-atoms of sodium and 8.8 mmol of the corresponding 5-cyano-3,4-dihydro-6-methoxy-2-pyridone (2) was refluxed for 8 to 20 h. The mixture was filtered at 80°C and the precipitate washed with diethyl ether and dried over phosphorous pentoxide to yield the sodium salts 8a-h. These were dissolved in 45 ml of anhydrous ethanol (or methanol for 8f-h), and 2.4 ml (8.8 mmol) of a 3.7N ethanolic solution of hydrogen chloride, freshly titrated with sodium hydroxide, were added with stirring, and ice/water cooling. After addition, the solution was stirred for 15 to 30 min at room temperature. The mixture was filtered and the precipitate stirred with 50 ml of water for 15 min. The resulting crystalline solid was filtered and dried in vacuo over phosphorous pentoxide. Recrystallization for analysis was performed from a mixture of ethyl acetate and hexane.

6-Cyanamino-5-cyano-3,4-dihydro-4-methyl-2-pyridone (3a); yield: 90%; mp 168°C (dec.); ir (KBr): 3220, 3120 (NH), 2240, 2205, 2175, 2150 (CN), 1755, 1740 (CO), 1615 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 4.91 (br s, 0.5H, NH), 4.71 (d, J 11 Hz, 0.5H, C₅H), 2.72-2.50 (m, 3H, CH and CH₂), 1.16 ppm (d, J 5.5 Hz, 3H, CH₃); ms: 176 (M⁺, 76). Anal. Calcd. for C₈H₈N₄O: C, 54.54; H, 4.58; N, 31.8. Found: C, 54.53; H, 4.58; N, 31.63.

6-Cyanamino-5-cyano-3,4-dihydro-3-methyl-2-pyridone (3b); yield: 74%; mp 145°C (dec.); ir (KBr): 3195, 3140 (NH), 2260, 2220-2190 (CN), 1740-1720 (CO), 1625 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 12.2 (br s, 1H, NH), 4.6 (br s, 1H, NH and C₅H), 2.9-2.7 (m, 1H, CH), 2.3-2.1 (m, 2H, CH₂), 1.1 ppm (2xd, J 6 Hz, 3H, CH₃); ms: 176 (M⁺, 100). Anal. Calcd. for C₈H₈N₄O: C, 54.54; H, 4.58; N, 31.8. Found: C, 54.71; H, 4.54; N, 31.96.

3-Cyanamino-4-cyano-4a,5,6,7,8,8a-hexahydroisoquinolin-1(2H)-one (3c); yield: 74%; mp 183 °C (dec.); ir (KBr): 3180, 3120 (NH), 2245, 2210-2195 (CN), 1735-1715 (CO), 1620 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 5.1-4.5 (m, 1H, NH and C₅H), 3.0-2.8 (m, 2H, CH), 2.0-1.0 ppm (m, 8H, CH₂); ms: 216 (M⁺, 27), 136 (100). Anal. Calcd. for C₁₁H₁₂N₄O: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.38; H, 5.55; N, 25.91.

6-Cyanamino-5-cyano-4-dimethoxymethyl-3,4-dihydro-2-pyridone (3d); yield: 80%; mp 153°C (dec.); ir (KBr): 3180, 3120 (NH), 2250, 2205-2180 (CN), 1735-1710 (CO), 1635 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 4.8-4.2 (br s, 2H, NH and CH), 3.4 (s, 6H, CH₃O), 3.0-2.5 ppm (m, 3H, CH and CH₂); ms: 236 (M⁺, 2), 75 (100). Anal. Calcd. for C₁₀H₁₂N₄O₃: C, 50.84; H, 5.12; N, 23.72. Found: C, 51.09; H, 5.10; N, 23.60.

6-Cyanamino-5-cyano-3,4-dihydro-4-phenyl-2-pyridone (3e); yield: 95%; mp 197°C (dec.); ir (KBr): 3180, 3120 (NH), 2260, 2210 (CN), 1740-1710 (CO), 1620 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 7.4 (m, 5H, H arom), 5.1-4.8 (br s, 1H, NH and C₅H), 3.9-3.8 (m, 1H, CH), 3.1-2.7 ppm (m, 2H, CH₂); ms: 238 (M⁺, 3), 131 (100). Anal. Calcd. for C₁₃H₁₀N₄O: C, 65.5; H, 4.2; N, 23.5. Found: C, 65.6; H, 4.35; N, 23.2.

6-Cyanamino-5-cyano-4-(2-furyl)-3,4-dihydro-2-pyridone (3f); yield: 63%; mp 168°C (dec.); ir (KBr): 3180, 3120 (NH), 2260, 2220-2185 (CN), 1750-1710 (CO), 1620 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 7.7 (m, 1H, furan ring), 6.45 (m, 2H, furan ring), 5.1-4.9 (br s, 1H, NH and C₅H), 4.2-4.0 (m, 1H, CH), 3.2-2.7 ppm (m, 2H, CH₂); ms: 228 (M⁺, 8), 121 (100). Anal. Calcd. for C₁₁H₈N₄O₂: C, 57.89; H, 3.53; N, 24.55. Found: C, 57.98; H, 3.53; N, 24.50.

6-Cyanamino-5-cyano-3,4-dihydro-4-(2-thienyl)-2-pyridone (3g); yield: 91%; mp 165°C (dec.); ir (KBr): 3160, 3120 (NH), 2250, 2220-2180 (CN), 1750-1715 (CO), 1620 cm^{-1} ; $^1\text{H-nmr}$ (DMSO-d_6): δ 7.5-7.4 (m, 1H, thiophene ring), 7.2-6.9 (m, 2H, thiophene ring), 5.1-4.7 (br s, 1H, NH and C_5H), 4.3-4.1 (m, 1H, CH), 3.2-2.8 ppm (m, 2H, CH_2); ms: 244 (M^+ , 2), 137 (100). Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{N}_4\text{OS}$: C, 54.09; H, 3.30; N, 22.94; S, 13.13. Found: C, 54.39; H, 3.28; N, 23.05; S, 12.99.

6-Cyanamino-5-cyano-3,4-dihydro-3,4-diphenyl-2-pyridone (3h); yield: 94%; mp 203°C (dec.); ir (KBr): 3200, 3100 (NH), 2250, 2220-2180 (CN), 1750-1710 (CO), 1625 cm^{-1} ; $^1\text{H-nmr}$ (DMSO-d_6): δ 7.2-7.0 (m, 10H, H arom), 5.1-5.0 (m, 1H, NH and C_5H), 4.3-4.2 ppm (m, 2H, CH); ms: 90 (100). Anal. Calcd. for $\text{C}_{19}\text{H}_{14}\text{N}_4\text{O}$: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.92; H, 4.70; N, 17.49.

ACKNOWLEDGEMENTS

Support of this work by a grant from the Comisión Asesora de Investigación Científica y Técnica of the Presidencia de Gobierno of Spain (Proyecto 0622/81) is gratefully acknowledged. Two of us (R. N. and M. G.) would like to thank the Ministerio de Educación y Ciencia of Spain for two grants within the Plan de Formación de Personal Investigador.

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Received, 21st December, 1984