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2-Methoxy-4-amino-5-pyrimidinecarbaldehyde (**2a**) as well as its 6-methyl **2b** and 6-phenyl derivatives **2c** were prepared by reduction of the corresponding aminopyrimidinecarbonitriles **1**. Catalytic hydrogenation of **1a**, **1b** gives 5-hydroxymethylpyrimidines **3a**, **3b**; under the same conditions **1c** afforded 5-aminomethylpyrimidine **4**. Condensation of **2** with carbonitriles, ketones and polyfunctional carbonyl compounds bearing the $-\text{CH}_2\text{CO}-$ moiety afforded the pyrido[2,3-*d*]pyrimidines and pyrimido-[4,5-*b*]quinoline derivatives.

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Following our report [1] of the cyclocondensation of carbonitriles, ketones and polyfunctional carbonyl compounds bearing the $-\text{CH}_2\text{CO}-$ moiety with heterocyclic aminoaldehydes, we describe the condensation reactions of 4-aminopyrimidine-5-carbaldehyde derivatives **2**, prepared by catalytic reduction of the corresponding 4-aminopyrimidine-5-carbonitriles **1** [2,3], with active methylene compounds.

The reduction of heterocyclic nitriles to aldehydes has been accomplished under a variety of different conditions [4-6]. Extensive experimentation by different methods of chemical and catalytic reduction of the nitrile group in compounds **1** revealed that hydrogenation using 10% Pd/C in dilute sulfuric acid was the best method. Although aldehydes are readily hydrogenated to the corresponding alcohols at room temperature and moderate pressures, under properly controlled conditions no similar reduction appears to occur, and good yields (61-78%) of the aldehydes **2** were obtained (Figure 1).

Koppel *et al.* [7] prepared a compound described as 4-amino-5-hydroxymethyl-2-methoxypyrimidine **3a**, which was formed from 4-amino-5-carbethoxy-2-methoxypyrimidine by treatment with lithium aluminum hydride. In our hands it was found that hydrogenation of

the compounds **1a**, **1b** with an excess of hydrogen yields hydroxymethylpyrimidines **3a**, **3b**; however, under the same conditions **1c** affords 6-phenyl-4-amino-5-aminomethyl-2-methoxypyrimidine **4**, due, probably, to the poor solubility of the intermediate aldimine which prevents its hydrolysis to aldehyde **2c**.

Analytical and spectroscopic data fully support the structural assignments for compounds **2**. The ^1H nmr spectra showed the presence of broad singlets corresponding to the protons of the primary amino groups and a singlet in the region δ 9.5-10 due to the proton of the formyl group. The ir spectrum of the aminoimidazolecarbaldehydes prepared in this work showed an absorption band at 1660 cm^{-1} due to CO stretching vibrations and no cyano group was observed.

Condensation of **2** with malononitrile in boiling methanol with piperidine as the catalyst has proved to be an excellent method for the synthesis of 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitriles **5**. These compounds are versatile synthetic intermediates and their preparation in virtually quantitative yields from aminopyrimidinecarbaldehydes **2** provide the opportunity for preparing a large number of polycondensed heterocyclic systems [8] for which, in many cases, alternate annelation methods are not readily available. However, 7-aminopyrido[2,3-*d*]pyrimidine-6-carbaldehydes could not be isolated from the corresponding aminonitriles **5**, and only the reduction products of the heterocyclic ring system **11** and **12** could be isolated (see Experimental).

Aminoaldehydes **2** are readily condensed with ethyl cyanoacetate under base-catalyzed conditions with formation of 6,7-functionalized pyridopyrimidines **6** and **7** which, in turn, are attractive starting materials for further ring annelations. With **2b** and **2c** cyclization takes place *via* intramolecular attack of the amino group on the nitrile function to give 7-aminopyrido[2,3-*d*]pyrimidines **6**. 2-Methoxy-4-amino-5-pyrimidinecarbaldehyde **2a**, however, as in the analogous quinoline synthesis [9], yielded

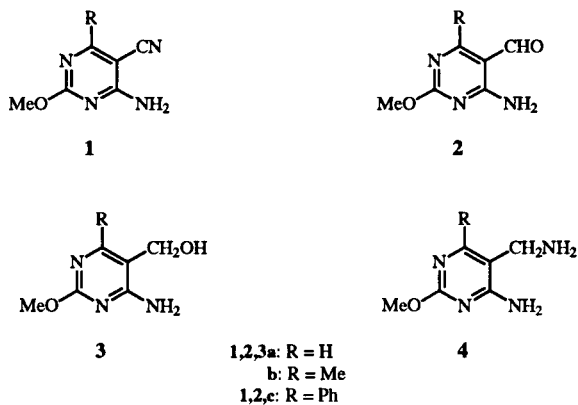
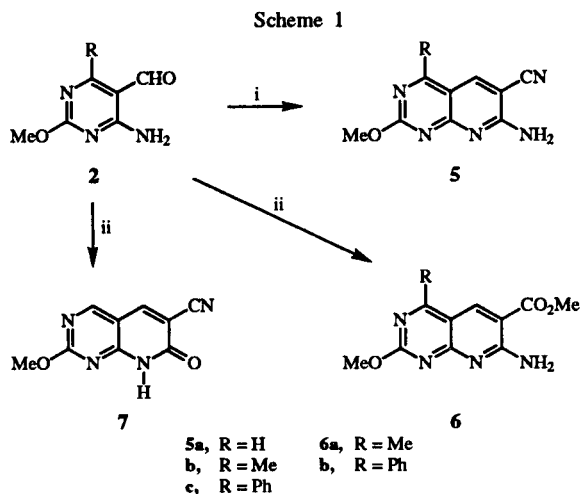


Figure 1

the 7-hydroxy derivative **7**. The infrared spectrum of **7** shows the presence of a conjugated nitrile group at 2210 cm^{-1} ; on the other hand, compounds **6** show a band at 1700 cm^{-1} due to the ester group, in addition to the strong N-H bands in the $3100\text{--}3400\text{ cm}^{-1}$ region, thus confirming the presence of a primary amino group (Scheme 1).



Reagents and conditions: i, CNCH_2CN , ethanol-piperidine, reflux; ii, $\text{CNCH}_2\text{CO}_2\text{Et}$, MeOH-MeONa , reflux.

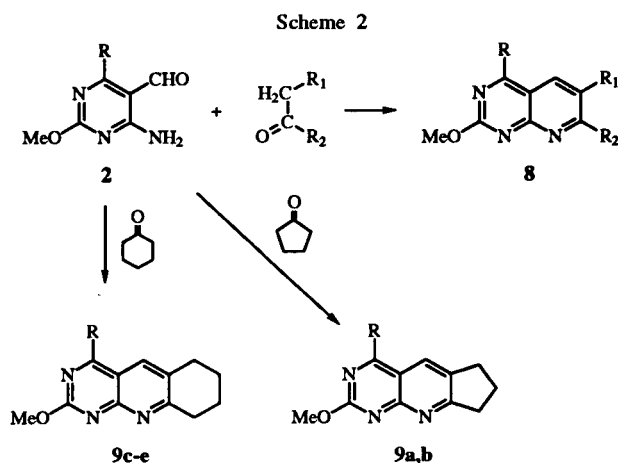
Condensation reactions of **2** with carbonyl compounds in the presence of methoxide ion gave the expected products **8a-l** in good yields. In this way, pyrimidoquinolines **9c-e** and polycyclic system **9a,b** were also prepared in good yields.

Some of the compounds **9** have a strong tendency to retain water of crystallization and high temperatures under reduced pressure were needed in order to get correct elemental analyses. However, compound **9b** tenaciously retains varying amounts of water, which could not be removed by using the above conditions.

In Friedländer reactions [10] with unsymmetrical aliphatic ketones, two different modes of cyclization should be theoretically possible, depending on whether the α -methyl or the α -methylene group undergoes condensation with the carbonyl group of the aminoaldehyde component. For linear ketones only one direction of ring closure was observed, although it is conceivable that small amounts of the isomeric products [11] were also formed but remained undetected in the reaction mixture. Thus base-catalyzed condensation of **2** and methyl ethyl ketone resulted in the formation of 6,7-dimethylpyrido[2,3-*d*]-

pyrimidine derivatives **8c**, **8g** and **8k**. The absence of the isomeric product was confirmed by nmr spectroscopy of the reaction product. Typically, compounds **8c**, **8g** and **8k** exhibited the presence of two singlets in the region $\delta\text{ 2.4--3.1}$ corresponding to the 6 and 7-methyl groups.

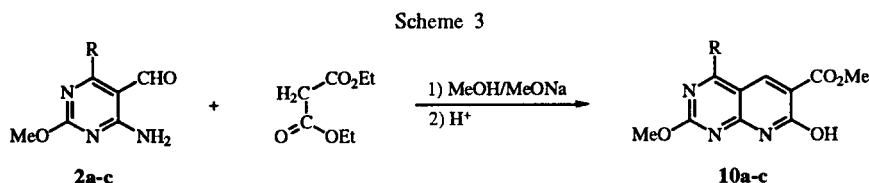
The structures of the heterocyclic condensed system **8** and **9** were fully supported by their analytical and spectroscopic properties. Particularly significant is the presence of the pyridine ring proton ($\delta\text{ 8.0--8.5}$, 5-H) in the nmr spectrum of compounds **8** (Scheme 2).



8a , R = H, R ₁ = H, R ₂ = Me	9a , R = Me
b , R = H, R ₁ = H, R ₂ = Ph	b , R = Ph
c , R = H, R ₁ = Me, R ₂ = Me	c , R = H
d , R = H, R ₁ = Et, R ₂ = Me	d , R = Me
e , R = Me, R ₁ = H, R ₂ = Me	e , R = Ph
f , R = Me, R ₁ = H, R ₂ = Ph	
g , R = Me, R ₁ = Me, R ₂ = Me	
h , R = Me, R ₁ = Et, R ₂ = Me	
i , R = Ph, R ₁ = H, R ₂ = Me	
j , R = Ph, R ₁ = H, R ₂ = Ph	
k , R = Ph, R ₁ = Me, R ₂ = Me	
l , R = Ph, R ₁ = Et, R ₂ = Me	

The reaction of **2** with diethyl malonate in the presence of sodium methoxide as a catalyst afforded, with transesterification of the ethyl ester group, the pyrido[2,3-*d*]-pyrimidine derivatives **10** in good yields. However, it was surprising that no cyclocondensation products could be isolated using some Michael reagents bearing acetyl groups such as ethyl acetoacetate and acetylacetone either under basic or acidic conditions (Scheme 3).

In summary, in this paper we report the preparation of 4-amino-5-pyrimidinecarbaldehydes **2** readily obtained from the respective 4-amino-5-pyrimidinecarbonitriles **1**.



These compounds **2** are suitable precursors for the synthesis of other heterocyclic fused systems. Thus, pyrido[2,3-*d*]pyrimidines and pyrimido[4,5-*b*]quinoline derivatives were obtained in good yields.

EXPERIMENTAL

Melting points were determined on a Büchi 530 or on a Gallenkamp open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Perkin Elmer 781 instrument in potassium bromide pellets, and nmr spectra were recorded at 300 MHz on a Varian VXR 300S spectrometer. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane as the internal standard. Microanalyses were performed by the Universidad Complutense Microanalytical Service. The reactions were monitored by tlc performed on silica gel plates (Merck 60-F) using chloroform-ethanol or toluene-ethyl acetate as the eluant.

General Procedure for the Reduction of the Aminopyrimidine-carbonitriles **1**.

A mixture of the corresponding aminopyrimidinecarbonitrile (27.1 mmol), sulfuric acid (6 ml) and 10% Pd/C (0.30 g) in water (30 ml) was hydrogenated in a Parr apparatus at room temperature and at an initial pressure of 50 psi until the calculated amount of hydrogen was absorbed (1 hour). After removal of the catalyst, the pH of the filtrate was adjusted to 8 with concentrated ammonium hydroxide. The solid which precipitated was filtered, washed with water and recrystallized to give the corresponding aminopyrimidinecarbaldehyde.

4-Amino-2-methoxypyrimidine-5-carbaldehyde (**2a**).

This compound was obtained from 4-amino-2-methoxypyrimidine-5-carbonitrile (**1a**) by following the above general procedure in a yield of 80%, white crystals, mp 187–189° (from water) [lit [12]].

4-Amino-6-methyl-2-methoxypyrimidine-5-carbaldehyde (**2b**).

This compound was obtained from 4-amino-6-methyl-2-methoxypyrimidine-5-carbonitrile (**1b**) by following the above general procedure in a yield of 67%, white crystals, mp 164–166° (from ethanol:water 1:1, v/v); ir (potassium bromide): 3360, 3280, 3140 (NH₂), 1660 (aldehyde CO) cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 10.1 (1H, s, CHO), 8.2 (2H, br s, NH₂), 3.8 (3H, s, MeO), 2.5 (3H, s, 6-Me).

Anal. Calcd. for C₇H₉N₃O₂ (167.17): C, 50.28; H, 5.44; N, 25.14. Found: C, 50.34; H, 5.43; N, 25.18.

4-Amino-6-phenyl-2-methoxypyrimidine-5-carbaldehyde (**2c**).

This compound was obtained from 4-amino-6-phenyl-2-methoxypyrimidine-5-carbonitrile (**1c**) by following the above general procedure in a yield of 61%, white crystals, mp 180–182° (from ethanol:water 2:1, v/v); ir (potassium bromide): 3360, 3260, 3120 (NH₂), 1660 (aldehyde CO) cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 9.6 (1H, s, CHO), 8.3 (2H, br s, NH₂), 7.5 (5H, s, phenyl protons), 3.9 (3H, s, MeO).

Anal. Calcd. for C₁₂H₁₁N₃O₂ (229.24): C, 62.86; H, 4.85; N, 18.33. Found: C, 62.58; H, 4.94; N, 18.31.

4-Amino-5-hydroxymethyl-2-methoxypyrimidine (**3a**).

A mixture of 4-amino-2-methoxypyrimidine-5-carbonitrile (**1a**) (10.0 mmol), sulfuric acid (5 ml) and 10% Pd/C (0.20 g) in water (30 ml) was hydrogenated in a Parr apparatus at room temperature and an initial pressure of 45 psi for about 3 hours. After removal of the catalyst, the pH of the filtrate was adjusted to 8 with concentrated ammonium hydroxide, and the solution was evaporated to dryness. The crude product was subjected to silica gel column chromatography. Elution of the column with chloroform-ethanol (10:1, v/v) gave a crystalline substance which was recrystallized from water to yield 0.82 g (53%) of **3a**, mp 172° [lit [7]174°].

4-Amino-5-hydroxymethyl-6-methyl-2-methoxypyrimidine (**3b**).

This compound was similarly prepared from 4-amino-6-methyl-2-methoxypyrimidine-5-carbonitrile (**1b**) in 46% yield as a white crystals, mp 221–222°; ir (potassium bromide): 3400, 3320, 3150 (NH₂), 1600, 1560 (C=N), 1460 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 6.52 (2H, br s, NH₂), 4.91 (1H, t, J = 5.4 Hz, CH₂OH), 4.37 (2H, d, J = 5.4 Hz, CH₂OH), 3.74 (3H, s, MeO), 2.25 (3H, s, 6-Me).

Anal. Calcd. for C₇H₁₁N₃O₂ (169.18): C, 49.68; H, 6.57; N, 24.84. Found: C, 49.58; H, 6.61; N, 24.69.

4-Amino-5-aminomethyl-6-phenyl-2-methoxypyrimidine (**4**).

This compound was prepared in 43% yield from compound **1c** by a procedure analogous to that described for the preparation of **3a**. The product was recrystallized from ethyl acetate:cyclohexane (4:1, v/v), as white needles, mp 182–183°; ir (potassium bromide): 3390, 3300, 3180 (NH₂), 1650, 1590 (C=N), 1450 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): 7.7–7.3 (7H, m, phenyl protons, NH₂), 7.0 (2H, br s, NH₂), 3.8 (3H, s, MeO), 3.6 (2H, s, CH₂).

Anal. Calcd. for C₁₂H₁₄N₄O (230.27): C, 62.58; H, 6.14; N, 24.33. Found: C, 62.39; H, 6.24; N, 23.88.

General Procedures for the Preparation of 7-Aminopyrido[2,3-*d*]pyrimidine-6-carbonitriles.

A mixture of aminopyrimidinecarbaldehyde (1.0 mmol), malononitrile (2.0 mmol), and piperidine (2.0 mmol) in dry ethanol (20 ml) was stirred at room temperature for 1 hour. The solid which precipitated was filtered, washed with water and dried. The compounds obtained were purified on a column filled with silica gel. Elution with ethyl acetate:toluene mixture (1:1, v/v) gave the corresponding 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitriles which were recrystallized from ethanol.

7-Amino-2-methoxypyrido[2,3-*d*]pyrimidine-6-carbonitrile (**5a**).

This compound was obtained from aminopyrimidinecarbaldehyde **2a** (153 mg, 1.0 mmol) and malononitrile (132 mg, 2.0 mmol) by following the above general procedure in a yield of 97%, mp 260° dec; ir (potassium bromide): 3390, 3300, 3180 (NH₂), 2210 (CN), 1650 (C=N), 1210 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 8.2 (1H, s, 4-H), 7.8 (1H, s, 5-H), 7.0 (2H, br s, NH₂), 3.9 (3H, s, MeO).

Anal. Calcd. for C₉H₇N₅O (201.19): C, 53.72; H, 3.51; N, 34.81. Found: C, 53.67; H, 3.72; N, 34.56.

7-Amino-4-methyl-2-methoxypyrido[2,3-*d*]pyrimidine-6-carbonitrile (**5b**).

This compound was obtained from aminopyrimidinecarbaldehyde **2b** (167 mg, 1.0 mmol) and malononitrile (132 mg, 2.0

mmoles) by following the above general procedure in a yield of 95%, mp > 230°; ir (potassium bromide): 3320, 3100 (NH₂), 2210 (CN), 1600, 1550 cm⁻¹; ¹H nmr (trifluoroacetic acid): δ 9.1 (1H, s, 5-H), 4.5 (3H, s, MeO), 3.3 (3H, s, Me).

Anal. Calcd. for C₁₀H₉N₃O (215.21): C, 55.80; H, 4.22; N, 32.54. Found: C, 56.07; H, 4.46; N, 32.26.

7-Amino-4-phenyl-2-methoxypyrido[2,3-*d*]pyrimidine-6-carbonitrile (**5c**).

This compound was similarly prepared from aminopyrimidinecarbaldehyde **2c** (229 mg, 1.0 mmole) by cyclocondensation reaction with malononitrile (132 mg, 2.0 mmoles) in 97% yield as a white crystals, mp 252–260° dec; ir (potassium bromide): 3200, 3020 (NH₂), 2210 (CN), 1650, 1600, 1550 (C=N) cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 8.5 (1H, s, 5-H), 7.6 (5H, s, phenyl protons), 6.9 (2H, br s, NH₂), 4.0 (3H, s, MeO).

Anal. Calcd. for C₁₅H₁₁N₅O (277.29): C, 64.96; H, 4.01; N, 25.26. Found: C, 64.89; H, 4.32; N, 25.11.

Methyl 7-Amino-4-methyl-2-methoxypyrido[2,3-*d*]pyrimidine-6-carboxylate (**6a**).

Compound **2b** (200 mg, 1.2 mmoles) and ethyl cyanoacetate (271 mg, 2.4 mmoles) were dissolved in a solution of sodium methoxide-methanol, prepared from sodium (20 mg) and dry methanol (20 ml). The reaction mixture was refluxed for 0.5 hours. After cooling, the mixture was neutralized with 10% acetic acid, and concentrated under reduced pressure to give a residue, which was poured into ice-water. The solid that precipitated was collected by filtration, recrystallized from ethanol, and identified as **6a** (80%), mp 262–264°; ir (potassium bromide): 3420, 3290, 3120 (NH₂), 1700 (methyl ester), 1620 cm⁻¹; ¹H nmr (trifluoroacetic acid): δ 9.2 (1H, s, 5-H), 4.5 (3H, s, MeO), 4.1 (3H, s, CO₂Me), 3.2 (3H, s, Me).

Anal. Calcd. for C₁₁H₁₂N₄O₃ (248.24): C, 53.21; H, 4.88; N, 22.57. Found: C, 53.10; H, 4.77; N, 22.76.

Methyl 7-Amino-4-phenyl-2-methoxypyrido[2,3-*d*]pyrimidine-6-carboxylate (**6b**).

Similarly, the cyclization of the compound **2c** (1.2 mmoles) with ethyl cyanoacetate (2.4 mmoles) gave methyl 7-amino-4-phenyl-2-methoxypyrido[2,3-*d*]pyrimidine-6-carboxylate (**6b**) (98%), mp 260°; ir (potassium bromide): 3420, 3380, 3110 (NH₂), 1700 (methyl ester), 1640 cm⁻¹; ¹H nmr (trifluoroacetic acid): δ 9.1 (1H, s, 5-H), 7.8 (5H, s, phenyl protons), 4.5 (3H, s, MeO), 4.1 (3H, s, CO₂Me).

Anal. Calcd. for C₁₆H₁₄N₄O₃ (310.31): C, 61.92; H, 4.51; N, 18.06. Found: C, 61.81; H, 4.63; N, 18.01.

6-Cyano-2-methoxypyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**7**).

This compound was prepared from **2a** and ethyl cyanoacetate by the same procedure as **6a**, in 85% yield, as white needles, mp >300°; ir (potassium bromide): 3200–2500 (NH), 2210 (CN), 1680 (CO), 1620, 1550 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 12.9–12.5 (1H, br s, NH), 8.8 (1H, s, 4-H), 8.5 (1H, s, 5-H), 3.9 (3H, s, MeO).

Anal. Calcd. for C₉H₆N₄O₂ (202.17): C, 53.46; H, 3.00; N, 27.72. Found: C, 53.61; H, 3.12; N, 27.50.

General Procedure for the Cyclization Reactions of Compound **2** with Active Methylene Compounds.

A mixture of compound **2** (1.5 mmoles) and the corresponding methylene compound (3.0 mmoles) were dissolved in a solu-

tion of sodium methoxide-methanol, prepared from sodium (20 mg) and dry methanol (15 ml). The reaction mixture was refluxed for a variable time (monitored by tlc). When the starting material according to tlc had disappeared, the mixture was concentrated under reduced pressure to give a residue, which was poured into ice-water; the precipitate filtered off, dried and recrystallized. In case of no precipitate the aqueous solution was neutralized (pH 6–7) with 10% acetic acid and kept in the refrigerator overnight. The solid that precipitate was collected by filtration and identified as the corresponding pyridopyrimidine.

7-Methyl-2-methoxypyrido[2,3-*d*]pyrimidine (**8a**).

This compound was obtained from aminopyrimidinecarbaldehyde **2a** (230 mg, 1.5 mmoles) and acetone (174 mg, 3.0 mmoles) by following the above general procedure, by refluxing for 9 hours, in 75% yield, mp 157–159° (from cyclohexane-ethyl acetate 4:1, v/v); ir (potassium bromide): 1620, 1550, 1480 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 9.3 (1H, s, 4-H), 8.3 (1H, d, J = 4 Hz, 5-H), 7.4 (1H, d, J = 4 Hz, 6-H), 4.0 (3H, s, MeO), 2.7 (3H, s, Me).

Anal. Calcd. for C₉H₉N₃O (175.19): C, 61.69; H, 5.19; N, 23.99. Found: C, 61.76; H, 5.15; N, 23.22.

7-Phenyl-2-methoxypyrido[2,3-*d*]pyrimidine (**8b**).

This compound was obtained from aminopyrimidinecarbaldehyde **2a** (230 mg, 1.5 mmoles) and acetophenone (360 mg, 3.0 mmoles) by following the above general procedure, by refluxing for 2 hours, in 65% yield, mp 154–156° (from aqueous ethanol); ir (potassium bromide): 1620, 1610, 1550, 1480 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 9.4 (1H, s, 4-H), 8.5 (1H, d, J = 4 Hz, 5-H), 8.4–8.0 (3H, m, 6-H, 2, 6-H), 7.6–7.3 (3H, m, 3, 4, 5-H), 4.1 (3H, s, MeO).

Anal. Calcd. for C₁₄H₁₁N₃O (237.26): C, 70.86; H, 4.68; N, 17.71. Found: C, 70.58; H, 4.79; N, 17.50.

6,7-Dimethyl-2-methoxypyrido[2,3-*d*]pyrimidine (**8c**).

This compound was obtained from aminopyrimidinecarbaldehyde **2a** (1.5 mmoles) and ethyl methyl ketone (3.0 mmoles) by following the above general procedure, by refluxing for 8 hours, in 60% yield, mp 176–178° (from water); ir (potassium bromide): 1620, 1550, 1480 cm⁻¹; ¹H nmr (deuteriochloroform): δ 9.3 (1H, s, 4-H), 8.1 (1H, s, 5-H), 4.5 (3H, s, MeO), 3.1 (3H, s, Me), 2.8 (3H, s, Me).

Anal. Calcd. for C₁₀H₁₁N₃O (248.24): C, 63.46; H, 5.87; N, 22.21. Found: C, 63.38; H, 6.02; N, 21.93.

6-Ethyl-7-methyl-2-methoxypyrido[2,3-*d*]pyrimidine (**8d**).

This compound was obtained from aminopyrimidinecarbaldehyde **2a** (1.5 mmoles) and 2-pentanone (3.0 mmoles) by following the above general procedure, by refluxing for 8 hours, in 49% yield, mp 110–112° (from water); ir (potassium bromide): 1610, 1580, 1470 cm⁻¹; ¹H nmr (deuteriochloroform): δ 9.2 (1H, s, 4-H), 7.9 (1H, s, 5-H), 4.2 (3H, s, MeO), 2.9 (2H, c, Ethyl), 2.7 (3H, s, Me), 1.4 (3H, t, Ethyl).

Anal. Calcd. for C₁₁H₁₃N₃O (203.24): C, 64.99; H, 6.46; N, 20.68. Found: C, 64.87; H, 6.29; N, 20.39.

4,7-Dimethyl-2-methoxypyrido[2,3-*d*]pyrimidine (**8e**).

This compound was obtained from aminopyrimidinecarbaldehyde **2b** (250 mg, 1.5 mmoles) and acetone (174 mg, 3.0 mmoles) by following the above general procedure, by refluxing for 14 hours, in 78% yield, mp 126–128° (from toluene); ir

(potassium bromide): 1610, 1590, 1500 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 8.4 (1H, d, $J = 4$ Hz, 5-H), 7.3 (1H, d, $J = 4$ Hz, 6-H), 4.0 (3H, s, MeO), 2.8 (3H, s, Me), 2.6 (3H, s, Me).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}$ (189.22): C, 63.46; H, 5.87; N, 22.21. Found: C, 63.03; H, 5.74; N, 22.05.

7-Phenyl-4-methyl-2-methoxyprido[2,3-*d*]pyrimidine (8f).

This compound was obtained from aminopyrimidinecarbaldehyde **2b** (250 mg, 1.5 mmoles) and acetophenone (360 mg, 3.0 mmoles) by following the above general procedure, by refluxing for 2 hours, in 66% yield, mp 128–130° (from aqueous ethanol); ir (potassium bromide): 1600, 1580, 1550 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 8.6 (1H, d, 5-H), 8.4–8.0 (3H, m, 6-H, 2',6'-H), 7.6–7.4 (3H, m, 3',4',5'-H), 4.1 (3H, s, MeO), 2.9 (3H, s, Me).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$ (251.29): C, 71.68; H, 5.22; N, 16.72. Found: C, 71.59; H, 5.36; N, 16.63.

4,6,7-Trimethyl-2-methoxyprido[2,3-*d*]pyrimidine (8g).

This compound was obtained from aminopyrimidinecarbaldehyde **2b** (250 mg, 1.5 mmoles) and methyl ethyl ketone (216 mg, 3.0 mmoles) by following the above general procedure, by refluxing for 1 hour, in 78% yield, mp 155–157° (from aqueous ethanol); ir (potassium bromide): 1610, 1580, 1550 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 8.2 (1H, s, 5-H), 4.0 (3H, s, MeO), 2.8 (3H, s, Me), 2.6 (3H, s, Me), 2.4 (3H, s, Me).

Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}$ (203.24): C, 64.99; H, 6.46; N, 20.68. Found: C, 64.62; H, 6.45; N, 20.61.

6-Ethyl-4,7-dimethyl-2-methoxyprido[2,3-*d*]pyrimidine (8h).

This compound was obtained from aminopyrimidinecarbaldehyde **2b** (1.5 mmoles) and 2-pentanone (3.0 mmoles) by following the above general procedure, by refluxing for 5 hours, in 49% yield, mp 122–124° (from ethyl acetate-hexane 4:1, v/v); ir (potassium bromide): 1610, 1580, 1460 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 8.0 (1H, s, 5-H), 4.2 (3H, s, MeO), 2.9 (3H, s, Me), 2.8 (2H, c, Ethyl), 2.7 (3H, s, Me), 1.4 (3H, t, Ethyl).

Anal. Calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}$ (217.27): C, 66.32; H, 6.97; N, 19.34. Found: C, 66.32; H, 6.81; N, 19.25.

4-Phenyl-7-methyl-2-methoxyprido[2,3-*d*]pyrimidine (8i).

This compound was obtained from aminopyrimidinecarbaldehyde **2c** (344 mg, 1.5 mmoles) and acetone (174 mg, 3.0 mmoles) by following the above general procedure, by refluxing for 24 hours, in 87% yield, mp 176–178° (from ethyl acetate-cyclohexane); ir (potassium bromide): 1610, 1570, 1490 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 8.3 (1H, d, $J = 8$ Hz, 5-H), 7.7–7.8 (5H, m, phenyl protons), 7.4 (1H, d, $J = 8$ Hz, 6-H), 4.1 (3H, s, MeO), 2.7 (3H, s, Me).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$ (251.29): C, 71.68; H, 5.22; N, 16.72. Found: C, 71.03; H, 5.21; N, 16.66.

4,7-Diphenyl-2-methoxyprido[2,3-*d*]pyrimidine (8j).

This compound was obtained from aminopyrimidinecarbaldehyde **2c** (344 mg, 1.5 mmoles) and acetophenone (360 mg, 3.0 mmoles) by following the above general procedure, by refluxing for 8 hours, in 90% yield, mp 124–126° (from aqueous ethanol); ir (potassium bromide): 1610, 1600, 1580 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 7.5–8.4 (12H, m, 5-H, 6-H, phenyl protons), 4.1 (3H, s, MeO).

Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}$ (313.36): C, 76.65; H, 4.83; N, 13.41. Found: C, 76.69; H, 4.99; N, 13.52.

4-Phenyl-6,7-methyl-2-methoxyprido[2,3-*d*]pyrimidine (8k).

This compound was obtained from aminopyrimidinecarbaldehyde **2c** (344 mg, 1.5 mmoles) and methyl ethyl ketone (216 mg, 3.0 mmoles) by following the above general procedure, by refluxing for 9 hours, in 74% yield, mp 155–157° (from ethanol-water 1:4, v/v); ir (potassium bromide): 1620, 1590, 1560 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 8.0 (1H, s, 5-H), 7.6 (5H, s, phenyl protons), 4.0 (3H, s, MeO), 2.6 (3H, s, Me), 2.4 (3H, s, Me).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}$ (265.31): C, 72.42; H, 5.71; N, 15.84. Found: C, 71.98; H, 5.68; N, 15.55.

6-Ethyl-4-phenyl-7-methyl-2-methoxyprido[2,3-*d*]pyrimidine (8l).

This compound was obtained from aminopyrimidinecarbaldehyde **2c** (344 mg, 1.5 mmoles) and 2-pentanone (258 mg, 3.0 mmoles) by following the above general procedure, by refluxing for 4 hours, in 51% yield, mp 129–130° (from ethyl acetate-hexane); ir (potassium bromide): 1610, 1590, 1560 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 8.1 (1H, s, 5-H), 7.7–7.8 (2H, m, 2',6'-H), 7.5–7.6 (3H, m, 3',4',5'-H), 4.2 (3H, s, MeO), 2.8 (3H, s, Me), 2.7 (2H, c, Ethyl), 1.3 (3H, t, Ethyl).

Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}$ (275.31): C, 74.15; H, 4.77; N, 15.26. Found: C, 73.90; H, 4.55; N, 14.99.

General Procedure for the Preparation of Tricyclic Systems

A mixture of aminopyrimidinecarbaldehyde **2** (1.5 mmoles) and cyclopentanone or cyclohexanone (2.0 mmoles) in sodium methoxide solution (20 mg of sodium dissolved in 20 ml of methanol) was refluxed for 2 hours. After cooling, the mixture was neutralized (pH 6–7) with 10% acetic acid concentrated. The solution was then evaporated under reduced pressure and the resulting residue was crushed with ice-water (30 ml). The solid obtained was collected by filtration, washed with water followed by ethanol and dried.

4-Methyl-2-methoxycyclopenta[5,6]pyrido[2,3-*d*]pyrimidine (9a).

This compound was obtained from aminopyrimidinecarbaldehyde **2b** (250 mg, 1.5 mmoles) and cyclopentanone (168 mg, 2.0 mmoles) by following the above general procedure in a yield of 62%, mp 132° (from ethyl acetate-hexane mixture); ir (potassium bromide): 1620, 1570, 1510 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 8.1 (1H, s, 5-H), 4.2 (3H, s, MeO), 3.2 (2H, t, 8-H), 3.1 (2H, t, 6-H), 2.9 (3H, s, Me), 2.2 (2H, q, 7-H).

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}$ (215.25): C, 66.94; H, 6.10; N, 19.52. Found: C, 66.75; H, 6.16; N, 19.47.

4-Phenyl-2-methoxycyclopenta[5,6]pyrido[2,3-*d*]pyrimidine (9b).

This compound was obtained from aminopyrimidinecarbaldehyde **2c** (344 mg, 1.5 mmoles) and cyclopentanone (168 mg, 2.0 mmoles) by following the above general procedure in a yield of 71%, mp 96–98° (from aqueous ethanol); ir (potassium bromide): 1620, 1590, 1560 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 8.1 (1H, s, 5-H), 7.5–7.8 (5H, m, phenyl protons), 4.2 (3H, s, MeO), 3.2 (2H, t, 8-H), 3.1 (2H, t, 6-H), 2.2 (2H, q, 7-H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}$ (277.33): C, 73.61; H, 5.46; N, 15.15. Found: C, 73.37; H, 5.39; N, 14.89.

2-Methoxy-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline (9c).

This compound was obtained from aminopyrimidinecarbaldehyde **2a** (230 mg, 1.5 mmoles) and cyclohexanone (196 mg, 2.0

mmoles) by following the above general procedure in a yield of 79%, mp 161° (from water); ir (potassium bromide): 1610, 1590, 1540 cm⁻¹; ¹H nmr (deuteriochloroform): δ 9.2 (1H, s, 4-H), 7.9 (1H, s, 5-H), 4.2 (3H, s, MeO), 3.2 (2H, t, 9-H), 3.0 (2H, t, 6-H), 1.8-2.1 (4H, m, 7, 8-H).

Anal. Calcd. for C₁₂H₁₃N₃O (215.25): C, 66.94; H, 6.10; N, 19.52. Found: C, 66.75; H, 6.04; N, 19.55.

4-Methyl-2-methoxy-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline (9d).

This compound was similarly prepared from aminopyrimidinecarbaldehyde **2b** (1.5 mmoles) by cyclocondensation with cyclohexanone (2.0 mmoles) in 77% as a white solid, mp 144-146°; ir (potassium bromide): 3540 (OH), 1610, 1580, 1550 cm⁻¹; ¹H nmr (deuteriochloroform): δ 8.0 (1H, s, 5-H), 4.2 (3H, s, MeO), 3.2 (2H, t, 9-H), 3.0 (2H, t, 6-H), 2.8 (3H, s, Me), 1.8-2.1 (4H, m, 7, 8-H).

Anal. Calcd. for C₁₃H₁₅N₃O•3/5H₂O (240.08): C, 65.02; H, 6.81; N, 17.50. Found: C, 64.90; H, 6.80; N, 17.59.

4-Phenyl-2-methoxy-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline (9e).

This compound was similarly prepared from aminopyrimidinecarbaldehyde **2c** (1.5 mmoles) by cyclocondensation with cyclohexanone (2.0 mmoles) in 72%; ir (potassium bromide): 1610, 1590, 1560 cm⁻¹; ¹H nmr (deuteriochloroform): δ 8.0 (1H, s, 5-H), 7.5-7.8 (5H, m, phenyl protons), 4.2 (3H, s, MeO), 3.2 (2H, t, 9-H), 2.9 (2H, t, 6-H), 2.0 (2H, q, CH₂), 1.9 (1H, q, CH₂).

Anal. Calcd. for C₁₈H₁₇N₃O (291.35): C, 74.19; H, 5.89; N, 14.42. Found: C, 74.03; H, 5.82; N, 14.05.

General Procedure for the Cyclization of Compounds **2** with Diethyl Malonate.

A mixture of the corresponding aminopyrimidinecarbaldehyde **2** (1.5 mmoles) and diethyl malonate (2.0 mmoles) in sodium methoxide solution (20 mg of sodium dissolved in 20 ml of methanol) was refluxed for 15 hours. The reaction mixture was then evaporated under reduced pressure. The resulting residue was dissolved in ice-water (10 ml) and acidified (pH 5-6) with dilute acetic acid. The solid obtained was collected by filtration, washed with water and recrystallized from ethanol as white needles.

Methyl 7-Hydroxy-2-methoxypyrido[2,3-*d*]pyrimidine-6-carboxylate (**10a**).

This compound was obtained from aminopyrimidinecarbaldehyde **2a** (230 mg, 1.5 mmoles) and diethyl malonate (2.0 mmoles) by following the above general procedure in a yield of 72%, mp 226-228°; ir (potassium bromide): 3200, 1700 (methyl ester), 1630, 1480 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 9.0 (1H, s, 4-H), 8.5 (1H, s, 5-H), 4.0 (3H, s, MeO), 3.8 (3H, s, CO₂Me).

Anal. Calcd. for C₁₀H₉N₃O₄ (235.20): C, 51.06; H, 3.86; N, 17.87. Found: C, 50.80; H, 4.03; N, 18.04.

Methyl 7-Hydroxy-4-methyl-2-methoxypyrido[2,3-*d*]pyrimidine-6-carboxylate (**10b**).

This compound was obtained from aminopyrimidinecarbaldehyde **2b** (250 mg, 1.5 mmoles) and diethyl malonate (2.0 mmoles) by following the above general procedure in a yield of 25%, mp 224-226°; ir (potassium bromide): 3220, 1700 (methyl ester), 1610, 1460 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 12.4-12.0 (1H, br s, OH-NH), 8.4 (1H, s, 5-H), 4.0 (3H, s, MeO), 3.8 (3H, s, CO₂Me), 2.6 (3H, s, Me).

Anal. Calcd. for C₁₁H₁₁N₃O₄ (249.24): C, 53.00; H, 4.46; N, 16.86. Found: C, 52.70; H, 4.60; N, 16.78.

Methyl 7-Hydroxy-4-phenyl-2-methoxypyrido[2,3-*d*]pyrimidine-6-carboxylate (**10c**).

This compound was obtained from aminopyrimidinecarbaldehyde **2c** (344 mg, 1.5 mmoles) and diethyl malonate (2.0 mmoles) by following the above general procedure in a yield of 95%, mp 238°; ir (potassium bromide): 3220, 2940, 1740 (methyl ester), 1660 (CO), 1600 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 12.6 (1H, s, NH), 8.3 (1H, s, 5-H), 7.6 (5H, s, Ph), 4.0 (3H, s, MeO), 3.7 (3H, s, CO₂Me).

Anal. Calcd. for C₁₆H₁₃N₃O₄ (311.30): C, 61.72; H, 4.22; N, 13.50. Found: C, 61.74; H, 4.29; N, 13.82.

Reduction Reactions of Pyrido[2,3-*d*]pyrimidine-6-carbonitriles.

7-Amino-5,8-dihydro-2-methoxypyrido[2,3-*d*]pyrimidine-6-carbonitrile (**11**).

7-Amino-2-methoxypyrido[2,3-*d*]pyrimidine-6-carbonitrile **5a** (241 mg, 1.2 mmoles) in anhydrous tetrahydrofuran (10 ml) was added under an atmosphere of dry nitrogen to a suspension of lithium aluminum hydride (140 mg, 3.6 mmoles) in 25 ml of anhydrous tetrahydrofuran. The mixture was stirred at room temperature for 3 hours, hydrolyzed with dilute ammonium hydroxide, and then extracted with ethyl acetate. The extracts were concentrated under reduced pressure to give a residue, which was subject to silica gel column chromatography. Elution with ethyl acetate-toluene (4:1, v/v) gave a solid product, which was recrystallized from ethanol, and identified as **11** (140 mg, 69%); ir (potassium bromide): 3460, 3380, 3200-2700 (NH, NH₂), 2220 (CN), 1620 (C=N), 1560 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 9.6 (1H, s, 4-H), 6.4 (2H, br s, NH₂), 4.2 (2H, s, 5-H), 3.7 (3H, s, MeO).

Anal. Calcd. for C₉H₉N₃O (203.20): C, 53.19; H, 4.47; N, 34.47. Found: C, 52.98; H, 4.51; N, 34.16.

4-Amino-5,8-dihydro-5-phenyl-7-ethoxypyrido[2,3-*d*]pyrimidine-6-carbonitrile (**12**).

4-Amino-5-phenyl-7-ethoxypyrido[2,3-*d*]pyrimidine-6-carbonitrile (500 mg, 1.7 mmoles) in anhydrous tetrahydrofuran (10 ml) was added under an atmosphere of dry nitrogen to a suspension of lithium aluminum hydride (77 mg, 2.0 mmoles) in 25 ml of anhydrous tetrahydrofuran. The mixture was stirred at 0° for 3 hours and then, acidified (pH 5-6) with dilute sulfuric acid and concentrated under reduced pressure. After the mixture had cooled, the precipitate was collected by filtration, washed with water followed by ethanol and dried. Recrystallization from ethanol gave 161 mg (55%) of **12**, mp 236-238°; ir (potassium bromide): 3460, 3300, 3200-2700 (NH, NH₂), 2200 (CN), 1640, 1560 cm⁻¹; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 10.4-9.5 (1H, br s, NH), 7.9 (1H, s, 2-H), 7.2 (5H, s, Ph), 6.4 (2H, br s, NH₂), 4.7 (1H, s, 5-H), 4.2 (2H, c, EtO), 1.3 (3H, t, EtO).

Anal. Calcd. for C₁₆H₁₅N₃O (293.33): C, 65.52; H, 5.15; N, 23.88. Found: C, 65.22; H, 5.08; N, 23.78.

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