AN UNEQUIVOCAL SYNTHESIS OF 4-AMINO-1,5,6,8-TETRAHYDROPYRIDO[2,3-*d*]PYRIMIDINE-2,7-DIONES AND 2-AMINO-3,5,6,8-TETRAHYDROPYRIDO[2,3-*d*]PYRIMIDINE-4,7-DIONES

Jose I. BORRELL[1], Jordi TEIXIDO[2], Blanca MARTINEZ-TEIPEL[3], Blanca SERRA[3], Josep Lluis MATALLANA[3], Marta COSTA[3] and Xavier BATLLORI[4]

Departament de Quimica Organica, CETS Institut Químic de Sarria, Universitat Ramon Llull, Via Augusta 390, E-08017 Barcelona, Spain; e-mail: [1] jibor@iqs.url.es, [2] jteix@iqs.url.es, [3] synth@iqs.url.es, [4] xbatl@iqs.url.es

Received February 27, 1996
Accepted March 24, 1996

An unequivocal set of procedures for the synthesis of 4-amino-1,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-2,7-diones (**7**) and 2-amino-3,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-4,7-diones (**8**), in a maximum of four steps from an α,β-unsaturated ester **1**, is reported. Thus, the acid hydrolysis of the 2,4-diaminopyrido[2,3-*d*]pyrimidines **3** yields the 4-amino-2-oxopyrido[2,3-*d*]pyrimidines **7** while the cyclization of the Michael adducts **9** (formed by reaction of **1** and methyl cyanoacetate) with guanidine affords the corresponding 2-amino-4-oxopyrido[2,3-*d*]pyrimidines **8**. Both isomers were also obtained by hydrolysis of the 4-amino-2-bromo- and 2-amino-4-bromo-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **5** and **6**, respectively.

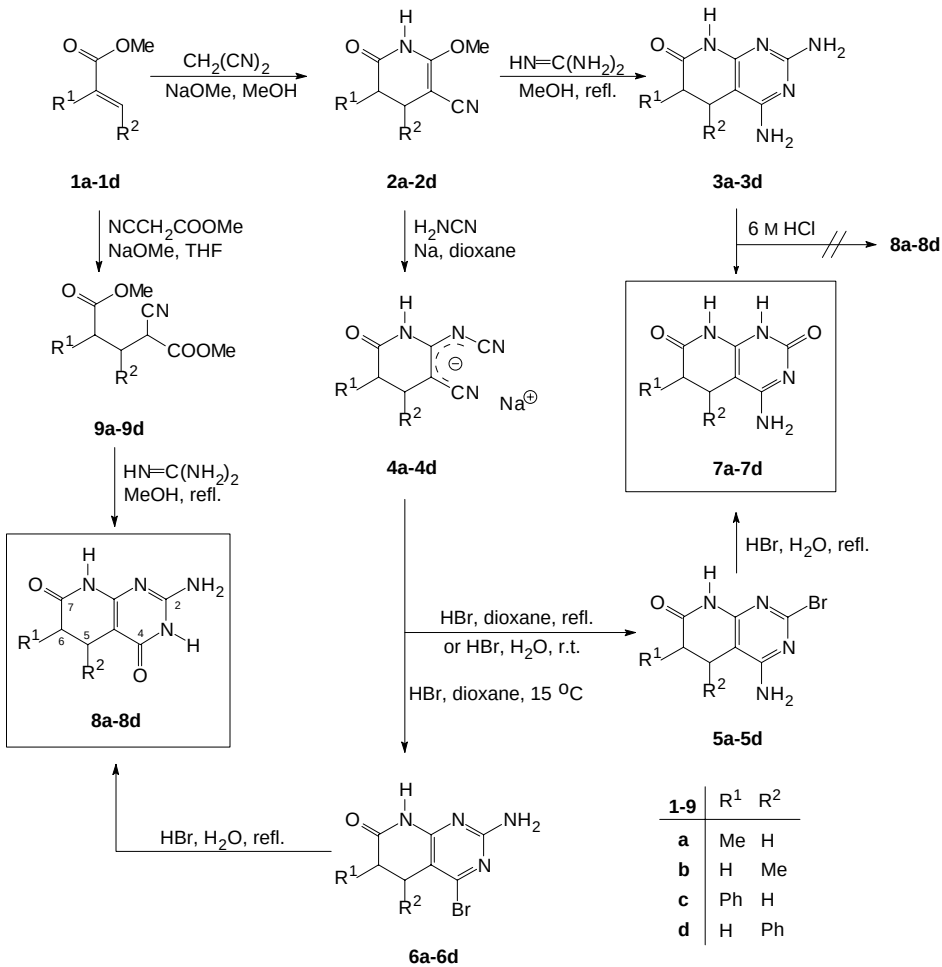
Key words: 4-Oxopyrido[2,3-*d*]pyrimidines; 2-Oxopyrido[2,3-*d*]pyrimidines; Dinitrile cyclization; Michael reaction.

During the past years our group has developed a general procedure for the synthesis of 5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines starting from α,β-unsaturated esters[1] (Scheme 1). The procedure starts by the condensation of an α,β-unsaturated ester **1** with malononitrile and sodium methanolate in methanol at reflux to afford the corresponding 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles **2** in moderate to good yields depending on the nature of R^1 and R^2. This reaction has been tested with a wide range of alkyl, aryl or heteroaryl substituted esters.

The subsequent treatment of the pyridones **2** with quanidine in methanol at reflux afforded in all cases the 2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **3** in good yields[2] (75–97%). On the other hand, the substitution of the methoxy group of pyridones **2** by cyanamide, carried out in dioxane at reflux in the presence of a stoichiometric amount of sodium, gave the sodium salts **4** in quantitative yields. Treatment of salts **4** with an equimolar amount of hydrogen chloride in ethanol afforded the corresponding cyanoamino substituted pyridones[2]. Cyclization of the later compounds with HBr in dioxane yielded both the positional isomers **5** and **6** depending on the thermal

level employed. Thus, when the reaction was carried out at low temperature (10–15 °C) the 2-amino-4-bromo-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **6** were preferently formed, but when it was done at high temperature (95–100 °C) the 4-amino-2-bromo substituted compounds **5** were selectively obtained[3,5]. Finally, these halogen derivatives were found to be excellent substrates for aromatic nucleophilic substitution by a wide range of nitrogen nucleophiles[6].

Very recently, in connection with a project concerning the synthesis of a series of folic acid analogs, we needed an unequivocal method to obtain 4-amino-1,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-2,7-diones **7** and 2-amino-3,5,6,8-tetrahydropyrido-4,7-diones **8**. The present paper deals with the results obtained in such study.



SCHEME 1

EXPERIMENTAL

Melting points were determined on a Büchi–Tottoli apparatus and are uncorrected. IR spectra were recorded on a BOMEM Michelson 100 (FTIR) or a Perkin–Elmer 683 spectrophotometers. ^{1}H and ^{13}C NMR spectra (δ, ppm; *J*, Hz) were measured in $(CD_3)_2SO$ (compounds **5**, **6**; $CDCl_3$ (compounds **9**) or CF_3COOD (**7**, **8**) on a Perkin–Elmer R-24 (^{1}H NMR, 60 MHz) or a Varian Gemini 300 spectrometer using TMS or sodium 2,2,3,3-tetradeuteriotrimethylsilylpropionate as an internal standard. Mass spectra (*m*/*z* (%), EI, 70 eV) were performed on a HP 5995 A spectrometer. Elemental analyses were obtained on a Carlo–Erba CHNS-O/EA 1108 analyzer. Column chromatography was carried out on silica gel (70–230 mesh). Compounds **2–4**, **6a** and **6b** were prepared according to reported procedures[3–6].

4-Amino-2-bromo-6-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5a**)

An amount of 2.08 g (10.6 mmol) of the sodium salt **4a** were treated with 30 ml of 45% aqueous HBr at room temperature for 16 h. The solution was neutralized with aqueous ammonia while cooling on an ice bath. The solid was filtered off and washed with water, methanol and diethyl ether and dried over phosphorus pentoxide to give 2.05 g (76%) of **5a**, m.p. 264–265 °C. IR spectrum: 3 360 and 3 320 (NH_2), 3 180 (NHCO); 1 695 (C=O), 1 645, 1 595, 1 560. ^{1}H NMR spectrum: 1.2 d, 3 H, ^3J = 5.8 Hz (Me); 2.2–3.0 m, 3 H (H-6 and 2 × H-5); 7.1 brs, 2 H (NH_2); 10.5 brs, 1 H (NH). ^{13}C NMR spectrum: 148.5 (C-2), 162.1 (C-4), 92.6 (C-4a), 25.0 (C-5), 33.8 (C-6), 172.9 (C-7), 156.9 (C-8a), 15.3 (Me). Mass spectrum: 258 (M^+ + 2, 88), 256 (M^+, 100), 241 (17), 201 (10), 177 (24). For $C_8H_9BrN_4O$ (257.1) calculated: 37.37% C, 3.53% H, 31.08% Br, 21.79% N; found: 37.25% C, 3.45% H, 31.07% Br, 21.58% N.

4-Amino-2-bromo-5-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5b**)

Prepared as given above starting from 2.00 g (10.5 mmol) of **4b**, reaction time 20 h, yield: 1.92 g (71%) of **5b**, m.p. 273–274 °C (ref.[3] gives 273–275 °C).

4-Amino-2-bromo-6-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5c**)

Prepared as given for the compound **5a** starting from 1.62 g (6.2 mmol) of **4c**, reaction time 1 h, yield: 1.42 g (72%) of **5c**, m.p. 284–285 °C. IR spectrum: 3 500 and 3 310 (NH_2), 3 240 and 3 120 (NHCO), 1 715 (C=O), 1 645, 1 605, 1 570. ^{1}H NMR spectrum: 2.9 and 3.0 m, 2 H, ^2J = 16.4, ^3J (5,6-*trans*) = 10.1, ^3J (5,6-*cis*) = 7.2 (2 × H-5); 3.9 dd, 1 H, ^3J = 10.1 and ^3J = 7.2 (H-6); 7.1 brs, 2 H (NH_2); 7.3 m, 5 H (Ph), 10.9 brs, 1 H (NH). ^{13}C NMR spectrum: 161.4 (C-2), 151.0 (C-4), 103.1 (C-4a), 30.0 (C-5), 45.7 (C-6), 171.9 (C-7), 158.3 (C-8a), 127.1, 128.1, 128.4 and 138.5 (Ph). Mass spectrum: 320 (M^+ + 2, 35), 318 (M^+, 36), 241 (27), 201 (31), 118 (100). For $C_{13}H_{11}BrN_4O$ (319.2) calculated: 48.92% C, 3.47% H, 25.04% Br, 17.55% N; found: 48.81% C, 3.11% H, 24.94% Br, 17.27% N.

4-Amino-2-bromo-5-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5d**)

Prepared as given above starting from 1.00 g (3.8 mmol) of **4d**, reaction time 6 h, yield: 1.00 g (80%) of **5d**, m.p. > 300 °C. IR spectrum: 3 350 and 3 325 (NH_2), 3 190 (NHCO), 1 705 (C=O), 1 650, 1 590, 1 555. ^{1}H NMR spectrum: 2.6 and 3.1 m, 2 H, ^2J = 16.2, ^3J (6,5-*trans*) = 7.5, ^3J (6,5-*cis*) = 1.2 (2 × H-6); 4.3 dd, 1 H, ^3J = 7.5 and 1.2 (H-5); 7.2 m, 5 H (Ph). ^{13}C NMR spectrum: 149.5 (C-2), 162.1 (C-4), 95.3 (C-4a), 33.1 (C-5), 38.4 (C-6), 168.8 (C-7), 157.4 (C-8a), 126.7, 127.1, 128.7 and 140.8 (Ph). Mass spectrum: 320 (M^+ + 2, 100), 318 (M^+, 96), 241 (55), 239 (5). For $C_{13}H_{11}BrN_4O$

(319.2) calculated: 48.92% C, 3.47% H, 25.04% Br, 17.55% N; found: 49.02% C, 3.26% H, 24.88% Br, 17.63% N.

2-Amino-4-bromo-6-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6c**)

A stream of dry hydrogen bromide was bubbled through a suspension of 1.52 g (5.8 mmol) of the sodium salt **4c** in anhydrous dioxane (140 ml) at 10–15°C until saturation (15 min) and the resulting suspension was stirred at room temperature for 2 h. The mixture was concentrated in vacuo, the residue was suspended in methanol (50 ml) and neutralized with 2 M methanolic ammonia. The solvent was eliminated in vacuo, the solid obtained was suspended in water (100 ml), filtered, washed with water and dried over phosphorus pentoxide to give 1.57 g of a 75 : 25 isomeric mixture of **6c** and **5c**. The solid was extracted with ethanol in a Soxhlet apparatus for 5 h to afford 0.63 g (34%) of **6c**, m.p. > 300 °C. IR spectrum: 3 355 (NH_2), 3 210 (NHCO), 1 690 (C=O), 1 655, 1 620, 1 545. ^{1}H NMR spectrum: 3.0 m, 2 H (H-5); 4.0 m, 1 H (H-6); 6.9 brs, 2 H (NH_2); 7.3 m, 5 H (Ph); 10.9 brs, 1 H (NH). ^{13}C NMR spectrum: 148.7 (C-2), 162.0 (C-4), 92.7 (C-4a), 25.3 (C-5), 45.3 (C-6), 171.4 (C-7), 156.8 (C-8a), 127.0, 128.2, 128.4 and 139.0 (Ph). Mass spectrum: 320 (M^+ + 2, 40), 318 (M^+, 41), 241 (47), 201 (51), 118 (100). For $C_{13}H_{11}BrN_4O$ (319.2) calculated: 48.92% C, 3.47% H, 25.04% Br, 17.55% N; found: 48.64% C, 3.48% H, 24.95% Br, 17.51% N.

2-Amino-4-bromo-5-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**6d**)

Prepared as given above for the compound **6c** starting from 1.52 g (5.8 mmol) of **4d**, yield: 1.30 g (70%) of **6d**, m.p. > 300 °C. IR spectrum: 3 320 (NH_2), 3 180 (NHCO), 1 690 (C=O), 1 655, 1 610, 1 535. ^{1}H NMR spectrum: 2.6 and 3.2 m, 2 H, ^2J = 16.0, ^3J (6,5-*trans*) = 7.2, ^3J (6,5-*cis*) = 1.2, (2 × H-6); 4.3 dd, 1 H, ^3J = 7.2 and ^3J = 1.5 (H-5); 7.0 brs, 2 H (NH_2); 7.2 m, 5 H (Ph); 10.9 brs, 1 H (NH). ^{13}C NMR spectrum: 161.6 (C-2), 152.4 (C-4), 105.4 (C-4a), 38.4 (C-5), 39.1 (C-6), 170.3 (C-7), 158.9 (C-8a), 126.5, 126.9, 128.8 and 141.7 (Ph). Mass spectrum: 320 (M^+ + 2, 52), 318 (M^+, 51), 241 (100), 239 (23), 162 (13). For $C_{13}H_{11}BrN_4O$ (319.2) calculated: 48.92% C, 3.47% H, 25.04% Br, 17.55% N; found: 48.95% C, 3.23% H, 24.74% Br, 17.84% N.

Dimethyl 2-Cyano-4-methylglutarate (**9a**)

Methyl cyanoacetate (38.60 g, 0.39 mol) was added dropwise to a solution of sodium (8.97 g, 0.39 mol) in methanol (80 ml). The mixture was heated at reflux for 10 min and then 39.00 g (0.39 mol) methyl methacrylate (**1a**) were added dropwise. The mixture was refluxed for 1.5 h, cooled and neutralized with acetic acid. The solution was concentrated in vacuo, the residue was poured into water and extracted with diethyl ether. The organic extracts were dried ($MgSO_4$), evaporated at reduced pressure and the residue was distilled to afford 39.80 g (51%) of **9a**, b.p. 110–115 °C/0.27 kPa. IR spectrum (neat): 2 950, 2 250 (CN), 1 750 (C=O), 1 440. ^{1}H NMR spectrum (60 MHz): 1.3 d, 3 H, J = 5.3 (Me); 1.8–2.8 m, 3 H (H-3 and H-4); 3.7 m, 1 H (H-2); 3.7 s, 3 H (COOMe); 3.8 s, 3 H (COOMe).

Dimethyl 2-Cyano-3-methylglutarate (**9b**)

Prepared as given above using 19.30 g (0.20 mol) methyl cyanoacetate, 4.50 g (0.20 mol) sodium in 40 ml methanol and 19.50 g (0.20 mol) methyl crotonate (**1b**) to give 25.40 g (66%) of **9b**, b.p. 144–147 °C/0.40 kPa. IR spectrum (neat): 2 960, 2 250 (CN), 1 750 (C=O), 1 440. ^{1}H NMR spectrum (60 MHz): 1.3 d, 1.5 H, J = 3.8 (Me); 1.4 d, 1.5 H, J = 3.0 Hz (Me); 2.6 m, 3 H (H-3 and H-4); 3.7 s, 3 H (COOMe); 3.8 s, 3 H (COOMe); 4.0 m, 1 H (H-2).

Dimethyl 2-Cyano-4-phenylglutarate (**9c**)

Prepared as given above using 0.62 g (6.2 mmol) methyl cyanoacetate, 0.14 g (6.2 mmol) sodium in 5 ml methanol and 1.00 g (6.2 mmol) methyl atropate (**1c**) to give 0.91 g (56%) of **9c**, b.p. 142–145 °C/0.27 kPa. IR spectrum (neat): 3 020, 2 250 (CN), 1 750 (C=O), 1 610 and 1 500 (C=C), 765, 700. ^{1}H NMR spectrum (60 MHz): 2.3–3.5 m, 3 H (H-3 and H-4); 3.9 s, 3 H (COOMe); 4.1 s, 3 H (COOMe); 4.3 m, 1 H (H-2); 7.4 s, 5 H (Ph).

Dimethyl 2-Cyano-3-phenylglutarate (**9d**)

Prepared as given above using 4.95 g (0.05 mol) methyl cyanoacetate, 1.15 g (0.05 mol) sodium in 15 ml methanol and 8.10 g (0.05 mol) methyl cinnamate (**1d**) to give 7.67 g (57%) of **9d**, b.p. 166–170 °C/0.27 kPa. IR spectrum (neat): 3 010, 2 240 (CN), 1 745 (C=O), 1 600 and 1 500 (C=C), 755, 700. ^{1}H NMR spectrum (60 MHz): 3.0 m, 2 H (H-4); 3.6–4.0 m, 7 H (2 × COOMe and H-3); 4.3 d, 1 H, J = 4.5 (H-2); 7.3 s, 5 H (Ph).

4-Amino-6-methyl-1,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-2,7-dione (**7a**)

A. A suspension of **3a** (0.50 g, 2.6 mmol) in 6 M hydrochloric acid (20 ml) was heated at reflux for 48 h. The resulting solution was allowed to cool and neutralized with 30% NaOH. The solid thus obtained was filtered off, washed with water and methanol and dried over phosporus pentoxide to afford 0.49 g (98%) of **7a** as a white solid, m.p. > 300 °C. IR spectrum: 3 500 (NH_2), 3 320 and 3 040 (NHCO), 2 930, 2 840, 1 715 and 1 695 (C=O), 1 630, 1 605, 1 520. ^{1}H NMR spectrum: 1.4 d, 3 H, J = 6.6 (Me); 2.5 m, 1 H (H-6); 3.0 m, 2 H (H-5). ^{13}C NMR spectrum: 15.8 (Me), 25.6 (C-5), 36.7 (C-6), 85.3 (C-4a), 150.7 (C-2), 151.6 (C-8a), 159.3 (C-4), 178.3 (C-7). Mass spectrum: 194 (M^+, 100), 179 (46). For $C_8H_{10}N_4O_2$ (194.2) calculated: 49.48% C, 5.19% H, 28.85% N; found: 49.45% C, 5.25% H, 28.73% N.

B. A suspension of **5a** (0.15 g, 0.6 mmol) in 45% aqueous HBr (5 ml) was heated at reflux for 4 h. The resulting solution was cooled and neutralized with NaOH pellets. The solid was filtered, washed with water, methanol, diethyl ether and dried over phosphorus pentoxide to give 0.10 g (96%) of **7a**.

4-Amino-5-methyl-1,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-2,7-dione (**7b**)

A. The same procedure as described for **7a** (*A*) was used starting from 0.47 g (2.44 mmol) of **3b** and 20 ml 6 M hydrochloric acid to give, after 96 h at reflux, 0.42 g (89%) of **7b**, m.p. > 300 °C. IR spectrum: 3 500 (NH_2); 3 300 and 3 020 (NHCO), 2 910, 2 830, 1 715 and 1 695 (C=O), 1 650, 1 615, 1 515. ^{1}H NMR spectrum: 1.3 d, 3 H, J = 4.8 (Me); 2.8–3.0 m, 2 H (H-6); 3.3 m, 1 H (H-5). ^{13}C NMR spectrum: 18.7 (Me), 25.3 (C-5), 38.6 (C-6), 90.7 (C-4a), 150.5 (C-2), 150.7 (C-8a), 158.8 (C-4), 175.3 (C-7). Mass spectrum: 194 (M^+, 25), 179 (100). For $C_8H_{10}N_4O_2$ (194.2) calculated: 49.48% C, 5.19% H, 28.85% N; found: 49.52% C, 5.28% H, 29.13% N.

B. As given in procedure *B* but using 0.42 g (1.6 mmol) of **5b** to afford 0.19 g (60%) of **7b**.

4-Amino-6-phenyl-1,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-2,7-dione (**7c**)

A. From **3c**: As given above starting from 0.47 g (1.84 mmol) of **3c** and 20 ml 6 M hydrochloric acid to give 0.38 g (81%) of **7c**, m.p. > 300 °C. IR spectrum: 3 500 (NH_2); 3 300 and 3 040 (NHCO), 2 930, 2 830, 1 735 and 1 700 (C=O), 1 650, 1 625, 1 515. ^{1}H NMR spectrum: 3.1 m, 2 H (H-5); 4.1 m, 1 H (H-6); 7.2–7.4 m, 5 H (Ph). ^{13}C NMR spectrum: 25.7 (C-5), 47.6 (C-6), 85.3 (C-4a), 129.5 (C-2′), 130.9 (C-4′), 131.2 (C-3′), 135.8 (C-1′), 150.4 (C-2), 151.0 (C-8a), 159.0 (C-4),

176.6 (C-7). Mass spectrum: 256 (M^+, 100), 179 (24). For $C_{13}H_{12}N_4O_2$ (256.3) calculated: 60.93% C, 4.72% H, 21.86% N; found: 60.79% C, 4.79% H, 21.88% N.

B. From **5c**: As given above but using 0.50 g (1.6 mmol) of **5c** to afford 0.30 g (76%) of **7c**.

4-Amino-5-phenyl-1,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-2,7-dione (**7d**)

A. From **3d**: As given above starting from 0.75 g (2.94 mmol) of **3d** and 20 ml of 6 M hydrochloric acid to give 0.40 g (53%) of **7d**, m.p. > 300 °C. IR spectrum: 3 500 (NH_2), 3 305 and 3 045 (NHCO), 2 930, 2 840, 1 700 (C=O), 1 650, 1 625, 1 510. ^{1}H NMR spectrum: 3.1–3.3 m, 2 H (H-6); 4.4 m, 1 H (H-5); 7.2–7.3 m, 5 H (Ph). ^{13}C NMR spectrum: 36.0 (C-5), 40.3 (C-6), 87.9 (C-4a), 127.9 (C-2′), 131.2 (C-4′), 131.9 (C-3′), 138.2 (C-1′), 150.4 (C-2), 152.0 (C-8a), 159.1 (C-4), 174.2 (C-7). Mass spectrum: 256 (M^+, 100), 179 (92). For $C_{13}H_{12}N_4O_2$ (256.3) calculated: 60.93% C, 4.72% H, 21.86% N; found: 60.77% C, 4.81% H, 21.95% N.

B. From **5d**: As given above but using 0.50 g (1.6 mmol) of **5d** to afford 0.34 g (85%) of **7d**.

2-Amino-6-methyl-3,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-4,7-dione (**8a**)

A. A suspension of **6a** (0.30 g, 1.17 mmol) in 45% aqueous HBr (5 ml) was heated at reflux for 4 h. The resulting solution was cooled and neutralized with NaOH pellets. The solid was filtered, washed with water, methanol, diethyl ether and dried over phosphorus pentoxide to give 0.15 g (68%) of **8a**, m.p. > 300 °C. IR spectrum: 3 500–3 000 (N–H), 1 695 and 1 650 (C=O), 1 595 and 1 535 (C=C). ^{1}H NMR spectrum: 1.3 d, 3 H, J = 6.0 (Me); 2.5 m, 1 H (H-5); 2.9 m, 1 H (H-6); 3.0 m, 1 H (H-5). ^{13}C NMR spectrum: 15.4 (Me), 24.8 (C-5), 36.4 (C-6), 94.3 (C-4a), 147.5 (C-8a), 153.0 (C-2), 162.9 (C-4), 179.4 (C-7). Mass spectrum: 194 (M^+, 100), 179 (98). For $C_8H_{10}N_4O_2$ (194.2) calculated: 49.48% C, 5.19% H, 28.85% N; found: 49.32% C, 5.38% H, 28.83% N.

B. Guanidine carbonate (2.20 g, 13.0 mmol) was added to a solution of sodium (0.60 g, 26.0 mmol) in methanol (50 ml). The mixture was heated at reflux for 15 min. The sodium carbonate formed was filtered and washed with methanol. 2.50 g (13.0 mmol) of compound **9a** were added to the filtrate and the resulting mixture was heated at reflux for 24 h. The precipitate formed was filtered, washed with methanol and dried over phosphorus pentoxide to give 2.08 g (82%) of **8a**.

2-Amino-5-methyl-3,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-4,7-dione (**8b**)

A. From **6b**: As given above but using 0.30 g (1.2 mmol) of **6b** to afford 0.10 g (43%) of **8b**, m.p. > 300 °C. IR spectrum: 3 500–3 000 (N–H), 1 670 and 1 635 (C=O), 1 595 (C=C). ^{1}H NMR spectrum: 1.2 d, 3 H, J = 7.0 (Me); 2.7 and 3.0 m, 2 H, ^2J = 17.0, ^3J (6,5-*trans*) = 7.0 (2 × H-6); 3.36 m, 1 H (H-5). ^{13}C NMR spectrum: 18.9 (Me), 25.2 (C-5), 38.5 (C-6), 99.9 (C-4a), 146.8 (C-8a), 153.1 (C-2), 163.2 (C-4), 176.8 (C-7). Mass spectrum: 194 (M^+, 15), 179 (100). For $C_8H_{10}N_4O_2$ (194.2) calculated: 49.48% C, 5.19% H, 28.85% N; found: 49,60% C, 5.17% H, 28.58% N.

B. From **9b**: As given above but using 2.50 g (13.0 mmol) of **9b**, 0.60 g (26.0 mmol) sodium in methanol (50 ml) and guanidine carbonate (2.20 g, 13.0 mmol) to yield 2.06 g (82%) of **8b**.

2-Amino-6-phenyl-3,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-4,7-dione (**8c**)

A. From **6c**: As given above but using 0.35 g (1.1 mmol) of **6c** to afford 0.06 g (19%) of **8c**, m.p. > 300 °C. IR spectrum: 3 500–3 000 (N–H), 1 690 and 1 625 (C=O), 1 600 and 1 540 (C=C), 770, 700. ^{1}H NMR spectrum: 3.0 and 3.2 m, 2 H, ^2J = 17.0, ^3J (5,6-*trans*) = 11.0, ^3J (5,6-*cis*) = 7.0 (2 × H-5); 4.0 dd, 1 H ^3J (5,6-*trans*) = 11.0, ^3J = (5,6-*cis*) = 7.0 (H-6); 7.2–7.3 m, 5 H (Ph). ^{13}C NMR spectrum: 25.4 (C-5), 48.1 (C-6), 94.9 (C-4a), 129.8, 130.8, 131.3 and 136.6 (Ph), 147.7 (C-8a),

153.1 (C-2), 159.9 (C-4), 178.0 (C-7). Mass spectrum: 256 (M^+, 100), 179 (48). For $C_{13}H_{12}N_4O_2$ (256.3) calculated: 60.91% C, 4.72% H, 21.87% N; found: 60.78% C, 4.84% H, 22.06% N.

B. From **9c**: As given above but using 2.50 g (9.6 mmol) of **9c**, 0.44 g (19.1 mmol) sodium in methanol (50 ml) and guanidine carbonate (1.72 g, 9.6 mmol) to give 2.00 g (82%) of **8c**.

2-Amino-5-phenyl-3,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-4,7-dione (**8d**)

A. From **6d**: As given above but using 0.12 g (0.4 mmol) of **6d** to afford 0.06 g (62%) of **8d**, m.p. > 300 °C. IR spectrum: 3 500–3 000 (N–H), 1 685 and 1 650 (C=O), 1 600 and 1 535 (C=C), 740, 690. ^{1}H NMR spectrum: 3.0–3.3 m, 2 H (2 × H-6); 4.5 m, 1 H (H-5); 7.1–7.3 m, 5 H (Ph). ^{13}C NMR spectrum: 35.3 (C-5), 39.1 (C-6), 98.0 (C-4a), 127.8, 130.3, 131.2 and 140.6 (Ph), 147.9 (C-8a), 153.2 (C-2), 159.8 (C-4), 176.0 (C-7). Mass spectrum: 256 (M^+, 63), 179 (100). For $C_{13}H_{12}N_4O_2$ (256.3) calculated: 60.91% C, 4.72% H, 21.87% N; found: 61.12% C, 4.85% H, 21.92% N.

B. Starting from **9d**. As given above using 2.50 g (9.6 mmol) of **9d**, 0.44 g (19.1 mmol) sodium in methanol (50 ml) and guanidine carbonate (1.72 g, 9.6 mmol) to give 1.91 g (78%) of **8d**.

RESULTS AND DISCUSSION

The starting point for our research was the work of Trattner et al. on the selective hydrolysis o 2,4-diaminopyrimidine systems[7]. According to this author, the treatment of 2,4-diaminopyrimidines with 6 M hydrochloric acid always causes the hydrolysis of the 4-amino group. The reaction was particularly fast (< 0.5 h) in the case of 2,4-diamino-7-butyl-6-propylpyrido[2,3-*d*]pyrimidine which afforded the corresponding 4-oxo derivative in 80% yield (90% when 3.5 M sulfuric acid was used). The hydrolysis of the 2-amino group only was observed after the transformation of the 4-amino group.

Taking these results into account, we carried out the treatment of the 2,4-diaminopyrido[2,3-*d*]pyrimidine **3a** with 6 M hydrochloric acid. The reaction afforded a carbonyl compound in almost quantitative yield, to which the 4-oxo substituted structure **8a** was initially assigned in accordance with the work of Trattner. In order to confirm such assignment, we decided to obtain unequivocally the two possible positional isomers **7a** and **8a**. Consequently, we synthesized the sodium salt **4a** and we converted it to the 2-amino-4-bromopyrido[2,3-*d*]pyrimidine **6a** by using hydrogen bromide in dioxane at 15 °C. On the other hand, we found that the treatment of **4a** with concentrated hydrobromic acid at room temperature is a much more favorable method for the synthesis of the corresponding 4-amino-2-bromo isomer **5a**.

Once the two bromo substituted positional isomers **5a** and **6a** were obtained, we treated them with boiling concentrated hydrobromic acid to respectively afford the 4-amino-2-oxo- and 2-amino-4-oxopyrido[2,3-*d*]pyrimidines **7a** and **8a** in fairly good yields. Surprisingly, when the compound obtained by the acid hydrolysis of the 2,4-diaminopyrido[2,3-*d*]pyrimidine **3a** was compared with the unequivocally assigned oxo derivatives, we found that it was in fact the 4-amino-2-oxopyrido[2,3-*d*]pyrimidine **7a**. That is to say, contrary to the prediction of Trattner, the hydrolysis proceeds on the theoretically less reactive amino group.

We have proved the general applicability of this method by carrying out the acid hydrolysis of the 2,4-diaminopyrido[2,3-*d*]pyrimidines **3b–3d** which afforded the corresponding 4-amino-2-oxopyrido[2,3-*d*]pyrimidines **7b–7d**. Similarly, the hydrolysis of the bromo substituted isomers **5b–5d** and **6b–6d**, obtained by cyclization of the sodium salts **4b–4d** with HBr in water at the room temperature and HBr in dioxane at 15 °C, respectively, yielded the corresponding oxo derivatives **7b–7d** and **8b–8d**.

The procedure described so far is a good method for the synthesis of 4-amino-1,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-2,7-diones **7** in three steps from an α,β-unsaturated ester through the sequence **1** → **2** → **3** → **7**, however, it is far from being an efficient method for the synthesis of 2-amino-3,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-4,7-diones **8**. These compounds are obtained through a four steps sequence **1** → **2** → **4** → **6** → **8** that includes a treatment with gaseous hydrogen bromide in dioxane at 15 °C in which the 4-bromo substituted intermediates **6** are only selectively formed.

This fact and the great interest of the 4-oxo substituted isomers in connection with folic acid analogues let us to search a more convenient way to obtain 2-amino-3,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-4,7-diones **8**. A bibliographic search revealed that Schoffstall described in 1971 a synthesis for **8a** by cyclization of the Michael adduct **9a** (formed by reaction of **1a** and ethyl cyanoacetate) and guanidine (1 : 1) in ethanol at room temperature (14% overall yield)[8]. In order to extend this reaction for the synthesis of the 2-amino-4-oxopyrido[2,3-*d*]pyrimidines **8a–8d**, we decided to carry out a careful revision of the work of Schoffstall. Then, we obtain the corresponding Michael adducts **9a–9d** (50–66% yield) and we treated them with guanidine (1 : 1) in ethanol at reflux in order to increase the yield of the pyridopyrimidine formed. However, although the yields were increased, in no case they were greater than 50%. The substitution of ethanol by solvents of a higher boiling point (*tert*-BuOH or DMF) did not increase the yields.

The analysis of the products left in solution after the filtration of the 4-oxo derivatives seemed to indicate the presence of open chain products, formed by reaction of two molecules of the corresponding Michael adduct **9a–9d** and one molecule of guanidine, which do not evolve to the cyclized compounds. In order to avoid the formation of these products, we decided to use a twofold molar excess of guanidine respect to the Michael adducts **9a–9d**. Such treatment resulted in the formation of the 2-amino-4-oxopyrido[2,3-*d*]pyrimidines **8a–8d** in high yield (78–82%).

This result completes an unequivocal set of procedures for the synthesis of 4-amino-1,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-2,7-diones **7** and 2-amino-3,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-4,7-diones **8** in a maximum of four steps from an α,β-unsaturated ester.

Support of this work by a grant from the Comissió Interdepartamental de Recerca i Innovació Tecnològica (CIRIT) within the Programa de Química Fina (QFN93-4420) is gratefully acknowledged. One of us (J. L. M.) would like to thank the CIRIT for a grant within the Formació de Personal

Investigador en Arees Prioritaries del Pla de Recerca. Two of us (B. S. and B. M.) are grateful to the Fundacio Juan Salaner for a grant.

REFERENCES

1. Victory P., Borrell J. I.: Trends Heterocycl. Chem. *3*, 235 (1993); and references therein.
2. Victory P., Nomen R., Colomina O., Garriga M., Crespo A.: Heterocycles *23*, 1135 (1985).
3. Victory P., Garriga M.: Heterocycles *23*, 1947 (1985).
4. Victory P., Garriga M.: Heterocycles *23*, 2853 (1985).
5. Victory P., Garriga M.: Heterocycles *24*, 3053 (1986).
6. Victory P., Crespo A., Garriga M., Nomen R.: J. Heterocycl. Chem. *25*, 245 (1988).
7. Trattner R. B., Elion G. B., Hitchings G. H., Sharefkin D. M.: J. Org. Chem. *29*, 2674 (1964).
8. Schoffstall A. M.: J. Org. Chem. *36*, 2385 (1971).