Synthesis and Structural Study of Novel 5-Aryl Substituted 2-Amino-4,7-dioxopyrido[2,3-*d*]pyrimidines

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The title compounds **4a-c** have been prepared in a one-step procedure from 2,4-diamino-6-hydroxypyrimidine (**1**) and the corresponding arylidene substituted Meldrum's acids **2a-e** in very good yields. Semiempirical theoretical calculations (AM1) reveal two favoured conformations (**A** and **B**) for compounds **4a-e**. The ^{1}H-nmr determinations, by using Karplus and Altona equations, clearly indicate that conformation **A**, with the aryl group on C5 in a pseudoaxial position, is that predominant in solution. The calculated charge density values for the olefinic carbons are in agreement with the experimental *push-pull* effect observed in the ^{13}C-nmr spectra.

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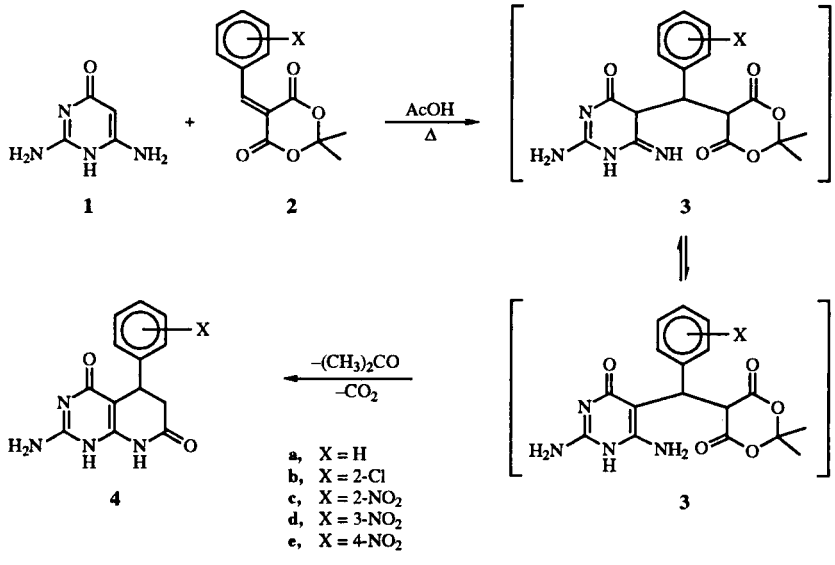
2-Aminopyrido[2,3-*d*]pyrimidines present interesting biological properties, and as some recent applications, they have been used as dihydrofolate reductase inhibitors and as antitumor agents [1]; some of them have shown antimicrobial activity [2], diuretics properties [3] and activity against platelet aggregation [4].

Regarding the synthesis of 2-aminopyrido[2,3-*d*]pyrimidines, some synthetic procedures starting from suitable 2,6-diamino-4-oxopyrimidine have been previously reported [5]. Recently, we have described novel 5-aryl substituted 2,4,7-trioxo and 4,7-dioxo-2-thioxopyrido-[2,3-*d*]pyrimidines [6], which have been prepared by refluxing equimolecular amounts of 6-amino-2,4-dioxotetrahydropyrimidine or 6-amino-4-oxo-2-trioxotetrahydropyrimidine in acetic acid with the appropriate 5-arylidene substituted Meldrum's acid. In this case, the formation of the pyrido[2,3-*d*]pyrimidine takes place in dilute solutions due to the low solubility of the starting materials in acetic acid, thus increasing the reaction time and decreasing the yield.

In this paper we report the synthesis of novel 2-amino-5-aryl-1,4,5,6,7,8-hexahydro-4,7-dioxopyrido[2,3-*d*]-pyrimidines (**4**) as novel dihydropyridine-containing ring systems. Semiempirical calculations and ^{1}H-nmr studies were carried out in order to determine the more favoured conformation for the novel compounds.

The reaction was carried out by refluxing equimolecular amounts of 2,4-diamino-6-hydroxypyrimidine (**1**) in acetic

Scheme



acid with the appropriate 5-arylidene substituted Meldrum's acid **2**. The pyrido[2,3-*d*]pyrimidines **4a-e** were obtained as stable crystalline solids easily purified by recrystallization from ethanol (See Experimental) (Scheme).

Compounds **2a-e** were prepared by following procedures described in the literature. Thus, equimolecular amounts of Meldrum's acid and the appropriate aldehydes were refluxed in the presence of triethylamine as the basic catalyst [7]. It is important to underline that the better solubility of the starting pyrimidine in acetic acid leads to a reduction of the reaction volume resulting in strikingly higher yields and lower reaction times in comparison with those previously reported in the synthesis of 5-aryl substituted 2,4,7-trioxo or 4,7-dioxo-2-thioxopyrido[2,3-*d*]-pyrimidines [6].

The reaction proceeds through a Hantzsch-like mechanism by conjugated addition of the enamine compounds **1** to the α,β-unsaturated carbonyl compound **2** to give the intermediate **3**, followed by an imino-enamine tautomerism and subsequent 6-*exo-trig* cyclization [8]. After loosing acetone and carbon dioxide, novel compounds **4a-e** were obtained and characterized by their analytical and spectroscopic data. In addition to the amino and carbonyl bands at 3450-3180 cm^{-1} (NH) and 1725-1670 cm^{-1} (C=O), the ir spectra of compounds **4c-e** clearly show the NO_2 bands at 1530 and 1350 cm^{-1}. The ^1H nmr spectra showed the NH protons at δ 10.7, 10.2 and 6.65 (assignment by NOE experiment to NH-1, NH-8 and NH_2 respectively), and the coupled pyridine protons on C6 and C5 as a double doublet centered at δ (C6) 3.20-2.99 and δ (C5) 4.3 respectively (See Experimental). The ^{13}C nmr spectra of compounds **4** present the pyridine carbonyl group at δ 171.4-170.2. The carbonyl group at C4 appears at δ 161.0 and C2 at δ 157.8-156.5. A *push-pull* effect is observed in the olefinic carbons C4a and C8a due to the electronic behaviour of their substituents. Thus, C4a appears at low δ values (89.9-91.7) and C8a gives a peak at low field values (δ 155). This result agrees with those previously observed for other related molecules [9]. The assignment of the remaining carbons of the molecule was carried out by DEPT-135° experiments (See Experimental).

The mass spectra of compounds **4a-e** shows the presence of the respective molecular ions with a relevant intensity and the base peak at m/z = 280 in all cases, due to the loss of the aryl group to form a stable ion. This result is in agreement with those previously observed for other related molecules [10].

We have carried out the determination of the favoured geometry for compounds **4a-e** with the quantum chemical AM1 method and found two favoured conformations (**A** and **B**) for these compounds with similar heats of formation. In the case **A**, the aryl substituent at carbon C5 lies in a pseudoaxial position, while in **B** the aryl substituent is in a pseudoequatorial position. In both cases the pyridone ring showed a twisted conformation (See Figure). The calculated heat of formation for the favoured geometries show that conformation **A** is 3-4 kcal/mol more stable than conformation **B** (see Table 1).

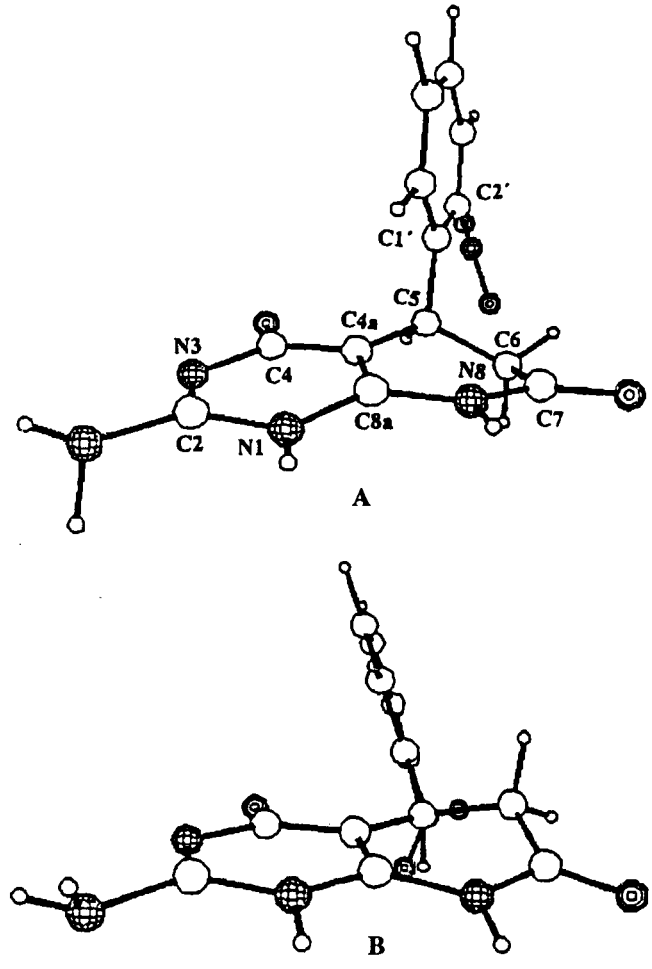


Figure. Favoured Conformations (**A** and **B**) for Compound **4c**.

Table 1

Heats of Formation (kcal/mol) for the Favoured Conformations **A** and **B** of Compounds **4a-e**

Compound	Conformation A	Conformation B
4a	7.31	11.69
4b	3.12	6.46
4c	15.15	17.65
4d	11.55	14.77
4e	10.33	14.45

Table 2 shows the most relevant geometric data for the most stable conformation **A**. In this conformation, as shown by the magnitude of the torsion angles (Table 2) the pyrimidine ring was found to be planar, being essentially located in a coplanar position to the pyridone ring. The magnitude of the C4a-C5-C1'-C2' torsion angle, shows that the plane of the phenyl ring is approximately

bisecting the pyridone ring. This interring orientation is preferred in all investigated *ortho* phenyl substituted derivatives **4b** and **4c** because it minimizes the steric strain imposed by the *ortho* phenyl substituent.

Table 2

Most Relevant Bond Distances (Å), Valence Angles (°) and Dihedral Angles (°) for the Conformation A of the Compounds **4a-e**

	4a	**4b**	**4c**	**4d**	**4e**
Bond Distances					
N1-C2	1.423	1.426	1.424	1.425	1.424
C2-N3	1.326	1.324	1.325	1.326	1.327
N3-C4	1.415	1.417	1.416	1.414	1.413
C4-C4a	1.474	1.476	1.476	1.475	1.474
C4a-C5	1.492	1.489	1.490	1.491	1.491
C5-C6	1.522	1.526	1.526	1.520	1.522
C6-C7	1.509	1.508	1.506	1.509	1.509
C7-N8	1.404	1.404	1.403	1.405	1.404
N8-C8a	1.404	1.404	1.403	1.405	1.404
C4a-C8a	1.384	1.384	1.385	1.384	1.385
Valence Angles					
C2-N1-C8a	117.89	117.88	118.14	118.01	118.03
C2-N3-C4	119.66	119.80	119.78	119.72	119.69
Dihedral Angle					
N1-C2-N3-C4	5.49	-4.45	4.30	-3.72	5.30
C2-N3-C4-C4a	1.21	4.40	1.01	3.36	0.70
N3-C4-C4a-C8a	-4.46	-5.16	-3.45	-4.09	-3.90
C4-C4a-C8a-N1	1.13	5.83	0.65	5.04	1.20
C4a-C8a-N1-C2	5.12	-5.51	4.21	-5.09	4.39
C8a-N1-C2-N3	-8.81	4.91	-7.09	4.52	-7.99
C2'-C1'-C5-C4a	-99.72	-23.20	-27.32	-97.42	-100.32
C7-N8-C8a	120.71	120.75	120.74	120.74	120.72
C4a-C5-C6	110.75	110.82	111.38	110.93	110.90
N8-C7-C6-C5	-30.35	-30.95	-29.40	-30.98	-30.47
C7-C6-C5-C4a	42.46	42.08	39.45	41.72	42.20
C6-C5-C4a-C8a	-30.80	-29.73	-26.07	-29.64	-30.05
C5-C4a-C8a-N8	3.66	2.94	-0.45	3.39	2.80
C4a-C8a-N8-C7	12.09	11.75	13.73	10.88	12.48
C8a-N8-C7-C6	2.31	3.34	2.20	3.94	2.41

In order to establish which of both conformers, **A** or **B**, is found in solution, we compared the experimental coupling constants between H6-H5 and H6'-H5 with those calculated by the Karplus [11] and Altona [12] equations using the theoretical dihedral angles obtained by AM1 calculations (Table 3).

The calculated $^3J_{HH}$ values together to those obtained from the ^1H nmr spectra are summarized in Table 4. The calculated coupling constants for conformation **A** are in good agreement with the found experimental data while those calculated for conformation **B** are far apart. This result cleary indicates that conformation **A** is the one observed in solution, thus confirming the higher stability of this conformation as predicted by the above theoretical calculations.

Table 3

Dihedral Angles (°) for the Favoured Conformations A and B

Compound	Dihedral angle	Conformation A	Conformation B
4a	H6'-C6-C5-H5	-79.21	160.51
	H6-C6-C5-H5	39.39	42.39
4b	H6'-C6-C5-H5	-79.92	144.82
	H6-C6-C5-H5	38.60	27.48
4c	H6'-C6-C5-H5	-82.36	144.03
	H6-C6-C5-H5	34.99	26.70
4d	H6'-C6-C5-H5	-79.63	156.25
	H6-C6-C5-H5	38.83	38.27
4e	H6'-C6-C5-H5	-79.06	147.88
	H6-C6-C5-H5	39.41	30.24

Table 4

Experimental and Calculated by Karplus and Altona Equations $^3J_{HH}$ Values

	Conformation	$^3J_{HH}$ Karplus		$^3J_{HH}$ Altona		$^3J_{HH}$ exp.	
		$J_{6,5}$	$J_{6',5}$	$J_{6,5}$	$J_{6',5}$	$J_{6,5}$	$J_{6',5}$
4a	**A**	7.20	2.16	6.29	1.12	7.6	1.0
	B	11.83	6.72	11.23	6.05		
4b	**A**	7.33	2.13	6.42	1.08	8.6	1.4
	B	8.98	9.49	8.39	8.86		
4c	**A**	7.89	2.04	7.02	1.00	8.4	1.4
	B	9.36	9.09	8.72	8.50		
4d	**A**	7.29	2.14	6.38	1.10	7.5	1.2
	B	7.38	11.29	10.69	6.74		
4e	**A**	7.20	2.17	6.29	1.12	7.5	1.2
	B	8.60	10.02	8.00	9.39		

The charge density values for the more relevant atoms are collected in Table 5. The calculated values for the olefinic carbons, C4a and C8a are in agreement with the experimental *push-pull* effect observed in the ^{13}C-nmr spectra. This finding can be accounted for by the presence of the two nitrogen atoms on C8a and their electronic effect and the electron withdrawing effect of the carbonyl group on C4a.

The calculated dipole moment for the Conformation **A** of the novel fused heterocycles **4a-e** are shown in Table 6. It is worth mentioning that compounds **4a,b** exibit values similar to other related molecules [9]. However, compounds **4c-e** bearing a nitro group on the phenyl ring in C5 show a higher value and, particularly, when the nitro substituent is located at the *para* position.

As expected, the primary amino group on C2 shows a low nucleophilic character and, consequently, all atempts carried out for the derivatization of this $-NH_2$ group such as Schiff's base formation and reaction with diethyl malonate under basic conditions were met with futility. This finding could be rationalized on the basis of the low charge density calculated for the amino group (Table 5) in comparison with that calculated for the nitrogen atom in the aniline molecule (-0.412) used as reference.

In conclusion, we have carried out the synthesis of novel 2-aminopyrido[2,3-*d*]pyrimidines **4** from the readily available 2,4-diamino-6-hydroxypyrimidine **1** and the arylidene substituted Meldrum's acids **2a-e**. Theoretical calculations confirm the electronic *push-pull* effect observed in the ^{13}C nmr spectra and show a distorted geometry with two posible favoured conformations. The experimental and theoretical values of $^3J_{HH}$ and the calculated heat of formation show that the conformation **A** is the favoured one.

Table 5

Charge Density Values for the atoms in Conformation A for Compounds **4a-e**

Compound	N1	C2	N3	C4	C4a	C7	C8a	N8	NH_2
4a	-0.305	0.232	-0.289	0.329	-0.289	0.322	0.217	-0.346	-0.322
4b	-0.309	0.229	-0.288	0.324	-0.297	0.324	0.215	-0.351	-0.322
4c	-0.310	0.231	-0.286	0.323	-0.309	0.320	0.223	-0.353	-0.321
4d	-0.308	0.236	-0.284	0.327	-0.304	0.318	0.225	-0.349	-0.322
4e	-0.307	0.237	-0.286	0.330	-0.304	0.318	0.228	-0.347	-0.323

The compounds now reported **4a-e** can be considered as promising candidates for further functionalization, leading to other fused heterocyclic systems containing the 1,4-dihydropyridine moiety.

Table 6

Dipole Moment for Conformation A for Compounds **4a-e**

Compound	Dipole Moment (D)
4a	5.53
4b	6.35
4c	9.25
4d	9.82
4e	9.96

EXPERIMENTAL

Melting points were determinated in capillary tubes in a Electrothermal 9100 apparatus and are uncorrected. The nmr spectra were recorded on a Bruker AC spectrometer (250 MHz-^{1}H and 62.0 MHz-^{13}C). Chemical shifts are given as δ values against tetramethylsilane as the internal standard. The ir spectra were measured with a SPEKORD instrument as potassium bromide pellets. Mass spectra were obtained with a TRIO 1000 machine. Microanalyses were performed by the Servicio de Microanálisis of Universidad Complutense de Madrid. The reactions were monitored by tlc performed on silica-gel plates (Merck $60F_{250}$) and using benzene:methanol (6:3) as the eluent.

Meldrum's acid, benzaldehyde, *o*-chlorobenzaldehyde, *o*-nitrobezaldehyde, *m*-nitrobenzaldehyde, *p*-nitrobenzaldehyde, triethylamine, and 2,4-diamino-6-hydroxypyrimidine were obtained from commercial sources (Aldrich and Merck) and were used without further purification. Aromatic aldehydes were distilled before use. The geometry optimization was carried out with the semiempirical AM1 method by using the MOPAC molecular orbitals set. Previously, the molecular geometry was optimized by using Allinger's Molecular Mechanics with PCMODEL program. Calculations were performed on a PC 486/33 computer. The theorical coupling constants were obtained using the Karplus [11] and Altona [12] equations.

5-Arylidene-2,2-dimethyl-1,3-dioxan-4,6-diones **2a-e** were obtained by the standard procedure [7].

2-Amino-5-aryl-4,7-diozo-1,4,5,6,7,8-hexahydropyrido[2,3-*d*]-pyrimidines **4a-e**.

General Procedure.

A mixture of 2,4-diamino-6-hydroxypyrimidine (**1**) and the corresponding arylidene-2,2-dimethyl-1,3-dioxane-4,6-dione **2a-e** in glacial acetic acid (30 ml) was refluxed for a variable length of time (5-12 hours monitored by tlc). The solid that precipitated was collected by filtration and washed with glacial acetic acid and water until neutral *p*H. Further purification was accomplished by recrystallization from ethanol

2-Amino-4,7-dioxo-5-phenyl-1,4,5,6,7,8-hexahydropyrido-[2,3-*d*]pyrimidine (**4a**).

This compound was obtained by following the above general procedure, refluxing **1** and **2a** for 5 hours in 89% yield, mp 393°; ir (potassium bromide): 3425, 3350, 3185 (N-H), 1705, 1685 (C=O) and 1555-1450 (Ph) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.72 (1H, s, NH-1), 10.36 (1H, s, NH-8), 7.29-7.14 (5H, m, Ph), 6.69 (2H, s, NH_2), 4.13 (1H, dd, H-5, $J_{5,6}$ = 7.6 Hz, $J_{5,6'}$ = 1.0 Hz, X part of ABX), 2.99 (1H, dd, H-6, $J_{6,5}$ = 7.7 Hz, $J_{6,6'}$ = 16.2 Hz A part of ABX), 2.49 (1H, dd, H-6', $J_{6',6}$ = 16.0 Hz, $J_{5,6}$ = 1.0 Hz B part of ABX); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 171.4 (C7), 161.4 (C4), 156.5 (C2), 155.2 (C8a), 143.7 (C1'), 128.5 (C3', C5'), 126.5 (C2', C4', C6'), 91.7 (C4a), 38.6 (C6), 32.9 (C5); ms: m/z (intensity %) 257 (M^+, 20), 256 (98), 213 (10), 179 (100), 162 (15), 137 (25), 94 (18), 43 (35).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$ (256.26): C, 60.93; H, 4.72; N, 21.86. Found: C, 61.07; H, 4.91; N, 22.07.

2-Amino-5-(2'-chlorophenyl)-4,7-dioxo-1,4,5,6,7,8-hexahydro-pyrido[2,3-*d*]pyrimidine (**4b**).

This compound was obtained by following the above general procedure, refluxing **1** and **2b** for 8.5 hours in 80% yield, mp >400°; ir (potassium bromide): 3445, 3340, 3190 (N-H); 1700, 1680 (C=O) and 1550-1440 (Ph) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.71 (1H, s, NH-1), 10.27 (1H, s, NH-8), 7.48-6.88 (4H, m, Ph), 6.65 (2H, s, NH_2), 4.46 (1H, dd, H-5, $J_{5,6'}$ = 8.6 Hz, $J_{5,6}$ = 1.4 Hz, X part of ABX), 3.04 (1H, dd, H-6, $J_{6,5}$ = 8.6 Hz, $J_{6,6'}$ = 16.3 Hz A part of ABX), 2.36 (1H, dd, H-6', $J_{6',6}$ = 16.2 Hz, $J_{5,6'}$ = 1.4 Hz B part of ABX); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 170.3 (C7), 161.1 (C4), 157.8 (C2), 155.4 (C8a), 139.9 (C1'), 132.5 (C2'), 129.8 (C3'), 128.5 (C4'), 127.5 (C6'), 127.3 (C5'), 89.9 (C4a), 37.4 (C6), 30.7 (C5); ms: m/z (intensity %) 292 (M^+ + 1, 16), 290 (M^+, 50), 255 (60), 213 (15), 179 (100), 162 (5), 137 (10), 94 (4), 75 (7), 43 (42).

Anal. Calcd. for $C_{13}H_{11}N_4O_2Cl$ (290.71): C, 53.71; H, 3.81; N, 19.27. Found: C, 53.53; H, 3.89; N, 19.08.

2-Amino-5-(2'-nitrophenyl)-4,7-dioxo-1,4,5,6,7,8-hexahydropy-rido[2,3-*d*]pyrimidine (**4c**).

This compound was obtained by following the above general procedure, refluxing **1** and **2c** for 9 hours in 95% yield, mp >400°; ir (potassium bromide): 3420, 3330, 3190 (N-H); 1710, 1680 (C=O), 1525 (NO_2), 1550-1465 (Ph) and 1350 (NO_2) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.71 (1H, s, NH-1), 10.41 (1H, s, NH-8), 7.93-7.14 (4H, m, Ph), 6.68 (2H, s, NH_2), 4.50 (1H, dd, H-5, $J_{5,6}$ = 8.4 Hz, $J_{5,6'}$ = 1.4 Hz, X part of ABX), 3.18

(1H, dd, H-6, $J_{6,5}$ = 8.4 Hz, $J_{6,6'}$ = 16.0 Hz, A part of ABX), 2.40 (1H, dd, H-6', $J_{6',6}$ = 16.5 Hz, $J_{5,6'}$ = 1.4 Hz, B part of ABX); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 170.2 (C7), 161.1 (C4), 157.2 (C2), 155.4 (C8a), 148.7 (C2'), 137.9 (C1'), 133.8 (C5'), 128.1 (C4'), 128.0 (C6'), 124.6 (C3'), 90.3 (C4a), 38.0 (C6), 29.2 (C5); ms: m/z (intensity %) 301 (M^+, 60), 284 (64), 267 (25), 253 (85), 179 (100), 162 (20), 155 (15), 137 (20), 94 (15), 43 (50).

Anal. Calcd. for $C_{13}H_{11}N_5O_4$ (301.26): C, 51.83; H, 3.68; N, 23.25. Found: C, 51.56; H, 3.82; N, 23.17.

2-Amino-5-(3'-nitrophenyl)-4,7-dioxo-1,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidine (**4d**).

This compound was obtained by following the above general procedure, refluxing **1** and **2d** for 12 hours in 83% yield, mp 356-359°; ir (potassium bromide): 3420, 3385, 3180, (N-H); 1690, 1675 (C=O), 1530 (NO_2), 1560-1455 (Ph), 1350 (NO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.32 (1H, s, NH-1), 10.27 (1H, s, NH-8), 8.07-7.58 (4H, m, Ph), 6.66 (2H, s, NH_2), 4.29 (1H, dd, H-5, $J_{5,6}$ = 7.5 Hz, $J_{5,6'}$ = 1.2 Hz, X part of ABX), 3.04 (1H, dd, H-6, $J_{6,5}$ = 7.9 Hz, $J_{6,6'}$ = 16.5 Hz, A part of ABX), 2.56 (1H, dd, H-6', $J_{6,6}$ = 16.4 Hz, $J_{5,6'}$ = 1.4 Hz, B part of ABX); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 170.7 (C7), 161.4 (C4), 156.9 (C2), 155.3 (C8a), 147.9 (C3'), 146.1 (C1'), 133.4 (C6'), 130.2 (C5'), 121.6 (C4'), 121.1 (C2'), 90.7 (C4a), 38.0 (C6), 32.8 (C5); ms: m/z (intensity %) 301 (M^+, 40), 284 (10), 254 (10), 179 (100), 162 (8), 137 (15), 94 (10), 43 (35).

Anal. Calcd. for $C_{13}H_{11}N_5O_4$ (301.26): C, 51.83; H, 3.68; N, 23.25. Found: C, 51.90; H, 3.72; N, 23.31.

2-Amino-5-(4'-nitrophenyl)-4,7-dioxo-1,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidine (**4e**).

This compound was obtained by following the above general procedure, refluxing **1** and **2e** for 9 hours in 89% yield, mp >400°; ir (potassium bromide): 3380, 3370, 3150, (N-H), 1710, 1690 (C=O), 1540 (NO_2), 1560-1480 (Ph), 1350 (NO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.32 (1H, s, NH-1), 10.27 (1H, s, NH-8), 8.07-7.58 (4H, m, Ph), 6.66 (2H, s, NH_2), 4.29 (1H, dd, H-5, $J_{5,6}$ = 7.5 Hz, $J_{5,6'}$ = 1.2 Hz, X part of ABX), 3.04 (1H, dd, H-6, $J_{6,5}$ = 7.9 Hz, $J_{6,6'}$ = 16.5 Hz A part of ABX), 2.56 (1H, dd, H-6', $J_{6',6}$ = 16.4 Hz, $J_{5,6}$ = 1.4 Hz B part of ABX); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 170.5 (C7), 161.4 (C4), 156.9 (C2), 155.3 (C8a), 151.8 (C4'), 146.2 (C1'), 127.8 (C3', C5'), 123.7 (C2', C6'), 90.4 (C4a), 38.4 (C6), 33.1 (C5); ms: m/z (intensity %) 301 (M^+, 90), 284 (15), 254 (10), 179 (100), 162 (25), 137 (30), 43 (45).

Anal. Calcd. for $C_{13}H_{11}N_5O_4$ (301.26): C, 51.83; H, 3.68; N, 23.25. Found: C, 51.54; H, 3.97; N, 23.41.

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REFERENCES AND NOTES

[1] A. Gangjee, A. Vasudevan, F. Queener and R. Kisliuk, *J. Med. Chem.*, **38**, 1778 (1995); A. Gangjee, U.S. Patent 5,508,281 (1996); *Chem. Abstr.*, **125**, 33667a, (1996); A. Gangjee, A. Vasudevan, F. Queener and R. Kisliuk, *J. Med. Chem.*, **39**, 1438 (1996).

[2] S. A. K. Sharma and L. Prakash, *Heterocyclic Commun.*, **1**, 89 (1994).

[3] A. Monge, V. Martinez, C. San Martín and M. A. Simon, Spanish Patent ES 2,056,742 (1994); *Chem. Abstr.*, **122**, 105912q (1995).

[4] G. Hou, D. Gravier, F. Casadebaig, J. Dupin, H. Bernard and M. Boiseau, *Pharmazie*, **50**, 719 (1995).

[5] J. Quiroga, J. García, B. Insuasty, N. Mendoza, M. Purgo and H. Meier, *An. Quim.*, **90**, 300 (1994).

[6] R. Rodríguez, M. Suárez, E. Ochoa, A. Morales, L. González, N. Martín, M. Quinteiro, C. Seoane and J. L. Soto, *J. Heterocyclic Chem.*, **33**, 45 (1996). See references cited therein.

[7] G. D. Krapivin and V. E. Savodnik, *Khim. Geterotsicl. Soedin.*, 1453 (1990).

[8] The Baldwin nomenclature for classifying ring closures is used here. See J. E. Baldwin and M. J. Lusch, *Tetrahedron*, **38**, 2939 (1982).

[9] Y. Verdecia, M. Suárez, A. Morales, E. Rodríguez, E. Ochoa, L. González, N. Martín, M. Quinteiro, C. Seoane and J. L. Soto, *J. Chem. Soc., Perkin Trans 1*, 947 (1996); N. Martín, J. L. Segura, C. Seoane, J. L. Soto, M. Morales and M. Suárez, *Liebigs Ann. Chem.*, 827 (1991); N. Martín, M. Quinteriro, C. Seoane, J. L. Soto, A. Mora, M. Suárez, E. Ochoa, A. Morales and J. R. del Bosque, *J. Heterocyclic Chem.*, **32**, 235 (1995); A. Morales, E. Ochoa, M. Suárez, Y. Verdecia, L. González, N. Martín, M. Quinteiro, C. Seoane and J. L. Soto, *J. Heterocyclic Chem.*, **33**, 103 (1996).

[10] U. Rose, *Arzneim.-Forsh./Drug Res.*, **39**, 1393 (1989).

[11] H. Günther, NMR Spectroscopy, John Wiley & Sons Ltd. Second Ed, New York, 1995, p 115.

[12] C. A. G. Haasnoot, F. A. A. M. de Leeuw, C. Altona, *Tetrahedron*, **36**, 2783 (1980).