Synthesis of Pyrimido[4,5-*b*]quinolines in the Reaction of 6-Aminopyrimidines with Dimedone and Benzaldehydes

J. Quiroga*, A. Hormaza and B. Insuasty

Department of Chemistry, Universidad del Valle, A.A. 25360 Cali, Colombia

A. J. Ortíz, A. Sánchez and M. Nogueras

Department of Inorganic and Organic Chemistry, Universidad de Jaén 23071 Jaén, Spain

Received May 12, 1997

The reaction of 6-aminopyrimidines **1a,b** with dimedone (**2**) and *p*-substituted benzaldehydes **3a-d** in ethanol afforded in all cases new regiospecific synthesis of tricyclic, linear 5-aryl-5,6,7,8,9,10-hexahydropyrimido[4,5-*b*]quinolines **4a-h** in good yields. The linear structures and hence the regiospecificity of the reaction were established by nmr measurements.

J. Heterocyclic Chem., **35**, 231 (1998).

Introduction.

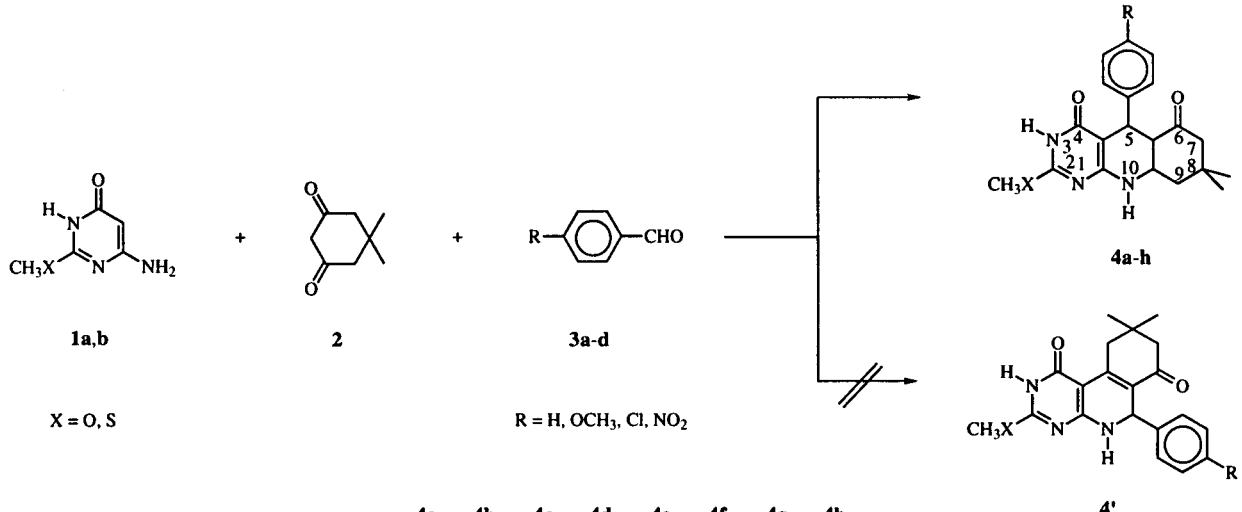
The research on the dihydropyridine systems is of current interest due to their exceptional properties as calcium antagonists [1-3] and as powerful arteriolar vasodilators [4,5]. Our recent works has provided an efficient method for the synthesis of various fused heterocyclic compounds containing the dihydropyridine moiety [6-9].

In this paper we describe a versatile synthesis of novel 5-aryl-5,6,7,8,9,10-hexahydropyrimido[4,5-*b*]quinoline derivatives as dihydropyridine containing ring systems. There was reported a significant inhibition of dihydrofolate reductase by 5-deazafolic acid lends further support for the synthesis of this system as an analog of 5-deazafolic acid [10-12]. The work has resulted in development of a new direct and simple synthetic entry into the pyrimido[4,5-*b*]quinoline ring system.

Results and Discussions.

The preparation of pyrimido[4,5-*b*]quinolines **4a-h** have been carried out by refluxing for 20-30 minutes equimolecular amounts of 6-aminopyrimidine **1** in absolute ethanol with dimedone **2** and the appropriate benzaldehyde derivative **3**. The new compounds were obtained in good yields (see Scheme 1) as stable crystalline solids and easy purified by recrystallization from ethanol. The one-step cyclocondensation reaction can afford linear and/or angular products **4/4'**.

Scheme 1



	4a	4b	4c	4d	4e	4f	4g	4h
X	O	O	O	O	S	S	S	S
R	H	OCH_3	Cl	NO_2	H	OCH_3	Cl	NO_2
mp, C°	316	307	319	282	366	345 (d)	350	346 (d)
Yield, %	75	78	80	85	78	80	85	88

The cyclocondensation of amines **1a,b** with **2** and **3** gave regiospecifically the linear isomer, hexahydropyrimido[4,5-*b*]quinoline **4**. In each case the reaction gave a single product as determined on tlc. The support for the linear structures of **4a-h** was provided from ^{1}H-nmr spectra in particular with respect to the chemical shift of the 5-H and singlet of 10-H.

The ^{1}H-nmr spectra of compounds **4a-h** (dimethyl sulfoxide-d_6, see Table 1) contain three relatively sharp singlets at 11.90-12.33, 4.81-5.00 and 9.71-9.98 ppm for 3-H, 5-H and 10-H. We have synthesized several 5,7-diaryl-5,8-dihydropyrido[2,3-*a*]pyrimidines and reported the 5-H and 10-H protons at δ 4.50-4.70 and 8.20-8.50 ppm respectively [7,8]. The fact that 5-H and 10-H are not coupled is a evidence for the linear structure **4** and discard the angular **4'**. In the last one, coupling between methynic proton and NH must be observed.

In the ^{13}C-nmr spectra, the number of signals belonging to quaternary, tertiary, secondary and primary carbon atoms for compounds **4a-h** could be determined (DEPT experiment, see Table 2). It is worth mentioning that these compounds showed in their ^{13}C-nmr spectra signals for C-9a and C-10a at higher δ values 150-156 ppm. In contrast, carbon atoms C-4a and C-5a appeared at unusually lower δ values, 94.8-98.1 and 108.5-109.9 ppm respectively. These findings could be accounted for by the strong push-pull effect of the amino and carbonyl groups linked to the C-4a C-l0a and C-5a C-9a double bonds.

The assignment of the signals in the ^{1}H- and ^{13}C-nmr spectra of **4a-h**, is supported by ^{1}H,^{1}H COSY technique and ^{1}H,^{13}C shift correlation, as well as by comparison with data previously published for similar systems [7-9,13].

Table 1

^{1}H NMR Data of **4a-h**, δ Values in DMSO-d_6, TMS as Internal Standard

Compound	CH_3X s	CH_3 s		3-NH s	5-H s	7-CH_2 dd		9-CH_2 dd		10-NH s	Phenyl m
4a	3.92	1.00	1.09	11.96	4.88	2.09	2.11	2.46	2.51	9.77	7.11-7.21
4b	3.90	1.00	1.09	11.90	4.81	2.09	2.17	2.43	2.50	9.71	6.73-7.08
4c	3.88	0.89	1.01	12.02	4.86	2.01	2.18	2.41	2.48	9.82	7.19-7.26
4d	3.90	0.90	1.09	12.10	5.00	2.04	2.24	2.41	2.51	9.98	7.32-8.12
4e	2.50	0.91	1.01	12.29	4.90	2.00	2.17	2.46	2.50	9.76	7.10-7.19
4f	2.51	0.91	1.01	12.29	4.88	2.00	2.17	2.44	2.50	9.79	6.74-7.10
4g	2.50	0.90	1.09	12.33	4.90	2.01	2.37	2.47	2.53	9.82	7.18-7.26
4h	2.51	0.90	1.03	12.30	5.00	2.03	2.22	2.51	2.55	9.93	7.48-8.10

Table 2

^{13}C NMR Data of **4a-h**, δ values in DMSO-d_6, TMS as Internal Standard

Compound	CH_3X	CH_3	C-2	C-6	C-4a	C-5	C-5a	C-4	C-7	C-8	C-9	C-9a	C-10a	Phenyl *i*	Phenyl *o*	Phenyl *m*	Phenyl *p*
4a	54.6	26.6 28.8	156.5	193.9	95.9	32.0	109.7	162.0	50.2	33.5	39.9	150.9	152.3	146.8	125.6	127.5	129.4
4b	54.8	26.7 28.9	157.2	193.9	96.2	32.0	109.9	162.0	50.2	32.6	40.0	152.2	156.4	139.2	128.3	113.0	150.6
4c	54.6	26.7 28.8	156.6	193.9	95.5	32.0	109.3	162.0	50.1	33.3	40.0	151.1	152.4	145.7	127.5	129.3	130.1
4d	54.7	26.7 28.8	154.2	193.9	94.8	31.1	108.7	161.8	50.0	34.5	40.0	151.6	152.6	145.6	123.1	128.8	145.4
4e	12.6	26.7 28.9	159.5	193.8	97.9	33.5	109.5	161.5	50.1	33.5	40.5	150.9	152.1	146.7	127.4	127.6	125.7
4f	12.6	26.7 28.8	157.3	193.8	98.1	32.5	109.7	161.5	50.1	33.0	39.6	151.2	153.5	138.9	128.4	113.1	150.6
4g	12.7	26.7 28.8	160.0	193.8	97.5	32.0	109.2	161.5	50.1	33.3	39.6	151.1	151.8	145.4	127.6	129.3	130.2
4h	12.6	26.7 28.7	153.9	193.8	96.8	32.0	108.5	162.8	49.9	34.5	39.6	151.6	151.8	145.7	123.0	128.8	140.0

EXPERIMENTAL

Melting points were determined in a Buchi Melting Point Apparatus and are uncorrected. The ^{1}H- and ^{13}C-nmr spectra were run on a Bruker DPX 300 spectrometer operating at 300 MHz and 75 MHz respectively, using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra were scanned on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) operating at 70 or 30 eV. The elemental analysis have been obtained using LECO CHNS-9OO equipment.

General Procedure for the Preparation of the Substituted Pyrimido[4,5-*b*]quinolines **4**.

A solution of 1 mmole of 6-aminopyrimidine **1**, 1 mmole of dimedone **2** and 1 mmole of benzaldehyde **3** in 15 ml of absolute ethanol was stirred at reflux for 20-30 minutes. The cycled products **4** were isolated by cooling, followed by filtration, washing with ethanol, drying and recrystallized from ethanol.

8,8-Dimethyl-5,6,7,8,9,10-hexahydro-2-methoxy-5-phenylpyrimido[4,5-*b*]quinoline-4,6-dione **4a**.

This compound was obtained according to general procedure as white crystals. The mass spectrum shows the following peaks: ms: (30 eV) m/z (%) 351 (M$^+$, 15), 336 (2), 274 (100), 242 (7), 218 (8), 190 (6), 147 (3), 83 (5), 43 (4).

Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.45; H, 6.13; N, 11.90.

8,8-Dimethyl-5,6,7,8,9,10-hexahydro-2-methoxy-5-(4-methoxyphenyl)pyrimido[4,5-*b*]quinoline-4,6-dione **4b**.

This compound was obtained according to general procedure as white crystals. The mass spectrum shows the following peaks: ms: (30 eV) m/z (%) 381 (M$^+$, 24), 366 (4), 296 (4), 274 (100), 42 (6), 218 (8), 190 (5), 149 (22), 83 (25), 57 (52), 43 (57).

Anal. Calcd. for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found: C, 66.05; H, 6.13; N, 11.09.

5-(4-Chlorophenyl)-8,8-dimethyl-5,6,7,8,9,10-hexahydro-2-methoxy pyrimido[4,5-*b*]quinoline-4,6-dione **4c**.

This compound was obtained according to general procedure as white crystals. The mass spectrum shows the following peaks: ms: (30 eV) m/z (%) 385 (M$^+$, 16), 275 (18), 274 (100), 83 (12), 57 (16), 45 (27), 44 (56), 43 (33).

Anal. Calcd. for $C_{20}H_{20}N_3O_3Cl$: C, 62.26; H, 5.22; N, 10.89. Found: C, 62.35; H, 5.26; N, 10.80.

8,8-Dimethyl-5,6,7,8,9,10-hexahydro-2-methoxy-5-(4-nitrophenyl)pyrimido[4,5-*b*]quinoline-4,6-dione **4d**.

This compound was obtained according to general procedure as pale yellow crystals. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) 396 (M$^+$, 2), 274 (17), 218 (2), 141 (4), 83 (13), 43 (100).

Anal. Calcd. for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13. Found: C, 60.05; H, 5.13; N, 14.20.

8,8-Dimethyl-5,6,7,8,9,10-hexahydro-2-methylthio-5-phenylpyrimido[4,5-*b*]quinoline-4,6-dione **4e**.

This compound was obtained according to general procedure as white crystals. The mass spectrum shows the following peaks: ms: (30 eV) m/z (%) 367 (M$^+$, 9), 313 (8), 290 (34), 264 (8), 236 (10), 152 (8), 83 (49), 57 (93), 43 (100).

Anal. Calcd. for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.40. Found: C, 65.45; H, 5.73; N, 11.44.

8,8-Dimethyl-5,6,7,8,9,10-hexahydro-5-(4-methoxyphenyl)-2-methylthiopyrimido[4,5-*b*]quinoline-4,6-dione **4f**.

This compound was obtained according to general procedure as white crystals. The mass spectrum shows the following peaks: ms: (30 eV) m/z (%) 397 (M$^+$, 34), 382 (10), 290 (100), 242 (16), 206 (6), 186 (6), 158 (6), 83 (24), 57 (38), 43 (52).

Anal. Calcd. for $C_{21}H_{23}N_3O_3S$: C, 63.46; H, 5.83; N, 10.57. Found: C, 63.41; H, 5.73; N, 10.50.

5-(4-Chlorophenyl)-8,8-dimethyl-5,6,7,8,9,10-hexahydro-2-methylthiopyrimido[4,5-*b*]quinoline-4,6-dione **4g**.

This compound was obtained according to general procedure as white crystals. The mass spectrum shows the following peaks: ms: (30 eV) m/z (%) 386 (M$^+$-15, 4), 290 (100), 242 (13), 83 (16), 43 (20).

Anal. Calcd. for $C_{20}H_{20}N_3O_2SCl$: C, 59.77; H, 5.02; N, 10.46. Found: C, 59.71; H, 5.10; N, 10.40.

8,8-Dimethyl-5,6,7,8,9,10-hexahydro-2-methylthio-5-(4-nitrophenyl)pyrimido[4,5-*b*]quinoline-4,6-dione **4h**.

This compound was obtained according to general procedure as pale yellow crystals. The mass spectrum shows the following peaks: ms: (30 eV) m/z (%) 290 (M$^+$-$C_6H_4NO_2$, 14), 83 (10), 71 (10), 69 (12), 57 (23), 55 (21), 44 (100), 43 (50).

Anal. Calcd. for $C_{20}H_{20}N_4O_4S$: C, 58.24; H, 4.89; N, 13.58. Found: C, 58.31; H, 4.83; N, 13.50.

Acknowledgment.

The authors thank the COLCIENCIAS and Universidad del Valle for financial support of this work.

REFERENCES AND NOTES

[1] F. Bossert and W. Vater, *Med. Res. Rev.*, **9**, 291 (1989).

[2] D. J. Trigle, D. A. Langs and R. A. Janis, *Med. Res. Rev.*, **9**, 123 (1989).

[3] A. Fleckenstein and G. Grun, *Arzneim. Forsch.*, **22**, 334 (1972).

[4] S. Kazda and R. Towart, *Br. J. Pharmacol.*, **72**, 582P (1981).

[5] R. Alajarin, J. Alvarez-Builla, J. J. Vaquero, C. Sunkel, J. Fau, P. Statkow and J. Sanz, *Tetrahedron Asymetry*, **4**, 617 (1993).

[6] V. D. Orlov, J. Quiroga and N. N. Kolos, *Khim. Geterosikl. Soedin.*, **9**, 1247 (1987).

[7] J. Quiroga, B. Insuasty, A. Sánchez, M. Nogueras and H. Meier, *J. Heterocyclic Chem.*, **29**, 1045 (1992).

[8] J. Quiroga, B. Insuasty, M. Pungo, L. Mendoza and H. Meier, *An. Quim.*, **90**, 300 (1994).

[9] J. Quiroga, A. Hormaza, B. Insuasty, M. Nogueras, A. Sánchez, N. Hanold and H. Meier, *J. Heterocyclic Chem.*, **34**, 521 (1997).

[10] A. Gangjee, K. A. Ohemeng, J. J. Tulachka, F.-T. Lin and A. A. Katoh, *J. Heterocyclic Chem.*, **22**, 1149 (1985).

[11] A. Gangjee, J. K. O'Donnell, T. J. Bardos and T. I. Kalman, *J. Heterocyclic Chem.*, **21**, 873 (1984).

[12] S. R. Stone, J. A. Montgomery and J. F. Morrison, *Biochem. Pharmacol.*, **33**, 175 (1984).

[13] N. Martin, M. Quintero, C. Seoane, J. L. Soto, A. Mora, M. Suarez, E. Ochoa, A. Morales and J. R. del Bosque, *J. Heterocyclic Chem.*, **32**, 235 (1995).