Reactions of 6-Aminopyrimidines with 2-Dimethylaminomethylenetetralone. Regiospecific Synthesis of 5,6-Dihydrobenzo[*h*]pyrimido[4,5-*b*]quinolines.

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Benzo[*h*]pyrimido[4,5-*b*]quinolines (**3**) have been synthesized *via* a regiospecific cyclocondensation reaction between 6-aminopyrimidines (**1**) and 2-dimethylaminomethylentetralone hydrochloride (**2**). The linear structure of the final compounds were determined by nmr measurements, especially by ^{1}H,^{1}H-, ^{1}H,^{13}C COSY and DEPT experiments.

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Introduction.

The pyrido[2,3-*d*]pyrimidine derivatives present interesting biological properties. Thus, recent works showed that these compounds have been used as dihydrofolate reductase inhibitors as antitumor agents [1-3]; some of them have shown a broad spectrum of antimicrobial - activity [4-7], diuretic properties [8] and activity against platelet aggregation [9].

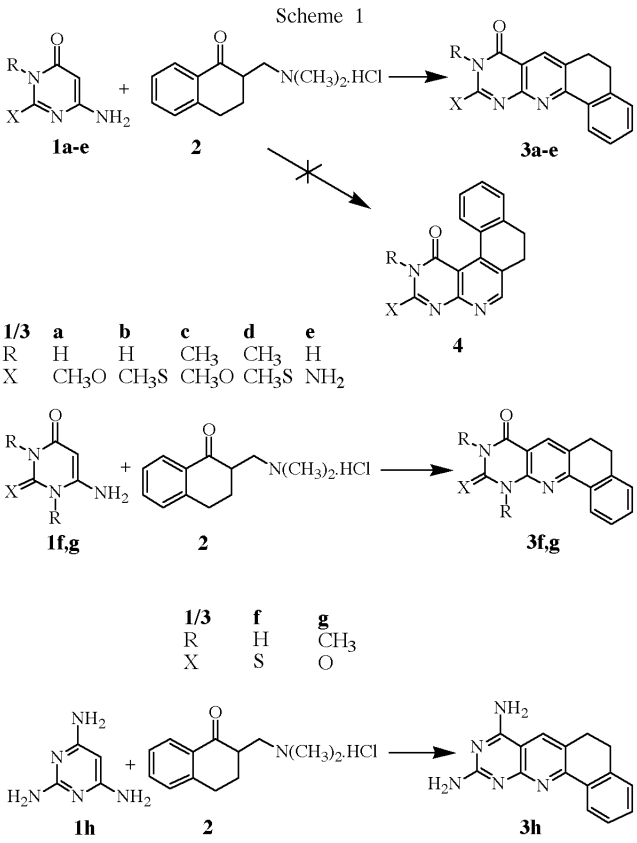
As part of our continuing interest in the reaction of aminopyrimidines with α,β-unsaturated compounds and their precursors [10-16], in this work we studied the cyclocondensation reaction between the 6-aminopyrimidines **1** and the hydrochloride of the Mannich base **2** (2-dimethylaminomethylentetralone hydrochloride).

Results and Discussion.

Thus, the reaction of equimolar amounts of aminopyrimidines **1a-h** and 2-dimethylaminomethylentetralone hydrochloride **2** in absolute ethanol at reflux yield the linear dihydrobenzo[*h*]pyrimido[4,5-*b*]quinolines **3a-h** in good yields (60-70%) as unique products (Scheme 1).

The Mannich bases (**2**) are relatively unstable and easily lose the amino group forming vinyl ketones [17-20]. Addition of vinyl ketone, resulting from elimination of dimethylamine hydrochloride from **2**, to the nucleophilic 5 carbon atom of the pyrimidine ring and subsequent cyclization with water elimination gives **3a-h**. On the other hand, the addition of the amino group of **1** to the β-C atom of vinyl ketone followed by cyclization can afford **4**. The cyclocondensation of amines **1a-h** with **2** gave regiospecifically the linear isomer, dihydrobenzo[*h*]-pyrimido[4,5-*b*]quinolines **3a-h**. In each case, the reaction gave a single product as determined on tlc. The support for the linear structures for **3** was provided from ^{1}H-nmr spectra in particular with respect to the chemical shift of the H-7 proton.

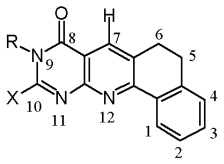
Scheme 1



The formation of **3a-h** is assumed to proceed by a Michael type addition of the most nucleophilic ring carbon atom in the aminopyrimidine to the activated double bond of vinyl ketone [11,15,16]. The intermediate formed Michael adduct, cyclic and by water elimination yield dihydrobenzo[*h*]pyrimido[4,5-*b*]-quinolines **3a-h** (Scheme 1).

The ^{1}H nmr spectra of compounds **3a-h** (see Table 1) contain one singlet at 8.18-8.61 ppm for the H-7 proton and signals at 2.94-3.06 ppm for methylene protons of the C(5)H_2-C(6)H_2 fragment.

Table 1
^{1}H-NMR Data of **3a-h** δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl Sulfoxide-d_6, 300 MHz



Compound	5-CH_2	6-CH_2	7-CH	Aromatic protons				9-R	10-X
				H-1	H-2	H-3	H-4		
3a	2.95	3.00	8.22	7.45	7.38	8.30	7.35	12.47	4.02
3b	2.95	3.03	8.25	7.46	7.38	8.30	7.35	12.57	2.63
3c	2.99	3.05	8.25	7.42	7.33	8.42	7.29	3.50	4.19
3d	3.00	3.06	8.32	7.40	7.37	8.53	7.38	3.64	2.79
3e[a]	3,00	3,10	8,61	8,24	7,50	7,60	7,46	[b]	[b]
3f[c]	2.94	2.99	8.18	7.45	7.41	8.23	7.35		
3g[d]	2.99	2.99	8.23	7.41	7.38	8.34	7.22	3.81	
3h[e]	2.95	2.99	8.42	7.43	7.37	8.25	7.34		

[a] Trifluor acetic acid and dimethyl sulfoxide-d_6 (50%) as solvent. [b] Appears together H_3O^+ signal. [c] 9-H and 11-H at 12,54 and 13,08 ppm respectively. [d] 9-CH_3 and 11-CH_3 at 3,81 and 3,49 ppm respectively. [e] 8-NH_2 and 10-NH_2 at 8,31 and 7,20 ppm respectively.

In the ^{13}C-nmr spectra of compounds **3**, the number of signals belonging to quaternary, tertiary, secondary and primary carbon atoms were determined (DEPT experiments, Table 2). It is worth mentioning that these compounds **3a-h** showed in their ^{13}C-nmr spectra the signals for C-11a at higher δ value 156-161 ppm and, in contrast, carbon atoms C-7a appeared at unusually low δ values (103-113 ppm).

Table 2
^{13}C-NMR Data of **3a-h** δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl Sulfoxide-d_6, 75 MHz

	3a	**3b**	**3c**	**3d**	**3e**[a]	**3f**	**3g**	**3h**
C-1	130.4	130.5	130.1	130.7	127,6	130.9	130.9	130.5
C-2	127.0	127.0	126.5	127.3	129,3	127.0	127.3	127.0
C-3	125.7	125.8	126.0	127.1	135,3	125.7	126.2	125.4
C-4	128.1	128.1	127.5	127.9	130,4	128.2	128.2	128.1
C-4a	139.4	139.4	139.0	139.5	143,1	139.6	139.5	139.5
C-5	27.2	27.0	27.3	28.0	28,1	26.9	27.9	27.3
C-6	26.7	26.7	26.9	27.9	27,6	26.3	27.0	26.9
C-6a	128.5	129.8	128.5	130.4	132,4	128.7	127.2	126.4
C-7	134.5	134.3	134.7	135.1	141,9	135.1	136.3	132.5
C-7a	112.7	113.7	111.4	112.7	112,2	110.5	108.9	103.7
C-8	162.6	161.1	161.7	161.9	161,3	150.3	149.7	154.5
C-10	156.2	155.3	155.1	161.4	155,0	175.4	151.7	162.9
C-11a	157.6	159.6	157.3	156.0	152,0	159.6	161.5	159.4
C-12a	156.9	156.9	155.5	158.6	156,4	156.3	156.7	156.5
C-12b	133.3	133.1	132.9	133.5	129,2	132.4	133.2	133.0

[a] Trifluor acetic acid and dimethyl sulfoxide-d_6 (50%) as solvent. CH_3S for **3b** and **3d** 12.9 and 15.3 ppm, respectively; CH_3O for **3a** and **3c** 54.8 and 55.6 ppm, 9-CH_3 for **3c** and **3d** 27.8 and 30.4 ppm, respectively; 9-CH_3 and 11-CH_3 for **3g** 29.4 and 28.4 ppm, respectively.

The determination of linear structures was based on the signals assignment in the ^{1}H- and ^{13}C-nmr spectra of **3a-h**, which is supported by ^{1}H,^{1}H COSY technique and ^{1}H,^{13}C shift correlation, as well as by comparison with ^{1}H nmr and ^{13}C nmr data which has been previously established by us [14-16] and others [25-28] for similar systems. HMBC experiments indicate a two-bond correlation between H-7 and C-7a and three-bond correlations between the H-7 proton and C-8 and between the H-7 proton and C-6. These experiments rule out the formation of the angular structure **4** (Scheme 1).

EXPERIMENTAL

Melting points were determined on a Buchi Melting Point Apparatus and are uncorrected. The ^{1}H- and ^{13}C nmr spectra were recorded 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 5989-B mass spectrometer (EI, 70 eV). Samples were introduced *via* a DIP. The elemental analysis were obtained using a LECO CHNS-900.

General procedure for the Preparation of the 5,6-Dihydrobenzo[*h*] pyrimido[4,5-*b*]quinolines **3**.

A solution of 6-aminopyrimidines **1a-h** (2.0 mmoles) and an equimolar amount of the 2-dimethylaminomethylentetralone (2-[(dimethylamino)methyl]-3,4-dihydro-1-(2*H*)-napthalenone) hydrochloride **2** (2.0 mmoles) in ethanol (10 ml) with a catalytic amount of triethylamine (5 drops) was refluxed for 1-12 hours (tlc monitoring), and allowed to cool overnight. The resulting white precipitate was filtered, washed with ethanol and recrystallized from ethanol (the products **3e-h** were recrystallized from a mixture water/dimethylformamide) to afford 60-72 % of the desired products **3a-h**.

10-Methoxy-5,6-dihydro-9*H*-benzo[*h*]pyrimido[4,5-*b*]quinolin-8-one (**3a**).

This compound was obtained according to the general procedure as yellow crystals, mp 238 °C, yield 60%. The mass spectrum shows the following peaks: ms:(70 eV) m/z (%) = 280 (34), 279 (M^+, 100), 278 (22), 264 (11), 221 (10), 193 (10).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.65; H, 4.83; N, 11.93.

10-Methylthio-5,6-dihydro-9*H*-benzo[*h*]pyrimido[4,5-*b*]quinolin-8-one (**3b**).

This compound was obtained according to the general procedure as yellow crystals, mp 283 °C, yield 65%. The mass spectrum shows the following peaks: ms:(70 eV) m/z (%) = 296 (26), 295 (M^+, 100), 294 (12), 221 (21), 193 (10).

Anal. Calcd. for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 65.15; H, 4.13; N, 14.09.

10-Methoxy-9-methyl-5,6-dihydro-9*H*-benzo[*h*]pyrimido-[4,5-*b*]quinolin-8-one (**3c**).

This compound was obtained according to general procedure as white crystals, mp 215 °C, yield 70%. The mass spectrum shows the following peaks: ms:(70 eV) m/z (%) = 294 (21), 293

(M^+, 100), 292 (10), 279 (23), 278 (22), 264 (22), 193 (11), 44 (56), 43 (33).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.55; H, 5.26; N, 14.48.

10-Methythio-9-methyl-5,6-dihydro-9*H*-benzo[*h*]pyrimido-[4,5-*b*]quinolin-8-one (**3d**).

This compound was obtained according to the general procedure as pale yellow crystals, mp 233 °C, yield 62%. The mass spectrum shows the following peaks: ms:(70 eV) m/z (%) = 310 (24), 309 (M^+, 100), 308 (10), 295 (14), 265 (17), 264 (71), 263 (28), 235 (14), 234 (11), 222 (21), 193 (13), 192 (11).

Anal. Calcd. for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.58. Found: C, 66.05; H, 4.73; N, 13.40.

10-Amino-5,6-dihydro-9*H*-benzo[*h*]pyrimido[4,5-*b*]quinolin-8-one (**3e**).

This compound was obtained according to the general procedure as pale yellow crystals, mp > 360 °C, yield 63%. The mass spectrum shows the following peaks: ms:(70 eV) m/z (%) = 265 (19), 264 (M^+, 100), 263 (27), 84 (17), 66 (18).

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.25; H, 4.63; N, 21.34.

10-Thioxo-5,6,10,11-tetrahydro-9*H*-benzo[*h*]pyrimido-[4,5-*b*]quinolin-8-one (**3f**).

This compound was obtained according to the general procedure as pale yellow crystals, mp 349 °C, yield 65%. The mass spectrum shows the following peaks: ms:(70 eV) m/z (%) = 282 (21), 281 (M^+, 100), 280 (10), 223 (10).

Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94. Found: C, 64.11; H, 3.79; N, 14.80.

9,11-Dimethyl-5,6-dihydro-11*H*-benzo[*h*]pyrimido[4,5-*b*]quinolin-8,10-dione (**3g**).

This compound was obtained according to general procedure as pale yellow crystals, mp 255 °C, yield 72%. The mass spectrum shows the following peaks: ms:(70 eV) m/z (%) = 294 (23), 293 (M^+, 100), 292 (19), 265 (17), 264 (16), 181 (16).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.71; H, 5.10; N, 14.40.

8,10-Diamino-5,6-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline (**3h**).

This compound was obtained according to the general procedure as yellow crystals, mp > 360 °C, yield 68%. The mass spectrum shows the following peaks: ms:(70 eV) m/z (%) = 264 (22), 263 (M^+, 100), 262 (24), 220 (10).

Anal. Calcd. for $C_{15}H_{13}N_5$: C, 68.43; H, 4.98; N, 26.60. Found: C, 68.31; H, 4.83; N, 26.50.

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