NOVEL BARBITURIC ACID DERIVATIVES, URACIL-PYRIDINIUM SALTS AND POLYCONDENSED OXOPYRIMIDINES

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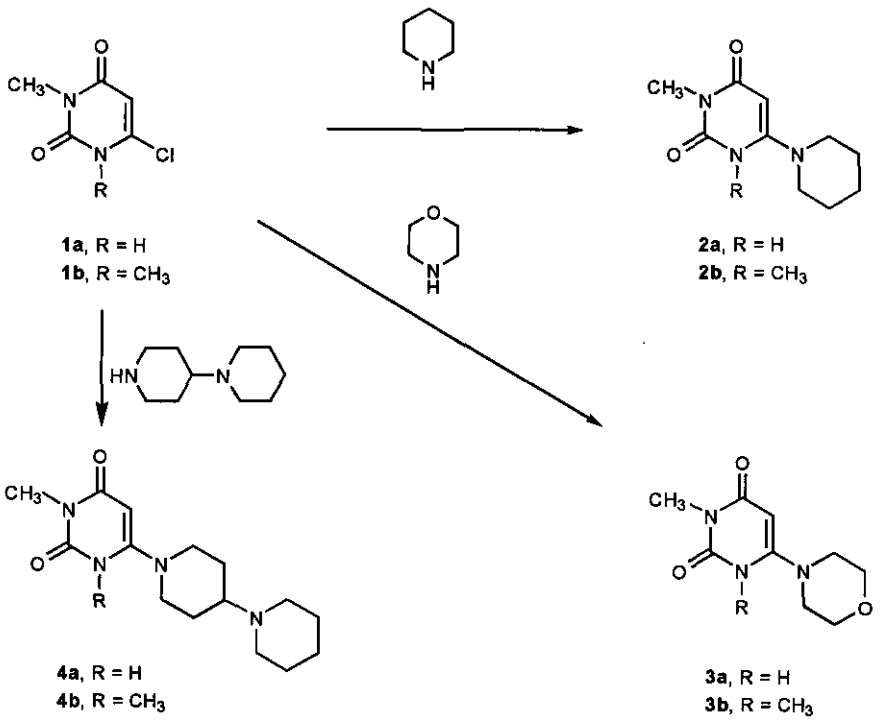
Abstract - Nucleophilic substitution of the 6-chloropyrimidines (**1**) with piperidine, morpholine, 4-(piperidin-1-yl)piperidine and 4-dimethylaminopyridine yielded the corresponding 6-aminosubstituted pyrimidines (**2**), (**3**), (**4**), and (**5**), respectively. The barbiturates (**9**) and (**10**) were formed either starting from the chloroaldehyde (**7**), or by applying Knoevenagel reaction to the barbituric acid (**13**) with 2-formylaminohetarenes. Cyclocondensation of the chloroaldehyde (**11**) with 2-aminopyridines resulted in the formation of the tricycle (**12**) which is also accessible by initial Knoevenagel reaction of the barbituric acid (**14**) and subsequent cyclization of the resulting barbiturates (**15**). Analogously, the new ring system (**17**) was formed upon treatment of **14** with 2-formylaminopyrimidine and subsequent cyclization.

As a result of their pharmacological, biological, physiological, and medical significance, substituted and condensed pyrimidines form a class of compounds of importance and still growing interest.[1] Since the pharmacological activity of barbituric acid derivatives was recognized,[2] intense studies have been devoted to preparation and properties,[3] physiological effects[4] and biochemical mechanisms of action,[4] and structure-activity relationships.[5] The chemistry and widespread use of uracils as active principles have recently been

reviewed.[6] Among the substituted or heterocondensed 1,3-dimethyluracils, modern competitive and reversible antagonists of α_1-adrenoreceptors[7] and antibiotics[8] are found.

This paper describes the preparation and properties of novel substituted uracils, new uracil-pyridinium salts, barbituric acid derivatives and of heterocondensed pyrimidines of potential biological interest. Furthermore, we report on the representative of a new ring system.

Halogen displacement reactions of 6-chlorouracils with a wide variety of heteroalicyclic amines are known to be fast and efficient.[9] As further examples we present the results of the reaction of the 6-chloro-pyrimidine-(1H,3H)-2,4-diones (**1**) with either morpholine, piperidine or 4-(piperidin-1-yl)piperidine, which formed the uracils (**2**), (**3**), and (**4**) within a few minutes. Compound (**2b**) has been mentioned but not characterized in the literature[10] (Scheme 1).



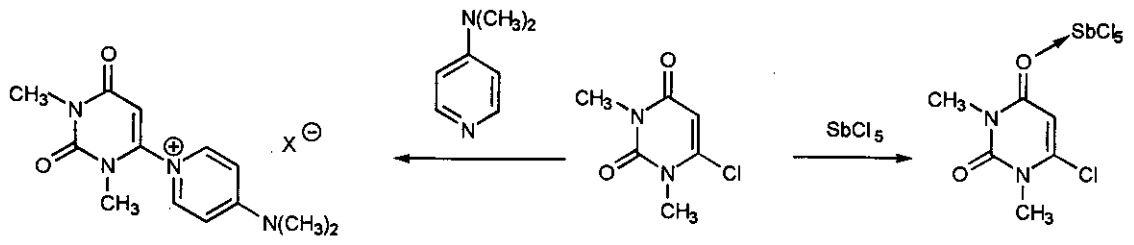
Scheme 1

Nucleophilic substitutions with heteroaromatic nucleophiles, forming hetarenium salts of uracil, have not been reported up to now. We want to present here that this reaction could be carried out successfully using

4-dimethylaminopyridine (DMAP) as nucleophile. Its basicity (pK_a = 9.70), intermediate between the values of piperidine (pK_a = 11.22) and morpholine (pK_a = 8.70), exceeds the basic strength of pyridine (pK_a= 5.23) by far. However, the substitution afforded very high reaction temperatures. Despite low polarity (E_T^N= 0.225),[11] best results were achieved using boiling 1,2-dichlorobenzene as solvent to give 4-dimethylamino-1-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)pyridinium chloride (**5a**) as amorphous grey solid (Scheme 2).

In the course of our studies we sought methodologies which would permit milder reaction conditions. As *ab initio* calculations[12] and experimental data[13] of complexes of nucleobases confirm coordination at O(4), addition of Lewis acids should facilitate S_NAE-substitution at C-6 by stabilization of the intermediary Meisenheimer adduct. This is a related effect to the well-known acceleration of S_N-reactions by suitable substitution at C-5 with strong electron withdrawing substituents.[14] Indeed, in the presence of equimolar amounts of antimony pentachloride in 1,2-dichloroethane, known to be a non-coordinative solvent (D_N^N= 0.00),[15] the 6-chloropyrimidine (**1b**) underwent ready reaction with 4-dimethylaminopyridine, forming the orange colored hexachloroantimonate (**5b**) in 85% yield. The mechanism was strongly supported by the isolation of a stable coordination compound (**6**), formed in quantitative yield upon treatment of **1b** with $SbCl_5$. Whereas the nmr spectra of **1b** remain nearly unchanged upon complexation, the FABMS of **6** showed both the fragmentation pattern of 6-chlorouracil (m/z 174) and $SbCl_5$ (m/z 299). The elemental analysis indicated a molecular formula $C_6H_7N_2O_2Cl_6Sb$ being consistent with a 1:1 complex.
Presence of sodium tetraphenylborate in ethyl acetate yielded the corresponding 4-dimethylamino-1-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)pyridinium tetraphenylborate (**5c**) as nearly colorless precipitate. In the latter case, sodium chloride was formed which could very easily be removed from the reaction mixture.

Furthermore, we studied possibilities to achieve intramolecular substitution reactions at C-6 of 6-chloropyrimidines. We chose 6-chloro-5-formyl-1,3-dimethylpyrimidine-(1H,3H)-2,4-dione (7) as starting



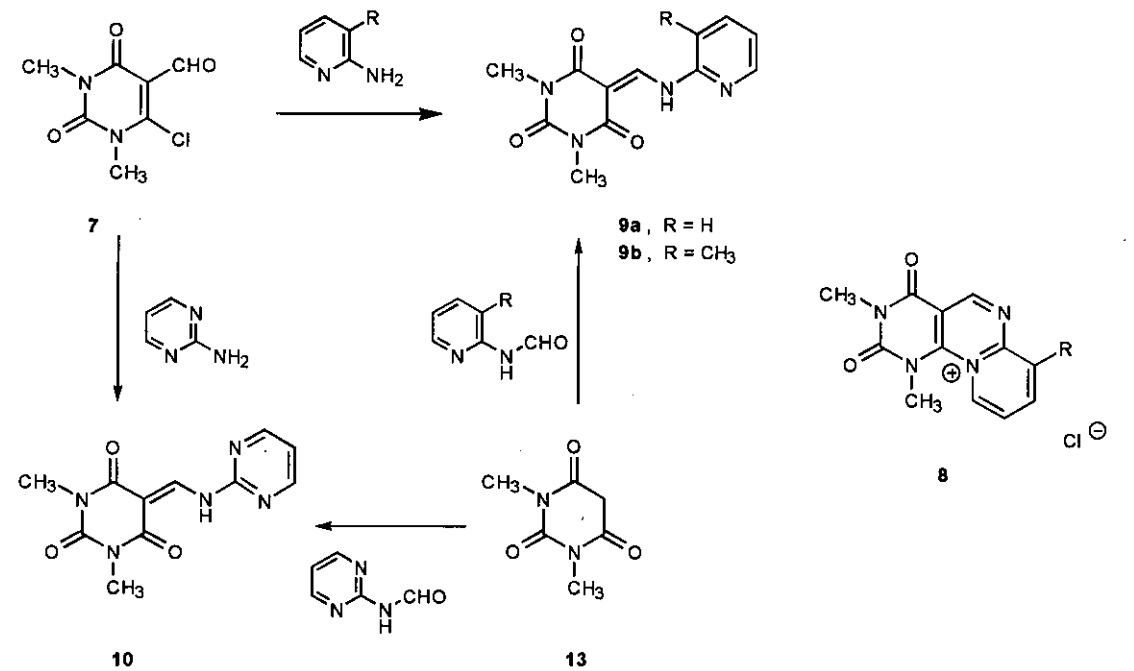
5a, X = Cl
5b, X = $SbCl_6$
5c, X = BPh_4

1b

6

Scheme 2

material to try two-step cyclization reactions with suitably substituted bifunctional nucleophiles. Surprisingly, with 2-aminopyridine no stable tricyclic salt (**8**) was formed. Instead, the new barbituric acid derivative (**9a**) was isolated, formally formed by ring cleavage of **8** by the addition of water at C-6 of the pyrimidine moiety. Analogously, 2-amino-3-methylpyridine gave **9b**. The reaction could easily be transmitted to 2-amino-pyrimidine which yielded the 1,3-dimethyl-5-(pyrimid-2-ylamino)methylenepyrimidine-(1H,3H)-2,4,6-trione (**10**). Taking the flood of studies into consideration which are directed toward seeking insight into the bioactivities of barbiturates, our new compounds will be of great interest as potential drugs.



7

9a, R = H
9b, R = CH_3

8

10

13

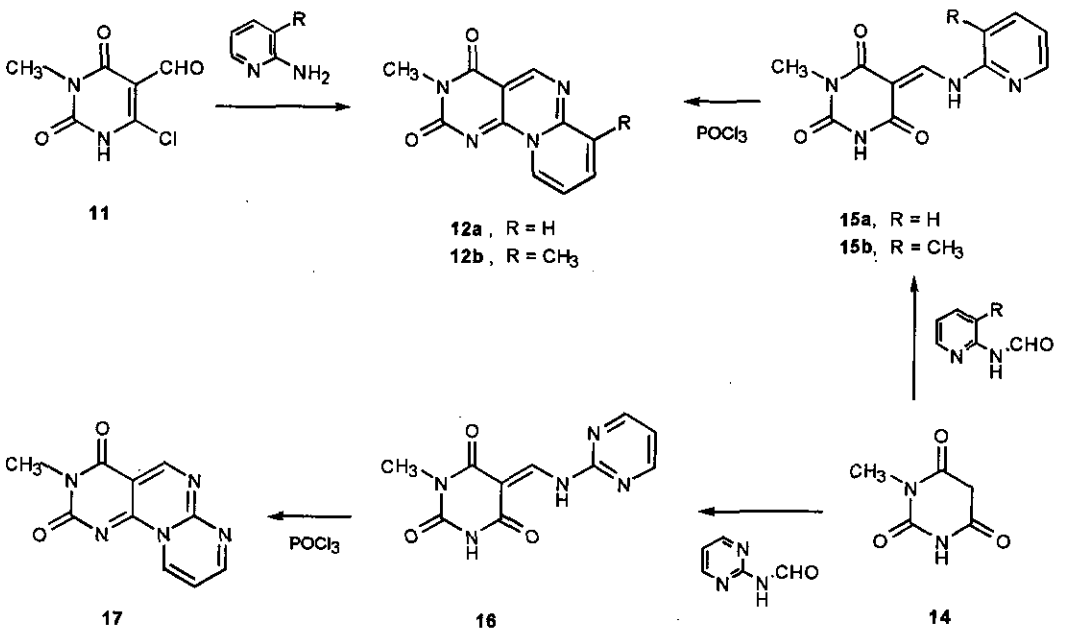
Scheme 3

However, the use of 6-chloro-5-formyl-3-methylpyrimidine(1H,3H)-2,4-dione (**11**) as starting material should allow stabilization of the intermediary tricyclic cation by deprotonation to give an uncharged conjugated molecule. As expected, the resulting 3H-pyrido[2,1-b]pyrimido[4,5-d]pyrimidine-2,4-diones (**12**) were stable against air and moisture (Scheme 4). Compound (**12a**) had already found interest as $FADH_2$ model compound,[16] but neither a detailed preparation procedure nor analytical data were given. However, this preparative method suffered from relatively low yield due to laborious isolation from the reaction mixture so that a better route was developed.

Thus, in an alternative access the barbituric acid derivatives (**9**) and (**10**) could also be formed starting from 1,3-dimethylpyrimidine-(1H,3H)-2,4,6-trione (**13**) upon Knoevenagel reaction with the 2-formylamino-pyridines and 2-formylaminopyrimidine, respectively, either readily obtained by treatment of the corresponding 2-aminohetarenes with absolute formic acid[17] (Scheme 3).

This reaction could also successfully be applied to 3-methylpyrimidine-(1H,3H)-2,4,6-trione (**14**) to give the new barbituric acid derivatives (**15**) and (**16**), respectively. Subsequent cyclization could be achieved with phosphorous oxychloride to give the 3H-pyrido[2,1-b]pyrimido[4,5-d]pyrimidine-2,4-diones (**12**) and the new ring system 8-methyl-8H-dipyrimido[2,1-b:4′,5′-d]pyrimidine-7,9-dione (**17**). This two-step preparation starting from barbituric acids provides a convenient and efficient approach to both tricyclic systems. These are of great biological interest because of their close relationship to known enzyme model compounds[16] (Scheme 4).

Due to the unsymmetrical substitution pattern of the pyrimidine moiety, either **15** and **16** were formed as a 1:1 mixture of E/Z isomers. As a result, pairs of signals were observed in the nmr spectra. The nitrogen bound proton of the -CH=NH-group of e.g. **15b** showed two separate dubletts (D_2O exchangeable) at 12.20 and 12.08 ppm and the coupling =CH moiety gave two overlapping dubletts at 9.19 ppm ($\Delta\,\delta = 0.012$ ppm) with an integration ratio of 1:1, respectively. The N(1)-H-group appeared as two separate singlets at 11.42 and 11.22 ppm. In the ^{13}C nmr spectra, the signals of C-2, C-4, C-5, C-6 and N-CH_3 appeared twice. The hydrogen bonding of the compounds (**15**) and (**16**) was shown by a broad ν_{NH} absorption band at 3379 cm^{-1}.



Scheme 4

EXPERIMENTAL

The ^{1}H and ^{13}C nmr spectra were obtained on a Bruker ARX 300 spectrometer, and chemical shifts are reported in ppm relative to tetramethylsilane. The following instruments were used: ir-spectrometer Nicolet 205 (400 - 4000 cm^{-1}); mass spectrometer AMD M-40 (AMD Intectra GmbH Harbstedt); melting points are uncorrected.

General procedure for the syntheses of the 6-substituted pyrimidine-2,4-diones 2 and 3. A stirred solution of the 6-chloropyrimidine [for **2a**, **3a**: 2.73 g (17 mmol) **1a**; for **2b**, **3b**: 3.00 g (17 mmol) **1b**] in 40 ml of methanol [**2a**, **3a**] or water [**2b**, **3b**] was treated with the nucleophile [**2a**,**b**: 20 ml of piperidine; **3a**,**b**: 20 ml of morpholine]. After a short refluxing the crystals were filtered off and recrystallized.

3-Methyl-6-piperidinopyrimidine-(1H,3H)-2,4-dione (2a) was obtained as colorless crystals, yield: 2.95 g (83%); mp 96 - 98°C (MeOH); ^{1}H nmr ($CDCl_3$): δ 7.81 (s, br, 1H; NH), 5.67 (s, 1H; CH), 3.27 (s, 3H;

Me), 3.15 (m, 4H; 2 CH_2), 1.85 (m, 4H; 2 CH_2), 1.68 (m, 2H; CH_2); ^{13}C nmr ($CDCl_3$): δ 165.29, 158.33, 155.37, 97.40, 47.67, 27.43, 22.83, 22.47; ir (KBr): 1653.7, 1557.2, 1545.5, 1467.8 cm^{-1}; ms: m/z (rel. int.) 209.2 (100%). Anal. Calcd for $C_{10}H_{14}N_3O_2$·HCl: C, 49.08; H, 6.18; N, 17.17. Found: C, 48.93; H, 6.62; N, 16.71.

1,3-Dimethyl-6-piperidinopyrimidine-(1H,3H)-2,4-dione (2b) was obtained as colorless crystals; yield: 2.30 g (59%); mp 77°C (H_2O); ^1H nmr ($CDCl_3$): δ 5.21 (s, 1H; CH), 3.37 (s, 3H; N-CH_3), 3.31 (s, 3H; N-CH_3), 2.87 (m, 4H; 2 CH_2), 1.68 (m, 6H; 3 CH_2); ^{13}C nmr ($CDCl_3$): δ 163.23, 160.18, 152.88, 87.40, 51.34, 32.43, 27.49, 25.04, 23.59; ir (KBr): 1655, 1435, 1196 cm^{-1}; ms: m/z 223. Anal. Calcd for $C_{11}H_{17}N_3O_2$: C, 59.25; H, 7.68; N, 18.80. Found: C, 59.04; H, 7.08; N, 17.69.

3-Methyl-6-morpholinopyrimidine-(1H,3H)-2,4-dione (3a) was obtained as colorless needles; yield: 2.69 g (75%); mp 268°C (MeOH); ^1H nmr ($CDCl_3$): δ 10.46 (s, 1H; br; NH), 4.97 (s, 1H; 5-H), 3.81 (m, 4H; 2 CH_2), 3.31 (m, 4H; 2 CH_2), 3.24 (s, 3H; N-CH_3); ^{13}C nmr ($CDCl_3$): δ 26.72, 46.48, 65.93, 79.46, 153.23, 153.66, 163.95; ir (KBr): 3219.3, 3175.6, 1712.8, 1640.0, 1468.6, 1119.5 cm^{-1}; ms: m/z 211. Anal. Calcd for $C_9H_{13}N_3O_3$: C 51.18; H, 6.20; N, 19.90. Found: C, 50.88; H, 6.30; N, 19.76.

1,3-Dimethyl-6-morpholinopyrimidine-(1H,3H)-2,4-dione (3b) was obtained as colorless crystals; yield: 2.01 g (53%); mp 159 - 160°C (H_2O); ^1H nmr ($CDCl_3$): δ 5.25 (s, 1H; CH), 3.84 (t, ^3J = 4.0 Hz, 4H; -CH_2-N-CH_2-), 3.41 (s, 3H; N-CH_3), 3.30 (s, 3H; N-CH_3), 2.97 (t, ^3J = 4.0 Hz, 4H; -CH_2-O-CH_2-); ^{13}C nmr ($CDCl_3$): δ 162.77, 158.92, 152.53, 87.67, 65.71, 50.27, 32.23, 27.40; ir (KBr): 1661, 1441, 1362 cm^{-1}; ms: m/z = 225. Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.19; H, 6.82; N, 18.23.

Synthesis of the 6-[4-(piperidin-1-yl)piperidin-1-yl]pyrimidine-(1H,3H)-2,4-diones (4). To a stirred solution of the 6-chlorouracil [0.30 g (1.7 mmol) of 6-chloro-1,3-dimethylpyrimidine-(1H,3H)-2,4-dione

(**1a**), 0.30 g (1.8 mmol) of 6-chloro-3-methylpyrimidine-(1H,3H)-2,4-dione (**1b**)] in 40 ml of abs. MeOH, 0.35 g (2 mmol) of 4-(piperidin-1-yl)piperidine was added. After the reaction mixture had been heated under reflux for 0.5 h, the MeOH was distilled off.

3-Methyl-6-[4-(piperidin-1-yl)piperidin-1-yl]pyrimidine-(1H,3H)-2,4-dione (**4a**) was isolated by treatment of the residue with ether as colorless crystals; yield: 0.45 g (85%); mp 160°C (MeOH); ^{1}H nmr (DMSO-d_6): δ 5.40 (s, 1H; CH), 3.35 - 1.42 (m, 22H); ^{13}C nmr (DMSO-d_6): δ 163.84, 155.54, 153.87, 94.67, 59.03, 49.28, 26.69, 26.05, 24.98, 24.22, 23.70; ir (KBr): 1660, 1608, 1462 cm^{-1}; ms: m/z (%) = 292 (24) [M$^+$]. Anal. Calcd for $C_{15}H_{24}N_4O_2$: N, 19.16. Found: N, 19.06.

1,3-Dimethyl-6-[4-(piperidin-1-yl)piperidin-1-yl]pyrimidine-(1H,3H)-2,4-dione (4b) was obtained by recrystallization of the yellowish residue from EtOH as colorless crystals; yield: 0.46 g (88%); mp 115°C (MeOH); ^{1}H nmr (DMSO-d_6): δ 5.18 (s, 1H; CH), 3.36 - 1.54 (m, 25H); ^{13}C nmr (DMSO-d_6): δ 161.98, 159.00, 152.18, 86.77, 61.63, 48.46, 32.29, 27.14, 25.06, 22.78, 22.44, 21.53; ir (KBr): 1654, 1440, 1011 cm^{-1}; ms: m/z (%) = 306 (61). Anal. Calcd for $C_{16}H_{26}N_4O_2$: N, 18.28. Found: N, 18.53.

4-Dimethylamino-1-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)pyridinium chloride (5a). A solution of 3.00 g (17.2 mmol) of **1b** and 2.11 g (17.2 mmol) of 4-dimethylaminopyridine in 45 ml of 1,2-dichlorobenzene was heated under reflux for 5 h. After cooling, the resulting precipitate was filtered off, washed with ethyl acetate and dried in vacuo. The salt (**5a**) was obtained as nearly colorless crystals; yield: 3.6 g (73%); mp 220-223°C (EtOAc); ^{1}H nmr (DMSO-d_6): δ 3.04 (s, 3H; N-CH_3), 3.17 (s, 3H; N-CH_3), 3.32 (s, 6H; NMe_2), 6.28 (s, 1H; 5-H), 7.29 (d, ^{3}J= 7.7 Hz, 2H; β-H), 8.42 (d, ^{3}J= 7.7 Hz, 2H; α-H); ^{13}C nmr (DMSO-d_6): δ 27.89, 31.74, 40.29, 99.73, 107.82, 140.60, 148.88, 150.80, 156.55, 161.14; ir (KBr): 1702.8, 1673.0, 1595.7 cm^{-1}; ms (FAB in NBA) (%): m/z 261.1 (100%). Anal. Calcd for $C_{13}H_{17}N_4O_2Cl \cdot 0.5\ H_2O$: C, 51.07; H, 5.62; N, 18.36. Found: C, 50.99; H, 6.36; N, 18.16.

4-Dimethylamino-1-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)pyridinium hexachloroantimonate (5b). A vigorously stirred solution of 1.74 g (10 mmol) of 6-chloro-1,3-dimethylpyrimidine-(1H,3H)-2,4-dione **(1b)** and of 1.22 g (10 mmol) 4-dimethylaminopyridine in 40 ml of 1,2-dichloroethane was treated dropwise under Ar with 2.99 g (10 mmol) of antimony pentachloride in 10 ml of the same solvent. After the solution was heated under reflux for 1 h, the precipitate was separated by filtration, washed with 15 ml of boiling 1,2-dichloroethane and dried in vacuo. Compound **(5b)** was obtained as orange crystals; yield: 5.06 g (85%); mp 226-231°C (1,2-dichloroethane); ^{1}H nmr (DMSO-d_6): δ 3.04 (s, 3H; N-CH_3), 3.25 (s, 3H; N-CH_3), 3.31 (s, 6H, NMe_2), 6.26 (s, 1H; 5-H), 7.25 (d, ^{3}J= 7.0 Hz, 2H; β-H), 8.36 (d, ^{3}J= 7.0 Hz, 2H; α-H); ^{13}C nmr (DMSO-d_6): δ 27.90, 31.76, 40.33, 99.72, 107.84, 140.52, 148.84, 150.80, 156.55, 161.13; ir (KBr): 1717, 1673, 1649 cm^{-1}. Anal. Calcd for $C_{13}H_{17}N_4O_2Cl_6Sb$: C, 26.21; H, 2.88; N, 9.40. Found: C, 24.90; H, 2.99; N, 9.40.

4-Dimethylamino-1-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)pyridinium tetraphenylborate (5c). An emulsion of 0.7 g (4.0 mmol) of 6-chlorouracil **(1b)**, 0.5 g (4.1 mmol) of 4-dimethylaminopyridine and 1.41 g (4.1 mmol) of sodium tetraphenylborate in 45 ml of ethyl acetate was refluxed for 3 h. After cooling, the precipitate was collected by filtration and treated with 40 ml of boiling ethanol. Drying in vacuo yielded 2.1 g (91%) of the salt **(5c)** as nearly colorless solid; mp 239-240°C (EtOAc); ^{1}H nmr (DMSO-d_6): δ 3.02 (s, 1H; N-CH_3), 3.25 (s, 1H; N-CH_3), 3.27 (s, 6H; NMe_2), 6.26 (s, 1H; 5-H), 6.79 (t, ^{3}J= 7.2 Hz, 4H; p-H of BPh_4^-), 6.92 (t, ^{3}J= 7.2 Hz, 8H; m-H of BPh_4^-), 7.19 (m, 8H; o-H of BPh_4^-), 7.23 (d, ^{3}J= 8.1 Hz, 2H; β-H), 8.35 (d, ^{3}J= 8.1 Hz, 2H; α-H); ^{13}C nmr (DMSO-d_6): δ 27.90, 31.72, 40.25, 99.73, 107.79, 121.40, 125.21 (Q, $^2J_{BC}$= 3.0 Hz), 135.42, 140.52, 148.86, 150.80, 156.52, 161.13, 163.24 (Q, $^1J_{BC}$= 49.8 Hz); ir (KBr): 1714.0, 1683.2, 1647.8 cm^{-1}; ms (FAB in NBA): m/z = 261.2 (82%; M^+). Anal. Calcd for $C_{37}H_{37}N_4O_2B \cdot 0.5\ H_2O$: C, 75.38; H, 6.33; N, 9.50. Found: C, 75.34; H, 6.72; N, 9.29.

General procedures for the syntheses of the 1,3-dimethyl-5-(pyridin-2-ylamino)methylenepyrimidine-(1H,3H)-2,4,6-triones (9) and the 3-methyl-5-(pyridin-2-ylamino)methylenepyrimidine-

(1H,3H)-2,4,6-triones (15). Method A: A solution of 6-chloro-5-formyl-1,3-dimethylpyrimidine-(1H,3H)-2,4-dione (7) [for **9a**: 0.66 g (3 mmol); for **9b**: 1.70 g (8 mmol)] and the corresponding 2-aminopyridine [for **9a**: 0.20 g (3 mmol); for **9b**: 0.80 g (8 mmol)] in 45 ml of DMF was heated under reflux for 5 h. After cooling to room temperature the precipitate was collected by filtration and recrystallized from DMF. 0.52 g (63%) of compound **9a** and 1.51 g (64%) of **9b** were obtained as colorless needles, respectively;

Method B: A solution of the barbituric acid [for **9a,b**: 1.50 g (10 mmol) **13**; for **15a**: 2.00 g (14 mmol) **14**; for **15b**: 1.40 g (10 mmol) **14**] and the corresponding 2-formylaminopyridine [for **9a**: 1,28 g (10 mmol); for **9b**: 1.49 g (11 mmol); for **15a**: 1.70 g (14 mmol); for **15b**: 1.36 g (10 mmol)] in 10 ml of EtOH was heated under reflux for 2 h. After cooling, the precipitate was collected by filtration and recrystallized from EtOH.

1,3-Dimethyl-5-(pyridin-2-ylamino)methylenepyrimidine-(1H,3H)-2,4,6-trione (9a) was obtained in 77% yield (2.15 g), which proved to be identical with all respects to the compound obtained by method A; mp 200°C (EtOH); ^{1}H nmr ($CDCl_3$): δ 12.10 (d, ^{3}J =12.0 Hz, 1H; NH-CH), 9.41 (d, ^{3}J= 12.0 Hz, 1H; CH-NH), 8.43 (d, ^{3}J = 4.8 Hz, 1H; α-H), 7.74 (dd, ^{3}J= 7.8 Hz, ^{3}J= 6.0 Hz, 1H; γ-H), 7.16 (dd, ^{3}J= 7.1 Hz, ^{3}J= 4.9 Hz, 1H; β-H), 7.02 (d, ^{3}J= 8.0 Hz, 1H; β'-H), 3.36 (d, 6H, 2 N-CH_3); ^{13}C nmr ($CDCl_3$): δ 165.15, 162.46, 151.84, 151.20, 149.55, 149.17, 138.84, 121.23, 112.62, 94.18, 28.05, 27.35; ir (KBr): 1660, 1644, 1431 cm^{-1}; ms: m/z (%) = 260 (68)[M$^+$]. Anal. Calcd for $C_{12}H_{12}N_4O_3$: C, 55.33; H, 4.61; N, 21.51. Found: C, 55.20; H, 4.18; N, 21.32.

1,3-Dimethyl-5-(3-methylpyridin-2-ylamino)methylenepyrimidine-(1H,3H)-2,4,6-trione (9b) was obtained in 76% yield (2.12 g) as colorless needles; mp 232°C (EtOH); ^{1}H nmr ($CDCl_3$): δ 12.38 (d, ^{3}J= 12.7 Hz, 1H; CH-NH), 9.53 (d, ^{3}J= 12.7 Hz, 1H; CH-NH), 8.27 (d, ^{3}J= 4.8 Hz, 1H; α-H), 7.55 (d, ^{3}J= 7.6 Hz, 1H; γ-H), 7.07 (dd, ^{3}J= 7.5 Hz, ^{3}J= 4.8 Hz, 1H; β-H), 3.37 (s, 6H; 2 N-CH_3), 2.41 (s, 3H; C-CH_3); ^{13}C nmr ($CDCl_3$): δ 165.46, 162.40, 151.83, 151.27, 147.96, 146.49, 139.62, 121.11, 94.39, 27.01, 27.37, 16.13; ir (KBr) 1660, 1581, 1422, 1334 cm^{-1}; ms: m/z = 274 [M$^+$]. Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.87; H, 5.10; N, 20.41. Found: C, 57.40; H, 5.07; N, 20.26.

3-Methyl-5-(pyridin-2-ylamino)methylenepyrimidine-(1H,3H)-2,4,6-trione (15a) was obtained as colorless crystals; yield: 2.02 g (58%); mp > 300°C (EtOH); ^{1}H nmr (DMSO-d_6; mixture of two E/Z isomers) : δ 11.83 (d, ^{3}J = 13.0 Hz, 1H; NH-CH), 11.27 (s, 0.5H; NH-C=O), 11.13 (s, 0.5H; NH-C=O), 9.17 (d, ^{3}J = 13.0 Hz, 1H; CH-NH), 8.44 (m, 1H; α-H), 7.88 (m, 1H; γ-H), 7.57 (m, 1H; β-H), 7.26 (m, 1H; β'-H), 3.16 (s, 1.5H; N-CH_3), 3:14 (s, 1.5H; N-CH_3); ^{13}C nmr (DMSO-d_6): δ 164.78/164.39, 163.14/162.40, 150.92/ 150.86, 149.93, 149.01, 148.43, 139.25, 121.13, 113.72, 93.97/93.92, 26.75/26.16; ir (KBr) 1702, 1623, 1428, 1321 cm^{-1}; ms: m/z (%) = 246 (14)[M$^+$]. Anal. Calcd for $C_{11}H_{10}N_4O_3$: C, 53.60; H, 4.06; N, 22.74. Found: C, 53.41; H, 4.64; N, 22.59.

3-Methyl-5-(3-methylpyridin-2-ylamino)methylenepyrimidine-(1H,3H)-2,4,6-trione (15b) was isolated in 65% yield (1.71 g) as pale reddish crystals; mp 280°C (EtOH); ^{1}H nmr (DMSO-d_6; mixture of E/Z isomers): δ 12.14 (d, ^{3}J= 13.0 Hz, 1H; NH-CH), 11.42 (s, 0.5H; NH-C=O), 11.22 (s, 0.5H; NH-C=O), 9.19 (d, ^{3}J= 13.0 Hz, 1H; NH-CH), 8.30 (m, 1H; CH), 7.78 (m, 1H; CH), 7.21 (m, 1H; CH), 3.17 (s, 1.5 H; N-CH_3), 3.14 (s, 1.5H; N-CH_3), 2.35 (s, 3H, C-CH_3); ^{13}C nmr (DMSO-d_6): δ 165.90/165.44, 162.94/162.21, 150.87, 149.28/148.63, 147.71, 146.19, 140.16, 121.38, 94.39/94.25, 26.78/26.30, 15.50; ir (KBr): 1686, 1640, 1412 cm^{-1}; ms: m/z = 260 [M$^+$]. Anal. Calcd for $C_{12}H_{12}N_4O_3$: C, 55.33; H, 4.61; N, 21.53. Found: C, 56.63; H, 4.96; N, 21.83.

General syntheses for 1,3-Dimethyl-5-(pyrimidin-2-ylamino)methylenepyrimidine-(1H,3H)-2,4,6-trione (10) and 3-Methyl-5-(pyrimidin-2-ylamino)methylenepyrimidine-(1H,3H)-2,4,6-trione (16).

Method A: To a stirred solution of 1.00 g (5 mmol) of 6-chloro-5-formyl-1,3-dimethylpyrimidine-(1H,3H)-2,4-dione and 0.48 g (5 mmol) of 2-aminopyrimidine in 10 ml of EtOH was refluxed for 1 h. After cooling, the precipitate were filtered off and recrystallized from DMF to give 0.95 g (72%) of **10** as colorless crystals.

Method B: A solution of the barbituric acid [for **10**: 1.50 g (10.5 mmol) **13**; for **16**: 1.40 g (10 mmol) **14**] and 2-formylaminopyrimidine [for **10**: 1.35 g (11 mmol); for **16**: 1.50 g (12 mmol)] in 30 ml of EtOH was heated under reflux for 2.5 h. After cooling, the precipitate was filtered off and recrystallized from EtOH. Compound (**10**) was obtained as colorless crystals which proved to be identical with respect to all spectroscopical and analytical data to the compound obtained by method A; yield: 1.66 g (60%); mp 220°C (EtOH); ^{1}H nmr ($CDCl_3$): δ 11.94 (d, ^{3}J= 12.8 Hz, 1H; NH), 9.39 (d, ^{3}J= 12.8 Hz, 1H; C=CH-N), 8.64 (d, ^{3}J= 4.8 Hz, 2H; 2 CH), 7.14 (t, ^{3}J = 4.8 Hz, 1H; CH), 3.37 (s, 6H; 2 CH_3); ^{13}C nmr ($CDCl_3$): δ 164.42, 162.21, 158.68, 156.40, 151.69, 151.30, 117.92, 95.62, 28.07, 27.42; ir (KBr): 1665, 1602, 1413, 1285 cm^{-1}; ms: m/z = 261. Anal. Calcd for $C_{11}H_{11}N_5O_3$: C, 50.13; H, 4.36; N, 26.73. Found: C, 50.57; H, 4.24; N, 26.81.

Compound (**16**) was obtained as orange crystals; yield: 1.75 g (70%); mp 287°C (EtOH); mixture of E/Z isomers; ^{1}H nmr ($CDCl_3$): δ 11.58 (m, 2H; 2 NH), 9.05 (s, 1H; C=C<u>H</u>-NH), 8.78 (d, ^{3}J= 4.9 Hz, 2H; α,γ-H), 7.37 (dd, ^{3}J= 4.9 Hz, ^{3}J= 4.8 Hz, 1H; β-H), 3.14 (s, 3H; N-CH_3); ^{13}C nmr ($CDCl_3$): δ 159.34, 156.07, 151.02, 149.44, 118.40, 95.65, 26.63; ir (KBr): 1696, 1605, 1404 cm^{-1}; ms: m/z (%) = 247 (87)[M^+]. Anal. Calcd for $C_{10}H_9N_5O_3$: C, 48.54, H, 3.64; N, 28.33. Found: C, 48.58; H, 3.90; N, 28.58.

3,7-Dimethyl-3<u>H</u>-pyrido[2,1-<u>b</u>]pyrimido[4,5-<u>d</u>]pyrimidine-2,4-dione (12b). Synthesis starting from the chloroaldehyde (**11**): A mixture of compound (**11**) [1.10 g (5 mmol)] and 0.50 g (5 mmol) of 2-amino-3-methylpyridine in 35 ml of DMF was heated under reflux for 3 h. After cooling overnight, the precipitate was separated by filtration, recrystallized from DMF and dried over calcium chloride. Compound (**12b**) was obtained as yellowish crystals; yield: 0.65 g (53%); mp > 300°C (DMF); ^{1}H nmr ($CDCl_3$): δ 9.81 (d, ^{3}J = 7.0 Hz, 1H; α-H), 9.27 (s, 1H; C=CH-N), 8.06 (d, ^{3}J= 7.0 Hz, 1H; γ-H), 7.53 (t, ^{3}J ≈ ^{3}J= 7.0 Hz, 1H; β-H), 3.50 (s, 3H; N-CH_3), 2.78 (s, 3H; C-CH_3); ^{13}C nmr ($CDCl_3$): δ 162.23, 157.25, 154.61, 154.29, 150.53, 139.75, 136.91, 127.89, 119.21, 103.68, 28.01, 18.41; ir (KBr): 1615, 1533,

1484 cm^{-1}; ms: m/z = 242 [M^+]. Anal. Calcd for $C_{12}H_{10}N_4O_2 \cdot 0.5\ H_2O$: C, 57.32; H, 4.77; N, 22.29. Found: C, 57.54; H, 4.54; N, 22.30.

General syntheses of the tricycles (12a,b) and (17) by cyclization. The barbituric acid derivatives (**15a,b**) and (**16**), respectively [0.74 g (3 mmol) **15a**; 0.61 g (2.3 mmol) **15b**; 0.75 g (3 mmol) **16**] were treated with 6 ml (64.4 mmol) of phosphorous oxychloride. The resulting emulsion was heated until a clear solution was obtained, and heated under reflux for further 4 h. After the excessive phosphorous oxychloride had been distilled off in vacuo, the remaining yellowish oil was taken up in warm DMF. After cooling, the resulting precipitate was separated by filtration and was recrystallized [**12a,b**: from DMF; **17**: from chloroform].

3-Methyl-3H-pyrido[2,1-b]pyrimido[4,5-d]pyrimidine-2,4-dione (12a) was obtained as yellowish crystals; yield: 0.40g (75%); mp 285°C [lit.,[16]: 285°C].

3,7-Dimethyl-3H-pyrido[2,1-b]pyrimido[4,5-d]pyrimidine-2,4-dione (12b) was obtained as yellowish crystals; yield 0.41 g (73%); mp > 300°C (DMF); for spectroscopical data see aforementioned synthesis.

***8-Methyl-8H-dipyrimido[2,1-b:4',5'-d]pyrimidine*-7,9-dione (17)** was obtained as greenish crystals; yield: 0.51 (73%); mp > 300°C ($CHCl_3$); ^{1}H nmr ($CDCl_3$): δ 10.09 (d, ^{3}J= 7.0 Hz, 1H; α-H), 9.43 (s, 1H, C=CH-N), 9.40 (d, ^{3}J= 6.3 Hz, 1H; γ-H), 7.62 (dd, ^{3}J= 7.0 Hz, ^{3}J= 6.3 Hz, 1H; β-H), 3.50 (s, 3H; N-CH_3); ^{13}C nmr measurement was not possible due to insufficient solubility; ir (KBr): 1682, 1507 cm^{-1}; ms: m/z (%) = 229 (100)[M^+]. Anal. Calcd for $C_{10}H_7N_5O_2$: N, 30.58; Found: N, 31.17.

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