82. Pteridines

Part XLI[1])

Synthesis and Properties of 6,7,8-Trimethyl-4-thiolumazine

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The first representative of the 8-substituted 4-thiolumazine series has been synthesized. In a sequence of reactions, 4,6-dichloropyrimidin-2-(1*H*)-one (**1**) is first converted into 4-chloro-6-(methylamino)pyrimidin-2(1*H*)-one (**6**), then the Cl-atom displaced by the thioxo group (→ **7**) followed by a coupling reaction with 4-chlorophenyldiazonium chloride to introduce the necessary N-function into the 5-position (→ **9**; *Scheme 1*). Reduction of the *p*-chlorophenylazo group leads to the 6-(methlyamino)-4-thiouracil-5-amine (**10**) which on condensation with diacetyl gives 6,7,8-trimethyl-4-thiolumazine (**8**). The physical properties of **8** are compared with the 2-thio analog and 6,7,8-trimethyllumazine indicating that **8** possesses the highest acidity and the longest UV absorption.

1. Introduction. – The interesting physical and chemical properties of the 8-substituted 2-thiolumazines [14] prompted us to investigate in the same manner the 8-substituted 4-thiolumazine analogs. The interaction of the 4-thioxo function with the cross-conjugated π-electron system will be of most importance for the molecular features. Molecules of this type have so far not been described in literature.

2. Syntheses. – It is a known fact that uracils [2] [3] and analogous condensed systems like lumazines [4] [5] and xanthines [6–10] can be selectively thiated by P_4S_{10} at the 4- and 6-position, respectively. Analogous reactions with 8-substituted lumazines [11], however, failed under a broad variety of reaction conditions giving a complex mixture of many reaction products, maybe due to the higher reactivity of the quinonoid-type π-electron system. Surprisingly, the direct thiations of 6-(methylamino)- and 6-[(2-hydroxyethyl)-amino]uracil revealed also difficulties, and no pure products could be isolated from the reaction mixtures.

Another approach to synthesize this type of compounds has, therefore, been developed starting from 4,6-dichloropyrimidin-2(1*H*)-one (**1**) which was first obtained by *Robins et al.* [12] from 2-thiobarbituric acid in four steps and recently synthesized by *Kazimierczuk et al.* [13] by selective base hydroylsis of 2,4,6-trichloropyrimidine (**2**). On repeating the latter experiment, we realized that a 75% yield [13] of **1** cannot be obtained since the material always contained substantial amounts of the isomeric 2,6-dichloropyrimidin-4(3*H*)-one (**3**). We optimized the reaction and found that treatment of **2** in dioxane with

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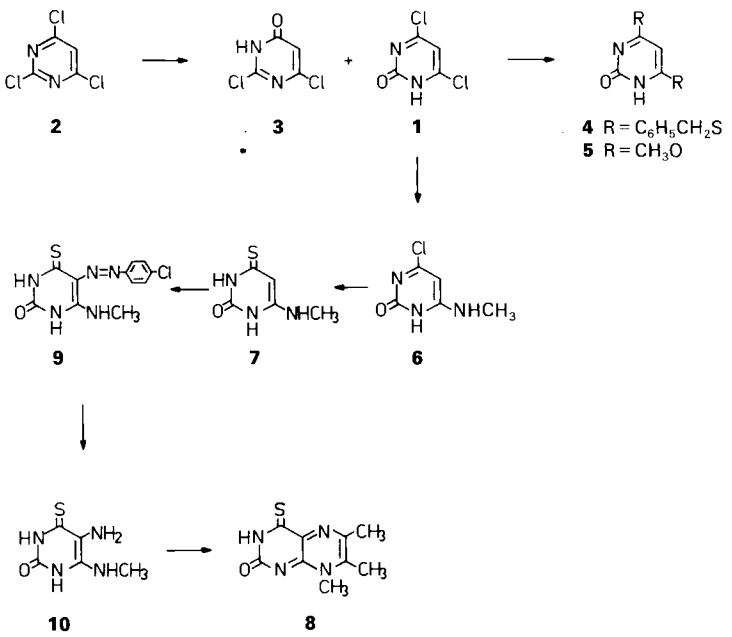
Scheme 1



aqueous NaOH solution at 25–40° yielded **1**/**3** in a *ca.* 1:1 ratio. Isomer **1** separated from the solution as a relatively insoluble sodium salt in almost pure form and 45% yield. The isomer **3** was isolated as the neutral species in 47% yield from the filtrate on careful acidification to pH 2–3. Acid hydrolyses lead one step further forming 6-chlorouracil from **1**, **2**, and **3** as the main reaction product.

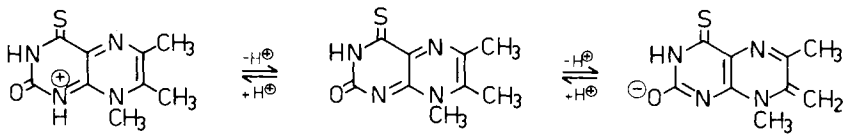
Attempts to displace one Cl-atom in **1** by S-nucleophiles such as HS^- or thiolates were not successful. Only the disubstituted products were formed, even on working with stoichiometric amounts. An excess of phenylmethanethiol in DMF yielded 29% of 4,6-bis(benzylthio)pyrimidin-2-(1*H*)-one (**4**). With MeOH (**1**), reacted similarly, even at room temperature, giving 4,6-dimethoxypyrimidin-2(1*H*)-one (**5**). Reactions with primary amines at room temperature, fortunately, led to a selective monosubstitution, even in presence of an excess of the amine. Thus 4-chloro-6-(methylamino)pyrimidin-2(1*H*)-one (**6**) was obtained in 72% yield from **1** and $MeNH_2$.

The displacement of the remaining Cl-atom in **6** could finally be achieved with NaHS in ethyleneglycol at 150°, giving 6-(methylamino)-4-thiouracil (**7**) in 59% yield. Similar attempts with H_2S or thiourea in EtOH, however, did not work so well. The next step in the synthesis of 6,7,8-trimethyl-4-thiolumazine (**8**) was the coupling reaction of **7** with 4-chlorophenyldiazonium chloride at neutral pH to form, in quantitative yield, the 5-(4-chlorophenylazo)-6-(methylamino)-4-thiouracil (**9**). Reductive cleavage of the azo group was most efficient with $(NH_4)_2S$ and gave 65% yield of 5-amino-6-(methylamino)-4-thiouracil (**10**). Finally, condensation of **10** with diacetyl in DMF/aqueous HCl solution led, in a clean reaction and 67% yield, to **8** which separated from the reaction solution in analytically pure form.

3. Physical Data and Structures. – The characterization and structural elucidation of the newly synthesized compounds were performed by elemental analyses, pK_a determinations, and ^{1}H-NMR and UV spectra *(Tables 1* and *2)*. It is interesting to note that the 4,6-dichloropyrimidin-2(1*H*)-one (**1**) is a much stronger acid than its 2,6-dichloro isomer **3**, as seen from the pK_a and as also reflected in the chemical shifts of the NH signals *(Table 1)*. The UV spectra of the 4-thiouracil derivatives **7** and **10** show, on anion formation, a hypsochromic shift of the long-wavelength band which is attributed to N(3) rather than N(1) deprotonation. Furthermore, protonation of **10** is again associated with a hypsochromic shift and must take place, therefore, at the 5-NH_2 group which looses its interaction with the π-electron system of the ring on monocation formation. Thus, the neutral species of **7** and the monocation form of **10** reveal almost identical UV spectra.

A comparison of the UV spectra of 6,7,8-trimethyllumazine with its 2-thio derivative [14] and 4-thio derivative **8** *(Table 2)* indicates as a characteristic feature a gradual bathochromic shift of the long-wavelength absorption band of the corresponding molecular species in this order. Considering the neutral form **8** as the standard, then both cation and anion formation is associated with a hypsochromic shift of the long-wavelength absorption band. N(1) Protonation causes the blue shift in the cation **11**, whereas the site of deprotonation to form the anion **12** is located in the 7-CH_3 group showing C–H acidity in accordance to analogous results [11] [14] in the lumazine and pterin series *(Scheme 2)*.

Scheme 2



11 **8** **12**

Furthermore, the basic pK_a values can be taken as an additional confirmation of the N(1) protonation of **8** since 6,7,8-trimethyl-2-thiolumazine [14] is expectedly the least basic derivative of this series due to the electronic influence of the thioxo group onto the adjacent ring N-atom as the most likely basic center in this type of molecules.

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Table 1. *Physical Data of Pyrimidine Derivatives*

	pK_a in H_2O	UV spectrum[a]) λ_{max} [nm]			lg ε			pH	Molecular form[b])	^{1}H-NMR spectrum ((D$_6$)DMSO; δ [ppm]) H–C(5)	NH	Substituents
3	5.30	208	260		3.89	4.02		3.0	○	6.8	10.5	
		218	282		3.92	4.14		8.0	–			
1	4.05	[227]	[273]	303	[3.82]	[3.44]	3.77	2.0	○	7.4	13.5	
		227		294	4.01		3.82	7.0	–			
4		275	314	321	3.96	4.30	4.31	MeOH	○	6.4	11.9	4.4 (*s*, 2 CH_2); 7.3 (*m*, 2 C_6H_5)
5		264			3.87			MeOH	○	5.45	10.7	3.8 (*s*, 2 CH_3O)
6	3.15	214	280		3.89	4.11		1.0	+	5.7	9.7	2.8 (*s*, CH_3N);
	9.05	[222]	[286]	297	[3.92]	[3.90]	3.95	5.0	○			7.8 (br. *s* H–N(1))
		205	[228]	283	4.28	[3.94]	3.99	11.0	–			
7	6.92		248	322		3.91	4.59	2.0	○	5.5	10.9	2.7 (*d*, CH_3NH);
		227		306	4.24		4.42	10.0	–		(br. *s*, 2H)	6.8 (br. *s*, CH_3N*H*)
10	2.76		245	321		3.83	4.56	0.0	+		11.7	2.9 (*d*, CH_3N)
	6.36		247	344		3.95	4.31	4.0	○		(*s*, 1H)	
		226		323	4.25		4.21	11.0	–		8.8 (*s*, 1H)	

[a]) Values in brackets refer to shoulders. [b]) ○ = neutral form, – = monoanion, + = cation.

Table 2. *Physical Data of 8-Substituted Lumazines*

	pK_a in H_2O	UV spectrum[a]) λ_{max} [nm]				lg ε				pH	Molecular form[b])	^{1}H-NMR spectrum ((D$_6$)DMSO; δ [ppm])
6,7,8-Trimethyl-lumazine	0.85	244			358	4.04			4.18	–2.7	+	10.91 (*s*, NH);
	9.90	256	275		402	4.17	4.05		4.09	7.0	○	3.75 (*s*, CH_3N);
		244	[267]	313	364	4.30	[3.84]	4.35	3.78	13.0	–	2.40 (*s*, $CH_3C(7)$); 2.38 (*s*, $CH_3C(6)$)
6,7,8-Trimethyl-2-thiolumazine	–0.57	227	[260]	291	390	3.71	[3.90]	4.17	4.16	–2.3	+	12.4 (*s*, NH);
	8.23	238	257	318	433	3.81	3.85	4.36	4.11	4.0	○	4.00 (*s*, CH_3N);
		[246]	287	318	[350]	[4.07]	4.43	4.27	[3.74]			2.68 (*s*, $CH_3C(7)$);
		[370]	383	[398]	[423]	[3.84]	3.87	[3.80]	[3.49]	11.0	–	2.57 (*s*, $CH_3C(6)$)
6,7,8-Trimethyl-4-thiolumazine (**8**)	0.08	250	288	322	405	3.82	3.98	3.77	4.09	–2.3	+	12.50 (*s*, NH);
	6.97	252	299	342	458	4.02	4.13	3.53	4.14	4.0	○	3.91 (*s*, CH_3N);
		221	246	[341]	362	4.21	4.18	[4.23]	4.43	10.0	–	2.63 (*s*, $CH_3C(7)$); 2.55 (*s*, $CH_3C(6)$)

[a]) Values in brackets refer to shoulders. [b]) ○ = neutral form, – = anion, + = cation.

Experimental Part

General. TLC: precoated silica-gel thin-layer sheets *F1500 LS254* and cellulose thin-layer sheets *F1440 LS254* from *Schleicher & Schüll.* Prep. TLC: silica gel *60 PF_{254} (Merck).* Prep. column chromatography: silica gel *Merck 60* (0.063–0.2 mm). M.p.: *Büchi* apparatus, model Dr. *Tottoli;* no corrections. UV/VIS: *Cary* recording spectrometer, model *118, Applied Phys. Corp.* and *Perkin-Elmer,* model *lambda 5;* λ_{max} in nm (lg ε). ^{1}H-NMR: *Bruker WP-80 CW* and *WM-250* in δ (ppm) relative to TMS. The pK_a determinations were performed by the spectrophotometric method [15].

1. *4,6-Dichloropyrimidin-2(1H)-one* (**1**). To a soln. of 36.7 g (0.2 mol) of 2,4,6-trichloropyrimidine (**2**) [16] in 600 ml of dioxane, 20 g (0.5 mol) of NaOH in 160 ml of H_2O are added with vigorous stirring. A precipitate separates out gradually, and after 4 h, the mixture is concentrated *in vacuo* to a small volume forming a thick paste. H_2O is added till a clear soln. is obtained on boiling (300 ml). On cooling and standing in the ice-box, colourless crystals are separated: 19.23 g (43%). Evaporation of the filtrate to 100 ml gives a second crop: 1.0 g (2%). Recrystallization from 0.2N NaOH yields an anal. pure sample of the sodium salt of **1** · 1.5 H_2O: colourless needles. M.p.180° (beginning dec.). Anal. calc. for $C_4HCl_2N_2NaO \cdot 1.5\ H_2O$ (214.0): C 22.45, H 1.88, N 13.09; found: C 22.54, H 1.80, N 12.89.

Free **1** is obtained by dissolving 6.42 g (30 mmol) of the sodium salt of **1** · 1.5 H_2O in 70 ml of H_2O, cooling to 5°, and careful acidification to pH 2 by 5N HCl. The precipitate is collected, washed with little cold H_2O, and dried in a vacuum desiccator over KOH: 4.38 g (87%), colourless crystal powder. M.p. 157° ([12] [13]: much higher m.p., indicating a high content of the sodium salt). Anal. calc. for $C_4H_2Cl_2N_2O$ (165.0): C 29.12, H 1.22, N 16.98; found: C 29.13, H 1.23, N 16.94.

2. *2,6-Dichloropyrimidin-4(3H)-one* (**3**). The reaction filtrate of the preceding procedure is cooled with ice and then gently acidified by 5N HCl to pH 2. The obtained precipitate is washed with little cold H_2O and dried in a vacuum desiccator over KOH: 16.6 g (47%). Recrystallization from H_2O gives colourless crystals. M.p. 170–171°. Anal. calc. for $C_4H_2Cl_2N_2O$ (165.0): C 29.12, H 1.22, N 16.98, Cl 42.98; found: C 29.26, H 1.30, N 17.01, Cl 42.82.

3. *4,6-Bis(benzylthio)pyrimidin-2(1H)-one* (**4**). A soln. of 0.3 g (1.4 mmol) of sodium salt of **1** · 1.5 H_2O and 0.9 g of phenylmethanethiol in 5 ml of DMF is stirred for 1 day at r.t. After addition of 0.7 ml of Et_3N, the mixture is heated for 15 min to 80°. After cooling, 15 ml of H_2O are added, the precipitate is collected and dried: 0.14 g (29%). Recrystallization from i-PrOH yields colourless needles. M.p. 187–188°. Anal. calc. for $C_{18}H_{16}N_2OS_2$ (340.5): C 63.50, H 4.74, N 8.23; found: C 63.34, H 4.66, N 8.21.

4. *4,6-Dimethoxypyrimidin-2(1H)-one* (**5**). For 4 h, 0.2 g (1.2 mmol) of **1** in MeOH (8 ml) are stirred at r.t. After evaporation, the residue is recrystallized from MeOH (3 ml) and H_2O (10 ml): colourless needles, 0.077 g (45%). M.p. 256°. Anal. calc. for $C_6H_8N_2O_3$ (156.1): C 46.15, H 5.16, N 17.94; found: C 46.22, H 5.22, N 17.68.

5. *4-Chloro-6-(methylamino)pyrimidin-2(1H)-one* (**6**). *a)* To a soln. of 0.35 g (1.6 mmol) of sodium salt of **1** · 1.5 H_2O in H_2O (15 ml), 50% aq. $MeNH_2$ soln. (6 ml) is added and then stirred at r.t. for 4 days. After 1 day, a clear soln. is obtained, from which a precipitate separates gradually. The mixture is evaporated and the residue recrystallized from H_2O (25 ml) by addition of AcOH (1 ml): colourless crystals, 0.9 g (70%). M.p. 216–217° (dec.). Anal. calc. for $C_5H_6ClN_3O \cdot 0.25\ H_2O$ (164.1): C 36.60, H 3.99, N 25.61; found: C 36.53, H 4.04, N 25.64.

b) Sodium salt: at r.t., 5.2 g (24.3 mmol) of sodium salt of **1** · 1.5 H_2O in H_2O (100 ml) and 50% aq. $MeNH_2$ soln. (20 ml) are stirred for 4 days. The mixture is then heated to boiling, 5N NaOH (7 ml) added, and the mixture chilled over night. The precipitate is collected and dried: colourless crystal powder, 3.61 g (74%). M.p. 255° (dec.). Anal. calc. for $C_5H_5ClN_3NaO \cdot H_2O$ (199.6): C 30.09, H 3.54, N 21.06; found: C 29.89, H 3.39, N 21.02.

6. *6-(Methylamino)-4-thioxopyrimidin-2(1H)-one* (**7**). *a)* To a hot soln. of 1 g of 70% NaHS in 4 ml of ethyleneglycol are added 0.55 g (3 mmol) of **6**. The mixture is heated to 150° for 30 min, diluted with H_2O (30 ml), treated with charcoal, the hot soln. filtered, and the filtrate poured into a hot soln. of H_2O (30 ml) and AcOH (5 ml). The sulfur is filtered off, the filtrate concentrated to 30 ml and then chilled over night. The precipitate is collected and dried: 0.28 g (59%). Recrystallization from H_2O with charcoal and a small amount of $Na_2S_2O_4$ gives colourless crystals: 0.155 g (33%). M.p. 262–263° (dec.). Anal. calc. for $C_5H_7N_3OS$ (157.2): C 38.21, H 4.49, N 26.73, S 20.46; found: C 38.37, H 4.54, N 26.87, S 21.05.

b) In a 40% aq. soln. of $MeNH_2$, 6.87 g (32 mmol) of sodium salt of **1** · 1.5 H_2O are stirred at r.t. for 2 days. Then, another 20 ml of $MeNH_2$ are added, and the mixture is stirred for 5 h at 50°. The clear soln. is evaporated, ethyleneglycol (25 ml) and 12 g of 70% NaHS are added, the mixture is heated for 30 min to 150°, the diluted with H_2O (50 ml), acidified to pH 3, and chilled over night. The precipitate which contains much sulfur is recrystallized from H_2O (140 ml) with charcoal: colourless crystals, 3.08 g (61%). M.p. 262° (dec.).

7. *4,8-Dihydro-6,7,8-trimethyl-4-thioxopteridin-2(3H)-one* (**8**). For 1 h, **10**·HCl·H_2O (0.23 g, 1 mmol) and diacetyl (0.4 ml) in 0.1N HCl (20 ml) and DMF (5 ml) are heated to 80°. The precipitate is collected after cooling and partial evaporation, washed with H_2O and acetone, and dried: red crystals, 0.15 g (67%). M.p. > 300°. Anal. calc. for $C_9H_{16}N_4OS$ (222.3): C 48.63, H 4.53, N 25.21, S 14.43; found: C 48.61, H 4.65, N 25.07, S 14.32.

8. *5-(4-Chlorophenylazo)-6-(methylamino)-4-thioxopyrimidin-2(1H)-one* (**9**). A soln. of 0.8 g of NaOH, 5.3 g of $NaHCO_3$, and 3.15 g (20 mmol) of **7** in H_2O (250 ml) is cooled to 5°, and then 1M 4-chlorobenzenediazonium chloride (25 ml) is slowly added with vigorous stirring. A red precipitate is formed and the foaming broken by addition of little EtOH. After stirring for 15 min, the mixture is acidified to pH 2, heated to 60°, and then filtered by suction. The precipitate is washed with H_2O and dried at 100°: red crystal powder, 5.9 g (98%). M.p. 236–237° (dec.). The material is pure enough for further reactions. UV (pH 13; 25% MeOH): 297 (4.37), 407 (4.28).

9. *5-Amino-6-(methylamino)-4-thioxopyrimidin-2(1H)-one* (**10**). In 20% aq. $(NH_4)_2S$ soln. (2.1 g, 7.1 mmol) is heated in an autoclave to 120° for 2 h. The precipitate is collected after cooling and washed with $CHCl_3$ and the filtrate extracted twice with $CHCl_3$. The aq. filtrate is evaporated and the residue recrystallized together with the first precipitate from 1N HCl (50 ml) with charcoal: colourless crystals, 0.75 g (46%). M.p. > 250° (dec.). Anal. calc. for $C_5H_8N_4OS \cdot HCl \cdot H_2O$ (236.7): C 26.49, H 4.89, N 24.72; found: C 26.34, H 5.05, N 24.48.

Concentration of the filtrate to half of its volume and addition of conc. NH_3 to pH 6 yielded 0.24 (19%) of the free base **10** as brownish solid.

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