Novel Pyrimidine and Pyrimido[1,2-*a*]pyrimidine Derivatives. By-products of a Guanidine Based Thymine Synthesis

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The isolation, structural elucidation, directed preparation and some derivatives of three previously unknown heterocycles is reported. Arising from a guanidine based thymine synthesis, these novel compounds exhibit substituted and fused pyrimidine structures repectively.

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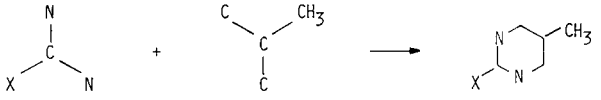
To date several 2',3'-dideoxynucleoside analogs and in particular 3'-azido-3'-deoxythymidine (AZT) have proven to be effective in the fight against the human immunodeficiency virus (HIV), the probable agent of AIDS [2]. On this account β-thymidine is one of the nucleosides of increasing importance, as it acts as a starting material for AZT itself as well as for other substituted or unsubstituted dideoxynucleoside derivatives, and which is therefore manufactured in technical quantities. According to classical nucleoside synthesis strategy, its preparation results from a glycosidation step of a protected sugar derivative, in this case being 2-deoxy-D-ribose, and a nucleobase, which in this case is thymine.

The preparation of thymine is well documented [3]. Amongst other possibilities of constructing this pyrimidine compound, reaction of a C-3-unit, bearing a methyl substituent at the posterior 5-position, with urea or one of its derivatives, is a preferred synthetic pathway. Suitable urea derivatives comprises thiourea [4], *S*-alkylisothiourea [5], *O*-alkylisourea [6] and guanidine [7] (see Scheme 1).

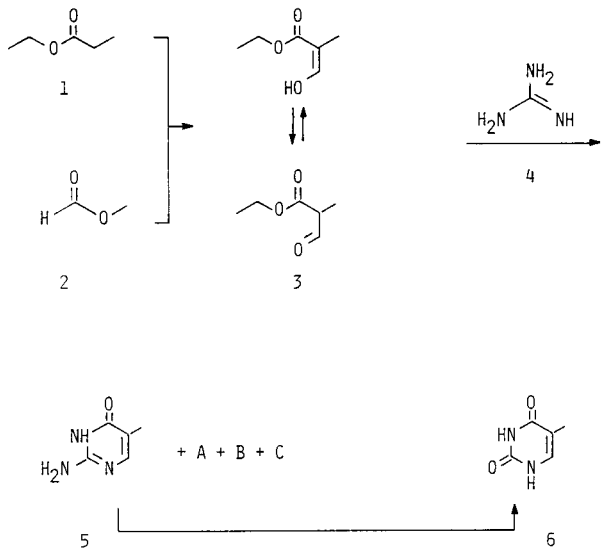
Scheme 1



When applying urea itself (X = O in Scheme 1) thymine is formed directly [8], while in all other cases at least one additional step is necessary to generate the carbonyl function. However, as urea needs troublesome accessable starting material, unfavourable reaction conditions, and the product suffers from low yield, the other aforementioned derivatives are more conveniently applied.

In connection with our engagement in the development of an optimized manufacturing procedure for β-thymidine, we also investigated various possibilities of thymine synthesis more exhaustively. The known reaction of ethyl propionate **1** and methyl formate **2** with guanidine **4** proceeds *via* ethyl 2-formyl-propionate **3** [9], which in due course is processed further with **4**, affording 5-methylisocytosine (2-amino-5-methyl-pyrimidin-4-one) **5** [7]. Subsequently the latter is desaminated to thymine **6** according to procedures which have been described for the analogous compounds uracil [10] and 5-fluoro-uracil [11] (see Scheme 2).

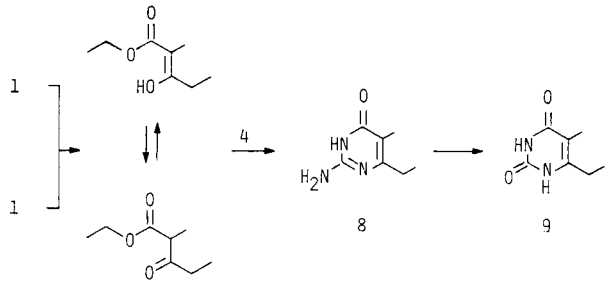
Scheme 2



When studying the first step of this sequence in detail, several by-products were detected *via* tlc in small amounts, in addition to the main product **5**. By enrichement from mother liquors three of them, **A**, **B**, **C**, could be isolated and identified. The first, **A**, is less polar than **5** in a chloroform/ethanol/concentrated aqueous ammonia 10:10:1 solvent system. The two others, **B** and **C**, exhibit lower Rf values (Rf: **A** = 0.60, **5** = 0.46, **B** = 0.41, **C** = 0.18).

The less polar compound **A** was obtained as a white, crystalline material, which melts under decomposition at 296° and showed an empirical formula $C_7H_{11}N_3O$. It forms a monotrimethylsilyl as well as a bistrimethylsilyl derivative which are both capable for gc analysis. From ^{1}H-nmr spectrum a methyl group and an ethyl group could be assigned, whereas the signals for H-5 and H-6 of the pyrimidine ring are missed. These data suggests **A** to be 6-ethyl-5-methylisocytosine (2-amino-6-ethyl-5-methylpyrimidin-4-one) **8**. Its formation can be explained by a self condensation of two molecules of **1** affording ethyl 2-propionylpropionate **7**. This reacts with **4** in a similar way as **3** does, to yield **8** (see Scheme 3).

Scheme 3



The verification of this reaction sequence was confirmed by a directed synthesis of **8** starting with **1** and **4** or using preformed **7** [12] and **4** as starting materials. In the latter case **8** was obtained in excellent (>85%) yield.

Much to our surprise **8** has never been mentioned in the literature. For further structural proof it was therefore converted to the known uracil derivative **9** [13], by reaction with sodium nitrite/hydrochloric acid. Compound **9** could also be isolated as an impurity from the desamination of the crude reaction mixture of **5** to **6**. Our data of **9** are in good agreement with the literature. Thus the structure of **A** was unambiguously assigned to be **8**.

Compounds **B** and **C**, with lower Rf-values than **5**, exhibit identical empirical formulas, $C_9H_9N_3O_2$, with a molecular mass of 191, thus giving evidence for being structural isomers. Compound **C**, which is the most polar compound, was isolated as a monohydrate. Both substances represent white crystalls with rather high decomposition points (above 300°).

The presence of three nitrogen atoms in the molecule indicated the incorporation of only one guanidine moiety. The remaining eight C-atoms suggest two C-4-units, for which **3** could act as a possible source. Considering this, the molecules in question could hypothetically be constructed from **5** and another **3**, which would also contribute the second oxygen as a carbonyl function. In fact, the ir findings showed the existence of amide bands in both compounds. It was further obvious from the ^{1}H-nmr that **C** contains two identical methyl groups at 2.18 ppm, whereas **B** shows two different signals for the methyl protons at 2.15 and 2.23 ppm respectively (see Experimental). For the unequivocal assignment of different possible structures an X-ray single crystal analysis was performed. Compound **C** was amenable to measurement as obtained from its crystallization, as a monohydrate, whereas no satisfactory crystals could be obtained from **B**. It was therefore converted to its hydrochloride.

For both crystal structures, **B** and **C**, intensity data were collected at room temperature on a Philips PW 1100 diffractometer with a graphite monochromator. MoKα radiation was used (λ = 0.71069 Å). The maximum 2θ was 50°. The number of unique reflections measured for **B** and **C** were 1791 and 1688, respectively. The 1346 reflections with Fo $\geq 2\sigma$(Fo) were used in the subsequent calculations for **C** and all 1791 reflections for **B**. The structures were solved by direct methods. Hydrogen atoms were located in difference maps. The methyl groups were treated as rigid groups. The non-methyl hydrogens were included in the Fc calculations but their parameters were not refined. The final agreement indices are R = 0.057 and Rw (F) = 0.059 for **C** and R = 0.060 and Rw (F) = 0.067 for **B** (see Figures 1 and 2). Atomic parameters are listed in Tables 1 and 2. Bond distances are listed in Table

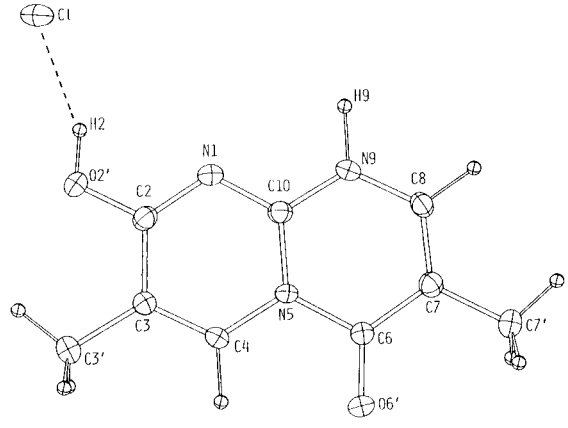


Figure 1. Molecular Structure of **B** (**10**). The dashed line represents a hydrogen bond.

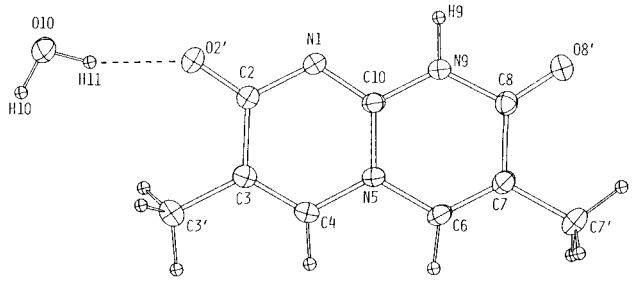


Figure 2. Molecular Structure of **C** (**11**). The dashed line represents a hydrogen bond.

Table 1

Fractional Coordinates for **B (10)**

	x	y	z	U(eq)
Cl	0.1216(1)	1.0322(1)	0.2248(0)	0.042(1)
N(1)	0.3704(4)	0.7099(2)	0.1494(1)	0.033(1)
C(2)	0.5010(4)	0.7939(2)	0.1162(2)	0.031(1)
O(2')	0.4552(4)	0.9115(2)	0.1232(1)	0.045(1)
C(3)	0.6953(5)	0.7643(2)	0.0703(2)	0.031(1)
C(3')	0.8411(5)	0.8635(3)	0.0346(2)	0.043(1)
C(4)	0.7406(4)	0.6414(2)	0.0622(2)	0.029(1)
N(5)	0.6047(3)	0.5522(2)	0.0964(1)	0.025(1)
C(6)	0.6712(5)	0.4236(2)	0.0901(2)	0.030(1)
O(6')	0.8338(4)	0.3922(2)	0.0495(1)	0.047(1)
C(7)	0.5339(4)	0.3376(3)	0.1318(2)	0.031(1)
C(7')	0.6045(5)	0.2035(3)	0.1305(2)	0.043(1)
C(8)	0.3512(5)	0.3796(3)	0.1704(2)	0.031(1)
N(9)	0.2984(4)	0.5032(2)	0.1744(1)	0.032(1)
C(10)	0.4245(4)	0.5910(3)	0.1401(2)	0.028(1)

Table 2

Fractional Coordinates for **C (11)**

	x	y	z	U(eq)
N(1)	0.2855(1)	0.0293(3)	0.1272(2)	0.037(1)
C(2)	0.2199(1)	-0.0260(4)	0.1010(2)	0.036(1)
O(2')	0.1905(1)	-0.0759(3)	0.17303(1)	0.058(1)
C(3)	0.1875(1)	-0.0563(3)	0.0074(2)	0.033(1)
C(3')	0.1146(1)	-0.1187(4)	-0.0365 (2)	0.044(2)
C(4)	0.2244(1)	-0.0200(4)	-0.0767(2)	0.035(1)
N(5)	0.2913(1)	0.0388(3)	-0.0479(2)	0.032(1)
C(6)	0.3300(1)	0.0779(4)	-0.1211(2)	0.037(2)
C(7)	0.3936(1)	0.1379(4)	-0.0952 (2)	0.035(1)
C(7')	0.4357(2)	0.1835(5)	-0.1717(2)	0.052(2)
C(8)	0.4246(1)	0.1639(4)	0.0134(2)	0.033(1)
O(8')	0.4827(1)	0.2160(3)	0.0457(1)	0.047(1)
N(9)	0.3829(1)	0.1264(3)	0.0810(2)	0.033(1)
C(10)	0.3182(1)	0.0631(3)	0.0548(2)	0.030(1)
O(10)	0.0777(1)	-0.2127(3)	0.2310(1)	0.055(1)

Table 3

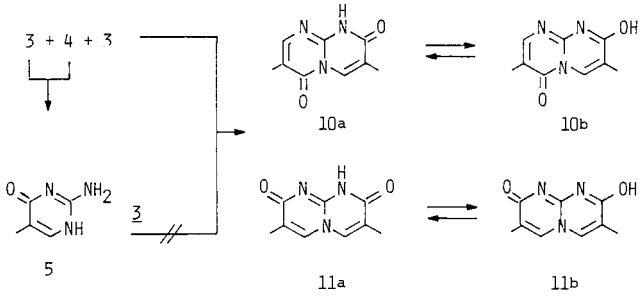
Bond Lengths (Å)

	Compound **B (10)**	Compound **C (11)**
N(1)-C(2)	1.322(3)	1.379(3)
N(1)-C(10)	1.332(3)	1.306(3)
C(2)-O(2')	1.302(3)	1.237(3)
C(2)-C(3)	1.435(4)	1.459(4)
C(3)-C(3')	1.507(4)	1.509(4)
C(3)-C(4)	1.359(4)	1.333(4)
C(4)-N(5)	1.386(3)	1.390(3)
N(5)-C(6)	1.445(3)	1.405(3)
N(5)-C(10)	1.373(3)	1.371(3)
C(6)-O(6')	1.220(3)	–
C(6)-C(7)	1.426(4)	1.329(4)
C(7)-C(7')	1.504(4)	1.502(4)
C(7(-C(8)	1.352(4)	1.460(4)
C(8)-0(8')	–	1.220(3)
C(8)-N(9)	1.369(4)	1.388(3)
N(9)-C(10)	1.343(3)	1.358(3)

3. Lists with anisotopic vibrations parameters, H-atom parameters and Fo/Fc data have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, Fachabt. III, Physik und Astronomie, D-7514 Eggenstein-Leopoldshafen 2. The data are available on request by quoting the Number CSB-54004.

From this study **B** turned out to be **10** and **C** to be **11**. The formation of both the pyrimido[1,2-*a*]pyrimidine derivatives is a result of the condensation of 2 moles 2-formylpropionate **3** with guanidine **4** by attack in different patterns. As several experiments failed to react preformed **5** with **3**, it seems unlikely that 5-methylisocytosine **5** is an intermediate in the formation of **10** and **11**. Presumably open chained disubstituted guanidine derivatives, which are not capable of isolation under the applied reaction conditions, must act as precursors of the fused two-ring system (see Scheme 4).

Scheme 4



While it is evident from the structural formulas that for both compounds lactam-lactim tautomerism is possible, only the keto forms **10a** and **11a** respectively are present in the solid state of the crystals, measured by X-ray. This

Scheme 5

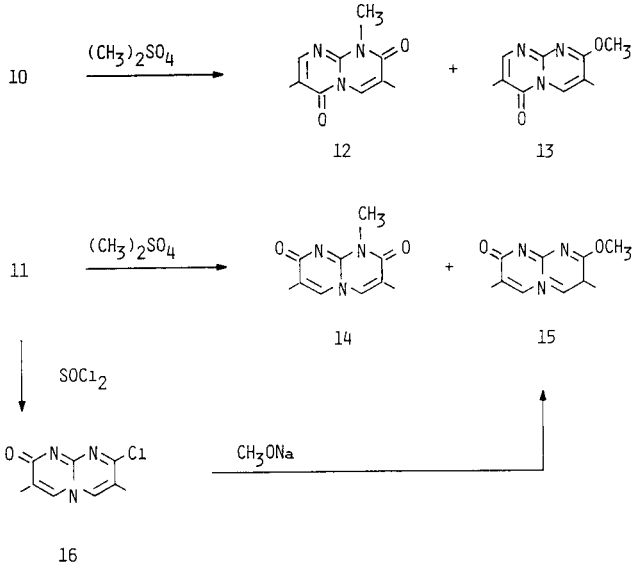


Table 4
Chemical Properties of Products

No.	Formula	MW	mp °C	Solvent	Analysis Calcd./Found C	H	N
5	$C_5H_7N_3O$	125.1	294 dec	water	47.99	5.64	33.58
					47.99	5.65	33.50
8	$C_7H_{11}N_3O$	153.2	296 dec	water	54.88	7.24	27.43
					54.71	7.24	27.50
9	$C_7H_{10}N_2O_2$	154.2	254-255 dec	water	54.88	6.54	18.17
					54.55	6.55	18.10
10	$C_9H_9N_3O_2$	191.2	> 330 dec	acetic acid	56.54	4.74	21.98
					56.52	4.77	22.00
11	$C_9H_9N_3O_2$	191.2	> 330 dec [a]	2*N* acetic acid	51.67	5.30	20.09 [a]
					51.74	5.34	20.20
12	$C_{10}H_{11}N_3O_2$	205.2	188	water	58.53	5.40	20.48
					58.39	5.41	20.50
13	$C_{10}H_{11}N_3O_2$	205.2	203-204 [a]	water	53.80	5.87	18.82 [a]
					53.79	5.81	18.70
14	$C_{10}H_{11}N_3O_2$	205.2	> 300 dec [a]	water	53.80	5.87	18.82 [a]
					53.79	5.84	19.00
15	$C_{10}H_{11}N_3O_2$	205.2	> 300 dec	water	58.53	5.40	20.48
					58.22	5.25	20.60
16	$C_9H_8ClN_3O$	282.5	> 200 dec [b]	decomposes	-.-	-.-	-.-

[a] Monohydrate. [b] Dihydrochloride.

Table 5
^{13}C NMR Chemical Shifts (δ ppm) in Deuterium Oxide Relative to External TMS

Conditions: Bruker AC 200; frequency 50.32 MHz
pulse : 3μsec = 30°
temperature : 297° K
size : 31 K datapoints
FID : 0,3 Hz linebroadening; 0,1 Hz gaussianbroadening; zerofilling to 64 k
sweep : 11628 Hz
resolution : 0,355 Hz/datapoint
number of scans : typical 40.000

Compound	C-2	C-3 [a]	C-4	C-6	C-7 [a]	C-8	C-9a	C-10/C-11[a]	$N\text{-}CH_3$	$O\text{-}CH_3$
10	161.72	114.78	136.01	155.46	121.28	130.45	145.50	(11.68/11.72)	–	–
11	164.53	121.03	138.17	138.17	121.03	164.53	147.31	(12.01/12.01)	–	–
12	156.42	116.22	137.06	159.36	121.50	129.25	146.93	(12.36/13.15)	30.43	–
13 [b]	134.08	113.38	168.12	143.29	118.35	156.38	146.40	(11.65/11.84)0	–	39.21
14	159.82	116.27	134.16	140.61	121.80	168.14	146.59	(10.90/12.06)	29.65	–
15 [b]	170.54	117.92	140.47	136.21	124.92	161.16	147.74	(11.56/12.15)	–	57.38

[a] Shifts of C-3 and C-7 respectively; C-10 and C-11 may be interchanged. [b] Assignments of C-atoms in concordance with formula of **13** and **15**. All data recorded and prepared by Mr. D. Schlosser, Analytical Dept. of Chem. Fabrik Pfersee, Augsburg, Germany.

confirms the known preference for the lactam structure of heterocycles containing an amide moiety [14]. From methylation experiments with different agents however, the equilibrium in solution could be demonstrated. Two monomethyl derivatives from each of the parent compounds are obtainable which could be clearly distinguished by spectroscopic data. By reacting **11** with diazomethane, methyl iodide or dimethyl sulfate, the N^1-methyl derivative **14** results predominantly. Dimethyl sulfate and **10** yields a mixture of N^1-methyl **12** and *O*-methyl **13** products, which could be separated. The *O*-methyl derivative **15** of the symmetric diketone **11** is most favourably prepared *via* the chlorination derivative **16** and subsequent halogen-methoxy exchange (See Scheme 5).

The first literature reference of a pyrimido[1,2-*a*]pyrimidine compound is from 1955 [15]. Several other derivatives

in various hydrogenation stages and different substitution patterns of the parent ring system have been reported since then. But none of these are identical to our thymine derived by-products. Thus, in addition to **8** compounds **10-16** also represent novel structures.

Substances **8**, **10** and **11** are substituted or fused isocytosines respectively and therefore exhibit structural properties, which should make them capable of glycosidations. By reacting these unusual nucleobases with sugar derivatives or their open chained analogues, novel types of nucleosides should result. We are presently investigating this aspect of biological interest.

EXPERIMENTAL

Melting points below 250° were determined on a Buechi 535 apparatus, those above 250° on an Electrothermal Melting Point Apparatus. The ir spectra were recorded on a Bruker IFS 85 FT-IR-spectrometer as potassium bromide disks. The ^{1}H-nmr spectra were obtained on a Varian EM 360 60 MHz ^{1}H-nmr-spectrometer in the following solvent system: deuterium oxide/deuterium chloride/3-(trimethylsilyl)propionic acid-d_4, sodium salt. The uv data were measured on a Varian UV-VIS 90 spectrometer in 0.1 *N* sodium hydroxide solution. Mass spectra were obtained on a Finnigan MAT 4510 quadrupol mass spectrometer as electron impact spectra (70 eV). Elemental analysis were performed by Mikroanalytisches Labor Pascher, D-5480 Remagen-2. The chemical properties of the compounds are listed in Table 4, the ^{13}C-nmr data in Table 5.

5-Methylisocytosine (**5**) [and By-products **8**, **10** and **11**].

Sodium methoxide (108.0 g, 2 moles) was suspended in a mixture of 153.2 g (1.5 moles) of ethyl propionate (**1**) and 150 ml of DMF. Methyl formate (**2**) (60.0 g, 1 mole) was added over a period of 2 hours. Stirring was continued, and after 30 minutes a solution of 95.5 g (1 mole) of guanidine hydrochloride (**4**•HCl) in 350 ml of methanol was added rapidly and the reaction mixture was refluxed for 2 hours. After cooling to 30° and adjusting the *p*H to 6.0 with concentrated hydrochloric acid the slurry was kept at 0-5° for 30 minutes. The solid was collected, washed with methanol, crystallized from water and dried *in vacuo* to yield 95.0 g (76%) of **5**; ir: ν 3368, 3165, 1669, 1648, 1549, 1499, 1394, 1232, 1033, 784, 605, 483 cm^{-1}; uv: λ max 228 nm (ϵ 4 908) 278 nm (ϵ 3 983); ^{1}H-nmr: δ 1.93 (d, J = 1.5 Hz, 3H, CH_3-5), 7.50 (q, J = 1.5 Hz, 1H, H-6); ms: (m/z) 125 (M^+, 100), 124 (12), 110 (3), 97 (11), 96 (18), 84 (17), 82 (22), 70 (5), 69 (5), 56 (8), 55 (34), 43 (48).

From mother liquors and washings by-products **8**, **10**, and **11** could be isolated only in mg amounts. Increased quantities of these compounds were obtained by modified synthetic routes.

Thymine (**6**).

Desamination of **5** according to the method described later to synthesize 6-ethyl-5-methyluracil (**9**) gave thymine (**6**) in 80% yield.

6-Ethyl-5-methylisocytosine (**8**).

Method 1.

A mixture of 21.6 g (0.4 mole) of sodium methoxide, 30 ml of DMF and 51.06 g (0.5 mole) of ethyl propionate (**1**) was stirred at 30° for 2 hours. After addition of a solution of 19.1 g (0.2 mole) of guanidine hydrochloride (**4**•HCl) in 70 ml of methanol the slurry was refluxed for 2 hours, then cooled to 30°, neutralized with concentrated hydrochloric acid and kept at 0-5° for 30 minutes. Solids were removed by filtration, the filtrate was evaporated *in vacuo* to give 0.6 g (2%) of **8**.

Method 2.

Sodium methoxide (5.4 g, 0.1 mole) was suspended in 7.5 ml of DMF, 7.9 g (0.05 mole) ethyl 2-propionylpropionate (**7**) [12] was added at temperatures not exceeding 20°. After addition of a solution of 4.8 g (0.05 mole) of guanidine hydrochloride (**4**•HCl) in 17 ml of methanol the mixture was heated to reflux for 3 hours, then cooled and neutralized with concentrated hydrochloric acid. The solid was collected and washed with methanol and water. It was crystallized from water to yield 6.6 g (86%) of **8**; ir: ν 3356, 3098, 1650, 1505, 1381, 1228, 788, 535, 486 cm^{-1}; uv: λ max 229 nm (ϵ 7 439), 278 nm (ϵ 7 431); ^{1}H-nmr: δ 1.22 (tr, J = 7.2 Hz, 3H, H_3C-CH_2-6), 1.94 (s, 3H, CH_3-5), 2.65 (q, J = 7.2 Hz, 2H, H_3C-CH_2-6); ms: (m/z) 153 (M^+, 100), 154 (9), 152 (72), 138 (32), 125 (13), 124 (14), 110 (31), 82 (19), 69 (7), 67 (8), 56 (13), 55 (24), 43 (53).

6-Ethyl-5-methyluracil (**9**).

A suspension of 15.3 g (0.1 mole) of **8** in 40 ml of 20% hydrochloric acid was warmed to 70°. A solution of 13.8 g (0.2 mole) of sodium nitrite in 23 ml of water was added drop by drop over a period of 6-8 hours. The reaction mixture was cooled to 0-5°, and after 2 hours the precipiate was filtered, washed with water and dried *in vacuo* to give 11.7 g (76%) of **9**; ir: ν 3160, 1707, 1649, 1454, 1382, 1196, 769, 524, 474 cm^{-1}; uv: λ max 218 nm (ϵ 9 365), 271 nm (ϵ 6 378); ^{1}H-nmr: δ 1.20 (tr, J = 7.2 Hz, 3H, H_3C-CH_2-6), 1.90 (s, 3H, CH_3-5), 2.62 (q, J = 7.2 Hz, 2H, H_3C-CH_2-6); ms: (m/z) 154 (M^+, 100), 155 (9), 153 (45), 139 (5), 126 (9), 125 (6), 111 (6), 110 (5), 83 (12), 82 (83), 68 (6), 67 (7), 56 (46), 55 (17).

3,7-Dimethyl-1*H*-pyrimido[1,2-*a*]pyrimidine-2,6-dione (**10**) and 3,7-Dimethyl-1*H*-pyrimido[1,2-*a*]pyrimidine-2,8-dione (**11**).

To a suspension of 8.1 g (0.15 mole) of sodium methoxide in 11.5 ml of DMF a mixture of 8.37 g (0.082 mole) of ethyl propionate (**1**) and 4.5 g (0.075 mole) of methyl formate (**2**) was added at 25-30° over a period of 2 hours. The solution was stirred further for 30 minutes at ambient temperature, cooled to 0° and partly neutralized by addition of 4.6 g (0.1 mole) of formic acid, maintaining the temperature at 0-10°. A solution of 4.8 g (0.05 mole) of guanidine hydrochloride (**4**•HCl) in 13 ml of methanol was then added, the slurry was refluxed for 3 hours and cooled to 0-5° for 1 hour. The solids were collected, washed with methanol and dried *in vacuo* to yield 13.0 g of a mixture of **5**, **8**, **10** and **11**. This material was refluxed with 80 ml of 2 *N* acetic acid for 10 minutes. The slurry was filtered while hot, the residue washed successively with 2 *N* acetic acid and methanol and dried *in vacuo*. Crystallization from DMF and acetic acid gave 0.82 g (8.6%) of **10**; ir: ν 3076, 1682, 1648, 1565, 1472, 1377, 1211, 969, 772 cm^{-1}; uv: λ max 234 nm (ϵ 22 045), 323 nm (ϵ 8 012); ^{1}H-nmr: δ 2.15 (d, 3H, CH_3-7), 2.23 (d, 3H, CH_3-3), 7.93 (q, 1H, H-8), 8.70 (q, 1H, H-4); ms: (m/z) 191 (M^+, 100), 192 (10), 190 (10), 163 (28), 162 (72), 134 (11), 110 (10), 109 (24), 81 (13), 54 (34), 53 (20); crystal data: $C_9H_9N_3O_2$•HCl; MW = 227.65; monoclinic, space group $P2_1/c$; cell parameters: a = 5.853(1), b = 10.779(2), c = 16.291(4) Å, β = 93.54(3)°; Z = 4; calculated density = 1.474 g cm^{-3}; absorption coefficient μ = 3.0 cm^{-1}.

The 2 *N* acetic acid mother liquor was concentrated *in vacuo* to a volume of 25 ml, the precipitate was collected, washed with water and dried *in vacuo*. Crystallization from DMSO and 2 *N* acetic acid yielded 0.86 g (8.2%) of **11** monohydrate; ir: ν 3468, 3400, 3034, 1698, 1661, 1610, 1547, 1421, 1396, 1383, 1264, 780 cm^{-1}; uv: λ max 237 nm (ϵ 45 954), 287 nm (ϵ 8 836); ^{1}H-nmr: δ 2.18 (d, 6H, CH_3-3, CH_3-7), 8.30 (q, 2H, H-4, H-6); ms: (m/z) 191 (M^+, 100), 192 (10), 163 (23), 162 (13), 151 (37), 134 (6), 123 (17), 122 (20), 95 (7), 82 (7), 69 (23), 54 (17), 53 (10); crystal data: $C_9H_9N_3O_2 \cdot H_2O$; MW = 209.20; monoclinic, space group C2/c; cell parameters: a = 20.184(4), b = 7.321(2), c = 13.337(4) Å, β = 102.50(3)°; Z = 8; calculated density = 1.444 g cm^{-3}; absorption coefficient μ = 0.70 cm^{-1}.

1,3,7-Trimethyl-1*H*-pyrimido[1,2-*a*]pyrimidine-2,6-dione (**12**) and 3,7-Dimethyl-8-methoxy-pyrimido[1,2-*a*]pyrimidin-4-one (**13**).

To **10** (19.1 g, 0.1 mole), suspended in 120 ml (0.12 mole) of *N* sodium hydroxide, 13.9 g (0.11 mole) of dimethyl sulfate was added, maintaining the temperature between 25° and 35°. After stirring the mixture for 2 hours the solid was collected and crystallized from water to give 6.5 g (32%) of **12** as fine white needles; ir: ν 3089, 1690, 1657, 1604, 1541, 1465, 1387, 1207, 962, 770 cm^{-1}; uv: λ max 219 nm (ϵ 11 495), 310 nm (ϵ 17 406); ^{1}H-nmr: δ 2.12 (d, 3H, CH_3-7), 2.19 (d, 3H, CH_3-3), 3.70 (s, 3H, H_3C-N-1), 7.92 (q, 1H, H-8), 8.63 (q, 1H, H-4); ms: (m/z) 205 (M^+, 100), 206 (11), 204 (9), 177 (33), 176 (53), 162 (14), 149 (10), 148 (24), 134 (12), 123 (17), 95 (7), 55 (17), 54 (20), 42 (34).

The mother liquors were extracted with methylene chloride. Evaporation of methylene chloride *in vacuo* gave a solid residue. This material was purified by flash chromatography (silica gel-methylene chloride:methanol 9:1, v/v) and crystallized from water to yield 7.1 g (35%) of **13**; ir: ν 3089, 1696, 1661, 1638, 1551, 1378, 1350, 1209, 783 cm^{-1}; uv: λ max 217 nm (ϵ 14 804) 292 nm (ϵ 15 895); ^{1}H-nmr δ 2.18 (d, 3H, CH_3-3), 2.32 (d, 3H, CH_3-7), 3.91 (s, 3H, H_3C-O-8), 8.16 (q, 1H, H-2), 8.96 (q, 1H, H-6); ms: (m/z) 205 (M^+, 100), 206 (11), 204 (2), 190 (5), 177 (27), 176 (52), 162 (17), 150 (6), 149 (7), 148 (23), 134 (13), 122 (12), 83 (12), 69 (17), 42 (37).

1,3,7-Trimethyl-1*H*-pyrimido[1,2-*a*]pyrimidine-2,8-dione (**14**).

To 5.2 g (0.025 mole) of **11** monohydrate, suspended in 52.0 ml (0.052 mole) of *N* sodium hydroxide 6.3 g (0.05 mole) of dimethyl sulfate was added at 25° to maximum 40°. The mixture was stirred overnight at room temperature and then cooled to 0°. The solid was collected, washed with water and acetone and dried *in vacuo* to give 4.5 g (81%) **14** monohydrate; ir: ν 3527, 3391, 1702, 1687, 1660, 1625, 1522, 1455, 1392, 1380, 1260, 1244, 1100, 973, 919, 778 cm^{-1}; uv: λ max 221 nm (ϵ 34 328), 285 nm (ϵ 14 380); ^{1}H-mnr: δ 2.18 (d, 3H, CH_3-7), 2.27 (d, 3H, CH_3-3), 3.70 (s, 3H, H_3C-N-1), 8.23 (q, 1H, H-4), 8.47 (q, 1H, H-6); ms: (m/z) 205 (M^+, 100), 206 (11), 204 (1), 177 (17), 176 (27), 165 (32), 162 (14), 148 (10), 137 (14), 136 (13), 83 (33), 56 (10), 54 (12).

3,7-Dimethyl-8-methoxypyrimido[1,2-*a*]pyrimidin-2-one (**15**).

To 100 ml of thionyl chloride, containing 0.5 ml of DMF 10.46 g (0.05 mole) of **11** monohydrate was added in small portions. When gas evolution had ceased, the slurry was heated to gentle reflux until evolution of gas had stopped again. After cooling and evaporating the excess of thionyl chloride *in vacuo* the white residue was suspended in diethyl ether, stirred for 30 minutes, collected and washed with ether. The solid was dried *in vacuo* over potassium hydroxide to yield 13.7 g (97%) of crude 8-chloro-3,7-dimethylpyrimido[1,2-*a*]pyrimidin-2-one dihydrochloride (**16**), which was processed further without purification. To a solution of 7.0 g (0.13 mole) of sodium methoxide in 340 ml of methanol **16** (11.3 g, 0.04 mole) was added in small portions, maintaining the temperature between 20° and 25°. Stirring was continued for 2 hours and the reaction mixture was cooled to 0-5°. The white solid was collected, washed with methanol and crystallized from water to yield 2.8 g (34%) of **15**; ir: ν 3016, 1674, 1652, 1602, 1509, 1473, 1460, 1392, 1369, 1279, 1246, 1035, 995, 784 cm^{-1}; uv: λ max 237 nm (ϵ 46 617), 287 nm (ϵ 9 377); ^{1}H-nmr: δ 2.17 (d, 3H, CH_3-3), 2.28 (d, 3H, CH_3-7), 4.23 (s, 3H, H_3C-O-8), 8.25 (q, 1H, H-6), 8.47 (q, 1H, H-4); ms: (m/z) 205 (M^+, 100), 206 (12), 177 (26), 176 (23), 165 (25), 162 (13), 150 (20), 148 (19), 147 (11), 137 (11), 136 (13), 107 (11), 83 (30), 66 (8), 54 (16).

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