

PTERIDINES, LXX¹ - SYNTHESIS AND PROPERTIES OF 1,8-ALKYLENE-BRIDGED LUMAZINES

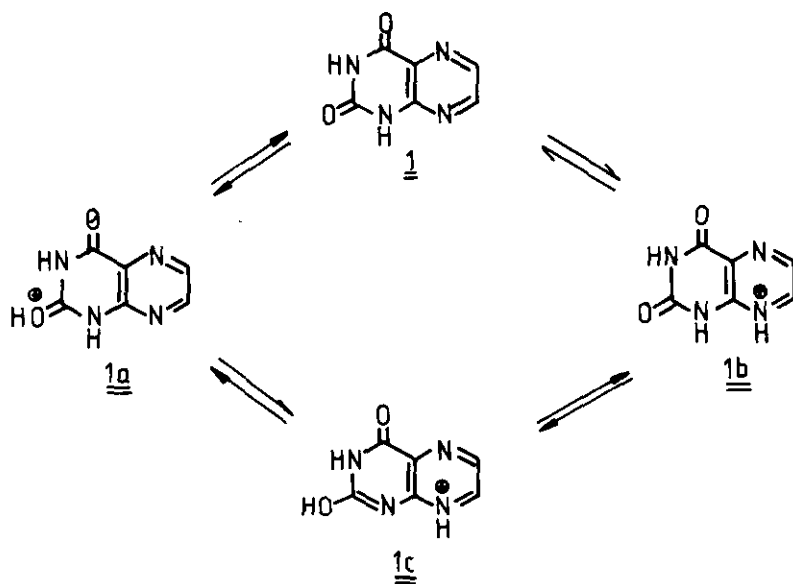
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ABSTRACT - A new type of lumazine derivatives (24-30) with a 1,8-alkylene bridge has been synthesized to study the protonation site in lumazine (1) itself. Comparisons of UV-data, however, do not allow a clear decision in this respect but indicate possibly the presence of a mixture of at least two cationic species. The structures of the newly synthesized compounds have been proven by UV- and NMR-spectra as well as pK_a measurements and elementary analyses. 8- β -Hydroxyethyl-7-oxo-7,8-dihydrolumazines (15-17) show an easy cyclization to the corresponding 1,8-ethano-bridged derivatives 18-20 on boiling with DMF.

The structure of lumazine (1) which favours the tautomeric 2,4-dioxo-1,2,3,4-tetrahydro form² reveals that this system will possess very weak basic properties recognizable only in the superacidic H_0 -region. This fact may be the reason why little attention has been drawn to this problem. Only Lippert and Prigge³ investigated the lumazine system in more detail and came to the conclusion that the most basic position is located at the O^{2-} and not the N-8 atom. Since both cationic species 1a and 1b are, however, resonance stabilized and the basicity of an amide function is very similar to that of the pyrazine nucleus, it is difficult to see why the 1H, 2-OH, 3-H-tautomer (1a) should be energetically favoured over the 1-H, 3-H, 8-H protonated form (1b).

There is even a further possibility 1c for the cation formation indicating a very complex system in general which may even consist of a mixture of different cation species. Since also very little NMR-studies have been carried out in this field and the results from ^{13}C -NMR-investigations⁴ of lumazine are not at all conclusive due to the fact that 1 is only partially protonated in trifluoroacetic acid we believe that a more precise answer to the open question of protonation could be



derived from UV-comparisons of the various N- and O-blocked models. The UV-spectra of the cations of lumazine (1) and its 8-methyl derivative⁵ (Fig. 1) look very similar what the shape and wave lengths of the absorption bands are concerned, whereas the differences in the extinctions may be due to hyperconjugative influences of the methyl substituent.

These increments have to be taken into account as seen from the physical data of the 1- and 3-monomethyl as well as the 1,3-dimethyl derivatives listed in tab. 1. N-1 substitution is in general be associated with a stronger bathochromic shift of the longwave absorption band than N-3 methylation. The spectral analogy of the cations of 1,3-dimethyl-lumazine and 2-methoxy-3-methyl-4-oxo-3,4-dihydropteridine (Fig. 1) may be explained by protonation at O² and N-1 respectively or in both cases at N-8, which is much more likely.

In order to narrow down the complex problem to a more fixed situation the synthesis of 1,8-alkylene-bridged lumazine derivatives as models for the 1b tautomer have been undertaken. There are two general routes starting from 1- and 8- ω -hydroxy-alkyllumazines respectively which after sulfonation at the terminal hydroxy groups may intramolecularly quaternize the peri-located ring N-atoms.

The first series of compounds have been obtained by Isay-condensations⁶ of 5,6-diamino-1- β -hydroxyethyluracil (3)⁷ which is derived from 6-amino-1- β -hydroxyethyl-

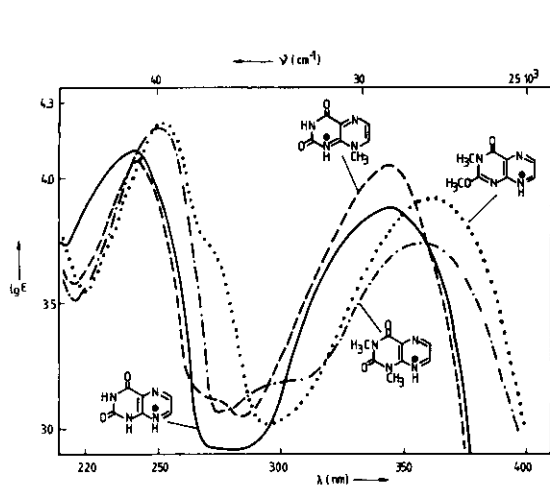


Fig. 1 - UV-Absorption spectra of the cations of lumazine (1) ($H_0 = -4.9$) —, 8-methyl- ($H_0 = -3.0$) —, 1,8-ethano- ($H_0 = -3.0$) —, 1,3-dimethyl- ($H_0 = -6.1$) —, 2-methoxy-3-methyl-4-oxo-3,4-dihydro-pteridin ($H_0 = -4.0$)

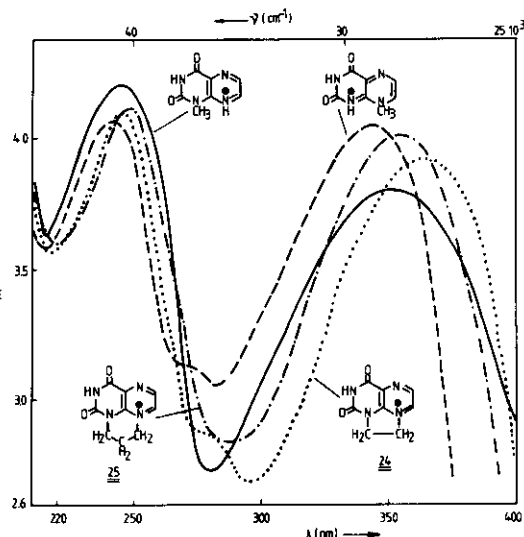
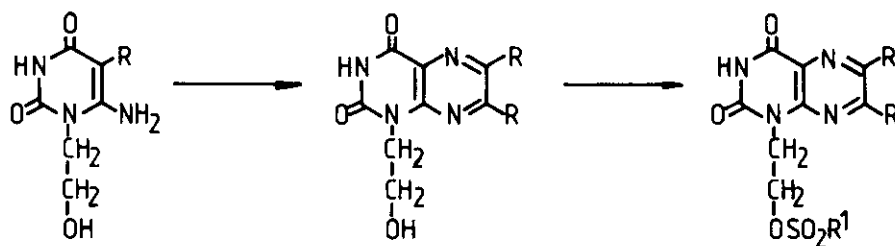


Fig. 2 - UV-Absorption spectra of 1-methyl- ($H_0 = -4.9$) —, 8-methyl- ($H_0 = -3.0$) —, 1,8-ethano- ($H_0 = -3.0$) —, 1,3-dimethyl- ($H_0 = -6.1$) —, 2-methoxy-3-methyl-4-oxo-3,4-dihydro-pteridin ($H_0 = -4.0$)

uracil (1) after nitrosation (2) and reduction, on treatment with glyoxal, diacetyl and benzil yielding 1-β-hydroxyethyl- (4) and its 6,7-dimethyl- (5) and 6,7-diphenyl derivative (6) respectively. Treatment of 5 with p-toluene sulfonylchloride in pyridine to form the corresponding tosyl derivative 7 did not proceed very well and gave only an impure product, whereas the mesylation to 8 as well as of 6 to 9 could be achieved in good yields.



	R
<u>1</u>	H
<u>2</u>	NO
<u>3</u>	NH ₂

	R
<u>4</u>	H
<u>5</u>	CH ₃
<u>6</u>	C ₆ H ₅

	R	R ¹
<u>7</u>	CH ₃	CH ₃ -C ₆ H ₄
<u>8</u>	CH ₃	CH ₃
<u>9</u>	C ₆ H ₅	CH ₃

Tab. 1 - UV-Absorption Spectra of Lumazines

-lumazine	pK _a in H ₂ O	UV - Absorption Spectra		pH	Mole- cular Form
		$\lambda_{\max}$ (nm)	lg ϵ		
1- β -Hydroxyethyl-(4)	8.54 $\pm$ 0.04	211 234 [250] 330 243 285 337	4.00 4.10 [3.95] 3.84 4.22 3.52 3.89	5.0 12.0	o -
1- β -Hydroxyethyl-6,7-dimethyl-(5)	9.14 $\pm$ 0.07	[228] 250 332 212 243 277 338	[4.06] 3.94 3.94 4.11 4.22 3.40 3.97	5.0 12.0	o -
1- β -Hydroxyethyl-6,7-diphenyl-(6)	8.86 $\pm$ 0.05	222 276 365 212 [220] 267 366	4.44 4.21 4.16 4.46 [4.38] 4.30 4.18	5.0 12.0	o -
8- β -Hydroxyethyl-7-oxo-7,8-dihydro-(15)	3.51 $\pm$ 0.03 12.79 $\pm$ 0.1	280 332 214 258 287 350	3.91 3.91 4.67 3.82 4.11 4.27	0.0 7.0	o -
8- β -Hydroxyethyl-6-methyl-7-oxo-7,8-dihydro-(16)	4.00 $\pm$ 0.03 13.15 $\pm$ 0.1	282 327 215 [250] 290 347	4.13 4.14 4.50 [3.68] 4.04 4.13	0.0 7.0	o -
8- β -Hydroxyethyl-6-phenyl-7-oxo-7,8-dihydro-(17)	3.31 $\pm$ 0.06 12.94 $\pm$ 0.05	232 288 353 217 [242] 297 372	4.13 4.07 4.29 4.54 [4.00] 4.08 4.32	0.0 7.0	o -
1,8-Ethano-7-oxo-7,8-dihydro-(18)	8.54 $\pm$ 0.05	215 275 325 215 255 274 338	4.19 4.06 4.08 4.15 3.99 3.73 4.07	5.0 12.0	o -
1,8-Ethano-6-methyl-7-oxo-7,8-dihydro-(19)	8.99 $\pm$ 0.09	214 275 320 215 252 275 335	4.14 4.02 4.06 4.20 4.02 3.76 4.11	5.0 12.0	o -
1,8-Ethano-6-phenyl-7-oxo-7,8-dihydro-(20)	8.94 $\pm$ 0.1	214 235 284 350 212 [235] 262 360	4.22 3.93 3.91 4.12 4.35 [4.11] 4.10 4.30	5.0 12.0	o -
Lumazine	-3.34 $\pm$ 0.1	240 [280] 343 226 [240] 323	4.11 [2.92] 3.88 4.02 [3.87] 3.84	-4.9 0.0	+ o
1-Methyl-	-3.26 $\pm$ 0.1	245 [295] 352 231 [245] 329	4.20 [2.94] 3.80 4.12 [3.94] 3.89	-4.9 0.0	+ o
3-Methyl-	-3.09 $\pm$ 0.1	242 [287] 342 230 [247] 323	4.13 [3.33] 3.86 4.15 [3.73] 3.89	-4.9 0.0	+ o
1,3-Dimethyl-	-3.04 $\pm$ 0.1	250 [294] 356 235 [253] 330	4.20 [3.18] 3.74 4.21 [3.79] 3.88	-6.1 0.0	+ o
8-Methyl-	-0.10 $\pm$ 0.1	240 [274] 344	4.07 [3.12] 4.05	-3.0	+
1,8-Ethano-7-hydroxy-7,8-dihydro-(24a)	1.25 $\pm$ 0.08 10.81 $\pm$ 0.1	246 [280] 364 220 269 296 [232] 277 [302]	4.10 [2.87] 3.92 4.05 4.22 3.88 [4.06] 4.12 [3.85]	-1.0 6.0 13.0	+ o -
1,8-Propano-7-hydroxy-7,8-dihydro-(24b)	3.21 $\pm$ 0.08	248 355 217 277 301 217 283 [308]	4.11 4.18 4.26 3.98 4.23 4.22 [3.92]	0.0 6.0 13.0	+ o -
6,7-Dimethyl-	-1.65 $\pm$ 0.05	236 347 245 328	4.16 3.99 3.90 4.01	-4.9 1.0	+ o
1,6,7-Trimethyl-	-1.84 $\pm$ 0.1	246 [265] 355 228 250 332	4.25 [3.95] 3.93 4.09 3.98 3.99	-5.0 1.0	+ o
3,6,7-Trimethyl-	-1.56 $\pm$ 0.07	243 [286] 348 232 [248] 329	4.21 [3.24] 4.02 4.14 [3.87] 4.02	-4.9 1.0	+ o
1,3,6,7-Tetramethyl-	-1.33 $\pm$ 0.08	251 [290] 358 235 [253] 332	4.28 [3.25] 3.94 4.21 [3.91] 3.98	-4.0 1.0	+ o
6,7,8-Trimethyl-	0.85 $\pm$ 0.1	244 356	4.11 4.23	-3.0	+
1,8-Ethano-6-methyl-7-methylene-7,8-dihydro-(26)	3.02 $\pm$ 0.03 10.35 $\pm$ 0.1	246 370 228 302 355 216 300 363	4.16 4.06 4.08 4.41 3.60 4.32 4.27 3.75	0.0 7.0 12.0	+ o -
1,8-Ethano-3,6-dimethyl-7-methylene-7,8-dihydro-(27)	3.23 $\pm$ 0.1	250 [290] 372 224 302 355	4.20 [3.21] 4.05 4.11 4.31 3.48	0.0 7.0	+ o
1,8-Propano-6-methyl-7-methylene-7,8-dihydro-(28)	3.85 $\pm$ 0.1 10.56 $\pm$ 0.1	251 365 230 [286] 314 [365] 218 311 364	4.08 4.10 4.02 [3.97] 4.32 [3.47] 4.23 4.31 3.68	1.0 7.0 12.0	+ o -
6,7-Diphenyl-	-3.89 $\pm$ 0.1	235 292 405 [220] 272 362	4.28 4.01 4.10 [4.43] 4.16 4.17	-5.5 5.0	+ o
1-Methyl-6,7-diphenyl-	-3.64 $\pm$ 0.1	245 298 415 220 277 365	4.23 3.95 4.05 4.35 4.13 4.09	-5.5 0.0	+ o
5-Methyl-6,7-diphenyl-	-3.28 $\pm$ 0.1	247 280 410 223 272 363	4.28 4.00 4.14 4.45 4.12 4.19	-5.5 0.0	+ o
1,3-Dimethyl-6,7-diphenyl-	-3.23 $\pm$ 0.1	[240] 252 [290] 415 227 275 364	[4.27] 4.33 [4.04] 4.15 4.43 4.21 4.19	-5.5 0.0	+ o
8-Methyl-6,7-diphenyl-	0.36 $\pm$ 0.1	[240] 255 286 400	[4.05] 4.04 4.09 4.05	-3.0	+
1,8-Ethano-7-hydroxy-6,7-diphenyl-7,8-dihydro-(30)	1.74 $\pm$ 0.05 10.68 $\pm$ 0.1	[230] 284 415 231 276 337 243 280 347	[4.15] 4.15 4.06 4.23 4.20 4.09 4.18 4.07 4.06	-1.0 6.0 13.0	+ o -
1,8-Propano-7-hydroxy-6,7-diphenyl-7,8-dihydro-(31)	2.89 $\pm$ 0.05 10.15 $\pm$ 0.1	[260] 283 400 231 286 350 [234] 287 356	4.14 4.08 4.29 4.25 4.09 [4.20] 4.17 4.09	0.0 6.0 12.0	+ o -
8-Methyl-6,7-diphenyl-7,8-dihydro-	0.21 $\pm$ 0.1 6.13 $\pm$ 0.1	[242] 275 417 237 292 373 250 [287] 385	[4.08] 4.46 4.10 4.27 4.26 4.07 4.27 [4.11] 4.11	-2.0 5.0 8.0	+ o -

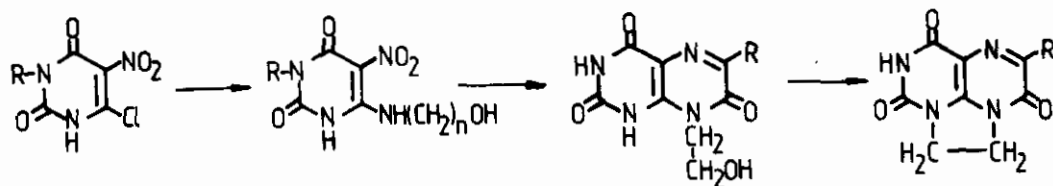
+ = cation, o = neutral form; - = monoanion.

[] = shoulder.

The series of the 8-substituted lumazines was based on the high reactivity of 6-chloro-5-nitrouracil (10)⁸ and its 3-methyl derivative (11)⁹ which reacted with ethanolamine and 3-hydroxypropylamine to the corresponding 6- ω -hydroxyalkylamino-5-nitrouracils 12-14 in high yields. Catalytic reduction of the nitro group in 12 to the 5-amino group with Pd/C/H₂ and subsequent condensation with ethyl glyoxylate-hemiacetal, ethyl pyruvate and ethyl phenylpyruvate led to the corresponding 8-substituted 7-oxo-7,8-dihydrolumazines 15¹⁰, 16¹¹ and 17. These compounds show presumably due to their relatively strong acidic character an interesting further cyclization reaction with loss of one mole of water on boiling in DMF forming the 1,8-ethano-7-oxo-7,8-dihydrolumazines 18-20 in good yields. The 6- ω -hydroxyalkylamino-5-nitrouracils 12-14 behave analogously and cyclize in boiling DMF to imidazo[1.2-c]-(21, 22) and pyrimido[1.2-c]-pyrimidines (23).

Compound 21 was believed to be formed¹² on short boiling of 4-(2'-hydroxyethylamino)-5-nitrouracil (12) in 1N HCl, but reinvestigation of this reaction indicated that the starting material of Cresswell and Wood⁸ could not have been 12 according to the published procedure and its relatively strong acidic character but the corresponding ethanalammonium salt, which was converted to the free 12 on acid treatment. This result is then in agreement with the mentioned fact of almost identical UV-spectra of starting and reaction product, the elementary analysis, which contained 1 mol of water, and the melting point of 275°C identical with our sample. 21, however, analyzes for C₆H₆N₄O₄, melts at 345°C and does show very little change in the long wave UV-absorption according to the blocking of the N-1 position. Measurements of the pK_a of 12 and 21 furthermore offers an easy differentiation of these structures because of the large differences in the acidic properties of 5-nitro-1- and 3-methyluracil derivatives¹³ respectively.

Conversion of the new imidazo-[1.2-c]- and pyrimido-[1.2-c]-pyrimidines 21-23 to the corresponding 1,8-alkylene-bridged lumazines 24-30 was achieved by catalytic reduction of the nitro group and subsequent condensation with glyoxal, diacetyl, and benzil. The reaction with glyoxal afforded acidic catalysis and 24 and 25 respectively have been isolated in form of the lumazinium-chlorides, whereas from the condensations with diacetyl and benzil the corresponding 6-methyl-7-methylene-7,8-dihydro-(26-28) and 6,7-diphenyl-7-hydroxy-7,8-dihydrolumazines (29, 30) respectively have been obtained. 26 and 29 are also formed on prolonged boiling of 8 and 9 respectively in pyridine or toluene showing an intramolecular quaterniza-

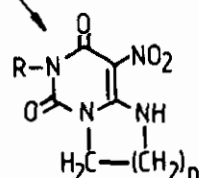


	R
<u>10</u>	H
<u>11</u>	CH ₃

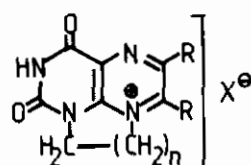
	R	n
<u>12</u>	H	2
<u>13</u>	CH ₃	2
<u>14</u>	H	3

	R
<u>15</u>	H
<u>16</u>	CH ₃
<u>17</u>	C ₆ H ₅

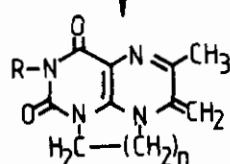
	R
<u>18</u>	H
<u>19</u>	CH ₃
<u>20</u>	C ₆ H ₅



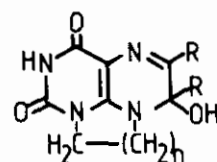
	R	n
<u>21</u>	H	1
<u>22</u>	CH ₃	1
<u>23</u>	H	2



	R	n
<u>24</u>	H	1
<u>25</u>	H	2
<u>26a</u>	CH ₃	1
<u>28a</u>	CH ₃	2
<u>29a</u>	C ₆ H ₅	1
<u>30a</u>	C ₆ H ₅	2



	R	n
<u>26</u>	H	1
<u>27</u>	CH ₃	1
<u>28</u>	H	2



	R	n
<u>29</u>	C ₆ H ₅	1
<u>30</u>	C ₆ H ₅	2
<u>24a</u>	H	1
<u>25a</u>	H	2

tion reaction at the peri-N-8 position.

The structures of the newly synthesized compounds 24-30 are based on UV- and NMR-spectra as well as pK_a -measurements and elementary analysis. The cations of the 1,8-alkylene-bridged lumazines represent the blocked lumazinium-cation form 1b whereby some specific structural features seem to be responsible for minor spectral differences. The 1,8-ethano-bridged derivatives show in general a bathochromic shift of the spectrum compared with the 1,8-propano analogues due perhaps to some internal strain in the five-membered ring which could also be seen from the pronounced differences in the basic pK_a -values. The better model for UV-comparisons are therefore the latter compounds, which are in agreement with the cations of the 1-methylated lumazines (Fig. 2,3,5).

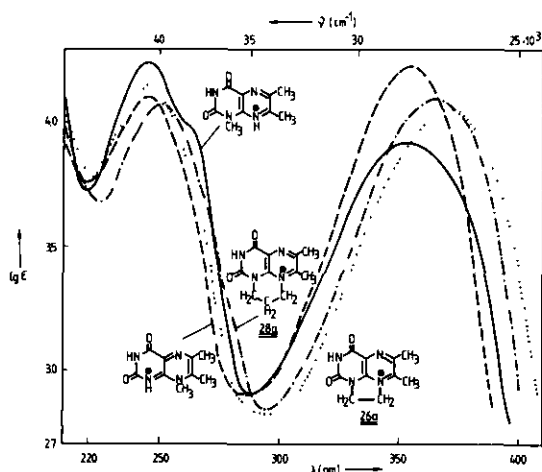


Fig. 3 - UV-Absorption spectra of 1,6,7-trimethyl- ($H_0 = -5.0$) —, 6,7,8-trimethyl- ($H_0 = -3.0$) ----, 1,8-ethano-6,7-dimethyl- (26a) (pH = 0.0), and 1,8-propano-6,7-dimethyl- (28a) (pH = 1.0) - - - - -.

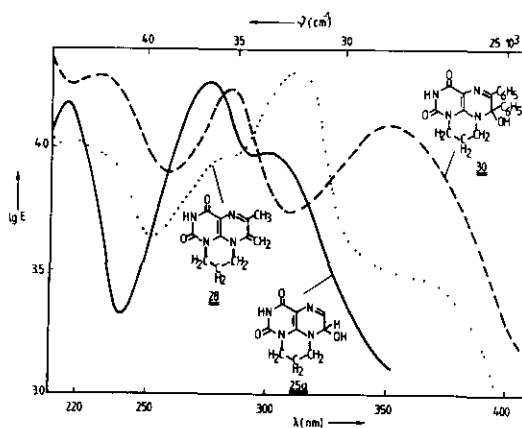


Fig. 4 - UV-Absorption spectra of the neutral forms of 1,8-propano-7-hydroxy-7,8-dihydro- (25a) (pH 6.0) —, 1,8-propano-7-hydroxy-6,7-diphenyl-7,8-dihydro- (30) (pH 6.0) ----, and 1,8-propano-6-methyl-7-methylene-7,8-dihydrolumazine (28) (pH 7.0)

Dramatic structural changes take place in the 1,8-alkylene-bridged cases going from the cations to the neutral species which do not show any indication of a zwitter-ion formation. The 6,7-H (24a, 25a) and 6,7-diphenyl derivatives (29, 30) form covalent hydrates by nucleophilic addition of a hydroxide ion to C-7 forming a formal 7,8-dihydrolumazine structure⁴ associated with a hypsochromic shift of the long wave absorption band of about 50-80 nm (Fig. 4).

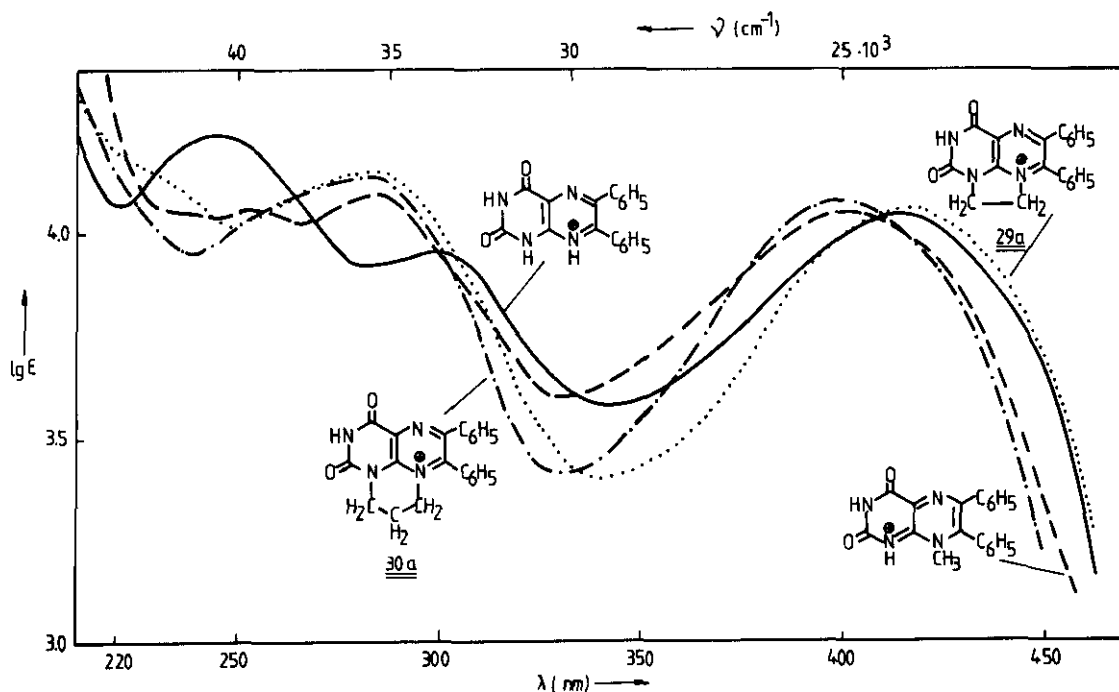


Fig. 5 - UV-Absorption spectra of 1-methyl-6,7-diphenyl- ($H_o = -5.5$) —, 8-methyl-6,7-diphenyl- ($H_o = -2.7$) ----, 1,8-ethano-6,7-diphenyl (29a) ($H_o = -1.0$), and 1,8-propano-6,7-diphenyllumazinium-cation (30a) ($H_o = -2.0$) - · - · - ·.

The 1,8-bridged 6,7-dimethylumazinium cations show in contrary to these results deprotonation at the activated 7-methyl group yielding a neutral species with an exocyclic methylene group in position 7 (26–28). These findings correlate nicely with former observations¹⁴ at neutral species of 8-substituted 6,7-dimethyl pterins and at the anions of 8-substituted 6,7-dimethylumazines. These structural features can also be seen in the NMR-spectra showing two characteristic doublets for the exocyclic methylene group (Tab. 2).

Furthermore the internal strain in the 1,8-ethano-bridged compounds can be seen in these spectra if taken in TFA. The N-1, N-8-bounded methylene groups absorb in 24, 26, 27 and 29 at much lowerfield than in the corresponding 1,8-propano-bridged derivatives 25, 28 and 30 respectively.

Tab. 2 - 100 MHz-NMR-Spectra of 1,8-Alkylene-bridged Lumazines
(δ values in ppm, TMS internal standard).

-lumazine	Substituent at			Alkylene Bridge			Solvent
	N-3	C-6	C-7				
1,8-Ethano-7-oxo-7,8-dihydro-(18)		7.65s(1)		4.2 m(4)			[D ₆]DMSO
1,8-Ethano-6-methyl-7-oxo-7,8-dihydro-(19)		2.27s(3)		4.2 m(4)			[D ₆]DMSO
1,8-Ethano-6-phenyl-7-oxo-7,8-dihydro-(20)		7.40m(3) 8.10m(2)		4.3 m(4)			[D ₆]DMSO
1,8-Ethano-(24)		9.2 d(1)	9.30d(1)	5.00t(2)	5.70t(2)		TFA
1,8-Propano-(25)		9.05d(1)	9.22d(1)	4.55t(2)	5.14t(2)	2.80m(2)	TFA
1,8-Ethano-6,7-dimethyl-(26)	10.70bs(1)	2.92s(3) 2.10s(3)	3.02s(3) 4.10d(1)	4.90t(2) 3.8 - 4.3 m(4)	5.44t(2)		TFA [D ₆]DMSO
1,8-Ethano-3,6,7-trimethyl-(27)	3.60s(3) 3.20s(3)	2.88s(3) 2.16s(3)	3.00s(3) 4.35d(1)	4.90t(2) 3.8 - 4.3 m(4)	5.40t(2)		TFA [D ₆]DMSO
1,8-Propano-6,7-dimethyl-(28)		2.96s(3) 2.14s(3)	3.09s(3) 4.26d(1)	4.46t(2) 3.38t(2)	4.92t(2) 3.84t(2)	2.80m(2) 2.10m(2)	TFA [D ₆]DMSO
1,8-Ethano-6,7-diphenyl-(29)	10.68bs(1)	7.20 - 7.80m(10) 7.20 - 7.90m(10)	8.0 s(1)	4.83t(2) 3.8 - 4.2 m(4)	5.30t(2)		TFA [D ₆]DMSO
1,8-Propano-6,7-diphenyl-(30)		7.30 - 7.90m(10) 7.15 - 7.90m(10)	8.05s(1)	4.54t(2) 3.2 - 3.8 m(4)	4.78t(2)	2.64m(2) 1.82m(2)	TFA [D ₆]DMSO

s = Singulett; bs = broad singulett; d = dublett; t = triplett; m = multipllett.

EXPERIMENTAL

UV-Spectra were taken with a Cary Recording Spectrometer, model 118, of Applied Physics. - ¹H-NMR-Spectra were measured with a Jeol JNM-MH-100. - Chromatographical studies were performed on thin layer sheets of Schleicher & Schüll, silica gel F 1500 LS 254 and cellulose F 1440 LS 254. - All substances were dried in a vacuum desiccator over P₄O₁₀ or in the oven at 100°C. - The melting points have not been corrected.

β -Hydroxyethylurea¹⁵. - 150 g (1.43 mole) nitrourea¹⁶ were added to a solution of 84 g (1.38 mole) ethanolamine in 200 ml ethanol with stirring. After 2 days reaction at room temp. the ethanol was removed in an evaporator, whereby the residue started to crystallize. The crude product was recrystallized from ethanol/dioxane yielding 121 g (85 %) colourless crystals of mp. 93°C. Lit.¹⁵ mp. 94-95°C.

6-Amino-1- β -hydroxyethyluracil (1)⁷. - 30 g Ethanolurea were added to a solution of 12.85 g natrium in 345 ml of ethanol and then 32.6 g ethyl cyanoacetate dropwise added followed by 10 h boiling under reflux with stirring. The reaction solution was then concentrated to half of its volume, diluted with 50 ml of water

and slightly acidified by glacial acetic acid. On cooling the precipitate was collected, yielding 33 g (67 %) colourless crystals of mp. 255°C. Lit.⁷ mp. 256°C.

6-Amino-1-β-hydroxyethyl-5-nitrosouracil (2). - A suspension of 66 g 1 in 1.5 l ethanol/water (1/1) was heated to boiling and then during 1 h 130 ml isoamylnitrite added dropwise. The starting material dissolved before the separation of violet crystals started. The reaction mixture was cooled after 1.5 h, the precipitate collected, yielding after drying at 80°C 55 g (71 %) violet crystals of mp. > 200°C (decomp.).

5,6-Diamino-1-β-hydroxyethyluracil (3)⁷. - 7.0 g 2 were added gradually with stirring to 40 ml of conc. ammonia whereby an orange ammonium salt was formed. It was then diluted with 50 ml of water, heated to 70°C and then a solution of 15 g sodium dithionite in 45 ml water added effecting a colour change from red to yellow. The precipitate was collected after cooling, washed with little water, and dried to give 4.5 g (70 %) crystals of mp. 255°C. Lit.⁷ mp. 246°C.

1-β-Hydroxyethyl-lumazine (4). - 3.0 g 3 were dissolved in a mixture of 45 ml of water and 6 ml of acetic acid, then 5 ml of a 40 % aqueous solution of glyoxal added and 30 min. boiled under reflux. On cooling a precipitate separates out, which was collected and recrystallized from ethanol/water yielding 3.1 g (92 %) colourless needles of mp. 263°C.

$C_8H_8N_4O_3$ (208.2) Calc. C 46.15 H 3.90 N 26.92

Found C 45.79 H 3.90 N 27.45.

6,7-Dimethyl-1-β-hydroxyethyl-lumazine (5). - 1.0 g 3 and 0.6 ml of diacetyl were boiled under reflux in 15 ml of water and 2 ml of glacial acetic acid for 20 min. A yellowish precipitate was formed, which was collected after cooling and yielded on recrystallization from 30 ml of water 0.9 g (71 %) yellowish needles of mp. 284-286°C (decomp.).

$C_{10}H_{12}N_4O_3$ (236.2) Calc. C 50.85 H 5.12 N 23.72

Found C 50.71 H 5.10 N 23.79.

1-β-Hydroxyethyl-6,7-diphenylumazine (6). - 8.0 g 3 were heated in 100 ml of water and 16 ml of glacial acetic acid with stirring to 80°C and then a solution of 10 g benzil in 100 ml of ethanol dropwise added. It was then boiled for 1 h under reflux forming a yellow precipitate. After cooling the crystals have been collected and treated at room temp. with 60 ml of acetone, filtered, and the re-

sidue recrystallized from ethanol/charcoal to yield 14.0 g (91 %) colourless crystals of mp. 239°C.

$C_{20}H_{16}N_4O_3$ (360.4) Calc. C 66.66 H 4.47 N 15.55
Found C 66.61 H 4.63 N 15.43.

1-β-Mesyloxyethyl-6,7-dimethylumazine (8). - 0.5 g 5 were dissolved in 20 ml of pyridine and then the solution cooled in ice water to about 2°C before dropwise slow addition of 1.8 ml of mesylchloride with stirring. The reaction mixture was poured after 1 h reaction at 2-4°C into 20 ml of ice water, yielding a colourless precipitate. The crystals were collected by suction, washed with water and dried in a vacuum desiccator over P_4O_{10} yielding 0.6 g (90 %) colourless crystals which start to decompose gradually at 150°C.

$C_{11}H_{14}N_4O_5S$ (314.3) Calc. C 42.03 H 4.49 N 17.82
Found C 42.23 H 4.44 N 17.94.

1-β-Mesyloxyethyl-6,7-diphenylumazine (9). - 1.0 g 6 was treated in 20 ml of pyridine with 3.5 ml of mesylchloride analogously to the preceding procedure to yield 1.2 g (90 %) colourless crystals of mp. 181-184°C (decomp.).

$C_{21}H_{18}N_4O_5S$ (438.5) Calc. C 57.52 H 4.14 N 12.78
Found C 57.55 H 4.27 N 12.52.

6-β-Hydroxyethylamino-5-nitrouracil (12)⁸. - 1.91 g (0.01 mole) 6-Chloro-5-nitrouracil (10)⁸ were suspended in 20 ml of ethanol and then 1.5 ml of aminoethanol added. The mixture was refluxed for 5 min. and the precipitate collected after cooling. The substance was dissolved in boiling water by addition of ammonia and reprecipitated when hot by acidification with dilute HCl. After cooling the precipitate was filtered and dried, yielding 1.73 g (80 %) of colourless crystals with mp. 270°C (decomp.).

$C_6H_8N_4O_5$ (216.2) Calc. C 33.33 H 3.73 N 25.92
Found C 33.44 H 3.86 N 25.57.

6-β-Hydroxyethylamino-3-methyl-5-nitrouracil (13). - 2.05 g (0.01 mole) 6-Chloro-3-methyl-5-nitrouracil (11)⁹ were refluxed in 20 ml of ethanol with 1.8 ml of aminoethanol in a water bath. The precipitate was collected after cooling, dissolved in hot water by addition of a small amount of ammonia, and then reprecipitated with 1N HCl to yield 2.0 g colourless crystals. Further recrystallization from 50 ml of water gave 1.6 g (70 %) colourless needles of mp. 213-215°C.

$C_7H_{10}N_4O_5$ (230.2) Calc. C 36.52 H 4.38 N 24.34
 Found C 36.44 H 4.28 N 24.12.

6-~~P~~-Hydroxyethylamino-5-nitouracil (14). - 9.55 g (0.05 mole) 6-Chloro-5-nitouracil (10)⁸ were added to a solution of 15 ml of 3-aminopropanol in 75 ml of water and then refluxed for 5 min. The hot solution was acidified with 5N HCl to pH 1 yielding colourless crystals on cooling. The precipitate was collected and recrystallized from 100 parts of water yielding 8.6 g (75 %) colourless needles of mp. 260°C (decomp.), on further heating the material solidified again and showed a second mp. at 320°C.

$C_7H_{10}N_4O_5$ (230.2) Calc. C 36.52 H 4.38 N 24.34
 Found C 36.70 H 4.43 N 24.59.

8-~~B~~-Hydroxyethyl-7-oxo-7,8-dihydrolumazine (15)¹⁰. - 5.0 g of 12 were reduced catalytically with Pd/C and H_2 in 300 ml of water at normal pressure in a shaking apparatus. The reduction of the nitro group was complete after 12 h. The catalyst is removed by suction, the filtrate acidified to pH 6, and then 8 ml of ethyl glyoxylate-hemiacetal added, whereby a yellow precipitate separated. After filtration the precipitate was boiled in 100 ml of 1N sodiumbicarbonate for 30 min. under reflux and then acidified with 5N HCl. On cooling 4.0 g (77 %) colourless crystals of mp. 325°C were obtained. Lit.¹⁰ mp. 326°C.

8-~~B~~-Hydroxyethyl-6-methyl-7-oxo-7,8-dihydrolumazine (16)¹¹. - 2.0 g of 12 were reduced catalytically analogous to the preceding procedure to the corresponding 5-amino compound, which was condensed with 4 ml of methylpyruvate. After 30 min. of reflux the precipitate was collected after cooling and yielded on recrystallization from 1N HCl with charcoal 1.1 g (50 %) slightly yellowish crystals of mp. > 330°C (decomp.).

8-~~B~~-Hydroxyethyl-7-oxo-6-phenyl-7,8-dihydrolumazine (17). - 2.0 g of 12 were reduced catalytically with Pd/C and H_2 analogously to the procedure 15 and then the 5-amino compound condensed with 3.5 g of phenylglyoxylic acid by 30 min. refluxing. The reaction solution is then acidified to pH 0, the precipitate collected after cooling and purified by recrystallization from DMF/water to yield 2.0 g (74 %) of yellow crystals with mp. > 320°C.

$C_{14}H_{12}N_4O_4 \times H_2O$ (318.3) Calc. C 52.83 H 4.43 N 17.60
 Found C 52.83 H 4.52 N 17.30.

1,8-Ethano-7-oxo-7,8-dihydrolumazine (18). - 0.5 g 15 were boiled under reflux in 10 ml of dimethylformamide for 10 h and then evaporated to dryness. The residue gave on recrystallization from ethanol 0.4 g (87 %) colourless crystals of mp. $> 335^{\circ}\text{C}$ (decomp.).

$\text{C}_8\text{H}_6\text{N}_4\text{O}_3 \times \text{H}_2\text{O}$ (224.2) Calc. C 42.86 H 3.60 N 24.90

Found C 43.15 H 3.40 N 24.84.

1,8-Ethano-6-methyl-7-oxo-7,8-dihydrolumazine (19). - 0.3 g 16 were refluxed in 20 ml DMF for 10 h and then the mixture evaporated to dryness. The residue yielded on recrystallization from ethanol 0.12 g (51 %) colourless crystals of mp. $> 345^{\circ}\text{C}$ (decomp.).

$\text{C}_9\text{H}_8\text{N}_4\text{O}_3$ (220.2) Calc. C 49.09 H 3.66 N 25.45

Found C 49.07 H 3.72 N 25.53.

1,8-Ethano-7-oxo-6-phenyl-7,8-dihydrolumazine (20). - 0.5 g 17 were boiled in 20 ml of DMF for 10 h under reflux. After evaporation the precipitate was recrystallized from DMF/water to yield 0.33 g (75 %) yellowish needles of mp. $> 350^{\circ}\text{C}$.

$\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}_3$ (282.3) Calc. C 59.57 H 3.57 N 19.85

Found C 59.41 H 3.54 N 19.76.

8-Nitro-5,7-dioxo-2,3,4,5,6,7-hexahydroimidazo[1,2-c]-pyrimidine (21). - 3.2 g 12 were boiled in 50 ml of dimethylformamide for 5 h. The solution was diluted by 50 ml of ethanol during cooling, whereby a colourless precipitate (2.5 g) separated. Recrystallization from water with charcoal yielded 2.1 g (72 %) colourless needles of mp. 345°C (decomp.).

$\text{C}_6\text{H}_6\text{N}_4\text{O}_4$ (198.1) Calc. C 36.37 H 3.05 N 28.28

Found C 36.62 H 3.37 N 28.43.

6-Methyl-8-nitro-5,7-dioxo-2,3,4,5,6,7-hexahydroimidazo[1,2-c]-pyrimidine (22). - 1.0 g of 13 was boiled under reflux in 10 ml of DMF for 2 h. The reaction mixture was evaporated to dryness and the residue recrystallized from water with charcoal to yield 0.75 g (81 %) colourless crystals of mp. 290°C .

$\text{C}_7\text{H}_8\text{N}_4\text{O}_4$ (212.2) Calc. C 39.62 H 3.80 N 26.41

Found C 39.56 H 4.07 N 26.20.

9-Nitro-6,8-dioxo-1,2,3,4,5,6,7,8-octahydropyrimido[1.2-c]-pyrimidine (23). -

2.0 g of 14 were boiled under reflux in 20 ml of DMF for 5 h. On cooling colourless crystals separated (1.3 g) which yielded on recrystallization from water 1.1 g (60 %) colourless needles of mp. 324°C (decomp.).

$C_7H_8N_4O_4$ (212.2) Calc. C 39.62 H 3.80 N 26.41
Found C 39.92 H 3.81 N 26.37.

1,8-Ethano-lumazinium-chloride (24). - 1.5 g 21 were suspended in 100 ml of water and then reduced catalytically with PtO_2/H_2 with shaking in a hydrogenation apparatus. The reaction was finished after 10 h at room temp.. The solution was acidified with 3 ml of conc. HCl, the catalyst filtered off, and the filtrate was then added dropwise with strong stirring to 40 ml of 40 % aqueous glyoxal. After 1 h stirring at room temp. the reaction mixture was evaporated and the residue made anhydrous by coevaporation with ethanol/benzene mixture. The reaction mixture was then boiled under reflux in 250 ml of methanolic HCl for 1 h and then the solid collected from the hot solution by suction. This product was recrystallized from methanolic HCl, washed with methanol and ether and dried at 80°C to yield 0.9 g (53 %) crystalline powder of mp. > 300°C (decomp.).

$C_8H_7N_4O_2 \cdot Cl \times H_2O$ (244.6) Calc. C 39.19 H 3.71 N 22.67
Found C 39.32 H 3.60 N 22.90.

1,8-Propano-lumazinium-chloride (25). - 5.0 g of 23 were dissolved in 100 ml of formic acid, heated to boiling and then gradually added 8 g zinc powder. The reaction mixture was refluxed for 10 min., filtered from insoluble material and the filtrate concentrated to dryness. The residue was boiled in 60 ml of saturated methanolic HCl for 60 min., whereby a precipitate separated. The crystal powder consisting of 9-amino-6,8-dioxo-1,2,3,4,5,6,7,8-octahydropyrimido[1.2-c]-pyrimidine-hydrochloride (2.7 g) was collected after cooling, washed with methanol and dried in a vacuum desiccator over P_4O_{10} .

$C_7H_{10}N_4O_2 \times HCl$ (218.6) Calc. C 38.46 H 5.07 N 25.63
Found C 38.39 H 5.14 N 25.61.

1.1 g of the hydrochloride were dissolved in 10 ml of water, combined with a solution of 0.5 g trimeric glyoxalhydrate in 10 ml of water and then refluxed

for 30 min.. The dark red solution was treated with charcoal, filtered and then evaporated to dryness. Treatment of the residue with saturated methanolic HCl yielded 0.54 g (42 %) yellowish crystals of mp. $>330^{\circ}\text{C}$.

$\text{C}_9\text{H}_9\text{N}_4\text{O}_2\text{]Cl} \times \text{H}_2\text{O}$ (258.7) Calc. C 41.79 H 4.29 N 21.66

Found C 41.63 H 4.21 N 21.61.

1,8-Ethano-6-methyl-7-methylene-7,8-dihydrolumazine (26). - a) 1.0 g 21 was reduced catalytically over PtO_2 in 150 ml of water in a hydrogenation apparatus with shaking. The catalyst was filtered off, the filtrate acidified with 4 ml of glacial acetic acid and then 1 ml of diacetyl added. The reaction solution was heated to 80°C and then cooled in an ice box. The separated crystals were collected and dried at 100°C to yield 0.6 g (55 %) yellowish needles of mp. 286°C (decomp.).

$\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}_2$ (218.2) Calc. C 55.04 H 4.62 N 25.68

Found C 55.23 H 4.56 N 25.55.

b) 2.5 g 8 were suspended in 100 ml of pyridine and then heated slowly within 20 min. to boiling. After refluxing for 10 min. a slightly brownish precipitate separated on cooling and yielded after recrystallization from ethanol/water 1.0 g (63 %) yellowish crystals of mp. 287°C . The material was chromatographically and spectrophotometrically identical with the substance a).

1,8-Ethano-3,6-dimethyl-7-methylene-7,8-dihydrolumazine (27). - 2.1 g (0.01 mole) of 22 were reduced catalytically over Pd/C with H_2 in a shaking hydrogenation apparatus. After reduction over night the catalyst was filtered off and the filtrate treated with 3 ml of diacetyl and boiling under reflux for 10 min.. The reaction mixture was concentrated to a smaller volume, the formed precipitate collected and then purified by recrystallization from water to yield 0.8 g (34 %) yellowish crystals of mp. 284°C (decomp.).

$\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_2$ (232.2) Calc. C 56.89 H 5.21 N 24.13

Found C 56.99 H 5.27 N 24.41.

1,8-Propano-6-methyl-7-methylene-7,8-dihydrolumazine (28). - 0.55 g 9-Amino-6,8-dioxo-1,2,3,4,5,6,7,8-octahydropyrimido[1.2-c]-pyrimidine-hydrochloride described in procedure 25 were dissolved in 5 ml of water and then 0.5 ml of diacetyl added, whereby a precipitate was formed. On boiling for 10 min. a clear

solution was obtained, which was neutralized to pH 5 with dilute ammonia before cooling. The separated precipitate (0.46 g) was collected and purified by recrystallization from water to yield 0.18 g (31 %) yellowish needles of mp. 281-283°C (decomp.).

$C_{11}H_{12}N_4O_2$ (232.2) Calc. C 56.89 H 5.21 N 24.13
Found C 56.70 H 5.18 N 23.89.

1,8-Ethano-7-hydroxy-6,7-diphenyl-7,8-dihydrolumazine (29). - a) 1.0 g 21 was reduced catalytically over PtO_2/H_2 in a hydrogenation apparatus and after filtration of the catalyst 1.2 g benzil in 30 ml of ethanol added. The mixture was boiled under reflux for 90 min., the precipitate collected and purified by recrystallization from ethanol/water to yield 1.1 g (61 %) yellowish crystals of mp. 236°C (decomp.).

$C_{20}H_{16}N_4O_3$ (360.36) Calc. C 66.70 H 4.48 N 15.55
Found C 66.82 H 4.42 N 15.60.

b) 1.0 g 2 was boiled under reflux in 35 ml of toluene for 14 h. After cooling the precipitate was collected and purified by repeated recrystallization from ethanol/water to yield 0.5 g (72 %) yellowish crystals of mp. 236°C (decomp.).

1,8-Propano-7-hydroxy-6,7-diphenyl-7,8-dihydrolumazine (30). - 1.09 g (5 mmole) of 9-Amino-6,8-dioxo-1,2,3,4,5,6,7,8-octahydropyrimido[1.2-c]-pyrimidine-hydrochloride described under procedure 25 were dissolved in 20 ml of ethanol/water (1/1) and after addition of 1.5 g benzil the mixture boiled under reflux for 1 h. The mixture will then be neutralized with dilute ammonia to pH 5, the precipitate filtered off and purified by recrystallization from water/ethanol to yield 1.2 g (65 %) yellowish crystals of mp. 217-219°C (decomp.).

$C_{21}H_{18}N_4O_3$ (374.4) Calc. C 67.36 H 4.85 N 14.97
Found C 66.80 H 4.82 N 14.63.

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