PYRIMIDINES, XXXII[1]: SYNTHESIS AND PROPERTIES OF PYRIDO-[2,3-d]PYRIMIDINE-2,4-DIONES (5-DEAZALUMAZINES)

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Dedicated to Prof. Dr. Masamoto Hamana on the occasion of his 75th birthday.

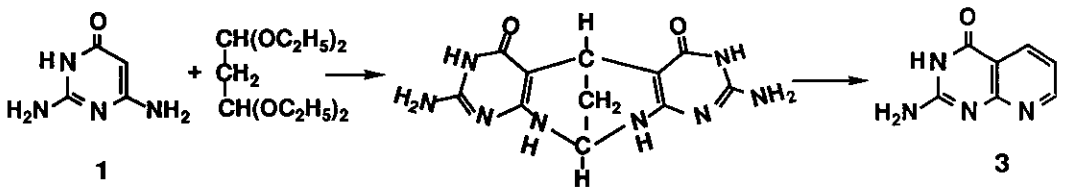
Abstract - Pyrido[2,3-d]pyrimidine-2,4-dione (8) and its N-methyl derivatives (9-11) as well as the corresponding 6-nitro analogues (12-15) have been synthesized by condensation reactions from 6-aminouracils (4-7). Reduction of compounds (4-7) led to the 6-aminopyrido[2,3-d]pyrimidine-2,4-diones (18-21). Diazotization of the amino group afforded two crystalline diazonium salts (26,27), the Sandmeyer reaction gave 6-halo compounds (28-31) and coupling reactions with secondary amines led to a series of 6-triazenopyrido[2,3-d]pyrimidine-2,4-diones (32-39). Treatment of the 6-nitropyrido[2,3-d]pyrimidine-2,4-diones (12-14) with sodium borohydride resulted in a reduction of the pyrido moiety to form the 5,6,7,8-tetrahydro derivatives (40-42).

INTRODUCTION

The pyrido[2,3-d]pyrimidine system[2,3] has attracted some attention due to its structural relationship to the naturally occurring pteridines.[4] The synthetic approach to this class of compounds (5-deazapteridines) can either be achieved from appropriate pyridine precursors[5-8] by annelation of the pyrimidine ring or by the reverse sequence of reactions attaching the pyridine moiety to a properly substituted pyrimidine derivative.[8] We have especially been interested in a systematic study of the pyrido[2,3-d]-pyrimidine-2,4-diones as structural analogues of the lumazines, which have been subject to intensive investigations in our laboratory.[9-22] Condensation reactions of 5-acyl- and 5-ethoxycarbonyl-6-aminopyrimidines, respectively, have been achieved with a great variety of ketones, esters, and nitriles,[23] whereas 6-aminopyrimidines reacted only in the expected manner if the 5-position is activated for electrophilic substitutions by the presence of additional electron-donating groups like OH, NH_2, SH at the C-2- and C-4-ring atoms. This type of pyrimidines condense effectively with 1,3-dicarbonyl compounds and 3-aminoacrolein derivatives. Furthermore cyclization reactions of 6-aminopyrimidines with enamines[24] and ring-transformations[25,26] are additional approaches to form pyrido[2,3-d]pyrimidines.

SYNTHESES

We based our syntheses of the various types of pyrido[2,3-d]pyrimidine derivatives on condensation reactions of 6-aminopyrimidines with appropriately functionalized C_3 building blocks. The approach of Price et al.[27] condensing 2,6-diaminopyrimidin-4-one with malonaldehyde ethylacetal leads in the first step to an intermediate which owes a much more complex structure (2) according to the nmr spectrum than the formerly proposed Schiff base assignment.[27] Heating of 2 in conc. H_2SO_4 to 160°C or prolonged reflux



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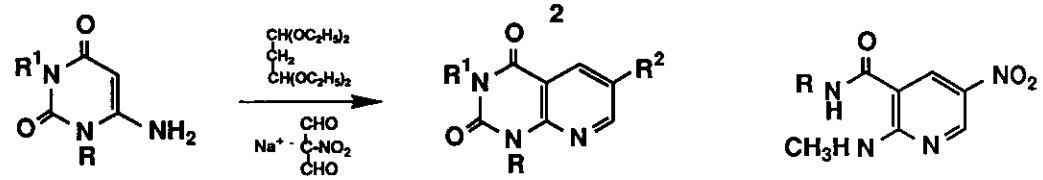
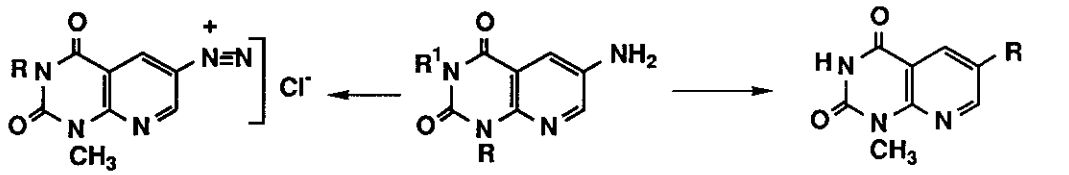


	R	R^1
4	H	H
5	CH_3	H
6	H	CH_3
7	CH_3	CH_3

	R	R^1	R^2
8	H	H	H
9	CH_3	H	H
10	H	CH_3	H
11	CH_3	CH_3	H

	R	R^1	R^2
12	H	H	NO_2
13	CH_3	H	NO_2
14	H	CH_3	NO_2
15	CH_3	CH_3	NO_2

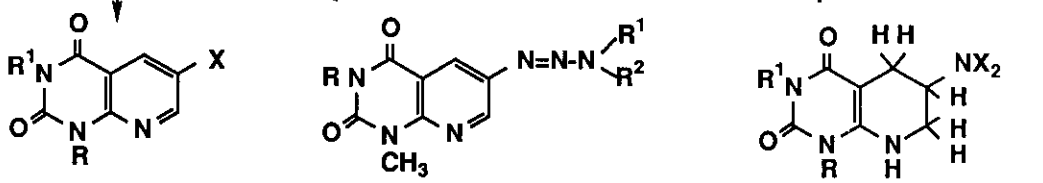
	R
16	H
17	CH_3



	R
26	H
27	CH_3

	R	R^1
18	H	H
19	CH_3	H
20	H	CH_3
21	CH_3	CH_3

	R
22	$N=CHC_6H_5$
23	$NHCH_2C_6H_5$
24	$N=CH-N(CH_3)_2$
25	NHCHO



	R	R^1	X
28	CH_3	H	Cl
29	H	H	Br
30	CH_3	H	Br
31	H	CH_3	Br

	R	R^1	R^2
32	H	C_2H_5	C_2H_5
33	H	$CH_2CH_2CH_2CH_2$	
34	H	$CH_2CH_2OCH_2CH_2$	
35	CH_3	$CH_2CH_2OCH_2CH_2$	
36	H	CH_3	CH_2COOH
37	H	CH_3	$CH_2CH_2C_6H_5$
38	H	C_2H_5	$CH_2C_6H_5$
39	H	CH_3	$CH-CH-C_6H_5$ (CH3, OH)

	R	R^1	X
40	H	H	O
41	CH_3	H	O
42	H	CH_3	O
43	CH_3	H	H

in glacial acetic acid formed in high yield the 2-aminopyrido[2,3-d]pyrimidin-4-one (3). 6-Aminouracil (4) and its 1-methyl- (5), 3-methyl- (6), and 1,3-dimethyl derivatives (7) show the same reaction behaviour and could be converted with 1,1,3,3-tetraethoxypropane via the condensed tetracyclic intermediates, which have however not been purified and characterized, in a similar manner into the corresponding pyrido[2,3-d]pyrimidine-2,4-diones (8-11). Compound (8),[7,28] (10),[29] and (11)[28,30] have been synthesized before, following entirely different approaches.

The 6-aminouracils (4-7) have also been condensed with sodium nitromalonodialdehyde according to the method of Lee et al.[31] to give the corresponding 6-nitropyrido[2,3-d]pyrimidine-2,4-diones (12-14). This reaction is base catalized and works best in 1 % NaOH under reflux temperature. 12 and 14 are formed without side products, whereas 13 showed some alkali sensitivity leading under nucleophilic attack of OH^- at the C-2 position to partial ring opening and formation of 2-methylamino-5-nitropyridine-3-carboxamide (16). Reaction at 80°C avoided ring-opening and 13 was obtained in 61 % yield. 1,3-Dimethyl-5-nitropyrido[2,3-d]pyrimidine-2,4-dione (15), on the other hand, was not available from 6-amino-1,3-dimethyluracil (7) in a similar manner due to its even higher alkali lability forming always 2-methylamino-5-nitropyridin-3-N-methylcarboxamide (17) as a breakdown product of 15. Mild methylation of 13 with dimethyl sulfate/alkali at room temperature led, however, in 68 % yield to the desired compound (15).

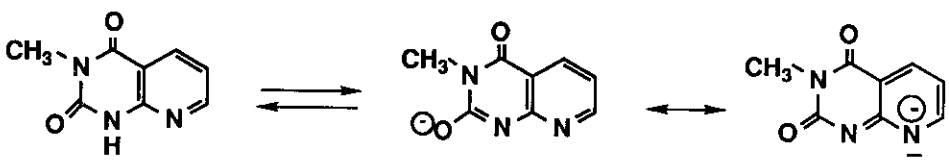
The 6-nitropyrido[2,3-d]pyrimidine-2,4-diones (12-15) have then also been reduced catalytically with Pd/C and hydrogen to the corresponding 6-amino derivatives (18-21) in good yields. The reactivity of the 6-amino groups was studied in different ways to show its synthetic potential. Reaction of 19 with benzaldehyde gave the Schiff's base (22), which could be converted into 6-benzylamino-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (23) by sodium borohydride reduction. In a similar manner 19 reacted with dimethyl-

formamidedimethylacetal to the corresponding dimethylaminomethylenimino derivative (24), which hydrolysed in dilute acid to 6-formylamino-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (25). Diazotization with isoamyl nitrite in ethanol/HCl led in the case of 13 and 15, respectively, to the formation and isolation of crystalline diazonium chloride salts (26,27). Analogous diazotizations in aqueous medium under Sandmeyer conditions afforded the 6-chloro- and 6-bromopyrido[2,3-d]pyrimidine-2,4-diones (28-31) in good yields. Finally the solid diazonium salts (26) and (27), respectively, were coupled with a series of secondary amines such as diethylamine, pyrrolidine, morpholine, sarcosine, (-)-ephedrine, N-methylphenethylamine, and N-ethylbenzylamine to afford the corresponding 6-triazeno derivatives (32-39).
A somewhat unexpected result was observed on reduction of the 6-nitropyrido[2,3-d]pyrimidine-2,4-diones (12-14) with sodium borohydride in aqueous ammonia leading to the 5,6,7,8-tetrahydro derivatives (40-42). The fact that the pyridine ring is reduced without altering the substituents is documented already in literature.[32-34] 5,6,7,8-Tetrahydro-1-methyl-6-nitropyrido[2,3-d]pyrimidine-2,4-dione (41) was furthermore subject to catalytic hydrogenation with Adams catalyst, which has to be reduced first to Pt before adding the educt, otherwise only partial conversion to the amino derivative (43) takes place.

PHYSICAL PROPERTIES

The newly synthesized compounds have been characterized by elemental analysis, uv and ^{1}H-nmr spectra and the determination of their pK_a values (Tables 1 and 2). Pyrido[2,3-d]pyrimidine-2,4-dione (8) and its methyl derivatives (9-11) are relatively weak bases with a basic pK_a around 0. Cation formation should take place at the N-8 position and causes a weak bathochromic shift of the long wavelength absorption band. The first acidic pK_a of 8 was found at 9.15, but this value represents an equilibrium

pK_a of the two possible anion species due to the fact that the 1- (9) and 3-methyl derivative (10), respectively, have almost identical acidities. We encounter here the same situation like in uracil[35] and lumazine,[9] where ionization of N_1-H and N_3-H also takes place simultaneously affording a 1:1 mixture of the monoanions. This behaviour is also reflected in the uv spectra of the monoanion species of 8, 9, and 10, since 1-methylpyrido-[2,3-d]pyrimidine-2,4-dione (9) reveals only a small bathochromic shift of 5 nm, whereas the 3-methyl isomer (10) is shifted on anion formation by 31 nm as expected from its much better resonance stabilization.



The monoanion spectrum of pyrido[2,3-d]pyrimidine-2,4-dione (8) is a composite of the two related anion species expressed by the two long wavelength absorption bands at 311 and 342 nm. Similar considerations are valid for the 6-nitropyrido[2,3-d]pyrimidine-2,4-dione series, which shows expectedly a higher acidity induced by the nitro group, which again influences the ionization of N_1-H more strongly and favouring the corresponding monoanion to a larger extent in the equilibrium mixture.

The 6-aminopyrido[2,3-d]pyrimidine-2,4-diones (18-21) absorb as neutral species at 352-356 nm due to the electron-donating effect of the amino group. Cation formation causes a strong hypsochromic shift to the region of 310-315 nm and revealing spectra which are almost superimposable with the neutral forms of 8-11. This similarity indicates that the protonation site is located at the exocyclic amino groups and not at the ring nitrogen as commonly observed with structurally related nitrogen heterocycles, in general,

Table 1. Physical Data of Pyrido[2,3-d]pyrimidine-2,4-diones

*pyrido[2,3-d]pyrimidine-2,4-dione	pK_a in H_2O	uv - Absorption Spectra λ_{max} (nm)					uv - Absorption Spectra log ε					pH	Molecular Form
Pyrido[2,3-d]pyrimidine-2,4-dione (8)	0.00 9.15 13.35	205 211 212	234 240 [236] 235	264 262	310 305 311	342 338	4.33 4.50 4.39	3.85 3.78 [3.93] 4.21	3.90 3.84	4.02 3.77 3.69	3.35 3.73	-3.0 7.0 11.0 2N KOH	+ o - --
1-Methyl-* (9)	-0.25 9.56	206 213 214	246 249 236	[266]	315 309 314		4.28 4.53 4.40	3.83 3.91 4.20	[3.42]	4.01 3.83 3.89		-3.0 7.0 12.0	+ o -
3-Methyl-* (10)	0.03 9.50	206 212 216	237 [241] [235]	265	311 305	336	4.26 4.24 4.43	3.98 [3.82] [4.05]	4.11	4.01 3.84	3.75	-3.0 7.0 12.0	+ o -
1,3-Dimethyl-* (11)	-0.57	209 215	242 [230]		316 309		4.25 4.21	4.04 [4.00]		4.01 3.83		-3.0 7.0	+ o
6-Nitro-* (12)	7.43 12.21	204 211		[290] [330]	311	354	4.39 4.31		[4.04]	4.15 [4.12]	4.19	5.0 10.0	o -
			235	270		383		4.12	3.81		4.24	14.0	--
1-Methyl-6-nitro-* (13)	8.27	208 207	[230]	[296] 265	315 332		4.40 4.34	[4.09]	[4.06] 3.99	4.23 4.15		3.0 12.0	o -
3-Methyl-6-nitro-* (14)	7.64	208 212	[224]	[290] [256]	313	362	4.36 4.35	[4.16]	[4.00] [3.66]	4.14	4.24	3.0 12.0	o -
1,3-Dimethyl-6-nitro-* (15)		[209]	[229]		315		[4.37]	[4.11]		4.17		MeOH	o
6-Amino-* (18)	2.09 9.41 13.56	211 216 224	242	260 265	309	354 357	4.53 4.36 4.31	3.94	4.09 3.97	3.77	3.66 3.68	-1.0 7.0 12.0	+ o -
			235	269		370		4.25	4.02		3.72	2N KOH	--

Continuation see next page!

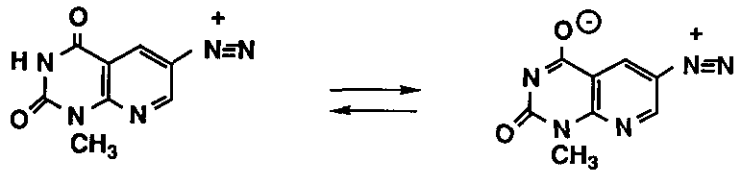
Table 1. Continuation -

*pyrido[2,3-d]pyrimidine-2,4-dione	pK_a in H_2O	uv - Absorption Spectra λ_{max} (nm)	uv - Absorption Spectra log ε	pH	Molecular Form
6-Amino-1-methyl-* (19)	2.02 9.71	212 250 314 216 261 356 231 352	4.51 4.02 3.77 4.42 4.17 3.71 4.39 3.79	-1.0 7.0 12.0	+ o -
6-Amino-3-methyl-* (20)	2.10 10.00	211 [230] [245] 310 223 258 352 224 273 373	4.48 [4.03] [3.87] 3.76 4.37 4.02 3.66 4.33 4.20 3.69	-1.0 7.0 12.0	+ o -
6-Amino-1,3-dimethyl-* (21)	2.04	215 235 [249] 315 223 263 356	4.48 4.06 [3.95] 3.76 4.38 4.09 3.68	-1.0 7.0	+ o
6-Benzylamino-1-methyl-* (23)	1.29 9.71	213 252 316 208 [218] 271 375 242 [268] 365	4.55 4.13 3.75 4.38 [4.37] 4.27 3.59 4.42 [4.16] 3.70	-1.0 7.0 13.0	+ o -
6-Dimethylaminomethylenamino-1-methyl-* (24)		206 [234] 283 352	4.39 [4.11] 4.43 3.73	MeOH	o
6-Formylamino-1-methyl-* (25)		[206] 216 266 334	[4.28] 4.35 4.34 3.72	MeOH	o
1-Methyl-*-6-diazonium chloride (26)	6.98	232 333 248 [312] 350	4.06 4.33 4.06 [3.92] 4.11	3.0 9.0	+ ±
1,3-Dimethyl-*-6-diazonium chloride (27)		232 333	4.10 4.31	3.0	+

[ ] = shoulder; + = cation; o = neutral molecule; - = monoanion; -- = dianion.

and 3-aminopyridine and 3-aminoquinoline, in special. This rare case of amino group protonation may be due to the fact that the pyridine ring-N-atom possesses in the pyrido[2,3-d]pyrimidine-2,4-dione system an unusual low basicity.

The 1-methylpyrido[2,3-d]pyrmidine-2,4-dione-6-diazonium chloride (26) again is an interesting compound, since its diazonium function reveals an even stronger acidifying effect than the nitro group bringing the acidic pK_a down to 6.98. Deprotonation leads in this case the zwitterion formation (26a) and a bathochromicity of the long wavelength band.



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The ^{1}H-nmr spectra are relatively simple and show no peculiarities (Table 2). The signals of the aromatic protons in compounds (8-11) appear as doublets of doublets indicating longrange couplings between H-C(5) and H-C(7). The coupling constants are found for $J_{5,6}$ = 7-8 Hz, $J_{6,7}$ = 4.5 Hz, and $J_{5,7}$ = 2 Hz. The additional nitro group in 12-15 causes the expected down-field shifts of the aromatic protons, which is even more pronounced in the diazonium salts (26) and (27), respectively. The electron-donating amino group in 18-21 effects an up-field shift in comparison to the unsubstituted analogues and the presence of a halo-atom in 6-position does not alter the chemical shifts of the aromatic protons significantly. It is also noteworthy that the 1-methyl group has always a lower chemical shift than the 3-methyl group.

Table 2. ^{1}H-Nmr Data of Pyrido[2,3-d]pyrimidine-2,4-dione in DMSO-d_6

*pyrido[2,3-d]pyrimidine-2,4-dione		N-H	H-C(7)	H-C(5)	H-C(6)	N-CH_3		6-Subst
Pyrido[2,3-d]pyrimidine-2,4-dione	(8)	11.53bs 11.38bs	8.59dd	8.25dd	7.24dd			
1-Methyl-*	(9)	11.69bs	8.69dd	8.31dd	7.29dd	3.47s		
3-Methyl-*	(10)	11.93bs	8.60dd	8.29dd	7.26dd		3.24s	
1,3-Dimethyl-*	(11)		8.70dd	8.31dd	7.31dd	3.54s	3.28s	
6-Nitro-*	(12)	12.44bs 11.86bs	9.39d	8.76d				
1-Methyl-6-nitro-*	(13)	12.12bs	9.48d	8.81d		3.55s		
3-Methyl-6-nitro-*	(14)	12.73bs	9.41d	8.80d			3.26s	
1,3-Dimethyl-6-nitro-*	(15)		9.50d	8.87d		3.62s	3.32s	
6-Amino-*	(18)	11.40bs	8.08d	7.46d				
6-Amino-1-methyl-*	(19)	11.40bs	8.12d	7.51d		3.42s		5.43bs
6-Amino-3-methyl-*	(20)	11.40bs	8.04d	7.47d			3.21s	5.36bs
6-Amino-1,3-dimethyl-*	(21)		8.10d	7.53d		3.55s	3.26s	5.44bs
1-Methyl-*-6-diazonium chloride	(26)	12.45bs	9.82d	9.44d		3.54s		
1,3-Dimethyl-*-6-diazonium chloride	(27)		9.80d	9.49d		3.63s	3.32s	
6-Chloro-1-methyl-*	(28)	11.88bs	8.75d	8.30d		3.46s		
6-Bromo-*	(29)	11.83bs 11.58bs	8.70d	8.33d				
6-Bromo-1-methyl-*	(30)	11.83bs	8.80d	8.36d		3.44s		
6-Bromo-3-methyl-*	(31)	12.11bs	8.72d	8.36d			3.22s	

ACKNOWLEDGEMENT

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EXPERIMENTAL

Tlc: Precoated cellulose thin-layer sheets F 1440 and silica gel thin-layer sheets F 1500 LS 254 from Schleicher & Schüll. Prep. tlc on silica gel 60 PF_{254} (Merck) and preparative column chromatography on silica gel (Merck 60, 0.063-0.2 mesh). UV/VIS: Uvikon 820, Kontron and Lambda 5 and 15, Perkin Elmer: λ_{max} nm (log ε). ^{1}H-Nmr: Bruker WM 250; δ (ppm) relative to TMS. pK: determinations were performed by the spectrophotometric method.[36] Mp: Büchi apparatus, model Dr. Tottoli; no corrections.

2-Aminopyrido[2,3-d]pyrimidin-4-one (3).[27] - In 280 ml of hot H_2O 6.7 g (53 mmol) of 2,4-diamino-4-pyrimidone (1) were dissolved, 6 ml of AcOH and 4.6 g (21 mmol) of 1,1,3,3-tetraethoxypropane were added and the mixture refluxed for 3.5 h. After cooling the precipitate was collected, washed with H_2O and EtOH and dried at 100°C in the oven to give 7.4 g (97 %) of an almost colorless chromatographically pure powder of 2, mp > 300°C. ^{1}H-Nmr (DMSO-d_6): 9.72 (br s, 2H, NH); 5.92 (br s, 4H, NH_2); 4.73 (br s, 1H, CH); 4.01 (br s, 1H, CH); 1.66 (br s, 2H, CH_2).

a) 1.8 g (6.25 mmol) of 2 were heated in 18 ml of conc. H_2SO_4 at 160°C for 2 h. After cooling the solution was poured on ice, diluted with H_2O to 250 ml and then treated with solid $NaHCO_3$ till pH 3. The resulting precipitate was filtered and discarded. The filtrate was then neutralized by solid $NaHCO_3$ to pH 6-7, the new precipitate was collected, washed with H_2O and dried at 100°C to yield 0.62 g (61 %) of 3 as a colorless powder, mp > 300°C.

b) 3.0 g (100 mmol) of 2 were refluxed in 90 ml of AcOH for 8 h. The resulting precipitate was collected after cooling and standing overnight. Washing with H_2O and EtOH and drying at 100°C gave 1.53 g (91 %) of 3 as a colorless powder, mp > 300°C. Both materials a) and b) are chromatographically identical. Uv (pH 13): 217 (4.28); 239 (4.28); 265 (3.88); 330

(3.81). ^{1}H-Nmr (DMSO-d_6): 8.62 (dd, 1H, H-C(7)); 8.21 (dd, 1H, H-C(5)); 7.12 (dd, 1H, H-C(6)); 6.75 (br s, 2H, NH_2).

Pyrido[2,3-*d*]pyrimidine-2,4-dione (**8**).[28] - A mixture of 2.54 g (20 mmol) of 6-aminouracil (**4**) and 4.0 g (18 mmol) of 1,1,3,3-tetraethoxypropane in 350 ml of H_2O was refluxed for 4 h. The yellowish precipitate was collected after cooling and gave on drying 2.02 g (66 %) of the intermediate. This material (1.0g, 3.3 mmol) was heated in 10 ml of conc. H_2SO_4 at 160°C for 2 h. The mixture was poured on ice, the brown precipitate was filtered off and the filtrate was neutralized to pH 7 by solid $NaHCO_3$. The newly developed precipitate was collected, washed with H_2O and EtOH and gave 0.5 g crude product. Recrystallization from 18 ml of AcOH/H_2O 4:1 yielded 0.35 g (66 %) of a colorless powder, mp > 320°C. Anal. Calcd for $C_7H_5N_3O_2$: C, 51.55; H, 3.09; N, 25.77. Found: C, 51.47; H, 3.12; N, 25.80.

1-Methylpyrido[2,3-*d*]pyrimidine-2,4-dione (**9**). - A mixture of 2.82 g (20 mmol) of 6-amino-1-methyluracil and 5 ml (22 mmol) of 1,1,3,3-tetraethoxypropane in 200 ml of H_2O and 50 ml of EtOH was refluxed for 3 h. It was then evaporated to dryness and the residue was heated with 5 ml of conc. H_2SO_4 at 160°C for 2 h. After cooling the reaction mixture was poured on ice (50 g) and the precipitate was collected on standing overnight. Recrystallization from H_2O yielded 0.86 g (48 %) of **9** as yellowish crystals, mp 285°C. Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.19; H, 4.00; N, 23.75.

3-Methylpyrido[2,3-*d*]pyrimidine-2,4-dione (**10**).[29] - Analogous to the preceding procedure from 2.82 g (20 mmol) of 6-amino-3-methyluracil (**6**). The strongly acidic reaction solution was neutralized by solid $NaHCO_3$ after treatment with ice. The precipitate was recrystallized from H_2O with char-

coal to give 0.37 g (10 %) of 10 as colorless crystals, mp 270°C. Lit.,[29] 274°C. Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 33.72. Found: C, 54.31; H, 4.11; N, 24.01.

1,3-Dimethylpyrido[2,3-d]pyrimidine-2,4-dione (11).[28] - A mixture of 3.1 g (20 mmol) of 6-amino-1,3-dimethyluracil (7) and 4.4 g (20 mmol) of 1,1,3,3-tetraethoxypropane in 50 ml of H_2O was refluxed for 4 h. After cooling the precipitate was collected, washed with EtOH and dried to yield 2.59 g (75 %) of the tetracyclic intermediate in form of colorless needles, mp 308°C. Anal. Calcd for $C_{15}H_{18}N_6O_4$: C, 52.02; H, 5.24; N, 24.27. Found: C, 51.67; H, 5.39; N, 24.16. Reaction of 1.41 g (4 mmol) of this compound in 5 ml conc. H_2SO_4 at 160°C for 2 h led to the desired cyclization. The reaction mixture was poured on ice (80 g), the precipitate was collected and then recrystallized from 50 ml of EtOH to yield 0.43 g (56 %) of colorless crystals, mp 160°C. Lit.,[28] 164°C. Anal. Calcd for $C_9H_9N_3O_2$: c, 56.54; H, 4.47; N, 21.98. Found: C, 56.58; H, 4.87; N, 22.21.

6-Nitropyrido[2,3-d]pyrimidine-2,4-dione (12).[31] - In 250 ml of 1 % NaOH are heated 19.5 g (0.15 mol) of 4 and 26.0 g (0.16 mol) of sodium nitromalonaldehyde monohydrate[37] for 5 h under reflux. The precipitate was collected after cooling to give 21.9 g (70 %) of 12 as its sodium salt. The product was dissolved in 240 ml of hot 1 N NaOH, treated with charcoal, filtered and acidified with AcOH/H_2O (1:1) to yield 17.4 g (56 %) of 12 in form of a yellowish powder, mp > 320°C. Anal. Calcd for $C_7H_4N_4O_4$: C, 40.39; H, 1.94; N, 26.92. Found: C, 40.20; H, 1.91; N, 26.81.

1-Methyl-6-nitropyrido[2,3-d]pyrimidine-2,4-dione (13). - A solution of 28.2 g (0.2 mol) of 5 in 700 ml of 1% NaOH and 32.0 g (0.2 mol) sodium nitromalonaldehyde monohydrate was heated with stirring to 80°C for 2 h.

The precipitate was collected after cooling (31.8 g), then again dissolved in 250 ml of boiling H_2O, treated with charcoal, filtered and the filtrate was acidified with conc. HCl to pH 4. The precipitate was filtered off, washed with H_2O and EtOH and dried at 100°C to give 27.2 g (61 %) of a colorless powder, mp 245-247°C. Anal. Calcd for $C_8H_6N_4O_4$: C, 43.25; H, 2.72; N, 25.22. Found: C, 43.40; H, 2.62; N, 25.07.

3-Methyl-6-nitropyrido[2,3-d]pyrimidine-2,4-dione (14). - A solution of 0.70 g (5 mmol) of 6 and 1.2 g (7.5 mmol) of sodium nitromalonaldehyde monohydrate in 20 ml of 1% NaOH was refluxed for 4.5 h. The precipitate was collected after cooling, then dissolved in 20 ml of boiling H_2O and the solution was acidified by glacial acetic acid to yield 0.54 g (44 %) of 14 as a colorless powder, mp 285-287°C. Anal. Calcd for $C_8H_6N_4O_4$: C, 43.25; H, 2.72; N, 25.22. Found: C, 43.70; H, 2.70; N, 25.37.

1,3-Dimethyl-6-nitropyrido[2,3-d]pyrimidine-2,4-dione (15). - To a solution of 4.44 g (20 mmol) of 13 in 500 ml of 0.05 N NaOH were added dropwise with stirring 3 ml (30 mmol) of dimethyl sulfate in 30 ml of MeOH at room temperature. The pH is kept at the end of the methylation at 7 by adding little 1 N NaOH. After stirring for another hour it was acidified by 1 N HCl to pH 4, the separating precipitate was collected and then recrystallized from EtOH to yield 2.8 g (59 %) colorless crystals, mp 192-194°C. Anal. Calcd for $C_9H_8N_4O_4$: C, 45.77; H, 3.41; N, 23.72. Found: C. 45.62; H, 3.51; N, 23.58.

2-Methylamino-5-nitropyridine-3-carboxamide (16). - a) 2.2 g (0.01 mol) of 13 were refluxed in 20 ml (0.1 mol) of 5 N NaOH for 1 h. The precipitate was collected after cooling and purified by recrystallization from H_2O to give 1.57 g (80 %) of yellow crystals, mp 243-245°C.

b) A mixture of 1.41 g (10 mmol) of 5 and 1.7 g (11 mmol) of sodium nitromalonaldehyde monohydrate in 35 ml of 1 % NaOH was refluxed for 4.5 h. On cooling a precipitate was obtained (0.29 g), which gave on recrystallization from H_2O 0.192 g (10 %) of yellow crystals, mp 243-246°C. ^{1}H-Nmr (DMSO-d_6): 9.49 (q, 1H, NH); 9.04 (d, J = 3 Hz, 1H, H-C(6)); 8.75 (d, J = 3 Hz, 1H, H-C(4)); 8.42 + 7.69 (br s, 2H, NH_2); 3.03 (m, 3H, N-CH_3). Anal. Calcd for $C_7H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56. Found: C, 43.09; H, 3.87; N, 28.55.

2-Methylamino-5-nitropyridine-3-N-methylcarboxamide (17). - a) 0.47 g (2 mmol) of 15 were refluxed in 10 ml (10 mmol) of 1 N NaOH for 1 h. The precipitate was collected after cooling and gave on recrystallization from H_2O/EtOH 0.315 g (75 %) of yellow crystals, mp 240°C.
b) A mixture of 1.55 g (10 mmol) of 7 and 1.89 g (12 mmol) of sodium nitromalonaldehyde monohydrate in 30 ml of 1 % NaOH was refluxed for 2.5 h. On cooling the precipitate was collected and gave on recrystallization from H_2O/EtOH 1.25 g (59 %) yellow crystals, mp 240°C.
^{1}H-Nmr (DMSO-d_6): 9.25 (q, 1H, NH); 9.03 (d, J = 2 Hz, 1H, H-C(6)); 8.86 (q, 1H, NHCO); 8.65 (d, J = 2 Hz, 1H, H-C(4)); 3.03 (m, 3H, N-CH_3); 2.77 (m, 3H, CH_3-NHCO). Anal. Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.79; N, 26.75. Found: C, 45.76; H, 4.75; N, 26.48.

6-Aminopyrido[2,3-d]pyrimidine-2,4-dione (18).[31] - In 1 l of H_2O were dissolved 5.0 g (24 mmol) of 12 by addition of a minimum amount of ammonia. Reduction was achieved by 0.8 g of Pd/C (5 %) under H_2 atmosphere in a shaking apparatus. The theoretical amount of H_2 was taken up after 5 h. The mixture was heated to boiling, filtered and the filtrate was evaporated to dryness. The residue was dissolved in 100 ml of 0.25 N NaOH and the hote solution was added dropwise to 75 ml of boiling 0.5 N AcOH. After coo-

ling the precipitate was collected, washed with H_2O and dried at 100°C to yield 3.8 g (89 %) of a colorless powder, mp > 320°C. Anal. Calcd for $C_7H_6N_4O_2$: C, 47.19; H, 3.39; N, 31.45. Found: C, 47.08; H, 3.33; N, 31.50.

6-Amino-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (19). - A mixture of 8.88 g (40 mmol) of 13 and 0.4 g of Pd/C (5 %) in 800 ml of EtOH and 200 ml of AcOH was hydrogenated in a shaking apparatus. The reduction was achieved after 3 h. The catalyst was filtered off, the filtrate was evaporated to dryness and the residue was reprecipitated from hot dilute NaOH by addition of 50 % AcOH. After cooling the precipitate was collected, washed with H_2O and dried at 100°C to give 6.17 g (80 %) of a yellowish powder, mp 316-319°C. The substance could also be recrystallized from a large amount of H_2O. Anal. Calcd for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.16. Found: C, 49.88; H, 4.02; N, 28.91.

6-Amino-3-methylpyrido[2,3-d]pyrimidine-2,4-dione (20). - To a solution of 1.8 g (8.1 mmol) of 10 1 N ammonia (150 ml) was added 0.2 g of Pd/C (5 %) and then catalytically 10 reduced under H_2 atmosphere in a shaking apparatus. The catalyst was filtered off after 5 h, the filtrate was evaporated and the residue recrystallized from 600 ml of H_2O to yield 1.09 g (70 %) of a yellowish powder, mp > 300°C. Anal. Calcd for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.16, Found: C, 49.72; H, 4.09; N, 29.13.

6-Amino-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4-dione (21). - A suspension of 3.2 g (13.6 mmol) of 15 in 400 ml of EtOH and 100 ml of AcOH was reduced catalytically with 0.4 g of Pd/C (5 %) in a shaking apparatus. After uptake of 920 ml of H_2 the mixture was heated, filtered hot and the filtrate evaporated to dryness. The residue was recrystallized from 250 ml of EtOH to yield 2.37 g (84 %) of yellow crystals, mp 211-212°C. Anal. Calcd

for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.54; H, 4.80; N, 27.12.

6-Benzylideneimino-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (22). - A suspension of 0.576 g (3 mmol) of 21 in 60 ml of AcOH was treated with 1.06 g (0.01 mol) of freshly destilled benzaldehyde with stirring for 1 h at room temperature. The precipitate was filtered off, washed with EtOH and then recrystallized from the same solvent to give 0.65 g (77 %) of a yellowish powder, mp 273-275°C. Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.19; H, 4.25; N, 20.08.

6-Benzylamino-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (23). - In 40 ml of AcOH were treated 0.53 g (2.7 mmol) of 21 with 1.0 g (9 mmol) of benzaldehyde with stirring for 1 h. The suspension was cooled with ice and then 0.38 g (10 mmol) of $NaBH_4$ were added gradually. The solid material was dissolved and soon afterwards a new precipitate separated. It was stirred for 45 min, filtered and then recrystallized from 350 ml of EtOH and 150 ml of H_2O to yield 0.623 g (82 %) of yellowish needles, mp 265-267°C. Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.79; H, 5.17; N, 19.73.

6-(N,N-Dimethylaminomethylenimino)-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (24). - A solution of 0.384 g (2 mmol) of 19 in 20 ml of dry DMF was treated with 0.66 ml of N,N-dimethylformamide dimethyl acetal for 18 h at room temperature. It was then evaporated to dryness in high vacuum, the residue was dissolved in $CHCl_3$, put onto a silica gel column and eluted with $CHCl_3$/MeOH (97:3). The main fraction was evaporated and the residue was recrystallized from dry EtOH to give 0.453 g (74 %) of colorless crystals, mp 185-186°C. Anal. Calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30;

N, 28.32. Found: C, 53.32; H, 535; N, 28.08.

6-Formylamino-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (25). - 0.494 g (2 mmol) of 24 were refluxed in 150 ml of H_2O and 1 ml of AcOH for 45 min. On cooling colorless crystals were separated to give 0.376 g (85 %) of 25, mp 302°C. Anal. Calcd for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 48.84; H, 3.58; N, 25.26.

1-Methylpyrido[2,3-d]pyrimidine-2,4-dione-6-diazonium chloride (26). - A suspension of 3.56 g (18.5 mmol) of 13 in 250 ml of EtOH and 15 ml (37.5 mmol) of 2.5 N methanolic HCl was cooled to 0°C and then 2.5 ml (18.5 mmol) of isoamyl nitrite added with stirring for 1 h and warming up to room temperature. The precipitate was filtered off, washed with dry EtOH and dry ether. Drying in a vacuum desiccator over P_4O_{10} yielded 3.8 g (86 %) of a slightly brownish powder, mp 175°C. Anal. Calcd for $C_8H_6N_5O_2Cl$: C, 40.10; H, 2.52; N, 29.23. Found: C, 40.55; H, 2.56; N, 28.99.

1,3-Dimethylpyrido[2,3-d]pyrimidine-2,4-dione-6-diazonium chloride (27). - A solution of 0.824 g (4 mmol) of 15 in 40 ml of dry EtOH and 3.2 ml (8 mmol) of 2.5 N methanolic HCl was cooled to 0°C and then 0.54 ml (4 mmol) of isoamyl nitrite added with stirring. After 45 min, the solution was dropped into 400 ml of dry ether under stirring, the precipitate was collected, washed with ether and dried in a vacuum desiccator to give 0.973 g (78 %) of a slightly brownish powder, mp 116°C. Anal. Calcd for $C_9H_8N_5O_2Cl \cdot H_2O$: C, 39.79; H, 3.71; N, 25.78. Found: C, 39.81; H, 3.78; N, 25.58.

6-Chloro-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (28). - To a hot solution of 0.65 g (2.6 mmol) of $CuSO_4$. 5 H_2O in 3 ml of H_2O were added 0.23 g of NaCl and then a solution of 0.17 g (1.3 mmol) of Na_2SO_3 in little H_2O. The resulting precipitate was collected, washed several times with H_2O and then dissolved in conc. HCl. This solution of the CuCl catalyst was treated with a cooled solution of 0.48 g (2 mmol) of 26 in 8 ml of conc. HCl and then heated to 70°C for 45 min. The reaction mixture was neutralized with a saturated aqueous $NaHCO_3$ solution and the precipitate was filtered off, washed and dried (0.36 g). The crude material was heated with 70 ml of EtOH, filtered and the filtrate was evaporated to half of its colume to yield 0.272 g (64 %) of colorless crystals, mp 258-259°C. Uv (MeOH): 212 (4.41); 254 (4.12); 324 (3.74); [335 (3.64)]. Anal. Calcd for $C_8H_6N_3O_2Cl$: C, 45.41; H, 2.86; N, 19.86. Found: C, 45.70; H, 2.81; N, 19.45.

6-Bromopyrido[2,3-d]pyrimidine-2,4-dione (29). - The CuBr catalyst was prepared analogous to the preceding procedure using 0.39 g of NaBr. The precipitate was dissolved in conc. HBr and then added to a solution of 0.356 g (2 mmol) of 12 in 5 ml of half conc. HBr treated at 0°C with 0.166 g (2.4 mmol) of $NaNO_2$ for diazotization. The reaction mixture was heated to 80°C for 30 min. After cooling the precipitate was collected and recrystallized from 320 ml of H_2O to give 0.36 g (73 %) of a colorless powder, mp 346-348°C. Uv (MeOH): 210 (4.42); 251 (4.13); 321 (3.74); [330 (3.69)]. Anal. Calcd for $C_7H_4N_3O_2Be$: C, 34.74; H, 1.67; N, 17.36. Found: C, 34.83; H, 1.66; N, 17.44.

6-Bromo-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (30). - Analogous treatment of 0.384 g of 13 according to the preceding procedure led to 0.48 g of crude material, which was recrystallized from 80 ml of EtOH to give 0.378 g (74 %) of colorless crystals, mp 259-261°C. Uv (MeOH): 217 (4.60);

245 (4.30); 330 (3.85); [343 (3.74)]. Anal. Calcd for $C_8H_6N_3O_2Br$: C, 37.52; H, 2.36; N, 16.41. Found: C, 37.63; H, 2.25; N, 16.33.

6-Bromo-3-methylpyrido[2,3-d]pyrimidine-2,4-dione (31). - 0.384 g of 14 were treated analogous to the preceding procedure to give 0.31 g (60 %) of colorless crystals, mp 314°C. Uv (MeOH): 214 (4.44); 250 (4.0); 322 (3.75); [331 (3.70)]. Anal. Calcd for $C_8H_6N_3O_2Br$: C, 37.52; H, 2.36; N, 16.41. Found: C, 37.93; H, 2.13; N, 16.24.

6-Triazenopyrido[2,3-d]pyrimidine-2,4-diones (32-39). General procedure. - 1 Mmol of the pyrido[2,3-d]pyrimidine-2,4-dione-6-diazonium chloride (26, 27) was suspended in 10 ml of ice-water, the appropriate amine was added and after stirring for 5 min the solution was acidified by conc. HCl to pH 4-5. The precipitate was collected and purified by recrystallization.

6-(N,N-Diethyltriazeno)-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (32). - From 0.239 g (1 mmol) of 26 and 3.6 g (0.05 mol) of diethylamine 0.232 g (83 %) of 32 were obtained as crude material. Recrystallization from 60 ml of MeOH gave 0.157 g (57 %) of yellowish crystals, mp 248°C. Uv (MeOH): 209 (4.36); [234 (3.87)]; 309 (4.39); [358 (3.98)]. Anal. Calcd for $C_{12}H_{16}N_6O_2$: C, 52.12; H, 5.84; N, 30.42. Found: C, 52.14; H, 5.57; N, 30.10.

1-Methyl-6-(N,N-tetramethylenetriazeno)pyrido[2,3-d]pyrimidine-2,4-dione (33). - From 0.239 g (1 mmol) of 26 and 1.4 g (0.02 mol) of pyrrolidine 0.256 g (93 %) of 33 were obtained in form of chromatographically pure, yellowish crystals, mp 271°C. Uv (MeOH): 209 (4.35); [236 (3.87)]; 311 (4.39); [360 (3.98)]. Anal. Calcd for $C_{12}H_{14}N_6O_2$: C, 52.55; H, 5.14; N, 30.64. Found: C, 51.98; H, 5.14; N, 30.35.

N-(1-Methyl-2,4-dioxotetrahydropyrido[2,3-d]pyrimidin-6-yl)diazomorpholine (34). - From 0.239 g (1 mmol) of 26 and 3.5 g (0.04 mol) of morpholine 0.263 g (90 %) of 34 were obtained as crude material. Purification was ahcieved by careful dissolution in 1 N NaOH and neutralization by HCl to pH 6 to give 0.217 g (75 %) of yellowish crystals, mp 283°C. Uv (MeOH): 208 (4.37); [234 (3.84)]; 308 (4.37); [352 (4.04)]. Anal. Calcd for $C_{12}H_{14}N_6O_3$: C, 49.65; H, 4.86; N, 28.95. Found: C, 49.45; H, 4.62; N, 28.68.

N-(1,3-Dimethyl-2,4-dioxotetrahydropyrido[2,3-d]pyrimidin-6-yl)diazomorpholine (35). - From 0.253 g (1 mmol) of 27 and 1.74 g (0.02 mol) of morpholine 0.23 g (75 %) of 35 were obtained as crude material. Recrystallization from EtOH gave 0.161 g (53 %) of yellowish crystals, mp 211°C. Uv (MeOH): 211 (4.35); [234 (3.99)]; 306 (4.39); [356 (4.05)]. Anal. Calcd for $C_{13}H_{16}N_6O_3$: C, 51.31; H, 5.30; N, 27.62. Found: C, 51.58; H, 5.19; N, 27.75.

1-Methyl-6-(N-methyl-N-carboxymethyltriazeno)pyrido[2,3-d]pyrimidine-2,4-dione (36). - From 0.239 g (1 mmol) of 26 and 0.17 g (1.2 mmol) of sarcosine 0.262 g (89 %) of 36 were obtained as yellowish crystals, mp 275-276°C. Uv (MeOH): 208 (4.35); [230 (3.95)]; 308 (4.32); [358 (3.96)]. Anal. Calcd for $C_{11}H_{12}N_6O_4$: C,45.20; H, 41.14; N, 28.76. Found: C, 44.83; H, 4.58; N, 28.55.

1-Methyl-6-(N-methyl-N-β-phenylethyltriazeno)pyrido[2,3-d]pyrimidine-2,4-dione (37). - From 0.239 g (1 mmol) of 26 and 0.5 ml of N-methylphenethylamine 0.296 g (87 %) of 37 were obtained as a yellowish powder, mp 185-186°C. Uv (MeOH): 207 (4.52); [236 (3.94)]; 309 (4.40); [359 (3.98)]. Anal. Calcd for $C_{17}H_{18}N_6O_2$: C, 60.34; H, 5.36; N, 24.84. Found: C, 59.83; H, 5.14; N, 24.68.

6-(N-Benzyl-N-ethyltriazeno)-1-methylpyrido[2,3-d]pyrimidine-2,4-dione (38). - From 0.239 g (1 mmol) of 26 and 0.5 ml of N-ethylbenzylamine 0.278 g (82 %) of 38 were obtained as yellowish crystals, mp 198-201°C. Uv (MeOH): 207 (4.52); [239 (3.91)]; 309 (4.40); [359 (4.01)]. Anal. Calcd for $C_{17}H_{18}N_6O_2$: C, 60.34; H, 5.36; N, 24.84. Found: C, 60.47; H, 5.38; N, 24.54.

1-Methyl-6-(N-methyl-N-β-hydroxy-α-methyl-β-phenylethyltriazeno)pyrido-[2,3-d]pyrimidine-2,4-dione (39). - From 0.239 g (1 mmol) of 26 and 0.38 g (2.3 mmol) of (-)-ephedrine 0.335 g (91 %) of 39 were obtained as a yellowish powder, mp 211-213°C. Uv (MeOH): 208 (4.50); [232 (3.97)]; 309 (4.40); [360 (3.95)]. Anal. Calcd for $C_{18}H_{20}N_6O_3$: C, 58.69; H, 5.47; N, 22.81. Found: C, 58.60; N, 5.66; N, 22.82.

Synthesis of 6-nitro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine-2,4-diones (40-42). General procedure. - 2 Mmol of the 6-nitropyrido[2,3-d]pyrimidine-2,4-dione were dissolved in 15 ml of H_2O and 2 ml of conc. NH_4OH. The Solution was cooled to 5-8°C and then 0.08 g (2 mmol) of sodium borohydride were added. It was stirred 10 min at 5°C and then 1 h at room temperature till the red color of the solution has disappeared. It was then concentrated to half of the colume and acidified by AcOH to form a precipitate which was purified by recrystallization.

6-Nitro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (40). - From 0.36 g (2 mmol) of 12 were obtained 0.308 g (72 %) of 40 as a crude material. Recrystallization from 60 ml of H_2O gave 0.237 g (56 %) of colorless crystals, mp >320°C. Uv (MeOH): 202 (4.17); [228 (3.65)]; 271 (4.23). Anal. Calcd for $C_7H_8N_4O_4$: C, 39.63; H, 3.80; N, 26.41. Found: C, 39.70; H, 4.02; N, 26.32.

1-Methyl-6-nitro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (41). - From 0.444 g (2 mmol) of 13 were obtained 0.37 g (82 %) of 41 as a crude product, which was recrystallized from 50 ml of H_2O to give 0.294 g (65 %) of colorless crystals, mp 297°C. Uv (MeOH): 203 (4.23); [230 (3.60)]; 274 (4.22). Anal. Calcd for $C_8H_{10}N_4O_4$: C, 42.48; H, 4.46; N, 24.77. Found: C, 42.22; H, 4.50; N, 24.70.

3-Methyl-6-nitro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (42). - From 0.444 g (2 mmol) of 14 were obtained 0.333 g (70 %) of 42 as a crude product, which gave on recrystallization from 35 ml of H_2O 0.256 g (57 %) of colorless crystals, mp >280°C (decomp.). Uv (MeOH): 204 (4.19); [230 (3.58)]; 270 (4.22). Anal. Calcd for $C_8H_{10}N_4O_4$: C, 42.48; H, 4.46; N, 24.77. Found: C, 42.50; H, 4.37; N, 24.72.

6-Amino-1-methyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (43). - In 100 ml of H_2O 0.1 g of PtO_2 was reduced under H_2 atmosphere in a shaking apparatus to form the Pt catalyst. The 0.452 g of 41 were added and the reduction was continued till the theoretical amount of H_2 (135 ml) was consumed. The catalyst was filtered off, the filtrate was evaporated to dryness and the residue was treated with 20 ml of 2.5 N methanolic HCl to give 0.324 g crude material. Purification was achieved by dissolving in little H_2O and addition of saturated methanolic HCl. The resulting precipitate was filtered off, washed with ether and gave after drying 0.15 g (50 %) of colorless crystals of the dihydrochloride monohydrate salt, mp >340°C. Uv (pH 4): [234 (3.50)]; 278 (4.26). Anal. Calcd for $C_8H_{12}N_4O_2 \cdot 2\,HCl \cdot H_2O$: C, 33.46; H, 5.61; N, 19.51. Found: C, 33.94; H, 5.70; N, 19.64.

REFERENCES

1. Paper XXXI: Z. S. Salih, P. Stegmüller, and W. Pfleiderer, J. Heterocycl. Chem., 1988, 25, 1443.
2. W. J. Irwin and D. G. Wibberley, Advan. Heterocycl. Chem., 1969, 10, 149.
3. E. Lunt and C. G. Newton, 'Comprehensive Heterocyclic Chemistry', ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, Vol. 3, Part 2 B, 199.
4. W. Pfleiderer, 'Comprehensive Heterocyclic Chemistry', ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, Vol. 3, Part 2 B, 263.
5. L. Klisiecki and E. Sucharda, Roczniki Chem., 1923, 3, 251.
6. V. Oakes, R. Pascoe, and N. H. Rydon, J. Chem. Soc., 1956, 1045.
7. R. K. Robins and G. H. Hitchings, J. Am. Chem.Soc., 1955, 77, 2256.
8. R. K. Robins and G. H. Hitchings, J. Am. Chem. Soc., 1958, 80, 3449.
9. W. Pfleiderer, Chem. Ber., 1957, 90, 2582.
10. W. Pfleiderer, Chem. Ber., 1957, 90, 2588.
11. W. Pfleiderer, Chem. Ber., 1957, 90, 2604.
12. W. Pfleiderer, Chem. Ber., 1957, 90, 2617.
13. W. Pfleiderer, Chem. Ber., 1957, 90, 2624.
14. W. Pfleiderer, Chem. Ber., 1957, 90, 2631.
15. W. Pfleiderer, Chem. Ber., 1958, 91, 1671.
16. W. Pfleiderer and G. Nübel, Chem. Ber., 1960, 93, 1406.
17. W. Pfleiderer, Chem. Ber., 1962, 95, 749.
18. G. Nübel and W. Pfleiderer, Chem. Ber., 1962, 95, 1605.
19. W. Pfleiderer, J. W. Bunting, D. D. Perrin, and G. Nübel, Chem. Ber., 1966, 99, 3503.
20. W. Pfleiderer and H. Deiss, Chem. Ber., 1971, 104, 780.
21. W. Pfleiderer and R. Mengel, Chem. Ber., 1971, 104, 3842.

22. W. Pfleiderer and W. Hutzenlaub, Chem. Ber., 1973, 106, 3149.
23. G. Evens and P. Caluwe, J. Org. Chem., 1975, 40, 1438.
24. E. E. Garcia, Synth. Commun., 1973, 3, 397.
25. K. Hirota, Y. Kitade, and S. Senda, Heterocycles, 1980, 14, 407.
26. K. Hirota, Y. Kitade, and S. Senda, J. Org. Chem., 1981, 46, 846.
27. R. Bernetti, F. Mancini, and C. C. Price, J. Org. Chem., 1962, 27, 2863.
28. A. C. McLean and F. S. Spring, J. Chem. Soc., 1949, 2582.
29. L. Capuano, M. Welter, and R. Zander, Chem. Ber., 1969, 102, 3698.
30. T. Itoh, T. Imini, H. Ogura, N. Kawahara, T. Nakajima, and K. A. Watanabe, Heterocycles, 1983, 20, 2177.
31. T. C. Lee and G. Salemnick, J. Org. Chem., 1975, 40, 3608.
32. E. F. Scriven, 'Comprehensive Heterocyclic Chemistry', ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, Vol. 2, 279.
33. S. Yamada and Y. Kikugawa, Chem. and Ind., 1966, 2169.
34. S. Yamada and Y. Kikugawa, Chem. and Ind., 1967, 1325.
35. K. Nakanishi, N. Suzuki, and F. Yamazaki, Bull. Chem. Soc. Japan, 1961, 34, 53.
36. A. Albert and E. P. Serjeant, 'The Determination of Ionization Constants', Chapman and Hall Ltd., Lomdon, 1971, 44,
37. P. E. Fanta, C. S. Hamilton, and P. J. Vanderhorst, Org. Synth. Coll., 1963, Vol. 4, 844.

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