Synthesis of 8-Methylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones and Their Use in the Oxidation of Alcohols

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Received July 16, 1985

A new-type pyridodipyrimide, 8-methylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones were prepared by the condensation of 6-alkyl- or 6-aryl-amino-2-methylpyrimidin-4(3*H*)-ones with 2,4,6-trichloropyrimidine-5-carbaldehyde or 3-alkyl-6-chloro-5-formyluracils. The pyridodipyrimidines thus obtained oxidized alcohols under neutral conditions to yield the corresponding carbonyl compounds and a significant autorecycling in the oxidation was observed.

J. Heterocyclic Chem., **23**, 241 (1986).

In relation to our studies on the biomimetic oxidations mediated by 5-deazaflavins and analogues [1], we have recently found that some pyridodipyrimidines showed strong ability and remarkable autorecycling toward oxidation of alcohols [2]. The pyridodipyrimidines are the structurally cyclized compounds of the amino analogues of the Hantzsch esters and have a conjugated system similar to that of 5-deazaflavins.

In order to gain more information about the oxidizing ability of this ring system, we have now prepared several 8-methylpyrido[2,3-*d*:6,5-*d'*]pyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones **5** as a new type of pyridodipyrimidine.

Scheme I

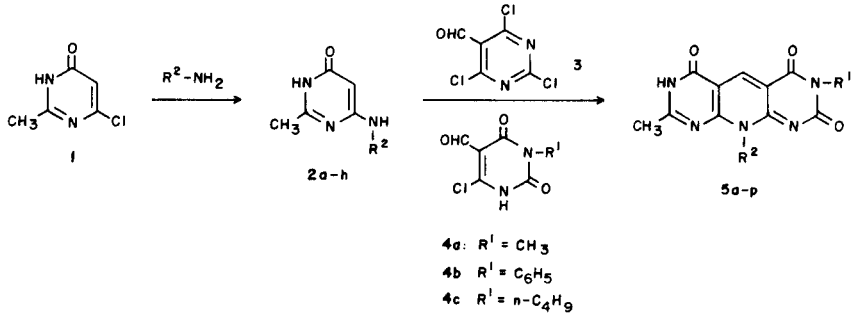
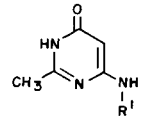


Table I

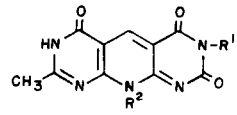
6-Alkyl- and 6-Arylamino-2-methylpyrimidin-4(3*H*)-ones



Compound No.	R¹	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2a	*n*-C_4H_9	66	144	$C_9H_{15}N_3O$	59.64	8.34	23.19	59.46	8.51	23.64
2b	*n*-C_8H_{17}	67	142	$C_{13}H_{23}N_3O$	63.96	10.29	18.65	64.12	10.57	18.22
2c	*n*-$C_{12}H_{25}$	75	132	$C_{17}H_{31}N_3O$	69.58	10.64	14.32	69.35	10.45	14.08
2d	*n*-$C_{18}H_{37}$	77	114	$C_{23}H_{43}N_3O$	73.15	11.48	11.13	72.35	11.42	10.89
2e	C_6H_5	90	282	$C_{11}H_{11}N_3O$	65.67	5.51	20.88	65.38	5.62	20.64
2f	3-CH_3-C_6H_4	95	309	$C_{12}H_{13}N_3O$	66.95	6.09	19.52	66.67	5.95	19.88
2g	3,4CH_3)$_2$-C_6H_3	90	312	$C_{13}H_{15}N_3O$	68.10	6.59	18.33	67.95	6.51	18.52
2h	3-CH_3O-C_6H_4	92	242	$C_{12}H_{13}N_3O_2$	62.32	5.67	18.17	62.52	5.95	17.91

Table II

8-Methylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones and Their Chemical Shifts of C-5 Protons

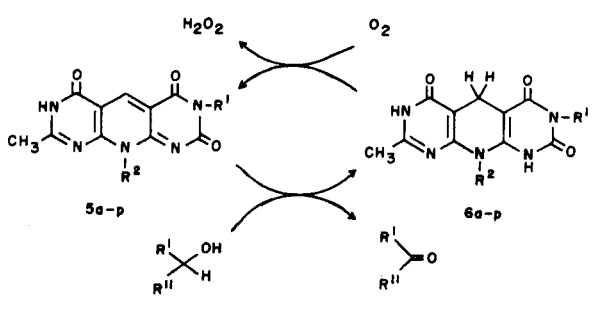


Compound No.	R^1	R^2	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	^{1}H-nmr δ (ppm)
5a	H	*n*-C_4H_9	50	>330	$C_{14}H_{15}N_5O_3$	55.80	5.02	23.25	55.60	5.23	22.99	9.83
5b	H	*n*-C_8H_{17}	72	>330	$C_{18}H_{23}N_5O_3$	60.49	6.49	19.60	60.76	6.51	19.38	9.86
5c	H	*n*-$C_{12}H_{25}$	70	>330	$C_{22}H_{31}N_5O_3$	63.90	7.56	16.94	63.63	7.29	17.12	9.80
5d	H	*n*-$C_{16}H_{37}$	70	240	$C_{28}H_{43}N_5O_3$	67.57	8.71	14.07	67.25	8.54	14.32	9.78
5e	CH_3	*n*-C_4H_9	50	271	$C_{15}H_{17}N_5O_3$	57.13	5.43	22.21	57.00	5.39	22.57	9.77
5f	CH_3	*n*-C_8H_{17}	53	263	$C_{19}H_{25}N_5O_3$	61.44	6.78	18.86	61.38	6.85	18.62	9.92
5g	CH_3	*n*-$C_{12}H_{25}$	52	255	$C_{23}H_{33}N_5O_3$	64.61	7.78	16.38	64.16	8.02	16.43	9.90
5h	CH_3	*n*-$C_{18}H_{37}$	53	139	$C_{29}H_{45}N_5O_3$	68.07	8.86	13.67	67.72	8.66	13.62	9.77
5i	CH_3	C_6H_5	73	>330	$C_{17}H_{13}N_5O_3$	60.89	3.91	20.89	61.03	4.11	20.53	9.91
5j	CH_3	3-CH_3-C_6H_4	80	>330	$C_{18}H_{15}N_5O_3$	61.88	4.33	20.05	62.05	4.64	19.70	9.90
5k	CH_3	3,4-$(CH_3)_2C_6H_3$	83	>330	$C_{19}H_{17}N_5O_3$	62.80	4.72	19.28	62.99	4.50	19.62	9.95
5l	CH_3	3-CH_3O-C_6H_4	80	>330	$C_{18}H_{15}N_5O_4$	59.17	4.14	19.17	60.01	4.43	18.93	9.90
5m	C_2H_5	*n*-C_8H_{17}	51	295	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17	62.66	6.82	18.52	9.90
5n	C_2H_5	*n*-$C_{12}H_{25}$	50	257	$C_{24}H_{35}N_5O_3$	65.28	7.99	15.85	65.03	8.21	15.52	9.85
5o	*n*-C_4H_9	*n*-C_8H_{17}	48	231	$C_{22}H_{31}N_5O_3$	63.90	7.56	16.94	63.77	7.78	17.18	9.85
5p	*n*-C_4H_9	*n*-$C_{12}H_{25}$	39	193	$C_{26}H_{39}N_5O_3$	66.49	8.37	14.91	66.28	8.56	15.03	9.83

The requisite starting materials, 6-alkyl- and 6-arylamino-2-methylpyrimidin-4(3*H*)-ones **2**, were prepared by the known procedure [3]. Namely, the reaction of 6-chloro-2-methylpyrimidin-4(3*H*)-one (**1**) [4] with appropriate alkyl-or arylamines in *n*-butyl alcohol gave the compounds **2** (Scheme 1) (Table 1).

Treatment of the 6-alkyl- or 6-arylamino-2-methylpyrimidin-4(3*H*)-ones **2** thus obtained with 2,4,6-trichloropyrimidine-5-carbaldehyde (**3**) [5] or 3-alkyl-6-chloro-5-formyluracils **4** [5,6] gave the corresponding pyridodipyrimidines **5**. The structures of compounds **5** were established on the basis of the satisfactory analytical and spectral data, and particularly, by the presence of the characteristic C-5 proton at δ 9.77-9.95 in ^{1}H-nmr spectra (Table 2).

Scheme 2



It has been found that the 8-methylpyrido[2,3-*d*:6,5-*d'*]-dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones **5** obtained here oxidized cyclopentanol and ℓ-menthol under neutral conditions to yield cyclopentanone and ℓ-menthol and, furthermore, a significant autorecycling in the oxidation was

Table III

Autorecycling Oxidation of Cyclopentanol and ℓ-Menthol by the Compounds **5**

Compound No.	Yield (%) [a,b]	of cyclopentanone	Yield (%) [a,b]	of ℓ-menthone
5a	6356	(10.3)	—	—
5b	11016	(12.7)	2744	(6.0)
5c	12112	(13.2)	3979	(8.7)
5d	9273	(8.5)	4894	(10.7)
5e	6502	(9.0)	—	—
5f	20667	(23.7)	8570	(17.5)
5g	9715	(10.7)	9350	(17.1)
5h	9155	(8.4)	7104	(15.6)
5i	6372	(8.7)	4998	(11.9)
5j	7219	(9.8)	4176	(9.3)
5k	10800	(12.5)	5487	(11.8)
5l	trace	—	3240	(6.9)
5m	11968	(14.1)	7350	(14.9)
5n	13620	(14.1)	5877	(10.4)
5o	10351	(11.5)	—	—
5p	12426	(12.0)	—	—

[a] Based on the pyridodipyrimidine. [b] Based on the starting alcohols given in parentheses.

observed. Namely, 1,5-dihydro-8-methylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones **6** initially formed are reoxidized to the original compounds **5** by the air which is included in the substrate or comes in naturally from outside, and thus the compounds **5** act as a turnover catalyst. As shown in Table 3, the compounds **5** exhibited in general autorecycling oxidation toward cyclopentanol and ℓ-menthol. Especially, compound **5f**, which possesses *n*-octyl substituent, an outstanding oxidizing power.

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Identity of the compounds was confirmed by comparison of the ir spectra determined in Nujol on a JASCO IR-A1 spectrometer. The nmr spectra were determined with a Hitachi R-24B spectrometer with tetramethylsilane as an internal standard.

6-Alkylamino-2-methylpyrimidin-4(3*H*)-ones **2a-d**.

A solution of 6-chloro-2-methylpyrimidin-4(3*H*)-one (**1**) (30 mmoles) and an alkylamine (60 mmoles) in 1-butanol (50 ml) was refluxed for 3 hours. After cooling, the crystals which separated are collected by filtration and recrystallized from ethanol to give colourless needles (Table 1).

6-Arylamino-2-methylpyrimidin-4(3*H*)-ones **2e-h**.

A mixture of **1** (30 mmoles) and an arylamine (90 mmoles) was fused at 200° for 10 minutes. After cooling, the crystals which separated were collected by filtration and recrystallized from ethanol to give colourless prisms (Table 1).

10-Alkyl-8-methylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones **5a-d**.

A mixture of **2a-d** (3 mmoles) and 2,4,6-trichloropyrimidine-5-carbaldehyde (**3**) (3 mmoles) was heated in acetic acid (20 ml) at 80° for 20 hours. After cooling, the crystals which separated were filtered off. Recrystallization from ethanol gave yellow powder (Table 2).

10-Alkyl-3,8-dimethylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones **5e-h**.

A mixture of **2a-d** (3 mmoles) and 6-chloro-5-formyl-3-methyluracil (**4a**) (3 mmoles) was heated in ethyl acetate (20 ml) under reflux for 2 hours. After cooling, the separated crystals were collected by filtration and recrystallized from ethanol to give yellow needles (Table 2).

10-Aryl-3,8-dimethylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones **5i-l**.

A mixture of **2e-h** (3 mmoles) and **4a** (3 mmoles) was heated in DMF (20 ml) at 50° for 1 hour. After cooling, the crystals which separated were filtered off. Recrystallization from DMF gave yellow powder (Table 2).

10-*n*-Octyl- and 10-*n*-Dodecyl-10-alkyl-8-methylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones **5m-p**.

These compounds were prepared by the same procedure as that for **5a-d**, from **2b,c** and the corresponding 3-alkyl-6-chloro-5-formyluracils **4b,c**. Recrystallization from ethanol gave yellow powder (Table 2).

Oxidation of Cyclopentanol of ℓ-Menthol by **5**. General Procedure.

A mixture of **5** (15 mg) with cyclopentanol (3 ml) or ℓ-menthol (3 g), was constantly stirred in a flask joined with a condenser at 115° (for cyclopentanol) or 120° (for ℓ-menthol) for 25 hours. After reaction, the reaction mixture was diluted with ether, and the catalyst **5** thus separated was filtered off. The filtrate was treated with a 2*N* hydrochloric acid solution of 2,4-ditrophenylhydrazine to give the corresponding 2,4-dinitrophenylhydrazone.

Acknowledgement.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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