Synthesis of Pyrido[3,2-*d*]pyrimidines by Intramolecular Cycloaddition of Azahexatrienes

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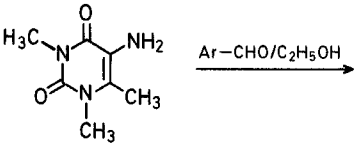
Intramolecular cycloaddition of aza-analogs of hexatrienes has recently been shown to offer a useful method for the construction of various heterocycles, i.e. purine, pyrazolo[3,4-*d*]pyrimidine, pteridine, pyrimido[4,5-*e*]-*as*-triazine, pyrimido[4,5-*c*]pyridazine, pyrimido[4,5-*d*]pyrimidine, pyrimido[5,4-*d*]pyrimidine, and pyrimido[4,5-*b*]quinoline[1]. We now report a new, facile synthesis of pyrido[3,2-*d*]pyrimidine derivatives **5** by intramolecular cycloaddition of azahexatriene intermediates. The pyrido[3,2-*d*]pyrimidines may be of considerable medicinal interest since they can be regarded not only as 8-deazapteridines but also as 5-azaquinazolines[2].



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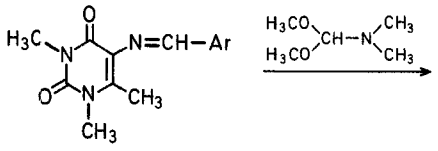
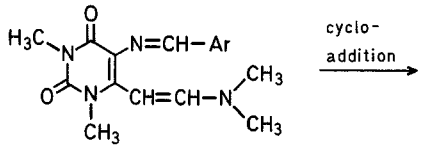
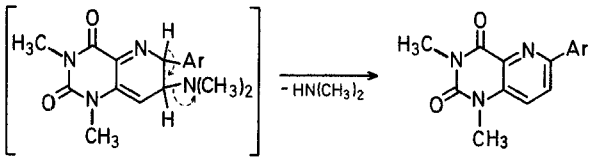


2a-h



3a-h



4a-h **5a-h**

	Ar		Ar
a		e	H_3C
b	Br	f	H_3CO
c	Cl	g	H_3CO, H_3CO
d	Cl, Cl	h	O, O

The key intermediates, 5-benzylideneamino-1,3,6-trimethyluracils **(2a–h)**, were prepared in 83–97% yields by refluxing of 5-amino-1,3,6-trimethyluracil **(1)**[3] with the appropriate benzaldehydes in ethanol for 3 h (Table 1).

Treatment of **2a** with excess dimethylformamide dimethyl acetal at 130 °C for 7 h afforded 5-benzylideneamino-6-(2-dimethylaminovinyl)-1,3-dimethyluracil **(3a)** and 1,3-dimethyl-6-phenylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **(5a)** in 7 and 74% yield, respectively. The compound **5a** was readily precipitated out from the reaction mixture and **3a** was isolated by concentration of the filtrate. In analogy with the above result, the reaction of other uracils **2b–h** with dimethylformamide dimethyl acetal provided the corresponding dimethylaminovinyluracils **(3b–h)** and pyridopyrimidines **(5b–h)** in 2–35 and 48–93% yields, respectively (Table 2).

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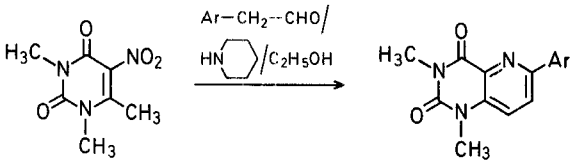
Table 1. 5-Benzylidenamino-1,3,6-trimethyluracils **2a–h**

Compound	Yield [%]	m.p.[a] [°C] (solvent)	Molecular[b] formula
2a	90	155.6° (C_2H_5OH)	$C_{14}H_{15}N_3O_2$ (257.3)
2b	95	174.9° (DMF/C_2H_5OH)	$C_{14}H_{14}BrN_3O_2$ (336.2)
2c	95	167.3° (DMF/C_2H_5OH)	$C_{14}H_{14}ClN_3O_2$ (291.8)
2d	94	201.7° (DMF/C_2H_5OH)	$C_{14}H_{13}Cl_2N_3O_2$ (326.2)
2e	90	162.4° (C_2H_5OH)	$C_{15}H_{17}N_3O_2$ (271.3)
2f	83	151.8° (C_2H_5OH)	$C_{15}H_{17}N_3O_3$ (287.3)
2g	97	204.6° (DMF/C_2H_5OH)	$C_{16}H_{19}N_3O_4$ (317.3)
2h	90	215.9° (DMF)	$C_{15}H_{15}N_3O_4$ (301.3)

[a] Melting points were taken on a Mettler FP-61 melting point apparatus.

[b] All products gave satisfactory microanalyses (C ±0.25%; H ±0.21%; N ±0.19%).

identical with a sample prepared by the reaction of 1,3,6-trimethyl-5-nitrouracil (**6**)[3] with phenylacetaldehyde in ethanol containing piperidine.



6 **5a**

I.R. spectra were recorded on a JASCO IR-E spectrophotometer. ^{1}H-N.M.R. spectra were determined at 100 MHz with a JEOL JNM-PS-100 spectrometer using tetramethylsilane as internal standard. U.V. spectra were performed on a Hitachi 124 spectrophotometer. Mass spectra were taken on a JEOL JMS D-300 spectrometer by a direct-inlet system at 70 eV.

5-Benzylidenamino-1,3,6-trimethyluracils 2a–h; General Procedure:

A mixture of the uracil **1**[3] (0.85 g, 0.005 mol) and an appropriate benzaldehyde (0.006 mol) in ethanol (20 ml) is heated under reflux for 3 h. After the reaction mixture has been cooled to ambient temperature, the precipitated solid is filtered, washed with ethanol, and recrystallized to give the corresponding product **2a–h** (see Table 1).

Table 2. 5-Benzylideneamino-6-(2-dimethylaminovinyl)-1,3-dimethyluracils **3a–h** and 6-Aryl-1,3-dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **5a–h**

Starting material	Reaction time [h]	Product 3				Product 5			
		Compound	Yield [%]	m.p.[a] [°C] (solvent)	Molecular[b] formula	Compound	Yield [%]	m.p.[c] [°C] (solvent)	Molecular[d] formula
2a	7	**3a**	7	160–163° (CH_3OH)	$C_{17}H_{20}N_4O_2$ (312.4)	**5a**	74	247.7° (DMF/C_2H_5OH)	$C_{15}H_{13}N_3O_2$ (267.3)
2b	10	**3b**	6	175–177° (C_2H_5OH)	$C_{17}H_{19}BrN_4O_2$ (391.3)	**5b**	67	215.6° (DMF)	$C_{15}H_{12}BrN_3O_2$ (346.2)
2c	10	**3c**	8	171–173° (C_2H_5OH)	$C_{17}H_{19}ClN_4O_2$ (346.9)	**5c**	49	198.3° (DMF/C_2H_5OH)	$C_{15}H_{12}ClN_3O_2$ (301.8)
2d	10	**3d**	7	174–175° (CH_3OH)	$C_{17}H_{18}Cl_2N_4O_2$ (381.3)	**5d**	85	239.9° (DMF)	$C_{15}H_{11}Cl_2N_3O_2$ (336.2)
2e	10	**3e**	2	154–158° (CH_3OH)	$C_{18}H_{22}N_4O_2$ (326.4)	**5e**	92	210.3° (DMF)	$C_{16}H_{15}N_3O_2$ (281.3)
2f	10	**3f**	5	180–181° (CH_3OH)	$C_{18}H_{22}N_4O_3$ (342.4)	**5f**	87	182.2° (DMF/C_2H_5OH)	$C_{16}H_{15}N_3O_3$ (297.3)
2g	15	**3g**	2	179–182° (CH_3OH)	$C_{19}H_{24}N_4O_4$ (372.4)	**5g**	93	220.3° (DMF)	$C_{17}H_{17}N_3O_4$ (327.3)
2h	20	**3h**	35	198–201° (DMF/C_2H_5OH)	$C_{18}H_{20}N_4O_4$ (356.4)	**5h**	48	285.0° (DMF)	$C_{16}H_{13}N_3O_4$ (311.3)

[a] Due to the thermal instability of **3a–h**, their melting points were taken on a YANACO micro-hot-stage melting point apparatus and are uncorrected.

[b] All products gave satisfactory microanalyses (C ±0.32%; H ±0.17%; N ±0.25%).

[c] Melting points were taken on a Mettler FP-61 melting point apparatus.

[d] All products gave satisfactory microanalysis (C ±0.29%; H ±0.14%; N ±0.12%).

On the basis of these findings, it would appear that the reaction of **2** with dimethylformamide dimethyl acetal leading to **5** proceeds through the initial formation of **3**, which possesses an azahexatriene-type structure. This could undergo intramolecular cycloaddition to the dihydropyridopyrimidine **4** and subsequent aromatization accompanied by elimination of dimethylamine.

The structures of **3** and **5** were established by microanalyses and spectral data. In addition, compound **5a** was

5-Benzylidenamino-6-(2-dimethylaminovinyl)-1,3-dimethyluracils 3a–h and 6-Aryl-1,3-dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones 5a–h; General Procedure:

A suspension of the appropriate uracil **2** (0.002 mol) in dimethylformamide dimethyl acetal (3 ml) is heated at 130 °C (reaction time, see Table 2). After the reaction mixture has cooled to ambient temperature, the precipitated solid is filtered, washed with ethanol, and recrystallized to give the corresponding product **5a–h**.

The filtrate, from which product **5** has been removed, is concentrated in vacuo and the residue is triturated with chilled methanol.

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The separated solid is filtered and recrystallized to give the corresponding product **3a–h** (see Table 2). [Prior to recrystallization, the crude products **3b** and **3c** are subjected to column chromatography through activated alumina with ethyl acetate/chloroform (50:50).]

As typical examples, the spectral data of **3a** and **5a** are shown below.

3a: M.S.: $m/e = 312$ ($M^{\oplus}$).

I.R. (Nujol): $\nu_{C=O} = 1665$ cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 2.97$ (s, 6H, $N(CH_3)_2$), 3.24 (s, 3H, NCH_3), 3.48 (s, 3H, NCH_3), 4.90 (d, 1H, $J = 12$ Hz, —CH=CH—N—), 7.24–7.84 (m, —CH=CH—N— and 5H$_{arom}$), 9.48 ppm (s, 1H, —CH=N). On proton spin decoupling, the vinyl proton signal is $\delta = 7.48$ ppm (d, 1H, $J = 12$ Hz).

U.V. (ethanol): λ_{max} (log ε) = 279 (4.40), 350 (4.14), 395 nm (4.14).

5a: M.S.: $m/e = 267$ ($M^{\oplus}$).

I.R. (Nujol): $\nu_{C=O} = 1702$, 1650 cm^{-1}.

^{1}H-N.M.R. (CF_3COOD): $\delta = 3.59$ (s, 3H, NCH_3), 3.90 (s, 3H, NCH_3), 7.68–8.16 (m, 5H$_{arom}$), 8.71 (d, 1H$_{arom}$, $J = 9$ Hz), 8.87 ppm (d, 1H$_{arom}$, $J = 9$ Hz).

U.V. (ethanol): λ_{max} (log ε) = 277 (4.33), 335 (3.66).

Compound **5a** is alternatively prepared as follows: a suspension of the uracil **6**[3] (1.0 g, 0.005 mol) and phenylacetaldehyde (0.90 g, 0.0075 mol) in ethanol (30 ml) containing piperidine (2.55 g, 0.03 mol) is heated under reflux for 10 h. The reaction mixture is concentrated in vacuo to one-third of the volume. The separated solid is filtered and recrystallized from dimethylformamide/ethanol to give **5a**; yield: 0.21 g (16%); which is identical in all respects with the sample obtained above.

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