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Synthesis of Cyclooctapyrimidine-2,4-diones by Photocycloaddition of 6-Chloro-1,3-dimethyluracil to Benzenes in the Presence of Trifluoroacetic Acid[1]

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Photoreaction of 6-chloro-1,3-dimethyluracil in benzene and monosubstituted benzenes furnished cycloaddition products, cyclooctapyrimidine-2,4-dione derivatives, in the presence of trifluoroacetic acid.

Keywords cyclooctapyrimidine-2,4-dione; photocycloaddition; 6-chloro-1,3-dimethyluracil; benzene; monosubstituted benzene; acid-catalyzed photoreaction

Although there are numerous publications describing the photocycloaddition reaction of uracil and its derivatives to olefins from the organic and biological points of view,[2] the photocycloaddition to benzene has not yet been reported. We have recently reported that the photoreaction of 5-halo-1,3-dimethyluracils (halogen: Br[3], Cl[4] and F[5]) was significantly affected by the presence of acid and proceeded differently depending on the halogen on the uracil ring and the reaction systems. In our continuing studies on the scope of this reaction, we aimed to extend our work to the photoreaction of 6-halo-1,3-dimethyluracils with substituted benzenes. We now report that, in the presence of an acid, the photoreaction of 6-chloro-1,3-dimethyluracil in benzene or its monosubstituted derivatives leads to the formation of the phtocycloaddition products, 1,3-dimethylcyclooctapyrimidine-2,4-diones, probably *via ortho*-cycloaddition.

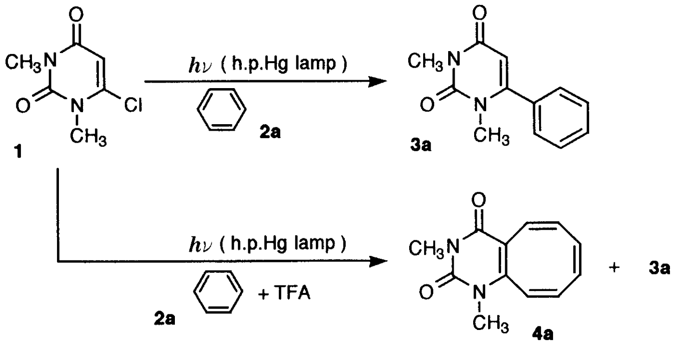


Chart 1

TABLE I. Photolysis of 6-Chloro-1,3-dimethyluracil (**1**) in Benzene (**2a**)

Acid	(mmol)	Lamp	Yields (%)[a,b] **3a**	Yields (%)[a,b] **4a**	Consumed **1** (%)[a]
None		h.p.[c]	3.6 (33)	— (—)	11
None		l.p.[d]	3.7 (25)	2.5 (17)	15
TFA	(0.05)	h.p.[c]	1.6 (3.9)	25.5 (62)	41
TFA	(1.2)	h.p.[c]	2.3 (3.3)	22 (32)	69
TFA	(0.05)	l.p.[d]	3.7 (11.5)	14 (44)	32
TFA	(1.2)	l.p.[d]	2.1 (8.8)	9.0 (37.5)	24
AcOH	(0.05)	h.p.[c]	3.5 (16.5)	1.3 (6.2)	21
AcOH	(1.25)	h.p.[c]	4.1 (14.5)	2.9 (10)	28
$ZnCl_2$	(0.05)	h.p.[c]	13 (18)	28 (39.5)	71
H_2SO_4	(0.05)	h.p.[c]	19 (24)	19 (24)	79
H_2SO_4	(1.25)	h.p.[c]	17 (61)	— (—)	28

a) Yields were determined by HPLC. *b*) Yields given in parentheses are based on **1** consumed. *c*) Reaction time, 10 h. *d*) Reaction time, 3 h.

A simple photolysis of a solution of 6-chloro-1,3-dimethyluracil (**1**) in benzene (**2a**) with a high-pressure mercury (h.p. Hg) lamp (>300 nm) for 10 h afforded 1,3-dimethyl-6-phenyluracil (**3a**)[3] in low yield (3.6%), together with a large amount of unreacted **1** (89%). By contrast, the addition of trifluoroacetic acid (TFA) (0.05 mmol) to the solution gave rise to the formation of 1,3-dimethylcyclooctapyrimidine-2,4-dione (**4a**) in appreciable yield (62%, based on 41% **1** consumed), while the formation of **3a** was suppressed significantly (3.9%) (Chart 1). The reaction in the presence of zinc chloride, despite deposition on the bottom of the reaction tube, proceeded smoothly to afford **4a** in 39.5% yield (based on 71% **1** consumed), together with **3a** in 18% yield. Sulfuric acid was also effective to some extent for the formation of **4a**, whereas acetic acid was much less effective. These results are summarized in Table I.

Ultraviolet (UV) irradiation of a solution of **1** in benzene (**2a**) in the presence of TFA (0.05 mmol) with a low-pressure mercury (l.p. Hg) lamp (254 nm) afforded **4a** with **3a** but in lower **4a**/**3a** ratio (3.8) than that observed for the reaction with the h.p. Hg lamp (16) (Table I).

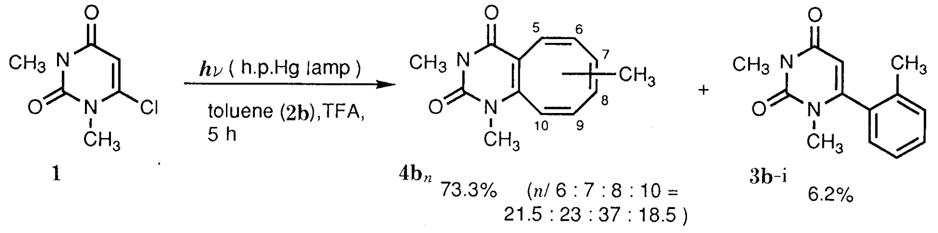
The structural assignment of **4a** was made essentially on the basis of the mass spectrum (MS) and the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. The MS of **4a** showed the molecular ion peak (M^{+}) at m/z 216 (100%). The ^{1}H-NMR spectrum (acetone-d_6) exhibited two sharp signals at 3.23 and 3.31 ppm due to the N^3- and N^1-methyl groups and peaks ascribable to six vinyl protons between 5.95—6.35 ppm. The ^{1}H–^{1}H shift correlated spectroscopy (acetone-d_6) δ (ppm)[6] exhibited peaks ascribed to 5-H at δ 6.11 ($J_{5-6}=11.49$; $J_{5-7}=-0.11$ Hz), 6-H at δ 5.97 ($J_{6-7}=3.91$; $J_{6-8}=-0.34$; $J_{6-9}=0.89$ Hz), 7-H at δ 6.03 ($J_{7-8}=11.58$; $J_{7-9}=-0.10$), 8-H at δ 6.07 ($J_{8-9}=3.21$), 9-H at δ 6.33 ($J_{9-10}=11.48$), and 10-H at δ 6.22. The observation of the nuclear Overhauser effect (NOE) between the peaks due to N^1-methyl and 10-H confirmed the assignment of the peak at δ 6.22 to 10-H.

On the basis of the above observations, the preparative-scale UV irradiation of **1** and benzene (**2a**) was carried out in the presence of TFA with the h.p. Hg lamp, and the cycloadduct **4a** was produced in practical yield (48.6%, based on 41.8% **1** consumed) (Table II). We have further

TABLE II. Photoreaction of 6-Chloro-1,3-dimethyluracil (**1**) in Benzenes (**2**) in the Presence of Trifluoroacetic Acid

2x	Reaction time (h)/lamp	TFA (mmol)	Yields[a] (%) of **3x**-i—iii Isomer ratio (%); i,	ii,	iii	**4x**$_n$ Isomer ratio (%); $n=$ 5,	6,	7,	8,	9,	10	Consumed **1** (%)
2a	10/h.p.	50		8.8				48.6				41.8
2b	5/h.p.	2		6.2				73.3				14.6
			[100,	—,	—]	[—,	21.5,	23,	37,	—,	18.5]	
2c	10/l.p.	2		34.5				8.3				49.5
			[66,	14,	20]	[100,	—,	—,	—,	—,	—]	
2d	5/l.p.	2		18.7				41.5				28.9
			[58,	26,	16]	[13,	34,	16,	19.5,	17.5,	—]	

[a] Yields are given on the basis of **1** consumed.



Yields; based on **1** consumed (14.6%).

Chart 2

conducted the photoreaction of **1** in various monosubstituted benzenes (toluene (**2b**), anisole (**2c**), fluorobenzene (**2d**), chlorobenzene (**2e**)) under similar conditions. The photoreaction with toluene (**2b**) afforded four isomeric 1,3-dimethyl-*n*-methyl (=1,3,*n*-trimethyl)cyclooctapyrimidine-2,4-diones (**4b**$_n$) in fair total yield (73.3%, based on 14.6% **1** consumed) ($n=6$, 7, 8, 10; **4b**$_6$, 18.5%; **4b**$_7$, 16.4%, **4b**$_8$, 25.3%; **4b**$_{10}$, 13.0%), together with 1,3-dimethyl-6-(2-tolyl)uracil (**3b**-i)[3] (6.2%) (Chart 2).

The reaction with anisole (**2c**) under similar conditions was sluggish and no cycloadduct (**4c**) was obtained.[7] However, the reaction with the l.p. Hg lamp in place of the h.p. Hg lamp gave the expected cycloaddition product, 1,3-dimethyl-5-methoxycyclooctapyrimidine-2,4-dione (**4c**$_5$) as a single regioisomer, albeit in low yield (8.3%) (based on 49.5% **1** consumed). The reaction with fluorobenzene (**2d**) was preliminarily examined with the h.p. Hg lamp in a Pyrex test tube and the l.p. Hg lamp in a quartz test tube (5 h). In comparison with the reaction using the l.p. Hg lamp, the reaction with the h.p. Hg lamp gave the corresponding cyclooctapyrimidine derivatives (**4d**) and the 6-aryl derivatives (**3d**), in a higher **4d**/**3d** ratio (4.5) (l.p. Hg lamp, **4d**/**3d**=3), but proceeded more slowly (conversion of **1**, 19.0%; **4d**, 5.8%) than the reaction with the l.p. Hg lamp did (conversion of **1**, 36.7%; **4d**, 10.1%). Therefore, the reaction of **2d** was carried out with the l.p. Hg lamp under similar conditions to those employed for **2c**, to give five regioisomeric 1,3-dimethyl-*n*-fluorocyclooctapyrimidine-2,4-diones (**4d**$_n$, $n=5$, 6, 7, 8, 9) in a total of 41.5%, together with 1,3-dimethyl-6-(*n*-fluorophenyl)uracils ($n=$ 2,3,4; **3d**-i, **3d**-ii, **3d**-iii) in 11%, 4.7%, and 3.0% (total yield 18.7%), respectively (yields are based on 28.9% **1** consumed). The results are summarized in Table II. The photoreaction with **2e** either with the h.p. Hg lamp or with the l.p. Hg lamp failed to yield the isolable amounts of a cycloaddition product or a substitution product. In this reaction, significant amounts of aromatic materials were obtained from the non-polar fraction, the NMR spectra of which showed the absence of a uracil moiety in the molecules. Presumably most of the incident light was not used for the activation of the uracil moieties but for the decomposition of **2e**, probably through simple homolysis of the C–Cl bond or *via* excimer formation.[8]

The structural assignments for the cyclooctapyrimidines (**4b**—**d**) were made essentially on the basis of their NMR spectra, especially a) the H–H coupling constants analogous with those of **4a** between the vinyl protons (J_{5-6}, J_{7-8}, $J_{9-10}=$ *ca.* 11—12 Hz; J_{6-7}, $J_{8-9}=$ *ca.* 3—4 Hz; ${}^{F-H}J_{5-6}$, ${}^{F-H}J_{7-8}$, ${}^{F-H}J_{9-10}=$ *ca.* 14—16 Hz; ${}^{F-H}J_{6-7}$, ${}^{F-H}J_{8-9}=0$—1 Hz), and b) the observation of the nuclear Overhauser effects (NOE) between N^1-methyl and 10-H, and between C-methyl (**4b**) or O-methyl (**4c**) and the neighboring protons. These spectral data are listed in Tables III and IV.

The UV spectrum of **1** (λ_{max} 262 nm) (0.08 mM) was shifted *ca.* 6 nm to the red in cyclohexane by the addition of TFA (9 eq molar). This new spectrum was insensitive to the added **2a**, whereas the fluoresence of this solution (emission λ_{max} at 330 nm with excitation at 285 nm) was quenched efficiently (*ca.* 65%) by **2a** (0.09 mM). Furthermore, addition of a triplet quencher, piperylene, to the reaction with **2a** had no effect on the formation of **4**, suggesting that the present cycloaddition may proceed *via* the singlet excited state of protonated **1** or the charge transfer complex of **1** and TFA.

The changes in the **4**/**3** ratio depending on the light source empolyed may be attributed to the excitation processes: a) the reactions in **2a**, **b**, and **d** with the h.p.

TABLE III. ^{1}H-NMR Chemical Shifts δ (ppm) for 1,3-Dimethylcyclooctapyrimidine-2,4-diones (**4a**—**d**)

	N^1–CH_3	N^3–CH_3	5-H	6-H	7-H	8-H	9-H	10-H	C–CH_3	O–CH_3
4a$^{a,b)}$	3.31	3.23	6.11	5.97	6.03	6.07	6.33	6.22		
4b$_6$$^{c)}$	3.33	3.35	5.94	—	6.01	5.93	6.30	6.02	1.87	
4b$_7$$^{c)}$	3.33	3.36	5.92	6.14	—	5.74	6.26	5.97	1.80	
4b$_8$$^{c)}$	3.35	3.36	6.15	6.02	5.78	—	6.23	5.95	1.83	
4b$_{10}$$^{a,b)}$	3.28	3.22	6.24	6.00	5.95	6.10	6.08	—	1.97	
4c$_5$$^{c)}$	3.32	3.35	—	5.19	6.14	5.89	6.38	6.21	—	3.70
4d$_5$$^{c)}$	3.36	3.37	—	5.83	5.99	6.08	6.49	6.40		
4d$_6$$^{c)}$	3.35	3.36	5.98	—	5.97	6.25	6.38	6.16		
4d$_7$$^{d)}$	3.31	3.36	6.45	5.92	—	5.78	6.27	6.15		
4d$_8$$^{a)}$	3.35	3.24	6.13	5.92	5.83	—	6.34	6.57		
4d$_9$$^{e)}$	3.30	3.36	6.28	6.16	6.40	5.99	—	6.09		

a) Acetone-d_6. *b)* Determined by using an NMR analyzing program, LAOCN3.[6] *c)* $CDCl_3$. *d)* $CDCl_3$: acetone-d_6 = 1 : 1. *e)* CD_3OD.

TABLE IV. Spin–Spin Coupling (^{1}H–^{1}H and ^{1}H–F) Constants (J = Hz) for 1,3-Dimethylcyclooctapyrimidine-2,4-diones (**4a**—**d**)

	5-6	5-7	5-8	5-9	6-7	6-8	6-9	7-8	7-9	7-10	8-9	9-10
4a$^{a,b)}$	11.5	−0.1			3.9	−0.3	0.9	11.6	−0.1		3.2	11.5
4b$_6$$^{c)}$								11.5			3.4	11.5
4b$_7$$^{c)}$	11.4										3.4	11.4
4b$_8$$^{c)}$	11.4				3.4							11.5
4b$_{10}$$^{a,b)}$	11.2	−0.3	0.2	−0.1	3.9	−0.3	1.0	11.4	−1.3		3.7	
4c$_5$$^{c)}$					3.9		1.0	11.2	0.6		3.6	11.5
4d$_5$$^{c)}$	13.7	—	2.0	—	3.9	1.0	1.5	11.2	1.0	—	3.4	11.7
4d$_6$$^{c)}$	15.6						3.4	11.6	1.0	0.6	3.4	11.6
4d$_7$$^{d)}$	11.2							15.1	5.8		3.9	11.2
4d$_8$$^{a)}$	11.2	1.0	1.0		4.4	6.5	1.0	15.9			1.0	11.2
4d$_9$$^{e)}$	11.7				3.9		3.9	11.7				14.2

a) Acetone-d_6. *b)* Determined by using an NMR analyzing program, LAOCN3.[6] *c)* $CDCl_3$. *d)* $CDCl_3$: acetone-d_6 = 1 : 1. *e)* CD_3OD.

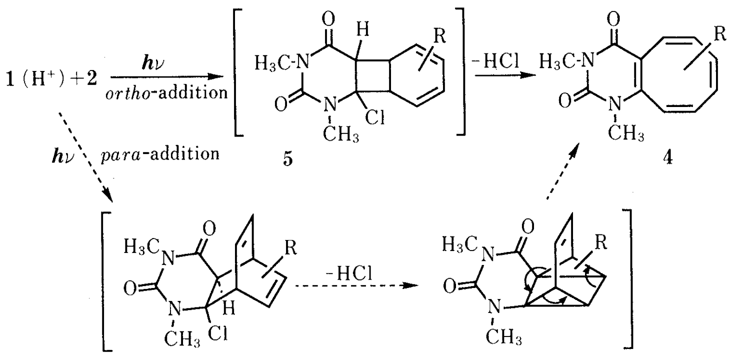


Chart 3

Hg lamp (>300 nm) are presumed to be derived from the initial excitation of protonated **1**, since, under the conditions used, the incident light (302 nm) is absorbed preferentially by protonated **1** (97% in **2a**, 93% in **2b**, and 98% in **2d**, respectively); in the case of anisole (**2c**), **2c** absorbs the 302 nm incident light considerably (53%), resulting in significant suppression of the reaction; b) the reaction with the l.p. Hg lamp may be initiated from the excited aromatic molecules (**2**), since the incident 254 nm light is absorbed predominantly by **2** (98—99%).

There are two possible modes of cycloaddition leading to the formation of cyclooctapyrimidines (**4**), *i.e.*, *ortho*- and *para*-cycloaddition (Chart 3).[9] However, in view of the reports that photocycloaddition of olefins to benzenes generally involves *ortho* and/or *meta*-cycloaddition depending on the electron donor–acceptor relationships of the addends, whereas *para*-cycloaddition occurs only in some special cases,[10] it seems more plausible that the cycloadducts (**4**) resulted from the *ortho*-cycloaddition intermediate (**5**) followed by a subsequent ring opening process and simultaneous elimination of hydrogen chloride.

The importance of the presence of the 5-H and the C^6–Cl for the formation of cyclooctapyrimidines (**4**) was suggested by the following results: a) photolysis of 6-chloro-1,3-dimethylthymine is benzene in the presence of TFA afforded only 1,3-dimethyl-6-phenylthymine and 1,3-dimethylthymine; and b) no product was obtained from the photoreaction of 1,3-dimethyluracil in benzene under similar conditions.

Although the details of the reaction mechanism remain unclear, it is noteworthy that the present reaction provides the first example of the synthesis of cycloaddition products of uracil moiety to benzenes.[11] Further studies on the synthetic application of this reaction are in progress.

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were measured with a JEOL JNM-EX400 (400 MHz) spectrometer, and chemical shifts are given on the δ (ppm) scale with tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were determined on a Shimadzu GCMS 9100-MK spectrometer at 70 eV. UV and fluoresence spectra were taken on Shimadzu UV-240 and Shimadzu RF-540 instruments, respectively. Short-column chromatography was performed on Kieselgel Si-60 (Merck). Reverse-phase column chromatography (RP-LC) was conducted on LiChroprep RP-18 size B (Merck) with an FMI pump (Fluid Metering, Inc.). Reverse-phase high-performance liquid chromatography (RP-HPLC) was performed either on a Wakosil II-5C18-100 column eluting with aqueous methanol (30—70%) (25 cm × 4.6 mm i.d., for analytical scale) or on a Shim-pac PREP-ODS (25 cm × 20 mm i.d., for preparative scale) (Shimadzu), using a Shimadzu LC-6A apparatus with monitoring at 254 nm. Similarly, silica gel HPLC (Si-HPLC) was conducted on a Shim-pac PREP-Sil (25 cm × 20 mm i.d.), using the same apparatus. UV irradiation was carried out externally with a 500 W h.p. Hg lamp (Eiko-sha) in a degassed Pyrex tube (>300 nm) or with a 60 W l.p. Hg lamp (Eiko-sha) in an argon-filled quartz test tube (254 nm) on a merry-go-round apparatus at room temperature. For preparative-scale photoreactions, UV irradiation was carried out externally with the h.p. Hg lamp in a doughnut type Pyrex vessel (500 ml), or internally with the l.p. Hg lamp in a Pyrex vessel (500 ml), under an argon atmosphere at room temperature.

Materials 6-Chloro-1,3-dimethyluracil (**1**)[12] and 6-chloro-1,3-dimethylthymine[13] were prepared according to the reported methods.

General Procedure for the Photolysis of 6-Chloro-1,3-dimethyluracil (1) in Benzene (2a) in the Presence of Various Acids (Analytical Scale) Photolysis of a solution of **1** (0.025 mmol) in **2a** (5 ml) was carried out in the absence or in the presence of an acid with the h.p. Hg lamp in a degassed Pyres tube (>300 nm) on a merry-go-round apparatus for 10 h, and the reaction mixture was subjected to RP-HPLC analysis, using 5-chloro-1,3-dimethyluracil as an internal standard.

General Procedure for the Photoreaction of 6-Chloro-1,3-dimethyluracil (1) with Benzenes (2) (Preparative Scale) A solution of **1** (1 mmol) and TFA in a substituted benzene (**2a**—**d**) (200 ml) was irradiated with a lamp as described above. The reaction mixture was concentrated *in vacuo*, and the residual oil was passed through a short column of silica gel with hexane, CH_2Cl_2, CH_2Cl_2–ether and ether, successively. The CH_2Cl_2–ether eluate was submitted to RP-HPLC and/or Si-HPLC.

Photoreaction of 1 in Benzene (2a) After photoreaction with the h.p. Hg lamp, the reaction mixture was passed through a short column of silica gel, and the ethereal eluate was submitted to Si-HPLC with ether–hexane (1 : 1) to afford 1,3-dimethylcyclooctapyrimidine-2,4-dione (**4a**) (44.0 mg, 20.4%) and 1,3-dimethyl-6-phenyluracil (**3a**) (7.8 mg, 3.7%), together with the recovered **1** (101.5 mg, 58.2%). **4a**: mp 130—131 °C (from isopropanol). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 221 (18500), 247.5 (10300), 305 (2080). MS *m/z* (%): 216 (M^+, 100), 159 (42), 131 (90). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59, N, 12.96. Found: C, 66.60; H, 5.61; N, 12.92.

Photoreaction of 1 in Toluene (2b) After photoreaction with the h.p. Hg lamp, the reaction mixture was passed through a short column of silica gel, and the ethereal eluate was submitted to RP-LC first with 25% aqueous methanol, then with 60% aqueous methanol to give **1** (149.0 mg, 85.4%), and a mixture of the photoproducts. The mixture was further submitted to Si-HPLC (ether–hexane, 40—42%) to afford 1,3,10-trimethylcyclooctapyrimidine-2,4-dione (**4b**$_{10}$) (4.4 mg, 1.9%), **4b**$_6$ (colorless oil, 6.3 mg, 2.7%), and a mixture of **4b**$_7$, **4b**$_8$, and 1,3-dimethyl-6-(2-tolyl)uracil (**3b**-i). The mixture was recrystallized from hexane to give **3b-i** (2.0 mg, 0.9%) and a mixture of **4b**$_7$ and **4b**$_8$ (5.6 mg, 2.4% and 8.4 mg, 3.7%, based on the NMR spectrum).

1,3,6-Trimethyl-cyclooctapyrimidine-2,4-dione (**4b**$_6$): Colorless oil, MS *m/z* (%): 231 (29), 230 (M^+, 100), 229 (24), 215 (19), 190 (13), 173 (40), 172 (17), 158 (29). HRMS: Calcd: $C_{13}H_{14}N_2O_2$: 230.1055. Found: 230.1080.

1,3,8-Trimethylcyclooctapyrimidine-2,4-dione (**4b**$_8$): HRMS (mixture of **4b**$_7$ and **4b**$_8$): Calcd. $C_{13}H_{14}N_2O_2$: 230.1055. Found: 230.1049.

1,3,10-Trimethylcyclooctapyrimidine-2,4-dione (**4b**$_{10}$): Colorless oil. MS *m/z* (%): 231 (23), 230 (M^+, 100), 229 (25), 215 (32), 173 (34), 172 (20), 158 (46). HRMS: Calcd: $C_{13}H_{14}N_2O_2$: 230.1055. Found: 230.1030.

Photoreaction of 1 in Anisole (2c) After photoreaction with the l.p. Hg lamp, the reaction mixture was passed through a short column of silica gel, and the hexane–CH_2Cl_2 (1 : 1) eluate was submitted to RP-LC with 30% aqueous methanol to furnish **1** (88.0 mg, 50.5%) and a mixture of products. The mixture was further submitted to RP-HPLC (33% aqueous methanol) to afford 1,3-dimethyl-5-methyloxycyclooctapyrimidine-2,4-dione (**4c**$_5$) (10.2 mg, 4.1%), 1,3-dimethyl-6-(2-methoxyphenyl)uracil (**3c**-i)[3] (28.0 mg, 11.4%), and a mixture of the *meta* (**3c**-ii)[3] and the *para* isomers (**3c**-iii)[3] (fraction 1) (14.8 mg), successively. Fraction 1 was further submitted to Si-HPLC with 25% ethyl acetate in hexane to afford **3c**-ii (6.0 mg, 2.4%) and **3c**-iii (8.2 mg, 3.3%), respectively.

1,3-Dimethyl-5-methoxycyclooctapyrimidine-2,4-dione (**4c**$_5$): Yellowish oil. HRMS: Calcd: $C_{13}H_{14}N_2O_3$: 246.1005. Found: 236.1006.

Photoreaction of 1 in Fluorobenzene (2d) After photoreaction with the l.p. Hg lamp, the reaction mixture was passed through a short column of silica gel with hexane, CH_2Cl_2, and CH_2Cl_2–ether, successively. The CH_2Cl_2–ether (1 : 1) eluate was submitted to RP-LC with 25% aqueous methanol to give **1** (124.0 mg, 71%) and a fraction containing a mixture of photoproducts. The fraction was extracted with chloroform, then the extract was dried over anhydrous Na_2SO_4, and evaporated. The residual mixture (92 mg) was further subjected to reverse-phase HPLC (36% aqueous methanol) to afford 1,3-dimethyl-5-fluorocyclooctapyrimidine-2,4-dione (**4d**$_5$) (5.6 mg), **4d**$_6$ (9.3 mg, 4.0%), a mixture of **4d**$_7$, **4d**$_8$, and **4d**$_9$ (fraction 1) (17.9 mg), a mixture of 1,3-dimethyl-6-(*n*-fluorophenyl)-uracil (**3d**-ii, $n=3$) and **3d**-iii ($n=4$) (fraction 2) (5.2 mg), and **3d**-i (7.2 mg, 3.1%), successively. Fraction 1 was subjected to Si-HPLC with 20% ethyl acetate in hexane to give **4d**$_9$ (5.0 mg, 2.1%), **4d**$_8$ (5.4 mg, 2.3%), and **4d**$_7$ (4.6 mg, 2.0%), successively. Pure **4d**$_5$ (3.7 mg, 1.6%) was obtained by passage through a short column of alumina. Fraction 2 was further submitted to Si-HPLC with 3% ethyl acetate in CH_2Cl_2 to afford **3d**-ii (3.2 mg, 1.4%) and **3d**-iii (2.0 mg, 0.9%), respectively.

1,3-Dimethyl-5-fluorocyclooctapyrimidine-2,4-dione (**4d**$_5$): Colorless oil. MS *m/z* (%): 235 (23), 234 (M^+, 100), 177 (30), 176 (19). HRMS: Calcd: $C_{12}H_{11}FN_2O_2$: 234.0804. Found: 234.0801.

1,3-Dimethyl-6-fluorocyclooctapyrimidine-2,4-dione (**4d**$_6$): Yellowish crystals, mp 142—143 °C (hexane). MS *m/s* (%): 235 (19), 234 (M^+, 100), 177 (31), 176 (16). HRMS: Calcd: $C_{12}H_{11}FN_2O_2$: 234.0804. Found: 234.0801.

1,3-Dimethyl-7-fluorocyclooctapyrimidine-2,4-dione (**4d**$_7$): mp 148.5—149.5 °C (hexane). HRMS: Calcd: $C_{12}H_{11}FN_2O_2$: 234.0804. Found: 234.0778.

1,3-Dimethyl-8-fluorocyclooctapyrimidine-2,4-dione (**4d**$_8$): Yellow crystals, mp 138—139 °C (from hexane). MS *m/z* (%): 235 (20), 234 (M^+, 100), 177 (33), 176 (29). HRMS: Calcd: $C_{12}H_{11}FN_2O_2$: 234.0804. Found: 234.0783.

1,3-Dimethyl-9-fluorocyclooctapyrimidine-2,4-dione (**4d**$_9$): Yellow crystals, mp 138—139 °C (from hexane). MS *m/z* (%): 235 (19), 234 (M^+, 100), 217 (11), 177 (40), 176 (33). HRMS: Calcd: $C_{12}H_{11}FN_2O_2$: 234.0804. Found: 234.0793.

1,3-Dimethyl-6-(2-fluorophenyl)uracil (**3d**-i): Colorless oil. ^{1}H-NMR (CD_3OD) δ[6]: 3.19 (3H, s, N–CH_3), 3.36 (3H, s, N–CH_3), 5.73 (1H, s, 5-H), 7.30 (1H, ddd, $J=9.9$, 8.5, 1.1 Hz, 3′-H), 7.36 (1H, ddd, $J=7.6$, 7.5, 1.1 Hz, 5′-H), 7.45 (1H, ddd, $J=7.5$, 7.4, 1.7 Hz, 6′-H), 7.61 (1H, dddd, $J=8.5$, 7.6, 5.5, 1.7 Hz, 4′-H). MS *m/z* (%): 235 (12), 234 (M^+, 77), 233 (35), 215 (20), 136 (100). HRMS: Calcd: $C_{12}H_{11}FN_2O_2$: 234.0804. Found: 234.0789.

1,3-Dimethyl-6-(3-fluorophenyl)uracil (**3d**-ii): Colorless crystals, mp 119—120 °C (from hexane). ^{1}H-NMR ($CDCl_3$) δ[6]: 3.23 (3H, s, N–CH_3), 3.41 (3H, s, N–CH_3), 5.71 (1H, s, 5-H), 7.07 (1H, ddd, $J=8.8$, 2.4, 1.5 Hz, 2′-H), 7.13 (1H, ddd, $J=7.8$, 1.5, 1.0 Hz, 6′-H), 7.22 (1H, tdd, $J=8.3$, 2.4, 1.0 Hz, 4′-H), 7.49 (1H, ddd, $J=8.3$, 7.8, 5.9 Hz, 5′-H). MS *m/z* (%): 235 (13), 234 (M^+, 83), 233 (61), 176 (39), 136 (100). *Anal.* Calcd for $C_{12}H_{11}FN_2O_2$: C, 61.53; H, 4.73; N, 11.96. Found: C, 61.55; H, 4.60; N, 11.77.

1,3-Dimethyl-6-(4-fluorophenyl)uracil (**3d**-iii): Colorless crystals, mp 144.5—145.5 °C (from benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ[6]: 3.22 (3H, s, N–CH_3), 3.41 (3H, s, N–CH_3), 5.69 (1H, s, 5-H), 7.20 (2H, tdd, $J=8.8$, 2.4, 0.4 Hz, 3′ and 5′-H), 7.35 (2H, dddd, $J=8.8$, 4,8, 2.4, 0.4 Hz, 2′ and 6′-H). MS *m/z* (%): 235 (14), 234 (M^+, 87), 233 (64), 176 (38), 136 (100). *Anal.* Calcd for $C_{12}H_{11}FN_2O_2$: C, 61.53; H, 4.73; N, 11.96. Found: C, 61.72; H, 4.61; N, 11.81.

References and Notes

1) K. Seki, N. Kanazashi, and K. Ohkura, *Heterocycles*, **32**, 229

(1991).

2) D. Bryce-Smith, "Photochemistry," Vol. 6—17, The Royal Society of Chemistry, Cambridge, 1975—1986.

3) K. Seki, K. Matsuda, Y. Bando, and K. Ohkura, *Chem. Pharm. Bull.*, **36**, 4737 (1988).

4) K. Ohkura, K. Matsuda, and K. Seki, *Heterocycles*, **32**, 1371 (1991).

5) K. Seki and K. Ohkura, *Nucleosides and Nucleotides*, **11**, 521 (1992).

6) Determined by using a NMR analyzing program, revised for NEC PC9801 use by Dr. H. Ogawa (Computer Center, Tokyo University) on the basis of the LAOCN3 QCPE library program (#111 by A. A. Bother-By and S. M. Castellano, 1966; Chemistry Department, Room 204, Indiana University, Bloomington, Indiana 47401).

7) The analytical-scale photoreaction of **2c** (5 h) gave **4c** in 0.8% yield and **3c** in 6.4% yield, along with unreacted **1** (80%).

8) M. Kojima, H. Sakuragi, and K. Tokumaru, *Chem. Lett.*, **1981**, 1539.

9) E.Grovenstein Jr., T. C. Campbell, and T. Shibata, *J. Org. Chem.*, **34**, 2418 (1969); D. Bryce-Smith, A. Gilbert, and J. Grzonka, *J. Chem. Soc., Chem. Commun.*, **1970**, 498.

10) J. Mattay, *Tetrahedron*, **41**, 2405 (1985); K. N. Houk, *Pure Appl. Chem.*, **54**, 1633 (1982).

11) A successful photocycloaddition of **1** to alkenes has been reported; C. Kaneko and N. Shimomura, *Tetrahedron Lett.*, **23**, 257 (1982).

12) W. Pfleiderer and K.-H. Schündehütte, *Justus Liebigs Ann. Chem.*, **612**, 158 (1958).

13) G. Strauss, *Justus Liebigs Ann. Chem.*, **638**, 205 (1960).