at atmospheric pressure and room temperature for 20 min. The catalyst was filtered off through Celite, and the filtrate was evaporated to afford 0.193 g (96%) of compound **9a**: mp 141–142 °C (chloroform); IR (KBr) 3523 (br), 3342 (br), 1772 cm^{-1}; ^1H NMR δ 1.7–2.0 (m, 4 H), 2.5–2.7 (m, 2 H), 4.0–4.5 (m, 4 H), 4.8 (s, 1 H (OH)), 5.7 (s, 1 H (OH)), 7.2 (s, 5 H); ^{13}C NMR δ 25.4, 34.4, 36.5, 75.4, 75.9, 78.6, 87.3, 108.5, 126.4, 129.0, 129.1, 142.9, 175.7; MS *m/e* (relative intensity) 294 (M, 3), 129 (27), 119 (33), 117 (21), 104 (66), 91 (100); $[\alpha]_D$ = +36° (*c* 1.0). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 60.85; H, 6.21.

2-Butyl-3-oxo-L-gulonolactone 3,6-Hemiketal (9b). Compound **9b** was prepared in 91% yield from **6b** by the same procedure as **9a**. Compound **9b**: mp 89–90 °C (spontaneous crystallization); IR (KBr) 3423 (br), 1785 cm^{-1}; ^1H NMR δ 0.8–1.9 (m, 9 H), 3.9–4.7 (m, 4 H); ^{13}C NMR δ 14.1, 23.5, 25.5, 34.5, 75.4, 75.9, 78.7, 87.3, 108.5, 175.8; MS *m/e* (relative intensity) 232 (M, <1), 119 (53), 102 (40), 101 (21), 85 (100), 57 (34); $[\alpha]_D$ = +29° (*c* 1.5). Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.88; H, 7.08.

2-Cyclohexyl-3-oxo-L-gulonolactone 3,6-Hemiketal (9i). Compound **9i** was prepared in 96% yield from **6i** by the same procedure as **9a**. Compound **9i**: mp 148–149 °C (chloroform); IR (KBr) 3504, 3382 (br), 1788 cm^{-1}; ^1H NMR δ 1.0–2.0 (m, 11 H), 4.0–4.6 (m, 4 H + 1 H (OH)), 4.8 (br s, 1 H (OH)); ^{13}C NMR δ 26.6, 26.9, 27.6, 42.9, 75.0, 75.9, 80.6, 87.9, 108.6, 175.4; MS *m/e* (relative intensity) 258 (M, <0.5), 119 (25), 102 (28), 85 (68), 81 (100), 71 (25), 55 (82), 41 (62); $[\alpha]_D$ = +40° (*c* 1.0). Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.65; H, 7.08.

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Registry No. 1, 50-81-7; **3a**, 21040-45-9; **3c**, 6737-11-7; **3d**, 2442-10-6; **3g**, 1191-16-8; **3h**, 10500-12-6; **3i**, 14447-34-8; **4a**, 106625-69-8; **4b**, 121725-70-0; **4c**, 106625-68-7; **4e**, 1469-70-1; **4f**, 70122-91-7; **4g**, 116504-03-1; **4h**, 121740-92-9; **4i**, 119825-50-2; **6a**, 127855-06-5; **6b**, 117383-61-6; **6d**, 127855-07-6; **6e**, 117383-59-2; **6f**, 117383-60-5; **6g**, 127855-08-7; **6h** (isomer 1), 127855-09-8; **6h** (isomer 2), 127855-10-1; **6i** (isomer 1), 127855-11-2; **6i** (isomer 2), 127855-12-3; **7**, 15042-01-0; **9a**, 127855-13-4; **9b**, 127820-02-4; **9i**, 127820-03-5; **10a**, 127880-39-1; 3,3-dicinnamylpentane-2,4-dione, 106536-22-5.

Cerium(IV)-Mediated Halogenation at C-5 of Uracil Derivatives

Jun-ichi Asakura*,† and Morris J. Robins‡

Department of Biochemistry, Kinki University School of Medicine, Ohno-higashi, Osaka-sayama, Osaka 589, Japan, and Department of Chemistry, Brigham Young University, Provo, Utah 84602

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Treatment of protected uracil nucleosides **1** or **2** with elemental iodine or metal halogenides and ceric ammonium nitrate (CAN) at 80 °C gave the corresponding protected 5-halouracil nucleosides **3a–f** in excellent yields. Treatment of the resulting crude **3a–f** with 0.1 M NaOMe/MeOH at ambient temperature gave the corresponding 5-halouridines **4a–f** in high overall yields from **1** or **2**. Further, 5-halouracils **9a–f** were prepared in good yields by treatment of 1,3-dimethyluracil (**7**) or uracil (**8**) with elemental iodine, metal halogenides, or hydrochloric acid and CAN. Halouridines **4a–e** also were obtained in good yields by treatment of unprotected uracil nucleosides **5** or **6** with halogen sources as above and CAN.

Halogen-substituted nucleosides and related compounds have been shown to exhibit interesting chemotherapeutic, biochemical, and biophysical properties.[1] A number of 5-substituted uracil derivatives, especially 2′-deoxyuridines, have been investigated extensively for the experimental and clinical treatment of neoplastic and viral diseases.[2] In addition, they have been utilized as intermediates for a variety of synthetic transformations of related compounds of biological interest.[3-5] Recently, it has been shown that 5-iodouracil derivatives undergo high-yield coupling with terminal alkynes to give 5-alkynyluracil nucleosides with antiviral activity,[6] and such products can be transformed into fluorescent 5-substituted compounds for automated DNA sequencing.[7] Therefore, new methods for the convenient synthesis of 5-halouracil derivatives are of current interest in nucleoside chemistry.

Halogenated pyrimidine and purine nucleosides have been prepared by direct reaction with halogens. Iodination of pyrimidine bases takes place under vigorous conditions. For example, Prusoff and co-workers described the first 5-iodination of uridine and 2′-deoxyuridine using an iodine/nitric acid system.[8] Dale et al. have effected iodination of ill-defined 5-mercuriuridine derivative mixtures in aqueous alcohol.[9] *N*-Iodosuccinimide has been utilized for iodination of pyrimidine nucleosides.[10] Iodine monochloride has been found to give high yields of 5-iodo-

† Kinki University School of Medicine.
‡ Brigham Young University.

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Table I. Results of the CAN-Mediated Halogenation[a] of Acetylated Uracil Nucleosides 1 and 2 and Deacetylation[b] of Their Halonucleosides 3

entry	compd	MS (mol equiv)	CAN, mol equiv	solvent[c]	time, h	product (yield, %)[d] 3	4[e]
1	1	I_2 (0.6)	0.5	MeCN	1.0	**3a** (96)	**4a** (93)
2	1	NaI (1.2)	0.5	MeCN	48.0	**3a** (0)[f]	
3	1	NaI (1.2)	1.0	MeCN	48.0	**3a** (63)[g]	
4	1	NaI (1.2)	2.0	MeCN	8.0	**3a** (93)	**4a** (90)
5	1	LiI (1.2)	2.0	MeCN	1.0	**3a** (95)	**4a** (94)
6	1	LiBr (1.2)	2.0	MeCN	1.5	**3b** (91)	**4b** (87)
7	1	LiCl (1.2)	2.0	MeCN	24.0	**3c** (90)	
8	1	LiCl (1.2)	2.0	MeCN/AcOH (1:1)	6.0	**3c** (94)	**4c** (88)
9	2	I_2 (0.6)	0.5	MeCN	1.0	**3d** (92)	**4d** (90)
10	2	LiI (1.2)	2.0	MeCN	1.0	**3d** (93)	**4d** (89)
11	2	LiBr (1.2)	2.0	MeCN	1.5	**3e** (90)	**4e** (85)
12	2	LiCl (1.2)	2.0	MeCN/AcOH (1:1)	6.0	**3f** (95)	**4f** (94)

[a] Halogenation reactions were effected with 0.5 mmol of starting material at 80 °C. [b] Deacetylation was carried out with crude halogenated **3** in 0.1 M NaOMe/MeOH (8 mL) at ambient temperature for 1 h. [c] Solvent volume was 8 mL. [d] Isolated yields of purified products. [e] Overall yields from starting material **1** or **2**. [f] A major amount of starting material remained, and partial deacetylation occurred (TLC analysis). [g] Starting material remained, and deacetylated products were formed (TLC analysis).

uracil products under mild conditions.[11] The 5-bromination of uracil derivatives has been effected with Br_2/acetic anhydride,[12] Br_2/H_2O,[13] Br_2/dimethylformamide,[14] and *N*-bromosuccinimide.[15] Chlorination of uracil derivatives has been realized using elemental chlorine[13a,16] or *N*-chlorosuccinimide in acetic acid[17,18] to provide the 5-chlorouracils. It has been found that treatment of uracil compounds with iodobenzene dichloride in warm acetic acid gave good yields of the 5-chloro products.[11] Ryu and MacCoss discovered that 3-chloroperoxybenzoic acid serves as an oxidant to effect chlorination and bromination of nucleosides in aprotic solvents containing hydrogen chloride or bromine.[19]

Recently lanthanide compounds have been used as shift reagents and reagents for organic synthesis.[20] Sugiyama has demonstrated that ceric ammonium nitrate (ammonium hexanitratocerate(IV), CAN) and elemental iodine or iodine salts effect iodination of benzenoid aromatics.[21] We have shown that protected uracil nucleosides are converted to their 5-iodo counterparts by elemental iodine in the presence of CAN as the in situ oxidant (generation of an electrophilic iodo species).[22] We now present general procedures for CAN-mediated halogenation at C-5 of uracil derivatives.

Halogenations of acetylated uracil nucleosides **1** and **2** were effected by their treatment with elemental iodine or metal halogenides and CAN at 80 °C. Deacetylation of the crude halogenated uracil nucleosides **3a–f** was carried out with 0.1 M NaOMe/MeOH at ambient temperature for 1 h. All products were purified by silica gel column chromatography or recrystallization and characterized by elemental analyses and spectroscopic (NMR, mass, UV) properties. These results are summarized in Table I.

It was found that treatment of acetylated uracil nucleosides **1** or **2** with 0.6 mol equiv of elemental iodine and 0.5 mol equiv of CAN in acetonitrile (MeCN) gave excellent isolated yields of the corresponding acetylated 5-iodo products **3a** and **3d**. This CAN-mediated halogenation reaction proceeded well with alkali-metal halogenides (sodium iodide, lithium iodide, lithium bromide, and lithium chloride) as halogen sources. However, treatment of **1** with 1.2 mol equiv of NaI and 0.5 mol equiv of CAN did not give acetylated 5-iodouridine (**3a**) after 48-h reaction time, and partial deacetylation of **1** occurred (TLC analysis) (Table I, entries 2 and 3). Halogenation with metal halogenides required excess CAN. Iodination with LiI proceeded more readily than with NaI (Table I, entries 4 and 5). Bromination of the acetylated nucleosides **1** and **2** were effected with CAN/LiBr in MeCN at 80 °C to give high isolated yields of the acetylated 5-bromo products **3b** and **3e**. Triacetylated 5-chlorouridine (**3c**) was obtained in 90% yield with CAN/LiCl in MeCN at 80 °C for 24 h. However, the use of MeCN/AcOH (1:1) as solvent accelerated this chlorination (Table I, entries 7 and

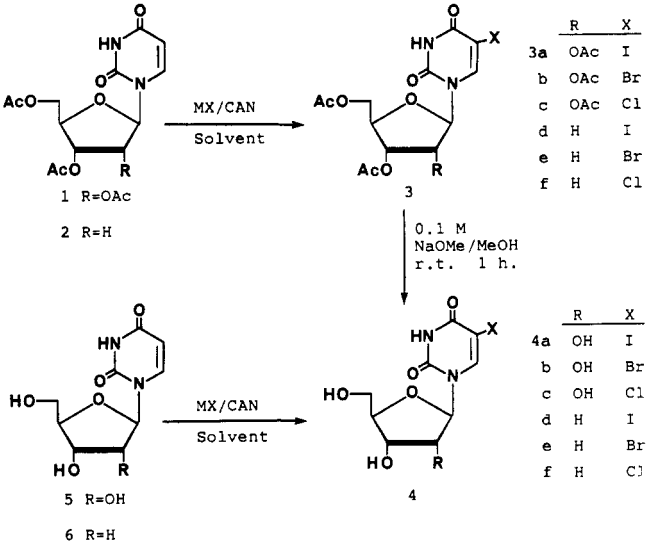

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Table II. Results of the CAN-Mediated Halogenation of Unprotected Uracil Nucleosides 5 and 6[a]

compd	MX (mol equiv)	CAN, mol equiv	solvent[b]	temp, °C	time, h	product (yield, %)[c]
5	I_2 (0.6)	0.5	AcOH	80	0.5	**4a** (80)
5	LiI (1.2)	2.0	AcOH	80	0.5	4a (78)
5	LiBr (1.2)	2.0	AcOH	80	0.5	**4b** (82)
5	LiCl (1.2)	2.0	AcOH	80	4.0	*d*
5	HCl[e]	2.0	MeOH[e]	70	8.0	**4c** (83)
6	I_2 (0.6)	0.5	AcOH	80	0.5	**4d** (77)
6	LiI (1.2)	2.0	AcOH	80	0.5	4d (73)
6	LiBr (1.2)	2.0	AcOH	80	0.5	**4e** (81)
6	HCl[e]	2.0	MeOH[e]	70	7.0	*f*

[a] Halogenation reactions were effected with 0.5 mmol of starting nucleosides. [b] Solvent volume was 8 mL. [c] Isolated yields of purified products. [d] Some starting material remained, and several products were formed (TLC analysis). [e] Concentrated hydrochloric acid/MeOH (3:5, 8 mL) was used. [f] Chlorination and decomposition reactions were competitive (TLC analysis).

Table III. Results of the CAN-Mediated Halogenation of 1,3-Dimethyluracil (7) and Uracil (8)[a]

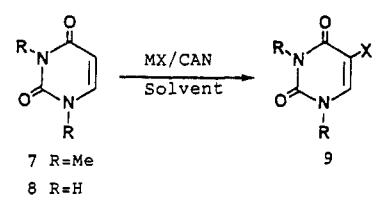
compd	MX (mol equiv)	CAN, mol equiv	solvent[b]	temp, °C	time, h	product (yield, %)[c]
7	I_2 (0.6)	0.5	MeCN	80	2.5	9a (88)
7	LiI (1.2)	2.0	MeCN	80	3.0	**9a** (85)
7	LiBr (1.2)	2.0	MeCN	80	0.5	**9b** (80)
7	LiCl (1.2)	2.0	MeCN/AcOH (1:1)	80	4.0	**9c** (74)
8	I_2 (0.6)	0.5	MeOH	70	5.0	**9d** (80)
8	LiI (1.2)	2.0	MeOH	70	3.0	**9d** (82)
8	LiBr (1.2)	2.0	MeOH	70	6.0	**9e** (83)
8	LiCl (1.2)	2.0	MeOH	70	48.0	**9f** (tr)[d]
8	LiCl (1.2)	2.0	MeOH/AcOH (1:1)	70	24.0	**9f** (tr)[d]
8	HCl[e]	2.0	MeOH[e]	70	5.5	**9f** (82)

[a] Halogenation reactions were effected with 150 mg of starting 7 or 8. [b] Solvent volume was 8 mL. [c] Isolated yields of purified products. [d] Starting material was mainly unchanged (TLC analysis). [e] Concentrated hydrochloric acid/MeOH (3:5, 8 mL) was used.

8). This may result from the enhanced solubility of LiCl in MeCN/AcOH or the enhanced oxidation potential of CAN in acidic solution.[23] Acetylated 5-chloro-2′-deoxyuridine (**3f**) also was obtained in high yield (95%) with LiCl/CAN in MeCN/AcOH as solvent. Treatment of the crude acetylated 5-halouracil nucleosides **3a–f** with 0.1 M NaOMe/MeOH gave the 5-halouracil nucleosides **4a–f** in high overall yields from **1** or **2** (Table I).

It was found that halogenation of unprotected uridine (**5**) or 2′-deoxyuridine (**6**) could be effected with halogen sources in the presence of CAN in AcOH (or HCl/H_2O/MeOH). These results are shown in Table II. The 5-iodo- and 5-bromouracil nucleosides **4a,b,d,e** were obtained in good yields with elemental iodine, LiI, or LiBr, and CAN in acetic acid at 80 °C for 0.5 h. However, chlorination of **5** and **6** by LiCl/CAN in AcOH did not proceed cleanly. The chlorination rate was slow, and acetylation occurred slowly in the acetic acid solution. Treatment of uridine (**5**) with concentrated aqueous hydrochloric acid and CAN in MeOH at 70 °C for 8 h gave 5-chlorouridine (**4c**) in 83% yield. Attempted chlorination of 2′-deoxyuridine (**6**) under the same conditions resulted in competitive chlorination and decomposition.

Halogenations of 1,3-dimethyluracil (**7**) and uracil (**8**) were effected with several halogen sources and CAN at 70 or 80 °C. The 5-halogenated uracil derivatives **9a–f** were obtained in good yields. These results are summarized in Table III.



7 R=Me
8 R=H

9

	R	X
9a	Me	I
b	Me	Br
c	Me	Cl
d	H	I
e	H	Br
f	H	Cl

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The CAN-mediated halogenation reactions presumably occur by attack of an electron-deficient halogen species (formed by in situ oxidation) at C-5 of the uracil ring.[5]

$$\text{CAN} + \text{MX} \rightarrow \tfrac{1}{2}X_2 + \text{Ce(III)}$$

$$\tfrac{1}{2}X_2 + \text{CAN} \rightarrow \text{“}X^+\text{”} + \text{Ce(III)}$$

$$\text{“}X^+\text{”} + \text{uracil compd} \rightarrow \text{5-halouracil compd}$$

Attempted fluorination with LiF/CAN failed, as expected, since the fluoride/fluorine oxidation potential is higher than that of Ce(IV)/Ce(III).[24]

In summary, the CAN-mediated halogenation of uracil derivatives described herein has advantages over other available methods. It gives good to excellent yields of 5-halouracil products. Reagents are readily available, and the lithium halide salts are easy to weigh and handle. Mild reaction conditions are employed with short reaction times, except for chlorination, and workup procedures are straightforward. This CAN-mediated halogenation also is useful with other organic compounds such as enones (to be published separately).

Experimental Section

General Procedures. Melting points were determined in glass capillary tubes and are uncorrected. Proton NMR spectra were recorded with a Jeol JNM GX-400 spectrometer at 400 MHz with tetramethylsilane as internal standard. Me_2SO-d_6 was used as solvent unless otherwise noted. Electron-impact high-resolution mass spectra were determined by the Mass Spectroscopy Laboratory, Kinki University, on a Jeol HX-100 spectrometer. Elemental analyses were performed by the Analytical Center of Dainippon Pharmaceuticall Co., Ltd. UV spectra were obtained in MeOH with a Hitachi 323 spectrophotometer. MeCN and MeOH were refluxed over and distilled from calcium hydride. Other solvents used were dried and distilled by ordinary methods.

(24) F_2/F^-, 2.87 V; Ce(IV)/Ce(III), 1.44 V; Cl_2/Cl^-, 1.36 V; Br_2/Br^-, 1.07 V; I_2/I^-, 0.535 V. *Handbook of Chemistry and Physics*, 52nd ed.; Weast, R. C., Ed.; The Chemical Rubber Co.: Cleveland, OH, 1971, pp D-111–D-113.

CAN, iodine, metal halogenides, and hydrochloric acid were of the highest chemical grade commercially available. CAN and metal halogenides were dried over P_2O_5 under vacuum at 60 or 100 °C for several hours before use. Reaction progress was monitored by TLC with Merck silica gel 60 F-254 plastic sheets. Merck silica gel 60 or Wakogel C-200 was used for column chromatography. Chromatographic solvents used: A, $CHCl_3$/acetone, 4:1; B, $CHCl_3$/acetone, 9:1; C, EtOAc/*i*-PrOH/H_2O, 4:1:2, upper phase. Flash evaporations were conducted at reduced pressure. Reactions were heated in an oil bath at the indicated temperature.

Iodination of Acetylated Uracil Nucleosides 1 or 2. Method A. A mixture of **1**[25] or **2**[26a] (0.5 mmol), iodine (76 mg, 0.3 mmol), CAN (137 mg, 0.25 mmol), and MeCN (8 mL) was stirred at 80 °C for 1 h. Reaction progress was monitored by TLC (solvent A). Solvent was evaporated, and the residue was partitioned between a cold[27] mixture of EtOAc (20 mL), saturated NaCl/H_2O (10 mL), and 5% $NaHSO_3$/H_2O (5 mL). The aqueous layer was extracted with EtOAc (10 mL × 2). The combined organic layer was washed carefully[27] with cold 5% $NaHSO_3$/H_2O (5 mL) followed by saturated NaCl/H_2O (15 mL) and H_2O (15 mL × 2), dried ($MgSO_4$), and evaporated. The crude 5-iodo products were purified by column chromatography (**3a**) or recyrstallization (**3d**).

5-Iodo-2′,3′,5′-tri-*O*-acetyluridine (3a). Crude **3a** was purified by column chromatography (Merck silica gel 60, 230–400 mesh, 40 g, 2.2 × 30 cm, solvent B). Appropriately pooled fractions were evaporated and coevaporated with Et_2O (10 mL × 2) to give 238 mg (96%) of **3a** as a TLC homogenous (solvent A) colorless solid glass: ^{1}H NMR δ 2.06, 2.07, 2.08 (3 s, 3 H, 3 H, and 3 H, OAc's), 4.22–4.28 (m, 2 H, H-5′,5″), 4.32–4.36 (m, 1 H, H-4′), 5.33–5.36 (m, 1 H, H-3′), 5.46 ("t", *J* = 5.7 Hz, 1 H, H-2′), 5.87 (d, *J* = 5.0 Hz, 1 H, H-1′), 8.18 (s, 1 H, H-6), 11.84 (br s, 1 H, NH); UV λ_{min} 246 nm (ε 2700), λ_{max} 283 nm (ε 8200); HR-MS for M$^+$, calcd *m/z* 495.9981, found 495.9954. Anal. Calcd for $C_{15}H_{17}IN_2O_9$: C, 36.31; H, 3.45; N, 5.65; I, 25.57. Found: C, 36.31; H, 3.46; N, 5.48; I, 25.69.

5-Iodo-3′,5′-di-*O*-acetyl-2′-deoxyuridine (3d). The crude product was recrystallized from EtOH to give 201 mg (92%) of colorless needles of **3d**: mp 160.5–162 °C (lit. mp 157–159 °C,[6a] 158–160 °C[28]); ^{1}H NMR δ 2.07, 2.11 (2 s, 3 H and 3 H, OAc's), 2.29–2.48 (m, 2 H, H-2′,2″), 4.20–4.29 (m, 3 H, H-4′,5′,5″), 5.17–5.19 (m, 1 H, H-3′), 6.11 (t, *J* = 7.1 Hz, 1 H, H-1′), 8.05 (s, 1 H, H-6), 11.74 (br s, 1 H, NH); UV λ_{min} 246 nm (ε 1800), λ_{max} 285 nm (ε 7600); HR-MS for M$^+$, calcd *m/z* 437.9925, found 437.9923. Anal. Calcd for $C_{13}H_{15}IN_2O_7$: C, 35.63; H, 3.45; N, 6.39; I, 28.96. Found: C, 35.91; H, 3.63; N, 6.16; I, 28.99.

Method B. A mixture of the acetylated nucleosides **1** or **2** (0.5 mmol), LiI (80 mg, 0.6 mmol), CAN (548 mg, 1.0 mmol), and MeCN (8 mL) was stirred at 80 °C for 1 h. Evaporation of solvent, workup, and product purification were accomplished as in method A. Yields of purified products are given in Table I.

Bromination of Acetylated Nucleosides 1 or 2. A mixture of **1** or **2** (0.5 mmol), LiBr (52 mg, 0.6 mmol), CAN (548 mg, 1.0 mmol), and MeCN (8 mL) was stirred at 80 °C for 1.5 h. Reaction progress was monitored by TLC (solvent A). Solvent was evaporated, and the resulting residue was partitioned between EtOAc (20 mL) and saturated NaCl/H_2O (10 mL). The aqueous layer was extracted with EtOAc (10 mL × 2). The combined organic layer was washed with H_2O (15 mL × 2), dried ($MgSO_4$), and evaporated. The resulting crude **3b** and **3e** were purified by column chromatography (Merck silica gel 60, 230–400 mesh, 40 g, 2.2 × 30 cm, solvent B).

5-Bromo-2′,3′,5′-tri-*O*-acetyluridine (3b). Appropriately pooled fractions were evaporated and coevaporated with Et_2O (10 mL × 2) to give 204 mg (91%) of **3b** as a TLC homogeneous (solvent A) colorless solid glass: ^{1}H NMR δ 2.066, 2.074 (2 s, 3 H and 6 H, OAc's), 4.23–4.29 (m, 2 H, H-5′,5″), 4.33–4.36 (m, 1 H, H-4′), 5.33–5.36 (m, 1 H, H-3′), 5.48 ("t", *J* = 5.1 Hz, 1 H, H-2′), 5.89 (d, *J* = 5.1 Hz, 1 H, H-1′), 8.21 (s, 1 H, H-6), 11.98 (s, 1 H, NH); UV λ_{min} 241 nm (e 2700), λ_{max} 276 nm (ε 10400); HR-MS for M$^+$ calcd *m/z* 448.0118, found 448.0096. Anal. Calcd for $C_{15}H_{17}BrN_2O_9$: C, 40.11; H, 3.81; N, 6.24; Br, 17.79. Found: C, 39.84; H, 3.62 N, 6.04; Br, 17.95.

5-Bromo-3′,5′-di-*O*-acetyl-2′-deoxyuridine (3e). Appropriately pooled fractions were evaporated and coevaporated with EtOH/Et_2O (1:2, 10 mL × 3) to give 176 mg (90%) of **3e** as a TLC homogeneous (solvent A) colorless crystalline powder. An analytical sample was recrystallized from EtOH to give colorless needles: mp 152.5–153 °C; ^{1}H NMR δ 2.06, 2.08 (2 s, 3 H and 3 H, OAc's), 2.29–2.54 (m, 2 H, H-2′,2″), 4.18–4.27 (m, 3 H, H-4′,5′,5″), 5.17–5.20 (m, 1 H, H-3′), 6.13 (t, *J* = 7.1 Hz, 1 H, H-1′), 8.06 (s, 1 H, H-6), 11.90 (s, 1 H, NH); UV λ_{min} 241 nm (ε 2200), λ_{max} 278 nm (ε 9400); HR-MS for M$^+$, calcd *m/z* 390.0064, found 390.0059. Anal. Calcd for $C_{13}H_{15}BrN_2O_7$: C, 39.92; H, 3.87; N, 7.16; Br, 20.43. Found: C, 39.81; H, 3.68; N, 7.09; Br, 20.61.

Chlorination of Acetylated Nucleosides 1 or 2. A mixture of **1** or **2** (0.5 mmol), LiCl (25 mg, 0.6 mmol), CAN (548 mg, 1.0 mmol), and MeCN/AcOH (1:1, 8 mL) was stirred at 80 °C for 6 h. Workup utilized the same procedures as bromination of **1** and **2**.

5-Chloro-2′,3′,5′-tri-*O*-acetyluridine (3c). Crude **3c** was purified by column chromatography (Merck silica gel 60, 230–400 mesh, 40 g, 2.2 × 30 cm, solvent B). Appropriately pooled fractions were evaporated and coevaporated with Et_2O (10 mL × 3) to give 190 mg (94%) of **3c** as a TLC homogeneous (solvent A) colorless solid glass: ^{1}H NMR δ 2.06, 2.07 (2 s, 6 H and 3 H, OAc's), 4.23–4.29 (m, 2 H, H-5′,5″), 4.32–4.37 (m, 1 H, H-4′), 5.34 (t, *J* = 5.9 Hz, 1 H, H-3′), 5.48 (t, *J* = 5.1 Hz, 1 H, H-2′), 5.89 (d, *J* = 5.1 Hz, 1 H, H-1′), 8.15 (s, 1 H, H-6), 12.01 (br s, 1 H, NH); UV λ_{min} 237 nm (ε 1900), λ_{max} 273 nm (ε 9700); HR-MS for M$^+$, calcd *m/z* 404.0623, found 404.0614. Anal. Calcd for $C_{15}H_{17}ClN_2O_9$: C, 44.51; H, 4.23; N, 6.92; Cl, 8.76. Found: C, 44.22; H, 4.13; N, 6.74; Cl, 8.75.

5-Chloro-3′,5′-di-*O*-acetyl-2′-deoxyuridine (3f). The residue was coevaporated with EtOH/Et_2O (1:2, 10 mL × 3) to give a crystalline powder. This was recrystallized from EtOH to give 165 mg (95%) of **3f** as colorless fine needles: mp 174.5–175 °C; ^{1}H NMR δ 2.06, 2.07 (2 s, 3 H and 3 H, OAc's), 2.29–2.54 (m, 2 H, H-2′,2″), 4.18–4.27 (m, 3 H, H-4′,5′,5″), 5.17–5.20 (m, 1 H, H-3′), 6.13 (t, *J* = 6.4 Hz, 1 H, H-1′), 8.01 (s, 1 H, H-6), 11.93 (br s, 1 H, NH); UV λ_{min} 238 nm (ε 1700), λ_{max} 275 nm (ε 9700); HR-MS for M$^+$, calcd *m/z* 346.0568, found 346.0571. Anal. Calcd for $C_{13}H_{15}ClN_2O_7$: C, 45.03; H, 4.36; N, 8.08; Cl, 10.23. Found: C, 44.99; H, 4.22; N 8.04; Cl, 10.30.

Deacetylation Procedure. After halogenation and workup, the crude acetylated 5-halouridine compound **3a–f** was stirred with 0.1 M NaOMe/MeOH (8 mL) for 1 h at ambient temperature. Reaction progress was monitored by TLC (solvent C). Addition of 2 mL of H_2O was followed by neutralization (pH ~6) with Dowex 50W-X8 (H^+) ion-exchange resin. The resin was filtered and washed with 50% aqueous MeOH (20 mL). The combined filtrate and washings were evaporated and coevaporated with EtOH/EtOAc/toluene (1:1:2, 10 mL × 2). The resulting crude product was purified by recrystallization or column chromatography.

5-Iodouridine (4a). The crystalline product was recrystallized from MeOH/Et_2O (diffusion[26b]) to give 174 mg (94% from **1**) of **4a** as colorless needles: mp 208–209 °C dec (lit. mp 205–208 °C dec,[8a] 208–210 °C dec[11]); ^{1}H NMR δ 3.54–3.70 (m, 2 H, H-5′,5″), 3.85–3.87 (m, 1 H, H-4′), 3.96–3.99 (m, 1 H, H-3′), 4.01–4.05 (m, 1 H, H-2′), 5.07, 5.26, 5.42 (d, t, and d, 1 H, 1 H, and 1 H, OH's), 5.72 (d, *J* = 4.6 Hz, 1 H, H-1′), 8.48 (s, 1 H, H-6), 11.65 (br s, 1 H, NH); UV λ_{min} 246 nm (ε 1500), λ_{max} 286 nm (ε 7300); HR-MS for M$^+$, calcd *m/z* 369.9662, found 369.9653. Anal. Calcd for $C_9H_{11}IN_2O_6$: C, 29.21 H, 3.00; N, 7.57; I, 34.29. Found: C, 29.37; H, 2.89; N, 7.45; I, 34.41.

5-Iodo-2′-deoxyuridine (4d). The crystalline solid was recrystallized from H_2O to give 159 mg (90% from **2**) of **4d** as colorless needles: mp 164–184 °C dec (lit. mp 160–180 °C dec,[8b] 160 °C dec[28]); ^{1}H NMR δ 2.10–2.14 (m, 2 H, H-2′,2″), 3.54–3.64 (m, 2 H, H-5′,5″), 3.78–3.80 (m, 1 H, H-4′), 4.23–4.25 (m, 1 H, H-3′), 5.14, 5.24 (t and d; 1 H and 1 H; OH's), 6.09 (t, *J* = 6.6 Hz, 1 H, H-1′), 8.39 (s, 1 H, H-6), 11.65 (s, 1 H, NH); UV λ_{min} 246 nm (ε

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2100), λ_{max} 285 nm (ϵ 8500); HR-MS for M^+, calcd m/z 353.9713, found 353.9704. Anal. Calcd for $C_9H_{11}IN_2O_5$: C, 30.53; H, 3.13; N, 7.91; I, 35.84. Found: C, 30.60; H, 3.00; N, 7.83; I, 35.90.

5-Bromouridine (4b). The crude material was dissolved in 1 mL of MeOH, silica gel (Wakogel C-200, 1 g) was added, and the mixture was dried overnight at room temperature over P_2O_5. This was applied to a dry-packed column (Wakogel C-200, 23 g, 1.1 × 42 cm) and eluted with solvent C. Appropriately pooled fractions were evaporated, coevaporated with EtOH/EtOAc/toluene (1:1:2, 10 mL × 2), and further dried at room temperature over P_2O_5 to give 141 mg (87% from 1) of **4b** as a TLC homogeneous (solvent C) colorless crystalline powder. An analytical sample was recrystallized from MeOH/Et_2O (diffusion[26b]) to give colorless needles: mp 203–204 °C dec (lit. mp 181–184 °C dec[29]); ^1H NMR δ 3.55–3.72 (m, 2 H, H-5′,5″), 3.86–3.87 (m, 1 H, H-4′), 3.97–4.01 (m, 1 H, H-3′), 4.03–4.06 (m, 1 H, H-2′), 5.08, 5.28, 5.43 (d, t, and d; 1 H, 1 H, and 1 H, OH's), 5.73 (d, J = 4.8 Hz, 1 H, H-1′), 8.49 (s, 1 H, H-6), 11.82 (s, 1 H, NH); UV λ_{min} 242 nm (ϵ 2400), λ_{max} 279 nm (ϵ 10600); HR-MS for M^+, calcd m/z 321.9801, found 321.9815. Anal. Calcd for $C_9H_{11}BrN_2O_6$: C, 33.46; H, 3.43; N, 8.67; Br, 24.73. Found: C, 33.51; H, 3.19; N, 8.59; Br, 24.79.

5-Bromo-2′-deoxyuridine (4e). The crude product was treated as **4b** to give a TLC homogeneous (solvent C) crystalline powder of **4e** (131 mg, 85% from **2**) and analytically pure fine needles: mp 173.5–175.5 °C dec (lit. mp 187–189 °C[13b]); ^1H NMR δ 2.12–2.15 (m, 2 H, H-2′,2″), 3.55–3.66 (m, 2 H, H-5′,5″), 3.79–3.81 (m, 1 H H-4′), 4.22–4.26 (m, 1 H, H-3′), 5.17, 5.25 (t and d; 1 H and 1 H; OH's), 6.11 (t, J = 6.5 Hz, 1 H, H-1′), 8.40 (s, 1 H, H-6), 11.77 (br s, 1 H, NH); UV λ_{min} 242 nm (ϵ 1800), λ_{max} 279 nm (ϵ 9700); HR-MS for M^+, calcd m/z 305.9851, found 305.9848. Anal. Calcd for $C_9H_{11}BrN_2O_5$: C, 35.20; H, 3.61; N, 9.12; Br, 26.02. Found: C, 35.18; H, 3.48; N, 9.01; Br, 26.19.

5-Chlorouridine (4c). The crude product was treated as **4b** to give a TLC homogeneous (solvent C) crystalline powder of **4c** (123 mg, 88% from **1**) and analytically pure needles: mp 212–214 °C dec (lit. mp 217–217.5 °C,[13a] 245 °C,[30] 220–223 °C dec[31]); ^1H NMR δ 3.57–3.71 (m, 2 H, H-5′,5″), 3.86–3.87 (br m, 1 H, H-4′), 3.98–4.00 (br m, 1 H, H-3′), 4.05 (br s, 1 H, H-2′), 5.08, 5.28, 5.43 (3 br s, 1 H, 1 H, and 1 H, OH's), 5.74 (d, J = 4.6 Hz, 1 H, H-1′), 8.41 (s, 1 H, H-6), 11.85 (br s, 1 H, NH); UV λ_{min} 239 nm (ϵ 1800), λ_{max} 277 nm (ϵ 10600); HR-MS for M^+, calcd m/z 278.0306, found 278.0301. Anal. Calcd for $C_9H_{11}ClN_2O_6$: C, 38.79; H, 3.98; N, 10.05; Cl, 12.72. Found: C, 38.83; H, 3.75; N, 10.05; Cl, 12.80.

5-Chloro-2′-deoxyuridine (4f). The crude product was treated as **4b** to give a TLC homogeneous (solvent C) crystalline powder of **4f** (123 mg, 94% from **2**) and analytically pure fine needles: mp 169–170.5 °C (lit. mp 178–179.5 °C[32]); ^1H NMR δ 2.09–2.15 (m, 2 H, H-2′,2″), 3.56–3.65 (br m, 2 H, H-5′,5″), 3.79–3.81 (m, 1 H, H-4′), 4.25 (br s, 1 H, H-3′), 5.16, 5.25, (2 br s, 1 H and 1 H, OH's), 6.11 (t, J = 6.4 Hz, 1 H, H-1′), 8.32 (s, 1 H, H-6), 11.83 (br s, 1 H, NH); UV λ_{min} 238 nm (ϵ 1600), λ_{max} 277 nm (ϵ 10000); HR-MS for M^+ calcd m/z 262.0357, found 262.0323. Anal. Calcd for $C_9H_{11}ClN_2O_5$: C 41.16; H, 4.22; N, 10.67; Cl, 13.56. Found: C, 41.17; H, 4.08; N, 10.66; Cl, 13.59.

5-Iodo-1,3-dimethyluracil (9a). Method A. A mixture of 1,3-dimethyluracil (**7**) (150 mg, 1.07 mmol), iodine (163 mg, 0.64 mmol), CAN (293 mg, 0.54 mmol), and MeCN (8 mL) was stirred at 80 °C for 2.5 h. Reaction progress was monitored by TLC (solvent C). The mixture was evaporated, and the residue was treated with cold[27] $CHCl_3$ (20 mL), saturated NaCl/H_2O (10 mL), and 5% $NaHSO_3$/H_2O (5 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL × 2), and the combined organic layer was washed carefully with cold 5% $NaHSO_3$/H_2O (5 mL), saturated NaCl/H_2O (15 mL), and H_2O (15 mL × 2), dried (Na_2SO_4), evaporated, and coevaporated with EtOH (10 mL × 2) to give a colorless crystalline powder. This product was recrystallized from EtOH to give 251 mg (88%, in two crops) of **9a** as colorless fine needles: mp 210–230 °C (sublimation); ^1H NMR ($CDCl_3$) δ 3.42, 3.43 (2 s, 3 H and 3 H, NMe's), 7.65 (s, 1 H, H-6); UV λ_{min} 247 nm (ϵ 1800), λ_{max} 287 nm (ϵ 7800); HR-MS for M^+, calcd m/z 265.9552, found 265.9540. Anal. Calcd for $C_6H_7IN_2O_2$: C, 27.09; H, 2.65; N, 10.53; I, 47.70. Found: C, 27.14; H, 2.66; N, 10.31; I, 47.60.

Method B. A mixture of **7** (150 mg, 1.07 mmol), LiI (172 mg, 1.28 mmol), CAN (1.174 g, 2.14 mmol), and MeCN (8 mL) was stirred at 80 °C for 3 h. Workup as in method A gave 242 mg (85%, in two crops) of **9a**.

5-Bromo-1,3-dimethyluracil (9b). A mixture of **7** (150 mg, 1.07 mmol), LiBr (112 mg, 1.28 mmol), CAN (1.174 g, 2.14 mmol), and MeCN (8 mL) was stirred at 80 °C for 0.5 h. Reaction progress was monitored by TLC (solvent C). The mixture was evaporated, and the residues was partitioned between $CHCl_3$ (20 mL) and saturated NaCl/H_2O (10 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL × 2), and the combined organic layer was washed with saturated NaCl/H_2O (15 mL) and H_2O (15 mL × 2), dried (Na_2SO_4), evaporated, and coevaporated with EtOH (10 mL × 2) to give a colorless crystalline powder. This was recrystallized from EtOH to give 186 mg (80%, in two crops) of **9b** as colorless prisms: mp 183–184 °C (sublimation); ^1H NMR ($CDCl_3$) δ 3.42, 3.44 (2 s, 3 H and 3 H, NMe's), 7.54 (s, 1 H, H-6); UV λ_{min} 245 nm (ϵ 1700), λ_{max} 282 nm (ϵ 8500); HR-MS for M^+, calcd m/z 217.9691, found 217.9721. Anal. Calcd for $C_6H_7BrN_2O_2$: C, 32.90; H, 3.22; N, 12.79; Br, 36.48. Found: C, 33.06; H, 3.03; N, 12.95; Br, 36.48.

5-Chloro-1,3-dimethyluracil (9c). A mixture of **7** (150 mg, 1.07 mmol), LiCl (54 mg, 1.28 mmol), CAN (1.174 g, 2.14 mmol), and MeCN/AcOH (1:1, 8 mL) was stirred at 80 °C for 4 h. Workup as for **9b** gave a colorless crystalline powder that was recrystallized from EtOH/*n*-hexane to give 138 mg (74%, in two crops) of **9c** as colorless fine needles: mp 140–148 °C (sublimation); ^1H NMR ($CDCl_3$) δ 3.41, 3.44 (2 s, 3 H and 3 H, NMe's), 7.42 (s, 1 H, H-6); UV λ_{min} 242 nm (ϵ 1200), λ_{max} 280 nm (ϵ 8900); HR-MS for M^+, calcd m/z 174.0196, found 174.0216. Anal. Calcd for $C_6H_7ClN_2O_2$: C, 41.28; H, 4.04; N, 16.05; Cl, 20.31. Found: C, 41.14; H, 3.97; N, 15.83; Cl, 20.31.

5-Iodouracil (9d). Method A. A mixture of uracil (**8**) (150 mg, 1.34 mmol), iodine (204 mg, 0.80 mmol), CAN (367 mg, 0.67 mmol), and MeOH (8 mL) was stirred at 70 °C for 5 h. Reaction progress was monitored by TLC (solvent C). Solvent was evaporated, and coevaporation with EtOH/H_2O (2:1, 10 mL × 3) gave a colorless solid powder that was crystallized from EtOH/H_2O (1:1) to give 255 mg (80%) of colorless fine needles of **9d**. An analytical sample was recrystallized from EtOH/H_2O (1:1): mp 198 °C dec–245 °C sublimation–264 °C (lit. mp 272 °C dec[33]); ^1H NMR δ 7.88 (s, 1 H, H-6), 11.10–11.40 (2 br s, 2 H, NH's); UV λ_{min} 244 nm (ϵ 2200), λ_{max} 280 nm (ϵ 7500); HR-MS for M^+, calcd m/z 237.9239, found 237.9215. Anal. Calcd for $C_4H_3IN_2O_2$: C, 20.19; H, 1.27; N, 11.77; I, 53.32. Found: C, 20.33; H, 1.16; N, 11.58; I, 53.09.

Method B. A mixture of **8** (150 mg, 1.34 mmol), LiI (215 mg, 1.61 mmol), CAN (1.467 g, 2.68 mmol), and MeOH (8 mL) was stirred at 70 °C for 3 h. Workup as in method A gave colorless fine needles of **9d** (261 mg, 82%).

5-Bromouracil (9e). A mixture of **8** (150 mg, 1.34 mmol), LiBr (139 mg, 1.61 mmol), CAN (1.467 g, 2.68 mmol), and MeOH (8 mL) was stirred at 70 °C for 6 h. Workup as for **9d** gave a colorless solid powder that was crystallized from H_2O to give 212 mg (83%, in two crops) of **9e**. An analytical sample was recrystallized from H_2O: mp 245 °C dec–270 °C sublimation–296 °C (lit. mp 293 °C[29]); ^1H NMR δ 7.90 (s, 1 H, H-6), 11.15–11.55 (2 br s, 2 H, NH's); UV λ_{min} 240 nm (ϵ 1600), λ_{max} 276 nm (ϵ 7800); HR-MS for M^+, calcd m/z 189.9377, found 189.9366. Anal. Calcd for $C_4H_3BrN_2O_2$: C, 25.16; H, 1.58; N, 14.67; Br, 41.84. Found: C, 25.09; H, 1.46; N, 14.46; Br, 41.93.

5-Chlorouracil (9f). A mixture of **8** (150 mg, 1.34 mmol), CAN (1.467 g, 2.68 mmol), and freshly mixed concentrated hydrochloric acid/MeOH (3:5, 8 mL) was stirred at 70 °C for 5.5 h. Workup as for **9d** gave a residue that was crystallized from H_2O/EtOH to give 161 mg (82% in two crops) of **9f**. An analytical sample was recrystallized from H_2O/EtOH: mp 250 °C sublimation–280 °C dec–303 °C (lit. mp >325 °C dec[11]); ^1H NMR δ 7.85 (s, 1 H, H-6), 11.21, 11.55 (2 s, 1 H and 1 H, NH's); UV λ_{min} 237 nm (ϵ

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1200), λ_{max} 274 nm (ϵ 7600); HR-MS for M^+, calcd m/z 145.9883, found 145.9864. Anal. Calcd for $C_4H_3ClN_2O_2$: C, 32.79; H, 2.06; N, 19.19; Cl, 24.19. Found: C, 32.69; H, 2.04; N, 18.86; Cl, 24.14.

Halogenation of Unprotected Nucleosides 5 or 6. A mixture of **5** or **6** (0.5 mmol), halogen sources as above, CAN, and solvent (see Table II) was stirred at 70 or 80 °C. Reaction progress was monitored by TLC (solvent C). After halogenation was complete, the mixture was evarpoated and coevaporated with EtOH/toluene (1:2, 10 mL × 3) and then H_2O/EtOH (1:2, 10 mL × 3). The residual **4d** was twice recrystallized from H_2O/MeOH to give 136 mg (77%, in two crops) of **4d** as colorless crystals. The residual **4a**, **4b**, **4c**, or **4e** was coevaporated with solvent C (10 mL × 2) and dissolved in a minimum volume of that solvent. This sample was applied to a dry-packed columm (Merck silica gel 60, 70–230 mesh, 55 g, 2.2 × 27 cm) and eluted with solvent C. Appropriately pooled fractions were evaporated and coevaporated with toluene/EtOH (2:1, 10 mL × 2) to give a colorless crystalline solid. This was recrystallized from MeOH/Et_2O (diffusion[26b]) to an analytically pure product: **4a**, 147 mg, 80%; **4b**, 132 mg, 82%; **4c**, 115 mg, 83%; **4e**, 124 mg, 81%.

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Photoinduced Molecular Transformations. 110.[1] Formation of Furoquinolinones via β-Scission of Cyclobutanoxyl Radicals Generated from [2 + 2] Photoadducts of 4-Hydroxy-2-quinolone and Acyclic and Cyclic Alkenes. X-ray Crystal Structure of (6aα,6bβ,10aβ,10bα)-(±)-10b-Acetoxy-6a,6b,7,8,9,10,10a,10b-octahydro-5-methylbenzo[3,4]cyclobuta[1,2-*c*]quinolin-6(5*H*)-one[2,3]

Hiroshi Suginome,* Kazuhiro Kobayashi, Masahito Itoh, and Shinzo Seko

Organic Synthesis Division, Faculty of Engineering, Hokkaido University, Sapporo 060, Japan

Akio Furusaki

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060, Japan

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Several [2 + 2] photocycloadducts were prepared by the photoaddition of 4-acetoxy-2-quinolone or 4-hydroxy-*N*-methyl-2-quinolone with cyclic and acyclic olefins. The photoaddition of 4-acetoxy-2-quinolone with cyclopentene gave, exclusively, cis-cisoid-cis adduct while that with 1-methoxycyclopentene gave, exclusively, a head-to-head cis-transoid-cis adduct. Photoaddition with cyclohexene, on the other hand, afforded cis-cisoid-cis together with cis-transoid-cis adducts. The molecular structure of the latter was determined by an X-ray crystallographic analysis of its *N*-methyl derivative. Photoadditions of 4-acetoxy-2-quinolone and 4-hydroxy-*N*-methyl-2-quinolone with ethyl vinyl ether, 2-methoxypropene, isopropenyl acetate, and vinyl benzoate were all regioselective, each giving the corresponding single or double stereoisomers of head-to-head adduct(s). The photolysis of the hypoiodites generated from cyclobutanols derived from the photocycloadducts between 4-acetoxy-2-quinolone and cyclopentene or 2,3-dimethylbut-2-ene induced regioselective rearrangements of the corresponding alkoxyl radicals to give 2,3-furo-4-quinolinones. In contrast, 3,4-furo-2-quinolinones are regioselectively formed when the hypoiodites generated from cyclobutanols derived from the photoadducts of 4-acetoxy-2-quinolone with vinyl ethyl ether, isopropenyl acetate, or 1-methoxycyclopentene in benzene are irradiated. Both 3,4-furo-2-quinolinone and 2,3-furo-4-quinolinone are formed when the hypoiodites of cyclobutanols derived from the photoadducts between 4-hydroxy-2-quinolone and vinyl esters in benzene are irradiated. The pathways leading to the 2,3-furo-4-quinolinones and 3,4-furo-2-quinolinones as well as the selectivity in the formation of the two isomeric furoquinolinones from the cyclobutanoxyl radicals are discussed.

The [2 + 2]π cycloaddition is one of the most synthetically useful photoreactions. Numerous applications of both inter- and intramolecular [2 + 2] photoaddition to the synthetic problems have been reported using a variety of conjugated and nonconjugated cyclic and acyclic alkenes.[4] One of the remarkable applications is photoaddition of an alkene to an enolyzed 1,3-diketone or its acetate to form a β-ketocyclobutanol or its acetate, which can ionically fragment to give a 1,5-diketone by retro-aldolization.[5]

As part of our investigation to explore the potential of the β-scission of alkoxyl radicals for organic synthesis,[6] we

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