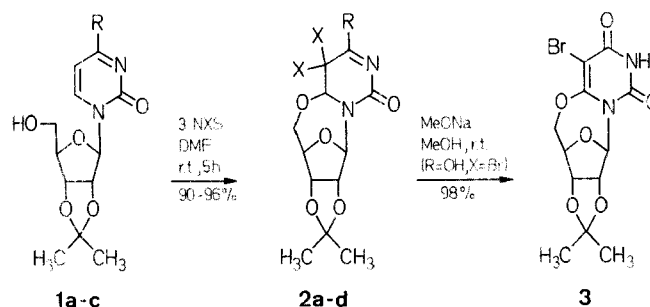


possessing biological activities and as a tool for conformational studies of naturally occurring nucleosides and nucleotides. Along this line, various types of the cyclonucleosides have been synthesized.¹

We now report here a facile synthesis of hitherto unknown 5'-*O*,6-cyclo-5,5-dihalogeno-5,6-dihydro-2',3'-*O*-isopropylidene-pyrimidine nucleosides **2**, which contain convertible functional groups in the molecule, starting from the readily available 2',3'-*O*-isopropylidene-pyrimidine nucleosides **1**. The unique feature of this method is that the reaction involves dihalogenation accompanying intramolecular 5'-*O*,6-cyclization.



NXS = *N*-bromo- or *N*-chlorosuccinimide

1	R
a	OH
b	NH ₂
c	NHCOC ₆ H ₅

A Facile Synthesis of 5'-*O*,6-Cyclo-5,5-dihalogeno-5,6-dihydropyrimidine Nucleosides

Magoichi Sako, Takao Saito, Keiji Kameyama, Kosaku Hirota, Yoshifumi Maki*

Gifu Pharmaceutical University, 6-1, Mitahora-higashi 5 Chome, Gifu 502, Japan

Treatment of 2',3'-*O*-isopropylidene-pyrimidine nucleosides (**1**; uridine and cytidine) with excess *N*-halogenosuccinimides in an aprotic solvent at ambient temperature results in the exclusive formation of the corresponding 5'-*O*,6-cyclo-5,5-dihalogeno-5,6-dihydro-2',3'-*O*-isopropylidene-pyrimidine nucleosides **2**.

Cyclonucleosides can be utilized as key intermediates in the synthesis of partially modified nucleosides and nucleotides

Treatment of 2',3'-*O*-isopropylideneuridine (**1a**) with 3 equivalents of *N*-bromosuccinimide (NBS) in dry *N,N*-dimethylformamide at ambient temperature for 5 h led to the formation of 5'-*O*,6-cyclo-5,5-dibromo-5,6-dihydro-2',3'-*O*-isopropylideneuridine (**2a**) in a high yield. No formation of other products in this reactions was shown by TLC analysis of the reaction mixture. The structure of **2a** was determined from microanalytical and spectral data and by its chemical conversion. For example, no characteristic UV absorption of the uracil ring was observed. The ¹H-NMR spectrum of **2a** showed two methine proton signals at δ 3.84 and 4.40 (2 d, 2H, each $J = 13$ Hz, C₅-H),

Table. 5'-*O*,6-Cyclo-5,5-dihalogeno-5,6-dihydro-2',3'-*O*-isopropylidene-pyrimidine Nucleosides **2**

2	R	X	Reaction Time (h)	Yield ^a (%)	m. p. (°C) ^b (solvent)	Molecular Formula ^c	¹ H-NMR (DMSO- <i>d</i> ₆ /TMS) ^d δ , J (Hz)
a	OH	Br	5	89	228–230 (EtOH)	C ₁₂ H ₁₄ Br ₂ N ₂ O ₆ (442.1)	3.84, 4.40 (2d, 2H, each $J = 13$, C ₅ -H); 4.56 (br s, 1H, C ₄ -H); 4.80, 4.94 (2d, 2H, each $J = 6$, C ₂ -H and C ₃ -H); 5.32 (s, 1H, C ₆ -H); 6.15 (s, 1H, C ₁ -H)
b	OH	Cl	48	90	248 (dec.) (EtOAc)	C ₁₂ H ₁₄ Cl ₂ N ₂ O ₆ (353.2)	3.84, 4.43 (2d, 2H, each $J = 13.5$, C ₅ -H); 4.56 (br s, 1H, C ₄ -H); 4.73, 4.94 (2d, 2H, each $J = 6$, C ₂ -H and C ₃ -H); 5.65 (s, 1H, C ₆ -H); 6.15 (s, 1H, C ₁ -H)
c	NH ₂	Br	2	86	196–198 (EtOAc)	C ₁₂ H ₁₅ Br ₂ N ₃ O ₅ (441.1)	3.86, 4.40 (2d, 2H, each $J = 13$, C ₅ -H); 4.50 (br s, 1H, C ₄ -H); 4.76, 4.91 (2d, 2H, each $J = 6$, C ₂ -H and C ₃ -H); 4.93 (s, 1H, C ₆ -H); 6.21 (s, 1H, C ₁ -H)
d	NHCOC ₆ H ₅	Br	1	96	206–207 (EtOAc)	C ₁₉ H ₁₉ Br ₂ N ₃ O ₆ (545.2)	3.90, 4.41 (2d, 2H, each $J = 12$, C ₅ -H); 4.59 (br s, 1H, C ₄ -H); 4.84, 4.94 (2d, 2H, each $J = 6$, C ₂ -H and C ₃ -H); 5.33 (s, 1H, C ₆ -H); 6.18 (s, 1H, C ₁ -H)

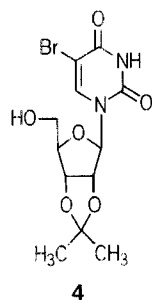
^a Yield of isolated product based on **1**.

^b Uncorrected, measured on a Yanagimoto micro hot-stage apparatus.

^c Satisfactory microanalyses obtained: C \pm 0.27, H \pm 0.19, N \pm 0.05.

^d Obtained on a Hitachi R-24B (60 MHz) spectrometer.

which are characteristic of the 5'-*O*,6-cyclopyrimidine nucleosides,² and a methine proton signal at δ 5.32 (s, C₆-H) in addition to signals assignable to an imide proton δ 11.33 (br) and protons in the protected sugar portion. On treatment of **2a** with sodium methoxide under a mild conditions, 5-bromo-5'-*O*,6-cyclo-2',3'-*O*-isopropylideneuridine (**3**) was obtained almost quantitatively. Reduction of **2a** with zinc-acetic acid gave **1a** in a high yield, along with a trace amount of 5-bromo-2',3'-*O*-isopropylideneuridine (**4**) which was identified by comparison with an authentic sample.³

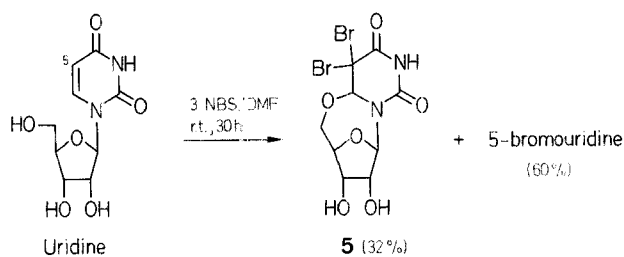


Analogous cyclization was also observed in the reaction of 2',3'-*O*-isopropylidene protected cytidine derivatives **1b** and **1c** with *N*-chlorosuccinimide (NCS) and NBS, respectively.

The results of these reactions are summarized in the Table.

N,N-Dimethylacetamide or acetonitrile also can be used as solvent, whereas the employment of the protic solvent such as alcohols in this reaction causes deprotection of the sugar moiety.

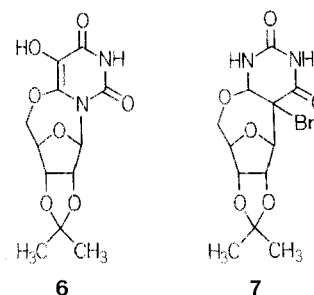
In contrast to the above results, bromination of unprotected uridine under the conditions analogous to the case of **1a** gave only a small amount of the corresponding pyrimidine cyclonucleoside (**5**) even after the prolonged reaction time; 5-bromouridine⁴ was obtained as a main product.⁵



These observations clearly indicate that the 2',3'-*O*-isopropylidene protection in the ribofuranosyl ring and the use of an aprotic solvent are requisite for the 5'-*O*-6-cyclization described here.

When the bromination of **1a** was carried out by using one equivalent of NBS, **4** was obtained in 85% yield, together with a trace amount of **2a**. The product **4** was easily converted into **2a** under the same conditions using excess NBS described above. These facts indicate that **4** is an intermediate for the formation of **2a** in the reaction of **1a** with excess NBS. An analogous reaction sequence has been proposed for the formation of 2'-*O*,6':5'-*O*,6-dicyclo-(β -D-arabinofuranosyl)-5,5-dibromo-5,6-dihydrouracil in the reaction of 2'-*O*,6-cyclouridine with bromine or NBS.⁶

Application of this procedure to the 5'-*O*,6-cyclization of 2',3'-*O*-isopropylidene protected 5-hydroxyuridine and pseudouridine allowed the formation of 5'-*O*,6-cyclo-5-hydroxy-2',3'-*O*-isopropylideneuridine (**6**) and 5-bromo-5'-*O*,6-cyclo-5,6-dihydro-2',3'-*O*-isopropylidene pseudouridine (**7**).



5'-*O*,6-Cyclo-5,5-dihalogeno-5,6-dihydro-2',3'-*O*-isopropylidene-pyrimidine Nucleosides (**2**); General Procedure:

A solution of 2',3'-*O*-isopropylidene pyrimidine nucleosides (**1**; ~ 2 mmol) and *N*-halogenosuccinimide (~ 6 mmol) in dry DMF (10 mL) is stirred at ambient temperature until disappearance of **1** (monitored by TLC analysis). After removal of the solvent, the residue is washed with a small amount of EtOH and the solid mass recrystallized from EtOH or EtOAc to give an analytically pure sample (Table).

5-Bromo-5'-*O*,6-cyclo-2',3'-*O*-isopropylideneuridine (**3**):

A solution of 5'-*O*,6-cyclo-5,5-dibromo-5,6-dihydro-2',3'-*O*-isopropylideneuridine (**2a**; 100 mg, ~ 0.2 mmol) and NaOMe (61 mg, ~ 1 mmol) in MeOH (20 mL) is stirred overnight at ambient temperature. The mixture is neutralized by using ion-exchange resin (Amberlite CG-120 B) and then the solvent is removed under reduced pressure. The residue is recrystallized from EtOH to give **3** as colorless crystals; yield: 80 mg (98%); m. p. 222–224°C.

C₁₂H₁₃BrN₂O₆ calc. C 39.91 H 3.63 N 7.76
(361.2) found 40.04 3.60 7.83

MS: *m/e* = 361 (M⁺), 346.

¹H-NMR (CDCl₃): δ = 1.32, 1.45 (2 br s, each 3 H, 2 C-Me); 4.08, 4.63 (2 br d, 2 H, each *J* = 12 Hz, 2 C₅-H); 4.68 (s, 1 H, C₄-H); 4.86, 5.00 (2 d, 2 H, each *J* = 6 Hz, C₂-H and C₃-H); 6.29 (s, 1 H, C₁-H); 9.17 (br, 1 H, NH).

5'-*O*,6-Cyclo-5,5-dibromo-5,6-dihydrouridine (**5**):

A mixture of uridine (490 mg, ~ 2 mmol), *N*-bromosuccinimide (1.07 g, ~ 6 mmol), and dry DMF (10 mL) is stirred for 30 h at ambient temperature. After removal of the solvent under reduced pressure, the residual oil is chromatographed on silica gel (CHCl₃ as eluent) to give 5-bromouridine⁴; yield: 388 mg (60%) and **5**; yield: 257 mg (32%); m. p. 155–157°C.

C₉H₁₀Br₂N₂O₆ calc. C 26.89 H 2.51 N 6.97
(402.0) found 26.98 2.53 6.84

IR (KBr): ν = 3430, 3200, 1720, 1690 cm⁻¹.

¹H-NMR (DMSO-*d*₆): δ = 3.80–4.50 (m, 5 H, C₂-H, C₃-H, C₄-H, and 2 C₅-H); 5.28 (s, 1 H, C₆-H); 6.00 (d, 1 H, *J* = 2 Hz, C₁-H); 11.18 (s, 1 H, NH).

5'-*O*,6-Cyclo-5-hydroxy-2',3'-*O*-isopropylideneuridine (**6**):

A mixture of 5-hydroxy-2',3'-*O*-isopropylideneuridine (300 mg, ~ 1 mmol), *N*-bromosuccinimide (200 mg, ~ 1.1 mmol), and dry DMF (5 mL) is stirred for 0.5 h at ambient temperature and then evaporated under reduced pressure. The residue is washed with EtOH (5 mL) and recrystallized from EtOH to give **6**; yield 235 mg (79%); m. p. > 300°C.

C₁₂H₁₄N₂O₇ calc. C 48.32 H 4.73 N 9.39
(298.3) found 48.16 4.81 9.30

MS: *m/e* = 298 (M⁺), 283, 240.

IR (KBr) ν = 3190, 3120, 1720, 1660, 1640 cm⁻¹.

¹H-NMR (DMSO-*d*₆): δ = 1.20, 1.43 (2 br s, each 3 H, 2 C-Me); 3.78, 4.58 (2 br d, 2 H, each *J* = 13 Hz, 2 C₅-H); 4.54 (s, 1 H, C₄-H); 4.83, 4.95 (2 br d, 2 H, each *J* = 6 Hz, C₂-H and C₃-H); 6.20 (s, 1 H, C₁-H); 11.32 (br, 1 H, NH).

5-Bromo-5'-*O*,6-cyclo-5,6-dihydro-2',3'-*O*-isopropylidene pseudouridine (**7**):

A mixture of 2',3'-*O*-isopropylidene pseudouridine (114 mg, ~ 0.4 mmol), *N*-bromosuccinimide (214 mg, ~ 1.2 mmol), and dry DMF (5 mL) is stirred for 3 h at ambient temperature and then evaporated under reduced pressure. The residue is recrystallized from EtOH to give **7**; yield: 90 mg (62%); m. p. 160°C (decomp.).

$C_{12}H_{15}BrN_2O_6$ calc. C 39.69 H 4.16 N 7.71
(363.2) found 39.50 4.12 7.84

MS: $m/e = 363$ (M^+). 348.

IR (KBr): $\nu = 3260, 1720\text{ cm}^{-1}$.

$^1\text{H-NMR}$ (DMSO- d_6): $\delta = 1.27, 1.44$ (2 br s, each 3 H, 2 C-Me); 3.69, 4.03 (2 d, 2 H, each $J = 13$ Hz, 2 $C_{5'}$ -H); 4.48 (m, 1 H, $C_{4'}$ -H); 4.55–4.80 (m, 3 H, $C_{1'}$ -H, $C_{2'}$ -H, and $C_{3'}$ -H); 4.90 (d, 1 H, $J = 4.5$ Hz, C_6 -H); 8.74 (d, 1 H, $J = 4.5$ Hz, $N_1\text{H}$); 11.06 (br, 1 H, $N_3\text{H}$).

Received: 2 September 1986; revised: 31 March 1987

- (1) Pertinent reviews on the chemistry of the pyrimidine cyclonucleosides:
Fox, J.J. *Pure Appl. Chem.* **1969**, *18*, 223.
Ikchara, M., Ueda, T. *J. Synth. Org. Chem. Jpn.* **1974**, *32*, 402.
- (2) Cadet, J., Kan, L.-S., Wang, S.Y. *J. Am. Chem. Soc.* **1978**, *100*, 6715.
- (3) Ueda, T. *Chem. Pharm. Bull.* **1960**, *8*, 455.
Smrt, J., Sorm, F. *Collect. Czech. Chem. Commun.* **1960**, *25*, 553.
Kochetkov, N.K., Budovsky, E.I., Shibaev, V.N., Yeliseeva, G.I., Grachev, M.A., Demushkin, V.P. *Tetrahedron* **1963**, *19*, 1207.
- (4) Wang, S.Y. *Photochem. Photobiol.* **1962**, *1*, 37.
- (5) Analogous results have been already observed in the reaction of unprotected 2'-deoxycytidine with iodine-iodic acid; cf.: Chang, P.K. *J. Org. Chem.* **1965**, *30*, 3913.
- (6) Maruyama, T., Kimura, S., Sato, Y., Honjo, M. *J. Org. Chem.* **1983**, *48*, 2719.