Chem. Pharm. Bull. 26(9)2664—2667(1978)

UDC 547.853.3.04 : 546.261-38.04

Synthesis of 6,5′-*S*- and 6,5′-*N*-Cyclouridines (Nucleosides and Nucleotides. XXII[1])

Hideo Inoue and Tohru Ueda

Faculty of Pharmaceutical Sciences, Hokkaido University[2]

(Received January 24, 1978)

Treatment of 5′-acetylthio-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine, prepared from 2′,3′-*O*-isopropylidene-5-bromouridine, with sodium methoxide in methanol afforded 5′-deoxy-5′-thio-2′,3′-*O*-isopropylidene-*S*^{6},5′-cyclouridine. Deacetonation of the product gave 5′-deoxy-5′-thio-*S*^{6},5′-cyclouridine, a sulfur-bridged cyclouridine fixed in the "*anti*" conformation. Starting from the 5′-amino derivative a *N*^{6},5′-cyclouridine was similarly prepared. The nuclear magnetic resonance and mass spectra of a series of *O*-, *N*- and *S*-cyclouridines were compared and the characteristic features were discussed.

Keywords——synthesis; pyrimidine cyclonucleosides; intramolecular cyclization; uridine; NMR; mass

It has been well known that the cyclo (or anhydro)-nucleosides are useful intermediates in the derivatization of the base and/or sugar moieties in the nucleoside conversions.[3,4] Furthermore the cyclonucleosides have been utilized as the model of conformationally fixed nucleosides around the glycosylic linkage.[4,5] We have been continuing the synthesis of sulfur-bridged[6] and nitrogen-bridged[7] pyrimidine nucleosides. The present work describes the synthesis of 6,5′-*S*- and 6,5′-*N*-cyclouridines, the uridines fixed in the "*anti*"-conformation.

Fox and co-workers have described[8] the formation of *O*^{6},5′-cyclo-2′,3′-*O*-isopropylideneuridine (**2**) by treatment of 2′,3′-*O*-isopropylidene-5-bromouridine (**1**) in an alkoxide solution. The reaction proceeded by the attack of the 5′-hydroxyl group of **1** to the 6-position followed by dehydrobromination to **2**. Under the reaction conditions the *N*^{3}-proton dissociated so that the attack of the 5′-hydroxyl group was retarded and required 17 hour's refluxing for the completion of the reaction. On the other hand it is reasonable to expect that the replacement of the 5′-hydroxyl group of **1** with sulfhydryl or amino group would facilitate the reaction and give the *S*- or *N*-cyclonucleosides more readily, because of the high nucleophilicities of sulfur and nitrogen nucleophiles as compared with the oxygen. In fact, 5′-deoxy-5′-mercapto-2′,3′-*O*-isopropylideneuridine is known to exist as the 6,5′-epithio form (**3**).[9]

2′,3′-*O*-Isopropylidene-5′-*O*-tosyl-5-bromouridine (**4**), prepared from **1**, was treated with potassium thioacetate in dimethylformamide at room temperature to afford a 5′-acetylthio-5′-deoxy derivative (**5**). The 5-bromo function of **4** was intact under the reaction conditions adopted although the conversion of the 5-bromouracil to the 5-acetylthio derivative with potassium thioacetate was observed in certain cases.[10] Treatment of **5** with 10 equivalents

1) Part XXI: H. Inoue and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **26**, 2657 (1978).
2) Location: *Kita-12, Nishi-6, Kita-ku, Sapporo, 060 Japan.*
3) L. Goodman, "Basic Principles in Nucleic Acid Chemistry," Vol. 1, ed. by P.O.P. Ts'o, Academic Press, N.Y., 1974, p. 93.
4) M. Ikehara and T. Ueda, *Yuki Gosei Kagaku*, **32**, 402 (1974).
5) M. Ikehara, *Accounts of Chem. Res.*, **2**, 47 (1969).
6) T. Ueda and S. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **22**, 930 (1974).
7) T. Ueda, S. Shibuya, and J. Yamashita, *Abstr. Paper 1st Symposium on Nucleic Acids Chemistry*, p. 71, Osaka, 1973.
8) B.A. Otter, E.A. Falco, and J.J. Fox, *J. Org. Chem.*, **34**, 1390 (1969).
9) B. Bannister and F. Kagan, *J. Am. Chem. Soc.*, **82**, 3363 (1960).
10) L. Szabo, T.I. Kalman, and T.J. Bardos, *J. Org. Chem.*, **35**, 1434 (1970).

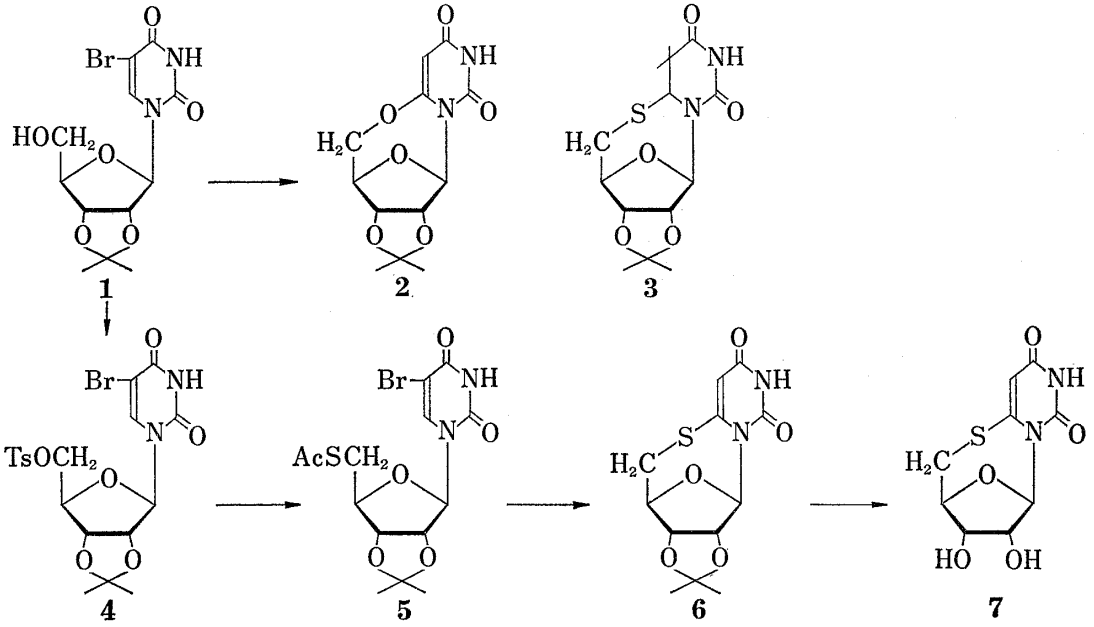

Chart 1

of sodium methoxide in methanol at room temperature for three hours afforded 5′-deoxy-5′-thio-2′,3′-*O*-isopropylidene-*S*^{6},5′-cyclouridine (**6**). Determination of the structure of **6** was made by ultraviolet (UV), mass, and nuclear magnetic resonance (NMR) spectra and elemental analyses. The detection of the geminal coupling of the 5′-methylene protons in **6** by NMR measurement is a characteristic feature of the cyclonucleoside formation. The deacetonation of **6** was performed in 50% formic acid at 70° to give 5′-deoxy-5′-thio-*S*^{6},5′-cyclouridine (**7**).

For the synthesis of 6,5′-*N*-cyclouridine, 5′-amino-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**9**) was used as the starting material. Compound **9** was also reported to exist as the 6,5′-epimino form (**8**).[11] Treatment of **8** in warm acetic acid followed by the addition of 1.2 equivalents

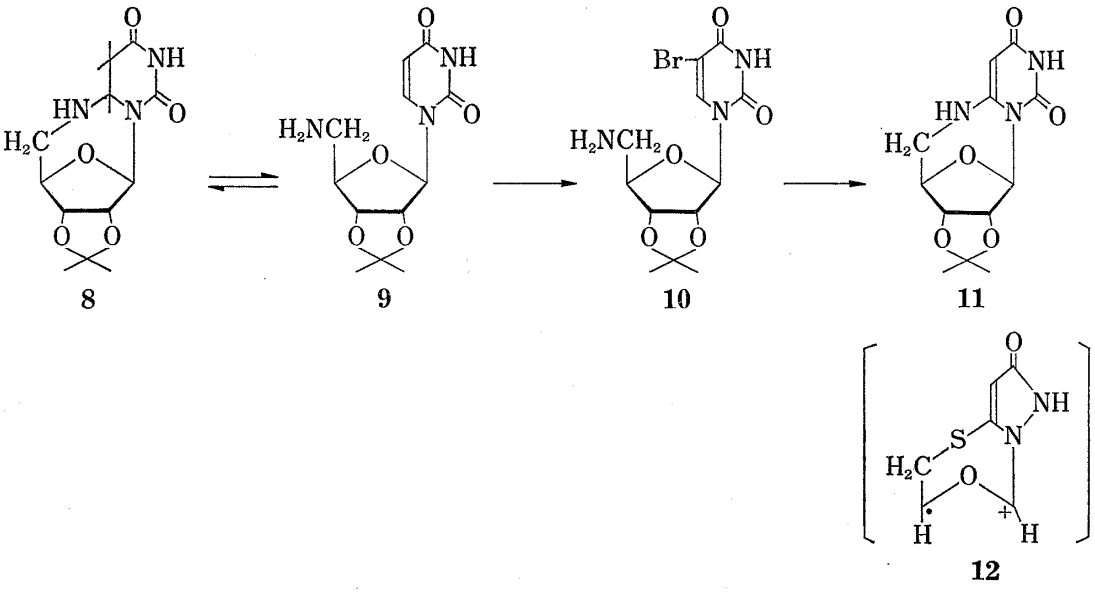

Chart 2

11) K. Isono and T. Azuma, *Chem. Pharm. Bull.* (Tokyo), **20**, 193 (1970).

of bromine gave the 5-bromo derivative (**10**). Refluxing of **10** in pyridine furnished 5′-amino-5′-deoxy-2′,3′-*O*-isopropylidene-N^6,5′-cyclouridine (**11**). The structure of **11** was also confirmed by the spectral and elemental analyses. Attempt to remove the isopropylidene group of **11** in acidic conditions resulted in a degradation probably giving a barbituric acid nucleoside.

Certain common features of the cyclonucleosides in mass and NMR spectra are to be described. The mass spectra of three cyclonucleosides(**2, 6, 11**) gave very similar fragmentation patterns showing fragment ions of M—15, M—57, M—87, M—118 and M—129, respectively (see experimental). These results imply that the fragmentation occurred similarly as to retain the cyclo-linkages in all cases. In the fragment ions of **7**, *m/e* 170 was detected which was in accord with the result of the fragmentation of O^6, 5′-cyclouridine which gave M—88.[12] The structure of this ion may be represented as **12** according to the previous report.[12]

Table I. NMR Chemical Shifts (δ) of 6,5′-Cyclouridines

Proton at	Compound **11** ppm	**11** *J* (Hz)	**2** ppm	**2** *J* (Hz)	**6** ppm	**6** *J* (Hz)	**7** ppm	**7** *J* (Hz)
N^3	10.86bs		11.39bs		11.58bs		11.53bs	
5	4.95 s		5.30 s		5.98 s		5.98 s	
1′	6.39 s		6.27 s		6.56 s		6.48 d	1′,2′=2
2′	4.74 s		4.98 d	2′,3′=6	5.25 d	2′,3′=6	4.93 q	2′,3′=6
3′	4.74 s		4.90 d		4.94 d		4.22 d	
4′	4.46m		4.61m		4.79m		4.61m	
5′a	(3.35 q	4′,a=2)	4.62 q	4′,a=1	(3.29 q	4′,a=2)	3.16m	
5′b	(3.02 q	4′,b=1 a,b=14)	4.01 q	4′,b=1 a,b=13	(2.97 q	4′,b=3 a,b=15)	3.16m	
N^6	6.83bd	a,NH=6						

The solvent used was DMSO-d_6, with D_2O added in the case of **7**. The data in parentheses are those measured in $CDCl_3$–DMSO-d_6 (3:1), which gave better separations.

The NMR chemical shifts of the cyclonucleosides (**2, 6, 7, 11**) were summarized in Table I. The common features as the cyclonucleosides are seen in the low field shifts of the anomeric protons as compared to that of uridine (5.76 ppm), probably due to the fixation of the carbonyl group as to exhibits a deshielding magnetic anisotropy to the anomeric protons of the respective nucleosides. From the coupling constants between 4′-H and 5′-Ha or 5′-Hb in **2, 6** and **11** the conformations of the cyclo linkages are determined as the "endo" mode as have been observed in the 2,5′-cyclonucleosides.[6] Also to be noticed is the low field shifts of the signals of 2′-H and 3′-H in an increasing order of the atomic radii of the hetero atoms on the bridge in **11, 2** and **6.**

The reactions of these cyclonucleosides and the synthesis of 6,2′-*S*- and -*N*-cyclonucleosides are in progress in our laboratories and the results will be reported elsewhere.

Experimental

Melting points were determined on a Yamato melting point apparatus MP-1 and are uncorrected. Mass spectra (MS) were measured on a Hitachi RMU-6E Spectrometer. NMR spectra were measured on a Hitachi R-20B Spectrometer using tetramethylsilane as the internal standard. Elemental analyses were performed by the members of the Analytical Room of this faculty.

2′,3′-*O*-Isopropylidene-5′-*O*-tosyl-5-bromouridine (4)——Compound **1**[8] (10 g) and *p*-toluenesulfonyl chloride (7 g) were dissolved in 40 ml of pyridine under cooling and kept for 21 hr at room temperature. After adding 2 ml of water the mixture was poured into 3000 ml of ice-water under stirring. The separated precipitates were collected and crystallized from MeOH–EtOH to give 10.2 g (72%) of **4**, mp 160—161°.

12) E.G. Lovett and D. Lipkin, *J. Am. Chem. Soc.*, **95**, 2312 (1973).

Anal. Calcd. for $C_{19}H_{21}BrN_2O_8S$: C, 44.10; H, 4.09; Br, 15.46; N, 5.42; S, 6.20. Found: C, 44.14; H, 4.15; Br, 15.65; N, 5.37; S, 6.17. UV λ_{max}^{EtOH} 275 nm (ε, 12400).

5′-Acetylthio-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (5)——Compound **4** (5.18 g) and $KOCSCH_3$ (prepared from 1.0 g of KOH in MeOH, 10 ml, and 1.2 ml of CH_3CSOH, azeotropically dried with benzene) were dissolved in 40 ml of DMF and kept for 36 hr at room temperature. After concentration of the mixture under diminished pressure the residue was partitioned with 200 ml of EtOAc and 100 ml of H_2O. The organic layer was washed twice with 40 ml of H_2O, dried over Na_2SO_4, and concentrated to leave a residue. This was crystallized from acetone–hexane to give 2.39 g of **5**, mp 159—162°. From the mother liquor additional 0.36 g (total yield, 65%) of **5** was obtained through a silica gel column chromatography with 2% EtOH in $CHCl_3$. Recrystallization of **5** gave an analytically pure sample, mp 160—162.5°. *Anal.* Calcd. for $C_{14}H_{17}BrN_2O_6S$: C, 39.94; H, 4.07; Br, 18.98; N, 6.65; S, 7.62. Found: C, 40.16; H, 4.17; Br, 18.22; N, 6.66; S, 8.18. UV λ_{max}^{EtOH} 276 nm (ε, 9100); MS *m/e*: 420 (M^+); NMR ($CDCl_3$) δ: 9.75 (bs, 1, N^3–H), 7.67 (s, 1, 6-H), 5.65 (d, 1, 1′-H), 5.03 (dd, 1, 2′-H), 4.71 (dd, 1, 3′-H), 4.25 (m, 1, 4′-H), 3.28 (bs, 2, 5′-H), 2.39 (s, 3, AcS), 1.55, 1.35 (s, 3+3, Me_2C).

5′-Deoxy-5′-thio-2′,3′-*O*-isopropylidene-*S*^{6}-5′-cyclouridine (6)——Compound **5** (423 mg) was dissolved in 0.5 N $NaOCH_3$ in MeOH (20 ml) and kept for 3 hr at room temperature. Acetic acid (0.6 ml) was added to the reaction solution and it was evaporated to leave a residue. The residue was partitioned with EtOAc and H_2O and the organic layer was dried over Na_2SO_4 and evaporated to leave a sirup. The $CHCl_3$ solution of the sirup was applied to a silica gel column (silica gel 25 g) and eluted with 2% EtOH in $CHCl_3$. The eluate was evaporated and the residue was crystallized from EtOH to give 248 mg (83%) of **6**, mp 250° (dec.). *Anal.* Calcd. for $C_{12}H_{14}N_2O_5S$: C, 48.36; H, 4.74; N, 9.40; S, 10.76. Found: C, 48.07; H, 4.69; N, 9.52; S, 10.62. UV λ_{max}^{EtOH} 292 nm (ε, 10400); MS *m/e*: 298 (M^+), 283 (base peak), 241, 211, 180, 169, 152. NMR: see Table I.

5′-Deoxy-5′-thio-*S*^{6},5′-cyclouridine (7)——Compound **6** (101 mg) was dissolved in 10 ml of 50% HCO_2H and kept at 70° for 2 hr. The solution was concentrated and the residue was crystallized from aqueous EtOH to give 74 mg (85%) of **7**, mp 255° (dec.). *Anal.* Calcd. for $C_9H_{10}N_2O_5S$: C, 41.86; H, 3.90; N, 10.85; S, 12.43. Found: C, 41.91; H, 3.96; N, 10.66; S, 12.34. UV $\lambda_{max}^{H_2O}$ 293 nm (ε, 11300), $\lambda_{max}^{OH^-}$ 289 nm (ε, 10000). MS *m/e*: 258 (M^+), 229, 170 (M−88), 169, 144 (base peak), 126. NMR: see Table I.

5′-Amino-5′-deoxy-2′,3′-*O*-isopropylidene-*N*^{6},5′-cyclouridine (11)——Compound **8**[11] (901 mg) was dissolved in 20 ml of AcOH and kept for 4 hr at 50°. The *Rf* value on a thin-layer chromatography (silica gel, $CHCl_3$–EtOH, 10: 1) of the solution changed from 0.30 to 0.04 (*Rf* for **9**). To the solution was added 0.9 g of KOAc and 0.2 ml of Br_2, and kept for 21 hr at room temperature. The mixture was evaporated, added EtOH, and evaporated again to a dryness. The UV of the residue ($\lambda_{max}^{H_2O}$ 277 nm, $\lambda_{max}^{OH^-}$ 274 nm) showed that the bromination of **9** to **10** was complete. Without further purification the residue was taken in 50 ml of pyridine and heated under reflux for 15 min. After evaporation of the solvent the residue was partitioned with EtOAc (100 ml) and H_2O (20 ml). The organic layer was dried over Na_2SO_4 and concentrated to give the crystalline precipitate (**11**, 551 mg, 62%). Recrystallization from EtOH afforded an analytically pure **11**; mp 270° (dec.). *Anal.* Calcd. for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.37; H, 5.56; N, 14.91. UV λ_{max}^{EtOH} 276 nm (ε, 22300). MS *m/e*: 281 (M^+), 266 (base peak), 224, 194, 163, 152. NMR: see Table I. Treatment of **11** in 50% HCO_2H at 70° for 2 hr, or at room temperature for 3 days, gave a compound which showed no appreciable UV absorptions in acidic condition, and a maximum at 260 nm in alkaline solution. Treatment of **11** in 98% HCO_2H for 3 days afforded a deacetonated compound contaminated with **11**.

Mass Spectra of 2′,3′-*O*-Isopropylidene-*O*^{6},5′-cyclouridine (2)——Mass spectra of **2** was measured at 80 eV at the heating temperature of 140°. The ion peaks detected were as follows; 282 (M^+), 267 (base peak), 225, 195, 164, 153, 136, and 110.

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