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# Pyrimidine *S*- and *N*-Cyclonucleosides. Synthesis of 6,2′(and 5′)-*S*- and *N*-Cyclouridines (Nucleosides and Nucleotides. XXXII[1])

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The synthesis of *S*- and *N*-cyclouridines, which are "anti"-fixed cyclonucleosides, is described. Bromination of $S^2$,2′-cyclo-2-thiouridine afforded the 5-bromo derivative. Cleavage of the $S^2$,2′-cyclo linkage of the 5-bromo derivative with methoxide resulted in the formation of $S^6$,2′-cyclo-2-*O*-methyluridine by intramolecular conversion of the $S^2$,2′-linkage to an $S^6$,2′-linkage, and this was further converted to the corresponding $S^6$,2′-cyclo derivatives of uridine, isocytidine and 2-thouridine. Similarly, 2′,3′-*O*-isopropylidene-$S^2$,5′-cyclo-2-thiouridine was converted to the 2′,3′-*O*-isopropylidene-$S^6$,5′-cyclo derivatives of uridine, isocytidine, and 2-thiouridine. 6-Methylaminouridine was cyclized by treatment with diphenyl carbonate to $N^6$,2′-cyclo-6-methylaminouridine. Cyclization with triphenylphosphine and diethyl azodicarboxylate gave the $N^6$,5′-cyclo derivative of 6-methylaminouridine.

**Keywords**——N-cyclonucleosides; uridine; 2-thiouridine; isocytidine; S-cyclonucleosides; bromination; intramolecular conversion; NMR; UV

The cyclonucleosides are of interest in nucleoside chemistry in that both the sugar and base portions are involved in the reactions, and they have been utilized for the transformation of naturally occurring nucleosides to derivatives of biochemical and pharmacological interest. Furthermore, the cyclonucleosides themselves can serve as conformationally fixed models of nucleosides.[3]

In the case of pyrimidine nucleosides, various oxygen-bridged cyclonucleosides have been prepared from uridine and cytidine. It is likely that sulfur- or nitrogen-bridged cyclonucleosides will be useful for further derivatizations, since the sulfur or nitrogen in the cyclo linkages can be expected to show unique reactivity. We have already synthesized $S^2$, 2′(3′ and 5′)-cyclo-2-thiouridines from uridine.[4,5] $S^2$, 2′-Cyclo-2-thiouridine has been converted to 1-(2,3-dideoxy-2,3-epithio-β-D-lyxofuranosyl)-uracil[6] and 2′-deoxy-2′,6-epithio-β-D-arabinofuranosyl-5,6-dihydrouracil.[7] These derivatizations were initiated by the cleavage of the *S*-cyclo linkage of the cyclo-2-thio-uridine. The $S^2$, 2′(3′ and 5′)-cyclo-2-thiouridines are assumed to be conformationally fixed in the "syn" form, the substituent at position 2 (in these *S*-cyclo derivatives, sulfur) being situated on or inside the ribose ring.

We report here the synthesis of 6,5′- and 6,2′-*S*-cyclouridines, the "anti" type cyclonucleosides, from 2,5′- and 2,2′-*S*-cyclo-2-thiouridines via the intramolecular conversion of the *S*-cyclo linkages. In addition, 6,2′- and 6,5′-*N*-cyclo-6-methylaminouridines were also synthesized. A preliminary account of the present work has appeared.[8]

1) Part XXXI: A. Matsuda, K. Niizuma, and T. Ueda, *Chem. Pharm. Bull.*, **28**, 876 (1980).
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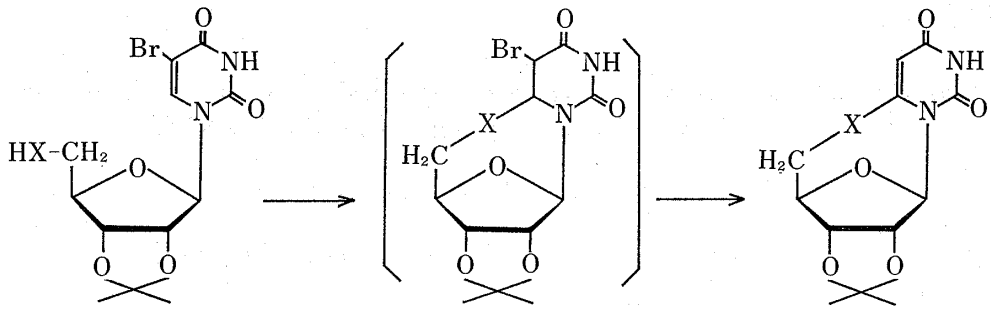


Chart 1

We have previously synthesized 6,5′-*S*- and 6,5′-*N*-cyclouridines.[9] In these cases the cyclo linkages were constructed by the attack of the 5′-thiol (or 5′-amino) group on position 6 of the 5-bromouracil moiety, followed by elimination of hydrogen bromide, as shown in Chart 1. The present method is unique in that the *S*-cyclo derivatives of 2-substituted-4-pyrimidinones including uracil can be obtained.

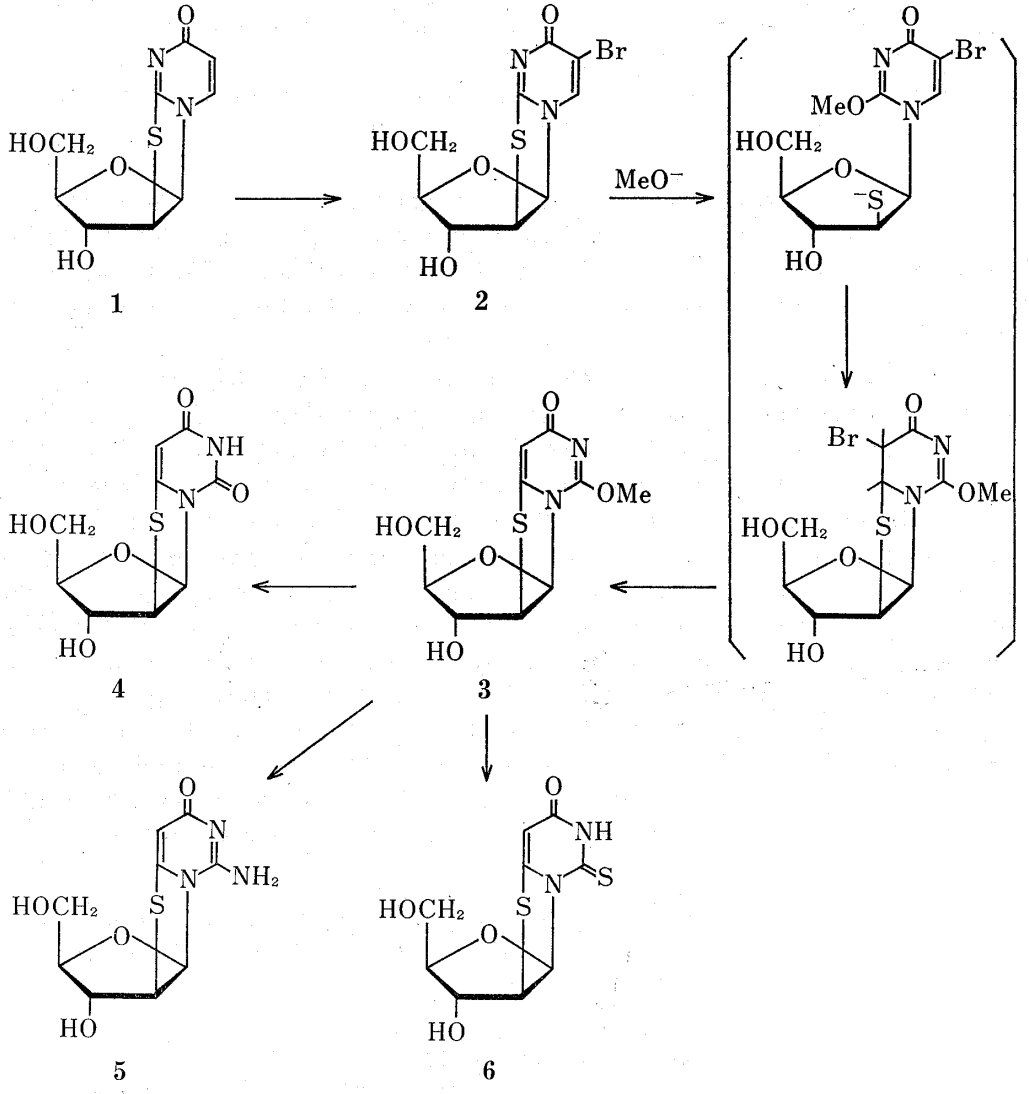


Chart 2

9) H. Inoue and T. Ueda, *Chem. Pharm. Bull.*, 26, 2664 (1978).

Treatment of $S^2$,2′-cyclo-2-thiouridine[5] (**1**) with excess bromine in methanol-pyridine at room temperature afforded the 5-bromo derivative (**2**). Treatment of **2** with sodium methoxide in methanol at room temperature gave a product (**3**). The product showed the molecular formula of *S*-cyclouridine having a methoxy group instead of a bromo group, as judged by mass spectral and elemental analyses. The nuclear magnetic resonance (NMR) spectrum of **3** showed that the proton at position 6 had been lost, and a proton corresponding to position 5 had appeared.

Based on these findings, together with the results of reactions described below, the structure of **3** was assigned as $S^6$,2′-cyclo-2-*O*-methyluridine. The reaction path leading **3** from **2** is postulated to be as follows: the attack of a methoxide ion at position 2 of **2** generates the 2′-mercaptide ion, which adds to position 6. Elimination of hydrogen bromide from the 5,6-dihydro intermediate furnishes the product **3** (Chart 2). Since the *S*-cyclo linkage of **1** was stable to methoxide treatment, the introduction of bromine must have enhanced the reactivity at position **2** towards methoxide ion.

Compound **3** was found to be a useful substrate for further substitution at position 2. Treatment of **3** with 0.1 N sulfuric acid afforded $S^6$,2′-cyclouridine (**4**). Ammonolysis of **3** with methanolic ammonia at room temperature gave $S^6$,2′-cycloisocytidine (**5**). Sulfhydrolysis of **3** in hydrogen sulfide-pyridine likewise gave $S^6$,2′-cyclo-2-thiouridine (**6**). The ultraviolet (UV), NMR and mass spectra of these compounds support the indicated structures.

The synthesis of $S^6$,5′-cyclouridines was next undertaken by a similar approach. Treatment of 2′,3′-*O*-isopropylidene-$S^2$,5′-cyclo-2-thiouridine[6] (**7**) with an excess of bromine afforded the 5-bromo derivative (**8**) in low yield. Oxidation of the bridged sulfur in **7** by bromine may be the main side reaction, but this was not examined further. Cleavage of the sulfur bridge in **8** with sodium methoxide in methanol proceeded readily at room temperature to give 2′,3′-*O*-isopropylidene-$S^6$,5′-cyclo-2-*O*-methyluridine (**9**). Treatment of **9** with 0.1 N sulfuric acid, methanolic ammonia, and hydrogen sulfide in pyridine afforded the $S^6$,5′-cyclo derivatives of uridine (**10**),[9] isocytidine (**11**), and 2-thiouridine (**12**), respectively.

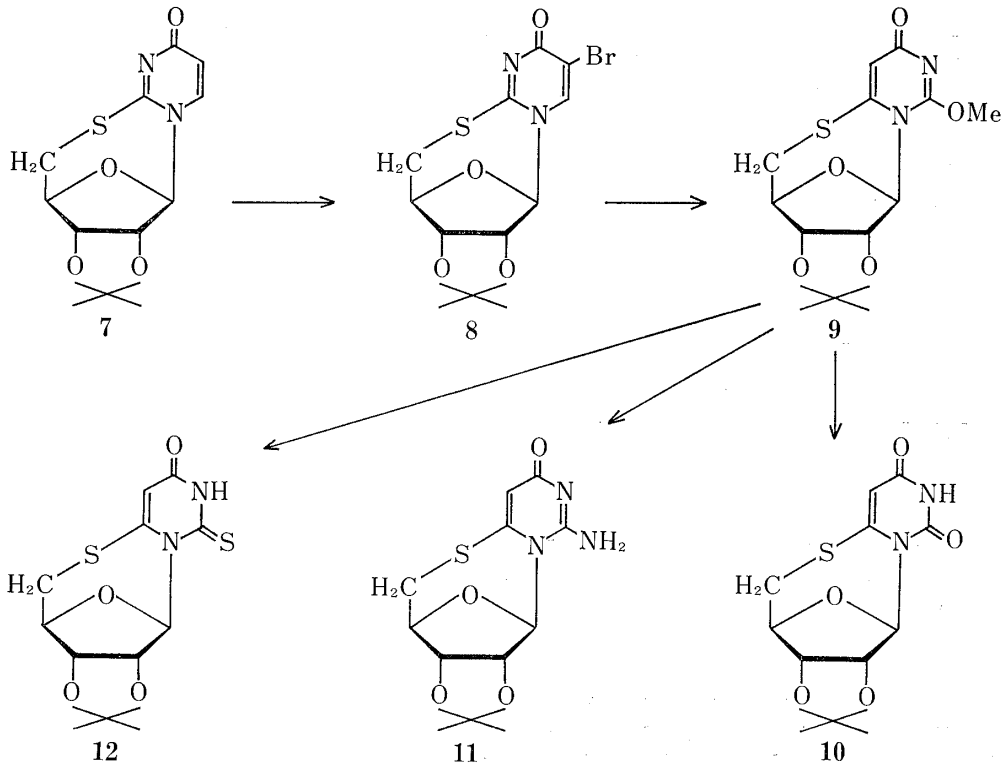


Chart 3

For the synthesis of nitrogen-bridged "anti"-fixed cyclouridines, a similar sequence of reactions was attempted. 5-Bromoisocytidine (**13**)[10] was prepared by the direct 2,5′-*O*-cyclization[11] of 5-bromouridine, followed by ammonolysis. Treatment of **13** with diphenyl carbonate in dimethylformamide (DMF)[12] afforded $N^2$,2′-cyclo-5-bromoisocytidine (**14**). Starting from 2′,3′-*O*-isopropylidene-5-bromouridine (**15**), the $O^2$,5′-cyclization and successive ammonolysis gave 2′,3′-*O*-isopropylidene-5-bromoisocytidine (**16**). Cyclization of **16** with triphenylphosphine and diethyl azodicarboxylate[11] gave the $N^2$,5′-cyclo derivative (**17**). Attempts to cleave the *N*-cyclo linkage of **14** and **17** with successive intramolecular conversion to the $N^6$,2′(5′)-cyclo derivatives under various conditions were unsuccessful. The $C^2$—$N^2$ bonds in **14** and **17** seemed to be resistant to basic attack and complex decompositions of the pyrimidine ring were observed instead.

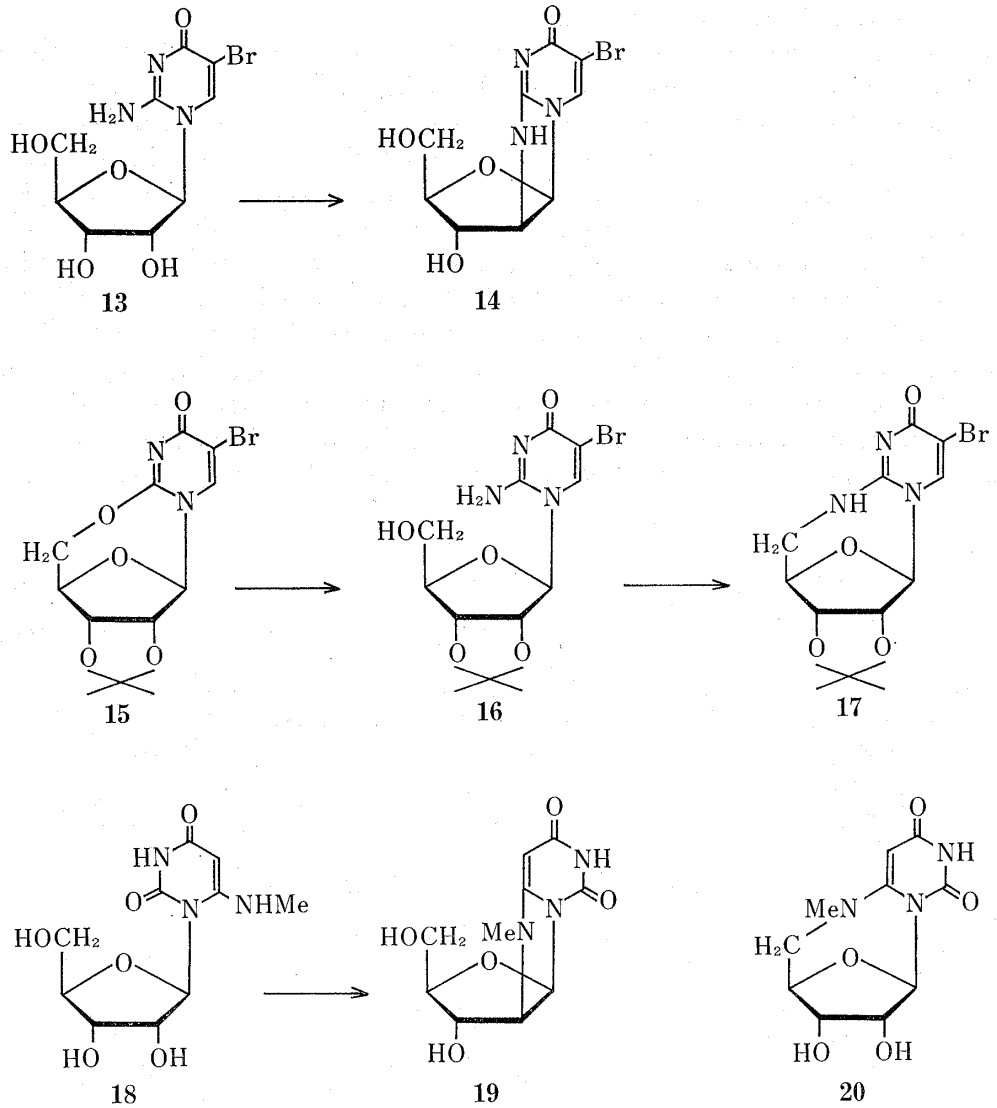


Chart 4

10) J. Doskocil, A. Holy, and J. Filip, *Nucleic Acids Res.*, **1**, 1209 (1974).
11) *a*) M. Wada and O. Mitsunobu, *Tetrahedron Lett.*, **1972**, 1279; *b*) S. Shibuya, A. Kuninaka, and H. Yoshino, *Chem. Pharm. Bull.*, **22**, 719 (1974); *c*) J. Kimura, Y. Fujisawa, T. Sawada, and O. Mitsunobu, *Chem. Lett.*, **1974**, 641.
12) A. Hampton and A.W. Nichol, *Biochemistry*, **5**, 2076 (1966).

Therefore, another route was investigated, utilizing 6-methylaminouridine (**18**). Compound **18**, prepared by deacetonation of the 2′,3′-*O*-isopropylidene derivative,[13] was treated with diphenyl carbonate in DMF. The sole product obtained was the expected $N^6$,2′-cyclo-6-methylaminouridine (**19**). The exclusive cyclization through the nitrogen rather than the carbonyl oxygen at position 2 of **18** may be a reflection of higher nucleophilicity of the nitrogen compared to oxygen. The direct cyclization of **18** with diethyl azodicarboxylate and triphenylphosphine gave $N^6$,5′-cyclo-6-methylaminouridine (**20**). The 2′,3′-*O*-isopropylidine derivative of **20** was also obtained.

The characteristic features of these *S*- and *N*-cyclouridine (mass, NMR and circular dichroic (CD) spectra) as compared with those of the "syn"-fixed cyclonucleosides as well as the usual nucleosides were studied, and will be reported separately.

## Experimental

Melting points were determined with a Yanaco MP-3 melting point apparatus and are uncorrected. Silica gel for column chromatography was Wakogel C-200. UV spectra were recorded on a Shimadzu UV-300 recording spectrophotometer. NMR spectra were taken with a JEOL JNM-FX 100 FT NMR spectrometer. Mass spectra were taken with a JEOL JMS-D 300 spectrometer. Ribonucleosides used in this study were purchased form Yamasa Shoyu Co. Ltd.

***S*²,2′-Cyclo-5-bromo-2-thiouridine** (**2**)——$S^2$,2′-Cyclo-2-thiouridine[4] (**1**, 0.8 g) was dissolved in 80 ml of MeOH and 16 ml of pyridine. Bromine (2.6 g) was added to the solution at room temperature and the solution was stirred overnight. The solvent was removed *in vacuo* and the residue was applied to a column (silica gel, 50 g). The eluate with 20% EtOH in $CHCl_3$ was concentrated and the residue was crystallized from EtOH to give 0.57 g (54%) of **2**, mp 238—240° (dec.). *Anal.* Calcd for $C_9H_9BrN_2O_4S$: C, 33.67; H, 2.83; N, 8.73; Br, 24.90; S, 9.99. Found: C, 33.60; H, 2.85; N, 8.63; Br, 25.32; S, 9.79. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 233 (22400), 270 (sh, 8000). NMR (DMSO-$d_6$) $\delta$: 8.43 (s, 1, 6-H), 6.36 (d, 1, 1′-H, $J$=6.3 Hz), 4.34 (m, 2, 2′,3′-H), 4.03 (m, 1, 4′-H), 3.44 (m, 2, 5′-H). MS (*m/e*): 322, 320 ($M^+$).

***S*⁶,2′-Cyclo-2-*O*-methyluridine** (**3**)——Compound **2** (1.0 g) was dissolved in 50 ml of MeOH containing 0.5 g of NaOMe, and the solution was stirred overnight at room temperature. After neutralization of the solution with Amberlite IR-120 ($H^+$) resin, the solvent was removed *in vacuo* and the residue was crystallized from EtOH to give 0.71 g (85%) of **3**, mp 211—212°. *Anal.* Calcd for $C_{10}H_{12}N_2O_5S$: C, 44.12; H, 4.44; N, 10.29; S, 11.78. Found: C, 43.92; H, 4.42; N, 10.12; S, 11.52. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 215 (17800), 273 (16400), 280 (ind., 14700). $\lambda_{min}^{H_2O}$ 245 (4800). NMR (DMSO-$d_6$) $\delta$: 6.43 (d, 1, 1′-H, $J$=5.8 Hz), 5.80 (s, 1, 5-H), 4.26 (d, 1, 2′-H), 4.23 (bs, 1, 3′-H), 3.91 (m, 1, 4′-H), 3.90 (s, 3, 2-O-Me), 3.44 (m, 2, 5′-H). MS (*m/e*): 272 ($M^+$).

***S*⁶,2′-Cyclouridine** (**4**)——Compound **3** (100 mg) was dissolved in 20 ml of 0.1 N $H_2SO_4$ and the solution was stirred overnight at room temperature. After neutralization of the solution with Dowex-1 ($HCO_3^-$ form) resin, the solvent was removed *in vacuo* and the residue was crystallized from EtOH to give 60 mg (63%) of **4**, mp 234—235°. *Anal.* Calcd for $C_9H_{10}N_2O_5S$: C, 41.86; H, 3.90; N, 10.85; S, 12.42. Found: C, 41.78; H, 3.85; N, 10.62; S, 12.29. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 218 (8000), 280 (18400). $\lambda_{min}^{H_2O}$: 242 (2600). $\lambda_{max}^{0.1N\ NaOH}$: 277 (14800). $\lambda_{min}^{0.1N\ NaOH}$: 247 (4200). NMR (DMSO-$d_6$) $\delta$: 11.17 (bs, 1, $N^3$–H), 6.37 (d, 1, 1′-H, $J$=6.1 Hz), 4.62 (d, 1, 5-H, $J$=1.7 Hz), 4.25 (d, 1, 2′-H), 4.23 (bs, 1, 3′-H), 3.92 (m, 1, 4′-H), 3.48 (m, 2, 5′-H). MS (*m/e*): 258 ($M^+$).

***S*⁶,2′-Cyclo-isocytidine** (**5**)——Compound **3** (100 mg) was dissolved in 30 ml of MeOH saturated with $NH_3$, and the stoppered solution was kept at room temperature for 5 hr. The solution was concentrated and the residue was crystallized from EtOH to give 73 mg (77%) of **5**, mp 231—232°. *Anal.* Calcd for $C_9H_{11}N_3O_4S$: C, 42.02; H, 4.31; N, 16.33; S, 12.47. Found: C, 41.62; H, 4.34; N, 16.10; S, 12.26. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 219 (22600), 277 (12800). $\lambda_{min}^{H_2O}$: 250 (4100). $\lambda_{max}^{0.1N\ HCl}$: 226 (10100), 281 (16300), 290 (infl., 12600). $\lambda_{min}^{0.1N\ HCl}$: 215 (7700), 248 (4500). NMR (DMSO-$d_6$) $\delta$: 7.07 (bs, 2, $NH_2$), 6.44 (d, 1, 1′-H, $J$=6.1 Hz), 5.51 (s, 1, 5-H), 4.25 (d, 1, 2′-H), 4.23 (s, 1, 3′-H), 3.94 (m, 1, 4′-H), 3.47 (m, 2, 5′-H). MS (*m/e*): 258 (M+1).

***S*⁶,2′-Cyclo-2-thiouridine** (**6**)——$H_2S$ gas was bubbled into a solution of 100 mg of **3** in 20 ml of pyridine, then the flask was sealed and the solution was stirred for 18 hr at room temperature. The solvent was removed *in vacuo* and the residue was crystallized from EtOH to give 77 mg (76%) of **6**, mp 266—268°. *Anal.* Calcd for $C_9H_{10}N_2O_4S_2$: C, 39.42; H, 3.68; N, 10.22; S, 23.39. Found: C, 39.40; H, 3.86; N, 10.05; S, 23.42. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 212 (14900), 231 (14600), 260 (infl., 10900), 282 (19600). $\lambda_{min}^{H_2O}$: 222 (12500), 244 (8800). $\lambda_{max}^{0.1N\ NaOH}$: 228 (20100), 248 (20000), 275 (11300), 294 (11100). $\lambda_{min}^{0.1N\ NaOH}$: 238 (18900), 268 (10900), 285 (10700). NMR (DMSO-$d_6$) $\delta$: 12.49 (bs, 1, $N^3$H), 6.82 (d, 1, 1′-H, $J$=5.9 Hz), 5.96 (d, 1, 5-H, $J$=2.0 Hz), 4.32 (d, 1, 2′-H), 4.28 (s, 1, 3′-H), 3.96 (m, 1, 4′-H), 3.52 (m, 2, 5′-H). MS (*m/e*): 274 ($M^+$).

13) Y. Mizuno, Y. Watanabe, and K. Ikeda, *Chem. Pharm. Bull.*, **22**, 198 (1974).

***S*²,5′-Cyclo-2′,3′-*O*-isopropylidene-5-bromo-2-thiouridine (8)**——Compound 7[4] (3.2 g) was dissolved in MeOH (50 ml) and pyridine (30 ml), and $Br_2$ (9.0 g) was added to the solution. After stirring the solution for 3 hr at room temperature, the solvent was removed *in vacuo* and the residue was taken up in EtOH. The evaporation of the solvent was repeated several times and the residue was partitioned with $CHCl_3$ and $H_2O$. The organic layer was applied to a column of silica gel (100 g) and the column was eluted with $CHCl_3$–EtOH (20: 1). The fraction containing 8 were concentrated *in vacuo* and the residue was crystallized from EtOH to give 0.7 g (18%) of **8**, mp 160—162°. *Anal.* Calcd for $C_{12}H_{13}BrN_2O_4S \cdot 1/2H_2O$: C, 38.93; H, 3.81; N, 7.57; Br, 21.59; S, 8.66. Found: C, 38.74; H, 3.83; N, 7.49; Br, 21.94; S, 8.42. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 251 (15600), 275 (sh., 10200). $\lambda_{min}^{H_2O}$: 224 (5000). NMR ($CDCl_3$) $\delta$: 7.77 (s, 1, 6-H), 5.47 (s, 1, 1′-H), 5.24 (d, 1, 2′-H, $J$=5.7 Hz), 4.92 (d, 1, 3′-H), 4.95 (bs, 1, 4′-H), 3.57 (dd, 1, 5′-Ha), 2.82 (dd, 1, 5′-Hb, $J_{4',a}$=1.9 Hz, $J_{4',b}$=3.2 Hz, $J_{a,b}$=14.9 Hz), 1.53, 1.38 (s, 3+3, $CMe_2$). MS (*m/e*): 362, 360 ($M^+$).

**2′,3′-*O*-Isopropylidene-*S*⁶,5′-cyclo-2-*O*-methyluridine (9)**——Compound **8** (300 mg) was taken up in 50 ml of MeOH containing 140 mg of NaOMe and kept at room temperature for 5 hr. After neutralization of the solution with Amberlite IR-120 ($H^+$) resin, the solvent was removed *in vacuo*. The residue was taken up in THF, the insoluble material being filtered off, and the solvent was removed *in vacuo* to leave an amorphous material (210 mg, 81%). A part of the product was crystallized from AcOEt–hexane to give pure **9**, mp 178—179°. *Anal.* Calcd for $C_{13}H_{16}N_2O_5S$: C, 50.00; H, 5.16; N, 8.97; S, 10.27. Found: C, 49.79; H, 5.15; N, 8.83; S, 10.41. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 248 (8200), 284 (12600). $\lambda_{min}^{H_2O}$: 238 (7900), 255 (8100). NMR ($CDCl_3$) $\delta$: 6.57 (s, 1, 1′-H), 6.37 (s, 1, 5-H), 5.22 (d, 1, 2′-H, $J$=5.6 Hz), 4.88 (d, 1, 3′-H), 4.88 (bs, 1, 4′-H), 3.29 (dd, 1, 5′-Ha), 2.79 (dd, 1, 5′-Hb, $J_{4',a}$=2.1 Hz, $J_{4',b}$=2.8 Hz, $J_{a,b}$=14.5 Hz), 4.05 (s, 3, OMe), 1.57, 1.38 (s, 3+3, $CMe_2$). MS (*m/e*): 312 ($M^+$), 297 (M-15).

**2′,3′-*O*-Isopropylidene-S⁶,5′-cyclouridine (10)**[9]——Compound **9** (180 mg) was dissolved in 20 ml of MeOH and 1 ml of 0.1 N $H_2SO_4$, and the solution was stirred for 3 hr at room temperature. After neutralization of the solution with Dowex-1 ($HCO_3^-$) resin, the solvent was removed *in vacuo* and the residue was crystallized from EtOH to give 110 mg (74%) of **10**, mp 260° (250°[9]). *Anal.* Calcd for $C_{12}H_{14}N_2O_5S$: C, 48.36; H, 4.74; N, 9.40; S, 10.76. Found: C, 48.15; H, 4.77; N, 9.35; S, 10.63. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 212 (7900), 292 (11900). $\lambda_{min}^{H_2O}$ 237 (3000). $\lambda_{max}^{0.1N\ NaOH}$: 287 (10400) $\lambda_{min}^{0.1N\ NaOH}$: 258 (2600). NMR ($CDCl_3$) $\delta$: 9.0 (bs, 1, N³H), 6.81 (s, 1, 1′-H), 6.09 (d, 1, 5-H, $J$=2.0 Hz), 5.18 (d, 1, 2′-H, $J$=5.4 Hz), 4.86 (d, 1, 3′-H), 4.83 (bs, 1, 4′-H), 3.33 (dd, 1, 5′-Ha), 2.81 (dd, 1, 5′-Hb, $J_{4',a}$=2.2 Hz, $J_{4',b}$=2.7 Hz, $J_{a,b}$=14.4 Hz), 1.55, 1.37 (s, (3+3, $CMe_2$). MS (*m/e*): 298 ($M^+$), 283 (M-15).

**2′,3′-*O*-Isopropylidene-S⁶,5,-cyclo-isocytidine (11)**——Compound **9** (60 mg) was kept in 20 ml of MeOH saturated with $NH_3$ at room temperature overnight. The solvent was removed *in vacuo* and the residue was crystallized from EtOH to give 46 mg (82%) of **11**, mp 257—260° (dec.). *Anal.* Calcd for $C_{12}H_{15}N_3O_4S$: C, 48.48; H, 5.09; N, 14.14; S, 10.79. Found: C, 48.48; H, 5.17; N, 13.54; S, 10.85. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 210 (19000), 225 (infl., 12200), 286 (8400). $\lambda_{min}^{H_2O}$: 260 (5100). NMR ($CDCl_3$) $\delta$: 7.31 (bs, 2, $NH_2$), 6.24 (s, 1, 1′-H), 6.05 (s, 1, 5-H), 5.26 (d, 1, 2′-H, $J$=5.7 Hz), 4.92 (d, 1, 3′-H), 4.86 (bs, 1, 4′-H), 3.23 (dd, 1, 5′-Ha), 2.95 (dd, 1, 5′-Hb, $J_{4',a}$=2.0 Hz, $J_{4',b}$=2.5 Hz, $J_{a,b}$=14.5 Hz), 1.53, 1.31 (s, 3+3, $CMe_2$). MS (*m/e*): 297 ($M^+$), 282 (M-15).

**2′,3′-O-Isopropylidene-S⁶,5′-cyclo-2-thiouridine (12)**——$H_2S$ gas was absorbed into a solution of **9** (100 mg) in 30 ml of pyridine. The sealed solution was stirred overnight at room temperature. After removal of the solvent, the residue was crystallized from EtOH to give 87 mg (87%) of **12**, mp>300°. *Anal.* Calcd for $C_{12}H_{14}N_2O_4S_2$: C, 45.86; H, 4.49; N, 8.92; S, 20.41. Found: C, 45.83; H, 4.46; N, 8.73; S, 20.34. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 212 (14300), 235 (sh., 9600), 280 (18600). $\lambda_{min}^{H_2O}$: 256 (3300). $\lambda_{max}^{0.1N\ NaOH}$: 252 (18500), 262 (18800), 305 (sh., 6100). $\lambda_{min}^{0.1N\ NaOH}$: 235 (13300). NMR ($CDCl_3$) $\delta$: 9.70 (bs, 1, N³H), 7.81 (s, 1, 1′-H), 6.36 (s, 1, 5-H), 5.25 (d, 1, 2′-H, $J$=5.6 Hz), 4.86 (d, 1, 3′-H), 4.89 (bs, 1, 4′-H), 3.41 (dd, 1, 5′-Ha), 2.80 (dd, 1, 5′-Hb, $J_{4',a}$=2.3 Ha, $J_{4',b}$=2.3 Hz, $J_{a'b}$=14.2 Hz), 1.58, 1.31 (s, 3+3, $CMe_2$). MS (*m/e*): 314 ($M^+$).

**5-Bromoisocytidine (13)**——a) $O^2$,5-Cyclo-5′-bromouridine: A mixture of 5-bromouridine (10 g), triphenylphosphine (17 g), and diethyl azodicarboxylate (18 ml) in 100 ml of dioxane was stirred for 5 hr at room temperature. Water (10 ml) was then added to the solution and the mixture was refluxed for 30 min. The solution was concentrated to *ca.* 30 ml *in vacuo* and ether was added to effect precipitation. The solvent was removed by decantation and the residual sirup was collected and crystallized from EtOH to give 4.5 g (48%) of $O^2$,5′-cyclo-5-bromouridine, mp 228—230° (dec.). *Anal.* Calcd for $C_9H_9N_2O_5Br$: C, 35.44; H, 2.97; N, 9.19; Br, 26.20. Found: C, 35.38; H, 3.01; N, 9.10; Br, 25.99. UV $\lambda_{max}^{H_2O}$ 250 nm (sh), 258 nm. $\lambda_{min}^{H_2O}$: 222 nm. NMR (DMSO-$d_6$) $\delta$: 8.64 (s, 1, 6-H), 5.64 (s, 1, 1′-H), 4.45 (d, 1, 2′-H, $J$=6.3 Hz), 4.35 (d, 1, 3′-H), 4.48 (bd, 1, 4′-H), 4.50 (dd, 1, 5′-Ha), 4.20 (dd, 1, 5′-Hb, $J_{4',a}$=1.2 Hz, $J_{4',b}$=1.4 Hz, $J_{a,b}$=13.2 Hz). MS (*m/e*): 306, 304 ($M^+$).

b) The above compound (1.0 g) was taken up in 200 ml of MeOH saturated with $NH_3$ and kept overnight at room temperature in a sealed tube. Removal of the solvent and crystallization of the residue gave 0.9 g (85%) of **13**, mp 185—187°.[14] *Anal.* Calcd for $C_9H_{12}BrN_3O_5$: C, 33.57; H, 3.76; N, 13.05; Br, 24.82. Found: C, 33.40; H, 3.77; N, 13.05; Br, 24.91. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 272 (5700). $\lambda_{min}^{H_2O}$: 256 (4500). $\lambda_{max}^{0.1N\ HCl}$: 227 (9400),

14) This compound was reported to be amorphous.[10]

275 (8200). $\lambda_{min}^{0.1N\ HCl}$: 217 (9000), 253 (4700). NMR (DMSO-$d_6$) $\delta$: 8.20 (s, 1, 6-H), 7.14 (bs, 2, $NH_2$), 5.50 (m, 3, 2′,3′,5′-OH), 5.46 (d, 1, 1′-H, $J$=5.8 Hz), 3.98 (m, 3,2′,3′,4′-H), 3.64 (m, 2, 5′-H). MS (*m/e*): 306, 304 (M−17), 189 (B+1).

**N²,2′-Cyclo-5-bromoisocytidine (14)**——Compound **13** (0.5 g) was dissolved in 5 ml of DMF. Diphenyl carbonate (0.46 g) and $NaHCO_3$ (45 mg) were added to the solution and the mixture was heated for 80 min at 120°. After cooling and separating the insoluble material from the solution, 1 ml of 28% $NH_4OH$ was added and the mixture was kept for 30 min. The solvent was then removed *in vacuo* and the residue was triturated with $CHCl_3$. The precipitate was collected and crystallized from EtOH to give 0.27 g (57%) of **14**, mp 252—254° (dec.). *Anal.* Calcd for $C_9H_{10}BrN_3O_4$: C, 35.56; H, 3.31; N, 13.82; Br, 26.29: Found: C, 35.33; H, 3.38; N, 13.53; Br, 26.53. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 226 (14800), 280 (4200), $\lambda_{min}^{H_2O}$: 221 (14600), 263 (3100). $\lambda_{max}^{0.1N\ NaOH}$: 237 (17300), 305 (1100). $\lambda_{min}^{0.1N\ NaOH}$: 280 (900). $\lambda_{max}^{0.1N\ HCl}$: 227 (7600), 283 (4000). $\lambda_{min}^{0.1N\ HCl}$: 218 (7000), 258 (2200). NMR (DMSO-$d_6$) $\delta$: 8.63 (bs, 1, NH), 8.17 (s, 1, 6-H), 6.14 (d, 1, 1′-H, $J$=6.6 Hz), 5.63 (d, 1, 3′-OH), 4.93 (t, 1, 5′-OH, $J$=5.3 Hz), 4.24 (d, 1, 2′-H), 4.10 (d, 1, 3′-H, $J_{3',OH}$=4.2 Hz), 4.02 (t, 1, 4′-H, $J_{4',5'}$=6.6 Hz), 3.21 (m, 2, 5′-H). MS (*m/e*): 305, 303 ($M^+$).

***O*²,5′-Cyclo-2′,3′-*O*-isopropylidene-5-bromouridine (15)**——2′,3′-*O*-Isopropylidene-5-bromouridine[15] (5.0 g), triphenylphosphine (4.0 g), and diethyl azodicarboxylate (3 ml) were taken up in 50 ml of dioxane and the suspension was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was partitioned with ether and $H_2O$. The aqueous layer was concentrated and the residue was crystallized from MeOH to give 3.0 g (63%) of **15**, mp 258—261° (dec.). *Anal.* Calcd for $C_{12}H_{13}BrN_2O_5 \cdot 1/2H_2O$: C, 40.71; H, 3.81; N, 7.91; Br, 22.58. Found: C, 40.78; H, 3.76; N, 8.03; Br, 22.52. UV $\lambda_{max}^{EtOH}$: nm ($\varepsilon$): 248 (8600), 265 (infl., 7700). $\lambda_{min}^{EtOH}$: 222 (3700). NMR ($CDCl_3$) $\delta$: 7.71 (s, 1, 6-H), 5.39 (s, 1, 1′-H), 4.99 (d, 1, 2′-H, $J$=5.6 Hz), 4.93 (d, 1, 3′-H), 4.71 (bt, 1, 4′-H), 4.50 (dd, 1, 5′-Ha), 4.22 (dd, 1, 5′-Hb, $J_{4',a}$=1.5 Hz, $J_{4',b}$=1.0 Hz, $J_{a,b}$=13.0 Hz), 1.53, 1.37 (s, 3+3, $CMe_2$). MS (*m/e*): 346, 344 ($M^+$), 331, 329 (M—15).

**2′,3′-*O*-Isopropylidene-5-bromoisocytidine (16)**——A solution of **15** (2.0 g) in 200 ml of MeOH saturated with $NH_3$ was heated at 60° overnight in a sealed tube. The solvent was removed *in vacuo* and the residue was crystallized from THF to give 2.0 g (95%) of **16**. Recrystallization of **16** from EtOH gave a pure sample, mp 213—215°.[16] *Anal.* Calcd lor $C_{12}H_{16}BrN_3O_5$: C, 39.81; H, 4.46; N, 11.61; Br, 22.08. Found: C, 39.74; H, 4.44; N, 11.59; Br, 21.96. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 272 (5900). $\lambda_{min}^{H_2O}$: 255 (4700). MS (*m/e*): 363, 361 ($M^+$), 348, 346 (M−15).

***N*²,5′-Cyclo-2′,3′-*O*-isopropylidene-5-bromoisocytidine (17)**——A mixture of **16** (0.5 g), triphenylphosphine (0.43 g), and diethyl azodicarboxylate (0.28 ml) in 5 ml of THF was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was applied to a column of silica gel (20 g). The eluate with $CHCl_3$–EtOH (10: 1) was concentrated and the residue was crystallized from EtOH to give 0.44 g (93%) of **17**, mp 229—231° (dec.). *Anal.* Calcd for $C_{12}H_{14}BrN_3O_4$: C, 41.90; H, 4.10; N, 12.22; Br. 23.23. Found: C, 42.09; H, 4.19; N, 12.02; Br, 23.11. UV $\lambda_{max}^{H_2O}$: nm ($\varepsilon$): 225 (24100), 270 (sh, 5000). NMR (DMSO-$d_6$) $\delta$: 8.31 (s, 1, 6-H), 7.37 (bs, 1, NH), 5.78 (s, 1, 1′-H), 4.79 (d, 1, 2′-H, $J$=5.9 Hz), 4.68 (d, 1, 3′-H), 4.54 (bs, 1, 4′-H), 3.32 (dd, 1, 5′-Ha), 3.19 (dd, 1, 5′-Hb, $J_{4',a}$=2.5 Hz, $J_{4',b}$=1.4 Hz, $J_{a,b}$=14.2 Hz), 1.41, 1.27 (s, 3+3, $CMe_2$). MS (*m/e*): 345, 343 ($M^+$), 330, 328 (M−15).

**6-Methylaminouridine (18)**——2′,3′-*O*-Isopropylidene-6-methylaminouridine[13] (3.5 g) was dissolved in 120 ml of 50% $HCO_2H$ and kept overnight at room temperature. The solvent was removed *in vacuo* below 35°, and the residue was applied to a column of silica gel (100 g). The eluate with EtOH–$CHCl_3$ (1: 5) was concentrated to give 2.5 g (83%) of **18** as an amorphous material. A part of the product was crystallized from EtOH–$CHCl_3$ to give pure **18**, mp 135—136°. *Anal.* Calcd for $C_{10}H_{15}N_3O_6$: C, 43.95; H, 5.53; N, 15.38. Found: C, 43.81, H, 5.67; N, 15.13. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 274 (23600). $\lambda_{min}^{H_2O}$: 242 (1700). $\lambda_{max}^{0.1N\ NaOH}$: 276 (17100). $\lambda_{min}^{0.1N\ NaOH}$: 247 (2000). NMR (DMSO-$d_6$) $\delta$: 10.56 (bs, 1, $N^3H$), 7.12 (m, 1, 6-NH), 6.25 (d, 1, 1′-H, $J$=7.3 Hz), 5.71 (bt, 1, 5′-OH), 5.25, 5.06 (each d, 2′,3′-OH, $J$=6.3 and 4.4 Hz), 4.48 (d, 1, 5-H, $J_{3,5}$=2 Hz), 4.32 (m, 1, 2′-H), 4.02 (m, 1, 3′-H), 3.89 (m, 1, 4′-H), 3.62 (m, 2, 5′-H), 2.62 (s, 3, NMe).

***N*⁶,2′-Cyclo-6-methylaminouridine (19)**——A Mixture of **18** (1.0 g), diphenyl carbonate (1.2 g), and $NaHCO_3$ (10 mg) in 8 ml of DMF was stirred for 1 hr at 100°. After cooling, the separated crystals were collected (0.45 g). Addition of EtOH to the mother liquor afforded 0.26 g of crystals (total 76%) of **19**. Recrystallization of **19** from EtOH gave a pure sample, mp 278—280° (dec.). *Anal.* Calcd for $C_{10}H_{13}N_3O_5$: C, 47.06; H, 5.13; N, 16.47. Found: C, 46.73; H, 5.16; N, 16.47. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 268 (27600). $\lambda_{min}^{H_2O}$: 238 (2200). $\lambda_{max}^{0.1N\ NaOH}$: 272 (19200). $\lambda_{min}^{0.1N\ NaOH}$: 245 (2600). NMR (DMSO-$d_6$) $\delta$: 10.32 (bs, 1, $N^3H$), 6.09 (d, 1, 1′-H. $J$=6.2 Hz), 4.13 (d, 1, 2′-H), 4.16 (bs, 1, 3′-H), 3.93 (m, 1, 1, 4′-H), 3.23 (m, 2, 5′-H), 4.56 (d, 1, 5-H, $J$=1.6 Hz), MS (*m/e*): 255 ($M^+$).

***N*⁶,5′-Cyclo-6-methylaminouridine (20)**——A Mixture of **18** (0.5 g), triphenylphosphine (0.5 g), and diethyl azodicarboxylate (0.5 ml) in 30 ml of dioxane was stirred for 4 hr at room temperature. After addition of $H_2O$ (2 ml) followed by stirring for 30 min, the solution was concentrated and the residue was taken up in EtOH. The resulting crystals were collected and recrystallized from aqueous EtOH to give 0.3 g

15) T. Ueda, *Chem. Pharm. Bull.*, **8**, 455 (1960).
16) This compound was reported to be amorphous.[10]

(64%) of **20**, mp 274—276° (dec.). *Anal.* Calcd for $C_{10}H_{13}N_3O_5$: C, 47.06; H, 5.13; N, 16.47. Found: C, 47.21; H, 5.14; N, 16.13. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 284 (20000). $\lambda_{min}^{H_2O}$: 248 (2000). $\lambda_{max}^{0.1N\ NaOH}$: 283 (15600). $\lambda_{min}^{0.1N\ NaOH}$: 252 (2300). NMR (DMSO-$d_6$) $\delta$: 10.97 (bs, 1, $N^3H$), 6.27 (s, 1, 1′-H), 5.31, 4.98 (each d, 2, 2′,3′-OH), 4.84 (d, 1, 5-H, $J_{3,5}$=1.7 Hz), 4.23 (bs, 1,4′-H), 4.16 (m, 1, 2′-H), 4.14 (m, 1, 3′-H), 3.36 (dd, 1, 5′-Ha), 3.05 (dd, 1, 5′-Hb, $J_{4',a}$=2.5 Hz, $J_{4',b}$=1.0 Hz, $J_{a,b}$=14.2 Hz), 2.80 (s, 3, NMe). MS (*m/e*): 255 ($M^+$).

***N*$^6$,5′-Cyclo-2′,3′-*O*-isopropylidene-6-methylaminouridine**——2′,3′-*O*-Isopropylidene-6-methylaminouridine (0.5 g) was treated with 0.5 g of triphenylphosphine and 0.5 ml of diethyl azodicarboxylate in 5 ml of DMF at room temperature for 4 hr. After work-up as described above, the $N^6$,5′-cyclo derivative was obtained from aqueous EtOH as crystals (0.32 g, 67%), mp 300°. *Anal.* Calcd for $C_{13}H_{17}N_3O_5$: C, 52.87; H, 5.80; N, 14.23. Found: C, 52.96; H, 5.88; N, 14.20. UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon$): 284 (20900). $\lambda_{min}^{H_2O}$: 247 (1800). $\lambda_{max}^{0.1N\ NaOH}$: 282 (15500). $\lambda_{min}^{0.1N\ NaOH}$: 250 (1900). NMR ($CDCl_3$) $\delta$: 10.00 (bs, 1, $N^3H$), 6.65 (s, 1, 1′-H), 5.02 (bs, 1, 5-H), 4.70 (s, 1, 2′-H), 4.70 (s, 1, 3′-H), 4.47 (bs, 1, 4′-H), 3.26 (dd, 1, 5′-Ha), 3.24 (dd, 1, 5′-Hb, $J_{4',a}$= 1.0 Hz, $J_{4',b}$=1.0 Hz, $J_{a,b}$=14.1 Hz). MS (*m/e*): 295 ($M^+$), 280 (M−15).

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