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Synthesis of 2′-Deoxy-6,2′-methano-cyclouridine (Nucleosides and Nucleotides. LIX[1])

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2′-Deoxy-6,2′-methano-cyclouridine, a carbon-bridged cyclonucleoside fixed in a high-anti conformation, was synthesized. Treatment of a 3′,5′-*O*-protected 6-cyano-2′-*O*-imidazolylthiocarbonyluridine with tri-*n*-butyltin hydride afforded a 6,2′-oxomethano-cyclouridine derivative in low yield. Base treatment of 5-bromo-2′-deoxy-2′(*S*)-ethoxycarbonylmethyl-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine resulted in an intramolecular Michael reaction followed by dehydrobromination to give the 6,2′-cyclonucleoside. The latter was de-ethoxycarbonylated by treatment with sodium chloride and water in dimethylsulfoxide followed by desilylation to furnish the title compound.

Keywords——uridine; *C*-cyclo-2′-deoxyuridine; nucleoside conformation; NMR; CD

Our current interest in stereochemical studies of the interactions of nucleosides and nucleotides with the enzymes utilizing them requires the use of carbon-bridged cyclonucleosides in which the glycosyl torsion angles are fixed at particular values.[2] In the pyrimidine nucleoside series, we have reported the preparation of 6,5′-,[3] 6,5′-methano-,[4] 6,3′-methano-,[5] and 6,2′-ethano-[6] cyclouridines. This paper describes the synthesis of 2′-deoxyuridine bridged between the 6- and 2′-position by a methylene bridge. A preliminary account of this work has appeared.[7]

In a previous study we made use of a 6-cyano-5′-deoxy-5′-iodouridine derivative for intramolecular radical cyclization between the 5′-position and the 6-cyano carbon.[4] It seems highly probable that similar cyclization should occur in a 6-cyanouridine if the methylene radical could be generated at the 2′-position, giving the 6,2′-bridged imine. We have also reported that the 2′-deoxygenation of ribonucleosides to 2′-deoxyribonucleosides can be performed by treatment of the 2′-*O*-imidazolylthiocarbonyl derivative with tri-*n*-butyltin hydride.[8] Since this reaction proceeds *via* the initial formation of the 2′-radical, this reaction might be adaptable for the present purpose.

5-Bromo-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (**1**) was treated with sodium cyanide in dimethylformamide (DMF)[9] at room temperature to give the crystalline 6-cyano derivative (**2**). Compound **2** was treated with thiocarbonyldiimidazole in acetonitrile to give the 2′-*O*-imidazolylthiocarbonyl derivative (**3**), which was then treated with tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN). After acid treatment of the reaction mixture, a product (**4**) was obtained which gave a positive test with a carbonyl reagent. The ultraviolet (UV) absorption maximum at 308 nm indicated an extension of the conjugation of the uracil system and another maximum at 261 nm should be that of the hydrate form of the ketone group of **4**. Similar hydration has been noted in 8,5′-cyclo-5′-oxo-2′,3′-*O*-isopropylideneadenosine,[10] and it appears to be a general feature in sterically hindered cyclic ketones. The nuclear magnetic resonance (NMR) spectra of **4** showed a low-field shift of the anomeric proton signal and a high field shift of the 2′-proton signal. These results strongly support the presence of a carbonyl bridge between C-6 and C-2′, as shown in **4**. However, the

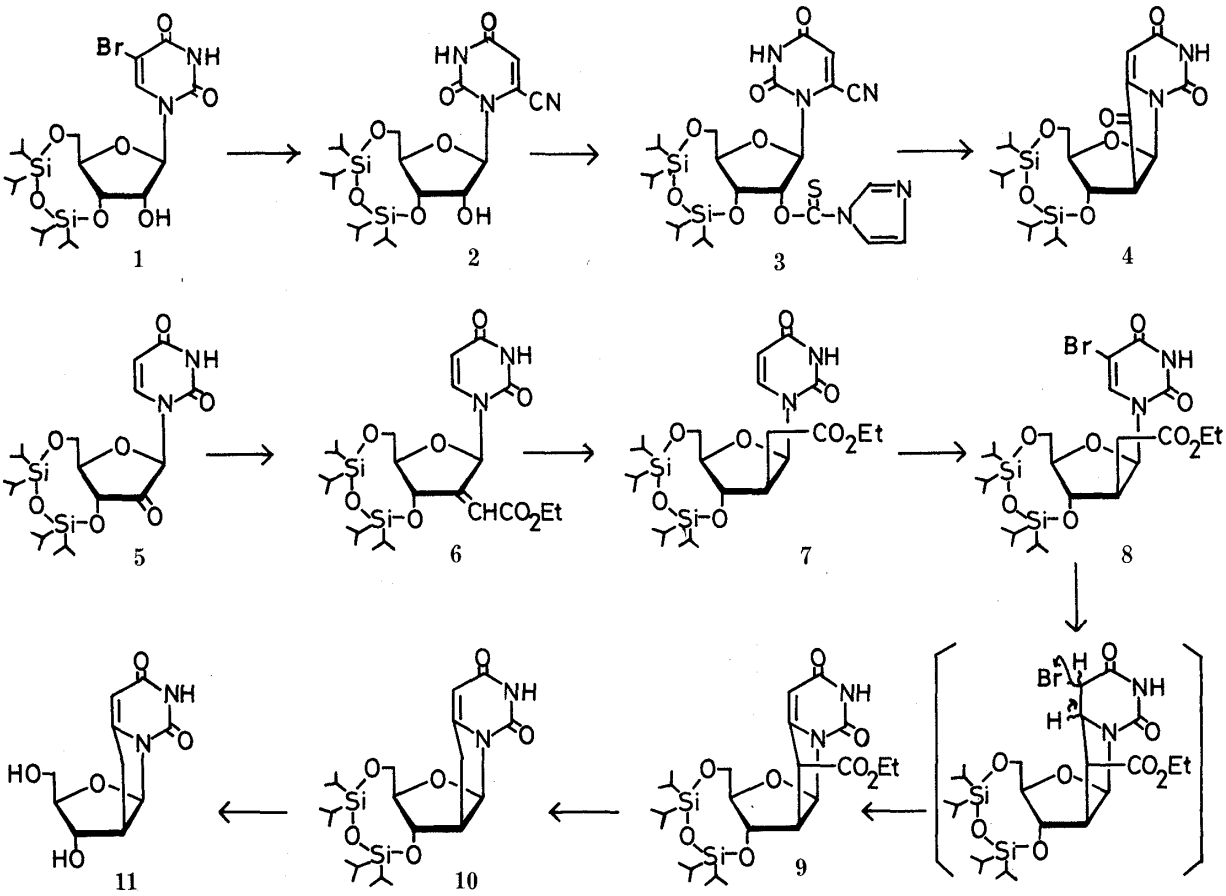

Fig. 1

yield of **4** was very low (8%) probably due to the *syn* preference of the 6-cyanouridine derivative in terms of the glycosyl bond rotation. Therefore we tried a different approach to the 6,2′-bridging.

In the synthesis of 2′-deoxy-6,2′-ethano-cyclouridine[6] we developed a route for the preparation of the 2′-deoxy-2′(*S*)-ethoxycarbonylmethyluridine derivative (**7**) from a 2′-ketouridine (**5**) *via* the 2′-ethoxycarbonylmethylene compound (**6**). Compound **7** was treated with bromine to give the 5-bromo derivative (**8**). Treatment of **8** with potassium *tert*-butoxide or sodium hydride did not give the expected product, but treatment with 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) in refluxing dioxane afforded the expected cyclo compound (**9**) by a Michael addition of the generated 2′′-carbanion to C-6 of the base portion, followed by dehydrobromination in 65% yield. The NMR spectrum of **9** showed the presence of a proton of C-5 at 5.7 ppm, in place of that of C-6, which is split by an allyl-coupling with the bridge methine proton. The UV spectrum of **9** (λ_{max} at 263 nm) in an alkaline medium showed a red shift (λ_{max} at 345 nm) due to dissociation of the bridge methine. A similar red shift due to dissociation of the methylene group connected to the C-6 of uracil had been observed in a 6-cyanomethyluridine derivative.[11] Although the stereochemistry at the bridge-head of **9** was not elucidated, it seems from the NMR data that only one diastereomer was obtained in this reaction. Heating of **9** in dimethylsulfoxide (DMSO) with a little more than an equimolar amount of water and sodium chloride at 140 °C[12] resulted in de-ethoxycarbonylation to afford the 6,2′-methano-cyclo compound (**10**). Deprotection of **10** with tetra-*n*-butylammonium fluoride in tetrahydrofuran furnished 2′-deoxy-6,2′-methano-cyclouridine (**11**), which was obtained in a crystalline form. The structure of **11** was fully

confirmed by the elemental analysis, NMR, and mass spectral data. The circular dichroism (CD) spectrum of **11** showed a strong negative ellipticity at the main absorption region (similar to that of 2′-deoxy-6,2′-ethano-cyclouridine[6]), as expected.

The present novel sequence of an ionic cyclization reaction should have a wide applicability for the synthesis of various carbon-bridged purine and pyrimidine cyclonucleosides.[13]

Experimental

All mealting points were determined on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. UV spectra were measured with a Shimadzu UV-240 spectrophotometer. NMR spectra were taken on a JEOL JNM-FX 100FT or 200FT spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in ppm (δ), and signals are described as s(singlet), d(doublet), t(triplet), q(quartet), m(multiplet) or br(broad). Mass spectra (MS) were taken on a JEOL D-300 spectrometer. CD spectra were taken on a JEOL J-40 spectropolarimeter at room temperature. The starting nucleoside, uridine, was from Yamasa Shoyu Co. Silica gel used for column chromatography or preparative thin layer chromatography (pTLC) was Wako gel C-200.

5-Bromo-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (1)——5-Bromouridine (5.0 g, 15.5 mmol) in 40 ml of pyridine was treated with 5.3 g (1.1 eq) of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[14] in an ice bath, and the mixture was kept at room temperature for 3.5 h. A small amount of H_2O was added to the solution under stirring and the solvent was evaporated off *in vacuo*. The residue was partitioned between EtOAc–H_2O and the organic layer was passed through a Whatman 1-PS filter paper. The filtrate was concentrated and the residue was taken up in $CHCl_3$, and applied to a column of silica gel (200 g). The eluate with 2% MeOH–$CHCl_3$ was concentrated to leave 7.4 g (85%) of **1** as a foam. UV λ_{max}^{MeOH} : 277 nm. This was used for the next step without further purification.

6-Cyano-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (2)——A mixture of **1** (3.1 g, 5.48 mmol) and NaCN (0.40 g, 1.5 eq) in 15 ml of DMF was stirred at room temperature for 34 h. The mixture was poured into 50 ml of EtOAc, a small volume of H_2O was added, and the whole was neutralized with 4 ml of 1 N HCl. The organic layer was washed with H_2O, and filtered through a Whatman 1-PS filter paper, then the filtrate was concentrated. The residue was taken up in $CHCl_3$ and applied to a column of silica gel (90 g). The eluate with 0.5% MeOH–$CHCl_3$ was concentrated to leave 1.72 g (61%) of **2** as a foam, which was crystallized from EtOAc–*n*-hexane, mp 127—129 °C. UV λ_{max}^{MeOH}: 283 nm. NMR ($CDCl_3$): 8.85 (1H, br s, NH-3), 6.28 (1H, s, H-5), 5.84 (1H, d, H-1′, J=2.9 Hz), 4.81 (1H, dd, H-3′, $J_{2',3'}$=6.8 Hz), 4.54 (1H, m, H-2′), 4.1—3.8 (3H, m, H-4′,5′), 3.34 (1H, d, HO-2′). MS *m/z*: 468 (base peak, M−43). *Anal.* Calcd for $C_{22}H_{37}N_3O_7Si_2$: C, 51.63; H, 7.29; N, 8.21. Found: C, 51.56; H, 7.31; N, 8.21.

6-Cyano-2′-*O*-imidazolylthiocarbonyl-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (3)——Compound **2** (1.34 g, 2.62 mmol) was dissolved in 40 ml of CCl_4, thiocarbonyldiimidazole (570 mg, 1 eq) was added and the mixture was refluxed for 1 h. The solvent was evaporated off *in vacuo*. The residue was taken up in benzene, and applied to a column of silica gel (40 g). The eluate with benzene–EtOAc (4 : 1) was concentrated to leave 775.7 mg (48%) of crude **3** as a foam. This was used for the next step without further purification.

2′-Deoxy-6,2′-oxomethano-cyclo-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (4)——Compound **3** (332 mg, 0.534 mmol) was dissolved in 50 ml of toluene in an atmosphere of argon. A mixture of *n*-Bu_3SnH (0.28 ml, 1.9 eq) and AIBN (50 mg) in 2 ml of toluene was added dropwise to the solution over a period of 1 h under reflux. After additional refluxing for 1 h, a small volume of AcOH–H_2O–MeOH was added to the solution at room temperature and the mixture was stirred for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in $CHCl_3$, and subjected to pTLC. The plate was developed three times with $CHCl_3$–MeOH (20 : 1) and the appropriate band was eluted with $CHCl_3$–MeOH (5 : 1). The extract was concentrated and the residue was crystallized from EtOAc–*n*-hexane to give 20.0 mg (8%) of **4**, mp 190 °C (dec.). UV λ_{max}^{MeOH}: 260, 308 nm. $\lambda_{max}^{1N\,NaOH-MeOH}$: 315 nm. NMR ($CDCl_3$): 8.36 (1H, br s, HN-3), 6.36 (1H, d, H-1′, J=6.1 Hz), 6.18 (1H, s, H-5),4.52 (1H, dd, H-3′, $J_{2',3'}$=4.4 Hz), 4.2—4.0 (2H, m, H-5′), 3.8 (1H, m, H-4′), 3.48 (1H, m, H-2′). MS *m/z*: 453 (base peak, M−43). *Anal.* Calcd for $C_{22}H_{36}N_2O_7Si_2 \cdot 0.5H_2O$: C, 52.24; H, 7.37; N, 5.54. Found: C, 52.11; H, 6.98; N, 5.59.

5-Bromo-2′-deoxy-2′(*S*)-ethoxycarbonylmethyl-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (8)——Compound **7**[6] (152.5 mg, 0.273 mmol) was dissolved in 5 ml of AcOH containing 67 mg of NaOAc. Bromine (15 μl, 1.1 eq) was added to the solution and the mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in dioxane. The solution was heated to reflux for 10 min and the solvent was evaporated off. The residue was partitioned between $CHCl_3$ and H_2O and the organic layer was applied to a column of silica gel (5 g). From the eluate with $CHCl_3$–EtOAc (8 : 1), 127 mg (73%) of **8** was obtained after evaporation of the solvent. The product was crystallized from EtOAc–*n*-hexane, mp 137—139 °C. UV λ_{max}^{MeOH}: 278 nm. NMR ($CDCl_3$): 8.40 (1H, br s, HN-3), 7.89 (1H, s, H-6), 6.18 (1H, d, H-1′, J=7.1 Hz), 4.3—4.0 (5H, m, H-3′,5′, OCH_2CH_3), 3.8 (1H, m, H-4′), 3.1 (1H, m, H-2′, $J_{2',2''a}$=4.1 Hz, $J_{2',2''b}$=10.0 Hz), 2.64 (1H, dd, H-2″a, $J_{a,b}$=16.8 Hz), 2.21 (1H, dd, H-2″b). MS *m/z*: 593, 591 (M−43). *Anal.* Calcd for $C_{25}H_{43}BrN_2O_8Si_2$: C, 47.23; H, 6.82; Br,

12.57; N, 4.41. Found: C, 47.36; H, 6.97; Br, 12.76; N, 4.40.

2′-Deoxy-2″-ethoxycarbonyl-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-6,2′-methano-cyclouridine (9)——Compound **8** (1.60 g, 2.52 mmol) and DBU (1.9 ml, 5 eq) were dissolved in 15 ml of dioxane. The system was flushed with Ar, and the solution was refluxed under Ar for 6.5 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and H_2O, while the aqueous layer was neutralized by the addition of 1 N HCl. The organic layer was passed through a Whatman 1-PS filter paper and the filtrate was concentrated. The residue was taken up in a small volume of $CHCl_3$ and applied to a column of silica gel (50 g). The eluate with $CHCl_3$–EtOAc (10 : 1) was concentrated to leave 907.7 mg (65%) of **9** as a foam. UV λ_{max}^{MeOH}: 263 nm. $\lambda_{max}^{1\,N\,NaOMe-MeOH}$: 345 nm. NMR ($CDCl_3$): 8.05 (1H, br s, HN-3), 6.17 (1H, d, H-1′, J=6.3 Hz), 5.78 (1H, dd, H-5), 4.27 (2H, q, OEt), 4.2 (1H, m, H-3′), 4.1—3.9 (4H, m, H-4′,5′, H-2″, $J_{5,2''}$=1.2 Hz), 3.4 (1H, m, H-2′), 1.32 (3H, t, OEt).

2′-Deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-6,2′-methano-cyclouridine (10)——Compound **9** (1.04 g, 1.87 mmol) was dissolved in 10 ml of DMSO, then H_2O (50 μl; 1.5 eq) and NaCl (100 mg, 1 eq) were added to the solution. The mixture was heated at 145 °C for 6 h under stirring. The reaction mixture was poured into EtOAc–H_2O and the organic layer was passed through a Whatman 1-PS filter paper. The filtrate was concentrated *in vacuo*, then the residue was taken up in $CHCl_3$, and applied to a column of silica gel (30 g). The eluate with $CHCl_3$–EtOAc (9 : 1) was concentrated to leave 284.5 mg (32%) of **10** as a foam. UV λ_{max}^{MeOH}: 263 nm. $\lambda_{max}^{1\,N\,NaOMe-MeOH}$: 260 nm. NMR ($CDCl_3$): 8.04 (1H, br s, HN-3), 6.11 (1H, d, H-1′, J=5.9 Hz), 5.57 (1H, s, H-5), 4.2 (1H, m, H-3′), 4.1—3.9 (3H, m, H-4′,5′), 3.2—3.0 (3H, m, H-2′,2″). MS m/z: 439 (M−43).

2′-Deoxy-6,2′-methano-cyclouridine (11)——Compound **10** (120 mg, 0.249 mmol) was dissolved in 3 ml of THF and 1 M tetra-*n*-butylammonium fluoride in THF (0.5 ml, 4 eq) was added to the solution. The mixture was stirred at room temperature for 1 h, and the solvent was evaporated off. The residue was partitioned between $CHCl_3$ and H_2O, and the aqueous layer was separated, and concentrated to dryness. The residue was dissolved in a small volume of MeOH and adsorbed on silica gel. The gel was dried *in vacuo* and placed on top of a column of silica gel (5 g). The eluate with 8% MeOH–$CHCl_3$ was concentrated and the residue was crystallized from aqueous MeOH to give 42.4 mg (71%) of **11**, mp 195—198 °C. UV $\lambda_{max}^{H_2O}$: 262 nm (ε, 11100). CD (H_2O): 261 nm (θ=−25400). NMR (DMSO-d_6+D_2O): 6.02 (1H, d, H-1′, J=5.6 Hz), 5.43 (1H, s, H-5), 4.0—3.8 (2H, m, H-3′,4′), 3.35 (2H, d, H-5′, J=4.6 Hz), 3.2—2.8 (3H, m, H-2′,2″). MS m/z: 240 (M). *Anal.* Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.85; H, 5.09; N, 11.63.

References and Notes

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