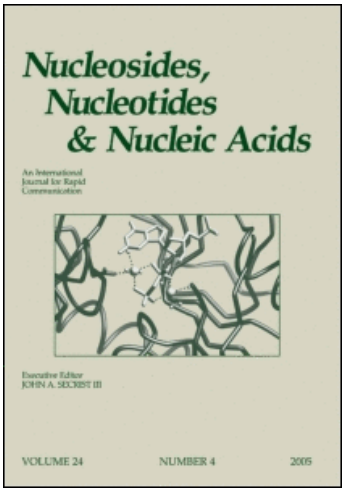

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SYNTHESIS OF 2',3'-DIDEOXY-6,3'-METHANO-CYCLOURIDINE AND A FURANOSYL TO PYRANOSYL RING-ISOMERIZATION IN THE C-CYCLO-NUCLEOSIDE (NUCLEOSIDES AND NUCLEOTIDES. 53[1])

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ABSTRACT

Synthesis of a C-cyclouridine fixed by a 6,3'-methylene unit, 2',3'-dideoxy-6,3'-methano-cyclouridine, was accomplished by utilizing a 3'-hydroxymethyluridine via an intramolecular radical addition as the key step. A furanosyl to pyranosyl ring-isomerization was observed in this reparation and the mechanism for this isomerization is presented.

In our continuing studies of the synthesis of carbon-bridged cyclonucleosides we have reported the pyrimidine cyclonucleosides bridged betweeen the 6 and 5'[2] or 6 and 2' positions[3] as models of the fixed anti form of pyrimidine nucleosides. It has been recognized that, in the binding of nucleotide-utilizing enzymes to the substrates, the glycosyl torsion angles of the nucleotides are one of the most important determinants.[2] The cyclonucleosides in which the glycosyl torsion angles are fixed in various degrees are therefore crucial for more precise studies of the stereochemistry of nucleotide interactions with the enzymes.

This paper describes a sythesis of 2',3'-dideoxy-6,3'-methano-cyclouridine where the glycosyl torsion angle is fixed by the 6,3'-methylene unit, together with the furanosyl to pyranosyl lactol ring-isomerization during the cyclization.[3] We have recently synthesized[4] the 3'-branched chain derivatives of 2'-deoxyuridine, namely 2',3'-dideoxy-3'(R and S)-

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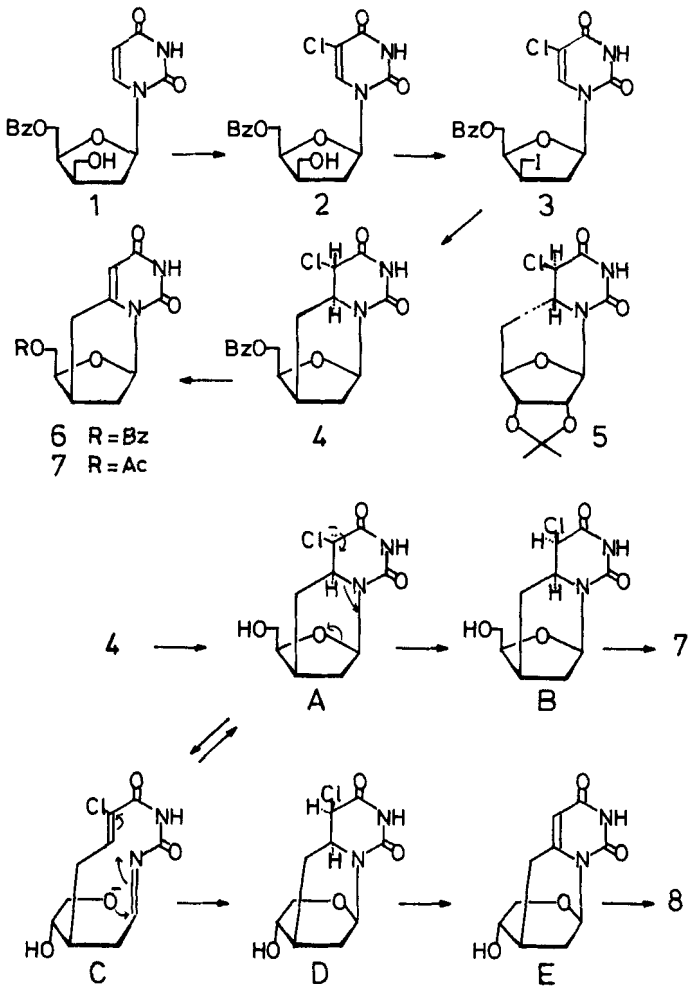
hydroxymethyluridines, via the deaminative ring contraction of the 3'-amino-2',3'-dideoxyglucopyranosyluracils.

One of the intermediates, 5'-O-benzoyl-2',3'-dideoxy-3'(S)-hydroxymethyluridine (1),[4] seemed to be a suitable starting material for this purpose. Treatment of 1 with chlorine and sodium acetate afforded the 5-chloro derivative (2). Compound 2 was treated with p-toluenesulfonyl chloride and 4-dimethylaminopyridine in pyridine followed by lithium iodide to give the 3'(R)-iodomethyl derivative (3). The radical cyclization between the 6 and 3'-position of 3 was performed by the addition of a mixture of tri-n-butylstannane and azobis-isobutyron-trile to 3 in benzene at reflux and furnished the cyclodihydro derivative (4) in 68% yield. The Structure of 4, obtained as an amorphous powder, was confirmed by instrumental analyses. The radical addition of the 3'-methylene carbon to the 6-position was highly stereospecific giving the 5(S),6(S)-derivative. It is interesting to note that, in the radical cyclization of 5'-deoxy-5'-bromo-2',3'-O-isopropylidene-5-chloro-uridine, the 5'-methylene radical attacked from the "rear" side to give the 5(R),6(R)-diastereomer (5).[2]

Treatment of 4 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene under reflux gave a crystalline product (6) isolated by preparative thin layer chromatography. The structure of 6 was confirmed by instrumental analyses to be 5'-O-benzoyl-2',3'-dideoxy-6,3'-methano-cyclouridine. Compound 6 was converted to the 5'-O-acetyl derivative (7) by methanolysis followed by acetylation. Compound 7 was obtained in a crystalline form suitable for the X-ray diffraction analysis.[5] Compound 4 was directly converted to 7 by treatment with sodium methoxide in methanol followed by acetic anhydride in pyridine. If sodium ethoxide in ethanol was used instead, a small amount of crystalline product (8) was separated, of which mass spectra showed the same molecular ion peak as that of 7. However, the NMR spectrum was different from that of 7. The structure of 8 was finally confirmed by the X-ray diffraction method[6] to be 4'-O-acetyl-2',3'-dideoxy-6,3'-methano-ß-D-erythro-pentopyranosyluracil. Although we have been un-



successful in finding reproducible conditions for this conversion, a possible route from 4 to 8 can be depicted.

In the elimination of HCl from 4 to give 6, prior epimerization of the 5-position to give B should occur via the anion A. In the furanose to pyranose isomerization, the electron flow in A must have occurred to give ring opened intermediate C, which recyclized to give D, and successive dehydrochlorination gave the product E, isolated as the 4'-O-acetate 8. Treatment of 6 or 7 with base under various conditions did not give the pyranoside, which ruled out the possibility of the route starting with the dissociation of

the 3''-proton of 6. Although we are unaware of any precedent report on this type of lactol ring-isomerization accompanied by the pyrimidine ring opening, the anomerization of 5-formyluridine[7] or 5-acetyluridine[8] has been observed which involved similar ring opening of the base moiety. In these cases the lactol ring isomerization was not observed.

The circular dichroism spectra (CD) of 7 showed a negative Cotton band at its main absorption region which is in contrast to that of the 6,5'-cyclouridines.[2] It should be emphasized that the sign of the CD band in the pyrimidine nucleosides is not a direct reflection of so called "syn-anti" conformation as have been generally accepted. The glycosyl torsion angle (χ) of 7 was determined as 79.3° and that of 6,5'-cyclouridine can be estimated by the molecular model to be about 50°. The transitional torsion angle for the reversal of the sign of the CD bands would therefore be in between. Since both cyclonucleosides are regarded as the anti type, one should be very careful to estimate preferred syn-anti conformations of pyrimidine nucleosides in solution by the CD spectra alone. Closer study on this point will be presented separately.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus MP-3 and were uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL FX100-FT or FX200-FT spectrometer in $CDCl_3$ as the solvent with tetramethylsilane as an internal standard. Chemical shifts were reported in ppm (δ), and signals were described as s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad). All exchangeable protons were confirmed by addition of D_2O. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-240 sepctrophotometer. CD spectra were measured on a JASCO J-40 spectropolarimeter at room temperature. Thin layer chromatography was carried out on Merck pre-coated plate $60F_{254}$. Silica gel for column chromatography was from Wako Co., C-200.

5'-O-Benzoyl-2',3'-dideoxy-3'(S)-hydroxymethyl-5-chlorouridine (2)---- Compound 1[4] (828 mg) and NaOAc (676 mg) were

dissolved in a mixture of DMF (5 mL) and AcOH (15 mL), and 2.2 mL of 1.24 M Cl_2 in AcOH (1.15 eq) was added to the solution under cooling in an ice bath. The solution was stirred overnight at room temperature and the solvent was removed in vacuo. The residue was partitioned with $CHCl_3$ and H_2O, and the organic layer was passed through a Whatman 1-PS filter paper. The filtrate was concentrated, and applied to a column of silica gel. The eluate with 5%-MeOH in $CHCl_3$ was concentrated to leave a foam of 2 (526 mg, 62%). UV λ_{max}^{MeOH}: 276 nm. Ms (m/z): 235 (sugar)$^+$, 147, 145 (B+1)$^+$. NMR (DMSO-d_6, 100 mHz): 11.85 (br, 1, HN^3), 8.03 (s, 1, H-6), 8.02-7.92 (m, 2, Bz), 7.75-7.44 (m, 3, Bz), 5.95 (dd, 1, H-1', J= 7 and 8 Hz), 4.93 (t, 1, HO, J= 4 Hz), 4.80-4.40 (m, 3, H-4',5'), 3.57 (m, 2, H-3''), 1.97 (m, 1, H-3'). The 2'-protons were buried in the peaks of DMSO and H_2O.

5'-O-Benzoyl-2',3'-dideoxy-3'(R)-iodomethyl-5-chlorouridine (3)---- Compound 2 (530 mg) was treated with TsCl (2.0 g) and 4-dimethylaminopyridine (600 mg) in 20 mL of pyridine at room temperature overnight under stirring. The solution was neutralized with 1 N $NaHCO_3$ and the solvent was removed in vacuo. The residue was partitioned with $CHCl_3$ and 1 N $NaHCO_3$, and the organic layer was passed through a Whatman 1-PS filter paper. The filtrate was concentrated to dryness and the residue was dried in vacuo overnight. This was dissolved in 15 mL of methyl ethyl ketone and the solution was refluxed with LiI (784 mg) for 3 h. The solvent was removed and the residue was treated with $CHCl_3$-H_2O, the organic layer was separated, and concentrated. The concentrate was applied to a column of silica gel. The eluate with $CHCl_3$-AcOEt (10·2) was concentrated to leave 388 mg (57%) of 3 as a foam. Ms (m/z): 345 (sugar)$^+$, 148, 146 (B+1)$^+$, 217 (sugar-HI)$^+$, 105 (Bz)$^+$, base peak. NMR (100 mHz): 8.73 (br, s, 1, HN^3), 8.05-7.90 (m, 2, Bz), 7.81 (s, 1, H-6), 7.67-7.37 (m, 3, Bz), 6.02 (dd, 1, H-1', J= 5.0 and 8.3 Hz), 4.81-4.44 (m, 3, H-4',5'), 3.28 (br s, 2, H-3''), 3.15-2.83 (m, 2, H-2'a,b), 1.94 (m, 1, H-3').

5'-O-Benzoyl-2',3'-dideoxy-6(S),3'-methano-5(S)-chloro-5,6-dihydrouridine (4)---- To a solution of 3 (123 mg) in

10 mL of benzene a mixture of tributylstannane (83 µL, 1.3 eq) and AIBN (25 mg) in 2 mL of benzene was added dropwise for 30 min under reflux in argon atmosphere. The solvent was removed and the residue was applied to a preparative tlc plate and developed with $CHCl_3$-AcOEt (2:1). The appropriate band was eluted with $CHCl_3$-AcOEt (1:1) and the solvent was evaporated to leave a powder of 4 (62 mg, 68%). Ms (m/z): 349, 347 $(M-17)^+$, 349, 346 $(M-18)^+$, 329 $(M-Cl)^+$, 328 $(M-HCl)^+$, 244, 242 $(M-BzOH)^+$, 105 $(Bz)^+$, base peak. NMR (200 mHz,+D_2O): 8.05 (d, 2, BZ, J= 7.3 Hz), 7.63-7.42 (m, 3, Bz), 6.34 (d, 1, H-1', J= 4.9 Hz), 4.57 (dd, 2, H-5'), 4.33 (m, 1, H-4'), 4.27 (d, 1, H-5, J= 12.2 Hz), 3.92 (m, 1, H-6, $J_{5,6}$= 12.2 Hz, $J_{6,3''a}$= 11 Hz, $J_{6,3''b}$= 5.8 Hz), 2.74 (br t, 1, H-3'), 2.54 (m, 1, H-3''a), 2.24 (m, 1, H-2'a), 1.88 (d, 1, H-2'b, $J_{2'a,b}$= 11.7 Hz), 1.71 (m, 1, H-3''b, $J_{3''a,b}$= 13.2 Hz).

5'-O-Benzoyl-2',3'-dideoxy-6,3'-methanouridine (6)---- Compound 4 (50 mg) and DBU (43 µL, 2.3 eq) in 4 mL of benzene were stirred for 100 min at 65°. The solution was neutralized with AcOH-benzene and the solvent was removed in vacuo, and the residue was crystallized from MeOH to give 20 mg (67%) of 5, mp 226-229°. Ms (M/z): 328 $(M)^+$, 206 $(M-BzOH)^+$, 193, 163, 105 $(Bz)^+$, base peak. NMR (100 mHz): 8.54 (br s, 1, HN^3), 8.02 (m, 2, Bz), 7.59-7.34 (m, 3, Bz), 6.51 (d, 1, H-1', J= 4.2 Hz), 5,56 (s, 1, H-5), 4.44 (br s, 3, H-4',5'), 3.01 (br s, 2, H-3''a,b), 2.88 (br s, 1, H-3'), 2.40 (m, 1, H-2'a), 2.07 (d, 1, H-2'b, $J_{2'a,b}$= 12.5 Hz). UV λ_{max}^{MeOH}: 268 nm. Anal. Calcd for $C_{17}H_{16}N_2O_5 \cdot 1/4H_2O$: C, 61.35; H, 5.00; N, 8.41. Found: C, 61.30; H, 4.77; N, 8.31.

5'-O-Acetyl-2',3'-dideoxy-6,3'methanouridine (7)---- a) Compound 6 (40 mg) was dissolved in 3 mL of 0.5% NaOH-MeOH and the solution was stirred for 1 h at room temperature. After neutralization with Dowex 50 (H^+) resin, the solution was evaporated in vacuo and the residue was partitioned with $CHCl_3$ and H_2O. The aqueous layer was concentrated, the residue dried in vacuo at 60° for 5 h, and dissolved in 2 mL of pyridine containing 0.1 mL of Ac_2O. The solution was stirred for 5 h at room temperature and MeOH was added to the mixture. The solution was evaporated and the residue was crystallized

from EtOH to give 24 mg (74%) of 7, mp 206-208°. The crystal was subjected to the X-ray diffraction analysis. Ms (m/z): 266 $(M)^+$, 224, 206, 193, 164, 163(base peak), 150, 120, 81, 43. UV λ_{max}^{MeOH}: 267 nm, ε = 10400. CD in MeOH: 265 nm, θ = -17800. NMR (200 mHz): 8.06 (br s, 1, HN^3), 6.47 (d, 1, H-1', J= 4.4 Hz), 5.56 (s, 1, H-5), 4.31-4.12 (m, 3, H-4',5'), 2.96 (d, 1, H-3''a), 2.94 (d, 1, H-3''b, $J_{3''a,b}$= 16 Hz), 2.84 (br s, 1, H-3'), 2.41 (m, 1, H-2'a), 2.08 (s, 3, Ac), 2.06 (d, 1, H-2'b, $J_{2'a,b}$= 12.2 Hz).

b) Compound 4 (27 mg) was dissolved in 2 mL of abs.MeOH containing 98 uL of 2 N NaOMe-MeOH (2.5 eq) and the solution was stirred for 15 min at 60°. After neutralization with dil.HCl the solvent was removed in vacuo. The residue was dissolved in 2 mL of pyridine containing 0.1 mL of Ac_2O and the solution was stirred for 6 h at room temperature. A small volume of MeOH was added and the solvent was removed, the residue was taken up in $CHCl_3$. After washing with H_2O, the $CHCl_3$ layer was dried through Whatman 1-PS filter paper and concentrated. The residue was crystallized from MeOH to give 9 mg (46%) of 7. The physical properties were identical with those obtained by the method a).

4'-O-Acetyl-2',3'-dideoxy-6,3'-methano-β-D-erythro-pentopyranosyluracil (8)---- Compound 4 (27 mg) was treated in 2.5 eq. of NaOEt in EtOH (2 mL) by similar manner as described in method b) for 7 from 4. A crystal of 8 (8 mg) was obtained from MeOH. This was subjected to the X-ray diffraction.[6] Ms (m/z): 266 $(M)^+$, 206 $(M-AcOH)^+$, 189, 163, 150, 81 (base peak). UV λ_{max}^{MeOH}: 266 nm. NMR (200 mHz): 7.98 (br s, 1, HN^3), 6.16 (br s, 1, H-1'), 5.53 (s, 1, H-5), 4.73 (br s, 1, H-4'), 3.84 (d, 1, H-5'a, $J_{5'a,b}$= 12.2 Hz), 3.74 (dd, 1, H-5'b, $J_{4',5'b}$= 2.0 Hz), 3.12 (dd, 1, H-3''a), 2.85 (d, 1, H-3''b, $J_{3''a,b}$= 18 Hz), 2.70)m, 1, H-2'a), 2.46 (m, 1, H-3'), 1.72 (d, 1, H-2'b, $J_{2'a,b}$= 15 Hz). This reaction was not reproducible to give 8, and in other runs 7 was obtained as the sole product.

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