SYNTHESIS OF 6,5'-CYCLO-5'-DEOXYURIDINE: A PYRIMIDINE NUCLEOSIDE FIXED IN ANTI CONFORMATION[1]

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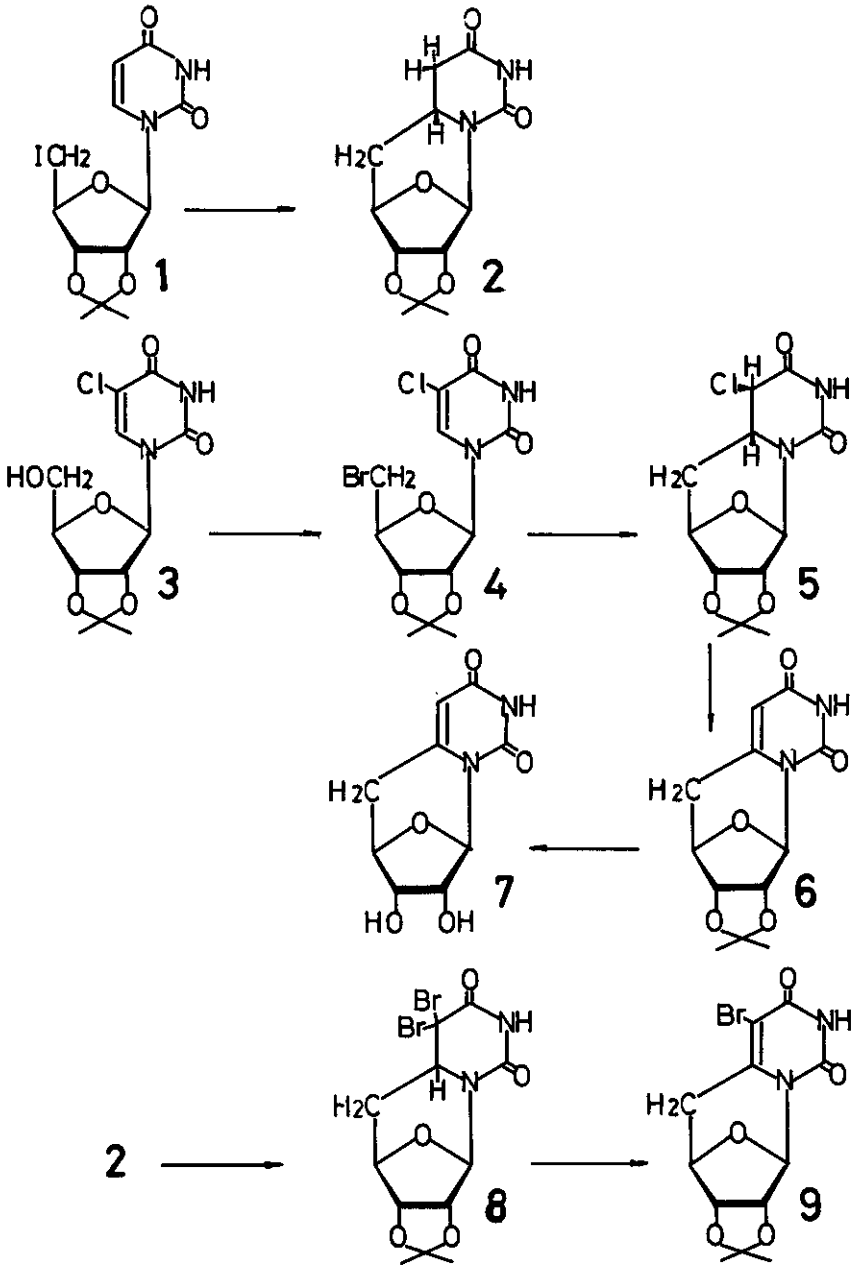
Abstract ——— Treatment of 2',3'-O-isopropylidene-5'-bromo-5'-deoxy-5-chloro-uridine with tri-n-butylstannane gave the 6,5'-cyclo-5,6-dihydro derivative, which was de-hydrochlorinated and deacetonated to furnish 6,5'-cyclo-5'-deoxy-uridine, a fixed anti conformer of uridine. Bromination of a 6,5'-cyclo-5,6-dihydrouridine gave the 5-bromo derivative of the title compound.

It has generally been recognized that the syn-anti conformation around the N-glycosylic bonds of nucleosides is the determinant of the nucleosides and nucleotides for exhibiting various biological activities[2]. We have recently synthesized fixed anti conformer of purine nucleosides, namely, 8,5'-cyclo-5'-deoxy-adenosine and -guanosine, and their phosphate derivatives. These were utilized in the conformational analysis on the interaction of guanylate and ribonuclease T_1[3].

We wish to report a versatile method of the synthesis of a fixed anti conformer of uridine, 6,5'-cyclo-5'-deoxyuridine, for similar studies of pyrimidine specific ribonucleases.

Fox and co-workers have reported[4] the synthesis of 6,5'(R and S)-cyclouridines by the method involving an intramolecular aldol reaction of 2',3'-O-isopropylidene-5-hydroxyuridine-5'-aldehyde. We have recently reported an intramolecular radical addition of 2',3'-O-isopropylidene-5'-deoxy-5'-iodouridine (1) by tri-n-butylstannane to form 2',3'-O-isopropylidene-6,5'-cyclo-5'-deoxy-5,6(R)-dihydrouridine (2)[5]. This reaction would be suitable for the preparation of 6,5'-cyclopyrimidine nucleosides provided that the 5,6-unsaturation can be accomplished from 2. This was realized by the following two routes.

Treatment of 2',3'-O-isopropylidene-5-chlorouridine (3) with carbon tetrabromide and triphenylphosphine in dimethylformamide[6] afforded the 5'-bromo-5'-deoxy derivative (4, mp 212.5-213.5°C) in high yield. The dropwise addition of a mixture of tri-n-butylstannane and azobisisobutyronitrile in benzene to the refluxing suspension of 4 in benzene resulted in a formation of 2',3'-O-isopropylidene-6,5'-cyclo-5,6-dihydro-5-chlorouridine (5, mp 278°C, decomp., m/e 304, 302 [M^+]) as highly insoluble crystals in 78 % yield. The NMR analysis of 5 showed that the configuration at 5 and 6 positions should be R and R.


ICH2
1
H2C
2
HOCH2
3
BrCH2
4
5
6
7
HO
OH
Br
8
9

Treatment of 5 with sodium ethoxide in ethanol gave the expected 6,5'-cyclouridine derivative [6, mp 288°C, m/e 266[M^+], UV λ_{max}^{MeOH}, nm (ε): 270 (8900), CD in MeOH [θ]: 264 (+13300)]. The deacetonation of 6 in 0.1 N HCl in aqueous methanol furnished 6,5'-cyclo-5'-deoxyuridine [7, mp 298°C, decomp., m/e 226 [M^+], UV $\lambda_{max}^{H_2O}$, nm (ε): 272 (9200), λmin: 235.5 (1400), $\lambda_{max}^{pH\ 11}$: 270 (7270), λmin: 244 (3000), CD in H_2O nm [θ]: 263 (+10600), NMR (DMSO-D_6-D_2O): δ 2.66 (d, 1, 5'-Ha), 3.06 (dd, 1, 5'-Hb, $J_{a,b}$= 20 Hz, $J_{4',5'b}$= 7 Hz), 4.07 (s, 2, 2',3'-H), 4.38 (d, 1, 4'-H), 5.40 (s, 1, 5-H), 5.78 (s, 1, 1'-H)].

Compound 6 can also be prepared from 2',3'-O-isopropylidene-5'-deoxy-5'-iodo-5-bromouridine or other 5,5'-dihalogeno derivatives, since the initial attack of the tributyltin radical should occur at the haloalkyl portion.

As the alternative route for the preparation of 6, the 5,6-unsaturation from 2 would also be promising. Treatment of 2 with various dehydrogenating agents, however, met with little success. Treatment of 2 with N-bromosuccinimide in carbon tetrachloride resulted in a formation of a mixture of the 5,5-dibromo-5,6-dihydro derivative (8) and the 5-bromo derivative (9), the latter being the major product. Brief treatment of the mixture with sodium ethoxide in ethanol afforded pure 9 [mp 225-226°C, m/e 346, 344 [M^+], 341, 339 [M^+-CH_3], UV λ_{max}^{MeOH}: 283 nm; ε, 10000, CD in MeOH, nm [θ]: 280 (+10060), 239 (0), 221 (-5400), NMR ($CDCl_3$): δ 1.33, 1.52 (s, 3+3, isopropylidene), 2.67 (dd, 1, 5'-Ha, $J_{4',5'a}$= 0.9 Hz, $J_{a,b}$= 19 Hz), 3.23 (dd, 1, 5'-Hb, $J_{4',5'b}$= 6.8 Hz), 4.70 (m, 3, 2',3',4'-H), 6.21 (s, 1, 1'-H), 8.61 (bs, 1, N^3-H)]. The yield of 9 from 2 was 59 %. Treatment of 9 with tri-n-butylstannane also afforded 6[7].

The present procedure for the synthesis of 6,5'-cyclo-5'-deoxyuridine involving a highly specific radical cyclization would facilitate further manipulation of various cyclopyrimidine nucleosides and such experiment is being extensively undertaken.

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References and notes

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7. Satisfactory elemental analyses were obtained for the crystalline compounds described in this report.

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