

SYNTHESIS OF 6,5'-CYCLO-5'-DEOXYURIDINE: A PYRIMIDINE NUCLEOSIDE
FIXED IN ANTI CONFORMATION¹

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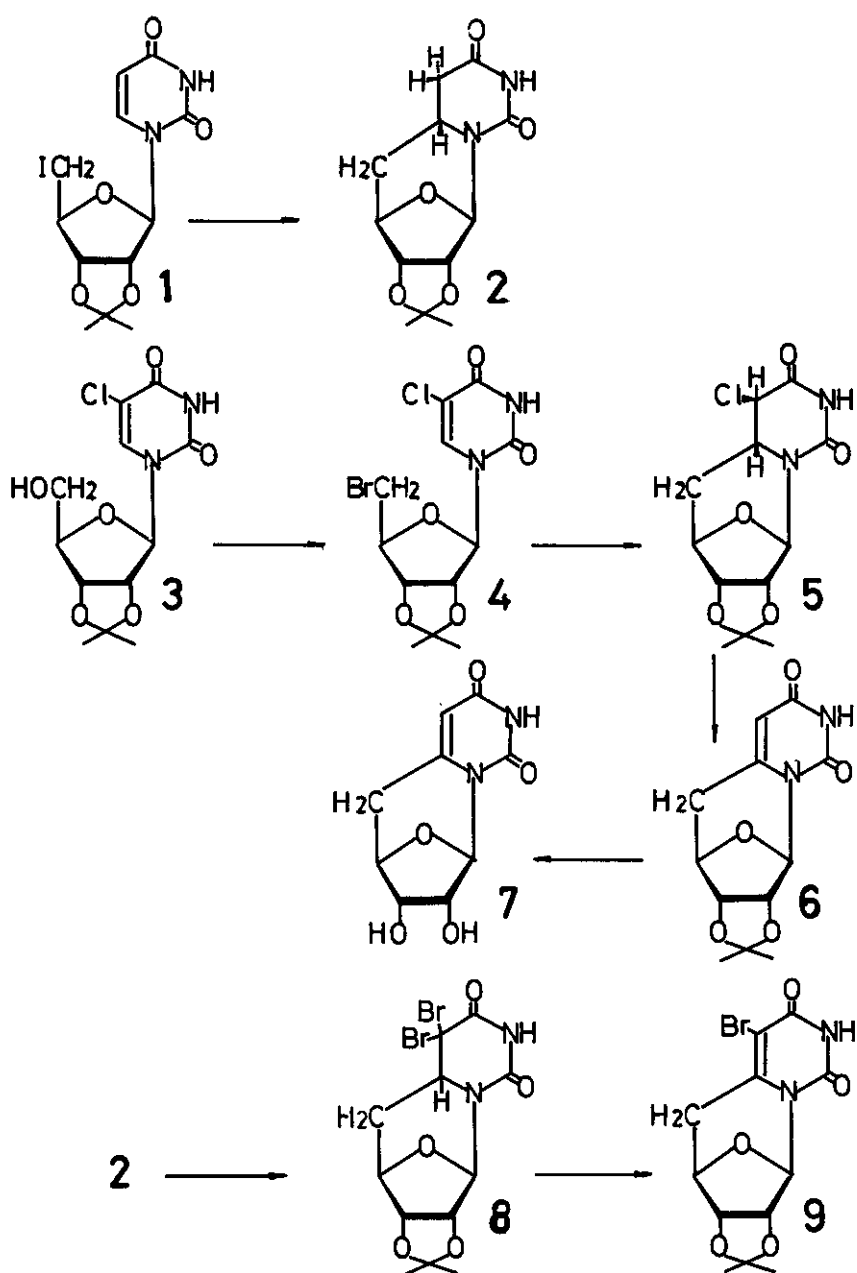
Abstract — Treatment of 2',3'-O-isopropylidene-5'-bromo-5'-deoxy-5'-chloro-uridine with tri-n-butylstannane gave the 6,5'-cyclo-5,6-dihydro derivative, which was de-hydrochlorinated and deacetonated to furnish 6,5'-cyclo-5'-deoxy-uridine, a fixed anti conformer of uridine. Bromination of a 6,5'-cyclo-5,6-dihydrouridine 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 activities². 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 T₁³.

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 reported⁴ 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 dimethylformamide⁶ 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.



Treatment of 5 with sodium ethoxide in ethanol gave the expected 6,5'-cyclo-uridine derivative [6, mp 288°C, m/e 266 [M^+], UV $\lambda_{\max}^{\text{MeOH}}$, nm (ϵ): 270 (8900), CD in MeOH [θ]: 264 (+13300)]. The deacetylation 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 $\lambda_{\max}^{\text{H}_2\text{O}}$, nm (ϵ): 272 (9200), λ_{\min} : 235.5 (1400), $\lambda_{\max}^{\text{pH } 11}$: 270 (7270), λ_{\min} : 244 (3000), CD in H_2O nm [θ]: 263 (+10600), NMR ($\text{DMSO}-d_6$ - 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 [$M^+ - \text{CH}_3$], UV $\lambda_{\max}^{\text{MeOH}}$: 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 6⁷.

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

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References and notes

1. This paper constitutes Part XXXVIII of "Nucleosides and Nucleotides". Part XXXVII, K. Fukukawa, T. Ueda, and T. Hirano, *Chem. Pharm. Bull.*, 1981, **29**, 597.
2. For example, see: a) K. K. Ogilvie, L. Slotin, and P. Rheault, *Biochem. Biophys. Res. Commun.*, 1971, **45**, 297. b) M. Ikehara, I. Tazawa, and T. Fukui, *Biochem.*, 1969, **8**, 736. c) T. Oshima and K. Imahori, *J. Biochem.*, 1971, **70**, 197.
3. A. Matsuda and T. Ueda, *Nippon Kagaku Kaishi*, 1981, 845 and references therein.
4. a) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, 1976, **41**, 3133. b) B. A. Otter,

- E. A. Falco, and J. J. Fox, J. Org. Chem., 1978, 43, 481.
5. Y. Yamagata, S. Fujii, T. Fujiwara, K. Tomita, and T. Ueda, Biochim. Biophys. Acta, 1981, in press.
6. J. P. H. Verheyden and J. G. Moffatt, J. Org. Chem., 1972, 37, 2289.
7. Satisfactory elemental analyses were obtained for the crystalline compounds described in this report.

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