SYNTHESIS AND PROPERTIES OF SULFUR- AND NITROGEN-BRIDGED 6,2'- AND 6,5'-PYRIMIDINE CYCLONUCLEOSIDES

Susumu Shibuya and Tohru Ueda

Faculty of Pharmaceutical Sciences, Hokkaido Univeristy

Sapporo, 060, Japan

Cyclonucleosides are useful intermediates for the chemical transformations of nucleosides. As the continuing studies on the synthesis and reactions of pyrimidine cyclonucleosides, we report the synthesis of sulfur- and nitrogen-bridged 6,2'- and 6,5'-cyclonucleosides starting from S^2,2'-cyclo- and S^2,5'-cyclo-2-thiouridines and 6-methylaminouridine.

S^2,2'-Cyclo-2-thiouridine(I) was treated with methyl iodide and NaOMe in MeOH at room temperature to give 1-(2-deoxy-2-methylthio-β-D-arabinofuranosyl)-2-methoxy-4-pyrimidinone(II). Compound II was converted to 1-(2-deoxy-2-methylthio-β-D-arabinofuranosyl)uracil(III) by alkaline hydrolysis. The product III was, in turn, acetylated, thiated, methylated, and then aminated to give 1-(2-deoxy-2-methylthio-β-D-arabionfuranosyl)cytosine.

Treatment of I with Br_2 in MeOH and pyridine gave S^2,2'-cyclo-1-(2-deoxy-β-D-arabinofuranosyl)-5-bromo-2-thiouracil(IV) in 54% yield. Treatment of IV with NaOMe in MeOH afforded S^6,2'-cyclo-1-(2-deoxy-β-D-arabinofuranosyl)-2-methoxy-4-pyrimidinone(V). The conversion of IV to V should have proceeded by the sequence of a) methanolysis with aryl-S fission, b) addition of the 2'-SH to the 5,6-double bond, and c) elimination of hydrogen bromide. Compound V was converted to S^6,2'-cyclo-uridine, -2-thiouridine, and -isocytidine by treatment with aqueous acid, H_2S in pyridine, and NH_3 in MeOH, respectively.

Similarly, 2',3'-O-isopropylidene S^2,5'-cyclo-2-thiouridine was brominated and the product was treated with NaOMe to give the S^6,5'-cyclo-O^2-methyluridine derivative, which was then converted to the 2',3'-O-isopropylidene derivatives of S^6,5'-cyclo-uridine, -2-thiouridine, and -isocytidine, respectively. For the synthesis of N^6,2'- and N^6,5'-cyclonucleosides, we made use of 6-methylaminouridine(VI), which was synthesized by a careful deprotection of 2',3'-O-isopropylidene-6-methylaminouridine. Treatment of VI with diphenyl carbonate in DMF afforded N^6,2'-cyclo-N^6-methyluridine. N^6,5'-Cyclization of VI was accomplished, in high yield, by the treatment with triphenylphosphine and diethyl azodicarboxylate.

The NMR spectra of these cyclo compounds are well agreeable with the 6,2'- and 6,5'-cyclo structures. The comparisons of the signals of these cyclo compounds with the natural pyrimidine nucleosides revealed that the anomeric protons are shifted to downfield by 0.5-2 ppm, probably due to the deshielding effects of the substituents at their 2-positions. These cyclonucleosides showed characteristic CD spectra. 6,2'-Cyclonucleosides exhibited negative CD bands, whereas the 6,5'-cyclo compounds showed large positive CD bands around the B_{2u} region. The magnitudes of the positive bands of the non-cyclo pyrimidine nucleosides were very weak probably reflecting their free rotations about the glycosylic linkages.