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SYNTHESIS OF SPIRO AND BICYCLIC NUCLEOSIDES FROM RIBOSE NITRILE OXIDE WITH DIMETHYL ACETYLENEDICARBOXYLATE

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Abstract: A new spiro nucleoside strutural type (5b) and two new bicyclic nucleoside structural types (6 and 7) were synthesized from the reaction of ribose nitrile oxide with dimethyl acetylenedicarboxylate.

In connection with our recent studies[1] directed towards the synthesis of acyclonucleosides which have received considerable attention as antiviral drugs,[2] we synthesized a ribose nitrile oxide derivative (2) which would yield the corresponding chiral acyclonucleosides by the reaction with various 1,3-dipolarophiles.

From this experiment, we found the following facts: Compound (2) was stable at 0 °C and changed gradually into a ribose hydroximolactone (4) at room temperature; 2 reacted with dimethyl acetylenedicarboxylate (DMAD) at 0 °C to give the expected chiral acyclonucleoside (3); the reaction of 4 with DMAD gave a new class of spironucleoside (5b) and bicyclic nucleosides (6 and 7). Herein we wish to present the preparations and structure determinations of 3, 5b, 6, and 7.

A mixture of 2,3-O-isopropylidene-5-O-trityl-D-ribose oxime (1)[3] (0.5 mmol) and DMAD (4 mmol) was allowed to react with aqueous 5 % NaOCl solution (2 ml) in the presence of triethylamine (0.02 ml) (stirring for 6 h, 0 °C). Purification by t.l.c. (silica gel, CH_2Cl_2) gave 3a in 43 % yield (white crystals, m.p. 59-61 °C). On treatment with HCl-MeOH, 3a was easily deprotected to give 3b. The structure of 3a was determined by its spectroscopic data (especially νOH = 3500 cm^{-1}) together with elemental analysis.

N-Hydroxy-2,3-O-isopropylidene-5-O-trityl-D-ribonimido-1,4-lactone (4) was prepared by the same method as described in 3a without DMAD (stirring for 20 min, r.t.); 99.5 %, white crystals, m.p. 152-153 °C.[4]

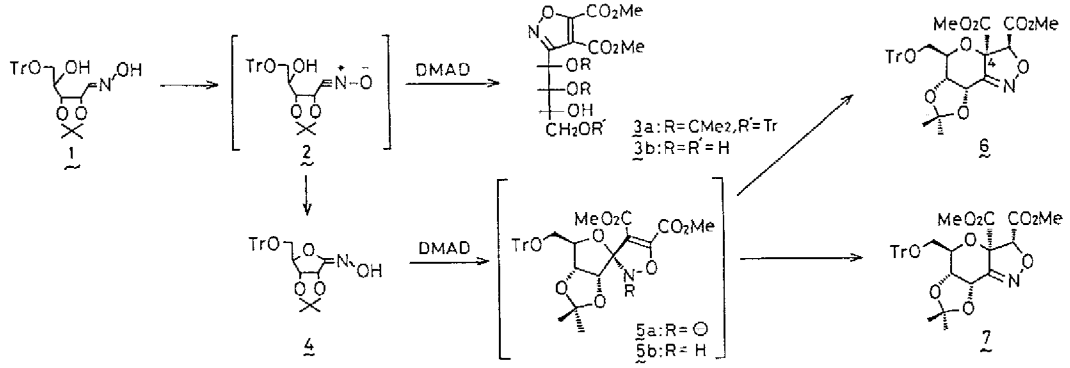
Next, 4 (0.5 mmol) was allowed to react with DMAD (0.8 mmol) and triethylamine (0.07 ml) in dry CH_2Cl_2 (1 ml) (stirring for 2 h, r.t.). Purification by t.l.c. (silica gel, AcOEt : hexane = 2 : 3) gave a 27 : 10 mixture of diastereoisomeric bicyclic nucleosides (6) and (7) in 85 % yield; Compound (6) was isolated by recrystallization from Et_2O-hexane (white needles, m.p.

149-150 °C); 7 was also obtained by t.l.c. purification (silica gel, THF : hexane = 1 : 2, white powder, m.p. 71 °C).

The structures of 6 and 7 were determined by the differences of chemical shift values for ester groups in ^1H- and ^{13}C-nmr. The structure of 4S-isomer is ruled out due to the steric hindrance between trityloxymethyl and ester groups. The formation of 6 and 7 are considered to proceed through an intermediate, spironucleoside (5a).

Thus, we attempted to trap 5a: A lithium salt of 4 generated with n-BuLi was treated with DMAD in THF at -20 °C to give 5b in 20 % yield. The structure of 5b was determined by n.O.e. obsevation (14.2 %) between $CO_2\underline{Me}$ of C-4 and $\underline{CH}_2OTr$. Further, the THF solution of 5b was stirred with equimolar LDA at room temperature to give 6 and 7 quantitatively.

Recently reports on spiro and bicyclic nucleosides have appeared for the first time.[5] The present compounds (5b, 6, and 7) are new type of nucleosides and seem interest in biological activity. Studies designed to uncover the chemistry of spiro and bicyclic nucleosides are in progress.



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