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NUCLEOSIDES XXVI. A FACILE SYNTHESIS OF 2,2'-ANHYDRO-ARABINO PYRIMIDINE NUCLEOSIDES (1)

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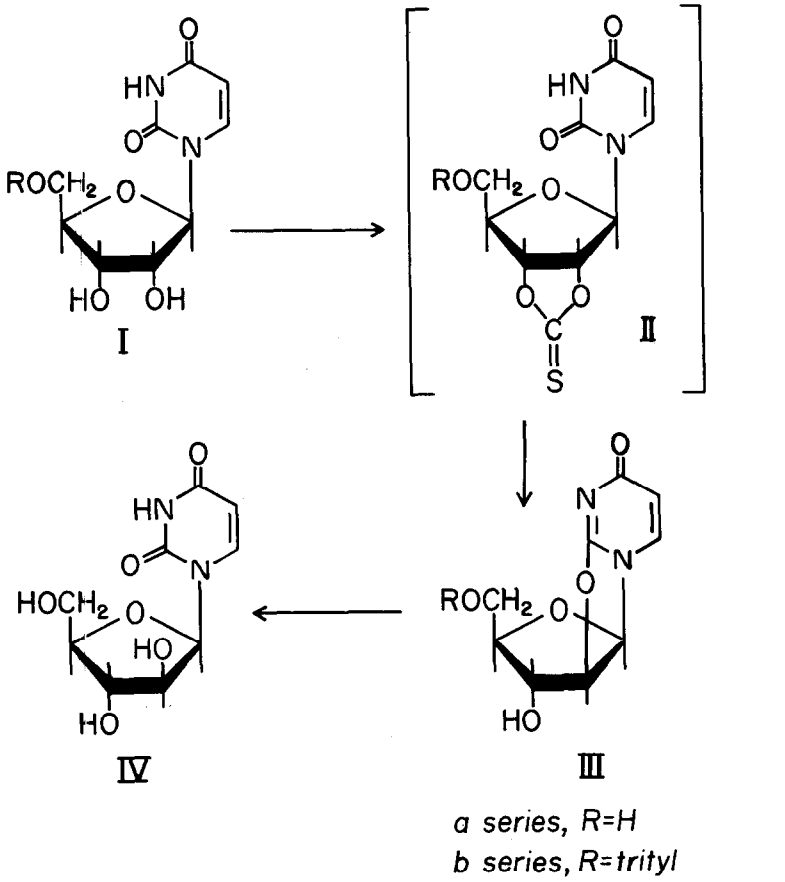
Corey and Winters (2) reported the reaction of 1,2-diols with thiocarbonyldiimidazole (3) to afford cyclic thionocarbonate derivatives which were then treated with trimethyl phosphite to yield olefins. In our attempt to apply this reaction to the synthesis of uridine nucleosides containing a 2,3-double bond in the carbohydrate moiety (4) an unexpected transformation was encountered which results in a simple and direct synthesis of certain anhydro nucleosides and thereby of the biologically-important 1-β-D-arabinofuranosyl pyrimidines.

Treatment of 5'-O-trityluridine (Ib) (5) with one equivalent of thiocarbonyldiimidazole in refluxing toluene under anhydrous conditions for one hour yielded, after cooling and filtration, a white, sulfur-free precipitate which was 2,2'-anhydro-1-(5'-O-trityl-β-D-arabinofuranosyl)uracil (IIIb, see figure). After recrystallization from methanol, needles were obtained, m.p. 217-219°, $[\alpha]_D^{23}$ - 18° (c, 0.4 in methanol). A second recrystallization from ethanol gave platelets, m.p. 219-221°. A melting point of 210-214° was reported (6) for IIIb with $[\alpha]_D^{26}$ - 19°. A mixed melting point of IIIb with an authentic sample (7) synthesized previously by an alternate route (6) gave 212-220°. The ultraviolet and infra-red spectra of the two samples



were identical. The overall yield of recrystallized IIIb from I (see figure) was 85%.

The structure of product IIIb was confirmed further by treating it with methanolic hydrogen chloride to effect de-tritylation. After removal of solvent, an aqueous solution of the residue was treated with Dowex-1 (acetate) to remove chloride ions. Solvent was removed and the residue was

crystallized from hot ethanol with the addition of water to effect solution. The 2,2'-anhydro nucleoside (IIIa) was obtained, m.p. 246-248° (no dec.). Brown, Todd and Varadarajan (8) reported m.p. 234-236° (dec.) and Codington, Doerr and Fox (6) reported 238-240° (no dec.). An authentic specimen (7) of 2,2'-anhydro-arabinosyluracil prepared by the reported route (6) gave a m.p. of 241-245° and showed no depression when admixed with the de-tritylated product obtained from IIIb. Both samples gave identical ultraviolet spectra in water with twin peaks at 223 and 249 mμ and a slight shoulder at ∿270 mμ (9). Finally, treatment of IIIa with dilute alkali at room temperature yielded as expected 1-β-D-arabinofuranosyluracil (IV, "spongouridine") as the sole product. All these data establish IIIb as 2,2'-anhydro-1-(5'-O-trityl-β-D-arabinosyl)uracil.

Uridine itself reacts directly with one equivalent of thiocarbonyldiimidazole in refluxing toluene for 45 minutes to give a precipitated brownish oil which, after trituration with alcohol, filtration of the solid and recrystallization (decolorization with charcoal) from 95% ethanol yielded the 2,2'-anhydro nucleoside (IIIa) in 40% yield. This material was identical with IIIa obtained by the de-tritylation of IIIb described above.

It is most likely that the thionocarbonate II (or a related thiocarbamate precursor) is an intermediate in the conversion of I → III. The fact that intermediate II was not isolated is readily ascribed to the presence of the 2-carbonyl of the pyrimidine moiety as a neighboring group which participated in the formation of III. It is also clear that the thionocarbonate of II (or a thiocarbamate group, e.g., -O-C(=S)-N-CH=N-CH=CH) behaved as a leaving group in the presence of the 2-carbonyl under the reaction conditions employed.

The scope of this reaction in the nucleoside area is under investigation

in our laboratory.

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