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The Chemical Transformation of Uridine to an α-L-Lyxo Nucleoside via a 4'-Unsaturated Intermediate

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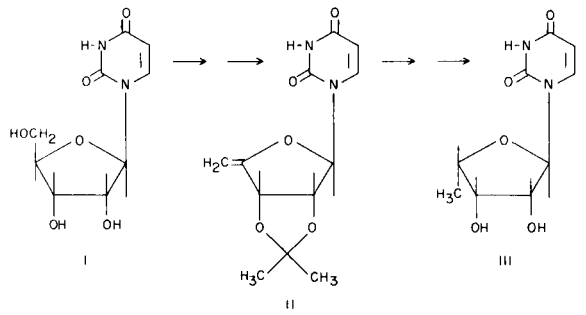
Sir:

We wish to report the synthetic conversion of 1-(β-D-ribopentofuranosyl)uracil (I) (uridine) to 1-(5-deoxy-α-L-lyxopentofuranosyl)uracil (III) *via* the unsaturated nucleoside 1-(2,3-*O*-isopropylidene-5-deoxy-β-D-erythropent-4-enofuranosyl)uracil (II).

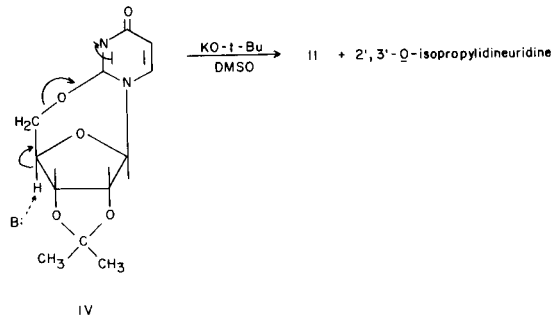


Interest in unsaturated carbohydrates (1) and unsaturated nucleosides (2) has been stimulated by the discovery of antibiotics containing unsaturated sugars (3,4). Hough and Otter (5) recently reported the preparation of 3-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-β-L-threopent-4-enofuranose and other furanoid vinyl ethers from the corresponding primary halogen derivatives by an extension of the silver fluoride/pyridine method (6) to the furanose series. Verheyden and Moffatt (7) have since successfully applied this procedure to 2',3'-di-*O*-acetyl-5'-iodo-5'-deoxyuridine.

We have been investigating the mild base-catalyzed E_2 elimination of *p*-toluene sulfonate from the 5'-position of several nucleosides as an extension of our earlier syntheses of 2',3'-unsaturated furanosyl adenine nucleosides by the same procedure (2b).

Reaction of 5'-*O*-*p*-toluenesulfonyl-2',3'-*O*-isopropylideneuridine (8) with potassium *t*-butoxide in *t*-butyl alcohol at room temperature for two hours gave a quantitative yield of II which was freed from trace impurities observed on tlc by elution from a neutral alumina column with chloroform:ethanol 8:2. The 4'-unsaturated nucleoside (II) crystallized from isopropyl alcohol as large shining crystals of the alcoholate. The product was dried over phosphorus pentoxide at 40° to yield the hemialcoholate, m.p. 50-60° (poorly defined), $C_{12}H_{14}N_2O_5 \cdot 1/2\ C_3H_8O$ requires: C, 54.74; H, 6.10; N, 9.46. Found: C, 54.86; H, 6.11; N, 9.39; λ max (EtOH), 258 mμ (ε, 9,500). The p.m.r. spectrum of II in deuteriochloroform showed the 5'-methylene group as two peaks (doublets with secondary splitting) centered at δ 4.44 and 4.63. The peaks corresponding to the 2' and 3' protons (doublets J 6 cps) were centered at δ 5.38 and 5.08 respectively. The peak for the anomeric proton overlapped the one peak of the 5 proton doublet at δ 5.77. Peaks corresponding to 4' and 5'-protons in the starting material were absent. The presence of one-half mole of isopropyl alcohol was also confirmed by integration of its corresponding peaks in the spectrum.

In order to explore further (2a) the generality of the base-catalyzed elimination in this system, 2',3'-*O*-isopropylidineuridine-O^2,5'-cyclonucleoside (IV) (9) was treated with excess potassium *t*-butoxide in dimethylsulfoxide at room temperature for 5 minutes. Using commercial potassium *t*-butoxide and taking no special precautions in the drying of reagents, a



20% yield of II was obtained. The infrared spectra (potassium bromide) of the hemialcoholate crystals from the two different preparations of II were superimposable in every detail as were the p.m.r. spectra in deuteriochloroform. The chromatographic mobility of the two samples of II were also identical in four different systems. The remainder of the cyclonucleoside IV was converted to 2',3'-*O*-isopropylidineuridine (as identified by UV spectra and cochromatography in four different systems) pre-

sumably by facile basic hydrolysis (9). It is interesting to note that cyclonucleosides (IV) have been prepared from the corresponding 5'-*p*-toluenesulfonate by treatment with *t*-butoxide in dimethylformamide at 100° (10).

It has been observed recently (11) that hydrogenation of exocyclic methylene groups on oxygen containing rings with palladium charcoal catalyst proceeds in a stereospecific manner. Similar results have been obtained with isopropylidine-blocked carbohydrates (12,13).

A solution of 1 g. of 1-(2,3-*O*-isopropylidine-5-deoxy-β-D-erythropent-4-enofuranosyl)uracil (II) hemialcoholate in ethanol was hydrogenated over 0.7 g. of 5% palladium on charcoal at 5 psi for 45 minutes. A 91% yield of 1-(2,3-*O*-isopropylidine-5-deoxy-α-L-lyxopentofuranosyl)uracil was obtained as needles from chloroform, 60-90° petroleum ether, m.p. 151-152°. $C_{12}H_{16}N_2O_5$ requires: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.91; H, 6.06; N, 10.27; λ max (EtOH), 260 mμ (ε, 9,650). A solution of 0.4 g. of this isopropylidine derivative in 20 ml. of 20% aqueous formic acid was heated on a steam bath for one hour. The solvents were removed and the colorless residue crystallized from methanol to give 0.28 g. (82%) of 1-(5-deoxy-α-L-lyxopentofuranosyl)uracil (III), m.p. 228-230°, $[\alpha]_D^{29}$ -60.1° (c 1.16, H_2O). $C_9H_{12}N_2O_5$ requires: C, 47.36; H, 5.30; N, 12.28. Found: C, 47.58; H, 5.46; N, 12.36; λ max (EtOH), 262 mμ (ε, 9,600).

The 4'-epimer of III, 1-(5-deoxy-β-D-ribopentofuranosyl)uracil (5'-deoxyuridine) (14) was synthesized for direct comparison. Similar treatment of 5'-deoxy-2',3'-*O*-isopropylidineuridine (14) with 20% aqueous formic acid gave needles from methanol, m.p. 184.5-186.5°, $[\alpha]_D^{29}$ + 9.91° (c 1.01, H_2O) (lit. (14) m.p. 176-178°); λ max (EtOH), 261 mμ (ε, 10,000).

The pmr spectra of these two 5'-deoxynucleosides in deuterium oxide exhibited very similar patterns. The doublet for the 5'-CH_3 of III was centered at δ 1.31 and the corresponding peak for 5'-deoxyuridine was shifted downfield 0.13 δ. The aromatic ring proton peaks were also shifted and the spectrum of a mixture of the two compounds gave multiple splitting. These diastereoisomers were resolved on SilicAR TLC-7GF (Mallinckrodt Chemical Works) using the upper phase of EtOAc:*n*-PrOH:H_2O 4:1:2 $R_{5'\text{-deoxyuridine}}/R_{III}$ = 1.09.

It was found that the isopropylidine blocked 4'-epimers exhibited slightly different chromatographic mobility in chloroform:acetone (8:2) on SilicAR TLC-7GF (Mallinckrodt Chemical Works). A mixture of these epimers with a 9/1 ratio of 1-(2,3-*O*-isopropylidine-5-deoxy-α-L-lyxopentofuranosyl)uracil/2',3'-*O*-isopropylidine-5'-deoxyuridine was resolved by the above chromatographic system with two developings. The original ethanol solution containing the total reduction product (s) of the 4'-exocyclic nucleoside II was chromatographed in the above system and no spot corresponding to 2',3'-*O*-isopropylidine-5'-deoxyuridine could be detected after three developings of the plate. Therefore, this reduction is certainly stereoselective to an extent of greater than 90% if not stereospecific. In contrast, the platinum-catalyzed hydrogenation of Angustmycin A tri- or tetra-acetate gave an epimeric mixture (4).

Further studies on the elimination-synthesis of 4'-unsaturated nucleoside analogs of Angustmycin A as well as this biologically interesting (15) antibiotic *per se* are in progress in our laboratory (16).

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(16) This research was supported by Institutional Research Grant CA-08109 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

Received April 18, 1967 Salt Lake City, Utah 84112