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NUCLEIC ACID RELATED COMPOUNDS. 13. 1-(2-DEOXY-D-ERYTHRO-PENT-1-ENOFURANOSYL)URACIL. SYNTHESIS OF THE FIRST 1',2'-UNSATURATED PYRIMIDINE NUCLEOSIDE, A FURANOID N,O-KETENE ACETAL.[1,2]

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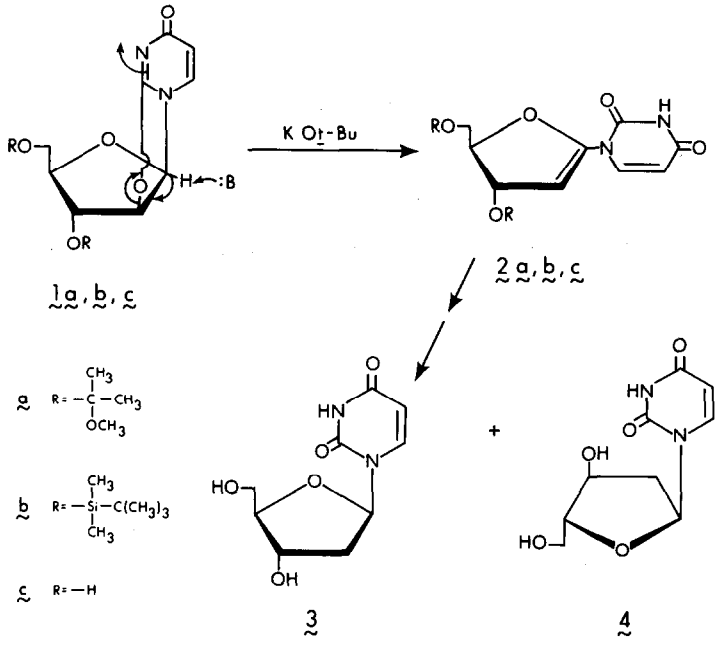
We wish to report the synthesis of 1-(2-deoxy-D-erythro-pent-1-enofuranosyl)uracil (2c) from uridine involving intramolecular elimination of the uracil O^2 from blocked 1-β-D-arabinofuranosyluracil-O^2→2'-cyclonucleosides as the key step.

The nucleoside antibiotic angustmycin A was originally assigned a structure with adenine attached to the 1'-position of a 1',2'-unsaturated sugar.[3] However, the presence of an exocyclic methylene function was later proved[4] and only very recently has an adenine 1',2'-unsaturated nucleoside been described.[5] Intramolecular elimination of O^2 from uracil and thymine cyclonucleosides has been used to obtain 2',3';[6] 3',4';[7] and 4',5'[8] unsaturated products. We now wish to describe the first such access into the 1',2'-unsaturated series as a route to the interesting cyclic N,O acetal structure 2c. Hydrogenation of 2a and deblocking provides 2'-deoxyuridine (3) and its α-anomer, 1-(2-deoxy-α-D-erythro-pentofuranosyl)uracil (4).

Treatment of 1-β-D-arabinofuranosyluracil-O^2→2'-cyclonucleoside (1c) (which is readily available in one step from uridine[9]) with 2-methoxypropene in the presence of p-toluenesulfonic acid[10] gave the corresponding 3',5'-bis-O-(2-methoxyprop-2-yl) derivative 1a in 85% yield.[11] Treatment of 1a with potassium tert-

butoxide in N,N-dimethylformamide effected extremely rapid intramolecular elimination to give 2a, which was isolated in 76% yield.[11] Attempted deblocking of 2a using various mildly acidic conditions gave major quantities of uracil (due to the acid lability of the N,O-ketene acetal function) along with 2c.



Cyclonucleoside 1c was treated with tert-butyldimethylsilyl chloride/imidazole[12] to give the 3',5'-bis-O derivative 1b.[11] Analogous reaction of 1b with KOt-Bu in DMF gave the crystalline blocked 1',2'-unsaturated nucleoside 2b in 50% yield [11] plus 28% of 1-(5-O-tert-butyldimethylsilyl-β-D-arabinofuranosyl)-uracil-$O^2 \rightarrow 2'$-cyclonucleoside.[11] It has been noted previously that nucleosides containing a free hydroxyl group fail to undergo elimination reactions[4] and no significant side reactions of this partially deblocked cyclonucleoside occurred during the short (∿ 1 min.) reaction time. Attempted elimination using DMSO as solvent gave complex mixtures.

Deblocking of 2b with tetraethylammonium fluoride in pyridine or DMF[12] gave 1-(2-deoxy-D-erythro-pent-1-enofuranosyl)uracil (2c), mp 141.5-143.5°; $[\alpha]_D^{25}$ + 108.4° (c 0.76, MeOH); uv (MeOH) max 273 nm (ε 9,270) min 241 nm (ε 5,320), (aqueous buffer, pH 7) max 265.5 nm (ε 9,050) min 237 nm (ε 5,650), (0.1 N NaOH) 261 nm (ε 8,060) min 245 nm (ε 7,680); nmr (DMSO-d_6-D_2O, TMS internal) δ 7.80 (d,

J_{6-5} = 8.0 Hz, 1, H^6), 5.73 (d, J_{5-6} = 8.0 Hz, 1, H^5), 5.35 (d, $J_{2'-3'}$ = 2.5 Hz, 1, $H^{2'}$), 4.71 ("t", $J_{3'-2'}$ ∿ 2.5 Hz, $J_{3'-4'}$ ∿ 3.0 Hz, 1, $H^{3'}$), 4.28 (m, 1, $H^{4'}$), 3.50 ("d", $J_{5',5''-4'}$ ∿ 5.2 Hz, 2, $H^{5'}$, $H^{5''}$); mass spectrum (70 eV, 140° direct probe) m/e 226.0592 (rel. int. 1.8%, calcd. for $C_9H_{10}N_2O_5$, M^+ 226.0590), 208 (45.4%, M-H_2O), 165.0430 (100%,208-HNCO), 112 (75%, BH^+); Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 48.01; H 4.43; N, 12.51.

The deblocked compound (2c) is extremely sensitive to acid. It consistently gave a uv spectrum of uracil in acidified solutions. Upon standing on the bench top, crystalline 2c decomposed in a few days to give uracil plus a smaller quantity of material exhibiting light blue-white fluorescence when visualized on chromatograms under a 2537 Å light source (presumably the corresponding furan derivative[5]). Addition of methanolic ammonia to column chromatography solvents and during recrystallizations effectively retarded hydrolysis, but the analytical sample of 2c prepared using these precautions had a detectable (tlc) trace of uracil contamination.

Treatment of 1-(2-bromo-2-deoxy-β-D-ribofuranosyl)uracil with hydroxycobalamin (vitamin B_{12}s) under reducing conditions was reported to yield 2c.[13] No isolation of product was reported and their structural assignment was based on colors produced with qualitative reagent sprays on paper chromatograms.

In view of the marked lability of 2c, especially in even mildly acidic solutions, it seemed improbable that it would have survived the described acidification to pH 5, evaporation to dryness, and phenolic extraction.[13] Paper chromatography systems were described which markedly separated the product of the hydroxycobalamin reaction and uracil. However, several of these contain acetic or formic acid and water. When 2c was subjected to chromatography using these systems[13] (on Whatman No. 1 paper), degradation to uracil and the fluorescent material uniformly occurred. The uv spectra of 2c in water at pH 7 (max 265.5 nm) and 0.1 N sodium hydroxide (max 261 nm) do not correspond with that reported (max 278 nm).[13] (The spectrum of the presumed Δ^1-compound in Fig. 1 of Ref. 13, which reportedly was obtained at pH 12-13, resembles that of uracil in basic solution.) We must therefore conclude that the structure of that product was not 2c and that the present report outlines the first described 1',2'-un-

saturated pyrimidine nucleoside.

Hydrogenation of 2a in ethyl acetate (polar protic solvents result in extensive uracil formation) over 5% Pd·C followed by acidic deblocking gave good conversion to a 1:1 mixture of the β and α anomers[14] of 2'-deoxyuridine (3 and 4, respectively). This sequence demonstrates a practical conversion of a β-ribonucleoside to its α-2'-deoxy counterpart with no furanoside ring cleavage[15] or other epimerization complications.

It is interesting to note that 2c corresponds to the uracil-N[1] enamine of the furanoid lactone. Studies on other examples of this cyclic N,O-ketene acetal system as well as investigation of the chemistry and synthetic possibilities opened by this novel structure in nucleoside chemistry are in progress.

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