

SYNTHESIS OF 2,4'-ANHYDRO-1-(5'-DEOXY-5'-BROMO-
2',3'-O-ISOPROPYLIDENE- α -L-LYXOSYL)URACIL

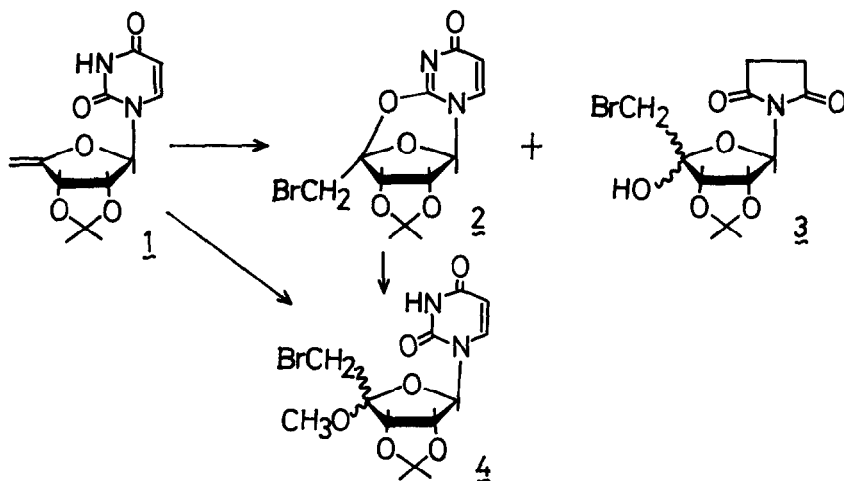
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In a recent paper¹, the results obtained by regiospecific addition of hypobromous acid to 6-benzamido-9-(5-deoxy-2,3-O-isopropylidene- β -D-erythro-pent-4-enofuranosyl)purine² have been described. In this reaction, the competitive participation of N³-lone pair electrons in the intermediary 4',5'-bromonium ion effected an anomalous ring opening of the base moiety. On the basis of a similar mechanistic consideration, we have envisaged a route to hitherto unknown 2,4'-anhydro-pyrimidinucleosides, using 4',5'-didehydro-pyrimidinucleosides and hypobromous acid. This report deals with a successful synthesis and the structural elucidation of 2,4'-anhydro-1-(5'-deoxy-5'-bromo-2',3'-O-isopropylidene- α -L-lyxosyl)uracil (2).

N-Bromosuccinimide (NBS) (1 equiv) and 1-(5-deoxy-2,3-O-isopropylidene- β -D-erythro-pent-4-enofuranosyl)uracil (1)³ (1 equiv) were combined into an ice-cold stirred mixture (1:1, v/v) of water and dioxane. After 10 min, the separated crystalline solid (2) was collected. Extraction of the filtrate with ethyl acetate gave a second crop. The total yield of 2 was 35% after re-crystallization from methanol at below 40^o: mp 172-174^o; λ max (methanol) nm (ϵ) 229 (13200) and 245 (8900, inflection); ir (KBr) 1650 cm⁻¹ (ν C=O); nmr (DMSO-d₆) 1.82 (s, 3, methyl), 1.95 (s, 3, methyl), 3.88 (d, 1, J_{gem} = 15 Hz, H_{5,a}), 3.98 (d, 1, J_{gem} = 15 Hz, H_{5,b}), 5.00 (d, 1, J_{2',3'} = 6 Hz, H₂, or H₃), 5.18 (d, 1, J_{2',3'} = 6 Hz, H₃, or H₂), 5.92 (d, 1, J_{2',6'} = 7.5 Hz, H₅),



6.25 (s, 1, $H_{1,}$) and 7.70 ppm (u, 1, $J_{5,6}=7.5$ Hz, H_6); mass m/e 344, 346 (M^+), 329, 331 (M^+-CH_3), 286, 288 ($M^+-CH_3COCH_3$), 269, 271 ($M^+-CH_3COCH_3-OH$), 265 (M^+-Br), 258, 260 ($M^+-CH_3COCH_3-CO$), 251 (M^+-BrCH_2) and 207 ($M^+-CH_3COCH_3-Br$). The ethyl acetate extract separated from **2** was chromatographed on a silica gel column using chloroform/ethyl acetate (1:1) to give the bromohydrin **3**¹ in 17% yield on the basis of **1**. On stirring a methanolic solution of **2** in the presence of barium carbonate at room temperature overnight, 1-(2',3'-O-isopropylidene-4'-methoxy-4'-bromomethyl-3-D-erythrofuranosyl)uracil (**4**) was obtained in 20% yield after preparative thin layer chromatography: mp 235-237° (from methanol); λ_{max} (methanol) 262 nm (ϵ 7000); nmr (DMSO- d_6) 1.34 (s, 3, methyl), 1.50 (s, 3, methyl), 3.07 (s, 3, methoxyl), 3.53 (d, 1, $J_{gem}=11$ Hz, $H_{5,a}$), 3.84 (d, 1, $J_{gem}=11$ Hz, $H_{5,b}$), 4.75 (u, 1, $J_{2,3}=6$ Hz, H_3), 5.29 (dd, 1, $J_{2,3}=6$ Hz, $J_{1,2}=1.5$ Hz, H_2), 5.65 (dd, 1, $J_{5,6}=8$ Hz, $J_{5,NH}=2$ Hz, H_5), 6.13 (d, 1, $J_{1,2}=1.5$ Hz, H_1) and 7.58 ppm (d, $J_{5,6}=8$ Hz, H_6); mass m/e 361, 363 (M^+-CH_3), 345, 347 (M^+-CH_3O), 297 (M^+-Br), 287, 289 ($M^+-CH_3O-CH_3COCH_3$), 283 (M^+-BrCH_2), 265 and 267 (M^+-base). The presence of ions ($M-CH_3O$)⁺ and ($M-BrCH_2$)⁺ and absence of any ion at m/e 331 and 343 ($M^+-CH_3OCH_2$)⁺ precluded a structure with a methoxyl at C₅, and a bromine atom at C₄, for compound **4**. Hence, the precursory compound (**2**) must

have a 2,4'-anhydro-bridge. Compound 4 was more conveniently obtained by refluxing 2 in 60% aqueous methanol for 3 hr (yield 29%). From the aqueous layer of the initial reaction, uracil and succinimide were recovered in unspecified yields. On the other hand, reaction of equimolar NBS and 1 in anhydrous methanol for 1 week, followed by silica gel column chromatography with the use of a solvent mixture, chloroform/ethyl acetate, 3:1, gave a yield of 14% of 4, a major part of the starting material being recovered. Thus, the structure of compound 4 was chemically established. The formation of 2 from 1 is mechanistically favoured on the basis of the generally accepted higher stability of an intermediate cation charged at the branched carbon atom (C₄). An intramolecular nucleophilic attack by 2-oxygen atom would reasonably form a 2,4'-anhydro-bridge. A similar intermediary carboxonium ion had been proposed for the formation of 5'-deoxy-5'-bromo-2',3'-O-isopropylidene-N³→4'-cycloadenosine bromide from the corresponding 4',5'-dehyaroadenosine derivative and bromine.⁵ The cyclonucleoside 2 is highly sensitive to nucleophiles⁶ and would be a promising intermediate for 4'-substituted uracil nucleosides.

References and Footnotes

1. Tadashi Sasaki, Katsumaro Minamoto, and Kaneaki Hattori, *J. Amer. Chem. Soc.*, 95, 1350 (1973).
2. I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffatt, *J. Amer. Chem. Soc.*, 93, 4323 (1971).
3. M. J. Robins, J. R. McCarthy, Jr., and R. K. Robins, *J. Het. Chem.*, 4, 313 (1967).
4. N. K. Kochetkov, N. S. Wulfson, O. S. Chizhov, and B. M. Zolotarev, *Tetrahedron*, 19, 2209 (1963).
5. Compound 2 reacts with excess ethanolic ammonia at room temperature to give a couple of products, whose structures are under investigation.