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A Convenient Synthesis of 1-(2′,3′-Dideoxy-β-D-*erythro*-hex-2′-enopyranosyl)uracil

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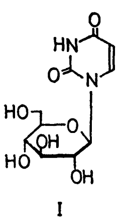
Synopsis. 2,2′-Anhydro-1-(4′,6′-*O*-benzylidene-3′-*O*-methylsulfonyl-β-D-mannopyranosyl)urasil, prepared smoothly from β-D-glucopyranosyluracil in three steps, was converted into the corresponding unsaturated nucleoside in a good yield by the action of sodium iodide. The unsaturated nucleoside was then debenzylidenated with acid to afford the title compound.

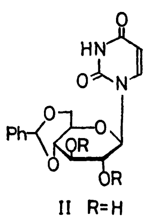
Our recent attention has focussed on the synthesis of unsaturated sugars[1] and nucleosides.[2] In our previous publications,[2] a new synthetic route of the 2′,3′-unsaturation of thymine pyranoside *via* 2,2′-anhydronucleoside has been described, its reaction mechanism has also been discussed. We wish now to report an application of this reaction to the uracil nucleoside series, which can be considered as potent intermediates for the synthesis of such antibiotics[3] as blasticidin S and amicetin.

β-D-Glucopyranosyluracil (I)[4] was converted into the benzylidene derivative (II) in a 68% yield by treatment with benzaldehyde in the presence of zinc chloride. The subsequent sulfonylation of II with methanesulfonyl chloride in pyridine proceeded smoothly to afford a new crystalline product, the 2′,3′-di-*O*-mesyl derivative (III) (89%). Anhydronucleoside (IV) was prepared in an 89% yield by the treatment of III with an equivalent amount of sodium benzoate in *N*,*N*-dimethylformamide (DMF) at an elevated temperature.

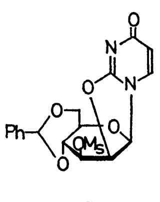
The refluxing of IV with a 20-fold excess of sodium iodide and zinc dust in DMF for 2 h gave the unsaturated nucleoside (V) in a 33% yield. The treatment of IV with a 20-fold excess of sodium iodide in DMF for 1 h under reflux gave V in a 37% yield, along with about a 40% recovery of the starting material. When the reaction time of this reaction was prolonged until 4 h, the unsaturated nucleoside (V) was obtained in a 67% yield. Thus, the unsaturation was performed successfully in the uracil nucleoside series using the anhydronucleoside as a substrate. The structure of V could be easily confirmed by NMR. The vinylic protons at δ 6.50 and 5.70 with the characteristic coupling constant of $J_{2',3'}$= 10 Hz appeared in the spectrum.



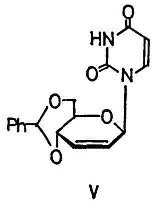
I



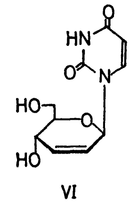
II R=H
III R=Ms



IV



V



VI

After several screenings, DMF was found to be the most suitable solvent for the elimination reaction.

Compound (V) was treated with 80% aqueous acetic acid for 15 min under reflux to give a new crystalline product, VI, in a 50% yield. The overall yield of VI from I was 18%.

Experimental

All the melting points are uncorrected. The NMR data were recorded at 100 MHz with a JEOL PS-100 instrument.

1-(4′,6′-O-Benzylidene-β-D-glucopyranosyl)uracil (II). A suspension of 4 g of β-D-glucopyranosyluracil (I) and 13 g of freshly melted zinc chloride in 70 ml of benzaldehyde was shaken for 30 h. The resulting clear solution was stirred into ether (500 ml). The precipitate thus formed was filtered and then recrystallized from methanol to afford 3.6 g (68%) of the benzylidene nucleoside (II) as colorless needles; mp 278—281 °C (dec);[5] $[\alpha]_D^{22}$ −8° (*c* 1.0 in DMF). Found: C, 55.91; H, 5.07; N, 7.56%. Calcd for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 5.07; N, 7.73%.

1-(4′,6′-O-Benzylidene-2′,3′-di-O-methylsulfonyl-β-D-glucopyranosyl)uracil (III). Into a cooled (0 °C) suspension of the benzylidene nucleoside (II) (11 g) in pyridine (450 ml), we stirred drop by drop methanesulfonyl chloride (8.5 ml). The reaction mixture was kept for 15 h at room temperature. The subsequent addition of the reaction mixture, which had been concentrated to a small volume, into ice water (2 l) with vigorous stirring gave a colored precipitate. The subsequent crystallization of the precipitate from acetone–ethanol afforded 14 g (89%) of III; mp 189—192 °C (dec); $[\alpha]_D^{22}$ −12° (*c* 1.0 in DMF); UV (EtOH) λ_{max} 255 nm (log ε 3.74); NMR [$(CD_3)_2SO$] δ=7.80 (1H, d, $J_{5,6}$= 8.8 Hz, H-6), 7.38 (5H, C_6H_5), 6.20 (1H, broad d, $J_{1',2'}$= 7.5 Hz, H-1′), 5.68 (1H, d, $J_{5,6}$=8.8 Hz, H-5), 5.66 (1H, s, PhCH), 5.15—5.40 (2H, m, H-2′ and -3′), 3.30 (4H, m, H-4′, -5′, -6′, and -6″), 3.16 (3H, s, CH_3SO_2), and 3.10 (3H, s, CH_3SO_2). Found: C, 44.01; H, 4.25; N, 5.41%. Calcd for $C_{19}H_{22}N_2O_{11}S_2$: C, 44.26; H, 4.07; N, 5.33%.

2,2′-Anhydro-1-(4′,6′-O-benzylidene-3′-O-methylsulfonyl-β-D-mannopyranosyl)urasil (IV). A mixture of the methanesulfonylated nucleoside (III) (13.5 g, 26 mmol) and sodium benzoate (4.6 g, 32 mmol) in DMF (500 ml) was heated at 120—130 °C with stirring for 1.5 h. The reaction mixture was then vigorous stirred into ice water (4 l) to give a crystalline product. Recrystallization from acetone afforded 9.8 g (89%) of the anhydronucleoside (IV); mp 215—216 °C (dec); $[\alpha]_D^{22}$ −130° (*c* 0.5 in DMF); UV (EtOH) λ_{max} 225 and 245 nm (log ε 3.90 and 3.89); NMR [$(CD_3)_2SO$]

δ=7.95 (1H, d, $J_{5,6}$=8 Hz, H-6), 7.40 (5H, C_6H_5), 6.13 (1H, $J_{1',2'}$=3 Hz, H-1'), 5.90 (1H, d, $J_{5,6}$=8 Hz, H-5), 5.77 (1H, s, PhCH), 5.55 (1H, q, $J_{2',3'}$=5 Hz, $J_{3',4'}$=10 Hz, H-3'), 5.35 (1H, q, $J_{1',2'}$=3 Hz, $J_{2',3'}$=5 Hz, H-2'), 3.8—4.3 (4H, m, H-4', -5', -6', and -6"), 3.22 (3H, s, CH_3SO_2). Found; C, 50.87; H, 4.26; N, 6.60%. Calcd for $C_{18}H_{18}N_2O_8S$: C, 51.18; H, 4.27; N, 6.64%.

General Procedure for the Unsaturation of the Anhydronucleoside (IV). A mixture of IV (210 mg, 0.5 mmol) and sodium iodide (1.5 g, 10 mmol) in the appropriate solvent (DMF, hexamethylphosphotriamide, or 1,3-dimethyl-2-imidazolidinone,[6] 20 ml) was refluxed for an appropriate time with stirring. The addition of water (30 ml) to the reaction mixture while it was hot gave the crystalline starting material (IV), which was identified by IR. To the filtrate we then added ethyl acetate (50 ml), and the organic layer was washed with thiosulfate and water, dried over Na_2SO_4, and evaporated. The crystals thus obtained were recrystallized from acetone to afford *1-(4',6'-O-benzylidene-2',3'-dideoxy-β-*D-erythro-*hex-2'-enopyranosyl)uracil (V)*; mp 228—230 °C (dec); $[\alpha]_D^{22}$ +32° (*c* 0.75 in DMF); UV (EtOH) λ_{max} 257 nm (log ε 3.75); NMR [$(CD_3)_2SO$] δ=7.45 (1H, d, $J_{5,6}$=8 Hz, H-6), 7.40 (5H, C_6H_5), 6.52 (1H, d, $J_{1',2'}$=3 Hz, H-1'), 6.50 (1H, d, $J_{2',3'}$=10 Hz, H-3'), 5.70 (1H, d, $J_{2',3'}$=10 Hz, H-2'), 5.70 (1H, s, PhCH), 5.65 (1H, d, $J_{5,6}$=8 Hz, H-5), 3.7—4.5 (4H, m, H-4', -5', -6', and -6"). Found: C, 61.24; H, 4.84; N, 8.25%. Calcd for $C_{17}H_{16}N_2O_5\cdot 1/4H_2O$: C, 61.29; H, 4.96; N, 8.41%.

*1-(2',3'-Dideoxy-β-*D-erythro-*hex-2'-enopyranosyl)uracil (VI).* A mixture of V (140 mg) in 80% aqueous acetic acid (10 ml) was refluxed for 15 min; then, after cooling, the clear solution was evaporated to a syrup. Preparative TLC (silica gel, 10 v/v% EtOH–benzene) of the syrup afforded a pure product (VI) (50 mg, 50%); mp 161—163°; $[\alpha]_D^{22}$ +84° (*c* 0.33 in EtOH); NMR [$(CD_3)_2SO$] δ=7.34 (1H, d, $J_{5,6}$=9 Hz, H-6), 6.28 (1H, q, $J_{1',2'}$=$J_{1',3'}$=2.0 Hz, H-1'), 6.15 (1H, dt, $J_{2',3'}$=10 Hz, $J_{1',3'}$=$J_{3',4'}$=2.0 Hz, H-3'), 5.64 (1H, dt, $J_{2',3'}$=10 Hz, $J_{1',2'}$=$J_{2',4'}$=2.0 Hz, H-2'), 5.62 (1H, d, $J_{5,6}$=9 Hz, H-5), 4.04 (1H, m, H-4'), and 3.2—3.8 (3H, m, H-5', -6', and -6"). Found: C, 50.35; H, 5.05; N, 11.79%. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.0; H, 5.04; N, 11.66%.

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References

1) T. Yamazaki, H. Sugiyama, N. Yamaoka, K. Matsuda, and S. Seto, *Carbohydr. Res.*, **50**, 278 (1976); *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1981.

2) T. Yamazaki, H. Shiraishi, K. Matsuda, H. Sugiyama, S. Seto, and N. Yamaoka, *J. Chem. Soc., Chem. Commun.*, **1975**, 518. T. Yamazaki, K. Matsuda, H. Sugiyama, S. Seto, and N. Yamaoka, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1654.

3) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley Interscience, New York (1970), p. 170.

4) Compound (I) was prepared by the method used for nitromethane-mercury cyanide [N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965)].

5) F. W. Lichtenthaler, T. Ueno, and P. Voss, *Bull. Chem. Soc. Jpn.*, **47**, 2304 (1974).

6) F. Kondo, D. Sc. Thesis, Tohoku University (1976).