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SYNTHESIS OF 1-(2-Deoxy-β-D-ERYTHRO-PENTOFURANOSYL)-5-ETHYNYL-1,2,3,4-TETRAHYDROPYRIMIDINE-2,4-DIONE (5-ETHYNYL-2'-DEOXYURIDINE)[1]

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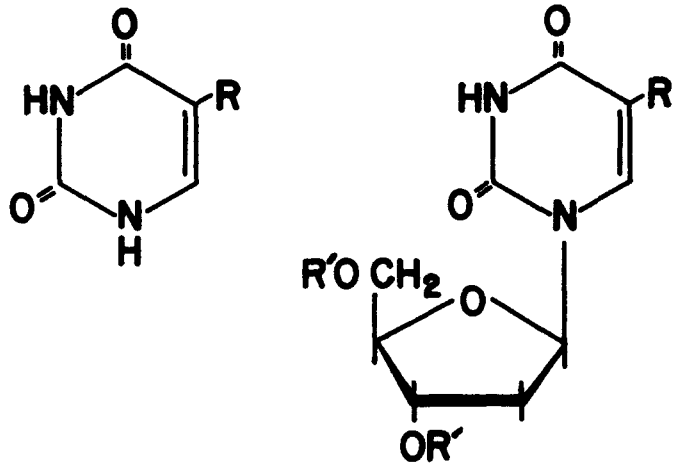
We have recently synthesized 5-vinyl-2'-deoxy-uridine[2], a thymidine analog, which showed marked antiviral activity against Herpes Simplex type I and type II[3]. This finding and the fact that various drugs incorporating the acetylenic function[4] can behave as specific inhibitors for certain enzymatic systems, suggested the synthesis of 5-ethynyl-2'-deoxyuridine.



I: R= CHO
II: R= CH=CBr$_2$
III: R= C≡CH

IV: R= CH=CBr$_2$, R'=p-CH$_3$C$_6$H$_4$CO
V: R= CH=CBr$_2$, R'=H
VI: R= C≡CH, R'=H

The Wittig reaction, utilizing (dichloromethylene)- or (dibromomethylene) triphenylphosphorane, has been a useful method for the conversion of aldehydes into dihaloalkenes[5,6] and, resently, a method

for the transformation of dibromoalkenes to acetylenes[7], by treatment with butyllithium, has been reported. When a DMF solution of 5-formyluracil (I) was treated with (dibromomethylene)triphenylphosphorane (prepared from carbon tetrabromide, triphenylphosphine, and zinc dust[7]) in methylene chloride at room temperature for 24 hr, 5-(2,2-dibromovinyl) uracil (II) was obtained in 70% yield. II, m.p. 278-280° (dec); λ max (methanol) 295 nm (ε 10,450), 244 nm (11,320) (sh.), 234 nm (10,800), mass spectrum m/e 296, 294 (M^+), nmr (DMSO-d_6) δ 7.21(s, 1H, CH=CBr_2), 7.93 (s, 1H, H-6), 11.25 (m, 2H, NH).

While treatment of II, or its bis(trimethylsilyl) derivative, with butyllithium produced only a complex mixture of products, reaction of a suspension of II in THF and phenyllithium at 0° gave 5-ethynyluracil (III), which was purified by silica gel chromatography with ethyl acetate (yield 52%). III, m.p. >300° (dec), λ max (methanol) 284 nm (ε 9,450), 225 nm (ε 10,330); mass spectrum m/e 136 (M^+), nmr (DMSO-d_6) δ 3.98 (s, 1H, C≡CH), 7.80(d, 1H, J_{NH-6}= 5Hz, H-6), 11.25 (m, 2H, NH); i.r. (KBr) 2110 cm^{-1} (C≡C).

For preparation of the 2'-deoxyribonucleoside derivative of III, 5-(2,2-dibromovinyl) uracil (II) was converted to its bis (trimethylsilyl) derivative by refluxing with hexamethyldisilazane in toluene, in the presence of a catalytic amount of ammonium sulfate. Condensation of the crude trimethylsilyl derivative with 2-deoxy-3,5-di-O-p-toluoyl-D-erythro-pentofuranosyl chloride[8] in 1,2-dichlorethane at 0-5°, in the presence of $SnCl_4$, gave a mixture (71% yield) of the blocked β nucleoside IV and its α-anomer, in an approximately 3:1 ratio. A relatively large fraction of the β-anomer IV was separated from the mixture by crystallization from acetone. The remaining mixture, containing some IV and the α-anomer was chromatographed on silica gel in benzene-ethyl acetate (8:2) to separate the anomers. The combined yield of IV, recrystallized from ethanol, was 47% m.p. 212-213°, nmr (DMSO-d_6) δ 6.31(t, 1H, $J_{1'-2'}$= 6.5Hz, H-1'), 7.14(s, 1H, CH=CBr_2), 8.25(s, 1H, H-6), 11.7(s, 1H, NH).

The α-anomer, 5-(2,2-dibromovinyl)-2-deoxy-α-uridine, was obtained in 19 % yield; nmr (acetone-d_6) δ 6.35(d of d, 1H, $J_{1'-2'-2''}$=1.0 and 6.0 Hz, H-1'), 7.17(s, 1H, CH=CBr_2), 8.55(s, 1H, H-6).

Assignment of the β-configuration to the nucleoside IV was made on the basis of its nmr spectrum, wherein the anomeric proton appeared as the characteristic triplet[9]. The nmr spectrum of the α-anomer of IV gave a pair of doublets for the anomeric proton.

Removal of the protecting groups from IV was readily achieved by treatment with NaOMe in methanol, and afforded 5-(2,2-dibromovinyl)-2'-deoxyuridine (V), which after recrystallization from ethanol, was

obtained in 93% yield; V, m.p. 195-196°; λ max(methanol) 297 nm (ε 10,637). 235 nm (ε 11,685); nmr (DMSO-d_6) δ 6.19(t, 1H, $J_{1'-2'}$ = 7.0Hz, H-1'), 7.24(s, 1H, CH= CBr_2), 8.42(s, 1H, H-6), 11.66(br.s, 1H, NH). 5-(2,2-Dibromovinyl)-2'-deoxyuridine (V) was silylated by refluxing with hexamethyldisilazane and trimethylchlorosilane in toluene for 2 hr. Treatment of the silylated V with phenyllithium in THF at -50° for 1 hr and at 0° for 45 min., followed by hydrolysis for 1 hr at 25° with acetic acid in methanol, gave crude 5-ethynyl-2'-deoxyuridine (VI). Compound VI was purified by silica gel chromatography in ethyl acetate and crystallization from an ethanol-acetone mixture; yield 19%, m.p. 196-197°; λ max(methanol) 287 nm (ε 10,902), 225 nm(ε 9,596); mass spectrum m/e 252 (M^+); nmr (DMSO-d_6) δ 4.08(s, 1H, C≡CH), 6.10(t, 1H, $J_{1'-2'}$ = 6.5 Hz, H-1'), 8.30(s, 1H, H-6), 11.60(s, 1H, NH).

Satisfactory analytical data were obtained for compounds II-VI.

The pronounced biological activity of some of the compounds and the preparation and activity of other acetylenic nucleoside derivatives is being presented in a separate communication.

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