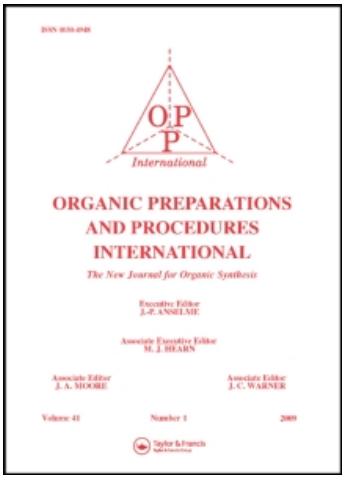

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SYNTHESIS OF URACIL-5-PHOSPHINIC AND 5-THIOPHOSPHONIC ACIDS

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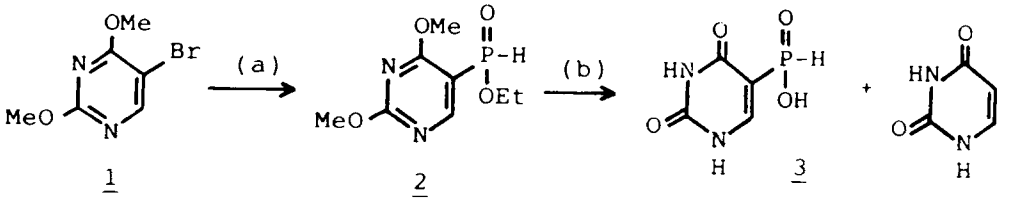
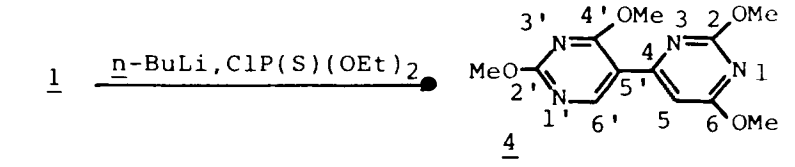
5-Substituted uracil and uracil nucleosides such as 5-fluorouracil or 5-iodo-2'-deoxyuridine[1] are useful in the treatment of certain types of cancer and viral diseases. A previous paper[2] disclosed briefly uracil-5-phosphonic acid (3) and the present paper describes in detail the synthesis of 3 and the related thio analogue 6.

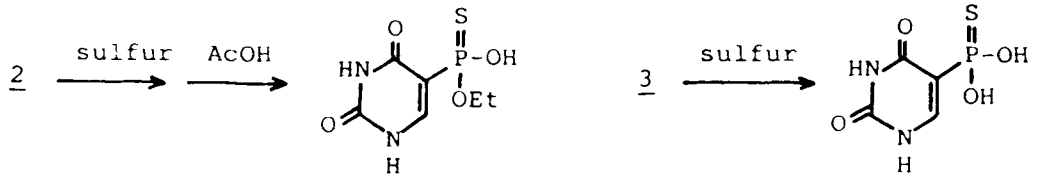


a) n-BuLi,ClP(OEt)$_2$ b) HCl,EtOH

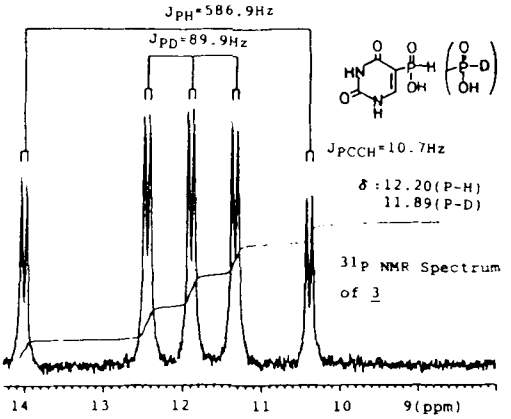
Although treatment of 2 with 10% hot acetic acid gave 3 as the major product in 18% yield, heating of 2 with 1 N ethanolic hydrochloric acid provided 3 in 38% yield and with only a trace of uracil. The reaction of 1 with n-butyllithium, followed by treatment with diethyl chlorothiophosphate furnished 4[4] as a sole product, resulting from the intermolecular



condensation of 1 in the presence of n-butyllithium. Thiation of 2 with sulfur in benzene gave an oil which, because of its lability to usual manipulation, was subjected to immediate hydrolysis with 10% acetic acid to give uracil-5-ethyl hydrogen thiophosphonate (5) , whose structure was assigned based on the



elemental analysis, MS and ^{1}H NMR spectrum. The ester linkage in 5 was quite resistant to hydrolysis, and treatment of 5 with 1 N hydrochloric acid resulted in fission of the C-P bond to give uracil. Thiation of 3 with sulfur was carried out in ethanol to afford uracil-5-thiophosphonic acid (6) as a white powder. Compound 6 migrated faster than 3 toward the anode by PE (phosphate buffer, 7.5). The spectrum of 3 in water displayed a ^{31}P signal directly bound to hydrogen as a double doublet at δ 12.20 ppm with J_{PH} 586.9 Hz and J_{PCCH} 10.7 Hz, while in deuterium oxide deuterium exchange occurred and the ^{31}P signal directly bound to deuterium appeared as a double triplet at δ 11.89 ppm with J_{PD} 89.9 Hz and J_{PCCH} 10.7 Hz. Owing to the slow deuterium exchange of P-H to P-D, both double doublet and double triplet signals were detectable in the spectrum (Fig. 1). The signal of ^{31}P in 6 appeared as a doublet at δ 56.19 ppm with J_{PCCH} 11.2 Hz, whose very low value was



similar to that of dimethyl phenylthiophosphonate;[5] this result also supports structure 6.

EXPERIMENTAL SECTION

All mps were determined on a Yanagimoto micromelting point apparatus (hot stage type) and are uncorrected. HPLC was conducted with a Shimadzu LC-2 model using a column packed with Nucleosil 10DMA (10μ) and a mobile phase of 10 mM phosphate buffer (pH 5.3). UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. ^{1}H NMR spectra were recorded with a JOEL GX-400 (400 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard and in D_2O with sodium 3-(trimethylsilyl)propionate as an internal standard, respectively. Paper electrophoresis (PE) was carried out at 22V/cm using 0.01 M phosphate buffer.

Ethyl 5-(2,4-Dimethoxypyrimidinyl)hydrogenphosphinate (2).- n-Butyllithium (23 ml of 1.7 M in hexane, 39.1 mmol) was added dropwise to a stirred solution of 5-bromo-2,4-dimethoxypyrimidine[3] (1)(5.13 g, 26.0 mmol) in THF (100 ml) below -70° under argon. After 1 hr, diethyl chlorophosphite (12 ml, 69.9 mmol) was added to the mixture and stirring was continued for additional 1 hr. Then 20% ammonium formate (20 ml) was added and the solution was warmed to room temperature with stirring. The syrup obtained after removal of the solvent was partitioned between benzene (50 ml) and water (50 ml). The organic layer was dried over $MgSO_4$ and concentrated to 10 ml and chromatographed over a column of silica gel G (ϕ 4.1X25 cm) using $CHCl_3$-AcOEt (1:1)(2 l) to give a pale yellowish oil. The oil was crystallized from ether to give colorless needles (4.43 g, 65 %), mp. 59-61°.

Anal. Calcd. for $C_8H_{13}N_2O_4P$: C, 41.03; H, 5.60; N, 11.96

Found: C, 40.88; H, 5.62; N, 11.95

UV(MeOH): λ max 258nm. MS m/z: 232 (M^+), 204 ($M^+-C_2H_4$), 188 ($M^+-C_2H_4O$). ^{1}H NMR ($CDCl_3$): δ 8.63 (1H, d, J_{HCCP}= 7.2 Hz, H-6),

4.1 (8H, m, $-C\underline{H}_2CH_3$ and $-OC\underline{H}_3$), 1.40 (3H, t, J_{HCCP}= 5.4 Hz, $-CH_2C\underline{H}_3$).

Uracil-5-phosphinic Acid (3).

Method A.- A solution of 2 (1.04 g, 4.47 mmol) in 10% acetic acid (50 ml) was refluxed for 4 hrs. After cooling, the solvent was evaporated in vacuo and the residue was chromatographed over a column of DEAE-cellulose (bicarbonate, ϕ 2.0 X 20 cm) with a gradient from water (1 l) and 0.05 M triethylammonium bicarbonate (TEAB) (1 l). The third fraction was collected and evaporated to dryness. The caramel obtained after repeated azeotropic distillation with water was dissolved in a water (2 ml) and passed through a column of Amberlite IR 120B (H^+, ϕ 2.0 X 10 cm). The eluent was evaporated and the solid was crystallized from EtOH (2 ml) to afford colorless needles of 3 (139 mg, 18%), mp.192.5-195°. PC: (n-BuOH-conc.NH_4OH-H_2O, 5:2:3) R_f 0.24. PE(0.01 M phosphate buffer, pH 3.9) $M_{UPA}{}^6$ 1.13. UV(MeOH): λ max 261 nm. MS m/z: 176 (M^+). ^{1}H NMR (D_2O): δ 8.28 (1H, d, J_{HCCP} 11.6 Hz, H-6). The first fraction was evaporated and crystallized from a small portion of water to obtain a white solid (37 mg, 7.4%) identified as uracil by TLC ($CHCl_3$-MeOH, 3:1): Rf 0.65.

Anal. Calcd. for $C_4H_5N_2O_4P$: C, 27.29; H, 2.86; N, 15.91

Found: C, 27.52; H, 2.97; N, 15.56

UV(0.1N HCl): λ max 261 nm (ε 9000). UV(H_2O): λ max 261 nm (ε 7600). UV(0.1N NaOH): λ max 284 nm (ε 9600).

Method B.- A solution of 2 (1.05 g, 4.54 mmol) in EtOH (20 ml) containing 1 N HCl (5 ml) was refluxed for 2.5 hrs. After cooling, the mixture was evaporated to dryness in vacuo to afford a syrup, which was dried azeotropically with EtOH to give color-

less needles (296 mg, 37%), which had the same spectroscopic data with those of the sample obtained in the method A.

2,2',4',6-Tetramethoxy-4,5'-bipyrimidine(4).- n-Butyllithium (1.7 M in hexane (4.6 ml), 7.8 mmol) was added to a cooled (-78°C) solution of 1 (1.00 g, 4.57 mmol) in THF (20 ml) under argon. After stirring for 1 hr, diethyl chlorothiophosphate (1.88 ml, 12 mmol) was added dropwise and the mixture was stirred for 2 hrs and treated in a similar manner to that described in the section of 2 to furnish white crystals (217 mg, 34%), mp.146-147°, lit.[4] mp.151-152°. UV(0.05N HCl): λ max 248, 290, 305(sh) nm. UV(MeOH): λ max 252, 292, 305(sh) nm. UV(0.1N NaOH): λ max 250, 288, 305(sh) nm.

Anal. Calcd. for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14

Found: C, 51.98; H, 5.19; N, 19.79

MS m/z: 278 (M^+), 263 (M^+-CH_3). ^{1}H NMR ($CDCl_3$): δ 9.29 (1H, s, H-6'), 7.10 (1H, s, H-5), 4.13, 4.06, 4.03, 4.01 (each 3H, $-OCH_3$).

Ethyl Hydrogen Uracil-5-thiophosphonate (5).- A suspension of 2 (951 mg, 12.3 mmol) and sulfur (394 mg, 12.3 mmol) in benzene (10 ml) was refluxed for 4 hrs. After cooling, an insoluble material was removed by decantation and the organic phase was extracted twice with water (10 ml). Combined extracts were chromatographed over a column of DEAE-cellulose (bicarbonate, ϕ 2.0 X 15 cm) with a gradient from H_2O (500 ml) and 0.05 M TEAB (500 ml). The eluate was evaporated to dryness. The residue was dried azeotropically with water and dissolved in 10 % acetic acid. The solution was refluxed overnight and purified by DEAE-cellulose column chromatography (bicarbonate, ϕ 2.0 X 15 cm) with a gradient from H_2O (500 ml) and 0.08 M TEAB (500 ml).

The eluate was treated in a similar manner to that described above to remove TEAB and passed through a column of Amberlite IR 120B (H^+, ϕ 2.0 X 9.0 cm). Evaporation of the effluent to dryness afforded a syrup, which was triturated with a small amount of EtOH to give white crystals (60.6 mg, 6.2%), mp.206-207°.

Anal. Calcd. for $C_6H_9N_2O_4PS$: C, 30.51; H, 3.81; N, 11.86
Found: C, 30.11; H, 3.77; N, 11.77

UV(MeOH): λ max 267 nm. MS m/z: 236 (M^+). ^1H NMR (D_2O): δ 8.64 (1H, d, J_{HCCP} 10.6 Hz, H-6). 4.31 (2H, m, $-C\underline{H}_2CH_3$), 1.71 (3H, t, J_{HCCP} 7.0 Hz, $-CH_2C\underline{H}_3$).

Uracil-5-thiophosphonic Acid (6).- A suspension of 3 (100 mg, 0.56 mmol) and sulfur (90 mg, 5.6 mmol) in EtOH (10 ml) was refluxed for 3 days and evaporated to dryness. The residue was partitioned between benzene (20 ml) and H_2O (20 ml) and the aqueous layer was chromatographed over a column of DEAE cellulose (bicarbonate, ϕ 2.2 X 15 cm) with a gradient from H_2O (500 ml) and 0.08 M (500 ml) TEAB. The eluate was evaporated to dryness and the residue was treated in the usual manner to that described in the section of 6. The residue was triturated with AcOEt to afford a white powder (26.5 mg, 23%), mp. 191-193°. PE: (0.01 phosphate buffer, pH 3.9) $M_{UPA}{}^6$ 1.31.

Anal. Calcd. for $C_4H_5N_2O_4PS\cdot 0.5H_2O$: C, 22.11; H, 2.76; N, 12.90
Found: C, 22.25; H, 2.56; N, 12.82

UV(0.1N HCl): λ max 266 nm (ε 7430). UV(H_2O): λ max 267 nm (ε 6900). UV(0.1N NaOH): λ max 289 nm (ε 9400). ^1H NMR (D_2O): δ 8.51 (1H, d, J_{HCCP} 12.50 Hz, H-6).

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6. Ratio of migration distance of the sample to that of uracil-5-phosphonic acid (UPA).

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