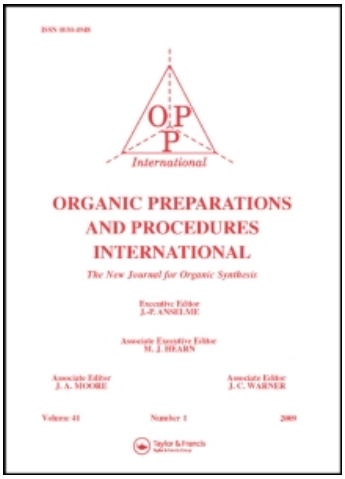

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AN IMPROVED SYNTHESIS OF 1-(2-HYDROXYETHYL)URACIL

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AN IMPROVED SYNTHESIS OF 1-(2-HYDROXYETHYL)URACIL†

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(01/03/95)

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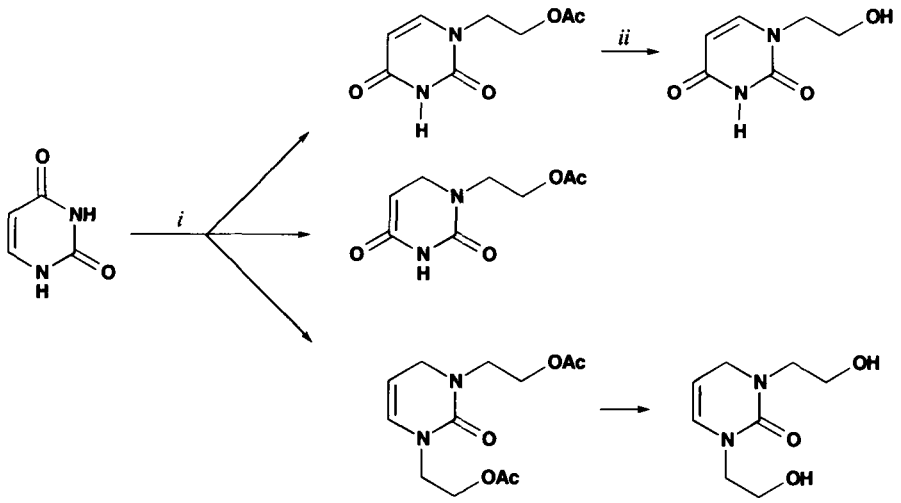
1-(2-Hydroxyethyl)uracil (**3**) finds wide application in biological science as a starting material of coenzymes and vitamins.[1] Inaki and Takemoto[2] prepared **3** from 2,4-diethoxypyrimidine and ethylene bromohydrin in a multiple-step synthesis to form 1-(2'-hydroxyethyl)-4-ethoxy-2-pyrimidone which was then converted to **3** with dilute acid. Nishimura and Iwai[3] synthesized **3** in 60% overall yield by first silylating uracil with hexamethyldisilazane to give 2,4-*bis*(trimethylsilyloxy) pyrimidine followed by reaction with 2-bromoethyl acetate (ten days at 85°). We now report one-step preparation of the key intermediate, 1-(2-acetoxyethyl) uracil **2** from uracil in 40% yield by a direct alkylation.

Reaction of uracil with sodium hydride in DMF furnished the corresponding sodium salt which was treated with excess 2-bromoethyl acetate to afford **2** (40%) and the dialkylated product **5** (18%). The corresponding monoalkylated **4** was not found.



i) NaH, $BrCH_2CH_2OAc$, DMF, 80° ii) MeOH, HCl, 65°

These results are particularly interesting in view of the few reported direct monoalkylation of uracil. 1-Benzyluracil has been synthesized by direct monoalkylation with benzyl chloride of uracil in aqueous sodium hydroxide.[4] The reduction of the 5,6-double bond of N-alkylated uracils with lithium *tris*-*s*-butylborohydride afforded the corresponding 5,6-dihydro derivatives and the method also could be used for alkylation of the 5-position of *n*-alkyluracils to give 5-alkyl-5-6-dihydrouracil derivatives.[5]

1,3-Dimethyluracil has been obtained by methylation with diazomethane, dimethyl sulfate, or methyl iodide.[6] Uracil 1-acetic acid has been synthesized by monoalkylation with chloroacetic acid of uracil in aqueous potassium hydroxide;[7] unfortunately, these conditions are not suitable for use of 2-bromoethyl acetate.

EXPERIMENTAL SECTION

Melting points were recorded in capillary tubes. IR spectra were recorded using a Perkin Elmer 16PC spectrometer and values are expressed in cm^{-1} ^1H NMR spectra were obtained using a Varian FT-80A spectrometer and chemical shifts are reported in δ ppm with TMS as the internal reference. The elemental analyses were performed on a Carlo-Erba 1106 ele-mental analyzer.

1-(2-Acetoxyethyl)uracil (2).- To a stirred suspension of 7 g (0.062 mole) of uracil **1** in 75 mL of dry DMF was added 2.37 g (0.062 mole) of a 80% sodium hydride suspension in oil (prewashed with sodium-dried *n*-hexane (bp. 69°) to remove the oil in one portion. After stirring for 2 hrs protected from moisture the mixture was treated with a solution of 25.0 g (0.149 mole) of 2-bromoethyl acetate in 15 mL of DMF and heated to 80° for 14 hrs. After that time, an additional portion of 12.5 g (0.074 mole) of 2-bromoethyl acetate was added. The temperature was then raised to 150° and held at that temperature until all the solids had dissolved and fine crystals of sodium bromide had begun to precipitate (about 30 min.). The reaction mixture was cooled and evaporated to dryness at 60° and 1mm. The residue was extracted with 300 mL of ethyl acetate, the extract was filtered to remove unreacted uracil, washed with two 200 mL portions of water, dried over magnesium sulfate and evaporated *in vacuo* to leave 10 g of a yellow oil which solidified. Crystallization from ethyl acetate and ethanol gave 4.93 g (40%) of 1-(2-acetoxyethyl) uracil (**2**) as a colorless solid, mp 136°. IR ($CHCl_3$): 1740, 1715, 1655, 1460, 1360, 1240 and 1140 cm^{-1}; UV (H_2O): λ_{max} 267 5 nm (ε = 9,800); ^1H NMR (80 MHz $CDCl_3$): δ 3.6 (s, 3H), 4.0 (t, 2H), 4.2 (t, 2H), 5.7 (d, 1H), 7.4 (d, 1H), 11.3 (s, 1H).

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.43; H, 5.07; N, 13.54

It was identical in all respects with an authentic sample.[2] The presence of **5** was in mother liquor was confirmed by nmr as well as by elemental analysis.

1,3-Di(2-acetoxyethyl)uracil (5).- The ethyl acetate mother liquor obtained from crystallization of **2** was evaporated and the residue was dissolved in chloroform and extracted. After evaporation of the dried chloroform solution, a yellow oil was obtained which slowly crystallized. The yield of **5** was 2.93 g (18%), mp. 50-52°; ^1H NMR (80 MHz, $CDCl_3$): δ 3.6 (s, 3H), 4.0 (t, 2H), 4.3 (t, 3H), 5.7 (d, 1H), 7.4 (d, 1H).

Anal. $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.86. Found: C, 51.29; H, 6.23; N, 10.46

Compound **5** was refluxed with 50 mL of methanol and 1 mL of hydrochloric acid for 5 hrs and the solvent was evaporated. The residue was recrystallized from ethanol to give 1.15 g (73%) of 1,3-*bis*(2-hydroxyethyl)uracil (**6**) as needles, mp 153°. ^1H NMR (80 MHz, DMSO-d_6): δ 5.4 (5H) and 7.5 (6H).

Anal. Calcd. $C_8H_{12}N_2O_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 48.60; H, 5.45; N, 13.93

The properties of **6** were identical in all respects with those of an authentic sample of compound.[8] No 3-(2-acetylethyl)uracil could be detected by column and thin layer chromatography (silica gel).

1-(2-Hydroxyethyl)uracil (3).- A mixture of 2 g (0.010 mole) of 1-(2-acetoxyethyl)uracil **2** was refluxed with 50 mL of methanol and 1 mL of hydrochloric acid at 65° for 1 hr. The solvent was evaporated at reduced pressure and the residue was extracted with four portions of ethanol (total 250 mL). The extract was evaporated to dryness and the residue was crystallized from ethanol to give 1.15 g (73%) of **3** as colorless needles, mp 138-139°. ^{1}H NMR (80 MHz, D_2O): δ 3.8 (t, 2H), 4.0 (t, 2H), 5.7 (d, 1H), 7.4 (d, 1H).

Anal. Calcd. $C_6H_8N_2O_3$: C, 46.15; H, 5.17; N, 17.97. Found: C, 46.40; H, 5.23; N, 17.83

The compound was identical with an authentic sample.[9,10]

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