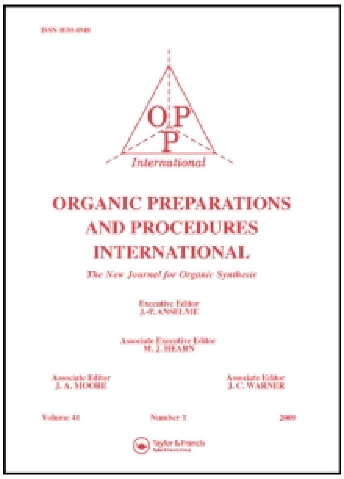

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REACTIONS OF CYCLIC DERIVATIVES OF URACIL AND THYMINE

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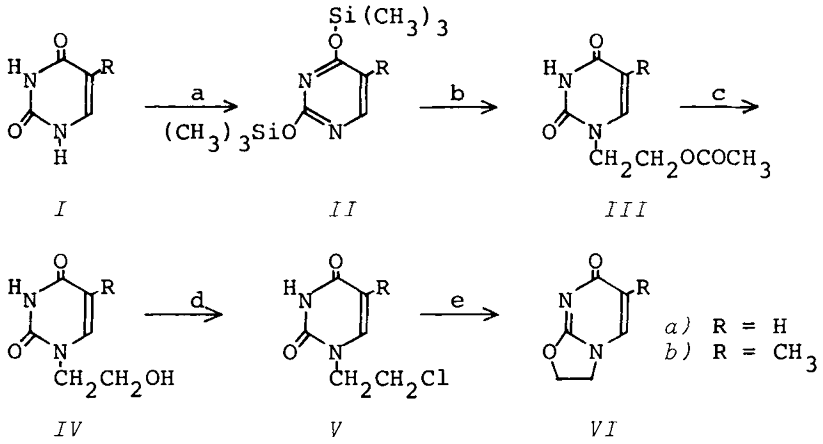
Dedicated to Professor C.G. Overberger on the Occasion of his 60th Birthday

Recently, cyclic derivatives of uracil and thymine, 1,2-O-ethanouracil (*VIa*) and 1,2-O-ethanothymine (*VIb*) were found to undergo polymerization with a cationic initiator by ring-opening process.[1] With number of reagents, these cyclic derivatives of the pyrimidine bases had reactivities similar to that cyclonucleotides[2] and were useful as intermediates for the synthesis of pyrimidine derivatives. This paper presents the reactions of compound *VI* with various reagents.

Compounds *VIa* and *VIb* were prepared from uracil or thymine as shown on the next page. Compounds *II*-*V* were known, but the procedure for preparation of *IV* from uracil or thymine was improved over that previously reported.[3]

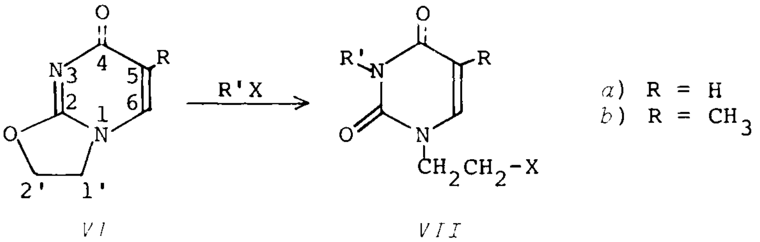
Compound *VI* with various acids gave the 2'-substituted 1-ethyluracil or -thymine derivatives (*VII*). By reaction with hydrochloric acid in aqueous solution or in methanol solution, compound *VI* gave the hydroxyethyl derivative (*IV*)



a) Hexamethyldisilazane b) 2-Bromoethyl acetate c) Methanol, H^+ d) Thionyl chloride, Dioxane e) DBU, DMF

or the chloroethyl derivative (*V*). When hydrobromic acid was used instead of hydrochloric acid in methanol, the bromoethyl derivative (*VIII*) was obtained.

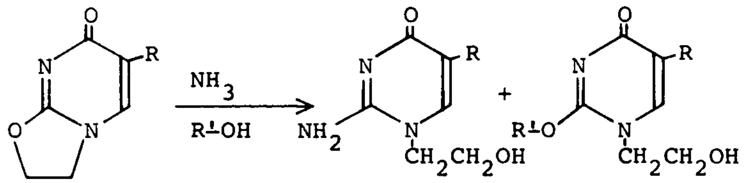
Acetate (*III*) was obtained from *VI* by reaction with acetic acid. Similarly polyacrylate (*IX*) and polymethacrylate (*X*) containing uracil or thymine were obtained by reaction with polyacrylic acid or polymethacrylic acid.[4] Thiolacetic acid and *VI* gave thioacetate (*XI*) which was lead to a thiol compound by hydrolysis.[5]



VIII) R' = H,X = Br *IX*) R' = H,X = $-\text{OCO}\overset{+}{\text{C}}\text{HCH}_2\text{+}$ *X*) R' = H, X = $-\text{OCO}\overset{+}{\text{C}}(\text{CH}_3)\text{CH}_2\text{+}$ *XI*) R' = H,X = $-SCOCH_3$ *XII*) R' = $-CH_3$, X = I *XIII*) R' = $-CH_3$, X = $-SO_3PhCH_3$

The ring-opening polymerization of monomer *VI* initiated by methyl iodide or methyl *p*-toluenesulfonate was reported.[1] When excess amounts of these initiators were reacted with monomer *VI*, the iodide (*XII*) or the tosylate (*XIII*) were obtained. The tosylate (*XIII*) was identified by IR and NMR spectra, but a pure compound could not be isolated because of low crystallinity of *XIII*.

In contrast to the reaction with acids, treatment of compound *VI* with ammonia in alcohol gave C-2 substituted pyrimidine derivatives *XIV* - *XVI*. In this reaction, 1,2-O-ethanouracil (*VIa*) and 1,2-O-ethanothymine (*VIb*) gave different products. The uracil derivative (*VIa*) gave the isocytosine derivative (*XIVa*) in high yield at room temperature. Small amounts of the 2-methoxypyrimidine derivative (*XVa*) and a polymer were obtained as by-products. On the other hand, the thymine derivative *VIb* gave the 2-methoxypyrimidine derivative (*XVb*) or 2-ethoxy derivative (*XVIb*) along with starting material *VIb*. At higher temperature (50-70°), the same systems formed polymers. This type of polymer was also obtained from the polymerization initiated by sodium methoxide.[6]



VI *XIV* *XV*) R' = CH_3

a) R = H *b*) R = CH_3 *XVI*) R' = CH_2CH_3

EXPERIMENTAL

1,2'-Chloroethyluracil (*Va*).- To a solution of *VIa* (1.4g, 10mmol) in 50mL of methanol, was added 5.0mL of conc. hydrochloric acid at 25°, and the solution was stirred for 2 hr. After evaporation of the solvent, the residue was washed with a small amount of cold water. Recrystallization from ethanol gave 1.4g (82%) of *Va* as colorless needles, mp. 162-163°, lit.[3] 163-164°.

1,2'-Bromoethylthymine (*VIIIb*).- To a solution of *VIb* (0.50g, 3.3mmol) in 30mL of methanol, was added 4.5mL of hydrobromic acid (48% aqueous solution) at 25°, and the mixture was stirred for 2 hr at 25°. The precipitated product was filtered and was recrystallized from ethanol to give 0.50g of *VIIIb* as colorless needles (65%), mp. 209-210°, lit.[7] 197-198°.

1,2'-Acetylthioethyluracil (*XIa*).- Compound *VIa*(1.0g, 7.3 mmol) was added to 10g of thiolacetic acid at room temperature and was stirred for 0.5 hr. Then the mixture was heated at 40° for 1 hr. After excess thiolacetic acid was distilled under reduced pressure, the residue was recrystallized from ethanol to give 1.26g (81%) of needles, mp. 168-170°. IR(KBr): 1690, 1460, 1360, 1240, 1140 cm^{-1}. UV(H_2O): λ_{max} = 267.5nm (ε = 9,800). ^{1}H-NMR (100MHz, DMSO-d_6): 2.32 (s, 3H), 3.13 (t, 2H), 3.80 (t, 2H), 5.50 (d, 1H), 7.58 (d, 1H), 11.3 (s, 1H) δ ppm. MS(m/e): 214.

Anal. Calcd. for $C_8H_{11}O_3N_2S$: C, 44.84; H, 4.71; N, 13.08; S, 14.96. Found: C, 44.67; H, 4.57; N, 13.28; S, 15.15.

1,2'-Acetylthioethylthymine (*XIb*).- Compound *VIb* (1.0g, 6.6 mmol) was added to 10g of thiolacetic acid, and the mixture was stirred for 1 hr at 25°. After excess thiolacetic acid was distilled under vacuum, the residue was washed with ethyl ether. The obtained solid was recrystallized from ethanol to give 1.1g (70%) of plates, mp. 169-170°. IR(KBr): 1690,1480, 1370, 1230, 1150 cm^{-1}. UV(H_2O): λ_{max} = 274.0nm (ε = 9,400). ^{1}H-NMR (100MHz, DMSO-d_6): 1.75 (s, 3H), 2.32 (s, 3H), 3.12 (t, 2H), 3.80 (t, 2H), 7.48 (s, 1H), 11.13 (s, 1H) δ ppm.

Anal. Calcd. for $C_9H_{12}O_3N_2S$: C, 47.36; H, 5.30; N, 12.27; S, 14.07. Found: C, 47.17; H, 5.24; N, 12.17; S, 14.12.

1,2'-Iodoethyl-3-methyluracil (*XIIa*).- To a solution of *VIa* (0.50g, 3.6mmol) in 10mL of DMF, was added 7mL (112mmol) of methyl iodide, and the mixture was stirred for 10 days at 25°. Excess methyl iodide and the solvent were distilled under vacuum, and ethyl ether was added to the oily residue and the mixture was stirred for 1 hr. After filtration, the filtrate was concentrated to give 0.75g (74%) of needles, mp. 94-96°. IR(KBr): 1700, 1650, 1460, 1410, 1360, 1240, 1150, 810, 760 cm^{-1}. UV(H_2O): λ_{max} = 266.0nm (ε = 10,000).

Anal. Calcd. for $C_7H_9O_2N_2I$: C, 30.02; H, 3.24; N, 10.00; I, 45.31. Found: C, 29.75; H, 3.04; N, 10.01; I, 45.36.

1,2'-Iodoethyl-3-methylthymine (*XIIb*).- To a solution of *VIb* (0.4g, 2.6mmol) in 10mL of DMF, was added 4mL (64mmol) of methyl iodide, and the solution was stirred for 10 days at 25°. Excess methyl iodide and DMF were distilled under vacuum, and ethyl ether was added to the residue. After filtration, the filtrate was concentrated to give 0.31g (40%) of plates, mp. 114-115°. IR(KBr): 1700, 1660, 1640, 1480, 1360, 1190, 770 cm^{-1}. UV(H_2O): λ_{max} = 271.5nm (ε = 10,300). ^{1}H-NMR (100MHz,

$CDCl_3$): 1.95 (s, 3H), 3.34 (s, 3H), 3.40 (t, 2H), 4.08 (t, 2H), 7.04 (s, 1H) δ ppm.

Anal. Calcd. for $C_8H_{11}O_2N_2I$: C, 32.67; H, 3.77; N, 9.53; I, 43.15. Found: C, 32.50; H, 3.68; N, 9.49; I, 43.22.

1,2'-Hydroxyethyl-isocytosine (*XIVa*).- A solution of *VIa* (1.0g, 7.3mmol) in 200mL of methanol saturated with ammonia was stirred for 10 days at room temperature. After evaporation of methanol, the residue was washed with ethyl acetate, and the obtained solid was recrystallized from ethanol to give 0.90g (80%) of needles, mp. 211-212°. IR(KBr): 3320, 3160, 1640, 1570, 1510, 1440, 1130, 1110, 1050, 820 cm^{-1}. UV(H_2O): λ_{max} = 261.5nm (ε = 5,500). ^1H-NMR (100MHz, DMSO-d_6): 3.60 (t, 2H), 3.80 (t, 2H), 5.13 (s, 1H), 5.50 (d, 1H), 6.95 (s, 2H), 7.24 (d, 1H) δ ppm. MS (m/e): 155.

Anal. Calcd. for $C_6H_9O_2N_3$: C, 46.44; H, 5.85; N, 27.08. Found: C, 46.32; H, 5.74; N, 26.92.

1,2'-Hydroxyethyl-2-methoxy-5-methylpyrimidine-4-one (*XVb*).- A solution of *VIb* (1.0g, 6.6mmol) in 150mL of methanol saturated with ammonia was stirred for 10 days at room temperature. After evaporation of methanol, 200mL of ethyl acetate was added to the residue and was stirred for 0.5 hr at 60°. After filtration, the filtrate was concentrated to dryness. Recrystallization from benzene gave 0.38g (31%) of granules, mp. 128-130°. IR(KBr): 3300, 1650, 1600, 1530, 1500, 1300, 1220, 1080, 1010, 790, 750 cm^{-1}. UV(H_2O): λ_{max} = 262.0nm (ε = 9,200). ^1H-NMR (100MHz, DMSO-d_6): 1.78 (s, 3H), 3.60 (s,3H), 3.85 (s, 4H), 5.00 (s, 1H), 7.46 (s, 1H) δ ppm.

Anal. Calcd. for $C_8H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21.

Found: C, 52.00; H, 6.49; N, 15.34.

1,2'-Hydroxyethyl-2-ethoxy-5-methylpyrimidine-4-one (*XVIb*).- A solution of *VIb* (0.60g, 4.0mmol) in 100mL of ethanol saturated with ammonia was stirred for 10 days at 30°. After evaporation of ethanol, the residue was recrystallized from ethyl acetate to give 0.25g (34%) of needles, mp. 133-135°. IR(KBr): 3310, 1660, 1610, 1520, 1480, 1400, 1320, 1300, 1220, 1150, 1080, 1040, 800 cm^{-1}. UV(H_2O): λ_{max} = 261.0nm (ε = 7,900). ^{1}H-NMR (100MHz, DMSO-d_6): 1.38 (t, 3H), 1.84 (s,3H), 3.88 (s, 4H), 4.18 (q, 2H), 5.16 (s, 1H), 7.15 (s, 3H). Anal. Calcd. for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.48; H, 6.93; N, 14.20.

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