Synthesis of *N*-(2,3-Dihydroxypropyl) Derivatives of Nucleic Bases

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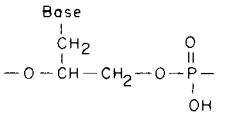
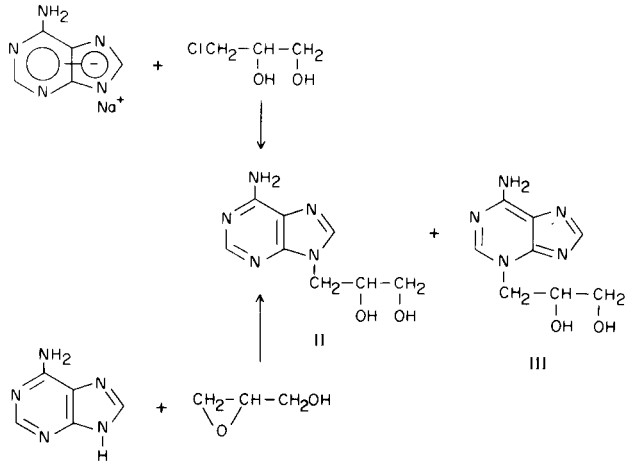
In preceding papers (1-6) of this series, the synthesis and polymerization of *N*-vinyl and *N*-methacryloyloxyethyl derivatives of pyrimidines and purines were studied, and base-base interactions between two synthetic nucleic acid chains were observed for the different pairs. In connection with this study, synthesis of alkyl chain polymers containing nucleic bases as side groups, and synthesis of polymeric analogues, the main chain of which also contains hetero atoms such as oxygen, nitrogen and phosphorus, was of interest. We now wish to report on the synthesis of *N*-(2,3-dihydroxypropyl) derivatives of the nucleic bases, to be used in the synthesis of new polymeric substances with phosphate linkages in the main chain (I).



I

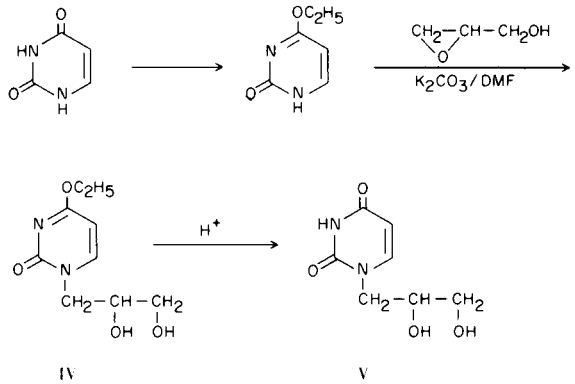
Dihydroxypropylation of the pyrimidine and purine bases was carried out by the reaction of the bases with glycerol α-chlorohydrin or glycidol in dimethylformamide solution. Treatment of adenine with sodium hydride afforded its sodium salt which was subjected to the reaction with glycerol α-chlorohydrin at 60-70°. Two dihydroxypropylated isomers of adenine (II, III) were obtained in a ration (II/III) of about ¼. The dihydroxypropylation of adenine was also achieved by the reaction of adenine with glycidol in dimethylformamide solution at 60-70°, using potassium carbonate as a catalyst. In this case, the ratio II/III was about 3/1. The sites of dihydroxypropyl substitution, namely the 9- and 3-positions, were determined by ultraviolet spectroscopy, λ max in an aqueous solution at near 260 and 270 mμ corresponding to 9- and 3-substituted adenine, respectively (7). Compounds II and III showed λ max at 262 and 274 mμ, respectively.



II III

Dihydroxypropylation of uracil was effected by condensation with an equimolar amount of glycidol under reaction conditions similar to those in the case of adenine. However, the reaction was accompanied by the formation of a byproduct, probably the disubstituted derivative, so that further purification by chromatography over cellulose powder was necessary.

In order to prepare 1-substituted uracil selectively, uracil was initially converted to 4-ethoxy-2-keto-1,2-dihydropyrimidine (8). This compound was then treated with glycidol to afford its dihydroxypropylated derivative (IV), which gave 1-(2,3-dihydroxypropyl) uracil (V) by treatment with dilute hydrochloric acid.

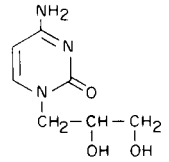


IV V

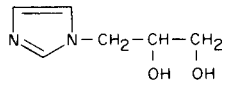
Cytosine provided the corresponding dihydroxypropyl compound (VI) by reaction with an excess amount of glycidol in a similar procedure as was used for uracil. The corresponding propanediol derivative was also obtained by condensation of imidazole with glycidol (VII). All the derivatives were identified by elementary analysis together with ir, nmr and uv spectra. They showed ultraviolet absorption spectra typical for substitution at the 1-position. In the nmr spectra, the alcohol protons, the C_1 protons

and the C_2 and C_3 protons in the propanediol groups appeared in the region of 4.5-5.5, 6.7 and 5.5-6.5 τ, respectively.

The synthesis of oligomers and polymers from these propanediol derivatives which is now in progress will be reported in the near future.



VI



VII

EXPERIMENTAL (9)

9- and 3-(2,3-Dihydroxypropyl)adenine (II, III).

i) Reaction of Adenine with Glycerol α-Chlorohydrin.

A mixture of adenine (5.0 g., 0.037 mole) and sodium hydride (2.1 g., 0.043 mole) in dimethylformamide (100 ml.) was stirred at room temperature for 1 hour. To the resulting suspension was added glycerol α-chlorohydrin (3.7 ml., 0.042 mole) dropwise, and the mixture was stirred at 60-70° for 20 hours. Solid material was collected by filtration and the filtrate was evaporated under reduced pressure. Recrystallization of the solid residue from ethanol gave 9-substituted derivative, II (3.2 g., 41%), m.p. 207-209°; nmr (DMSO-d_6) τ 1.9 and 2.0 (2s, 2, Ad.$C_{2,8}$-H), 2.8 (br s, 2, Ad.C_6-NH_2), 5.0 (v br, 2, Pro.$C_{2,3}$-OH), 5.5-6.5 (m, 3, Pro. $C_{2,3}$-H) and 6.7 (br d, 2, Pro.C_1-H); uv λ max (ε) 261 mμ (13,100), *p*H 7; ir (potassium bromide) ν 3250 (OH), and 1040, 1080 (primary and secondary alcohol C-O); tlc: Rf 0.39.

Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.90; H, 5.26; N, 33.47. Found: C, 45.88; H, 5.39; N, 33.66.

The solid material collected above was recrystallized from water to give the 3-substituted derivative, III (2.0 g., 26%), m.p. >300° dec.; nmr (DMSO-d_6, 125°) τ 1.8 and 2.2 (2s, 2, Ad.$C_{2,8}$-H), 4.6 (br s, 4, Ad.C_6-NH_2 and Pro.$C_{2,3}$-OH), 5.5-6.5 (m, 3, Pro.$C_{2,3}$-H) and 6.7 (br d, 2, Pro.C_1-H); uv λ max (ε) 273 mμ (15,000) *p*H 7, 274 mμ (18,800) *p*H 1, 272 mμ (16,900) *p*H 13; ir (potassium bromide) ν 3300 (OH), and 1050, 1080 (primary and secondary alcohol C-O); tlc: Rf 0.31.

Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.90; H, 5.26; N, 33.47. Found: C, 46.11; H, 5.17; N, 33.53.

ii) Reaction of Adenine with Glycidol.

A mixture of adenine (1.0 g., 0.0074 mole), glycidol (0.5 ml., 0.0075 mole) and a trace of anhydrous potassium carbonate in dimethylformamide (40 ml.) was stirred at 60° for 20 hours. After filtering off undissolved materials, the solution was evaporated under reduced pressure. The solid residue finally obtained was recrystallized from ethanol to give colorless needles of II (0.53 g., 34%). Recrystallization of the filtered material gave colorless plates of III (0.17 g., 11%).

1-(2,3-Dihydroxypropyl)uracil (V).

Uracil (1.1 g., 0.010 mole) and glycidol (0.86 g., 0.012 mole) was allowed to react as in the case of adenine. After the filtration of the unreacted uracil (0.3 g.,), the solution was evaporated to dryness under reduced pressure. The residue was chromatographed over cellulose powder. Elution with 1-butanol saturated with water gave 0.1 g. of the product, which was then recrystallized from 2-propanol to give colorless needles, m.p. 143-144°; nmr (DMSO-d_6) τ -1.15 (br s, 1, Ur.N_3-H), 2.5 and 4.5 (2s, 2, Ur.$C_{5,6}$-H), 5.5 (br s, 2, Pro.$C_{2,3}$-OH), 5.8-6.5 (m, 3, Pro. $C_{2,3}$-H) and 6.7 (br d, 2, Pro.C_1-H); uv λ max 265 mμ; ir (potassium bromide) ν 3370, 3420 (OH), and 1040, 1080 (primary and secondary alcohol C-O).

Anal. Calcd. for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 44.92; H, 5.50; N, 14.97.

Compound V was also obtained by heating a 10% hydrochloric acid solution of IV for 30 minutes on the steam bath, evaporating to dryness and recrystallizing from 2-propanol.

1-(4-Ethoxy-1,2-dihydro-2-keto-1-pyrimidyl)-2,3-propanediol (IV).

Dimethylformamide solution (15 ml.) containing 4-ethoxy-1,2-dihydro-2-ketopyrimidine (1.4 g., 0.01 mole), glycidol (0.8 g., 0.011 mole) and a trace of anhydrous potassium carbonate was stirred at 60-65° for 5 hours. The solution was then evaporated to dryness under reduced pressure. The residue was chromatographed over 60 g. of silica gel. Elution with benzene-ethanol solution (3:1 v/v %) gave 0.8 g. of the propanediol derivative. The product was then recrystallized from benzene-ethanol to give white rods, m.p. 112.5-113.5°; nmr (DMSO-d_6) τ 2.25, 4.15 (2d, 2, J = 7 Hz, Ur.C_5 and C_6-H), 5.65 (br s, 2, Pro.$C_{2,3}$-OH), 5.75 (q, 2, J = 7 Hz, Ur. C_4-CH_2-), 6.0-6.5 (m, 3, Pro. $C_{2,3}$-H), 6.7 (d, 2, J = 5 Hz, Pro. C_1-H) and 8.75 (t, 3, J = 7 Hz, Ur. C_4-CH_3); uv, λ max 274 mμ; ir (potassium bromide) ν 3150, 3300 (OH) and 1040, 1110 (primary and secondary alcohol C-O).

Anal. Calcd. for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.42; H, 6.72; N, 13.45.

1-(2,3-Dihydroxypropyl)cytosine (VI).

Cytosine (1.1 g., 0.01 mole) and a trace of anhydrous potassium carbonate was suspended in dimethylformamide (30 ml.). At 60-70°, glycidol (4.5 ml., 0.068 mole) was added to this suspension in five 0.9 ml. portions at intervals of 12 hours. At the end of the reaction, the suspension became clear. The solvent was then evaporated under reduced pressure. The residue was chromatographed on cellulose powder. Elution with the same solvent as above afforded 0.5 g. of the product, which was then recrystallized from water or 1-propanol to give thin leaves, m.p. 178-179°; nmr (DMSO-d_6) τ 2.5, 4.3 (2d, 2, J = 7 Hz, Cy.$C_{6,5}$-H), 2.85 (s, 2, Cy.C_4-NH_2), 5.5 (br s, 4, Pro.$C_{2,3}$-OH and water), 5.8-6.6 (m, 3, Pro.$C_{2,3}$-H) and 6.7 (br d, 2, J = 4-5 Hz, Pro.C_1-H); uv λ max 272 mμ; ir (potassium bromide): ν 3450, 3500 (OH) and 1020, 1060 (primary and secondary alcohol C-O).

Anal. Calcd. for the monohydrate $C_7H_{11}N_3O_3 \cdot H_2O$: C, 41.37; H, 6.45; N, 20.68. Found: C, 41.20; H, 6.41; N, 20.61.

1-(2,3-Dihydroxypropyl)imidazole (VII).

A solution of imidazole (0.68 g., 0.01 mole) and glycidol (1.35 g., 0.01 mole) in dioxane (10 ml.) was stirred at 60° for 4-5 hours. The solution was evaporated under reduced pressure. The oily residue was chromatographed over cellulose powder. Elution with 1-butanol saturated with water gave 0.6 g. of the product, which was then recrystallized from acetonitrile to afford colorless prisms, m.p. 77-78°; nmr (DMSO-d_6) τ 2.4, 2.9 and 3.1 (3 br s, 3, Im. $C_{2,5,4}$-H), 5.15 (s, 2, Pro.$C_{2,3}$-OH), 5.7-6.4 (m, 3, Pro.$C_{2,3}$-H), 6.7 (br d, 2, Pro.C_1-H); uv λ max 220 mμ; ir (potassium bromide): ν 1040, 1090 (primary and secondary alcohol C-O).

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.57; H, 7.07; N, 19.76.

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(9) Melting points were determined on a Yanaco micro melting point apparatus, and are uncorrected. Infrared spectra were obtained on JASCO IR-G spectrometers. Ultraviolet spectra were obtained with a HITACHI 124 spectrophotometer in aqueous solutions. Nmr spectra were determined on a JEOL M-JNM-3H-60 spectrometer using TMS as an internal standard. In nmr data the symbols are m, multiplet, s, singlet, d, doublet and br, broad. Thin layer chromatography was carried out on glass plate coated with Nagel Cellulose powder MN 300 G using the solvent, 1-butanol saturated with water.