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Studies on Nucleosides and Nucleotides. XII.[1] Syntheses of 3′-Amino-3′-deoxypentofuranosylcytosines[2]

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1-(3′-Amino-3′-deoxy-β-D-arabinofuranosyl)cytosine derivatives (IX), (X), and (XI) were prepared from 1-(3′-azido-3′-deoxy-β-D-arabinofuranosyl)uracil (III) *via* 4-thiouracil derivative (VII). Attempts to prepare 2′,3′-epoxide (XVII) of down-configuration from di-O-mesyl derivative (XVI) with sodium hydroxide was failed and instead 2,2′-anhydronucleoside (XVIII) was obtained.

Recently, a number of analogues of the aminonucleoside, 6-dimethylamino-9-(3′-amino-3′-deoxy-β-D-ribofuranosyl)purine derived from the antibiotic puromycin, have been prepared[4] for the purpose of the investigation of biological activity and structure relationship. On the other hand, several 1-(3′-amino-3′-deoxy-β-D-ribofuranosyl)-uracils and -cytosines were prepared by kissman, *et al.*[5], and they reported that none of these compounds had any significant antitumour and trypanocidal activities. However, it was of interest for us to study more extensively on the biological activity of cytosine derivatives having amino group in the sugar moiety. We attempted, therefore, to synthesize 1-(3′-amino-3′-deoxy-β-D-arabinofuranosyl)- and 1-(3′-amino-3′-deoxy-β-D-xylofuranosyl)-cytosines by the nucleophilic substitution reaction of secondary sulfonyloxy group of pyrimidine nucleosides reported in previous paper.[1,6]

The starting material, 1-(3′-azido-3′-deoxy-β-D-arabinofuranosyl)uracil (III), which was converted into 1-(3′-amino-3′-deoxy-β-D-arabinofuranosyl) cytosines (IX), (X), (XI), was obtained by the hydrolysis of 2,2′-anhydro-1-(3′-azido-3′-deoxy-β-D-arabinofuranosyl)uracil (II). The compound (II) was afforded by the reaction of I with sodium azide as described in previous paper.[6a] The other synthetic routes of III from 1-(2′,3′-epoxy-β-D-lyxofuranosyl)isocytosine (IV)[6b] and 1-(3′-O-tosyl-β-D-arabinofuranosyl)uracil (V)[1] were successful. As shown in Chart 1, the reaction of IV with sodium azide in the existence of benzoic acid in the solution of dimethylformamide (DMF) gave II. It appears likely that 1-(3′-azido-3′-deoxy-β-D-arabinofuranosyl)isocytosine was really formed in this reaction as an intermediate, and subsequently rearranged to the 2,2′-anhydro-arabinonucleoside (II) by the attack of 2′-hydroxy group on C-2. The compound (II) thus obtained was identical with an authentic specimen prepared from I. The compound (III) was also obtained from V with sodium azide in DMF at 100° for five hours. In this case, it was considered that 1-(2′,3′-epoxy-β-D-lyxofura-

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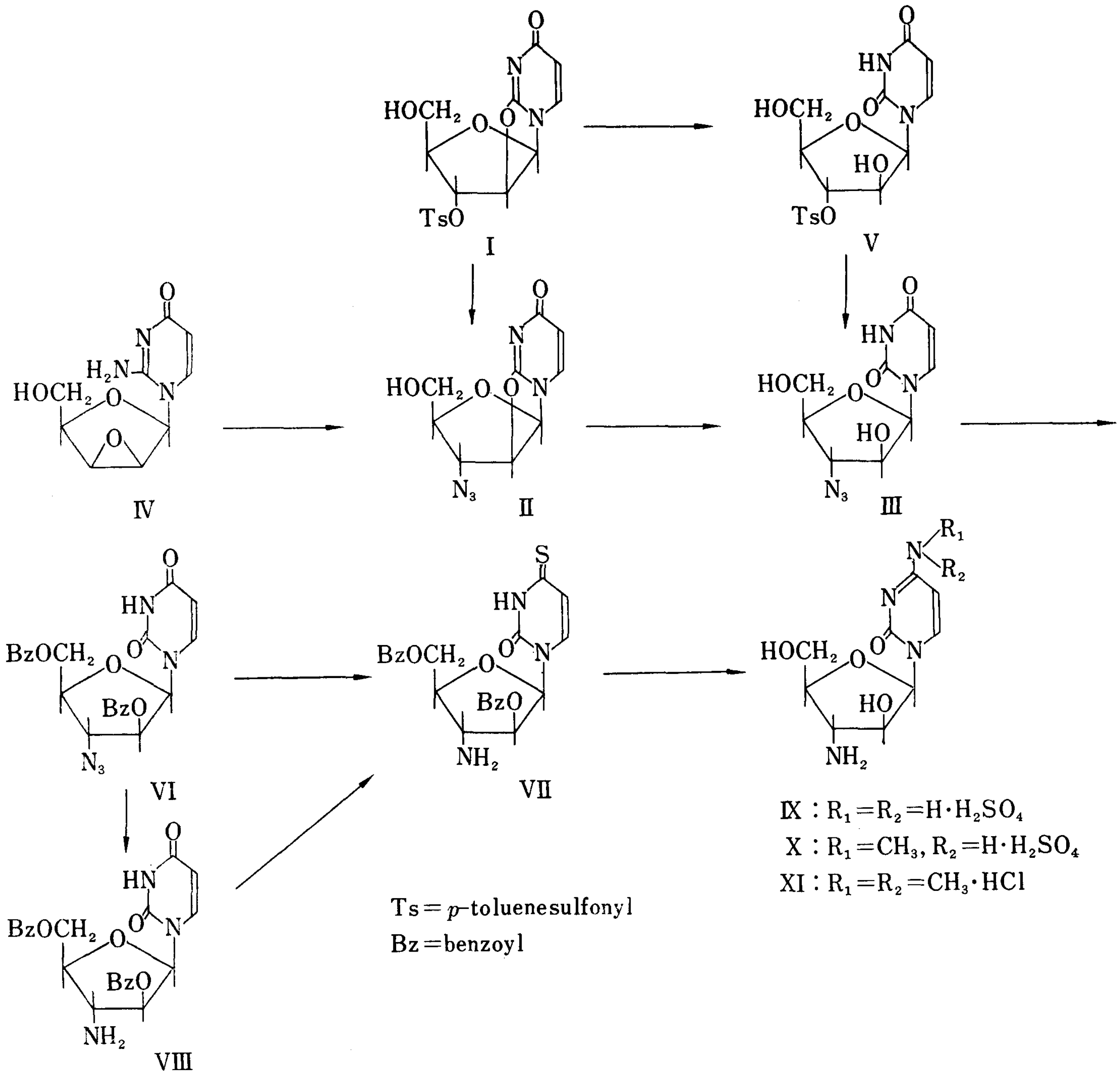
[1] Part XI: M. Hirata, *Chem. Pharm. Bull.* (Tokyo), **16**, 437 (1968).
[2] A part of this work was presented at the General Meeting of Pharmaceutical Society of Japan, Kyoto, April 1967.
[3] Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
[4] B.R. Baker, J.P. Joseph, and J.H. Williams, *J. Am. Chem. Soc.*, **77**, 1(1955); H.M. Kissman, C, Pidacks, and B.R. Baker, *ibid.*, **77**, 18 (1955); B.R. Baker, and R.E. Schaub, *ibid.*, **77**, 2396 (1955); B.R. Baker, R.E. Schaub, and H.M. Kissman, *ibid.*, **77**, 5911 (1955); L. Goldman, J.W. Marsico, and R.B. Angier, *ibid.*, **78**, 4173 (1956).
[5] H.M. Kissman and M.J. Weiss, *J. Am. Chem. Soc.*, **80**, 2575 (1958).
[6] *a*) M. Hirata, *Chem. Pharm. Bull.* (Tokyo), **16**, 291 (1968); *b*) M. Hirata, *ibid.*, **16**, 430 (1968).



IX : $R_1 = R_2 = H \cdot H_2SO_4$
X : $R_1 = CH_3, R_2 = H \cdot H_2SO_4$
XI : $R_1 = R_2 = CH_3 \cdot HCl$

Ts = *p*-toluenesulfonyl
Bz = benzoyl

Chart 1

nosyl)uracil would be the intermediate of the reaction because sodium azide reacted easily with tosylate (V).

Since direct thiation of III at position 4 would require suitable blocking groups for sugar hydroxyls, III was treated with benzoyl chloride to prepare 1-(3′-azido-3′-deoxy-2′,5′-di-O-benzoyl-β-D-arabinofuranosyl)uracil (VI). The thiation of VI with phosphorous pentasulfide in refluxing pyridine gave the yellow crystalline material (VII), whose ultraviolet absorption spectra were similar to those of 4-thiouracil derivatives, but the infrared (IR) spectra of VII had no characteristic band of azido group (4.8 μ). The structure of VII was established as follows. After hydrogenation of VI on Pd–catalyst to 1-(3′-amino-3′-deoxy-2′,5′-di-O-benzoyl-β-D-arabinofuranosyl)uracil (VIII), which was treated with phosphorous pentasulfide under similar conditions described above to obtain VII. Ultraviolet (UV) absorption spectra, infrared spectra, and melting point of the yellow crystals thus obtained were completely identical with those of VII. From this result, the structure of VII was established as 1-(3′-amino-3′-deoxy-2′,5′-di-O-benzoyl-β-D-arabinofuranosyl)-4-thiouracil. It was very interesting that thiation of VI with phosphorous pentasulfide was accompanied by reduction of azido group. This hydrogenation mechanism of azido group could be explained by the reaction of VI with hydrogen sulfide in pyridine. Thus, it was rigidly established that

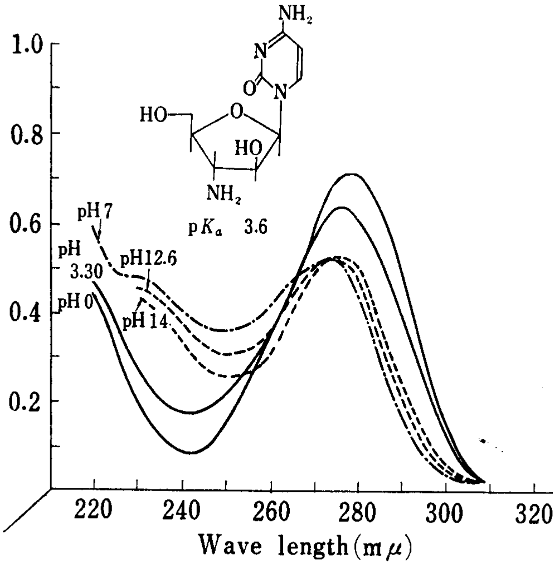


Fig. 1. Ultraviolet Spectra of IX

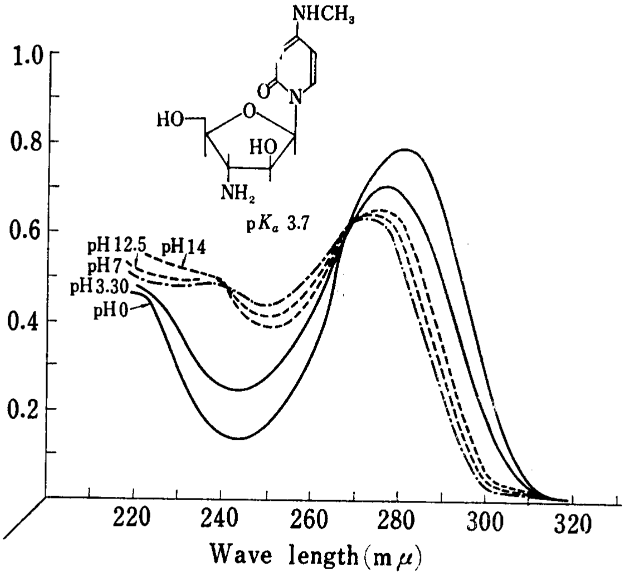


Fig. 2. Ultraviolet Spectra of X

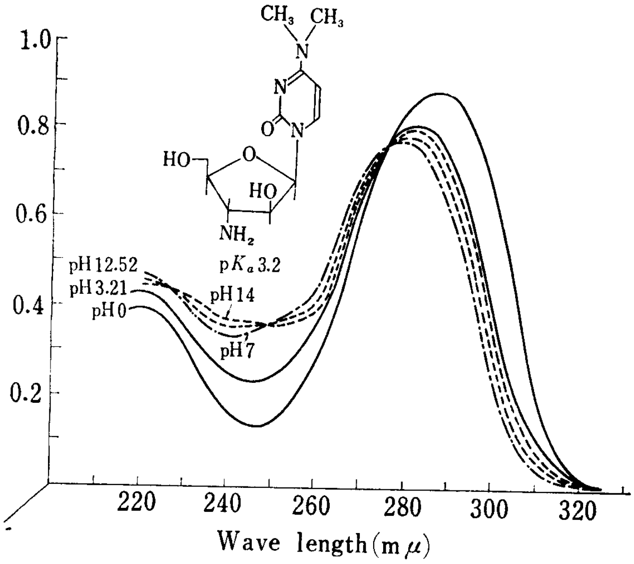
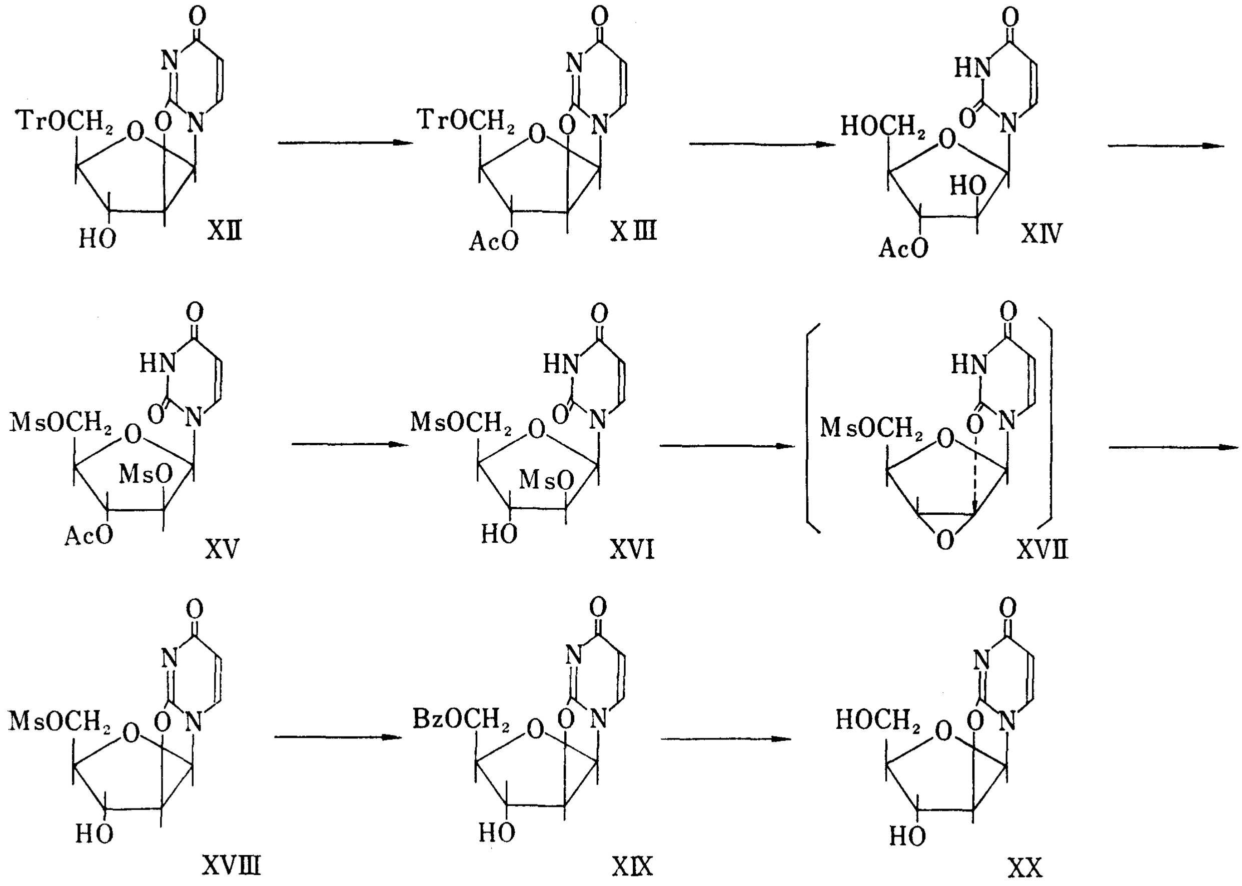


Fig. 3. Ultraviolet Spectra of XI

hydrogenation of VI in the reaction with phosphorous pentasulfide was occured by hydrogen sulfide liberated in the reaction.

The compound (VII) was treated with ethanolic ammonia in a sealed tube, and 1-(3′-amino-3′-deoxy-β-D-arabinofuranosyl)cytosine sulfate (IX) was obtained as pale yellow needles, whose ultraviolet absorption spectra (Fig. 1) showed the same as those of cytidine, but IX travelled further toward the anode than both of cytidine and 1-(3′-amino-3′-deoxy-β-D-arabinofuranosyl)uracil in electrophoresis. Similarly, N^4-methyl-1-(3′-amino-3′-deoxy-β-D-arabinofuranosyl) cytosine sulfate (X) and N^4-dimethyl-1-(3′-amino-3′-deoxy-β-D-arabinofuranosyl)cytosine hydrochloride (XI) were obtained from VII and ethanolic monomethylamine and dimethylamine, respectively. As shown in Fig. 1, 2, and 3, ultraviolet absorption spectra of IX, X, and XI were very similar each other, but slight difference was observed in apparent pK_a values of these compounds, whose pK_a values were 3.6, 3.7, and 3.2, respectively. The formation of monoacidic base salt in the case of XI presumably depends on the weak basicity in comparison with IX and X.

The author further attempted to synthesize isomer of IX, 1-(3′-amino-3′-deoxy-β-D-xylofuranosyl)cytosine having 3′-amino group in up-configuration. In the reaction of pyrimidine nucleoside having 3′-sulfonyloxy group of down-configuration with nucleophilic reagent like sodium azide, azide group was not introduced in up-configuration but down-configuration as described previously.[6a)] Considering this fact, we desired to prepare 1-(3′-amino-3′-deoxy-β-D-xylofuranosyl)uracil by the reaction of 1-(2′,3′-epoxy-β-D-ribofuranosyl)uracil (XVII) with ammonia.



Tr = triphenylmethyl Ac = acetyl Ms = methanesulfonyl Bz = benzoyl

Chart 2

As shown in Chart 2, 2,2′-anhydro-1-(5′-O-trityl-β-D-arabinofuranosyl)uracil (XII)[7] was acetylated with acetic anhydride in pyridine to 2,2′-anhydro-1-(3′-O-acetyl-5′-O-trityl-β-D-arabinofuranosyl)uracil (XIII). Acidic hydrolysis of XIII with aqueous acetic acid at 100°, the reaction product gave two spots with different *Rf* values on thin-layer chromatography (TLC) (silicagel; solvent: chloroform: acetone=1:1), which were definitely separated. A silicagel column chromatography of the product gave 1-(3′-O-acetyl-β-D-arabinofuranosyl)uracil (XIV), mp 167—169°, whose structure was confirmed by the transformation to a compound, 1-β-D-arabinofuranosyluracil, which was obtained by hydrolysis of XIV with methanolic ammonia. Another product which was shown as a minor spot was assigned as 1-(3′-O-acetyl-β-D-ribofuranosyl)uracil, which was probably obtained by the effect of a neighbouring acetoxy-group as suggested by Brown, *et al.*[8]

Treatment of XIV with mesyl chloride in pyridine gave 1-(3′-O-acetyl-2′,5′-di-O-mesyl-β-D-arabinofuranosyl) uracil (XV) and XV was deacetylated by methanolic ammonia to 1-(2′,5′-di-O-mesyl-β-D-arabinofuranosyl)uracil (XVI), mp 164—165.5°. In treatment of XVI with an equivalent sodium hydroxide in water, 1-(2′,3′-epoxy-5′-O-mesyl-β-D-ribofuranosyl)-uracil (XVII) was not obtained, but 2,2′-anhydronucleoside (XVIII) deduced from its characteristic ultraviolet absorption spectra, was obtained as the sole product. The structure of XVIII was established as follows. After the substitution of mesyl group of XVIII with benzoyl group by sodium benzoate, the benzoate (XIX) was converted with methanolic ammonia into 2,2′-anhydro-1-β-D-arabinofuranosyluracil (XX), which was identified by

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[7] J.F. Codington, I. Doerr, D.V. Praag, A. Bendich, and J.J. Fox, *J. Am. Chem. Soc.*, **83**, 5030 (1961).

[8] D.M. Brown, D.B. Parihar, and Sir A. Todd, *J. Chem. Soc.*, **1958**, 4242.

comparison with an authentic specimen. Therefore, the structure of XVIII was established as 2,2′-anhydro-1-(5′-O-mesyl-β-D-arabinofuranosyl)uracil.

It is assumed that in the reaction of XVI with sodium hydroxide, a transitory formed 2′,3′-epoxide (XVII) would be rearranged to anhydronucleoside (XVIII) by the attack of carbonyl group of pyrimidine moiety to C–2′ of the sugar moiety. It is interesting that the attack occured on C–2′ exclusively in this reaction. Similar reaction was reported[9] independently that on treatment of 3-O-tosylxylofuranosyluracil derivatives with methanolic sodium methoxide gave 2,2′-anhydronucleoside.

The biological activities of cytosine derivatives (IX), (X), and (XI) will be reported elsewhere.

Experimental

All melting points are uncorrected. Paper chromatography (PPC) was performed by the ascending technique using Toyo Roshi No. 51 filter paper. Ultraviolet absorption spectra were measured with Hitachi Model EPS-2U Spectrophotometer. Buffer solution was prepared as described previously.[6b)]

2,2′-Anhydro-1-(3′-azido-3′-deoxy-β-D-arabinofuranosyl)uracil (II)——IV (1.15 g, 5 mmoles), NaN_3 (0.8 g, 12.5 mmoles), and benzoic acid (1.2 g, 10 mmoles) were dissolved in DMF (5 ml) and the solution was heated at 100° for 3 hr in a sealed tube. After removal of the solvent, the residue was chromatographed through a celite column (solvent: methyl ethylketone (MEK) saturated with H_2O). Evaporation of the eluate gave colorless needles. Recrystallization from MeOH gave 0.45 g (38%) of II, mp 177—179°, undepressed on admixture with an authentic sample.[6a)]

1-(3′-Azido-3′-deoxy-β-D-arabinofuranosyl)uracil (III)——V (400 mg, 1 mmole), NaN_3 (130 mg, 2 mmoles) were dissolved in DMF (5 ml) and MeOH (2 ml) and the solution was heated at 100° for 5 hr in a sealed tube. After evaporation of the solvent *in vacuo*, the residue was treated with H_2O to induce crystallization. Recrystallization from MeOH–EtOH gave 130 mg (50%) of colorless needles, mp 171—172° (decomp.), undepressed on admixture with an authentic sample.[6a)]

1-(3′-Azido-3′-deoxy-2′,5′-di-O-benzoyl-β-D-arabinofuranosyl)uracil (VI)——To a solution of III (10 g, 37 mmoles) in pyridine (100 ml), benzoylchloride (12.3 g, 96 mmoles) was added at 5—10° under stirring, and it was kept at 40° for 4 hr. The solution was evaporated to a syrup *in vacuo*, and it was treated with H_2O to induce crystallization. Recrystallization from benzene gave 17 g (90%) of colorless needles, mp 120°. $[\alpha]_D^{22}$ +112.1° (c=0.94, pyridine). UV λ_{max}^{MeOH} mμ(ε): 232 (23300), 261 (8100); λ_{min}^{MeOH} mμ(ε): 252 (7900). *Anal.* Calcd. for $C_{23}H_{19}O_7N_5$: C, 57.85; H, 4.01; N, 14.68. Found: C, 57.95; H, 3.71; N, 14.38.

1-(3′-Amino-3′-deoxy-2′,5′-di-O-benzoyl-β-D-arabinofuranosyl)uracil (VIII)——(A) VI (4.8 g, 10 mmoles) was dissolved in EtOH (90 ml) and pyridine (10 ml) and the solution was catalytically hydrogenated over 40% Pd–C (0.9 g) at room temperature. Uptake of hydrogen was completed in 30 min. After removal of catalyst and solvent, colorless needles, mp 212—213° (decomp.), were obtained in yield of 3.5 g (78%). $[\alpha]_D^{22}$ 140.6° (c=0.98, pyridine). UV λ_{max}^{MeOH} mμ (ε): 231.5 (30400), 263 (10200); λ_{min}^{MeOH} mμ (ε): 251.5 (9200). *Anal.* Calcd. for $C_{23}H_{21}O_7N_3$: C, 61.19; H, 4.88; N, 9.33. Found: C, 60.81; H, 4.46; N, 9.49.

(B) A solution of VI (100 mg) in refluxing pyridine (10 ml) was treated with bubbling H_2S for 40 min. After removal of the solvent *in vacuo*, the residue was triturated with MeOH. Recrystallization from MeOH gave 60 mg (65%) of colorless needles, mp 211—213° (decomp.), undepressed on admixture with an authentic sample prepared by method (A).

1-(3′-Amino-3′-deoxy-2′,5′-di-O-benzoyl-β-D-arabinofuranosyl)-4-thiouracil (VII)——(A) VI (4.8 g, 10 mmoles) and phosphorous pentasulfide (6.7 g, 30 mmoles) were dissolved in pyridine (100 ml) and the solution was refluxed for 4 hr. It was concentrated to about 20 ml *in vacuo* and poured into H_2O (1 liter) under stirring. The pale yellow powder of VII was obtained in yield of 3.9 g (80%). Recrystallization from EtOH gave fine yellow needles, mp 219—221° (decomp.). $[\alpha]_D^{23}$ +236.2° (c=1.08, pyridine). UV λ_{max}^{EtOH} mμ (ε): 233 (32900), 341 (21900); λ_{min}^{EtOH} mμ (ε): 290 (5800). *Anal.* Calcd. for $C_{23}H_{21}O_6N_3S$: S, 6.86. Found: S, 6.83.

(B) VIII (4.5 g, 10 mmoles) and phosphorous pentasulfide (6.7 g, 30 mmoles) were dissolved in pyridine (100 ml) and the solution was treated as described above. Recrystallization from EtOH gave fine yellow needles, 4.1 g (90%), mp 219—221° (decomp.), undepressed on admixture with the specimen prepared by method (A). UV and IR spectra of these substances were identical.

1-(3′-Amino-3′-deoxy-β-D-arabinofuranosyl)cytosine Sulfate (IX)——A suspension of VII (4.7 g, 10 mmoles) in EtOH (100 ml) was cooled to 0° and was saturated with NH_3. It was heated at 100° for 5 hr in a sealed tube. After removal of the solvent, the residue was dissolved in H_2O and the solution was chromatographed through a columm of Amberite IR-120 (H-form), which was eluted with dilute aqueous

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9) E.J. Reist, J.H. Osiecki, L. Goodman, and B.R. Baker, *J. Am. Chem. Soc.*, **83**, 2208 (1961).

NH_3. Evaporation of the eluates gave a syrup, and, after it was diluted with a small portion of H_2O, it was adjusted to pH 3—4 by addition of 10% H_2SO_4 to form crystalline sulfate. Recrystallization from EtOH–H_2O gave 1 g (30%) of pale yellow needles, mp 235—236° (decomp.). $[\alpha]_D^{24}$ +88.9° (c=0.81, H_2O). UV $\lambda_{max}^{H_2O}$ mμ (ε): 228 (9100) (shoulder), 272 (10600); $\lambda_{min}^{H_2O}$ mμ (ε): 251 (7000). *Anal.* Calcd. for $C_9H_{14}O_4N_4 \cdot H_2SO_4$: C, 31.56; H, 4.41; N, 16.39; S, 9.38. Found: C, 31.76; H, 4.72; N, 16.43; S, 9.41.

N^4-Methyl-1-(3′-amino-3′-deoxy-β-D-arabinofuranosyl)cytosine Sulfate (X)——A suspension of VII (4.7 g, 10 mmoles) in EtOH (100 ml) was cooled to 0° and was saturated with $MeNH_2$. It was heated at 100° for 5 hr in a sealed tube and was treated as decribed above. Pale yellow needles of X, mp 188—190° (decomp.), were obtained in yield of 1.06 g (30%). $[\alpha]_D^{24}$ +75.8° (c=1.04, H_2O). UV$\lambda_{max}^{H_2O}$ mμ (ε): 234 (8000) (shoulder), 273 (11800); $\lambda_{min}^{H_2O}$ mμ (ε): 248 (7230). *Anal.* Calcd. for $C_{10}H_{16}O_4N_4 \cdot H_2SO_4$: C, 33.89; H, 5.12; N, 15.82; S, 9.04. Found: C, 33.95; H, 5.22; N, 15.61; S, 8.99.

N^4-Dimethyl-1-(3′-amino-3′-deoxy-β-D-arabinofuranosyl)cytosine Hydrochloride (XI)——A suspension of VII (4.7 g, 10 mmoles) in EtOH (100 ml) was cooled to 0° and was saturated with Me_2NH. It was heated at 100° for 5 hr in a sealed tube and was treated as described above. Pale yellow needles of XI, mp 225° (decomp.), were obtained in yield of 0.91 g (29%). $[\alpha]_D^{24}$ +72.4° (c=1.01, H_2O). UV $\lambda_{max}^{H_2O}$ mμ (ε): 220 (9920) (shoulder), 280 (13700); $\lambda_{min}^{H_2O}$ mμ (ε): 241 (6900). *Anal.* Calcd. for $C_{11}H_{18}O_4N_4 \cdot HCl$: C, 43.04; H, 6.20; N, 18.26; Cl, 11.57. Found: C, 42.89; H, 6.35; N, 17.99; Cl, 11.70.

2,2′-Anhydro-1-(3′-O-acetyl-5′-O-trityl-β-D-arabinofuranosyl)uracil (XIII)——To a suspension of XII (2.35 g, 5 mmoles) in pyridine (30 ml), acetic anhydride (2 g, 20 mmoles) was added at room temperature. The solution was allowed to stand overnight, then it was evaporated to a syrup, and it was treated with H_2O. The crystalline material, 2.3 g (90%), mp 80—90°, was used to the next process without further purification.

1-(3′-O-Acetyl-β-D-arabinofuranosyl)uracil (XIV)——Raw XIII (12 g), above described, was suspended in the mixture of AcOH (80 ml), H_2O (10 ml), and MeOH (10 ml), and the suspension was heated on a boiling water bath for 6 hr. After concentration of the solution, tritylcarbinol was removed by filtration and the mother liquor was evaporated to dryness *in vacuo*. In order to remove a small amount of impure byproduct, the residue was chromatographed through a silicagel column, and was developed with $CHCl_3$–acetone (1:1). The fractions containing XIV were evaporated to yield 3.65 g (56%) of colorless needles, mp 167—169°. $[\alpha]_D^{24}$ +101.8° (c=0.91, H_2O). UV λ_{max}^{MeOH} mμ (ε): 263 (12600); λ_{min}^{MeOH} mμ (ε): 231 (2500). *Anal.* Calcd. for $C_{11}H_{14}O_7N_2$: C, 46.15; 4.93; N, 9.78. Found: C, 46.37; H, 4.65; N, 9.84.

1-(3′-O-Acetyl-2′,5′-di-O-mesyl-β-D-arabinofuranosyl)uracil (XV)——In the solution of XIV (1 g, 3.5 mmoles) in pyridine (5 ml), mesyl chloride (1 g, 10.5 mmoles) was gradually added at 5° and the solution was allowed to stand at room temperature overnight. After removal of the solvent, the residue was treated with H_2O. An amorphous powder, thus obtained, was chromatographed through a silicagel column and was eluted with $CHCl_3$–acetone (1:1). The fractions containing XV were evaporated to yield 1 g (65%) of homogeneous form. *Anal.* Calcd. for $C_{13}H_{18}O_{11}N_2S_2$: N, 6.33. Found: N, 6.50.

1-(2′, 5′-Di-O-mesyl-β-D-arabinofuranosyl)uracil (XVI)——XV (1 g, 2.26 mmoles) was dissolved in 15% NH_3–MeOH (20 ml) and the solution was allowed to stand for 2 hr. Then it was evaporated under reduced pressure to dryness and the residue was triturated with EtOH to induce crystallization. Recrystallization from EtOH–acetone gave colorless needles, mp 164—165.5°, in yield of 0.8 g (90%). $[\alpha]_D^{24}$+89.7° (c=0.90, pyridine). UV λ_{max}^{MeOH} mμ (ε): 260 (11400); λ_{min}^{MeOH} mμ (ε): 229 (2600). *Anal.* Calcd. for $C_{11}H_{16}O_{10}N_2S_2$: C, 33.00; H, 4.00; N, 7.00. Found: C, 33.42; H, 4.04; N, 7.29.

2,2′-Anhydro-1-(5′-O-mesyl-β-D-arabinofuranosyl)uracil (XVIII)——XVI (440 mg, 1 mmole) was dissolved in H_2O (5 ml) containing NaOH (44 mg, 1.1 mmole) and immediately colorless needles were separated out from the solution. Recrystallization from H_2O gave 240 mg (80%) of colorless pillars, mp 215—216° (decomp.). $[\alpha]_D^{24}$ −41.8° (c=0.37, DMF). UV λ_{max}^{MeOH} mμ (ε): 226 (10600), 247 (8900); λ_{min}^{MeOH} mμ (ε): 239 (8300). *Anal.* Calcd. for $C_{10}H_{12}O_7N_2S$: C, 39.47; H, 3.95; N, 9.21; S, 10.52. Found: C, 39.45; H, 4.03; N, 9.29; S, 10.35.

2,2′-Anhydro-1-(5′-O-benzoyl-β-D-arabinofuranosyl)uracil (XIX)——XVIII (200 mg, 0.66 mmole) and Na benzoate (140 mg, 0.99 mmole) were dissolved in DMF (3 ml) and the solution was heated at 120° for 4 hr in a sealed tube. The solution was evaporated *in vacuo* and the residue was treated with H_2O to induce crystallization. Recrystallization from EtOH gave 60 mg (28%) of colorless needles, mp 190—192°. $[\alpha]_D^{24}$ +13.4° (c=0.47, pyridine). UV λ_{max}^{MeOH} mμ (ε): 229 (26000); λ_{min}^{MeOH} mμ (ε): 250 (10200). *Anal.* Calcd. for $C_{16}H_{14}O_6N_2$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.51; H, 4.32; N, 8.77.

2,2′-Anhydro-1-β-D-arabinofuranosyluracil (XX)——XIX (25 mg, 0.08 mmole) was dissolved in 15% NH_3–MeOH (1 ml) and the solution was allowed to stand at room temperature for 2 hr. It was evaporated *in vacuo* and the resulting material was recrystallized from MeOH to give 8 mg (48%) of colorless needles, mp 235°, undepressed on admixture with an authentic sample.

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