[Chem. Pharm. Bull. 16( 3 ) 437—443 (1968)]

UDC 547.963.3.07

# Studies on Nucleosides and Nucleotides. XI.[1] Nucleophilic Substitution of Secondary Sulfonyloxy Groups of Pyrimidine Nucleosides. IV. Deamination in Isocytosine Derivatives and Dealkoxylation in 2-O-Alkyl-pyrimidine Nucleosides[2]

MIYOSHI HIRATA

*Central Research Laboratory, Daiichi Seiyaku Co., Ltd.*[3]

(Received April 25, 1967)

1-(2',3'-Epoxy-β-D-lyxofuranosyl)isocytosines (I) and (II) were easily deaminated by heating with aqueous hydrogen chloride, yielding 2,2'-anhydro-1-(3'-chloro-3'-deoxy-β-D-arabinofuranosyl)uracil (III), and 1-(3'-chloro-3'-deoxy-β-D-arabinofuranosyl)uracil (IV). And other isocytosine derivatives (VIII), (X), (XI), and (XVI) were also deaminated by heating at 80° for several minutes in acetic acid to corresponding anhydronucleosides, *i.e.* VII, IX, and XV, while 2',3'-O-isopropylideneisocytidine (XVII) and isocytidine (XVIII) were not deaminated.

Furthermore, demethoxylation of 2-O-methylpyrimidine nucleosides was studied. In the reaction of 2,5'-anhydro-1-(2,3'-di-O-acetyl-β-D-arabinofuranosyl) uracil (XXI) with triethylamine in methanol, 2-O-methyl-1-β-D-arabinofuranosyluracil (XXII) was not obtained, but IX as a sole product. This phenomenon showed that XXII was the intermediate. However, 2-O-methyl-1-(2',3'-epoxy-β-D-lyxofuranosyl)uracil (XXIII), 2-O-methyl-1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)uracil (XXIV) and 2-O-methyluridine (XXV) were not demethoxylated by heating at 80° in acetic acid.

Therefore, deamination in isocytosine derivatives and demethoxylation in 2-O-methylpyrimidine derivatives required one hydroxy group of up form in 2'-position or 2',3'-epoxide ring of lyxo-form.

The preceding paper described the reaction of 2',3'-di-O-tosyluridine with methanolic ammonia and the spectroscopic properties of 2-substituted pyrimidine nucleosides. This paper deals with the chemical properties of aforementioned 2-amino- and 2-methoxypyrimidine nucleosides.

Isocytosine derivatives have been generally less investigated than cytosine derivatives. In the study of chemical properties of the isocytosine derivatives, of particular interest was the easy deamination of them. Cytidine was rather stable against acid,[4] but the isocytosine

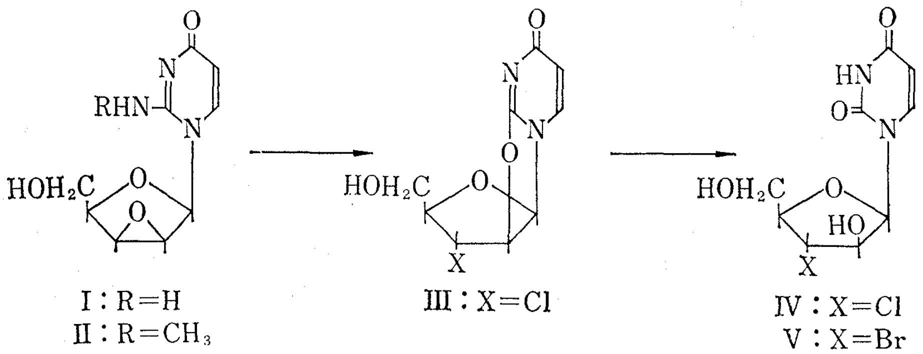

Chart 1

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1) Part X: *Chem. Pharm. Bull.* (Tokyo), **16**, 430 (1968).

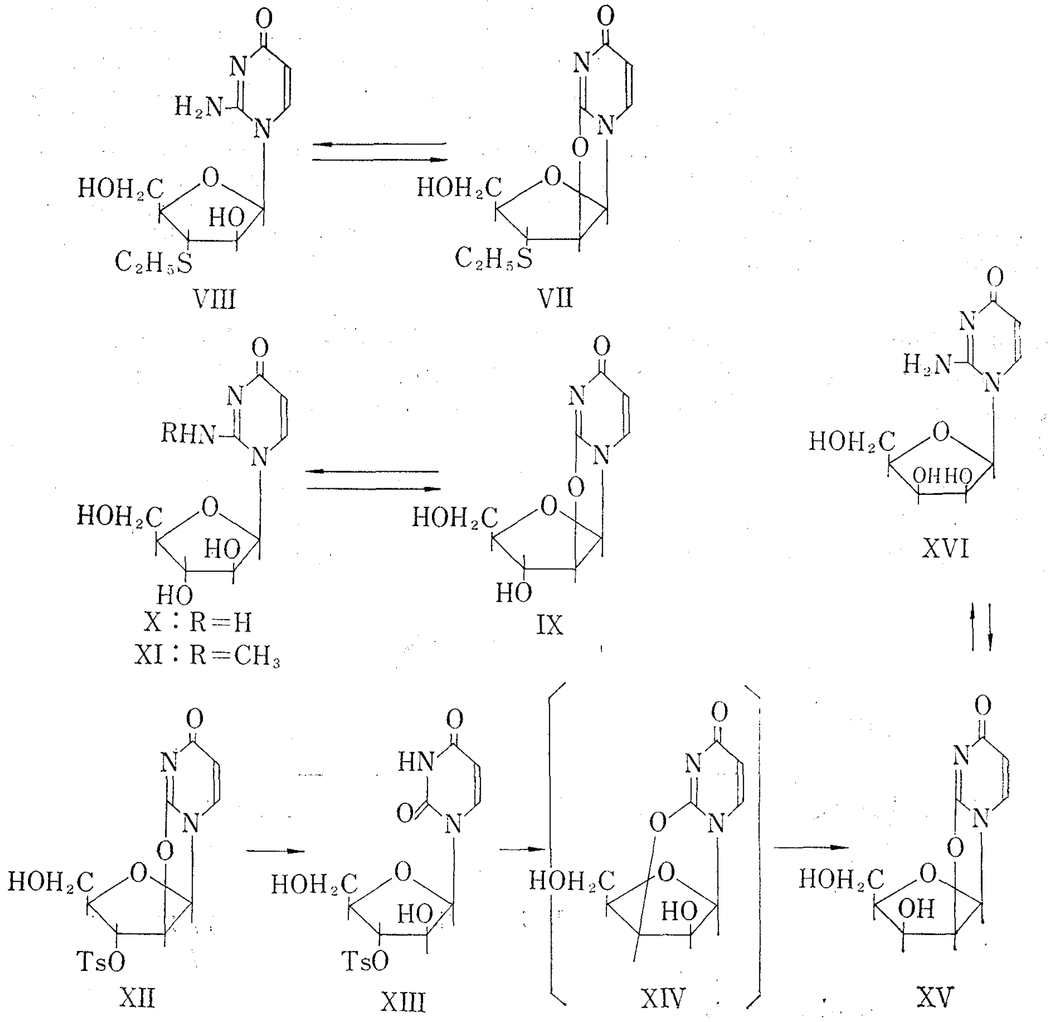
2) Preliminary communication of this work appeared in *Chem. Pharm. Bull.* (Tokyo), **13**, 1258 (1965).

3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*

4) P. Reichard, *Acta. Chem. Scand.*, **3**, 422 (1949). [*C.A.*, **43**, 8510*e* (1949)].

derivatives were unstable under the similar conditions. These properties suggested that there would be a relationship between the amino group in 2-position of the base moiety and the configuration of hydroxy group of the sugar moiety.

As shown in Chart 1, 1-(2',3'-epoxy-β-D-lyxofuranosyl)isocytosine (I) or 2-N-methyl-1-(2',3'-epoxy-β-D-lyxofuranosyl)isocytosine (II) was treated with 5% hydrochloric acid at 80° for several hours to form 2,2'-anhydro-1-(3'-chloro-3'-deoxy-β-D-arabinofuranosyl)-uracil (III) and 1-(3'-chloro-3'-deoxy-β-D-arabinofuranosyl)uracil (IV), whereas treatment of I or II with 5% hydrobromic acid resulted in the formation of 1-(3'-bromo-3'-deoxy-β-D-arabinofuranosyl)uracil (V). Furthermore, the hydrochloride (VI) of I yielded quantitatively III when directly heated in capillary tube at 140° for a moment or at 100° in dimethylformamide (DMF) for seven hours. The structures of these compounds (III), (IV), and (V) were confirmed as follows. The compound (V) was identified by comparison with an authentic 1-(3'-bromo-3'-deoxy-β-D-arabinofuranosyl)uracil.[5] The compound (III) showed two maxima at 223 and 250 mμ in ultraviolet absorption spectra which were characteristic of 2,2'-anhydronucleosides, and III was converted to IV by hydrolysis with dilute hydrochloric acid. The structure of IV was determined on the basis of elemental analysis and ultraviolet absorption spectrum which was very similar to that for V.



Ts=p-Toluenesulfonyl

Chart 2

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[5] Part IX: *Chem. Pharm. Bull.* (Tokyo), **16**, 291 (1968).

In order to explore this novel deamination more extensively, the studies were focussed on the relationship between the amino group in 2–position of the base moiety and the hydroxy groups in the sugar moiety in various isocytosine derivatives, which were prepared from anhydronucleosides and methanolic ammonia or methylamine in the same manner as Brown, *et al.*[6]

As shown in Chart 2, reaction of 2,2′–anhydro–1–(3′–deoxy–3′–ethylthio–β–D–arabinofuranosyl)uracil (VII),[5] and 2,2′–anhydro–1–β–D–arabinofuranosyluracil (IX) with methanolic ammonia or methylamine gave respectively 1–(3′–deoxy–3′–ethylthio–β–D–arabinofuranosyl)isocytosine (VIII), 1–β–D–arabinofuranosylisocytosine (X), and 2–N–methyl–1–β–D–arabinofuranosylisocytosine (XI). Moreover, in order to examine the influence of 3′–hydroxy group of up–configuration, 1–β–D–lyxofuranosylisocytosine (XVI) was synthesized from 2,2′–anhydro–1–(3′–O–tosyl–β–D–arabinofuranosyl)uracil (XII) *via* 1–(3′–O–tosyl–β–D–arabinofuranosyl)uracil (XIII) and 2,3′–anhydro–1–β–D–lyxofuranosyluracil (XIV). In this synthetic route, XIV was prepared by the method which Fox[7] had used for the synthesis of 2,3′–anhydronucleoside. Recent studies[8] demonstrated on the basis of both chemical and ultraviolet absorption spectral evidences, that the crystalline anhydronucleoside isolated from the reaction of 1–(3′,5′–di–O–mesyl–β–D–arabinofuranosyl)uracil in boiling water was 2,2′–anhydro–1–(5′–O–mesyl–β–D–lyxofuranosyl)uracil resulting by attack of the anionic 2′–hydroxy group on C–2 of 2,3′–anhydronucleoside. This report required a reexamination of the assigned structure of XIV.

The ultraviolet absorption spectra and *Rf* values of XIV agreed closely with those of 2,2′–anhydro–1–β–D–lyxofuranosyluracil (XV) prepared by an unambiguous route,[9] and the infrared spectra of XIV were completely identical with those of XV.[10] As a result, it appears

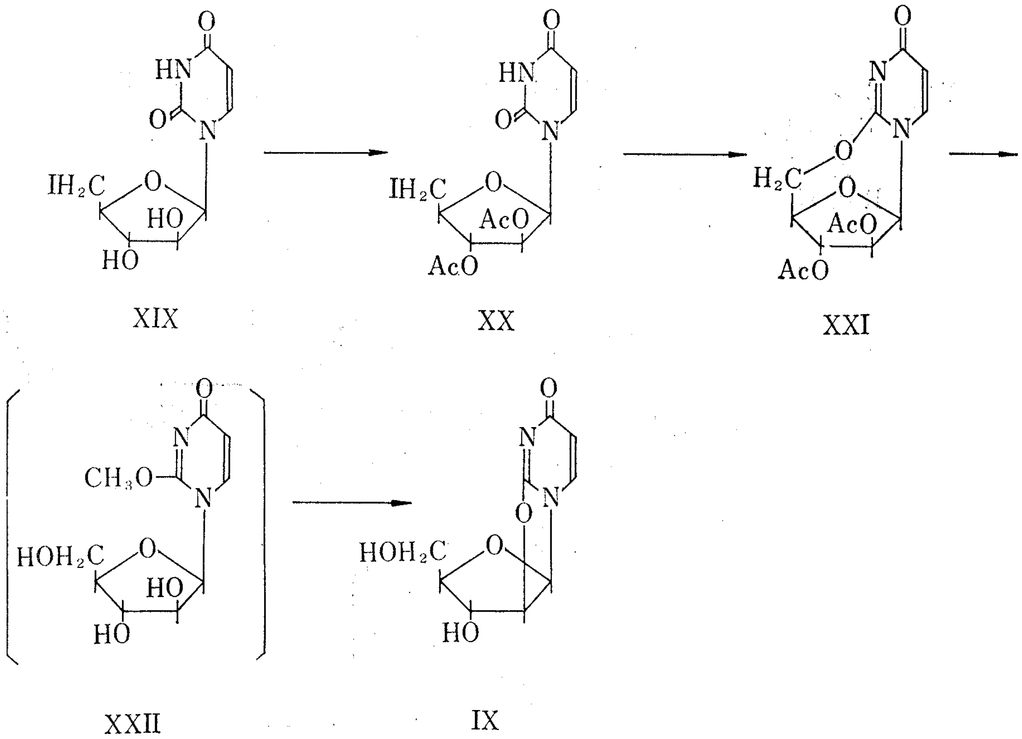

Chart 3

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[6] D.M. Brown, Sir A. Todd, and S. Varadarajan, *J. Chem. Soc.*, **1957**, 868.
[7] R. Fecher, J.F. Codington, and J.J. Fox, *J. Am. Chem. Soc.*, **83**, 1889 (1961).
[8] J.F. Codington, I.L. Doerr, and J.J. Fox, *J. Org. Chem.*, **30**, 476 (1965).
[9] N.C. Yung and J.J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).
[10] The author wishes to express his deep gratitude to Prof. Jack J. Fox of Sloan–Kettering Institute for his kind suggestion to determine the structure of XIV.

likely that the 2,3′-anhydro compound (XIV) was really formed, and subsequently rearranged to the 2,2′-anhydro lyxosylnucleoside (XV) by the attack of 2′-hydroxy group on C-2. Treatment of XV with methanolic ammonia gave 1-β-D-lyxofuranosylisocytosine (XVI).

The compounds (VIII), (X), (XI), (XVI), 1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-isocytosine (XVII),[6] and isocytidine (XVIII)[6] were tried to be deaminated. Then VIII, X, XI, and XVI were deaminated respectively to VII, IX and XV by heating for several minutes at 80° in glacial acetic acid, whereas XVII and XVIII were not deaminated under the same conditions. The compound (X and XI) were also deaminated directly at 180—200° in capillary tube. Consequently, it was concluded that the deamination required a chemical structures such as 2′-up-configurated hydroxy group or 2′,3′-epoxide ring in lyxo configuration. By the way, Brown[6] showed that IX melts at 234—236°, and X melts at almost same temperature, 235—236°, but the present paper demonstrated that X was converted into IX in the measurement of melting point.

Furthermore, demethoxylation of 2-O-methylpyrimidine nucleosides was examined. As shown in Chart 3, 1-(5′-deoxy-5′-iodo-β-D-arabinofuranosyl)uracil (XIX)[11] was acetylated by usual method to 1-(5′-deoxy-5′-iodo-2′,3′-di-O-acetyl-β-D-arabinofuranosyl)uracil (XX). In spite of repeated attempts, it was not possible to obtain XX in crystalline form, but the homogeneity of XX was confirmed by paper chromatography. According to Brown's procedure,[6] XX was treated with silver acetate in refluxing methanol, giving 2,5′-anhydro-1-(2′,3′-di-O-acetyl-β-D-arabinofuranosyl)uracil (XXI) in crystalline form. In treatment

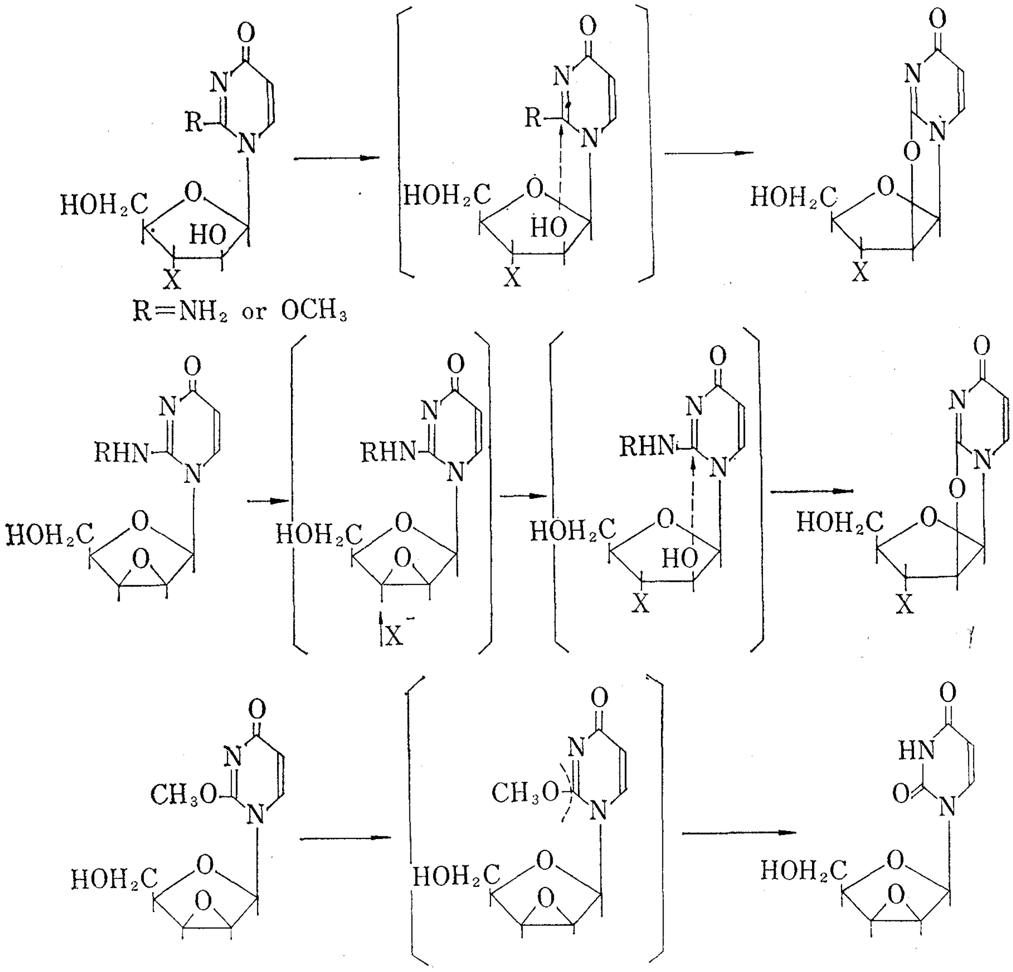

Chart 4

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[11] I.L. Doerr, J.F. Codington, and J.J. Fox, *J. Org. Chem.*, **30**, 467 (1965).

of XXI with triethylamine in methanol 2–O–methyl–1–β–D–arabinofuranosyluracil (XXII) was not obtained and in stead 2,2′–anhydrouridine (IX) was obtained as the sole product. This phenomenon showed that XXII is the intermediate which is demethoxylated to IX by the attack of 2′–hydroxy group of up–configuration to C–2 of the base moiety. In the case of the following compounds, 2–O–methyl–1–(2′,3′–epoxy–β–D–lyxofuranosyl)uracil (XXIII),12) 2–O–methyl–1–(2′,3′–O–isopropylidene–β–D–ribofuranosyl)uracil (XXIV),6) and 2–O–methyluridine (XXV)6) were not demethoxylated by heating at 80° in glacial acetic acid for several minutes.

The mechanism of the formation of anhydronucleosides by deamination or demethoxylation would be explained as shown in the following Chart 4; if these reactions had involved simple hydrolysis ($S_N1$), they would have occurred without regard to the configuration of 2′–hydroxy group of the sugar moiety. Since these reactions occurred only when 2′–hydroxy group was in up-configuration, these reactions involved attack by 2′–hydroxy group of up–configuration ($S_N2$). Recently, Fox, *et al.*8) reported independently that hydrolysis of 5′–O–mesyl– and 5′–iodo–arabinofuranosyluracil under slightly acidic conditions gave IX by attack of 2′–hydroxy group of up–configuration.

The fact that reaction of I and II with hydrochloric acid afforded anhydronucleoside (III), while treatment of XXIII with the same reagent gave 1–(2′,3′–epoxy–β–D–lyxofuranosyl)uracil1) instead of anhydronucleoside, showed that 2–methoxy group of the base moiety was less stable than 2–amino group, and that attack to 2–methoxy group by hydrogen chloride was faster than attack to the epoxide ring.

It was very interesting that the bridged oxygen of anhydronucleosides (VII), (IX), and (XV) was formed from 2′–hydroxy group of the sugar moiety, though the bridged oxygen of anhydronucleoside (VII) in previous papers resulted from 2–carbonyl group of the base moiety.

## Experimental12)

**2,2′-Anhydro-1-(3′-chloro-3′-deoxy-β-D-arabinofuranosyl)uracil (III) and 1-(3′-Chloro-3′-deoxy-β-D-arabinofuranosyl)uracil (IV)**——I (230 mg, 1 mmole) was dissolved in 5% HCl (1.2 ml, 1.5 mmoles) and the solution was heated at 80° for 2 hr. After concentration of the solvent *in vacuo*, the separated crystalline material was collected and recrystallization from MeOH to colorless prisms, mp 220—222° (decomp.), 100 mg (40%). $[\alpha]_D^{21}$ −8.5° ($c=0.47$, MeOH). *Rf*: 0.31 ($H_2O$–saturated methylethylketone (MEK)). UV $\lambda_{max}^{H_2O}$ m$\mu$ ($\varepsilon$): 223 (7400), 250 (6700). $\lambda_{min}^{H_2O}$ m$\mu$ ($\varepsilon$): 235 (5400). *Anal.* Calcd. for $C_9H_9O_4N_2Cl$: C, 44.17; H, 3.69; N, 11.45. Found: C, 44.44; H, 3.89; N, 11.44.

The mother liquor was chromatographed through a celite column and was eluted with $H_2O$–saturated MEK. Fractions showing a spot at *Rf* 0.66 (solvent: described above) were concentrated to dryness and the residue was crystallized from MeOH to yield 50 mg (19%) of IV, colorless needles, mp 159—160°. $[\alpha]_D^{22}$ +22.3° ($c=0.67$, $H_2O$). UV $\lambda_{max}^{MeOH}$ m$\mu$ ($\varepsilon$): 262 (8800). $\lambda_{min}^{MeOH}$ m$\mu$ ($\varepsilon$): 229 (1400). *Anal.* Calcd. for $C_9H_{11}O_5N_2Cl$: C, 41.41; H, 4.19; N, 10.67. Found: C, 41.06; H, 4.27; N, 10.63.

**1-(3′-Bromo-3′-deoxy-β-D-arabinofuranosyl)uracil (V)**——I (2.3 g, 10 mmols) was dissolved in 5% HBr (25 ml, 15 mmoles) and the solution was heated at 80° for 7 hr. After concentration of the solvent, the separated crystalline material was recrystallized from MeOH to colorless needles, mp 181—183° (decomp.), 660 mg (20%). On admixture of this compound with the authentic sample5) showed no depression.

**1-(2′,3′-Epoxy-β-D-lyxofuranosyl)isocytosine hydrochloride (VI)**——I (234 mg, 1 mmole) was dissolved in 0.1 N HCl (10 ml) and the solution was, after addition of EtOH, evaporated twice at 40°. Colorless leaflets, mp 145—147° (decomp.) were obtained in yield of 206 mg (79%). Beilstein test: positive. $[\alpha]_D^{22}$ +22.3° ($c=0.67$, $H_2O$). *Anal.* Calcd. for $C_9H_{12}O_4N_3Cl$: C, 41.39; H, 4.62; N, 16.06. Found: C, 41.67; H, 4.84; N, 15.67.

**2,2′-Anhydro-1-(3′-chloro-3′-deoxy-β-D-arabinofuranosyl)uracil (III)**——A) A small amount of VI was heated directly in a melting apparatus at 140° for about 10 min. Examination of the resulting substance by

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12) All melting points are uncorrected. Paper chromatography (ppc) was carried out on Toyo Roshi No. 51 filter paper.

ppc (solvent: $H_2O$–saturated MEK) showed one spot at *Rf* 0.36. UV spectrum of this substance was identical with III.

B) A small amount of VI was dissolved in DMF (2 ml) and the solution was heated at 100° for 7 hr. After evaporation of the solvent, the residual material was examined by ppc (same solvent). It showed one spot at *Rf* 0.36. UV spectrum of this material was identical with III.

**1-(3′-Deoxy-3′-ethylthio-β-D-arabinofuranosyl)isocytosine (VIII)**——VII (270 mg, 1 mmole) was dissolved in $NH_3$–saturated MeOH (30 ml) and the solution was allowed to stand at room temperature for 2 days. After evaporation of the solvent, the residue was dissolved in MeOH and after addition of acetone, the resulting solution was kept at room temperature overnight, during which crystallization occurred. Colorless prisms of VIII, mp 115—122°, were obtained in yield of 275 mg (96%). An analytical sample obtained by recrystallization from MeOH–acetone melted at 135—138°. $[\alpha]_D^{22}$ +99.1° ($c$=0.93, MeOH). UV $\lambda_{max}^{H_2O}$ m$\mu$ ($\varepsilon$): 256 (13600). $\lambda_{min}^{H_2O}$ m$\mu$ ($\varepsilon$): 248 (12700). *Anal.* Calcd. for $C_{11}H_{17}O_4N_3S$: C, 46.08; H, 5.97; N, 14.62; S, 11.16. Found: C, 45.71; H, 6.12; N, 14.56; S, 10.96.

**2,2′-Anhydro-1-(3′-deoxy-3′-ethylthio-β-D-arbinofuranosyl)uracil (VII)**——VIII (70 mg) was added to AcOH (1 ml) and the solution was heated at 80° for 5 min. After removal of the solvent *in vacuo*, the separeatd crystals were recrystallized from MeOH. Colorless needles of VII, mp 189—190°, were obtained in yield of 60 mg (90%). On admixture of this compound with the specimen described previously[5] showed no depression. UV spectra of these compounds were identical.

**2,2′-Anhydro-1-β-D-arabinofuranosyluracil (IX)**——A) X (60 mg) was dissolved in AcOH (2 ml) and the solution was heated at 80° for 5 min. After evaporation of the solvent, the residue was crystallized from MeOH to colorless needles, 50 mg (90%), mp 235—236°, undepressed on admixture with an authentic IX. UV spectra of these compounds were identical.

B) A samll amount of X was heated at 200° for several min, in melting apparatus. On admixture of crystals thus obtained with an authentic IX gave no depression.

**2-N-Methyl-1-β-D-arabinofuranosylisocytosine (XI)**——IX (2 g) was dissolved in 20% $CH_3NH_2$–EtOH solution and the solution was kept at room temperature for 40 hr. The solution was concentrated to dryness *in vacuo* and the residue was crystallized from MeOH to 1.85 g (84%) of XI, colorless needles. It decomposed at 180°. UV $\lambda_{max}^{H_2O}$ m$\mu$ ($\varepsilon$): 216 (19600), 254 (shoulder) (6200). *Anal.* Calcd. for $C_{10}H_{15}O_5N_3$: C, 46.69; H, 5.84; N, 16.34. Found: C, 46.50; H, 5.61; N, 15.52.

**2,2′-Anhydro-1-β-D-arabinofuranosyluracil (IX)**——A) A solution of XI (60 mg) in AcOH (2 ml) was heated at 80° for 5 min. After removal of the solvent, the separated crystals were recrystallized from MeOH. Colorless needles of IX, mp 237—238°, were obtained in yield of 50 mg (95%). A mixed mp with an authentic IX was 235—237°. UV spectra of these compounds were identical.

B) A small amount of IX was heated at 180—200° for several min in melting apparatus. On admixture of the crystals thus obtained with an authentic specimen gave no depression.

**1-(3′-O-Tosyl-β-D-arabinofuranosyl)uracil (XIII)**——XII (3.8 g, 10 mmoles) was dissolved in MeOH (80 ml) with slight warming and after cooling the solution, conc. HCl (5 ml) and $H_2O$ (15 ml) were added. After standing at room temperature for 4 days, the solution was neutralized with methanolic ammonia. The volume was reduced to 20 ml and this solution was allowed to stand at room temperature overnight. The separated white prisms of XIII, mp 150—156°, were collected. Yield, 2.3 g (57.7%). An analytical sample obtained by recrystallization from EtOH melted at 157—158°. $[\alpha]_D^{22}$ +68.8° ($c$=0.66, MeOH). UV $\lambda_{max}^{MeOH}$ m$\mu$ ($\varepsilon$): 225 (13800), 262 (6700). $\lambda_{min}^{MeOH}$ m$\mu$ ($\varepsilon$): 241 (4900). *Anal.* Calcd. for $C_{16}H_{18}O_8N_2S$: C, 48.20; H, 4.55; N, 7.03; S, 8.04. Found: C, 48.43; H, 4.61; N, 7.21; S, 8.00.

**2,2′-Anhydro-1-β-D-lyxofuranosyluracil (XV)**——A suspension of XIII (4 g, 10 mmoles) in $H_2O$ (2 liter) was heated on boiling water bath for several min with methyl red as an internal indicator. After cooling, the suspension was titrated with 1 N NaOH to pH 5 (methyl red). Heating was continued, and the evolved acid neutalized periodically until one equivalent of *p*–toluenesulfonic acid had been liberated in the reaction. This required about 6 hr. In order to remove Na tosylate, the solution thus obtained was passed through Amberite IRA–410 (OH–form) and Amberite IR–120 (H–form) columns, and the eluate was concentrated to dryness. The remaining crystalline material was recrystallized from MeOH to colorless pillars, mp 240—246°. Yield, 300 mg (14%). IR spectra of this compound were identical with those of an authentic 2,2′–anhydro–1–β–D–lyxofuranosyluracil.[9]

**1-β-D-Lyxofuranosylisocytosine (XVI)**——XV (100 mg) was dissolved in $NH_3$–saturated MeOH (5 ml) and the solution was heated at 80° for 2 hr. After cooling, it was concentrated to a syrup *in vacuo* and the syrup was crystallized from MeOH–EtOH to colorless fine prisms of XVI, mp 181—182°. Yield, 60 mg (56%). $[\alpha]_D^{22}$ +62.5° ($c$=0.67, $H_2O$). UV $\lambda_{max}^{H_2O}$ m$\mu$ ($\varepsilon$): 225 (shoulder) (14700), 256 (7700). $\lambda_{min}^{H_2O}$ m$\mu$ ($\varepsilon$): 247 (7400). *Anal.* Calcd. for $C_9H_{13}O_5N_3$: N, 17.27. Found: N, 16.80.

**2,2′-Anhydro-1-β-D-lyxofuranosyluracil (XV)**——XVI (30 mg) was dissolved in AcOH (1 ml) and the solution was heated at 80° for 5 min. After cooling, colorless needles, mp 243—244°, were separated out from the solution. Yield, 24 mg (85%). On admixture of this compound with an authentic sample described above showed no depression. IR and UV spectra of these substances were identical.

**Treatment of 1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)isocytosine (XVII) in AcOH**——A small amount of XVII was dissolved in AcOH and the solution was heated at 80° for 4 hr. XVII was not deaminated in this conditions.

**Treatment of Isocytidine (XVIII) in AcOH**———XVIII was treated as described above. Unchanged XVIII was recovered.

**2,5′-Anhydro-1-(2′,3′-di-O-acetyl-β-D-arabinofuranosyl)uracil (XXI)**——XIX[11] (500 mg) was suspended in $Ac_2O$ (5 ml) and pyridine (1 ml) and this suspension was kept at room temperature for 2 days. An yellowish solution thus obtained was, after addition of MeOH, evaporated to a syrup repeatedly. Examination of the syrup with ppc (solvent: *n*–BuOH: $H_2O$ (86:14)) showed a single spot at *Rf* 0.73. This material (XX) was used in the preparation of XXI, described below.

The above syrupy XX in MeOH (100 ml) was refluxed with AgOAc (1.4 g) for 30 min. Silver iodide began to separate as soon as the solution was brought to the boil. The hot solution was filtered and Ag ions were removed by $H_2S$. Concentration of the solution gave XXI, 260 mg (60% from XIX), which recrystallized from MeOH to colorless needles, melting at 245—246°. $[\alpha]_D^{23}$ $-55.2°$ ($c=0.72$, MeOH). UV $\lambda_{max}^{MeOH}$ m$\mu$ ($\varepsilon$): 236 (12600). $\lambda_{min}^{MeOH}$ m$\mu$ ($\varepsilon$): 213 (3700). *Anal.* Calcd. for $C_{13}H_{14}O_7N_2$: C, 50.32; H, 4.55; N, 9.04. Found: C, 50.38; H, 4.49; N, 8.96.

**2,2′-Anhydro-1-β-D-arabinofuranosyluracil (IX)**——To a solution of XXI (200 mg) in hot MeOH (80 ml) was added $Et_3N$ (6 ml), and the solution was kept at room temperature overnight. After evaporation to dryness, the residue was crystallized from MeOH to white needles, melting at 239—241° (decomp.). Yield, 110 mg (75%). On admixture of this compound with an authentic IX showed no depression. UV spectra of these two compounds were identical.

**Treatment of 2-O-methyl-1-(2′,3′-epoxy-β-D-lyxofuranosyl)uracil (XXIII) in AcOH**——A small amount of XXIII was dissolved in AcOH and the solution was heated at 80° for 10 min. Examination of this solution with ppc (solvent: $H_2O$–saturated MEK) showed a sole spot of XXIII.

**Treatment of 2-O-methyl-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)uracil (XXIV) and 2-O-methyluridine (XXV) in AcOH**——XXIV and XXV were treated as described above. Unchanged XXIV and XXV were recovered.

**Acknowledgement** The author wishes to express his deep gratitude to Prof. T. Ukita of the Faculty of Pharmaceutical Science, University of Tokyo, for reviewing this manuscript, and to the member of the Laboratory of Hygiene and Forensic Chemistry of the University for valuable discussions. He is indebted to Dr. T. Ishiguro, President, and Dr. M. Shimizu, Director of this Laboratory, for kind encouragement throughout the course of this work and for permission to publish this work, and to Dr. Takeo Naito, Head of Organic Chemistry Division of this Laboratory for kind guidance. Thanks are due to Mr. B. Kurihara and Miss E. Kosaka for elemental analyses.