Methyl Ether III: Recrystallized from $CHCl_3$–MeOH to give yellow needles, mp 179° (decomp.). *Anal.* Calcd. for $C_8H_9O_2N$; C, 63.56; H, 6.00; N, 9.27. Found: C, 63.77; H, 6.12; N, 9.19. λ_{max}^{MeOH} mμ (log ε): 257 (4.37), 372 (4.29). ν_{max}^{KBr} cm^{-1}: 3320, 3180, 1658, 1621, 1586, 1487, 1451, 1240, 1212, 1170, 987.

Bromination of II——Into a solution of II (33 mg) in EtOH (5 ml) cooled in an ice-bath, a solution of bromine (70 mg) in EtOH (3 ml) was added slowly. Colorless fine needles obtained by evaporation of the solvent were dissolved into H_2O and pH of the solution was adjusted to 7 with Na_2CO_3. The colorless needles which were separated out were filtered and washed with H_2O; 30 mg, mp 205—206°. *Anal.* Calcd. for $C_8H_8O_2NBr$; C, 41.74; H, 3.48; N, 6.09. Found: C, 41.51; H, 3.61; N, 5.86. λ_{max}^{MeOH} mμ (log ε): 274 (4.72), 322 (3.71). ν_{max}^{KBr} cm^{-1}: 3430, 3300, 3200, 1633, 1580, 1552, 1476, 1230, 800.

Bromination of III——A solution of bromine (40 mg) in EtOH (2 ml) was added dropwise to a solution of III (41 mg) in EtOH (3 ml) cooled in an ice-bath. After the reaction mixture was allowed to stand at room temperature for 1 hr, the crystals (50 mg) which were separated out were filtered and washed with EtOH. Recrystallization from EtOH gave yellow needles; mp 227—228° (decomp.). *Anal.* Calcd. for $C_8H_7O_2NBr_2$; C, 31.09; H, 2.27; N, 4.53. Found: C, 31.26; H, 2.24; N, 4.48. λ_{max}^{MeOH} mμ (log ε): 257 (4.26), 352 (3.88), 395 (4.13). ν_{max}^{KBr} cm^{-1}: 3450, 3270, 3100, 1626, 1612, 1565, 1475, 1450, 1374, 1232, 981, 742.

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A Convenient Synthesis of 1-β-D-Arabinofuranosylcytosine

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Cytosine arabinoside is effective as an antileukemic agent, and is otherwise also biologically active.[2] Therefore, the synthesis of this arabinoside seemed to be worthwhile and interesting. The purpose of this communication is to report, as a continuation of our studies of the synthesis of nucleosides, a convenient synthetic procedure for this nucleoside. Modification of the previously reported method[3] for the synthesis of the pyrimidine and purine nucleosides by using catalytic condensation reactions of acylated halogeno sugars with silyl purine and pyrimidine derivatives in organic solvents served as the basis of the synthesis.

In 1961, Goodman, *et al.*[4] successfully synthesized "Spongo" nucleosides of uracil derivatives, but did not attempt the preparation of arabinosyl cytosine (Ara-C). In their study, a 3-tosyl-D-xylofuranose derivative (II) was found suitable for synthesizing Ara-C. This together with the results of studies[3] described above, we started with the condensation of N^4-acetylcytosine (bistrimethylsilyl) (VI) with 5-O-carboethoxy-3-tosyl-2-acetylxylofuranosyl chloride (II).

Acetyl 5-O-carboethoxy-3-O-tosyl-2-O-acetyl-D-xylofuranoside (I)[4] was converted into the corresponding 1-chloroderivative (II) with hydrogen chloride in ether in the presence of acetyl chloride in the usual manner. This chloride (II) was allowed to react with bistrimethylsilyl-N^4-acetylcytosine (VI) in benzene for 12 hr at room temperature in the presence of mercuric bromide. After the solvent was removed by evaporation *in vacuo* to dryness, the

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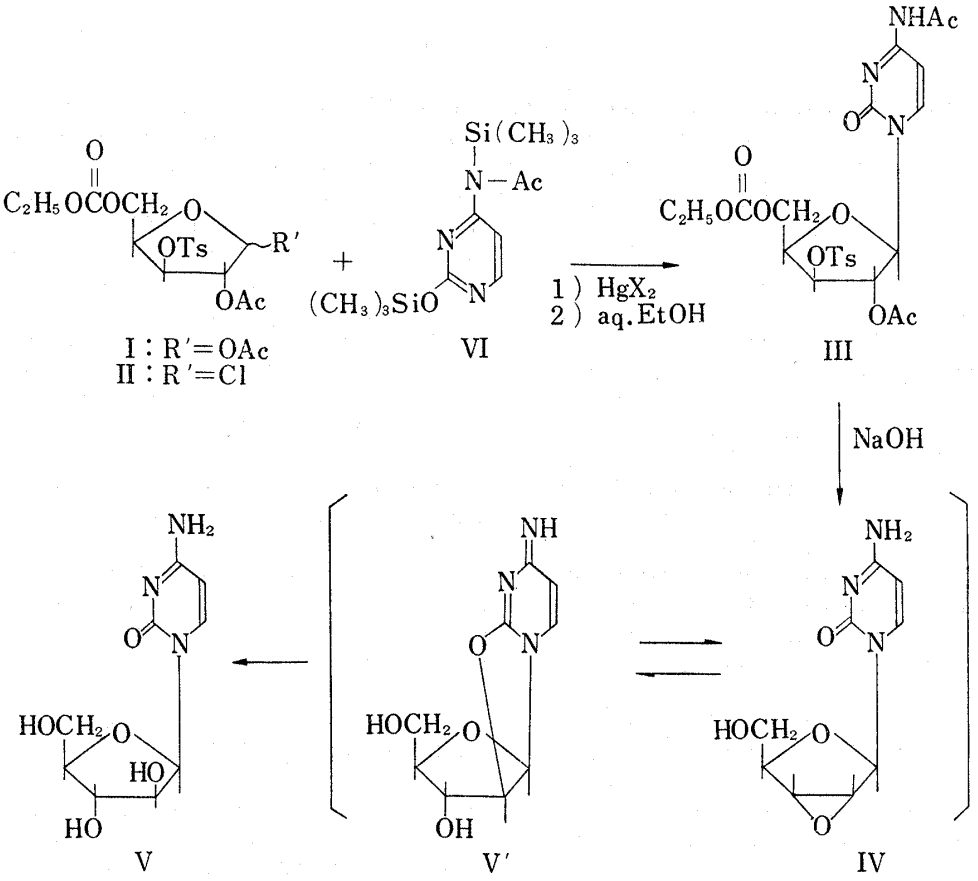

Chart 1

silyl group of the residue was removed with aqueous ethanol at room temperature to furnish the crude protected 1-β-D-xylofuranosylcytosine (III). The crude product was dissolved in chloroform and the solution was washed with 20% KI solution, water and dried over $MgSO_4$. The solvent was evaporated to dryness *in vacuo*. Chromatography of the residue on a silica gel column afforded pure 1-(5-O-carboethoxy-3-O-tosyl-2-O-acetyl-β-D-xylofuranosyl)-N^4-acetylcytosine (III), amorphous UV λ_{max}^{EtOH} mμ 227(sh) 248 and 297; λ_{min}^{EtOH} mμ 240 and 276, $[\alpha]_D^{20}$ −0.5 (C=4.0, $CHCl_3$) (Found: C, 49.56; H, 5.05; N, 7.60. $C_{23}H_{27}O_{11}N_3S$ requires C, 50.0; H, 4.93; N, 7.59), (92% yield). Deacylation of III was effected with sodium hydroxide to give the nucleoside (V), mp 213—214° $[\alpha]_D^{22}$ +146° (c=1.04, H_2O) UV $\lambda_{max}^{H_2O}$ mμ: (pH 2) 212, 278, (pH 12) 225 (infl), 272 (75% yield based on III) which was identical in its physical properties with an authentic sample[5] of 1-β-D-arabinofuranosylcytosine.

Chromatography of the alkali hydrolysate of III on silica gel afforded small amount of a cyclonucleosidelike compound (V′): λ_{max}^{EtOH} 231 mμ and 262 mμ.[6] This compound was readily converted into arabinosylcytosine (V) on treatment with alkali.

In view of this together with the study of Goodman, *et al.*,[4] it seemed reasonable to assume that III was converted into V *via* IV and V′. On the other hand, we observed that the intermediate (III) was also obtained in good yield by using the TMS fusion method,[7] direct method,[8] and $Hg(CN)_2$ method[9] for the condensation procedure instead of the method described above.

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Experimental

1,2-O-Isopropylidene-5-O-ethoxycarbonyl-D-xylofuranose (I′)——To a stirred solution of 1,2-O-isopropylidene-D-xylofuranose, which was prepared from 50 g of D-xylose by the method of Baker, *et al.*, in 184 ml of dry pyridine and 70 ml of dry $CHCl_3$ was added dropwise during a period of 1 hr 20 g of ethyl chloroformate at such a rate that the temperature was maintained at 0—5°. After being stirred for an additional 2 hr, the reaction mixture was kept at 0° overnight and poured into 800 ml of cold water with stirring. The product was extracted with $CHCl_3$ (140 ml×3). The combined extracts, washed with H_2O (200 ml×2) and dried with $MgSO_4$, were evaporated to dryness *in vacuo*. Recrystallization from 200 ml of 1:1 benzene–*n*-hexane gave 33.3 g (60%) of a product, mp 107—108°, which was suitable for the next step. $[\alpha]_D^{22}$ −12° (c=2.0, MeOH). *Anal.* Calcd. for $C_{11}H_{18}O_7$: C, 50.37; H, 6.92. Found: C, 50.10; H, 6.83.

1,2-O-Isopropylidene-5-O-ethoxycarbonyl-3-O-tosyl-D-xylofuranose (II′)——The compound (II′) was obtained from 16 g of I by the method of Baker, *et al.*[4] The crude product (II′) was crystallized from 70% EtOH giving crystals (18.59 g), mp 68—70°. $[\alpha]_D^{22}$ −11° (c=2.0, MeOH). *Anal.* Calcd. for $C_{18}H_{25}O_9S$: C, 51.78; H, 6.04. Found: C, 51.98; H, 5.79.

1,2-Di-O-Acetyl-5-O-ethoxycarbonyl-3-O-tosyl-D-xylofuranose (I)——Acetylation of 8.34 g of II′ with acetic anhydride according to the same procedure[4] before gave an 99% yield of a product as a colorless syrup suitable for the next step.

1-(5-O-Carboethoxy-3-O-tosyl-2-O-acetyl-β-D-xylofuranosyl)-N⁴-acetylcytosine (III)——A: To a solution of 2.76 g (6 mmoles) of I in 6.4 ml of AcCl was added 100 ml of saturated solution of HCl in dry ether at 0° and the solution was kept for 4 days at 0° in a cold room. The reaction mixture was evaporated *in vacuo* with protection from moisture and the residue was codistilled with 20 ml of anhydrous toluene *in vacuo* below 35°.

The azeotropic distillation with toluene was repeated until the syrup was completely free from acidic odor. The syrupy chloro sugar (II) thus obtained was dissolved in 35 ml of dry benzene and immediately used for the following condensation reaction.

To a solution of 2.14 g of bistrimethylsilyl-N⁴-acetylcytosine (VI) was added the benzene solution of chloro sugar (II) and 2.16 g of $HgBr_2$. After being kept at room temperature overnight, the mixture was extracted with $CHCl_3$ and the $CHCl_3$ solution was washed with 200 ml of 20% KI solution and water. After drying, the solution was evaporated *in vacuo* to leave a syrup. The syrup (3.4 g) was chromatographed on silica gel (50 g). The fraction eluted with benzene–$(CH_3)_2CO$ (9:1) gave protected nucleoside (III) 3.1 g (92% from II), amorphous, UV λ_{max}^{EtOH} mμ: 227 (sh), 248 and 297. λ_{min}^{EtOH} mμ: 240 and 276. $[\alpha]_D^{20}$ −0.5 (c=4.0, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{27}O_{11}N_3S$: C, 50.0; H, 4.93; N, 7.59. Found: C, 49.56; H, 5.05; N, 7.60.

1-β-D-Arabinofuranosylcytosine (V)——To a vigorous stirred solution of 3.31 g of III in 140 ml of MeOH and 26 ml of H_2O was added dropwise 7.12 ml of 1N NaOH during a period of 6 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was taken up in H_2O and applied to the top of a column packed with IRC resin (OH^- form), The column was washed with H_2O. The product was eluted with 50% MeOH. Fractions were checked on an UV spectrophotometer. UV absorbing fractions were collected and evaporated to dryness *in vacuo*. The residue was recrystallized from aq. EtOH giving 0.98 g of V in 75% yield based on III, mp 213—214° (corr.) $[\alpha]_D^{20}$ +146° (c=1.04, H_2O). UV $\lambda_{max}^{H_2O}$ mμ: (pH 2) 212, 278, (pH 12) 225 (infl), 272. V was identical in its physical properties with an authentic sample[5] of 1-β-D-arabinofuranosylcytosine.

B: A mixture of II (prepared from 2.76 g of I by the same method described above) 780 mg of $Hg(CN)_2$ and 1.5 g of anhydrous $CaSO_4$ was added to a solution of 450 mg of dry N⁴-acetylcytosine in 100 ml of CH_3NO_2 dried by azeotropic distillation. The mixture was refluxed for 20 hr with stirring. Crude III was isolated from reaction mixture in the manner described by Yamaoka, *et al.*[9] Chromatography of the crude IVon a silica gel column as described above afforded pure III, (amorphous) in a yield of 1.2 g (70%), which was identical in its physical properties with the sample synthesized by the method A.

C: A solution of II (6 mmol) and 918 mg of N⁴-acetylcytosine in 18 ml of CH_3CN was heated at 70° for 4 days with stirring.

The separation of crude III from reaction mixture was carried out by the procedure reported by Asai, *et al.*[8] Purification of crude III was carried out by the column chromatography as described above afforded III in a yield of 2.07 g (60%).

D: VI (357 mg) and II (1.2 mmol) were dissolved in 20 ml of dry benzene. After evaporation of the solvent, the residue was heated at 120° for 3 hr under reduced pressure (80—90 mmHg). The separation of crude III from the reaction mixture was carried out by the procedure reported by Nishimura, *et al.*[7] Chromatography of crude III afforded pure III in a yiled of 456 mg (80%).

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