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Studies on Nucleosides and Nucleotides. IX.[1] Nucleophilic Substitution of Secondary Sulfonyloxy Groups of Pyrimidine Nucleosides. II. Reaction of 2,2′-Anhydro-1-(3′-O-tosyl-β-D-arabinofuranosyl)uracil with Sodium Bromide, Sodium Ethanethiol, and Sodium Azide[2]

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Treatment of 2,2′-anhydro-1-(3′-O-tosyl-β-D-arabinofuranosyl)uracil (I) with sodium bromide, sodium ethanethiol, or sodium azide afforded 2,2′-anhydro-1-(3′-substituted-β-D-arabinofuranosyl)uracil (II), (III), or (IV). This result shows that 3′-tosyloxy group of I is displaced by above various nucleophiles without net inversion.

The preceding paper described the reaction of secondary tosyloxy groups of 2′-O-tosyluridine and 2′,3′-di-O-tosyluridine with alkali halides, and demonstrated that 2′-tosyloxy group was substituted with nucleophiles but 3′-tosyloxy group was not.

This paper deals with the reaction of 3′-tosyloxy group of 2,2′-anhydro-1-(3′-O-tosyl-β-D-arabinofuranosyl)uracil (I) with such nucleophiles as sodium bromide, sodium ethanethiol, and sodium azide.

Fox, *et al.*[4] converted 2,2′-anhydro-1-(5′-O-benzoyl-3′-O-mesyl-β-D-arabinofuranosyl)-uracil with sodium benzoate to 2,2′-anhydro-1-(3′,5′-di-O-benzoyl-β-D-arabinofuranosyl)-uracil and 1-(2′,3′,5′-tri-O-benzoyl-β-D-xylofuranosyl)uracil. In this reaction benzoyl group was introduced into both up and down configuration of 3′-position of the sugar moiety.

It is interesting to examine that the products obtained by treatment of I with sodium bromide, sodium ethanethiol, or sodium azide were in "arabino" or "lyxo" configuration.

The reaction of I with these reagents are shown in Chart 1. The reaction of I with sodium bromide in N,N-dimethylformamide (DMF) at 130° gave II, mp 223—225° (decomp.), the reaction of I with sodium ethanethiol in methanol at room temperature afforded III, mp 189—190°, and the treatment of I with sodium azide in DMF at 100° yielded IV, mp 177—179°. The structures of compounds (II), (III), and (IV) were established based on the following evidences. All of these compounds (II), (III), and (IV) exhibited the maxima in ultraviolet spectra at 221—224 and 250 mμ (twin maxima) and one shoulder at about 270 mμ which were in good agreement with the 2,2′-anhydronucleoside structure.[5] This fact suggested the possibility that the nucleophiles were introduced into position 3′. Treatment of II, III, and IV with dilute hydrochloric acid solution to cleave the anhydro bond gave V, mp 181—183° (decomp.), VI, mp 155—157°, and VII, mp 171—172° (decomp.), respectively, showing strong ultraviolet absorption maximum at about 260 mμ characteristic of aldopentofuranosyluracil. The reduction of V with Pd-carbonate and VI with Raney Ni catalyst, respectively, gave the deoxynucleoside (VIII), 1-(3′-deoxy-β-D-arabinofuranosyl)uracil,[6] mp 144—

1) Part VIII: *Chem. Pharm. Bull.* (Tokyo), **16**, 285 (1968).
2) Preliminary communication of this work appeared in *Chem. Pharm. Bull.* (Tokyo), **13**, 1258 (1965).
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
4) J.F. Codington, R. Fecher, and J.J.Fox, *J. Am. Chem. Soc.*, **82**, 2794 (1960).
5) N.C. Yung and J.J.Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).
6) During the preparation of this manuscript for publication, a report by J.P. Horwitz, J. Chua, M.A. DaRooge, M. Noel, and J.L. Klundt, *J. Org. Chem.*, **31**, 205 (1966), appeared in which they prepared VIII, mp 147—148°, from 1-(5′-O-benzoyl-3′-deoxy-3′-iodo-β-D-arabinofuranosyl)uracil by hydrogenolysis and following ester hydrolysis.

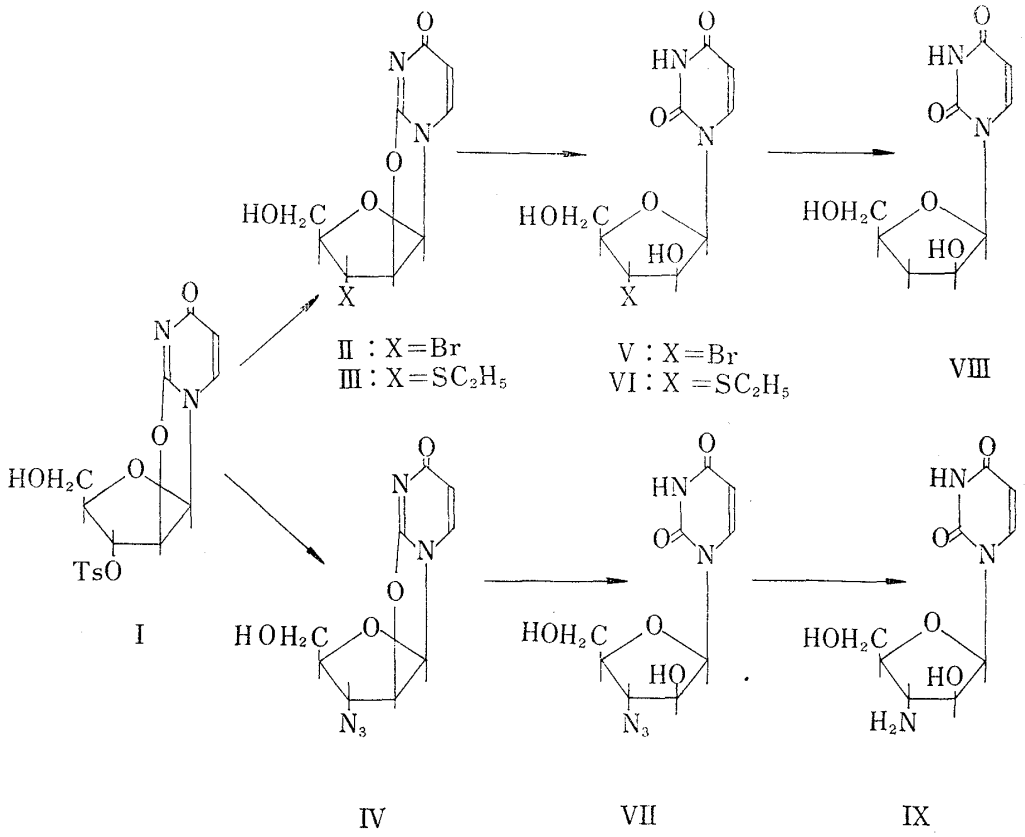

Chart 1

145°, which was negative in Dische-test (cystein-sulfuric acid). The reduction of VII over Pd-on-charcoal afforded IX, whose all physical properties were identical with those of 1-(3′-amino-3′-deoxy-β-D-arabinofuranosyl)uracil.[7] It is concluded that azido groups of IV and VII were in down configuration at 3′-position of the sugar moiety. It is also expected that bromine atom of II and V, and ethylthio groups of III and VI are in the same configuration as that of IV and VII.

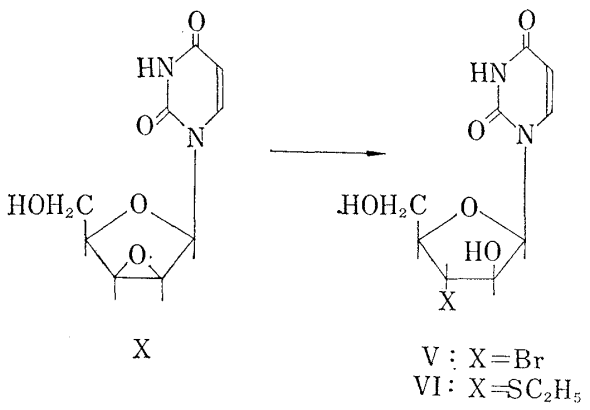

Chart 2

Alternative syntheses of V and VI were tried to establish these structures more rigidly (Chart 2). Previous studies[8-12] demonstrated that in the nucleophilic reactions of up-configurated 2,3-epoxide of sugar or nucleosides, nucleophiles were mainly introduced into down configuration at 3′-carbon atom through *trans* fission. As expected, reaction of X with hydrogen bromide in methanol at reflux temperature or with sodium ethanethiol in methanol at 70°, gave two ultraviolet absorbing spots on paper chromato-

7) J.F. Codington, R. Fecher, and J.J. Fox, *J. Org. Chem.*, **27**, 163 (1962).
8) J. Davoll, B. Lythgoe, and S. Tripett, *J. Chem. Soc.*, **1951**, 2230.
9) R. Allerton and W.G. Overent, *J. Chem. Soc.*, **1951**, 1480.
10) P.W. Kent, M. Stacey, and L.F. Wiggins, *J. Chem. Soc.*, **1949**, 1232.
11) S.P. James, F. Smith, M. Stacey, and L.F. Wiggins, *J. Chem. Soc.*, **1946**, 625.
12) C.D. Anderson, L. Goodman, and B.R. Baker, *J. Am. Chem. Soc.*, **81**, 898 (1959).

graphy in either case, and one of them was much stronger in ultraviolet absorption at 2536 Å (solvent: methylethylketone (MEK) saturated with water). The stronger absorbing spot was expected to be 3′–substituted–1–β–D–arabinofuranosyluracil. From respective reaction mixture 1–(3′–bromo–3′–deoxy–β–D–arabinofuranosyl)uracil, mp 181—183° (decomp.), or 1–(3′–deoxy–3′–ethylthio–β–D–arabinofuranosyl)uracil, mp 150—154°, was obtained. Melting points, infrared spectra, and *Rf*–values of the products prepared from X were identical with those of V and VI from I. It is thus established that bromine atoms of II and V, and ethylthio groups of III and VI were in down configuration and located at 3′–position.

Table I. Chemical Shifts and Coupling Constants of the Pyrimidine Nucleosides

Compound	Solvent	Chemical Shift (τ Value)		
		H6	H5	H_1'
2,2′–anhydro–1–(3′–azido–3′–deoxy–β–D–arabinofuranosyl)-uracil (IV)	DMSO	1.94	3.94	3.45 (J=6 cps)
1–(3′–bromo–3′–deoxy–β–D–arabinofuranosyl)uracil (V)	DMSO	2.35	4.45	3.90 (J=6 cps)
1–(3′–azido–3′–deoxy–β–D–arabinofuranosyl)uracil (VII)	DMSO	2.17	4.32	3.77 (J=6 cps)
1–(3′–amino–3′–deoxy–β–D–arabinofuranosyl)uracil (IX)	D_2O	1.77	3.86	3.54 (J=6 cps)

Nuclear magnetic resonance spectrum was determined on a J.N.H. 3H–60 spectrophotometer and tetramethylsilane was used as an internal reference.

Furthermore, in nuclear magnetic resonance spectra of IV, V, VII, and IX (Table I), all of these compounds showed the same value, about 6 cps, of coupling constant ($J_{1',2'}$) and this value was compatible with the assigned configuration of IV, V, VII, and IX.

From these results, in the reaction of I to II, III, or IV nucleophiles had replaced the 3′–tosyloxy group without net inversion.

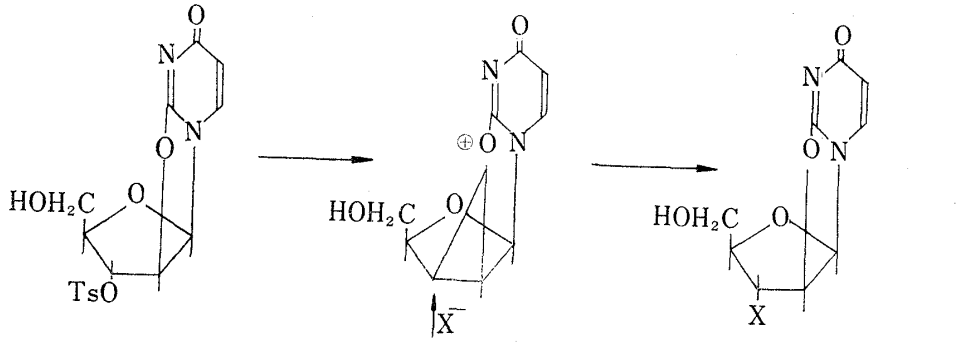

Chart 3

If nucleophilic reagents had attacked 3′–tosyloxy group without any anchimeric effects, the products would have been in lyxo configuration. A plausible mechanism for the formation of II, III, and IV, involved anchimeric assistance, as Fox[4] suggested (Chart 3). The bridged oxygen of I exerted an influence similar to that of a nucleophile upon 3′–carbon atom to form the transitory cyclic oxonium ion intermediate (XI), which was attacked at 3′ by nucleophiles to form II, III, and IV.

Experimental[13]

2,2′-Anhydro-1-(3′-bromo-3′-deoxy-β-D-arabinofuranosyl)uracil (II)——I (1.9 g, 5 mmoles) and dry NaBr (1.8 g, 18 mmoles) were dissolved in DMF (50 ml) and the solution was heated at 130° for 20 hr. The dark red solution was concentrated to dryness *in vacuo* and the residue was dissolved in acetone. The insoluble material was removed and the filtrate was chromatographed through a celite (100 g) column and was eluted with H_2O-saturated MEK. The fraction containing II (examined by UV rays) was evaporated under reduced pressure. Recrystallization from MeOH gave white needles, mp 223—225° (decomp.), in yield of 140 mg (10%). $[\alpha]_D^{20}$ −74.3° (c=0.66, MeOH). UV $\lambda_{max}^{H_2O}$ mμ (ε): 224 (10800), 250 (10800). $\lambda_{min}^{H_2O}$ mμ (ε): 234 (8800). *Anal.* Calcd. for $C_9H_9O_4N_2Br$: C, 37.38; H, 3.13; N, 9.69. Found: C, 37.70; H, 3.28; H, 9.99.

2,2′-Anhydro-1-(3′-deoxy-3′-ethylthio-β-D-arabinofuranosyl)uracil (III)——Fine powdered I (3.8 g, 10 mmoles), EtSH (1.86 g, 30 mmoles) and 1 N NaOMe (20 ml, 20 mmoles) were dissolved in MeOH (20 ml) and the solution was allowed to stand for 2 days at room temperature. The pale yellow solution was neutralized by bubbling of CO_2 and concentrated *in vacuo*. The residual solid was extracted with hot acetone (50 ml) repeatedly. After reducing the volume of the acetone extract to 40 ml and cooling, 1.4 g (52%) of colorless needles, mp 185—188°, were obtained. Recrystallization from acetone gave fine needles, mp 189—190°. $[\alpha]_D^{23}$ −106.9° (c=0.53, MeOH). UV $\lambda_{max}^{H_2O}$ mμ (ε): 223 (13200), 250 (12600). $\lambda_{min}^{H_2O}$ mμ (ε): 234 (10100). *Anal.* Calcd. for $C_{11}H_{14}O_4N_2S$: C, 48.95; H, 5.20; N, 10.38; S, 11.85. Found: C, 48.84; H, 5.44; N, 10.88; S, 11.81.

2,2′-Anhydro-1-(3′-azido-3′-deoxy-β-D-arabinofuranosyl)uracil (IV)——I (380 mg, 1 mmole) and dry NaN_3 (100 mg, 1.5 mmoles) were added to DMF (5 ml) and the mixture was heated at 100° for 5 hr. The yellow solution was concentrated to dryness *in vacuo* and the residue was extracted with acetone repeatedly. Concentration of the extract gave 125 mg (52%) of fine needles, mp 177—179°. $[\alpha]_D^{23}$ −177.4° (c=0.64, MeOH). UV $\lambda_{max}^{H_2O}$ mμ (ε): 221 (11900), 250 (11200). $\lambda_{min}^{H_2O}$ mμ (ε): 234 (9000). *Anal.* Calcd. for $C_9H_9O_4N_5$: C, 43.03; H, 3.61; N, 27.88. Found: C, 42.81; H, 3.75; N, 27.72.

1-(3′-Bromo-3′-deoxy-β-D-arabinofuranosyl)uracil (V) (A)——To a solution of X (2.5 g) in MeOH (150 ml), 48% HBr (12 g) was added and the solution was refluxed for 14 hr, then cooled. The insoluble material was removed and the filtrate was neutralized with methanolic ammonia. The solution was concentrated to a syrup which was chromatographed through a celite (100 g) column and was developed with H_2O-saturated MEK, and the eluate was evaporated to dryness. Recrystallization from EtOH gave colorless needles, mp 181—183° (decomp.), in yield of 600 mg (18%). $[\alpha]_D^{21.5}$ +89.4° (c=0.68, MeOH). UV $\lambda_{max}^{H_2O}$ mμ (ε): 262 (22100). $\lambda_{min}^{H_2O}$ mμ (ε): 231 (4300). *Anal.* Calcd. for $C_9H_{11}O_5N_2Br$: C, 35.18; H, 3.62; N, 9.17. Found: C, 35.28; H, 3.73; N, 9.52.

(B)——To a solution of II (90 mg) in MeOH (2 ml) was added 0.33N HCl (10 ml) and the solution was allowed to stand at room temperature for 2 days. After neutralizing with dil. NH_4OH, the solution was chromatographed through a cellulose powder column and was eluted with H_2O-saturated MEK. Concentration of the eluate gave needles, mp 181—183° (decomp.) were obtained in yield of 20 mg. The mixing melting point of this compound was not depressed on admixture with V prepared by method (A).

1-(3′-Deoxy-3′-ethylthio-β-D-arabinofuranosyl)uracil (VI) (A)——To a solution of EtSH (500 mg, 8 mmoles), 1N NaOMe (7 ml, 7 mmoles) in MeOH (3 ml), X (226 mg, 1 mmole) was added and the solution was heated at 70° in a sealed tube for 2.5 hr, then cooled. The solution was diluted with H_2O (10 ml) and it was chromatographed through a column of Amberite IRA-120 (H-form, 6 ml). The eluate was concentrated to a syrup (300 mg) which was dissolved in EtOH. After evaporation of EtOH solution, the residue was crystallized from acetone to V, colorless needles, mp 150—154°. Yield, 182 mg (63%). $[\alpha]_D^{21.5}$ +152.9° (c=0.66, MeOH). UV λ_{max}^{MeOH} mμ (ε): 263 (14700). λ_{min}^{MeOH} mμ (ε): 231 (2800). *Anal.* Calcd. for $C_{11}H_{16}O_5N_2S$: C, 45.89; H, 5.59; N, 9.72; S, 11.10. Found: C, 45.55; H, 5.72; N, 10.38; S, 11.13.

(B)——III (2 g) was suspended in 0.5N HCl (30 ml) and the suspension was kept at room temperature for 3 days with occasional shaking. In order to remove HCl, the solution was passed through a column of Amberite IRA-410 (OH-form, 15 ml), and the eluate was concentrated to about 7 ml, and the residue was allowed to stand at room temperature overnight, during which it was crystallized. The crystalline material was collected and washed with H_2O. Recrystallization from acetone gave 870 mg (40.6%) of colorless fine needles, mp 155—157°, undepressed on admixture with a sample prepared by method (A).

1-(3′-Azido-3′-deoxy-β-D-arabinofuranosyl)uracil (VII)——IV (2.4 g) was dissolved in 2% HCl (100 ml) and the solution was warmed at 80° for 30 min. After concentration of this solution, separated crystalline residue was recrystallized from MeOH-EtOH. Colorless needles of VII, mp 171—172° (decomp.) were obtained in yield of 2.2 g (81.5%). $[\alpha]_D^{23}$ +124.6° (c=0.81, MeOH). UV λ_{max}^{MeOH} mμ (ε): 262 (13500). λ_{min}^{MeOH} mμ (ε): 231 (3000). *Anal.* Calcd. for $C_9H_{11}O_5N_5$: C, 40.14; H, 4.09; N, 26.02. Found: C, 40.47; H, 4.31; N, 25.67.

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

1-(3′-Deoxy-β-D-arabinofuranosyl)uracil (VIII) (A)——V (1.2 g, 4 mmoles) in 50% MeOH (45 ml) was catalytically hydrogenated over 10% Pd–$CaCO_3$ (1.2 g) and hydrogen was absorbed in 10 min. After removal of catalyst and solvent, the residue was chromatographed through a celite (100 g) column and was eluted with H_2O–saturated MEK. The fraction having the UV absorption was collected. Recrystallization from EtOH, gave colorless fine needles, mp 144—145°. Yield 720 mg (81%). $[\alpha]_D^{21.5}$ +136.8° (c=0.62, MeOH). UV $\lambda_{max}^{H_2O}$ mμ (ε): 262 (8170). $\lambda_{min}^{H_2O}$ mμ (ε): 232 (1900). $\lambda_{max}^{0.1N\ HCl}$ mμ (ε): 264 (8100). $\lambda_{min}^{0.1N\ HCl}$ mμ (ε): 231 (1600). $\lambda_{max}^{0.1N\ NaOH}$ mμ (ε): 264 (6650). $\lambda_{min}^{0.1N\ NaOH}$ mμ (ε): 242 (3750). *Anal.* Calcd. for $C_9H_{12}O_5N_2$: C, 47.35; H, 5.29; N, 12.23. Found: C, 47.51; H, 5.43; N, 12.59.

(B)——To a solution of VI (567 mg, 2 mmoles) in 75% EtOH (30 ml), Raney–Ni (W–7, 8 ml) was added and was refluxed for 2 hr. After removal of catalyst and solvent, the residue was purified through a cellulose powder column to remove VI, and was developed with H_2O–saturated MEK. The fraction containing VIII was concentrated to a syrup and it was dissloved in EtOH (5 ml) and the solution was kept at room temperature overnight. The separated uracil (9 mg) was removed and the residue was concentrated to dryness. Recrystallization from acetone to yield 85 mg (18.6%) of colorless needles, mp 143—145°, undepressed on admixture with a sample obtained by method (A). IR spectra of these samples were identical.

1-(3′-Amino-3′-deoxy-β-D-arabinofuranosyl)uracil (IX)——VII (4.5 g, 16 mmoles) in warm MeOH (100 ml) was catalytically hydrogenated over 40% Pd–C (1.3 g) and hydrogen uptake ceased after 1hr. After removal of catalyst and solvent, the residue was crystallized from MeOH. Colorless needles of IX, mp 202—208° (decomp.), were obtained in yield of 3.18 g (81%). An analytical sample obtained by recrystallization from MeOH melted at 214—216° (decomp.). *Anal.* Calcd. for $C_9H_{13}O_5N_3$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.06; H, 5.46; N, 17.32.

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