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Studies on Nucleosides and Nucleotides. VIII.[1] Nucleophilic Substitution of Secondary Sulfonyloxy Groups of Pyrimidine Nucleosides. (1)[2]

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Treatment of 2′–O–tosyl–5′–O–trityluridine (I), 2′–O–tosyluridine (II), or 2′,3′–di–O–tosyluridine (XI) with various alkali chlorides or bromides afforded only 2′–halogenonucleosides, whereas in the reaction of alkali iodides with I or II were isolated 2,2′–anhydronucleosides accompanied with 2′–deoxy–2′–iodouridine derivatives. And in the reaction of XI with sodium iodide in DMF only 2,2′–anhydro–1–(3′–O–tosyl–β–D–arabinofuranosyl)–uracil (XIII) was obtained.

In recent years, nucleophilic substitution reaction of secondary sulfonyloxy groups of pyrimidine nucleosides has been investigated by several workers.[4–10]

The present series deals with the behavior of some sulfonylated derivatives of uridine toward nucleophilic reagents, such as alkali halides, sodium ethanethiol, sodium azide, and methanolic ammonia.

This paper describes the reaction of 2′–O–tosyluridine derivatives or 2′,3′–di–O–tosyluridine with alkali halides.

Brown, *et al.*[5] reported that in the reaction of 5′–O–acetyl–2′–O–tosyluridine with sodium iodide in acetonylacetone 5′–O–acetyl–2′–deoxy–2′–iodouridine was obtained, and assumed that this nucleophilic substitution proceeded through 2,2′–anhydrouridine derivative and therefore, iodine atom in 2′–position was in down–form. Furthermore, they[6] prepared 5′–O–acetyl–2′–deoxy–2′–iodouridine by treatment of 5′–O–acetyl–2,2′–anhydrouridine with sodium iodide in the presence of glacial acetic acid and identified this compound with the afore–mentioned 2′–deoxy–2′–iodouridine derivative. On the other hand, Fox, *et al.*[11] synthesized 2′–deoxy–2′–halogenouridines from 2,2′–anhydrouridine and hydrogen halides by alkyl–oxygen fission of the anhydro bond. Thus, it was assumed generally that in the reaction of pyrimidine nucleoside having 2′–sulfonyloxy group of down configuration with alkali halide, 2,2′–anhydronucleoside is formed first by rearward attack of the carbonyl group in the pyrimidine moiety and next the anhydronucleoside thus formed is cleaved to 2′–deoxy–2′–halogenopyrimidine nucleoside. However, in the reaction sequence 2,2′–anhydronucleoside was not isolated yet.

As shown in Chart 1, substitution reaction of 2′–O–tosyl–5′–O–trityluridine (I) with various alkali metal, alkali earth metal, and ammonium salts of hydrogen chloride or hydrogen

1) Part VII: *Chem. Pharm. Bull.* (Tokyo), **12**, 951 (1964).
2) Preliminary communication of this work appeared in *Chem. Pharm. Bull.* (Tokyo), **13**, 1258 (1965).
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5) D.M. Brown, D.B. Parihar, C.B. Reese, and A.R. Todd, *J. Chem. Soc.*, **1958**, 3035.
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9) J.P. Horwitz, J. Chua, and M. Noel, *J. Org. Chem.*, **29**, 2076 (1964).
10) K.F. Pfitzer and J.G. Moffatt, *J. Org. Chem.*, **29**, 1508 (1964).
11) J.F. Codington, I. Doerr, D.V. Praag, A. Bendich, and J.J. Fox, *J. Am. Chem. Soc.*, **83**, 5030 (1961).

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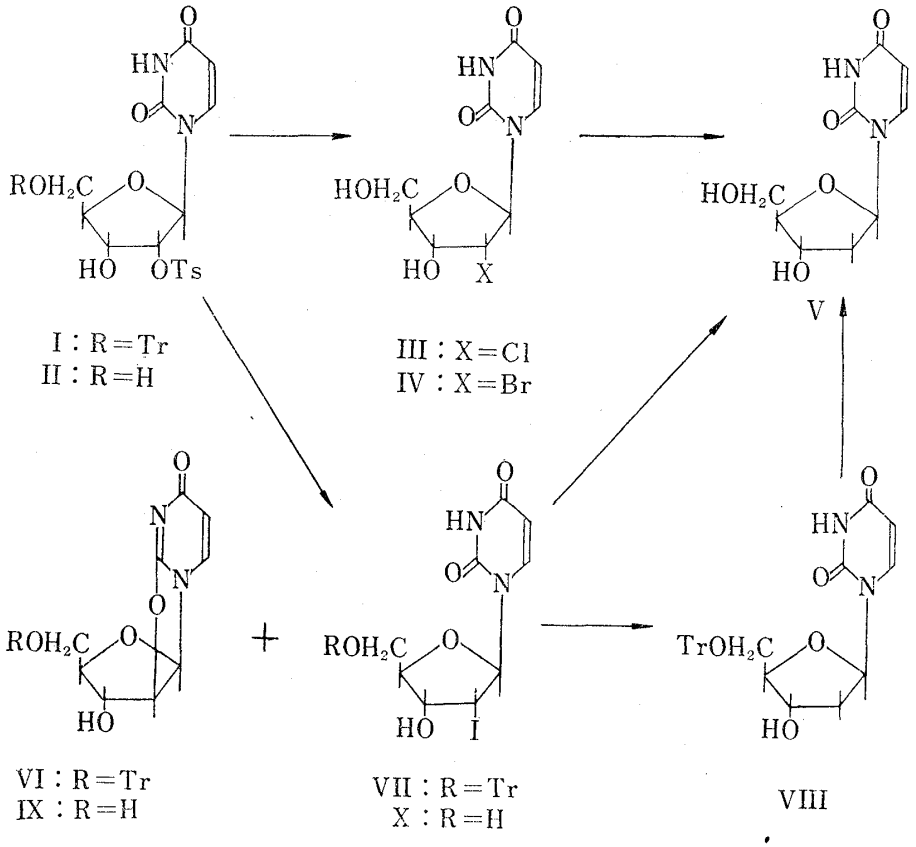

Tr=Trityl-, Ts=*p*-Toluenesulfonyl-

Chart 1

bromide, at100° for three to six hours in dimethylformamide (DMF) or acetone, was accompanied by detritylation and 2′-deoxy-2′-halogenouridine, *i.e.* 2′-chloro-2′-deoxyuridine (III) or 2′-bromo-2′-deoxyuridine (IV) in fairly good yield (Table I). The structures of compounds (III and IV) were confirmed by comparison with the authentic samples of III and IV prepared from 2,2′-anhydrouridine and hydrogen halides by the method of Fox, *et al.*,[11] and IV was easily converted into 2′-deoxyuridine (V) by hydrogenation in 50% alcohol over a palladium-carbonate catalyst. But in the case of I with sodium iodide in acetonylacetone at 85—95° for two and a half hours,2,2′-anhydro-1-(5′-O-trityl-β-D-arabinofuranosyl)uracil (VI) and 2′-deoxy-2′-iodo-5′-O-trityluridine (VII) were obtained. The compound (VII) had not

Table I. Reactions of 2′-O-Tosyluridines (I), (II) with Various Halides

Compound	Reagent	Solvent	Temp. (°C)	Time (hr)	Product	Yield
I	LiCl	DMF	100	6	III	83
I	LiBr	Me_2CO	100	3	IV	73
I	NaBr	DMF	100	5	IV	94
I	$CaBr_2$	DMF	100	6	IV	39
I	NH_4Br	DMF	100	4	IV	66
I	NaI	Acetonylacetone	85—95	2.5	VI (syrup)	67
					VII	29
I	NaI	Acetonylacetone	100	4	X[a] (syrup)	48
I	LiI	Me_2CO	100	3	X[a] (syrup)	50
I	KI	DMF	100	4	X[a] (syrup)	45
II	NaBr	DMF	90	7	IV	72
II	NaI	DMF	95	3	X[a] (cryst)	22

a) Existence of IX was examined by paper chromatography (solvent: H_2O-saturated MEK).

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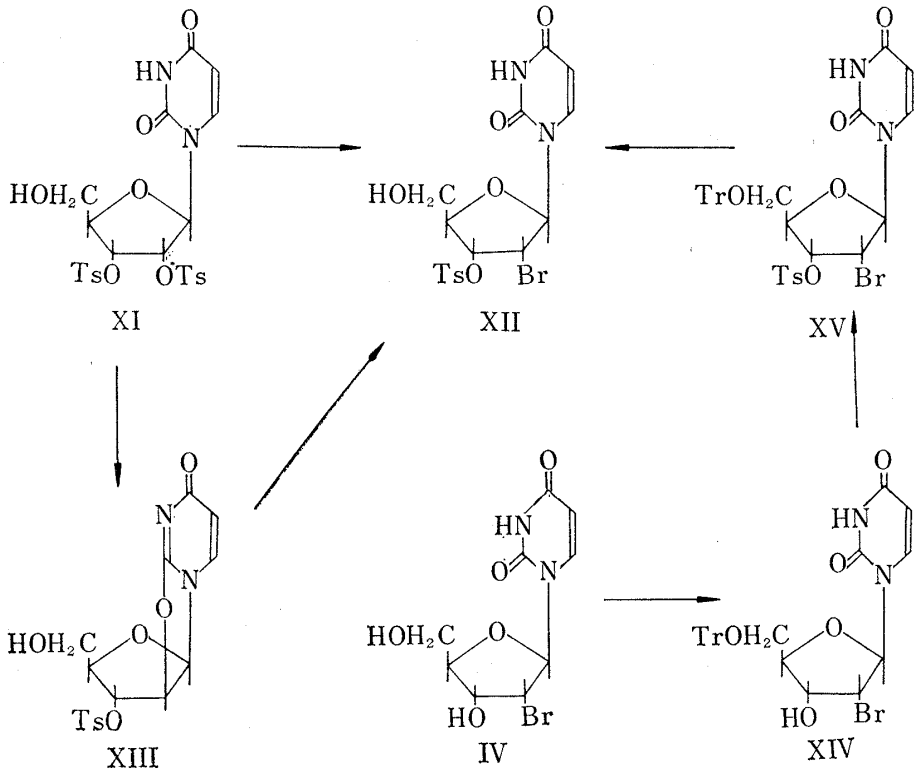
been crystallized yet, so it was reduced over a palladium catalyst to 2′–deoxy–5′–O–trityluridine (VIII), which was identified with an authentic sample prepared by tritylation of 2′–deoxyuridine, according to a reported procedure.[10] On the other hand, reaction of I with alkali iodide at 100° for three to four hours gave 2,2′–anhydro–1–β–D–arabinofuranosyluracil (IX) and 2′–deoxy–2′–iodouridine (syrup) (X). Hydrogenation of X also gave V. It was very interesting that 2,2′–anhydronucleoside derivatives (VI) and (IX) which had been assumed to be the intermediates of the reaction, were isolated from reaction mixture only when alkali iodide was used as alkali halide. The anhydronucleoside (VI) was also obtained from various reaction mixtures of I and sodium iodide (see Table II).

Table II. Anhydronucleoside (VI) Formation in Various Conditions from I

Reagent NaI (mol)	Solvent	Temp. (°C)	Time (hr)	Yield of VI (%)
2	Acetonylacetone	90—95	0.5	15
2	Acetonylacetone	90	2	19.5
2	Acetylacetone	90—95	3	23.5
2	DMF	90—95	3	15
2	*iso*–BuOH	90—95	3	5
2	Methyl cyanide	90—95	3	8

The same reaction was applied to 2′–O–tosyluridine (II). The compound (I) was difficult to obtain in pure crystalline form in good yield as indicated by Fox, *et al.*,[12] but pure crystalline II, mp 175—177° (decomp.), was easily derived from raw material of I by the cleavage of



Ts=*p*–Toluenesulfonyl–

Chart 2

12) J.F. Codington, I.L. Doerr, and J.J. Fox, *J. Org. Chem.*, **29**, 558 (1964).

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trityl group. In the reaction of II with alkali bromide, IV was obtained in similar yield as in the case of I. Treatment of II with alkali iodide also gave the 2,2′-anhydrouridine (IX) and 2′-deoxy-2′-iodouridine (X). In this experiment by use of silica gel column chromatography, X was obtained as crystalline form.

In order to extend this interesting reaction further, 2′,3′-di-O-tosyluridine (XI) was chosen as a starting material (Chart 2). Levene[13] reported that the reaction of XI with sodium iodide in acetone at 100° did not give substitution product. Treatment of XI with sodium bromide in DMF at 115° for four hours gave XII, mp 164—165°, by using a celite column chromatography (solvent: chloroform saturated formamide). But in the case of sodium iodide as a nucleophile under the same conditions, only XIII, mp 204—206° (decomp.), was obtained as crystalline form in poor yied by means of column chromatography. XIII gave negative halogeno test and showed two maxima at 227 and 245—252 mμ in ultraviolet absorption characteristic of 2,2′-anhydronucleoside. The structures of these compounds (XII and XIII) were established as follows. Compound (XIII) was identical with 2,2′-anhydro-1-(3′-O-tosyl-β-D-arabinofuranosyl)uracil prepared from the reaction of XI with one equivalent of sodium hydroxide solution, and XIII was converted into XII by treatment of XIII with *p*-toluenesulfonic acid and sodium bromide in DMF. Therefore, XIII was considered as the intermediate in this nucleophilic reaction of XI with sodium bromide. Then the structure of XII was confirmed by synthesis from IV by the treatment with tritylchloride in anhydrous pyridine by the usual method. 2′-Bromo-2′-deoxy-5′-O-trityluridine (XIV), mp 162—163°, thus obtained was tosylated in pyridine to 2′-bromo-2′-deoxy-3′-O-tosyl-5′-O-trityluridine (XV), an amorphous powder. The compound (XV), without further purification, was detritylated to 2′-bromo-2′-deoxy-3′-O-tosyluridine (XII) by alcoholic hydrogen chloride. The melting point of XII obtained from IV was not depressed on admixture with XII prepared from XI and sodium bromide, and the infrared spectra of the two substances were identical. Therefore, it may be concluded from the results of this investigation that in the nucleophilic substitution of XI with alkali halides, reaction proceeded through 2,2′-anhydronucleoside (XIII) as in the case of I and II, and that sulfonyloxy group of 3′-position was rather inactive than 2′-sulfonyloxy group. This conclusion was in accordance with that of Brown, *et al.*[14] and Yung and Fox.[15]

Reaction of I, II, or XI with alkali chlorides or bromides gave III, IV, or XII, respectively, and 2,2′-anhydronucleosides were not obtained. On the other hand, the formation of 2,2′-anhydronucleosides (VI), (IX), or (XIII) was observed only in the case of alkali iodides as nucleophile. The reasons for occurrence of anhydronucleosides are assumed that hydrogen iodide liberated in the reaction mixture has less reactivity[6] toward anhydronucleosides than other hydrogen halides, and it is easily oxidized to iodine, as a result failed to give 2′-deoxy-2′-iodouridine derivatives.

Experimental[16]

2′-O-Tosyluridine (II)——To a solution of I (5 g, 7.8 mmoles) in acetone (20 ml) was added 5N HCl (2 ml) and refluxed for 4 hr, and the solution was concentrated *in vacuo*. The separated crystals were washed with benzene and recrystallization from EtOH gave white needles, mp 175—177° (decomp.). Yield, 2.61 g (83%). $[\alpha]_D^{23}$ −32.1° (c=0.65, MeOH). UV λ_{max}^{EtOH} mμ (ε): 225—226 (12200), 262 (7450). λ_{min}^{EtOH} mμ (ε): 216 (11500), 243 (4700). *Anal.* Calcd. for $C_{16}H_{18}O_8N_2S$: C, 48.23; H, 4.59; N, 7.04; S, 8.05. Found: C, 48.50; H, 4.69; N, 6.94; S, 7.63.

13) P.A. Levene and R.S. Tipson, *J. Biol. Chem.*, **105**, 419 (1934).
14) D.M. Brown, D.B. Parihar, Sir A. Todd, and S. Varadarajan, *J. Chem. Soc.*, **1958**, 3028.
15) N.C. Yung and J.J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).
16) All melting points are uncorrected and paper chromatography (ppc) was carried out on Toyo Roshi No. 51 filter paper.

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2′-Bromo-2′-deoxyuridine (IV) (A)——A solution of I (3.2 g, 5 mmoles) and dry NaBr (1.03 g, 10 mmoles) in DMF (30 ml) was heated in a sealed tube for 4 hr at 100°. The yellowish solution was concentrated *in vacuo* and the resulting syrup was diluted with acetone (20 ml) and filtered off from Na tosylate. The filtrate was concentrated again *in vacuo* and the remaining syrup was shaken in a mixture of H_2O (3 ml) and benzene (20 ml), following to crystallize. These crystals, when allowed to stand at room temperature overnight, deposited 1.26 g (84%) of IV, mp 183—186° (decomp.). Recrystallization from EtOH gave white needles, mp 186—190° (decomp.), showed no depression on admixture with the substance synthesized by Fox.[11]

(B)——A solution of II (3.98 g, 10 mmoles) and NaBr (2.06 g, 20 mmoles) in DMF (30 ml) was heated in a sealed tube for 7 hr at 90°. IV, white needles, mp 186—190° (decomp.), were obtained in yield of 2.2 g (72%) by the procedure as described above.

2′-Deoxy-2′-iodo-5′-O-trityluridine (VII) and 2,2′-Anhydro-1-(5′-O-trityl-β-D-arabinofuranosyl)uracil (VI)——I (12.8 g, 20 mmoles) and dry NaI (9 g, 60 mmoles) were dissolved in freshly distilled acetonylacetone (120 ml) and the solution was heated for 2.5 hr at 85—95°. The insoluble Na tosylate was removed and washed with acetone. Filtrate and washing were evaporated to syrup *in vacuo*. The residual syrup was treated with H_2O (20 ml) and AcOEt (100 ml), and AcOEt layer was washed with 20% $Na_2S_2O_3$ (10 ml), and water, and evaporated again to syrup *in vacuo*. The syrup was diluted with acetone (40 ml) whereupon crystallization occurred. White leaflets of VI, mp 205—208°(decomp.) were obtained in yield of 2.7 g (29%). No depression in melting point was observed on admixture with an authentic sample prepared by Fox.[11] Concentration of the mother liquor gave 8 g of raw VII, as a syrup.

2′-Deoxy-5′-O-trityluridine (VIII)——To a solution of VII (8 g) described above in 80% EtOH (150 ml) was added 2.3 ml of 10% NH_4OH and the solution was hydrogenated over 10% Pd–$CaCO_3$ (4 g) at room temperature and pressure. Reaction was completed in 30 min, after removal of catalyst and solvent, the residue was dissolved in MeOH and poured into cold water with stirring. White powder thus precipitated was allowed to stand at room temperature overnight, and filtered. This powder was dissolved in EtOH whereupon crystallization occurred. Recrystallization from EtOH gave 2.8 g (44%) of VIII, white prisms, mp 189—192°. Then recrystallization from benzene, gave white prisms, mp 203—204°, showed no depression on admixture with the substance synthesized by Moffatt.[10]

2′-Deoxy-2′-iodouridine (X)——II (3.98 g) and NaI (3.0 g) were dissolved in DMF (30 ml) and the solution was heated in a sealed tube for 3 hr at 95°. The red solution was concentrated *in vacuo* and the resulting syrup was dissolved in acetone (20 ml) and filtered off from Na tosylate. The filtrate was chromatographed through a silica gel column, and was developed with acetone–AcOEt (9:1). The fractions containing X (examined by UV rays) were evaporated *in vacuo* to yield colorless needles. Recrystallization from MeOH–AcOEt gave X, fine needles, mp 145—147° (decomp.), in yield of 740 mg (22%). $[\alpha]_D^{22}$ +27.1° (c=0.66, H_2O). UV $\lambda_{max}^{H_2O}$ mμ (ε): 260 (11000). $\lambda_{min}^{H_2O}$ mμ (ε): 230 (3200). $\lambda_{max}^{0.1\,N\ HCl}$ mμ (ε): 260 (11000). $\lambda_{min}^{0.1\,N\ HCl}$ mμ (ε): 230 (3200). *Anal.* Calcd. for $C_9H_{11}O_5N_2I$: C, 30.50; H, 3.11; N, 7.92; I, 35.86. Found: C, 31.01; H, 3.41; N, 8.06; I, 35.43.

2′-Deoxyuridine (V)——IV (1.54 g, 5 mmoles) was dissolved in 50% EtOH (40 ml), 10% NH_4OH (0.85 g) added several times to keep pH 9, and the solution was hydrogenated over 10% Pd–$CaCO_3$ (1 g). Uptake of hydrogen (120 ml) was completed in 30 min. After removal of catalyst and solvent, the residual syrup was dissolved in H_2O (50 ml). The solution was chromatographed through a column of Amberite IRA-410 (OH-form, 30 ml), and was eluted with 10% AcOH (20 ml) and 0.5N AcOH (200 ml). Evaporation of the eluates gave a syrup which was crystallized from EtOH to colorless needles of V, 980 mg (85.5%), mp 158—162°, undepressed on admixture with an authentic sample.[5]

2,2′-Anhydro-1-(3′-O-tosyl-β-D-arabinofuranosyl)uracil (XIII) (A)——A hot solution of XI (11 g, 20 mmoles) in 1.1 liter of 50% EtOH was cooled to 50—55° and 1N NaOH was added quickly with stirring. The volume reduced to about 400 ml *in vacuo* and separated colorless needles were collected. Recrystallization from EtOH gave 5.3 g (70%) of XIII, mp 204—206° (decomp.). $[\alpha]_D^{24}$ −84.6° (c=0.69, MeOH). UV λ_{max}^{MeOH} mμ (ε): 227 (20300), 245—252 (shoulder) (8200). *Anal.* Calcd. for $C_{16}H_{16}O_7N_2S$: C, 50.52; H, 4.24; N, 7.36. Found: C, 50.57; H, 4.31; N, 7.62.

(B)——XI (2.8 g, 5 mmoles) and NaI (2.2 g, 15 mmoles) were dissolved in DMF (50 ml) and the solution was heated for 4 hr at 115°. After decolorization by $Na_2S_2O_3$ solution, the solution was concentrated *in vacuo*, and the remaining syrup was diluted with acetone and the insoluble material was removed. Concentration of the mother liquor gave light brown syrup and which was chromatographed through a celite(70 g)column, and was developed with methylethylketone (MEK) saturated with H_2O. The fractions showing UV absorption were evaporated *in vacuo*, and then the residue was re-chromatographed through a celite (50 g) column, and was eluted with $CHCl_3$ saturated with $HCONH_2$. Each fraction was examined by ppc (solvent: $HCONH_2$–saturated $CHCl_3$). Fractions showing a single spot at Rf 0.12, were evaporated to syrup *in vacuo*. The syrup was diluted with H_2O and was allowed to stand overnight. Colorless needles were recrystallized from EtOH to give 200 mg (12%) of XIII, mp 204—206° (decomp.), unchanged on admixture with XIII prepared by the procedure as described above. IR spectra of two substances were identical.

1-(2′-Bromo-2′-deoxy-3′-O-tosyl-β-D-ribofuranosyl)uracil (XII) (A)——XI (2.77 g, 5 mmoles) and NaBr (1.5 g, 15 mmoles) were dissolved in DMF (25 ml) and the solution was heated for 4 hr at 115° in a sealed

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tube. The tan-colored solution was evaporated to dryness *in vacuo* and the residue was dissolved in acetone (20 ml). Na tosylate (0.9 g, 90%) was removed and the mother liquor was reduced to about 10 ml, then poured into 500 ml of cold H_2O with stirring and allowed to stand overnight. The pale yellow powder was collected and washed with H_2O (2 g). It was chromatographed through a celite column (100 g, impregnated with $CHCl_3$–saturated $HCONH_2$) and was eluted with $HCONH_2$–saturated $CHCl_3$, and fractions of each 20 ml were collected. Fractions No. 50—65 were treated as above described to obtain an amorphous solid. Recrystallization from MeOH gave 940 mg (40.5%) of XII, colorless needles, mp 164—165°. $[\alpha]_D^{20}$ −74.3° (c=0.66, MeOH). UV λ_{max}^{MeOH} mμ (ε): 228 (18000), 258 (12600). λ_{min}^{MeOH} mμ (ε): 215 (14100), 241 (8300). *Anal.* Calcd. for $C_{16}H_{17}O_7N_2BrS$: C, 41.72; H, 3.68; N, 6.08; S, 6.96; Br, 17.35. Found: C, 41.66; H, 3.74; N, 5.92; S, 6.46; Br, 17.65.

(**B**)——XIII (1.15 g, 3 mmoles), NaBr (618 mg, 9 mmoles) and anhydrous *p*-toluenesulfonic acid (516 mg, 3 mmoles) were dissolved in DMF (40 ml) and the solution was heated at 100° for 6 hr in a sealed tube. The yellowish solution was treated as described above. The weight of colorless needles, mp 162—165°, was 500 mg (36%). This material was undepressed on admixture with XII described above. IR spectra of two substances were identical.

1-(2′-Bromo-2′-deoxy-5′-O-trityl-β-D-ribofuranosyl)uracil (XIV)——IV (4 g, 12 mmoles) and tritylchloride (6.6 g, 24 mmoles) were dissolved in pyridine (70 ml) and the solution was allowed to stand for 3 days at room temperature. After heating for 30 min at 50—60°, 10 drops of EtOH were added to the solution and allowed to stand for 1 hr at room temperature. It was concentrated to syrup and was poured into H_2O (200 ml) with stirring. The gummy product was extracted with ether and was triturated with petr. ether. The separated crystals were recrystallized from EtOH. XIV, white prisms, mp 162—163°, were obtained in yield of 4.8 g (67%). $[\alpha]_D^{23}$ +3.6° (c=0.83, MeOH). UV λ_{max}^{MeOH} mμ (ε): 261 (8300). λ_{min}^{MeOH} mμ (ε): 243 (5500). *Anal.* Calcd. for $C_{28}H_{25}O_5N_2Br$: C, 61.21; H, 4.59; N, 5.10; Br, 14.54. Found: C, 61.25; H, 4.62; N, 5.11; Br, 14.21.

1-(2′-Bromo-2′-deoxy-3′-O-toxyl-β-D-ribofuranosyl)uracil (XII)——To a solution of XIV (100 mg, 0.2 mmole) in pyridine (7 ml), tosylchloride (70 mg, 0.4 mmole) was added at 0—5°. The solution was allowed to stand at room temperature for 2 days. After removal of solvent *in vacuo*, the brownish residue was poured into H_2O (100 ml). A tan-colored solid was collected and washed with H_2O. The weight of brown amorphous powder, raw 1-(2′-bromo-2′-deoxy-3′-O-tosyl-5′-O-trityl-β-D-ribofuranosyl)uracil (XV), was 120 mg (94%). XV (100 mg, 0.14 mmole) was suspended in EtOH (5 ml) saturated with HCl at 0°, and this suspension was warmed at 50° for 30 min. The solution was concentrated to reddish syrup and it was, after addition of EtOH, evaporated repeatedly *in vacuo*. After extraction with ether to remove tritylcarbinol, the residue was added to EtOH–H_2O (1:3) and stored in refrigerator overnight. The separated yellowish needles were recrystallized from MeOH to give pale yellow fine needles, mp 163—165°. Yield, 20 mg (30%). On admixture of this compound with XII prepared by the method (A) gave no depression.

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