

Reaction of Hydrogen Halides on 2,3'-Anhydro-1-(β -D-xylofuranosyl)uracil¹⁾KIYOMI KIKUGAWA^{2a)} and TYUNOSIN UKITA²⁾Faculty of Pharmaceutical Sciences, University of Tokyo²⁾

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2,3'-Anhydro-1-(β -D-xylofuranosyl)uracil (IV) was allowed to react with sodium iodide in the presence of acetic acid. The major product isolated was proved to be 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil (V) whose structure was unambiguously established. The reaction of other halide ions on the anhydronucleoside (IV) furnished the same type of compounds, 1-(5'-chloro-5'-deoxy- β -D-xylofuranosyl)uracil (XVI) and 1-(5'-bromo-5'-deoxy- β -D-xylofuranosyl)uracil (XVII). By treatment of the compound (V) with silver acetate, 2,3'-anhydro compound (IV) was recovered, and it was supposed that 2,5'-anhydro-1-(β -D-xylofuranosyl)uracil (XII) initially produced was rearranged to the 2,3'-anhydro compound (IV) by a nucleophilic attack of 3'-up hydroxyl function of XII at C₂ carbon of the uracil moiety.

It has well been known that naturally occurring pyrimidine nucleosides, such as uridine, cytidine and thymidine give 2,2'-(in the case of ribonucleoside), 2,3'- or 2,5'-anhydronucleoside by intramolecular nucleophilic attack by the enolizable C₂ carbonyl group at the carbon atoms in the ribofuranosyl or deoxyribofuranosyl residue. As the anhydro-bonds in these nucleosides are splitted by nucleophilic reagents to furnish nucleoside derivatives in which the sugar hydroxyl groups in the original nucleoside are epimerized or substituted, the anhydropyrimidine nucleosides have widely been used as materials in the syntheses of several nucleoside derivatives.

The anhydropyrimidine nucleosides, such as 2',3'-O-isopropylidene-2,5'-anhydrouridine (I) and 2,2'-anhydro-1-(β -D-arabinofuranosyl)uracil (II), have been reported to react readily with ammonia and form isocytosine nucleosides.³⁻⁵⁾ These compounds I and II have also been reacted with hydrogen sulfide to form 5'-thio-5'-deoxyribofuranosyluracil derivatives and 2-thiouracil derivatives.^{4,6,8)} When I was treated with lithium azide,⁹⁾ sodium ethanethiol⁴⁾ or phosphate,¹⁰⁻¹²⁾ the corresponding 5'-substituted-5'-deoxyribofuranosyl-uracil derivatives were obtained. The derivatives of the compound (II) such as 2,2'-anhydro-1-(β -D-arabinofuranosyl)uracil could be cleaved by hydrogen halide to form 2'-halogeno-2'-deoxyribofuranosyluracil derivatives.^{13,14)} The above-cited reactions indicated that the

- 1) Papers read at the 88th Annual Meeting of Pharmaceutical Society of Japan held in Tokyo, April, 1968.
- 2) Location: Hongo, Tokyo; a) Present adress: Kokoku Rayon and Pulp Co., Ltd., 11277, Higashi-hama, Saeki, Oita.
- 3) D.M. Brown, A.R. Todd and S. Varadarajan, *J. Chem. Soc.*, **1957**, 868.
- 4) D.M. Brown, D.B. Parihar, A.R. Todd and S. Varadarajan, *J. Chem. Soc.*, **1958**, 3028.
- 5) I.L. Doerr and J.J. Fox, *J. Org. Chem.*, **32**, 1465 (1967).
- 6) R.W. Chambers and V. Kurkov, *J. Am. Chem. Soc.*, **85**, 2160 (1963).
- 7) N.K. Kochetkov, E.I. Budwsky, V.N. Shibaev, G.I. Yeliseeva, M.A. Grachev and V.P. Demushkin, *Tetrahedron*, **19**, 1207, (1963).
- 8) T. Sekiya and T. Ukita, *Chem. Pharm. Bull.* (Tokyo), **15**, 1498 (1967).
- 9) J.P. Horwitz, A.J. Tomson, J.A. Urbanski and J. Chua, *J. Org. Chem.*, **27**, 3045 (1962).
- 10) J. Žemlička and J. Smrt, *Tetrahedron Letters*, **1964**, 2081.
- 11) J. Nagyváry, *Biochemistry*, **5**, 1316 (1966).
- 12) Y. Mizuno, T. Sasaki, T. Kanai and H. Igarashi, *J. Org. Chem.*, **30**, 1533 (1965).
- 13) D.M. Brown, D.B. Parihar and A.R. Todd, *J. Chem. Soc.*, **1958**, 4242.
- 14) J.F. Codington, I.L. Doerr, D.V. Praag, A. Bendich and J.J. Fox, *J. Org. Chem.*, **29**, 558 (1964).

cleavage of the anhydro-bonds occurred in two directions *i.e.*, first, the nucleophiles attacked the C₂ carbon atom of uracil moiety to give 2-substituted uracil derivatives and second, the nucleophiles attacked the sugar carbon atom which has been concerned with the formation of the anhydro-bond with uracil residue. One exceptional case which is not involved in the above general reaction types has also been reported, namely, when II was treated with sodium ethanethiol, 3'-ethylthio-3'-deoxyxylofuranosyluracil was obtained, and the mechanism of this unique reaction was explained by Brown, *et al.*⁴⁾ by assuming that 2',3'-epoxy-ribofuranosyluracil (III) was formed as an intermediate compound.

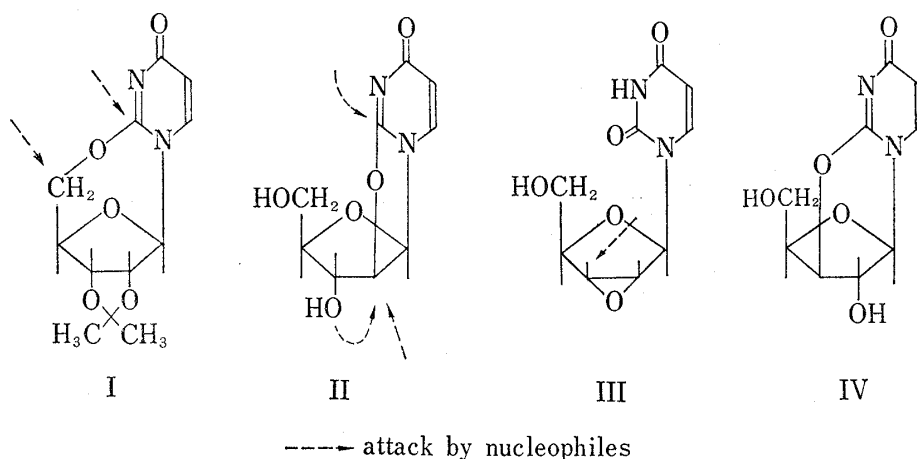


Chart 1

The anhydronucleoside, 2,3'-anhydro-1-(β-D-xylofuranosyl)uracil (IV) which was synthesized by Yung and Fox¹⁵⁾ and by Letters and Michelson¹⁶⁾ has not yet been applied as a starting material in the syntheses of nucleoside derivatives by above mentioned reactions, except the trial to cleave the anhydro-bond with phosphate anion by Mizuno, *et al.*¹²⁾ It is, therefore, interesting to apply this type of anhydronucleoside to react with nucleophiles and to investigate the reaction products.

This time, we observed a new type of reaction between 2,3'-anhydro-1-(β-D-xylofuranosyl)uracil (IV) and alkali halide in acid medium, and this paper deals with the interesting reaction and the properties of the resulted halogenonucleosides.

2,3'-Anhydro-1-(β-D-xylofuranosyl)uracil (IV) which was obtained by Fox's procedure¹⁵⁾ was treated with sodium iodide in the presence of acetic acid. The subsequent paper chromatography of the reaction mixture revealed that the anhydronucleoside (IV) was converted into two products. The major product (V), after separation from the other side product and the starting material by cellulose column chromatography, was isolated as granules in a yield of 50% showing mp 166—168°. The elemental analysis, ultraviolet absorption spectrum and high *R_f* values on paper chromatogram of this compound (V) indicated that V was an uridine analog which was substituted with one iodo group on the sugar moiety. The product (V) was catalytically reduced to a deoxynucleoside (VI) which showed lower *R_f* values than V. Metaperiodate titration studies indicated that the deoxynucleoside (VI) consumed slowly one mole of the reagent, thus the compound (VI) could not be 2'-deoxy- or 3'-deoxy-pentofuranosyl uracil that would consume no metaperiodate. The rate of periodate consumption of this compound was similar to the cases of xylofuranosyluracil or arabinofuranosyluracil which had *trans* vicinal hydroxyl groups. Paper chromatographic mobilities of the compound (VI) were apparently different from those of 2'-deoxyuridine and 3'-deoxyuridine. From these results, the deoxynucleoside (VI) must be 1-(5'-deoxy-β-D-xylofuranosyl)- or 1-(5'-deoxy-β-

15) N.C. Yung and J.J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).

16) R. Letters and A.M. Michelson, *J. Chem. Soc.*, **1961**, 1410.

D-arabinofuranosyl)uracil, and the parent iodo containing nucleoside (V) must have been 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)- or 1-(5'-iodo-5'-deoxy- β -D-arabinofuranosyl)uracil. 1-(5'-Iodo-5'-deoxy- β -D-arabinofuranosyl)uracil has been reported by Doerr, *et al.*¹⁷⁾ to melt at 188–190°, thus it is likely that the compound (V) which melted at 166–168° should be 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil, and, accordingly, the deoxynucleoside (VI) must be 1-(5'-deoxy- β -D-xylofuranosyl)uracil.

In order to confirm the structure of these compounds (V and VI) further investigations were performed. The iodo containing major product (V) was proved to be identical with the 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil by mixed melting point test, and comparison of infrared absorption spectra and *R_f* values, which was obtained from 1-(5'-O-mesyl- β -D-xylofuranosyl)uracil (VII)¹⁷⁾ by treatment with sodium iodide in acetone and melted at 165–

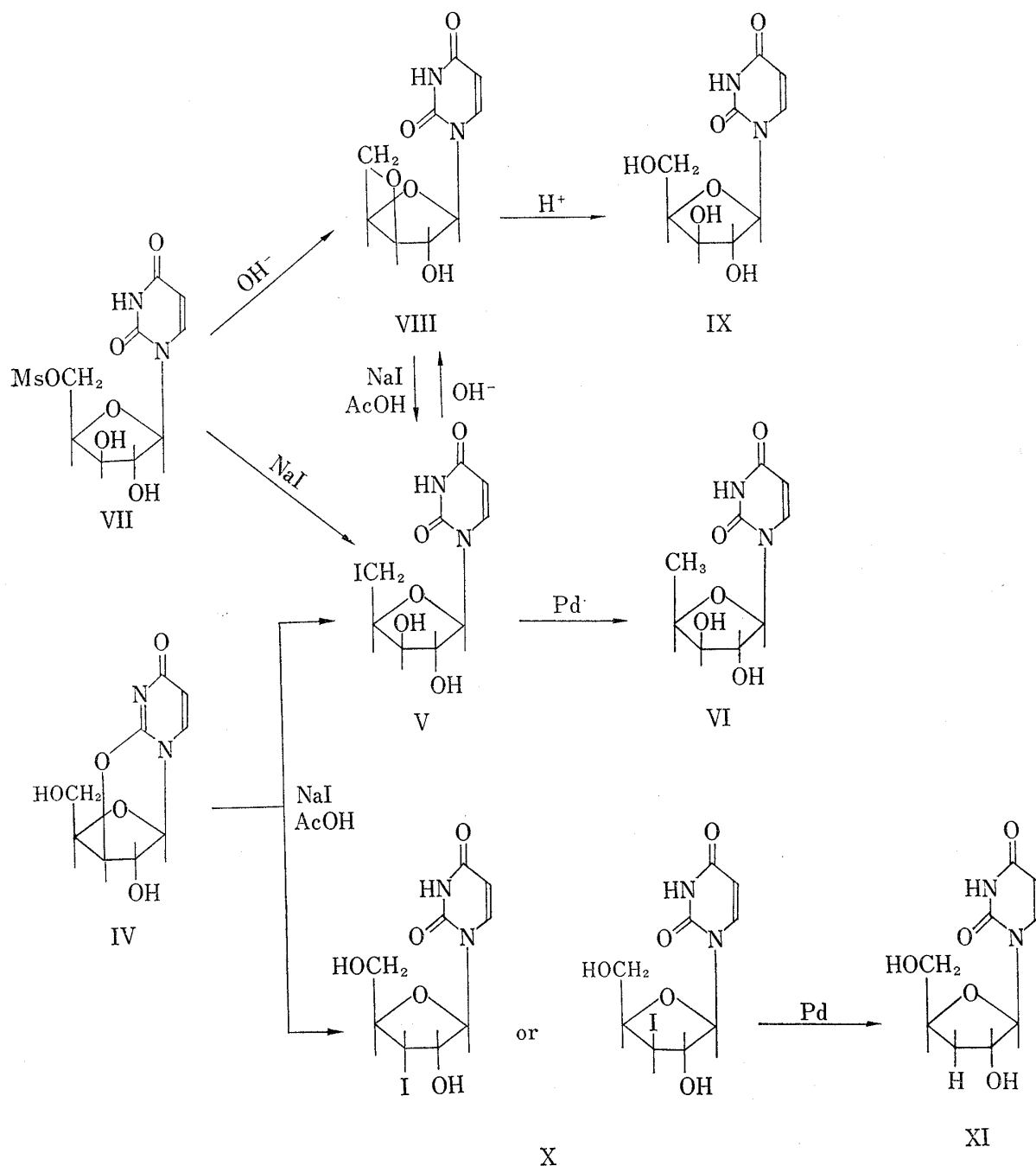


Chart 2

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

168°. The alkali treatments of the product as well as of the compound (VII)¹⁷ gave the same product, 1-(3',5'-epoxy- β -D-xylofuranosyl)uracil (VIII), which, on hydrolysis with acid, afforded a product having the same *Rf* value in paper chromatography and the mobility in paper electrophoresis with those of 1-(β -D-xylofuranosyl)uracil (IX). On treatment of 1-(3',5'-epoxy- β -D-xylofuranosyl)uracil (VIII) with sodium iodide in the presence of acetic acid, the iodo group was introduced into 5' position rather than 3' position to recover the compound (V), as was expected from the known property of the 3',5'-epoxy ring.¹⁸

From the results described above, it was concluded that the major product (V) obtained from IV was 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil.

The minor product (X) which was formed on treatment of 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV) with sodium iodide in the presence of acetic acid was isolated by separation using a cellulose column, but the yield of this product (X) was much lower than the product (V). The relatively high *Rf* values and the ultraviolet absorption spectra of this product indicated that the iodo group should be substituted on the sugar moiety of this compound. Reduction of X with palladium catalyst gave the product (XI), the *Rf* values of which coincided with those of 2'-, and 3'-deoxyuridine and was lower than those of X. The product (XI) consumed no metaperiodate, and did not show clearly positive reaction to cystein-sulfuric acid reagent.¹⁹ As 2'-deoxyuridine has been known to show strongly positive coloration with cystein-sulfuric acid, the compound (XI) should probably be 3'-deoxyuridine, and accordingly the compound (X) could be 1-(3'-iodo-3'-deoxy- β -D-xylofuranosyl)- or 1-(3'-iodo-3'-deoxy- β -D-ribofuranosyl)uracil. Because of the low yield of the product (X), further studies on the structural confirmation of this compound was not performed.

It was found that the reaction of the compound (IV) with hydrogen iodide and dioxane gave the same products (V and X) as with sodium iodide and acetic acid. Thus when hydrogen iodide was allowed to react with the anhydronucleoside (IV) for 3 hours at 100°, the product (X) was obtained in a higher yield than the product (V), so that this reaction seemed favorable to obtain the compound (X) in a better yield.

Brown, *et al.*³⁾ reported that 2',3'-di-O-acetyl-5'-iodo-5'-deoxyuridine was converted into 2,5'-anhydro derivative by treatment with silver acetate, thus the compound, 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil (V) would afford 2,5'-anhydro-1-(β -D-xylofuranosyl)uracil (XII) by the similar treatment. The compound (V) was refluxed with silver acetate in methanol, and the reaction mixture was subsequently applied to paper chromatography. The paper chromatogram revealed a spot of the product, the *Rf* value of which was the same as that of 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV). The ultraviolet absorption spectrum of the extract of this spot also indicated the characteristics of 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil and not those of the 2,5'-anhydro-1-(β -D-xylofuranosyl)uracil or 2,2'-an-

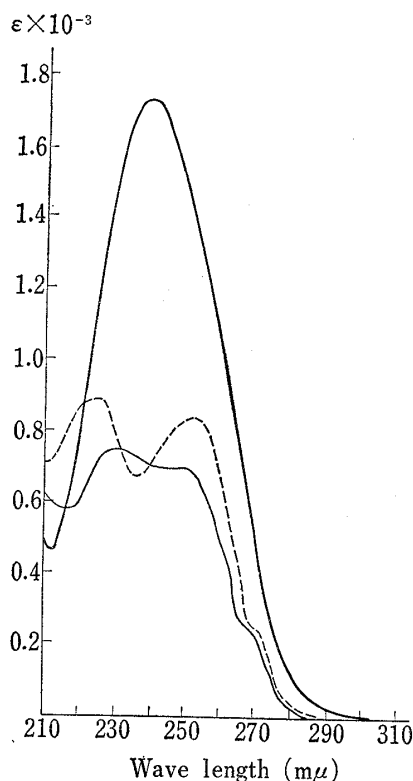


Fig. 1. Ultraviolet Absorption Spectra of Three Kinds of Anhydro-uracil-nucleosides

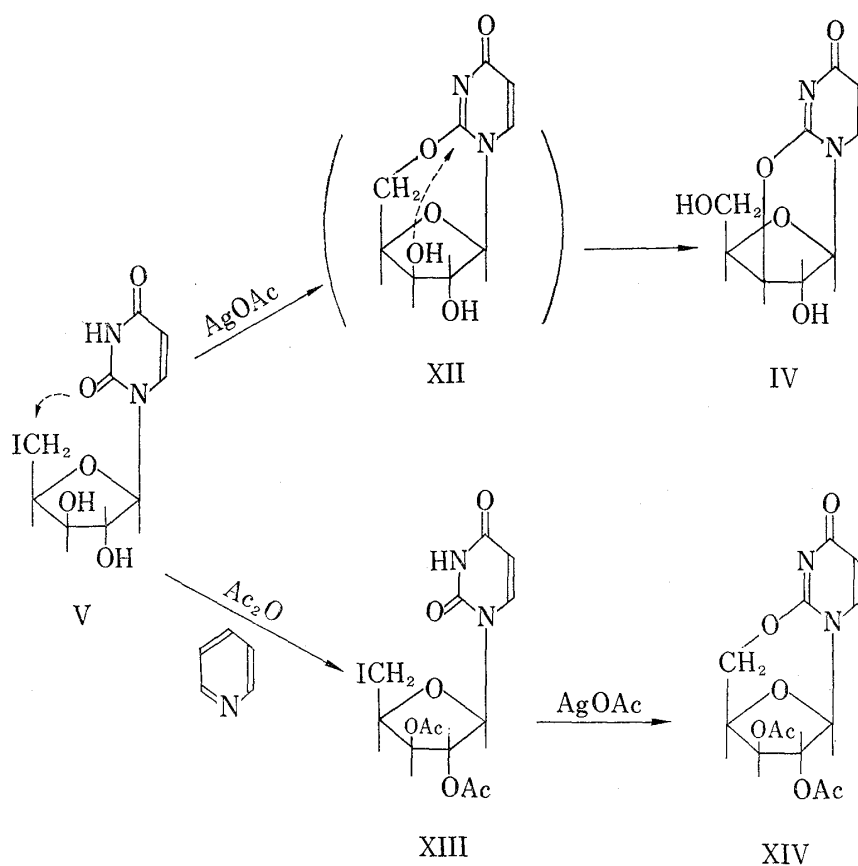
- ; 2',3'-di-O-acetyl-2,5'-anhydrouridine,
- - - ; 2,2'-anhydro-1-(β -D-arabinofuranosyl)uracil,
- ; 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil

All the spectra were measured in water.

18) I.P. Horwitz, J. Chua, J.A. Urbanski and M. Noel, *J. Org. Chem.*, **28**, 942 (1963).

19) J.G. Buchanan, *Nature*, **168**, 1091 (1951).

hydro-1- β -D-arabinofuranosyl)uracil. The comparison of the spectra of these compounds are given in Fig. 1, which shows that these three types of anhydro-nucleosides can be distinguished from each other. From these results, it should be assumed that the 2,5'-anhydro-1-(β -D-xylofuranosyl)uracil (XII) initially produced from the compound (V) by its treatment with silver acetate was converted to 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV) by a nucleophilic attack of 3'-up hydroxyl function of XII at C₂ carbon in the uracil moiety. This assumption was supported by a series of reaction. Thus the compound V was acetylated at 2' and 3'



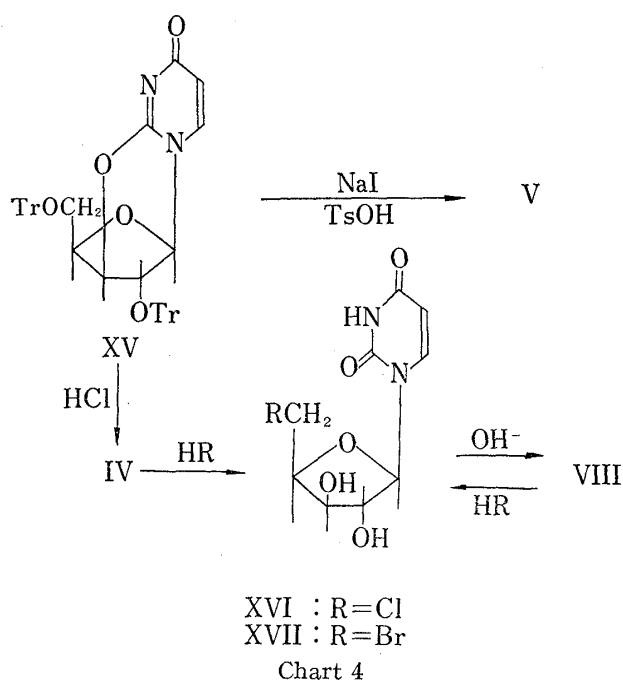
hydroxyl functions and the diacetate (XIII) was submitted to the treatment with silver acetate, the product (XIV) of this reaction gave an ultraviolet absorption spectrum characteristic to 2,5'-anhydro derivative. The molecular model of 2,5'-anhydro-1-(β -D-xylofuranosyl)uracil (XII) indicated that 3'-up hydroxyl function is close enough to the C₂ carbon to result in this rearrangement of the anhydro-bond. A similar rearrangement of the anhydro-bond has been reported in the case of 2,5'-anhydro-1-(β -D-arabinofuranosyl)uracil, thus 1-(5'-iodo-5'-deoxy- β -D-arabinofuranosyl)uracil afforded 2,2'-anhydro-1-(β -D-arabinofuranosyl)uracil by treatment with silver acetate.^{17,20)}

The results of the experiments described above, firmly established the structure of the major product (V) obtained by the action of sodium iodide on 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV) to be 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil.

Action of hydrogen chloride and hydrogen bromide on 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV) gave 5'-halogeno derivatives, 1-(5'-chloro-5'-deoxy- β -D-xylofuranosyl)uracil (XVI) and 1-(5'-bromo-5'-deoxy- β -D-xylofuranosyl)uracil (XVII), respectively.

5'-Chloro derivative (XVI) resisted to the reactions to convert the chloro group to iodo group, hydrogen atom or to form the anhydro-bond, thus XVI was inert to the treatments

20) T. Naito, M. Hirata, Y. Nakai, T. Kobayashi and M. Kanao, *Chem. Pharm. Bull.* (Tokyo), 13, 1258 (1965).



with sodium iodide, hydrogen in the presence of palladium or Raney Ni catalyst, or silver acetate. This compound (XVI), however, was derived into 1-(3',5'-epoxy- β -D-xylofuranosyl)uracil (VIII) by treatment with dilute alkali, which recovered the 5'-chloro derivative (XVI) by reaction with chloride ion in acidic medium, and these reactions supported the structure of XVI to be 1-(5'-chloro-5'-deoxy- β -D-xylofuranosyl)uracil. The bromo group of the nucleoside (XVII) revealed the similar reactions to the chloro group of the compound (XVI). When 2,3'-anhydro-1-(2',5'-di-O-trityl- β -D-xylofuranosyl)uracil (XV) was detritylated to 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV) by warming XV in ethanol

saturated with hydrogen chloride for 10 min at 70° according to Fox's procedure,¹⁵⁾ besides the desired anhydronucleoside (IV), a side product was isolated in a rather high yield of 34%. Recently, Kowollik and Langen²¹⁾ assumed this side product to be 3'-chloro-3'-deoxy-uridine, but we identified this side product with 5'-chloro-5'-deoxy compound (XVI), and this reaction could be explained by that the detritylation first occurred on the compound (XV) was followed by chlorination of the anhydronucleoside (IV). Thus, in order to obtain the anhydronucleoside (IV) in a better yield, detritylation must be performed under milder conditions.

As the reactions of halides on 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV) described above revealed an unexpected reaction, and the introduction of halogeno group into 3'-position of the sugar moiety was unsuccessful, the reaction was tested under several modified conditions. Thus, 2,3'-anhydro-1-(2',5'-di-O-trityl- β -D-xylofuranosyl)uracil (XV)¹⁵⁾ was treated with sodium iodide in the presence of benzoic acid or *p*-toluenesulfonic acid, but no reaction was observed in the presence of benzoic acid even when the reaction mixture was treated at 100° overnight. In the presence of *p*-toluenesulfonic acid, though the reaction proceeded, the isolated product was again 5'-iodo derivative (V), this observation indicated that, in this reaction, by detritylation, 2,3'-anhydro compound (IV) was initially formed. Other trial to introduce halogeno group into 3'-position of uridine did not give any successful results. Thus, 2',5'-di-O-trityl-3'-O-mesyluridine did not react with sodium iodide, though the similar reaction to 5'-O-trityl-3'-O-mesyl-2'-deoxyuridine yielded 5'-O-trityl-3'-iodo-2',3'-dideoxyuridine.²²⁾

The unexpected reaction of the compound (IV) to furnish the products (V, XVI and XVII), however, can be used as a convenient method to obtain 5'-halogeno-5'-deoxyxylosyl derivatives which could not so readily be obtained by the known procedures *via* 5'-mesyl (or tosyl)-xylofuranosyluracil, because it is very tedious to obtain 5'-sulfonyloxyxylosyluracils.¹⁷⁾ The mechanism of this unique cleavage of the anhydro-bond in pyrimidine nucleoside by nucleophiles seemed to involve a rearrangement of 2,3'-anhydro bond to 2,5'-anhydro bond. The detailed reaction mechanism will be discussed in a following paper.²³⁾

21) G. Kollolik and P. Langen, *Chem. Ber.*, **101**, 235 (1968).

22) K.E. Pfitzner and J.G. Moffatt, *J. Org. Chem.*, **29**, 1508 (1964).

23) K. Kikugawa, M. Ichino and T. Ukita, *Chem. Pharm. Bull. (Tokyo)*, **17**, 785 (1969).

Experimental²⁴⁾

Methods

Paper chromatography was carried out on Toyo Roshi No. 53 paper using solvent systems, (1) iso-PrOH–conc. NH_4OH – H_2O (7:1:2 v/v), (2) BuOH– H_2O (84:16 v/v), (3) BuOH–AcOH– H_2O (4:1:2 v/v). The R_f value of the spot obtained for individual solvent was represented by the symbol, R_f , with suffix corresponding to the number of the solvents. The spots were detected by ultraviolet absorption and coloration with periodate-benzidine reagent,²⁵⁾ or cystein–sulfuric acid reagent.¹⁹⁾

Paper electrophoresis was performed using 0.02M sodium borate buffer (pH 9.2) at 30 V/cm and 25° for 1 hr.

Cellulose powder (200–300 mesh) (Toyo Roshi Kaisha Ltd.) was used for the separation of the products by column chromatography.

Metaperiodate titration was performed as follows: the solutions of nucleosides of 1–3 mM concentration were treated with excess sodium metaperiodate at 25° and the remaining reagent was determined by iodometry according to the usual procedures.²⁶⁾

1-(5'-Iodo-5'-deoxy- β -D-xylofuranosyl)uracil (V)—Method A. From 2,3'-Anhydro-1-(β -D-xylofuranosyl)uracil (IV): A sealed tube containing 250 mg (1.15 mmoles) of 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV),¹⁵⁾ 1.0 g (7 mmoles) of NaI, 0.3 ml of AcOH and 5 ml of acetonylacetone (distilled and dried over molecular sieves 4A) was heated at 100° for 16 hr. The tube was opened and the solvent was removed *in vacuo*. The residual gum was applied onto a cellulose column (3 × 30 cm) and eluted with a mixed solvent BuOH– H_2O (84:16). The fractions containing a product which had R_{f2} value of 0.73 and absorbed ultraviolet ray were combined and evaporated to dryness under reduced pressure. The residual brownish gum was dissolved in water and extracted several times with small amounts of CHCl_3 . The aqueous layer was taken and evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH– H_2O mixture to furnish white granules, mp 166–168° (decomp.), which weighed 200 mg (yield, 50.0%). R_{f1} 0.71, R_{f2} 0.73, R_{f3} 0.73. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ m μ (ϵ): 261 (10600), $\lambda_{\text{min}}^{\text{H}_2\text{O}}$: 230 (3000), $\lambda_{\text{max}}^{0.1\text{NNaOH}}$: 2600 (8900), $\lambda_{\text{min}}^{0.1\text{NNaOH}}$: 242 (6500). $[\alpha]_D^{20}$: +9° ($c=0.15$ in H_2O). Anal. Calcd for $\text{C}_9\text{H}_{11}\text{O}_5\text{N}_2\text{I}$: C, 30.53; H, 3.13; N, 7.91; I, 35.85. Found: C, 31.01; H, 3.64; N, 8.20; I, 35.34.

Method B. From 2,3'-Anhydro-(2',5'-di-O-trityl- β -D-xylofuranosyl)uracil (XV): To a solution of 1.0 g (1.4 mmoles) of 2,3'-anhydro-(2',5'-di-O-trityl- β -D-xylofuranosyl)uracil (XV)¹⁵⁾ in 20 ml of dimethylformamide (DMF) were added 1.0 g (6.7 mmoles) of NaI and 240 mg of *p*-toluenesulfonic acid (1.4 mmoles). The mixture was heated at 100° overnight under prevention of the moisture. The solvent was then removed *in vacuo*, and the residual gum was treated with 80% AcOH at 100° for 20 min. Crystalline triphenyl carbinol was removed by filtration, and the filtrate was evaporated to dryness. The residual gum which gave only one ultraviolet absorbing spot in paperchromatography was purified through a cellulose column (2 × 28 cm) as was described in method A. On recrystallization from AcOEt, 45 mg (yield, 9%) of the product was obtained as colorless granules, mp 164–166°. This product showed no depression of melting point in the mixed fusion with the product obtained by method C.

Method C. From 1-(5'-O-Mesyl- β -D-xylofuranosyl)uracil (VII): A sealed tube containing 100 mg of 1-(5'-O-mesyl- β -D-xylofuranosyl)uracil (VII),¹⁷⁾ 1.0 g of NaI and 4 ml of acetone was heated at 100° overnight. The reaction mixture was evaporated to dryness and the residue was applied on a cellulose column (2 × 28 cm) to separate the iodo-containing nucleoside from the starting material. The column was eluted with the mixed solvent, BuOH– H_2O , and fractions containing the product were combined and evaporated to dryness. Recrystallization of the residue from AcOEt gave white granules, mp 165–168° (decomp.), which weighed 50 mg (yield, 45.5%). The product was coincided with that obtained by method A in every respect: mixed melting point, infrared spectra and R_f values on paper chromatograms.

Method D. From 1-(3',5'-Epoxy- β -D-xylofuranosyl)uracil (VIII): A sealed tube containing 125 mg of 1-(3',5'-epoxy- β -D-xylofuranosyl)uracil (VIII),¹⁷⁾ 1.0 g of NaI, 0.2 ml of AcOH and 4 ml of acetonylacetone was heated at 80–85° for 13 hr. From the reaction mixture solvent was removed *in vacuo*. The residual gum was dissolved in water and deionized by successive passing of the solution through Dowex 50 (H^+) and Dowex 1 (HCO_3^-) columns. The eluate was evaporated again to dryness and the residue was applied onto a cellulose column (2 × 28 cm) to separate the product from the starting material. The column was eluted with the mixed solvent, BuOH– H_2O , and the fractions that contained the product were combined and evaporated to dryness. Recrystallization of the residue furnished 23 mg (yield, 13%) of white granules, mp 164–166° (decomp.). R_{f1} 0.71, R_{f2} 0.73, R_{f3} 0.73. Anal. Calcd. for $\text{C}_9\text{H}_{11}\text{O}_5\text{N}_2\text{I}$: C, 30.53; H, 3.13; N, 7.94; I, 35.85. Found: C, 30.31; H, 3.29; N, 8.26; I, 35.87.

The product was coincided in every respect: mixed melting point, infrared spectra and R_f values, with that obtained by method A.

24) All melting points are uncorrected.

25) J.A. Cifonelli and F. Smith, *Anal. Chem.*, **26**, 1132 (1954).

26) J.J. Fox, N.C. Yung, J. Davoll and G.B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).

1-(5'-Deoxy- β -D-xylofuranosyl)uracil (VI)—A solution of 50 mg of 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil (V) in 5 ml of EtOH containing 200 mg of 5% palladium-barium sulfate as catalyst and 0.1 ml of triethylamine was shaken in hydrogen atmosphere for 10 hr under pressure of 760 mmHg at room temperature. The catalyst was removed by centrifugation and the supernatant was evaporated to dryness. The residue was crystallized from acetone, and recrystallized from mixed solvent, EtOH-H₂O, to give 35 mg (yield, 94%) of fine needles, mp 193–195° (decomp.). Rf_1 0.63, Rf_2 0.49, Rf_3 0.59. UV $\lambda_{\max}^{H_2O}$ m μ (ϵ): 263 (7400), $\lambda_{\min}^{H_2O}$: 241 (4100), $\lambda_{\max}^{0.1N NaOH}$: 263 (5300), $\lambda_{\min}^{0.1N NaOH}$: 247 (3900). $[\alpha]_D^{20}$: -26° ($c=0.1$ in H₂O). *Anal.* Calcd for C₉H₁₂O₅N₂·2H₂O: C, 40.91; H, 6.10; N, 10.60. Found: C, 41.17; H, 6.36; N, 10.35.

The Rf_2 value of this compound differed from that of 2'-deoxyuridine (Rf_2 0.37)²⁷ and the compound did not color with cystein-sulfuric acid²⁸ and not with periodate-benzidine test on a paper sheet. The consumption of metaperiodate by several nucleosides including this product (VI) was tested according to the usual procedures²⁶ and the results are listed below:

| Compound | Moles of IO ₄ ⁻ consumed per 1 mole of the compound tested in | | | |
|---------------------------|---|-------|-------|-------|
| | 1 hr | 24 hr | 48 hr | 72 hr |
| Uridine | 1.0 | 1.02 | — | — |
| Xylofuranosyl uracil (IX) | 0.12 | 0.37 | 0.73 | 0.94 |
| 2'-Deoxyuridine | 0.0 | 0.05 | 0.05 | 0.08 |
| Product (VI) | 0.12 | 0.38 | 0.76 | 0.96 |

The Compound (X) and Its Reduction Product (XI)—In method A described above, after 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil (V) was eluted from the cellulose column, fractions, which contained another product having Rf_2 value of 0.64, were obtained. These fractions were pooled and evaporated to dryness. The residue was crystallized from the mixed solvent of acetone-benzene to furnish 10 mg of white granules (X), mp 109–110°, UV $\lambda_{\max}^{H_2O}$ m μ : 261, $\lambda_{\min}^{H_2O}$: 262. Rf_2 0.64, Rf_3 0.67.

A solution of 1 mg of this compound (X) in 5 ml of EtOH containing a few mg of 5% palladium-barium sulfate and one drop of triethylamine was shaken in hydrogen atmosphere at room temperature and 760 mm Hg for 3 hr. The catalyst was removed by centrifugation and the supernatant evaporated to a small volume. In paper chromatography, the reduced product (XI) revealed spots having the same Rf values as those of 2'-deoxyuridine²⁷ (Rf_1 0.59, Rf_2 0.37, Rf_3 0.49), but it did not show strongly positive reaction to cystein-sulfuric acid reagent, which gave strongly positive coloration with 2'-deoxyuridine.

These results indicated that the compound (X) and the reduced product (XI) would be a 1-(3'-iodo-3'-deoxy- β -D-pentofuranosyl)uracil, and 3'-deoxyuridine, respectively.

1-(5'-Chloro-5'-deoxy- β -D-xylofuranosyl)uracil (XVI)—Method A. From 2,3'-Anhydro-1-(β -D-xylofuranosyl)uracil (IV): 2,3'-Anhydro-1-(β -D-xylofuranosyl)uracil (IV)¹⁵ (100 mg) was added to 10 ml of dioxane saturated with dry HCl, and the mixture was warmed overnight at 40° in a sealed tube. On paper chromatography, the reaction mixture gave one spot of the product. The mixture was evaporated to dryness, and the residue was dissolved in water, then passed through a column of Dowex 1 (HCO₃⁻) to remove chloride ion. The eluate was evaporated again to give a gum which was subsequently treated with acetone-benzene mixture to afford white plates in a quantitative yield, mp 85–90° (decomp.). Rf_1 0.67, Rf_2 0.61, Rf_3 0.66.

Method B. From 2,3'-Anhydro-1-(2',5'-di-O-trityl- β -D-xylofuranosyl)uracil (XV): 2,3'-Anhydro-1-(2',5'-di-O-trityl- β -D-xylofuranosyl)uracil (XV)¹⁵ (3.6 g) was placed in 50 ml of absolute EtOH saturated with hydrogen chloride at 0°, and the mixture was warmed at 70° for 10 min. The solution was concentrated at 40° *in vacuo* to give a syrup, which was then triturated several times with 20 ml of ether to remove triphenylcarbinol. The residue was dissolved in water and passed through Dowex 1 (HCO₃⁻) column to remove chloride ion. The neutralized eluate was evaporated to furnish a colorless syrup. On trituration with ethanol of the syrup, 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV) appeared as crystalline form, which was filtered and weighed 250 mg (yield, 22%), mp 195–200°.

After concentration of the filtrate to a syrup, it was applied onto a cellulose column (4×40 cm) and eluted with a mixed solvent of BuOH-H₂O (84 : 16). Ten milliliter aliquotes were collected and the fractions containing the compound (XVI) were pooled and evaporated to dryness. The residue was dissolved in acetone and to the solution benzene was added dropwise until slight turbidity was observed. Crystals which appeared on storing the mixture at room temperature was recrystallized from ethanol to give 450 mg (yield, 34%) of white plates of XVI, which melted at 85–90° (decomp.). Rf_1 0.67, Rf_2 0.61, Rf_3 0.66. UV

27) It was shown by Brown, *et al.*⁴) that 2'-deoxyuridine and 3'-deoxyuridine have the same Rf value in the solvent system (2).

28) It is known that 2'-deoxyuridine is rapidly and 3'-deoxyuridine is slowly colored by the reagent.⁴)

$\lambda_{\max}^{\text{H}_2\text{O}}$ m μ (ϵ): 263 (9600), $\lambda_{\min}^{\text{H}_2\text{O}}$: 230 (1800). $\lambda_{\max}^{0.1N \text{ NaOH}}$: 263 (7300), $\lambda_{\min}^{0.1N \text{ NaOH}}$: 242 (4700). $[\alpha]_D^{25}$: +8° ($c=0.23$ in H_2O). Anal. Calcd for $\text{C}_9\text{H}_{11}\text{O}_5\text{N}_2\text{Cl} \cdot 1/2\text{C}_2\text{H}_5\text{OH}$: C, 42.07; H, 4.94; N, 9.83; Cl, 12.4. Found: C, 42.54; H, 4.90; N, 9.67; Cl, 12.5.

Fractions from the cellulose column containing the compound (IV) were pooled and evaporated to a syrup, from which, by crystallization from EtOH, 230 mg (yield, 20%) of IV, mp 195–200°, was obtained. Thus, overall yield of 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV) in this reaction was 42%.

Method C. From 1-(3',5'-Epoxy- β -D-xylofuranosyl)uracil (VIII): To 5 mg of 1-(3',5'-epoxy- β -D-xylofuranosyl)uracil (VIII)¹⁷ was added dioxane containing 4M of dry hydrogen chloride. The mixture was warmed at 40° overnight. Paper chromatography of the reaction mixture indicated that the starting material was quantitatively converted to the product (XVI). Alkali treatment of the product (XVI) gave 1-(3',5'-epoxy- β -D-xylofuranosyl)uracil.

1-(5'-Bromo-5'-deoxy- β -D-xylofuranosyl)uracil (XVII)—Method A. From 2,3'-Anhydro-1-(β -D-xylofuranosyl)uracil (IV): A sealed tube containing 100 mg of 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV),¹⁵ 500 mg of NaBr, 0.1 ml of AcOH and 2 ml of DMF was heated at 100° overnight. From the reaction mixture, the solvent was removed *in vacuo* and the residue was put onto a cellulose column (2 \times 28 cm) to separate the product from the starting material. The column chromatography was performed using a mixed solvent of BuOH-H₂O (84 : 16). Fractions that contained the product having R_f value of 0.69 were evaporated to dryness, and the residual gum was treated with mixture of ethanol, acetone and benzene (1 : 5 : 5). On standing at room temperature white crystals appeared, which weighed 50 mg, and melted at 80°.

Method B. From 1-(3',5'-Epoxy- β -D-xylofuranosyl)uracil (VIII): A sealed tube containing 200 mg of 1-(3',5'-epoxy- β -D-xylofuranosyl)uracil (VIII),¹⁷ 1.0 g of NaBr, 0.2 ml of AcOH and 4 ml of DMF was heated at 100° overnight. The residue, which was obtained by removal of the solvent from the reaction mixture *in vacuo*, was applied on a cellulose column (2 \times 28 cm) and the column was eluted as described above. The fractions containing the product were pooled and evaporated to dryness to give a gum. On treatment of the gum as in method A, white crystals were obtained in a yield of 28% (100 mg), mp 80°. R_f 0.70, R_f 0.69, R_f 0.70. UV $\lambda_{\max}^{\text{H}_2\text{O}}$ m μ (ϵ): 262 (9900), $\lambda_{\min}^{\text{H}_2\text{O}}$: 232 (2800), $\lambda_{\max}^{0.1N \text{ NaOH}}$: 263 (8400), $\lambda_{\min}^{0.1N \text{ NaOH}}$: 243 (5300). Anal. Calcd for $\text{C}_9\text{H}_{11}\text{O}_5\text{N}_2\text{Br} \cdot \text{C}_2\text{H}_5\text{OH}$: C, 38.18; H, 4.94; N, 8.10; Br, 23.10; Found: C, 38.50; H, 5.23; N, 7.95; Br, 23.53.

This product was identical with the product obtained by method A in mixed melting point test and R_f values. This bromo-containing nucleoside was easily converted to 1-(3',5'-epoxy- β -D-xylofuranosyl)uracil (VIII) by alkali treatment.

Treatment of 1-(5'-Iodo-5'-deoxy- β -D-xylofuranosyl)uracil (V) with Silver Acetate—Several milligrams of 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil (V) was dissolved in methanol and to the solution was added small amount of silver acetate. The mixture was boiled for 30 min in a water bath. The application of the reaction mixture to paper chromatography indicated that the starting iodo-containing compound was quantitatively converted to a product having a lower R_f value (R_f 0.17) which was corresponding to that of 2,3'-anhydro-1-(β -D-xylofuranosyl)uracil (IV). The ultraviolet absorption spectra of the aqueous extract of the spot showed characteristics of the compound IV (λ_{\max} : 228, 249 m μ , λ_{\min} : 240 m μ , shoulder 270 m μ). When 2'-iodo-2'-deoxyuridine²⁹ and 5'-iodo-5'-deoxyuridine³ were treated with silver acetate under the same reaction condition, the each compound was converted almost completely to the corresponding anhydronucleoside; 2,2'-anhydro-1-(β -D-arabinofuranosyl)uracil (R_f 0.16 and UV $\lambda_{\max}^{\text{H}_2\text{O}}$: 221, 250 m μ , $\lambda_{\min}^{\text{H}_2\text{O}}$: 235 m μ , shoulder 270 m μ), and 2,5'-anhydrouridine (R_f 0.09, and UV $\lambda_{\max}^{\text{H}_2\text{O}}$: 240 m μ), respectively. (see Fig. 1).

2',3'-Di-O-acetyl-1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil (XIII) and Its Treatment with Silver Acetate—To a 3 ml of pyridine solution containing 15 mg (0.05 mmole) of 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil (V) was added 0.05 ml (0.5 mmole) of Ac₂O, and the mixture was kept at room temperature overnight. The mixture was coevaporated three times with EtOH *in vacuo* to dryness. White powder of 2',3'-diacetate (XIII) of V thus obtained weighed 20 mg and gave the following properties: R_f 0.84. UV $\lambda_{\max}^{\text{H}_2\text{O}}$: 260 m μ , $\lambda_{\min}^{\text{H}_2\text{O}}$: 232 m μ .

To a methanolic solution (1 ml) of 5 mg of the powder (XIII) was added 5 mg of silver acetate, and the mixture was boiled for 30 min in a water bath. Paper chromatography of the supernatant of the reaction mixture revealed the spot of a new product (R_f 0.41), which was eluted with warm water, and analyzed spectrophotometrically. The absorptions in the spectrum (λ_{\max} : 242 m μ , λ_{\min} : 213 m μ) of the product were quite identical with those of 2',3'-di-O-acetyl-2,5'-anhydrouridine obtained by similar treatment of 2',3'-di-O-acetyl-5'-iodo-5'-deoxyuridine.³ These properties of the product showed that 5'-iodo-nucleoside (V) when its 2' and 3' hydroxyl functions were blocked was converted into 2,5'-anhydro derivative (XIV).

1-(3',5'-epoxy- β -D-xylofuranosyl)uracil (VIII)—Method A. From 1-(5'-O-mesyl- β -D-xylofuranosyl)uracil (VII): The experimental procedure was entirely same as reported by Doerr, *et al.*¹⁷ The product was obtained in a yield of 47% and melted at 214–216° (decomp.)³⁰. R_f 0.53, R_f 0.33, R_f 0.46. UV

29) 2'-Iodo-2'-deoxyuridine²⁹ was kindly supplied by Dr. Hirata of Daiichi Pharmaceutical Co., Ltd.

30) Doerr, *et al.*¹⁷ did not describe the melting point of the compound (VIII).

$\lambda_{\max}^{\text{H}_2\text{O}}$ m μ (ϵ): 260.5 (9800), $\lambda_{\min}^{\text{H}_2\text{O}}$: 230 (2200), $\lambda_{\max}^{0.1N \text{ NaOH}}$: 262 (7800), $\lambda_{\min}^{0.1N \text{ NaOH}}$: 247 (5300). $[\alpha]_D^{25}$: -76° ($c=0.25$ in H_2O). *Anal.* Calcd for $\text{C}_9\text{H}_{10}\text{O}_5\text{N}_2$: C, 47.79; H, 4.46; N, 12.38. Found: C, 47.55; H, 4.50; N, 12.67.

Method B. From 1-(5'-Halogeno-5'-deoxy- β -D-xylofuranosyl)uracils (V, XVI and XVII): A solution of 30 mg of 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil (V) in 1 ml of 2N NaOH was heated at $50-60^\circ$ for 2 hr. Then the reaction mixture was deionized by successive passing through Dowex 50 (H^+) and Dowex 1 (HCO_3^-) columns. The eluate was evaporated to dryness and the residue was recrystallized from EtOH to afford 15 mg (yield, 78%) of flat crystals, mp $214-216^\circ$ (decomp.). Rf_1 0.53, Rf_2 0.33, Rf_3 0.46. *Anal.* Calcd for $\text{C}_9\text{H}_{10}\text{O}_5\text{N}_2$, C, 47.79; H, 4.46; N, 12.38. Found: C, 47.72; H, 4.58; N, 12.51.

The product was identical in mixed melting point test, infrared spectra and Rf values with that obtained by method A. 1-(5'-Chloro-5'-deoxy- β -D-xylofuranosyl)uracil (XVI) and 1-(5'-bromo-5'-deoxy- β -D-xylofuranosyl)uracil (XVII) were, respectively, treated as described above, and the products obtained were identical with that obtained from 1-(5'-iodo-5'-deoxy- β -D-xylofuranosyl)uracil (V) in every respect.

1-(3',5'-Epoxy- β -D-xylofuranosyl)uracil (VIII) thus obtained was treated with 0.25N H_2SO_4 for 1 hr at 100° . After neutralization with Dowex 1 (HCO_3^-), the solution was submitted to paper chromatography and paper electrophoresis. The product had a Rf_2 of 0.29 whereas Rf_2 values of the authentic 1-(β -D-arabinofuranosyl)uracil, 1-(β -D-xylofuranosyl)uracil, uridine and uracil were 0.32, 0.29, 0.23 and 0.34, respectively. The product moved 7.5 cm towards anode whereas the authentic 1-(β -D-arabinofuranosyl)uracil, 1-(β -D-xylofuranosyl)uracil, 1-(3',5'-epoxy- β -D-xylofuranosyl)uracil and uracil moved 2.5 cm, 7.5 cm, 2.3 cm and 2.5 cm towards anode, respectively. Ultraviolet absorption spectra of the product indicated the characteristics of N_1 substituted uracil. From these results the product obtained by acid hydrolysis of VIII was proved to be 1-(β -D-xylofuranosyl)uracil.

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