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Reactions of Methyl Iodide on 2,2′-Anhydro-1-(β-D-arabinofuranosyl)-uracil and 2,3′-Anhydro-1-(β-D-xylofuranosyl)uracil[1]

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The reactions of methyl iodide with 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (I) and 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil (VIII) afforded the products (II and IX) containing methyl and iodo groups, respectively. The structure of the product (II) was firmly established to be N_3-methyl-2′-iodo-2′-deoxyuridine, and that of the product (IX) to be N_3-methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil.

The reaction mechanism to afford the compound (IX) from VIII was assumed to proceed *via* an initial intermediate, quaternary salt (XXI), and followed by the second intermediate of a quaternary 2,5′-anhydro compound (XXIII), which was formed by an intramolecular attack by 5′-hydroxyl function at the C_2 carbon atom of the base moiety in XXI.

The fact that the antibiotic activity of puromycin entirely depends on the presence of the unique substituent at the 3′-carbon atom of this compound lead us to an investigation on the synthesis of the similar type of nucleosides starting from 2,3′-anhydropyrimidine–nucleoside. Brown, *et al.*[3] and Codington, *et al.*[4] reported that the reaction of hydrogen halides with 2,2′-anhydropyrimidine nucleosides yielded 2′-halogeno-2′-deoxynucleosides. It was supposed that the 2,3′-anhydropyrimidine nucleoside analogously provides the 3′-halogeno-3′-deoxypyrimidine nucleosides by the reaction with hydrogen halides.

In the previous paper,[5] however, we described that the action of hydrogen halides on 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil unexpectedly yielded 1-(5′-halogeno-5′-deoxy-β-D-xylofuranosyl)uracils and the structures of these products were firmly established.

This time, we investigated the reaction of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (I) and 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil (VIII) with methyl iodide. The reaction of methyl iodide with the compound (I) afforded N_3-methyl-1-(2′-iodo-2′-deoxy-β-D-ribofuranosyl)-uracil (II). This reaction demonstrated that the reagent acted on the compound (I) in two functions, methylation and iodination, and the iodo group was introduced into 2′-carbon atom of the nucleoside. The action of the reagent on 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil (VIII), however, gave N_3-methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil. These results indicated that the iodo group of the methyl iodide acted quite similarly as the halogen group of hydrogen halide on both anhydronucleosides I and VIII. Thus, in the case of the reaction with 2,3′-anhydronucleosides (VIII), the iodo group of methyl iodide was introduced into a unique position, 5′-carbon atom, analogously to the action of hydrogen iodide on VIII. The observations described above lead the authors to the assumption that the mechanism of the reactions of anhydronucleosides I and VIII with both hydrogen iodide and methyl iodide should be very similar and that the mechanism could be clarified by a research using the

1) Papers read at the 88th Annual Meeting of the 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, D.B. Parihar and A.R. Todd, *J. Chem. Soc.*, **1958**, 4242.
4) J.F. Codington, I.L. Doerr, D.V. Praag, A. Bendich and J.J. Fox, *J. Org. Chem.*, **29**, 558 (1964).
5) K. Kikugawa and T. Ukita, *Chem. Pharm. Bull.* (Tokyo), **17**, 775 (1969).

latter reagent, as the compound (VIII) reacted relatively milder with methyl iodide than with hydrogen iodide.

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil (I), which was synthesized according to Hampton's diphenylcarbonate methods[6] was treated with methyl iodide in dimethylformamide at room temperature for about 24—48 hr. A product (II), isolated in a yield of 77%, indicated that by this reaction one methyl and one iodo group were introduced to the parent compound. The methyl group in this product was proved to be attached at N_3 position of uracil moiety from the characteristic ultraviolet properties of this compound. Catalytic reduction of the product (II) with palladium produced a deoxy compound (III) which was identified with a compound obtained by methylation with diazomethane of 2′-deoxyuridine (IV).

When the reaction mixture of methyl iodide with 2,2′-anhydro–compound (I) was analyzed in early stage of the reaction by paper chromatography run in a solvent containing water, the chromatogram revealed three spots: that of the starting material (I) having the lowest *Rf* value, that of the product (II) having the highest *Rf* value and the third tailing spot having the medium *Rf* value, which corresponded to N_3-methyl-1-(β-D-arabinofuranosyl)uracil (V). On the final stage of the reaction, however, the similar chromatogram revealed only one spot

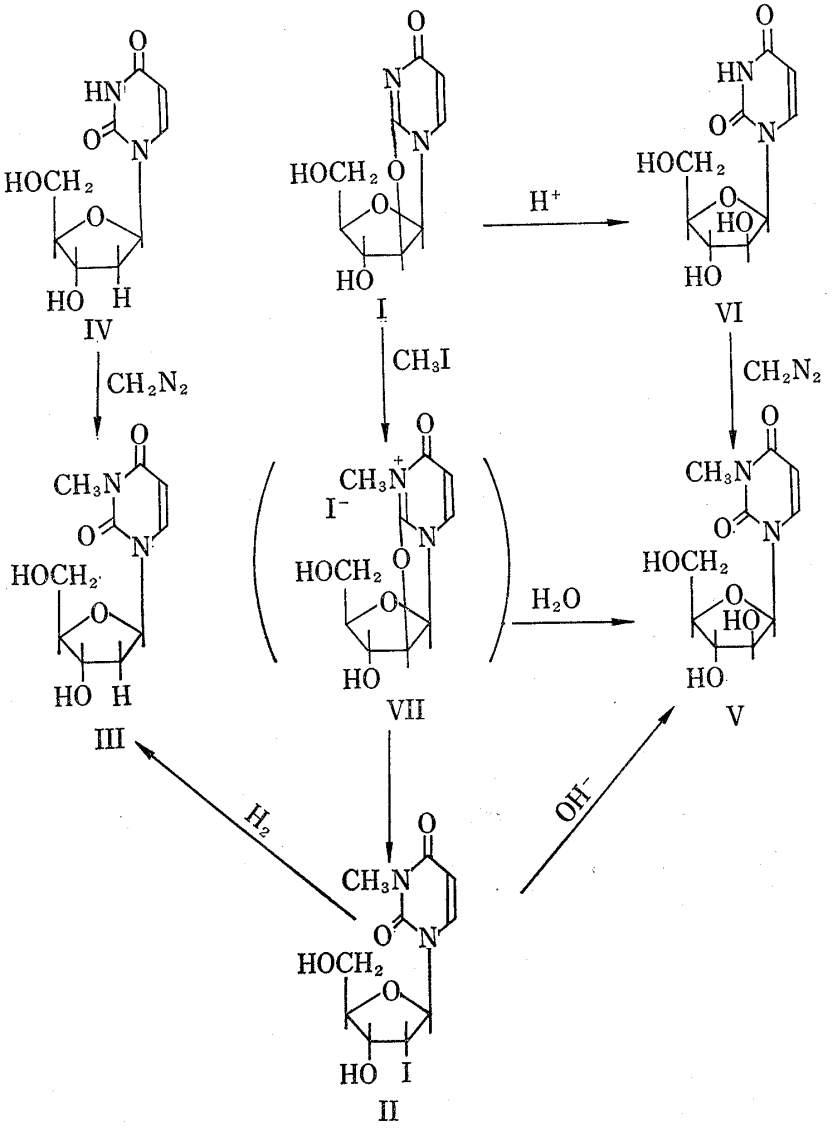


Chart 1

6) A. Hampton and A.M. Nichol, *Biochemistry*, **5**, 2076 (1966).

which corresponded to the product (II). The time course measured for the yield of the compound (V), which gave the medium *Rf* value, showed that the highest yield was obtained about 10 hours after the reaction started. As the compound (V) was found not to be converted to the product (II) by treatment with methyl iodide, the compound (V) was thought to be produced from some kind of intermediate which should give product (II).

When the reaction mixture was more carefully investigated, it was proved that in early step of the reaction, the mixture contained an intermediate compound which liberated acid on addition of water and the paper chromatogram of the acidic solution revealed the spot of the compound (V), but after completion of the reaction, the mixture showed neither liberation of the acid nor the occurrence of the compound (V) by the addition of the water. Accordingly, the compound (V) was assumed not to be an intermediate compound in the non-aqueous reaction of I to II, but it was formed from an intermediate compound during the paper chromatographic procedure. After treatment of an early stage reaction mixture with water, the compound (V) was isolated using cellulose column chromatography and it was proved to be N_3-methyl-1-(β-D-arabinofuranosyl)uracil by mixed fusion with an authentic sample obtained by treatment of 1-(β-D-arabinofuranosyl)uracil (VI) with diazomethane.

Thus the reaction mechanism should be explained as follows: the 2,2′-anhydro compound (I) is first methylated with methyl iodide at N_3-position to form quaternary salt (VII) which, in the presence of water, was hydrolyzed to the compound (V) with simultaneous liberation of hydrogen iodide. But in the absence of water, the intermediate (VII) must be iodinated by iodo ion at 2′-carbon atom *via* S_N2 type reaction. Thus, on reaction of methyl iodide with 2,2′-anhydro compound (I), not only methylation at the base residue but also iodination at the sugar moiety occurred to yield N_3-methyl-2′-iodo compound (II). The fact that the alkali treatment of the product (II) gave the compound (V) and the reaction mechanism described above indicated that the configuration of 2′-iodo group of the product (II) should probably be down type.

Murdock and Angier[7] reported earlier that the action of methyl iodide on 2,3′-anhydrocyclopentylthymine afforded the compound which had methyl group at N_3-position and iodo group at the cyclopentyl moiety, but they did not characterize the product well. In the next study, we reacted methyl iodide with 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil (VIII)[8] in dimethylformamide at room temperature for 2 days. Cleavage of the anhydrobond occurred with the formation of a crystalline product (IX) in a high yield. Elemental analysis and ultraviolet absorption properties of this product showed that the product (IX) should be the compound which had methyl group at N_3-position of the uracil moiety and iodo group at the carbon atom of furanosyl moiety. The product (IX) was identified by mixed fusion and comparisons of infrared spectra and *Rf* values with N_3-methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil which was synthesized by methylation with diazomethane of 1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil (X)[5] The deoxy compound (XI), which was obtained by catalytic reduction of the product (IX) with palladium, consumed 1 mole equivalent of metaperiodate, but the reaction was so slow as the case of xylofuranosyluracil,[9] indicating the presence of vicinal *trans* hydroxyl groups at 2′ and 3′ positions of this compound (Fig. 2). Thus, the structure, N_3-methyl-1-(5′-deoxy-β-D-xylofuranosyl)uracil, was proposed for the deoxy compound (XI).

If the compound (IX) had the above proposed structure, it should produce an 3′,5′-epoxy derivative by treatment with alkali. When the compound (IX) was warmed in an aqueous

7) K.C. Murdock and R.B. Angier, *J. Am. Chem. Soc.*, **84**, 3748 (1962).
8) N.C. Yung and J.J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).
9) The parent iodo containing compound (IX) consumed more than 1 mole of metaperiodate under the same condition, probably due to the promoted overoxidation by the halogeno group. The similar overoxidation was observed for 1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)- and 1-(5′-chloro-5′-deoxy-β-D-xylofuranosyl)uracils.[5]

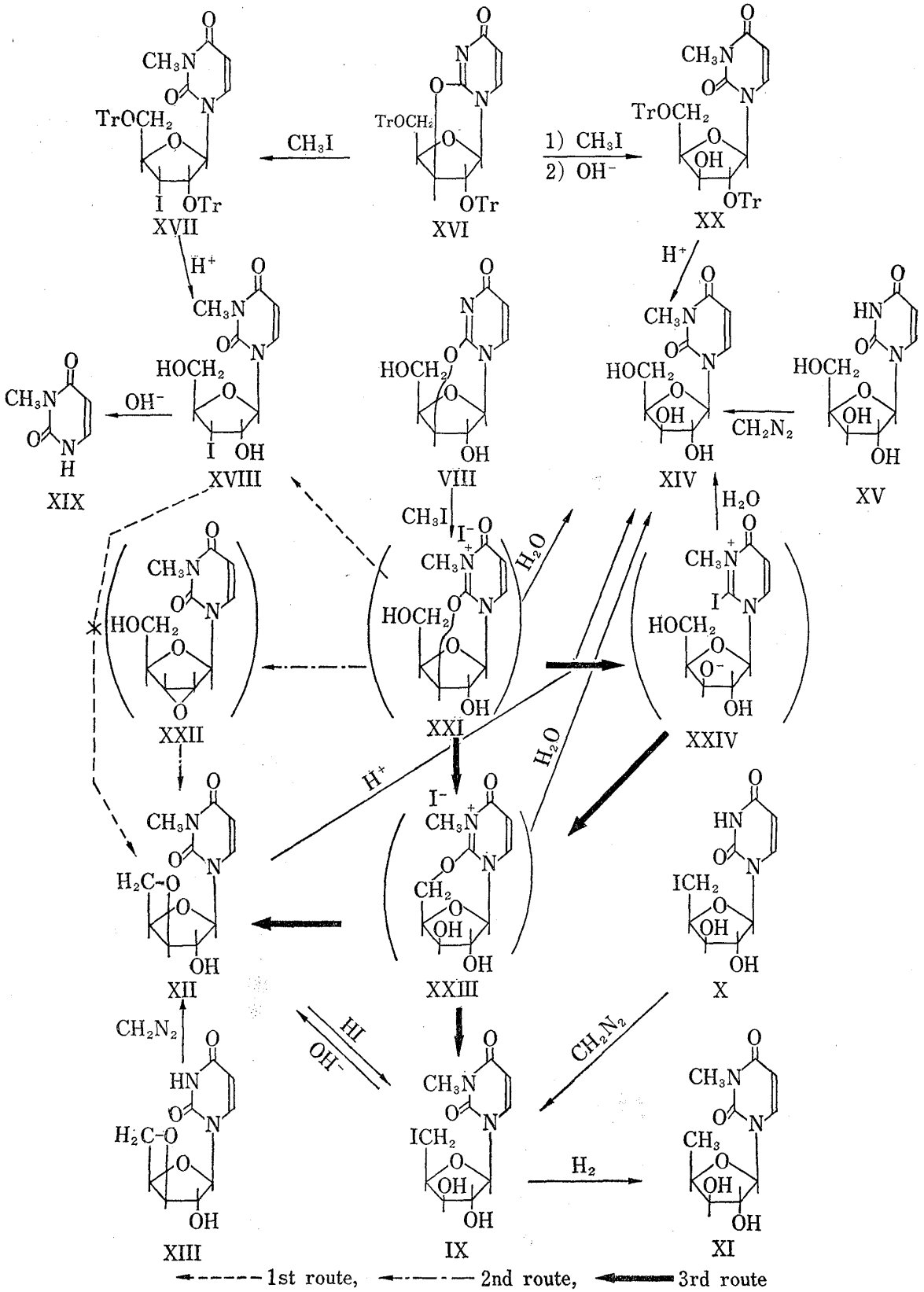


Chart 2

alkali, it gave a product (XII) in a high yield, which was quite identical with the compound obtained by reaction of 1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil (XIII)[5,10] with diazomethane. The structure of the compound (XII) was thus confirmed to be N_3-methyl-1-(3′,5′-epoxy-β-D-xylofuranoxyl)uracil. The epoxide (XII) was reversely converted into the parent iodo-containing compound (IX) by treatment with hydrogen iodide in a good yield. The results of the reactions described above fully supported the structure of the product (IX) to be N_3-methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil, which was produced from 2,3′-anhydro-compound (VIII) by reaction of methyl iodide.

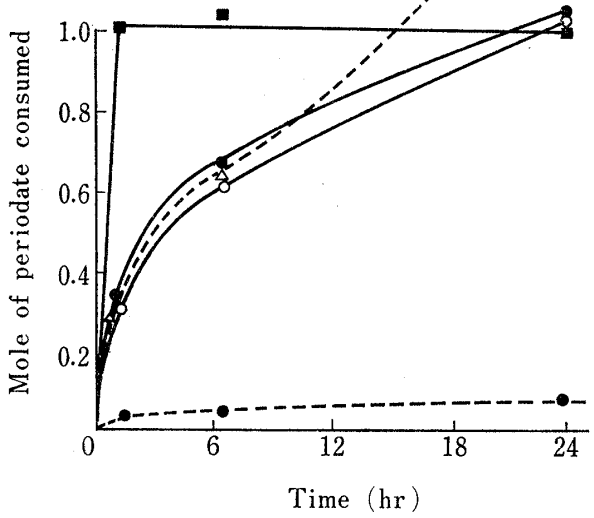


Fig. 1. Metaperiodate Consumption of the Nucleosides

···●··· : 2′-deoxyuridine (IV)
—○— : 1-(β-D-xylofuranosyl)uracil (XV)
···△··· : N_3-methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)-uracil (IX)
—●— : N_3-methyl-1-(5′-deoxy-β-D-xylofuranosyl)uracil (XI)
—■— : uridine

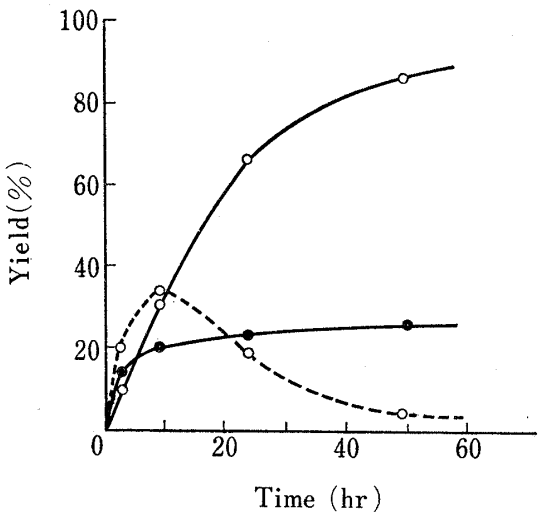


Fig. 2. Reaction Profile of 2,3′-Anhydro-1-(β-D-xylofuranosyl)uracil (VIII) with Methyl Iodide, and N_3-Methyl-1-(3′,5′-epoxy-β-D-xylofuranosyl) uracil (XII) with Methyl Iodide in the Presence of Hydrogen Iodide

The formation of the product (IX) (—○—) and hydrolysis product (XIV) of the intermediate compounds (···○···), respectively in the reaction of VIII with 7 molar excess of methyl iodide.

The formation of the product (IX) (—●—) in the reaction of XII with 7 molar excess of methyl iodide in the presence of an equimolar amount of hydrogen iodide.

In order to establish a synthetic procedure to introduce iodo group at the 3′-carbon atom of the ribosyl residue, 2,3′-anhydro-1-(2′,5′-di-O-trityl-β-D-xylofuranosyl)uracil (XVI) was heated with methyl iodide in dimethylformamide. An iodo-containing product (XVII) which was obtained in a good yield showed the elemental composition coincided with N_3-methyl-1-(2′,5′-di-O-trityl-3′-iodo-3′-deoxy-β-D-ribofuranosyl)uracil. Detritylation of the product with ether saturated with dry hydrogen chloride gave a product (XVIII). The elemental composition and ultraviolet absorption properties of this product (XVIII) were in good accordance with the structure, N_3-methyl-3′-iodo-3′-deoxyuridine. The product (XVIII) was well distinguished from the 5′-iodo derivative (IX) in melting points, thus the 5′-iodo derivative (IX) melted at 219—221° and the product (XVIII) melted at 202—205°, and the melting point depressed to 175° when both compounds were mixed. The comparisons of infrared spectra *Rf* values of these compounds also indicated that they were not indentical.

It was described above that the alkali treatment of the 5′-iodo derivative (IX) yielded 3′,5′-epoxycompound (XII), but the similar alkali treatment of 3′-iodo derivative (XVIII) did not give any trace of the epoxy compound but it resulted in the degradation of XVIII

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

to N_3-methyluracil (XIX). The results showed that by alkali treatment of 5′-iodo derivative, a nucleophilic attack of 3′-hydroxy function at 5′-carbon atom with simultaneous displacement of iodo group produced 3′,5′-epoxy compound (XII), but the similar nucleophilic attack of 5′-hydroxyl function at 3′-carbon atom hardly occurred in the case of 3′-iodo derivative (XVIII).[11]

When the reaction mixture of methyl iodide with 2,3′-anhydro compound (VIII) was detected by paper chromatography in an early stage of the reaction, besides the spots of the starting material and the final product, an additional tailing spot appeared on the chromatogram. In order to isolate this side product, the reaction mixture of methyl iodide with 2,3′-anhydro compound (VIII) in dimethylformamide at room temperature for 3 hr, was treated with small amount of water, because this product seemed to be produced from some intermediate compound by its contact with water and the products were fractionated by cellulose column chromatography. The side product thus isolated was proved to be identical by mixed melting point test, and comparisons of infrared spectra and *Rf* values with the authentic N_3-methyl-1-(β-D-xylofuranosyl)uracil (XIV) which was obtained by reaction of 1-(β-D-xylofuranosyl)uracil (XV) with diazomethane.

In Fig. 2 the reaction rates of the production of the final product (IX) and the hydrolysis product (XIV) of an intermediate compound in the reaction between methyl iodide and 2,3′-anhydro compound were plotted against time. The figure showed that the production of the compound (XIV) reached a maximum at 10 hours reaction, whereas the amount of the final product (IX) increased continuously. As the compound (XIV) did not give the final product (IX) by its treatment with methyl iodide, XIV must be produced by hydrolysis of an intermediate compound and the reaction time at which the yield of the compound (XIV) reached maximum should therefore indicate the time when the intermediate compound was produced in a maximum yield. It was found that on addition of water to the aliqout of reaction mixture taken in time intervals, the mixture was most acidic at the time when the compound (XIV) was produced in a maximum yield.

These results suggested that on reaction of methyl iodide with 2,3′-anhydro compound (VIII), the methylation at the uracil moiety resulted in the formation of an intermediate which liberated hydrogen iodide on contact with water, and which, in the reaction mixture, subsequently iodinated the sugar residue to give the final product (IX). This series of reaction was very similar to that observed in the reaction of methyl iodide with 2,2′-anhydro compound (I) as was described above. In the reaction of methyl iodide with 2′,5′-di-O-trityl-2,3′-anhydro compound (XVI), when the reaction mixture was made alkaline at an initial stage of the reaction, N_3-methyl-1-(2′,5′-di-O-trityl-β-D-xylofuranosyl)uracil (XX) was isolated in a high yield, the structure of which was confirmed by detritylation to the compound (XIV).

In the reactions mentioned above, iodination at the sugar residue always occurred after the methylation at N_3-position of the uracil moiety. Thus, when methyl iodide was allowed to react, for instance, with 2,3′-anhydro compound (VIII) it should give a first intermediate quarternary salt, namely, N_3-methyl-2,3′-anhydro-1-(β-D-xylofuranosyl)uracilyl iodide (XXI)

11) Horwitz, *et al.* (J.P. Horwitz, J. Chua and M. Noel, *Tetrahedron Letters*, **1966**, 1343) reported the action of sodium methoxide on 3′-O-tosyl-2′-deoxyadenosine afforded 1-(3′,5′-epoxy-2′-deoxy-β-D-xylofuranosyl) adenine in a low yield. So that we expected the similar nucleophilic attack of the primary hydroxyl function to secondary sulfonyloxy group in 3′-O-mesyluridine or N_3-methyl-3′-O-mesyluridine. 3′-O-Mesyluridine[8] and N_3-methyl-3′-O-mesyluridine which was synthesized by mesylation and detritylation of N_3-methyl-2′,5′-di-O-trityluridine prepared by methylation of 2′,5′-di-O-trityluridine[8] were treated in various alkaline conditions. In these cases, however, formation of 3′,5′-epoxy derivative was never observed, but in most cases cleavage of the glycosyl bond occurred except one case for the potassium butoxide treatment of 3′-O-mesyluridine, which yielded 2,3′-anhydro compound (VIII). These results indicated that the 3′-carbon atom of uridine and N_3-methyluridine which is substituted with O-mesyl or iodo group could not be attacked by 5′-hydroxyl function.

which could be converted to the final product through one of the following three theoretical routes.

The First Route: the iodide ion in the quarternary salt (XXI) attacks the 3′-carbon atom of the ribosyl moiety which was concerned with the formation of the anhydrobond and cleaves the anhydrobond to form N_3-methyl-3′-iodo-3′-deoxyuridine (XVIII). The 5′-hydroxyl function of the compound (XVIII) then attacks intramolecularly the 3′-carbon atom to afford N_3-methyl-1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil (XII) with simultaneous liberation of equimolar amount of hydrogen iodide. The compound (XII), in the presence of hydrogen iodide, is rapidly converted to the final 5′-iodo derivative (IX).

The Second Route: the 2′-hydroxyl function of the quaternary salt (XXI) attacks intramolecularly the 3′-carbon atom to form neutral N_3-methyl-2′,3′-epoxyuridine (XXII) with liberation of equimolar amount of hydrogen iodide, then 5′-hydroxyl function of XXII attacks the 3′-carbon atom in the presence of hydrogen iodide to form 3′,5′-epoxy-derivative (XII) whose epoxy ring is rapidly cleaved by iodo ion to afford the final product (IX). Thus this pathway involves, two intermediate compounds, XXII and XII between the quaternary salt (XXI) and the final product (IX).

The Third Route: the 5′-hydroxyl function of the quaternary salt (XXI), attacks the C_2 carbon atom of the uracil moiety to produce the second intermediate, N_3-methyl-2,5′-anhydro-1-(β-D-xylofuranosyl)uracilyl iodide (XXIII) accompanying a rearrangement of the anhydrobond. This intermediate (XXIII) will also be formed *via* a zwitter ionic compound, N_3-methyl-2-iodo-1-(β-D-xylofuranosyl)-4-pyrimidinone (XXIV) which is formed from XXI by the attack of iodo ion at its C_2 carbon atom of the uracil moiety. This intermediate (XXIII) could be converted to the final product (IX) through one of the following two possible routes. First, an intramolecular attack of the 3′-hydroxyl function in 2,5′-anhydro compound (XXIII) at the 5′-carbon atom would afford 3′,5′-epoxy compound (XII) and equimolar amount of hydrogen iodide. The subsequent attack of the iodo ion at the 5′-carbon atom in XII would afford the final product (IX).

Second, as was reported with the reactions of 2,5′-anhydrouridine derivatives,[12] the final product (IX) would be produced directly from the intermediate (XXIII) by the attack of iodo ion at the 5′-carbon atom.

The N_3-methyl-3′-iodo-3′-deoxyuridine (XVIII) which was prepared from 2′,5′-di-O-trityl derivative (XVI) was treated with methyl iodide in dimethylformamide at room temperature for several days, the same conditions used for the convertion of VIII to the product (IX), but the compound (XVIII) was inert to the reaction and did not give the 5′-iodo derivative (IX). Thus the possibility of involvement of the first route was completely excluded. Concerning with the second route, 3′,5′-epoxy derivative (XII) which was obtained by alkali treatment of the 5′-iodo derivative (IX) was reacted with methyl iodide in dimethylformamide in the presence of equimolecular amount of hydrogen iodide and the reaction rate of the formation of the final product (IX) was plotted against time and shown in Fig. 2. The figure indicated that the rate was much slower than that in the conversion of 2,3′-anhydro derivative (VIII) to the product (IX) by action of methyl iodide under the similar conditions. From the results, the 3′,5′-epoxy derivative (XII) could hardly be involved in the real pathway. Thus, the second route could also be eliminated from the consideration. The third route involves an additional quaternary salt (XXIII) and the iodo ion of this compound attacks the 5′-carbon atom to give the final product (IX). The occurrence of this reaction is readily

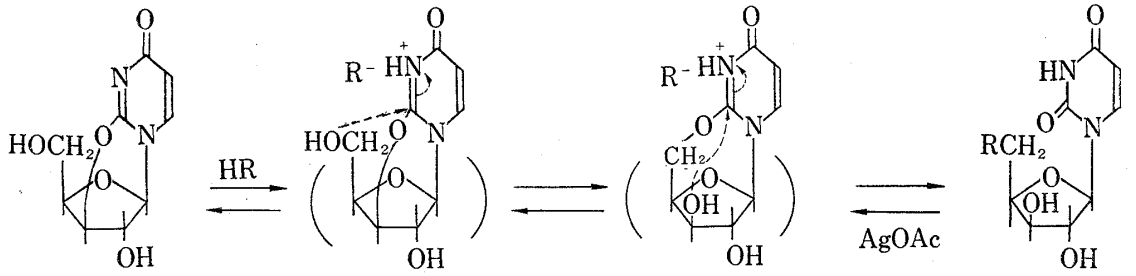
12) D.M. Brown, A.R. Todd and S. Varadarajan, *J. Chem. Soc.*, **1957**, 868; I.L. Doerr and J.J. Fox, *J. Org. Chem.*, **32**, 1465 (1967); D.M. Brown, D.B. Parihar, A.R. Todd and S. Varadarajan, *J. Chem. Soc.*, **1958**, 3028; R.W. Chambers and V. Kurkov, *J. Am. Chem. Soc.*, **85**, 2160 (1963); J.P. Horwitz, A.J. Tomson, J.A. Urbanski and J. Chua, *J. Org. Chem.*, **27**, 3045 (1962); J. Žemlička and J. Šmrt, *Tetrahedron Letters*, 1964, 2081; J. Nagyvary, *Biochemistry*, **5**, 1316 (1966); Y. Mizuno, T. Sasaki, T. Kanai and H. Igarashi, *J. Org. Chem.*, **30**, 1533 (1965).

acceptable as the analogous reaction has been reported for 2,5′-anhydrouridine derivative.[12] The real route, therefore, should be represented by: VIII→XXI→(XXIV)→XXIII→IX.

All of the proposed intermediate compounds (XXI, XXIV and XIII) involved in the third route seemed to be so unstable for detection or isolation that they all were hydrolysed to N_3-methyl-1-(β-D-xylofuranosyl)uracil (XIV) on contact with water.

The most probable route of the reaction of 2,3′-anhydro compound (VIII) with methyl iodide involves a rearrangement of the anhydro bond 2,3′ to 2,5′ in the convertion of the first intermediate N_3-methyl-2,3′-anhydro-1-(β-D-xylofuranosyl)uracilyl iodide (XXI) to the second intermediate N_3-methyl-2,5′-anhydro-1- (β-D-xylofuranosyl)uracilyl iodide (XXIII). The molecular model of the 2,3′-anhydro compound (VIII) indicated that the 5′-hydroxyl function of this compound is so closely positioned to the C_2 carbon atom of the uracil moiety and supported the easy occurrence of the rearrangement of the anhydrobond.

It has been reported in the preceeding paper[5] that the reaction of hydrogen halides with 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil gave 1-(5′-halogeno-5′-deoxy-β-D-xylofuranosyl) uracils (XXVII). The mechanism of that reaction could be explained by an analogus path-



VIII XXV XXVI XXVII

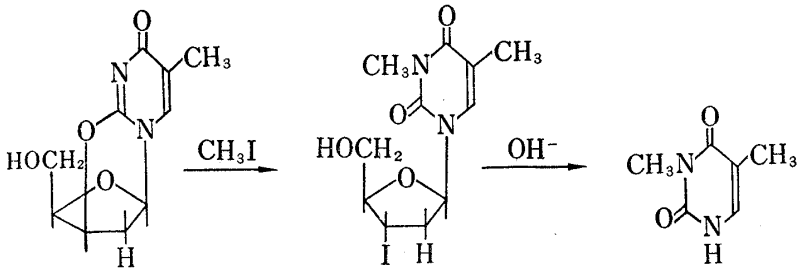
Chart 3

way, in which the methyl group in above third route was replaced with hydrogen, thus a protonation at the N_3-position of the uracil moiety of the anhydro compound (XXV) derived the rearrangement of anhydro bond to XXVI which was subsequently converted directly to the halogenonucleoside (XXVII). Together with our previous observation[5] that the action of silver acetate on 1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil initially formed 2,5′-anhydro compound which was then rearranged to 2,3′-anhydro compound, the results described above might give the conclusion that 2,3′-anhydroxylosyluracil and the 2,5′-anhydroxylosyluracil are interconvertible depending on the reaction conditions, and that the 2,5′-anhydro derivative is more reactive than the 2,3′-anhydro derivative.

Such a rearrangement of the anhydro bond 2,3′ to 2,5′ has never been known for 2,2′-anhydro pyrimidine nucleoside. The molecular models of the 2,2′-anhydro compounds, when compared with that of the 2,3′-anhydro derivatives indicated that the 5′-hydroxyl function positioned far from C_2 carbon atom of the base moiety.

In connection with the observation obtained above, it is noteworthy that 2,3′-anhydro thymidine did not indicate such rearrangement of anhydro bond as above by reaction with methyl iodide. Thus, when 2,3′-anhydro-1-(2′-deoxy-β-D-xylofuranosyl)thymine (XXVIII)[13,14] was allowed to react with methyl iodide in dimethylformamide, the product isolated was N_3-methyl-3′-iodo-3′-deoxythymidine (XXIX) whose *Rf* values were quite identical with those of the compound obtained by the reaction of methyl iodide with 5′-tritylated deriva-

13) A.M. Michelson and A.R. Todd, *J. Chem. Soc.*, **1955**, 816.
14) J.J. Fox and N.C. Miller, *J. Org. Chem.*, **28**, 936 (1963).



XXVIII XXIX XXX

Chart 4

tive of XXVIII and subsequent detritylation. Furthermore, the compound (XXIX), liberated N_3-methylthymine (XXX) in alkali treatment. It is also noteworthy that the phosphate ion attacked the 3′-carbon atom (not the 5′-carbon atom) of 2,3′-anhydro-1-(β-D-xylofuranosyl)-cytosine.[15] It is interesting that the difference of the sugar moiety or the base moiety of the 2,3′-anhydro compounds effects the cleavage of the anhydro bonds differently.

In conclusion, the action of methyl iodide on 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (I) and 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil (VIII) gave N_3-methyl-2′-iodo-2′-deoxyuridine (II) and N_3-methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil (IX), respectively. The reaction mechanism of the latter series was found to involve a rearrangement of the anhydro bond from the 2,3′ to the 2,5′ bond.

Experimental[16]

Methods

Paper chromatography was performed on Toyo Roshi No. 53 filter 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 *Rf* value of the spot obtained for individual solvent was represented by the symbol, *Rf*, with suffix corresponding to the number of the solvents. The spots were located by ultraviolet absorption of the compounds.

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

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

Metaperiodate titration was performed as follows: the solutions containing 1 to 3 mM of nucleoside were treated with excess sodium metaperiodate at 25° and the remaining reagent was determined iodometrically according to the usual procedures.[17]

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil (I)——The experimental procedure to synthesize this compound from uridine was entirely the same as reported by Hampton.[6] The product which was obtained in a yield of 65%, melted at 236—239° and showed the following properties: Rf_2 0.16, UV $\lambda_{max}^{H_2O}$ mμ (ε): 223 (8850), 251.5 (8400); $\lambda_{min}^{H_2O}$: 235.5 (6550), shoulder 270.5 (2380), $\lambda_{max}^{conc\ H_2SO}$: 219 (4840), 255.5 (6390), $\lambda_{min}^{conc\ H_2SO}$: 233.6 (4140).

N_3-Methyl-2′-iodo-2′-deoxyuridine (II)——To a suspension of 500 mg of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (I) in 10 ml of DMF, was added 1.0 ml of methyl iodide. The mixture was stirred vigorously at room temperature for 48 hr. The solvent was removed *in vacuo*, and the residue was crystallized from ethanol to afford 620 mg (yield, 77%) of pure product, mp 176° (decomp.). Rf_1 0.86, Rf_2 0.74, Rf_3 0.78. UV $\lambda_{max}^{H_2O}$ mμ (ε): 260 (8600), $\lambda_{max}^{H_2O}$: 232 (2500), $\lambda_{max}^{0.1N\ NaOH}$: 264 (10000), $\lambda_{min}^{0.1N\ NaOH}$: 237 (4200). $[\alpha]_D^{12°}$: +5° (c=0.25 in H_2O). *Anal.* Calcd for $C_{10}H_{13}O_5N_2I$: C, 32.62; H, 3.56; N, 7.61. Found: C, 32.95; H, 3.85; N, 7.58.

N_3-Methyl-2′-deoxyuridine (III)——Method A. From N_3-Methyl-2′-iodo-2′-deoxyuridine (II): To a solution of 330 mg of N_3-methyl-2′-iodo-2′-deoxyuridine (II) in 30 ml of 50% EtOH were added 300 mg of 5% palladium on $BaSO_4$ and 0.3 ml of triethylamine. The mixture was shaken in hydrogen atmosphere at 760 mmHg for 7 hr. The catalyst was removed by centrifugation, and the supernatant was passed through

15) Y. Mizuno and T. Sasaki, *Tetrahedron Letters*, **1965**, 4579.
16) All melting points are uncorrected.
17) J.J. Fox, N.C. Yung, J. Daroll and G.B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).

a Dowex 1 (HCO_3^-) column and the effluent was evaporated to dryness. The residual gum was crystallized from EtOAc to give 71 mg (yield, 33%) of plates, mp 98—100°. Rf_1 0.79, Rf_2 0.60, Rf_3 0.66. UV $\lambda_{max}^{H_2O}$ mμ: 262, $\lambda_{max}^{0.1N\ NaOH}$: 264. *Anal.* Calcd. for $C_{10}H_{14}O_5N_2$: C, 49.59; H, 5.82; N, 11.56. Found: C, 49.30; H, 5.72; N, 11.48.

Method B. From 2′-Deoxyuridine (IV): One milliliter of a dimethylformamide (DMF)-solution containing 100 mg of 2′-deoxyuridine (IV) was saturated with diazomethane. After standing the mixture at room temperature for 2 to 3 hr, the solvent was removed *in vacuo* to give a gum, which was purified by applying to a cellulose column (2 cm×28 cm) and eluting with the solvent of BuOH–H_2O (84:16). The eluate which contained the product was evaporated to dryness and the residue was crystallized from EtOAc to afford 85 mg (yield, 80%) of plates, mp 98—100°. Rf_1 0.79, Rf_2 0.60, Rf_3 0.66. UV $\lambda_{max}^{H_2O}$ mμ: 262, $\lambda_{max}^{0.1N\ NaOH}$: 264.

The mixed fusion of the products obtained by method A and method B did not show any depresson of the melting point.

N_3-Methyl-1-(β-D-arabinofuranosyl)uracil (V)——Method A. From 1-(β-D-arabinofuranosyl)uracil (VI): A solution of 50 mg of 1-(β-D-arabinofuranosyl)uracil (VI)[18] in 1 ml of DMF was saturated with diazomethane. The mixture was kept at room temperature for 2 to 3 hr, and the solution was evaporated to dryness. The residue was applied onto a cellulose column (2 cm×28 cm) and eluted with the mixed solvent, BuOH–H_2O (84:16). The fractions which contained V were evaporated to dryness and the residue was recrystallized from EtOAc to furnish the pure product melting at 163—164°. Rf_1 0.83, Rf_2 0.51, Rf_3 0.59.

Method B. From N_3-Methyl-2′-iodo-2′-deoxyuridine (II): A solution of 288 mg of N_3-methyl-2′-iodo-2′-deoxyuridine (II) in 50 ml of water was adjusted to pH 8.5 with sodium azide, and heated in a water bath for 8.5 hr. The mixture was successively passed through a Dowex 50 (H^+) and Dowex 1 (HCO_3^-) columns to remove inorganic salt. The effluent from the columns was evaporated to dryness to obtain crystals, which were recrystallized from EtOAc to give 174 mg (yield, 87%) of plates, mp 168—170°. Rf_1 0.83, Rf_2 0.51, Rf_3 0.59. UV $\lambda_{max}^{H_2O}$ mμ (ε): 262 (9400), $\lambda_{min}^{H_2O}$: 232 (2300), $\lambda_{max}^{0.1N\ NaOH}$: 261 (9300), $\lambda_{min}^{0.1N\ NaOH}$: 237 (3700). $[\alpha]_D^{12°}$: +22° (c=0.2 in H_2O). *Anal.* Calcd. for $C_{10}H_{14}O_6N_2$: C, 46.50; H, 5.46; N, 10.85. Found: C, 46.82; H, 5.47; N, 10.84.

The mixed melting point test of the compounds obtained by method A and method B did not show any depression.

Isolation of N_3-Methyl-1-(β-D-arabinofuranosyl)uracil (V) from the Reaction Mixture of Methyliodide and 2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil (I)——To a solution of 150 mg of 2,2′-anhydro-1-(β-D-arabinofruanosyl)uracil (I) in 3 ml of DMF was added 0.3 ml of methyl iodide. The solution was kept at room temperature for 4 hr and to it was added 1 ml of water. On application of the mixture to paper chromatography, three spots having Rf_2 values of 0.74 (II), 0.51 (V), and 0.16 (I) were observed. The mixture was evaporated to dryness and applied onto a cellulose column (2 cm×28 cm) and eluted with a mixed solvent of BuOH–H_2O (84:16), to separate into two products (II and V) and the starting material (I). The fractions containing the product (V) were evaporated to dryness and the residual gum was treated with EtOAc to give 40 mg of crystals which melted at 166—167°. Rf_1 0.83, Rf_2 0.51, Rf_3 0.59. The product did not show depression in a mixed fusion test with the authentic sample of N_3-methyl-1-(β-D-arabinofuranosyl)uracil.

N_3-Methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil (IX)——Method A. From 2,3′-Anhydro-1-(β-D-xylofuranosyl)uracil (VIII): A solution of 250 mg of 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil (VIII)[8] and 1.0 ml of methyl iodide in 10 ml of DMF was kept at room temperature for 2 days under complete prevention of the moisture. The solvent and excess methyl iodide were removed *in vacuo* below 65°. The residue was purified by recrystallization from EtOH to give 350 mg (yield, 86%) of the product (IX), mp 219—221° (decomp.). Rf_1 0.91, Rf_2 0.82, Rf_3 0.88. UV $\lambda_{max}^{H_2O}$ mμ (ε): 262 (10800), $\lambda_{min}^{H_2O}$: 232 (3400), $\lambda_{max}^{0.1N\ NaOH}$: 261 (10200), $\lambda_{min}^{0.1N\ NaOH}$: 238 (5300). $[\alpha]_D^{12°}$: +33° (c=0.15 in H_2O). *Anal.* Calcd. for $C_{10}H_{13}O_5N_2I$: C, 32.62; H, 3.56; N, 7.61. Found: C, 33.01; H, 3.57; N, 7.91.

Method B. From 1-(5′-Iodo-5′-deoxy-β-D-xylofuranosyl)uracil (X): About 30 equivalent moles excess of diazomethane was allowed to react with 50 mg of 1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil (X)[5] in 1 ml of DMF. After standing the mixture at room temperature for one hour, the solvent and excess of diazomethane were removed by evaporation and the resulting gum was crystallized from EtOH to afford 12 mg of crystals, mp 215—219° (decomp.). Rf_1 0.91, Rf_2 0.82, Rf_3 0.88.

The product was quite identical with that obtained by method A, in mixed fusion test and infrared spectra.

Method C. From N_3-Methyl-1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil (XII): A solution of 100 mg of N_3-methyl-1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil (XII) in 1 ml of 1N hydriodic acid was heated at 70° for 1 hr. The reaction mixture was passed through Dowex 1 (HCO_3^-) column to remove excess hydroiodic acid, and the eluate from the column was evaporated to dryness. The residue was crystallized from EtOH to afford the product (IX) in a yield of 70%, which melted at 219—221° (decomp.) and was identified by mixed fusion test with the compound obtained by method A.

18) D.M. Brown, A.R. Todd and S. Varadarajan, *J. Chem. Soc.*, **1956**, 2388.

The product (IX) obtained by method A consumed 1.4 equivalent moles of metaperiodate in a same time interval, in which 1-(β-D-xylofuranosyl)uracil consumed 1 equivalent mole of the metaperiodate (Fig. 1).

N_3-Methyl-1-(5′-deoxy-β-D-xylofuranosyl) uracil (XI)—N_3-Methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl) uracil (IX) (165 mg) was dissolved in 10 ml of EtOH containing 330 mg of 5%-palladium on $BaSO_4$ and 0.15 ml of triethylamine. The mixture was shaken in hydrogen atmosphere at 760 mmHg and room temperature for 10 hr. The catalyst was removed by centrifugation and the supernatant was evaporated *in vacuo* to dryness. Crystallization of the residual gum from ethyl acetate gave 88 mg (yield, 81%) of the product (XI), mp 146—148°. Rf_1 0.85, Rf_2 0.69, Rf_3 0.77. UV $\lambda_{max}^{H_2O}$ mμ (ε): 262 (7300), $\lambda_{min}^{H_2O}$: 232 (1600), $\lambda_{max}^{0.1N\ NaOH}$: 264 (7800), $\lambda_{min}^{0.1N\ NaOH}$: 235 (2000). $[\alpha]_D^{12°}$: +4° (c=0.25 in H_2O). *Anal.* Calcd. for $C_{10}H_{14}O_5N_2$: C, 49.59; H, 5.82; N, 11.56. Found: C, 49.67; H, 5.91; N, 11.71.

The product did not color with cystein–sulfuric acid reagent[19] and consumed 1 equivalent mole of metaperiodate slowly in the similar reaction rate as that observed for 1-(β-D-xylofuranosyl)uracil (Fig. 1).

N_3-Methyl-1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil (XII)——Method A. From N_3-Methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil (IX): To a solution of 120 mg (0.33 mmole) of N_3-methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil (IX) in 15 ml of 50% EtOH was added 3.5 ml (0.35 mmole) of 0.1N NaOH. The mixture was refluxed for 7 hr, and then passed through the columns of Dowex 50 (H^+) and Dowex 1 (HCO_3^-) successively to remove inorganic salts. The effluent was evaporated to dryness, and the residue was dissolved in a small amount of EtOAc, and to the solution was added petroleum ether until slight turbidity was observed. The precipitated crystals were recrystallized from the mixed solvents of EtOAc and petroleum ether to give 50 mg (yield, 63%) of the pure product, mp 118—120°. Rf_1 0.82, Rf_2 0.55, Rf_3 0.66. UV $\lambda_{max}^{H_2O}$ mμ (ε): 262 (9000), $\lambda_{min}^{H_2O}$: 232 (2700), $\lambda_{max}^{0.1N\ NaOH}$: 260 (8800), $\lambda_{min}^{0.1N\ NaOH}$: 237 (3700). $[\alpha]_D^{12°}$: −63° (c=0.15 in H_2O). *Anal.* Calcd. for $C_{10}H_{12}O_5N_2$: C, 49.99; H, 5.04; N, 11.66. Found: C, 49.84; H, 5.00, N, 11.81.

When the product (XII) was hydrolysed with 0.25N H_2SO_4 at 100° for 1 hr, it gave N_3-methyl-1-(β-D-xylofuranosyl)uracil (XIV) which was identified with authentic specimen by paper chromatography and paper electrophoresis and spectrophotometric analysis.

Method B. From 1-(3′,5′-Epoxy-β-D-xylofuranosyl)uracil (XIII): 1-(3′,5′-Epoxy-β-D-xylofuranosyl) uracil (XIII)[5,10] (100 mg) was treated with excess diazomethane in 3 ml of DMF at room temperature for 3 hr. The product was recrystallized from the mixture of EtOAc and petroleum ether as above to give 15 mg of the pure sample, mp 118—120°. (Rf_1 0.82, Rf_2 0.55, Rf_3 0.66) which was identified by mixed melting point test and comparison of infrared spectra with the product obtained by method A.

N_3-Methyl-1-(β-D-xylofuranosyl)uracil (XIV)——To a solution of 200 mg of 1-(β-D-xylofuranosyl)uracil (XV)[8] in 10 ml of water was added 50 ml of ethereal solution of 30 equivalent moles excess of diazomethane, and the mixture was vigorously shaken at room temperature for 30 minutes. The solvent was removed *in vacuo*, and the resulting syrup was applied onto a cellulose column (2 cm × 27 cm). The column was eluted with a mixed solvent of BuOH–H_2O (84:16) and the fractions which contained the product (XIV) were combined and evaporated to dryness. The residual syrup was recrystallized from EtOAc to give 50 mg (yield, 25%) of pure sample, mp 178—180°. Rf_1 0.79, Rf_2 0.50, Rf_3 0.60. UV $\lambda_{max}^{H_2O}$ mμ (ε): 262 (12800), $\lambda_{min}^{H_2O}$: 227 (3600), $\lambda_{max}^{0.1N\ NaOH}$: 261 (12400), $\lambda_{min}^{0.1N\ NaOH}$: 235 (4500). $[\alpha]_D^{12°}$: +16° (c=0.2 in H_2O). *Anal.* Calcd. for $C_{10}H_{14}O_6N_2$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.50; H, 5.46; N, 10.96.

Isolation of N_3-Methyl-1-(β-D-xylofuranosyl)uracil (XIV) from the Reaction Mixture of Methyliodide and 2,3′-Anhydro-1-(β-D-xylofuranosyl)uracil (VIII)——A mixture of 100 mg of 2,3′-anhydro-1-(β-D-xylofuranosyl) uracil (VIII)[8] 0.2 ml of methyl iodide and 2 ml of DMF was set aside at room temperature for 3 hr. The solvent and excess of methyl iodide were removed *in vacuo* to dryness, and the residue was applied to a cellulose column (2 cm × 28 cm) eluting with the mixed solvent, BuOH–H_2O (84:16). The fractions which contained a product having Rf_2 of 0.82 were pooled and evaporated to dryness. Crystallization of the residue from EtOH gave 30 mg of N_3-methyl-1-(5′-iodo-5′-deoxy-β-D-xylofuranosyl)uracil (IX), mp 218—220° (decomp.). The fractions which contained another product having Rf_2 of 0.50 were pooled and evaporated to dryness. The residue was crystallized from a mixture of ethyl acetate and ligroin (1:2) to give 20 mg of crude product, mp 155—175°. Recrystallization from ethyl acetate gave 10 mg of plates mp 180—182°. Rf_1 0.79, Rf_2 0.50, Rf_3 0.60. UV $\lambda_{max}^{H_2O}$ mμ: 265, $\lambda_{max}^{0.1N\ NaOH}$: 267. *Anal.* Calcd. for $C_{10}H_{14}O_6N_2$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.45; H, 5.46; N, 10.56.

In mixed melting point test and infrared spectra, the product was quite identical with authentic N_3-methyl-1-(β-D-xylofuranosyl)uracil (XIV).

N_3-Methyl-2′,5′-di-O-trityl-3′-iodo-3′-deoxyuridine (XVII)——2,3′-Anhydro-1-(2′,5′-di-O-trityl-β-D-xylofuranosyl)uracil (XVI)[8] (1.0 g) was dissolved in 9 ml of DMF, and to the solution was added 1.5 ml of methyl iodide. After keeping at room temperature overnight, the mixture was heated at 100° for 1 hr and subsequently evaporated to dryness. Crystallization of the residue from a mixture of $CHCl_3$, EtOAc and EtOH (1:1:1), gave 910 mg (yield, 77%) of the product, mp 235—245° (decomp.) which showed positive reaction in Beilstein test. *Anal.* Calcd. for $C_{48}H_{41}O_5N_2I$: C, 67.66; H, 4.86; N, 3.30. Found: C, 67.86; H, 5.16; N, 3.57.

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

N_3-Methyl-3′-iodo-3′-deoxyuridine (XVIII)——A suspension of 100 mg of N_3-methyl-2′,5′-di-O-trityl-3′-iodo-3′-deoxyuridine (XVII) in 50 ml of absolute ether was saturated with hydrogen chloride. The mixture was stored at 0° for 1 hr, and evaporated *in vacuo* to dryness under complete prevention of the moisture. The residue was extracted several times with ether and recrystallized from EtOH to furnish 10 mg (yield, 25%) of pure sample of XVIII, mp 202—205°. Rf_1 0.86, Rf_2 0.74, Rf_3 0.81. UV $\lambda_{max}^{H_2O}$ mμ: 262, $\lambda_{max}^{0.1N\ NaOH}$: 264. *Anal.* Calcd. for $C_{10}H_{13}O_5N_2I$: C, 32.62; H, 3.56; N, 7.61. Found: C, 32.41; H, 3.74; N, 8.15.

Mixed fusion of the compound (XVIII) with the products (IX) (mp 219—221°) and that (IX) (mp 215—219°) obtained by the methods A and B described above, respectively, revealed each depressed melting points of 175° and 187°.

Dilute alkali treatment of the compound (XVIII) and subsequent analysis of the product by paper chromatography indicated that the glycosyl bond of XVIII was cleaved to yield N_3-methyluracil (XIX) (UV $\lambda_{max}^{H_2O}$ mμ: 260, $\lambda_{max}^{0.1N\ NaOH}$: 284, Rf_2 0.66).

N_3-Methyl-1-(2′,5′-di-O-trityl-β-D-xylofuranosyl)uracil (XX)——A mixture of 0.3 g (0.4 mmole) of 2,3′-anhydro-1-(2′,5′-di-O-trityl-β-D-xylofuranosyl)uracil (XVI),[8] 3 ml of DMF and 0.1 ml (1.7 mmoles) of methyl iodide was kept at room temperature for 30 minutes. To the reaction mixture was added 0.2 ml of 2N NaOH (0.4 mmole), and 270 mg (yield, 92.5%) of crystals (mp 130°) obtained were collected. The product did not give positive Beilstein test but showed characteristic ultraviolet absorptions for N_1,N_3-disubstituted uracil. Recrystallization from a large amount of EtOH gave pure sample, mp 240° (decomp.). *Anal.* Calcd. for $C_{48}H_{42}O_6N_2 \cdot C_2H_5OH$: C,76.13; H, 6.14; N, 3.55. Found: C, 76.53, H, 5.62, N, 4.10.

The product (XX) was heated at 100° for 30 minutes in 80% AcOH to remove the trityl groups and the product was applied to paper chromatography and paper electrophoresis. The *Rf* values and electrophoretic mobilities of the detritylated compound were quite identical with those of N_3-methyl-1-(β-D-xylofuranosyl)uracil (XIV).

N_3-Methyl-3′-O-mesyluridine——A solution of 5.6 g of 2′,5′-di-O-trityluridine[8] in 100 ml of DMF was treated with large excess of diazomethane. The mixture was stored at room temperature overnight, and then evaporated to dryness. Crystallization of the residue gave 5.00 g (yield, 93%) of N_3-methyl-2′,5′-di-O-trityluridine. Recrystallization furnished pure sample, having mp 212—214°. *Anal.* Calcd. for $C_{48}H_{42}O_6N_2$: C, 77.60; H, 5.70; N, 3.77. Found: C, 77.60; H, 5.64; N, 3.55.

To a solution of 3.5 g of the above sample in 40 ml of pyridine was added 1 ml of mesyl chloride under cooling at 0°. The mixture was kept at 5° for 18 hr. After addition of a small amount of EtOH to the mixture, it was evaporated to dryness. The residual gum was washed well with water, dried and crystallized from a mixture of ethanol and ethyl acetate (1:1) to afford 2.87 g (yield, 75%) of N_3-methyl-2′,5′-di-O-trityl-3′-O-mesyluridine, mp 184—194°.

An ethanolic solution (50 ml) of 1.5 g of the above compound was saturated with dry hydrogen chloride and refluxed for 30 minutes. The solvent was removed *in vacuo*, and the residue was extracted several times with ether and then the resulting syrup was crystallized from EtOH to furnish 590 mg (yield, 96%) of N_3-methyl-3′-O-mesyluridine, mp 173—175°. Rf_1 0.83, Rf_2 0.59, Rf_3 0.64. UV $\lambda_{max}^{H_2O}$ mμ (ε): 260 (8500), $\lambda_{min}^{H_2O}$: 232 (2600), $\lambda_{max}^{0.1N\ NaOH}$: 262 (8600), $\lambda_{min}^{0.1N\ NaOH}$: 237 (3800). $[\alpha]_D^{12°}$: −12° (c=0.25 in H_2O). *Anal.* Calcd. for $C_{11}H_{16}O_8N_2S$: C, 39.29; H, 4.79; N, 8.33. Found: C, 39.34; H, 4.84; N, 8.21.

N_3-Methyl-1-(3′-iodo-2′,3′-dideoxy-β-D-ribofuranosyl)thymine (XXIX)——A mixture of 130 mg of 2,3′-anhydro-1-(2′-deoxy-β-D-xylofuranosyl)thymine (XXVIII),[14,15] 1 ml of methyl iodide and 10 ml of DMF was stored at room temperature for 48 hr. The reaction mixture was evaporated *in vacuo* to dryness, and the resulting syrup was recrystallized from a mixed solvent of EtOH–H_2O (1 : 2), to give 60 mg (yield, 45%) of the product, mp 114—116°. The product was positive to Beilstein test. Rf_1 0.96, Rf_2 0.89, Rf_3 0.92. UV $\lambda_{max}^{H_2O}$ mμ (ε): 267 (9100), $\lambda_{min}^{H_2O}$: 236 (2900), $\lambda_{max}^{0.1N\ NaOH}$: 267 (9400), $\lambda_{min}^{0.1N\ NaOH}$: 237 (3000)., $[\alpha]_D^{12°}$: +20° (c=0.2 in H_2O). *Anal.* Calcd. for $C_{11}H_{15}O_4N_2I$: C, 36.10; H, 4.13; N, 7.65. Found: C, 36.50; H, 4.38; N, 7.74.

2,3′-Anhydro-1-(5′-O-trityl-2′-deoxy-β-D-xylofuranosylthymine[14] (300 mg) was dissolved in 3 ml of DMF and treated with 0.2 ml of methyl iodide. After standing at room temperature for 3 days, the mixture was evaporated *in vacuo* to furnish 350 mg of a foam. The foam was heated at 100° in 80% AcOH for 30 minutes, and subsequently submitted to paper chromatography. *Rf* values of the resulting product were identical with those of the compound (XXIX).

The product (XXIX) was degradated into N_3-methylthymine (XXX) when it was heated at 100° for 1 hr in 0.1N NaOH, which gave the following properties: UV $\lambda_{max}^{H_2O}$ mμ: 264, $\lambda_{max}^{0.1N\ NaOH}$: 281. Rf_1 0.71, Rf_2 0.78, Rf_3 0.77.

Comparison of the Reaction Rate——A) The Reaction of 2,3′-Anhydro-1-(β-D-xylofuranosyl)uracil (VIII) with Methyl Iodide: A solution of 0.05 mmole of 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil (VIII)[8] and 0.34 mmole of methyl iodide in 0.5 ml of DMF was kept at room temperature. Aliquotes (0.1 ml) were withdrawn at adequate time intervals, and submitted to paper chromatography. Three spots, Rf_2 0.82, 0.50 and 0.17 (corresponding to the compounds IX, XIV and VIII respectively) were detected. The spots were extracted with 5 ml of water and the extracts analyzed spectrophotometrically at 260 mμ (in the case of IX and XIV), and at 250 mμ (in the case of VIII).

B) The Reaction of N_3-Methyl-1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil (XII) with Methyliodide–Hydrogen Iodide Mixture: A solution of 0.05 mmole of N_3-methyl-1-(3′,5′-epoxy-β-D-xylofuranosyl)uracil (XII), 0.34 mmole of methyl iodide and 0.5 ml of DMF containing 0.05 mmole of hydrogen iodide was kept at room temperature. Aliquotes (0.1 ml) were withdrawn at adequate time intervals, and analyzed as above. The estimated amount of the compound (IX) yielded was plotted against time. The results of these experiments are shown in Fig. 2.

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