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Methods of Synthesis of Pyrimidine Nucleosides

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The review describes the present state of knowledge about the synthesis of pyrimidine nucleosides. Together with a description of various methods of synthesis, their comparative characteristics are stated briefly. The bibliography includes 188 references.

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I. INTRODUCTION

The chemistry of nucleosides and nucleic acids is at present one of the most vigorously developing fields despite the considerable difficulties facing investigators engaged in it. The interest in the chemistry of nucleosides is quite understandable. There are good grounds for attributing to the analogues of nucleosides the capacity to influence heredity, to act on the development of viruses, and to suppress the growth of malignant tumors. Finally the availability of a large set of various nucleosides constitutes an essential condition for theoretical studies on the mechanism of the biosynthesis of nucleic acids and proteins, on the specificity of the relevant enzymes, etc.

In view of the great interest in the chemistry of nucleosides, the literatures in this field is exceptionally large. The compilation of a detailed review on the chemistry of all the groups of nucleosides became difficult a long time ago [1-6]. This is undoubtedly the reason why it has already been possible for some time to publish in the periodical literature reviews dealing with a particular single group of nucleosides [1,7,8] or one of the methods of synthesis [9,10]. Thus a very good review by Fox and Wempen [1], dealing only with the methods of synthesis of pyrimidine nucleosides (and yet including 6-7 pages of references), was published in 1959 in Advances in Carbohydrate Chemistry.

During more than ten years which have elapsed since the publication of the review, a number of earlier methods of synthesis have been further improved and have been given a theoretical basis (for example the metal salts and the Hilbert-Johnson methods). The silyl modification of the Hilbert-Johnson method has been developed.

The method involving the modification of existing nucleosides has been supplemented by a number of new reactions, for example nucleosides containing the 5',6- and 2',6-anhydro-linkages [11-15], sulphur [16,17], halogens [18,19], a double bond in the sugar residue [20], etc. have been obtained.

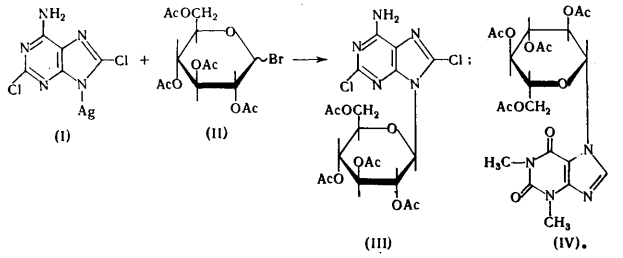
Considerable practical advances have been made in nucleoside chemistry. The possibility of clinical application of nucleosides as antiviral agents was demonstrated for the first time for the familiar thymidine analogue 2-deoxy-5-iodouridine in the treatment of herpetic affections of the eyes [21].

Data on the biological activities of a large number of synthetic nucleosides and the possibility of their clinical application can be found in a number of reviews [22-24].

The aim of the present review was to describe the present state of knowledge of the synthesis of pyrimidine nucleosides, including the literature up to the middle of 1971.

II. THE METAL SALTS METHOD

Fischer and Helferich [25] were the first to achieve the condensation of the silver salt of 2,8-dichloroadenine (I) and theophylline with 2,3,4,6-tetra-*O*-acetylglucopyranosyl bromide (II) which led to the synthesis of 2,8-dichloro-9-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)adenine (III) and 7-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-theophylline (IV) respectively:



(I) (II) (III) (IV).

After deactylation and dehalogenation of compound III, 9-(β-D-glucopyranosyl) adenine, the first synthetic nucleoside, was obtained.

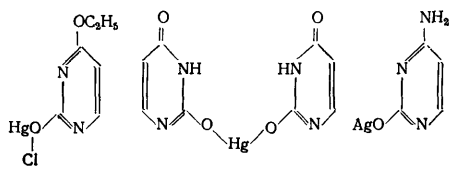
However, it was found that the silver salts of purines and pyrimidines containing the tautomeric group $-\overset{|}{N}-\overset{\|}{C}- \rightleftharpoons -N=\overset{|}{C}-$ (H, O, OH), such as uracil, cytosine, and theobromine, react with acetohalogeno-sugars to form products which reduce Fehling's reagent and are labile in relation to acids and alkalis. Fischer [26] suggested that these derivatives are probably *O*-glycosides.

Levene and Sobotka [27] reached the same conclusion on the basis of experiments in which the silver and potassium salts of cytosine and certain substituted uracils were condensed with glycosyl halides to form unstable products.

For this reason, the reaction of metals salts of pyrimidines with glycosyl halides was not investigated until the successful synthesis of nucleosides using mercury salts of purines [28] led to the investigation of the analogous pyrimidine derivatives and it was found [29,30] that

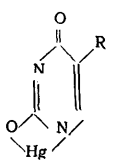
N-glycosides can be obtained from them in satisfactory yields; for example, thyminyl riboside and thyminyl xyloside were synthesised from dithyminylmercury and cytidine was obtained from *N*-acetylcytosinylmercury. It was noted that the reactions of certain mercury salts with deoxyribosyl halides take place with formation of *O*-deoxyribosides and not *N*-deoxyribosides [31]. In order to obtain *N*-deoxyribosides, it is necessary to employ the mercury salts of pyrimidine containing the pyrimidine base and mercury in proportions of 1 : 1. [32,33]

A number of hypotheses have been put forward to account for these results and the finding that the silver and mercury salts yield different products [34-36]. It was suggested that the chloromercury salt (V) of a pyrimidine, the dipyrimidine mercury compound (VI), and the silver salt (VII) of a pyrimidine are oxygen derivatives which react with glycosyl halides with the initial formation of *O*-glycosides, most of which rearrange to *N*-glycosides under the reaction conditions:



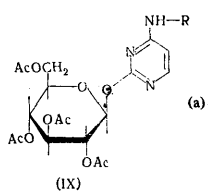
(V) (VI) (VII).

Since in monopyrimidine compounds of mercury, the heavy metal is probably also linked to the nitrogen atom, as in compound (VIII), these substances yield *N*-glycosides directly [37]:



(VIII) (R=H,CH$_3$, F, Br, I).

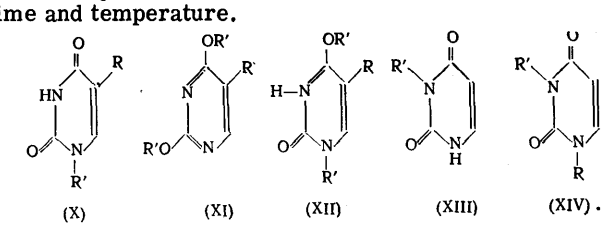
Fischer's method [26] (the preparation of the silver salt of cytosine and its condensation with acetobromoglucose in boiling xylene) was modified [38] but, as in Fischer's original work, the final product was an *O*-glycoside (IXa): [39]



(IX) (a) R = H; (b) R = CH$_3$CO.

On heating with mercury(II) bromide in xylene, the acetylated nucleoside (IXa) isomerises to an *N*-nucleoside with a very low yield. The best result was obtained in the condensation of the silver salts of *N*-acetylcytosine with acetobromoglucose in boiling xylene, compound (IXb) being formed. The reaction of the chloromercury salt of uracil (V) with acetobromoglucose, which has been reinvestigated, is of practical interest, but Ukite et al. [40] found that Fox's method [condensation of the chloromercury salt of 4-ethoxy-2(1*H*)-pyrimidinone with acetobromoglucose in boiling xylene] is not adequately reproducible.

Interesting data were obtained in a study of the reaction of metal salts of uracil and thymine [41-43] and also of 2-thiouracil [44] with acetobromoglucose and tribenzoylribofuranosyl chloride. The reaction of the silver salt of uracil with acetobromoglucose in toluene gives a mixture of five products [(Xa), [45] (XIa), (XIIa), (XIII), and (XIV) [42,43]], the proportions of which vary with reaction time and temperature.



(X) (XI) (XII) (XIII) (XIV).

[R' = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; (a) R = H; (b) R = CH$_3$]

A similar reaction with thymine yields the known compounds (Xb), [29] and (XIb) [46] and compound (XIIb), which was not characterised previously.

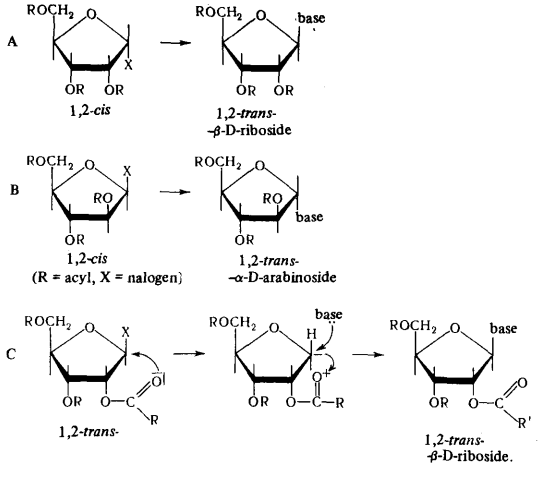
In the reaction of the silver salts of uracil and thymine with tribenzoylribofuranosyl chloride [41] in boiling xylene for 7 h, satisfactory yields of 1-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)-uracil and -thymine were obtained. Thus the views expressed in literature that the silver salts of uracil are incapable of undergoing the *N*-glycosylation reaction under the influence of acylglycosyl halides were disproved yet again [3]. The use of the mercury salt in the reaction with acylglycosyl halides leads to the formation of a more complex mixture of products and to a sharp decrease of the yield of the *N*-nucleoside [41].

A modification of the Helferich method [47-50], which was first employed by Fox and coworkers [47] to synthesise acylated pyrimidine nucleosides, is nowadays used fairly often for the synthesis of pyrimidine nucleosides. This method is suitable for the preparation of thymine and uracil derivatives without the preliminary isolation of mercury derivatives of the heterocyclic bases. Free bases are used in the synthesis but in the case of amino-derivatives it is desirable to protect the amino-group by acylation before the condensation reaction. However, it was shown recently that 2-thiocytosine [49] can be introduced into the reaction directly. Particularly high yields are obtained for pyrimidines containing electronegative groups at C$_{(5)}$.

1. Stereochemistry of the Synthesis of Nucleosides

The synthesis of nucleosides from acetobromoglucose having the α-configuration at C$_{(1)}$ leads to compounds with the β-configuration and therefore the reaction presumably involves an S$_N$2 mechanism with direct attack by the electrophilic C$_{(1)}$ atom of α-acetobromoglucose on the nucleophilic nitrogen atom of the pyrimidine or purine derivative. In the synthesis of natural β-nucleosides, syrupy ribofuranosyl halides containing a mixture of α- and β-forms are used as starting materials. In the synthesis of puromycin [51], crystalline 2,5-di-*O*-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl chloride yields exclusively the β-nucleoside. To account for these observations, Baker and coworkers [52,53] suggested that, in the condensation of the purine (or pyrimidine) derivative of a heavy metal with an acetylated glycosyl halide, the product is a nucleoside with a C$_{(1)}$-C$_{(2)}$-*trans*-configuration of the sugar regardless of the initial configuration of these atoms. Usually in the reactions of halogeno-sugars with the C$_{(1)}$-C$_{(2)}$-*cis*-configuration, there is a simple Walden inversion and the resulting nucleoside has the C$_{(1)}$-C$_{(2)}$-*trans*-configuration, which can be either the α- or β-form depending on the configuration of the sugar

(mechanism A and B).[2] $C_{(1)}$ -$C_{(2)}$-*trans*-halogeno-sugars are involved in two S_N2 reactions (with a double Walden inversion); initially the configuration at $C_{(1)}$ is inverted with participation of the adjacent $C_{(2)}$-acyloxy-group and the formation of an orthoester ion and then in the reaction of the base a second inversion takes place (mechanism C).[2]



Although the reaction mechanisms are completely different for the two anomeric halides, a nucleoside with a *trans*-arrangement $C_{(1)}$ and $C_{(2)}$ is formed in both cases regardless of the configuration of the anomeric halide at $C_{(1)}$ when the halogen atom is replaced by nucleophilic groups.

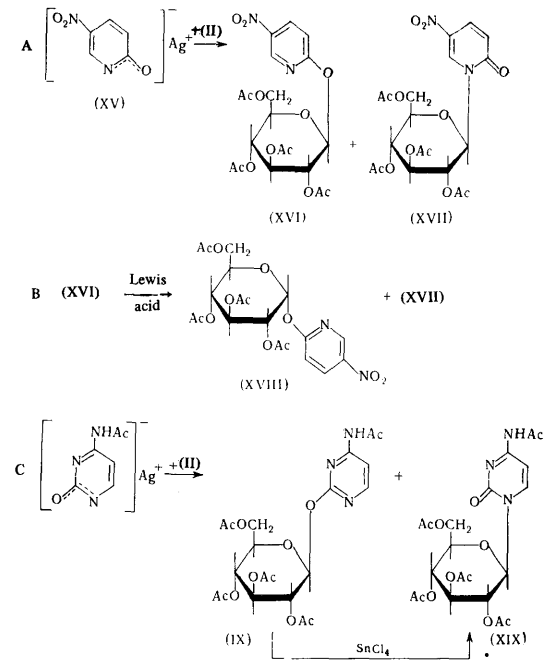
It has been shown that the rule is well founded and is actually employed at present to demonstrate a particular configuration. However, in certain cases a small amount of the other anomer is formed together with the one expected. Thus in the ribofuranosyl halide having a 2,3-cyclocarbonate protecting group and also in derivatives of 2-deoxy-D-ribose, there is no directing effect of the 2-acyloxy-group; in such cases the α- and β-forms of the nucleosides should be obtained and are in fact obtained[54,55].

2. The Mechanism of the Synthesis of Nucleosides

The mechanism of the synthesis of nucleosides and similar glycosides from glycosyl halides and metal salts of heterocyclic bases containing the $-\underset{\displaystyle H}{\overset{|}{N}}-\overset{\displaystyle O}{\overset{\|}{C}}-$ group has been investigated extensively in recent years[2,36,38,56,57,58]. It was shown in early investigations that mercury halides catalyse the O → N glycosyl rearrangement. Wagner and coworkers[59] demonstrated the possibility of such rearrangements for various heterocyclic systems.

It was observed that in certain cases heterocyclic *O*-glycosides do not rearrange to *N*-glycosides in the presence of mercury halides, products which are anomeric *O*-glycosides being obtained instead[60]. Thacker and Ulbricht reinvestigated the glycosides of 5-nitro-2-pyridone[57,58], since in Wagner's studies the aglycones (including 5-nitro-2-pyridone) were powerful electron acceptors.

The reaction of the silver salt of 5-nitro-2-pyridone (XV) with acetobromoglucose (II) is the *O*-glucoside (XVI) which was believed[60] to be the α-anomer on the basis of the method of synthesis (mechanism A). Treatment of this product with a Lewis acid (mercury bromide) in boiling xylene gives the isomeric *O*-glucoside (XVIII) which was assumed[60] to be the α-anomer (mechanism B)

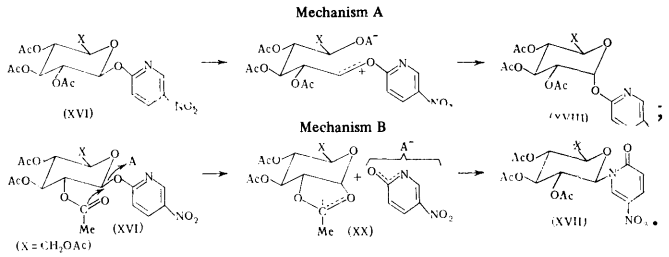


It was established by the NMR method[58] that compounds (XVI) and (XVIII) are in fact the β- and α-anomers and in addition thin-layer chromatography revealed the presence, together with compound (XVIII), of a product (XVII) which is a β-*N*-glycoside. Consequently an O → N rearrangement takes place in this case, its occurrence depending on the temperature, time, and the concentration of mercury bromide. The *N*-glucoside (XVII) was also isolated in a small amount when compound (XVI) was synthesised from the silver salt (XV).

The O → N rearrangement was studied using different Lewis acids[58]. When the pyridyl β-*O*-glucoside (XVI) was treated with tin(II) chloride, both anomerisation and rearrangement took place, while in the presence of $HgBr_2$ as the catalyst the anomerisation occurred virtually without rearrangement. The crystalline α-*O*-glucoside (XVIII) was obtained only when $HgBr_2$ was used as a catalyst, while in the presence of other Lewis acids the formation of the α-anomer was detected only by paper chromatography. The amount of the α-anomer formed when various catalysts are used decreases in the following sequence: $HgBr_2 > ZnBr_2 > CdCl_2 > SnCl_4 > SbCl_5 > TiCl_4$.

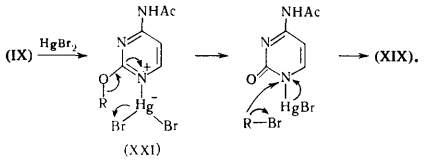
N-Acetylcytosinyl *O*-glucoside (XIX) also undergoes a rearrangement under the influence of tin(II) chloride to the β-*N*-isomer (IX) (mechanism C) but anomerisation was not observed under these conditions. The O → N glycosyl rearrangement catalysed by heavy metal salts ($SnCl_4$, $HgCl_2$, $HgBr_2$) was achieved by Schmidt and Farkas[46] [the di-*O*-glycosides of thymine (XIb) were converted into

thyminyl mono-*N*-glycosides (Xb)]. The thermal O → N glycosyl rearrangement of the readily hydrolysed *O*-glycoside 2-(tetra-acetyl-β-D-glucopyranosyl)hydroxypyrimidine was described recently [61]. The finding that in many cases the β-*O*-glycoside anomerises to the α-*O*-glycoside, while the α-*N*-isomer is not detected and that the rearrangement and the anomerisation take place at different rates and in different ways under different reaction conditions confirmed that two different mechanisms can operate in this case: (a) the formation of a complex of the catalyst and an oxygen atom of the sugar ring with subsequent ring opening and closure (anomerisation, mechanism A) and (b) the formation of a complex of the catalyst and the glycosidic oxygen, the formation of an ion pair, and the involvement of the adjacent 2-acyloxy-group (stereospecific rearrangement, mechanism B):



According to Wagner [59], the two products (XVII) and (XVIII) can be formed from the cyclic ion (XX), but in this case it is difficult to account for the formation of the α-*O*-glucoside and the absence of the α-*N*-glucoside.

The mechanism of the O → N glycosyl rearrangement, proposed previously by Ulbricht [36,38,56] and involving the formation of a complex of the catalyst with the ring nitrogen atom of the aglycone (XXI), was shown [61-65] to be inapplicable in all cases.

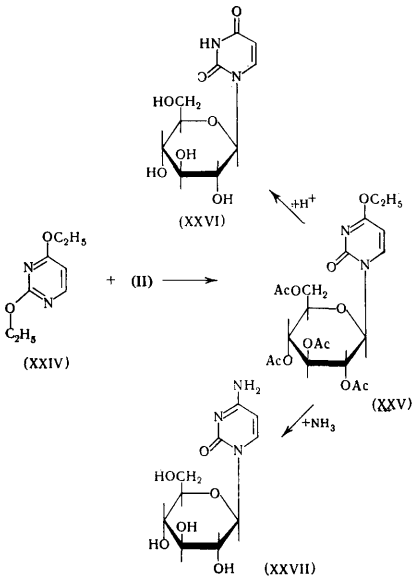


(R = 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)

III. THE HILBERT–JOHNSON METHOD

Previously it was believed that the glycosylation of the $N_{(1)}$-pyrimidine ring atom is impossible with pyrimidines containing the lactam—lactim tautomeric system $-\underset{\underset{O}{\|}}{C}-\underset{\underset{H}{|}}{N}- \rightleftharpoons -\underset{\underset{OH}{|}}{C}=N-$. However, Hilbert and Johnson [66,67], who restricted the tautomeric shift by employing 2,4-dialkoxypyrimidines, extended this reaction to *O*-acylglycosyl halides [45] after the successful synthesis of 4-alkoxy-1-methyl-2(1*H*)-pyrimidinone (XXIII) by treating 2,4-dialkoxypyrimidine (XXII) with methyl iodide.

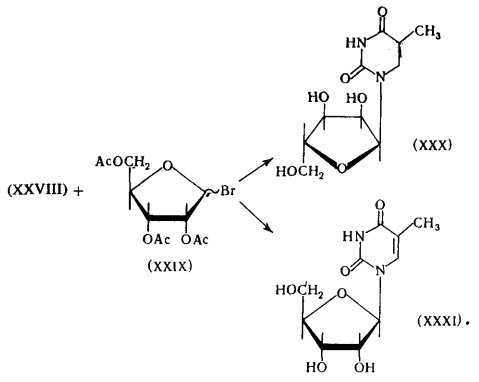
Thus, when 2,4-diethoxypyrimidine (XXIV) was treated with acetobromoglucose (II) (50°C, 48 h in the absence of a solvent), the $N_{(1)}$-glycosyl derivative (XXV) was obtained:



Treatment of compound (XXV) [45,68] with a solution of hydrogen chloride in ethanol or with a solution of ammonia in ethanol leads to the D-glucosides of uracil (XXVI) or (cytosine (XXVII). Many years later, Davoll et al. [69] reproduced these experiments [45,68] and established that the compounds obtained have the β-configuration.

Subsequently the reactions of 2,4-diethoxypyrimidine with L-arabinopyranosyl bromide, α-D-xylopyranosyl bromide, D-ribopyranosyl bromide, and α-D-galactopyranosyl bromide were carried out [70]. The first natural nucleoside obtained by the Hilbert–Johnson reaction was cytidine [71]. Its successful synthesis gave rise to further studies on the synthesis of pyrimidine nucleosides. For example, when 2,4-diethoxy-5-methylpyrimidine (XXVIII) was treated with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (XXIX) (at 60°C in the absence of a solvent), "5-methyluridine" (A) (XXX) was isolated after hydrolysis [72]. In contrast to compound (A), the thymine nucleoside (C) obtained enzymatically from thymine and ribosyl phosphate was cleaved by the nucleosidase from *Escherichia Coli* and had a different melting point. 5-Methyluridine (C), synthesised later by the mercury method [29], was found to be identical with compound (B). By converting compound (C) into spongothymidine [1-(β-D-arabinofuranosyl)thymine], [74] the β-configuration of compounds (B) and (C) was demonstrated. Compound (A) was identified as the α-anomer [75] and it was observed that 1-(α-D-ribofuranosyl)thymine (XXX) and 1-(β-D-ribofuranosyl)thymine (XXXI) are obtained in yields of

8.5 and 8% respectively when the reaction is carried out in benzene:

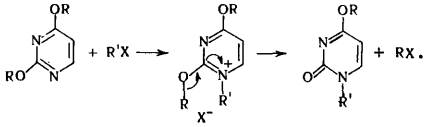


A mixture of 1-(α-D-ribopyranosyl)thymine and 1-(β-D-ribopyranosyl)thymine was obtained similarly from 2,3,4-tri-*O*-benzoyl-D-ribopyranosyl bromide [76].

Recently Sorm and coworkers [77] made a systematic study of the Hilbert–Johnson reaction. They investigated the role of the solvent, of various substituents in the 5-position of the pyrimidine ring, and of various protecting groups in the sugar component and studied the reaction yield and the ratio of the α- and β-anomers.

1. Reaction Mechanism

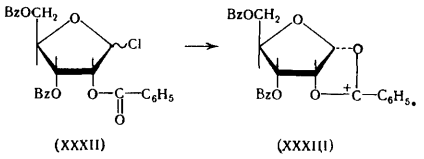
The reaction of 2,4-dialkoxypyrimidines with halogenoses (or with alkyl halides) was shown by Hilbert [78] to involve the formation of a quaternary salt as an intermediate. Later the mechanism of the Hilbert–Johnson reaction was investigated by Ulbricht [79]. His mechanism involves the formation of a quaternary nitrogen atom with subsequent attack by the halide ion:



It was shown recently [80] that a 2-alkoxy-group in the quaternary salt may be replaced by 2-oxo, 2-thio, and 2-amino-groups.

2. Stereochemistry of the Hilbert–Johnson Reaction

The effect of various factors on the ratio of the α- and β-anomers obtained by the Hilbert–Johnson reaction was investigated by Sorm and coworkers. The first papers [77,81] of this series were devoted to the synthesis of 2-deoxyuridine and thymidine, where the α-anomer predominates (for deoxy-sugars). It was established that the ratio of the α- and β-anomers in the Hilbert–Johnson method depends on the polarity of the solvent [81,82]. If, for example, the reaction of the halogenose (XXXII) with the base is carried out in benzene, a small amount of the corresponding α-anomer accompanies the main reaction product—the β-anomer. On the other hand, in a polar solvent the halogenose (XXXII), which is predominantly present in the β-configuration, gives rise to the ortho-ester cation (XXXIII), from which only the β-anomer may be formed.



The formation of the anomers is also influenced by the nature of the base and of the sugar component and by the protecting groups in the sugar residue [9]. Baker's "*trans*-rule" [52,53] is of limited applicability in the Hilbert–Johnson reaction, a mixture of α- and β-anomers being usually reformed.

3. Conditions of the Hilbert–Johnson Reaction

The absence or presence of the solvent plays an important role in the Hilbert–Johnson reaction. Best results are largely obtained in the presence of solvents although unfortunately systematic studies have not so far been made on this question. The reactions are carried out at temperatures ranging from 20° to 115°C. The reaction time was varied very markedly by investigators depending on the stability and reactivity of the halogenose employed. For example, the Hilbert–Johnson reaction of 2,4-dimethoxypyrimidine (in acetonitrile at room temperature) with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride requires 1–2 h, [83] while the reaction mixture with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride must be kept for several days [81,82]. If the halogenose is relatively stable and less reactive, the reaction must be carried out at an elevated temperature, for example in a boiling solvent, while with a reactive and relatively unstable halogenose the condensation is carried out at room temperature.

The application of molecular sieves [82–86] as hydrogen chloride acceptors gave satisfactory results because the formation of side products was largely suppressed. The use of mercury bromide (in acetonitrile and benzene) was recently investigated [82,84,86]. Thus, when compound (XXII) reacted with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride, the rate of reaction was higher in the presence of one or two equivalents of mercury bromide, but the yield of the anomer mixture was appreciably reduced owing to the rapid decomposition of the deoxyhalogenose. The amount of the β-anomer in the mixture increases under these conditions. In the reactions with stable halogenoses, the use of mercury(II) bromide gives rise to the possibility of reducing the reaction time (without lowering the yield) [86].

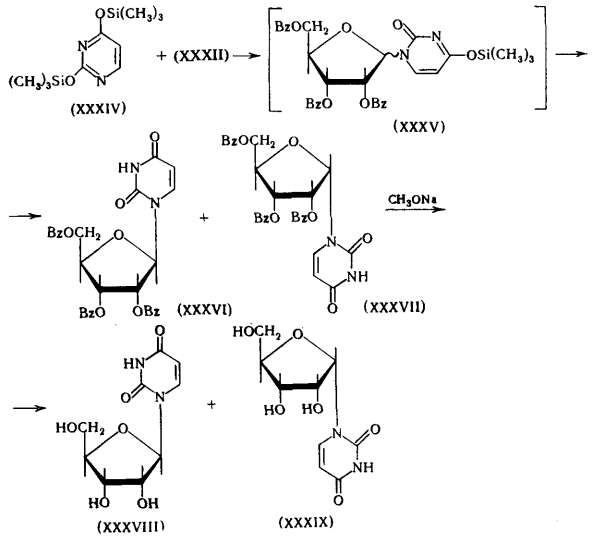
The side products usually formed in the Hilbert–Johnson reaction can be divided into four groups [9]: (1) substances obtained from the bases [for example uracil, 1-alkyluracils [45,70], 1,3-dialkyluracils [83], 4-alkoxy-2(1*H*)-pyrimidinones, and 4-alkoxy-1-alkyl-2(1*H*) pyrimidinones [70,84] may be formed from 2,4-dialkoxypyrimidines]; substances formed from the sugar component [84]; (3) side products obtained from the protected intermediate 4-alkoxy-1-glycosyl-2(1*H*)-pyrimidinones; (4) the *O*-glycosides mentioned above (they were first reported by Hilbert and Rist [87], who called them "*O*-nucleosides").

IV. THE TRIMETHYLSILYL METHOD

The trimethylsilyl method of synthesising nucleosides, the principle of which was discovered by Birkofer and coworkers [88-91] in studies on other nitrogen-containing compounds, was described by Nishimura and coworkers [92-97] and independently by Wittenburg [98-103]. The method is a modification of the Hilbert–Johnson method, but has a number of advantages. Silyl derivatives of pyrimidine bases can be obtained in high yields directly from pyrimidines such as uracil, thymine, and cytosine, the silyl derivatives being able to react with halogenoses under more severe conditions than their alkoxy-analogues. Compared with the Hilbert–Johnson method, the stage involving the hydrolysis of the alkoxy-group is virtually eliminated (the trimethylsilyl group is readily split off on treatment with aqueous alcohol).

Pyrimidine bases are sparingly soluble in organic solvents and have fairly high melting points. Their trimethylsilyl derivatives are liquids which can be distilled or crystals with a low melting point. Moreover, they dissolve readily in non-polar solvents, being completely decomposed by alcohol or water even in a neutral medium with liberation of the base.

The products of the silylation of dihydroxypyrimidines have the structure of bis-*O*-trimethylsilyloxypyrimidines (XXXIV).[92] The conversion of uracil into uridine (XXXVIII) and its anomer (XXXIX) may serve as an illustration of the trimethylsilyl method for the synthesis of nucleosides:



On treatment with chlorotrimethylsilane, uracil is readily converted into 2,4-bis(trimethylsilyloxy)pyrimidine (XXXIV) which on fusion (190°C) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride yields the protected nucleoside (XXXV); on dissolution in ethanol the latter gave a benzoylated nucleoside in the form of a mixture of anomers (XXXVI) and (XXXVII). They were separated and deacylated with formation of uridine (XXXVIII) and 1-(α-D-ribofuranosyl)uracil (XXXIX).

Using the trimethylsilyl method for the synthesis of nucleosides, Wittenburg suggested the following versions of the condensation reaction [98,102]. Method A: prolonged heating of the components in dry solvents such as benzene, toluene, dimethylformamide (DMF), nitromethane, and others; method B: fusion of the components at 90–100°C *in vacuo*; method C: reaction carried out in an absolute inert solvent (benzene) in the presence of silver perchlorate at room temperature; method D: interaction of the starting materials at room or elevated temperature in a solvent in the presence of mercury(II) compounds, such as HgO, mercury(II) acetate, $HgBr_2$, and $HgCl_2$.

These methods were investigated in the reaction of 2,4-bis-*O*-trimethylsilylthymine with α-acetobromoglucose and β-acetochloroglucose. The yields were 27 and 41% by methods A and B and 56–86% by methods C and D. The use of polar solvents (DMF, acetonitrile) in method A accelerates the reaction but lowers the yield owing to the easier decomposition of the halogeno-sugars.

The technique of the fusion method B resembles that of the Hilbert–Johnson reaction. On fusion of bistrimethylsilylthymine with acetobromoglucose at 110°C, the reaction begins after several minutes and terminates after 1–3 h. The yield increases when the reaction is performed in benzene in the presence of one equivalent of silver perchlorate (method C). The reaction proceeds very rapidly even at room temperature and heat is evolved. Presumably silver perchlorate initially reacts with acetobromoglucose to form silver bromide and tetraacetylglucosyl perchlorate ($AgClO_4$ and silylpyrimidine do not react with one another) [91]. Since acetylglucosyl perchlorate is highly reactive [104], a further reaction with formation of a 4-*O*-silylnucleoside and trimethylsilyl perchlorate takes place.

The reaction in which mercury compounds are used as catalysts [HgO, mercury(II) acetate, $HgBr_2$, $HgCl_2$] (method D), particularly when an almost equimolar mixture HgO and $HgBr_2$ is employed, takes place more smoothly. The bromotrimethylsilane formed initially is converted into hexamethyldisiloxane in the presence of mercury(II) oxide and the acetylated products is isolated in a very satisfactory yield in consequence of a shift of the reaction equilibrium.

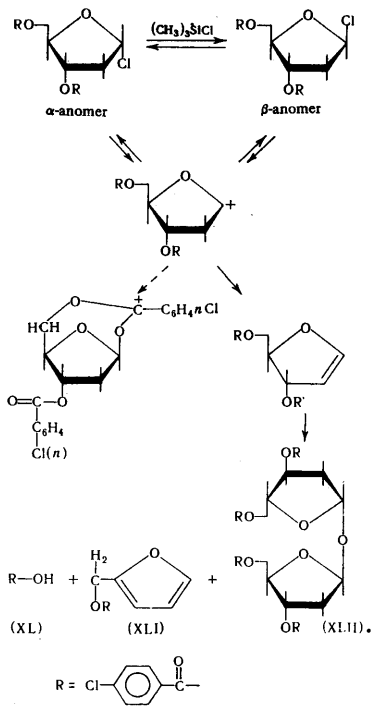
Wittenburg, who investigated the glycosylation of silyl derivatives of 6-substituted uracil derivatives [105] (6-methyluracil, 5,6-dimethyluracil, 5-bromo-6-methyluracil, 5-iodo-6-methyluracil, barbituric acid, and orotic acid and its esters) with acetobromoglucose or tribenzoylribofuranosyl chloride (method D was employed for glycosylation), concluded that the course of the reaction depends on the nature and position of the substituent in the pyrimidine ring. For example, in the glycosylation of the silyl derivative of 5,6-dimethyluracil under the above conditions, the $N_{(1)}$-glycoside was obtained almost exclusively, while in the reaction with 6-methyluracil the $N_{(3)}$-glycoside was formed preferentially together with appreciable amounts of the $N_{(1)}$-glycoside and the $N_{(1,3)}$-diglycoside. Other silyl derivatives listed above do not react with halogeno-sugars or with methyl iodide under the above conditions. Winkley and Robins [106] obtained similar results with silyl derivatives of 5,6-dimethyluracil and 6-methyluracil.

In this connection, it is noteworthy that the required $N_{(1)}$-glycosides of 6-methyluracil, barbituric acid [107], and orotic acid [108] were not obtained by the Hilbert–Johnson method either. However, Winkley and Robins [109] succeeded in synthesising 1-(β-D-ribofuranosyl)barbituric acid by the silyl method via condensation in acetonitrile at room temperature. Azacytidine [110], 2-deoxy-5-hydroxymethyluridine [111], and other derivatives of pyrimidine bases [112] were synthesised under these conditions.

Vorbruggen and Niedballa [113-115] suggested that the silyl derivative of pyrimidine bases be condensed with protected sugars in the presence of the Friedel–Krafts catalyst.

Stereochemical aspects. According to Wittenburg's data[102], a nucleoside with the $C_{(1)}-C_{(2)}$-*trans*-configuration was isolated as the main product in the interaction of 2,4-bis-(*O*-trimethylsilyl)thymine with α-acetobromoglucose. Traces of the α-anomer with the $C_{(1)}-C_{(2)}$-*cis*-configuration (i.e. traces of tetra-acetyl-α-D-glucopyranosylthymine), which proved to be identical with the α-glucopyranosylthymine obtained by Schmidt[46] by a modified Hilbert–Johnson method, were detected only in experiments by methods C and D. Treatment of bis-(trimethylsilyl)thymine with β-acetochloroglucose led to the same results. Hence Wittenburg concluded (without taking into account the amount of the anomers, which were detected by the chromatographic method alone) that the silyl method for the synthesis of pyrimidine nucleosides is rigorously stereospecific and fully obeys Baker's rule[52,53]. Nevertheless Nishimura and coworkers isolated α- and β-nucleosides[95,97] using adenine[96], uracil[95,97], and thymine[97] as aglycones. The Japanese workers concluded that the silyl method yields not only the β-anomers but also the α-anomers having the $C_{(1)}-C_{(2)}$-*cis*-configuration. Probably the formation of anomeric nucleosides depends to a very large extent on the reaction conditions (temperature, solvent, and catalyst).

A study of the factors influencing the stereospecificity of the silyl method for the synthesis of deoxynucleosides was made using as an example the reaction of 3,5-di-*p*-chlorobenzoyl-2-deoxy-α-D-ribofuranosyl chloride with the silyl derivatives of 5-mercaptouracil and thymine[116]. It was established that chlorotrimethylsilane has a major influence on the stereospecific course of the reaction. Under reaction conditions promoting the rapid removal of chlorotrimethylsilane from the reaction medium, the β-anomer is formed preferentially or exclusively. On the other hand, the addition of chlorotrimethylsilane to the reaction mixture promotes the formation of the α-anomer. It was found that chlorotrimethylsilane can cause the anomerisation of the halogenose under the reaction conditions;



To investigate the influence of chlorotrimethylsilane on the glycosyl chloride, the latter was allowed to stand in benzene in the presence and absence of chlorotrimethylsilane for several hours at room temperature. When the halogenose was allowed to stand for a long time in the absence of chlorotrimethylsilane in benzene solution (see scheme above), a small amount of compound (XLII) was isolated in addition to *p*-chlorobenzoic acid (XL) and furfuryl-*p*-chlorobenzoic acid. A carbonium ion can participate as an intermediate in the formation of all the degradation products of the glycosylhalogenose; the presence of chlorotrimethylsilane prevents the formation of the carbonium ion, stabilising the halogenose in the form of an equilibrium mixture of α- and β-anomers. In the condensation reaction, β-halogenose reacts much faster with bistrimethylsilylpyrimidine than the α-anomer and, as the latter is consumed, chlorotrimethylsilane is used to restore the equilibrium with inversion of the α-anomer to the β-anomer. Chlorotrimethylsilane does not anomerise the complete nucleoside.

Consequently the stereospecific formation of α- or β-deoxynucleosides can be explained solely on the basis of an S_N2 mechanism. Bearing in mind that the condensation reaction involves a nucleophilic attack by silylpyrimidine on glycosyl chloride with a single Walden inversion, the reaction of the pure α-halogenose should lead to the formation of the β-nucleoside; on the other hand, the reaction of the β-halogenose should tend to form the α-nucleoside.

Japanese workers found that, when bis(trimethylsilyl)-uracil and tribenzoylribofuranosyl chloride are fused together[95], bis(tribenzoylribosyl)uracil is formed together with the α- and β-anomers. The ultraviolet absorption spectrum of the debenzoylated product resembles that of 1,3-dimethyluracil[117]. However, the *O*-glycosides[102] formed when the mercury method is employed were not detected in the silyl method. Possibly, in the condensation of *O*-silyl derivatives with halogeno-sugars, there is a very fast migration of the sugar residue from the oxygen atom to the nitrogen atom with formation of an *N*-glycoside.

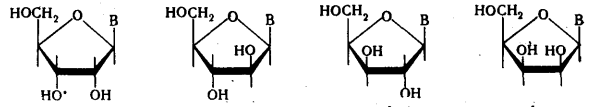
V. METHOD INVOLVING THE MODIFICATION OF THE SUGAR OR BASE IN THE COMPLETE NUCLEOSIDE

In nucleoside chemistry, there are many examples of reactions of nucleosides which involve changes both in the aglycone (halogenation, methylation, introduction of sulphur, deamination, etc.) and in the sugar component of the nucleoside, associated with the formation of anhydronucleosides (for example, a change in the configuration of the sugar residue or the introduction of a new functional group into the sugar moiety). Moreover, the changes in the aglycone are frequently results of the formation of anhydronucleosides.

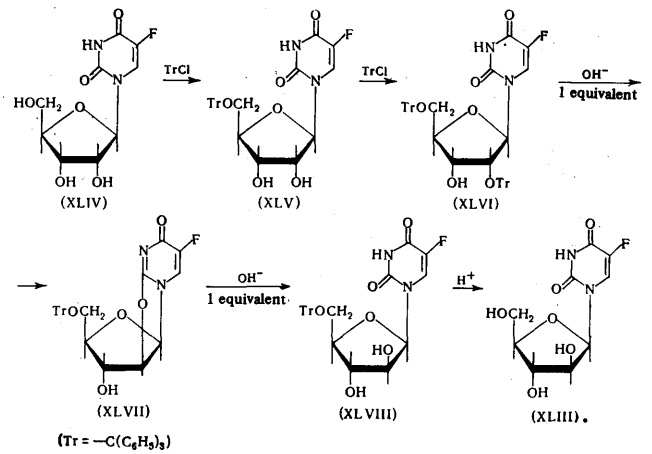
1. Transformations of Pyrimidine Nucleosides via Anhydronucleosides

The inversion of a hydroxy-group of the sugar was first described for thymidine; it occurred as a result of the formation of the 2,3′-anhydronucleoside, which is converted into 1-(β-D-deoxyxylofuranosyl)thymine on alkaline hydrolysis[118]. Subsequently similar results were obtained with ribonucleosides from which pyrimidine

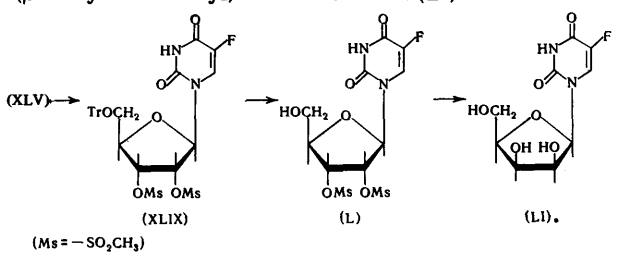
nucleosides with *lyxo*-, *xylo*-, and *arabino*-configurations are formed via the 2,2'- and 2,3'-anhydronucleosides.



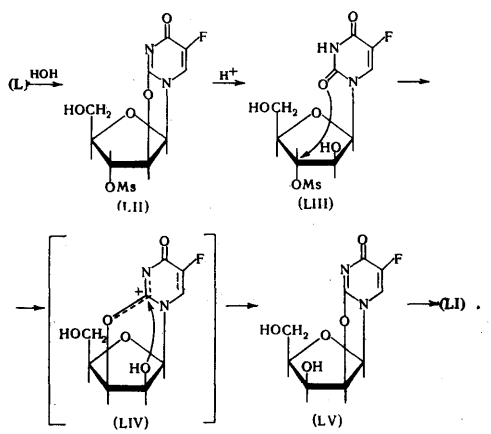
Thus 1-(β-D-arabinofuranosyl)urasil (spongouridine) [119] and 1-(β-D-arabinofuranosyl)thymine [120] were obtained in this way via the 2,2'-anhydronucleoside. A scheme for the synthesis of 1-(β-D-arabinofuranosyl)-5-fluorouracil (XLIII) [121] from 1-(β-D-ribofuranosyl)-5-fluorouracil (XLIV) via the trityl derivatives (XLV)–(XLVIII) is presented below:



When 5-fluoro-5'-trityluridine (XLV) was treated with methanesulphonyl chloride, 2',3'-dimethanesulphonyl-5'-tritylribofuranosyl-5-fluorouracil (XLIX) was obtained, its detritylation yielding the riboside (L); the removal of the methanesulphonyl groups by heating in water gave rise to 1-(β-D-lyxofuranosyl)-5-fluorouracil (LI):

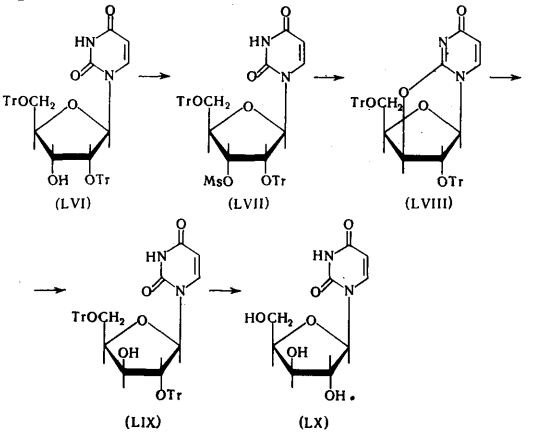


Compound (L) is converted into compound (LI) via a series of successive reactions [122]:

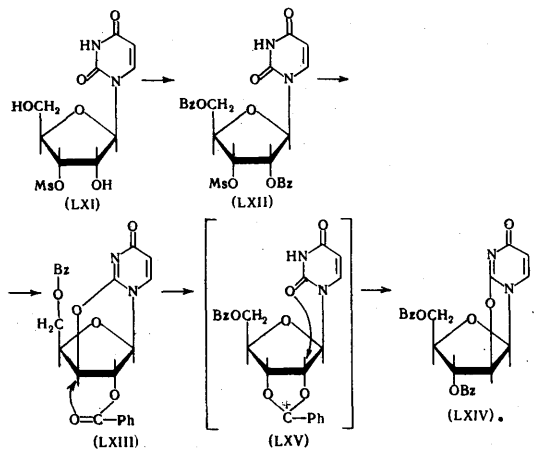


The first stage is the formation of the 2,2'-anhydronucleoside (LII) with liberation of methanesulphonic acid; next, in the presence of an acid catalyst, compound (LII) is cleaved to (LIII) and nucleophilic attack by the 2-carbonyl group on the $C_{(3)}$ carbon atom of the latter yields the 2,2'-anhydrolyxonucleoside (LIV). It is converted into the 2,2'-anhydrolyxonucleoside (LV) as a result of the attack by the OH group at $C_{(2)}$ on the carbonium ion (LIV). Hydrolysis of compound (LV) leads to (LI).

3-*O*-Methanesulphonyl derivatives of uradine are frequently employed to obtain 2,3'-anhydronucleosides, which are intermediates in the synthesis of both xylofuranosyl and arabinofuranosyl nucleosides [123]. Tritylation of uridine under appropriate conditions leads to crystalline 2',5'-di-*O*-trityluridine (LVI) which on methanesulphonation is converted into 3'-*O*-methanesulphonyl-2',5'-di-*O*-trityluridine (LVII). On treatment with sodium benzoate in dimethylformamide, (LVII) is converted into 2,3'-anhydro-2',5'-di-*O*-tritylxylonucleoside (LVIII). Its treatment with alkali and subsequent detritylation yields a single product—1-(β-D-xylofuranosyl)uracil (LX).



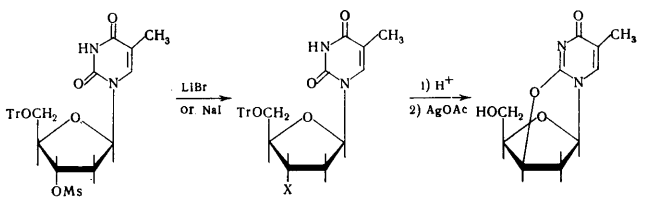
Detritylation of (LVII) yielded 3'-*O*-methanesulphonyluridine (LXI), the 3',5'-dibenzoyl derivative (LXII) of which gave the 2,3'-anhydroxylonucleoside (LXIII) on treatment with sodium benzoate [compound (LXIII) can be obtained also by the direct benzoylation of 2,3'-anhydroxylosyluracil]. When the anhydroxylonucleoside (LXIII) is heated up to its melting point, it isomerises rapidly to 2,2'-anhydro-3',5'-di-*O*-benzoylarabinonucleoside (LXIV), probably via a stage involving the formation of the orthoester ion (LXV) with participation of the adjacent acyl group.



The anhydronucleosides of pyrimidines proved to be convenient not only for the specific inversion of the hydroxy-groups of the sugar but also in the synthesis of 2-deoxynucleosides. Treatment of 5′-*O*-acetyl-2′-*O*-tosyluridine with sodium iodide leads to 5′-*O*-acetyl-2′-deoxy-2′- iodouridine from which 2-deoxyuridine is formed after hydrogenation and deacetylation [124]. The same iodo-derivative (with the ribose configuration) was obtained by treating with sodium iodide and acetic acid the 5′-*O*-acetyl-2,2′-anhydroarabinonucleoside, which can be formed from the iodo-derivative under the influence of a base [125]. Probably the anhydronucleoside is an intermediate in the substitution of toluene-*p*-sulphonyloxy-group by iodine, the final product being formed as a result of two substitutions at $C'_{(2)}$.

Thymidine was synthesised by the same method from 5′-*O*-acetyl-1-(β-D-ribofuranosyl)thymine [124]. 2,3′-Anhydroxylonucleoside is the initial compound in the synthesis of 3′-deoxyuridine [126].

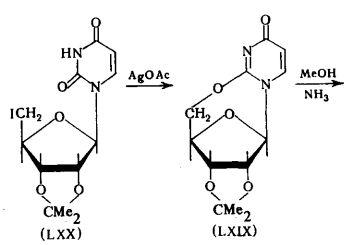
Anhydronucleosides can be used for the stereochemically controlled introduction of functional groups into secondary positions in the sugar residue. Michelson and Todd [118] synthesised 3′-deoxy-3′-halogenothymidine (LXVII) by treating 3′-methanesulphonyl-5′-tritylthymidine (LXVI) with sodium iodide or lithium bromide in acetone at 100°C. They suggested that (LXVI) has the *ribo*-configuration, since it can be inverted to give the 2,3′-anhydro-derivative (LXVIII):



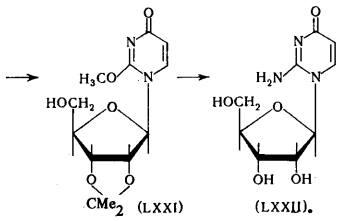
(LXVI) (X = Br, I) (LXVII) (LXVIII).

When 2,2′-anhydronucleosides are treated with anhydrous HBr, HCl, and HI, high yields of 2′-deoxy-2′-halogenonucleosides are formed [127]. It proved possible to obtain 3′-amino-3′-deoxythymidine and the 3′-deoxy-3′-phthalimidonucleoside from thymidine via the 2,3′-anhydro-derivative [128,129].

Anhydronucleosides are also used to replace the oxygen atom at the $C_{(2)}$ atom of the base by various substituents. Brown et al. showed that, when 2,5′-anhydro-2′,3′-isopropylidineuridine (LXIX) obtained from compound (LXX) is treated with a methanol solution of ammonia, the isocytosine derivative (LXXII) is formed via the 2-methoxy-nucleoside (LXXI). [126,130] 1-(β-D-Arabinosyl)isocytosine was synthesised from 2,2′-anhydroarabinosyluracil under the same conditions. Sulphur can be introduced into the heterocyclic ring via the 2,2′- and 2,5′-anhydronucleosides.

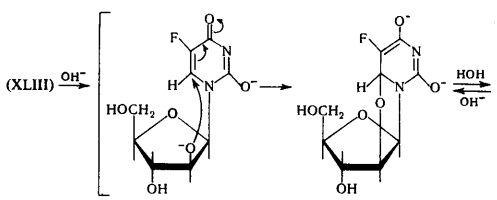


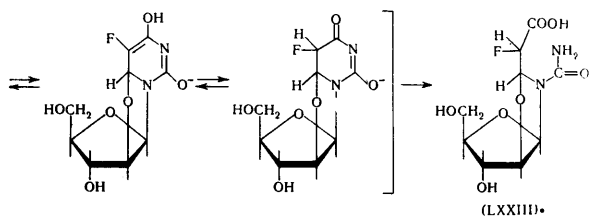
(LXX) (LXIX)



(LXXI) (LXXII).

Fox and coworkers made a detailed study of the behaviour of 5-halogeno-derivatives of spongouridine in an alkaline medium and showed that such nucleosides and their precursors (2,2′-anhydronucleosides) are unstable under these conditions [14,131-134]. For example, on treatment with alkali, 1-(β-D-arabinofuranosyl)-5-fluorouracil (XLIII) is converted into the 2′,6-anhydro-5-fluoro-5,6-dihydro derivative (LXXIII). It was suggested that the process proceeds via a 1,4-addition mechanism:

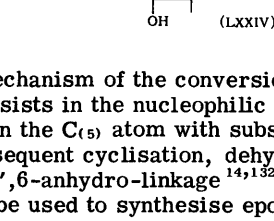




(LXXIII).

Compound (LXXIII) was one of the first products with a 2′,6′-anhydro-linkage obtained from nucleosides. The double bond is not reduced under the reaction conditions while the 3,4-bond is cleaved. The ease with which the 2′-OH anion having the *arabino*-configuration participates in the reaction is probably a property of pyrimidine nucleosides having the aglycone and 2′-OH in the *cis*-positions.

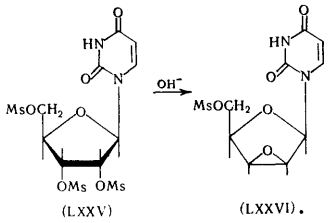
The study of the properties of the 2′,6-anhydro-5-fluoro-5,6-dihydro-derivative (LXXIII) led to the discovery of a new rearrangement of the aglycones of 5-halogeno-derivatives of arabinosyl nucleosides. The reaction of (LXXIII) with 1 *N* NaOH for 20 min at 60°C gives a crystalline halogen-free product (LXXIV):



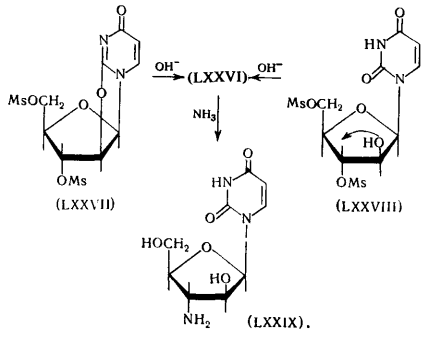
(LXXIV).

A possible mechanism of the conversion of (LXXIII) into (LXXIV) consists in the nucleophilic attack by the amide nitrogen on the $C_{(5)}$ atom with substitution of the fluorine and subsequent cyclisation, dehydrogenation, and cleavage of the 2′,6-anhydro-linkage [14,132]. Anhydronucleosides can be used to synthesise epoxy-derivatives

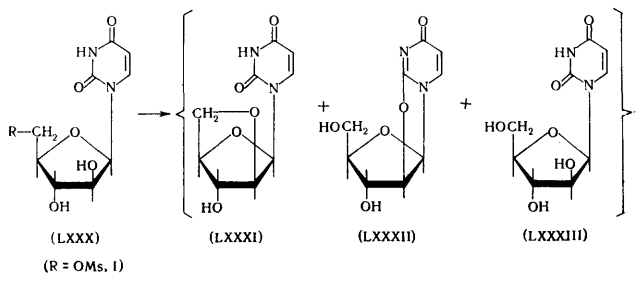
of nucleosides. Treatment of tri-*O*-methanesulphonyluridine (LXXV) with three equivalents of alkali gives a high yield of the 2',3'-epoxide (LXXVI):[135,136]



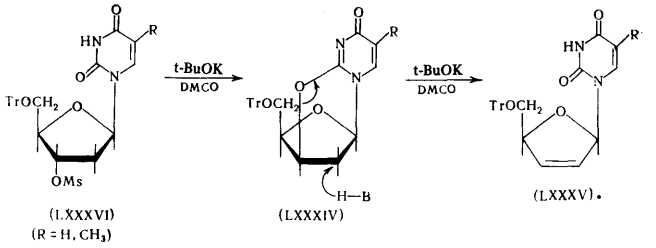
This reaction can probably proceed via the anhydronucleoside (LXXVII) and the arabinonucleoside (LXXVIII), since each is converted into an epoxide on treatment with alkali. On treatment with an alcoholic solution of ammonia at an elevated temperature, the epoxide is converted into 1-(3'-amino-3'-deoxy-β-D-arabinofuranosyl)uracil (LXXIX):[135]



In the course of a study of the hydrolytic cleavage of the 5'-iodo- or 5'-methanesulphonyloxy-derivatives of arabinosyluracil, evidence was obtained for intramolecular reactions involving anhydronucleosides[137]. Treatment of compound (LXXX) with boiling water results in the formation of three products: 2',5'-epoxynucleoside (LXXXI), 2,2'-anhydronucleoside (LXXXII), and 1-(β-D-arabinofuranosyl)uracil (LXXXIII). The last compound can be obtained by the hydrolysis of (LXXXII).

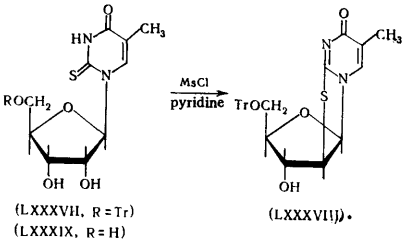


Recently Horwitz and coworkers showed[138,139] that certain anhydronucleosides can be used to synthesise derivatives unsaturated in the sugar moiety by a base-catalysed elimination reaction. Thus, on treatment with potassium t-butoxide in dimethyl sulphoxide (DMSO), the anhydronucleoside (LXXXIV) gives rise to a high yield of the Δ2',3'-nucleoside (LXXXV), which can also be obtained from the nucleoside (LXXXVI) under the same conditions:

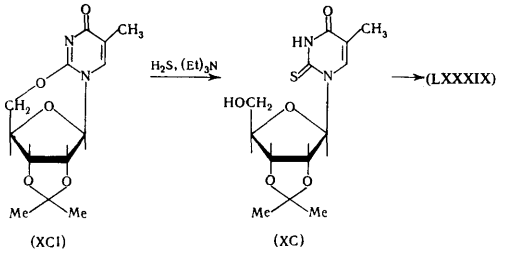


Detritylation of compound (LXXXV) yields "thymidinene" and "uridinene" respectively.

The first synthesis of an anhydronucleoside containing a sulphur atom instead of oxygen in the anhydride bridge was achieved by Shaw and Warrener, who observed that the $S_{(2)}$, 2'-anhydronucleoside (LXXXVIII) is formed in high yields on methanesulphonation of 5-methyl-2-thio-5'-*O*-trityluridine (LXXXVII).[140,141]

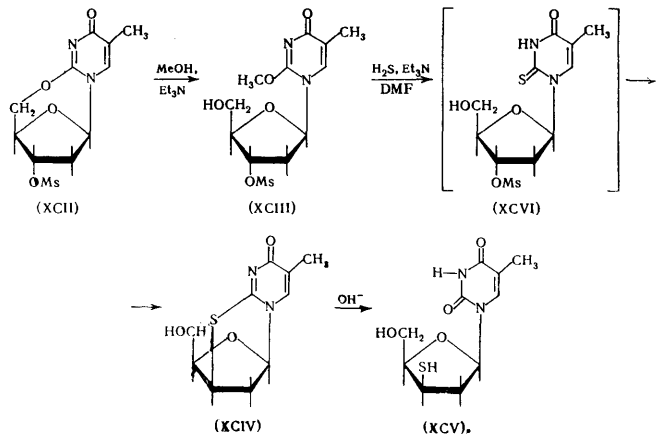


The initial compound (LXXXVII) was obtained by the tritylation of the thionucleoside (LXXXIX), which was synthesised from isopropylidene-2-thiouridine (XC), one of the products of the interaction of 2,5'-anhydro-2',3'-isopropylideneuridine (XCI) with hydrogen sulphide in the presence of triethylamine:



When the 2,5'-anhydronucleoside (XCII) is heated with methanol containing triethylamine, a high yield of the 2-methoxynucleoside (XCIII) is obtained; its treatment with hydrogen sulphide and triethylamine in DMF in 65°C for several hours leads to the $S_{(2)}$,3'-anhydronucleoside

(XCIV). The cleavage of the sulphide bridge with 0.1 *N* solution of alkali gives the 3′-mercaptonucleoside (XCV):



The 2-thionucleoside (XCVI), which was synthesised from compound (XCII) by treatment with hydrogen sulphide (in DMF) and triethylamine at room temperature, is an intermediate in the conversion of (XCIII) into (XCIV). Compound (XCVI) was converted into compound (XCIV) by refluxing in ethanol containing triethylamine.

The introduction of sulphur into the $C_{(4)}$-position in the pyrimidine ring is used as an intermediate reaction in the general method for the conversion of various uracil nucleosides into their cytosine analogues [142]. As a rule, treatment of uracil and its derivatives with phosphorus pentasulphide results in the introduction of the thio-group in the 4-position.

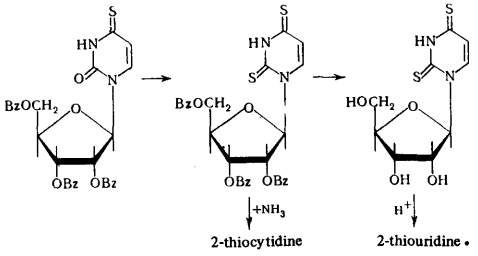
In model experiments with 1-methyluracil, the introduction of sulphur followed by amination yielded 1-methylcytosine; hence it was concluded that this reaction can be used also to synthesise nucleosides. In the latter case the hydroxy-groups of the sugar residue must be protected (with the benzoyl group) and pyridine must be employed as the reaction medium.

As a result of the introduction of the thio-group into ribo- and deoxyribopyrimidine nucleosides, reactive intermediates are obtained from which one can synthesise not only the principal natural nucleosides but also various 4-substituted analogues. Thus the 4-thio-compound was obtained from 3′,5′-di-*O*-benzoylthymidine and was converted by treatment with an alcoholic ammonia solution into 2-deoxy-5-methylcytidine. Uridine and 1-(β-D-ribofuranosyl)thymine were converted in this way into cytidine and 5-methylcytidine; likewise glycosyl-5-fluorocytosines were obtained from 5-fluorouridine and 2-deoxy-5-fluorouridine [143]. 5-Azacytidine is obtained in a similar way following the introduction of the thio-group into tri-*O*-benzoyl-5-azauridine with subsequent amination and debenzylation [144,145].

When acylated 4-thionucleosides (including 2-deoxy-derivatives) are treated with appropriate reagents, 4-alkylamino-, 4-hydrazino-, 4-hydroxylamino-, and other derivatives are formed [143].

When the thio-group in 4-thiothymidine and 4-thiouridine is removed with activated Raney nickel, the heterocyclic ring is fully hydrogenated with formation of 2-oxohexahydropyrimidine nucleosides. Such ready and extensive reduction is characteristic of 4-thiouracils and 2-hydroxypyrimidines and does not occur with 2-thiouracils and 4-hydroxypyrimidines [146].

Brown and Herper [147] succeeded in introducing sulphur directly at the $C_{(2)}$-position in 1-methyluracil by treatment with P_2S_5 in tetralin [147]. In 1968 Japanese workers achieved this reaction with the corresponding nucleosides [148]:



2. Halogenation of Nucleosides

In 1907 Wheeler and Johnson observed for the first time the decolorisation of bromine water by uracil and cytosine. Since then, this reaction has been used as a qualitative test for these substances. The colorimetric method for the determination of uracil and cytosine is also based on it [149]. The reaction likewise plays an important role in the synthesis of nucleoside derivatives, in particular 5-bromouridine [150].

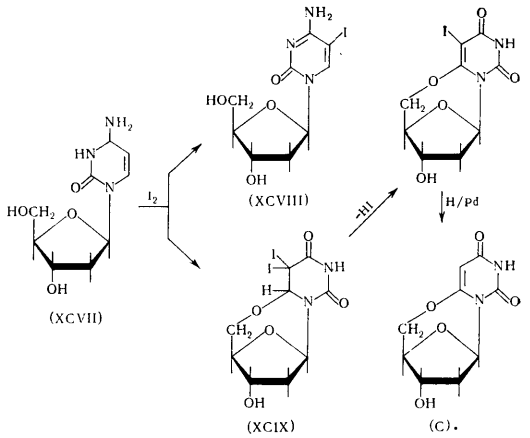
The halogenation of pyrimidine nucleosides takes place readily and leads to a modification of the heterocyclic ring without its cleavage. Usually nucleosides and bases are halogenated with the free halogen in an anhydrous solvent (the iodination reaction is an exception) in which substitution at the fifth carbon atom, where there is an excess of electron density, takes place [151-154].

The bromination of nucleosides usually occurs under very mild conditions and can be achieved in several ways: (a) in anhydrous solvents, for example in DMF, pyridine, formamide, and alcohol [155,156]; 5-bromo-derivatives of cytidine and deoxycytidine were obtained under the same conditions [155-157]; (b) with bromine water and subsequent lyophilisation [158] and (c) with simultaneous irradiation by ultraviolet light [159,160]. The mechanism of the halogenation reaction has been investigated in detail for the bromination of pyrimidine nucleosides [161-163].

As a rule uracil derivatives are chlorinated with a chlorine solution in dry carbon tetrachloride, which is added to a solution of the initial compound in glacial acetic acid. The reaction proceeds readily and terminates after several hours at room temperature or after several minutes on heating. It proved possible to obtain in this way 5-chlorouridine [158,164] and 5-chlorodeoxyuridine [165]. 5-Chlorocytidine cannot be obtained under similar conditions [159], because cytidine exists in a protonated form in glacial acetic acid and electrophilic attack is difficult. However, when the reaction mixture containing cytidine is irradiated by ultraviolet light, the reaction takes place smoothly, probably owing to a change in reaction mechanism, with radical substitution instead of electrophilic substitution.

The iodination of pyrimidine nucleosides takes place under much more severe conditions. Iodination methods have been developed and introduced into the synthetic chemistry of nucleosides by Prusoff [166,167]. The commonest iodination procedure involves heating the nucleosides with a chloroform solution of iodine in the presence of nitric acid. Modifications of this method consist in using different solvents, different nitric acid concentrations, or different heating times [166-170]. 5-Iodo-derivatives of uridine, deoxyuridine, etc. have been obtained in this way.

Another possible iodination procedure involves treatment with iodine in the presence of alkalis [166]. However, these methods cannot be used to synthesise 5-iodo-derivatives of cytidine and deoxycytidine, since under these iodination conditions the *N*-glycosidic bond is broken [171]. The replacement of nitric acid by another oxidising agent (for example iodic-acid) which does not affect the glycocidic linkage permits the successful iodination of cytidine and deoxycytidine (XCVII). [172] Together with deoxy-5-iodo-cytidine (XCVIII), a side product was isolated, which proved to be the anhydrodi-iodonucleoside (XCIX); the latter can be converted into the deiodinated product (C): [13]



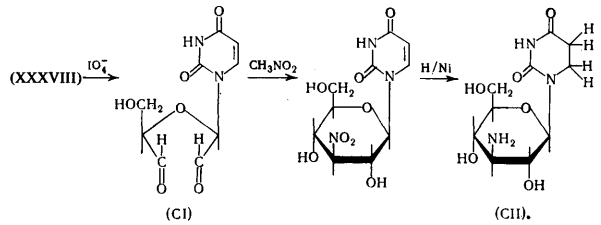
Bromine chloride and iodine chloride have been used as mild iodinating and brominating agents. Joshida et al. [173] believe that electrophilic substitution takes place in this case and suggest that in iodination and bromination by this method in DMF the formation of 5-halogenouridines is accompanied by the formation of 5-halogeno-5,6-dihydro-6-hydroxyuridine, as in bromination in aqueous solvents.

N-Halogenoamides and *N*-halogenoimides are effective halogenating agents, which made it possible to replace the hydrogen atom at the $C_{(5)}$-position of the pyrimidine ring under extremely mild conditions. Thus the use of *N*-chloro- and *N*-bromo-succinimides permits the synthesis of 5-chloro- and 5-bromo-derivatives in almost quantitative yields [174-180]. For iodination with *N*-iodo-succinimide in DMSO, it is necessary to add catalytic amounts of di-n-butyl disulphide [178,181], which is probably required to form an intermediate halogenating agent—n-butylsulphenyl iodide.

Fluorine-containing nucleosides are usually obtained from the corresponding fluoro-derivatives of pyrimidine using one of the direct methods of synthesis discussed above.

3. Oxidation of Nucleosides

Fox and coworkers [182] obtained nucleosides derived from 3'-amino-3'-deoxyaldoses by the periodate oxidation of uridine to the dialdehyde (CI) without the cleavage of the glycosidic linkage; the addition of nitromethane leads to cyclisation. 1-(3'-Amino-3'-deoxy-β-D-glucopyranosyl)-5,6-dihydrouracil (CII) was obtained after the reduction of the nitro-group:



Among the methods of synthesis of pyrimidine nucleosides discussed above, the silyl method is the most advantageous. This is clearly seen from the synthesis of 1-(β-D-xylofuranosyl)uracil and 5-bromouracil tribenzoates [183-187]. The yield of the first compound was 77% by the silyl method and 28% by the mercury method; in the synthesis involving the modification of the ribose residue of uridine, this compound was obtained in a yield of only 8%. [188]

As a preparative method, the modification procedure suffers from many disadvantages among which the large number of stages in the processes and the low yield of products are of primary importance. Nevertheless, this method permitted an appreciable expansion of the chemistry of nucleosides and led to the possibility of a wide variety of chemical transformations of the compounds.

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