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The synthesis and transformations of uronic acid nucleosides

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Contents

I.	Introduction	695
II.	Catalytic oxidation of nucleosides to uronic acid nucleosides	695
III.	Oxidation of nucleosides by nonspecific oxidants	696
IV.	Glycosylation of purine and pyrimidine heterocycles by uronic acids	698
V.	Synthesis of uronic acid nucleosides by modifying the sugar and heterocyclic base residues	704
VI.	Transformations of uronic acid nucleosides	706

Abstract. The results of studies on the synthesis and transformations of uronic acid nucleosides are surveyed. Various pathways leading to the synthesis of uronic acid nucleosides are examined, including methods involving specific and nonspecific oxidation of nucleosides, and the glycosylation and modification of the sugar residue or the heterocyclic base. The bibliography includes 97 references.

I. Introduction

Uronic acid nucleosides occupy a special place among the numerous modified nucleosides. Replacement of the primary hydroxy-group in nucleosides by a carboxy-group induces appreciable changes in the reactivities of other functional groups due both to the redistribution of electron density in the molecule and to conformational factors. Furthermore, the presence of a carboxy-group extends the possibilities of the syntheses based on nucleosides.

The interest in uronic acid nucleosides is caused primarily by the fact that they are a component of many antibiotics exhibiting a broad spectrum of biological activity.[1] There is much promise for derivatives of adenosine-5′-carboxylic acid, which are agonists of adenosine receptors and in the future may find extensive application in medical practice as hypotensive, cardiotonic, and thrombolytic agents.[2]

Progress in the synthesis of natural antibiotics, in devising new antibiotics, and also in the study of the biological action of uronic acid nucleosides with a wide variety of structures is in many respects determined by current advances in the development of methods for their preparation. The aim of the present review is to examine and treat systematically the existing methods of synthesis of uronic acid nucleosides and their transformations.

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II. Catalytic oxidation of nucleosides to uronic acid nucleosides

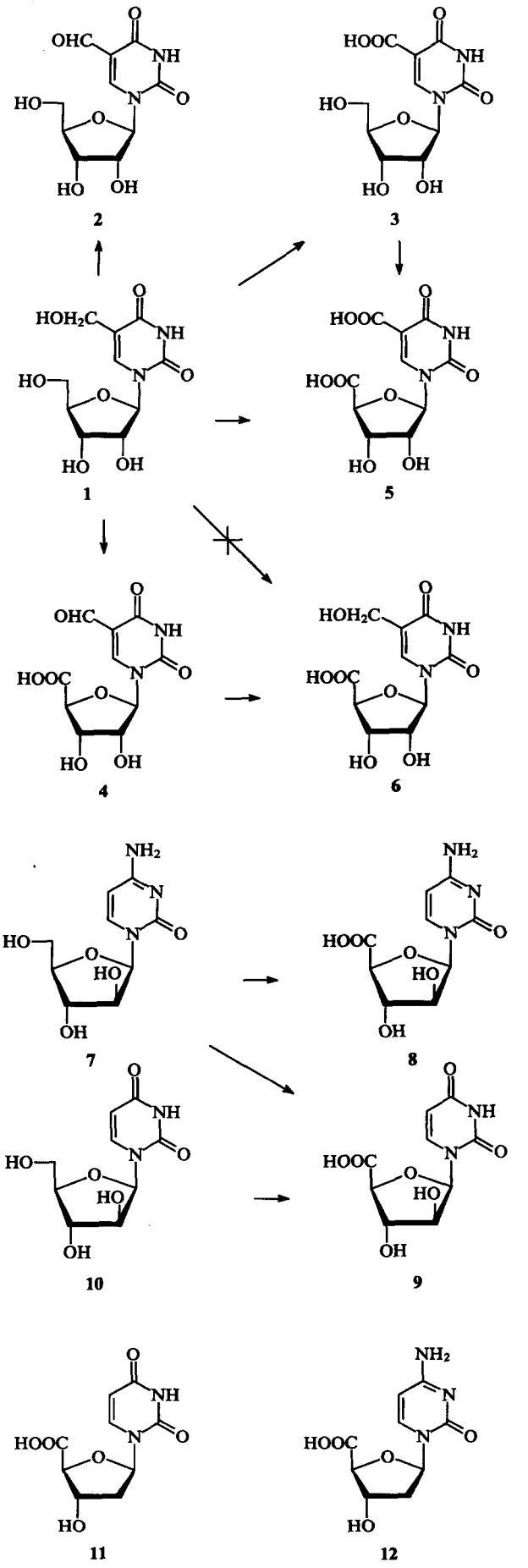
A general method of synthesis of uronic acid nucleosides, involving the selective oxidation of the primary hydroxy-group of the nucleoside to a carboxy-group by oxygen over a platinum catalyst, has been proposed by Todd and coworkers[3] in connection with the solution of the problem of the stepwise degradation of polynucleotides. The catalytic oxidation of uridine, thymidine, adenosine, guanosine, 3′-bromo-3′-deoxy-3-methylthymidine, 3-methylthymidine, thymidine 3′-phosphate and thymidylyl-(3′→5′)-thymidine was investigated. The corresponding nucleoside-5′-carboxylic acids were obtained and characterised. The oxidation of nucleosides to acids is usually carried out in a weakly alkaline medium at 50 – 60 °C by bubbling with finely dispersed oxygen in the presence of platinum on charcoal. The maintenance of a specified solution pH (~7.5) and a high rate of stirring are extremely important factors in the process.

It has been shown[4] that, when the reaction is carried out at room temperature in 50% acetic acid, three oxidation products are formed from 5-hydroxymethyluridine **1**: uridine-5-carboxaldehyde **2**, uridine-5-carboxylic acid **3**, and the aldehydoacid **4**. The oxidation of nucleosides **1** and **3** in the presence of sodium bicarbonate leads to the acid **5**. The reduction of compound **4** with sodium tetrahydroborate affords the nucleoside **6**, which cannot be obtained by direct oxidation of compound **1**.

Together with the acid **8**, its uracil analogue **9** was isolated from the reaction mixture in the oxidation of the arabinonucleoside **7**. Compound **9** can also be obtained by oxidising the uracil nucleoside **10**.

In the oxidation of 5-halo-derivatives of 2′-deoxyuridine and 2′-deoxycytidine, it was noted that the rate of reaction increases in the sequence H < Br < I.

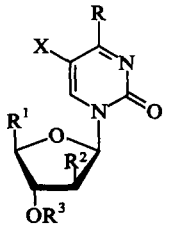
2′-Deoxyuridine-5′-carboxylic acid **11** and 2′-deoxycytidine-5′-carboxylic acid **12** were obtained by catalytic oxidation.



5-Fluoro-2′-deoxyuridine (FUDR) is known to exhibit an antitumour activity. However, the toxic 5-fluorouracil, formed as a result of its hydrolysis by phosphorylase, impairs the therapeutic properties of this preparation. Various attempts have been made to modify FUDR in such a way that it is stable toward phosphorylase and at the same time its ability to penetrate cell membranes is retained. It was found that these requirements are satisfied by 5-fluoro-2′-deoxyuridine-5′-carboxylic acid and its esters. These compounds are more resistant to hydrolysis, their toxicity is relatively low, and they exhibit a higher antitumour activity than FUDR.[5] When FUDR was oxidised in a weakly alkaline medium, the reaction products could not be isolated. Positive results were obtained on oxidation in a weakly acid medium (pH 6.81 ± 0.2).

Thymidine-5′-carboxylic acid has been obtained by the catalytic oxidation of nucleosides. Its nitriles, amides, and esters are inhibitors of thymidylate kinase of Walker 256 carcinoma.[6,7]

Catalytic oxidation of uracil and cytosine nucleosides afforded uronic acids and their derivatives having the general formula **13**.[8]



13

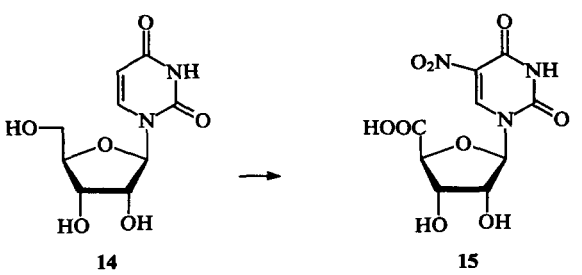
R = OH, NH_2;
R^1 = COOH, COOMe, CN;
R^2 = H, OH;
R^3 = H, COMe;
X = H, F, Br, I, Me.

It was observed that uracil nucleosides are oxidised at a higher rate than cytosine nucleosides. The ease of oxidation depends on the nature of the substituent in the 5-position in the pyrimidine ring and decreases in the sequence H > Me > F > Br > I. Thirty five compounds were obtained; the 5-bromo- and 5-iodouracil nucleosides of 2′-deoxyriburonamides possess an antiviral activity.

It is noteworthy that the method involving the catalytic oxidation of nucleosides suffers from disadvantages as well as having evident advantages. Thus the yields of the acids obtained by this method are as a rule fairly moderate (20%–50%), although they sometimes reach 70%–80%. Appreciable deviations from the activities of catalysts obtained by the same procedure, which results in a poor reproducibility of the results, have been noted. Compounds containing sulfur and amino-groups deactivate platinum catalysts. This method is relatively unsuitable for the preparative synthesis of amounts of nucleosides. A significant disadvantage is also the high cost of the catalyst. Methods for the synthesis of uronic acid nucleosides in which oxidants with a nonselective activity are used therefore merit attention.

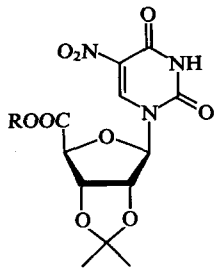
III. Oxidation of nucleosides by nonspecific oxidants

One of the first examples of uronic acid nucleoside synthesis was the oxidation of uridine **14** by nitric acid to 5-nitrouridine-5′-carboxylic acid **15**.[9]

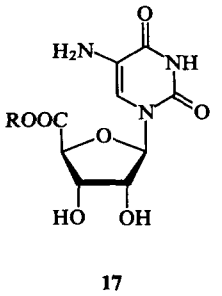


14 15

Later Fox and coworkers, [10] who repeated the synthesis of the acid **15**, confirmed its structure and obtained a series of its derivatives, including the acetonides of the esters **16** and the amine **17**.



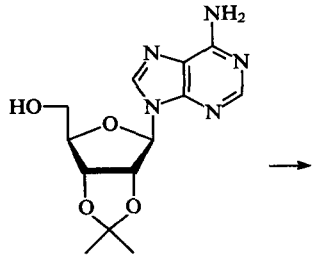
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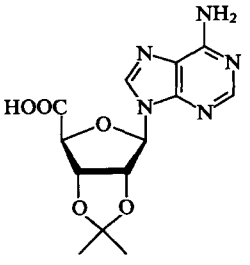
17

Oxidation of thymidine and 2′-deoxyadenosine by chromium trioxide afforded a low yield (~14%) of the corresponding acids. [11] Owing to the low selectivity of the oxidant, the secondary hydroxy-group is oxidised as well as the primary hydroxy-group. The ketoacids synthesised under these conditions are extremely unstable and decompose with formation of thymine and adenine. 2′-Deoxyadenosine-5′-carboxylic acid has been obtained in higher yield (28%) by oxidising 2′-deoxyadenosine with potassium permanganate in an alkaline medium. [12]

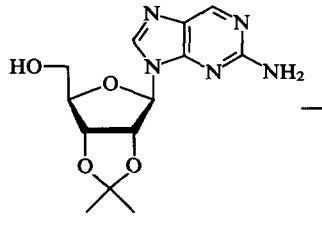
After an unsuccessful attempt at the catalytic oxidation of the adenosine acetonide **18** (the yield of the acids was 2%–5%), Harper and Hampton [13] oxidised it with chromium trioxide in various solvents. In all cases, the reaction mixtures contained several oxidation products. The acids **19** and **21** were obtained in satisfactory yields by oxidising the nucleosides **18** and **20** with potassium permanganate. [14, 15]



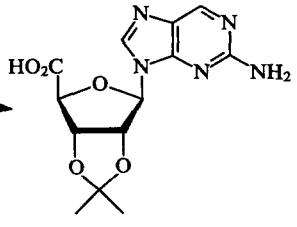
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19



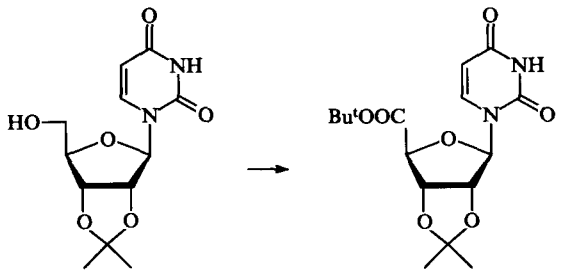
20



21

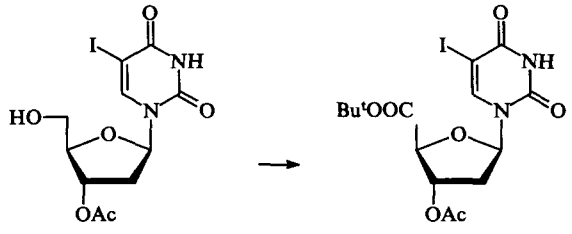
In the oxidation of isopropylidene derivatives of guanosine, inosine, and uridine by potassium permanganate, the only reaction product isolated has been oxalic acid. 2′,3′-*O*-Isopropylideneinosine-5′-carboxylic acid has been obtained in high yield using chromium peroxide in glacial acetic acid as the oxidant. [16]

A method of synthesis of guanosine-5′-carboxylic acid has not been described hitherto. In order to obtain derivatives of uridine-5′-carboxylic acid, Corey and Samuelsson [17] developed an unusual variant of the oxidation of 2′,3′-*O*-isopropylidene-uridine **22** coupled with esterification. Treatment of compound **22** with four equivalents of pyridinium dichromate in methylene chloride and dimethylformamide in the presence of acetic anhydride and *tert*-butyl alcohol leads to the formation of the *tert*-butyl ester of the acid **23**.



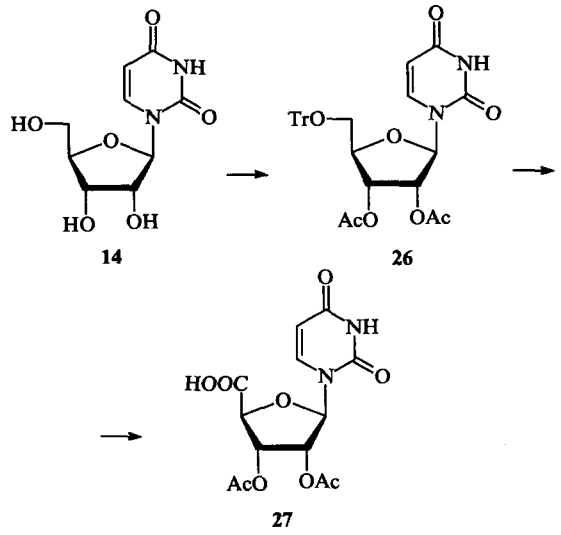
22 **23**

The ester **25** was obtained by this method from the deoxynucleoside **24**. [18]



24 **25**

A scheme has been developed for the synthesis of pyrimidine nucleosides of uronic acids involving the treatment of uridine **14** in pyridine initially with chlorotriphenylmethane and then with acetic anhydride, this being followed by the oxidation of the resulting fully substituted nucleoside **26** with chromium peroxide [chromium trioxide? (Ed.)] in acetone in the presence of 50% sulfuric acid (the Jones reagent). The diacetate **27** was obtained by this procedure in 50% yield. [19]

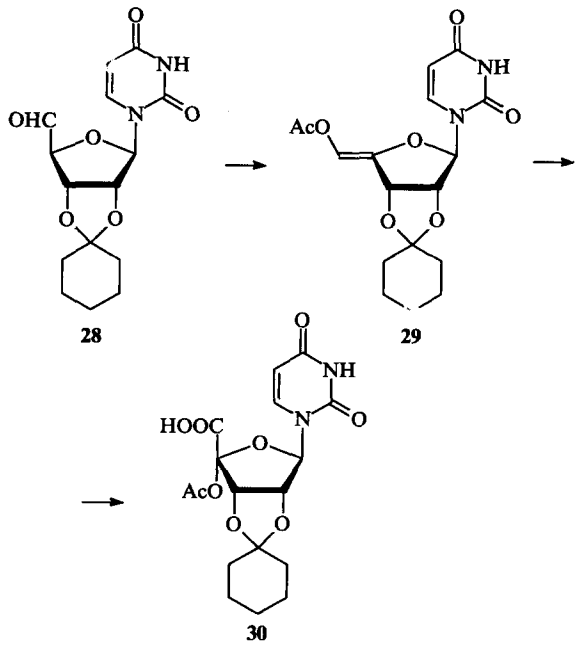


14 **26**

27

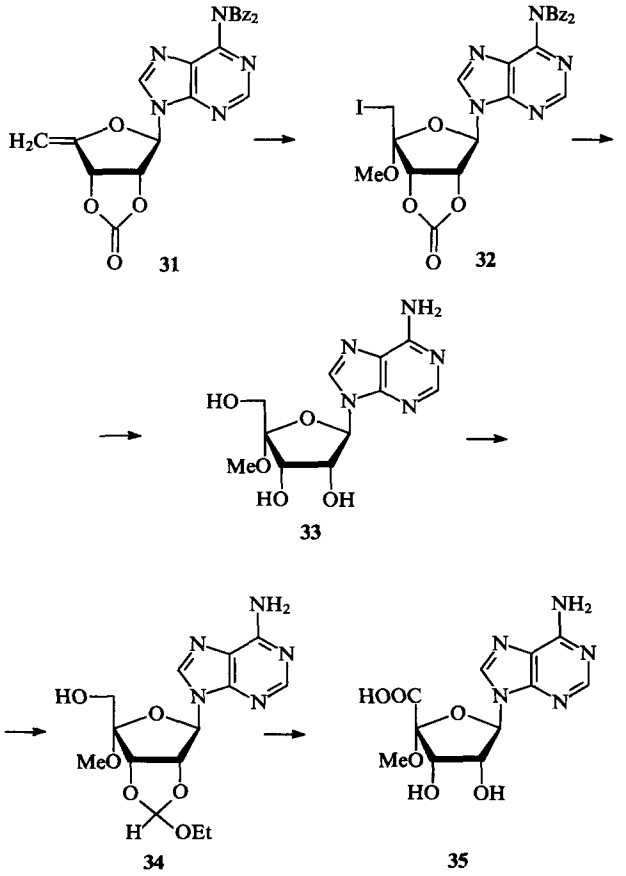
Tr = $C(Ph)_3$.

Nucleosides with an exocyclic double bond are convenient precursors in the synthesis of 4′-acetoxy- and 4′-methoxy-derivatives of nucleoside-5′-carboxylic acids. When the aldehyde **28** is heated with potassium carbonate in acetic anhydride, the enol acetate **29** is formed readily and its oxidation with *m*-chloroperbenzoic acid in methylene chloride gives the 4′-acetoxy-acid **30**. [20]



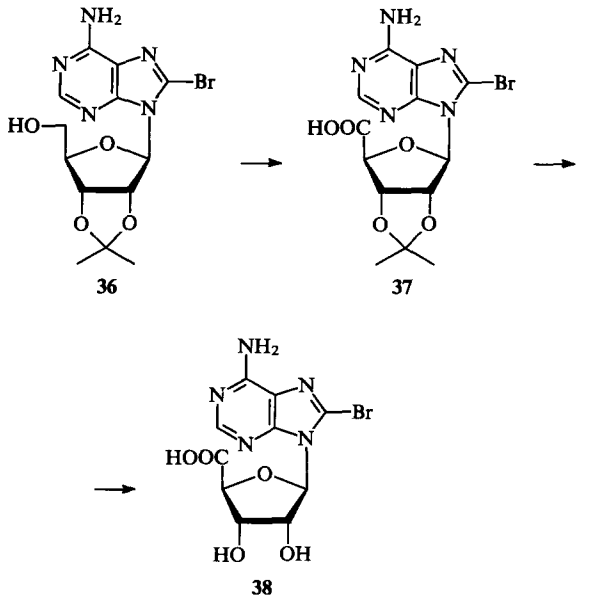
28 29 30

Treatment of the unsaturated nucleoside **31** with iodine leads to the selective formation of the iododeoxynucleoside **32**, which is converted into 4′-methoxyadenosine **33** as a result of hydrolysis, benzoylation, substitution of iodine by the benzyloxy-group, and ammonolysis. The oxidation by potassium permanganate of the ethoxymethylidene derivative **34** obtained from compound **33**, esterification, and the removal of the protecting group lead to the 4′-methoxy-acid **35**.[21]



31 32 33 34 35

Derivatives of adenosine-5′-carboxylic acid with various substituents in the 8-position in the adenine residue are of interest as potential agonists of adenosine receptors.[22] The acid **37** was obtained by oxidising the bromo-derivative **36** with potassium permanganate in an alkaline medium. Its controlled hydrolysis made it possible to remove the isopropylidene protecting group without appreciable cleavage of the *N*-glycosidic linkage, which in the presence of a bulky substituent in the 8-position is very sensitive to the action of acids. The esters obtained from the acids **37** and **38** were found to be able to form only primary amides on treatment with a mixture of primary and secondary amines. The secondary amines substitute the bromine atoms with a high degree of selectivity under these conditions, giving tertiary amines.[23]



36 37 38

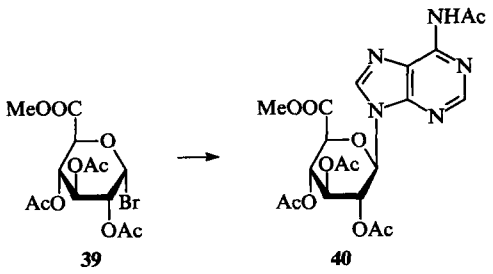
Oxidation of the acetonides of 8-aminoadenosine derivatives with potassium permanganate led to the complete decomposition of the purine residue.[22]

As can be seen from these examples, the oxidation of nucleosides by nonspecific oxidants encounters difficulties due to both the necessity for the preliminary protection of the secondary hydroxy-groups and the sensitivity of the heterocycles to oxidation, which appreciably limits the scope of this method.

The method involving the glycosylation of a wide variety of purine and pyrimidine heterocycles by uronic acid derivatives, for the preparation of which the range of oxidants employed in organic chemistry is in principle suitable, gives rise to extensive prospects for the synthesis of uronic acid nucleosides. The glycosylation of heterocycles by uronic acid derivatives has its specific features associated with the presence of a carboxy-group, which induces an appreciable redistribution of electron density in the molecule.

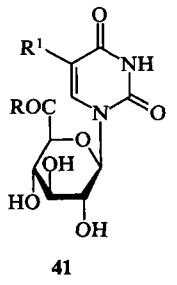
IV. Glycosylation of purine and pyrimidine heterocycles by uronic acids

There are numerous examples in the literature of the synthesis of nucleosides via the glycosylation of a wide variety of nitrogen-containing heterocycles by carbohydrate derivatives. At the same time, the use of uronic acid derivatives as glycosylating agents has only recently been systematically studied. Early attempts to synthesise uronic acid nucleosides include the condensation of the bromo-derivative **39** with 6-acetamido-9-chloromercuriopurine in the presence of cadmium carbonate and celite, which gave nucleoside **40** in 57% yield.[24]



39 40

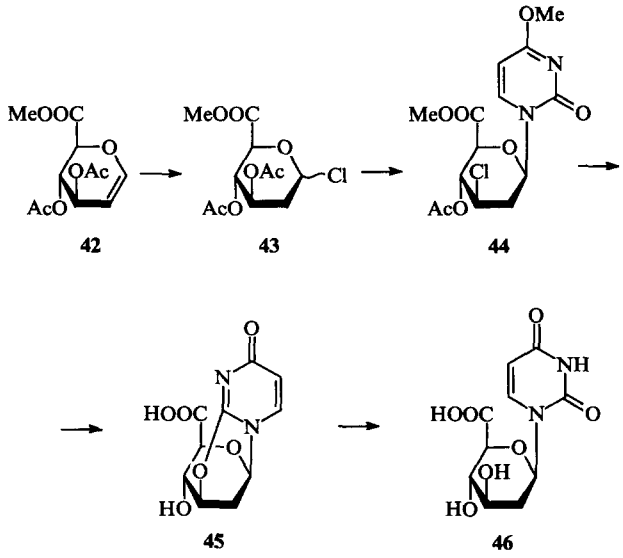
Hilbert and Johnson's method has been used to synthesise the pyrimidine nucleosides of D-glucopyranouronic acid: the glycosylation of 2,4-dialkoxypyrimidines by the bromo-derivative **39** gave the corresponding *N*-glycosides in 40%–60% yield, their methanolysis, ammonolysis, and alkaline hydrolysis giving rise to the uracil and thymine nucleosides of D-glucuronic acid and its methyl ester and amide having the general formula **41**.[25]



41

R = OH, OMe, NH_2;
R^1 = H, Me, Br, I.

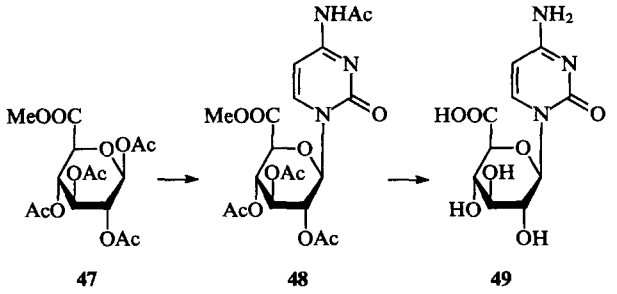
An interesting scheme for the synthesis of the nucleosides of 2-deoxypyranouronic acid has been described.[26] The chloro-derivative **43**, obtained by adding hydrogen chloride to the glycal **42**, was condensed with 2,4-dimethoxyuracil at 90–95 °C. Subsequent treatment of 3'-chloro-2',3'-dideoxy-β-nucleoside **44** with hydrogen chloride in methanol and with alkali afforded the cyclic nucleoside **45**. The opening of the anhydride ring by treatment with alkali led to the formation of the 2'-deoxynucleoside **46**.



42 43 44

45 46

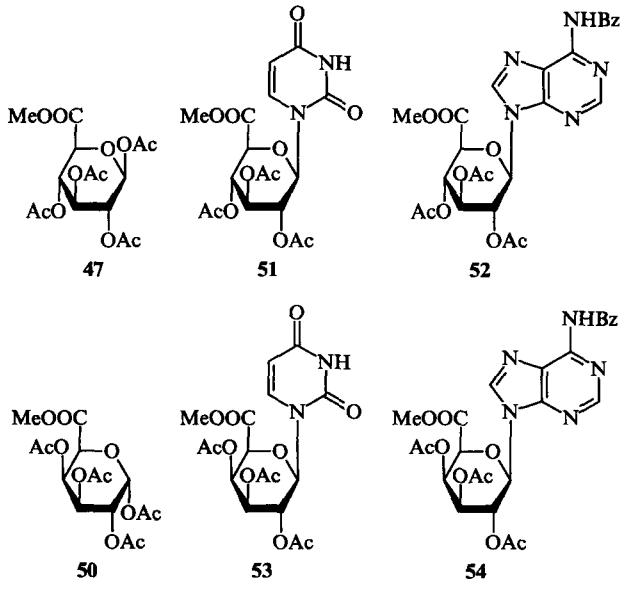
Fox and coworkers[27] synthesised the acid **49**, which is the cytosine nucleoside of D-glucuronic acid detected among the products of the biosynthesis of the antibiotic blasticidin S. Glycosylation of the silyl derivative of *N*(4)-acetylcytosine by the acetate **47** in the presence of $SnCl_4$ gave the nucleoside **48** in a low yield (20%). The required acid **49** was obtained by the alkaline hydrolysis of the latter.



47 48 49

The glycosylation of the silyl derivative of *N*-benzoylcytosine by the acetate **47** in the presence of three equivalents of $SnCl_4$ led to the benzoyl analogue of compound **48** in 70% yield.[28]

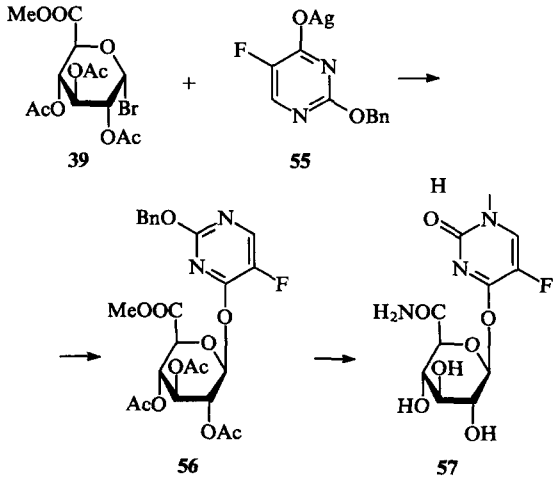
Lichtenthaler and coworkers[29,30] investigated the condensation of silyl derivatives of nitrogen-containing heterocycles with peracylated uronic acid esters in the presence of Lewis acids. It was found that, in the glycosylation of uracil and *N*(6)-benzoyladenine by the acetates **47** and **50**, the corresponding nucleosides **51**–**54** are formed in satisfactory yields only in the presence of 2.6 equivalents of $SnCl_4$.



47 51 52

50 53 54

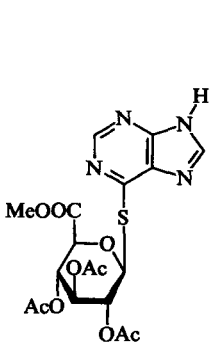
The *O*-glucuronide of 5-fluorouracil **57** has been obtained by condensing the silver salt of 5-fluorouracil **55** with the bromo-derivative **39** and by the subsequent removal of the protecting groups of the nucleoside **56**.[31]



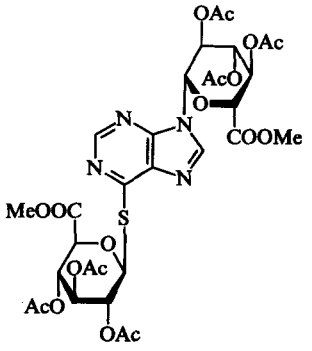
39 55

56 57

The reaction of bromo-derivative **39** with 6-mercaptopurine in DMF containing potassium carbonate afforded the *S*-glucuronide **58**. The reaction of **39** with the silver salt of 6-mercaptopurine and also the transglycosylation of the *S*-glucuronide **58** in the presence of $HgBr_2$ led to the formation of *N*(9),*S*-bisglucuronide **59**.[32,33]

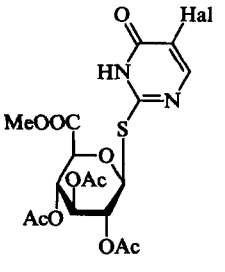


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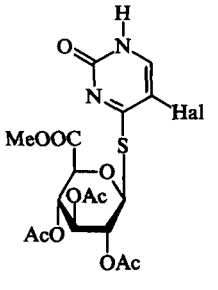


59

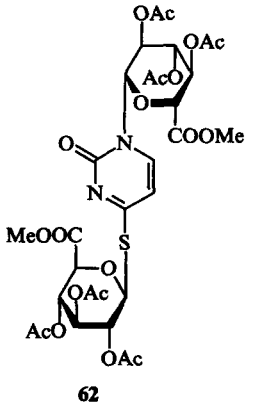
Methods for the synthesis of the *S*-glucuronides of 2- and 4-thiouracils, containing halogen atoms in the 5-position of the pyrimidine group, have been developed.[34] The best synthetic procedure was found to be the glycosylation of thiouracils by the acetate **47** in acetonitrile in the presence of 3.3 equivalents of $SnCl_4$. Together with the *S*-monoglucuronides **60** and **61**, a small amount of the *N*(1),*S*-bisglucuronide **62** was found, the latter being formed probably as a result of transglycosylation of the *S*-glucuronides.



60



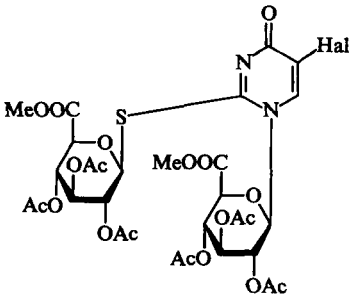
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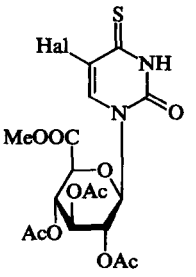
62

The corresponding 5-halo-derivatives have been obtained by halogenating the *S*-glucuronides and it was shown that 4-thiouracil glucuronides are halogenated less effectively than 2-thiouracil glucuronides. The fluorination of 4-thiouracil glucuronides led to cleavage of the *S*-glycosidic linkage.

The reactions of the *S*-glucuronides of 2, and 4-thiouracils and of their 5-halo-derivatives on treatment with Lewis acids have been investigated.[35] Refluxing of the *S*-glucuronides of 2-thiouracil and of its 5-halo-derivatives **60** in benzene in the presence of $HgBr_2$ led to the *N*(1),*S*-bisglucuronide **63** as a result of the transglycosylation reaction, whereas the *S*-glucuronides of the 5-halo-derivatives of 4-thiouracil gave predominantly the *N*(1),*S*-bisglucuronides **62** and insignificant amounts of the *N*(1)-glucuronides **64** as a result of the S → N transglycosylation of the nucleoside **61**.



63



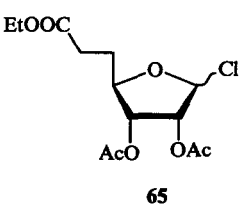
64

Mahrwald and Wagner[36] examined synthetic approaches to glucuronides of 2-hydroxy and 4-hydroxy- as well as 2-mercapto- and 4-mercaptopyrimidines.

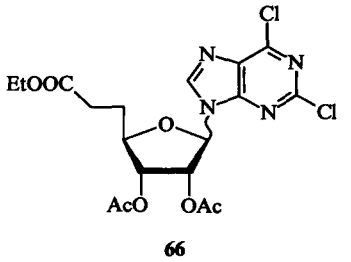
Glycosylation of 5-halouracils (Hal = F, Cl, Br, I) by the bromo-derivative **39** and the acetate **47** has been investigated.[37] The interaction of the bromo-derivative with silyl derivatives of 5-halouracils in benzene in the presence of $HgBr_2$ and $Hg(CN)_2$ led to the corresponding *N*(1)-nucleosides; the formation of small amounts of *N*(1), *N*(3)-bisglucuronides was observed. An increase in the yield of the *N*(1)-nucleosides on passing from uracil to 5-iodouracil was noted. The authors attributed this finding to the decreasing electronegativity of the halogens and the increasing basicity of the *N*(1) atom of the heterocycle.

The condensation of the silyl derivatives of 5-halouracils with the sugars **39** and **47** in acetonitrile and dichlorobutane in the presence of $SnCl_4$ afforded predominantly the *N*(1)-nucleosides, the *N*(3)-nucleosides being found in only two cases.

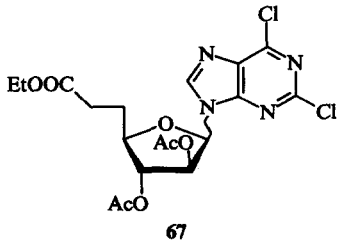
When the chlorosugar **65**, synthesised in six stages from allofuranose, was fused together with 2,6-dichloropurine in the presence of catalytic amounts of toluene-*p*-sulfonic acid with a yield of 47%, the formation of the α- and β-anomeric nucleosides of the D-ribose (compound **66**) and D-arabinose (compound **67**) series was observed.[38]



65

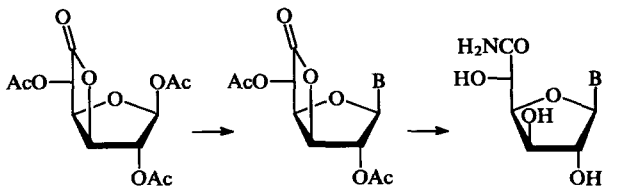


66



67

The condensation of silyl derivatives of uracil (U), *N*(4)-benzoylcytosine [*N*(4)-BzC], and also *N*(6)-benzoyladenine [*N*(6)-BzA] with the completely acetatoxylated glucurone **68** in the presence of three equivalents of $SnCl_4$ gave the nucleosides **69**–**71**, the ammonolysis of which led to the amides **72**–**74**.[39–41]



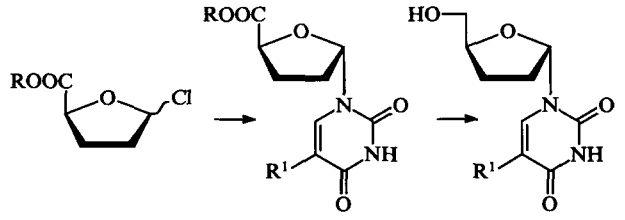
68

69: B = U; **72**: B = U;
70: B = *N*(4)-BzC; **73**: B = *N*(4)-BzC;
71: B = *N*(6)-BzA; **74**: B = *N*(6)-BzA.

The high stereospecificity of the condensation, leading to the formation of nucleosides only in the β-anomeric configuration, was demonstrated.

The nucleosides of glucurone and their derivatives have been synthesised by condensing the lactone **68** with the silyl derivatives of 5-fluoro-, 5-bromo-, and 5-iodo-uracil.[42] The condensation of the lactone with silylated uric acid, xanthine, and *N*(2)-acetylguanine has been investigated in dichlorobutane in the presence of trimethylsilyltrifluorosulfonic acid.[43] The formation of a mixture of the *N*(3)-, *N*(7)-, and *N*(9)-nucleosides was observed under these conditions.

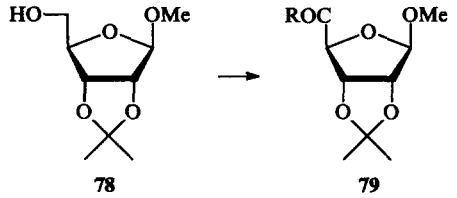
The nucleosides **76** have been synthesised by alkylating silylated pyrimidines by the chloro-derivatives of tetrahydrofurancarboxylic acid **75**. The reaction takes place at 20–30 °C with formation of racemic nucleosides having the *trans*-configuration. Reduction of the esters gave the dideoxynucleosides **77**. A small amount of the *cis*-isomer together with the *trans*-isomer was isolated following the alkylation of 5-fluoro-uracil by the chloro-derivative **75** at 100 °C with distillation of the chlorotrimethylsilane formed during the reaction.[44]



75 76 77

R^1 = Me, H, F.

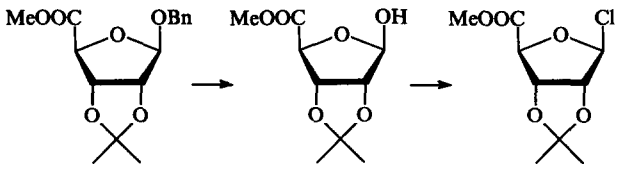
Schmidt and coworkers[45–47] have studied the glycosylation of pyrimidine and purine heterocycles by uronic acid derivatives. They developed methods for the preparation of derivatives of riburonic acid by oxidising the methyl riboside **78** with potassium permanganate. Because of their low reactivity in glycosylation reactions, the esters and amides **79** were found unlikely to be useful in the synthesis of nucleosides.[45]



78 79

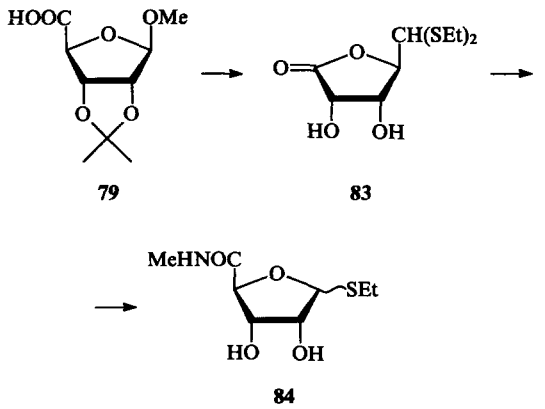
R = OH, OR^1, NR_2^2.

Chlorosugars are more active glycosylating agents. The sugar **81** with a free hemiacetal hydroxy-group was obtained by the hydrogenolysis of the riburonide **80**. Its treatment with thionyl chloride led to the β-anomer of the glycosyl chloride **82**.[46]



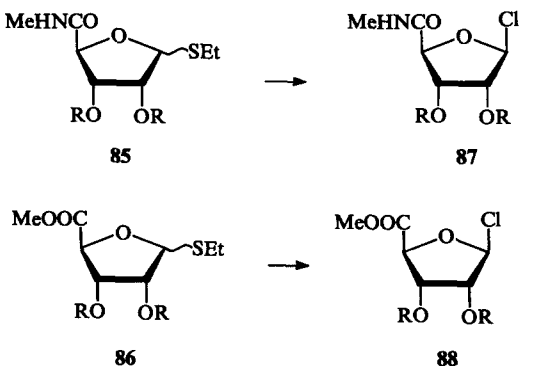
80 81 82

The use of the chloro-derivative **82** in order to obtain nucleosides proved to be of limited applicability for the following reason. In contrast to the isopropylidene derivatives of nucleosides, where the protecting group can be removed under the conditions of mild acid hydrolysis, the hydrolytic removal of the isopropylidene protecting group from uronic acid nucleosides requires severe conditions, which leads to appreciable cleavage of the glycosidic linkage. Methods have been described[47] for the synthesis of halo-derivatives of riburonic acid with benzylidene, benzyl, and benzoyl protecting groups. Treatment of the acid **79** with ethanethiol led to the synthesis of the diethylmercaptoacetal of the lactone **83**, which was transformed in two stages into the amide **84**.



79 83 84

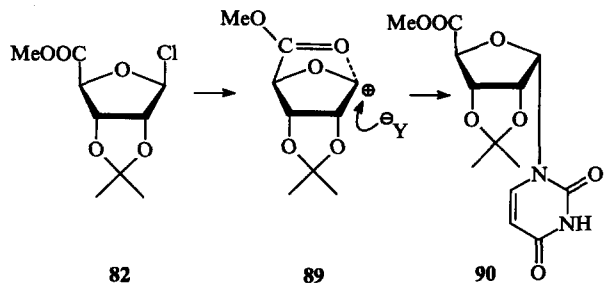
On treatment with chlorine, the benzylidene, benzyl, benzoyl, and acetyl derivatives of the amide **85** and the ester **86** were converted smoothly into the chloro-derivatives **87** and **88**.



85 87

86 88

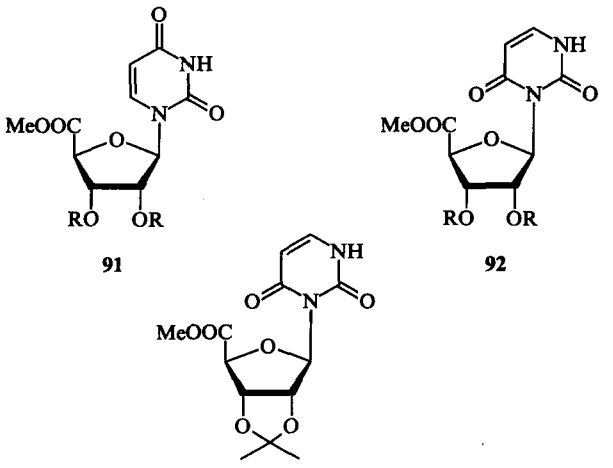
The stereochemical features of the glycosylation of pyrimidine heterocycles by the halo-derivatives of riburonic acid esters and amides with different protecting groups have been investigated. The method involving fusion of the chloro-derivative **82** with silylated uracil in the absence of a catalyst gave only the α-anomeric nucleoside **90**. The stereochemical result of this reaction is probably determined by the steric influence of the methoxycarbonyl group, which prevents the attack on the carbonium ion **89** by the nucleophile from the β-region.[48]



82 89 90

On fusion with uracil, the acetyl and benzoyl derivatives of the chloro-derivative **88** afforded a mixture of anomeric nucleosides, in which the β-anomer predominated. In this case, the stereochemical result was determined by neighbouring group participation, i.e. by the directing effect of the 2-*O*-acyl group.

When the condensation was carried out in benzene in the presence of silver perchlorate, the same behaviour was observed, but an increase in the fraction of the β-anomer was also noted in all cases. When $SnCl_4$ was used as the catalyst, the condensation led only to β-nucleosides, but appreciable amounts of the *N*(3)-nucleosides **92** were found in the reaction mixture under these conditions together with the *N*(1)-nucleosides **91**. Condensation of chloride **82** with uranyl gave only *N*(3) nucleoside **93**. Substitution of chlorine by the acetyl group produced the same result.

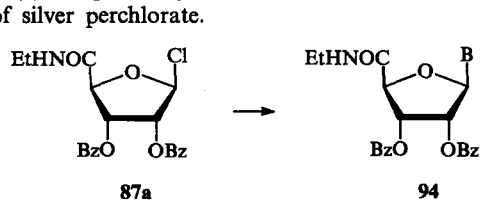


91 92

R = Ac, Bz. 93

The *N*(1)-α-, *N*(1)-β-, and *N*(3)-β-nucleosides have been obtained in proportions of 2 : 15 : 3 respectively by glycosylation of the silylated *N*(4)-acetylcytosine by the chloro-derivative **82** in the presence of $SnCl_4$. The condensation of the benzoate **88** led to the α- and β-anomers in proportions of 1 : 3 and the *N*(3)-nucleoside was not formed. Fusion with silver perchlorate did not alter significantly the stereochemical result of the reaction.

The ethylamides **94** were obtained in satisfactory yields by glycosylating silylated derivatives of uracil, *N*(4)-acetylcytosine [*N*(4)-AcC], and thymine (T) by the diethylamide **87a** in presence of silver perchlorate.



87a 94

B = U, *N*(4)-AcC, T.

The condensation of activated derivatives of D-riburonic and D-lyxuronic acids with various purines was investigated by Schmidt et al.[49] in order to estimate the effectiveness of the glycosylation of purines as a general method of synthesis of uronic acid nucleosides. The anomeric and regioisomeric [*N*(7),*N*(9)] nucleosides were separated by high performance column chromatography and structural assignments were reliably made on the basis of ^1H and ^{13}C NMR data.

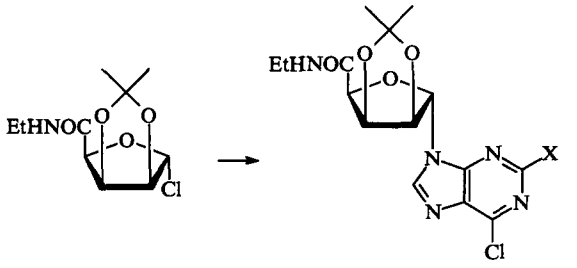
It was established that catalysis by mercury salts and also by $SnCl_4$ and $AgClO_4$ gave nucleosides in acceptable yield only in rare cases. Satisfactory results were obtained by fusing silylated purines with the methyl esters of chloro-derivatives of riburonic and lyxuronic acids with an isopropylidene protecting group. Together with the α- and β-anomers of the *N*(9)-nucleosides, the anomers of *N*(7)-nucleosides were isolated. The ratio of the anomers of the nucleo-sides obtained was shown to be independent of the anomeric configuration of the sugar. Condensation of the riburonic acid derivative with 6-chloropurine led to only one isomer — the α-*N*(7)-nucleoside.

In contrast to the esters, the amides of riburonic acid form exclusively the *N*(9)-nucleosides with approximately equal proportions of the anomers as a result of fusion with purines.

The use of acyl derivatives of riburonamides for condensation with halo-derivatives led to the preferential formation of the β-*N*(9)-nucleosides, as was in fact to be expected in view of the involvement of the 2-*O*-acyl groups.

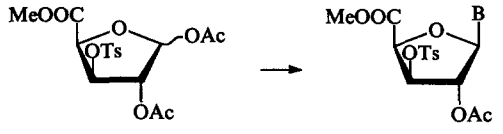
The condensation of purines with the methyl ester of the chloro-derivative of lyxuronic acid carrying an isopropylidene protecting group obeys in the main the same rules, but the formation of a considerable proportion of the β-nucleoside is somewhat unexpected, since all the substituents are then located on one side of the furanose ring.

Purine nucleosides of the ethylamide of lyxuronic acid **96** have also been obtained by fusing the chloro-derivative **95** with 6-chloro- and 2,6-dichloropurines. In contrast to the esters of lyxuronic acid, the condensation of the amide led to the formation of *N*(9)-nucleosides (with a 2 : 1 ratio of the α- and β-anomers) and only trace amounts of the *N*(7)-isomers.[50]



95 96, X = H, Cl.

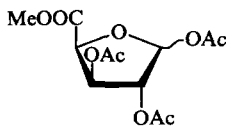
The reaction of alkoxyuronides with silylated nitrogen-containing heterocycles affords nucleosides in lower yields.[51] The 1-*O*-acetyl derivatives of sugars are less active glycosylating agents than alkyl glycosides and are more stable than halo-derivatives of sugars.[52] The condensation of acetate **97** with silylated uracil in the presence of an equimolar amount of $SnCl_4$ leads to the formation of the nucleoside **98** in 32% yield. When the amount of $SnCl_4$ was increased to three equivalents, the yield rose to 85%. The interaction of the acetate **97** with silylated derivatives of 5-fluorouracil, *N*(4)-benzoylcytosine, and *N*(6)-benzoyladenine afforded the corresponding nucleosides **99**–**101**. The formation of only the β-anomeric nucleosides was observed in all cases.[51,53]



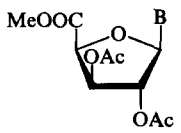
97, Ts = $MeC_6H_4SO_2$.

98: B = U;
99: B = 5-F-U;
100: B = *N*(4)-BzC;
101: B = *N*(6)-BzA.

On glycosylation with the xyluronic acid ester **102** in acetonitrile in the presence of three equivalents of $SnCl_4$, the silyl derivatives of uracil, 5-fluorouracil, and *N*(6)-benzoyladenine give the corresponding nucleosides **103**–**105** in moderate yields.[54]

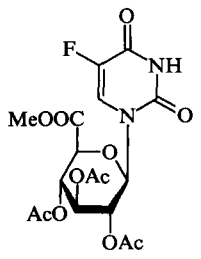


102

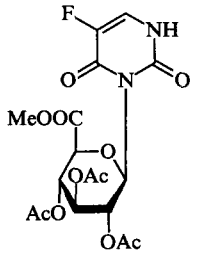


103: B = U;
104: B = 5-F-U;
105: B = *N*(6)-BzA.

The donor–acceptor complexes formed between the silylated pyrimidines and the Lewis acids, the so called *N*(1)-σ-complexes, are capable of reacting slowly with the sugar cation to form *N*(3)-nucleosides.[55]



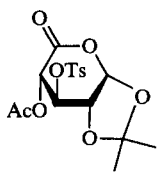
106



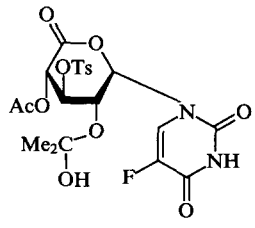
107

The glycosylation of 5-fluorouracil by the acetate **47** using three equivalents of $SnCl_4$ affords the *N*(1)-nucleoside **106** and the *N*(3)-nucleoside **107** in 36% and 6% yields respectively. The replacement of $SnCl_4$ by boron trifluoride etherate gave rise to approximately equal amounts (30.5% and 30%) of the isomeric nucleosides **106** and **107**.[56,57]

The formation of the α-anomeric nucleoside **109** was observed as a result of the glycosylation of 5-fluorouracil by the products of the acetolysis of the lactone **108**.[58,59]

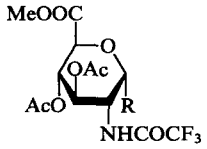


108

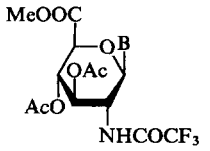


109

The first example of the synthesis of the nucleosides of 2-amino-2-deoxyuronic acids has been described by the present author and Kulinkovich.[60] The glycosylation of uracil by the acetate **110** in the presence of $SnCl_4$ proved to be unsuccessful. The condensation of the bromo-derivative **111** was also relatively ineffective. The nucleosides **112**–**114** were obtained in 26%, 36%, and 25% yields respectively by fusing the bromo-derivative **111** with the silylated heterocycles at 130 °C at a reduced pressure (40 Torr).

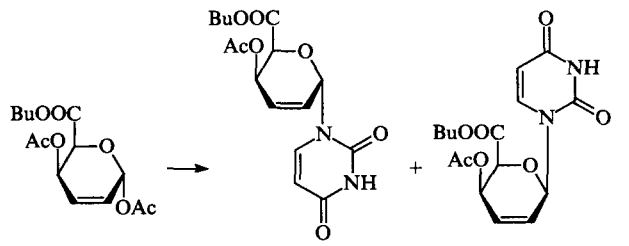


110: R = Ac;
111: R = Br;

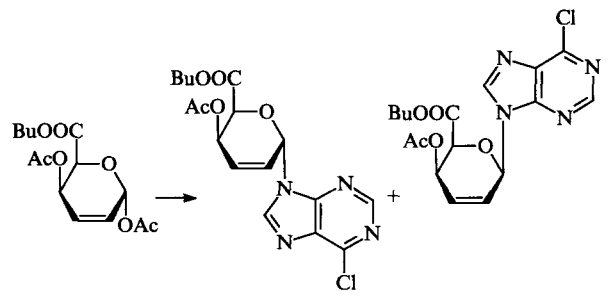


112: B = U;
113: B = 5-Br-U;
114: B = *N*(6)-BzA.

The ready availability of esters of the acid **115**, which are obtained in a single stage from diacetoxybuta-1,3-diene and alkyl glyoxylate, makes them convenient precursors in the synthesis of unsaturated uronic acid nucleosides.[61] The antimony pentachloride-catalysed reaction of the acetate **115** with silylated uracil afforded a mixture of the α-nucleoside **116** and the β-nucleoside **117** (overall yield 80%) with a 3:2 anomer ratio. In the case of thymine, the anomer ratio was 2. The α-nucleoside **118** and the β-nucleoside **119** were obtained in an overall yield of 75% and with the anomer ratio α:β = 2:1 by refluxing the acetate **115** in nitromethane with 6-chloropurine in the absence of a catalyst.

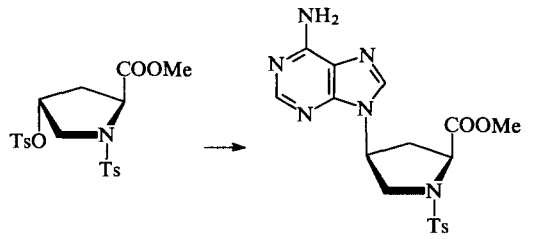


115 **116** **117**



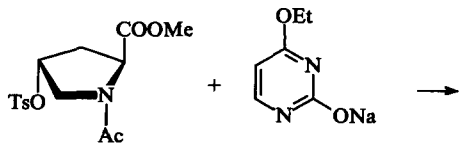
115 **118** **119**

Noncarbohydrate analogues of nucleosides are of undoubted interest as potential biologically active compounds. Certain derivatives of L-hydroxyproline have been used to synthesise them. Thus nucleophilic substitution of the *O*-tosyl group in compound **120** by the sodium salt of adenine led to the nucleoside analogue **121**.[62]

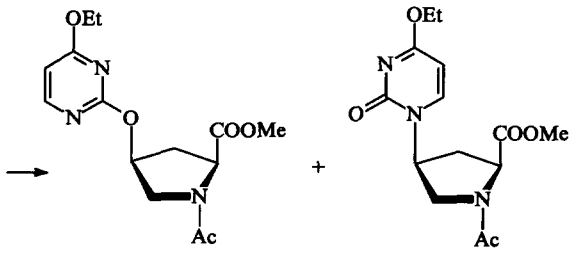


120 **121**

The similar substitution by the sodium salt of 4-*O*-ethyluracil in the pyrrolidine **122** afforded a low yield of the *O*-pseudoglycoside **123** and the *N*-pseudoglycoside **124**.[63]

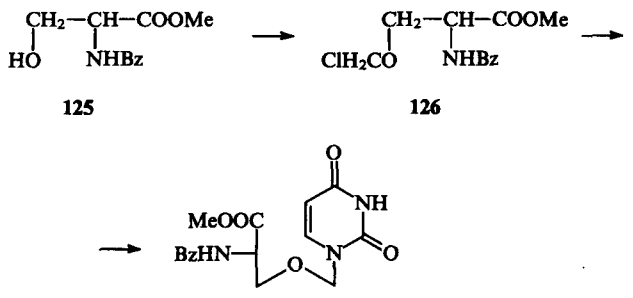


122



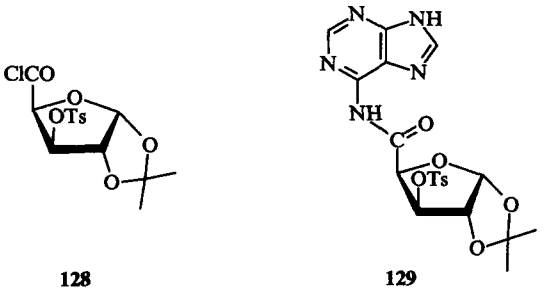
123 124

The possibility of using suitably substituted serine in the synthesis of acyclic analogues of polyoxine antibiotics has been demonstrated.[64] The unstable chloromethyl ether **126** has been obtained by chloromethylating the *N*-benzoyl-DL-serine ester **125**. The condensation of the ether with silylated uracil in acetonitrile led to the acyclic analogue **127** of polyoxine C.



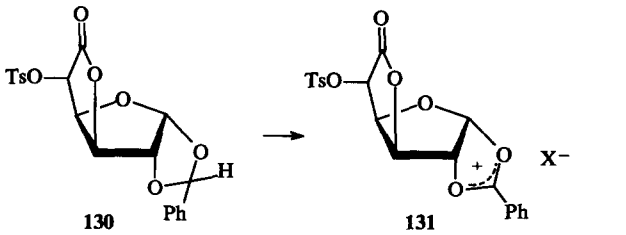
125 126 127

The uronic acid chloride **128** readily reacts with silylated *N*(6)-benzoyladenine to form the xyluronoyl derivative **129**.[65]

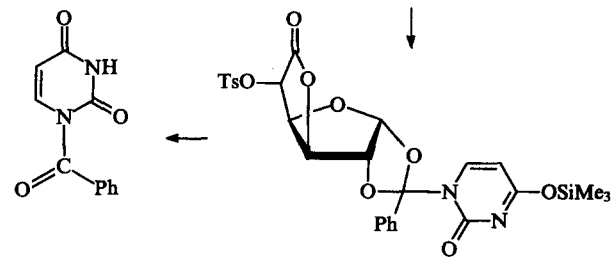


128 129

The intermediate formation of an acyloxonium salt has been postulated as the key stage in the mechanism of the synthesis of nucleosides via glycosylation. The generation of such a salt from the benzylidene derivative of the glucuronolactone **130** has been described.[66] The lactone was treated in acetonitrile with an equivalent amount of Ph_3CBF_4 or $Ph_3CCl/SnCl_4$ and the resulting salt **131** was condensed with silylated uracil. This led to the isolation of *N*(1)-benzoyluracil **132**, the yield of which varied from 30% to 50% in different experiments. Contrary to expectation, nucleoside products were not detected in the reaction mixture. The formation of the intermediate **133**, the hydrolysis of which leads to compound **132**, from the benzoxonium salt **131** appears most probable in this reaction.



130 131



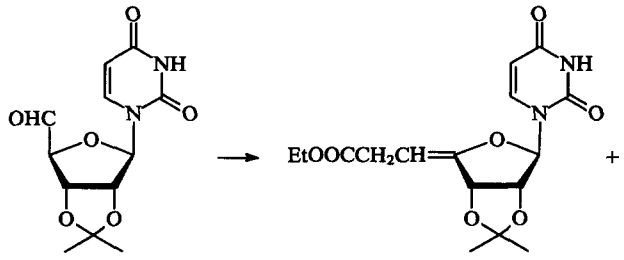
132 133

The structures of the intermediates in the glycosylation reaction differ from the canonical carbonium ion and the acyloxonium ion, although both structures can be formed sometimes, depending on the reaction conditions, which is indicated by the formation of α-anomeric nucleosides and acylated heterocycles.

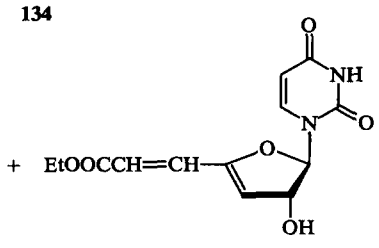
As can be seen from these data, the glycosylation of heterocycles by uronic acids has characteristic features due to the electron-accepting properties of the alkoxycarbonyl group, which is capable of forming stable complexes with Lewis acids. As a result, an excess of the condensing agent is required to obtain acceptable yields of the nucleosides. The presence of the alkoxycarbonyl group in the sugar molecule can appreciably influence the stereochemical result of the glycosylation reaction.

V. Synthesis of uronic acid nucleosides by modifying the sugar and heterocyclic base residues

One of the procedures in the synthesis of uronic acid nucleosides is the condensation of phosphoranes with nucleoside-5'-carboxaldehydes. The reaction of the aldehyde **134** with ethoxycarbonylmethylenetriphenylphosphorane afforded the two unsaturated nucleosides **135** and **136**.[67]

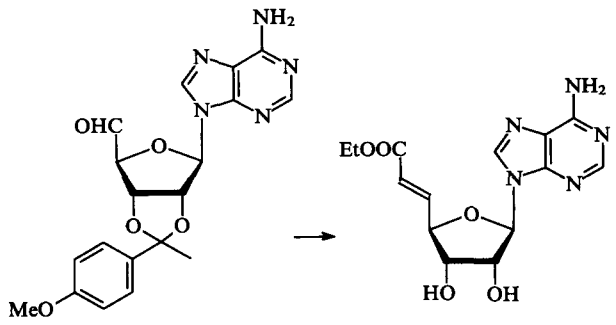


134 135



136

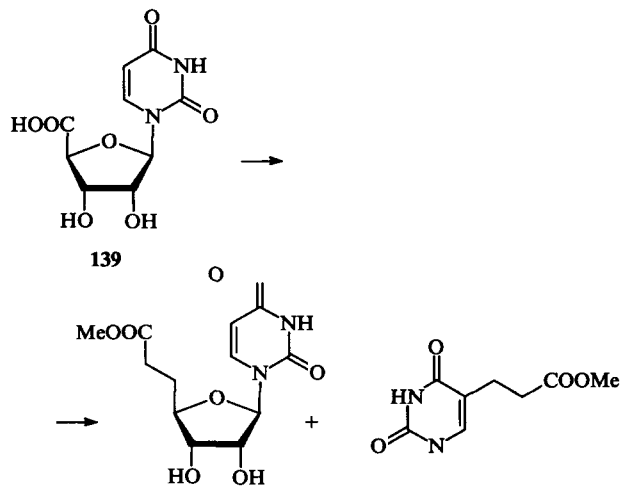
In contrast to the example quoted above, interaction of the aldehyde **137** and the phosphorane under similar conditions gave the nucleoside **138** in a low yield.[68]



137 138

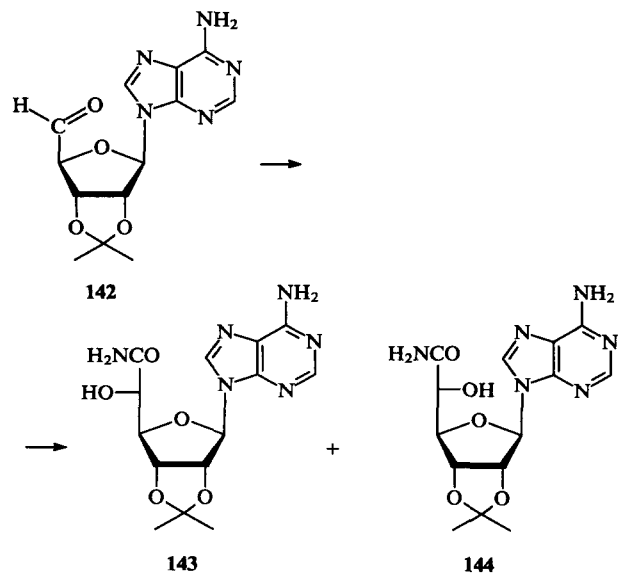
The synthesis of purine and pyrimidine nucleosides having a similar structure has been described.[69-72]

Nucleosides of this type can be obtained by the Kolbe anodic condensation of the acid **139** and the monomethyl ester of succinic acid.[67] The nucleoside **140** and the uracil derivative **141** were obtained by this reaction.



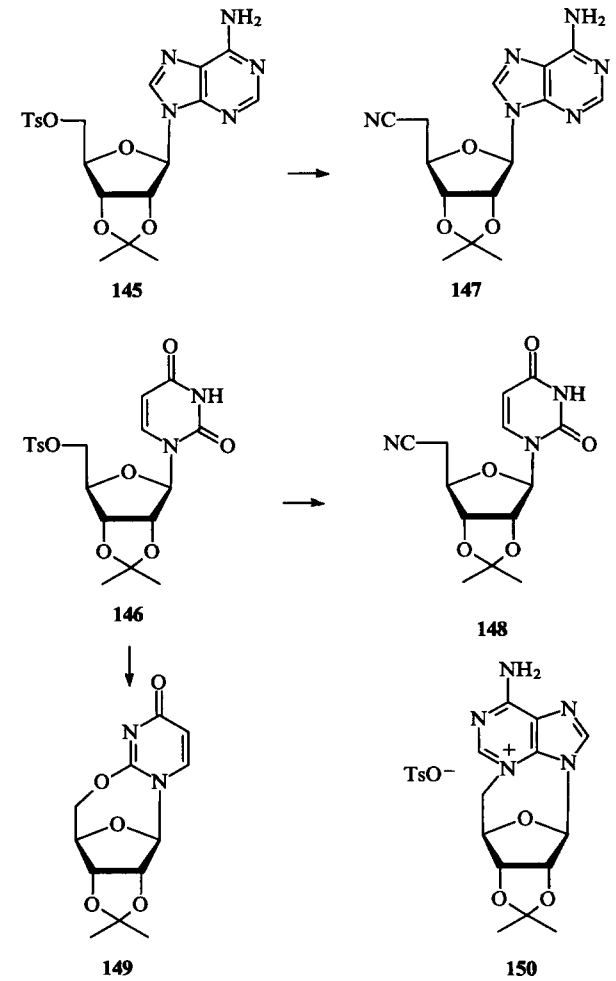
139 140 141

The exocyclic carbon chain of the nucleoside can be developed with simultaneous introduction of a carboxy-group by adding nucleophiles to the carbonyl group of nucleoside-5'-carboxaldehydes. The reaction between the aldehyde **142** and acetone cyanohydrin followed by treatment with hydrogen peroxide at pH 10 of the unstable α-hydroxynitriles formed led irreversibly to the two epimeric amides **143** and **144**.[73]



142 143 144

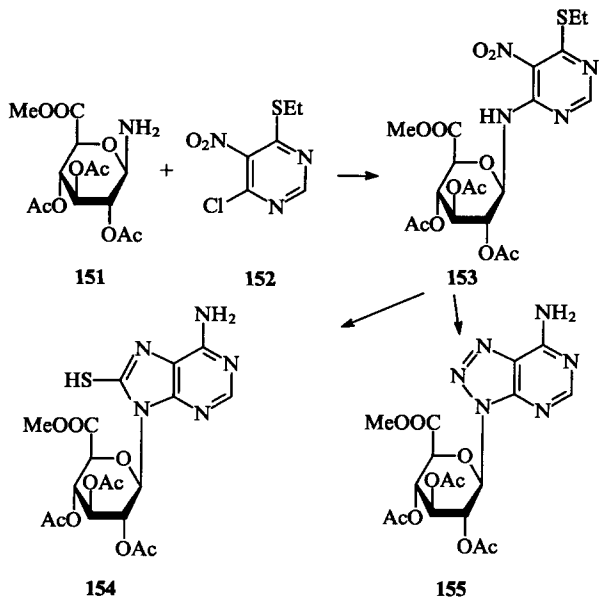
A method has been developed for the synthesis of nucleosides with a lengthened carbon chain from readily available 5'-*O*-tosyl derivatives of nucleosides.[74] The nitriles **147** and **148**, which were previously difficult to obtain, have been synthesised by treating tosylates of adenosine (compound **145**) and uridine (compound **146**) with potassium cyanide in the presence of a crown-ether. In the case of nucleoside **146**, the crown-ether-activated cyanide acts as a base and deprotonates the *N*(3) atom of the pyrimidine; intramolecular nucleophilic substitution results in the formation of a small amount of the cyclic nucleoside **149**. The purine cyclic nucleoside **150** has also been detected.



145 147 146 148 149 150

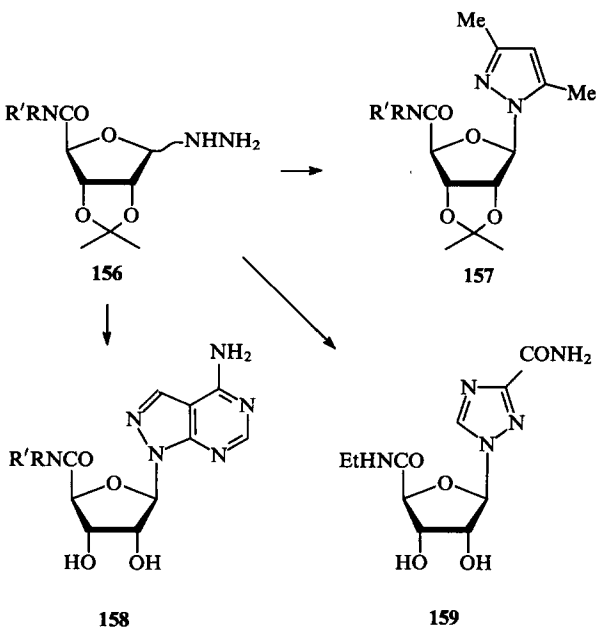
Another route to uronic acid nucleosides, involving modification of the sugar and heterocyclic base residues (the building-on method), is also possible. This variant was applied for the first time in the interaction of the amine **151** with the pyrimidine **152** in the presence of triethylamine.[75] The hydrogenolysis of the *N*-glycoside **153** and refluxing of the resulting amine in a carbon disulfide–pyridine mixture afforded the nucleoside **154**. The reduction of compound **153** with sodium nitrate in aqueous acetic acid led to the 8-azanucleoside **155** (see over).

The building-on method has been used successfully by Schmidt and coworkers[76] to synthesise a wide variety of heterocyclic derivatives of riburonic acid amides. The hydrazinoriburonamides **156** have been used as key compounds for their synthesis. Their condensation with acetylacetone, ethoxymethylenemalononitrile, and oxalic ester thioamide led to the formation of the pyrazole nucleoside **157**, the pyrazolopyrimidine nucleoside **158**, and the virazole analogue **159**.

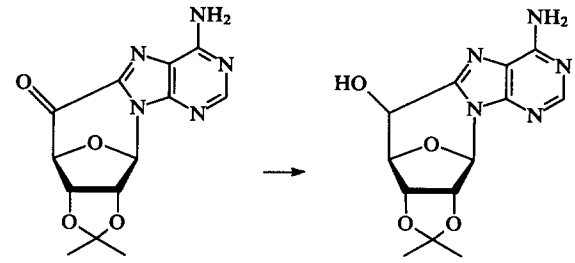


151 152 153

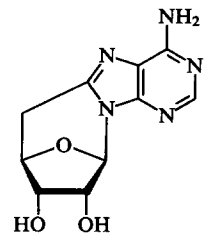
154 155



156 157 158 159

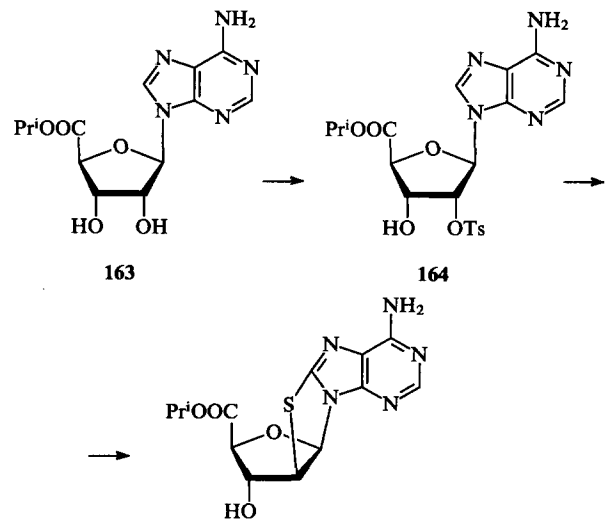


160 161



162

The use of the alkoxycarbonyl group of compound **163** as a kind of protecting group has made it possible to develop an alternative method of synthesis of 2′-deoxyadenosine.[79] Successive bromination and tosylation of the ester **163** afforded the nucleoside **164**, the treatment of which with thiourea gave rise to the *S*-anhydronucleoside **165**. Its reduction over Raney nickel gave 2′-deoxyadenosine in an overall yield of 10%.



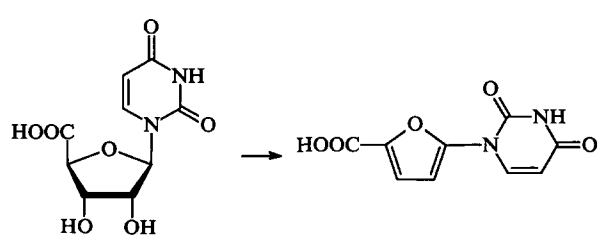
163 164 165

VI. Transformations of uronic acid nucleosides

The presence of the carboxy-group in nucleosides is significantly reflected in their chemical and conformational properties, which has led to new possibilities for the synthesis of diverse nucleosides, the preparation of which by traditional methods involves considerable experimental difficulties. The use of reactions characteristic of the carboxy-group makes it possible to synthesise a whole series of nucleosides with unusual structures. The synthesis of cyclic purine nucleosides may serve as confirmation of the foregoing. Treatment of the acid **19** with methyllithium afforded the ketone **160**, the reduction of which with sodium tetrahydroborate led to the cyclic nucleoside **161**, which is an analogue of deoxycycloadenosine **162**—the product of the photolysis of coenzyme B_{12}.[77] Adenosine-5′-carboxylic acid has been obtained by the photolytic oxidation of the nucleoside **162**.[78]

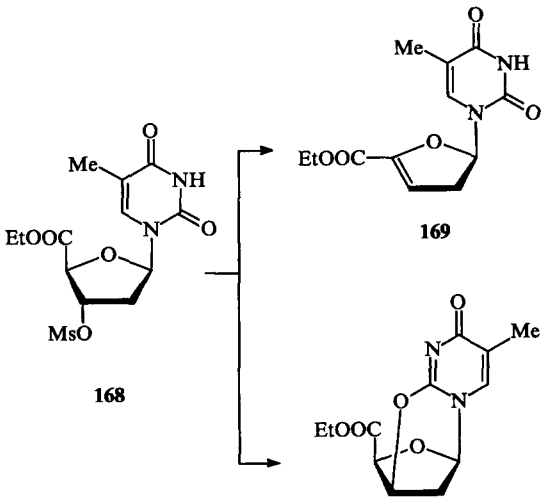
Uronic acids and their nucleosides are known[80] to be capable of giving, by β-elimination, unsaturated compounds, which are of undoubted interest for use in a wide variety of chemical reactions and also for the study of their unusual spectroscopic characteristics.

The β-elimination reaction is observed after brief heating of the acid **166** in acetic anhydride, whereupon the furan derivative **167** is formed.[3]



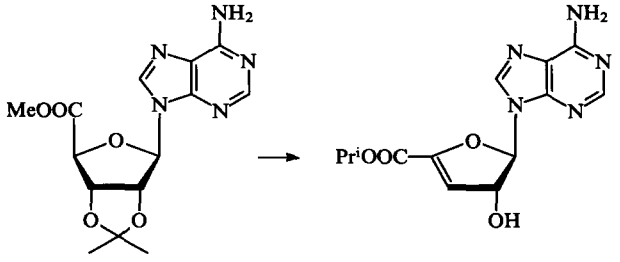
166 167

Uronic acid nucleosides are convenient precursors of 3',4'-unsaturated-nucleosides. Heating of the methanesulfonate **168** with triethylamine or sodium benzoate in DMF leads to the unsaturated nucleoside **169**, while heating with barium carbonate gives the cyclic nucleoside **170**.[81-83]



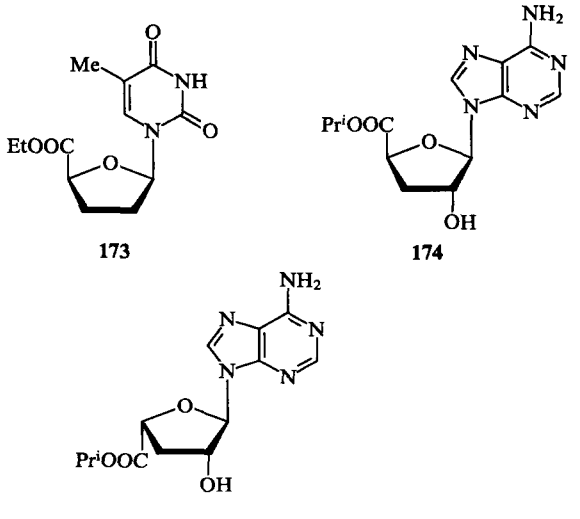
168 **169** **170**

The elimination reaction of acetonide **171** with formation of the unsaturated nucleoside **172** occurred only when sodium isopropoxide was used as the base.[84]



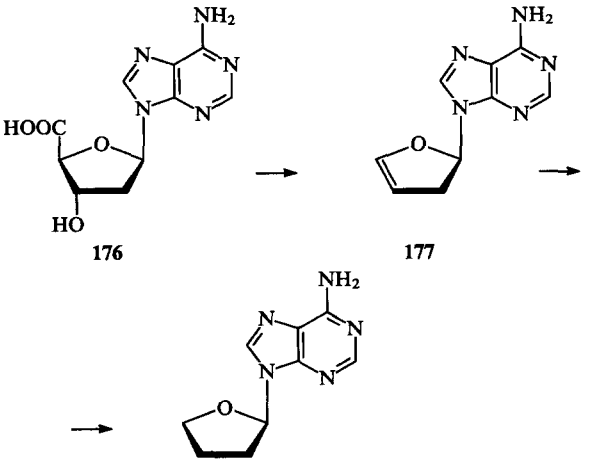
171 **172**

The nucleosides thus obtained were used in the synthesis of the D- and L-series of deoxynucleosides. The catalytic reduction of nucleoside **169** led stereoselectively to the D-isomer **173**, while reduction of nucleoside **172** gave the D- and L-isomers **174** and **175**. Deoxythymidine and deoxyadenosine have been obtained by reducing the esters **174** and **175**.[81,84]



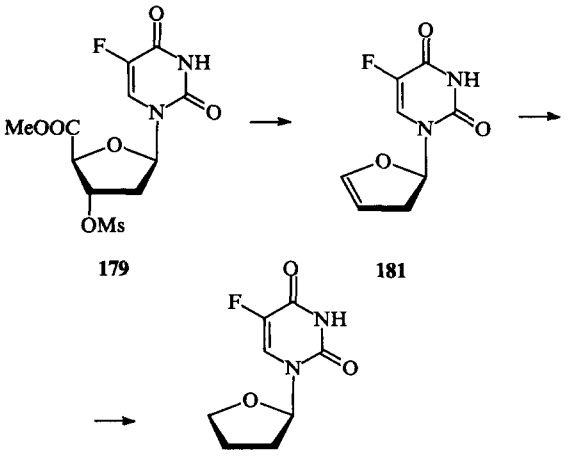
173 **174** **175**

An elimination reaction coupled with decarboxylation has been observed in a series of uronic acid nucleosides.[12] The interaction of nucleoside **176** with the dineopentyl acetal of dimethylformamide in DMF at 80-90 °C leads to a satisfactory yield of the unsaturated nucleoside **177**, the reduction of which makes it possible to obtain the optically active tetrahydrofuran nucleoside **178**.



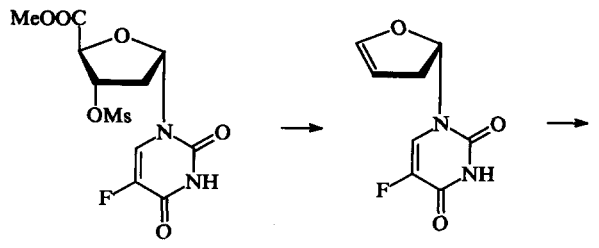
176 **177** **178**

An elimination reaction coupled with dealkoxycarbonylation has been described.[85] Heating of the α- and β-nucleosides **179** and **180** in aqueous pyridine with sodium bicarbonate gave the unsaturated nucleosides **181** and **182**, hydrogenolysis of which led to the optically active nucleosides **183** and **184** (ftorafur).

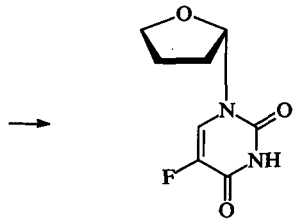


179 **181** **183**

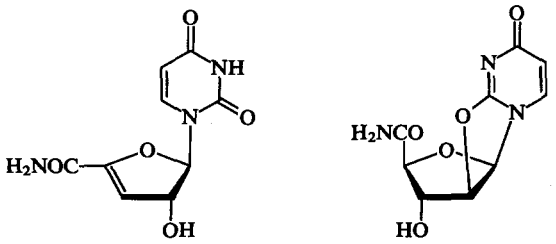
Nucleosides containing derivatives of 3-TsO-D-xyluronic acid as the carbohydrate fragment are readily converted into 3',4'-unsaturated and cyclic nucleosides on treatment with bases.[51,53] The nucleosides **185** and **186** were synthesised by treating the nucleoside **98** with a solution of ammonia in methanol. The nucleoside **185** was also obtained by treating compound **98** with sodium bicarbonate in boiling benzene with subsequent ammonolysis of the unsaturated nucleoside produced. The unsaturated purine nucleoside **187** was synthesised similarly from the tosylate **101**.



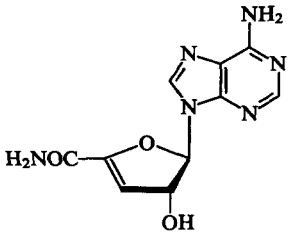
180 182



184

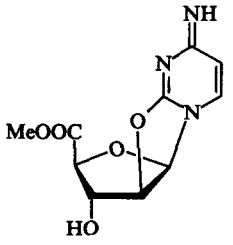


185 186



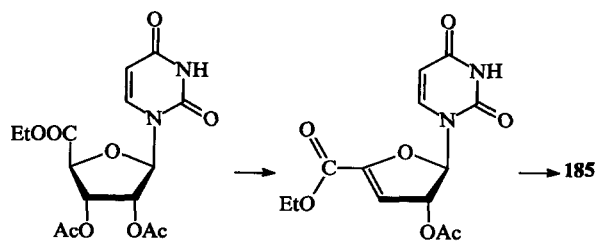
187

For the specific synthesis of the cyclic nucleoside **188**, the nucleoside **100** was initially deacetylated with hydrogen chloride in methanol and then treated with sodium bicarbonate. Under the selected conditions, the dominant process is the intermediate formation of the 2',3'-*O*-anhydronucleoside, which is subsequently converted into the *O*(2),2'-anhydronucleoside **188**.[86]



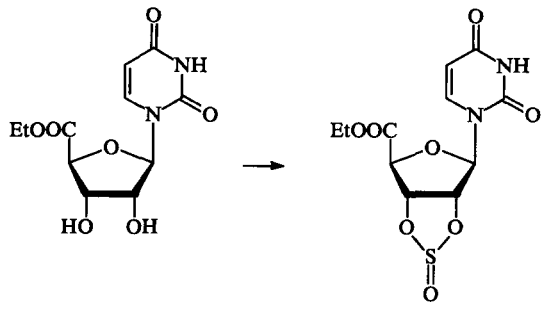
188

The amide **185** has been synthesised by a shorter route from the ester **189**, which was converted into the unsaturated nucleoside **190** on treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU). Ammonolysis gave the amide **185** in a satisfactory yield.[87]

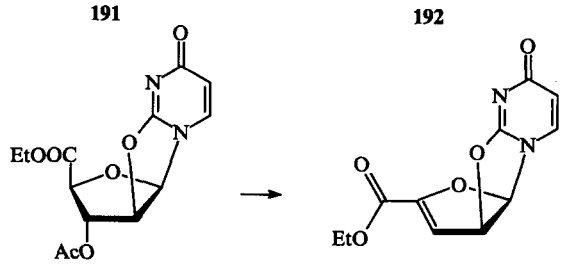


189 190

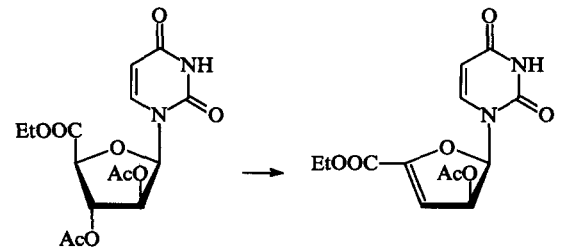
The synthesis of a nucleoside containing an anhydro-ring and a double bond together has been described.[87] Treatment of the ester **191** with thionyl chloride in acetonitrile led to the formation of the sulfite **192**, the heating of which with phthalimide in DMF led to cyclic and arabinosyl nucleosides. The acetates **193** and **194**, obtained from them, gave on treatment with DBU the unsaturated cyclic nucleoside **195** and the nucleoside **196**, which is isomeric in relation to compound **190**.



191 192

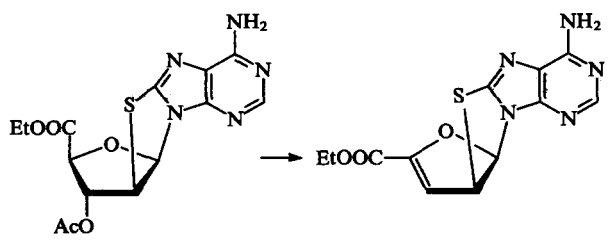


193 195



194 196

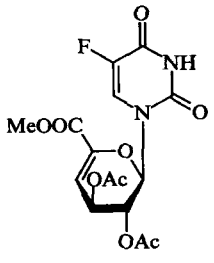
The unsaturated cyclic purine nucleoside **198** was obtained from the *S*-anhydronucleoside **197** on treatment with DBU.[88]



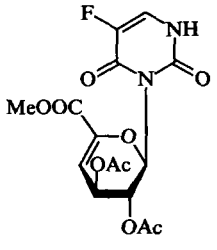
197 198

The Cotton effects observed in the circular dichroism (CD) spectra of the unsaturated nucleosides **195** and **198** are characterised by extremely high molar ellipticities, typical of systems with an internally dissymmetric chromophore.[87,88]

The 4',5'-unsaturated nucleosides **199** and **200** have been obtained by treating the *N*(1)- and *N*(3)-isomeric nucleosides **106** and **107** with DBU.[89,90]



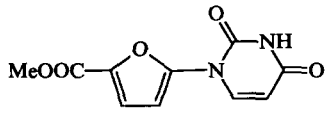
199



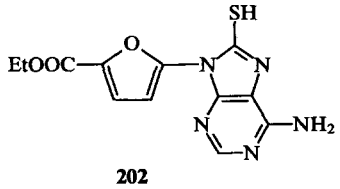
200

There exists in the literature a single point of view on the cause of the anomalies in the CD spectra of unsaturated nucleosides. It has been shown[87] that the sign and amplitude of the Cotton effect in the CD spectra of purine and pyrimidine nucleosides with a double bond in the carbohydrate fragment of the molecule depend on the position of the double bond, the asymmetry of the glycosidic carbon atom, and the sign of the pitch of the weakly or strongly bound internally disymmetric chromophore.

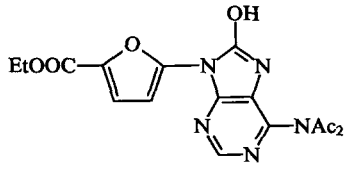
In the presence of an excess of DBU, unsaturated cyclic nucleosides are readily converted into the furancarboxylic acid derivatives **201**–**203**.[87,88,91]



201



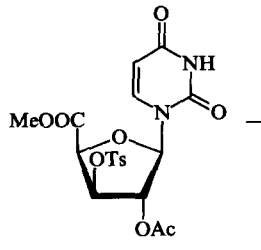
202



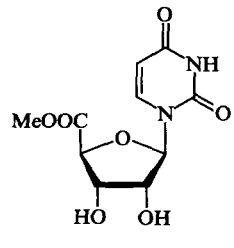
203

Compounds **201**–**203**, which have no asymmetric carbon atom, were found to be optically active.[92] The antiperiplanar conformation of the lone pair of the nitrogen atom (the sp^3-orbital) and of the σ(CO) orbital and their conjugation on passing from anhydronucleosides to furans stabilised the structure with a mutually perpendicular arrangement of the planes of the furan ring and of the nitrogenous base. The stabilisation of such structures as a result of the hindered rotation of the C–N bond leads to the appearance of stereoisomerism, which may be classified as related to the isomerism of allenes and biphenyls but is caused by the stereoelectronic anomeric effect.

Nucleophilic substitution of the halogens and of the methanesulfonyl and tosyl groups, which proceeds with inversion of the configuration, is one of the most widely used methods for specific transformations in the chemistry of carbohydrates and nucleosides. This method is unsuitable in the series of uronic acids when the group to be substituted is in the β-position relative to the alkoxycarbonyl group. The competing β-elimination reaction then takes place. It has been observed[93] that the nucleosides of 3-TsO-D-xyluronic acid can be converted smoothly into nucleosides with the D-ribo-configuration on treatment with phthalimide. Treatment of the nucleoside **98** with phthalimide in DMF at 130 °C gives rise to a mixture of positional acetate isomers, the deacetylation of which leads to the ribonucleoside **204**.

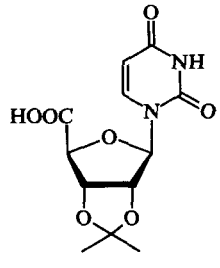


98

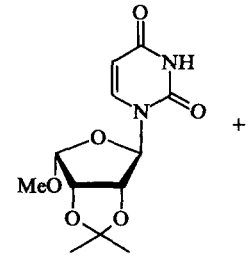


204

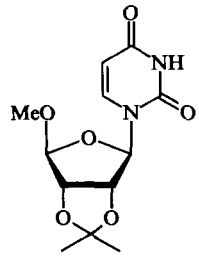
The results of the anodic oxidation of the acid **205** are interesting.[94] A mixture of the methoxynucleosides **206** and **207** has been obtained in a 35% overall yield by the electrolysis of the acid in methanol. The cyclic nucleoside **208** with an unusual structure was isolated from the reaction mixture together with the above compounds. Electrolysis of the nucleoside **205** in acetic acid afforded the acetates **209** and **210**.



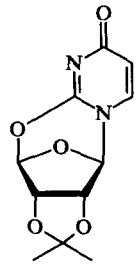
205



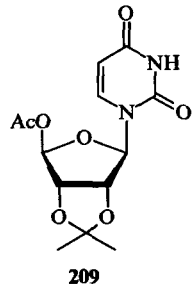
206



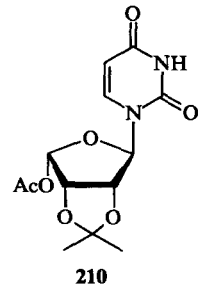
207



208



209



210

It is essential to note one other feature of uronic acid nucleoside. Anisochronicity of the diastereotopic protons in the ^1H NMR spectra of the ethyl and isopropyl esters has been observed only in nucleosides with an anhydro-ring or an isopropylidene protecting group. It has been shown that the observed anisochronicity, caused by the presence of anisotropic heterocycles in the chiral molecule, depends on the distance between the alkoxycarbonyl group and the anisotropic group and on their orientation relative to one another in space.[95–97]

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