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The Silyl Method of Synthesis of Nucleosides and Nucleotides

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Data on the silylation of pyrimidine and purine bases and on the application of trimethylsilyl derivatives of nitrogen-containing heterocycles in the synthesis of nucleosides, nucleotides, and their analogues have been reviewed systematically. The bibliography includes 205 references.

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I. INTRODUCTION

The silyl method discovered in 1963[1,2] rapidly gained a firm position among numerous methods for the synthesis of nucleosides. More than 500 syntheses of various nucleosides have already been carried out by the silyl method and their number continues to grow without interruption. This can be explained by the many advantages and distinctive features of the silyl method compared with others, particularly the Hilbert–Johnson method[3] of which it is a modification.

The principal stage in the synthesis of nucleosides by the silyl method is the interaction of silylated heterocyclic bases with acylated halogenoses. The silyl derivatives can be obtained in high yield directly from the heterocyclic bases (not only pyrimidines but also their aza-analogues, triazole, purine, and other nitrogen-containing condensed systems), while the trimethylsilyl groups remaining after the reaction can be readily removed by treating the product with water or alcohol. By varying the conditions of the reaction, it can be driven towards the preferential formation of the α- or β-anomer. The use of phosphorylated sugars in the reactions makes it possible to obtain nucleotides.

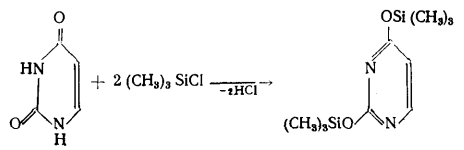
The first results obtained by the silyl method in the synthesis of nucleosides were described in a number of incomplete and now obsolete reviews[3-7] and examples of the silylation of heterocyclic bases published up to the middle of 1968 have been compiled in a table in a handbook on the silylation of organic compounds[8].

We have reviewed data on the silylation of pyrimidine and purine bases and on the application of trimethylsilyl derivatives of nitrogen-containing heterocycles in the synthesis of nucleosides† and nucleotides published up to May, 1973.

† Following Townsend and Revankar[9], in the present review the term "nucleosides" is applied to the *N*-glycosides of nitrogen-containing heterocycles.

II. SILYLATION OF PYRIMIDINES AND PURINES

When uracil is allowed to react with chlorotrimethylsilane in the presence of triethylamine, 2,4-bis(trimethylsilyl)uracil is obtained in 72% yield[1,10-21]:



The reaction is carried out in benzene[1] or dioxane[14,17], pyridine[22] or triethylamine being used as the hydrogen chloride acceptor.

When uracil is heated with hexamethyldisilazane, 2,4-bis(trimethylsilyl)uracil is formed in a high yield 90–96%).[23-27] To accelerate the silylation, chlorotrimethylsilane[28-33] or ammonium sulphate[29] is added to the reaction mixture.

For the purpose of chromatographic and mass-spectrometric analysis, uracil was silylated with *NO*-bis(trimethylsilyl)acetamide in the presence of a catalytic amount of chlorotrimethylsilane[31,34], ammonium chloride[31] (or without them[31,35,36]), and bis(trimethylsilyl)trifluoroacetamide[34,35].

In the silylation of thymine, a high yield (90–92%) of the 2,4-bis(trimethylsilyl) derivative is achieved both with chlorotrimethylsilane as the silylating agent[1,10,14,17,22,37] and on silylation with hexamethyldisilazane[11-13,16,20,21,23-25,28,30,32,38-43]. The latter reaction is carried out either in dimethylformamide (DMF) solution[38] or in an excess of hexamethyldisilazane[23]. The silylation of thymine with bis(trimethylsilyl)acetamide is carried out in acetonitrile solution[31] or at 100°C in the absence of solvent[34].

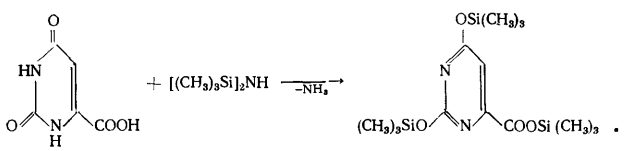
5-Alkyluracils[21,44], 5-alkoxymethyluracils[45], 5-substituted thiouracils[37,46], 6-chlorouracil[47], and 5- and 6-bromouracils[48] have also been silylated with chlorotrimethylsilane in the presence of triethylamine.

The reaction with hexamethyldisilazane yielded 2,4-bis(trimethylsilyl)derivatives of 5-trifluoromethyluracil[30,49,50], 5-alkoxyuracils[51], 5-alkoxymethyluracils[25,52],

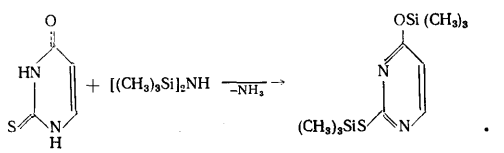
5-fluorouracil[25,30,50,53,54], 5-chlorouracil[25], 5-bromouracil[25], 5-iodouracil[25], 5-formyluracil[30,52,55], 5-alkyluracils[56], 5,6-dialkyluracils[57,58], 5-bromo-6-methyluracil[57], 5-iodo-6-methyluracil[57], 6-alkyluracils[57,58], 6-alkylthiouracils[59,60], and orotic acid esters[57]. 6-Vinyluracil has been silylated by bis(trimethylsilyl)acetamide in acetonitrile solution[61].

When 5-hydroxymethyluracil reacts with chlorotrimethylsilane in the presence of triethylamine[62] or with hexamethyldisilazane in the presence of chlorotrimethylsilane[30] or ammonium sulphate[52], all three hydroxy-groups are silylated with formation of a tris(trimethylsilyl) derivative. The reaction between barbituric acid and hexamethyldisilazane takes place quantitatively with formation of 2,4,6-tris(trimethylsiloxy)pyrimidine[53,63]. A similar tris(triethylsiloxy)-derivative is formed when barbituric acid reacts with aminotriethylsilane[64].

The carboxy-group of orotic acid is also silylated by hexamethyldisilazane, which leads to the formation of the trimethylsilyl ester of 2,4-bis(trimethylsilyl)orotic acid[57]:



When hexamethyldisilazane or its mixture with chlorotrimethylsilane reacts with 2-thiouracil[65,66], 5-alkyl-2-thiouracils[56,65-67], 5-ethoxycarbonylmethyl-2-thiouracil[66,68,69], 2,4-bis(trimethylsilyl) derivatives containing Si—O and Si—S bonds are formed. For example:

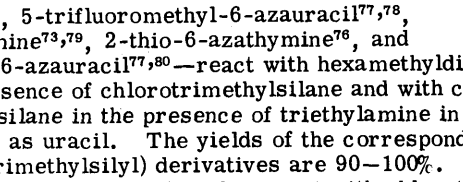


2-Selenouracil is silylated by hexamethyldisilazane similarly[70].

One trimethylsilyl group can be introduced with the aid of these reagents into the molecules of 4-*O*-ethyluracil[11,14,15,24,26], 4-*O*-ethylthymine[24,38,41,42], 4-methylthiopyrimidin-6-one[71], and 6-methyl-4-methylthiopyrimidin-2-one[58].

6-Azauracil[32,72-75] and its derivatives—2-thio-6-azauracil[65,76], 5-trifluoromethyl-6-azauracil[77,78], 6-azathymine[73,79], 2-thio-6-azathymine[76], and 5-bromo-6-azauracil[77,80]—react with hexamethyldisilazane in the presence of chlorotrimethylsilane and with chlorotrimethylsilane in the presence of triethylamine in the same way as uracil. The yields of the corresponding 3,5-bis(trimethylsilyl) derivatives are 90—100%.

When cytosine was allowed to react with chlorotrimethylsilane in the presence of triethylamine[1,10] or pyridine[22], the bis(trimethylsilyl) derivative containing Si—O and Si—N bonds was obtained in 70% yield:

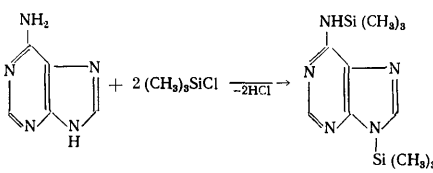


The use of hexamethyldisilazane as a silylating agent makes it possible to obtain *NO*-bis(trimethylsilyl)cytosine in 90% yield[24,29-31]. For the purpose of chromatography, cytosine has also been silylated with bis(trimethylsilyl)-acetamide[31,34,35] and bis(trimethylsilyl)trifluoroacetamide[31].

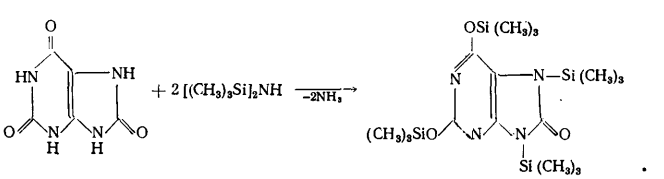
5-Methylcytosine[35], 6-methylcytosine[58], 4-acetylcytosine[1,10,16,20,24,28,32,81,82], 5-bromocytosine[83], 5-fluoro-4-*p*-toluoylcytosine[53], and 5-hydroxymethylcytosine[24] are silylated similarly.

High yields of trimethylsilyl derivatives are obtained also by the silylation with hexamethyldisilazane of other aminopyrimidines: 4-aminopyrimidin-6-one[71], 4-amino-6-hydroxypyrimidine-2-thione[59], 6-aminouracil[59], 5,6-diaminouracil[84,85], 6-alkoxy-2,4,5-triaminopyrimidines[86], and also 5-azacytosine[63,87,88], and 2-thio-5-azacytosine[87,89]. The hydrogen atom in all these hydroxy-, mercapto-, and amino-groups is substituted by the trimethylsilyl group.

When adenine[1,10,22,27], 6-benzoyladenine[1,10,11,15,28,32,90,91], hypoxanthine[1,10,14,15,91], xanthine[1,10,22], guanine[1,10,29], and theophylline[11,14,15] were allowed to react with chlorotrimethylsilane in the presence of triethylamine or pyridine, their mono-, bis-, and tris-(trimethylsilyl) derivatives were obtained respectively in 80—90% yield. In all cases one trimethylsilyl group is linked to a nitrogen atom of the imidazole ring. For example, the reaction with adenine proceeds as follows:



On heating with hexamethyldisilazane, hypoxanthine[22,23] is converted into 6,9-bis(trimethylsilyl)hypoxanthine; under analogous conditions, xanthine[29] gives rise to 2,6,9-tris(trimethylsilyl)xanthine; 6,9-bis(trimethylsilyl)-adenine is formed from adenine[29,31,92] and guanine[29] is converted into the 2,6,9-tris(trimethylsilyl) derivative. On heating with hexamethyldisilazane in an autoclave at 200°C (14 h), uric acid is converted into 2,6,7,9-tetrakis-(trimethylsilyl)uric acid in 70% yield[64,84]:



Tetrakis(triethylsilyl)uric acid was obtained in 90% yield by the reaction of uric acid with aminotriethylsilane[2,64,93,94].

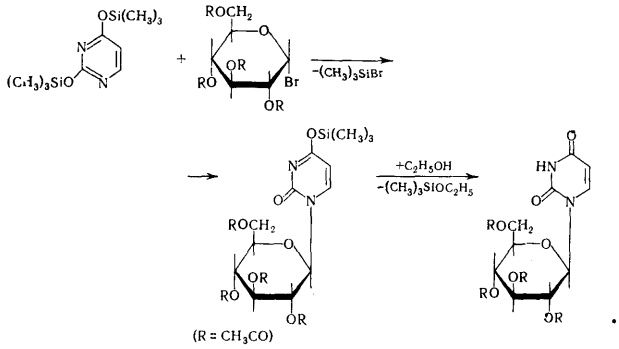
NO-Bis(trimethyl)acetamide has been used successfully in the silylation of hypoxanthine[34,35], xanthine[34,35], adenine[31,34,35], and guanine[31,34,35].

In contrast to the bases themselves, the *N*- and *O*-trimethylsilyl derivatives of hydroxy- and amino-pyrimidines are liquids or solids with comparatively low melting points and are readily soluble in non-polar solvents. They are purified by vacuum distillation or crystallisation. However, heterocyclic amines are frequently silylated by an excess of hexamethyldisilazane in the presence of a catalytic amount of chlorotrimethylsilane, the excess hexamethyldisilazane is removed after the reaction *in vacuo*, and the silyl derivative obtained is used subsequently in the synthesis of nucleosides without additional purification.

III. SYNTHESIS OF PYRIMIDINE NUCLEOSIDES

1. Uracil Nucleosides

Trimethylsilyl derivatives of hydroxypyrimidines react with acylhalogenoses, halogenotrimethylsilane being evolved and an acylated pyrimidine nucleoside being formed. Initially it was suggested that the reaction be carried out by fusing the reactants at 180—195°C at atmospheric pressure[1,12,23,28,95]. For example, when 2,4-bis(trimethylsilyl)uracil is fused with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide at 180—195°C, bromotrimethylsilane is evolved. The subsequent elimination of a second trimethylsilyl group by aqueous ethanol gives 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-uracil in 42% yield[95]:



The β-anomers were also obtained by the reaction of 2,4-bis(trimethylsilyl)uracil with 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl chloride[18,19,96] (yield 73%) and 3,5-di-*O*-acetyl-2-deoxy-2-trifluoroacetamido-D-xylofuranosyl chloride[97] (yield 48%).

Mixtures of anomers with the β-anomer predominating (about 80%) were obtained by the reactions of 2,4-bis(trimethylsilyl)uracil with 2,3,5-tri-*O*-benzoyl-4-thio-β-D-arabinofuranosyl chloride[20] and 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl bromide[98] at 130—140°C. On the other hand, when 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide is employed as the glycosidic component, both anomers are obtained in equal amounts[12], while on fusion with 2,3,5-tri-*O*-acetyl-D-lyxofuranosyl chloride the product is 1-(2,3,5-tri-*O*-acetyl-D-lyxofuranosyl)uracil containing 78% of the α-anomer[12].

The reactants were heated at 140°C in the vacuum generated by a water pump in order to synthesise 1-(2,3,4,5,6-penta-*O*-acetyl-1-ethylthio-D-glucosyl)-uracil (yield 45%).[99] The reaction of 2,4-bis(trimethylsilyl)uracil with 3-*C*-acetoxymethyl-2,5-di-*O*-acetyl-3-deoxy-3-phthalimido-D-ribofuranosyl chloride was carried out by refluxing their solution in benzene for two days. This led to the formation of the corresponding β-nucleoside in 23% yield[100].

The silyl method has been used successfully also to synthesise nucleoside analogues in the molecules of which the pyrimidine base is linked to tetrahydrofuran or tetrahydropyran[101,102,103]. For example, 2,4-bis(trimethylsilyl)uracil reacts at a temperature as low as -20°C with 2-chlorotetrahydrofuran, the product being 1-(2-tetrahydrofuryl)uracil[102].

When 2,4-bis(trimethylsilyl)uracil is fused together with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride at 190°C for 40 min, a mixture of anomeric 1-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)uracils is formed‡. The yields of the β- and α-anomers are 58 and 9% respectively[17,23,28]. When the reaction was carried out in benzene solution at room temperature in the presence of $AgClO_4$, the overall yield of the nucleoside (52%) did not increase[24,25]. The addition of $HgBr_2$ to the reaction mixture was much more effective—after a 3 h reaction with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide at room temperature, only the β-anomer was formed in 90% yield[32,105]. In an analogous reaction the yield of 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)uracil was 93%.[32]

The 1-β-anomer was formed in 59% yield in the reaction of 2,4-bis(trimethylsilyl)uracil with 2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-diethoxyphosphinylmethyl-D-ribofuranosyl chloride in the presence of a mixture of $HgCl_2$ and HgO.[33] The mixture of mercury(II) bromide and oxide proved to be a better catalyst than $AgClO_4$ also in the reaction of 2,4-bis(trimethylsilyl)uracil with 3,4-di-*O*-*p*-toluoyl-2-deoxy-D-ribopyranosyl chloride. In the first case the yield of the mixture of anomers ($\alpha:\beta$ = 77 : 23) was 78%, while in the second it was only 36%, but the anomer ratio remained almost the same (72 : 28).[26] The replacement of the *p*-toluoyl derivative by the *p*-nitrobenzoyl derivative in the reaction in benzene at room temperature in the presence of $HgBr_2$—HgO did not affect the yield and ratio of the anomers[26].

The employment of 1-(3,4,6-tri-*O*-tosyl-1-deoxy-β-D-psicofuranosyl) bromide instead of the chloride did not influence the yield of the β-nucleoside in its synthesis from 2,4-bis(trimethylsilyl)uracil in the presence of mercury(II) acetate (17%).[106]

In many cases the corresponding nucleosides were obtained in high yields also in the presence of $AgClO_4$. For example, the yields of 1-(2,3,4-tri-*O*-acetyl-L-arabinopyranosyl)uracil and 1-(2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl)uracil synthesised from 2,4-bis(trimethylsilyl)uracil and the corresponding bromo-sugars in the presence of $AgClO_4$ were 90 and 86%.[24,25] However, the yields of the nucleosides obtained by this method from 2,4-bis(trimethylsilyl)uracil and 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide, 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride, and 3,5-di-*O*-*p*-toluoyl-2-deoxyribofuranosyl chloride are much lower—44, 52, and 25% respectively[24,25].

When Lewis acids are used as catalysts in the synthesis of nucleosides by the silyl method, fully acylated sugars may be introduced into the reaction with 2,4-bis(trimethylsilyl)uracil. In the presence of antimony pentachloride a high yield of the nucleoside is achieved even at room temperature[107]. For example, when a solution of 2,4-bis(trimethylsilyl)uracil and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose in 1,2-dimethoxyethane is stirred for 100 min at 20°C in the presence of $SbCl_5$, 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)uracil is obtained in 55% yield. Much less satisfactory results are achieved when boron trifluoride-ether is employed[107].

Depending on the nature of the catalyst employed and the reaction temperature, the interaction of 2,4-bis(trimethylsilyl)uracil with triacetylglycal gives rise to different products. When the reaction is carried out at -20°C

‡ 2,3,5-Tribenzoyl-L-uridine was synthesised similarly[104].

in the presence of BF_3-ether, the product is 3-(4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hexeno-2-pyranosyl)-uracil ($\alpha:\beta = 35:32$). When a solution of the reactants in ethyl acetate is refluxed for 1 h, 1,2,3-trideoxy--3-(3'-uracilyl)-D-*arabino*-hex-1-enopyranose is formed in 78% yield, while in the presence of $SbCl_5$ an 87% yield of 1-(4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-eno-pyranosyl)uracil ($\alpha:\beta = 23:26$) is obtained[108]. $AlCl_3$, $TiCl_4$, and $SnCl_4$ have an effect similar to that of BF_3, but the yields of the reaction products are lower. $FeCl_3$, $SbCl_3$, and $Cu(BF_4)_2$ act like $SbCl_5$, while $BiCl_3$ and PCl_5 do not catalyse the reaction[108].

Condensation of 2,4-bis-(trimethylsilyl)uracil with triacetylgalactal in ethyl acetate solution in the presence of $SbCl_5$ at 23°C for 5 min leads to a mixture of anomers of 1-(4,6-di-*O*-acetyl-2,3-dideoxy-D-*threo*-hexeno-2-pyranosyl)uracil from which the crystalline α-anomer and the amorphous β-anomer were isolated in yields of 40 and 24% respectively[109].

2. Thymine Nucleosides

The reaction of 2,3,4-6-tetra-*O*-acetyl-α-D-gluco-pyranosyl bromide with 2,4-bis(trimethylsilyl)thymine results in the formation of 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thymine. Its yield depends to a considerable degree on the reaction conditions and the nature of the catalyst employed (Table 1).

Table 1. Dependence of the yield of 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thymine on the conditions of the reaction of 2,4-bis(trimethylsilyl)thymine with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[41,95].

Catalyst	Solvent	Reaction temp., °C	Duration, h	Yield, %
—	Benzene	100	20	27
—	—	100 (vacuum)	3	41
—	—	170—190	0.5	52
$AgClO_4$	ditto	20	0.25	61
$AgClO_4$	»	20	12	66
HgO	»	50	4	65
$HgCl_2$/HgO	»	50	4	72
$HgBr_2$/HgO	»	50	4	84
$HgBr_2$/HgO	»	110	5	86

Thus, while the yield of the 1-β-nucleoside in the reaction in boiling benzene is only 27% after 20 h, [41] at 170—190°C in a stream of nitrogen the yield is 52% after 30 min[95]. In the presence of $AgClO_4$ in benzene solution the yield reaches 61% after only 15 min at 20°C. The increase of the reaction time to 12 h has little influence on the yield. The maximum yield (86%) was achieved on refluxing a benzene solution of the reactants for 5 h in the presence of a mixture of $HgBr_2$ and HgO.[41] A mixture of $HgCl_2$ and HgO proved to be less active. The replacement of α-acetylbromoglucose by β-acetylchloroglucose reduced the yield of the nucleoside from 72 to 56%.[41]

In many cases the yields of the nucleosides obtained from 2,4-bis(trimethylsilyl)thymine in the presence of $HgBr_2$—HgO and $AgCl_4$ are similar. For example, the yields of 1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)-thymine were 88 and 78%,[41] which is much more than in the synthesis of the same compound by the mercury method (22%) [110] or by the Hilbert—Johnson method (13%);[111] the yields of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thymine were 80 and 75%,[41] which is also higher than the yields achieved by the mercury method (50%) [110] and the Hilbert—Johnson method (8% each of the α- and β-anomer)[112]; the yields of 1-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thymine were 45 and 50%,[41] those of 1-(3,5-di-*O*-*p*-toluoyl-2-deoxy-D-ribofuranosyl)thymine were 55 and 45% (with the same ratio of the α- and β-anomers equal to 31:69)[41], and those of 1-(3,4-di-*O*-acetyl-2-deoxy-D-xylopyranosyl)thymine were 88 and 80%.[40] However, in the last case the ratios of the anomers in the mixtures were not the same: in the presence of $AgClO_4$ the α- and β-anomers are formed in almost equal amounts (48:52), while in the presence of $HgBr_2$—HgO the α-anomer predominates (60:40).[40]

When 2,4-bis(trimethylsilyl)thymine reacts with 2-deoxy-3,5-di-*O*-*p*-nitrobenzoyl-D-ribofuranosyl chloride in the presence of $HgBr_2$—HgO, a mixture of anomers is obtained in 80% yield, in which the α-anomer also predominates (79:21).[42] The use of the *p*-toluoyl derivative in this reaction alters the ratio in favour of the β-anomer[41]. On the other hand, mercury acetate gives a greater amount of the α-anomer ($\alpha:\beta = 56:24$) also in the reaction of 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride in DMF at 20°C.[41]

The β-anomers are obtained by the reaction of 2,4-bis-(trimethylsilyl)thymine with 1-deoxy-3,4,6-tri-*O*-tosyl-D-psicofuranosyl bromide in the presence of mercury(II) acetate[106], with 2,4,6-tri-*O*-acetyl-3-deoxy-D-galacto-pyranosyl chloride and 2,5,6-tri-*O*-acetyl-3-deoxy-D-galactofuranosyl chloride in the presence of $AgClO_4$,[39] and with 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[43], 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyl chloride[113], 3,5,6-tri-*O*-acetyl-2-deoxy-2-(2',4'-dinitroanilino)-α-D-glucopyranosyl bromide[114], 3,5,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl chloride[115], 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoro-acetamido-α-D-glucopyranosyl bromide[116], 3,5-di-*O*-acetyl-2-deoxy-2-trifluoroacetamido-D-xylo-furanosyl chloride[13], and many other 2-trifluoroacetamido-halogenoses[113,115-117] at 120—140°C at water pump vacuum.

The interaction of 2,4-bis(trimethylsilyl)thymine with 2-deoxy-*C*-methyl-2-(R)-3,5-di-*O*-*p*-toluoyl-*erythro*-D-pentofuranosyl chloride in acetonitrile at room temperature for 24 h leads to a mixture of anomers from which 1-[2-deoxy-*C*-methyl-2(R)-3,5-di-*O*-*p*-toluoyl-*erythro*-D-pentofuranosyl]thymine was isolated in 42% yield[118].

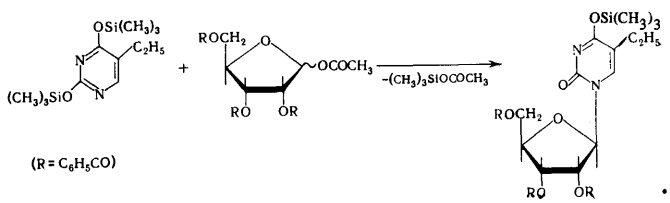
By using tin and antimony halides as catalysts, it is also possible to obtain thymine nucleosides from acylated sugars. Thus the reaction of 2,4-bis(trimethylsilyl)-thymine with 1,2,3-tri-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranose in 1,2-dichloroethane solution in the presence of $SnCl_4$ at 20°C for 4.5 h gave a 70% yield of 1-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-thymine[119]. In the analogous reaction with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in the presence of $SbCl_5$ in 1,2-dimethoxyethane solution the yield of the β-nucleoside was 35%.[107]

The same behaviour was observed in the reaction of 4-ethyl-2-trimethylsilylthymine[24,41,42] with halogenoses as for 2,4-bis(trimethylsilyl)thymine. For example, in the presence of $HgBr_2$—HgO the yield of 1-(2,3,4-triacetyl-α-L-arabinopyranosyl)-4-ethylthymine was higher than in

the presence of $AgClO_4$ (80 and 55% respectively)[41] and the ratio of the α- and β-anomers in the reaction with 2-deoxy-3,5-di-*O*-*p*-nitrobenzoyl-D-ribofuranosyl chloride was 64:36,[42] while in the reaction with the *p*-toluoyl derivative the β-anomer predominates (39:61).[41]

3. Nucleosides of Other 5-Substituted Uracils

The use of $SnCl_4$, $ZnCl_2$, $TiCl_4$, $AlCl_3$, or $BF_3.(C_2H_5)_2O$ as catalysts in the silyl synthesis of nucleosides in solution in 1,2-dichloroethane, acetonitrile, carbon disulphide, or DMF made it possible to employ instead of 1-halogeno-sugars the more stable and more readily available 1-alkoxy- or 1-acyloxy-derivatives[75,120]. For example, the reaction of 5-ethyl-2,4-bis(trimethylsilyl)-uracil with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in 1,2-dichloroethane at 22°C in the presence of $SnCl_4$ (0.72 mole per mole of sugar) for 4 h gave a 68% yield of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-ethyluracil[75]:



Under the same conditions 5-nitro-2,4-bis(trimethylsilyl)uracil was converted after 2 h into the β-nucleoside in 62% yield[75].

However, the synthesis of 2′,3′,5′-tri-*O*-benzoyl-5-butyluridine in the presence of the $HgCl_2$—HgO mixture gave much better results than when $SnCl_4$ was employed[56].

5-Allyl-1-(3,5-di-*O*-*p*-chlorobenzoyl-2-deoxy-β-D-ribofuranosyl)uracil was obtained in a low yield (23%) by the fusion method at 125—130°C *in vacuo* (25 mmHg).[44] The fusion method (at 185—195°C for 0.5 h) gave more satisfactory results (yield 70—88%) for 5-alkoxymethyluracils[45]. A mixture of anomers containing about 80% of the β-anomers was obtained.

When 5-benzyloxymethyl-2,4-bis(trimethylsilyl)-uracil was fused together with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride, 5-benzyloxymethyl-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl)uracil was obtained in 60.5% yield with an α- and β-anomer ratio of 1:4.[45] At room temperature in benzene solution the same reactants gave 66% of the nucleoside with an anomer ratio of 38:62. When the reaction was carried out in acetonitrile, the content of the α-anomer rose (66:34 for an overall yield of 71%)[52] and in the presence of $AgClO_4$ or $HgBr_2$ in benzene the main reaction product was the β-anomer[25,121]. In contrast, the reaction of 5-methoxy-2,4-bis(trimethylsilyl)uracil with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile solution for 45 h have a high yield (75%) of the β-nucleoside[51]. In the case of the analogous derivatives of 5-hydroxymethyluracil[52,62,121] the highest yield of the β-anomer (80—85%) was also observed when the reaction was performed in acetonitrile (30 h at 20°C)[62], while in benzene in the presence of $HgCl_2$ the yield of the α-anomer increased to 34% (for an overall yield of the anomers of 87%)[62]. The yield of the 5-formyluracil derivative was much lower (31%).[52,55]

A study of the reaction of 5-alkylthio-2,4-bis(trimethylsilyl)uracil and of 5-acetylthio-2,4-bis(trimethylsilyl)uracil with 3,5-di-*O*-*p*-chlorobenzoyl-2-deoxy-α-D-ribofuranosyl chloride showed that, under the conditions promoting the rapid removal of the chlorotrimethylsilane formed, the main reaction product is the β-nucleoside, while the addition of more chloromethylsilane to the reaction mixture results in the preferential formation of the α-anomer[37,46,122] (Table 2). In agreement with this finding, when the reaction of 5-acetylthio-2,4-bis(trimethylsilyl)uracil with 2,3,5-tri-*O*-*p*-chlorobenzoyl-α-D-ribofuranosyl chloride was carried out at 110°C *in vacuo*, the β-anomer was also formed[122].

Table 2. Dependence of the yield of the anomers of 1-(3,5-di-*O*-*p*-chlorobenzoyl-2-deoxy-D-ribofuranosyl)-5-methylthiouracil (I) and 5-acetylthio-1-(3,5-di-*O*-*p*-chlorobenzoyl-2-deoxy-D-ribofuranosyl)uracil (II) on the reaction conditions[37,46,122].

Solvent	Reaction temp., °C	Reaction time, h	Yield of (I), %	Anomer ratio $\alpha:\beta$	Yield of (II), %	anomer ratio $\alpha:\beta$
Benzene	80	1.5	51	18:82	45	More of α
Ditto	25	150	49	20:80	—	—
»	37	110	—	—	11	more of α
»	Azeotropic distillation with addition of benzene	—	36	β only	43	20:80
»	Azeotropic distillation with addition of benzene and $(CH_3)_3SiCl$	—	47	77:23	—	—
—	100–115 [without distillation of $(CH_3)_3SiCl$]	0.25	—	—	39	α only
—	100–110 (10–20 mmHg)	0.25	58	β only	50	β only

Depending on the structure of the pyrimidine derivative employed, the synthesis of 5-trifluoromethyl-1-(2-deoxy-3,5-di-*O*-*p*-nitrobenzoyl-D-ribofuranosyl)uracil from 5-trifluoromethyl-2,4-dimethoxypyrimidine and 5-trifluoromethyl-2,4-bis(trimethylsilyl)uracil can be driven towards the preferential formation of a particular anomer. In the reaction involving 5-trifluoromethyl-2,4-dimethoxypyrimidine the main reaction product was the α-anomer (83%), while the β-anomer predominated (67%) in the mixture of products in the reaction of the 2,4-bis(trimethylsilyl) derivative in the presence of mercury(II) acetate[49].

The β-anomer is also formed in 55% yield in the reaction of 5-trifluoromethyl-2,4-bis(trimethylsilyl)uracil with 3-deoxy-2,5-di-*O*-*p*-nitrobenzoyl-β-D-*erythro*-pentofuranosyl bromide in acetonitrile solution at room temperature[50].

The condensation of 5-halogeno-2,4-bis(trimethylsilyl)-uracils with various halogenoses (acetylbromoglucose, acetylbromogalactose, L-acetyl-bromoarabinose, 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride, and 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride) takes place at room temperature in benzene solution in the presence of $AgClO_4$ and the yields of products are high[25].

When 5-fluoro-2,4-bis(trimethylsilyl)uracil was heated with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride in boiling toluene, a mixture consisting of 25% of the α-anomer and 75% of the β-anomer was obtained[53].

β-Anomers are formed preferentially also in the reaction of 5-fluoro-2,4-bis(trimethylsilyl)uracil with 3-deoxy-2,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl

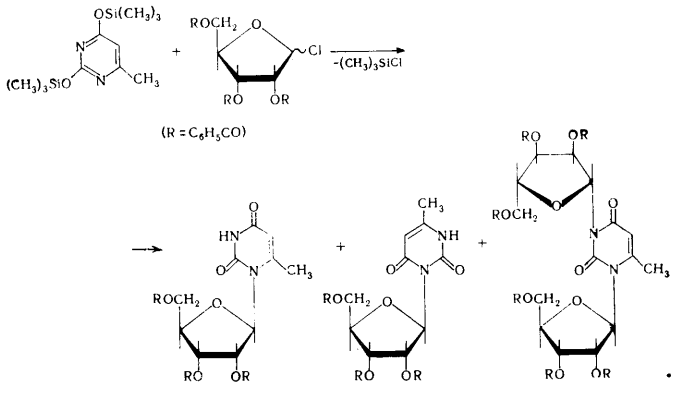
bromide[50] in acetonitrile at 20°C and with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide at 150°C at a reduced pressure[54].

The reaction of 5-fluoro-2,4-bis(trimethylsilyl)uracil with 2-chlorotetrahydrofuran yielded 5-fluoro-1-(2-tetrahydrofuryl)uracil[101,103] (fluorafur), which proved to be effective in the treatment of cancer of the gastrointestinal canal[123].

The reaction of trimethylsilyl derivatives of 5-bromo- and 5-iodo-uracils with 2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyl chloride in the presence of $HgBr_2$—HgO in benzene solution resulted in the formation of β-nucleosides in 36 and 43% yields respectively[96].

Nucleosides of 6-Substituted Uracils

Glycosylation of 6-methyluracil usually results in the formation of N_3-glycosides and $N_{1,3}$-diglycosides or a mixture of isomers[124]. This was also observed when an attempt was made to synthesise 6-methyluridine by the silyl method. The reaction of 6-methyl-2,4-bis(trimethylsilyl)uracil with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in acetonitrile solution at room temperature gave a low yield of the N_3-isomer[58]. An increase of the temperature of the reaction mixture to boiling and the addition of mercury(II) acetate resulted in a mixture of the N_1-, N_3-, and $N_{1,3}$-diribosyl derivatives in proportions of 4 : 11 : 33.[125] When the reaction was carried out in benzene in the presence of $HgBr_2$—HgO, a mixture of the same products was formed in proportions of 2 : 5 : 4.[57] The N_3-isomer also predominated (4 : 5 : 1) in the products of the reaction with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide:



In contrast, the reaction of 5,6-dimethyl-2,4-bis(trimethylsilyl)uracil with the same halogenoses in the presence of $HgBr_2$—HgO resulted in the formation of a high yield (about 90%) of the β-N_1-nucleosides (the yield of the $N_{1,3}$-derivatives was not more than 2—4%).[57]

In all other reactions of trimethylsilyl derivatives of 6-methylthiouracil[59,60], 6-aminouracil[59], 6-hydroxyuracil[59], and 6-chlorouracil[47] with various acylated halogenoses, N_3-derivatives were formed.

5. Nucleosides of Cytosine and Its 5- or 6-Substituted Derivatives

The reactions of 4-acetyl-2,4-bis(trimethylsilyl)-cytosine with 2,3,4-tri-*O*-acetyl-L-arabinopyranosyl chloride, 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosil chloride, 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide, 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride, and 2-deoxy-3,5-di-*O*-*p*-toluoylribofuranosyl chloride in the presence of $AgClO_4$ give rise smoothly to the corresponding nucleosides[24]. The maximum yield (70%) was observed for the galactose derivative[24]. The yield of 4-acetyl-1-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-cytosine in this reaction was only 38%,[24] which is nevertheless higher than in its synthesis by the fusion of the initial reactants at 180—195°C (15%).[23,95] When the reactants are fused at 100—120°C *in vacuo* (80—90 mmHg) with simultaneous distillation of the halogenotrimethylsilane formed, the yield of the nucleoside is sometimes greatly increased. For example, the condensation of 4-acetyl-2,4-bis(trimethylsilyl)cytosine with 2-*O*-acetyl-5-*O*-ethoxycarbonyl-3-*O*-tosyl-D-xylofuranosyl chloride at 120°C (80—90 mmHg) for 3 h gave 4-acetyl-1-(2-*O*-acetyl-5-ethoxycarbonyl-3-*O*-tosyl-β-D-xylofuranosyl)cytosine in 80% yield[81]. The yield increases to 92% when the reaction is carried out in benzene solution at room temperature in the presence of $HgBr_2$ for 12 h.[81]

Condensation at reduced pressure was also used to synthesise 1-(3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-galactopyranosyl)cytosine[113] and 1-(3,5,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucofuranosyl)cytosine[115].

The reaction of 2,4-bis(trimethylsilyl)cytosine with 2,5-*O*-benzoyl-3-deoxy-3-fluoro-D-xylofuranosyl bromide in acetonitrile at room temperature resulted in the formation in 4 days of the corresponding 1-β-nucleoside in 65% yield[126].

When $SnCl_4$ is employed as the catalyst, the 1-acetyl derivative of the sugar can be used also in the synthesis of nucleosides from cytosine and its derivatives[82,127].

On heating 4-acetyl-5-fluoro-2,4-bis(trimethylsilyl)-cytosine with 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide in toluene solution, a mixture is formed with a 40 : 60 ratio of the α- and β-anomers[53].

β-N_1-ribosyl derivatives are formed in the reaction of 6-methyl-2,4-bis(trimethylsilyl)cytosine and 4-acetyl-6-methyl-2,4-bis(trimethylsilyl)cytosine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in acetonitrile solution[125]. When ribosyl bromide is employed, their yield reaches 40% after 3 days[58]. The reaction with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride also yields the N_1-nucleoside in the form of an anomer mixture with the β-anomer predominating[58]. However, the reaction of 2,3,5-tri-*O*-benzoylribofuranosyl chloride with 5,6-dimethyl-2,4-bis(trimethylsilyl)cytosine yields the O_2-riboside as the main product. The ratio of the O_2- and N_1-derivatives is 76 : 24.[125] Similarly the reaction of the trimethylsilyl derivative of 6-amino-2-thiouracil with 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl bromide results in the formation of the β-S_2-derivative in 40% yield[59].

6. Derivatives of Various Hydroxy-, Thio-, Seleno-, and Amino-pyrimidines

When 2,4-bis(trimethylsilyl)-2-thiouracil[65], 5-benzyloxy-2,4-bis(trimethylsilyl)-2-thiouracil[68], 5-methoxy-2,4-bis(trimethylsilyl)-2-thiouracil[69], and 5-ethoxycarbonyl-2,4-bis(trimethylsilyl)-2-thiouracil[69] react with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in benzene solution at room temperature in the presence of $AgClO_4$, the β-anomers of N_1-ribofuranosides are formed in yields of 71—78%. Under the same conditions, 5-ethyl-2,4-bis(trimethylsilyl)-2-thiouracil reacts with

2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride to give a mixture of anomers with an overall yield of 82% and a 76 : 24 ratio of the α- and β-anomers[65,69].

A high yield (95%) of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-thiocytosine was achieved by the reaction of 2,4-bis(trimethylsilyl)-2-thiocytosine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in 1,2-dichloroethane solution in the presence of $SnCl_4$.[81] 2',3',5'-Tri-*O*-benzoyl-5-cyano-2-thiocytidine[128], 2',3',5'-tri-*O*-benzoyl-2-thiouridine[128], 2',3',5'-tri-*O*-benzoyl-5-butyl-2-thiouridine[56], and 2',3',5'-tri-*O*-benzoyl-2-selenouridine[70] were obtained by this procedure.

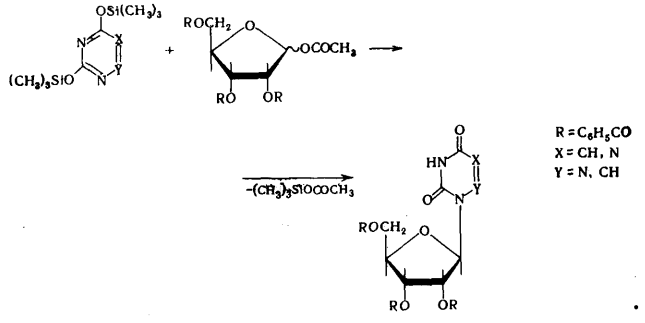
A number of nucleosides were obtained from 4,6-dihydroxy-[129], 4-amino-, and 4-alkylthio-6-hydroxypyrimidines[71]. For example, the reaction of 6-trimethylsiloxy-4-trimethylsilylaminopyrimidine with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride in acetonitrile at 20°C gave a 75% yield of 4-amino-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl)pyrimidin-6-one containing more than 90% of the α-anomer. Under the same conditions, 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide gives rise to the β-anomer in 61% yield[71].

7. 6-Aza-analogues of Pyrimidine Nucleosides

The synthesis of the nucleosides of 6-azauracil and 6-azathymine by the mercury method is complicated by the formation of a mixture of N_1- and N_3-isomers[130], while the Hilbert–Johnson method is inapplicable owing to the unavailability of the initial 3,5-dialkoxy-derivatives[131].

When 2,4-bis(trimethylsilyl)-6-azauracil is fused together with various halogenoses *in vacuo*[72,73] and also when the reaction is carried out in benzene or in toluene at room temperature in the presence of mercury(II) acetate[72,74], the corresponding β-N_1-nucleosides are formed in low yields. The use of $HgBr_2$ instead of $Hg(OCOCH_3)_2$ greatly increases the yield of nucleosides (to 90%).[32]

High yields of β-nucleosides are achieved when 1-*O*-acetyl derivatives[75,120,128,134,135] are employed instead of the halogenoses[132,133]. Thus the reaction of 2,4-bis-(trimethylsilyl)-6-azauracil with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in 1,2-dichloroethane solution at 22°C in the presence of $SnCl_4$ for 4 h resulted in the formation of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-azauracil in 92% yield[75]. When $SnCl_4$ is replaced by $ZnCl_2$ in this reaction and also when the latter is carried out in nitromethane, the yield of the product falls somewhat (83%). Other solvents proved to be less effective (Table 3)[128].



When 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl chloride is employed in this reaction, a mixture of 1-(2,3,5-tri-*O*-benzoyl-$\alpha\beta$-D-arabinofuranosyl)-6-azauracil containing 56% of the β-anomer is formed[75].

2,4-Bis(trimethylsilyl)-6-azathymine reacts in benzene with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-ribofuranosyl chloride even at room temperature. However, the yield of the β-N_1-nucleoside after interaction for 48 h was only 38%.[79] The increase of reaction temperature to 90°C in the absence of solvent has little effect on the yield of product[73]. When the reaction was carried out with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in boiling acetonitrile in the presence of $Hg(OCOCH_3)_2$, the yield of nucleoside rose to 68%,[79] while the use of the 1-*O*-acetyl derivative in the presence of $SnCl_4$ gave 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-azathymine in 77% yield[75].

Table 3. Dependence of the yield of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-azauracil on the nature of the solvent[75,128]*.

Solvent	Reaction temp., °C	Reaction time, h	Yield of nucleoside, %	
			unpurified	recrystallised
1,2-Dichloroethane	20	4	97	92
Acetonitrile	20	4	97	82.5
Tetrahydrofuran	65	3	98	75
Carbon tetrachloride	77	4	93	73
Dimethylformamide	153	4	77.5	68.5
Carbon disulphide	46	4	87	67
Benzene	80	6	80.5	66
Toluene	111	6	86	66
1,4-Dioxane	100	4	77	57

*5 mmoles of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose, 6.25 mmoles of 2,4-bis(trimethylsilyl)6-azauracil, 3.6 mmoles of $SnCl_4$, and 100 ml of the solvent were taken.

The corresponding 1-ribofuranosyl derivatives were obtained in 50% yield from 5-trimethylsiloxy-2,4-bis-(trimethylsilyl)methyl-6-azauracil[121,136,137] and 5-trifluoromethyl-2,4-bis(trimethylsilyl)-6-azauracil[78,138] in the presence of $Hg(OCOCH_3)_2$ in benzene at room temperature. In the second case the same yield of the nucleoside was achieved also by the fusion method[77]. The fusion method was likewise employed to synthesise derivatives of 5-bromo-6-azauracil[77,80].

The reaction of *OS*-bis(trimethylsilyl)-2-thio-6-azauracil with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in benzene solution in the presence of $AgClO_4$ resulted in the formation of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-thio-6-azauracil in 78% yield[65,139]. Similar yields of the β-anomers were achieved when 2,3,5-tri-*O*-acetyl-1-*O*-methyl-D-ribofuranose or 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose were employed as the glycosidic components and the reaction was carried out in the presence of $SnCl_4$.[75]

8. 5-Aza-analogues of Pyrimidine Nucleosides

The application of the silyl method gave rise for the first time to the possibility of synthesising the antibiotic

5-azacytidine by the direct glycosylation of the 1,3,5-triazine ring. For this purpose, 2,4-bis(trimethylsilyl)-5-azacytosine was condensed with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile solution at room temperature for 3 days and 5-azacytidine was obtained in 34% yield after the removal of protecting groups with ammonia[63]. 1-(2-Deoxy-$\alpha\beta$-D-ribofuranosyl)-5-azacytosine, 1-(β-D-ribofuranosyl)cyanuric acid, and 3-methyl-1-(β-D-ribofuranosyl)cyanuric acid were obtained similarly[63]. The addition of $HgBr_2$—HgO to the reaction mixture increases somewhat the yield of nucleosides[88]. When 2,4-bis(trimethylsilyl)-5-azacytosine is fused together with 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride at 195°C, the α-anomer is formed in 8% yield, while on carrying out the reaction at 20°C in methylene chloride for 11 days, the product is the β-anomer in 47% yield[63].

2,4-Bis(trimethylsilyl)-5-azacytosine reacts readily with 1-*O*-acetyl derivatives of sugars in 1,2-dichloroethane solution in the presence of $SnCl_4$. 1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-5-azacytosine and 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-azacytosine (in yields of 52 and 70%)[87,140] as well as 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-azacytosine (yield 55%)[87] were obtained in this way. A number of nucleosides of 2-thio-5-azacytosine were synthesised by similar procedures[87,89].

IV. SYNTHESIS OF NUCLEOSIDES CONTAINING CONDENSED PYRIMIDINE SYSTEMS

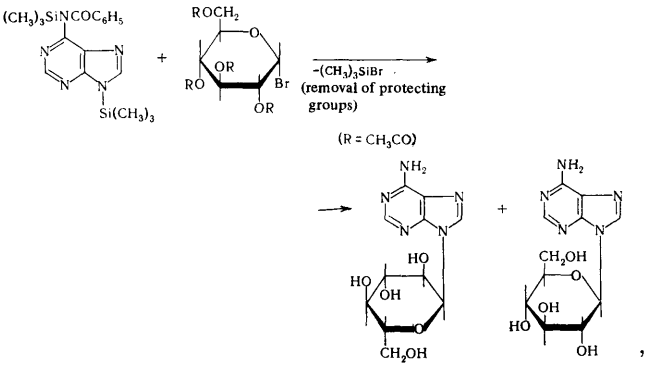
1. Purine Nucleosides

When 6,9-bis(trimethylsilyl)adenine was allowed to react with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile solution at 20°C the product contained 27% of the 3-β-nucleoside and 10% of the 9-β-nucleoside[92]. Under the same conditions, 8-bromo-6,9-bis(trimethylsilyl)adenine gave an 80% yield of the 3-β-nucleoside and a 7% yield of the 9-β-nucleoside. On replacing 1-bromoribose by the corresponding 1-*O*-acetyl derivative and on carrying out the reaction in the presence of $SnCl_4$, the yield of the 9-β-isomer was raised to 20%, which is still lower than the yield of the 3-β-nucleoside (39%).[92]

Condensation of 8-bromo-6,9-bis(trimethylsilyl)-adenine with 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl bromide in acetonitrile at 20°C for 24 h led to the formation of the 3-α-nucleoside in 73% yield, while condensation with 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride gave the 3-β-isomer (37%).[92]

On heating 6,9-bis(trimethylsilyl)-6-benzoyladenine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride at 150—160°C for 3.5 h and subsequent debenzoylation by sodium methoxide, adenosine was obtained[28]. A mixture of nucleosides containing the 9-β- and 7-β-isomers in proportions of 57 : 43 was obtained in benzene at room temperature in the presence of $HgBr_2$.[32,141] Under the same conditions, 3,5-di-*O*-benzoyl-2-*S*-benzyl-2-thio-D-ribofuranosyl chloride gives 22% of the 9-β-nucleoside, 5% of the 9-α-nucleoside, and 9% of a mixture of the 7-α- and 7-β-nucleosides, while 3,5-di-*O*-benzoyl-2-*S*-methyl-2-thio-D-ribofuranosyl chloride yields 34% of the 9-β-nucleoside, 10% of the 9-α-nucleoside, and 12% of a mixture of the 7-α- and 7-β-nucleosides[141].

9-β-D-Glucopyranosyladenine was obtained by the reaction of 6,9-bis(trimethylsilyl)-6-benzoyladenine with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride, while the reaction with α-acetylbromoglucose gave a mixture of 9-α- and 9-β-D-glucopyranosyladenines containing equal amounts of the anomers[23,90,91]:



6,9-Bis(trimethylsilyl)hypoxanthine reacts similarly[23,28,90,91].

In the synthesis of 2-acetamido-6-chloro-9-(2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl)-9*H*-purine the yield of the nucleoside increases somewhat following the addition of an excess of chlorotrimethylsilane, while an excess of the halogenose reduces it and an excess of the base has no effect whatever. The use of an excess of chlorotrimethylsilane together with mercury(II) cyanide promotes the decomposition of the sugar, best (almost quantitative) yields of the nucleoside being achieved in the presence of $Hg(CN)_2$ without the introduction of additional chlorotrimethylsilane. A mixture of the α- and β-anomers with the α-anomer predominating is then formed. The addition of chlorotrimethylsilane has little influence on the anomer ratio[142].

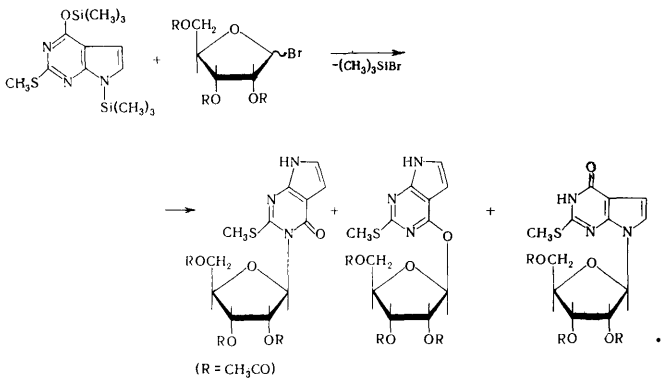
The first nucleoside obtained from xanthine by direct glycosylation was 3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)xanthine formed by the reaction of 2,6,9-tris(triethylsilyl)xanthine with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide in nitromethane in the presence of $AgClO_4$.[86,94] When the reaction is carried out with 2,6,9-tris(trimethylsilyl)xanthine in acetonitrile, the 3,7-β-diglucoside is obtained[143]. The 3,7-disubstituted product is formed also in the reaction with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride in acetonitrile at 35° or 65°C. Under milder conditions (polar solvent, room temperature), the products of this reaction are 7-(2-deoxyribosyl)- and 7,9-di-(2-deoxyribosyl)-xanthines[143]. The reaction of 2,6,9-tris(trimethylsilyl)-xanthine with 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2′,4′-dinitroanilino)glucopyranosyl bromide yields a mixture of products, among which the 1- and 7-glucosides were identified[143]. The condensation of 2,6,7,9-tetrakis(triethylsilyl)uric acid with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide, 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide, and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in toluene in the presence of $AgClO_4$ resulted in the formation of the 3-β-nucleosides in yields of 70, 56, and 90% respectively[2,86,94].

After the successful application of the silyl method in the synthesis of purine nucleosides, the range of condensed heterocycles employed in this reaction was greatly extended by the inclusion of systems in which the pyrimidine ring is linked not only to the imidazole ring but also to the pyrrole, pyrazole, triazole, benzene, pyridine, or pyrazine ring.

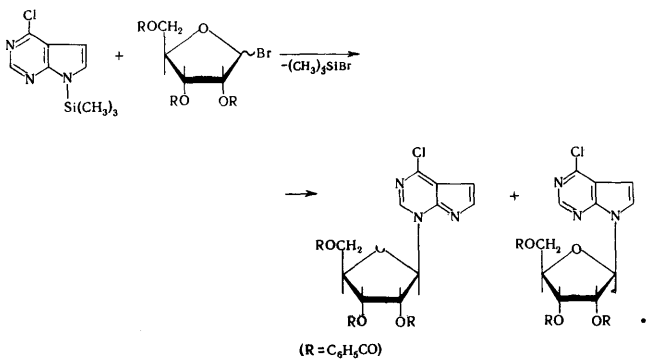
2. Derivatives of Pyrrolo[2,3-*d*]- and Pyrazolo[3,4-*d*]-pyrimidines

When 4-chloro-7-trimethylsilylpyrrolo[2,3-*d*]pyrimidine was allowed to act with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in boiling benzene in the presence of HgO for 18 h, a mixture of the 1-β- and 7-β-nucleosides was obtained, the yields of the isomers being 11 and 18% respectively[144]. Under the same conditions, the main products of the reaction with 4-chloro-5-cyano-6-methyl-7-trimethylsilylpyrrolo[2,3-*d*]pyrimidine are the 1-β- and 3-β-ribosides (yields 46 and 31%), while the 7-β-isomer is formed in a smaller amount (17%). The reaction of 4-chloro-2-methylthio-7-trimethylsilylpyrrolo[2,3-*d*]pyrimidine and 5-bromo-4-chloro-2-methylthio-7-trimethylsilylpyrrolo[2,3-*d*]pyrimidine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile at 25°C in the presence of Ag_2O for 3 days gives exclusively the 7-isomers in yields of 82 and 48% respectively[144].

A mixture of the 3-, and 4-, and 7-ribosides is formed in overall yields of 79 and 94% on ribosylation of 2-methylthio-4,7-bis(trimethylsilyl)pyrrolo[2,3-*d*]pyrimidin-4-one with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in boiling benzene in the presence of $HgBr_2$—HgO for 18 h or in acetonitrile at room temperature for 48 h:



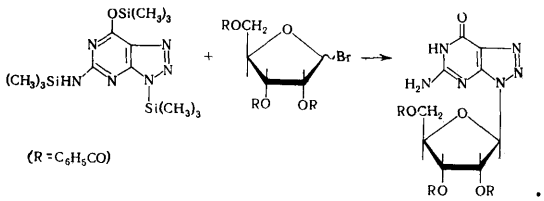
The 7-isomer predominates in the first case (64%) and the 4-isomer in the second (76%):[144]



The analogous reaction of 4-chloro-*N*-trimethylsilylpyrazolo[3,4-*d*]pyrimidine at 105—110°C *in vacuo* gave the 7-β-nucleoside in 30% yield[145].

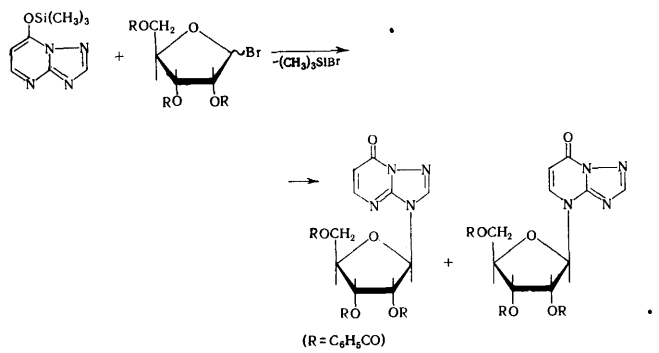
3. Derivatives of Triazolopyrimidines

When 3-tri-methylsilyl-5-7-trimethylsiloxy-trimethylsilylamino-v-triazolo[4,5-*d*]pyrimidine reacted with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile solution at 20°C for 6 days, 5-amino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-v-triazolo[4,5-*d*]pyrimidin-7-one was formed in 43.5% yield[146].



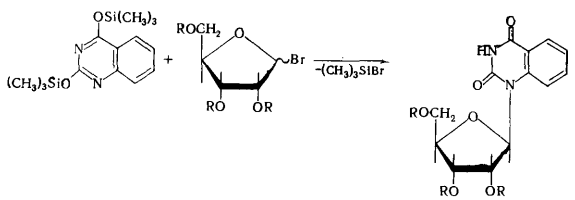
In contrast to this, the trimethylsilyl derivatives of thiazolo]5,4-*d*]pyrimidine-5,7-dione yielded a mixture of the 4-α- and 4-β-nucleosides[147]. A mixture of the 2- and 3-nucleosides (α- and β-anomers) was formed in the reaction of 7-methylthio-3-trimethylsilyl-v-triazolo-[4,5-*d*]pyrimidine with 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride at 120°C *in vacuo*[148].

When 7-trimethylsiloxy-*sym*-triazolo[2,3-*a*]pyrimidine reacts with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile at room temperature, a mixture of 3- and 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*sym*-triazolo-[2,3-*a*]pyrimidin-7-ones is obtained in which the amount of the 3-isomer exceeds by a factor of 1.7 that of the 4-isomer[149]:



4. Quinazoline Nucleosides

The reaction of 2,4-bis(trimethylsiloxy)quinazoline with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile at room temperature for 2 days resulted in the formation of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)quinazoline-2,4-dione in 80% yield[144]. A similar result was obtained when the reaction was carried out in boiling benzene in the presence of $HgBr_2$—HgO.[57]

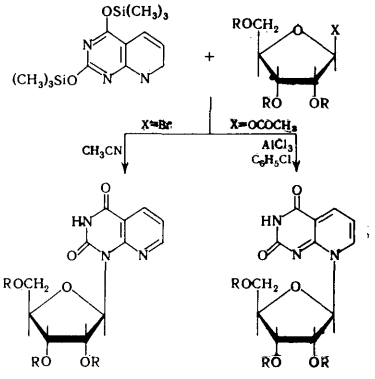


When 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranosyl chloride was employed in this reaction, the product was a mixture of anomers in 60% yield, from which it was possible to isolate 25.4% of the β-anomer and about 1% of the α-anomer[150].

β-Anomers were obtained on ribosylation of 2- and 4-trimethylsiloxyquinazolines in acetonitrile in the presence of $SnCl_4$.[151]

5. Pyrido[2,3-*d*]pyrimidine Nucleosides

The reaction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide with 4-trimethylsiloxy- and 2,4-bis(trimethylsiloxy)-pyrido[2,3-*d*]pyrimidine in acetonitrile results in the formation of the corresponding 1-β-nucleosides[152]. On the other hand, if the second compound is introduced into the reaction with tetra-*O*-acetyl-β-D-ribofuranose in chlorobenzene in the presence of $AlCl_3$ at 20°C, the product is 8-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-pyrido[2,3-*d*]pyrimidine-2,4-dione[152]:

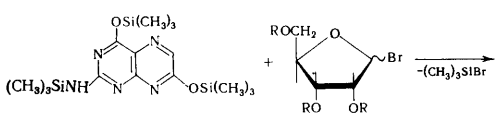


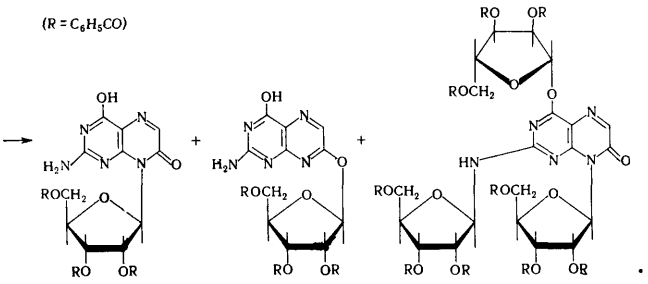
When tetra-*O*-acetyl-β-D-ribofuranose is heated with the bis(trimethylsilyl) derivative of 6-ethoxycarbonyl-2-methylthiopyrido[2,3-*d*]pyrimidine-4,5-dione at 155–160°C *in vacuo*, the 8-β-nucleoside is also formed[153].

6. Pteridine Nucleosides

The study of the reaction of trimethylsilyl derivatives of hydroxy- and amino-pteridines with halogenoses and fully acylated sugars established that, when the hydroxy-group is in the 7-position of pteridine (i.e. in the pyrazine ring), β-N_8-nucleosides are formed in most cases in the reaction with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in boiling benzene in the presence of $HgBr_2$—HgO,[154] and also with 1-*O*-acetyl-2,3,5-tribenzoyl-β-D-ribofuranose in the presence of $SnCl_4$ [155] or $ZnCl_2$.[156]

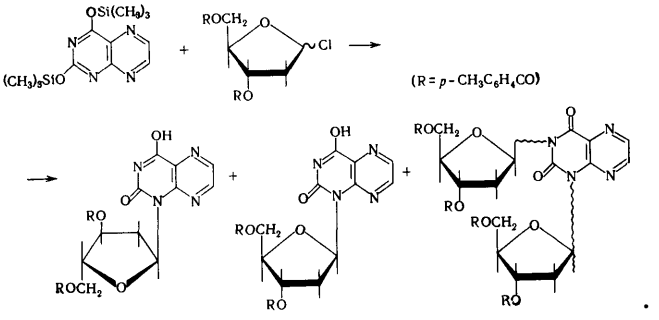
However, the 6-methyl-2-dimethylamino- [154,155] and 4-alkoxy-2-amino-derivatives[155] give rise to the formation of a mixture of the β-N_8- and β-O_7-isomers. The reaction with the 2-amino-7-hydroxy-derivative gives rise to the β-N_8-riboside (21%) and the 2,8-diriboside (4.5%).[156] But 2-amino-4,7-dihydroxypteridine yields, apart from the β-N_8- and β-O_7-isomers, also the 2,4,8-tririboside (4%):[155]





On the other hand, when the hydroxy-group is in the 2-position of pteridine (i.e. in the pyrimidine ring), then the reaction with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in the presence of $HgBr_2$—HgO yields the β-N_1-nucleoside[157] with a small admixture of the 1,3-diriboside in the case of the 2,4-dihydroxy-derivatives.

The reaction of 2,4-bis(trimethylsiloxy)pteridine and 2-trimethylsiloxy-4-trimethylsilylaminopteridine with 2-deoxy-3,5-di-*O*-*p*-toluoylfuranosyl chloride in the presence of $HgBr_2$—HgO gives rise to the formation of a mixture of 1-α-, 1-β-, and 1,3-dideoxyribosides in which the 1-β-anomer predominates[157]:

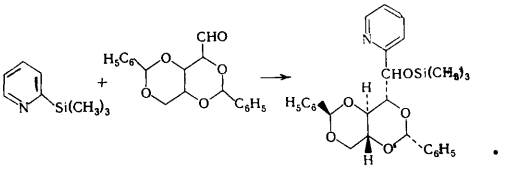


V. SYNTHESIS OF NUCLEOSIDES CONTAINING OTHER HETEROCYCLIC BASES

1. Pyridine Derivatives

The reaction of 2-trimethylsiloxypyridine with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide in nitromethane at 20°C in the presence of $AgClO_4$ gave 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-pyridone in 70% yield[86,94]. 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-hydroxy-2-pyridone was obtained in 68% yield from 2,4-bis-(trimethylsiloxy)pyridine and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile[158-160], while heating of the same silyl derivative with 2-deoxy-3,5-di-*O*-*p*-toluoylribofuranosyl chloride *in vacuo* at 110°C gave 4-hydroxy-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-αβ-D-ribofuranosyl)-2-pyridone[159,160]. The N_1-nucleosides of 4-hydroxy-5-methoxycarbonyl-2-pyridone were obtained in acetonitrile at room temperature[159,161].

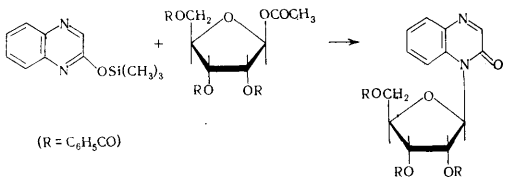
The enhanced reactivity of the Si—C bond in trimethyl-(2-pyridyl)silane permits its employment for the synthesis of *C*-nucleosides (for example, by the reaction with 2,4:3,5-di-*O*-benzylidene-D-ribose)[162]:



2. Pyridazine, Pyrazine, and Quinoxaline Nucleosides

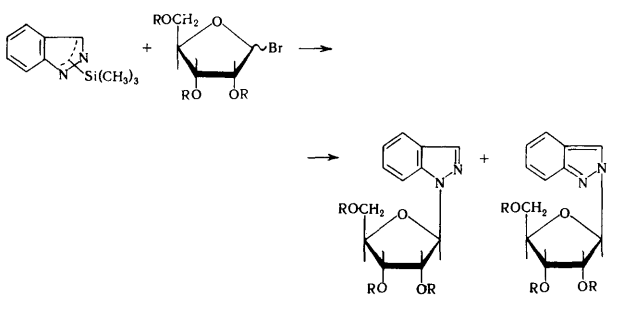
The reaction of 3,6-bis(trimethylsiloxy)pyridazine with 2-chlorotetrahydrofuran at temperatures between −20° and 10°C for 6 h or with 2-chlorotetrahydropyran at 15–50°C for 7 h in benzene solution resulted in the formation of analogues of pyridazine nucleosides—1-(2-tetrahydrofuryl(-3-hydroxypyridazin-6-one (yield 50%) and 3-hydroxy-1-(2-tetrahydropyranyl)pyradazin-6-one (yield 44.5%)—which inhibit DNA polymerase[163].

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydropyrazin-2-one was obtained by the reaction of 2-trimethylsiloxypyrazine with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in boiling 1,2-dichloroethane in the presence of $TiCl_4$.[164] 2-(Trimethylsiloxy)quinoxaline reacts similarly[165]. The yield of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)quinoxaline when the reaction was carried out in the presence of $SnCl_4$ did not exceed 10%, as in the presence of $HgBr_2$–HgO:[165]



3. Indazole Nucleosides

The 1- and 2-(β-D-ribofuranosyl)indazoles were obtained in proportions of 1:5 by heating *N*-trimethylsilylindazole with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide at 75–80°C *in vacuo* (1.5 mmHg) in the presence of sodium iodide[166]:



The 2-β-D-ribofuranosyl derivatives of 4-, 5-, and 6-nitroindazoles[166] and 3-cyanoindazole[167] were synthesised similarly. In the last case the yield of the nucleoside was 23%. The yield in boiling benzene in the presence of $HgBr_2$–HgO reached 85%.[167]

4. Pyrazole, Imidazole, Benzimidazole, and Imidazo-[4,5-*c*]pyridine Nucleosides

When 1-trimethylsilylbenzimidazole is fused *in vacuo* with various *O*-acylhalogenoses, a mixture of the α- and β-anomers of the corresponding N_1-nucleosides is formed[168-173]. The ratio of the anomers in the mixture obtained from 1-trimethylsilylbenzimidazole and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide is 43:57,[168] while in the case of the glucopyranosyl derivative the ratio is 56.5:43.5.[168]

Condensation of 2-chloro-1-trimethylsilylbenzimidazole with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide at 110°C in the presence of NaI resulted in the formation of 2-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-benzimidazole in 69% yield[174]. 2-Chloro-5,6-dimethyl-1-trimethylsilylbenzimidazole[175], 1-trimethylsilyl-2-trimethylsilylthiobenzimidazole[174], and 4,6-dichloro-1-trimethylsilylimidazo[4,5-*c*]pyridine[176] react similarly. The ratio of the α- and β-anomers in the synthesis of 1-(2,3,5-tri-*O*-acetyl-αβ-D-ribofuranosyl)-5-carbamoyl-4-(3,3-dimethyl-1-triazino)imidazole is 65:35.[177] Only the 1-β-riboside was isolated after the reaction of the analogous pyrazole derivative[178].

1-Methyl-2-trimethylsilylimidazole reacts with 1,6-diformyl-1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,5-pyranoside like trimethyl-(2-pyridyl)silane with formation of the corresponding *C*-nucleoside[162,179].

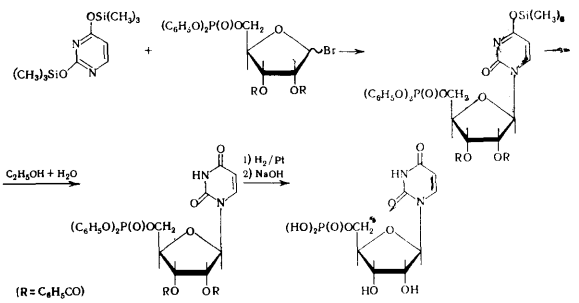
5. Triazole and Benzotriazole Nucleosides

The silyl method has been used successfully also in the synthesis of 1-(β-D-ribofuranosyl)urazole[180] and its 2- and 4-methylderivatives[180], 1-(β-D-2-deoxyribofuranosyl)-urazole[180], the methyl esters of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-3- and 5-carboxylic acids[181,182], and N_1-nucleosides of benzotriazole[170,171,183,184].

VI. SYNTHESIS OF NUCLEOTIDES

The commonest method of synthesising nucleotides involves the phosphorylation of the protected nucleoside. The possibility of the direct condensation of phosphorylated sugars with derivatives of pyrimidine or purine bases has been much less thoroughly investigated[185,186]. The silyl method proved to be very convenient for this purpose.

When 2,4-bis(trimethylsilyl)uracil was heated with 2,3-di-*O*-benzoyl-5-diphenylphosphoryl-D-ribofuranosyl bromide at 100–110°C for 30 min, 1-(2,3-di-*O*-benzoyl-5-diphenylphosphoryl-α-D-ribofuranosyl)uracil was formed in 38% yield together with its β-anomer in 11% yield[11,13,15]; after treatment with aqueous ethanol and catalytic dephenylation followed by deacylation, the latter was converted into uridine 5′-phosphate[11]:



Under analogous conditions, 2,3-di-*O*-benzoyl-5-diphenylphosphoryl-L-ribofuranosyl bromide gives the α- and β-anomers in yields of 34.5 and 18% respectively[16]. The yields of 1-[2,3,4-tri-*O*-acetyl-6-bis-(*p*-nitrophenyl)-phosphoryl-β-D-glucopyranosyl]uracil[11], 1-[2,3-di-*O*-benzoyl-5-diphenylphosphoryl-β-D-ribofuranosyl]-4-ethyluracil[11], and the α- and β-anomers of L-ribofuranosylthymine 5′-phosphate[16] are 18.5%, 35%, 34.3, and 17% respectively.

The α-anomer was obtained in 26% yield on heating 2,4-bis(trimethylsilyl)thymine with 2,3-di-*O*-benzoyl-5-diphenylphosphoryl-D-ribofuranosyl bromide at 100–110°C.[13] When the same reaction was carried out *in vacuo* (80–100 mmHg), the β-anomer was formed in 48% yield[15]. In the presence of $HgBr_2$ the reaction can be carried out in benzene at room temperature. The yield of the β-anomer then reaches 92% after 3 h.[32] In the presence of $HgBr_2$, 4-acetyl-1-(2,3-di-*O*-benzoyl-5-diphenylphosphoryl-β-D-ribofuranosyl)cytosine was also obtained in a high yield[32], while fusion of the reactants leads to a mixture of the α- and β-anomers in proportions of 68 : 32.[16,187]

6-Benzoyl-9-(2,3-di-*O*-benzoyl-5-diphenylphosphoryl-D-ribofuranosyl)adenine was obtained in 37.6% yield[14,15,187,188] and with a 43 : 57 ratio of the α- and β-anomers[188] by fusing 6-benzoyl-6,9-bis(trimethylsilyl)-adenine with 2,3-di-*O*-benzoyl-5-diphenylphosphoryl-D-ribofuranosyl bromide. When the reaction is carried out in benzene at room temperature in the presence of $HgCl_2$, the yield of the β-nucleotide is increased to 67% but a mixture of the 9- and 7-isomers is then formed in proportions of 58 : 42.[32]

Condensation of 6,9-bis(trimethylsilyl)hypoxanthine and trimethylsilyltheophylline with 2,3-di-*O*-benzoyl-5-diphenylphosphoryl-D-ribofuranosyl bromide at 100–110°C leads to the formation of 9-(2,3-di-*O*-benzoyl-5-diphenylphosphoryl-β-D-ribofuranosyl)hypoxanthine in 59.2% yield and of the 7-β-nucleotide of theophylline in 73% yield[11,15].

ADDENDUM

A series of studies on the synthesis of nucleosides and their analogues using trimethylsilyl derivatives of heterocyclic bases were published recently (from May to October, 1973), which is evidence of a growing popularity of the trimethylsilyl method of synthesis. For example, 2,3,5-tri-*O*-benzoyl-5-isopropyl- and 2,3,5-tri-*O*-benzoyl-5-t-butyl-uridines (*anti*-conformations)[189] as well as 1,2-dihydro-1-(3,5-di-*O*-*p*-chlorobenzoyl-2-deoxy-$\alpha\beta$-D-*erythro*-pentofuranosyl-2-oxopyrazine 4-oxide[190], which is an analogue of deoxyuridine, were resynthesised by this method. Condensation of 2,4-bis(trimethylsilyl)-uracil[191] and 5-trimethylsiloxy-2,4-bis(trimethylsilyl)-uracil[192] with 2-chlorotetrahydrofuran and with 2-chlorotetrahydropyran led to the formation of the corresponding N_1-tetrahydrofuryl and N_1-tetrahydropyranyl derivatives.

5-Hydroxy-1-(β-D-ribofuranosyl)pyrimidin-2-one[193] and 3-methoxycarbonyl-, 3-cyano-, and a number of other 3-substituted 1-(β-D-ribofuranosyl)-1,2,4-triazoles[194] were also successfully synthesised via the silyl derivatives of the bases. Studies have been made on the condensation of trimethylsilyl derivatives of thymine with acyclic sugars[195] and of a number of trimethylsilyl derivatives of uracil, 6-azauracil, and their 2-thio-derivatives with oligosaccharides[196].

Nucleoside analogues containing various condensed systems as the aglycones were obtained by the silyl method: 3-($\alpha\beta$-D-galactopyranosyl)-2-methyl-7-nitroimidazo[4,5-*c*]pyridine[197], 6-bromo-1-(β-D-glucopyranosyl)-2-methyl-1*H*-imidazo[4,5-*b*]pyridine[198], 6-bromo-1-(β-D-galactopyranosyl)-1*H*-imidazo[4,5-*b*]-pyridine[198], 5,6-dimethyl-1-(β-D-ribofuranosyl)imidazo-[4,5,*b*]-pyrazine[199], 2-β-D-(2,3,5-tri-*O*-benzoylribofuranosyl)- and 2-β-D-(2,3,4,6-tetra-*O*-acetylglucopyranosyl)-5,6-dihydro-4-hydroxymercapto-7*H*-pyrrolo[2,3-*d*]-pyrimidines[200], and 2-ethyl-6-(β-D-ribofuranosyl)oxazolo-[5,4-*d*]pyrimidin-7-one[201].

The synthesis of pteridine nucleosides from the trimethylsilyl derivatives of various hydroxy- and amino-pteridines was investigated in greater detail[202–204].

The employment of the trimethylsilyl method for the synthesis of pyrimidine nucleosides was also briefly considered in a recently published review devoted to the methods of synthesising pyrimidine nucleosides[205].

REFERENCES

1. T. Nishimura, B. Shimizu, and I. Iwai, Chem. Pharm. Bull. (Tokyo), 11, 1470 (1963).
2. L. Birkofer, A. Ritter, and H. P. Kühlthau, Angew. Chem., 75, 209 (1963).
3. G. E. Hilbert and T. B. Johnson, J. Amer. Chem. Soc., 52, 4489 (1930).
4. E. Lukevics, Candidate's Thesis, Institute of Organic Synthesis, Academy of Sciences of Latvian SSR, Riga, 1965.
5. B. Shimizu, Ann. Sankyo Res. Lab., 19, 1 (1967). Chem. Abs., 68, 96 054y (1968).
6. W. W. Zorbach, Synthesis, 329 (1970).
7. C. A. Dekker and L. Goodman, in "The Carbohydrates", New York–London, 1970, Vol. 2A, p. 1.
8. A. E. Pierce, "Silylation of Organic Compounds", Pierce Chem. Comp., Rockford, 1968.
9. L. B. Townsend and G. R. Revankar, Chem. Rev., 70, 389 (1970).
10. T. Nishimura and I. Iwai, Chem. Pharm. Bull. (Tokyo), 12, 352 (1964).
11. B. Shimizu, M. Asai, and T. Nishimura, Pharm. Bull. (Tokyo), 13, 230 (1965).
12. T. Nishimura and B. Shimizu, Pharm. Bull. (Tokyo), 13, 803 (1965).
13. T. Nishimura, B. Shimizu, and M. Futai, Biochim. Biophys. Acta, 129, 654 (1966).
14. Sankyo Co. Ltd., Dutch Appl. 6510 323 (1966); Chem. Abs., 65, 10 652f (1966).
15. B. Shimizu, M. Asai, and T. Nishimura, Chem. Pharm. Bull. (Tokyo), 15, 1847 (1967).
16. B. Shimizu, A. Saito, T. Nishimura, and M. Miyaki, Chem. Pharm. Bull. (Tokyo), 15, 2011 (1967).
17. I. Iwai, T. Nishimura, and B. Shimizu, in "Synthetic Procedures in Nucleic Acid Chemistry", New York, 1968, Vol. 1, p. 388.
18. B. N. Stepanenko and E. M. Kaz'mina, Trudy 1-go Moskov. Med. Inst., 61, 276 (1968).
19. B. N. Stepanenko and E. M. Kaz'mina, Trudy 1-go Moskov. Med. Inst., 181, 619 (1968).
20. R. L. Whistler, L. W. Doner, and U. G. Nayak, J. Org. Chem., 36, 108 (1971).
21. K. Golankiewicz, and L. Strekowski, Roczniki Chem., 45, 3 (1971).
22. T. Hashizume, S. Higa, Y. Sasaki, H. Yamazaki, H. Iwamura, and H. Matsuda, Agr. Biol. Chem., 30, 319 (1966).
23. Sankyo Co. Ltd., Belg. P. 639 885 (1964), Chem. Abs., 62, 16 364 (1965).
24. E. Wittenburg, Z. Chem., 4, 303 (1964).
25. E. Wittenburg, Angew. Chem., 77, 1043 (1965).
26. E. Wittenburg, Chem. Ber., 101, 2132 (1968).
27. Z. A. Martirosyan, V. I. Gunar, and S. I. Zav'yalov, Izv. Akad. Nauk SSSR, Ser. Khim., 1841 (1970).
28. T. Nishimura, B. Shimizu, and I. Iwai, Chem. Pharm. Bull. (Tokyo), 12, 1471 (1964).

29. Y. Sasaki and T. Hashizume, Anal. Biochem., 16, 1 (1966).
30. T. T. Sakai, A. L. Pagollotti, and D. V. Santi, J. Heterocycl. Chem., 5, 849 (1968).
31. C. W. Gehrke and C. D. Ruyle, J. Chromatog., 38, 473 (1968).
32. B. Shimizu and A. Saito, Agr. Biol. Chem., 33, 119 (1969).
33. H. P. Albrecht, G. H. Jones, and J. G. Moffatt, J. Amer. Chem. Soc., 92, 5511 (1970).
34. E. White, V. P. Krueger, and J. A. McCloskey, J. Org. Chem., 37, 430 (1972).
35. C. W. Gehrke, D. L. Stalling, and C. D. Ruyle, Biochem. Biophys. Res. Comm., 28, 869 (1967).
36. W. J. A. Van den Heuvel, J. L. Smith, P. Haug, and J. L. Beck, J. Heterocyl. Chem., 9, 451 (1972).
37. M. P. Kotick, C. Szantay, and T. J. Bardos, J. Org. Chem., 34, 3806 (1969).
38. E. Wittenburg, Chem. Ber., 99, 2380 (1966).
39. E. Wittenburg, Z. Chem., 7, 13 (1967).
40. E. Wittenburg, G. Etzold, and P. Langen, Chem. Ber., 101, 494 (1968).
41. E. Wittenburg, Chem. Ber., 101, 1095 (1968).
42. E. Wittenburg, Chem. Ber., 101, 1614 (1968).
43. M. L. Wolfrom and M. W. Winkley, J. Org. Chem., 33, 4227 (1968).
44. J. A. Montgomery and K. Hewson, J. Heterocycl. Chem., 2, 313 (1965).
45. G. L. Bubbar and V. S. Gupta, Canad. J. Chem., 48, 3147 (1970).
46. T. J. Bardos, M. P. Kotick, and C. Szantay, Tetrahedron Letters, 1759 (1966).
47. L. Pichat and G. Chatelain, Bull. Soc. chim. France, 1833 (1970).
48. L. Pichat, J. Deschamps, B. Massé, and P. Dufay, Bull. Soc. chim. France, 2110 (1971).
49. K. J. Ryan, E. M. Acton, and L. Goodman, J. Org. Chem., 31, 1181 (1966).
50. S. Nesnow, A. M. Mian, T. Oki, D. L. Dexter, and C. Heidelberger, J. Medicin. Pharmaceut. Chem., 15, 676 (1972).
51. M. G. Stout and R. K. Robins, J. Heterocycl. Chem., 9, 545 (1972).
52. M. P. Mertes and M. T. Shipchandler, J. Heterocycl. Chem., 8, 133 (1971).
53. Hoffman-La Roche, Dutch Appl. 6 610 360 (1967), Chem. Abs., 67, 91 093 (1967).
54. T. Kanai, M. Ichino, A. Hoshi, F. Kanzawa, and K. Kuretani, J. Medicin. Pharmaceut. Chem., 15, 1218 (1972).
55. M. P. Mertes and M. T. Shipchandler, J. Heterocycl. Chem., 7, 751 (1970).
56. E. H. Hamamura, K. Sato, and J. G. Moffat, J. Medicin. Pharmaceut. Chem., 15, 1061 (1972).
57. E. Wittenburg, Coll. Czech. Chem. Comm., 36, 246 (1971).
58. M. W. Winkley and R. K. Robins, J. Org. Chem., 33, 2822 (1968).
59. M. W. Winkley and R. K. Robins, J. Chem. Soc. (C), 791 (1969).
60. M. W. Winkley, J. Chem. Soc. (C), 1365 (1970).
61. R. S. Klein and J. J. Fox, J. Org. Chem., 37, 4381 (1972).
62. V. S. Gupta and G. L. Bubbar, Canad. J. Chem., 49, 719 (1971).
63. M. W. Winkley and R. K. Robins, J. Org. Chem., 35, 491 (1970).
64. W. Giessler, Dissertation, Köln, 1963.
65. H. Vorbrüggen, P. Strehlke, and G. Schulz, Angew. Chem., 81, 997 (1969).
66. H. Vorbrüggen, P. Strehlke (Schering A.-G.), South African P. 6 906 210 (1969); Chem. Abs., 73, 110 084v (1970).
67. H. Vorbrüggen and P. Strehlke (Schering A.-G.), BRD Appl. 1 955 402 (1971); Chem. Abs., 75, 36 575d (1971).
68. H. Vorbrüggen and P. Strehlke, Angew. Chem., 81, 998 (1969).
69. H. Vorbrüggen and P. Strehlke (Schering A.-G.), BRD Appl. 1 959 523 (1971); Chem. Abs., 75, 88 909k (1971).
70. D. S. Wise and L. B. Townsend, J. Heterocycl. Chem., 9, 1461 (1972).
71. M. W. Winkley and R. K. Robins, J. Org. Chem., 34, 431 (1969).
72. G. L. Tong, W. W. Lee, and L. Goodman, J. Heterocycl. Chem., 3, 226 (1966).
73. G. J. Durr, J. F. Keiser, and P. A. Ierardi, J. Heterocycl. Chem., 4, 291 (1967).
74. C. Cristescu, Rev. Roum. Chim., 31, 365 (1968).
75. U. Niedballa and H. Vorbrüggen, Angew. Chem., 82, 449 (1970).
76. H. Vorbrüggen, K. H. Kolb, U. Niedballa, and P. Strehlke (Schering A.-G.), BRD Appl. 1 955 695 (1971); Chem. Abs., 75, 49 513g (1971).
77. T. Y. Shen, W. V. Ruyle, and R. L. Bugianesi, J. Heterocycl. Chem., 2, 495 (1965).
78. A. Dipple and C. Heidelberger, J. Medicin. Pharmaceut. Chem., 9, 715 (1966).
79. M. Prystaš and F. Šorm, Coll. Czech. Chem. Comm., 34, 1104 (1969).
80. G. J. Durr and S. Hammond, J. Heterocycl. Chem., 7, 743 (1970).
81. B. Shimizu and F. Shimizu, Chem. Pharm. Bull. (Tokyo), 18, 1060 (1970).
82. D. H. Warnock, K. A. Watanabe, and J. J. Fox, Carbohydr. Res., 18, 127 (1970).
83. S. David and A. Lubineau, Compt. rend., 275C, 331 (1972).
84. L. Birkofer, H. P. Kühlthau, and A. Ritter, Chem. Ber., 93, 2810 (1960).
85. L. Birkofer and A. Ritter, Angew. Chem. Internat. Ed., 4, 417 (1965).
86. L. Birkofer, A. Ritter, and H. P. Kühlthau, Chem. Ber., 97, 934 (1964).
87. H. Vorbrüggen and U. Niedballa, Tetrahedron Letters, 3571 (1970).
88. A. Piskala and F. Šorm, BRD P. 1 935 028 (1970); Chem. Abs., 73, 45 793j (1970).
89. H. Vorbruggen and U. Niedballa (Schering A. -G.), BRD Appl., 2 032 424 (1972); Chem. Abs., 76, 113 492z (1972).
90. T. Nishimura and B. Shimizu, Agr. Biol. Chem., 28, 224 (1964).
91. See Ref. 17, p. 135.
92. C. G. Tindall, R. K. Robins, R. L. Tolman, and W. Hutzenlaub, J. Org. Chem., 37, 3985 (1972).
93. L. Birkofer and A. Ritter, Angew. Chem., 71, 372 (1959).
94. L. Birkofer and A. Ritter, Angew. Chem., 77, 414 (1965).
95. T. Nishimura and I. Iwai, Chem. Pharm. Bull. (Tokyo), 12, 357 (1964).
96. Z. S. Dubinkina, E. M. Kaz'mina, and B. N. Stepanenko, Dokl. Akad. Nauk SSSR, 204, 352 (1972).
97. M. L. Wolfrom and P. J. Conigliaro, Carbohydr. Res., 20, 391 (1971).

98. T. Kondo and T. Goto, Agr. Biol. Chem., 35, 625 (1971).
99. D. Horton and S. S. Kokrady, Carbohydrate Res., 24, 333 (1972).
100. H. Yanagisawa, O. M. Kinoshita, and S. Umezawa, Bull. Chem. Soc. Japan, 44, 3399 (1971).
101. S. Hillers, M. Lidaks, R. A. Zhuk, A. Berzina, K. Pecs, I. N. Getsova, and E. I. Bruk, Khim. Geterotsikl. Soed., 375 (1969).
102. D. Snikeris, R. A. Zhuk, E. I. Stankevich, G. Duburs, and S. Hillers, Khim. Geterotsikl. Soed., 170 (1969).
103. S. Hillers and R. A. Zhuk, Symposium, "7-oi Mezhdunarodnyi Simposium po Khimii Prirodnykh Soedinenii, Tezisy Dokladov" (The Seventh International Symposium on the Chemistry of Natural Products. Abstracts of Reports), Izd. Zinatne, Riga, 1970, p. 281.
104. A. F. Wu and E. Chargaff, Proc. Nat. Acad. Sci. USA, 63, 1222 (1969).
105. B. Shimizu and M. Miyagi (Sankyo Co., Ltd.), Japanese P. 21 872 (1971); Chem. Abs., 75, 77 229n (1971).
106. H. Hřebabecky, J. Farkaš, and F. Šorm, Coll. Czech. Chem. Comm., 37, 2059 (1972).
107. T. Ogawa, M. Yasui, and M. Matsui, Agr. Biol. Chem., 36, 913 (1972).
108. T. Kondo, H. Nakai, and T. Goto, Agr. Biol. Chem., 35, 1990 (1971).
109. T. Kondo, H. Nakai, and T. Goto, Tetrahedron Letters, 1881 (1972).
110. J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, J. Amer. Chem. Soc., 78, 2117 (1956).
111. D. W. Visser, I. Goodman, and K. Dittmer, J. Amer. Chem. Soc., 70, 1926 (1948).
112. J. Farkaš, L. Kaplan, and J. J. Fox, J. Org. Chem., 29, 1469 (1964).
113. M. L. Wolfrom, H. B. Bhat, and P. J. Conigliaro, Carbohydr. Res., 20, 375 (1971).
114. M. L. Wolfrom and H. B. Bhat, J. Org. Chem., 32, 2757 (1967).
115. M. L. Wolfrom, P. J. Conigliaro, and H. B. Bhat, Carbohydr. Res., 20, 383 (1971).
116. M. L. Wolfrom, H. B. Bhat, and P. McWain, see Ref. 17, p. 323.
117. M. L. Wolfrom and P. J. Conigliaro, Carbohydr. Res., 20, 369 (1971).
118. J. J. K. Novak, J. Šmejkal, and F. Šorm, Coll. Czech. Chem. Comm., 36, 3670 (1971).
119. G. Kowollik, G. Demirow, M. Schütt, and P. Langen, Z. Chem., 12, 106 (1972).
120. H. Vorbrüggen and U. Niedballa, see Ref. 103, p. 232.
121. E. Wittenburg, "The 21st International IUPAC Congress, Chemistry of Nucleic Acid Components, Abstracts of Papers, Prague, 1967", No. 18.
122. G. L. Szekeres and T. J. Bardos, J. Medicin. Pharmaceut. Chem., 13, 708 (1970).
123. "Fluorafur", Izd. Prospekt, Inst. Org. Sint., Akad. Nauk Latv. SSR, Riga, 1972.
124. J. J. Fox and I. Wempen, Adv. Carbohydr. Chem., 14, 335 (1959).
125. M. Prystaš and F. Šorm, Coll. Czech. Chem. Comm., 34, 2316 (1969).
126. J. A. Wright, D. P. Wilson, and J. J. Fox, J. Medicin. Pharmaceut. Chem., 13, 269 (1970).
127. K. A. Watanabe, I. M. Wempen, and J. J. Fox, Carbohydr. Res., 21, 148 (1972).
128. U. Niedballa and H. Vorbruggen (Schering A.-G.), BRD Appl. 1 919 307 (1971); Chem. Abs., 74, 88 267d (1971).
129. M. Prystaš, Coll. Czech. Chem. Comm., 33, 1813 (1968).
130. R. H. Hall, J. Amer. Chem. Soc., 80, 1145 (1958).
131. J. Gut, Adv. Heterocycl. Chem., 1, 204 (1963).
132. T. Nishimura, Methods Carbohydr. Chem., 6, 436 (1972).
133. U. Niedballa and H. Vorbrüggen (Schering A.-G.), BRD Appl. 1 943 428 (1971); Chem. Abs., 74, 100 361g (1971).
134. H. Vorbrüggen and U. Niedballa (Schering A.-G.), South African P. 2114 (1970); Chem. Abs., 75, 20 912a (1971).
135. H. Vorbrüggen and U. Niedballa, Angew. Chem., 83, 729 (1971).
136. M. Bobek, J. Farkaš, and F. Šorm, Coll. Czech. Chem. Comm., 32, 3581 (1967).
137. M. Bobek, J. Farkaš, and F. Šorm, "The 21st International IUPAC Congress, Chemistry of Nucleic Acid Components, Abstracts of Papers, Prague, 1967", No. 20.
138. T. Y. Shen, W. V. Ruyle, and R. L. Bugianesi, see Ref. 17, p. 355.
139. P. Fuchs, F. W. Garn, K. H. Kolb, and H. Vorbrüggen (Schering A.-G.), BRD Appl. 1 937 073 (1971); Chem. Abs., 74, 100 362r (1971).
140. H. Vorbrüggen and U. Niedballa (Schering A.-G.), BRD Appl. 2 012 888 (1971); Chem. Abs., 75, 14 862p (1971).
141. K. J. Ryan, E. M. Acton, and L. Goodman, J. Org. Chem., 36, 2646 (1971).
142. W. W. Lee, A. P. Martinez, L. Goodman, and D. W. Henry, J. Org. Chem., 37, 2923 (1972).
143. M. J. Covill, H. G. Garg, and T. L. Ulbricht, Tetrahedron Letters, 1033 (1968).
144. R. L. Tolman, G. L. Tolman, R. K. Robins, and L. B. Townsend, J. Heterocycl. Chem., 7, 799 (1970).
145. G. R. Revankar and L. B. Townsend, J. Chem. Soc. (C), 2440 (1971).
146. W. Hutzenlaub, R. L. Tolman, and R. K. Robins, J. Medicin. Phamaceut. Chem., 15, 879 (1972).
147. C. L. Schmidt, W. J. Rusho, and L. B. Townsend, Chem. Comm., 1515 (1971).
148. C. W. Smith, R. W. Sidwell, R. K. Robins, and R. L. Tolman, J. Medicin. Pharmaceut. Chem., 15, 883 (1972).
149. M. W. Winkley, G. F. Judd, and R. K. Robins, J. Heterocycl. Chem., 8, 237 (1971).
150. M. G. Stout and R. K. Robins, J. Org. Chem., 33, 1219 (1968).
151. M. G. Stout and R. K. Robins, J. Heterocycl. Chem. 6, 89 (1969).
152. B. H. Rizkalla, A. D. Broom, M. G. Stout, and R. K. Robins, J. Org. Chem., 37, 3975 (1972).
153. B. H. Rizkalla and A. D. Broom, J. Org. Chem., 37, 3980 (1972).
154. W. Pfleiderer, D. Autenrieth, and M. Schranner, Angew. Chem., 83, 971 (1971).
155. H. Schmid, M. Schranner, and W. Pfleiderer, Angew. Chem., 83, 972 (1971).
156. M. Ott and W. Pfleiderer, Angew. Chem., 83, 974 (1971).
157. G. Ritzmann, K. Harzer, and W. Pfleiderer, Angew. Chem., 83, 975 (1971).
158. M. J. Robins and B. L. Currie, Chem. Comm., 1547 (1968).

159. B. L. Currie, Diss. Abs., 30B, 5425 (1970).
160. B. L. Currie, R. K. Robins, and M. J. Robins, J. Heterocycl. Chem., 7, 323 (1970).
161. B. L. Currie, M. J. Robins, and R. K. Robins, J. Heterocycl. Chem., 8, 221 (1971).
162. T. Ogawa, M. Yasui, and M. Matsui, Agr. Biol. Chem., 36, 1443 (1972).
163. L. Avota, I. V. Turovskii, and S. Hillers, Khim. Geterotsikl. Soed., 1545 (1973).
164. M. Bobeck and A. Bloch, J. Medicin. Pharmaceut. Chem., 15, 164 (1972).
165. W. Pfleiderer and M. Schranner, Chem. Ber., 104, 1915 (1971).
166. G. R. Revankar and L. B. Townsend, J. Heterocycl. Chem., 7, 117 (1970).
167. G. R. Revankar and L. B. Townsend, J. Heterocycl. Chem., 5, 1329 (1968).
168. H. Bräuniger and A. Koine, Arch. Pharm., 296, 668 (1963).
169. H. Bräuniger and A. Koine, Arch. Pharm., 298, 641 (1965).
170. H. Bräuniger and A. Koine, Arch. Pharm., 298, 644 (1965).
171. H. Bräuniger and A. Koine, Arch. Pharm., 298, 708 (1965).
172. H. Bräuniger and A. Koine, Arch. Pharm., 298, 712 (1965).
173. T. Nishimura, Methods Carbohydr. Chem., 6, 441 (1972).
174. G. R. Revankar and L. B. Townsend, J. Heterocycl. Chem., 5, 477 (1968).
175. G. R. Revankar and L. B. Townsend, J. Heterocycl. Chem., 5, 615 (1968).
176. J. A. May and L. B. Townsend, Chem. Comm., 64 (1973).
177. R. P. Panzica and L. B. Townsend, J. Org. Chem., 36, 1594 (1971).
178. R. A. Earl, R. P. Panzica, and L. B. Townsend, J. Chem. Soc., Perkin 1, 2672 (1972).
179. T. Ogawa, M. Yasui, and M. Matsui, Agr. Biol. Chem., 36, 1445 (1972).
180. J. T. Witkowski and R. K. Robins, J. Org. Chem., 35, 2635 (1970).
181. J. T. Witkowski, R. K. Robins, and R. W. Sidwell, "Abstracts of the 163rd National Meeting of the American Chemical Society, Boston, 1972", MEDI 19.
182. J. T. Witkowski, R. K. Robins, R. W. Sidwell, and L. N. Simon, J. Medicin. Pharmaceut. Chem., 15, 1150 (1972).
183. H. Bräuniger and A. Koine, Arch. Pharm., 296, 665 (1963).
184. G. R. Revankar and L. B. Townsend, J. Heterocycl. Chem., 5, 785 (1968).
185. T. Ukita and H. Hayatsu, J. Amer. Chem. Soc., 84, 1879 (1962).
186. M. Matsui and A. Nobuhara, Agr. Biol. Chem., 27, 650 (1963).
187. T. Nishimura, B. Shimizu, and I. Iwai, see Ref. 121, No. 23.
188. B. Shimizu, T. Nishimura, and M. Ikehara, Agr. Biol. Chem., 31, 637 (1967).
189. M. Draminski and B. Fisher, Roczniki Chem., 47, 1205 (1973).
190. P. T. Berkowitz, T. J. Bardos, and A. Bloch, J. Medicin. Pharmaceut. Chem., 16, 183 (1973).
191. R. A. Earl and L. B. Townsend, J. Heterocycl. Chem., 9, 1141 (1972).
192. R. Brossmer and V. Eschenfelder, Annalen, 762, 160 (1972).
193. R. Wightman and A. Holy, Coll. Czech. Chem. Comm., 38, 1381 (1973).
194. J. T. Witkowski and R. K. Robins, BRD Appl. 2 220 246 (1972); Chem. Abs., 78, 84 766a (1973).
195. M. L. Wolfrom, H. B. Bhat, P. McWain, and D. Horton, Carbohydr. Res., 23, 289 (1972).
196. H. Vorbrüggen and U. Niedballa (Schering A.-G.), BRD Appl. 2 108 808 (1972); Chem. Abs., 77, 152 519d (1972).
197. N. S. Miroshnichenko, I. G. Ryabokon', and A. V. Stetsenko, Ukrain. Khim. Zhur., 39, 350 (1973).
198. N. S. Miroshnichenko, I. L. Shkrebtii, and A. V. Stetsenko, Ukrain. Khim. Zhur., 39, 277 (1973).
199. R. P. Panzica and L. B. Townsend, J. Chem. Soc., Perkin 1, 244 (1973).
200. V. S. Martynov and N. N. Preobrazhenskaya, Zhur. Org. Khim., 9, 1980 (1973).
201. V. D. Patil, D. S. Wise, and L. B. Townsend, J. Heterocycl. Chem., 10, 277 (1973).
202. W. Pfleiderer, D. Autenrieth, and M. Schranner, Chem. Ber., 106, 317 (1973).
203. G. Ritzmann and W. Pfleiderer, Chem. Ber., 106, 1401 (1973).
204. H. Schmid, M. Schranner, and W. Pfleiderer, Chem. Ber., 106, 1952 (1973).
205. B. N. Stepanenko, E. M. Kaz'mina, and Z. S. Dubinkina, Uspekhi Khim., 42, 1121 (1973) [Russ. Chem. Rev., No. 6 (1973)].

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