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THE USE OF PROTECTING GROUPS IN THE SYNTHESIS OF PURINE DERIVATIVES (REVIEW)

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Published data on the use of protecting groups in the synthesis of purine derivatives are reviewed and classified.

Keywords: aminopurines, guanosine acyclic analogs, hydroxypurines, medicines, nucleosides, nucleotides, protecting groups, thioxopurines, catalytic hydrogenation.

During the synthesis of derivatives of purine from amino-, hydroxy-, thio-, or chloropurines there is often a need at position 2, 6, 7, or 9 of the purine ring to insert a protecting group that can be removed after the necessary chemical operations and retained or replaced by another pharmacophoric group during the search for biologically active substances.

1. ALKYL (ARALKYL) PROTECTION OF POSITION 7(9)

The following basic rules were established on the basis of experimental data from a large number of papers and patents relating to the nucleophilic substitution of chloropurines, reported in the monographs [1, 2]: In the series of chloro-, dichloro-, and trichloropurines the most reactive is the chlorine atom at position 6, in second place is the chlorine atom at position 8, and in third place the chlorine atom at position 2 of the purine bicycle. This rule persists in the series of 7(9)-alkyl-2,6-, -2,8-, and -6,8-dichloropurines.

In the series of 7(9)-alkyl-2,6,8-trichloropurines the order of nucleophilic substitution of the chlorine atoms changes. In these compounds, unlike 2,6,8-trichloropurine, the most vulnerable center for nucleophilic attack is the chlorine atom at position 8 and then the chlorine atom at position 6 of the purine ring. The chlorine atom at position 2 was and remains the most inert in the series of 7(9)-alkyl-2,6,8-trichloropurines.

In the synthesis of 8-substituted purines from 2,6,8-trichloro-7-methylpurine (**1**) the founder of purine chemistry E. Fischer used the methyl group as protection. Thus, 2,6-dichloro-7-methylpurin-8-one (**2**) was obtained by the reaction of the trichloride **1** with KOH in aqueous solution at 20°C [3].

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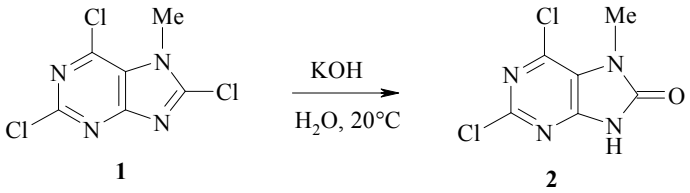
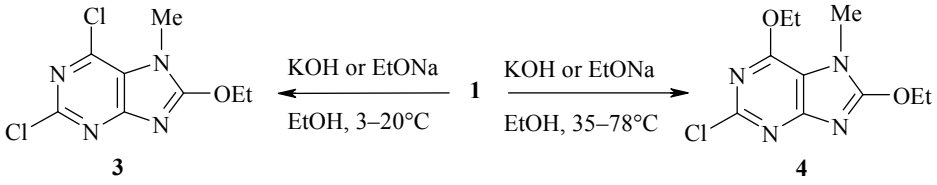
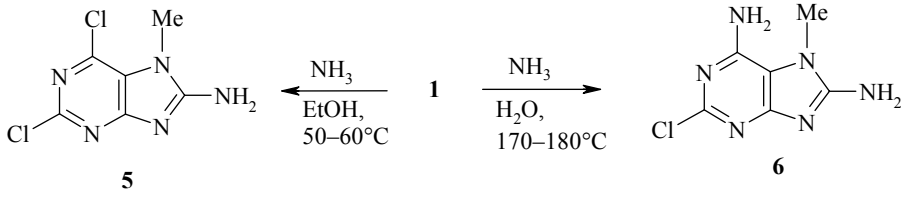


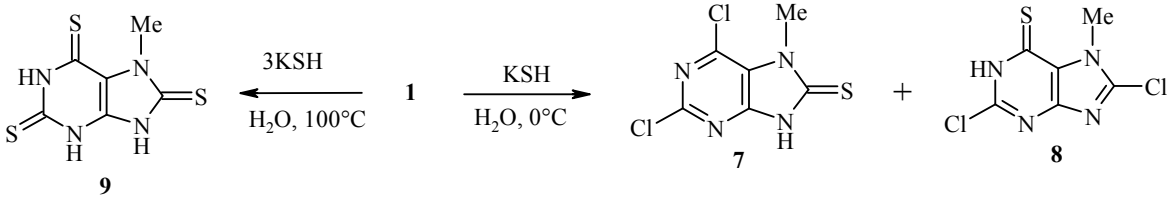
The reaction of the trichloride **1** with KOH [3] and sodium ethoxide [4] in anhydrous ethanol at 3-20°C leads to 8-ethoxypurine **3** (yield 58%) while the reaction at 35-78°C leads to 6,8-diethoxypurine **4**.



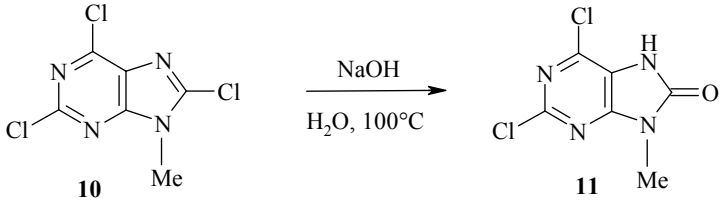
8-Aminopurine **5** was obtained by heating the trichloride **1** with ammonia in alcohol solution at 50-60°C (yield 85%) while 6,8-diaminopurine **6** (yield 71%) was obtained with 28% aqueous ammonia at 170-180°C [4].

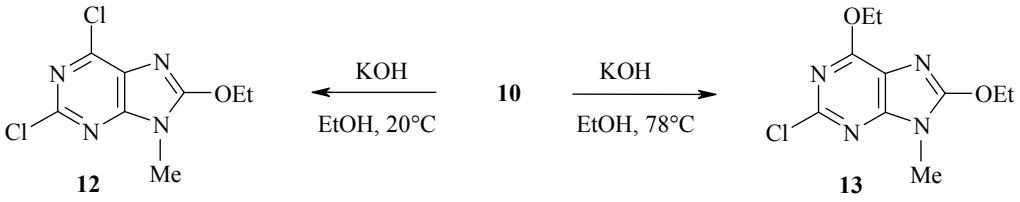


The reaction of the trichloride **1** with KSH at 0°C gave a mixture of 8-thioxo- and 6-thioxopurines **7** and **8** while reaction at 100°C with an excess of KSH gave the trithiopurine **9** [5].

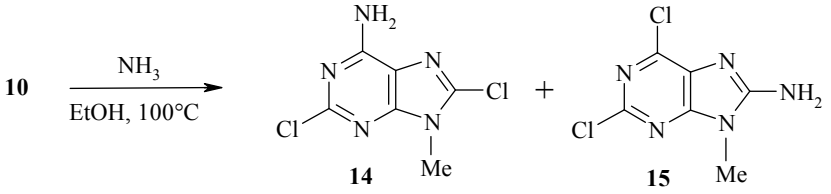


Stepwise substitution of the chlorine atom at position 8 and then at position 6 of the purine ring also occurs in the reactions of -2,6,8-trichloro-9-methylpurine (**10**) with nucleophiles. Thus, the purin-8-one **11** was obtained in the reaction of the trichloride **10** with sodium hydroxide in water while 8-ethoxypurine **12** (yield 70%) or 6,8-diethoxypurine **13**, depending on the temperature, was obtained with potassium hydroxide in ethanol [3].

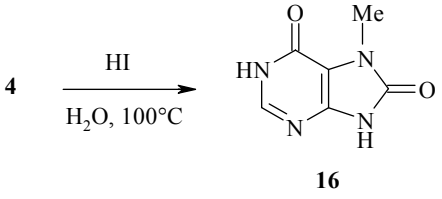




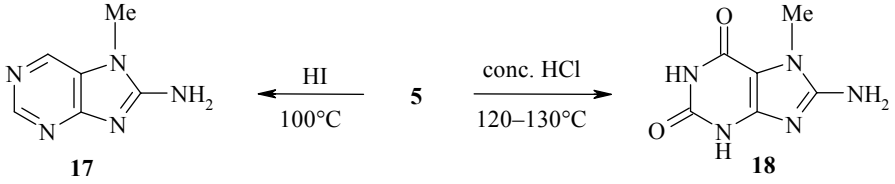
A departure from the rule presented above was observed in the reaction of the trichloride **10** with ammonia in alcohol solution at 100°C – a mixture of 6-amino- and 8-aminopurines **14** and **15** with a preference for the 6-isomer **14** was obtained [6].



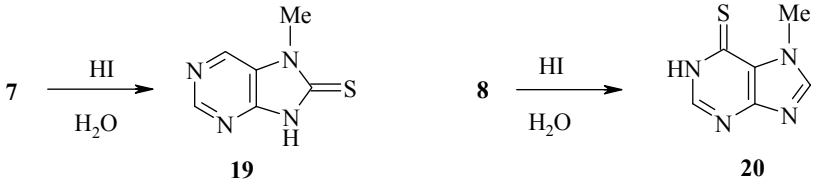
Some properties of the obtained compounds were described in [3, 4]. Thus, during the reduction of the diethoxy compound **4** with concentrated HI the ethoxy groups were hydrolyzed at the same time with the formation of 7-methylpurine-6,8-dione **16** [3].



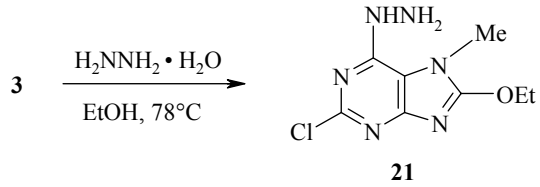
During the reduction of compound **5** in concentrated HI 8-amino-7-methylpurine **17** was obtained, and during its hydrolysis in concentrated HCl 8-amino-7-methylxanthine **18** was obtained [3].

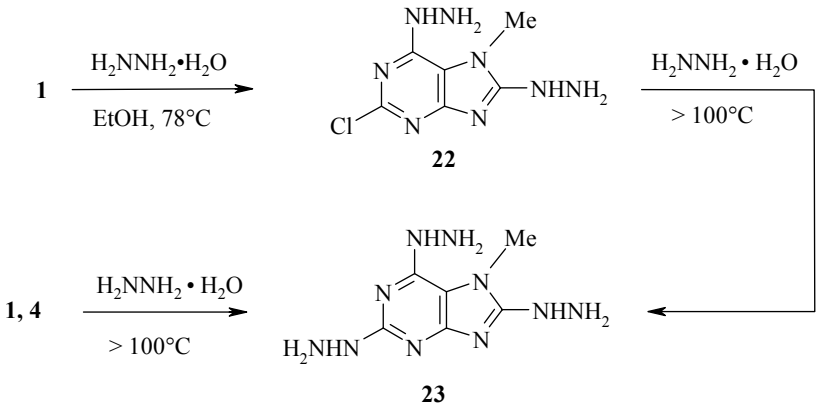


The reduction of chlorothiopurines **7** and **8** with concentrated HI led to the formation of 7-methyl-8-thioxo- and 7-methyl-6-thioxopurines **19** and **20** [5].



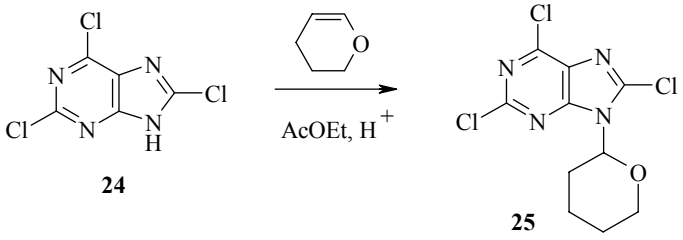
The reaction of the chloropurines **1**, **3**, and **4** with 80% hydrazine hydrate led to mono-, di-, and trihydrazinopurines **21**-**23**, depending on the temperature, boiling without a solvent, or boiling in alcohol solution (yields 41-95%) [4].



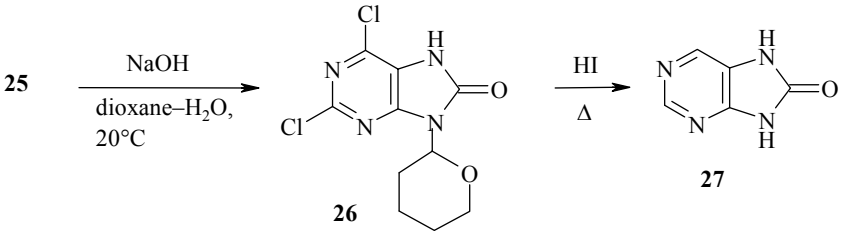


The use of 7(9)-methyltrichloropurines **1** and **10** in the synthesis of purine derivatives with a free NH group is prevented by the lack of a method for removing the methyl group from positions 7 and 9.

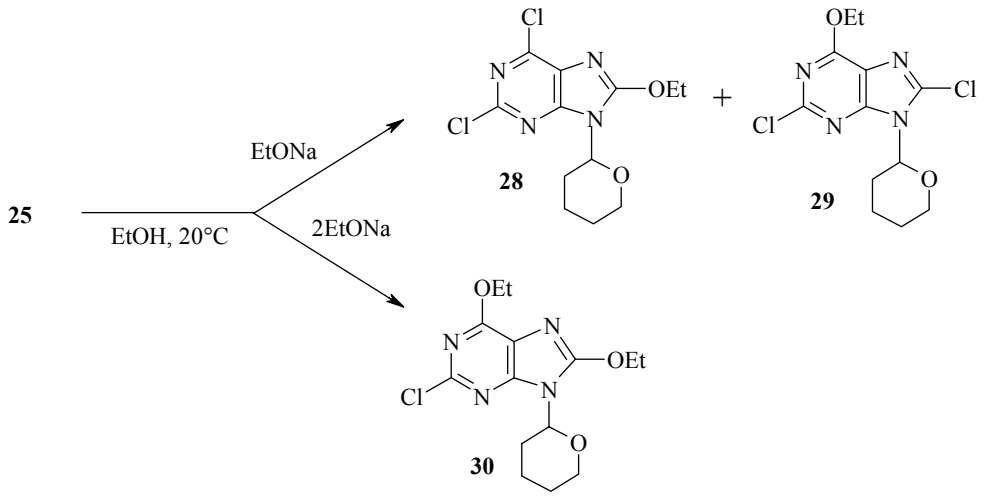
In [7] 2-tetrahydropyranyl protection was proposed for position 9 of the purine ring. The reaction of 2,6,8-trichloropurine **24** with 2,3-dihydropyran in ethyl acetate in the presence of *p*-toluenesulfonic acid leads to the formation of 2,6,8-trichloro-9-(tetrahydro-2-pyranyl)purine (**25**) (yield 61%) – a key compound in the synthesis of all the purine derivatives **26-39** presented below [7].



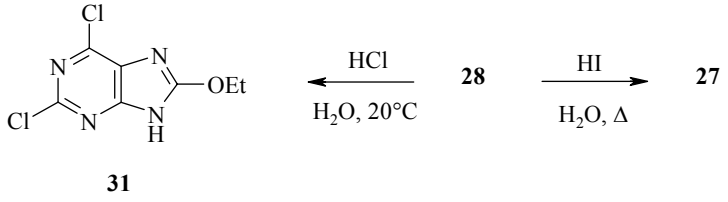
The reaction of the trichloride **25** with sodium hydroxide at 20°C gave the dichloride **26** (yield 43%), the reduction of which with concentrated HI led to the purin-8-one **27**.



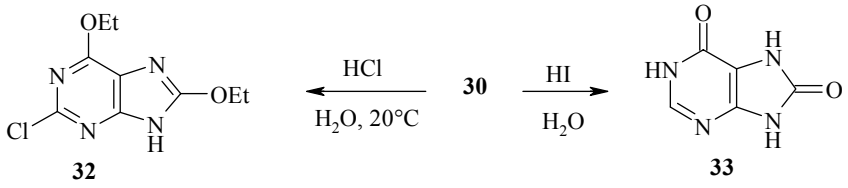
Depending on the amount (one or two moles) the reaction of the trichloride **25** with sodium ethoxide at 20°C leads to a mixture of the 8-ethoxy and 6-ethoxy isomers **28** and **29** (total yield 80%, content of the 8-isomer 70%) or 6,8-diethoxypurine **30** (yield 85%).



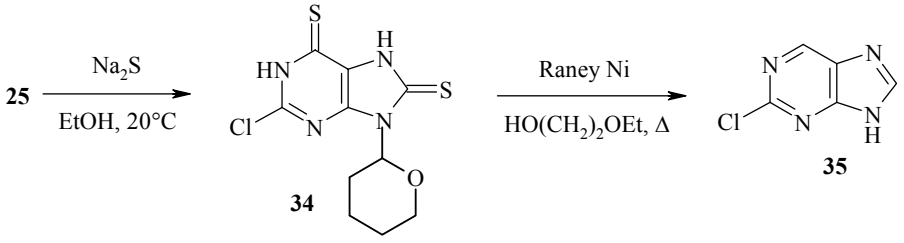
In 1 N HCl at 20°C the ethoxypurine **28** loses the tetrahydropyranyl group with the formation of the dichloropurine **31**, and during reduction with HI it is converted into the purinone **27**.



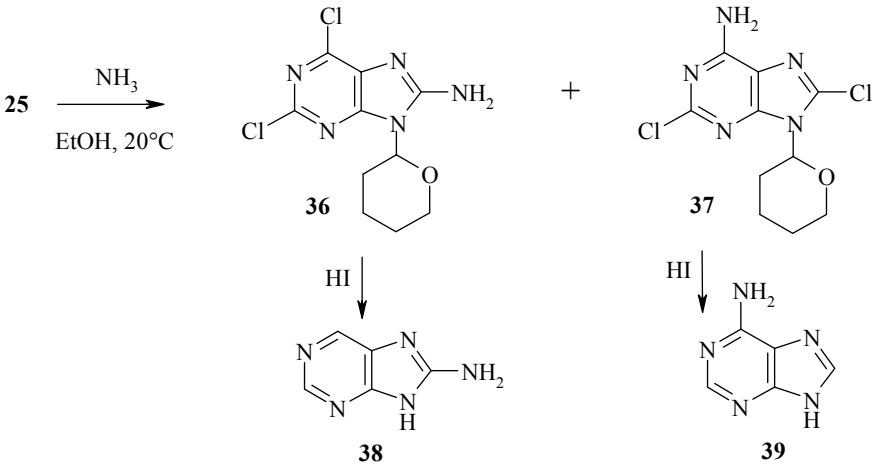
Under analogous conditions compound **30** is converted into 2-chloro-6,8-diethoxypurine **32** (yield 63%) and purine-6,8-dione **33** (yield 78%).



The reaction of the trichloride **25** with Na_2S at 20°C leads to the 6,8-dithiopurine **34** (yield 97%), the desulfurization of which with Raney nickel gives 2-chloropurine **35**.

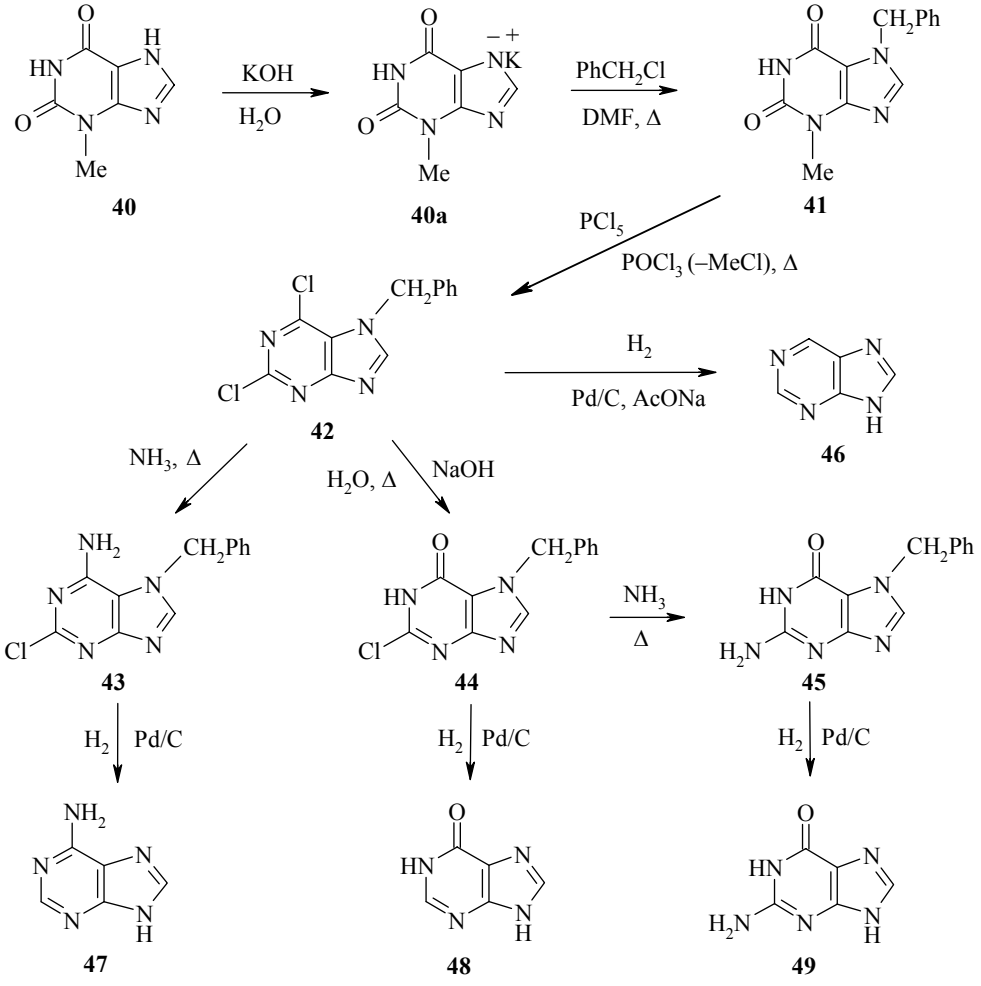


A mixture of isomers **36** (yield 69%) and **37** (yield 29%) is formed during the reaction of the trichloride **25** with ammonia in ethanol at 20°C. The amines **38** and **39** were obtained by the reduction of these compounds with 47% HI.



The main shortcomings of tetrahydropyranyl protection are the complexity of the synthesis, the low yields of the key compound **25** (61%), and the instability of the group in acidic media.

A more universal protecting group for the synthesis of purine derivatives from chloropurines is a benzyl group at position 7 of the purine ring. Its universality lies in the simplicity of introduction and removal. It is stable in both alkaline and acidic media, and its use makes it possible to use commercially available 3-methylxanthine **40** and its potassium salt **40a**, which are intermediates in the production of theobromine and caffeine [8].



The method is based on the introduction of the benzyl group at position 7 of the xanthine molecule **40**, realization of the necessary reactions at positions 2, 6, 8, or 9, and subsequent removal of the benzyl group by catalytic hydrogenation of the obtained compounds in the presence of a palladium catalyst. By this method it is possible to achieve debenzylation with simultaneous dechlorination of the chlorine derivatives of 7-benzylpurine without affecting other previously inserted functional groupings. The purine ring is not hydrogenated under the selected conditions (5-10% Pd/C, 80-95°C).

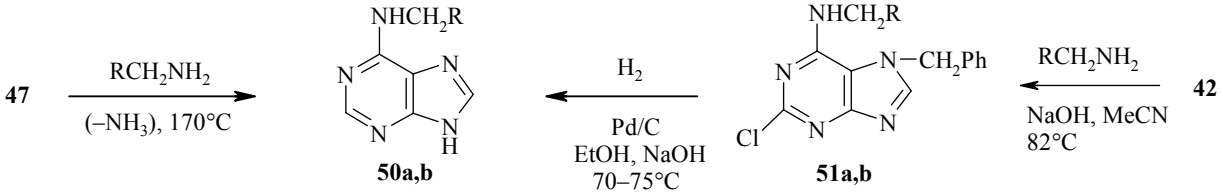
Examples of the use of benzyl protection for the synthesis of purine derivatives are presented above.

New methods for the synthesis of purine, adenine, hypoxanthine, and guanine **46**-**49** (yields 73, 77, 85, and 95% respectively) from xanthine **40** were developed according to a combined scheme through the intermediate compounds **42**-**45** (yields 87, 95, 95, and 81% respectively) [9-14].

Pure adenine, hypoxanthine, guanine, and purine were produced as commercial chemical reagents by crystallization of the industrial compounds, and adenine for injections was produced by fine chemical purification from extraneous impurities, microorganisms, and pirogens as the most important component of new preservatives for donated blood and erythrocyte mass having increased storage lives [15].

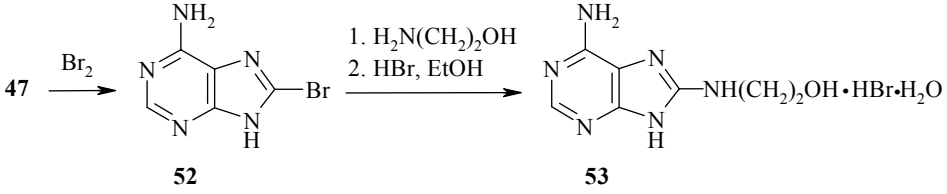
The high quality of the industrial adenine, hypoxanthine, and guanine makes it possible to use these compounds without additional purification in the synthesis of medicinal and agrochemical products. Thus, transamination of the amine **47** with furfuryl- and benzylamines by the method in [16] gave 54-55% yields of plant growth hormones (cytokinins [17]) – the natural hormone kinetin (**50a**) and its synthetic analog N(6)-benzyladenine (**50b**) [11, 12].

The cytokinins **50a**,**b** were also synthesized with high yields (66-69%) by another original method – by reaction of the dichloride **42** with furfuryl(benzyl)amines followed by simultaneous debenzylation and dechlorination of the intermediate compounds **51a**,**b** (yields 71-84%) [11, 12, 18].

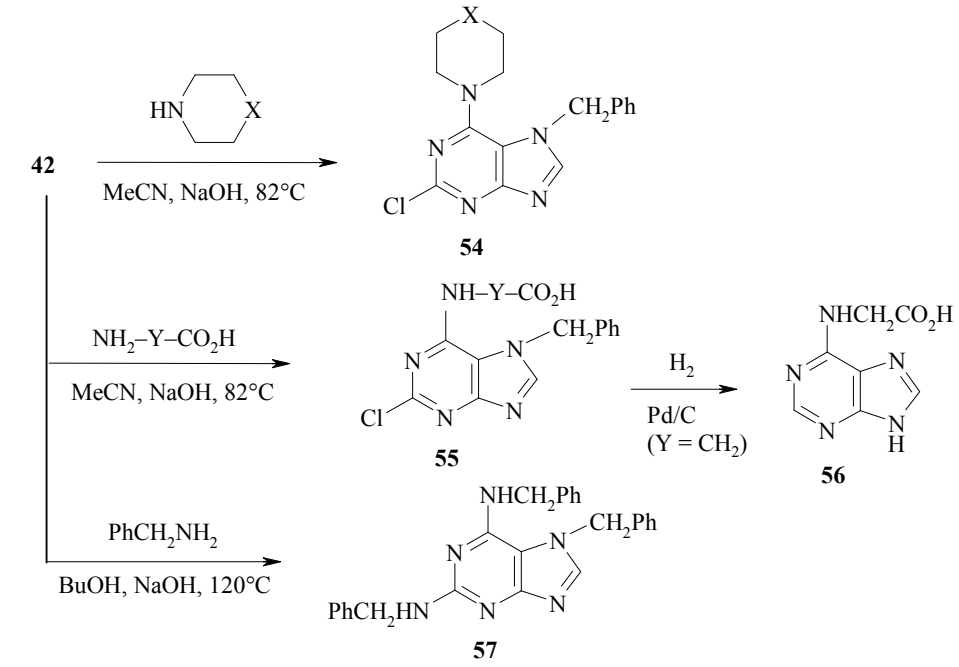


a R = 2-furyl; **b** R = Ph

The medical product ethadene – the hydrate of 6-amino-8-(2-hydroxyethylamino)purine hydrobromide **53** [20-22] – was obtained with a yield of 47% calculated on the adenine [11, 12] from the industrial amine **47** through the 8-bromoadenine **52** [19].



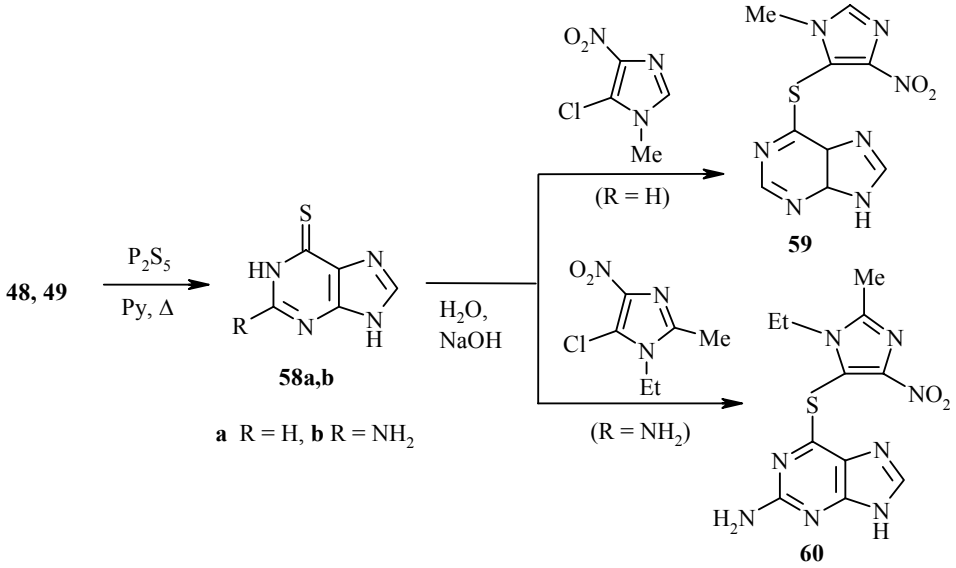
The N(6)-substituted 7-benzyladenines **54** and **55** (yields 70-91%) were synthesized by the reaction of the dichloride **42** with acyclic secondary amines and also α-, β-, and ω-amino acids in acetonitrile. The hydrogenation of some of these compounds, e.g., the acid **55** (Y = CH_2), gave purinyl-6-glycine (**56**) (yield 66%) [11, 12, 18]. Under more rigorous conditions, when the dichloride **42** is boiled with benzylamine in *n*-butanol, both chlorine atoms are substituted with the formation of the diamine **57** (yield 49%) [11, 12, 18].



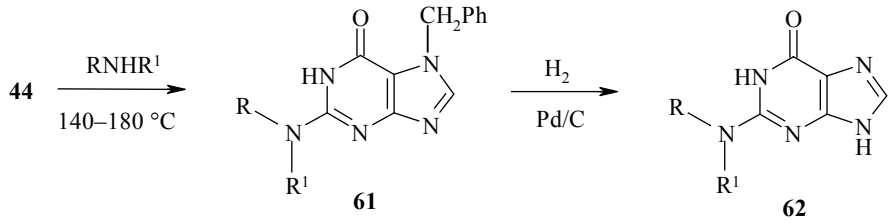
X = CH_2, O; Y = $(CH_2)_n$ (n = 1, 2, 5), CHMe, $CHCHMe_2$

The reaction of the industrial hypoxanthine **48** and guanine **49** with P_2S_5 in pyridine gave the medicinal products mercaptopurine **58a** (yield 70%) [12, 13, 23] and thioguanine **58b** (yield 26-27%) [12, 13, 24, 25] having antileucose activity [22].

The available thioxopurines **58a**,**b** were used as starting materials in the synthesis of the immunodepressant azathioprine **59** [22] (yield 85-88%) [12, 26, 27] and the new compound **60** (yield 79%), which had high immunodepressant activity in trials [12, 25, 28-30].

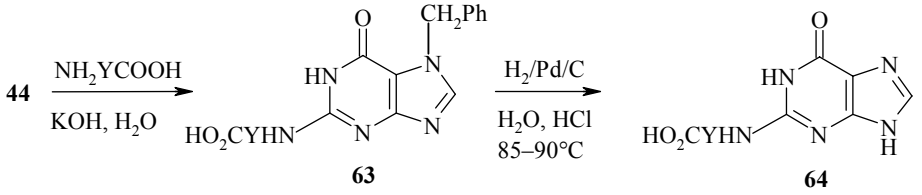


The reaction of 2-chloropurine **44** with primary and secondary amines gave the purines **61** (yields 67-92%), the hydrogenation of which led to a new synthesis of N(2)-alkyl(aryl, cycloalkyl)guanines **62** (yields 60-95%) [11, 12, 31, 32].



R = H, Alk; R^1 = Alk, Ph; NRR^1 = piperidyl, morpholyl

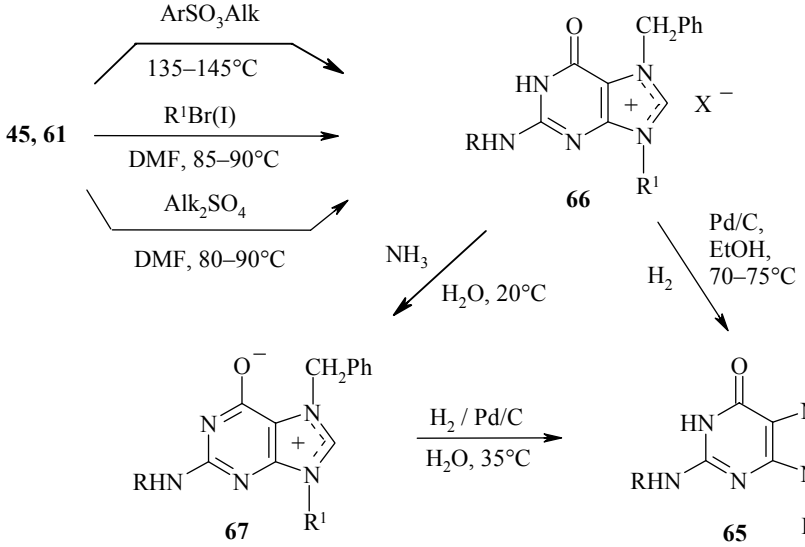
7-Benzyl-N(2)-guanylcarboxylic acids **63** (yields 70-95%) were synthesized by an analogous scheme by the reaction of the chloride **44** with α-, β-, γ-, and ε-amino acids, including the dibasic aspartic and glutamic acids, and the N(2)-guanylcarboxylic acids **64** (yields 61-90%) were obtained from them by hydrogenation [11, 12, 33].



Y = $(CH_2)_n$ (n = 1, 2, 3, 5), CHAlk (Ar), $CH(CH_2)_nCO_2H$ (n = 1, 2)

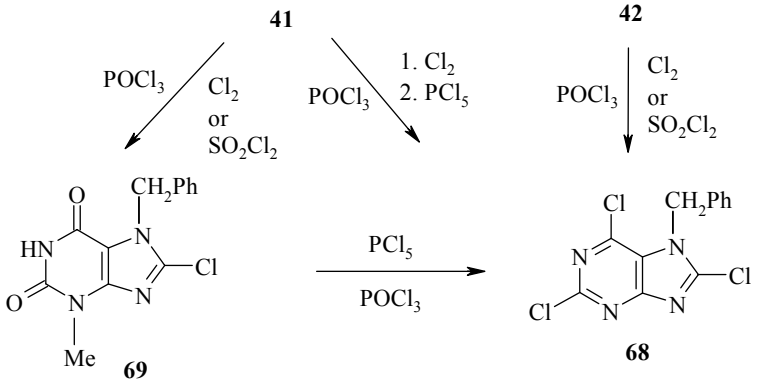
It is known that the alkylation of N(2),9-diacetyl- and 2,6,9-trimethylsilylguanines leads to the formation of mixtures of the 9-alkyl and 7-alkyl isomers, which can be separated by preparative chromatography on silica gel with large volumes of flammable solvents. The yields of the 9-substituted guanines are low [34-40].

In [11, 12, 41, 42] a new method for the production of 9-alkylguanines **65**, excluding the formation of the 7-alkyl isomers, was described. The method is based on the quaternization of 7-benzylguanine **45** and its N(2)-substituted derivatives **61** by alkyl halides, dialkyl sulfates, or arenesulfonate esters, resulting in the production of the quaternary salts **66** (yields 64-98%). The salts **66** were converted into the enol betaines **67** (yields 80-93%) by treatment with ammonia in aqueous solution. The catalytic hydrogenation of the quaternary salts **66** or enol betaines **67** leads to the 9-alkylguanines **65** (yields 50-76%) without the 7-isomers as impurities.

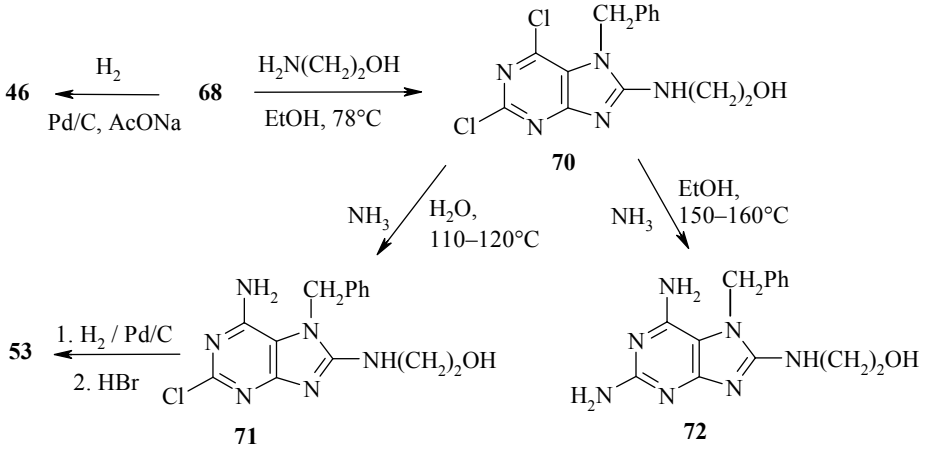


R = H, Alk Ar; RHN = NMe_2, $N(CH_2)_6$; R^1 = Alk, CH_2COOMe; Ar = Ph, 4-MeC_6H_4;
X = ClO_4, Br, $PhSO_3$, 4-$MeC_6H_4SO_3$

A study of the properties of 7-benzyl-2,6,8-trichloropurine (**68**), synthesized by chlorination of compounds **41** and **42** and 7-benzyl-8-chloro-3-methylxanthine (**69**) with chlorine, SO_2Cl_2, or PCl_5, was of scientific and practical interest. The yield of the chloride **69** was 76-78%, and the yield of the trichloride **68** was 87-93%. The previously described synthesis of compound **68** was very complicated [43].



It was established that the chlorine atom at position 8 is the most reactive in compound **68**, as in 7-methyltrichloropurine **1**. These properties of the trichloropurine **68** were utilized for preparative purposes in the synthesis of 8-amino-, 6,8-diamino-, and 2,6,8-triaminopurines **70**-**72** (yields 51-95%), purine **46** (yield 70-73%), and the medical product ethadene **53** (yield 65%) [11, 12, 44, 45].



As shown above, the use of 7-benzyl protection with the readily available 3-methylxanthine made it possible to develop new simple methods for the synthesis of a series of 6-, 2,6-, 6,8-, 2,6,8-, and 2,6,9-substituted purines. Under industrial conditions it is economically profitable to produce about 15 named chemical reagents, medical products, and agrochemical products by a combined scheme. In the search for new biologically active substances it was of interest to use 7-benzyl-substituted 3-methylxanthine, 2,6-dichloropurine, 2-chloroadenine, 2-chlorohypoxanthine, guanine, 2,6,8-trichloropurine, and 8-chloro-3-methylxanthine **41**-**45**, **68**, and **69** as starting materials [12].

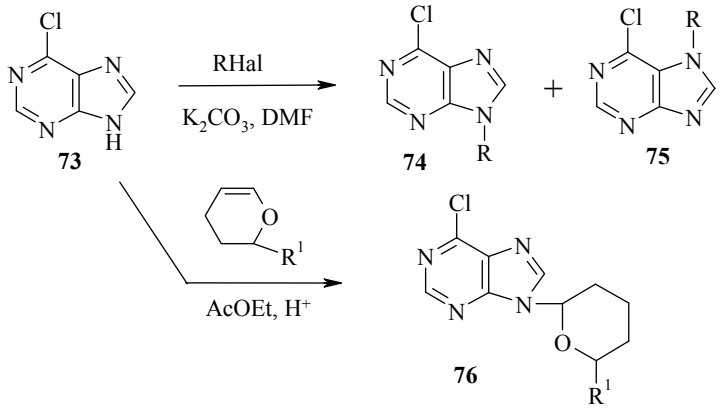
2. 6-CHLOROPURINE PROTECTION

Biologically active 9-alkyl(hydroxyalkyl)-substituted hypoxanthine, 6-thiopurine, adenine, and guanine, inaccessible by direct alkylation of the purine derivatives, were synthesized with 6-chloropurine protection.

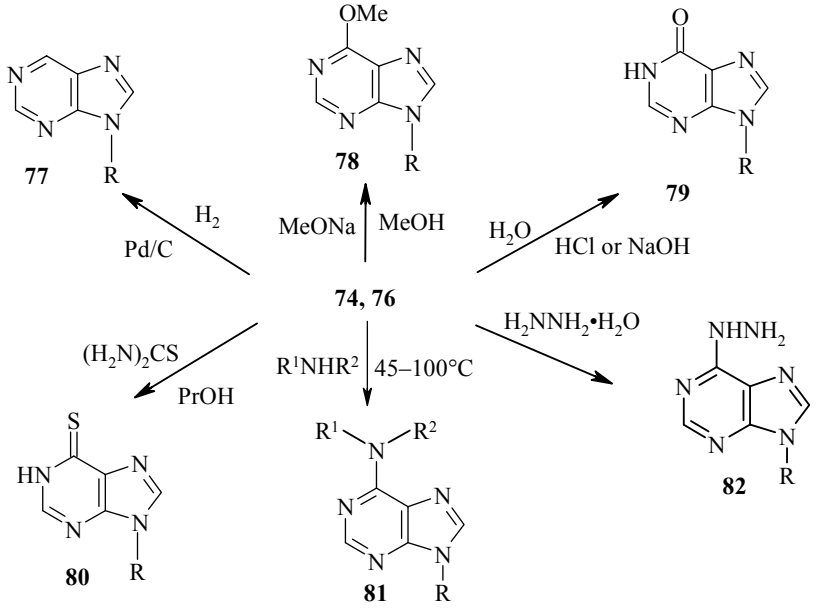
In [46-52] it was established that the alkylation of 6-chloropurine **73** with various halogen compounds in aprotic solvents (DMF, etc.) in the presence of anhydrous K_2CO_3 leads to mixtures of 9-alkyl- and 7-alkyl-6-chloropurines **74** and **75** with a preference for the 9-alkyl isomers (44-90%); the yield of the 7-isomers is 1-18% [46-49].

6-Chloro-9-tetrahydropyranylpurines **76** (yields 60-75%) were obtained by the reaction of the chloride **73** with 2,3-dihydropyrans in ethyl acetate in the presence of *p*-toluenesulfonic acid [53].

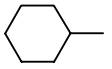
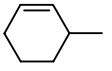
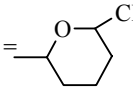
The alkylation of the thallium [54], silver [55], and mercury [56] salts of chloropurine **73** in DMF [54] or xylene [55, 56] leads to the 9-alkylpurines **74** [54-56].



R = Alk, $CH_2O(CH_2)$, *c*-C_6H_9, $(CH_2)_nOH$ (*n* = 2–4), $(CH_2)_mCOOAlk$ (*m* = 1, 2), $ArCH_2$; R^1 = H, CH_2OAc; Hal = Cl, Br, I



77, **79**–**82** R = Et, **77**–**80**, **82** R = $PhCH_2$, **77**, **81** R = CH_2COOEt, **81** R = CH_2CONH_2,

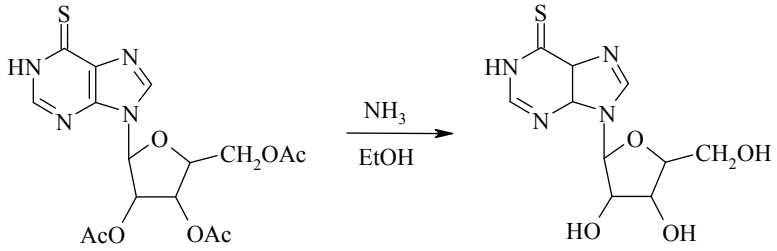
77 R =  , **79**, **80** R =  , **80**, **81** R = 

80 R = O-O-acylribofuranos-1-yl, **80**, **81** R = $(CH_2)_mCH(OEt)_2$ (*m* = 1, 2),
81 R = $(CH_2)_nOH$ (*n* = 2–4); R^1 = R^2 = H, Me, R^1 = H, R^2 = Alk, Ar, $NH(CH_2)_4NH_2$;
$R^1 + R^2 = (CH_2)_2$

Examples of the synthesis of purine derivatives on the basis of 6-chloropurines **74** and **76** are given above. Thus, the catalytic hydrogenation of 9-alkylchloropurines **74** and **76** gave 9-alkylpurines **77** [43, 44, 54], while nucleophilic reactions gave 9-substituted derivatives of 6-methoxypurine **78** [46], hypoxanthine **79** [39, 46, 47, 49-51, 57], 6-thiopurine **80** [46, 47, 49-51, 53, 55-57], 6-aminopurines **81** [39, 46, 52, 53, 57, 58], and 6-hydrazinopurine **82** [47, 57]. The yields of the purine derivatives **77**-**82** amount to 39-96% [46, 47, 53, 54].

In addition to thiourea [46, 47, 55, 57] NaHS [53], MeCOSK [55], and $(COSK)_2$ [56] were used in the synthesis of the thioxo compounds **80** by substitution of the chlorine atom by an SH group.

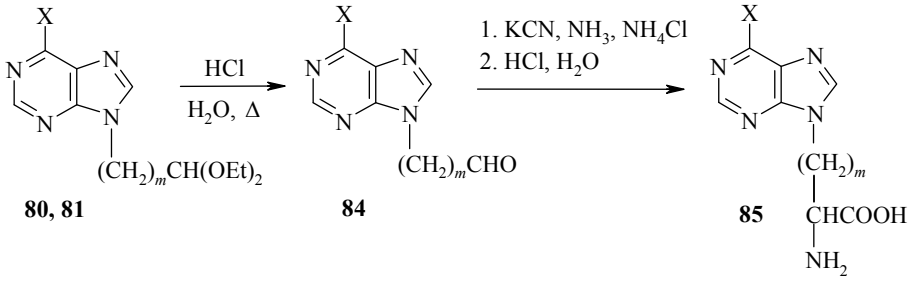
Some derivatives of **80** and **81** were subjected to further transformations in the search for antitumor agents. Thus, hydrolysis of the acylnucleoside **80** (R = 2,3,5-tri-O-acetylribofuranos-1-yl) in an alcohol solution of ammonia gave 9-(β-D-ribofuranos-1-yl)-6-thioxopurine **83** (yield 60%) [55].



80 **83**

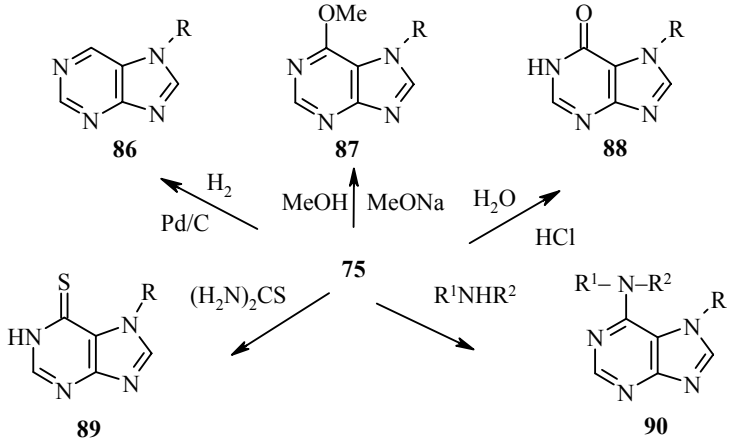
2-Amino-9-(β-D-ribofuranos-1-yl)-6-thioxopurine was obtained by a similar method [55, 56].

The 6-amino- and 6-mercaptopurinyl-9-α-amino acids **85** were synthesized from the acetals of **80** and **81** (R = $(CH_2)_mCH(OEt)_2$, m = 1, 2; X = SH, NH_2) through the intermediate aldehydes **84** by the Strecker–Zelinsky–Stadnikov cyanohydrin method [50, 51].



80, 81 **84** **85**

X = NH_2, SH; m = 1, 2



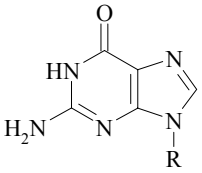
86 **87** **88**

89 **90**

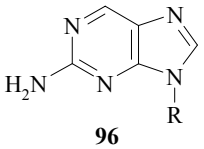
86–90 R = $PhCH_2$, **88–90** R = 4-$O_2NC_6H_4CH_2$; (**90** R = $(CH_2)_3OH$ at $R^1 = R^2$ = H; **90** $R^1 = R^2$ = H, Me)

7-Alkyl(aralkyl)-6-chloropurines **75** enter into the same reactions as their 9-isomers **74**. 7-Alkyl-(aralkyl)purines **86** and their 6-substituted derivatives **87-90** were obtained with yields of 57-93% [47-49].

6-Chloropurine protection was used for the synthesis of the acyclic analogs of guanosine nucleoside **91**, which have antiviral activity [22]: acyclovir, ganciclovir, buciclovir, and penciclovir, and also famciclovir – a derivative of 2-aminopurine (**92-96**, Table 1).

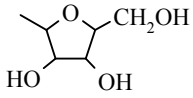


91–95



96

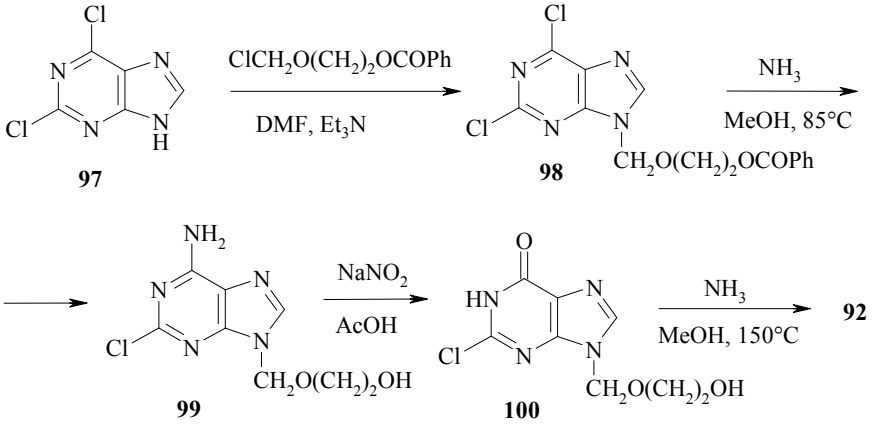
TABLE 1. Guanosine **91** and its Acyclic Analogs **92-96**

Com-pound	Name	R	Reference
91	Guanosine		[1, 2]
92	Acyclovir	$CH_2OCH_2CH_2OH$	[37–40, 59, 63–68]
92a	Valacyclovir	$CH_2OCH_2CH_2OOCCHCHMe_2$ (NH$_2$)	[59]
93	Ganciclovir	$CH_2OCH(CH_2OH)_2$	[34, 35, 38, 39, 60]
94	Buciclovir	$CH_2CH_2CH(OH)CH_2OH$	[61]
95	Penciclovir	$CH_2CH_2CH(CH_2OH)_2$	[39, 62]
96	Famciclovir	$CH_2CH_2CH(CH_2OCOMe)_2$	[62]

G. Elion was awarded a Nobel prize for the creation of acyclovir.

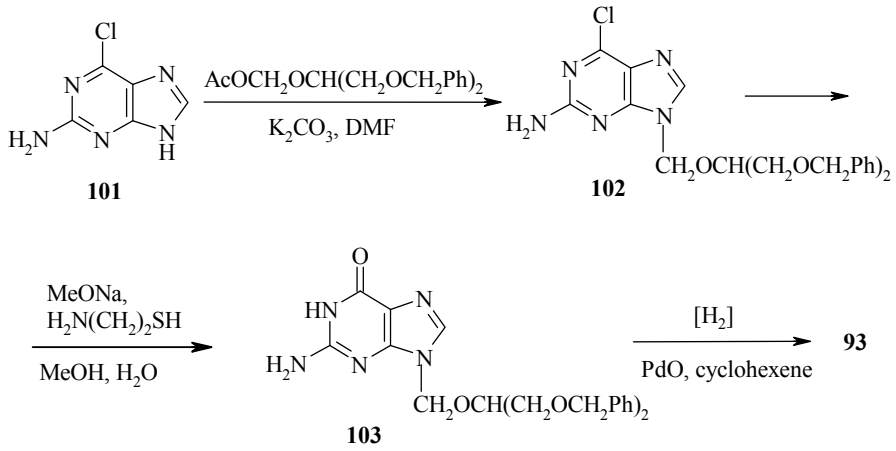
The principal preparative methods for the synthesis of medical preparations **92-96** were presented in the reviews [39, 59-62]. Several methods have been proposed for the production of acyclovir **92** – from 2,6-dichloropurine [59, 63], 2-chloro-6-iodo-purine [64], guanine [36-40, 58, 65-67], and 2-amino-6-chloropurine [68].

The first synthesis of acyclovir **92** from 2,6-dichloropurine (**97**) was realized according to the scheme [59, 63]:

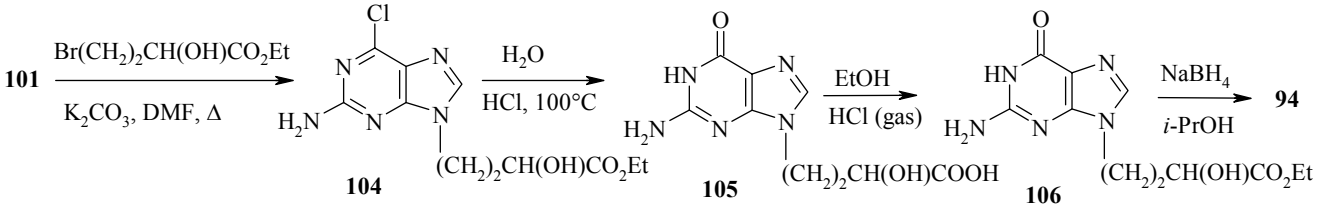


Simpler methods for the synthesis of acyclovir will be discussed below.

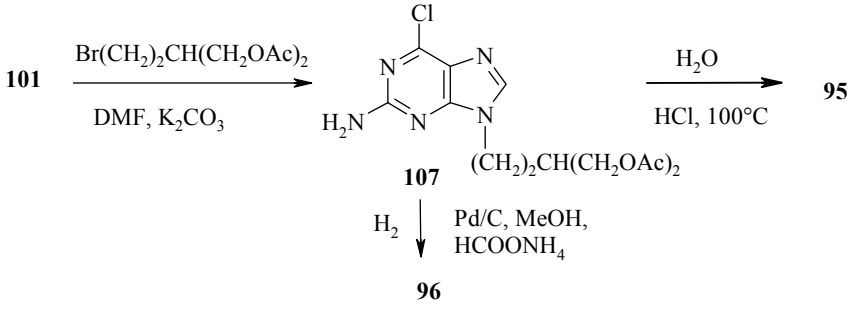
Ganciclovir **93** was produced from 2-amino-6-chloropurine **101** [34].



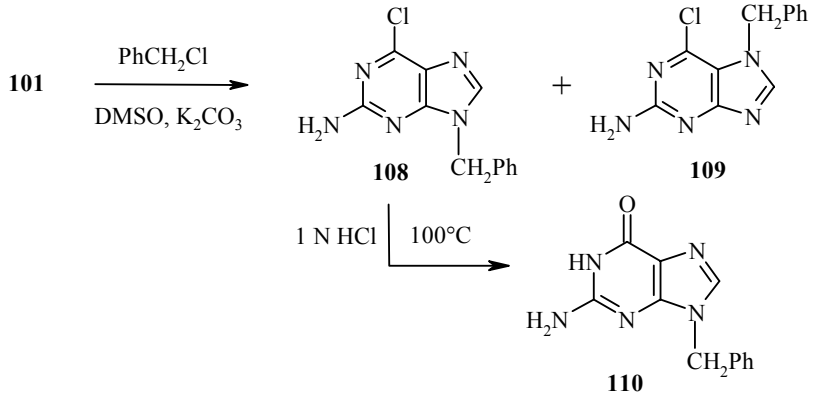
The synthesis of buciclovir **94** from the chloro amine **101** consists of four stages [60].



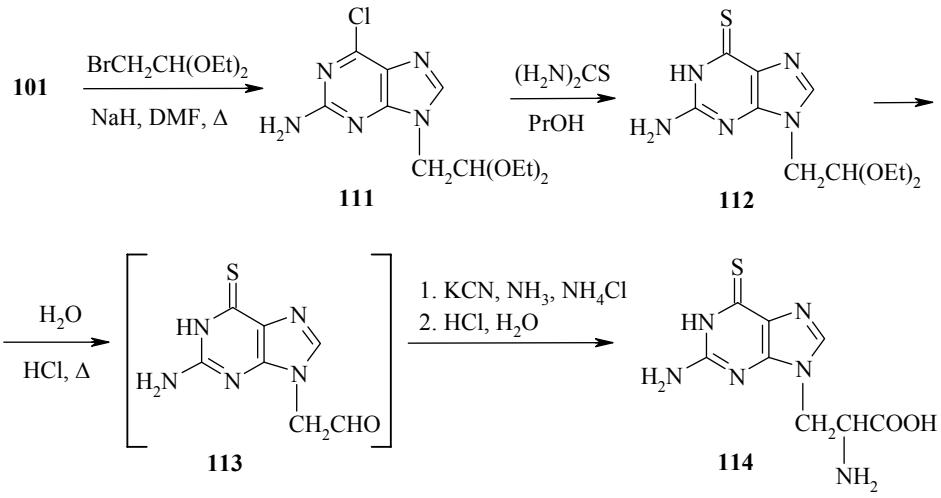
Penciclovir **95** and famciclovir **96** were obtained from the chloro amine **101** according to the combined scheme [62]:



Benzylation of the chloro amine **101** with benzyl chloride in dimethyl sulfoxide in the presence of K_2CO_3 leads to a mixture of isomers **108** and **109** with yields of 41 and 24% respectively. 9-Benzylguanine **110** was obtained by hydrolysis of the isomer **108** (yield 85%) [69].



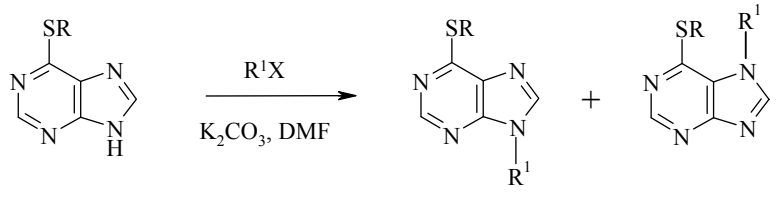
2-Amino-6-thioxopurinyl-9-α-alanine **114** was synthesized from the chloro amine **101** by the cyanohydrin method through the intermediate acetals **111** and **112** and the aldehyde **113**. The yields of compounds **111**, **112**, and **114** were 28, 72, and 50% respectively [70].



3. 6-ALKYL(ARALKYL)THIO PROTECTION

6-Alkyl(aralkyl)thio protection is used in the synthesis of 9-substituted purines, hypoxanthines, 6-thio- and 6-aminopurines which difficult to obtain by other methods.

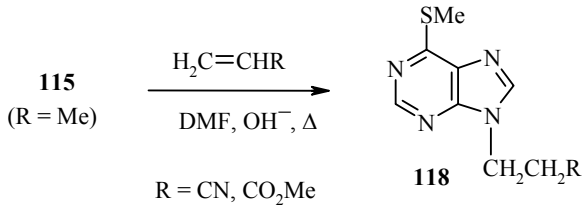
The alkylation of 6-alkyl(aralkyl)thiopurines **115** with 1-bromo-2-diethoxyethane [70], alkyl (aralkyl) halides, halo ketones, bromosteroids and 4-bromobenzenesulfonates of steroidal alcohols [71-73], the esters of haloacetic acids [74-76], and O-acetylribofuranosyl chloride [77] in an aprotic solvent in the presence of anhydrous K_2CO_3 leads to the formation of a mixture of isomers **116** and **117** with a preference for the 9-isomers **116** (yields 29-80%). The yields of the 7-isomers **117** are 5-13% [70, 73, 75].



R = Alk, CH_2Ar, $CHPh_2$; R^1 = Alk, Aralk, $CH_2CH(OEt)_2$, $ArCOCH_2$, steroid $–COCH_2$, O-acylribofuranosyl, $CH_2CONHCH(R^2)COOR^3$ (R^2 = H, Alk, CH_2Ar; R^3 = Et, $PhCH_2$);
X = Cl, Br, I, 4-$BrC_6H_4SO_2$

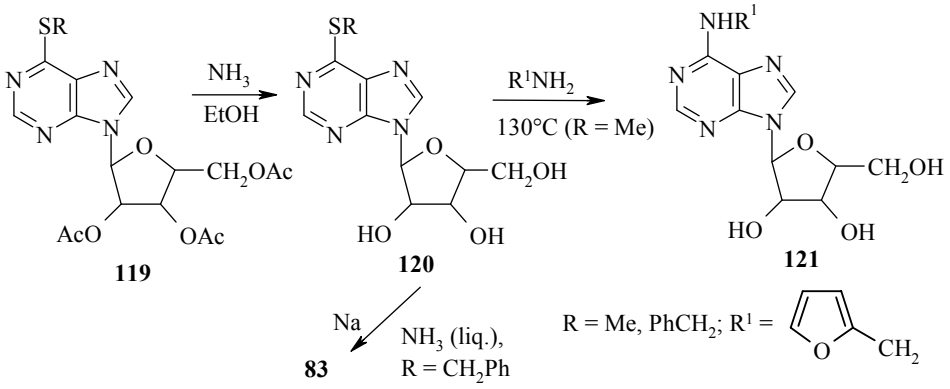
Compounds of the **116** type were also obtained by the reaction of the mercury salt of 6-methylthiopurine [78] and the silver salt of 6-benzylthiopurine [55] with O-acetylribofuranosyl chloride in xylene [55, 78].

The reaction of 6-methylthiopurine **115** (R = Me) with acrylonitrile and methyl acrylate in DMF in the presence of Rodionov's catalyst ($Ph_3N^+MeOH^-$) takes place like the β-addition of nucleophiles with the formation of the purines **118** (yields 35-74%) [75].

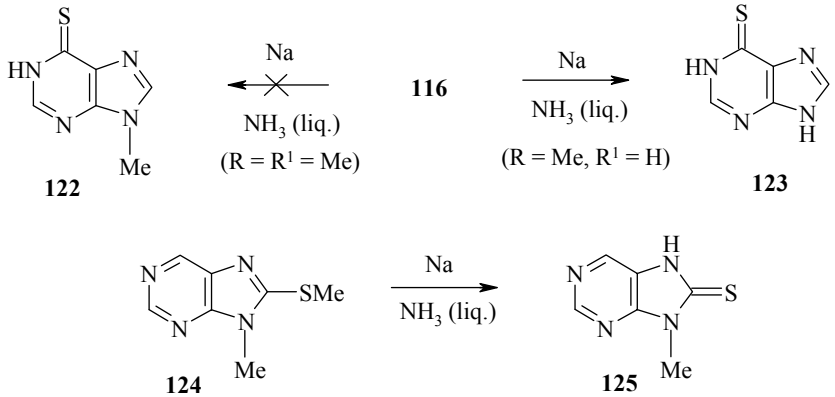


The transformations of the obtained 6-alkyl(aralkyl)thiopurines were studied in a series of papers. Thus, 6-methyl(benzyl)thionucleosides **120** were obtained by the hydrolysis of O-acylnucleosides **119** in an alcoholic solution of NH_3 [55, 78]. 9-(β-D-Ribofuranosyl)-6-thioxopurine **83** as a potential antitumor agent was obtained by the debenzylation of compound **120** (R = $PhCH_2$) by the action of sodium in liquid NH_3 [55]. Its 2-amino analog was obtained by a similar scheme [55].

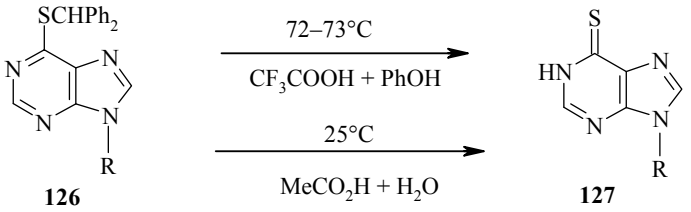
9-Ribofuranosylkinetin **121** was obtained by the reaction of the nucleoside **120** (R = Me) with 2-furfurylamine [78].



An attempt at the demetallation of 9-methyl-6-methylthiopurine **116** (R = R^1 = Me) to 9-methyl-6-thioxopurine **122** by the action of sodium in liquid NH_3 was unsuccessful. The reaction did not take place although 6-methylthiopurine is transformed under these conditions into 6-thioxopurine **123** with a yield of 40% while 9-methyl-8-methylthiopurine **124** is converted into 9-methyl-8-thioxopurine **125** with almost quantitative yield [79].

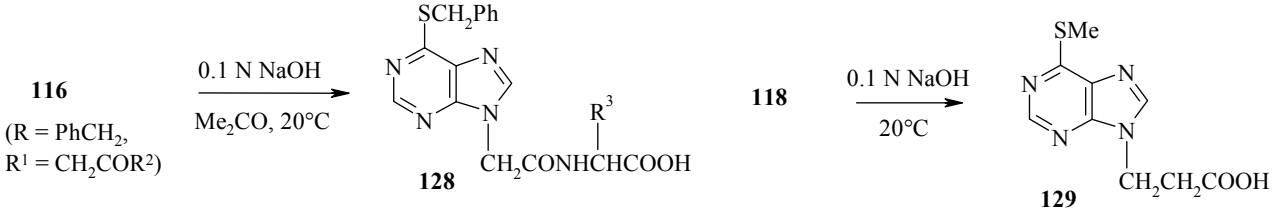


Unlike demetallation and debenzylation diphenylmethyl protection is removed under mild conditions – by briefly boiling (15-30 min) 6-diphenylmethylthio-9-alkyl(steroid)purines **126** in trifluoroacetic acid in the presence of phenol as catalyst. This reaction also takes place in aqueous acetic acid at 25°C, but the reaction time is increased to four days while the yield of compounds **127** is reduced to 60% [72, 73].



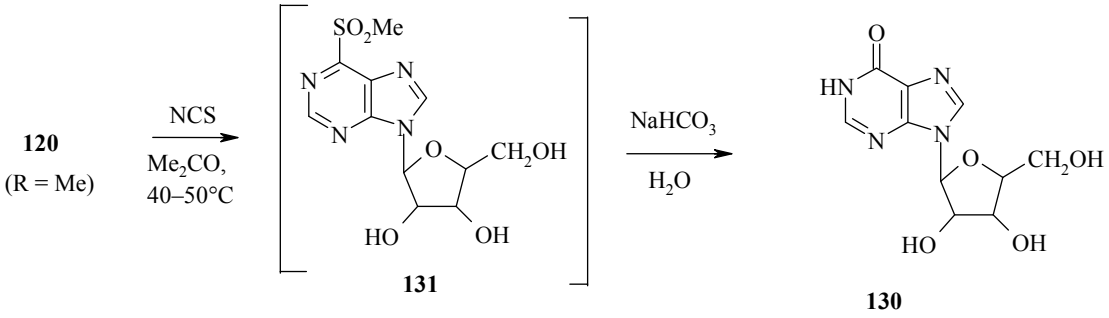
R = Et, $PhCH_2$, 4-$ClC_6H_4COCH_2$, steroid residues

Anticipating the more recent data on the high biological activity of the nucleosides of 6-methyl-, 6-benzyl-, or 6-(4-nitrobenzyl)thiopurines [80-87], the authors of [74, 75] kept the substituents at the sulfur atom at position 6 (6-SMe, 6-SCH_2Ph). The substituents at position 9 of the purine ring were changed, and here 6-benzylthio-9-acetylamino acids **128** (yields 62-75%) and 6-methylthio-9-β-propionic acid **129** (yields 74-87%) were obtained [75].

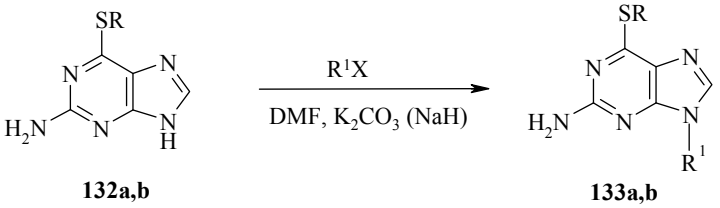


R^2 = $NHCHR^3COOR^4$; R^3 = H, Alk, $ArCH_2$; R^4 = Et, $PhCH_2$

An attempt at the hydrolysis of the nucleoside **120** (R = Me) to 9-(β-ribofuranosyl)hypoxanthine (inosine) **130** was unsuccessful. Oxidation of the sulfide **120** to the sulfone **131** with N-chlorosuccinimide (NCS) took place with simultaneous hydrolysis of the SO_2Me group and the formation of inosine **130** [77].

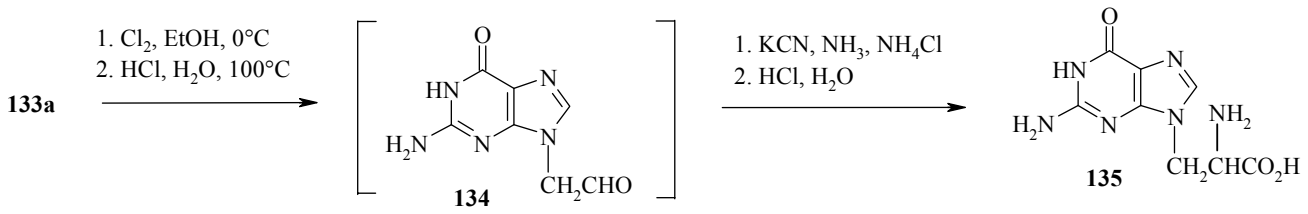


The reaction of 2-amino-6-methyl(diphenylmethyl)thiopurines **132a**,**b** with 1-bromo-2-diethoxyethane [70] and ethyl iodide [88] in dimethyl formamide in the presence of sodium hydride [70] or potassium carbonate [88] leads to 9-substituted 6-alkyl(aralkyl)thiopurines **133a**,**b** (yields 23-69%).

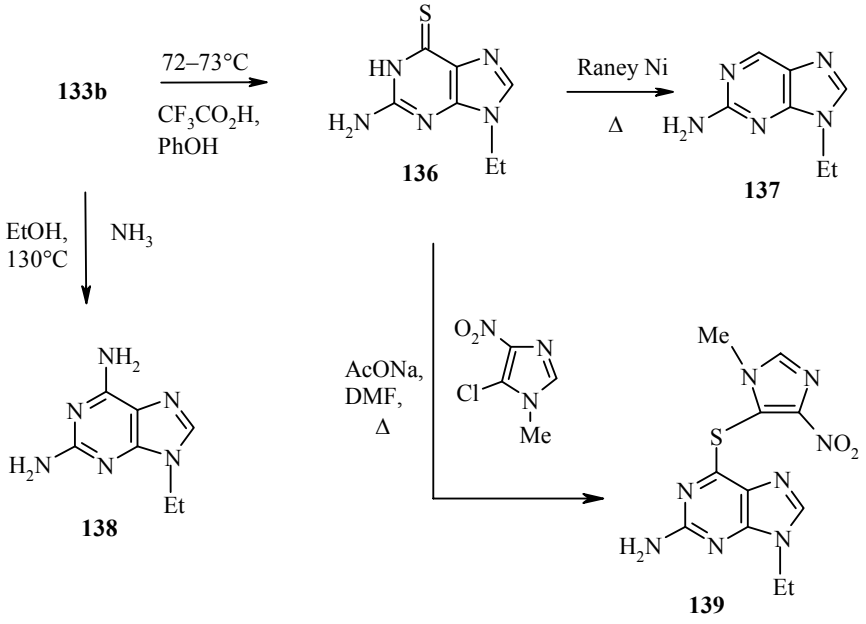


a R = Me, R^1 = $CH_2CH(OEt)_2$, X = Br ; **b** R = $CHPh_2$, R^1 = Et, X = I

Guanyl-9-α-alanine **135** was synthesized with a yield of 41% from compound **133a** by the cyanohydrin method through the intermediate aldehyde **134** [70].



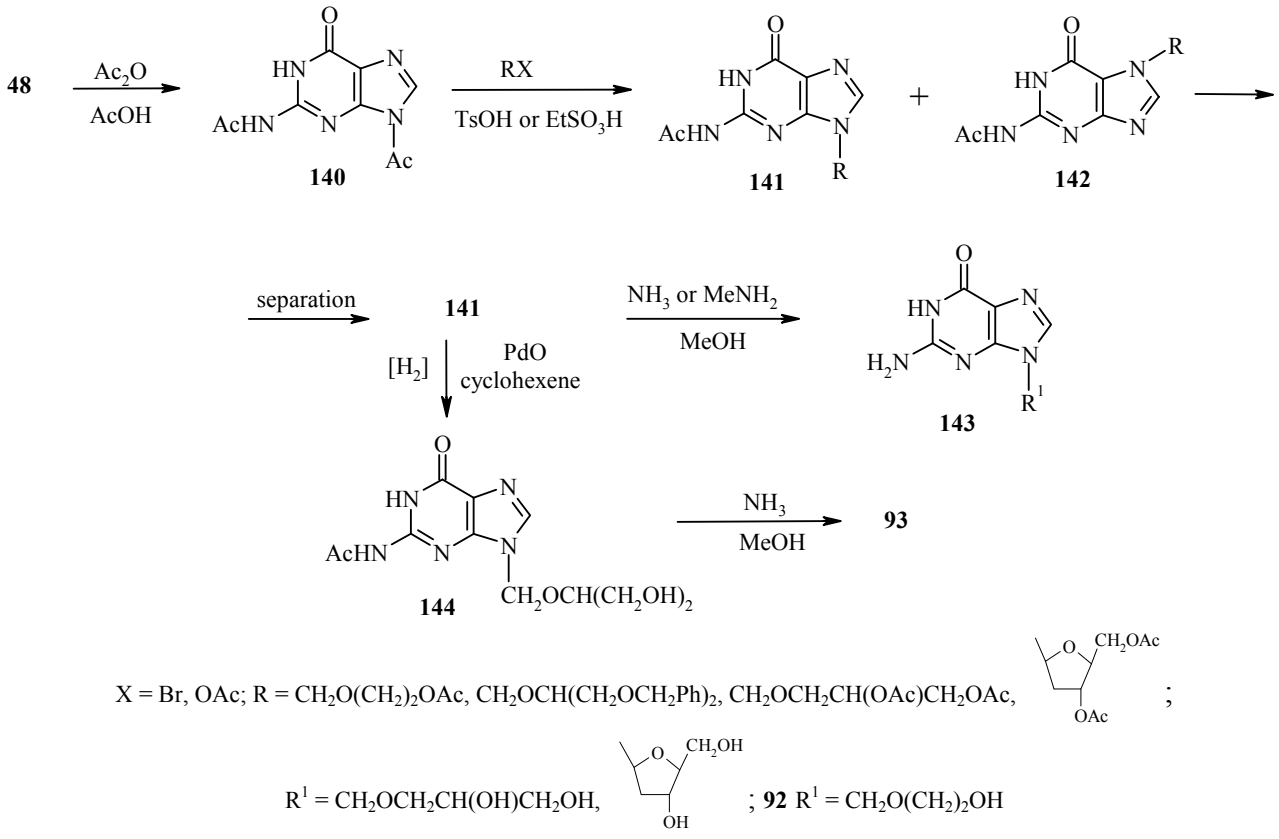
When boiled in trifluoroacetic acid in the presence of phenol compound **133b** is hydrolyzed to 9-ethylthioxoguanine **136**, the desulfurization of which with Raney nickel leads to 2-amino-9-ethylpurine **137**. 2,6-Diamino-9-ethylpurine **138** and 2-amino-6-(1-methyl-4-nitroimidazol-5-ylthio)-9-ethylpurine **139** were synthesized by the reaction of the thioether **133b** with ammonia and of the thioxopurine **136** with 5-chloro-1-methyl-4-nitroimidazole. The yields of compounds **136-139** were 81, 45, 85, and 80% respectively [88].



4. N(2),9-DIACETYL PROTECTION

This protection was used in the synthesis of acycloguanosines from guanine **48**, treatment of which with acetic anhydride gave N(2),9-diacetylguanine **140** (yield 76%) [40]. The reaction of the diacetate **140** with O-acylhalo sugars and α,ω-diacyl alcohols in the presence of alkane(arene)sulfonic acid as catalyst leads to a mixture of the isomers **141** and **142** (yields 60-92%) [35, 37-40]. The N- and O-acyl protecting groups are removed by treatment of the 9-isomers **141** with ammonia or methylamine in methanol, and the acycloguanosines **143** (yields 47-86%) [37, 38, 40], including acyclovir **92** (yield 84-86%) [37, 38, 40], and also 2'-deoxyguanosine [38] are formed.

For the production of ganciclovir **93** the 9-isomer **141** (R = $CH_2OCH(CH_2OCH_2Ph)_2$) is debenzylated to N(2)-acetylganciclovir **144**, hydrolysis of which gives the product **93** (yield 94%) [35, 38].



An attempt at the hydrolysis of the mixture of acyl isomers **141** and **142** (R = $CH_2O(CH)_2Oac$) led to a mixture of acyclovir **92** and its 7-isomer, which could not be separated [37].

5. TRIALKYLSILYL PROTECTION

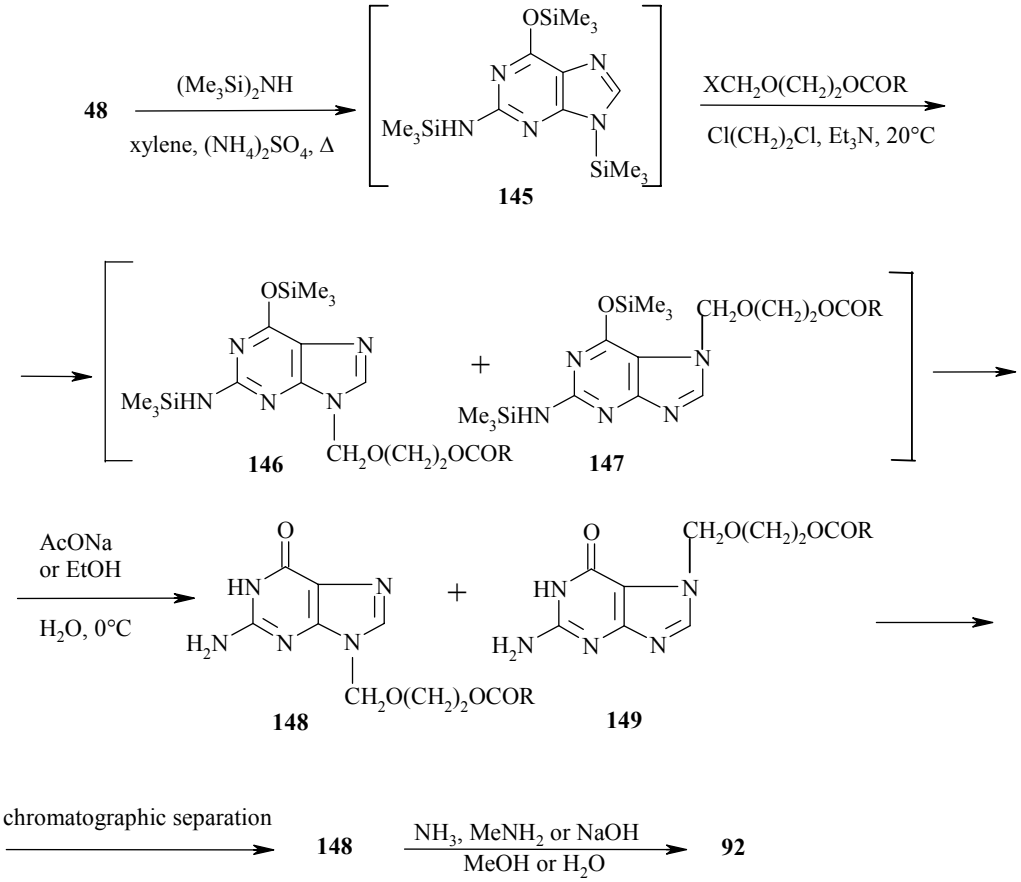
Trialkylsilyl protection is widely used in the synthesis of the nucleosides and nucleotides examined in detail in the review [89] and the monograph [90] and also the acyclic analogs of guanosine.

The essential feature of this protection involves trialkylsilylation of the purine bases, which takes place both at the functional groups of the pyrimidine part of the molecule and at the NH group of the imidazole ring. Trialkylchlorosilanes, trialkylaminosilanes, hexaalkyldisilazanes, and N,O-di(trialkylsilyl)acetamides have been described as silylating agents [89, 90]. The readily available trimethylchlorosilane (TMCS) and hexamethyldisilazane (HMDS) have been used most. In the first case the reaction is conducted in the presence of a base (triethylamine, pyridine), and in the second it is conducted in an excess of HMDS with heat in the presence of ammonium sulfate as catalyst, followed by removal of the reagent under vacuum.

The synthesized silyl-protected purine bases (yields 70-90%) enter into reaction with O-acyl(benzyl)-protected halo sugars or halo alcohols when heated without a solvent or in an organic solvent (benzene, acetonitrile, etc.) often in the presence of a salt of a heavy metal ($AgClO_4$, $HgCl_2$, et. al) as catalyst.

The trimethylsilyl and O-acyl protection is removed from the obtained intermediate silyl-containing compounds by treatment with aqueous ethanol or with sodium acetate in water and then with ammonia or sodium methoxide in water. The benzyl protection is removed by catalytic hydrogenation of the compounds in the presence of palladium. As a result mixtures of isomeric compounds are usually obtained, and they are

separated by preparative chromatography. The synthesis of acyclovir **92** from the guanine **48** through 2,6,9-tri-(trimethylsilyl)guanine **145** was described in a series of papers [37, 59, 66, 67]. Compounds **145-147** are not isolated in the pure form but are subjected to alkylation followed by removal of the silyl protection. This gives a mixture of the acyl derivatives **148** and **149**, from which the 9-isomer **148** is isolated, and the product **92** is obtained by deacylation (yield 84-86%). Deacylation of the mixture of compounds **148** and **149** leads to a mixture of acyclovir **92** and its 7-isomer in a ratio of 9:1, which could not be separated [37].



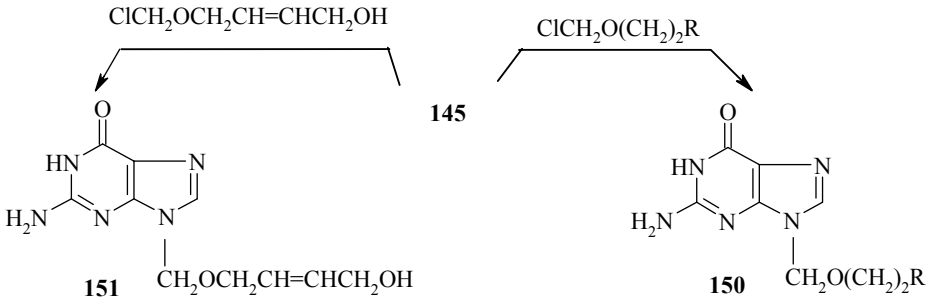
X = Cl, Br; R = Me, Ph

The synthesis of acyclovir from 2-acetyl- and N(2),9-diacetylguanines through N(2)-acetyl-2,6,9-tri-(trimethylsilyl)guanine was less successful with respect to the yield of the desired compound **92** and the large content of the 7-isomer [37].

A similar pattern – the formation of significant amounts of the side 7-isomer – was observed during the synthesis of ganciclovir **93** from guanine and 2-acetylguanine through their trimethylsilyl derivatives [67].

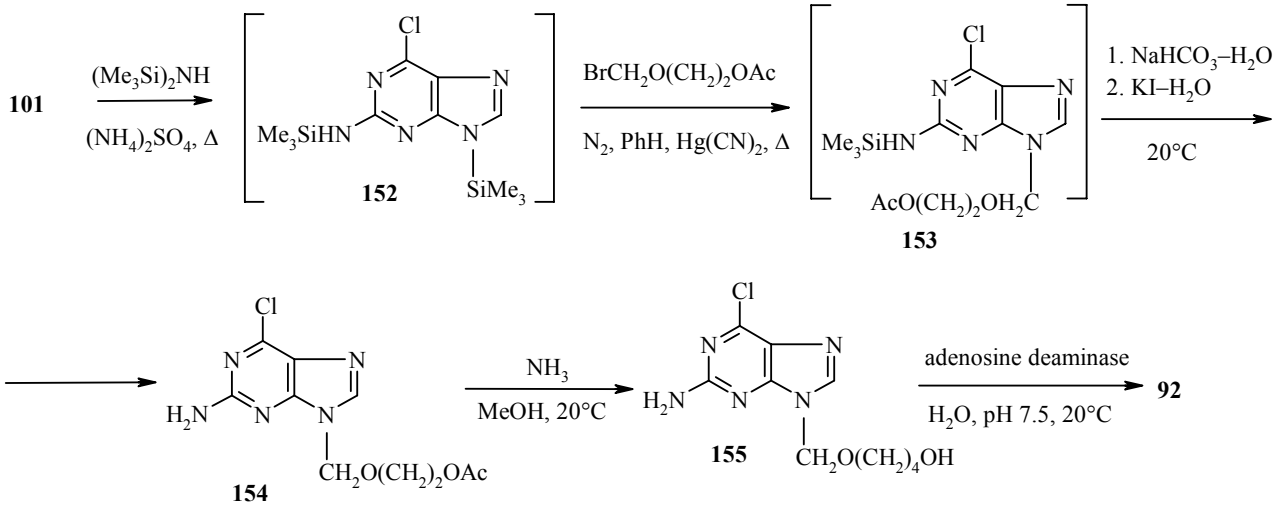
The authors [66] proposed an improved synthesis of compounds **92** and **93** by realizing the alkylation of silylguanine **145** in the presence of tetrabutylammonium fluoride, leading to an increased yield of the 9-alkyl-guanines **103** and **148**. Acyclovir **92** and ganciclovir **93** were obtained with yields of 90-92% by debenzoylation of compound **148** (R = Ph) and debenzylation of compound **103** by the methods described above.

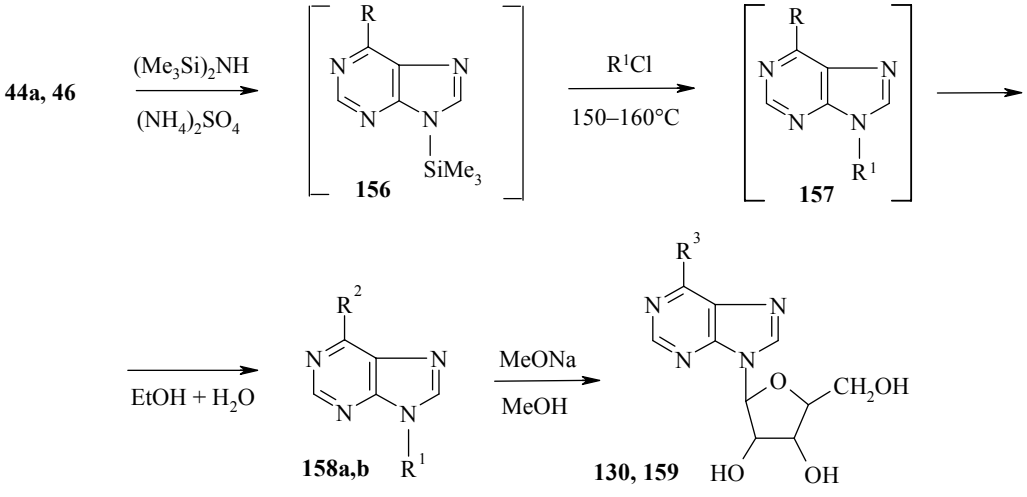
The N-isosteres of acyclovir **150** (yields 53-90%) [91] and 9-(6-hydroxy-2-oxa-4-hexenyl)guanine **151** (yield 32%) [92], exhibiting antiviral activity, were synthesized from guanine through silylguanine **145**.

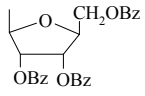


R = NH_2, NHAc, $NH(CH_2)_2OH$, $O(CH_2)_2NH_2$

High yields at all stages (~87%) were achieved during the synthesis of acyclovir **92** from aminochloropurine **101** through its 2,9-disilyl derivative **132** using enzymatic hydrolysis of the intermediate compound **155** at the last stage [68].





R = $BzNSiMe_3$, $OSiMe_3$; R^1 =  ; R^2 = NHBz, OH; **130** R^3 = OH,

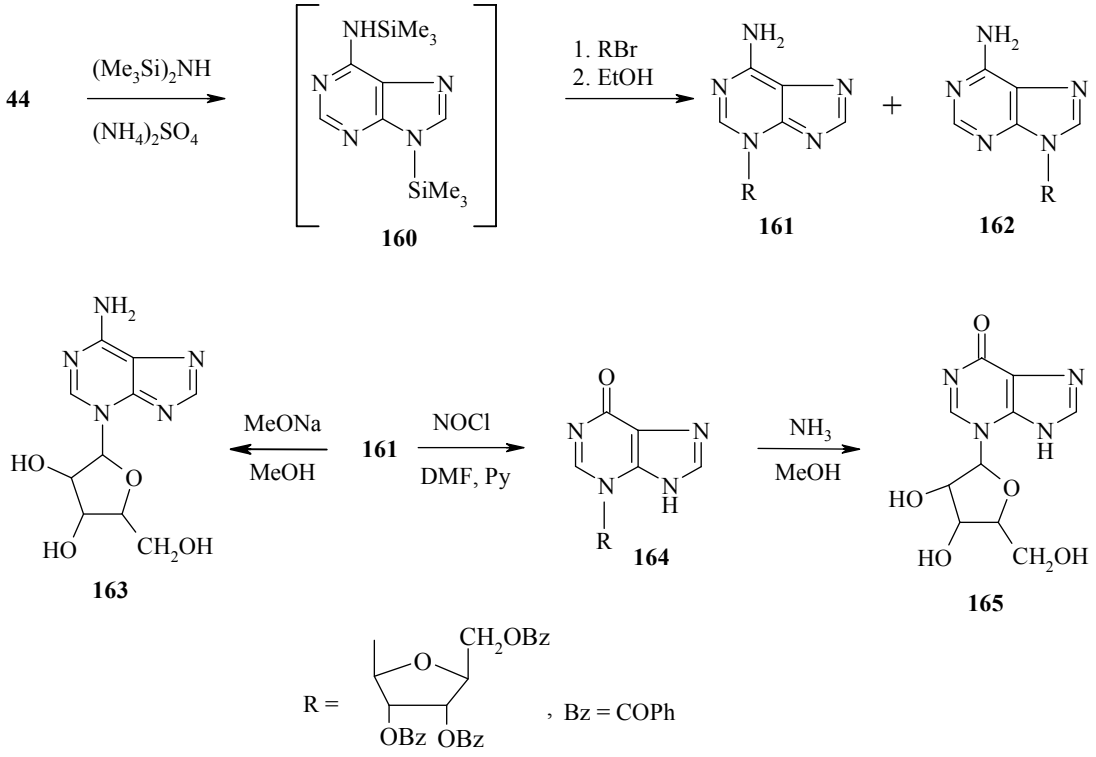
159 R^3 = NH_2; Bz = COPh

Ganciclovir **93** was synthesized from silylpurine **152** by an analogous scheme with higher yields (70-80%) of the intermediate compounds **102** and **103** than during the synthesis of this product from the chloro amine **101** without silyl protection [34].

Inosine **130** (R^3 = OH) and adenosine **159** (R^3 = NH_2) were synthesized with high yields (70-80%) by the silyl method from N(6)-benzoyladenine **44a** and hypoxanthine **46** by condensation of the silylpurines **156** with 2,3,5-tri-O-benzoylribofuranosyl chloride at 150-160°C followed by desilylation and debenzoylation of the intermediate compounds **157** and **158** [93].

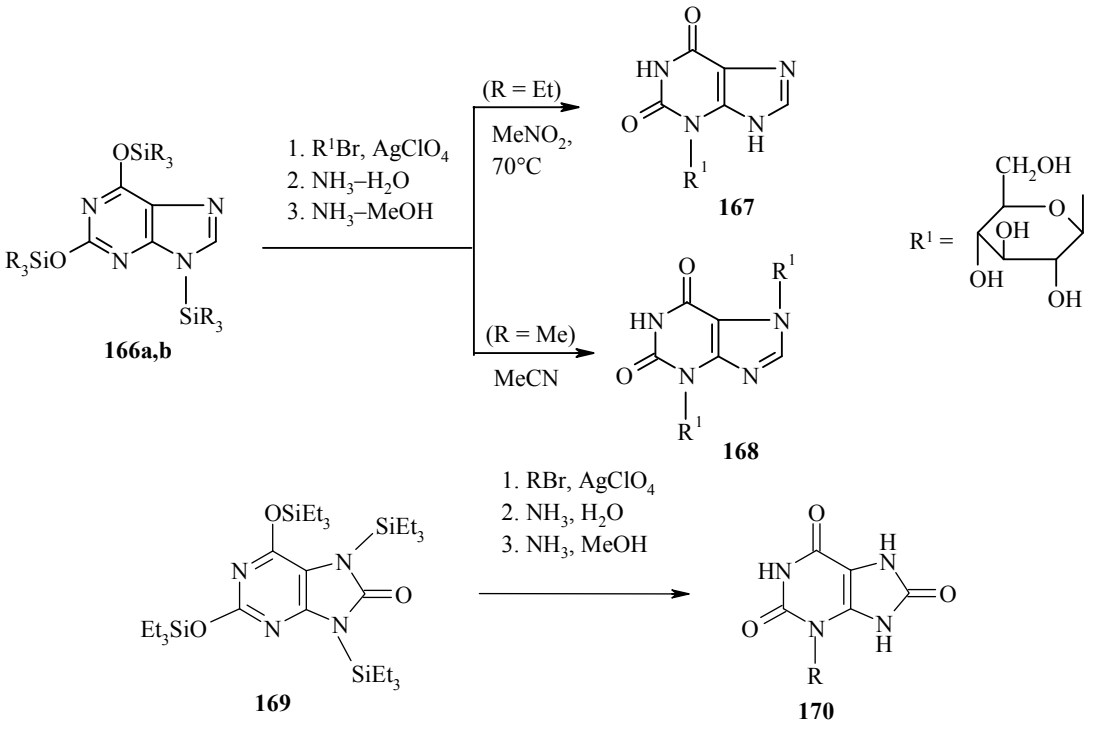
The reaction of silylpurine **156** (with R = $PhCONSiMe_3$) with 2,3,5-tri-O-benzoylribofuranosyl bromide in benzene in the presence of $HgBr_2$ at 20°C leads to a mixture of adenosine **159** and its 7-β isomer in a ratio of 57:43 [94, 95].

The condensation of 6,9-di(trimethylsilyl)adenine **160** with 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide in acetonitrile leads to a mixture of the 3-β-nucleoside **161** (yield 26-27%) and 9-β-nucleoside **162** (yield 10-18%). Hydrolysis of the nucleoside **161** by the action of sodium methoxide in methanol gave 3-β-D-ribofuranosyladenine **163** (yield 87%). The nucleoside **164** (yield 75%) was synthesized by treatment of the nucleoside **161** with nitrosyl chloride, and 3-β-D-ribofuranosylhypoxanthine (yield 91%) was obtained from the product by debenzoylation with ammonia in methanol [96].



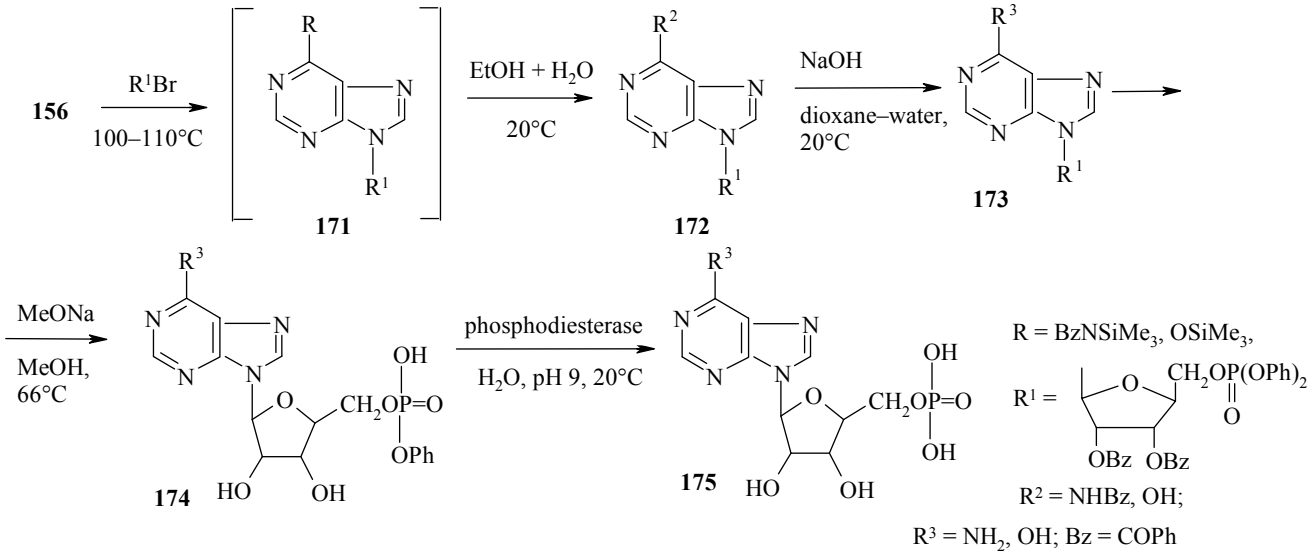
In the reaction of 2,6,9-tri(triethylsilyl)xanthine **166a** with acetobromoglucose in nitromethane in the presence of $AgClO_4$ 3-β-D-glucopyranosylxanthine **167** was obtained [97]. The same reaction with 2,6,9-tri-(trimethylsilyl)xanthine **166b** in acetonitrile led to the 3,7-β-D-dinucleoside **168** [98].

The reaction of 2,6,7,9-tetra(triethylsilyl)uric acid **169** in toluene in the presence of $AgClO_4$ leads to 3-β-nucleosides with yields of 56-90% irrespective of the structure of the O-acylhalo sugar [97].



R = β-D-glucopyranos-1-yl, β-D-ribofuranos-1-yl

A general method for the synthesis of nucleotides is phosphorylation of protected nucleosides. With silyl protection it is possible to produce nucleotides by the condensation of silylpurines with phosphoryl derivatives of sugars. Thus, the fusion of silylpurines **156** with 5-diphenylphosphoryl-2,3-di-O-benzoyl-D-ribofuranosyl bromide at 100-110°C gave 9-substituted silylpurines **171** [99, 100]. Treatment of the products with aqueous ethanol and then with NaOH in aqueous dioxane and with sodium methoxide in methanol gave compounds **174**. Hydrolysis of these esters by the action of phosphodiesterase in a buffer solution at pH 9 led to the production of 9-β-D-ribofuranosyl 5'-phosphates of adenine (5'-AMP) and hypoxanthine **175** (IMP). The yields of compounds **172-175** amounted to 38-59, 97, 88, and 39-42% respectively [99-101].



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