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To the memory of Academician A. Krayevsky

Synthesis of Thymidine Derivatives as Potential Pharmaceuticals against HIV/AIDS Infection*

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Abstract—Data on preparation methods for 3'-modified oxythymidines are summarized and systematized. A synthesis tree is presented permitting a selection of rational schemes for thymidine derivatives preparation, in particular those that can be potential anti-HIV/AIDS drugs.

I. INTRODUCTION

Crick and Watson discovery produced a powerful impact on the development of the nucleoside chemistry. Tens of reviews and thousands of original papers treat these unique biological and chemical objects. A special journal on this subject, Nucleotides & Nucleosides, has been published since 1981 that covers the most recent developments and discoveries in the chemistry and biochemistry of nucleosides and nucleotides. Since the middle of nineteen eighties a new trend appeared in the nucleoside chemistry for among the synthetic analogs of the natural nucleosides were discovered and put in production by the pharmaceutical industry the medicines against HIV infection. Their role in the cell metabolism consists in the termination of the chain elongation of the proviral DNA. The latter process occurs on the HIV *m*-RNA matrix and is governed by a highly specific viral enzyme reverse transcriptase (revertase) [1–4]. Therefore the drugs of this group were named NARTIs (nucleoside analogs of reverse transcriptase inhibitors) [5,6]. In the mentioned abnormal nucleoside the hydroxy group in 3' position can be replaced by a quasipharmacophore, e.g., azide group, as in AZT (3'-azido-2',3'-dideoxythymidine), or be simply removed as in d_4T (2',3'-dideoxy-2',3'-didehydrothymidine) [7].

The first preparation of the NARTIs group that since 1987 is firmly established on the market of the anti-HIV/ AIDS drugs is the 3'-azido-2',3'-dideoxythymidine (AZT, Retrovir). The screening of the biological activity and the problems of the clinical application of the AZT and the NARTIs of the next generation are extensively discussed in numerous publications [6, 8, 9–14] and on special Internet sites. At the same tame no comprehensive review appeared as yet on the chemical syntheses of the compounds that are extensively developed meeting the request of the molecular biology and medicine.

In the present paper are reviewed the publications on the synthesis of thymidine and its functional derivatives, potential ant-AIDS drugs, and the most important precursors thereof. We attempted to present

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also the preparation methods for 3'-substituted thymidines in a systematic form of a "synthesis tree".

Some among the studies reviewed were published before the discovery of the HIV virus by Gallo and Montagner (1984). However these fundamental investigations obviously play an important part in the strategy and tactics of the modern synthesis of the anti-HIV drugs.

II. HIV LIFE CYCLE

The modern strategy for synthesis of the anti-AIDS drugs is based on the knowledge of the structure and life cycle of the HIV virion. In its internal cavity are located two identical RNA molecules each containing about 5700 nucleotide rests, two types of internal proteins, p18 and p24 (the figures correspond to their molecular weight expressed in thousand Daltons), and specific viral enzymes [3, 16].

The viral envelope is built of glycoproteins, gp120 and gp41, and lipids. Retroviral RNA encodes the genes of viral proteins and the gen that activates the viral enzymes. The best studied are the functions of two among the HIV viral enzymes, reverse transcriptase (revertase), and protease (proteinase).

The HIV particle is first adsorbed on the surface of a T-lymphocyte, then injects into the cytoplasm the matrix *m*-RNA and the reverse transcriptase. The reverse transcriptase enzyme catalyzes the synthesis of proviral DNA on the matrix of viral RNA. Then DNA replication occurs, forms duplex DNA that invades the cell nucleus. The viral DNA gets built into the chromosomal DNA and further serves as a base for HIV virion replication. The replication includes the transcription of the viral RNA on the proviral DNA and the transfer of viral RNA into the ribosomal apparatus of the infected cell. Then under the guidance of the ribosome occurs the biosynthesis of the viral proteins [5].

The final stages of the HIV life cycle consist in the assembly of the virion particles. Here the important part belongs to the specific protease. This enzyme cleaves the viral proteins that have been formed from the viral genetic material into relatively short fragments facilitating the invasion of the new virions into the cells of the host body.

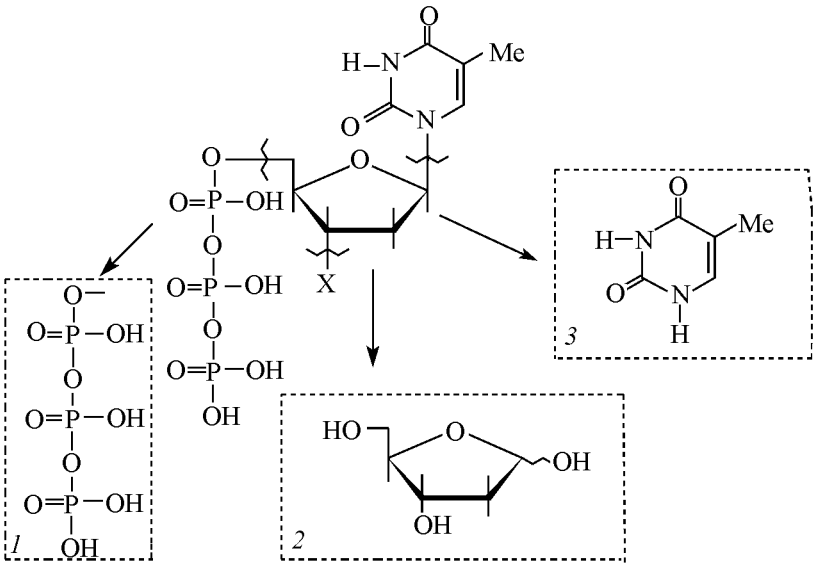
As seen from the above, the NARTIs preparations function at the first stage of HIV life cycle in the form of 2',3'-dideoxynucleoside-5'-triphosphate ddNTP [17–20]. The molecular design preceding the synthesis of the anti-HIV/AIDS drugs consists in modifying various fragments in the ddNTP structure.

We shall consider the structure of ddNTP by an example of thymidine derivatives to get more insight into the synthesis strategy of the anti-HIV drugs.

III. STRUCTURE OF 3'-SUBSTITUTED 2',3'-DIDEOXYTHYMIDINE-5'-TRIPHOSPHATES

Theoretically a modification can be preformed on any of the selected structural fragment: 1, triphosphate rest; 2, deoxyribose; 3, pyrimidine base, thymine (Scheme 1).

Scheme 1.



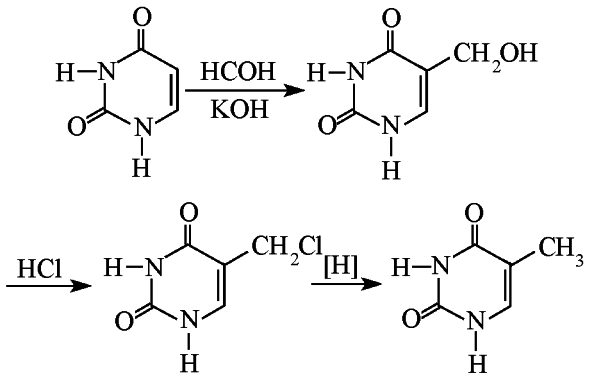
However to terminate the elongation of HIV proviral DNA the most important alterations are either the replacement of 3'-OH group by another pharmacophoric group acceptable for the active center of the enzyme, or the total absence of the substituent in the 3' position. Two approaches can be presumed to a solution of this structural problem. The first one involves the thymidine synthesis followed by multistage transformations. The second procedure consists of thymine condensation with the 5-*O*-protected 3-substituted 2,3-dideoxyfuranose or its derivatives. The vital reagents for both synthetic routes are thymine, ribothymidine, and thymidine.

IV. MAIN REAGENTS FOR THE SYNTHESIS OF 3'-SUBSTITUTED THYMIDINES

IV.1. Thymine

Thymine synthesis along Fischer procedure consists in preparation of 5,6-dihydrothymine from methacrylic acid and urea by fusion followed by bromination and dehydrobromination with alkali [21]. A condensation of β-methylmalic acid under catalysis with acid (oleum) or base is also known. As a source of the thymine carboxy group apart from urea serve ethyl α-methylpropionate or butyrate, also α,β-dibromomethylpropionyl chloride [22, 23]. All the above methods have a common drowback to provide a low yield of thymine.

The industrial process for thymine production is based on oxymethylation of uracil with paraformaldehyde in alkaline medium followed by hydrogenation under pressure of the obtained 5-oxymethyluracil in the presence of catalysts (Rh, PtO_2). This procedure was later simplified by converting the 5-hydroxymethyluracil into 5-chloromethyluracil by treating with hydrochloric acid. Then the latter compound was reduced by sodium borohydride in the presence of Pd/C under atmospheric pressure [24, 25].



The yield of thymine obtained in this process is fairly high, 80%.

IV.2. 1-(β-D-Ribofuranosyl)thymine (ribothymidine)

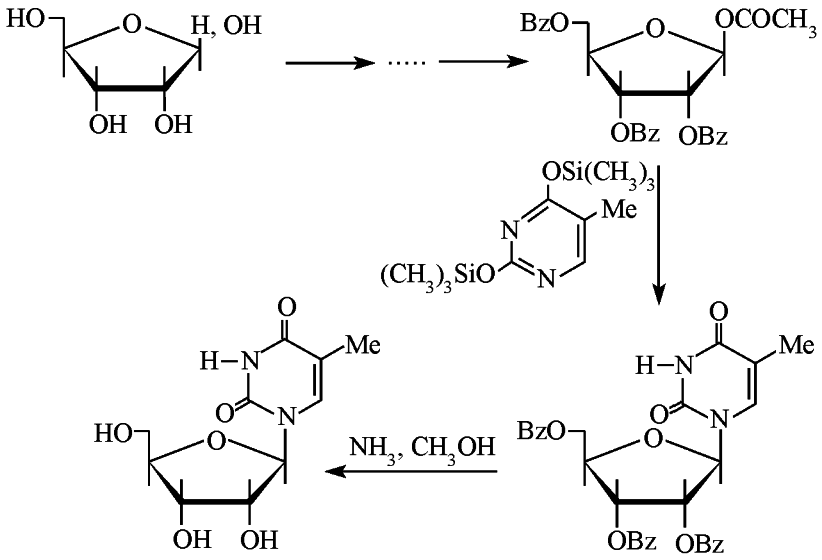
The 1-(β-D-Ribofuranosyl)thymine (ribothymidine) is a key reagent in synthesis of various nucleosides, thymidine included. The preparation of ribothymidine is commonly performed by condensation of the D-ribose derivatives with thymine [26–29]. A typical problem in this procedure is a stereodirectional synthesis. The spatial configuration of the glycoside bond in the ribothymidine is determined by converting the latter into 1-(D-arabinofuranosyl)-thymine via an intermediate 2,2'-anhydro derivative [27]. The ribothymidine was obtained for the first time in a 10% yield by condensation of 2,4-dimethoxy-5-methylpyridine with acetochlororibose (Hilbert–Johnson reaction). The low product yield is due to the difficulties in separation from the α-stereoisomer (anomer). In [27] is also described the ribothymidine synthesis by condensation of thymidine mercury salt with the 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride followed by debenzoylation of the 5'-*O*-protected nucleoside. The reaction afforded the target product in 50% yield. However here also the fraction of the α-anomer is significant. The stereoselective preparation of ribothymidine was successively carried out by protecting the thymine oxygen atoms with trimethylsilyl groups. Introduction of this protective group occurs at boiling the thymine in excess hexamethyldisilazane in the presence of ammonium salts in catalytic quantity, or by treating with trimethylchlorosilane taken in stoichiometric amount. The latter reaction is carried out in anhydrous solvent in the presence of a tertiary amine.

The condensation of the 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride with the bistrimethylsilyl thymine derivatives yields ribothymidine in 65–80% yield. It was established that the stereoselectivity of the process was considerably affected by temperature, reaction time, catalyst and solvent character [28]. The optimal combination of the temperature, catalysts, and the other parameters (Vorbruegen modification) was developed providing nearly complete stereoselectivity.

The ribothymidine can also be prepared from uridine [30] and by transglycosylation of thymine using inosine as substrate [31].

Later a complete procedure was developed for preparation of the ribothymidine from the D-ribose and thymine [29]. The conversion of the D-ribose into 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose

Scheme 2.



occurs in ~60% yield by methanolysis according to Fischer method with subsequent benzoylation in pyridine and acid acetolysis [32]. The benzoylation of methyl-β-D-ribofuranoside was also attempted under conditions of the phase-transfer catalysis. The condensation of a bistrimethylsilyl thymine derivative with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose occurs in dichloroethane or acetonitrile in the presence of trimethyliodosilane or silyl perfluoroethanesulfonate. In the process 1-(2',3',5'-tri-*O*-benzoyl)ribothymidine formed in 70–75% yield. Debenzoylation of the latter effected by solution of ammonia (NaOH or CH_3ONa) afforded the ribothymidine in 70% yield (Scheme 2).

IV.3. 1-(2'-Deoxy-β-D-ribofuranosyl)thymine (thymidine)

The commercial thymidine comes from two sources: It can be of biotechnological or synthetic origin. The former is a product of hydrolysis of a natural DNA effected with enzyme. The DNA is separated from a natural raw material, e.g., from the milt of salmon fish. here arises a problem of nucleosides separation. In the biotechnological synthesis of thymidine is preferably used the nucleoside phosphorylase produced by *E.Coli* bacteria since in this case the yield of thymidine approaches 70% [33]. Alongside the biotechnological thymidine in the processes of abnormal nucleosides preparation is extensively used the thymidine of synthetic origin. Just the synthetic thymidine is now prevailing in the market of the nucleoside raw materials.

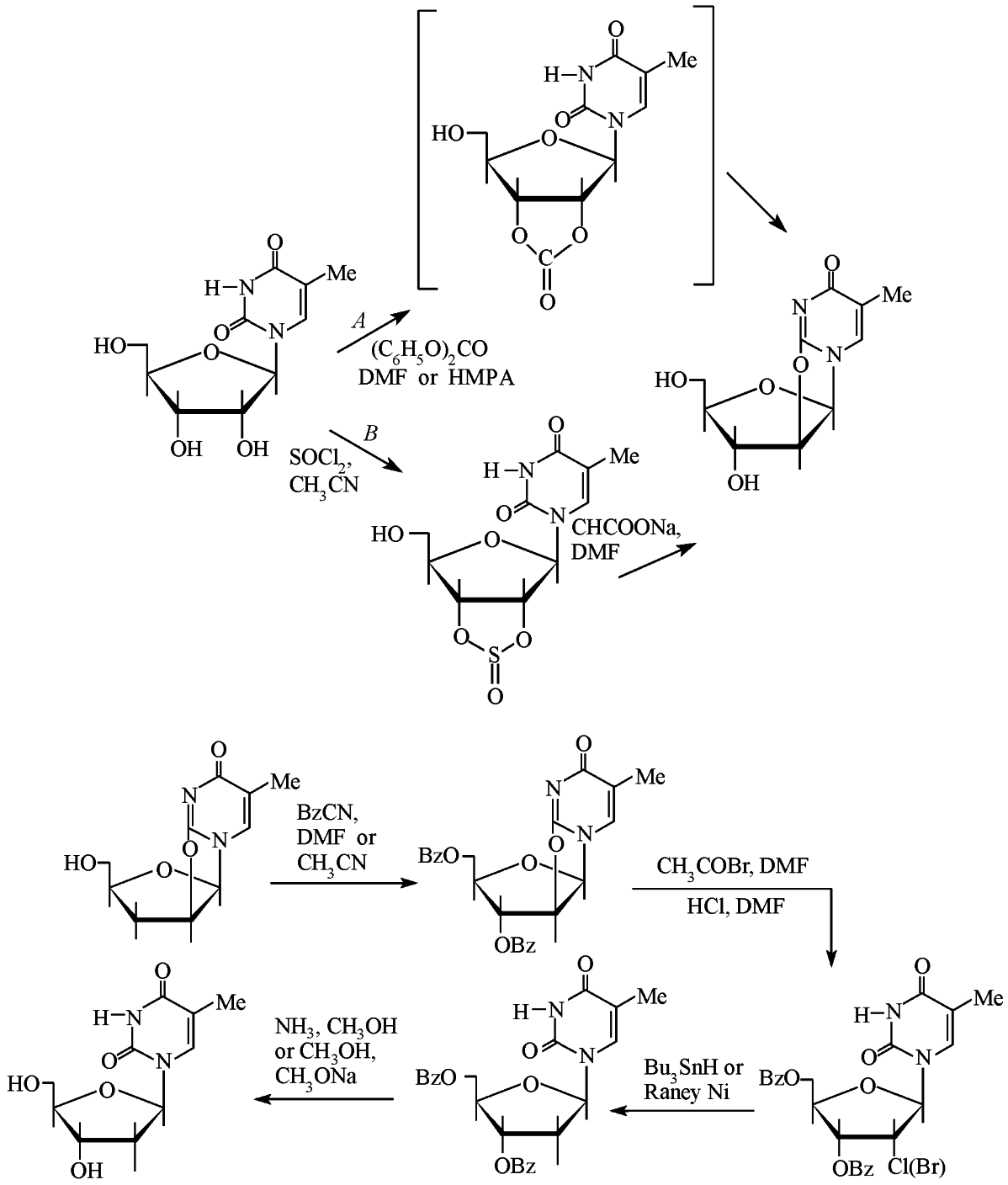
The thymidine was formerly mostly prepared by condensation of 3,5-di[*O*-(4-toluoyl)-2-deoxyribofuranosyl] chloride with a thymidine mercury salt. Both α- and β-enantiomers arise in this reaction, and also unstable deoxynucleosides impurities. On removing the protective toluoyl group the thymidine is isolated by chromatography or by fractional crystallization. Its yield in this procedure amounts to 40% [34]. If in this method instead of thymine mercury salt is used thymine bistrimethylsilyl derivative, the β-anomer of thymidine is obtained in a good yield [85–90% with respect to 3',5'-di-*O*-(4-toluoyl)-thymidine]. However certain precautions should be taken to reduce the fraction of the α-anomer. The highest β-thymidine yield is obtained when the reaction is carried out at room temperature and equimolar reagents ratio in the chlorinated hydrocarbons preventing the presence of the Lewis acids. The quality of the crystalline α-chloro-3,5-di-*O*-(4-toluoyl)-2'-deoxyribofuranose is crucial. The latter compound is prepared from the 2-deoxy-D-ribose [35, 36].

However now apparently the thymidine is most widely synthesized from ribothymidine. In this process a hydroxy group in 2' position is eliminated from the ribose fragment.

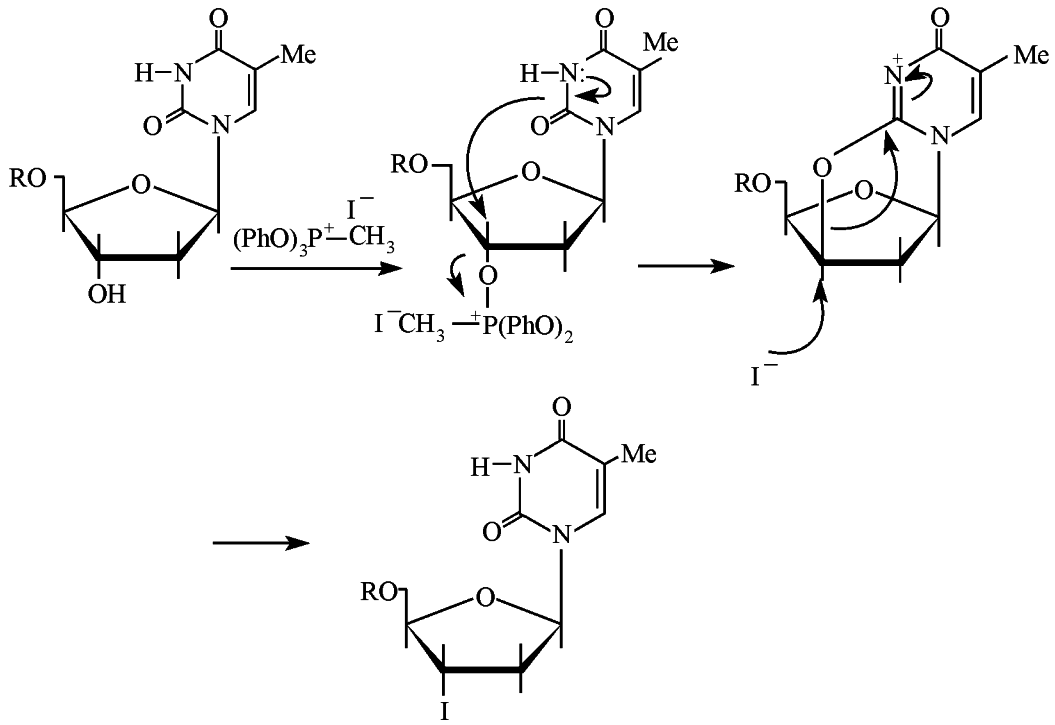
The synthesis of 2'-deoxyribonucleosides from the corresponding ribonucleosides is performed in five stages, and the key reagent is 2,2'-anhydronucleoside. This intermediate can be prepared either via cyclic carbonate (A) or cyclic sulfite (B) [37–40].

In the A procedure the intermediate cyclic carbonate is synthesized in two ways: either by treat-

ing ribothymidine with diphenyl carbonate in hexamethylphosphoramide or dimethylformamide with subsequent reaction with sodium hydrogen carbonate carried out without separation of the intermediate products to obtain the corresponding anhydronucleoside; or by treating with phosgene in toluene–pyridine mixture [41]. The B procedure involves preparation of nucleoside sulfinyl derivative by the action of thionyl chloride in acetonitrile [42]. The separated cyclic sulfide is heated in dimethylformamide with sodium acetate to furnish 2,2'-anhydronucleoside in 50–60% yield. Further the 3',5'-di-*O*-acyl-2,2'-anhydronucleoside is obtained that is converted stereospecifically into the corresponding 2'-halonucleoside. The latter is subjected to dehalogenation and deacylation to get the target 2'-deoxynucleoside in 40% yield.



Scheme 3.



R = Tr, Ac, *p*-NO_2Bz.

V. PROCEDURES FOR FUNCTIONAL GROUPS INTRODUCTION INTO 3' POSITION OF THYMIDINE

V.1. Successive Transformations of Functional Groups in Thymidine and Its Derivatives

Reactions with 3'-hydroxy group of thymidine. Synthetic procedures for preparation of 3'-substituted thymidine derivatives have been extensively developed since the beginning of nineteen sixties. The succession of reactions is usually as follows: selective protection of the hydroxy group in the 5' position; activation of the hydroxy group in 3' position by an appropriate, e.g., methanesulfonic, group; generation of a 2,3'-anhydro bond (formation of a C^3–O^2 bond); introduction of a substituent into 3' position with simultaneous rupture of the anhydro bond; deprotection, isolation, and purification of the target compound.

The hydroxy group in 5' position is protected by trityl, dimethoxytrityl, benzoyl, toluoyl, or some other group [43–48].

Glinski *et al*. described a procedure for preparation of 3'-(4-nitrophenylphosphate)-2'.3'-dideoxythymidine and its various salts under the action of 4-nitrophenyl dichlorophosphate [49].

Reaction of 5'-*O*-trityl-3'-hydroxythymidine with alkyl iodides (Alk = Me, Et, Bu) affording the corresponding 3-alkoxy derivatives was described by Hampton [50]. The synthesis of 3'-carbamate thymidine derivatives was reported in [51].

Verheyden and Moffatt [52] developed a synthesis method for 3'-iodothymidine based on reaction of the 3'-hydroxy group of the 5'-protected thymidine with methyl diphenoxyphosphoroiodide (Scheme 3).

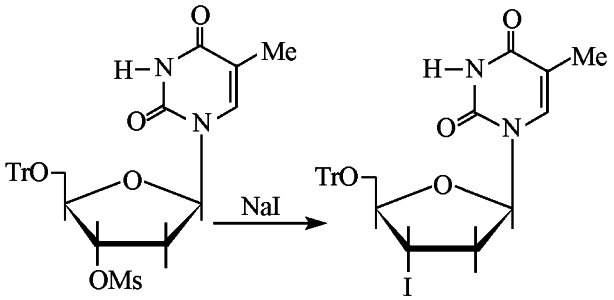
An intermediate in this process is 5'-protected-2,3'-anhydrothymidine.

In [53–56] are presented various schemes of 3'-oxythymidine syntheses from 3'-hydroxythymidine.

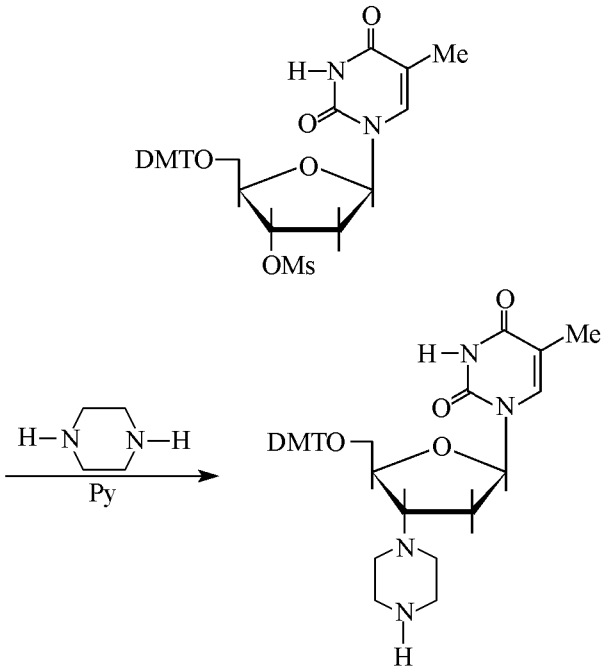
Transformations of 5'-*O*-protected 3'-methanesulfonyl-2',3'-dideoxythymidine (3'-mesylthymidine). The 3'-mesylthymidine is among the most important intermediates in the planned syntheses of various thymidine derivatives. Therefore the pioneering studies of the chemical transformations of 3'-mesylthymidine carried out by Fox [57–60] and Horwitz [61, 62] are still important and undergo further development even now [63–65].

In these studies was utilized the opportunity of the mesyl group replacement with various nucleophilic reagents. The mesyl group in 3' position is cleanly

substituted by iodine at treatment with sodium iodide [61, 66–68].



Similarly the reaction of 5'-dimethoxytrityl-3'-mesyl-2',3'-dideoxythymidine with piperazine in pyridine solution affords in high yield 3'-(piperazin-1-yl)-2',3'-dideoxythymidine protected with a dimethoxytrityl group (DMTO) [69].

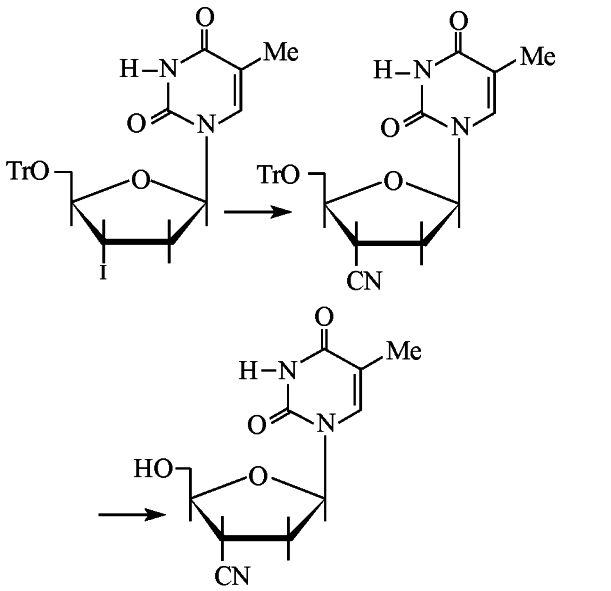


The analogous result is obtained at treating the 3'-mesylthymidine with the triphenoxyphosphonium iodide in DMF.

A separate group of methods concerns the preparation of 5'-*O*-protected 2,3'-anhydrothymidines from the corresponding 3'-mesyl-2',3'-dideoxythymidines.

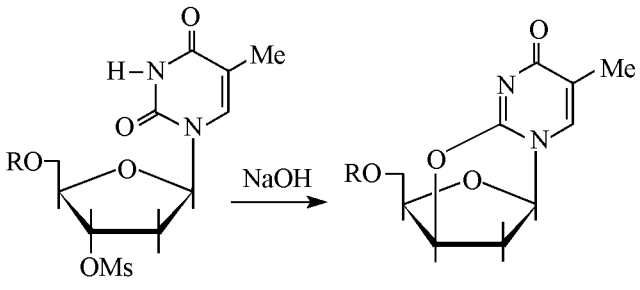
Several modifications of these procedures are known distinguished by the character of protective groups in 5' position and by reagents providing formation of the $C^{3'}$–O^{2} anhydro bond [70–72].

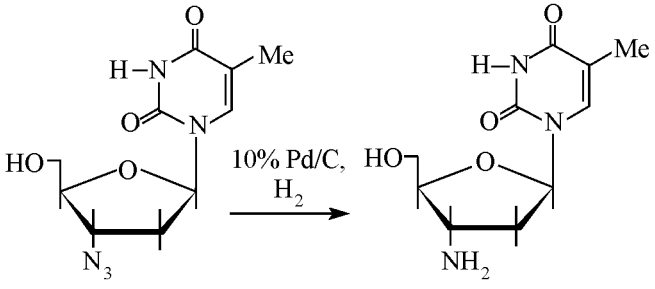
Transformations of the other functional groups in 3' position. The 3'-iodo-2',3'-dideoxythymidine was applied to the synthesis of the other 3'-derivatives, e.g., 3'-cyano- [66, 67], 3'-nitroso-, and 3'-nitro-2',3'-dideoxythymidine [73]. The halogen is replaced by the cyano group at treatment of the 3'-iodo-2',3'-dideoxythymidine with *tert*-*O*-butyl isocyanate [65, 66–68].



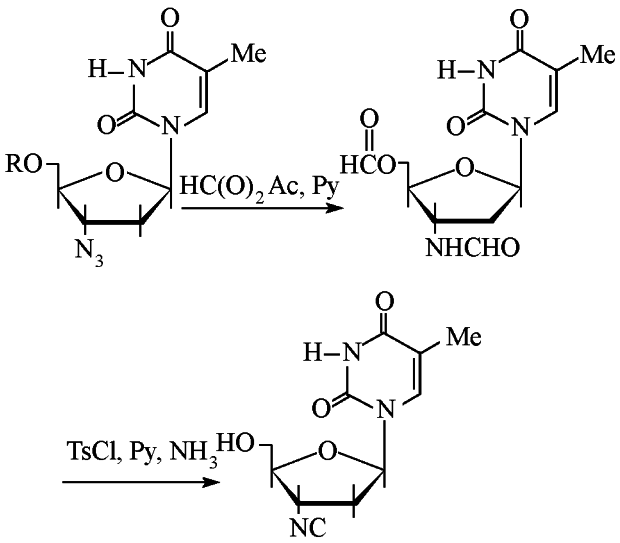
The 3'-iodo-2',3'-dideoxythymidine is also an intermediate in the synthesis of 3-allenyl-2',3'-dideoxythymidine [71].

The 3'-azido-2',3'-dideoxythymidine (AZT) is known to find wide application in the AIDS treatment. However the presence of a reactive azide group provides a possibility to use it also as a reagent in the synthesis of new thymidine derivatives. The azide group can be reduced into an amino group by hydrogen on a Pd/C catalyst [74].

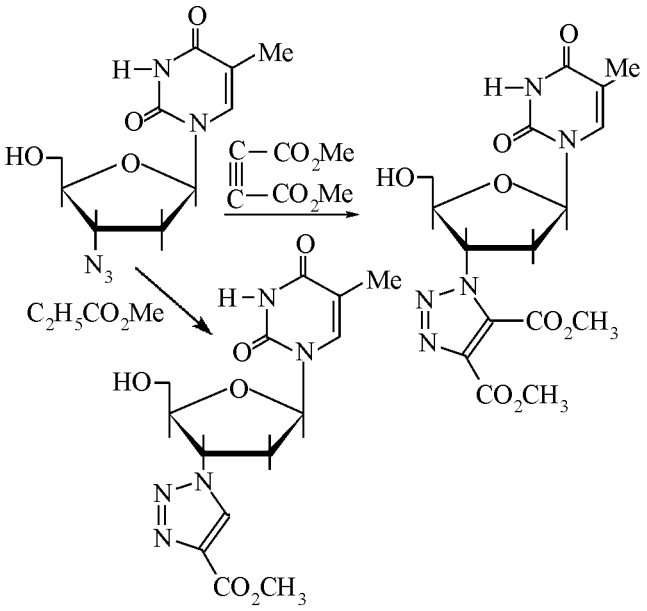




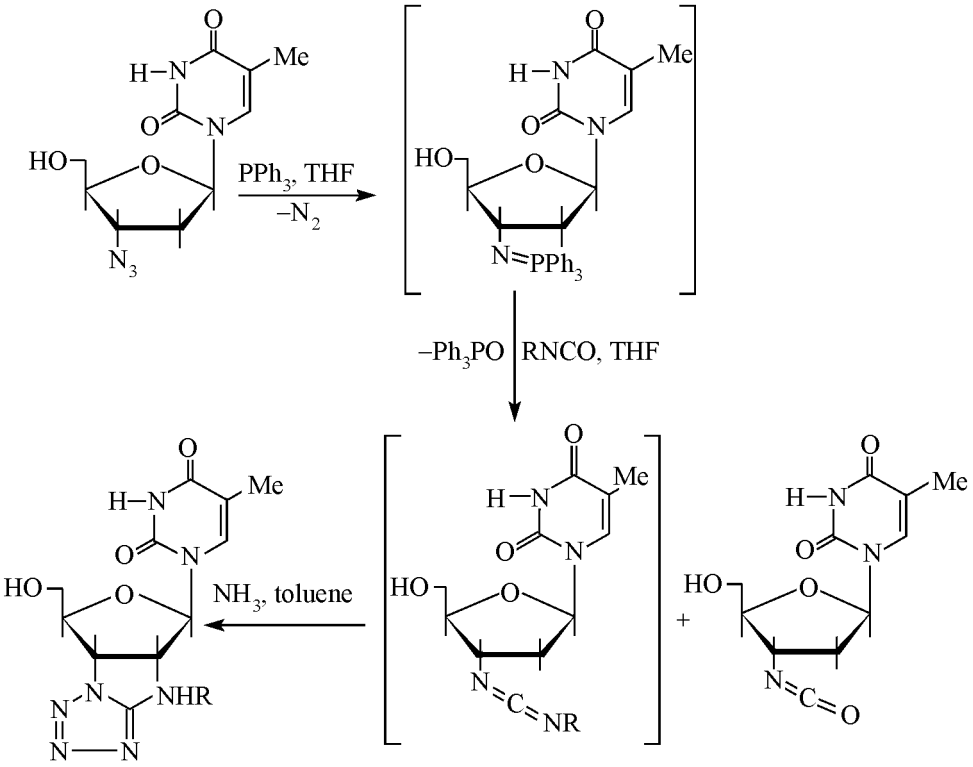
Certain modifications of this method furnish 3'-aminocyano- and 3'-amincarbamato-2',3'-dideoxythymidines [75]. Ugi *et al.* from 5'-*O*-substituted-3'-azido-2',3'-dideoxythymidine obtained 3'-formamido-2',3'-dideoxythymidine that in its turn was converted into 3-isocyano-2',3'-dideoxythymidine [76].



The 3'-isocyano-2',3'-dideoxythymidine was also prepared from 3'-azido-2',3'-dideoxythymidine via complicated intramolecular transformations [77]. Recently appeared publications on the use of the azide group in the synthesis of thymidine derivatives with 1,2,3-triazole or tetrazole substituents in the 3' position: 3'-(1,2,3-Traiazol-1-yl)-2',3'-dideoxythymidine derivatives were reported to be synthesized [78].

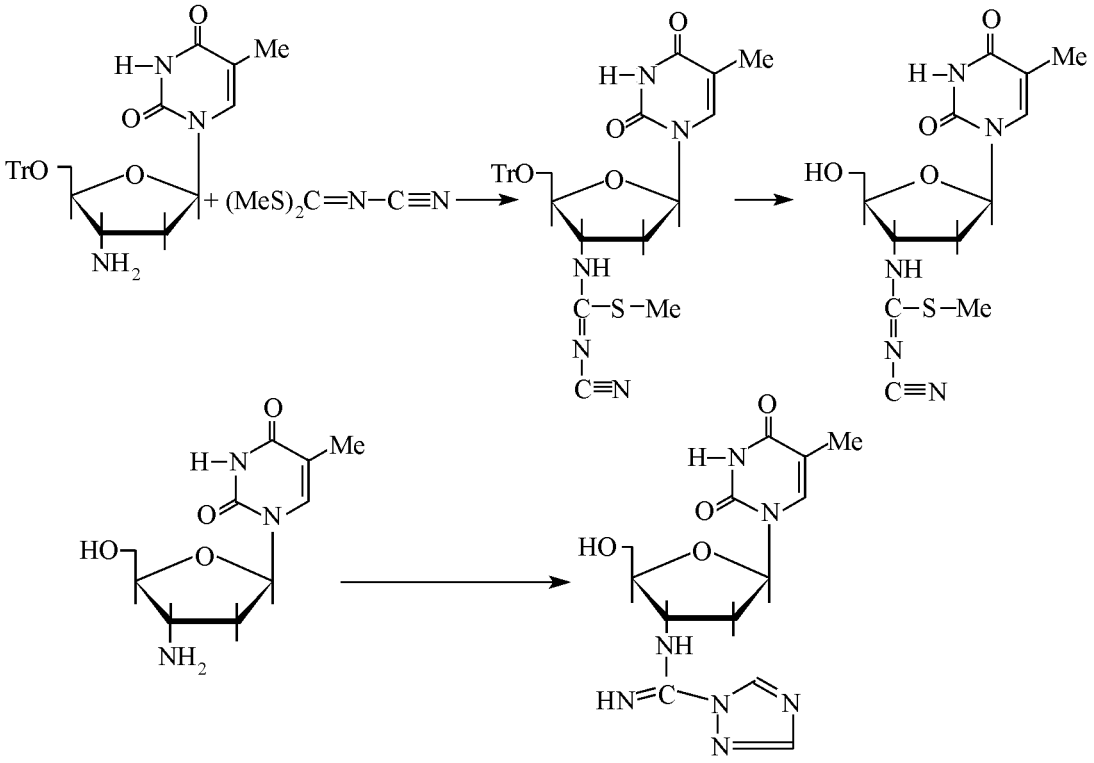


Scheme 4.



R = *t*-Bu, *i*-Bu, $C_{12}H_{25}$, $Cl(CH_2)_6$, Ph, 4-ClC_6H_4, 4-$CH_3C_6H_4$.

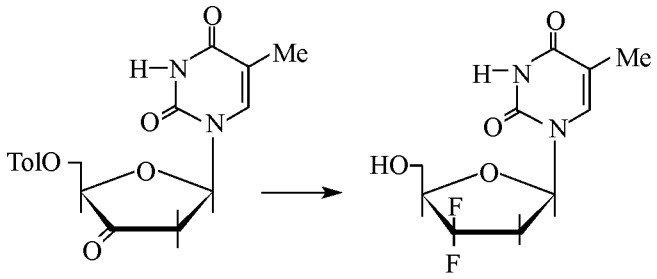
Scheme 5.



Finally the advantage was taken of the azide group reactivity to carry out a multistage synthesis of 3'-(5- R-aminotetrazol-1-yl)-2',3'-dideoxythymidine [79, 80] (Scheme 4).

The reactions of the amino group in the 3' position of thymidine are well studied and described [81, 82]. However the opportunities provided by this group for the planned synthesis of 3'-substituted thymidines apparently are not exhausted. We can prove it by an example of reaction between 5'-*O*-trityl-3'-amino-2',3'-dideoxythymidine and *N*-cyanamido-S,S-dimethyldithiocarbonate [83], and between 3'-amino-2',3'-dideoxythymidine and 1,1'-carbimidoyl-bis-(1,2,4-triazole) [84] (Scheme 5).

The 3'-oxo-2',3'-dideoxythymidine is fairly accessible and also can serve as an initial compound for preparation of 3'-modifies thymidines. Thus the



reaction of 5'-*O*-protected-3'-oxo-2',3'-dideoxythymidine with diethylaminosulfur trifluoride gave rise to 3',3'-difluoro-2',3'-dideoxythymidine.

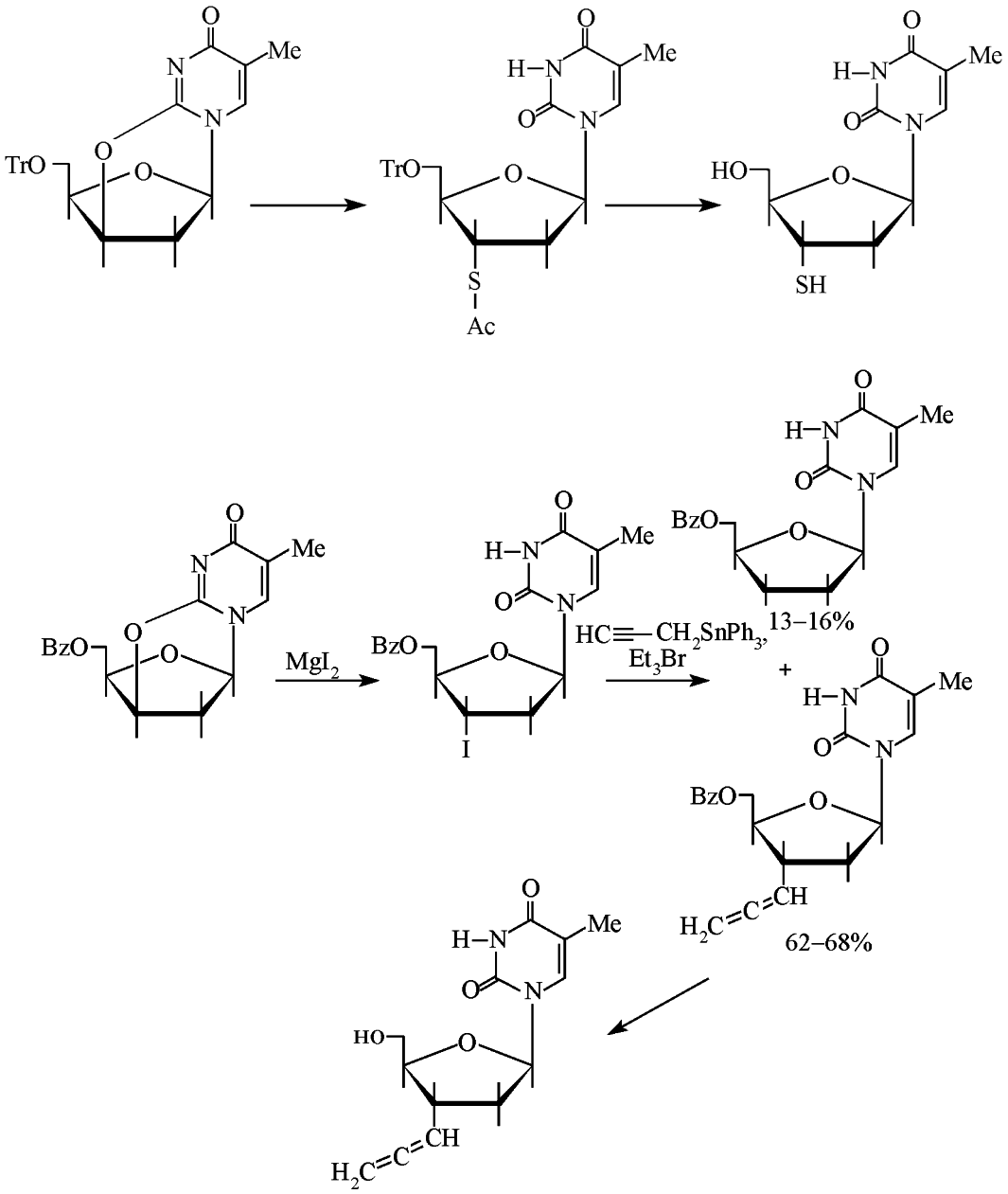
The drawbacks of these methods are the application of expensive reagents and low yield of the target products [85]. These studies were extended [86, 87] to the synthesis of 3'-fluoro-2',3'-dideoxythymidine from 3',3'-difluoro-2',3'-dideoxythymidine prepared by a procedure similar to that mentioned above.

According to Calvo-Mateo data [54] the reaction of 3'-oxo2',3'-dideoxythymidine with sodium cyanide afforded the corresponding 3'-cyano-2',3'-dideoxythymidine, and with ethynylmagnesium bromide formed the 3'-ethynyl-2',3'-dideoxythymidine [88].

Transformations of 5'-*O*-protected 2,3'-anhydrothymidine. Krayevsky *et al*. [89] demonstrated the possibility to prepare the 3'-mercapto-2',3'-dideoxythymidine from 5'-trityl-2,3'-anhydrothymidine via opening of the anhydro bond $C^{3'}$–O^{2} effected by potassium thioacetate (Scheme 6).

The synthesis of 3'-allenyl-2',3'-dideoxythymidine from 5'-benzoyl-2,3'-anhydrothymidine was described in [71]. In this reaction formed intermediately 5'-*O*-benzoyl-3'-iodo-2',3'-dideoxythymidine.

Scheme 6.



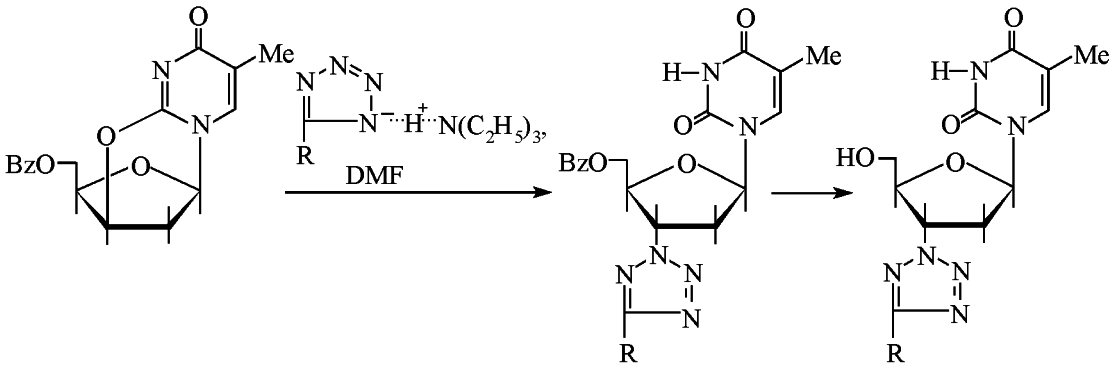
The reaction of 5'-*O*-benzoyl-2,3'-anhydrothymidine with magnesium iodide at heating in toluene gave rise to 3'-iodo-2',3'-dideoxythymidine. The latter provided the target product at treating with triphenylpropynyl-2-stannate in the presence of alkyl bromide as a catalyst.

The 3'-(isopropylthio)-2',3'-dideoxythymidine and 3'-phenylselenyl-2',3'-dideoxythymidine were obtained by reacting 5'-*O*-protected 2,3'-anhydrothymidine with 2-propylthiol and phenylselenide respectively [90].

In reaction of 5'-benzoyl-2,3'-anhydrothymidine with 5-substituted tetrazoles [91] and with their alkylammonium salts [92–96] were obtained for the first time 5'-*O*-benzoyl-3'-(5-R-tetrazol-2-yl)thymidines that on debenzoylation yielded 3'-(5-R-tetrazol-2-yl)-thymidines (Scheme 7).

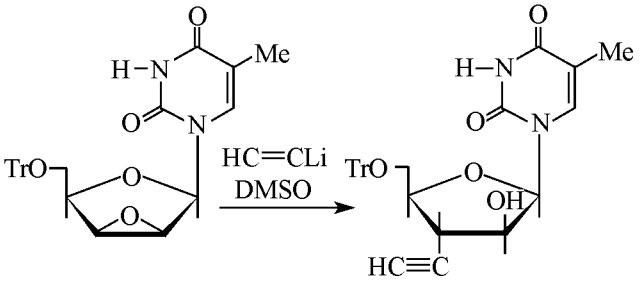
Transformations of 5'-*O*-protected 2',3'-epoxythymidine. The opening of the 2',3'-epoxy ring same as in analogous α-oxides [977-100] is effected by various reagents. As a result arises a mixture of two reaction products with substituents attached

Scheme 7.



R = H, CH_3, Ph, CH_2Ph, 4-FC_6H_4.

respectively to 2' and 3' positions. The reaction between the 5'-*O*-trityl-2',3'-lyxoepoxythymidine with the ethynyllithium in DMSO afforded 3'ethynyl-2',3'-dideoxythymidine [101].



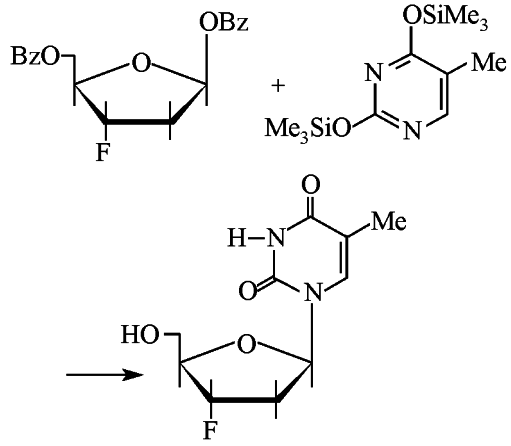
Hampton *et al*. mentioned a formation of 3'-ethylthio-2',3'-dideoxythymidine in a high yield in reaction of 5'-*O*-trityl-2',3'-xylo-epoxythymidine with ethanethiol in DMF. In [102] was described the cleavage of the 2',3'-epoxy ring effected by methylmagnesium iodide. Finally, the 3'-cyano-2',3'-didehydro-2',3'-dideoxythymidine and 3'-cyano-2',3'-dideoxythymidine were obtained successively in the reaction of 5'-*O*-trityl-2',3'-xylo-epoxythymidine with sodium cyanide [103].

V.2. Condensation of Ribofuranose Derivatives with Thymine (Building up of a Glycoside Bond)

This approach is feasible for preparation of a wide range of the 3'-modified nucleosides since the 3-substituted derivatives of deoxyfuranose are easily available.

The reaction of a silylated thymine with the 3,5-*O*-protected 2-deoxyribofuranose furnished the 3'-hydroxymethyl-2',3'-dideoxythymidine [104]; a simpler procedure for the synthesis od the 3'-modified thymidines utilizing unsilylated thymine was further developed [105, 106].

The 3'-fluoro-2',3'-dideoxythymidine was prepared in a good yield from the corresponding 3-fluoro-derivative of ribofuranose and the silylated thymine [107].



A similar procedure for preparation of 3'-fluoro-2',3'-dideoxythymidine was reported in [108].

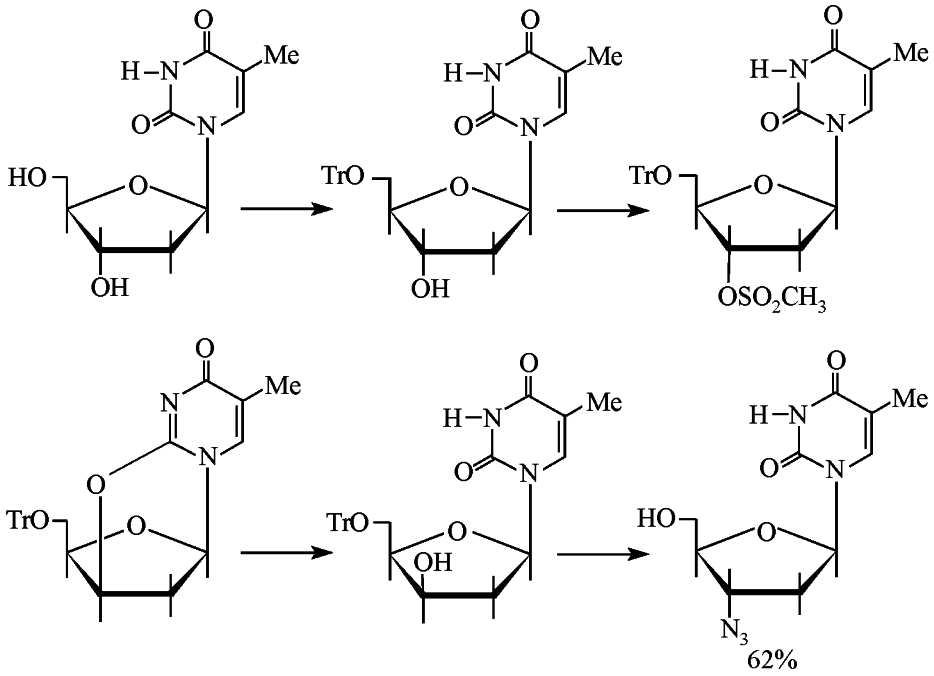
The synthesis of isomeric α- and β-derivatives of the 3'-cyano-2',3'-dideoxythymidine is comprehensively reported in [109].

Quite a number of 3'-modified nucleosides was obtained by condensation of ribofuranose derivatives with thymine [110–115].

V.3. Thymidine Derivatives Used in the Clinical Treatment of HIV/AIDS Infection

V.3.1. 3'-Azido-2',3'-dideoxythymidine (AZT). For AZT preparation were developed two methods:

Scheme 8.



either transformations of thymidine or ribothymidine, or condensation of thymine with protected 3-azido-2,3-dideoxyribofuranose (building up of the glycoside bond).

Let us consider the first method. The AZT was first prepared by Horwitz at the Michigan Cancer Foundation as a potential anti-cancer agent [59, 61, 72]. Above is given the simplified synthesis scheme (Scheme 8).

In [74] AZT was obtained by treating the intermediate 3'-mesyl derivative with lithium azide in DMF at 90–95°C.

The most difficult part of these syntheses is the chromatographic isolation of 2'-deoxylyxofuranosylthymidine since at the cleavage of the epoxy ring arise up to four products. Further is performed the tritylation, introduction of a mesyl group into the 3' position, then its substitution by an azide group effected by azides of lithium, sodium, ammonium, dimethylammonium etc. [116].

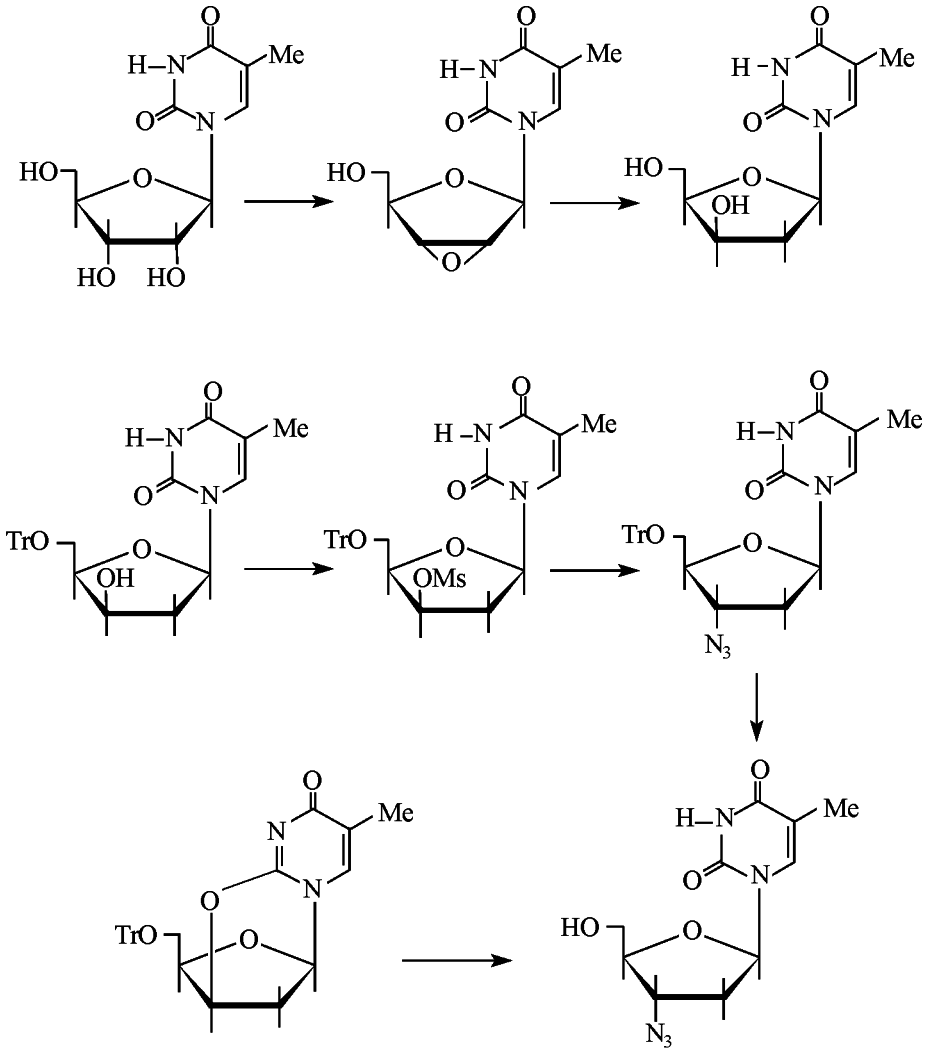
The protection of the furanose hydroxyls is performed with various groups [43–48, 17–119]. The frequently used is triphenylmethyl (trityl) group that shows high selectivity toward the OH group in 5' position. Apart from trityl protection are also used dimethoxytrityl and readily available benzoyl group [120]. As already mentioned, the activation of the hydroxy group in the 3' position is best performed with methanesulfonic group in pyridine solution. In its turn the azidation is carried out by the above named agents in an aprotic dipolar solvent within 9–140°C temperature range. The deprotection is further effected by acids or bases (Scheme 9).

Fox and Miller [58] developed an alternative synthesis of the 3'-azido-2',3'-dideoxythymidine. This approach consists in preparation of 5'-*O*-trityl-2'-deoxylyxofuranosylthymidine from the anhydro $C^{3'}$–O^{2}-nucleoside that was further activated by introducing a mesyl group into 3' position. Then azidation was carried out yielding a product with a reversed configuration at the $C^{3'}$ atom. Although the overall number of stages in this alternative procedure is greater, the yield of the azidation product is high enough. However the overall yield of the 3'-azido2',3'-dideoxythymidine does not exceed 20–30% [58].

The azidation of 5'-*O*-trityl-3'-*O*-mesyl-2',3'-dideoxythymidine is performed with the use of 5–7-fold excess of the azidizing agent. The reaction is carried out in DMF or hexamethyphosphoramide at 100–150°C [121]. It is possible to add some water into the reaction mixture to increase the solubility of the alkali metal azides in the aprotic dipolar solvent. Below is presented the azidation mechanism assumed in [121] (Scheme 10).

It was shown that different conditions of reaction give rise to dissimilar products, in particular,

Scheme 9.

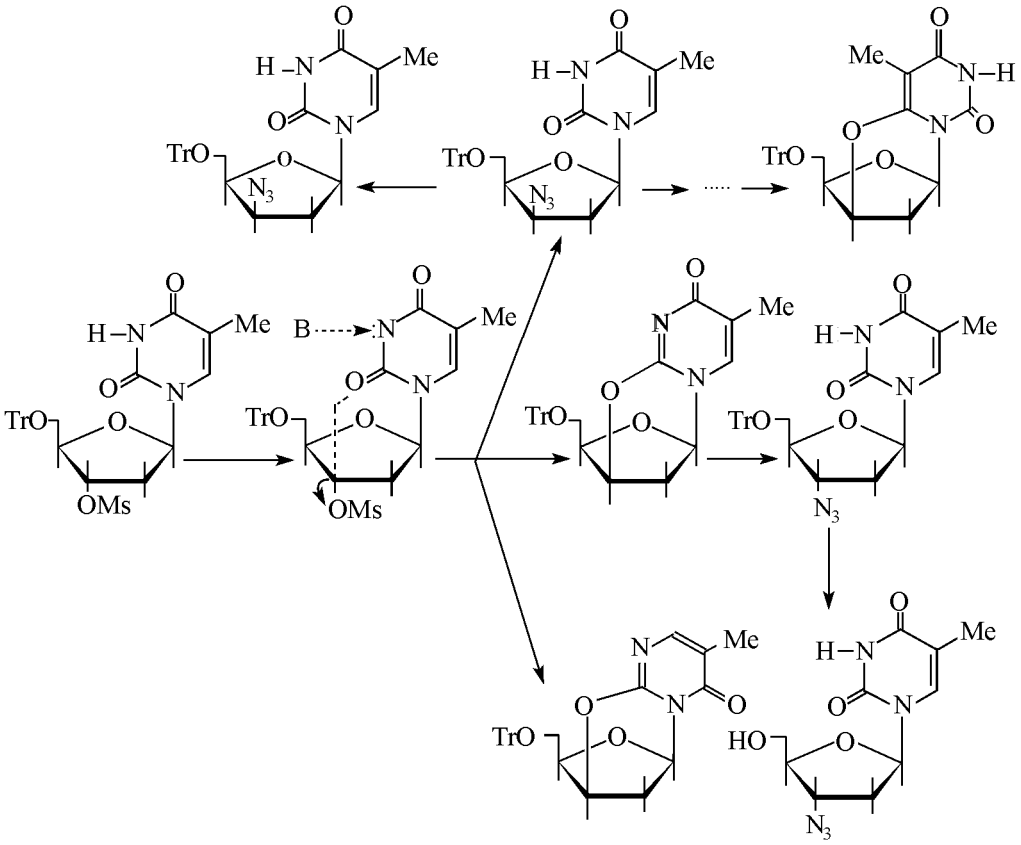


3'-azido-lyxo- and 3'-azidoerytrothymidine. In considering the mechanism of 3'-azido-2',3'-dideoxythymidine formation it should be taken into account that under specific conditions 5'-*O*-trityl-2,3'-anhydrothymidine can arise as intermediate (Scheme 10).

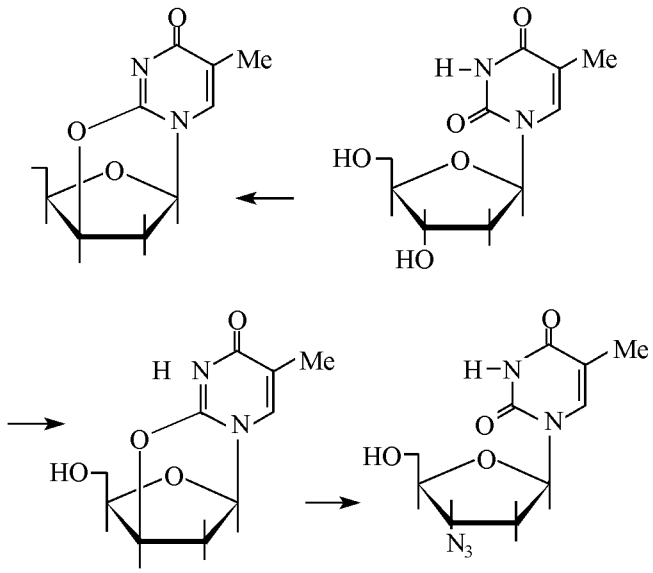
The further development of the AZT synthesis was dedicated to refining of the preparation methods for the anhydro $C^{3'}$–O^{2}-nucleosides. For instance, in the patent [122] and the study [123] was described a selective benzoylation and anhydrization of thymidine with benzoic acid in the presence of diethyl azodicarboxylate and triphenylphosphine in DMF. The resulting product, 5'-*O*-benzoyl-2,3'-anhydrothymidine, when treated with lithium azide in DMF at 150°C afforded 5'-*O*-benzoyl-2',3'-dideoxythymidine in 90% yield. A selective silylation of thymidine with *tert*-$BuSi(CH_3)_2Cl$ in anhydrous pyridine to yield 5'-*O*-*tert*-butyldimethylsilyl-2',3'-dideoxythymidine was described in [124]. The latter compound was treated with trifluoromethanesulfonic acid anhydride. The corresponding triflate thymidine derivative fairly readily cyclized into 5'-*O*-*tert*-butyldimethylsilyl-2,3'-anhydrothymidine. Its reaction with the sodium azide in DMF (5 h, 140°C) followed by deprotection with tetrabutylammonium fluoride provided AZT in 80% yield.

Glinski *et al*. [125] developed a synthesis of 3'-azido-2',3'-dideoxythymidine from 2,3-anhydrothymidine or its 5'-*O*-trityl derivative. The latter compound arose at treating thymidine or 5'-*O*-trityl-2',3'-dideoxythymidine with 2-chloro-1,1,2-trifluoroethylamine. The latter substance functioned as cyclizing agent that generated the anhydro bond [126].

Scheme 10.



It was also shown that conversion of 5'-*O*-trityl-3'-*O*-mesyl-2',3'-dideoxythymidine into the 5'-*O*-trityl-2,3'-anhydrothymidine could occur in the presence of phthalic acid derivatives.



The overall yield of the 3'-azido-2',3'-dideoxythymidine with respect to thymidine amounted to ~25%. The attempt to refine this scheme [127] did not notably increase the overall yield of AZT.

In [128, 129] was described a synthesis of 2,3'-anhydrothymidine and 3'-azido-2',3'-dideoxythymidine with the use of sulfur trifluoride. The treatment of 5'-*O*-trityl-2',3'-dideoxythymidine with derivatives of sulfur trifluoride in 1,4-dioxane at room temperature afforded in a high yield 5'-*O*-trityl-2,3'-anhydrothymidine that was further converted into AZT by azidizing agents. The formation of the 2,3'-anhydro compound was presumed to occur via the corresponding bridging 3'-*O*-, N-,S-fluoroethers.

An interesting alternative AZT synthesis was performed by treating 5'-*O*-protected thymidine in DMF by a mixture triphenylphosphine–tetrabromomethane–lithium azide [130]. The AZT yield amounted to 67%. A similar procedure was also reported in [131].

Fleet *et al.* [132] developed a multistage AZT synthesis from thymine and xylose via intermediate formation of a well crystallizing methyl-5-*O*-*tert*-

butyldiphenylsilyl-2-deoxy-α,β-xylofuranoside. The main stages of the process were as follows: conversion of the D-xylose into methyl-3,5-*O*-isopropylidene-α,β-D-xylofuranosides; deoxygenation by Barton procedure of the arising 2-*O*-[(methylthio)-thiocarbonyl]xylofuranosides; removing of the isopropylidene protection and selective silylation of the primary 5-OH group with *tert*-butyldiphenylchlorosilane; formation of 3-triflate derivative of the 1-*O*-methyl-5-*tert*-butyldiphenylxylofuranoside that was further transformed into the target 3-azido-2-deoxyribofuranoside. The condensation of methyl-3-azido-2,3-dideoxy-5-*O*-tertbutyldiphenylsilylribofuranoside with the thymine silyl ether resulted in 33% yield of β-anomer of 3'-azido-2',3'-dideoxythymidine (separated by chromatography) and in ~29% yield of the corresponding α-anomer.

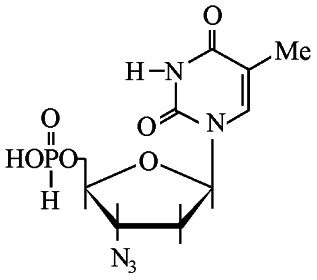
The synthesis of methyl-3-azido-2,3-dideoxy-5-*O*-*p*-toluoyl-D-ribofuranoside from xylose through 1,2,3,5-di-*O*-isopropylidene-D-xylose was described in [118, 133–135]. The product was further used in preparation of AZT by silyl procedure.

The condensation of 1-*O*-methyl or 1-*O*-acetyl-3-azido-2,3-dideoxy-D-ribofuranosides with thymine in the presence of $SnCl_4$ or $(CH_3)_3SiSO_3CF_3$ [136] results in a mixture of α- and β-anomers of 3'-azido-2',3'-dideoxythymidine.

The syntheses of 3'-azido-2',3'-dideoxythymidine were also carried out proceeding from xylose, D-mannitol [137–140], and also from 2',3'-cyclic thymidine derivatives [141].

The majority of the above mentioned methods are difficult for realization since they are multistage, require sophisticated chromatographic separation procedures of the formed isomer mixtures, and use potentially hazardous and expensive reagents: CS_2, NaH, $(CH_3)_3Si–SO_3CF_3$ etc.

A special attention should be drawn to the phosphorylated derivative of AZT, 5'-phosphonate, prepared by reaction of tris(1,3-imidazolyl)phosphorus with the 3'-azido-2',3'-dideoxythymidine.

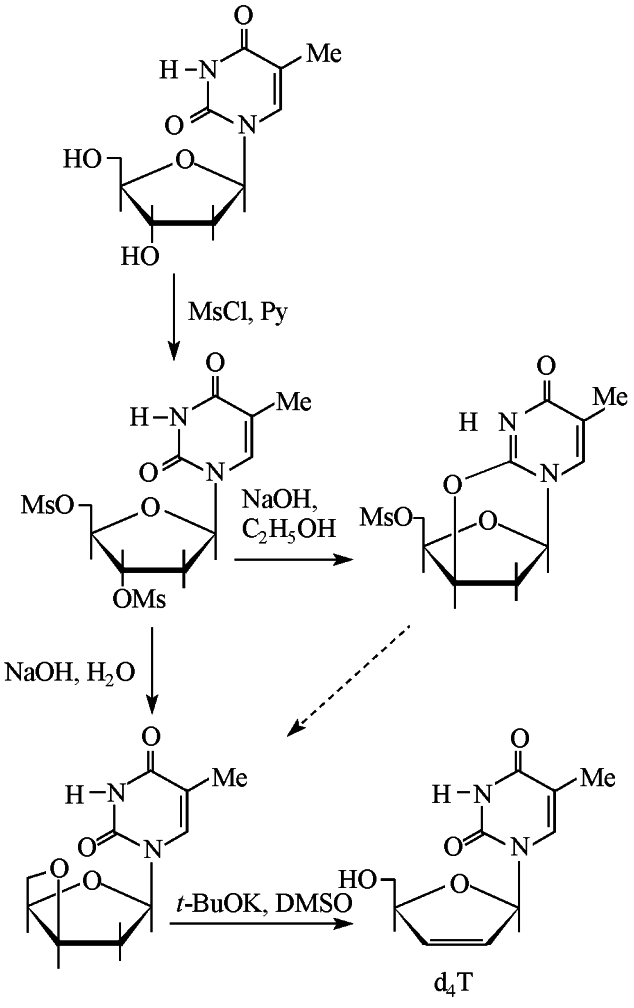


This compound was patented as an original Russian preparation "Phosphazide" for treating the HIV infection.

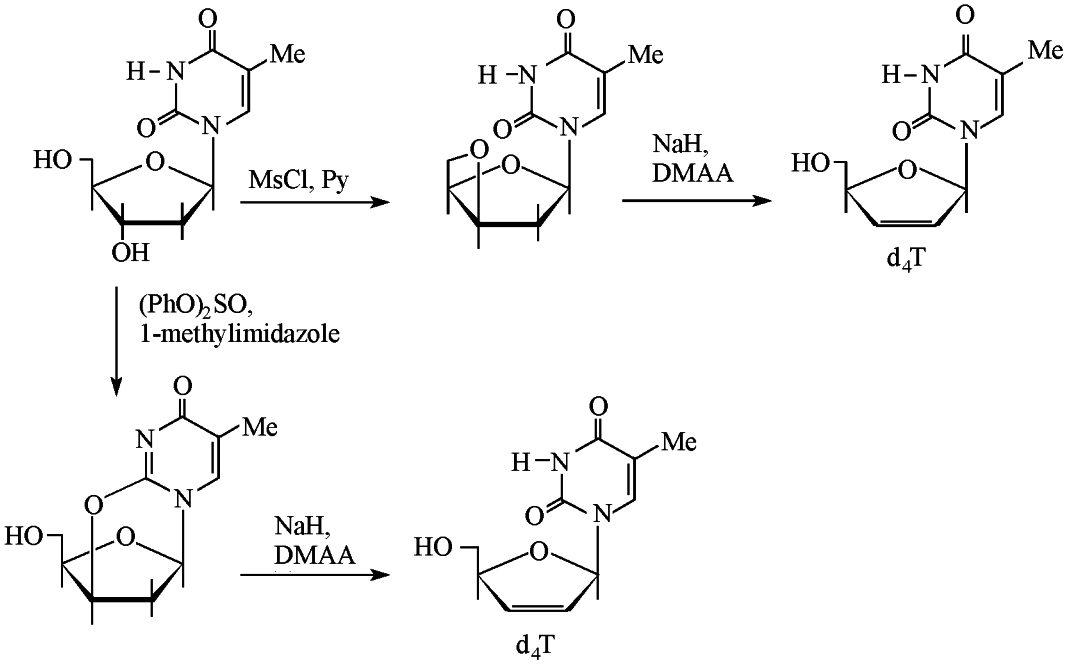
In conclusion to this chapter we would like to indicate as a trend the growing number of studies on the synthesis and investigation of phosphorylated nucleosides, in particular, those of thymidine [8, 9, 17, 142–148]. The phosphonates were shown to be less toxic than the original 3'-modified thymidines.

V.3.2. 2',3'-Dideoxy-2',3'-didehydrothymidine (d_4T). Horwitz *et al.* [62] synthesized 2',3'-dideoxy-2',3'-didehydrothymidine (d_4T) from thymidine by elimination reaction catalyzed with a base. They studied the transformation of 2',3'-deoxynucleosides prepared from 2'-deoxyuridine and thymidine into the respective 2',3'-unsubstituted nucleosides by the treatment with potassium *tert*-butylate in dimethyl sulfoxide.

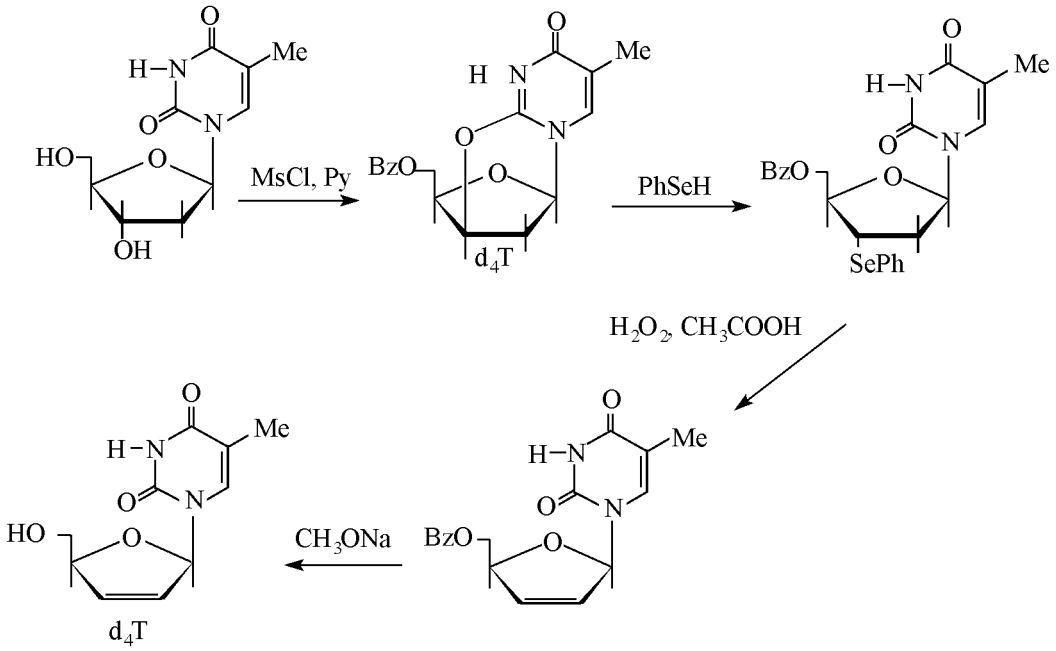
This procedure was further refined by Mansuri [149, 150].



Scheme 11.



Scheme 12.

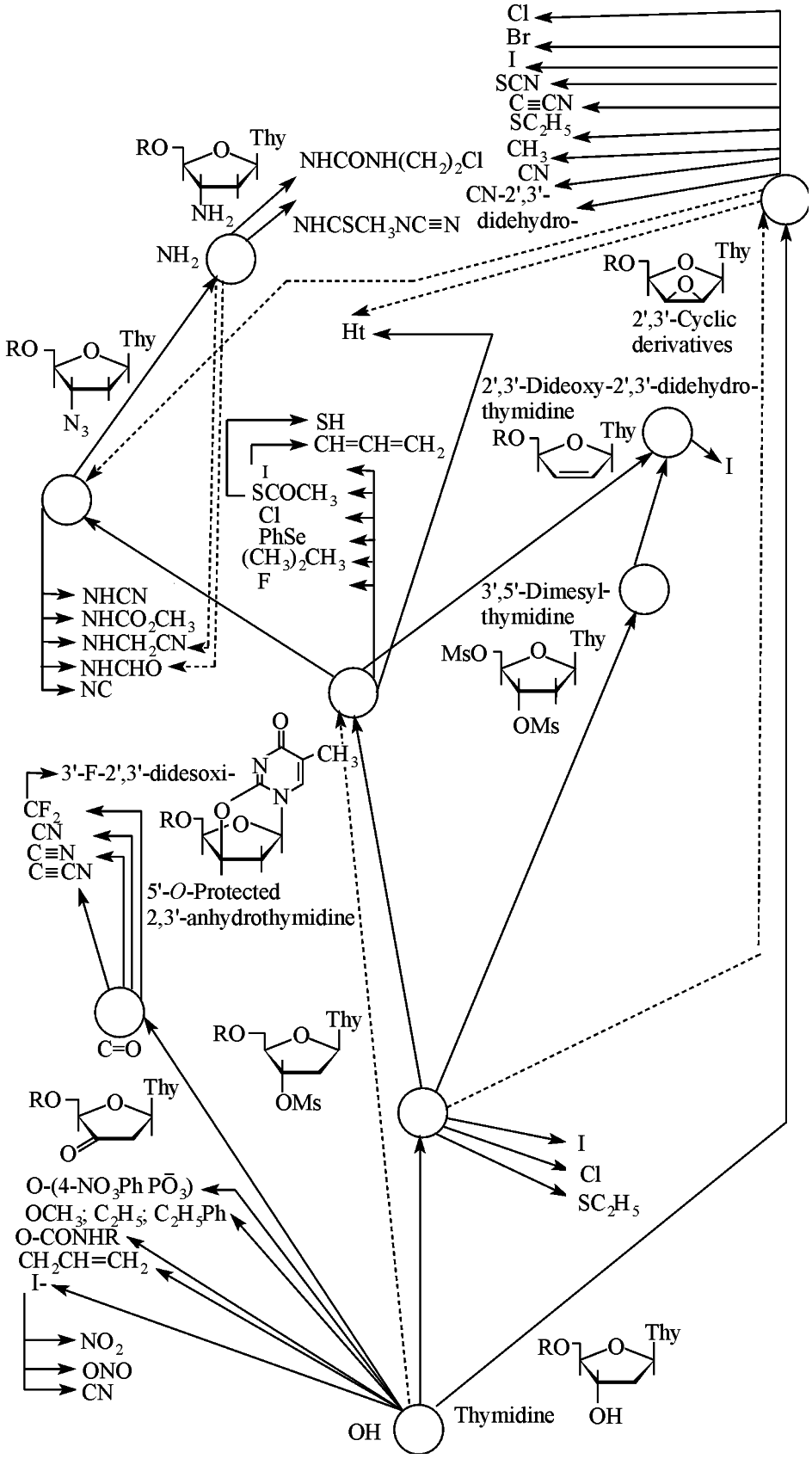


The first stage includes treatment of the thymidine with a slight excess of methanesulfonyl chloride in pyridine to yield 3',5'-mesyl-2',3'-dideoxythymidine. The latter is reacted with NaOH in water or ethanol to afford 2,3'-anhydrothymidine that at prolonged contact with the base is converted into the corresponding oxetane in 74% yield.

Although the reaction can proceed in various solvents, water is the most favorable since here the process is homogeneous.

The conversion of the thymidine into 2',3'-dideoxy-2',3'-didehydrothymidine is described in [151]. The procedure involves preparation of the cor-

Scheme 13. Synthesis tree for 3'-modified thymidines



responding oxetane derivative of thymidine or the 2,3'-anhydrothymidine. These compounds further are subjected to elimination (Scheme 11).

The oxetane derivative of thymidine was prepared by Horwitz method [62]. The elimination procedure was improved: sodium hydride (~3 mol equiv) in *N*,*N*-dimethylacetamide was used at heating to 100°C providing a high yield of the target compound. The thymidine can also be converted into 2,3'-anhydrothymidine by heating with excess diphenyl sulfite in the presence of 1-methylimidazole. The product is easily isolated from the reaction mixture in 65% yield. The heating of the unprotected 2,3'-anhydrothymidine with sodium hydride in the *N*,*N*-dimethylacetamide at 100°C for 30 min affords the d_4T in 81% yield. The overall yield in this procedure amounts to ~50%.

In [152] the d_4T and its analogs were obtained by deoxygenation of the 2', 3'-hydroxy groups along Garegg–Samuelson method in the system iodine–triphenylphosphine–imidazole. In this case the elimination occurs under mild conditions.

In [123] the d_4T was prepared through an intermediate phenylselenium derivative of thymidine (Scheme 12).

CONCLUSION

Within a short period (10–15 years) was made significant progress in syntheses and clinical studies of efficient anti-HIV drugs. Nearly all the modern compounds that are active at various stages of the HIV life cycle are the products of the fine organic synthesis [153–175]. Since the virus is highly resistant against medicines it is obvious that the search for new components of anti-HIV medical preparations will be growing. The structure of those compounds will depend on the newest developments in the molecular biology. At the same time it is clear that AZT and the other thymidine derivatives will retain in the years to come their significance for the mono and complex AIDS therapy as indispensable inhibitors of HIV revertase. The analysis of publications undertaken in this review revealed the most important pathways to the synthesis of modified thymidines, the significant intermediates and their relation to the target products. We hope that the synthesis tree constructed by us will be helpful for development of planned strategy and tactics for the synthesis of new HIV revertase inhibitors and for improvement of the preparation methods of the already known NARTIs group drugs. The circles in the scheme mark the key intermediates, unbroken arrows show the main pathways, and the dashed arrow correspond to the yet undeveloped but possible transitions (Scheme 13).

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