AZANUCLEOSIDES AND DEAZANUCLEOSIDES OF BIOLOGICAL INTEREST

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1. Introduction

1-1 The Rationale for the Design and Synthesis of Biologically Active Nucleosides.[1]

Major natural pyrimidine and purine nucleosides are given in Fig. 1. When structural analogs

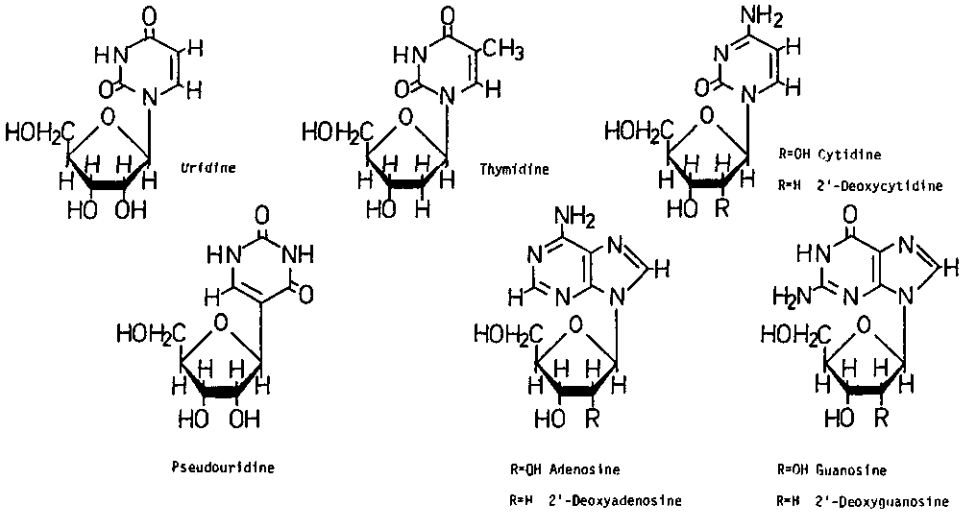


Fig. 1

Dedicated to the 75th birthday of Professor Kyosuke Tsuda.

of the natural purine and pyrimidine nucleosides are supplied exogenously to a cell, they can undergo a variety of transformations along numerous metabolic paths, and they can thereby effect the synthesis of proteins and carbohydrates and other cell constituents as well as the synthesis of nucleic acids.

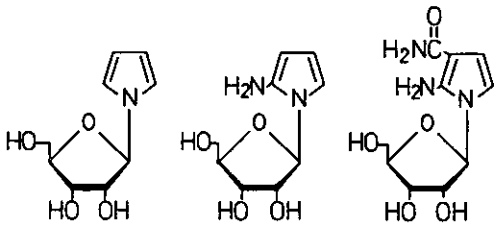
Although conceivably these metabolic paths are qualitatively similar in all living cells, selectivity of action, including permeability (the rate of entry of an analog into the cell) and stability against catabolic action and selectivity of its rate of absorption, distribution and elimination must be different.

From the standpoint of drug design, a number of questions, of course, arise. Why should we design nucleosides at all? What advantages do they hold over the normally less expensive base analog? How can we secure specificity of selectivity? It is not easy to answer these questions. Answers, if any, however, must be obtained from past biological, biochemical, and pharmacological experiences gained with synthetic nucleosides or with nucleoside antibiotics. Tentative criteria which can serve as guideline for the design and synthesis of more site-specific and target-selective nucleosides, must emerge from such past observations. Fortunately, during the past twenty years a veritable flood of nucleoside(especially adenosine) analogs, having a variety of biological activities has been obtained by synthesis or from natural sources. Thus, a correlation between the structural variations and the utilization by cells of these nucleosides has been clarified to some extent. For example, in the adenosine analogs the following salient features have emerged: (a) In order to be phosphorylated to the 5'-triphosphate level, the adenosine analog has to have a primary amino group at the C-6 position of the purine moiety. Compounds that belong in this category are 3'-deoxyadenosine; 3'-amino-3'-deoxyadenosine and 2-fluoroadenosine. These three nucleosides were also found to be potent inhibitors of nucleic acid synthesis. 7-Deazaadenosine, xylosyladenine, and arabinosyladenine were also phosphorylated to 5'-triphosphate level by microbial cells. Removal of the 6-amino group as in 3'-deoxynebularine resulted in complete absence of phospharylation by ascites cells. (b) 6-Methylaminopurine ribonucleoside was metabolized to the monophosphate level only.

Anyway a plethora of nucleoside analogs have been synthesized and biochemically examined and or evaluated as drugs. Therefore it is impossible to deal with all of them. Only a few selected examples will be touched on and besides emphasis will be laid upon aza- and deaza-analogs.[2] In addition to the above-mentioned reason, others are the following. The aza-analogs of pyrimidine and purine bases are an important group of antimetabolites which are theoretically derived by a replacement of the methine group of pyrimidine or purine nucleus with a nitrogen atom. This replacement represents, with an exception of the induced change in electron density in the nucleus, a relatively minor alternation of the structure of these substances as it does not change the functional groups, practically the molecular weight, and produces almost isosteric compounds. The replacement of the

methine group with a nitrogen atom can be effected in position 5 or 6 of pyrimidine base.[2] This results in analogs described as "5-aza" and "6-aza". With the purine bases the replacement can take place either in position 2 or 8,* this leading to 2- and 8-aza analogs, respectively. On the other hand, the replacement of azomethine group with methine group results in 3-deazapyrimidine with pyrimidine series, whereas such replacement results in the purine series in 1-, 3- and 7-deazapurine. Among important antimetabolites belong to aza- or deaza-nucleosides are, for example, 3-deazauridine,[3] 3-deazacytidine,[3] 3-deazaadenosine,[4] 7-deazaadenosine,[5] ribavirin,[6a] 6-aza-cytidine,[7] 5-aza-5,6-dihydrothymidine,[8] and 6-azauridine.[9] Some of these are in clinical use as antineoplastic agents.

2. Azaimidazole Nucleosides To our knowledge, deazaimidazoles nucleosides such as 1, 2, and 3 have never been reported. Preparation of deaza-imidazole nucleoside such as 3 must be of potential biological importance. However, it is anticipated by analogy with N-alkylated pyrrole derivatives that such nucleosides might be quite unstable and not be easily accessible.



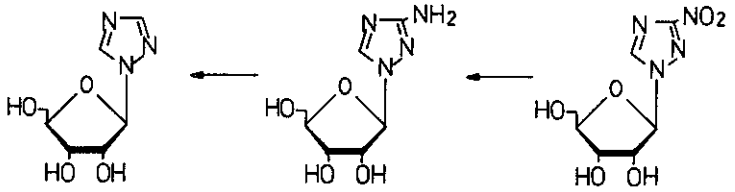
1 2 3

2-1 1-(β-D-Ribofuranosyl)-1,2,4-triazole Witkowski and Robins prepared the title analog during studies on pyrimidine nucleoside analogs. It was found to be biologically inactive.[10]

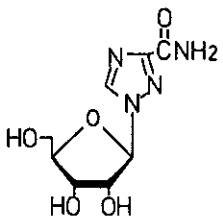
* In keeping with the title the present minireview occupies itself with those substances which were recently tested as aza or deaza analogs and further with substance which could be as such. For brevity the following abbreviations will be adopted. For instance, 1-deazaadenosine, 7-amino-3-β-D-ribofuranosyl-3H-imidazo[4,5-b]pyridine; 5-azacytidine, 1-β-D-ribofuranosyl-4-amino-1H,2H-triazin-2-one; 8-azaguanosine, 5-amino-3-β-D-ribofuranosyl-3H-6,7-dihydro-1,2,3-triazolo[4,5-d]pyrimidin-7-one; 8-azaadenosine, 7-amino-3-β-D-ribofuranosyl-3H-1,2,3-triazolo[4,5-d]pyrimidine; 3-deaza-adenosine, 4-amino-1-β-D-ribofuranosyl-1H-imidazo[4,5-c]pyridine and so on.

In addition, the left hand abbreviations refer to as full names on the right hand:

ABR	1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose
By	Benzyl
Bz	Benzoyl
HMDS	Hexamethyldisilazane
TAR	Tetra-O-acetyl-D-ribofuranose
TBRC(B)	2,3,5-tri-O-Benzoyl-D-ribofuranosyl Chloride(bromide)
TMS	Trimethylsilyl

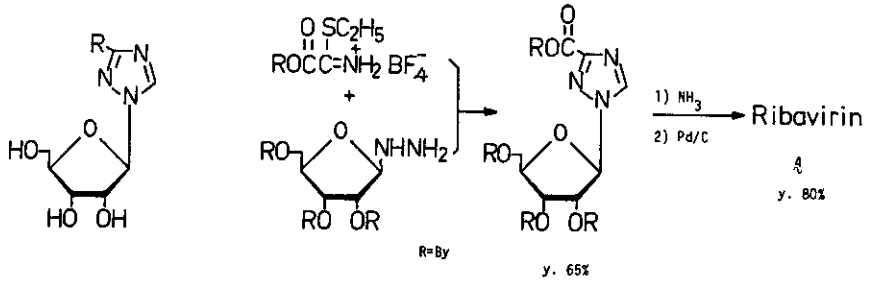


2-2 Ribavirin (or Virazole)[6] 1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide 4 (ribavirin or virazole) was synthesized by Robins et al.[11] who reported that this analog may be a broad-spectrum of antiviral agent in vitro.[6a, 12] Ribavirin also possesses strikingly strong inhibitory effects on influenza and parainfluenza virus replication in some animals. The drug has been licensed for human use in some countries. This analog undergoes easily transport into cells and phosphorylated.[13] Ribavirin 5'-phosphate can be regarded as a structural analog of AICAR 5'-phosphate that occupies a central position in the biosynthesis of purine nucleosides. This drug is a potent inhibitor against nucleic acid synthesis in viruses. It is conceivable that this may represent the major site of action of this antimetabolite. It is of interest in this regard that 4 failed to inhibit both eukaryotic DNA polymerase α and β and eukaryotic RNA polymerase I and II.

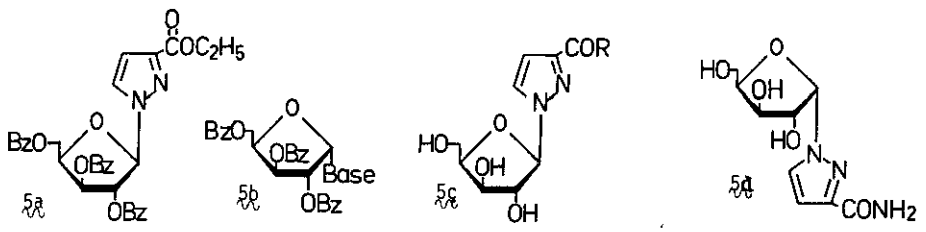


4

1-β-D-Ribofuranosyl-1,2,4-triazoles having substituents other than carbamoyl (R=$COOCH_3$, C≡N, $CSNH_2$, NO_2 and H) have been also prepared.[6d] Quite recently, Itoh et al. developed an improved and regioselective synthesis of 4 starting from cyanoformate.[6c] A series of analogs of the type 5 (structures are shown below) has been prepared by Russian workers. However, no reports regarding the

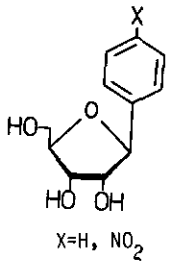


biological properties are available yet.[7]

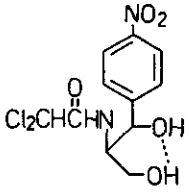


3. Deazapyrimidine Nucleosides

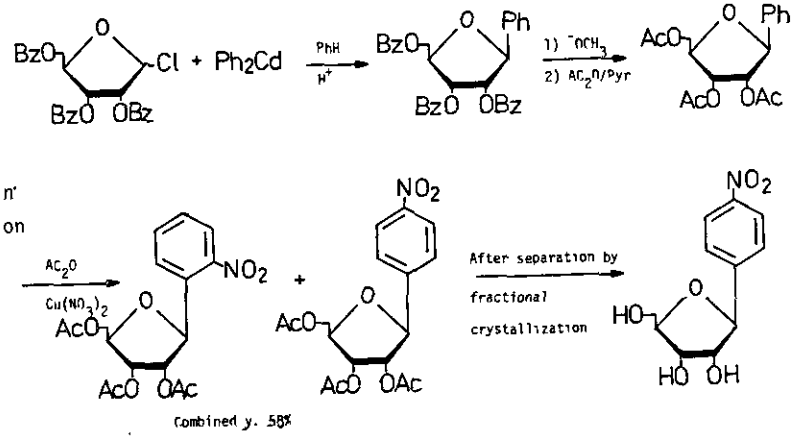
3-1 β-D-Ribofuranosylbenzene(Ribofuranosyl Analog of Chloramphenicol)[14] Since p-(5-dichloro-acetamido-5-deoxy-β-D-ribofuranosyl)nitrobenzene is considered as an analog of chloramphenicol (a potent inhibitor of protein biosynthesis) in "curled conformation", one might expect that X=NO_2 may be also an inhibitor of the synthesis. C-Glycosyl bond was made by "Cadmium method" as shown below: Thus, Mertes et al. prepared 2,6-dibenzyloxypyridyl-3-β-D-ribofuranoside.[15] By a similar technique, X=H was prepared and the β-configuration was initially and definitely determined with this compound.[13] Russian workers already had prepared D-ribopyranoside whose anomeric configuration was determined as β on the basis of large (7 Hz) coupling constant of $J_{1',2'}$ showing that adjacent hydrogens are located at trans and therefore the anomeric configuration is β. Periodate oxidation of the above D-ribofuranosylbenzene afforded a dialdehyde, which was reduced with $NaBH_4$ to the trialcohol 7. A similar oxidation and subsequent reduction of the above β-D-ribopyranosyl-benzene afforded a trialcohol which was found to be identical (mp, ord, and nmr) with the compound 7. Nitration of 6, followed by debloking afforded p-nitrobenzene-1-riboside.[6]



X=H, NO_2

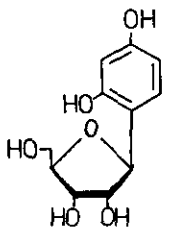


Chloramphenicol in "curled" conformation

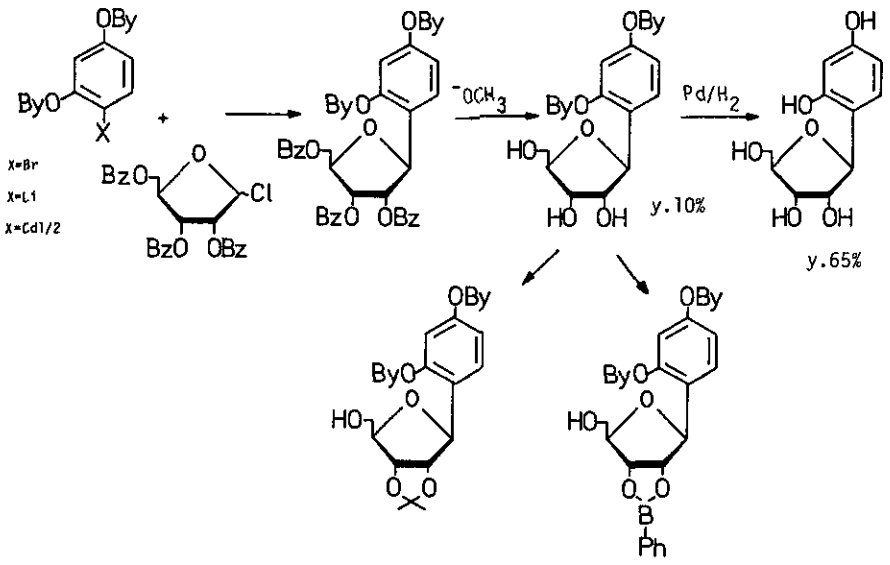


Combined y. 58%

3-2 1,3-Dideazauridine[17] This analog was prepared by "Cadmium method" from 1-lithio-2,4-dibenzyloxybenzene and 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride, as shown below. The structure was confirmed on the basis of combustion values and spectral (mass, nmr, and ir) data. The β-configuration at the anomeric position was based mainly on Imbach rule (Δδ=0.23) with its 2', 3'-O-isopropylidene derivative.

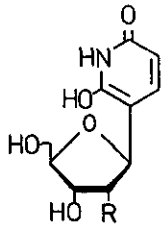


1-(β-D-Ribofuranosyl)-2,4-di-benzyloxybenzene (not de-blocked one) was found to be active against leukemia L1210 (50% inhibition at 7 x 10^{-6} M)



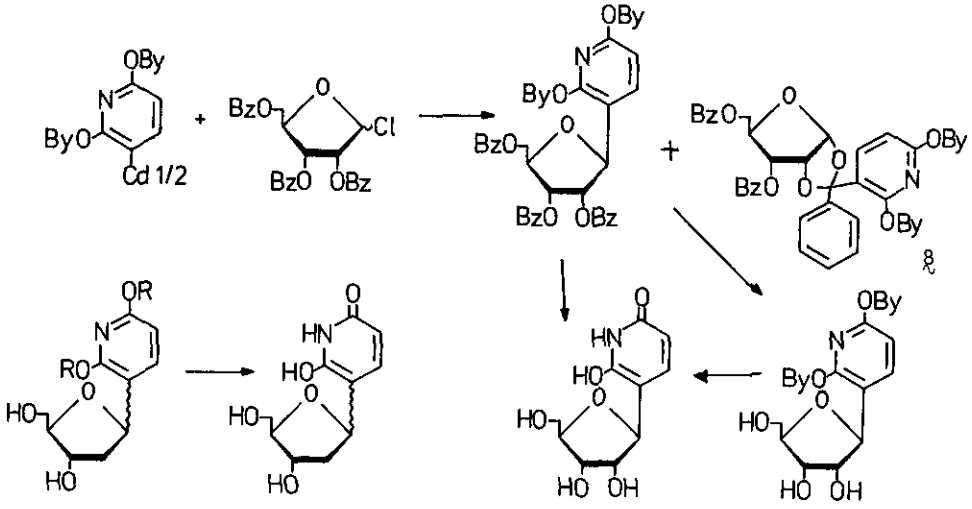
and against mammary carcinoma (50% inhibition at 5 x 10^{-6}M), but curiously enough, dideoxyuridine itself was much less active (leukemia 1210, 1 x 10^{-4}M).

3-3 1-Deazapyrimidine-1-D-ribofuranosides[18] This series of C-nucleosides was prepared as potential inhibitors of thymidylate synthetase, because B. R. Baker had suggested that the decreased electrondensity of the pyrimidine ring might enhance its electrostatic binding to the enzyme.



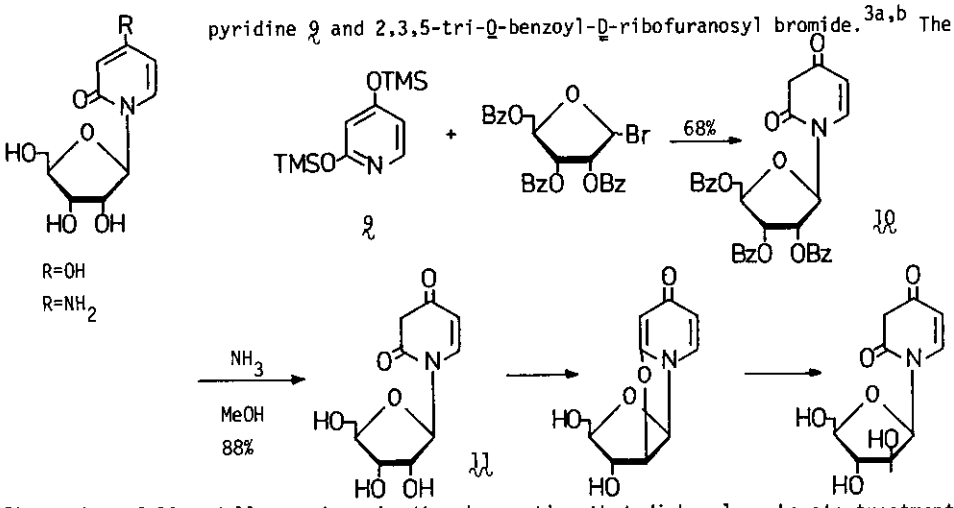
R=H or OH

As shown below, these C-nucleosides were also prepared by "Cadmium method".[15] The reaction of 2,6-di-benzyloxypyridine-3-cadmium derivative with TBRC led to the predominant formation of undesired ketal type product (8). A desired product, however, was isolated in



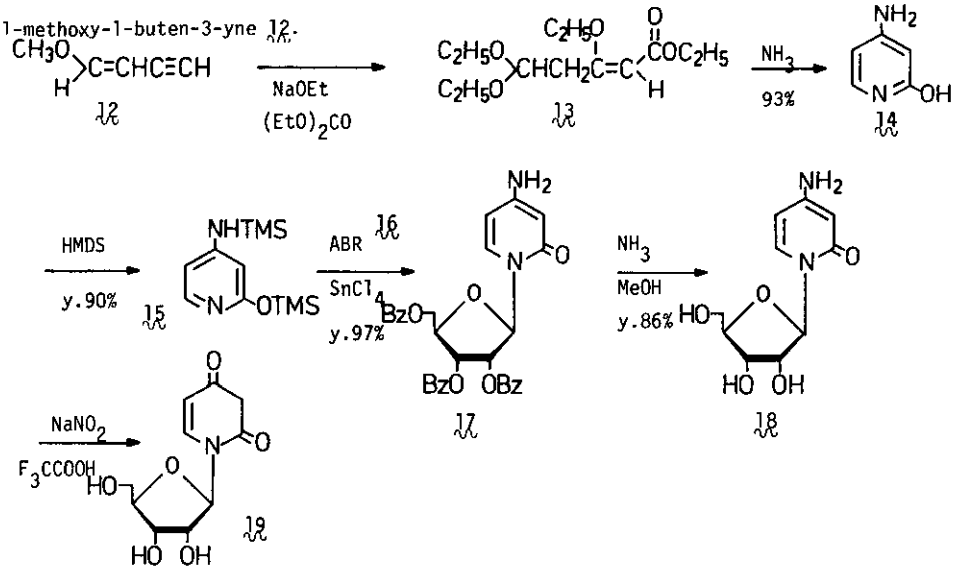
low yield (ca. 10%). These compounds were found to be quite unstable. No significant inhibition of thymidylate synthetase or dihydroreductase was observed in this series of compounds.

3-4 3-Deazauridine and 3-Deazacytidine (3-Deazapyrimidine-1-ribofuranoside)[3a,b] Two title compounds were prepared by Hilbert-Johnson procedure from 2,4-bis(trimethylsilyloxy)-pyridine 9 and 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide.[3a,b] The anomeric



configuration of 10 and 11 was shown by the observation that diphenyl carbonate treatment of 11 gave rise to the 2,2'-anhydro compound. It is of interest that in D_2O solution, H-3 of 11 was slowly replaced with deuterium.

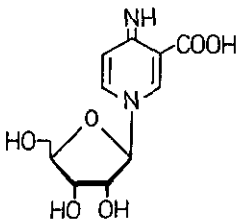
3-Deazacytidine was similarly prepared from 2-methoxy-4-acetamidopyridine and 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide. The structure was determined in a similar way, including the determination of the anomeric configuration. 3-Deaza-2'-deoxycytidine was also prepared.[3a] Quite recently (in 1977) an improved procedure of the synthesis of 3-deazapyrimidine ribosides was reported by Cook et al.[19] 3-Deazauridine and 3-deazacytidine were prepared in 70% overall yields, starting from 1-methoxy-1-buten-3-yne 12.



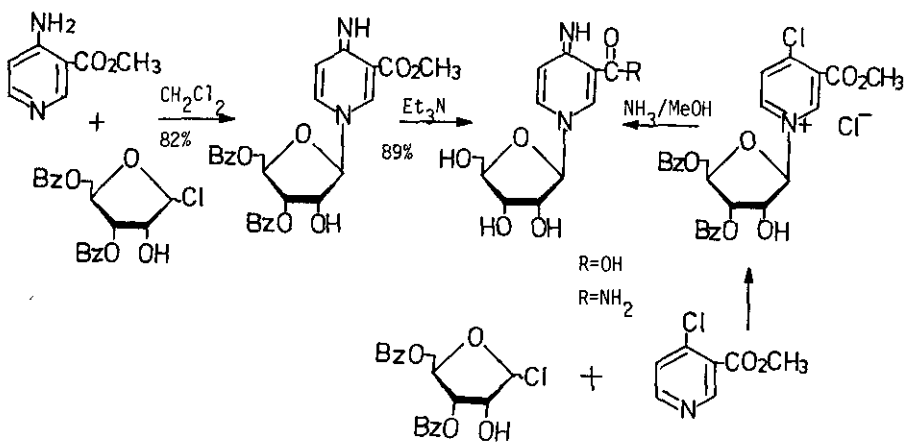
3-Deazauridine was shown to be active as antibacterial agent.[20] In addition, this drug posseses a wide spectrum of anti-RNA viral activity,[21] activity on cutaneous lesions in patients with nodular basal cell carcinoma, [22] and in vitro activity against neoplastic hepatic cell.[23]

3-5 1-(2-Deoxy-β-D-ribofuranosyl)-2(1H)pyridone This type of 3-deazapyrimidine-2'-deoxyribofuranoside and its nucleotides and also polynucleotides containing the analog were prepared and some properties were studied.[24]

3-6 Clitidine Clitidine was isolated from clitocybe acromelalga (Dokusasako in Japanese) by Matsumoto et al.[25] Marked increase in hyperemia and hyperesthesia in fingers and toes was observed on injection of this drug. It is to be noted that specific rotation of clitidine in aq. solution is $[\alpha]_D^{24}$-50.6, because common naturally occurring pyrimidine nucleosides have the specific rotation of plus sign. In nmr (DMSO) H-2 that is located in the vicinity of electron-attracting carboxyl group appears at 8.7 ppm as doublet having quite large long range coupling(J=1.5 Hz).



The chemical synthesis of clitidine starts from methyl 4-aminonicotinate. The reaction of the nicotinate (47 mg) with 3,5-di-O-benzoyl-D-ribofuranosyl chloride (97 mg) in CH_2Cl_2 at room temp.for 1 day gave rise to an excellent yield of N-ribosylated product having desired β-configuration. The assignment of configuration comes from the mode of reaction (presumably via 1,2-epoxido-D-ribofuranose)[26] and the result was further confirmed enzymatically. The site of ribosylation on the ring nitrogen rather than exo-nitrogen was chemically demonstrated as shown. Thus, the synthesis started from methyl 4-chloronicotinate, to lead to the formation of the same nucleoside. Almost

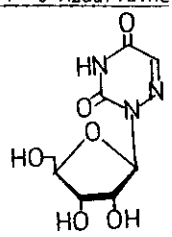


at the same time, the antibiotic was isolated and characterized by Ushizawa et al. and its physiological properties were extensively examined.[25b] Quite recently workers in the Institute of Immunological Sciences, Hokkaido University, studied on the biosynthesis of the antibiotic.[25c] In addition to clitidine and NAD, a number of pyridine (deazapyrimidine) nucleosides have been synthe-

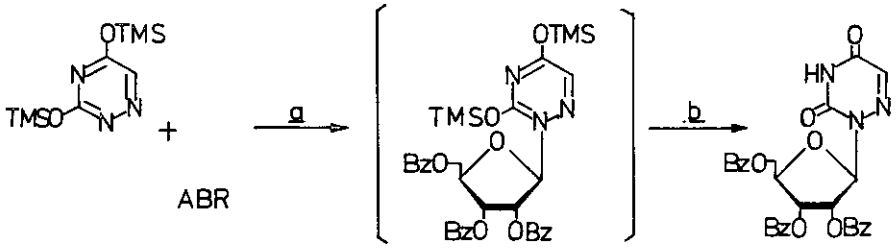
sized and their biological, biochemical, and physiological properties have been examined.[27]

4. Azapyrimidine Nucleosides

4-1 6-Azauridine



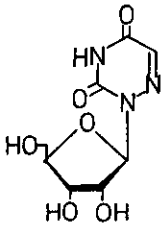
This drug was prepared by a number of different procedures. However, trimethyl-Si-blocked-Friedel-Crafts catalyzed Hilbert-Johnson method was found to be the method of chloice.[28] The reaction of 2,4-bis(trimethylsilyloxy)-6-aza-pyrimidine with ABR and $SnCl_4$ in 1,2-dichloroethane gave even on a 10 kg scale, after hydrolysis of thereactive intermediate, pure 2',3',5'-tri-O-benzoyl-6-azauridine in 93% yield. 6-Azauridine 5'-phosphate may be, above all, one of the most potent inhibitors against orotidine 5'-phosphate decarboxylase.



a. $SnCl_4/ClCH_2CH_2Cl$, 4 hr, 22°.

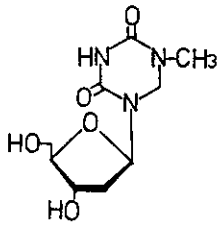
b. $H_2O/NaHCO_3$

c. $NH_3/MeOH$

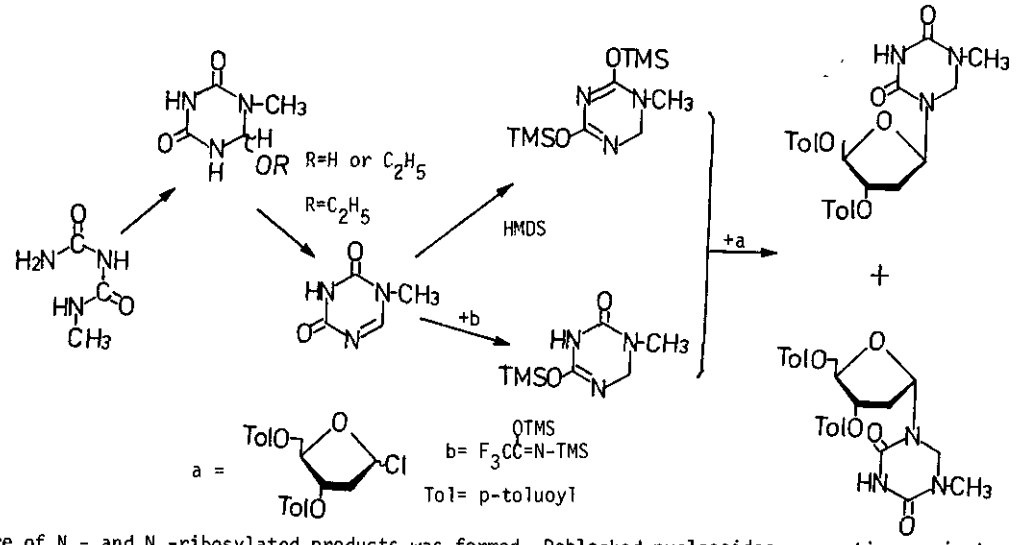


Among the above-mentioned several procedures was a method that was developed by Mizuno et al. who prepared the nucleoside via 4-methylthio-1-β-D-ribofuranoyl-2-pyrimidone. The latter was prepared by "Mercuri method" from 4-methylthio-2-pyrimidone.[28b]

4-2 5,6-Dihydro-5-azathymidine,[29, 30]

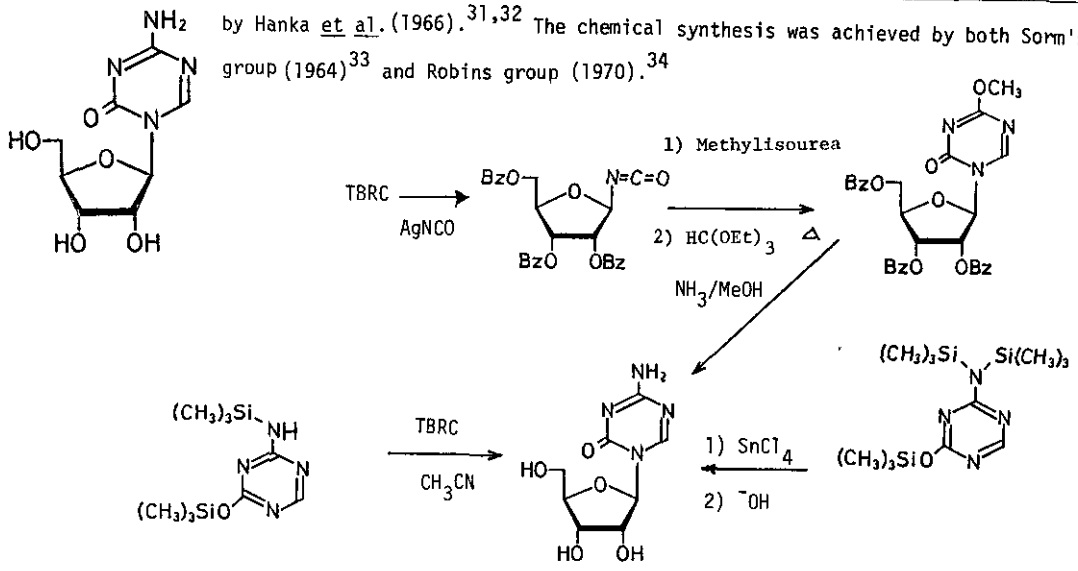


This antibotic with both antiviral and antibacterial activity was prepared by silyl ether modification of Hilbert-Johnson procedure.[28] On trimethylsilyl-ation, hexamethyldisilazane afforded bis-derivative, whereas bis(trimethyl-silyl) trifluoroacetamide in pyridine (25° for 18 h) gave rise mainly to mono-derivative. Configuration of N-glcosyl bond comes from the observation that in nmr, with β-anomer signals due to H-1' appear as triplet, while with α-anomer signals due to H-1' appear as characteristic quartet. Ratio of forma-tion of two anomers was found to be 1:1. Both antibiotics are in clinical use as antineoplastic agents. The corresponding riboside was also prepared. From the synthetic standpoint, it is of in-terest that the reaction of 5,6-dihydro-5-methyl-s-triazin-2,4-dione with ABR, TBRB, or tri-O-acetyl-D-ribofuranosyl bromide gave rise to N_3-riboside alone, whereas with tetra-O-acetyl-ribose, a

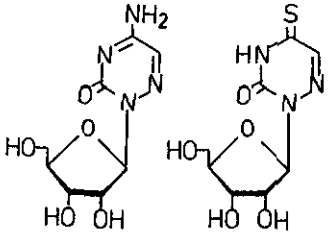


mixture of N_1- and N_3-ribosylated products was formed. Deblocked nucleosides are active against both herpes simplex type I and herpes simplex type II. Other analogs that belong to azapyrimidine nucleosides have been also prepared.[27 a,b,c,d]

4-3 5-Azacytidine 5-Azacytidine was isolated from a culture broth of streptoverticillium ladakanus, by Hanka et al. (1966).[31,32] The chemical synthesis was achieved by both Sorm's group (1964)[33] and Robins group (1970).[34]

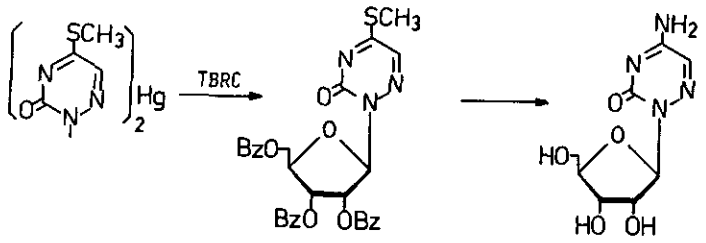


4-4 6-Azacytidine Sorm et al.[35] prepared azacytidine and some of its derivatives. The 4-thio-derivative was obtained from 2',3',5'-tri-O-acetyl- or 2',3',5'-tri-O-benzoyl-6-azauridine by treatment with phosphorus pentasulfide: this procedure afforded 4-thio-6-azauridine which was identified with 4-thio-6-azauracil by comparing the uv spectra each other. Treatment with ammonia produced 6-azacytidine; treatment

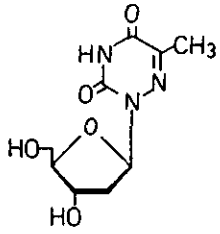


with hydrazine, hydroxylamine, and n-butylamine yielded the corresponding derivatives The uv spectra of 5-azacytidine are similar to those of uridine and 6-azauridine, but differ from those of cytosine and cytidine. On the other hand, the spectrum of the 4-methylamino derivative is different from that of 6-azacytidine and similar to that of cytidine.[36] The ir spectra of chloroform solution of 6-azacytidine and its derivatives show that these compounds, like the corresponding cytidine derivatives, exist in the amino form.

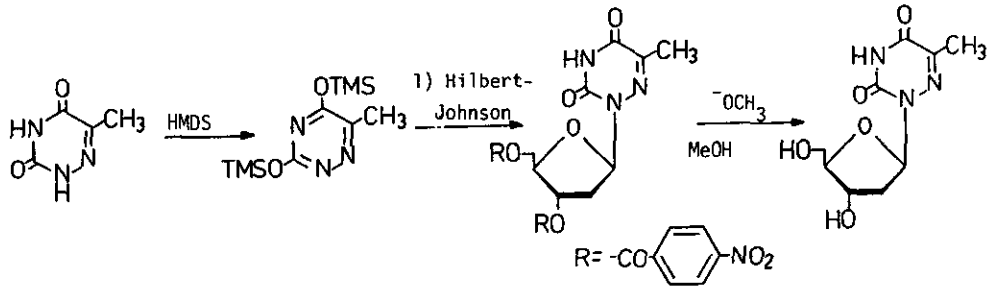
Mizuno et al. also prepared the same nucleoside in the following way.[37,38]



4-5 6-Azathymidine



6-Azathymidine [(2-deoxy-β-D-erythro-penrofuranosyl)-6-methyl-1,2,4-triazine-3,5-(2H,4H)-dione] is a strong inhibitor of the synthesis of nucleic acids and a much more potent antagonist of thymine and thymidine than is 6-azathymine[39,40] Plimil et al. are the first to obtain the analog as an amorphous solid by the "Mercuri salt method"(1963).[41] Quite recently(1978) the preparative procedure has been much improved by the application of TMS-Hibert-Johnson method and high yield of crystalline analog could be prepared. The outline of Shian and Prusoff's procedure is shown below.[42]

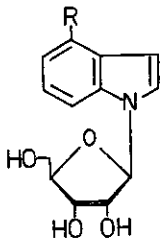


The assignment of β-configuration was based mainly on the observation that a signal(at 6.53 ppm) due to H-1' appears double-doublet($J_{1',2'}$, 5.88 Hz; $J_{1',2''}$ 6.22 Hz) typical of an anomeric proton of β-D-2'-deoxyriboside. Mitra and Saran have discussed about the conformation of 6-azapyrimidine nucleosides.[43]

5. Deazapurine Nucleosides

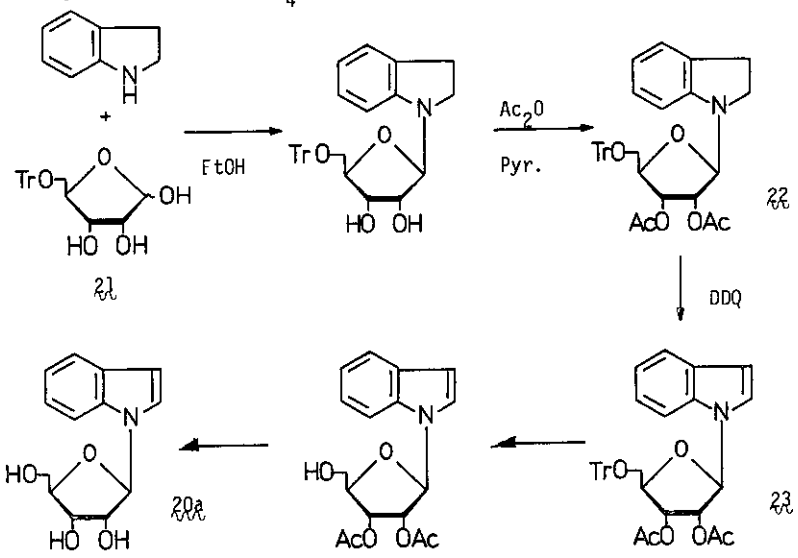
5-1 1-(β-D-Ribofuranosyl)indole and 4-Amino-1-(β-D-ribofuranosyl)indole(1,3,7-Trideazaadenosine)[44-46]

1-(β-D-Ribofuranosyl)indole (1,3,7-trideazaneblarine) is the first indole analog of nucleo-



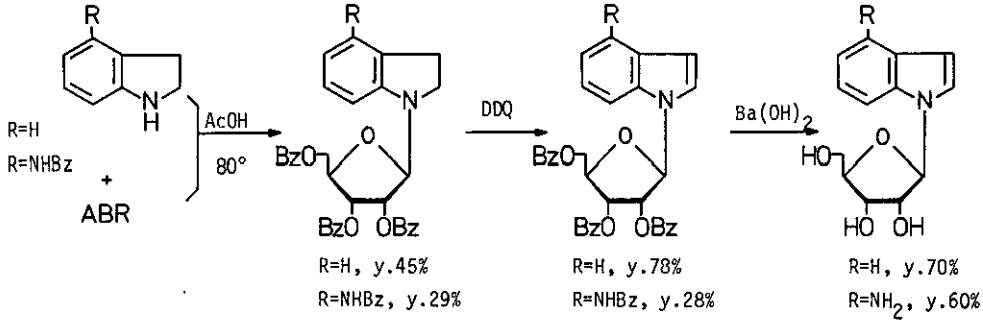
20 R=H or NH_2

side, which has been prepared in 1967 by the "indoline-indole method". This work has been stimulated by the discovery of tubercidin and toyocamycin which is pyrrolopyrimidine nucleoside analog. Thus, the condensation of 5-O-trityl-D-ribose 21 with indoline resulted in 5-O-tritylribofuranosylindoline whose acetylation led to 1-(5-O-trityl-2,3-di-O-acetyl-β-D-ribofuranosyl)indoline 22. Indole riboside 23 was obtained by dehydrogenation of the latter with dicyanodichloroquinone (DDQ) rather than chloranil. The detritylation (with 80% AcOH) and deacetylation (with $Ba(OMe)_2$) gave 1-(β-D-ribofuranosyl)indole. The structure was confirmed by nmr and ir spectral analysis as well as $NaIO_4$ oxidation[care must be exercised because indole ring may

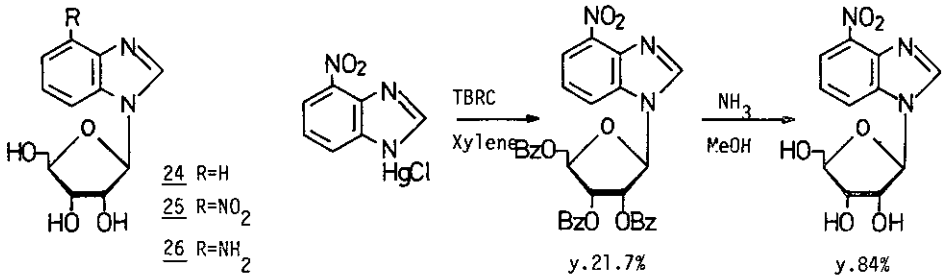


be able to consume the oxidant[44]], $[\alpha]_D^{20}$ -7.1° specific rotation being negative, but small.

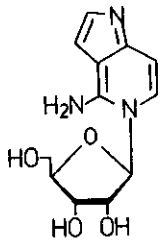
In the following year, Walton et al. also prepared 20a starting from TAR by indoline-indole method.[45] In addition 4-aminoindole-1-ribofuranoside(20b, 1,3,7-trideazaadenosine) was prepared by the same workers.[45] Walton[45] as well as Suvanov[44] noted the superiority of DDQ over chloranil in oxidation of indoline to indoles.



5-2 5-Nitrobenzimidazole Ribosides Mizuno et al. prepared benzimidazole ribofuranosides in the following way. However, they failed to prepare 1,3-dideoxyadenosine 26.[47]



5-3 Iso-3-deazatubercidin[48] 4-Amino-5-azaindole was obtained starting from 1-benzylpyrrole as shown. Thus, direct alkylation of the corresponding 4-benzamido derivative 43 with TBRB and subsequent debenzylation led to the corresponding N-5-8-D-ribofuranoside. The structure and configuration of this compound were deduced on the basis of spectroscopic data which were in good agreement with X-ray crystallographic data. This is the first example of di-deazaadenosine analogs .



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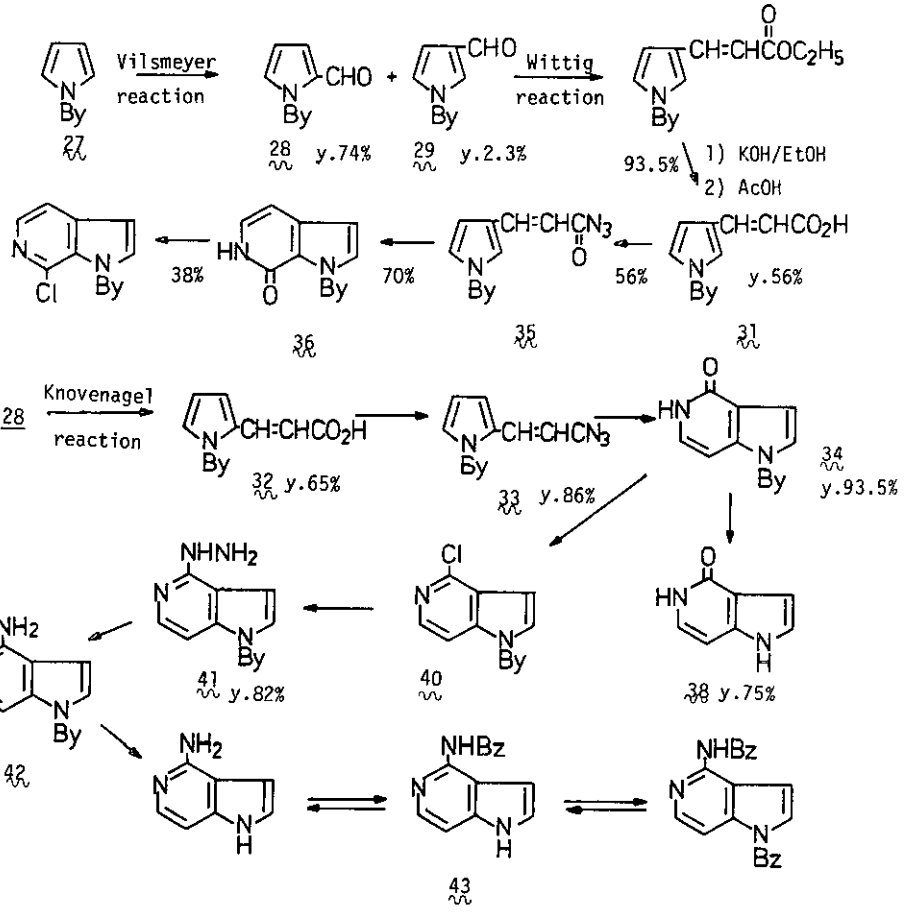
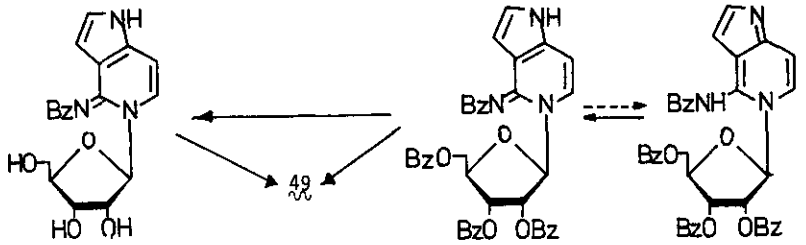
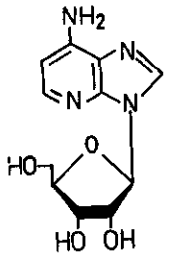


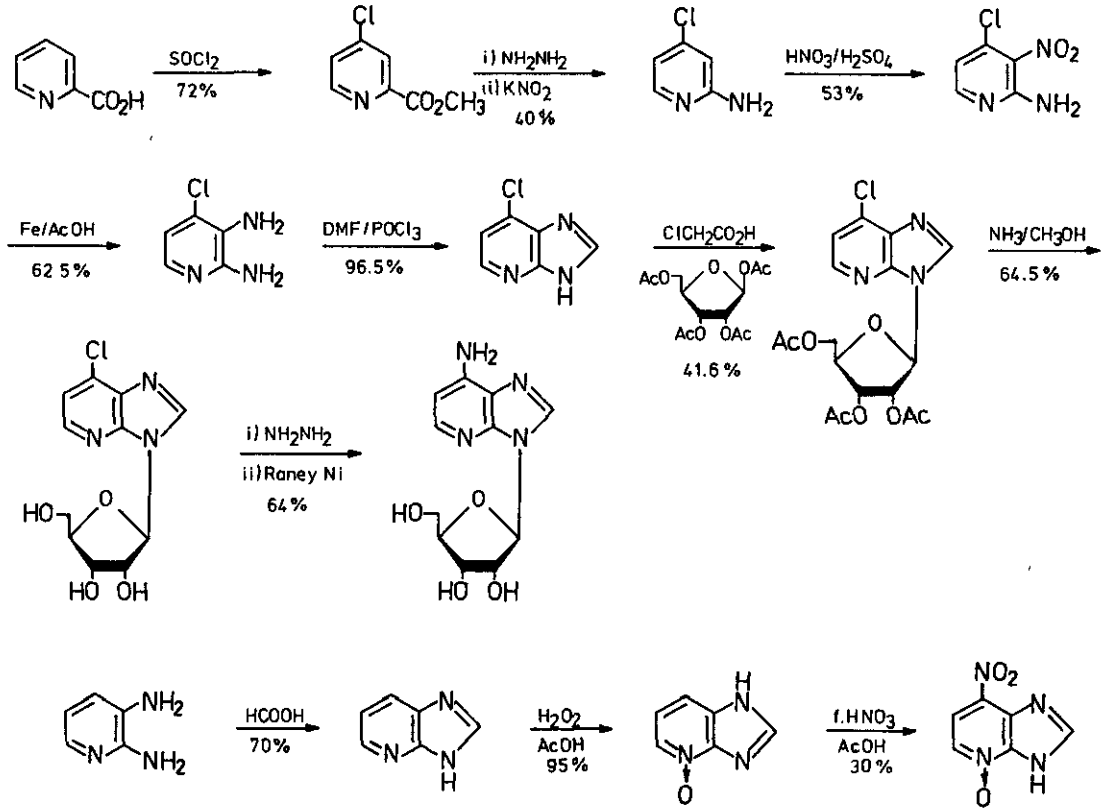


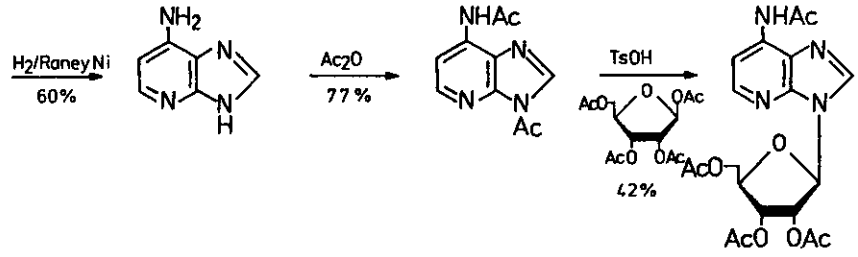
47 49 46 45

5-4 1-Deazaadenosine



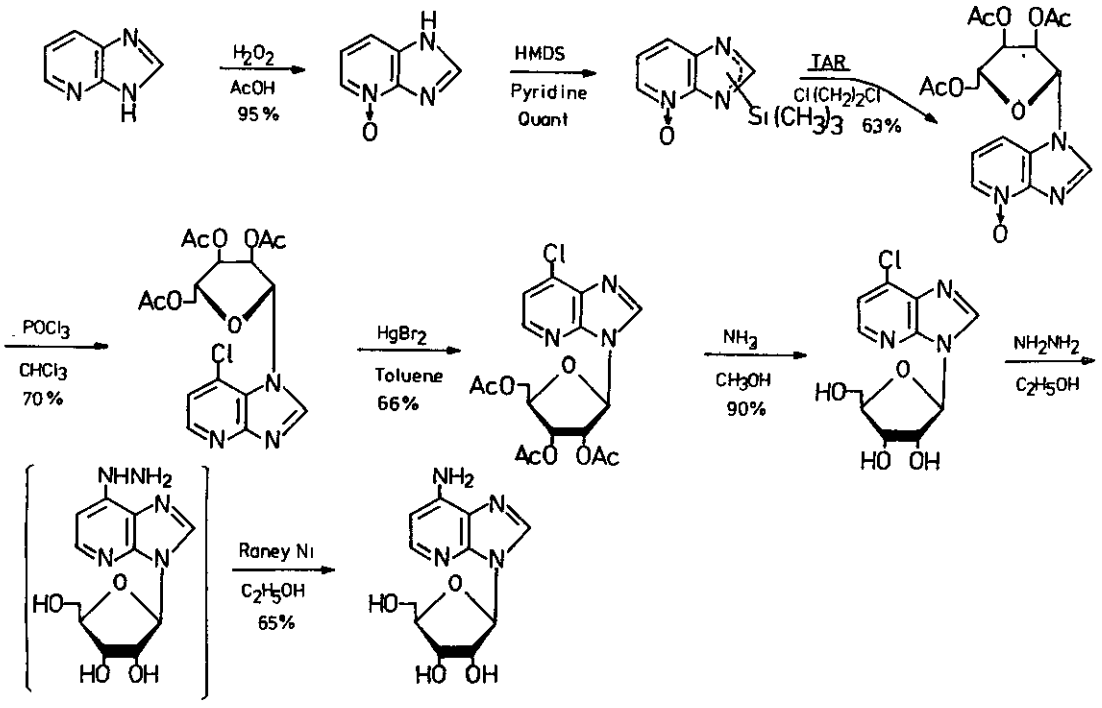
Anand et al. are the first to prepare 1-deazaadenosine.[51] De Roos and Salemink [49] then prepared the same analog from commercially available α-picolinic acid in 10 steps in quite unsatisfactory overall yields, as shown. N-Glycosyl bond was formed by fusion procedure. Itoh and his coworkers prepared the nucleoside by alternate route.[50] One of the key intermediates, 2'-3-diaminopyridine, could be prepared according to a reported procedure.[52] 1-Deazaadenosine was prepared from the 2,3-diaminopyridine as shown in an accompanying sheet.



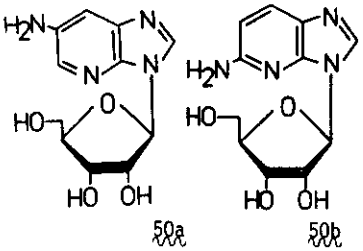


The site of ribosylation and the configuration of N-glycosyl bond will be discussed along with the case of 3-deazaadenosine synthesis. Itoh and his coworkers devised another synthesis which was able to much better overall yield, starting from 1-deazapurine, overall yield being ca. 20%.

Improved synthesis of 1-deazaadenosine This improved synthesis (Itoh et al.[53]) deserves some



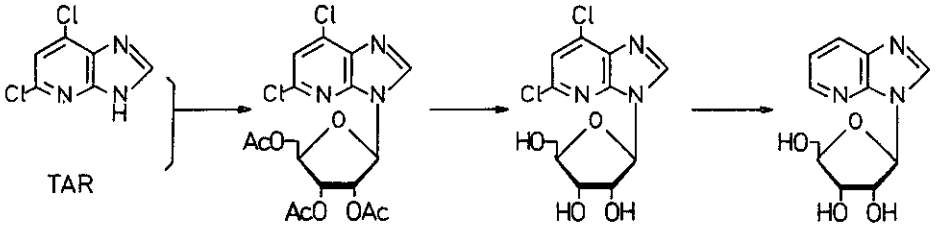
comments: Polonovski reaction took place in a regioselective way and in boiling toluene 9-substituted 1-deazapurine may be more thermodynamically stable and therefore $HgBr_2$-catalyzed migration of 7-ribosyl group to the position 9 took place.

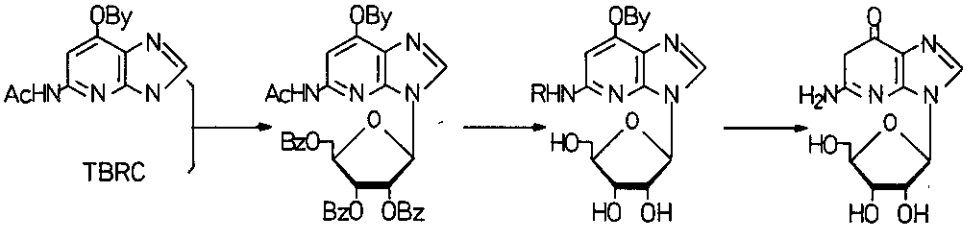


Itoh et al. have also prepared other adenosine analogues 50a and 50b.[54] This type of analogues are of interest, because these

will be useful as probes for screening the potential inhibitors against suicide-type enzyme such as S-adenosylhomocysteinase [56] and might have other interesting physiological properties.

5-5 1-Deazaguanosine[57] A fusion reaction of 5,7-dichloroimidazo[4,5-b]pyridine with TAR gave, after deacetylation, 5,7-dichloro-3-β-D-ribofuranosylimidazo[4,5-b]pyridine. The site of ribosylation and the anomeric configuration of the nucleoside obtained were determined by convertingit into the known 3-β-D-ribofuranosylimidazo[4,5-b]pyridine.[58] In a direct condensation of 5-acetamido-7-benzyloxyimidazo[4,5-b]pyridine[59,61] with TBRC in nitromethane, a riboside which was formed, afforded 1-deazaguanosine upon removal of the protecting group. The structure of this compound was confirmed by its conversion into the above β-D-ribofuranosyl-5,7-dichloroimidazo[4,5-b]pyridine.

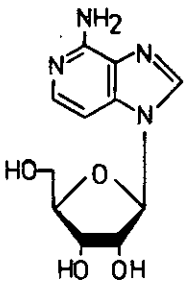




The structure of substituted nucleoside was confirmed by ir, nmr and uv spectra.

5-6 1-Deaza-6-thioguanosine and 1-Deaza-6-(methylthio)guanosine[60] 6-Substituted 1-deazaguanosines were prepared by Elliot and Montgomery starting from 2-acetamino-6-chloro-1-deazapurine and TARC.[60] 2-Amino-6-chloro-1-deazaguanosine was active against L-1210 mouse leukemia and was able to produce a 79% increase in life span of the mouse. The chloro-derivative was converted to thiol and methylthio-derivative by usual procedures.

5-7 3-Deazaadenosine 3-Deazaadenosine was initially prepared by Robins et al.[4b] and then by Mizuno and his coworkers via quite similar route, starting from 6-chloro-3-deazapurine.[62] In 1975 a slight modification was introduced by May and Townsend by use of 4,6-dichloroimidazo[4,5-c]pyridine as a starting material.[63] Montgomery et al. optimized the early conditions to prepare a high yield of the title analog , starting from the dichloro-3-deazapurine and TAR.[64] 3-Deazaadenosine has a potent activity against herpes simplex 1. In addition isobutylthio-5'-deoxy-3-deazaadenosine,[60]



S-3-deazaadenosyl-L-homocysteine and the dialdehyde of the latter was found to be biochemically active analogs.[67]

Until now we have reserved the discussion of the site of ribosylation and the determination of N-glycosyl bond formed in the synthesis of 1- and 3-deaza-adenosine.* Now the discussion will be touched on briefly. Mizuno et al.[58,65b] and Elguero et al.[65a] prepared in an unambiguous way each pair of 7- and 9-methyl-1- or 3-deazapurine, and 3-methyl-derivative. The site of ribosylation of 1- or 3-deazapurine could be determined by spectral comparison of product(s) with those of N-methyl counterparts. The β-configuration was assigned on the basis of the mode of reaction(Baker's 1,2-trans rule) and in the case of 1-deazapurine ribofuranosides, the β-configuration was further confirmed by the demonstration of 5',3-cyclonucleoside formation. In the case of ribosylation of chloro-deazapurines, the product(s) were subjected to catalytic hydrogenation leading to the known β-D-ribofuranosyl-1- or 3-deazapurines. Thus, 1- or 3-deazaadenosine was derived from the chloro-1- or 3-deazapurine riboside of the definite structure, respectively. 2'-Deoxy-3'-deazaadenosine was also prepared.[55]

5-8 8,5'-O-Cyclo-3-deazaguanosine[68] Tanaka and Ueda prepared the title compound from 1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid methyl ester which in turn recently became available from 2',3'-O-isopropyliden-5-bromouridine. One of key steps of their synthetic sequence is the introduction of cyanomethyl group on position 5 of the imidazoline moiety.

---

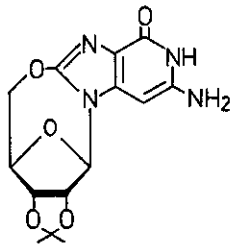
* We had a table of nmr data of 3-deazaadenosine made by Dr. Hurwitz(Detroit) and Dr. Endo(Fuji Kagaku) to show that reported chemical shifts, notably of H-8 of 3-deazaadenosine are different from sample to sample depending upon the sources(lit. 65).

Nmr Data of 3-Deazaadenosine(Numbers in parentheses refer to coupling constants in Hz)

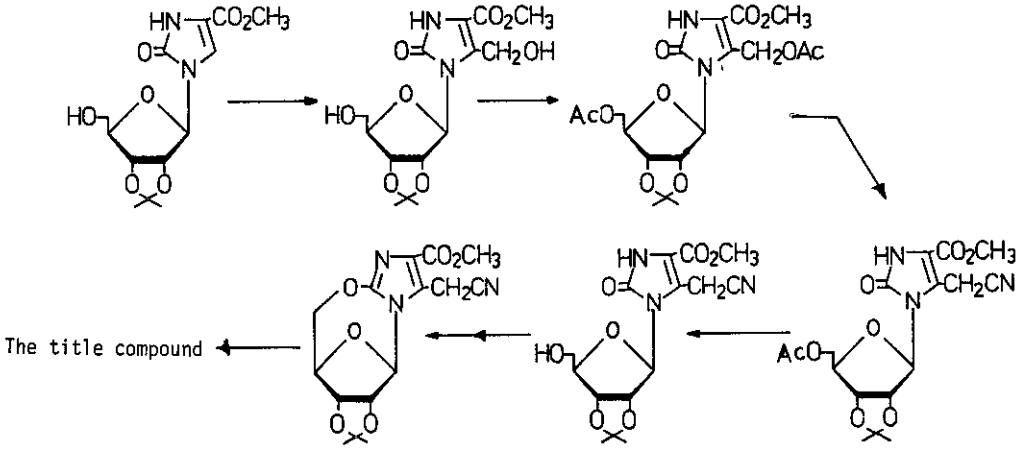
H_8	H_2	H_3	$H_{1'}$	H_6	reference	Lit.
8.72	7.79 (7.1)	7.46 (7.1)	5.98 (5.9)	8.52	TMS	a
8.24	7.66 (5.8)	6.90 (5.8)	5.75 (5.9)	6.11	TMS	Sample from NIH
8.30	7.69	6.93	5.78	6.14	DSS	Sample from NIH
8.77	7.83 (3.5)	7.47 (3.5)	5.99 (3.0)	8.63	TMS	63
8.3	7.7 (6.0)	6.9 (6.0)	5.8 (6.1)	6.2	TMS	64

a S. Kitano, Y. Mizuno, M. Uemura, K. Tori, M. Kamisaka, and K. Ajisaka, Biochem. Biophys. Res. Commun., 1980, 23, 347.

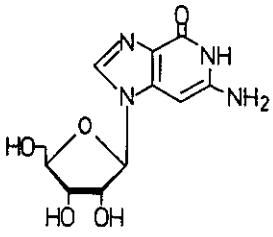
Regarding this matter, nmr spectral deta of 4-amino-3-β-D-ribofuranosyl-3H-imidazo[4,5-c]pyridine (a positional isomer of 3-deazaadenosine) whose synthesis has never been reported are highly desirable.



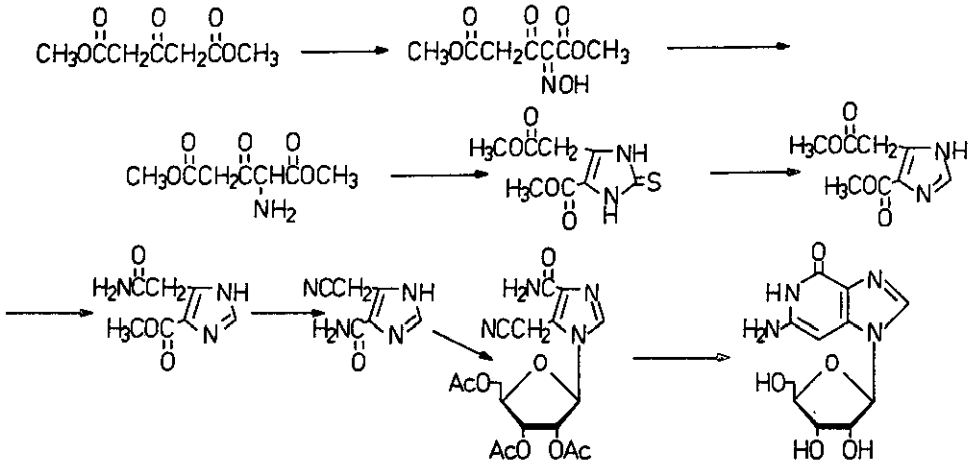
They successfully achieved the cyanomethylation by a series of reactions (hydroxymethylation→acetylation→substitution of the acetoxy group with cyano group). In the subsequent steps, they used a base-catalyzed ring closure which had been developed by Cook et al.[69] The acetoxy group could be quite easily displaced with cyano group. This displacement presumably took place via elimination and addition mechanism.



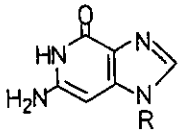
5-9 3-Deazaguanosine[69]



This analog may be useful biochemical tools employed to probe enzymatic transformations and also is active against the viral infection. The synthesis was achieved by Robins and coworkers in an ingeneous way.[69] One of key steps was ribosylation of 5-cyanomethylimidazole-4-carboxamide or 5-carbamoylmethyl-4-carbomethoxyimidazole. Another was a base-catalyzed ring closure of 1-β-D-ribofuranosyl-5-cyanomethylimidazole-4-carboxamide. Thus, the outline of synthetic sequence is shown below.



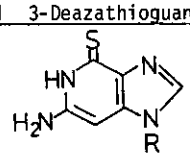
5-10 1-β-D-Arabinofuranosyl-3-deazaguanine Poonian et al.[71] prepared the title compound analogously.



R=β-D-arabinofuranosyl

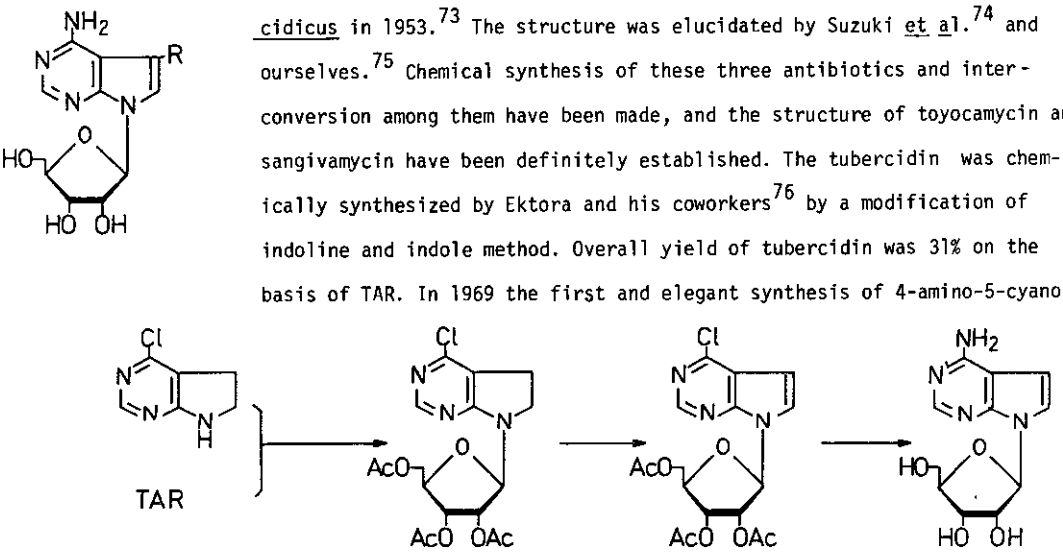
However, they experienced difficulty to isolate a pure sample of the analog, because glycosylation with sugar having non-participating blocking group gave rise to both a positional (N-1 and N-3) and anomeric mixture of arabinosides.

5-11 3-Deazathioguanosine[6-Amino-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine-4-thione][72] The title analog was prepared analogously. In this case, the anomeric configuration was confirmed to be β-D, on the basis of the fact that Δδ of the methyl group of the corresponding 2',3'-O-isopropylidene-3-deazathioguanosine is 0.22. The key step of their synthesis consists in the ribosylation of trimethylsilyl derivative of 4-bromo-6-acetamido-3-deazapurine with TBRC by mercury cyanide-nitromethane procedure.

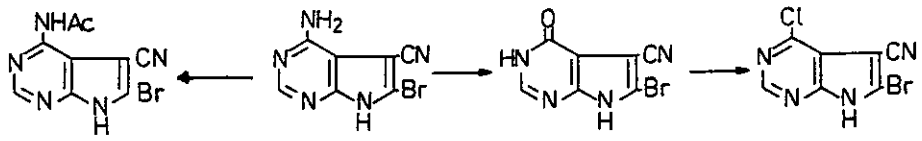


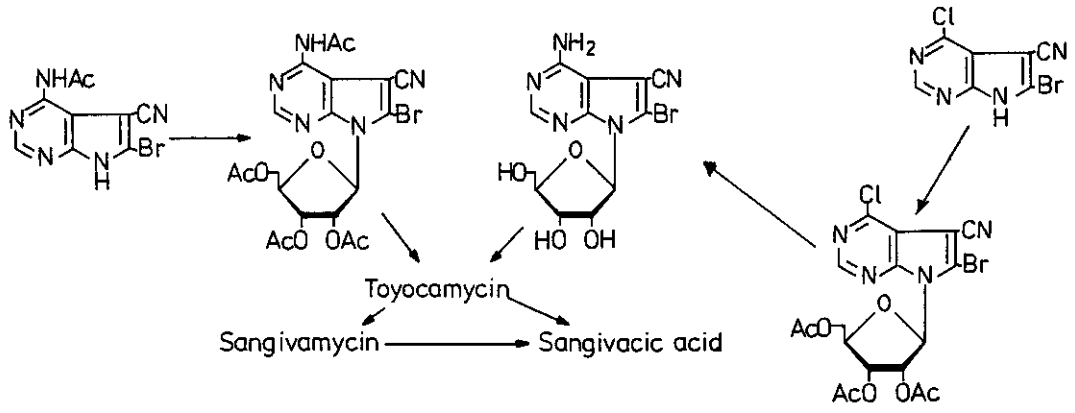
R=β-D-ribofuranosyl

5-12 Tubercidin, Toyocamycin, and Sangivamycin Tubercidin was isolated from Streptomyces tubercidicus in 1953.[73] The structure was elucidated by Suzuki et al.[74] and ourselves.[75] Chemical synthesis of these three antibiotics and interconversion among them have been made, and the structure of toyocamycin and sangivamycin have been definitely established. The tubercidin was chemically synthesized by Ektora and his coworkers[76] by a modification of indoline and indole method. Overall yield of tubercidin was 31% on the basis of TAR. In 1969 the first and elegant synthesis of 4-amino-5-cyano-



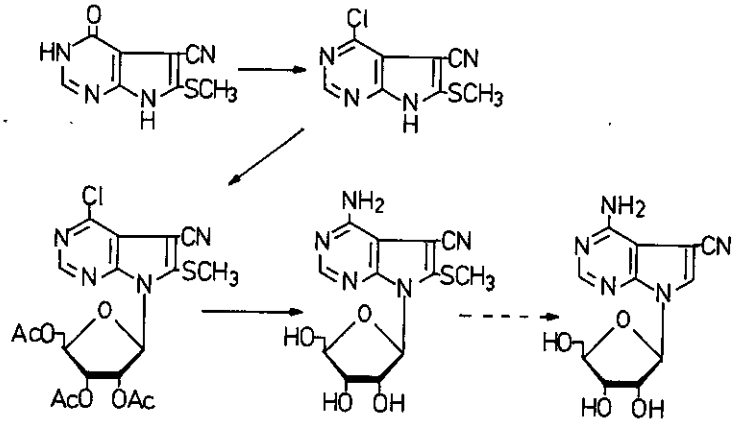
7-β-D-ribofuranosylpyrrolo[2,3-d]pyrimidine by direct ribosylation of a pyrrolo[2,3-d]pyrimidine was accomplished by the fusion procedure.[85]



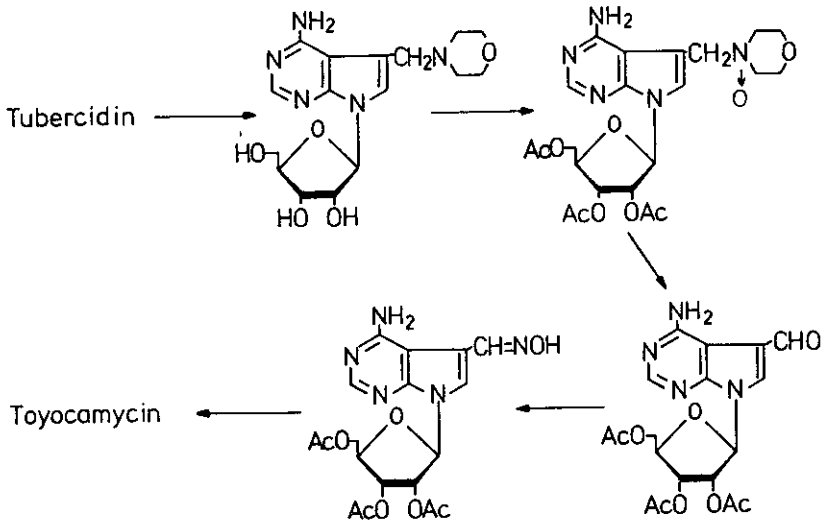


However, prior to the work in 1967, Tolman et al. failed to dethiate 4-amino-5-cyano-6-methylthiopyrrolo[2,3-d]pyrimidine into toyocamycin. The Raney nickel reduction gave rise to an untractable mixture, showing that the substituent on position 6 has a critical implication in the synthesis of 7-deazapurine nucleoside synthesis.[86]

All three of the above pyrrolopyrimidine nucleoside antibiotics are reported to possess cytotoxicity against HeLa cell in cell cultures and to exihibit remarkable activity against leukemia L1210 in mice.

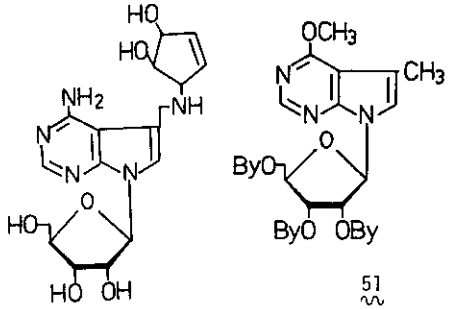


Ueda et al. were able to convert successfully tubercidin to toyocamycin.[77] The key step in this transformation is to introduce one carbon unit into the position 5 of the former. To this end, Mannich reaction has been used. The conversion of morpholinomethyl group into formyl group was effected by the N-oxidation and successive treatment with acetic acid of the product. The formyl derivative was converted into cyano group by way of the oxime. The outline of their synthetic scheme is shown on next page. The overall yield of toyocamycin from tubercidin was satisfactory.



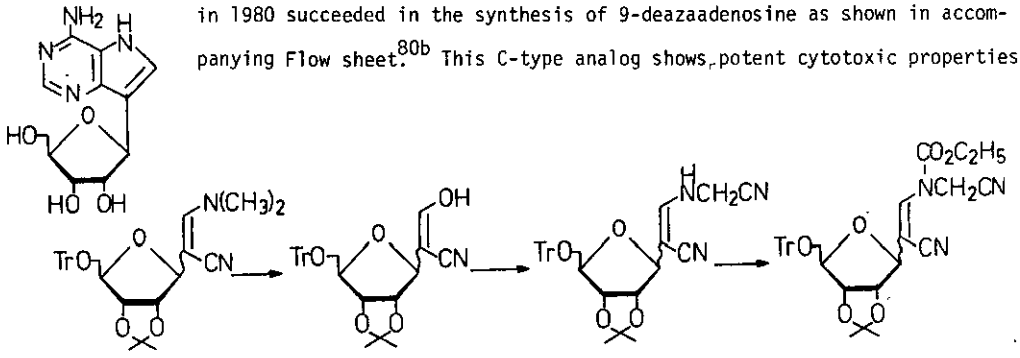
5-13 4-Amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-d]pyrimidine [78](Aratubercidin) Arabinofuranosyladenine is very important antiherpes agent. This stimulated the synthesis of the title compound.

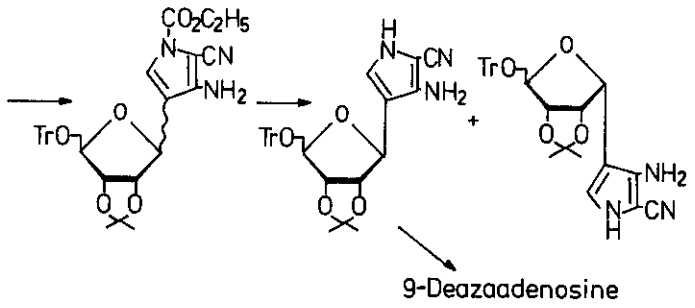
5-14 Queosine and Related Nucleosides In 1968 a nucleoside named Q was discovered in the first letter of the anticodon of tRNA whose corresponding codons consist of UApyrimidine, CApyrimidine, AApyrimidine, or GApyrimidine. A common feature is that adenosine is located in the middle of an anticodon ending in pyrimidine nucleoside. Recently. Goto et al. have definitely determined the absolute configuration regarding cyclopentene ring and concomitantly achieved the total synthesis of the nucleoside.[79] The synthetic sequence starts with 51 whose anomeric configuration has been rigorously established as β. Queosine was obtained in 10 steps. Concerning details of this elegant work, refer to the original paper.[79]



51

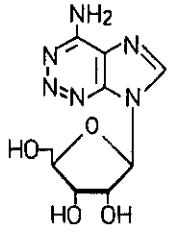
5-15 9-Deazaadenosine Lim and Klein who have already achieved the synthesis of 9-deazainosine[80a] in 1980 succeeded in the synthesis of 9-deazaadenosine as shown in accompanying Flow sheet.[80b] This C-type analog shows potent cytotoxic properties.



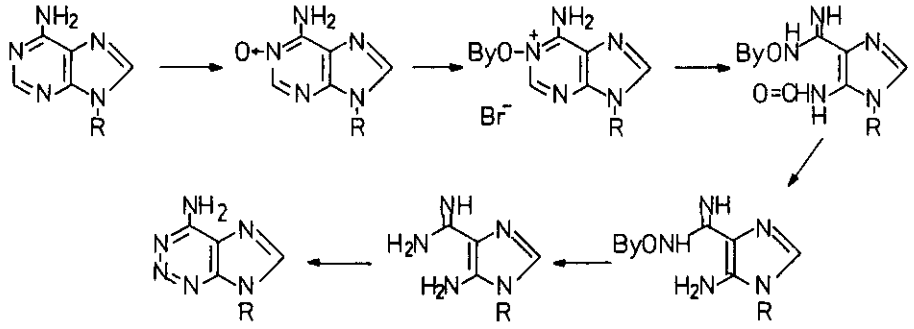


6 Azapurine Nucleosides

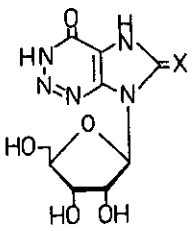
6-1 2-Azaadenosine

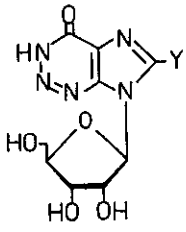


This analog has anticancer activity and other interesting biological properties for example, 2-azaadenosine is cytotoxic to human epidermic carcinoma cells in culture and shows consistent activity against L-1210 leukemia in both chronic and single-dose schedules. This analog was initially prepared by Montgomery and Thomas in 1969.[109] However, the report of Montgomety and Jeanette in "Nucleic Acid Chemistry" is the preparation of choice.[110]



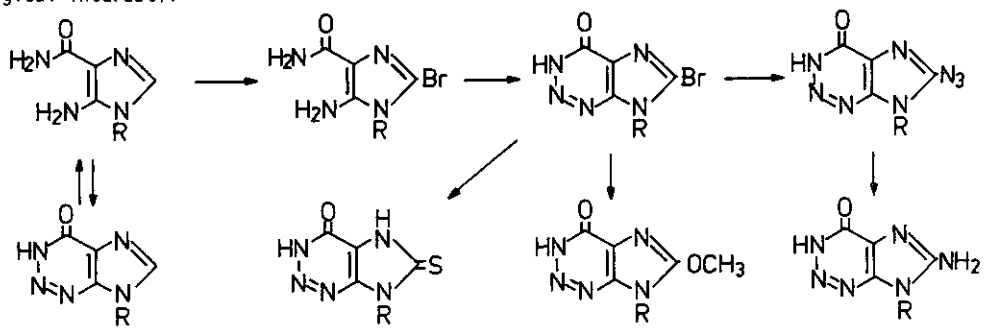
6-2 8-Substituted 2-Azainosine[89]



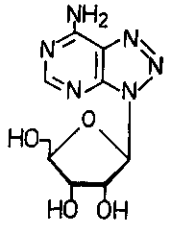


It is well established that halogen atom on the imidazole may be inert toward nucleophilic attack. However. in cases where the imidazole ring is fused with electron deficient triazine ring to form imidazo[4,5-d]-v-triazine system, halogen atom on the imidazole ring moiety of the fused ring system becomes more susceptible to nucleophilic displacement with a variety of nucleophiles. On the other hand, 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide(AICAR) and 4-hydroxy-(7-β-D-ribofuranosyl)-imidazo[4,5-d]-v-triazine(2-azainosine) are interconvertible; namely, hydrogenation in the presence of Raney Ni (for this purpose, hydrogenation over Pd/C was of no use) can effect opening of the triazine ring to give AICAR, whereas AICAR can be ring-closed to triazine system with HONO to afford 2-azainosine. Therefore, 2-azainosine can be viewed as "masked" AICAR whose halogen on the imidazole can be re-

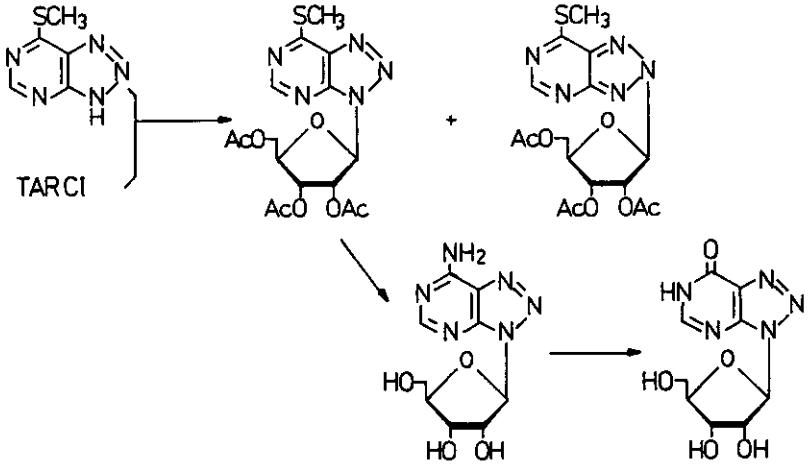
placed with nucleophile. As shown in an accompanying flow sheet, 2-azainosine is a key intermediate for the synthesis of 2-substituted imidazole ribosides (in addition to a potential antimetabolite of biological interest).



6-3 8-Azaadenosine[88] The title analog has attracted considerable attention as purine antagonists biological system, including virus and cancers. Since azapurines appear to function by incorporation as ribosyl derivatives, the synthesis, for biological testing, of the analog was undertaken. Synthetic sequence starts with the reaction of chloromercuri-derivative(7-amino-5-methylthio-v-triazolo[d]pyrimidine). Analogously, 8-azainosine was prepared by the same author(J. Davoll) in 1958. However, in elsewhere one wants to prepare these analogs, the directions written by Montgomery and Elliot in "Nucleic Acid Chemistry" are recommended.[89]



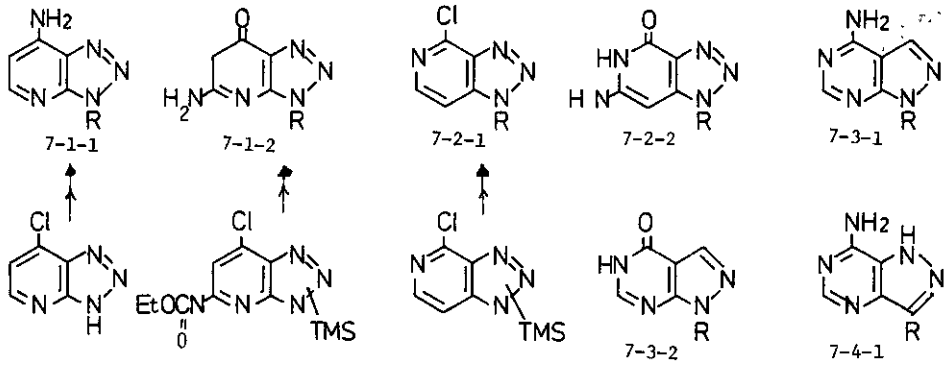
8-Azainosine was found to be incorporated into RNA in place of guanosine.[90]



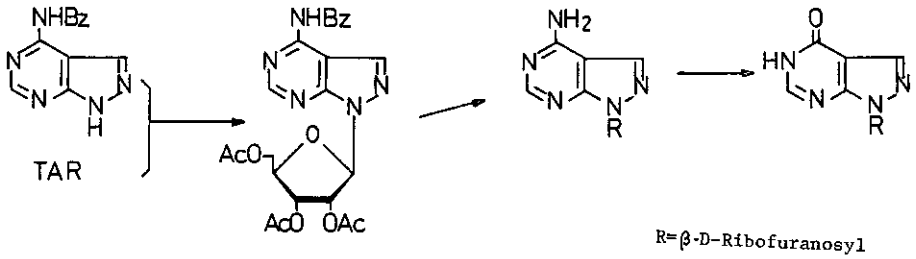
7. Deazaazapurine Nucleosides

1-Deaza-8-azaadenosine (7-1-1, De Roos and Salemink, 1971)[81], 1-deaza-8-azaguanosine(7-1-2, Cline, Panzica and Townsend, 1976)[82], 6-substituted 3-deaza-8-azapurine ribosides(7-2-1, May and Townsend, 1976)[83], 3-deaza-8-azaguanosine(7-2-2, Meyer et al, 1980)[84], 7-deaza-8-azaadenosine(7-3-1,

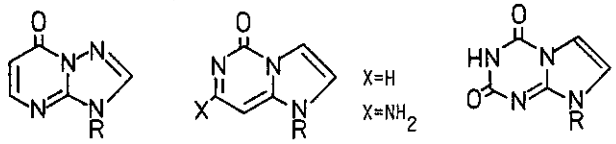
Montgomery, Clayton, and Fitagibbon, 1964; Krenitsky et al, 1967)[92,93] allopurinol-1-ribofuranoside (7-3-2, Krenitsky et al, 1967)[93] and formycin(7-4-1, 9-deaza-8-azaadenosine) fall into this category.



7-3-2 Allopurinol-1-ribofuranoside[93] In 1964, Montgomery et al. initially prepared 1-(β-D-ribofuranosyl-4-aminopyrazolo[3,4-d]pyrimidine.[92] The procedure was slightly improved by Krenisky et al.[93]



7-4-1 Formycin This antibiotic was discovered by Hori et al, in 1964 from culture broth of Norcardia interforma.[94] The structure was elucidated by X-ray analysis[95] and by other instrumental analysis.[96] Chemical synthesis has been achieved in a number of laboratories.[97,98,99,100] This antibiotic is one of C-nucleoside having potent antitumor activity and therefore the physical and chemical properties have been extensively examined to gain some information on the relationship between structure and function. For example, Zemlicka[101] examined the conformational specificity of adenosine deaminase by use of 5',8-cycloformycin and Lewis and Townsend studied on methylation of formycin to determine the tautomeric distribution.[102] In addition to the above deazaaza-analogs, nucleosides whose rings nitrogen atom is located at one of the ring juncture are known. For instance, we have a few analogs of this type:[103,104,105]

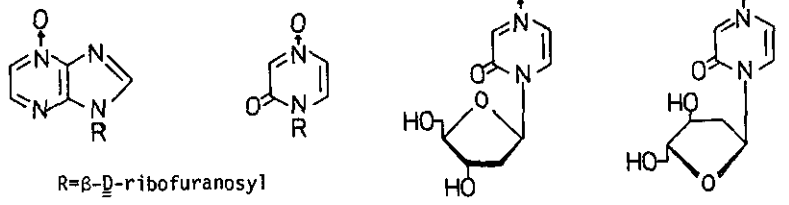


R=β-D-ribofuranosyl R=β-D-arabinofuranosyl

8-β-D-ribofuranosyl-2,4-dihydroxy-imidazo[1,2-a]-1,3,5-triazine

These analogs showed no significant antibacterial, antiviral, antifungal or cytotoxic effects. These compounds are also inactive against leukemia L1210 and Ehrlich ascites carcinoma in mice.[105]

8. Micellaneous Nucleosides Closely Related to Above-mentioned Nucleosides For example, following some inosine, uridine or 2'-deoxyuridine analogs were prepared from appropriate bases and TAR by Vorbrüggen procedure.[106,107,108]



R=β-D-ribofuranosyl

1.2-Dihydro-1-(β-D-ribofuranosyl)-2-oxopyrazine 4-oxide has showed moderate inhibitory activity against Streptococus faecium and Escherichia coli B, whereas 2'-deoxy-β-D-ribofuranoside counterpart exhibited approximately 10^6 times more effective against the same microbial system(ED_{50} 5 x 10^{-11}M and 4 x 10^{-11}M, respectively).

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