AZA AND DEAZA ANALOGS OF PURINE NUCLEOSIDES (REVIEW)

T. D. Miniker and M. N. Preobrazhenskaya

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Methods for the preparation of aza and deaza analogs of purine nucleosides, viz., nucleosides of imidazo[4,5-d]-v-triazines, imidazo[4,5-b]pyridines, and imidazo-[4,5-c]pyridines, and their properties are described. References to the synthesis of nucleosides of imidazo[4,5-d]pyridazines, imidazo[4,5-c]pyridazines, and imidazo[4,5-b]pyrazines are also given.

Among the antimetabolites of nucleic acids, purine nucleosides with different numbers and positions of nitrogen atoms in the aglycone are of great interest. These compounds include nucleosides of pyrrolo- and pyrazolopyrimidines, including antibiotics of the tubercidin (7-β-D-ribofuranosides of pyrrolo[2,3-d]pyrimidines) and formicin (3-β-D-ribofuranosides of pyrazolo[4,3-d]pyrimidines) series, which have high antimetabolite activity. Nucleosides of 8-azapurine (triazolo[4,5-d]pyrimidine), which display high cytotoxic activity, have been studied extensively. These compounds, which are deaza and aza analogs of purine nucleosides with respect to the imidazole ring, have been examined in monographs and reviews [1-3].

Nucleosides of benzimidazole, the preparation and properties of which have been discussed in an earlier review [4], are complete deaza analogs of purine nucleosides with respect to the pyrimidine part of the molecule. However, up until now there has been no review devoted to analogs of purine nucleosides that differ with respect to the position and/or number of nitrogen atoms in the six-membered ring. These compounds are also of interest as potential substrates or inhibitors of enzymes that participate in nucleic acid metabolism. They include such effective inhibitors of nucleic acid metabolism as 2-azaadenosine and 3-deazaguanosine, which have antitumorigenic activity. The present review is devoted to the synthesis and properties of aza and deaza analogs of purine nucleosides with respect to the pyrimidine part of the molecule.

The ordinary methods of glycosylation used in the chemistry of nucleosides [5], viz., condensation of silyl or mercury derivatives of a heterocycle with acyl halogenoses, fusion of the bases with acylated sugars, and building up of the heterocycle on the basis of a compound that already contains a carbohydrate fragment, have been employed to obtain these nucleosides. Except for the synthesis based on building up of the aglycone, all of the remaining synthetic methods in most cases lead to several isomeric nucleosides that differ with respect to the site of glycosylation of the heterocycle. In addition, the formation of α and β anomers is possible in each case. In the specific search for antimetabolites of purine metabolism isosteric analogs of natural nucleosides are of greatest interest, since it seems more likely that structures that are sterically close to natural nucleosides will be substrates or inhibitors of the enzymes of nucleic metabolism.

1. Preparation of Nucleosides of 2-Azapurines (Imidazo[4,5-d]-v-triazines)

Some of the most thoroughly studied types of aza analogs of purine nucleosides (I) are those in which the carbon atom in the 2 position is replaced by a nitrogen atom, viz., nucleosides of imidazo[4,5-d]-v-triazines (II) (see top of next page).

Nucleosides of 2-azapurines have been synthesized in most cases by building up the corresponding nucleosides of imidazole obtained by the usual methods of synthesis of nucleosides [6-11] and by opening of the adenosine or inosine ring [12-17]. Thus, the corresponding 2-azahypoxanthine nucleosides IVa-f were obtained by cyclization of 1-glycosyl-5-amino-4-carbamoylimidazoles IIIa-f [10-15]. The optimum conditions for the cyclization involve diazo-

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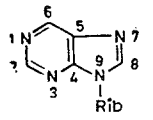
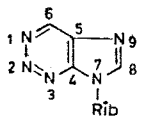


I

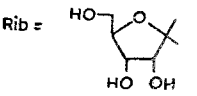
purine 9-ribofuranoside (the antibiotic nebularine)



II

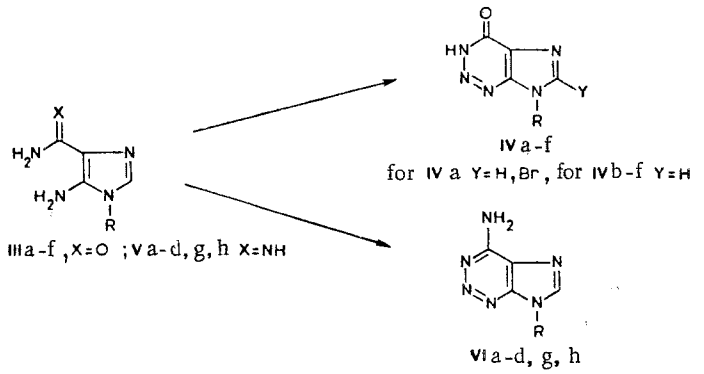
imidazo[4,5-b]-v-triazine (2-aza-purine) 7-ribofuranoside

Here and subsequently:



β-*D*-ribofuranosyl

tization with a solution of $NaNO_2$ in 6 N HCl at −25 to −30°C. Strongly acidic conditions suppress intramolecular diazo coupling, while low temperatures make it possible to avoid hydrolysis of the glycoside bond and to obtain 2-azahypoxanthine nucleosides from O-unsubstituted nucleosides of imidazole [6-8].



IIIa-f, X=O ; Va-d, g, h X=NH

IVa-f

for IVa Y=H, Br, for IVb-f Y=H

VIa-d, g, h

2-Azaadenosine glycosides VIa-d,g-i are obtained by cyclization of the corresponding 5-amino-4-carboxamidinoimidazole glycosides Va-d,g-i under the influence of nitrous acid [13-17].

The corresponding 2-azahypoxanthine nucleosides IVa (Y = H) and IVb were obtained by deamination of 2-azaadenine nucleosides VIa,b by means of adenosine deaminase [6]. 2-Azaadenine nucleosides that do not contain ribose or 2-deoxyribose are not substrates for adenosine aminase.

Only one example of the direct glycosylation of imidazo[4,5-d]-v-triazines has been described [18]. The condensation of 4-methylmercaptoimidazo[4,5-d]-v-triazine (VII) with 2,3,5-tri-O-acetyl-D-ribofuranosyl bromide in nitromethane in the presence of mercuric cyanide gave 7-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4-methylmercaptomidazo[4,5-d]-v-triazine (VIIIa), the deacetylation of which with ammonia in methanol led to 7-(β-D-ribofuranosyl)-4-methylmercaptoimidazo[4,5-d]-v-triazine (VIIIb).

VII

VIIIa, b

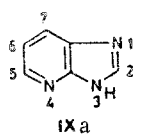
VIIIa Gly = Rib ; b Gly = Rib(Ac)

Here and subsequently: Rib(Ac) = 2,3,5-tri-O-acetyl-β-D-ribofuranosyl.

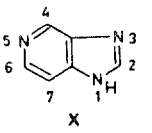
2. Preparation of 1- and 3-Deazapurine Nucleosides and Their Isomers

The detection of high antitumorigenic and antivirus activity of 7-deazapurine nucleosides (antibiotics of the tubercidin group) stimulated research on 1- and 3-deaza analogs of purine nucleosides. These nucleosides contain imidazopyridines IXa and X as nitrogen bases (see top of next page).

One of the chief methods for the glycosylation of 1- and 3-deazapurines is the synthesis on the basis of mercury derivatives. This method has been used for the preparation of nucleosides of imidazo[4,5-b]pyridine (IXa) that do not contain substituents in the aglycone [19, 20], the riboside of which can be regarded as an analog of the highly active antibiotic nebularine [9-β-D-ribofuranosylpurine (I)].

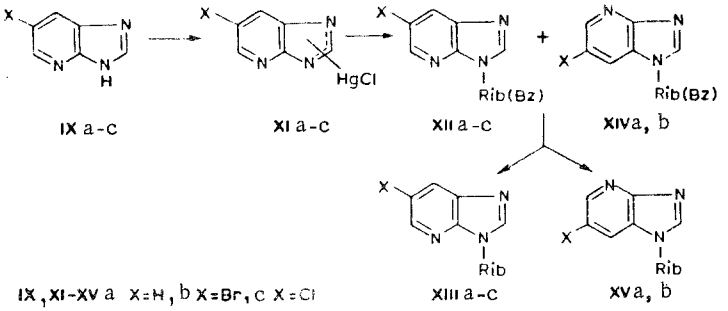


IXa
imidazo[4,5-b]pyridine
(1-deazapurine)



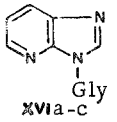
X
imidazo[4,5-c]pyridine
(3-deazapurine)

The reaction of imidazo[4,5-b]pyridine (IXa) with $HgCl_2$ yielded mercury derivative XIa, the condensation of which with 1-bromo-2,3,5-tri-O-benzoylribofuranose led to O-substituted nucleoside XIIa. The latter was converted by debenzoylation to 3-β-D-ribofuranosylimidazo-[4,5-b]pyridine (XIIIa). Similarly [19, 20], the condensation of XIa with the corresponding acyl halogenoses gave the glucopyranoside (XVIa), galactopyranoside (XVIb), and xylopyranoside (XVIc) of 1-deazapurine.



IX a-c XI a-c XII a-c XIVa, b

IX, XI-XV a X=H, b X=Br, c X=Cl XIII a-c XVa, b

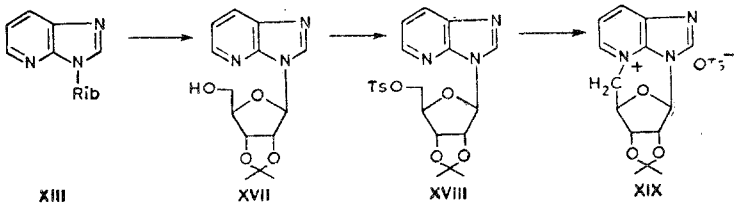


XVI a Gly = β-D-glucopyranosyl; b Gly = β-D-galactopyranosyl; c Gly = β-D-xylopyranosyl

XVIa-c

Here are subsequently: Rib(Bz) = 2,3,5-tri-O-benzoyl-D-ribofuranosyl

It was later demonstrated that 1-β-D-ribofuranosylimidazo[4,5-b]pyridine (XVa) is formed in addition to N_3 isomer XIIIa in the glycosylation of mercury derivative XIa [21-23]. The site of glycosylation was determined by comparison of the UV spectra of the nucleosides with the spectra of the corresponding N-alkyl derivatives of the heterocycle at various pH values. It is known that in purines the transition from an alkyl derivative to a glycoside derivative does not affect the position of the maximum in the UV spectra. It was shown that the UV spectra of the hypothetical 1-deazapurine riboside XIIIa and 1-methylimidazo[4,5-b]pyridine in a neutral medium coincide with respect to the character of the curve and the position of the maximum (λ_{max} 282 nm) [19]. However, further study [20-22] showed that the spectra of the 1-methyl derivative recorded at pH 0.5 and 12 differ markedly from the corresponding spectra of nucleoside XIIIa. The UV spectra of 3-methylimidazo[4,5-b]pyridine over all pH ranges are identical to the spectra of nucleoside XIIIa. On the basis of this, the 3-β-D-ribofuranosylimidazo[4,5-b]pyridine structure was assigned to riboside XIIIa. Riboside XIIIa was also converted to intramolecular quaternary salt XIX through isopropylidene derivatives XVII and XVIII; this is possible only for the N_3 isomer.

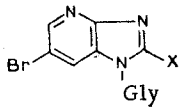


XIII XVII XVIII XIX

In connection with the fact that antivirus activity has been detected for chlorobenzimidazole nucleosides, their aza analogs, viz., 6-chloro- (XIIIc) and 6-bromoimidazo[4,5-b]-pyridine (XIIIb) nucleosides, have been synthesized on the basis of the corresponding mercury derivatives [20]. The debromination of XIIIb and XVb was another method for the preparation of 1-deazanebularine XIIIa and its isomer XVa [23].

The condensation of mercury derivative XIb or its 2-methyl derivative with the corresponding acetobromo sugars in xylene with subsequent deacetylation gave 6-bromoimidazo[4,5-b]-

pyridine glycosides, to which the authors assigned XX-XXII structures. Nucleosides XXI and XXII were also synthesized by condensation of silyl derivatives of the corresponding heterocycles with acetobromo sugars in somewhat higher yields than when the mercury derivatives were used as the starting compounds [24].

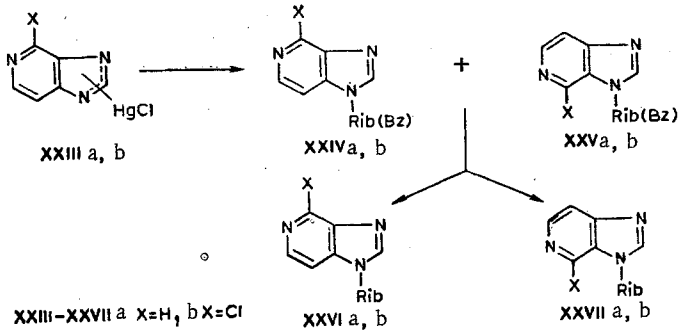


XX–XXII

XXa,b Gly = β-D-glucopyranosyl; XXIa,b Gly = β-D-galactopyranosyl;
XXIIa Gly = β-D-ribopyranosyl; XX-XXII a X = H; b X = CH_3

1-β-D-Ribofuranosylimidazo[4,5-c]pyridine (3-deazanebularine, XXVIa) and its 3-isomer XXVIIa were similarly obtained from mercury derivative XXIIIa [20, 22, 25].

The condensation of mercury derivative XXIIIa with tri-O-benzoylribofuranosyl chloride in xylene led to the formation of a mixture of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-imidazo[4,5-c]pyridine (XXIVa) and its 3-isomer XXVa in almost equal amounts. Debenzoylation of the two isomers gave 1- and 3-β-D-ribofuranosylimidazo[4,5-c]pyridines (XXVIa and XXVIIa, respectively) [20, 22, 25].

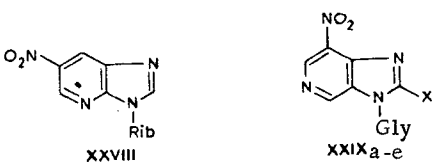


XXIII a, b; XXIVa, b; XXVa, b; XXIII–XXVII a X=H, b X=Cl; XXVI a, b; XXVII a, b

As mentioned above, the N_3-nucleoside is formed in preponderant amounts in the glycosylation of the mercury derivatives of imidazo[4,5-b]pyridines (1-deazapurines). Both possible positional isomers are formed in approximately equal amounts in the glycosylation of imidazo-[4,5-c]pyridines (3-deazapurines) by this method [21-23]. It is proposed that the effect of the nitrogen atom of the pyridine ring on the ratio of glycosylation products is manifested as follows: In imidazo[4,5-b]pyridines the nitrogen atom of the pyridine ring is adjacent to the imidazole ring, and its withdrawing inductive effect (—I effect) is evidently exerted more strongly on the nitrogen atom of the imidazole ring that is closest to it, viz., on N_3, and, in this connection, the formation of the 3-isomer is preferred. However, in the case of imidazo[4,5-c]pyridines the nitrogen atom of the pyridine ring is sufficiently remote from the imidazole ring, and both possible isomers are therefore probably formed in almost equal amounts [23].

3-Deazapurine riboside XXVIa was also obtained from the mercury derivative of 4-chloroimidazo[4,5-c]pyridine (XXIIIb) with subsequent dehalogenation of 4-chloro-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (XXVIb) over 20% palladium on carbon [25].

The mercury derivatives were used to synthesize 1- and 3-deazapurine riboside XXVIII and XXIXa, which contain a nitro group in the pyridine ring [20, 26]. It was assumed that the



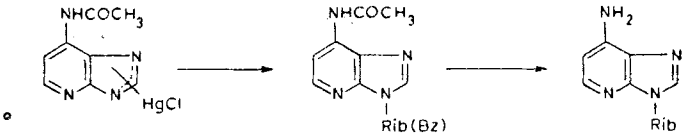
XXVIII; XXIXa-e

XXIX a X = H, Gly = Rib; b X = H, Gly = β-D-glucopyranosyl; c X = CH_3,
Gly = β-D-glucopyranosyl; d X = H, Gly = β-D-galactopyranosyl; e X = CH_3,
Gly = β-D-galactopyranosyl

introduction of a nitro group in the 1 position of the 1-deazapurine or in the 3 position of the 3-deazapurine would create an electronic characteristic of the molecule similar to that which is created by the presence of a nitrogen atom in the nebularine (I) ring.

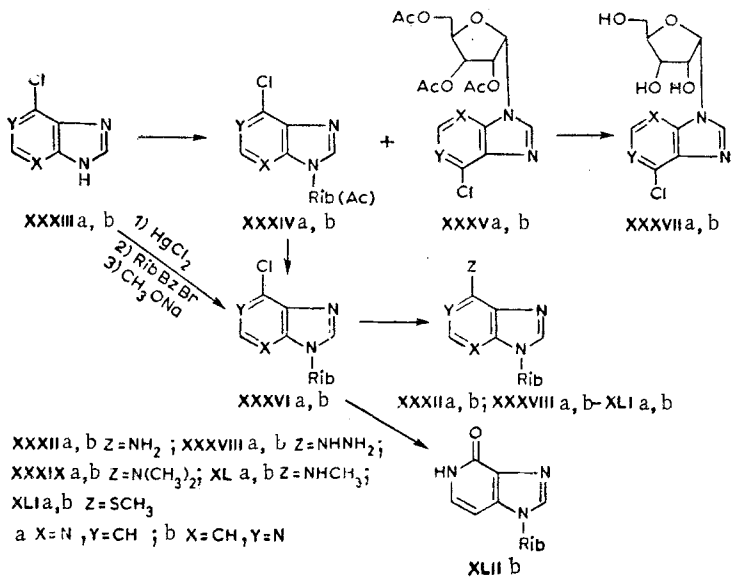
Glucopyranosides XXIXb,c and galactopyranosides XXIXd,e of 7-nitroimidazo[4,5-c]pyridine and its 2-methyl derivative were obtained by condensation of the corresponding heterocycles with acetobromoglucose in nitromethane in the presence of $Hg(CN)_2$ with subsequent removal of the protective groupings. A nucleoside in which the position of the sugar residue was not established was isolated as a result of condensation of the trimethylsilyl derivative of 2-methyl-7-nitroimidazo[4,5-c]pyridine with acetobromogalactose [27].

Of particular interest was the preparation of the corresponding amino derivatives, viz., the 1- or 3-deaza analogs of adenosine. 7-Amino-3-(β-D-ribofuranosyl)imidazo[4,5-b]pyridine (1-deazaadenosine, XXXIIa) was obtained through the mercury derivative [28] and by the fusion method [29]. The condensation of the mercury salt of 7-acetamidoimidazo[4,5-c]pyridine (XXX) with 2,3,5-tri-O-benzoylribofuranosyl chloride and subsequent removal of the O- and N-protective groupings gave 1-deazaadenosine (XXXIIa) [28]. Fusion of 7-chloroimidazo[4,5-b]-



XXX XXXI XXXIIa

pyridine (XXXIIIa) with tetraacetylribofuranose in the presence of chloroacetic acid gave a mixture of β- and α-O-substituted nucleosides (XXXIVa, XXXVa), after deacetylation and chromatographic separation of which individual anomers XXXVIa and XXXVIIa were isolated in 64.5 and 2.0% yields, respectively, based on starting XXXIIIa [29].

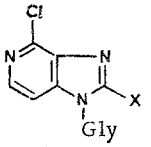


7-Chloro-3-(β-D-ribofuranosyl)imidazo[4,5-b]pyridine (XXXVIa) was used as the key compound for the preparation of substituted 1-deazapurine nucleosides XXXVIIIa-XLIa, including a 1-deazaadenosine nucleoside (XXXIIa) [29, 30].

A 3-deazaadenosine nucleoside (XXXIIb) and other 4-substituted 3-deazapurine nucleosides (XXXVIIIb-XLIIb) were similarly obtained by fusion of 4-chloroimidazo[4,5-c]pyridine (XXXIIIb) with tetraacetylribofuranose [31, 33].

Nucleoside XXXIIb was also obtained by condensation of chloride XXXIIIb with tribenzoylribofuranose in acetonitrile in the presence of mercuric cyanide [32]. In contrast to the fusion method [31], the condensation proceeds stereospecifically: The formation of a second position isomer and α anomers was not observed.

Analogs of nucleosides with various sugar residues (XLIII-XLVI) were obtained as in [34] by condensation of chloride XXXIIIb or its 2-methyl derivative with the corresponding acetobromo sugars in nitromethane in the presence of mercuric cyanide.

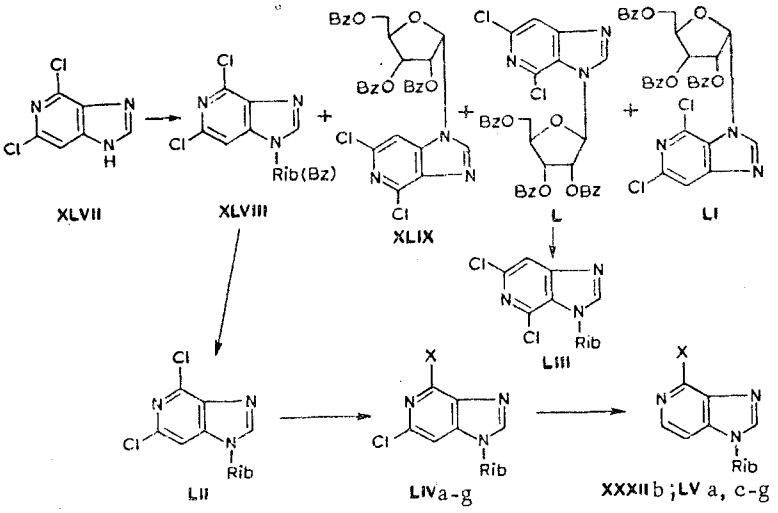


XLIII – XLVI

XLIII, X = H, Gly = β-D-glucopyranosyl; XLIV, X = CH_3, Gly = tetra-O-acetyl-β-D-glucopyranosyl; XLV, X = CH_3, Gly = tetra-O-acetyl-β-D-galactopyranosyl; XLVI, X = CH_3, Gly = tri-O-acetyl-β-D-ribofuranosyl

The synthesis of 3-deazaadenosine (XXXIIb) from 4-chloro derivative XXXIIIb is hindered by the low reactivity of the chlorine atom in nucleophilic substitution reactions, and it has therefore been proposed that 4,6-dichloroimidazo[4,5-c]pyridine (XLVII) be used as the key compound for the preparation of nucleoside XXXIIb [35, 36]. The introduction of a second chlorine atom in the 6 position of the heteroring decreases the electron density in the 4 position of the pyridine ring and increases the ability of the chlorine atom in the 4 position to undergo nucleophilic substitution. The condensation of the trimethylsilyl derivative of dichloroimidazo[4,5-c]pyridine (XLVII) with 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide in the presence of sodium iodide gave a mixture of 4,6-dichloroimidazo[4,5-c]pyridine 1- and 3-benzoylribofuranosides (XLVIII, L). The latter were converted to 1- and 3-(β-D-ribofuranosyl)-4,6-dichloroimidazo[4,5-c]pyridines (LII and LIII, respectively). 3-Deazaadenosine (XXXIIb) was obtained by reaction of nucleosides LII with ammonia and subsequent catalytic dehalogenation.

It was later demonstrated [37] that the reaction of the trimethylsilyl derivative of heterocycle XLVII with benzoylribofuranosyl bromide gives a mixture of four rather than two nucleosides; the mixture was separated into individual products, which were identified by means of the UV and PMR spectra as 4,6-dichloro-1-(2,3,5-tri-O-benzoyl-β- and α-D-ribofuranosyl)imidazo[4,5-c]pyridines (XLVIII, XLIX) and 4,6-dichloro-3-(2,3,5-tri-O-benzoyl-β- and α-D-ribofuranosyl)imidazo[4,5-c]pyridines (L, LI). It was shown that fusion of dichloro derivative XLVII with tetraacetylribofuranose takes place with the formation of only 4,6-dichloro-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine.

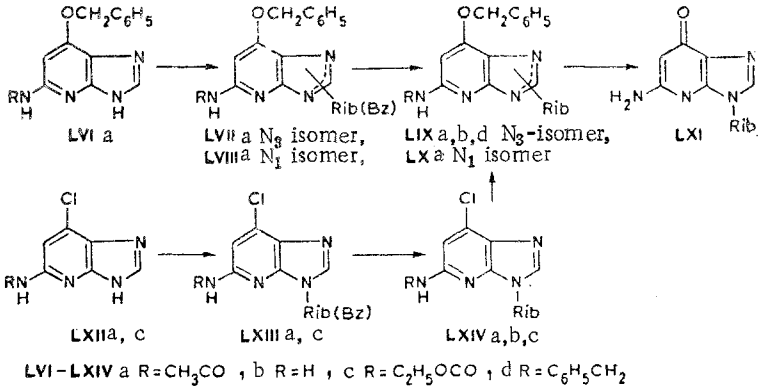


XXXII, LIV a X = $NHCH_3$; b X = NH_2; c X = OCH_3; d X = SCH_3; e X = $NHNH_2$; f X = $N(CH_3)_2$; g X = $SCH_2C_6H_5$

The reactions of 4,6-dichloro-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (LII) with various nucleophiles [NH_2CH_3, NH_3, $NaOCH_3$, $HSCH_3$, NH_2NH_2, $NH(CH_3)_2$, and $HSCH_2C_6H_5$] took place virtually exclusively at the C_4 atom and led to derivatives LIVa-g, which upon dehalogenation over palladium on carbon were converted to 4-substituted 1-(β-D-ribofuranosyl)imidazo[4,5-c]-pyridines (LVa,c-g), including 3-deazaadenosine (XXXIIb).

Various approaches to the synthesis of 1-deazaguanosine, viz., 5-amino-3-(β-D-ribofuranosyl)imidazo[4,5-b]pyridin-7-one (LXI), have been studied [38-41]. It was obtained in highest overall yield (52%) [38] by the reaction of the silyl derivative of 5-acetamido-7-benzyloxyimidazo[4,5-c]pyridine (LVIa) with tribenzoylbromoribose in refluxing toluene in the presence of mercuric cyanide. In addition to the principal N_3 isomer (LVIIa), its N_1

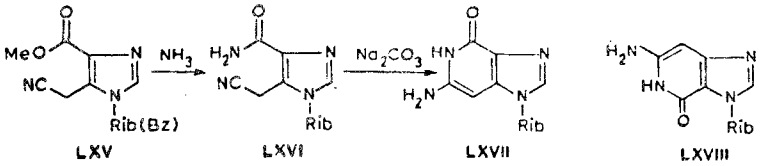
isomer, viz., 5-acetamido-7-benzyloxy-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazo[4,5-b]pyridine (LVIIIa) was also obtained in low yield (1.3%). Both LVIIa and LVIIIa were treated with sodium methoxide in a mixture of methanol with tetrahydrofuran, which led to the formation of 5-acetamido-7-benzoyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-b]pyridine (LIXa) and its N_1 isomer (LXa), respectively. Hydrolysis of nucleoside LIXa by refluxing in alcoholic alkali gave 5-amino-7-benzyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-b]pyridine (LIXb), which was converted to 1-deazaguanosine (LXI) after hydrogenolysis over 5-10% palladium on carbon.



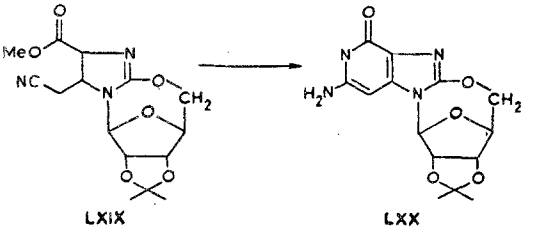
1-Deazaguanosine (LXI) was also obtained on the basis of silyl derivatives of 5-acetamido-7-chloroimidazo[4,5-b]pyridine (LXIIa) or the 5-ethoxycarbonyl derivative (LXIIc) in 30% overall yield [38-40]. This yield of nucleoside LXI is due to the low yields of intermediate LIXb or LIXd from the corresponding chloro derivatives LXIVa or LXIVb. The ability of the chlorine atom attached to C_7 to undergo nucleophilic substitution is hindered significantly as a consequence of the low electron-acceptor effect of the acylamido groups attached to the C_5 atom in LXIVa and LXIVc. In addition, hydrolysis of the acetamido group, which leads to the formation of amino chloro derivative LXIVb as a side product, is observed in the reaction of acetamido derivative LXIVa with sodium benzilate.

The direct condensation of 5-acetamido-7-benzyloxyimidazo[4,5-b]pyridine (LVIa) with tribenzoylribofuranosyl chloride in nitromethane in the presence of potassium cyanide and subsequent removal of the protective groupings gave 1-deazaguanosine (LXI) in 17% overall yield [41].

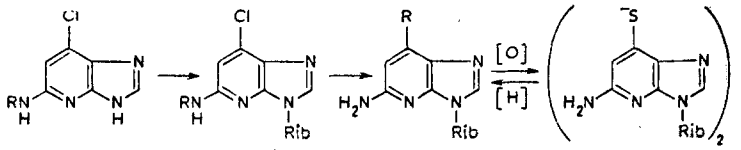
Aglycone buildup has been used for the synthesis of 3-deazaguanosine (LXVII) [42, 43]. 5-Cyanomethyl-4-carbamoyl-1-(β-D-ribofuranosyl)imidazole (LXVI) was isolated when 5-cyanomethyl-4-methoxycarbonyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazole (LXV) was treated with liquid ammonia. Compound LXVI was converted by refluxing in an alcohol solution of sodium carbonate to 3-deazaguanosine (LXVII) in 69% yield based on nucleoside LXV. Similarly, 7-β-D-ribofuranosyl-3-deazaguanosine (LXVIII) — an isomer of 3-deazaguanosine — was obtained in 80% yield in the cyclization of 4-cyanomethyl-5-methoxycarbonyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazole with liquid ammonia and sodium carbonate [42, 43].



The preparation of the 8,5'-O-anhydro derivatives of 8-hydroxy-3-deazaguanosine (LXX) by treatment of 2,5'-O-anhydro nucleoside LXIX with ammonia in methanol has been described [44].

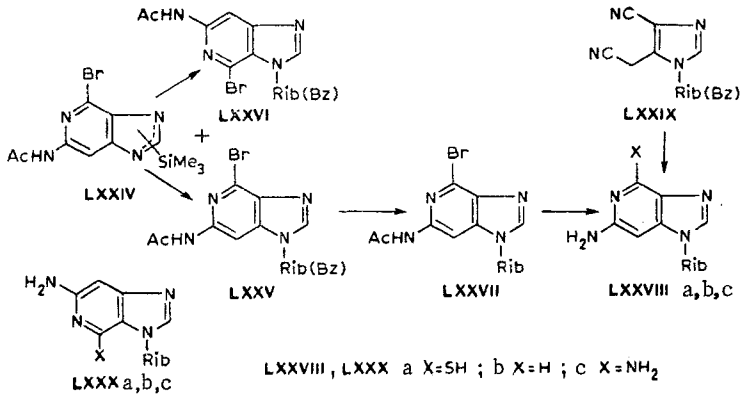


In connection with the fact that 6-thioguanosine has antitumorigenic activity *in vivo*, its 1- and 3-deaza analogs were obtained. 1-Deaza-6-thioguanosine (LXXI) was synthesized from 5-acetamido-7-chloroimidazo[4,5-b]pyridine (LXIIa) [45]. Condensation of the latter with 2,3,5-tri-O-acetyl-D-ribofuranosyl chloride in dichloroethane in the presence of molecular sieves and subsequent removal of the acetyl groups with sodium methoxide led to 5-amino-7-chloro-3-(β-D-ribofuranosyl)imidazo[4,5-b]pyridine (LXIVb). The reaction of nucleoside LXIVb with hydrogen sulfide or methyl mercaptan in the presence of sodium methoxide gives 1-deaza-6-thioguanosine (LXXI) or 1-deaza-6-methylmercaptoguanosine (LXXII), respectively.



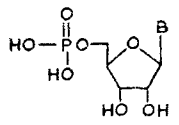
1-Deaza-6-thioguanosine (LXXI) was also obtained by the reaction of ethoxycarbonyl derivative LXIVc with excess anhydrous sodium hydrosulfide in dimethylformamide [38]. The reaction mass consisted of a difficult-to-separate mixture of three products, viz., chloro derivative LXIVb, 1-deaza-6-thioguanosine (LXXI), and disulfide LXXIII. The reaction mixture was treated with dimethyl sulfoxide, during which 1-deaza-6-thioguanosine (LXXI) was converted to disulfide LXXIII, which was isolated in 30% yield after column chromatography.

4-Bromo-6-acetamido-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (LXXVII) was used as the starting compound for the synthesis of 3-deaza-6-thioguanosine (LXXVIIIa) [46, 47]. During a search for the optimum conditions for the preparation of nucleoside LXXVII it was observed that the most convenient method is condensation of the silyl derivative of 4-bromo-6-acetamidoimidazo[4,5-c]pyridine (LXXIV) with tribenzoylribofuranosyl bromide in nitromethane in the presence of mercuric cyanide [47]; an easily separable mixture of 4-bromo-6-acetamido-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine (LXXV) and its N_3 isomer in 71 and 7% yields, respectively, is formed. 3-Deaza-6-thioguanosine (LXXVIIIa) was obtained by treatment of debenzoylated nucleoside LXXVII with a methanol solution of sodium sulfide, which leads to simultaneous replacement of the bromine atom in the 4 position by a thio group and deacetylation of the amino group in the 6 position of the pyridine ring.

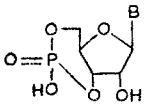


3-Deaza-6-thioguanosine (LXXVIIIa) was obtained in excellent yield in the cyclization of 4-cyano-5-cyanomethyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazole (LXXIX) with an alcohol solution of hydrogen sulfide in the presence of triethylamine with subsequent denenzoylation [48]. Similarly, an isomer of nucleoside LXXVIIIa, viz., 3-deaza-4-thioguanosine (LXXXa), was obtained in the cyclization of 5-cyano-4-cyanomethyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazole. Dethionation of nucleosides LXXVIIIa and LXXXa over Raney nickel led to 6(or 4)-amino-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (LXXVIIIb) and LXXXb, respectively. 3-Deaza analogs of 2,6-diaminopurine (LXXVIIIc and LXXXc) have also been obtained [48].

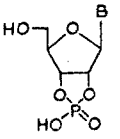
Natural nucleosides in the cell are phosphorylated under the influence of kinase and are converted successively to the corresponding nucleotides and deoxynucleotides. In order to react with enzymes of nucleic metabolism the nucleoside-antimetabolite should also be converted to the corresponding nucleotide-antimetabolite. Synthetic nucleotides are necessary for biochemical studies. The ordinary methods of the chemistry of nucleotides have been used for the synthesis of 5'-phosphates and cyclophosphates [5]. The preparation of 1-deazaadenylic (LXXXIa) [49], 3-deazaadenylic (LXXXIb) [32], 3-deazainosinic (LXXXIc) [32], and 3-deazaguanylic (LXXXId) [42, 43] acids, as well as 1- and 3-deazaadenosine 3',5'- and 2',3'-cyclophosphates (LXXXII and LXXXIII) [49], has been described.



LXXXI



LXXXII



LXXXIII

LXXXI a B = 1-deazaadenine, b B = 3-deazaadenine, c B = 3-deazahypoxanthine, d B = 3-deazaguanine

LXXXII B = 1- or 3-deazaadenine; LXXXIII B = 1- or 3-deazaadenine

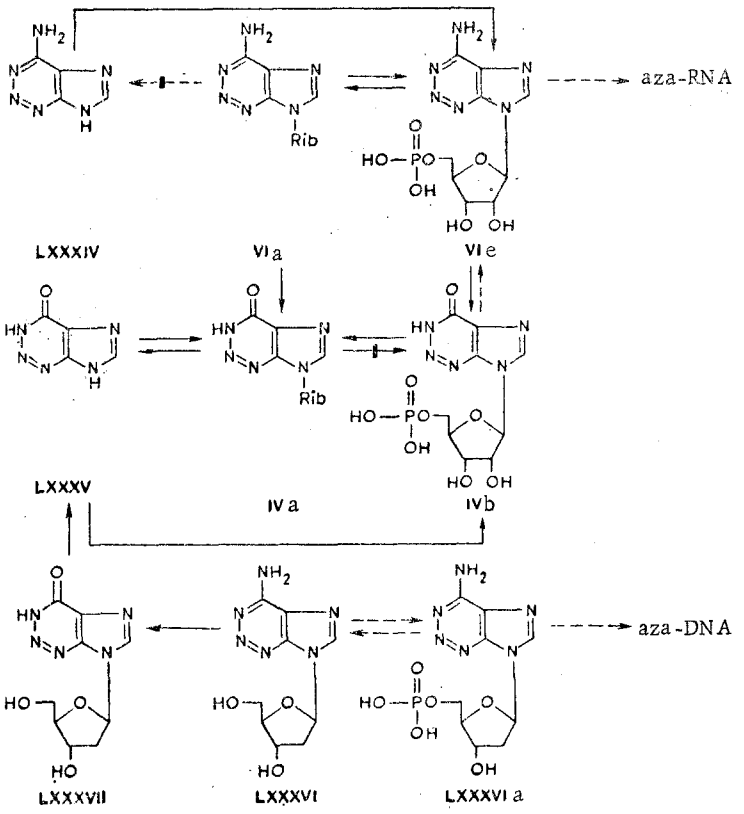
Data on methods for the synthesis of nucleosides of imidazo[4,5-d]pyridazines [50-52], imidazo[4,5-c]pyridazines [53], and imidazo[4,5-b]pyrazines [54, 55], which are structural isomers of purine nucleosides that differ with respect to the position of the nitrogen atoms in the pyrimidine part of the molecule, are not included in the present review.

3. Biological Properties of Aza and Deaza Analogs of Purine Nucleosides

Among the analogs of purine nucleosides examined in the present review, the most serious study has been devoted to the biological properties of 2-azapurine nucleosides and nucleotides. It is known that the first important step in the bioactivation of nucleosides or nucleic bases is their conversion to nucleotides (under the influence of the corresponding kinases in the case of nucleosides or phosphoribosyltransferases in the case of nucleic bases). Under the influence of adenosine kinase, 2-azaadenosine (VIa) is converted in cells to 2-azaadenylic acid (VIe), which is also formed from 2-azaadenine (LXXXIV) under the influence of phosphoribosyltransferase. 2-Azainosine (IVa) [from 2-azaadenosine (VIa)] or 2-azainosinic acid [from 2-azaadenylic acid (VIe)] is formed under the influence of adenosine deaminase. Under the influence of inosine phosphorylase, 2-azainosine (IVa) is converted to 2-azahypoxanthine (LXXXV), which gives 2-azainosinic acid (IVe) under the influence of hypoxanthine–guanine phosphoribosyltransferase. The interconversions of 2-azapurines are presented in the scheme given below. It is not clear whether 2-azaadenylic acid (VIe) is capable of being included in RNA. The cytotoxic activity of 2-azaadenosine (VIa) or 2-azainosine (IVa) is associated with their conversion to both 2-azaadenylic (VIe) and 2-azainosinic (IVe) acid. 2'-Deoxy-2-azaadenylic acid (LXXXVIa) is also cleaved in the organism to 2-azahypoxanthine (LXXXV), which is converted to 2-azainosinic acid (IVe); however, it is unclear whether it is included in DNA [12, 16]. It has been shown [14] that 2-azaadenosine in epidermoid carcinoma KV cell cultures is 20 times more toxic than 2-azaadenine and seven times more toxic than 2-azahypoxanthine. 2-Azainosine (IVa), 2'-deoxy-2-azaadenosine (VIb), and 2-azainosinic acid (IVe) are cytotoxic with respect to KV, HEp-2, and HeLa cell cultures [6]. 3'-Deoxy-2-azaadenosine (VIc) and 2-azaadenine β-arabinoside (VId), α-arabinoside (VIg), and β-xyloxide (VIh) are not cytotoxic with respect to a strain of HEp-2 cells [56]. Only 2-azaadenosine (VIa) displays activity in *in vivo* experiments with animals with transplantable tumors (a 35% increase in the lifetime of mice with L-1210 leucosis is observed). 2-Azainosine (IVa) and its tri-O-acetate, as well as 2-azainosinic acid (IVe), inhibit the growth of herpes and parainfluenza viruses and adenoviruses [14, 16].

Attempts have been made to link the ability of analogs of nucleosides to be substrates of the enzymes of purine metabolism with their conformational state. The conformation relative to the glycoside bond seems particularly important. Thus it has been proposed that a "high anti" conformation of the glycoside bond (angle φ = 140-165°) is preferred for 2-azaadenosine (VIa); the concentration of conformers with a "high anti" conformation is higher than that of adenosine. Precisely this conformation is favorable for the reaction with adenosine kinase, and 2-azaadenosine (VIa) is therefore a better substrate for adenosine kinase than adenosine. The enzyme protein kinase is bonded with cyclic adenosine monophos-

Interconversions of 2-azapurines in the organism



phate (cyclic AMP) in an anti conformation, and, in this connection, cyclic-2-aza-AMP is a weaker activator for protein kinase than cyclic AMP. It is known that cyclic-2-aza-AMP is a substrate for cyclic-AMP-phosphodiesterase [57].

It is still difficult to compose a biotransformation scheme similar to that presented for 2-azaadenosine for 1- or 3-deazapurine nucleosides. It seems of interest to investigate the ability of these analogs to be included in nucleic acids and to replace adenosine in coenzymes. This will be of help in understanding the role of the N_1 and N_3 functions as sites of bonding with the enzymes or as nucleophilic centers. In addition, the removal of one ring nitrogen atom substantially increases the basicity of the remaining atom and its ability to undergo protonation or to form hydrogen bonds. The conformation relative to the glycoside bond is changed substantially [particularly for 3-deazaadenosine (XXXIIb)], and this may also determine its ability to react with the enzymes of purine metabolism. It has been proposed that 3-deazapurines exist in solution primarily in the syn conformation. In this connection, 3-deaza-cyclic-AMP is a weak substrate for protein kinase, which is bonded with nucleosides in the anti conformation. 1-Deaza-cyclic-AMP is more active than cyclic AMP as a protein kinase activator; this constitutes evidence that the electronic effects at N_1 or N_3 are insignificant for this enzyme [58].

It has been shown that 3-deazaadenosine (XXXIIb) is an effective inhibitor of adenosine homocysteine hydrolase; it prevents replication and growth of Raus sarcoma virus. 5'-Deoxy-5'-ixobutylmercapto-3-deazaadenosine is also a powerful inhibitor of adenosine homocysteine hydrolase and, possibly, methylase, and suppresses the growth of Raus sarcoma virus and Gross leucosis [59].

Not one of the four known deaza analogs of mercaptopurine has cytotoxic activity [60]; this can be explained by their inability to undergo conversion in cells to the corresponding nucleotides or the inability of these nucleotides to bond allosterically with phosphoribosyl pyrophosphate—glutamine amido transferase. Like mercaptopurine, which has high antitumorigenic activity but is bioactivated with the participation of other enzymes (adenosine kinase), the deaza analogs of 6-methylmercaptopurine riboside are of greater interest. 1-Deaza-6-methylmercaptopurine riboside (XLIa) has 0.25% of the cytotoxicity of 6-methylmercaptopurine riboside [30]. It has been proposed that N_3 atom is more necessary for bonding with adenosine kinase or with phosphoribosyl pyrophosphate—glutamine amido transferase than the N_1 atom.

2-Amino-4-chloro-1-deazapurine (LXIIb) is active with respect to L-1210 leucosis, and its effect is eliminated by hypoxanthine; this constitutes evidence for the necessity of its conversion to the corresponding nucleotide for the manifestation of a cytotoxic effect [45]. 3-Deazaadenosine (XXXIIb) does not have antitumorigenic activity, but 6-chloro-4-dimethylamino-1-ribosylimidazo[4,5-c]pyridine (LIVf) is highly active with respect to L-1210 leucosis [36]. 1-Deazapurine riboside (XIIIa) has antivirus and cytotoxic activity [19, 20, 30], while 3-deazapurine riboside (XXIVa) is inactive [20].

From the point of view of the biological activity among deaza analogs of purine components of nucleic acid, 3-deazaguanine, 3-deazaguanosine, and 3-deaza-2'-deoxyguanosine and their phosphates are of greatest interest. These substances are antivirus preparations with a broad spectrum of activity. 3-Deazaguanine has low toxicity and is highly effective with respect to L-1210 leucosis and adenocarcinoma-755 in mice [42]. 3-Deazaguanine in the cell is evidently converted to a nucleoside, after which it is converted to a 2'-deoxynucleoside phosphate and incorporated in DNA. 3-Deazaguanine 2'-deoxyriboside is more cytotoxic than 3-deazaguanine or 3-deazaguanosine (LXVII). Hypoxanthine guanine phosphoribosyl transferase and adenine phosphoribosyl transferase participate in activation of 3-deazaguanine [61, 62].

LITERATURE CITED

1. R. J. Suhadolnic, Nucleoside Antibiotics, Vol. 1, Wiley, New York (1970); p. 298, Vol. 2, p. 68.
2. J. A. Montgomery, Progr. Med. Chem., 7, Part 1, 69 (1970).
3. J. A. Montgomery, Handbook of Experimental Pharmacology, Vol. 38, Springer Verlag, Berlin–New York (1974), p. 76.
4. L. B. Townsend and G. R. Revankar, Chem. Rev., 70, 389 (1970).
5. Z. A. Shabarova and A. A. Bogdanov, The Chemistry of Nucleic Acids and Their Components [in Russian], Khimiya, Moscow (1978).
6. M. Kawana, G. A. Ivanovics, R. J. Rousseau, and R. K. Robins, J. Med. Chem., 15, 841 (1972).
7. R. P. Panzica and L. B. Townsend, J. Heterocycl. Chem., 9, 623 (1972).
8. G. A. Ivanovics, R. J. Rousseau, M. Kawana, P. C. Srivastava, and R. K. Robins, J. Org. Chem., 39, 3651 (1974).
9. R. J. Rousseau and G. A. Ivanovics, U.S. Patent No. 3803126; Chem. Abstr., 80, 146489 (1974).
10. P. C. Srivastava, A. R. Newman, and R. K. Robins, J. Carbohydrates, Nucleosides, and Nucleotides, 3, 327 (1975).
11. B. Rayner, C. Tapiero, and J.-L. Imbach, J. Heterocycl. Chem., 10, 417 (1973).
12. J. A. Montgomery, A. G. Laseter, A. T. Shortnacy, S. J. Clayton, and H. J. Thomas, J. Med. Chem., 18, 564 (1975).
13. J. A. Montgomery and H. J. Thomas, J. Chem. Soc., Chem. Commun., 468 (1969).
14. J. A. Montgomery and H. J. Thomas, J. Med. Chem., 15, 182 (1972).
15. M. A. Stevens, H. W. Smith, and G. B. Brown, J. Am. Chem. Soc., 82, 3189 (1960).
16. J. A. Montgomery, R. D. Elliott, and H. J. Thomas, Ann. N. Y. Acad. Sci., 255, 292 (1975).
17. J. A. Montgomery and H. J. Thomas, J. Med. Chem., 15, 1334 (1972).
18. V. I. Ofitserov, V. S. Mokrushin, I. A. Korbukh, M. N. Preobrazhenskaya, and Z. V. Pushkareva, Zh. Org. Khim., 11, 909 (1975).
19. S. K. Chatterjee, M. M. Dhar, N. Anand, and M. L. Dhar, J. Sci. Ind. Res., 19C, 35 (1960).
20. P. S. Jain, S. K. Chatterjee, and N. Anand, Indian J. Chem., 1, 30 (1963).
21. Y. Mizuno, M. Ikehara, T. Itoh, and K. Saito, Chem. Pharm. Bull. (Tokyo), 11, 265 (1963).
22. Y. Mizuno, M. Ikehara, T. Itoh, and K. Saito, J. Org. Chem., 28, 1837 (1963).
23. Y. Mizuno, M. Ikehara, T. Itoh, and K. Saito, J. Org. Chem., 30, 4066 (1965).
24. N. S. Miroshnichenko, O. I. Shkrebtii, and A. V. Stetsenko, Ukr. Khim. Zh., 39, 274 (1973).
25. Y. Mizuno, T. Itoh, and K. Saito, J. Org. Chem., 29, 2611 (1964).
26. P. C. Jain and N. Anand, Indian J. Chem., 6, 123 (1968).
27. N. S. Miroshnichenko, I. G. Ryabokon', and A. V. Stetsenko, Ukr. Khim. Zh., 39, 344 (1973).
28. P. C. Jain, S. K. Chatterjee, and N. Anand, Indian J. Chem., 4, 403 (1966).

29. K. B. de Roos and C. A. Salemink, Recueil, 90, 654 (1971).
30. J. A. Montgomery and K. Hewson, J. Med. Chem., 9, 354 (1966).
31. R. J. Rousseau, L. B. Townsend, and R. K. Robins, Biochemistry, 5, 756 (1966).
32. Y. Mizuno, S. Tazawa, and K. Kageura, Chem. Pharm. Bull. (Tokyo), 16, 2011 (1966).
33. J. A. Montgomery and K. Hewson, J. Med. Chem., 9, 105 (1966).
34. A. V. Stetsenko and N. S. Miroshnichenko, Ukr. Khim. Zh., 39, 695 (1973).
35. J. A. May and L. B. Townsend, J. Chem. Soc., Chem. Commun., 64 (1973).
36. J. A. May and L. B. Townsend, J. Chem. Soc., Perkin I, 125 (1975).
37. J. A. Montgomery, A. T. Shortnacy, and S. D. Clayton, J. Heterocycl. Chem., 14, 195 (1977).
38. B. L. Cline, R. P. Panzica, and L. B. Townsend, J. Heterocycl. Chem., 15, 839 (1978).
39. B. L. Cline, R. P. Panzica, and L. B. Townsend, Proc. Utah Acad. Sci., 52, Part 1, 79 (1975).
40. B. L. Cline, R. P. Panzica, and L. B. Townsend, J. Heterocycl. Chem., 12, 603 (1975).
41. J. E. Schelling and C. A. Salemink, Recueil, 94, 153 (1975).
42. P. D. Cook, R. J. Rousseau, A. M. Mian, R. B. Meyer, P. Dea, G. A. Ivanovics, D. G. Streeter, J. T. Witkowski, M. G. Stout, L. N. Simon, and R. W. Sidwell, J. Am. Chem. Soc., 97, 2916 (1975).
43. P. D. Cook, R. J. Rousseau, A. M. Mian, P. Dea, R. B. Meyer, and R. K. Robins, J. Am. Chem. Soc., 98, 1496 (1976).
44. H. Tanaka and T. Ueda, J. Heterocycl. Chem., 16, 411 (1979).
45. R. D. Elliott and J. A. Montgomery, J. Med. Chem., 21, 112 (1978).
46. J. A. May and L. B. Townsend, J. Carbohydrates, Nucleosides, and Nucleotides, 2, 271 (1975).
47. J. A. May and L. B. Townsend, J. Carbohydrates, Nucleosides, and Nucleotides, 2, 371 (1975).
48. P. D. Cook and R. K. Robins, J. Org. Chem., 43, 289 (1978).
49. Y. Mizuno, S. Kitano, and A. Nomuro, Chem. Pharm. Bull. (Tokyo), 23, 1664 (1975).
50. J. A. Carbon, J. Org. Chem., 25, 579 (1960).
51. C. Tapiero, J.-L. Imbach, R. P. Panzica, and L. B. Townsend, J. Carbohydrates, Nucleosides, and Nucleotides, 3, 191 (1976).
52. P. D. Cook, P. Dea, and R. K. Robins, J. Heterocycl. Chem., 15, 1 (1978).
53. D. M. Halverson and R. N. Castle, J. Heterocycl. Chem., 1, 39 (1974).
54. R. P. Panzica and L. B. Townsend, Tetrahedron Lett., 13, 1013 (1970).
55. R. P. Panzica and L. B. Townsend, J. Chem. Soc., Perkin I, 244 (1973).
56. L. L. Bennett, P. W. Allan, J. W. Carpenter, and D. L. Hill, Biochem. Pharm., 25, 517 (1976).
57. T. Zimmerman, Biochem. Pharm., 17, 2533 (1968).
58. D. W. Miles, L. B. Townsend, P. Rodington, and H. Eyring, Proc. Natl. Acad. Sci. U.S.A., 73, 2384 (1976).
59. P. K. Chiang, G. L. Cantoni, and J. P. Bader, Biochem. Biophys. Res. Commun., 82, 417 (1978).
60. J. A. Montgomery and K. Hewson, J. Med. Chem., 8, 708 (1965).
61. P. Saunders and L.-Y. Chao, Proceedings of the 17th Annual Meeting of the AACR and the 15th Annual Meeting of the ASCO(1979), p. 897.
62. J. Khwaja, L. Momparler, J. Varven, and A. Mian, Proceedings of the 17th Annual Meeting of the AACR and the 15th Annual Meeting of the ASCO (1979), p. 613.