SYNTHESIS OF ANALOGS OF NUCLEOSIDES BY CREATION OF HETEROCYCLIC BASES (REVIEW)

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Primarily the studies of the author dealing with the synthesis of analogs of nucleosides by cyclization of derivatives of monosaccharides, viz., Schiff bases, hydrazones, thioureas, thiocarbamates, thiosemicarbazones, thiobiurets, and keto isothiocyanates, are correlated.

Modified nucleosides and their analogs are of great scientific and practical interest, since many of them have clearly expressed biological activity with a broad spectrum of activity. Compounds of this type are important instruments in the study of the relationship between the structure and functions of nucleic acids and problems of metabolism. A large number of analogs of nucleosides are finding wide application in medicine, for example, as effective anticancer and antivirus preparations. All of this is responsible for the interest in the synthetic chemistry of analogs of nucleosides.

There are three basic approaches to the preparation of these compounds: 1) modification of the natural nucleoside in the heterocyclic or carbohydrate part of the molecule; 2) the synthesis of an analog from two components, viz., an aglycone and a carbohydrate component; 3) the construction of the heterocyclic base of the analog of the nucleoside on the basis of the functional groupings of the carbohydrate component. The possibilities of the latter approach on the basis of the author's own studies are examined in the present review. For convenience, the material is grouped together with respect to the types of reactive groupings of the carbohydrate component used.

Schiff Bases [1]

This approach consists essentially in the condensation of diamines [in this case 5,6-diamino-1,3-dimethyluracil (I)] with protected aldehyde sugars in absolute methanol. As a result of the condensation of diamine I with di-O-benzylidene derivatives of D-ribose, D-xylose, and L-arabinose (RCHO), one obtains excellent yields of the corresponding Schiff bases (II), the oxidative cyclization of which under the influence of N-bromosuccinimide (NBS) in methanol at 0°C gives theophylline C-nucleosides (III) [1].

Treatment of III with acetic acid leads to debenzoylated tetrahydroxybutyltheophyllines (IV), the acetylation of which with acetic anhydride in pyridine gives the corresponding tetraacetates V. Unprotected sugars (R'CHO), which upon condensation with pyrimidine I give Schiff bases VI, can also be subjected to a similar reaction. Acetylation and subsequent cyclization of acetyl derivative VII by means of NBS lead to theophylline derivative V. It has been reported [2] that fusion of base I with D-ribonolactone leads to a theophylline C-nucleoside with a D-ribo configuration (VIII). However, the compound described differs from the compound that we obtained by the method indicated above. In our opinion, epimerization should be observed under such severe conditions, and one should doubt the configuration of VIII obtained in [2].

According to the data from the PMR spectra, the signals of the NH protons of III and V are observed at 13.50 and 12.12 ppm, respectively, while the signals of the NH protons of VIII and IX have chemical shifts of 8.15 and 7.62 ppm, respectively. Consequently, the nitrogen atom in the 7 position is protonated in III and V, whereas the nitrogen atom in the 9 position is protonated in VIII and IX.

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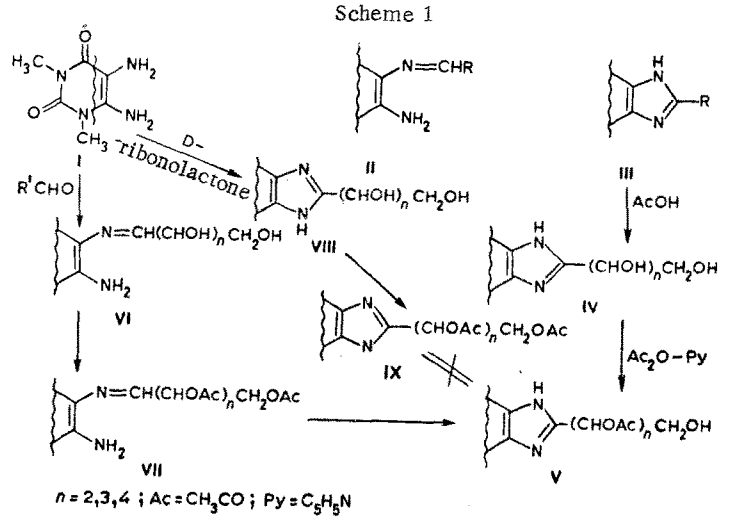
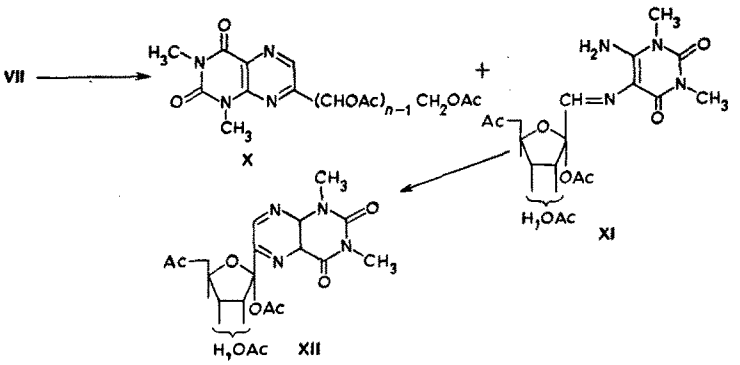
Scheme 1



To obtain C-nucleosides of pyrazole via a similar scheme, instead of pyrimidine I we used diaminomaleic acid nitrile.

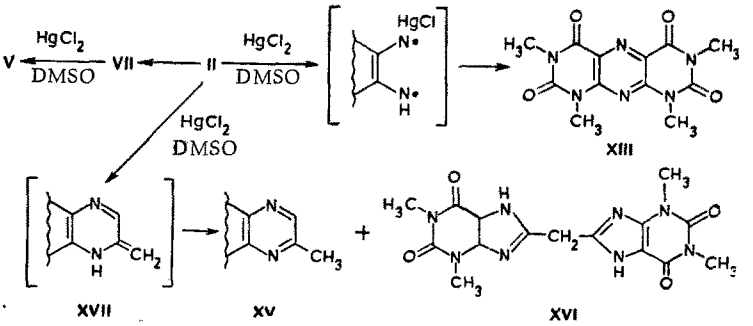
2,3-Dichloro-5,6-dicyano-1,4-benzoquinoline can also be used as the cyclizing agent. Refluxing in toluene for 10-30 h of acetylated Schiff base VII with this reagent leads to pteridine C-nucleosides (X). As a minor component in the reaction mixture we detected XI, by the reaction of which with ethyl orthoformate another pteridine C-nucleoside (XII) can be obtained. Treatment of XI with NBS in order to obtain the corresponding theophylline derivative was unsuccessful.

Scheme 2



The oxidative cyclization of Schiff bases can also be realized by means of mercuric chloride in dimethyl sulfoxide (DMSO) [3-5]. (Since the bonding of metal ions with nucleosides is of great biological interest, we simultaneously studied this problem by PMR spectroscopy [3].) In these studies we used Schiff bases with the general formula II, which were obtained by condensation of diaminopyrimidine I with aldehydes (D-glucose and D- and L-arabinose).

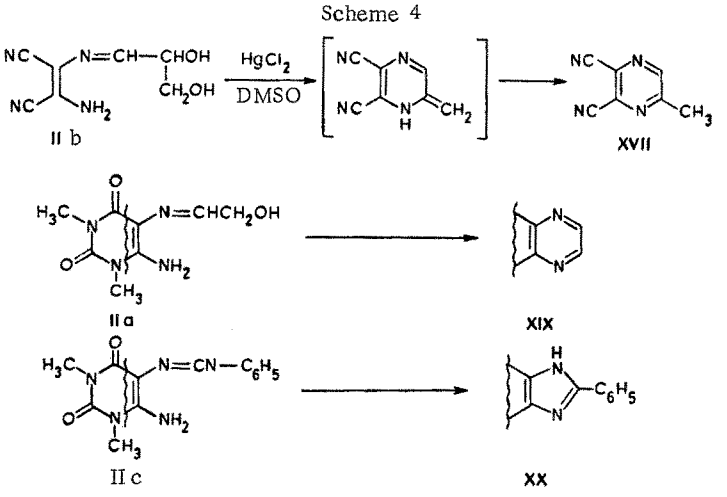
Scheme 3



Treatment of Schiff base II with one equivalent of mercuric chloride in DMSO at room temperature leads to pyrimidopteridine XIII in quantitative yield with the simultaneous

liberation of mercury metal. The reaction proceeds through intermediate diradical XIV, which was confirmed by a study of the EPR spectra of the reaction mixture. At the same time, similar treatment of acetates VII gives theophylline analogs of nucleosides V in 35-40% yields, as in the case of cyclization by means of NBS. Treatment of Schiff base IIa, obtained from pyrimidine I and (+)-glyceraldehyde, with mercuric chloride under similar conditions leads to 1,3,7-trimethylpteridine-2,4-dione (XV) in 63% yield and a bistheophylline derivative (XVI) in 15% yield. The structure of the intermediately formed XVII was confirmed by recording of the PMR spectra of the reaction mixture with time. 2,3-Dicyano-5-methylpyrazine (XVIII) was similarly obtained in 65% yield from the product of the condensation of diaminomaleic acid nitrile and (+)-glyceraldehyde. The products of the condensation of diamine I with glycolaldehyde (IIc) and benzaldehyde (IId) react with mercuric chloride in DMSO to give 1,3-dimethylpteridine-2,4-dione (XIX) and 8-phenyltheophylline (XX) in 62 and 100% yields, respectively.

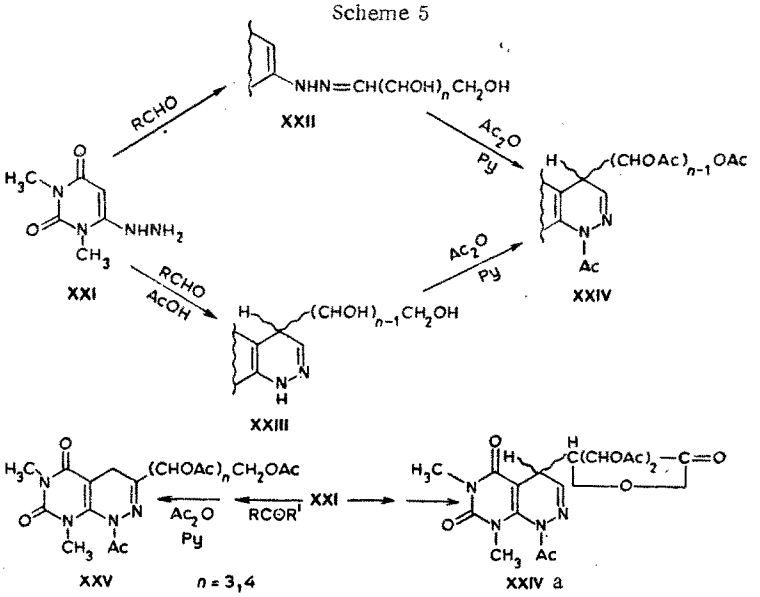
Scheme 4



Hydrazones [6]

The condensation of 7-hydrazino-1,3-dimethyluracil (XXI) with aldoses, ketoses, or lactones of sugars leads to the corresponding hydrazones XXII in good yields [6]; the latter can also be used as key compounds in the synthesis of analogs of nucleosides.

Scheme 5



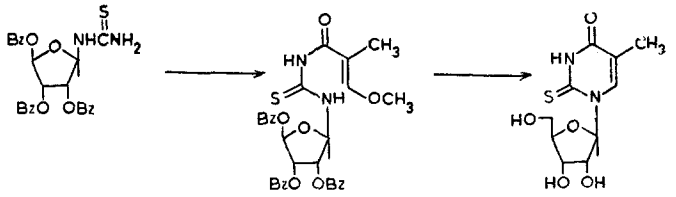
D-Arabinose, L-arabinose, D-glucose, and D-mannose have been used as the carbohydrate component (RCHO) in this method. If catalytic amounts of acetic acid are added to the reaction mixture, nucleoside analogs of pyrimido[4,5-c]pyridazine (XXIII) are formed in low yields. Hydrazones XXII with the above-listed aldehydo sugars were converted to acetylated analogs of pyrimido[4,5-c]pyridazine (XXIV) by treatment with acetic anhydride. Ketoses (D-fructose and L-sorbose) (RCOR') react with hydrazine XXI to give hydrazones, which undergo

cyclization under the influence of acetic anhydride to give acetylated 3-substituted pyrimido[4,5-c]pyridazines (XXV). Like the hydrazones of free aldehydo sugars, D-glucurono-lactone hydrazone undergoes cyclization to 4-substituted pyrimido[4,5-c]pyridazine under the influence of acetic anhydride.

Thioureas [7-9]

The synthesis of glycosyl-2-thiothymine from glycosylthiourea was previously realized by Ukita and co-workers [10] and Naito and Sano [11] via the following scheme:

Scheme 6

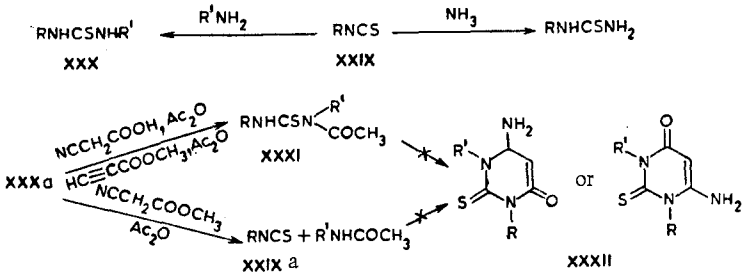


XXVI XXVII XXVIII

1-β-D-Ribofuranosyl-2-thiothymine (XXVIII) is obtained by treatment of 2,3,5-tri-O-benzoyl-β-D-ribofuranosylthiourea (XXVI) with 3-methoxy-2-methylaroyl chloride and subsequent cyclization of the intermediate thiourea XXVII.

Isocyanates and isothiocyanates are important reagents in the chemistry of heterocyclic compounds. We have found that glycosyl isothiocyanates XXIX, particularly, glucosyl isothiocyanate, are important key compounds in the synthesis of analogs of nucleosides, as demonstrated in Scheme 7. Treatment of glucosyl thioureide XXXa with cyanoacetic acid or methyl propiolate in acetic anhydride leads to the formation of thioureide XXXI but not to the expected cyclization product XXXII. However, the corresponding isothiocyanate XXIXa is formed by the action of methyl cyanoacetate in acetic anhydride on glucosyl thioureide XXXa [7].

Scheme 7



XXIX, XXX R = carbohydrate residue, R' = aryl, hetaryl

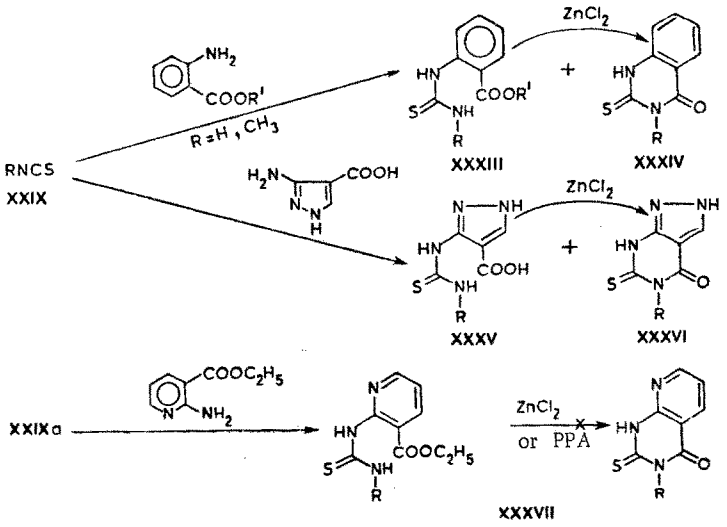
XXIX a, XXX a R = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl, $R^1 = C_6H_5$

The use of aromatic α-amino acids has proved to be more promising in this respect [9]. Thus refluxing glycosyl isothiocyanates XXIX with anthranilic acid in benzene leads to the formation of thioureides XXXIII and thioquinazoline glycosides XXXIV in approximately equal ratios. In the presence of zinc chloride the yield of the cyclization product increases, and the XXXIII:XXXIV ratio become 3:8. Thioureide XXXIII can be converted to cyclization product XXXIV by refluxing in toluene in the presence of zinc chloride. Similarly, 3-amino-pyrazole-4-carboxylic acid reacts in benzene with thioisocyanate XXIX to give thioureides XXXV and glycoside analogs of pyrazolo[4,5-e]pyrimidine (XXXVI) in a ratio of 4:5. In the presence of zinc chloride the yield of pyrazolopyrimidine XXXVI increases due to cyclization of thioureide XXXV. At the same time, the reaction of isothiocyanate XXIXa with ethyl 2-aminonicotinate gives thioureide XXXVII (95%), attempts to bring about the cyclization of which to the corresponding thioquinazolone by means of zinc chloride or polyphosphoric acid (PPA) were unsuccessful.

Yet another method for the creation of analogs of nucleosides is the cyclodesulfuration of glycosyl thioureides [12, 13].

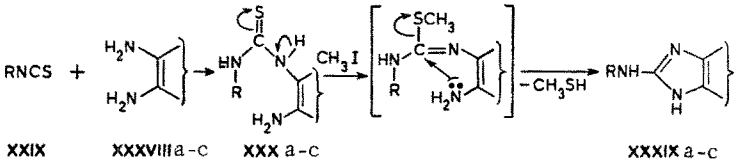
The reaction of glycosyl isothiocyanates XXIX with diamines XXXVIIIa-c leads to the formation of the corresponding thioureides XXXa-c in excellent yields. Treatment of the

Scheme 8



latter with methyl iodide gives the corresponding N-substituted glycosides XXXIXa-c in high yields. The process takes place through a step involving cyclodesulfuration by elimination of methyl mercaptan, as shown in Scheme 9.

Scheme 9



a o-diaminobenzene; b 2,3-diaminopyridine; c 5,6-diamino-1,3-dimethyluracil

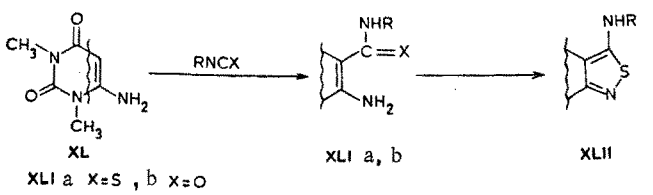
At the same time, the treatment of thioureide XXXa with lead tetraacetate with subsequent acetylation, although it does lead to the formation of benzimidazole XXXIXa, gives the cyclization product in very low yield.

The 8-glycosylaminotheophylline structure (XXXIXc) was confirmed by PMR spectroscopy. The signal of the proton of the amino group attached to C_8 of the purine ring is observed in the spectrum at 8.25-8.28 ppm, while the signal of the proton attached to N_7 appears at 11.55-11.82 ppm (protonation of the N_9 atom would lead to the appearance of a signal at 8-9 ppm [1]).

Thiocarbamides [7, 14]

The reaction of 6-amino-1,3-dimethyluracil (XL) with alkyl or aryl iso(thio)cyanates leads to the formation of the corresponding carbamoyluracils (XLIa, b). The oxidation of thiocarbamide XLIa with NBS at 0-5°C leads to N-substituted aminoisothiazolo[3,4-d]pyrimidines (XLII) in good yields, while attempts to cyclize carbamide XLIb under similar conditions to the corresponding oxazolopyrimidines were unsuccessful [7].

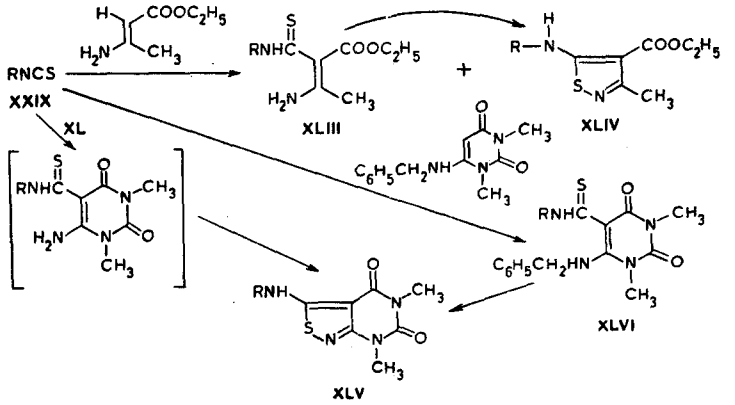
Scheme 10



Attempts to obtain thiopyrimidine nucleosides by treatment of glycosyl isothiocyanates XXIX with ethyl aminocrotonate were unsuccessful: Only thiocarbamides XLIII and aminoisothiazole nucleosides XLIV were formed. The yields of the nucleosides can be raised substantially, since thiocarbamides XLIII are readily cyclized to 5-glycosylaminoisothiazoles XLIV. Similar treatment of glycosyl isothiocyanates XXIX with 6-amino-1,3-dimethyluracil (XL) in dimethylformamide (DMF) gives 3-glycosylamino-5,7-dimethylisothiazolo[3,4-d]pyrimi-

dine-4,6-diones (XLV) in good yields. One might have expected that the reaction would proceed through the intermediate formation of thiocarbamide derivatives of the XLIII type; however, the latter were not detected. To confirm the mechanism of this reaction isothiocyanate XXIX (R = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) was therefore subjected to

Scheme 11



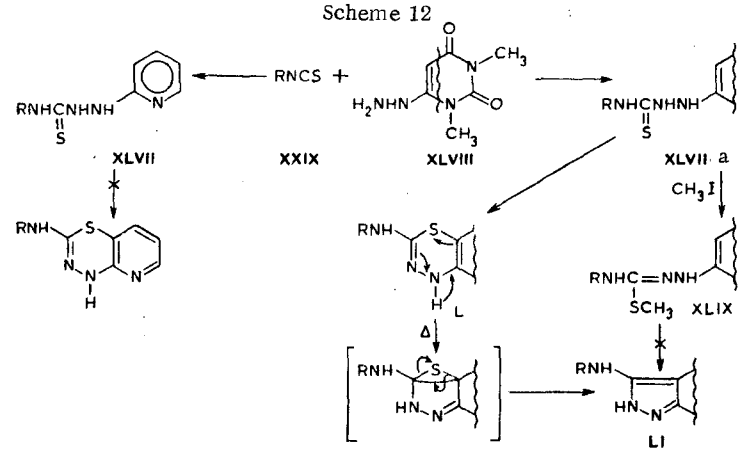
reaction with 6-benzylamino-1,3-dimethyluracil, and the resulting thiocarbamide, after debenzylation of the amino group by hydrogenation, was subjected to cyclization to isothioazolopyrimidine XLV.

Thiosemicarbazides [14]

Methods for the synthesis of analogs of nucleosides of theophylline, aminoisothiazole, and aminoisothiazolopyrimidine both by means of oxidative cyclization of Schiff bases and through glycosylthiocarboxamides have been previously examined. In this section we will examine the synthetic procedure for the preparation of nucleoside analogs of pyrazolopyrimidines by means of oxidation with N-bromosuccinimide (NBS) [14].

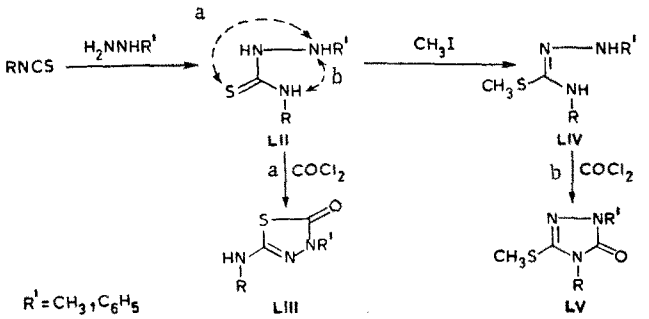
Glycosyl isothiocyanates XXIX react with 2-hydrazinopyridine to give N-glycosyl-2-(2-pyridylhydrazinyl)thiocarboxamides XLVII. However, attempts to cyclize XLVII by heating or under the influence of NBS were unsuccessful. The reaction of isothiocyanates XXIX with 6-hydrazino-1,3-dimethyluracil (XLVIII) gave N-glycosyl-2-(1,3-dimethyl-2,4-dioxo-6-pyrimidinylhydrazinyl)thiocarboxamides (XLVIIa), the structures of which were confirmed by data from the PMR and IR spectra. As in the case of XLVII, heating XLVIIa in refluxing xylene or o-dichlorobenzene does not lead to cyclization. On the other hand, the action of methyl iodide on thiocarboxamide XLVIIa (R = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) gives the corresponding N-glycosyl-S-methyl-2-(1,3-dimethyl-2,4-dioxo-6-pyrimidinylhydrazono)thiocarboxamide (XLIX). 2-Glycosylamino-6,8-dioxopyrimido[4,5-e]-1,3,4-thiadiazines (L) are formed in good yields (75-80%) by the action of NBS on thiocarboxamides XLVIIa. When L are refluxed in toluene, they undergo ring contraction due to desulfuration, as indicated in Scheme 12, and form 7-substituted pyrazolo[3,4-d]pyrimidine-4,6-diones (LI) in quantitative yields. Attempts to cyclize thiocarboxamide XLIX to pyrazolopyrimidine LI by means of NBS or by heating were unsuccessful.

Scheme 12



Glycosyl isothiocyanates XXIX react with methyl- and phenylhydrazine to give glycosyl thiosemicarbazones LII.

Scheme 13

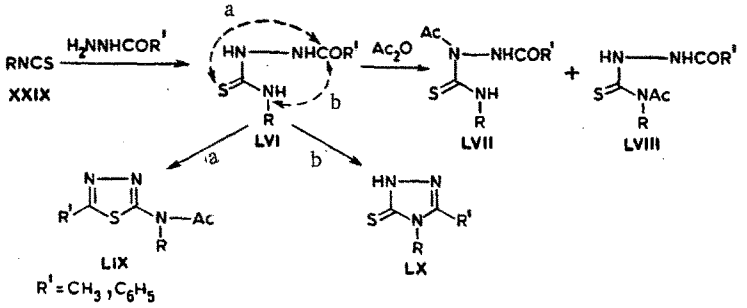


When semicarbazones LII are treated with phosgene, cyclization takes place via pathway a and leads to glycosylámino-1,3,5-thiadiazolones (LIII). On the other hand, the methylation of semicarbazones LII with methyl iodide gives glycosyl-S-methylthiosemicarbazide (LIV), which undergoes cyclization on treatment with phosgene via pathway b to give glycosyl-5-thio-1,2,4-triazolin-3-one (LV).

The reaction of isothiocyanates XXIX with acetyl- or benzoylhydrazine gives glycosylthiosemicarbazides LVI in good yields.

Treatment of LVI with acetic anhydride leads only to N-acetates LVII and LVIII in a ratio of 3:1. However, cyclization via pathway a to give glycosylamino-1,3,5-triazole LIX takes place when semicarbazide LVI is treated with sodium methoxide with subsequent treatment of the reaction mixture with acetic anhydride. However, when semicarbazide LVI is treated with polyphosphoric acid (PPA) or a mixture of phosphoric acid with acetic anhydride, cyclization proceeds via pathway b, and the reaction product is 4-glycosyl-1,2,4-thiazole-2-thione (LX).

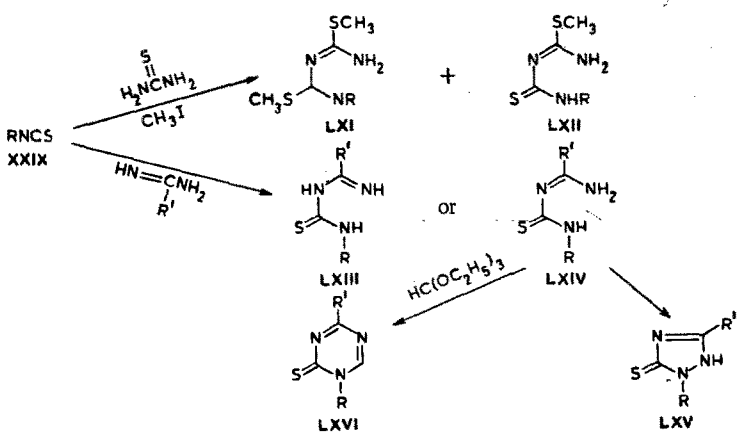
Scheme 14



Thiobiurets and Amidinoureas [15]

Derivatives of thiobiurets and amidinoureas of sugars are obtained from glycosyl isothiocyanates XXIX and amidine compounds of the $NH{=}C(R)NH_2$ type, where R = H, CH_3, OCH_3, SCH_3, and NH_2.

Scheme 15



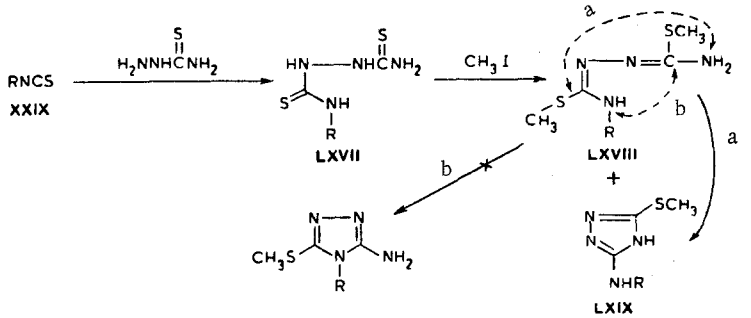
The reaction of isothiocyanate XXIX with thiourea and methyl iodide gives S-methyl- (LXI) and bis(S-methyl)-substituted (LXII) compounds in 52 and 46% yields, respectively. If S-methylthiourea is used as the nucleophile in this reaction, LXII is obtained in 93% yield. When amidine compounds are used as the nucleophiles, LXIII and LXIV are obtained in good yields. The cyclization of LXIV under the influence of NBS leads to glycosyl-1,2,4-triazole-3-thiones (LXV) in excellent yields, and the corresponding s-triazine glycosides LXVI are also formed in excellent yields when it reacts with ethyl orthoformate.

Bisthioureas [15]

Glycosyl-2,5-bisthioureas (LXVII) are obtained from glycosyl isothiocyanates XXIX and semicarbazide.

Treatment of LXVII with excess methyl iodide leads to the bis(S-methylated) derivative LXIII and glycosylamino-1,2,4-triazole LXIX in a ratio of 1:9. Heating LXIII in a suitable solvent also leads to its cyclization to triazole LXIX, i.e., the cyclization proceeds via

Scheme 16

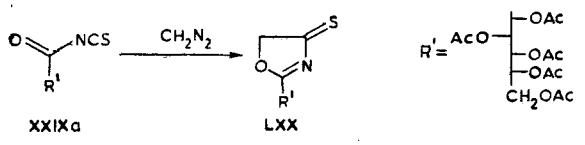


pathway a. However, we were unable to realize the cyclization of LXIII via pathway b; the expected nucleoside analog of 1,3,5-triazole was not obtained.

Keto Isothiocyanates [7, 16, 17]

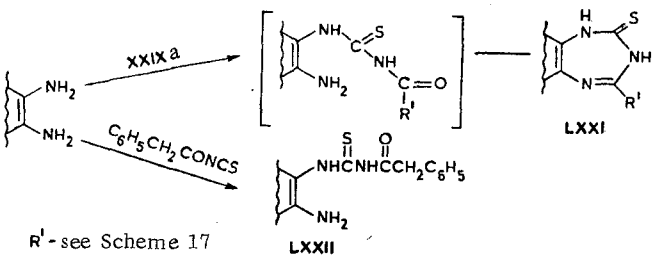
The use of D-gluconyl isothiocyanate as the key compound in the synthesis of analogs of nucleosides [7] and its reaction with nucleophilic reagents were summarized above. Here we will note only that the cyclization of isothiocyanate XXIXa with diazomethane leads to 2-(penta-O-acetyl)-D-gluconyl-4-thiooxazolone (LXX).

Scheme 17



Diamines (ethylenediamine, o-phenylenediamine, 5,6-diamino-1,3-dimethyluracil, and diaminomaleic acid nitrile) react with isothiocyanate XXIXa to give nucleoside analogs of triazepine-2-thione LXXI. We did not observe the formation of any intermediates in this reaction.

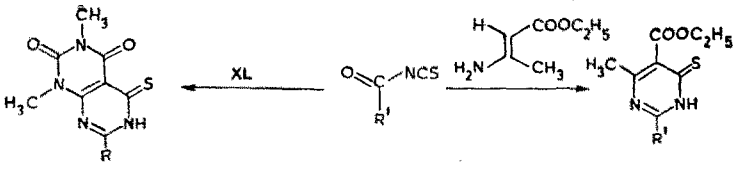
Scheme 18



At the same time, phenylacetyl isothiocyanate reacts with diamines to give LXXII, which are not capable of undergoing cyclization to triazepine derivatives.

In conclusion, one should note the reaction of isothiocyanate XXIXa with enamines.

Scheme 19



LXXIV R'-see Scheme 17 | XXIX a | LXXIII

The use of ethyl 2-aminocrotonate or 6-amino-1,3-dimethyluracil (XL) as enamines leads to D-gluconylpyrimidine LXXIII and D-gluconylpyrimidino[4,5-d]pyrimidine LXXIV, respectively, in good yields.

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