Translated from *Uspekhi Khimii*, 51 661-677 (1982) U.D.C. 547.917

Derivatives of Carbohydrates with Carbamide Fragments

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A systematic account is given of the results of experimental studies on the synthesis, structures, and properties of carbohydrate-containing derivatives of urea and its analogues—thiourea, selenourea, and iminourea (guanidine). The possibility of using them in the preparative chemistry of carbohydrates and in certain branches of the national economy is demonstrated. The prospects for the development of the chemistry of sugars with ureido-groups are outlined.

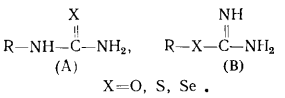
The bibliograph includes 123 references.

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I. INTRODUCTION

The products of the substitution of the hydroxy-groups of the carbohydrate chain, including the glycosidic hydroxyl $C_{(1)}$–OH by the residues of derivatives of urea and its analogues—thiourea, selenourea, and guanidine (iminourea)—must be included among ureidosugars, which form part of the large class of aminosugars and *N*-glycosylamines (*N*-glycosides).[1-4] A series of structural and chemical features make it possible to combine these compounds into a separate group among nitrogen-containing sugar derivatives. Among these features, one should include in the first place the polyfunctional nature of the carbamide fragments, manifested particularly by the effects involving neighbouring functional groups of the sugars. The presence of the carbonyl group in the immediate vicinity of the amino-group reduces markedly the basicity (pK_a) of the amino-group and hence the reactivity of the carbamide fragment in acid-catalysed nucleophilic addition and substitution reactions. In this respect the *N*-glycosidic linkage in *N*-glycosyl derivatives of carbamides approaches in its properties the glycosidic linkages in nucleosides. The fact that both the amino-group (A) and the oxygen, sulphur, and selenium atoms (B) can participate in the formation of a bond with the carbohydrate residue R must be regarded as one of the characteristic features of ureidosugars, the stability of derivatives with the iso-structure (B) increasing with increase of the nucleophilicity of the atom X. Stable iso-structures of carbohydrate derivatives of urea are unknown.



(A) (B)

X=O, S, Se.

In terms of certain structural and chemical features, ureidosugars resemble carbamic acid esters (carbanilates) and amides derived from sugars as well as *N*-acylation products. The preparative value of these derivatives in carbohydrate chemistry has been discussed in a number of studies[1-5] and they are not considered in the present review.

Different aspects of the technical employment of ureidosugars are limited mainly to *N*-glycosylureas, which have been used, for example, to obtain non-shrinking and crease-resistant cotton fabric[6], in compositions designed to increase the strength of paper[7], as detergents with improved disinfecting properties[8,9], and as feed preparations with a high content of *N*-glycosylurea to make good the protein nitrogen deficiency in the diet of animals[10,11]. A significantly more important trend towards their application in pharmacology, medicine, the health service, bio-organic chemistry, and molecular biology has arisen recently. The likelihood of the development of research into the chemistry of ureidosugars is associated primarily with the problem of the synthesis of carbohydrate-containing physiologically active substances with a low toxicity, a high solubility in water, and with selective action on the living organism.

As a preparation for medical purposes, urea has extremely modest possibilities[12]. Urea derivatives, the various pharmacological properties of which can be illustrated by examples of their utilisation as soporific, narcotic, antipyretic, analgesic, and anticonvulsant agents and in the treatment of diabetes, glycaemia, and in helminthiasis, are of significantly greater interest in this sense[12-14]. The fact that the carbamide residue is extremely common in nature and enters into the structures of biologically important substances of the pyrimidine series also merits special attention. Nitroso-derivatives of urea, guanidine, and biuret have acquired great practical importance for the treatment of malignant neoplasts[15-19]. An exceptionally high mutagenic activity and the ability to overcome the haematoencephalic barrier must be included among the characteristic features of *N*-nitrosoalkylureas.

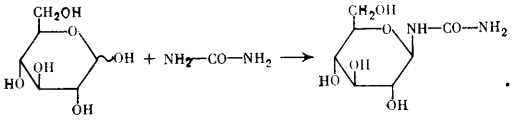
Bearing in mind the above considerations, it is to be expected that the development of experimental and theoretical studies in the field of carbohydrate-containing derivatives of urea and its analogues will lead to the discovery of ways of synthesising new effective medicinal drugs and intermediates for their preparation.

II. METHODS OF SYNTHESIS OF UREIDOSUGARS

Two main approaches are used in the synthesis of ureidosugars: direct interaction of carbohydrates with carbamides and their analogues under the conditions of acid catalysis and the formation of carbamide groups in the carbohydrate molecule on the basis of known reactions leading to the formation of derivatives of urea, thiourea, selenourea, and guanidine. The first pathway is suitable for the synthesis of derivatives involving the glycosidic centre. Among the methods of the second type, the iso(thio)cyanate

method has become most widely used, permitting the introduction of the carbamide residue into virtually any position in the carbohydrate ring.

The synthesis of *N*-glucosylurea (II) by the direct condensation of unsubstituted D-glucose (I) with urea in the presence of an inorganic acid as the catalyst was first achieved by Schoor[20]:

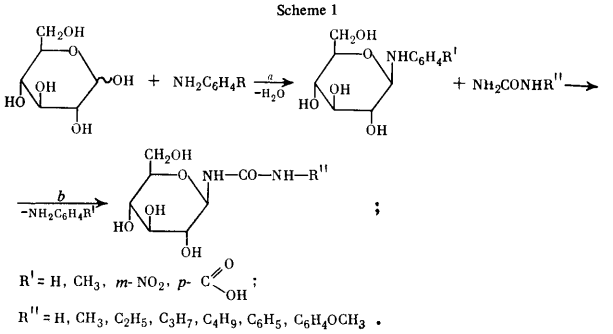


(I) (II)

The reaction was followed by measuring the optical rotation of the reaction solution. The crystalline product was obtained only after enzymatic cleavage of the unreacted D-glucose. Subsequently, the direct condensation method was improved somewhat[21-29] and extended to other mono- and di-saccharides, but no fundamental changes were introduced into the method of synthesis. Thus in the synthesis of *N*-β-D-glucopyranosylurea[21] a 1:1 mixture of glucose and urea is kept at 50 °C for seven days, evaporated, and the 1:2 adduct of glucosylurea and urea is crystallised. In order to isolate glucosylurea, the product is treated with boiling absolute ethanol for three days. In the synthesis of *N*-β-D-ribopyranosylurea[23] the reaction mixture is kept at 50 °C for ten days and the anomeric forms of the condensation product are isolated by preparative chromatography; the final yield does not exceed 15–20%.

A new, more effective method of synthesis of *N*-glycosylurea, using unprotected *N*-arylglycosides, has been discovered in recent years[30-32]. Kinetic studies have shown[2] that the replacement of the glycosidic hydroxyl by an *N*-arylaglycone increases the reactivity of $C_{(1)}$ in nucleophilic addition and substitution reactions as a result of which it is possible to facilitate the introduction of weakly basic aglycones under the conditions of acid catalysis. The set of reactions involving the $C_{(1)}$ atom in the synthesis of *N*-glycosylureas can be represented by the following scheme incorporating stages (*a*) and (*b*):

Scheme 1



R^{I} = H, CH_3, *m*-NO_2, *p*-$C(=O)OH$;

R^{II} = H, CH_3, C_2H_5, C_3H_7, C_4H_9, C_6H_5, $C_6H_4OCH_3$.

In order to obtain *N*-glycosylureas by the *N*-transglycosylation reaction, it is sufficient to heat for a very short time (10–30 min) a mixture of urea and the *N*-arylglycosides with an aglycone of moderate basicity in the presence of small amounts of added inorganic acid until the mixture becomes completely homogenised. The initial *N*-glycoside is sometimes precipitated on crystallisation together with the required product, but it can be readily removed by washing the precipitate with hot ethanol. Subsequent recrystallisation of the product from aqueous alcoholic solutions leads to chromatographically homogeneous *N*-β-D-glycopyranosylurea.

Scheme 1 shows that the arylamine plays in essence the role of a nucleophilic catalyst of the direct condensation of the monosaccharide with urea derivatives. To simplify the preparative procedure, *N*-glycosylureas can therefore be synthesised without the preliminary preparation of the corresponding *N*-arylglycoside and catalytic amounts of the arylamine can be used.

In the synthesis of glycosylureas by the direct condensation of unprotected sugars with urea, *N*,*N'*-diglycosylureas are always formed, their relative content in the reaction mixture depending on the ratio of the concentrations of the initial components:

$$2\rangle HC_1{-}OH + NH{-}CO{-}NH_2 \rightarrow \rangle HC_1{-}NH{-}CO{-}NH{-}C_1H\langle + 2H_2O\ .$$

N-Alkylureas do not condense with sugars at the site where the alkyl group is substituted.

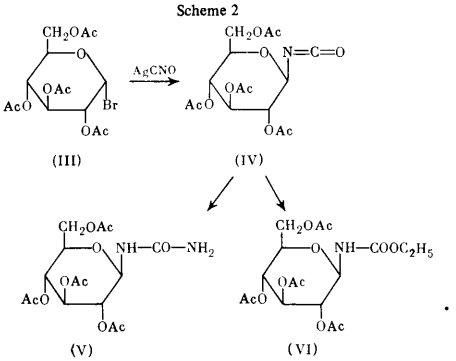
The *N*-triglycosylation method is nowadays the most promising for the synthesis of *N*-glycosylureas on a large scale. By altering the nature of the *N*-aglycone, it is possible to vary the rate of the substitution reaction and to synthesise anomeric forms at the kinetically controlled stages.

The isocyanate method, developed by Fischer[33] in 1914 and based on the interaction of acetyl-substituted glycosyl isocyanates with amines, proved to be effective in the synthesis of *N*-glycosylureas:

$$\rangle HC_1{-}N{=}C{=}O + NH_2R \rightarrow \rangle HC_1{-}NH{-}CO{-}NHR\ .$$

Thus, in the synthesis of *N*-β-D-glucopyranosylurea, treatment of tetra-*O*-acetyl-α-D-glycopyranosyl bromide (III) with silver cyanate in anhydrous xylene gives the glucosyl isocyanate (IV) which is converted into the final product (V) by teatment with an aqueous solution of ammonia. On the other hand, when compound (IV) is heated in an alcoholic solution, the glucosylurethane (VI) is formed (see the scheme below):

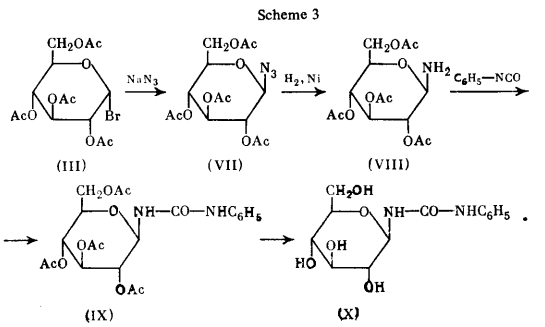
Scheme 2



(III) (IV) (V) (VI)

The carbamide residue can be formed at $C_{(1)}$ also by the reaction of *N*-glycosylamine with isocyanates, as shown for the formation of *N'*-phenyl-*N*-β-D-glucopyranosylurea (X) (see the scheme below):

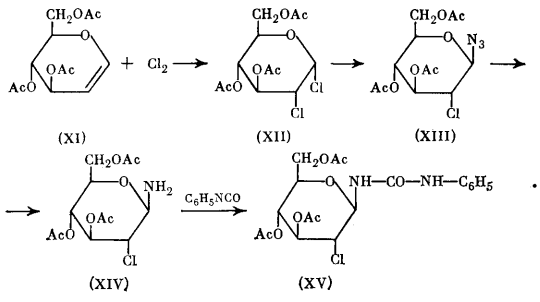
Scheme 3



(III) (VII) (VIII) (IX) (X)

The Fischer method has been improved[34-41] and its applicability in the synthesis of glycosylureas has been greatly extended. An an illustration, one may quote the synthesis of 2-chloro- and 2-bromo-derivatives of glycosylureas from acetylglycols[42]:

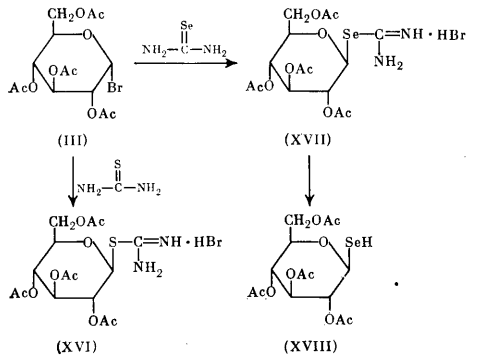
Scheme 4



Similarly sugar isothiocyanates with protected hydroxy-groups readily undergo addition reactions with amines and give rise to the corresponding *N*-glycosylthioureas.

The interaction of thiourea with acetylhalogeno-sugars leads to the formation of thioureido-sugars with the iso-structure. Thus treatment of acetobromoglucose (III) with thiourea results in the formation of tetra-*O*-acetyl-β-D-glucopyranosylisothiourea (XVI)—the so-called "isothiouronium salt":[48-51]

Scheme 5

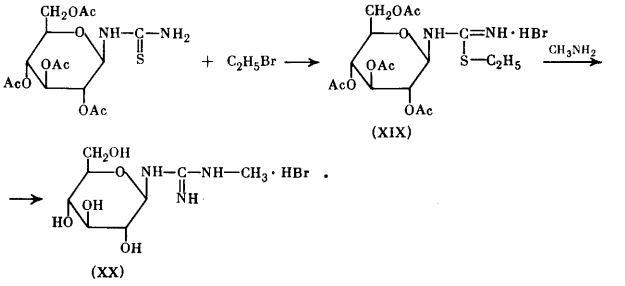


Derivatives of isothiourea are unstable and readily decompose under the influence of bases with formation of thioaldoses. A method of synthesis of alkylthioglycosides has been developed on this basis[52].

Selenourea behaves analogously[53-56]. On interaction with acetobromoglucose, it gives rise to tetra-*O*-acetyl-β-D-glucopyranosylisoselenourea (XVII), which decomposes on treatment with KOH solution to form the selenoglucoside (XVIII), which subsequently condenses to bis(tetra-*O*-acetyl-β-D-glucopyranosyl) diselenide.

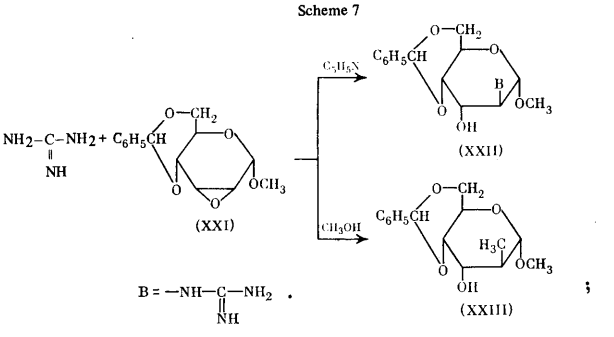
In contrast to urea and thiourea, guanidine does not undergo condensation reactions with unsubstituted sugars[4]. Guanidine-containing sugars can be conveniently obtained by the method involving the transformation of the thiourea fragment into a guanidine fragment by treatment with amines[57-59]. This procedure can be illustrated in relation to the synthesis of *N*-β-D-glucopyranosylguanidine (XX) from *S*-ethyl-substituted *N*-β-D-glucopyranosylthiourea (XIX) obtained by the reaction of *N*-β-D-glucopyranosylthiourea with ethyl bromide and subsequent treatment with methylamine[57,58]:

Scheme 6



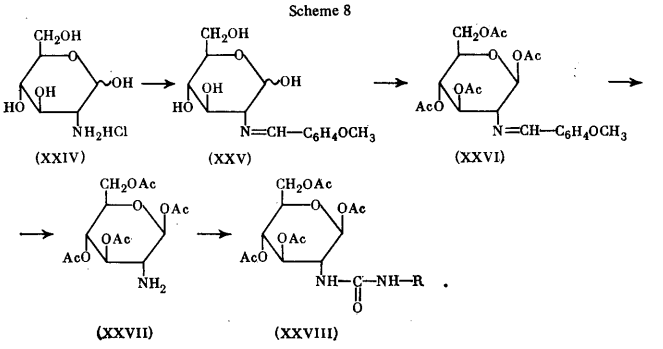
It has been possible[60-62] to introduce the guanidino-residue into the $C_{(2)}$ position by the direct treatment of 2,3-anhydro-4,6-*O*-benzylidene-α-D-methylallopyranoside (XXI) with guanidine, the mixture being subjected to prolonged heating in pyridine. When the treatment with guanidine was carried out in methanol, the methyl derivative (XXIII) was formed via the following scheme:

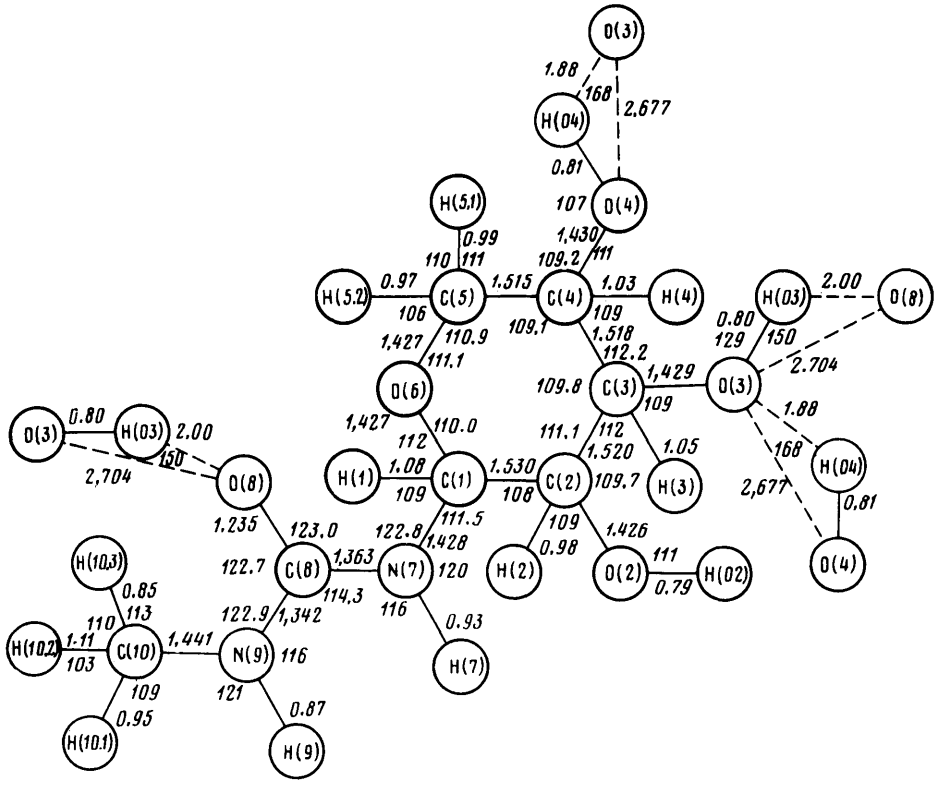
Scheme 7



The Fischer iso(thio)cyanate method, which is universal and preparatively simple, is mainly used to introduce carbamide or thiocarbamide fragments into positions in the carbohydrate ring other than the glycosidic centre at $C_{(1)}$. The applicability of this method of synthesis is determined by the practical availability of aminosugars with a specified position of the amino-group. The method of synthesis can be illustrated by the synthesis via Scheme 8 of *N*-substituted derivatives of 2-ureido-2-deoxysugars in which it is possible to isolate the following principal stages[63]: protection of the amino-group with the aid of anisaldehyde, exhaustive *O*-acetylation with acetic anhydride in pyridine, removal of the anisidine protection group, and condensation of the acetyl-substituted aminosugar with alkyl or aryl isocyanates. Treatment of the *O*-acetyl-substituted condensation products with an ammoniacal solution of methanol permits smooth deacetylation and the preparation of the unsubstituted derivatives of 2-ureido-2-deoxysugars:

Scheme 8





The bond lengths (Å) and valence angles (degrees) in *N*-methyl-*N*-β-D-xylopranosylurea. The oxygen atoms of the neighbouring groups forming hydrogen bonds with the given molecule (dashed lines) are also shown.

III. THE STRUCTURE AND PROPERTIES OF *N*-GLYCOSYLUREAS

The structure and properties of *N*-glycosylureas have been most thoroughly studied among ureidosugars. The structures of *N*-glycosylureas, demonstrated with the aid of traditional methods of carbohydrate chemistry—periodate oxidation, exhaustive acrylation, acid hydrolysis, and specific synthesis by the isocyanate method—have been described in a review[4]. In the vast majority of the known ureidosugars the carbohydrate residue exists in the cyclic, principally the pyranose form with a 1,2-*trans*-glycosidic linkage[24].

An X-ray diffraction study of *N*-methyl-*N'*-β-D-xylopyranosylurea showed[64] that the carbohydrate ring is in the $C_{(1)}$ conformation, while the carbamide residue has an almost planar trigonal structure (see Figure). The plane of the carbamide residue forms a dihedral angle of 4.5° with the plane of the carbohydrate ring. The valence angles at the atoms of the pyranose ring are close to the tetrahedral value, while the bond lengths are close to the standard $C(sp^3)$–$C(sp^3)$ and $C(sp^3)$–O bond lengths. The $C_{(8)}$–$N_{(7)}$ bond in the urea residue is somewhat lengthened, while the $C_{(8)}$–$N_{(9)}$ bond is somewhat shortened compared with the corresponding bonds in ureas.

The crystals of *N*-methyl-*N'*-β-D-xylopyranosylurea belong to the orthorhombic system ($P\ 2_12_12_1$ group): $a = 6.707$ Å; $b = 8.670$ Å; $c = 15.944$ Å; $\alpha_{calc} = 1.48$ g cm^{-3}; $Z = 4$. In the crystal lattice the molecules are "cross-linked" by hydrogen bonds and give rise to a two-dimensional network in the *ac* plane. Each molecule is involved in four intermolecular hydrogen bonds of the type O–H...O with participation of the OH groups at the $C_{(3)}$ (two bonds) and $C_{(4)}$ atoms as well as the C = O group of the urea residue. The hemiacetal oxygen ring atom and both NH groups are not involved in the system of hydrogen bonds. The hydrogen bonds apparently make the main contribution to the energy of the crystal[64].

The range 1400–1800 cm^{-1}, free from the absorption bands of the carbohydrate residues, is suitable for the identification of *N*-glycosylureas with unprotected OH groups on the basis of absorption spectra[65]. In this region there are characteristic "amide" absorption bands, which frequently make it possible to determine the nature of the substituents at the nitrogen atom (see Table). The band near 1560 cm^{-1}, which is associated with the deformation vibrations of the N–H bond ("the amide-II" band), is a reliable spectroscopic characteristic of the *N*-glycosidic linkage in *N*-glycosylureas. The absorption bands of free urea (at 1625 and 1680 cm^{-1}) do not change significantly when urea is incorporated into a monosaccharide. An absorption band at 1635–1645 cm^{-1} is characteristic of *N*,*N'*-diglycosylureas, while bands at 1630–1640 cm^{-1} (C = O) and 1585–1590 cm^{-1} (N–H) are characteristic of *N*-alkyl-substituted 2-ureido-2-deoxysugars[66]. The replacement of an alkyl substituent in these derivatives by a phenyl group shifts the stretching vibration frequency of the C = O group to 1690 cm^{-1} and lowers the frequency of the deformation vibrations of the N–H

bond to 1540 cm^{-1}. The introduction of a nitroso-group in the *N*-position results in a still greater shift (to 1710 to 1720 cm^{-1}) of the frequency of the C = O group in the –NH–CO–NHR fragment; at the same time the absorption band of the *N*-nitroso-group appears in the range 1450 to 1500 cm^{-1}. Acetylation of ureidosugars results in a marked levelling of the infrared spectra.

The characteristic signals of the anomeric proton and of the protons at the other carbon atoms of the carbohydrate skeleton in the NMR spectra are in general retained for *N*-glycosylureas and 2-ureido-2-deoxy-derivatives. The signal of the hydrogen atom linked to $C_{(1)}$ in the β-anomers of ureidosugars has a chemical shift δ = 6.00–6.34 p.p.m.; as a result of the interaction with the hydrogen atom at $C_{(2)}$, this signal is a doublet and the spin–spin coupling constant J = 9 Hz. The signals of the protons in the carbamide residue (–NH–CO–NH–) are in the range δ = 4.2–5.5 p.p.m. and, together with the signals of the protons of the carbohydrate ring, give rise to an extremely complex group whose complete analysis is possible at working frequencies of spectrometers in excess of 100 mHz.[66]

The "amide" absorption bands of certain *N*-glycosylureas and their derivatives.

Compound	Frequencies, cm^{-1}
N-β-D-Glucosylurea	1555, 1625, 1670
N-β-D-Galactosylurea	1565, 1635, 1663, 1680
N-β-D-Mannosylurea	1565, 1630, 1680
N-β-D-Xylosylurea	1560, 1615, 1680
N,N Di-D-mannosylurea	1575, 1650
N,N'-Di-D-xylosylurea	1585, 1645
N-Methyl-*N'*-β-D-glucosylurea	1572, 1672
N-Phenyl-*N'*-β-D-glucosylurea	1560, 1660
Urea	1629, 1681
N-Methylurea	1580, 1660
N,N-Dimethylurea	1530, 1634, 1680

The introduction of the carbamide *N*-aglycone leads to an appreciable decrease of the reactivity of the glycosidic centre in relation to nucleophiles without altering significantly the properties of the OH groups of the carbohydrate skeleton and the functional groups of the urea residue. Glycosylureas are stable in dilute solutions of acids and alkali and hydrolyse only in a highly acid medium.

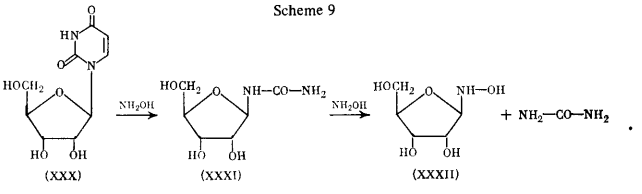
Glycosylureas give a negative response on treatment with reagents for the aldehyde group. In contrast to *N*-glycosides with aglycones of moderate and high basicity ($pK_a \cong$ 2–10), glycosylureas do not enter into transamination (*N*-transglycosylation), osazone formation, and anomerisation reactions and do not undergo the Amadori rearrangement under the conditions of the acid–base catalysis typical for these reactions[2,3]. However, it has been shown[27] that heating of tetra-*O*-acetyl-*N*-β-D-glucopyranosylurea in glacial acetic acid leads to the formation of an equilibrium mixture of anomers with approximately 14.5% of the α-anomer.

The reactivity of the glycosidic centre in sugars in relation to nucleophiles is determined by the effective positive charge on the $C_{(1)}$ atom, so that all the factors promoting an increase of the positive charge favour nucleophilic addition and substitution reactions. Such factors include acid catalysis, whose mechanism is described satisfactorily on the basis of the idea that the heteroatom in the glycosidic linkage is protonated.

The rate of the acid-catalysed nucleophilic reaction involving $C_{(1)}$ should increase with increasing basicity (pK_a) of the *N*-aglycone, which agrees with the results of kinetic studies[2]. The replacement of the oxygen atom in monosaccharides and *O*-glycosides by the more basic nitrogen atom in the *N*-glycosidic linkage increases, other experimental conditions being equal, the probability of the protonation of the glycosidic linkage and hence also the rate of nucleophilic reactions involving the $C_{(1)}$ atom. As regards glycosylureas, the pK_a for the basicity of the nitrogen atom involved in the *N*-glycosidic linkage is very low ($pK_a \cong$ 0.1) compared with *N*-aryl- and *N*-alkyl-glycosides. The probability of its protonation in moderately acid media is therefore very low. Furthermore, calculations have shown[67,68] that the most probable site of the protonation of urea is the oxygen atom. The protonation of the oxygen atom is energetically favourable, but it does not promote and actually lowers the reactivity of the $C_{(1)}$ centre owing to the decrease of the probability of the protonation of the nitrogen atom of the *N*-glycosidic linkage.

The above factors can account for the relatively high hydrolytic stability and low reactivity of glycosylureas in nucleophilic substitution reactions. In this respect the $C_{(1)}$–N bond in glycosylureas has properties approaching those of the *N*-glycosidic linkages in pyrimidine nucleosides and their analogues. For example, it is instructive that, in the hydroxylaminolysis of cytosine and uracil nucleosides, the heterocycle is the first to be cleaved, the *N*-aglycone being displaced from *N*-β-D-ribofuranosylurea (XXXI) only in the concluding stages of the reaction under fairly severe conditions (see the scheme below):[69]

Scheme 9



(XXX) (XXXI) (XXXII)

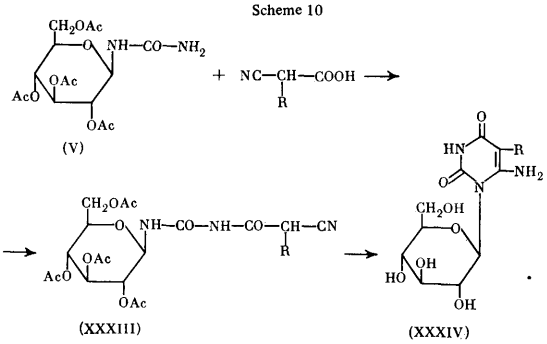
IV. THE REACTIONS OF UREIDOSUGARS AND THE SYNTHESES ON THEIR BASIS

1. The Synthesis of Nucleosides and Their Analogues

Glycosylureas and glycosylthioureas can serve as the starting materials for the synthesis of *N*-glycosides of the pyrimidine series by the cyclisation of the carbamide aglycone on the basis of the known reactions for the formation of pyrimidine systems. One of the first studies in this field was that of Goodman[70], who described the synthesis of 6-amino-*N*-β-D-glucopyranosyluracil (XXXIV) by the Trauber reaction involving the treatment of tetra-*O*-acetyl-β-D-glucopyranosylurea (V) with cyanoacetic acid and subsequent deacetylation of the condensation product (XXXIII) with an ethanol solution of ammonia. The removal of the acetyl protecting groups resulted also in the simultaneous cyclisation of the *N*-aglycone. Goodman obtained in this way a series

of alkyl- and aryl-substituted glucosyl derivatives of 6-aminouracil:

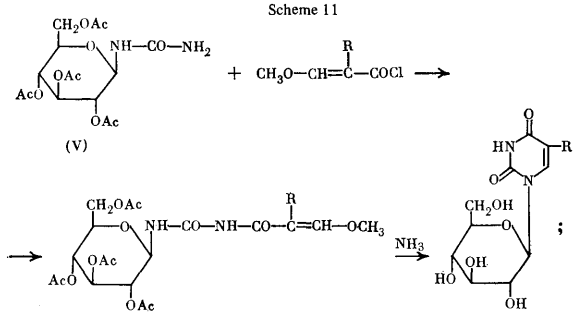
Scheme 10



(V) (XXXIII) (XXXIV)

Japanese investigators[71-76] synthesised pyrimidine *N*-glycosides by the condensation of fully *O*-acetylated *N*-glycosylureas and glycosylthioureas with the chlorides of acrylic and methacrylic acids. Thus β-D-glucopyranosylthymine (XXXVI) has been obtained by the reaction of tetra-*O*-acetyl-β-D-glucopyranosylurea (V) with 3-methoxy-2-methacrylic acid chloride and treatment of the condensation product, tetra-*O*-acetyl-β-D-glucopyranosyl-3-(3-methoxy-2-methylacryloyl)urea (XXXV), with a 3.3% solution of ammonia at 80 °C for 2 h. Under these conditions, the carbohydrate residue is deacetylated and the *N*-aglycone cyclises via Scheme 11. β-D-Arabinopyranosylthymine has been obtained analogously.

Scheme 11

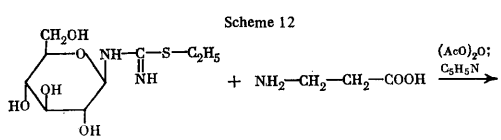


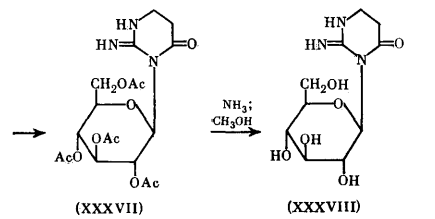
(V) (XXXV) R = CH_3. (XXXVI)

In these syntheses the yields of products reach 60–70% in the stage involving the condensation of the acid chloride with *O*-acetylated glycosylureas and 60% in the stage where the intermediate is deacetylated and cyclises. In terms of efficiency, the above method of synthesis of glycosylthymines is comparable to the method of Ralph and Shaw, which is based on the interaction of α-cyano-β-ethoxycarbonylacrylamide with glycosylamines (see Shabarov's review[77]).

Micheel and coworkers[57,58] synthesised analogues of nucleosides and *N*-glycosides with heterocyclic aglycones using *N*-glycosylthioureas. Thus the glycosyl derivative of hexahydropyrimidine (XXXVIII) has been obtained from *S*-ethyl-*N*-β-D-glucopyranosylthiourea via the following scheme:

Scheme 12





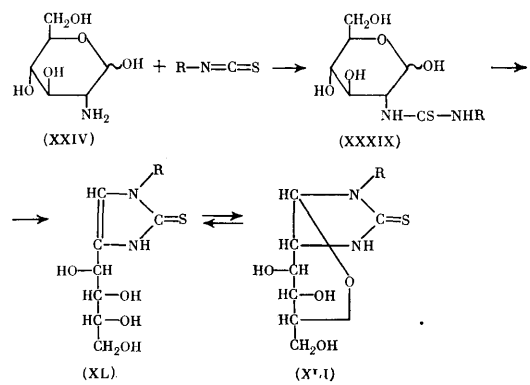
(XXXVII) (XXXVIII)

2. Reactions Involving Neighbouring Groups

In modern carbohydrate chemistry reactions with neighbouring group participation are used to invert the configuration of the carbon atoms and for the stereospecific synthesis of glycosides[1-5,78,79]. Under the conditions of acid catalysis, the collaboration effects frequently lead to migration of the functional groups to neighbouring carbon atoms via intermediate stages involving the formation of acetoxonium, oxazoline, and other heterocycles in the carbohydrate chain. An analogous picture has been observed also for ureidosugars.

The effect of the collaboration of the neighbouring groups in *O*-substituted sugars has been examined in detail[80] in relation to nucleophilic reactions of $C_{(1)}$-acetyl derivatives of sugars. Subsequently the ideas concerning the mechanism of the intramolecular reactions of neighbouring groups were developed by Lemieux[78], but, long before these studies, Neuberth and Wolf[81] established in 1901 that the reaction of D-glucosamine with allyl and phenyl isothiocyanates leads to the formation of stable derivatives of imidazoline-2-thione (XL) (see Scheme 13). It was later shown[82,83] by periodate oxidation and acetylation methods that the condensation product exists in the glucopyranose form (XLI) and it has been observed[84] that in alcoholic solutions the interaction of D-glucosamine with isothiocyanates leads initially to the formation of derivatives of 2-thioureido-2-deoxy-D-glucose (XXXIX), which then undergo an intramolecular cyclisation on treatment with glacial acetic acid with formation of the heterocycle (XL). The interaction of isothiocyanates with products of the Amadori rearrangement leads to analogous derivatives[85].

Scheme 13

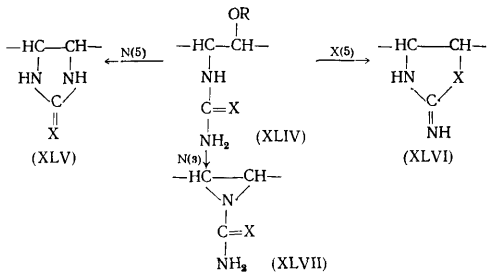


(XXIV) (XXXIX) (XL) (XLI)

Intramolecular cyclisation of the carbamide and thiocarbamide fragments in a series of alkyl(or aryl)-2-thioureido(or 2-ureido)-2-deoxy-D-glucopyranose yielded[63] a large number of derivatives of 3-alkyl(aryl)-1-aryl-4-(D-arabinotetrahydroxybutyl)-imidazolin-2-ones (imidazoline-2-thiones) (XL).

The mechanism of the collaboration process can be represented by a scheme which provides for intramolecular nucleophilic attack by the heteroatom of the functional group on a neighbouring carbon atom linked to a readily removed substituent (see Scheme 14). The carbamide substituents in general possess three potentially active nucleophilic centres capable of involvement in intramolecular substitution processes. Depending on which of the three centres attacks a neighbouring *trans*-substituent, there is a possibility of $N_{(5)}$-cyclisation with formation of the imidazole ring compound (XLV), $X_{(5)}$-cyclisation accompanied by the formation of heterocyclic structures of the type of (XLVI), and $N_{(3)}$-cyclisation leading to the closure of the aziridine ring (XLVII).

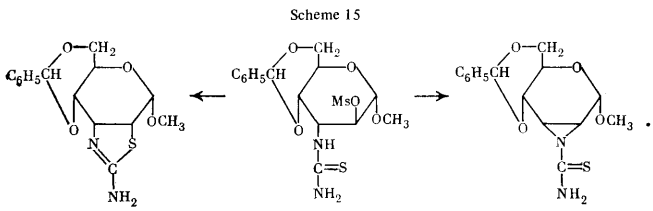
Scheme 14



(XLV) (XLIV) (XLVI) (XLVII)

In a series of studies[86-93] on the synthesis of analogues of nucleosides, reactions with involvement of carbamide[90-92], thiocarbamide[89,92-93] and guanidine[88-91] fragments were investigated in detail and empirical rules were formulated for the determination of the preferential mode of intramolecular cyclisation as a function of the positions of the attacking and leaving (sulphonate ester) groups and the basicity of the medium. As an example, one may quote reactions involving intramolecular substitution in the molecule of methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-methanesulphonyl-3-thioureido-α-D-altropyranoside (XLVIII). When compound (XLVIII) is kept in boiling pyridine for 1 h, a product with the thiazoline structure (XLIX) is formed in yields up to 70%. When it is treated with sodium methoxide, cyclisation with formation of the aziridine structure (L) takes place:

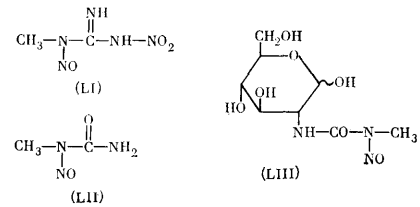
Scheme 15



(XLIX) (XLVIII) (L)

3. Carbohydrate Derivatives of *N*-Alkyl-*N*-Nitrosoureas

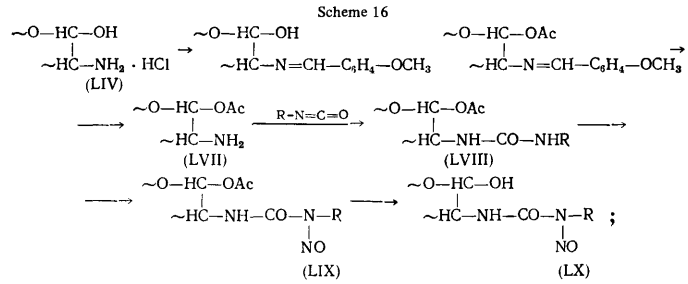
Sugar derivatives with *N*-alkyl-*N*-nitrosocarbamide fragments merit special consideration in view of their exceptionally important role in the chemotherapy of cancer[15,94]. Interest in compounds of this class arose at the beginning of the 1960s after the discovery of the high antileukaemic activity of 1-methyl-1-nitroso-3-nitroguanidine (LI) [95] and 1-methyl-1-nitrosourea (LII).[96] During the same years, the antibiotic streptozotocin was isolated from the culture liquid of streptomycin[97-101] and its structure was then readily demonstrated by specific synthesis from tetra-*O*-acetyl-D-glucosamine and methyl isocyanate with subsequent nitrosation and deacetylation of the condensation product[101]:



(LI) (LII) (LIII)

The preparative syntheses of a number of *N*-alkyl-substituted analogues of streptozotocin via Scheme 16 have been achieved[66,101,102].

Scheme 16



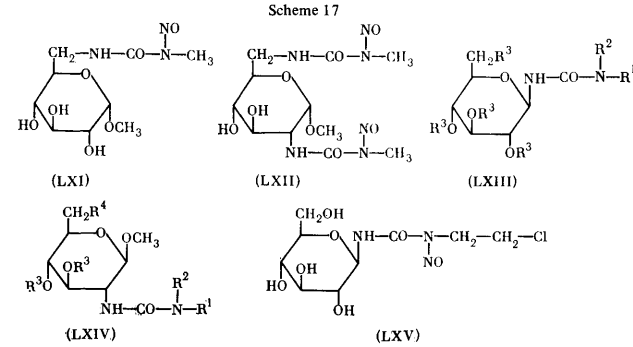
(LIV) (LVII) (LVIII) (LIX) (LX)

R=CH_3, C_2H_5, C_3H_7, C_4H_9 .

The discovery of streptozotocin and the determination of the spectrum of its therapeutic activity (antibiotic, antitumour, etc.) stimulated experimental research into the synthesis of a wide variety of carbohydrate-containing *N*-nitrosoureas as well as tests on their biological activity. In the search for syntheses of selectively acting antitumour agents with a high solubility and a low toxicity, methods of synthesis were developed during a comparatively short time for *N*-nitroso-derivatives of ureidosugars with various locations of the *N*-nitroso-carbamide fragments in the carbohydrate ring and with a wide variety of substituents and carbohydrate residues[103-117].

Japanese investigators achieved considerable successes in this field[104-111]. Derivatives of α-methyl-D-glucopyranoside with one [compound (LXI)] and two [compound (LXII)] methyl-*N*-nitrosocarbamide fragments, *N*-alkyl-*N*-nitroso-derivatives of *N*-β-D-glucosylurea (LXIII), and 1-methyl-β-D-glucosamine (LXIV) have been synthesised and their pharmacological activities have been largely tested (Scheme 17). The derivatives were synthesised by a fairly general method involving the interaction of glucosamine with alkyl isocyanates and nitrosation of the condensation products with sodium nitrite in acetic acid solutions.

Scheme 17



(LXI) (LXII) (LXIII) (LXIV) (LXV)

R′—CH_3, C_2H_5, C_3H_7, C_4H_9; R^2=H, NO; R^3=OH, OAc;
R^4=H, OH, OAc, OMs, NH—CO—N(NO)CH_3 .

It has been shown[118] that the replacement of the CH_3 group in *N*-methyl-*N*-nitrosurea by the 2-chloroethyl fragment increases the antitumour activity in relation to leukaemia; later, monosaccharide derivatives of 1-(2-chloroethyl)-3-(D-glucosyl)urea (LXV) were synthesised and preliminary tests on their antitumour activities were performed[110,119–122].

Comparative pharmacotoxicological studies established[123] that the addition of *N*-methyl-*N*-nitrosourea to the glycosidic centre in unprotected monosaccharides leads to a sharp decrease of the toxicity of the antitumour preparation and to a change of the spectrum of its action in relation to a number of experimental tumour models. It has also been shown that the toxicity and selectivity of the action of carbohydrate analogues of methylnitrosourea depend significantly on the nature of the monosaccharide carrier of the cytotoxic agent. This leads to the possibility for the specific regulation of the pharmacological properties of anticancer preparations by altering the structure of the carbohydrate unit.

REFERENCES

1. N.K.Kochetkov, A.F.Bochkov, B.A.Dmitriev, A.I.Usov, O.S.Chizhov, and V.N.Shibaev, "Khimiya Uglevodov" (Carbohydrate Chemistry), Izd.Khimiya, Moscow, 1967, p.671.
2. V.A.Afanas'ev, I.F.Strel'tsova, N.I.Trushkina, F.V.Pishugin, and O.V.Dronov, "Stroenie i Reaktsionnaya Sposobnost' N-Glikozidov" (The Structure and Reactivity of *N*-Glycosides), Izd. Ilim, Frunze, 1976, p.226.
3. A.F.Bochkov, V.A.Afanas'ev, and G.E.Zaikov, "Obrazovanie i Rasshcheplenie Glikozidnykh Svyazei" (The Formation and Cleavage of Glycosidic Linkages), Izd.Nauka, Moscow, 1978, p.180.
4. I.Goodman, Adv.Carbohydrate Chem., 1958, **13**, 215.
5. N.K.Kochetkov (Editor), Symposium "Metody Khimii Uglevodov" (Methods in Carbohydrate Chemistry), Izd.Mir, Moscow, 1967, p.512.
6. H.W.J.H.Meijer, US P.2612437 (1952); Chem.Abs., 1953, **47**, 1402.
7. H.W.J.H.Meijer, US P.2596268 (1952); Chem.Abs., 1952, **46**, 10636.
8. R.R.Stegermark, T.R.Steadman, and R.P.German, Ind.Eng.Chem., 1961, **53**, 212.
9. J.J.Oppelt, US P.2694719 (1954); Chem.Abs., 1955, **49**, 2639.
10. M.S.Dudkin, S.I.Grinshpun, and V.V.Kapustina, Zhur.Prikl.Khim., 1975, **48**, 833.
11. M.S.Dudkin, A.G.Bezusov, S.P.Karchevnaya, and S.I.Grinshpun, Khimiya Drevesiny, 1975(5), 36.
12. N.A.Preobrazhenskii and E.I.Genkin, "Khimiya Organicheskikh Dekarstvennykh Veshchestv" (The Chemistry of Organic Drugs), GNTI, Moscow–Leningrad, 1953, p.262.
13. G.A.Melent'eva, "Farmatsevticheskaya Khimiya" (Pharmaceutical Chemistry), Izd.Meditsina, E.[Erevan?], 1976, Vol.1, p.186.
14. M.D.Mashkovskii, "Lekarstvennye Sredstva" (Drugs), Izd.Meditsina, Moscow, 1978.
15. N.Emanuel', D.B.Korman, L.A.Ostrovskaya, L.B.Gorbacheva, and N.P.Dement'eva, "Nitrozoalkilmocheviny—Novyi Klass Protivoopukholevykh Preparatov" (Alkyl-Nitrosoureas—A New Class of Antitumour Preparations), Moscow, 1978, p.290.
16. N.M.Emanuel', "Kinetika Eksperimental'nykh Opukholevykh Protsessov" (Kinetics of Experimental Tumour Processes), Izd.Nauka, Moscow, 1977, p.320.
17. N.M.Emanuel', E.M.Vermel', I.A.Rapoport, S.A.Kruglyak, L.M.Dronova, and L.A.Ostrovskaya, Dokl.Akad.Nauk SSSR, 1965, **163**, 483.
18. L.A.Ostrovskaya, S.A.Kruglyak, and E.M.Vermel', Vop.Onkol., 1970(16), 46.
19. V.A.Afanas'ev and G.E.Zaikov, "V Mire Kataliza" (In the World of Catalysis), Izd.Nauka, Moscow, 1977.
20. M.N.Schoor, Rec.Trav.chim., 1903, **22**, 1.
21. B.Helferich and W.Kosche, Ber., 1926, **59**, 69.
22. J.G.Erickson and J.S.Keps, J.Amer.Chem.Soc., 1953, **75**, 4339.
23. M.N.Benn and A.S.Jones, J.Chem.Soc., 1960, **82**, 3837.
24. A.S.Jones and G.W.Ross, Tetrahedron, 1962, **18**, 189.
25. W.E.Jensen, A.S.Jones, and G.W.Ross, J.Chem. Soc., 1965, 2463.
26. E.Badawi, A.S.Jones, and M.Staseg, Tetrahedron, 1966, 281.
27. A.Gerecs, K.Barta, J.Hemely, and A.Rockenbauer, Magyar kem.folyoirat, 1975, **81**, 236; Ref.Zhur. Khim., 1976, 2E3.
28. N.G.Shkantova, M.S.Dudkin, and S.I.Grinshpun, Zhur.Prikl.Khim., 1967, **40**, 164.
29. O.Mitsuo, G.Dzyugo, and K.Saburo, J.Chem.Soc. (Japan), 1963, **66**, 948; Ref.Zhur.Khim., 1964, 11Zh366.
30. V.A.Afanasev and Zh.A.Dzhamanbaev, Izv.Akad. Nauk Kirgiz, SSR, 1973(2), 64.
31. V.A.Afanasev and Zh.A.Dzhamanbaev, Khim.Prirod. Soed., 1974(2), 176.
32. V.A.Afanasev and Zh.A.Dzhamanbaev, USSR P.382613 (1971); Byul.Izobret., 1973(23), 58.
33. E.Fischer, Ber., 1914, **47**, 1377.
34. T.B.Johnson and W.Bergmann, J.Amer.Chem.Soc., 1932, **54**, 3360.
35. T.B.Johnson and W.Bergmann, J.Amer.Chem.Soc., 1938, **60**, 1916.
36. B.Helferich and A.Mitrowsky, Chem.Ber., 1952, **85**, 1.
37. F.Micheel and W.Brunkhorst, Chem.Ber., 1955, **88**, 481.
38. G.Shaw and R.N.Werrener, Proc.Chem.Soc., 1957, 3511.
39. G.Shaw and R.N.Werrener, Proc.Chem.Soc., 1958, 81.
40. G.Shaw and R.N.Werrener, Proc.Chem.Soc., 1958, 153.
41. G.Shaw and R.N.Werrener, Proc.Chem.Soc., 1958, 157.

42. P.Boullanger, J.C.Martin, and G.Descotes, Bull. Soc.chim.France, 1973, 2149.
43. E.Fischer, Ber., 1920, **53**, 884.
44. K.M.Haring and T.B.Johnson, J.Amer.Chem.Soc., 1933, **55**, 395.
45. S.Müller and A.Wilhelms, Ber., 1941, **74**, 698.
46. M.H.Benn, Canad.J.Chem., 1963, **41**, 196.
47. C.J.Morel, Helv.Acta, 1961, **44**, 404.
48. M.Cerny, J.Vrkoc, and J.Stanek, Chem.Listy, Chem.Abs., 1958, **52**, 311, Chem.Abs., 1958, **52**, 10893.
49. M.Cerny, J.Vrkoc, and J.Stanek, Coll.Czech.Chem. Comm., 1959, **24**, 64.
50. M.Cerny and J.Pasak, Coll.Czech.Chem.Comm., 1961, **24**, 2084.
51. K.L.Matta, R.N.Girotra, and J.J.Barlow, Carbohydrate Res., 1975, **43**, 101.
52. E.Hardegger and R.M.Montavon, Helv.Chim.Acta, 1946, **29**, 1199.
53. G.Wagner and P.Nuhn, Arch.pharm., 1964(2), 81.
54. G.Wagner and P.Nuhn, Z.Chem., 1963, **3**, 64.
55. G.Wagner and P.Nuhn, Arch.pharm., 1964(8), 461.
56. R.A.Zingaro and I.K.Thomson, Carbohydrate Res., 1973, **29**, 147.
57. F.Micheel, W.Berlenbach, and K.Weichbrodt, Chem. Ber., 1952, **85**, 189.
58. F.Micheel and A.Heesing, Annalen, 1957, **604**, 31.
59. F.Micheel and W.Brunhorst, Chem.Ber., 1955, **88**, 481.
60. I.S.Lishanskii, Candidate's Thesis in Chemical Sciences, Institute of Macromolecular Compounds, USSR Academy of Sciences, Leningrad, 1950.
61. S.N.Danilov and I.S.Lishanskii, Zhur.Obshch.Khim., 1951, **21**, 366.
62. S.N.Danilov and I.S.Lishanskii, Zhur.Obshch.Khim., 1955, **25**, 2106.
63. C.J.Morel, Helv.Chim.Acta, 1961, **44**, 404.
64. B.K.Sadybakasov, M.A.Antipina, V.A.Afanas'ev, Zh.A.Dzhamanbaev, and Yu.T.Struchkov, Kristallografiya, 1978, **23**, 1267.
65. Zh.A.Dzhamanbaev, Candidate's Thesis in Chemical Sciences, Institute of Organic Chemistry, Academy of Sciences of Kirghiz SSR, Frunze, 1973.
66. F.Stoss, Diess.ETH, Prom., 1969(4423).
67. Yu.A.Panteleev and A.A.Lipovskii, Zhur.Strukt. Khim., 1976, **17**, 4.
68. Yu.A.Panteleev and A.A.Lipovskii, Zhur.Strukt. Khim., 1976, **17**, 9.
69. D.W.Verwoerd, H.Kohlhage, and W.Zillig, Nature, 1961, **192**, 1038.
70. I.Goodman, Federation Proc., 1956, **15**, 264.
71. N.Takeo, K.Tomogoshi, S.Mitsuji, and H.Nigoshi, Chem.and Pharmac., 1961, **9**, 249.
72. N.Takeo and S.Mitsuji, Chem.and Pharmac., 1961, **9**, 703.
73. N.Takeo and K.Tomogoshi, Chem.and Pharmac., 1962, **10**, 627.
74. S.Mitsuji, Chem.and Pharmac., 1962, **10**, 308.
75. S.Mitsuji, Chem.and Pharmac., 1962, **10**, 313.
76. S.Mitsuji, Chem.and Pharmac., 1962, **10**, 320.
77. Z.A.Shabarov, Uspekhi Khim., 1959, **28**, 369.
78. R.U.Lemieux, Adv.Carbohydrate Chem., 1954, **9**, 1.
79. L.Goodman, Adv.Carbohydrate Chem., 1967, **22**, 109.
80. H.S.Isbell and H.L.Frush, J.Res.Nat.Bur.Stand., 1949, **43**, 161.
81. C.Neuberh and H.Wolf, Ber., 1901, **34**, 3840.
82. F.G.Gonzalez and J.Fernandez-Bolanos, An.Real. Soc.espan.Fisica Quim., 1948, Ser.B, **44**, 233; Chem.Abs., 1949, **43**, 2988i.
83. F.G.Gonzalez and J.Fernandez-Bolanos, An.Real. Soc.espan.Fisica Quim., 1949, Ser.B, **45**, 1527; Chem.Abs., 1952, **46**, 6122.
84. F.Kruger and H.Rudi, Annalen, 1963, **669**, 146.
85. G.Huber, O.Schier, and J.Druey, Helv.Chim.Acta, 1960, **43**, 1787.
86. B.R.Baker and R.E.Schanb, J.Org.Chem., 1954, **19**, 646.
87. B.R.Baker, R.E.Schanb, and J.H.Williams, J.Amer. Chem.Soc., 1955, 77, 7.
88. B.R.Baker and T.Neilson, J.Org.Chem., 1964, **29**, 1047.
89. B.R.Baker and T.Neilson, J.Org.Chem., 1964, **29**, 1051.
90. B.R.Baker and T.Neilson, J.Org.Chem., 1964, **29**, 1057.
91. B.R.Baker and T.Neilson, J.Org.Chem., 1964, **29**, 1063.
92. B.R.Baker and T.L.Hullar, J.Org.Chem., 1965, **30**, 4038.
93. B.R.Baker and T.L.Hullar, J.Org.Chem., 1965, **30**, 4053.
94. P.S.Schein, J.Heal, D.Green, and P.V.Woolley, "Fundamentals of Cancer Chemotherapy", Basel, 1978, Vol.64.
95. M.O.Greene and J.Greenberg, Cancer Res., 1960, **20**, 1166.
96. N.M.Emanuel', E.M.Vermel', I.A.Rapoport, S.A.Kruglyak, L.M.Dronova, and L.A.Ostrovskaya, Dokl.Akad.Nauk SSSR, 1965, **163**, 483.
97. J.J.Vavra, C.De Boer, A.Dietz, L.J.Hanka, and W.T.Sokolski, Antibiot.Ann., 1959–1960, 230.
98. W.T.Sokolski, J.J.Vavra, and L.J.Hanka, Antibiot. Ann., 1959–1960, 241.
99. C.Lewis and A.R.Barliers, Antibiot.Ann., 1959–1960, 247.
100. R.R.Herr, T.E.Elle, M.E.Bergy, and H.K.Jahnke, Antibiot.Ann., 1959–1960, 236.
101. R.R.Herr, H.K.Jahnke, and A.D.Argouadelis, J.Amer.Chem.Soc., 1967, **89**, 4808.
102. A.Meier, Diss.ETH, Prom., 1969(4443).
103. J.S.Jochims and A.Seeliger, Tetrahedron, 1965, 2611.
104. T.Suami and T.Machinami, Bull.Chem.Soc.Japan, 1970, **43**, 2953.
105. T.Suami and T.Machinami, Bull.Chem.Soc.Japan, 1970, **43**, 3013.
106. T.Suami, Japan KoKai, 1976, **7652**, 160; Chem.Abs., 1977, **86**, 30032.
107. T.Machinami and T.Suami, Bull.Chem.Soc.Japan, 1973, **46**, 1013.
108. T.Suami and T.Machinami, Bull.Chem.Soc.Japan, 1975, **48**, 1333.
109. T.Machinami, K.Kobajashi, J.Hayakawa, and T.Suami, Bull.Chem.Soc.Japan, 1975, **48**, 3761.
110. T.Machinami, S.Nishigushi, J.Hagawa, T.Kikuchi, and T.Suami, Bull.Chem.Soc.Japan, 1975, **48**, 3763.
111. T.Suami, Japanese Appl.No.52-148025 (1977); Ref. Zhur.Khim., 1978, 21016.
112. D.Arndt and A.Graffi, DDR P.123457 (1976).
113. K.Goro and S.Junzo, US P.4057684 (1977).
114. G.P.Wheeler, B.J.Bowdon, Y.A.Grimsley, and H.H.Lloyd, Cancer Res., 1974, **34**, 194.
115. L.C.Panasci, P.A.Fox, and P.S.Schein, Cancer Res., 1977, **37**, 3321.
116. L.C.Panasci, D.Green, and R.Nagorney, Cancer Res., 1977, **37**, 2615.

117. D.M.Zimmer and B.K.Bhugan, Cancer Res., 1976, **40**, 281.
118. T.P.Johnston, C.S.McCaleb, P.S.Oplinger, and J.A.Montgomery, J.Medicin.Chem., 1966, **9**, 892.
119. J.L.Montero and J.L.Imbach, Compt.rend., C.279, 1974, 809.
120. J.L.Montero, A.Morujji, and J.Jiri, Europ.J.Med. Chem., 1976, **11**, 183.
121. P.A.Fox, L.C.Panasci, and P.S.Schein, Cancer, 1977, **37**, 783.
122. R.A.Nagourney, P.Fox, and P.S.Schein, Cancer, 1978, **38**, 65.
123. N.M.Emanuel', L.A.Ostrovskaya, and D.B.Korman, Symposium, "Vsesoyuznoe Soveshchanie: Aktual'nye Problemy Eksperimental'noi Khimioterapii Opukholei. Chernogolovka, 1980" (All-Union Conference: Urgent Problems in the Experimental Chemotherapy of Tumours. Chernogolovka, 1980), p.126.

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