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PROGRESS IN THE CHEMISTRY OF THE AMINODEOXY-SUGARS

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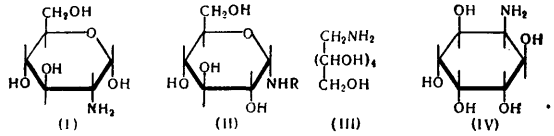
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I. INTRODUCTION

Aminodeoxy-sugars or glycosamines (I) [subsequently abbreviated to AS in the Russian text; this nomenclature has not been retained here (Ed. of Translation)] are carbohydrates containing amino-groups in place of alcoholic hydroxyl groups, and differ from *N*-glycosides (glycosylamines) (II), in the molecules of which the amino-group takes the place of a hemiacetal hydroxyl. A characteristic difference between aminodeoxy-sugars and *N*-glycosides is generally the stability of the carbon–nitrogen bond in the former and the lability of this bond in the latter[1-3]. Aminodeoxy-sugars are sometimes called "amino-sugars", but this term is not sufficiently unambiguous.

Compounds genetically related to the aminodeoxy--sugars are their reduction products — acyclic polyhydric alcohols containing amino-groups — the aminodeoxy-sugar alcohols† (III). Finally, compounds similar to the aminodeoxy-sugars and aminodeoxy-sugar alcohols are the aminodeoxy-derivatives of cyclic alcohols, *i.e.* polyhydroxycyclohexanes, called inosamines[5,6] (IV):



For a long time only two aminodeoxy-sugars — both of natural origin — were known: 2-amino-2-deoxy-D-glucose (glucosamine, 1878) and 2-amino-2-deoxy-D-galactose (galactosamine, 1914), whose configuration was established only in 1937–1939 [7] and 1945 [8] respectively. Individual synthetic aminodeoxy-sugars and aminodeoxy--sugar alcohols were prepared by Fischer and coworkers[9,10], Freudenberg, Helferich, Ohle, and others. Particular interest in aminodeoxy-sugars was aroused by the discovery of 2-deoxy-2-(*N*-methylamino)-L-glucose in the products arising from the extensive degradation of the antibiotic streptomycin[11]; later, other amino-sugars were found in a number of antibiotics. Individual inosamines were also found as components of antibiotics[5]. At the same time increasing attention was drawn to the discovery of aminodeoxy-sugars in biologically important polysaccharides and proteins. In this connection a large number of papers have been published in the last 15 years on the improvement of old methods and the development of new methods for the synthesis of aminodeoxy-sugars and aminodeoxy-sugar alcohols and the study of their properties, and also on the determination of the structure of a number of aminodeoxy-sugars of natural origin.

The importance of aminodeoxy-sugars at the present time is due to the fact that they are present in important macromolecular substances which are found in living organisms and in a number of cases exhibit biological activity; they also take part in the exchange of matter. They

† Aminodeoxy-sugar alcohols with an amino-group on a primary carbon atom are usually called glycamines[1]; it has been suggested[4] that this term be used for aminodeoxy-sugar alcohols in general.

arepresent in bacterial organisms, crabs' shells, insects, fungi, and soil compounds. Aminodeoxy-sugars are components of a number of antibiotics and oligosaccharides of human milk. Work is being carried out on the use of aminodeoxy-sugars and aminodeoxy-sugar alcohols as drugs, surface-active agents, and starting materials for the preparation of polymers, etc.

A number of reviews[2,12-18] and reference tables[19] devoted partly or entirely to aminodeoxy-sugars have been published; the paper by Foster and Horton[18] is particularly noteworthy‡. In the present review an attempt is made to describe the present state of this field. We have considered it advisable to restrict ourselves to the amino--derivatives of simple sugars. The volume and importance of the chemistry of the amino-polysaccharides are such that this subject requires separate treatment (see other reviews[17,18,20-24]).

II. SYNTHESIS OF AMINODEOXY-SUGARS AND AMINODEOXY-SUGAR ALCOHOLS

The methods for the synthesis of aminodeoxy-sugar and aminodeoxy-sugar alcohols can be divided into three groups: (1) the direct introduction of an amino-group into a sugar; this includes the specific methods for preparing 2-amino--2-deoxyaldoses and 1-amino-1-deoxyketoses; (2) the introduction of nitrogen-containing groups into a sugar and conversion of the former into amino-groups; (3) the conversion of aminodeoxy-sugars into other aminodeoxy--sugars and aminodeoxy-sugar alcohols. These methods are considered below in the order listed.

1. Direct Introduction of an Amino-Group into a Sugar

(a) Introduction of an amino-group by substitution. The most widely used method involves the introduction of amino-groups into the molecules of sugars (or sugar alcohols) by the action of ammonia (or amines) on the readily accessible sugar sulphonates (V)[25] according to the scheme:

$$\underset{(V)}{\text{Sug-OSO}_2\text{R}} + \text{NH}_3 \text{ (or NHR'R'')} \rightarrow \text{Sug-NH}_2 \text{ (or Sug-NR'R'')},$$

where R, R', and R'' are alkyl or aryl groups and Sug the residue formed by removing OH from the molecule of a monosaccharide or polyhydric alcohol.

The reaction takes place with varying ease, depending on the position of the group being replaced in the sugar molecule, the structure of the sugar, and the nature of the amine used. No differences were observed in the reactions of ammonia with a number of esters (the 3-*p*-toluene-, 3-ethane-, and 3-naphthalene-sulphonates of 1,2:5,6-di-*O*--isopropylidene-D-glucose[26]). In the case of the *p*-nitrobenzenesulphonates, however, solvolysis takes place instead of substitution[27].

The opinion exists that benzenesulphonates react with amines more readily than *p*-toluenesulphonates[28,29]. Although substitution at a secondary carbon atom is much more difficult than substitution at a primary carbon atom, cases of the direct formation of the corresponding amino--derivatives have been described: 3,5-methylene-2-*p*--toluenesulphonyl-1,4-xylitan reacts in good yield with butylamine at 120° and with aniline at 140°.[30]§

Substitution is also comparatively difficult in the 1-position in ketoses[26], but this is unimportant, since the corresponding amino-derivatives are more conveniently prepared by the Amadori rearrangement (see below).

The reaction rate evidently depends to a marked extent on steric factors: 1,5-di-*O*-benzenesulphonyl-D-mannitol reacts with aniline at 25°, whereas the corresponding 2,4:3,5-dimethylene derivative reacts only after boiling for 42 h in dioxan[28]. The replacement of the corresponding residues by amino-groups should apparently take place more readily in the case of compounds with an open chain (aminodeoxy-sugar alcohols or sugar thioacetals) than in the case of aminodeoxy-sugars; this was shown by the action of sodium iodide[31].

Substitution with the formation of aminodeoxy-sugars and aminodeoxy-sugar alcohols can generally be carried out only when the neighbouring hydroxyl groups are blocked with substituents which are not removed during amination. If this is not the case, the products are anhydro-compounds, which may undergo further changes[25]. 1,4-Anhydro--5-chloroxylitol, however, reacts smoothly with aqueous ammonia and a number of amines to give the 5-amino--derivatives of 1,4-anhydroxylitol[32]. Similarly, methyl 6-*p*-toluenesulphonyl-α-D-glucoside reacts with ammonia in methanol to form methyl 6-amino-6-deoxy-α-D-glucoside[33]. At the same time the analogous galactoside gives not the amino-sugar but the anhydrogalactoside[34].

The reaction of the sulphonates with amines and other nucleophilic reagents takes place with Walden inversion by an S_N2 mechanism[35]. This is confirmed by kinetic data: the reaction takes place according to a second-order equation and its rate is proportional to the nucleophilic power of the reagent[36]. The configuration of some previously--prepared aminodeoxy-sugars[37,38] were corrected on the basis of data obtained by Cope and Shen[35].

The significance of the nature of the amine was illustrated by the reaction of 1,2:3,4-di-*O*-isopropylidene-6--*p*-toluenesulphonyl-D-galactose with 16 different aromatic amines in butanol at 100°. The reaction rate was found to be greater, the greater the basic strength of the amine used: the yields of aminodeoxy-sugars were high in the case of anisidines, toluidines, and aniline, whereas in the case of nitroanilines, dichloroaniline and other weakly--basic amines, the reaction took place extremely slowly[36].

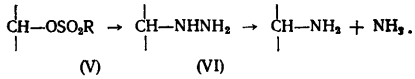
Glycoseens and secondary and tertiary amines[25,39] of the type $(\text{Sug})_2\text{NH}$ and $(\text{Sug})_3\text{N}$ are formed in side reactions. Unexpectedly, 6-iodo-1,2:3,4-di-*O*-isopropylidene-D-galactose reacted with ammonia in methanol to give the 6-methylamino-derivative of galactose, as a result of the reaction between the initially-formed aminodeoxy-sugar and the methyl iodide produced during the reaction[39].

The sulphonates react much more readily with liquid hydrazine than with ammonia solutions. Thus a method has been proposed for the synthesis of aminodeoxy-sugars (particularly those with an amino-group on a secondary

‡ *Note added in proof*. A number of additional reviews have recently been published[282-284].

§ *Note added in proof*. The methanesulphonyl group is readily replaced in 4-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-3-*O*--methanesulphonyl-D-mannitol[285].

carbon atom) by the hydrogenolysis of the hydrazine-derivatives (VI); this method avoids the difficulties associated with direct treatment with ammonia[40]:



(V) (VI)

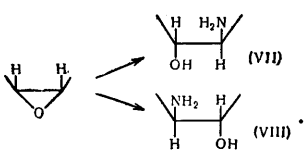
The reaction of sugar sulphonates with hydrazine at 150°, however, is accompanied by a large number of side reactions involving the formation of symmetrical and unsymmetrical disubstituted hydrazines, tri-substituted hydrazines, and reduction products — deoxymonosaccharides and thiols[41]. Steric factors are important: hydrazine reacts with the α-anomer, but not the β-anomer, of methyl 3,5-*O*-isopropylidene-2-*p*-toluenesulphonyl-L-xyloside[42].

The action of guanidine in methanol at 100° and 140° did not lead to the introduction of the guanidino-group into 1,2:5,6-di-*O*-isopropylidene-3-*p*-toluenesulphonyl-D-glucofuranose or 1,2:3,4-di-*O*-isopropylidene-6-*p*-toluenesulphonyl-D-galactopyranose; instead, solvolysis of the sulphonyl group took place[43,44].

Use is also made of the oldest method[10] in which an amino-group replaces a halogen atom in halogen-derivatives of sugars and sugar alcohols, particularly for the preparation of aminodeoxy-sugar alcohols[30,32,45]. The secondary amine was not formed by the action of ammonia on 1-chlorodimethylenexylitol, but was formed with the corresponding sulphonate[30].

A method for preparing halogeno-derivatives by the action of halogen-containing complexes of triphenyl phosphite on the sugar has been developed; in individual cases, migration of the alkylidene protection is observed[46]. A method for the introduction of halogen by the action of alkyl halides on the phosphinites of sugar alcohols has been proposed[47].

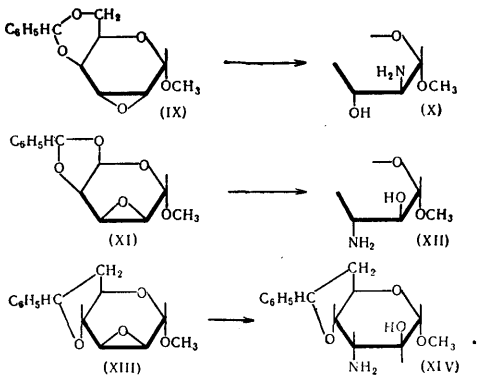
(b). The addition of ammonia and amines to sugar oxides is widely used in the synthesis of aminodeoxy-sugars[48,49]. When the oxide ring is split in this reaction, the resulting hydroxyl and amino-groups occupy the *trans*-position and the process in general takes place in two directions with the formation of the two possible isomeric aminodeoxy-sugars (VII) and (VIII):



(VII) (VIII)

In the case of the 5,6-anhydrides of hexofuranoses, only the 6-amino-derivatives are obtained[50,51]. In other cases the yield of isomers depends on the structure of the anhydride molecule and in particular on the pressure of additional rings. For example, ammonolysis of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-guloside (IX) gave only the 2-amino-2-deoxy-D-idose derivative (X) and the corresponding taloside (XI) gave the 3-amino-3-deoxy-D-idose derivative (XII).[52]

The 2,3-anhydromannoside (XIII) gives only the 3-amino-3-deoxy-D-altroside (XIV).[53] The ring opens with the production of groups in the axial position.

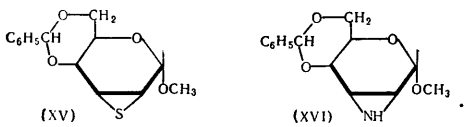


(IX) (X) (XI) (XII) (XIII) (XIV)

It has been proposed that the disulphonates be used directly instead of the anhydrides and that the ammonolysis be carried out in the presence of sodium methoxide: in this case the α-anhydride is first formed and immediately adds on ammonia. Thus methyl 4,6-*o*-benzylidene-2,3-di-*O*-toluenesulphonyl-α-D-galactopyranoside gave the corresponding derivative of 2-amino-2-deoxy-D-idose and 3-amino-3-deoxy-D-idose in 46% and 26% yields respectively[54].

The addition of ammonia to α-oxides is often used for the preparation of aminodeoxy-sugars with an amino-group on a secondary carbon atom. It has been noted that the use of the 5,6-anhydrides for the preparation of 6-amino-hexoses is less suitable than direct replacement of sulphonyl groups[55].

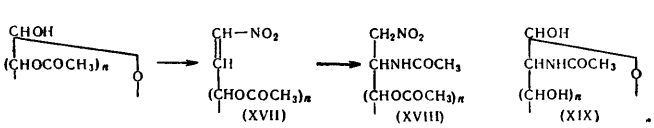
An attempt to use the corresponding thio-analogue (episulphide) instead of the α-anhydrides for the preparation of sulphur-containing aminodeoxy-sugars did not give satisfactory results: methyl 2,3-epithio-α-D-allopyranoside (XV) reacts with ammonia only at 100°, with the formation of a polymer[56]. The α-ethylenimine (XVI) has been obtained as a possible starting material in the synthesis of aminodeoxy-sugars[57].



(XV) (XVI)

Instead of the α-oxides, it is possible to use the β-oxides, which, as shown for the case of dianhydroxylitol, can be split by ammonia or amines at 140° to give the corresponding aminodeoxy-sugar alcohols[58].

(c). The addition of ammonia to unsaturated derivatives of sugars. The condensation of nitromethane with acetylated aldoses according to the usual scheme gives 1-nitro-substituted unsaturated alcohols (XVII) which can add on ammonia across the double bond with the formation of nitroacetamido-polyhydric alcohols (XVIII):



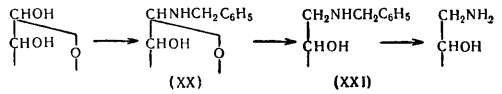
(XVII) (XVIII) (XIX)

The latter are converted into the sodium derivative and then treated with sulphuric acid to remove the nitro-group and give the acetylated aminodeoxy-sugars (XIX): usually,

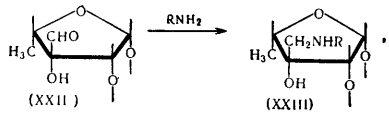
one epimer is obtained. By these reaction, D- and L--arabinose gave D- and L-mannosamine respectively[59] and D-xylose gave D-gulosamine, identical with the natural product obtained from the degradation of the antibiotic streptothricin[60].

An interesting paper by Paulsen[61] describes the preparation of derivatives of 5-amino-5-deoxyaldoses *via* unsaturated nitro-compounds.

(d). The reductive amination of aldoses and derivatives of aldonic acids with ammonia or amines in the presence of hydrogenating catalysts leads to the formation of aminodeoxy-sugar alcohols[62]. The best yields are obtained by starting from *N*-benzylglycosylamines (XX)[63]; the *N*-benzylglycamines (XXI) are formed initially and converted into aminodeoxy-sugar alcohols by hydrogenolysis.



Aminodeoxy-sugars can be obtained in this way from the ω-formyl derivatives of aldoses. This reaction has been carried out with streptomycin, whose component streptose (3-*C*-formyl-1-lyxomethylose) (XXII) is converted into an aminodeoxy-sugar residue (XXIII) according to the scheme:

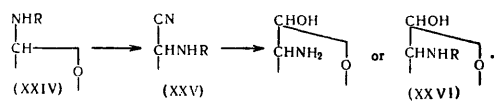


where R = H, C_8H_{17}, C_9H_{19}, $C_{12}H_{25}$, $C_{14}H_{29}$, or $C_{16}H_{33}$. The resulting *N*-alkyl-streptomycins exhibit antibacterial activity[64].

Reduction of the amide of alginic acid gives a polysaccharide with CH_2NH_2 groups[65].

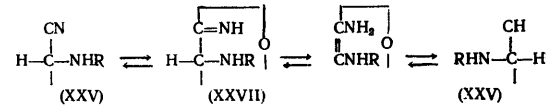
2. Methods for the Synthesis of 2-Amino-2-deoxyaldoses and 1-Amino-1-deoxyketoses

(a). The aminonitrile synthesis. The ordinary aminonitrile synthesis, used at an early date by Fischer[9] for the synthesis of glucosamine, was transformed by Kuhn and coworkers into an extremely fruitful method which has been used for the preparation of a number of 2-amino-2-deoxyaldoses[66]. The starting materials are the *N*-glycosides of the aldoses (XXIV), which with hydrogen cyanide give the aminonitriles (XXV); the latter undergo partial hydrogenation and hydrolysis:

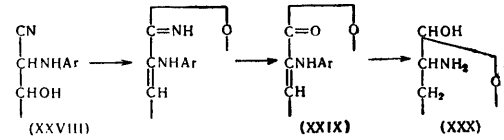


The benzyl or aryl aglycones (or the fluorene residue[67]) are split off under the conditions of the hydrogenation and give aminodeoxy-sugars with a primary amino-group; *N*-alkyl glycosides give *N*-alkyl-substituted aminodeoxy--sugars (XXVI, R = alkyl).

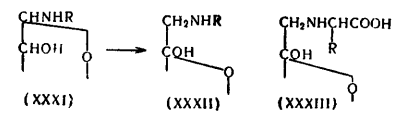
The mixture of epimeric aminodeoxy-sugars formed in this synthesis contains chiefly the epimer with the amino--group in the *trans*-position relative to a hydroxyl group on a neighbouring carbon atom. A method of directed epimerisation has been found; for example, the nitriles of *N*-benzylmannosaminic and *N*-benzylglucosaminic acids (from benzylarabinosylamine), when heated in dilute alcoholic solution, from equilibrium mixtures (~1:1) from which the first nitrile is separated by the addition of petrol. Hydrogenation of this compound gives mannosamine in 40% yield, calculated on the original arabinose[69]. D-Talosamine and D-allosamine were prepared in analogous fashion[67]. Epimerisation of the aminonitrile (XXV) takes place preferentially *via* the iminolactone (XXVII):



In individual cases a single aminodeoxy-sugar is obtained; for example, threose gives chiefly 2-amino-2-deoxy-D--xylose[69]. The action of alkali on *N*-phenyl-D-hexosaminic [2-deoxy-2-phenylamino-D-hexonic (Ed. of Translation)] nitriles (XXVIII) gives iminohexose-2,3-ene-1→4-lactones (XXIX), which are hydrogenated to 2-amino-2,3-dideoxyhexoses (XXX)[70]:

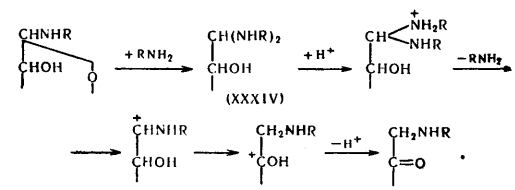


(b). The Amadori rearrangement and the reverse reaction. The Amadori rearrangement — the conversion of the *N*-glycosides of aldoses (XXXI) into *N*-substituted 1-amino-1-deoxyketoses (XXXII) — is the most effective method for preparing the compounds (XXXII)[13,16,71,72]:

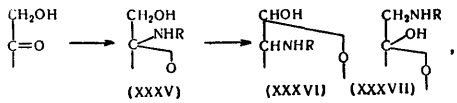


The yield of product increases with increase in the basic strength of the amine used for the formation of the *N*-glycoside[73,74]. The reaction was first applied to *N*-aryl glycosides, but was later extended to the *N*-alkyl derivatives[75-77], the derivatives of aliphatic-aromatic amines[78], and to amino-acids, from which 1-carboxyalkylamino-1--deoxyketoses (XXXIII) are formed[79-81]. Compounds of type (XXXIII) are of particular interest, since they have been found in liver and in micro-organisms[82]. The *N*-glycosides of uronic acids are converted into *N*-subtituted keto--acids in analogous fashion[83,84].

According to Micheel[85], the mechanism of the Amadori rearrangement includes a stage involving the intermediate formation of the *NN*-diacetal (XXXIV), which adds on a proton and undergoes further conversion according to the scheme:



The reaction which is the reverse of the Amadori rearrangement has been studied chiefly by Heyns and coworkers. This reaction, which is catalysed by acids or salts, makes it possible to obtain 2-amino-2-deoxyaldoses and their derivatives from ketoses. The reaction takes place with a ketosylamine or with *N*-alkyl ketosides (XXXV), including derivatives of amino-acids and peptides [86-89]:



(XXXV) (XXXVI) (XXXVII)

where R = H, alkyl, or CH(R')COOH.

Fructosylamine gives a mixture of glucosamine and mannosamine; the reaction of fructose with amino-acids gives the corresponding 2-carboxyalkylamino-derivatives of the epimers (XXXVI). The *N*-derivatives of 1-amino--1-deoxyketoses (XXXVII) are formed simultaneously.

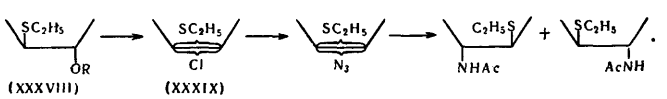
The theories of the Amadori rearrangement have been used to explain the mechanism of the complex reactions involved in the biosynthesis of aminodeoxy-sugars [16,90] and amino-acids [91] and also the reaction of melanoidin formation (the Maillard reaction) [16,92-94].

3. The Introduction of Nitrogen-Containing Groups into a Sugar and Conversion of the Former to Amino-Groups

(a). Conversion of sugar phenylhydrazones into aminodeoxy-sugar alcohols. New methods for bringing about this change have been developed [95]. Aminodeoxy-sugars are obtained by the reduction of the phenylhydrazones [95,96] or oximes [97] of the oxo-derivatives of monosaccharides. In connection with the development of a method for the selective oxidation of aldoses to 4-oxo-aldoses, the use of the latter for the synthesis of 4-amino--4-deoxyaldohexoses has been reported [98].

The usual method for the addition of nitromethane to aldoses makes it possible to obtain nitro-compounds which can be hydrogenated to amines. When applied to 5-formyl--1,2-*O*-isopropylidene-D-xylose, this method gave a mixture of stereoisomeric 6-amino-6-deoxy-D-glucose and -L-idose [99].

(b). Alcoholic hydroxyl groups in a sugar molecule can be replaced (*via* the sulphonyl group or a halogen atom) by azido-, cyano-, phthalimido-, and other groups, which are then converted into an amino-group in the usual way. For example, 6-amino-6-deoxy-D-glucose was obtained from the 6-*p*-toluenesulphonate of α-methyl glucoside *via* the azido-derivative [33]. Baker and coworkers [100] introduced the azido-group using the episulphonium ion (XXXIX) obtained by the action of thionyl chloride on the ethylthio-derivative of sugar sulphonates (XXXVIII):



(XXXVIII) (XXXIX)

Isomerisation and reversal of configuration take place during the reaction. An interesting feature is that similar changes take place in the molecules of nucleosides [101].

Recently, Baker and coworkers [102] showed that the methanesulphonyl group on a secondary carbon atom can be replaced directly by an azido-group and this made it possible to prepare derivatives of 4-amino-4-deoxy-D-glucose.

The phthalimide method has not been widely used, although the dimethylformamide used as solvent makes it possible to carry out the reaction between the sugar sulphonates and potassium phthalimide under comparatively mild conditions (at 90° and below); the phthalimido-derivatives of the aminodeoxy-sugars or aminodeoxy-sugar alcohols are split by heating with hydrazine in alcoholic solution [45].

The reaction of sugar sulphonates with ethyleneimine has given the ethyleneimino-derivatives, and from these the β-chloroethylamino-derivatives, which are of interest as anti-cancer agents (see below) [103].

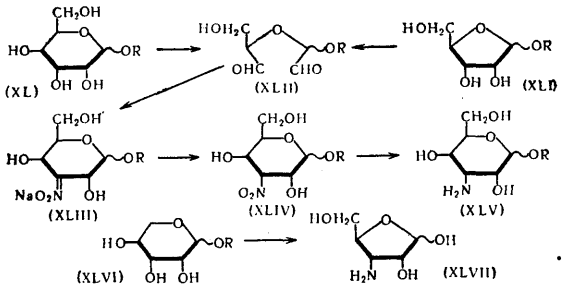
The condensation of monosaccharides with acrylonitrile (with subsequent hydrogenation of the condensation products) [39] or with esters of crotonic acid, with subsequent addition of an amine across the double bond [104] has been described.

Alkyl radicals containing amino-groups have been introduced into cellulose using epoxy- and diaminoepoxy-amines, which add on at the position of the hydroxyl groups [105,106].

A primary sulphonyl group can be replaced by a cyano--group either directly or *via* the iodide; the iodo-derivative can also be converted into the nitro-compound by substitution [107]. It is evidently possible to obtain amino-derivatives of sugars containing the $CH_2-CH_2-NH_2$ group, by hydrogenation of the resulting cyano-derivatives.

(c). The preparation of aminodeoxy-sugars from monosaccharides *via* uronic acids and their nitriles, which can be reduced to aminodeoxy--sugars, has also been carried out. This method has been used to synthesise 2,6-diamino-2,6-dideoxy-D-glucose (neosamine) from glucosamine derivatives [108]. Uronic acids are readily obtained by the catalytic oxidation of aldoses with oxygen according to Heyns' method [109].

(d). The synthesis of 3-amino-3-deoxymonosaccharides from dialdehydes, which are formed by the periodate oxidation of hexose and pentose glycosides and cyclised to the 3-nitro-derivatives of aldoses by the action of nitromethane, has also been developed. Hexopyranosides (XL) or pentafuranosides (XLI), *via* the dialdehydes (XLII), give the nitro-derivatives of the hexoses (XLIV), which give the corresponding 3-amino-3-deoxyhexoses (XLV) [110]. The pentapyranosides (XLVI) give dialdehydes which are converted into 3-amino-3-deoxy--pentoses (XLVII) [111]:



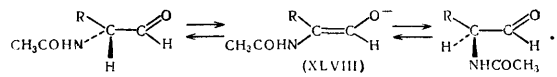
(XL) (XLII) (XLI) (XLIII) (XLIV) (XLV) (XLVI) (XLVII)

A method has been found for the spontaneous epimerisation, at the C_4 atom, of the sodium derivatives of nitro--compounds (XLIII) by allowing the compounds to stand in

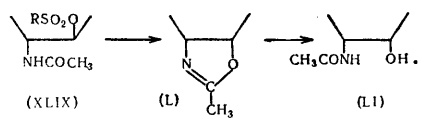
aqueous solution. From methyl α-D-glucopyranoside this method gave a mixture of the 3-amino-derivatives of D-glucose, D-mannose, D-galactose, and D-talose, in which the last two predominated[112]. Laevoglucosan gave a mixture of stereoisomeric 3-amino-1,6-anhydro-3--deoxy-hexoses with the gulo-, altro-, and ido-configurations[113]. Phenylhydrazine can be used instead of nitromethane for cyclisation of the dialdehyde, followed by hydrogenolysis of the resulting azo-compound[114].

4. Methods for Converting Aminodeoxy-Sugars into Other Aminodeoxy-Sugars and Aminodeoxy-Sugar Alcohols

(a). Epimerisation of aminodeoxy-sugars. It has been found possible to carry out the direct epimerisation of *N*-acetylglucosamine to *N*-acetylmannosamine[115] and of *N*-acetyl-D-galactosamine to *N*-acetyl-D-talosamine[116]. In the presence of 0.7 *N* ammonium hydroxide solution, 2-acetamido-2-deoxy-D-ribose is converted into an equilibrium mixture with the epimer in the ratio 2:1. The same equilibrium is established starting from the epimeric 2-acetamido-2-deoxy-D-arabinose. The corresponding monosaccharides are not epimerised under these conditions. The ease of conversion in the case of acetamidoaldoses is due to the inductive effect of the acetamido--group; it is assumed that an intermediate enolate ion (XLVIII) is formed[117]:



(b). Walden inversion in substitution reactions of aminodeoxy-sugars and aminodeoxy--sugar alcohols. Solvolysis of the α-sulphonates of *N*-acetylated aminodeoxy-sugar or aminodeoxy-sugar alcohols with these groups in the *trans*-position (XLIX) takes place with Walden inversion *via* the intermediate oxazoline ring (L), which is subsequently broken to give the *N*-acetyl aminodeoxy-sugars or aminodeoxy-sugar alcohols (LI) with the inverse configuration[118].



In practice, solvolysis is brought about by the action of sodium acetate with heating in a medium of methylcellosolve (2-methoxyethanol). This method is widely used in synthesis[119-123].

(c). Increase and decrease in the length of the aminodeoxy-sugar chain by the usual methods makes possible conversion from the 2-amino- to the 3-amino-derivatives of aldoses and back again. Thus Kuhn and coworkers, who increased the length of the carbon chain by the action of hydrogen cyanide, prepared 3-amino--3-deoxy-hexoses and -heptoses from the corresponding 2-amino-2-deoxy-pentoses and -hexoses respectively[124,125]. On the other hand, oxidation of the 3-amino-derivatives with periodate gave the 2-amino-2-deoxyaldoses; the latter are also formed by oxidising the corresponding thioacetals with peroxypropionic acid[126].

TABLE 1. Synthetic aminodeoxy-sugars and *N*-substituted aminodeoxy-sugars (obtained in the free form and as the *O*- and *N*-derivatives)*.

Sugar	Position and name of nitrogen-containing groups	References
1	2	3
I. Aminodeoxy-derivatives of sugars		
D-Threose	2-amino	131, 132
D-Erythrose	2-amino	131, 132
D-Arabinose	2-amino	69
D-Arabinose	3-amino	119
L-Arabinose	2-amino	133
L-Arabinose	3-amino	125
L-Arabinose	5-amino	134
D-Xylose	2-amino	69
D-Xylose	3-amino	131
D-Xylose	5-amino and substituted 5-amino	95, 96, 135, 136
D-Xylose	2,5-diamino	136
D-Lyxose	2-amino	38, 69
L-Lyxose	2-amino	42
D-Ribose	2-amino	38, 69, 117
D-Ribose	3-amino	111, 119, 137
D-Ribose	5-di-(2-chloroethyl)amino	103, 138
D-Ribose	5-(2-chloroethyl)ethylamino	138
D-Ribose	3,5-diamino	38
L-Ribose	2-amino	40
L-Ribose	3-amino	111
D-Allose	2-amino	19, 67
D-Allose	3-amino	27, 37, 53, 97, 113
D-Allose	3-ethylamino	139
D-Allose	3-ethyl-(2-chloroethyl)amino	139
D-Allose	3-(2-chloroethyl)amino	139
D-Allose	2,3-imino	57
D-Altrose	2-amino	19, 43, 140
D-Altrose	2-methylamino	43
D-Altrose	2-guanidino	43
D-Altrose	3-amino	56, 113, 126
D-Galactose	2-amino	19
D-Galactose	3-amino	112, 125
D-Galactose	6-amino	36, 141
D-Galactose	6-methylamino	39
D-Galactose	6-dimethylamino	142
D-Galactose	substituted 6-arylamino	36
D-Galactose	6-di-(2-chloroethylamino)	103
D-Glucose	2-amino and substituted 2-amino	19, 93
D-Glucose	3-amino	97, 112, 114
D-Glucose	3-dimethylamino	143
D-Glucose	4-amino	102
D-Glucose	6-amino	33, 50, 55, 99
D-Glucose	substituted 6-alkylamino	50, 144
D-Glucose	6-phenylamino	138
D-Glucose	6-benzylamino	138, 144
D-Glucose	6-dibenzylamino	51, 144
D-Glucose	5-pyridino	145, 146
D-Glucose	6-morpholino	51
D-Glucose	6-pyrrolidino	51
D-Glucose	6-piperidino	51, 144
D-Glucose	6-guanidino	50
D-Glucose	substituted 6-(2-chloroethyl)-amino	55, 138
D-Glucose	6-anilino	147
D-Glucose	2,6-diamino	108
L-Glucose	2-amino and substituted 2-amino	19
D-Gulose	2-amino	19, 60
D-Gulose	3-amino	113, 122, 125
L-Gulose	2-amino	19
D-Idose	2-amino	19, 52, 54
D-Idose	3-amino	52, 113, 122
L-Idose	2-amino	19
L-Idose	3-amino	122
L-Idose	5-amino	148
L-Idose	6-amino	99
D-Mannose	2-amino and substituted 2-amino	19, 59, 68, 93
D-Mannose	3-amino	112, 124, 149
D-Mannose	4-amino	8
D-Mannose	2,3-diamino	150
L-Mannose	2-amino	19, 59
D-Talose	2-amino	19, 54, 67
D-Talose	3-amino	112
D-Gluco-D--guloheptose	3-amino	125
D-Gluco-D--idoheptose	3-amino	125
D-Manno-D--galaheptose	3-amino	125
D-Threopentulose	5-amino	129
D-Erythropentulose	5-amino	129
L-Xylohexulose	5-amino	130
L-Xylohexulose	6-methylamino	130
L-Sorbose	1-amino and substituted 1-amino	71
D-Tagatose		76, 83, 89, 103,
D-Fructose		151–153
II. Aminodeoxy-derivatives of deoxy-sugars		
2-Deoxy-D-ribose	3-amino	100
6-Deoxy-D-altrose	3-amino	154
3-Deoxy-D-galactose	2-amino	70

TABLE 1. (cont'd).

Salt	Position and name of nitrogen-containing groups	References
1	2	3
II. Aminodeoxy-derivatives of deoxy-sugars		
6-Deoxy-L-galactose	2-amino	155, 156
6-Deoxy-L-galactose	3-amino	157
6-Deoxy-D-glucose	2-amino	158
6-Deoxy-D-glucose	3-amino	159
6-Deoxy-D-glucose	3-dimethylamino	159, 160
4,6-Dideoxy-D--glucose	3-dimethylamino	161
6-Deoxy-L-glucose	2-amino	158
6-Deoxy-L-glucose	3-amino	157
6-Deoxy-L-glucose	3-dimethylamino	159
3-Deoxy-D-mannose	2-amino	70
6-Deoxy-D-mannose	3-amino	162, 163
6-Deoxy-D-talose	2-amino	164
6-Deoxy-L-talose	3-amino	157
6-Deoxy-L-xylo-hexulose	5-amino	130
3-Deoxy-D-fructose	1-amino	165

* *Note added in proof*. Data have also been published on the synthesis of 2-amino-2-deoxy-L-xylose[286], 2,6-diamino-2,6-dideoxy-D-galactose[287], 2,4-diamino-2,4-dideoxy-D-glucose[288], 2,6-diamino-2,6-dideoxy-L-idose[289], 3-amino-3-deoxy-D-altro-γ-mannoheptose, 3-amino-3-deoxy-D-manno-D-taloheptose[290], 2,7-anhydro-4-amino-4-deoxyheptoses[291], 3-amino-3,5-dideoxy-L-idose[292], 2-amino-2,6-dideoxy-D-mannose[293], and 2-amino-2,6-dideoxy-D-talose[294]; improvements have been introduced in the synthesis of 6-amino-6-deoxy-D-glucose[295], 2-deoxy-2-amino-D-talose (talosamine)[116], 2-amino-2,6-dideoxy-L-mannose (L-rhamnosamine)[293], 2-amino-2,6-dideoxy-D-talose[294], 4-amino-4-deoxy-L-erythrose[303], 4-amino-4-deoxy-D-lyxose[304], 6-amino-6-deoxy- and 1,6-diamino-1,6-dideoxy-L-sorbose[305], 3-amino-3,5-dideoxy-D-xylose[306], derivatives of 5,6-diamino-5,6-dideoxy-D-glucose and -L-idose[307], 6-amino-6-deoxy-D-glucose[295], and 2-amino-2-deoxy-D-talose (talosamine)[116]. Data have also been published on the preparation of amino-derivatives of starch[308,309] and cellulose[310].

Decrease in the length of a chain with a non-reducing end is brought about by oxidising aminohexose furanosides with periodate, followed by reduction of the ω-formyl group. Finally, a combination of methods involving increase in the length of a chain, followed by decrease in the length of a chain with a non-reducing end, makes it possible to bring about "migration" of the amino-group — conversion of 2-amino-2-deoxyhexoses to 3-amino-3-deoxy-hexoses and -pentoses[125].

(d). Reduction of aminodeoxy-sugars and oxidation of aminodeoxy-sugar alcohols. The reduction of 1-amino-1-deoxyketoses gives an individual aminodeoxy-sugar alcohol or a mixture of aminodeoxy-sugar alcohols, depending on the conditions[127] (examples of the reduction of aminoaldoses are given by Foster *et al.*[128]). 1-Acetamido-1-deoxyketoses have been prepared by the oxidation of 1-acetamido-1-deoxy-sugar alcohols with *Acetobacter suboxydans* enzymes[129,130].

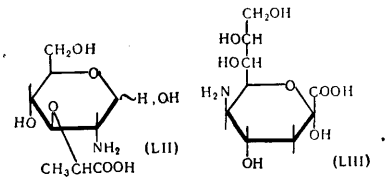
Thus there are at present a number of methods for preparing aminodeoxy-sugars with amino-groups on primary carbon atoms and on secondary carbon atoms in the 2- and 3-positions, and also the corresponding aminodeoxy-sugar alcohols. Methods for the synthesis of aminodeoxy-sugars with an amino-group on the fourth carbon atom (for pentoses and hexoses) and on the fifth carbon atom (for hexoses) have been little developed.

Table 1 gives the synthetic aminodeoxy-sugars and their *N*-substituted derivatives (with alkyl, aryl, or heterocyclic substituents) described in the literature¶. Many of these substances have been prepared in recent years[18]. The aminodeoxy-sugars can conveniently be divided into two groups: (1) aminodeoxy-derivatives of sugars, and (2) aminodeoxy-derivatives of deoxy-sugars, and can be further classified in the usual way as aldoses and ketoses, and as tetroses, pentoses, hexoses, and heptoses. Within the subgroups, the aminodeoxy-sugars are arranged in the alphabetical order of the monosaccharides [this refers to the Cyrillic alphabet; the order of the Russian version is retained in the translation and is no longer alphabetical (Ed. of Translation)].

III. AMINODEOXY-SUGARS OF NATURAL ORIGIN

Aminodeoxy-sugars are obtained from the degradation of a number of complex natural products present in animal and vegetable organisms, micro-organisms, soil substances, and antibiotics. In natural substances the primary amino-group of the aminodeoxy-sugars are usually acylated, most frequently with an acetic acid residue but also with sulphuric and other acids. A list of aminodeoxy-sugars of natural origin is given in Table 2.

Table 2 shows that, together with glucosamine and galactosamine, which are the most commonly-encountered nature aminodeoxy-sugars, the other aminodeoxy-sugars are also in most cases aminodeoxyaldohexoses. Only a few representatives of other types of aminodeoxy-sugars are encountered. Deoxygenated aminodeoxy-sugars with methylene and methyl groups are fairly widespread, and *N*-alkylated (methylated) aminodeoxy-sugars and diamino-derivatives are also encountered. In addition to aminodeoxy-sugars in the true sense, natural substances also contain the amino-acids: 2-amino-2-deoxy-D-galacturonic acid, muramic acid (LII), and sialic acids — the *N*-acyl derivatives of neuraminic acid (LIII). The latter are genetically related to mannosamine, which is formed when these acids are degraded.



In living organisms, aminodeoxy-sugars are found chiefly in the so-called mucoid substances. These include glucosamine, galactosamine, and sialic acids, together with other sugars, hexuronic acids, amino-acids, and lipids. Mucoid substances are usually subdivided into mucopolysaccharides, mucoproteins, and mucolipids, depending on the quantity of the corresponding components present[167]. There is, however, no generally-accepted classification. The term mucopolysaccharide (or amino-polysaccharide[208]) denotes a heteropolysaccharide with a high aminodeoxy-sugar content, and this class is subdivided into acidic (containing

¶ In general, only the latest published data for a given substance are quoted.

TABLE 2. Aminodeoxy-sugars of natural origin.

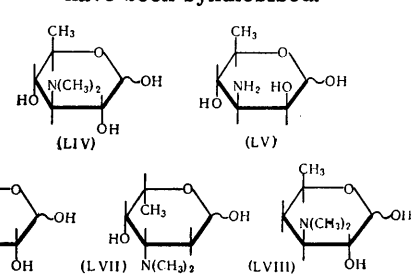
Name	Occurrence in natural products
3-Amino-3-deoxy-D-ribose	the antibiotic puromycin [166]
2-Amino-2-deoxy-D-galactose (galactosamine)	mucoid substances [14,167], bacteria polysaccharides [24], oligosaccharides of human milk [22], soil substances [168]
2-Amino-2,6-dideoxy-D-galactose (fucosamine)	bacteria polysaccharides [24,169]
2-Amino-2,6-dideoxy-L-galactose	bacteria polysaccharides [156]
2-Amino-2-deoxy-D-galacturonic acid	bacteria polysaccharides [24,170]
2-Amino-2-deoxy-D-glucose (glucosamine)	mucoid substances [14,167], bacteria polysaccharides and nucleotides [23,24], fungi, chitin of insects and crabs [21], oligosaccharides of human milk [22], soil substances [168], the antibiotics trehalosamine [171], paromomycin [172], racemomycin O [173], monomycin [174], and zygomycin [175] *
3-Amino-3-deoxy-D-glucose (kanosamine)	the antibiotics kanamycin A [176,177] kanamycin B [178], and kanamycin C [179]
6-Amino-6-deoxy-D-glucose	the antibiotic Kanamycin A [176]
3-Dimethylamino-3,6-dideoxy--D-glucose (mycaminose)	the antibiotics magnamycin (carbomycin), leucomycin [180], spiramycin [181]
2,6-Diamino-2,6-dideoxy-D--glucose (neosamine C)	the antibiotics neomycin C [182,183], zygomycin [184]*, paromomycin II [194]
2-Amino-2-deoxy-3-*O*-(2--carbethoxy)-D-glucose (muramic acid)	bacteria nucleotides and polysaccharides [23,24]
3-Dimethylamino-3,4,6--trideoxy-D-xylohexose (desosamine, picrocine)	the antibiotics methymycin [185], neomethymycin [186], picromycin [187], erythromycin A [188], erythromycin B [189], erythromycin C [190], oleandomycin [191], narbomycin [192]
2-Methylamino-2-deoxy-L--glucose	the antibiotics streptomycin, dihydrostreptomycin, hydroxystreptomycin, mannosidostreptomycin [11,64]
2-Amino-2-deoxy-D-gulose (gulosamine)	the antibiotic streptomycin [193]
2,6-Diamino-2,6-dideoxy-L--idose (paromose)	the antibiotics neomycin B, paromomycin I [194,311]
2-Amino-2-deoxy-D-mannose (mannosamine)	product of the enzymatic breakdown of sialic acids [195]
3-Amino-3,6-dideoxy-D--mannose (mycosamine)	the antibiotics nystatin [196], amphotericin B [197], pimaricin [198], trichomycin [199], candinin, candicidin [200]
Sialic acids	mucoid substances [14,195], bacteria polysaccharides [24], oligosaccharides of human milk [22]
2-Amino-2-deoxy-D-talose	mucoid substances [201]
2-Amino-2,6-dideoxy-D--talose (pneumosamine)	bacteria polysaccharides [164]
1-Deoxy-1-*N*-*o*-carboxyphenyl-ribulose	bacteria polysaccharides [202]
Substituted 1-amino-1-deoxy--D-fructose	liver [82]
4-Dimethylamino-4,6-dideoxy--D-glucose (amosamine)	the antibiotic amicetin [203]
3-Dimethylamino-2,3,6--trideoxy-L-lyxohexose (rhodosamine)	antibiotics rhodomycin, isorhodomycin [204,205], pyrromycin [206]
2-Amino-4-acetamido-2,4,6--trideoxyhexose	bacteria polysaccharides [207]

aminodeoxy-sugars themselves, hexuronic acids, and sulphuric acid) and "neutral" (containing aminodeoxy-sugars and sialic acids) compounds. Mucoproteins (mucoids) are complex proteins with mucopolysaccharides as prosthetic groups. The name glycoproteins has also been suggested for these substances [208]. Mucoid substances are sometimes subdivided into: (1) glycoproteins, (2) mucoproteins, and (3) mucoproteids [209]; the first two types of substance have strong covalent bonds between the carbohydrate and protein components, whereas the mucoproteids are complexes formed by polysaccharides and proteins by ionic and hydrogen bonds. Mucoid substances are present in the materials characterising the blood group (group-specific polysaccharides), in blood serum, in the material of the salivary gland, urine, connective tissue, the secretions of the sexual organs, the epithelial mucus of the digestive tract, and are components of enzymes, hormones, malignant growths, etc. [167].

The aminodeoxy-sugars found in bacteria include, in addition to glucosamine, galactosamine, muramic acid, and sialic acids, other less common aminodeoxy-sugars: 2-amino-2,6-dideoxy-D-galactose and -L-galactose, 2-amino-2,6-dideoxy-L-talose, etc. Here the aminodeoxy--sugars are components of polysaccharides and nucleotides [23,24].

An even greater variety of aminodeoxy-sugars is found in antibiotics, chiefly macrolides, streptomycins, and streptomycin-like antibiotics [64]. Antibiotics containing aminodeoxy-sugars generally have the chemical structure of *O*-glycosides of aminodeoxy-sugars; the antibiotic puromycin is an *N*-glycoside (nucleoside) of 3-amino-3-deoxy--D-ribose.

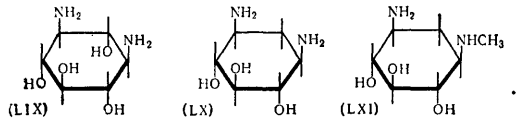
Work carried out in recent years has reduced considerably the list of aminodeoxy-sugars of unknown configuration and has revealed the nature of many aminodeoxy-sugars present in antibiotics. Thus it has been shown that the *N*-dimethylaminodeoxyhexose mycaminose, found in magnamycin (carbomycin) and other antibiotics and previously assigned the configuration of a D-altrose, is in fact 3,6-dideoxy-3-*N*-dimethylamino-D-glucose (LIV) [159,160]. Mycosamine (the aminodeoxyhexose of the antibiotics nystatin, pimaricin, etc.) is 3-amino-3,6-dideoxy-D-mannose (LV) [162,163]. The structure of two other aminodeoxy--sugars present in antibiotics — amosamine and rhodosamine — has recently been established. The former, a 4-aminohexose, is 4,6-dideoxy-4-dimethylamino-D-glucose (LVI) [203] and the latter is 2,3,6-trideoxy-3-dimethylamino-L--lyxohexose (LVII) [204]. It has been established by degradation, study of the nuclear magnetic resonance spectra, and synthesis that the extremely widespread amino-sugar desosamine (picrocine) is 3,4,6-trideoxy-3-dimethylamino-D-xylohexose (LVIII) [210-213]. Muramic acid [214,215] and *N*-acetylneuraminic acid [116,216] have been synthesised.



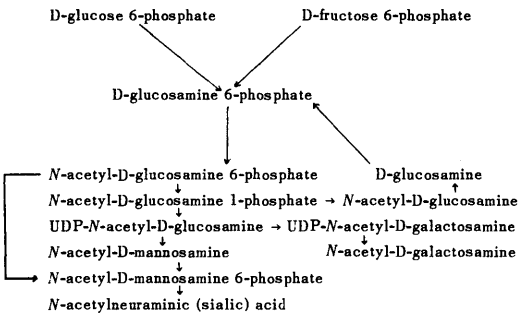
Among the substances related to aminodeoxy-sugars and found in natural products, not including riboflavine [62], are

* *Note added in proof.* Zygomycin was found to be idential with paromomycin [194,312].

the cyclic aminodeoxy-alcohols: streptamine (LIX) (in streptomycin and related antibiotics), 2-deoxystreptamine (LX) (in kanamycins, neomycins, and paromomycin), neo-inosamine-2 (IV) (in hygromycin)[5], 2-deoxy-*N*-methylstreptamine (LXI) (in hygromycin B [217]) and tetrahydroxy-1,3-bismethylaminocyclohexane (in the antibiotic actinospectacin)[218]:



The biosynthesis of aminodeoxy-sugars has been described in a number of reviews[17,208,219,220]. Glucosamine 6-phosphate is formed from the 6-phosphates of D-glucose or D-fructose using L-glutamine or ammonia[221]. Galactosamine is formed from glucosamine, as the uridine diphosphate (UDP) of the *N*-acetyl derivative; there are no data confirming that galactosamine is formed from galactose. On the other hand, there are enzymes which catalyse the conversion of glucosamine derivatives into mannosamine derivatives and the latter to sialic acids. These changes are outlined in the following simplified scheme:



Vitamin A plays an important part in the biosynthesis of aminodeoxy-sugars; it has also been established that vitamin C deficiency leads to an increase in the concentration of sialic acids and hexosamines in the organism[208]. The UDP-*N*-acetylglucosamine takes part in the formation of chitin[222].

IV. CHEMICAL REACTIONS AND PREPARATION OF DERIVATIVES OF AMINODEOXY-SUGARS

The most detailed studies have been made of the chemical reactions of 2-amino-2-deoxyaldoses, particularly glucosamine (reviewed by Foster and Horton[18]), and the genetically related 1-amino-1-deoxyketoses. Much attention is paid to the synthesis of the *N*-acyl derivatives of glucosamine, particularly with nature amino-acid residues, since these are models of glycopeptides[223-225]. A method has been developed for the selective *N*-acylation of aminodeoxy-sugars with carboxylic acids and amino-acids without blocking of the hydroxyl groups of the aminodeoxy-sugars[223,224]. *N*-Sulphonated aminodeoxy-sugars are being studied in detail[236,237].

The 2,5-dinitrophenyl[238], benzylsulphonyl[239], *N*-formyl[240], and ethoxycarbonyl[241] groups have been proposed for the protection of the amino-group in aminodeoxy-sugars. The *N*-methylation of *N*-acetylglucosamine has been described[242].

Analogues of glucosamine, containing urea and thiourea residues in place of the amino-group, have been synthesised; the urea-derivatives have been cyclised to the corresponding tetrahydroimidazole derivatives[243], which are also obtained by the action of isocyanates on glucosamine and 1-amino-1-deoxyfructose[244,245]. The preparation and hydrogenation of the Schiff's bases of glucosamine have been studied[246]. A number of new *N*-glucosaminides have been prepared[247], particularly *O*-β-(D,L-*trans*)-2-aminocyclohexyl glucosaminide[248], as a model of the antibiotic kanamycin.

The rate of hydrolysis of methyl glucosaminides has been studied[249]; it was found that the rates of hydrolysis and oxidation of methyl *N*-acylglucosaminides are lower, the stronger the acid forming the acyl residue; steric factors influence the oxidation[250]. 1-Chloro-substituted *N*-acylglucosamines with different acyl groups[251,252] and 1-*C*-phenyl-substituted glucosamine[253], 1-thioglucosamine[254], thioglucosaminides[255], and glucosamine 1-phosphate[256] have been prepared. It has been shown that the *O*-acetyl derivatives of glucosamine with a free amino-group are unstable: solvolysis at the $C_{(3)}$ atom takes place in alcholic solution under ordinary conditions[257]. 6-Thioglucosamine has been synthesised[258].

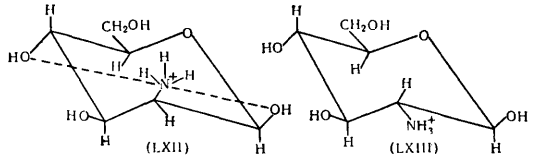
The conversion of aminodeoxy-sugars into imidazole derivatives and other heterocyclic compounds has been reviewed[259]. The action of aqueous ammonia converts glucosamine into a mixture of pyrazines[260]; pyrazines are also formed when the acetates of glucosamine or 1-amino-1-deoxyfructose are boiled in methanol[165]. As in the case of sugars without nitrogen-containing groups, lime water converts oligosaccharides containing glucosamine residues attached by 1,4-bonds into a mixture of different isosaccharinic acids[261].

Deamination of methyl 4,6-*O*-benzylideneglucosaminide with nitrous acid gives 2,5-anhydro-4,6-*O*-benzylidene-D-mannose, *i.e.* deamination is accompanied by splitting of the glycoside bond, whereas the corresponding altroside is converted into methyl 2,3-anhydro-4,6-*O*-benzylidene-D-alloside[241].

Synthetic polymers of glucosamine have also been prepared[262].

The Amadori rearrangement is still being actively studied[263]. Combination of Amadori products containing aromatic radicals with diazonium salts give triazines[264,265] or azo-compounds as a result of reaction with the aromatic nucleus[265].

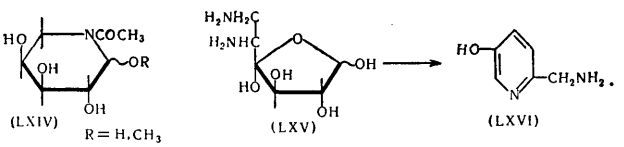
The basic strength of mannosamine is only one-third that of glucosamine, so that acylation of the former gives chiefly the *O*-acyl derivatives; mannosammonium chloride does not undergo mutarotation. This is due to the formation of a stable hydrogen bond between the ammonium- and the 1- and 4-hydroxyl groups in mannosamine (LXII); this bond is not present in glucosamine (LVIII)[266]:



The characteristic features and properties of aminodeoxy-sugars with structures different from those of 2-amino-2-

deoxyaldoses and 1-amino-1-deoxyketoses have been little studied. As in the case of glucosamine, the screening action of the $-NH_3^+$ group in a number of cases hinders the acid hydrolysis of the *O*-glucosides and acetals (ketals) of aminodeoxy-sugars, so that usually the *N*-acylated derivatives are subjected to hydrolysis. Depending on the structure of the molecule, however, reaction is also possible with substances containing a free amino-group: methyl 3-amino-3-deoxy-α-D-talopyranoside is converted into the aminodeoxy-sugar hydrochloride by heating with 2 *N* HCl at 98° for 2 h,[112] *i.e.* the reaction is similar to that with ordinary glycosides. Methyl 3-amino-3,6-dideoxy-D-altroside (2 *N* HCl, 12 h, 100°)[154] and methyl 3-amino-3-deoxy--D-glucoside (4 *N* HCl, 100°, 3 h)[177] are hydrolysed similarly. The hydrolysis of the analogous glycosides of 3-amino-3-deoxy-D-xylose and -D-ribose requires heating for a prolonged period (18–22 h) in 1 *N* HCl.[135] The reaction takes place comparatively readily when combined with anhydride-formation; the tendency to form 1,6-anhydrides is more marked for 3-amino-3-deoxyaldoses than for the corresponding 2-amino-derivatives[122]†.

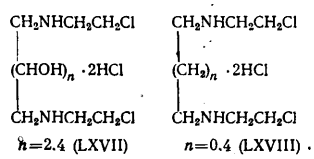
Very interesting results have recently been published on the cyclisation of aminodeoxy-sugars with an amino-group on the fifth carbon atom: 5-acetamido-5-deoxy-L-arabinose gives the cyclic form (LXIV) with an *N*-heteroatom[134]. Analogous results were obtained with 5-acetamido-5-deoxy--D-xylose[267,268]. In the case of 5-amino-5-deoxy-L-idose, however, only the *O*-furanoside bridge is formed[148]. 5,6--Diamino-5,6-dideoxyaldohexoses (LXV), at the moment of their formation, are converted into 2-aminomethyl-5--hydroxypyridine (LXVI)[61]:



(LXIV) (LXV) (LXVI)

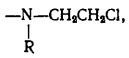
V. PRACTICAL APPLICATION OF AMINODEOXY-SUGARS AND AMINODEOXY-SUGAR ALCOHOLS

A number of aminodeoxy-sugar and aminodeoxy-sugar alcohol derivatives have been synthesised for use as drugs. To obtain anti-cancer agents, the *N*-β-chloroethyl group is introduced into the sugar molecules. The first and most active of these substances was 1,6-di-(2-chloroethylammonium)--1,6-dideoxy-D-mannitol dichloride, which was introduced into clinical practice under the name "Degranol"[269]. The synthesis of this compound and analogous compounds — derivatives of hexahydric and tetrahydric alcohols (LXVII)[270,271] — is achieved by replacing a sulphonyl group in the sugar or sugar alcohol molecule by an $NHCH_2CH_2OH$ or $N(CH_2CH_2OH)_2$ group followed by replacement of the hydroxyl by chlorine. In another method the ethyleneimine group is introduced and then split with hydrogen chloride. A more active compound than "Degranol" is its bromo-analogue — 1,6-di--(2-bromoethylammonium)-1,6-dideoxy-D-mannitol dibromide. Contrary to expectation, the corresponding iodo--derivative was found to have a low activity. Stereoisomers of "Degranol" — derivatives of D-sorbitol, dulcitol, D-iditol, and D-mannitol — are much less active; the dulcitol derivative shows the greatest activity.



It has been confirmed that a decisive part in the anti-carcinogenic activity of substances of this type is played by the system of hydroxyl groups of the polyhydric alcohol, since the corresponding β-chloroethylamino-derivatives of hexane and ethane (LXVIII) are quite inactive[269]. The further introduction of methanesulphonyl groups in the "Degranol" decreases the cumulative effect[272]. Vargha and coworkers also prepared di-*N*-(β-chloroethyl) derivatives of D- and L-glucosamine, 6-amino-6-deoxy-D-galactose, ethyl 5-amino-5-deoxy-D-ribofuranoside, 1-amino--1-deoxy-D-fructose and -L-sorbose; all these substances were found to be toxic[103]‡.

Baker and coworkers synthesised a number of derivatives of 6-amino-6-deoxy-D-glucose[55,138], 5-amino-5--deoxy-D-ribose,[138] and 3-amino-3-deoxy-D-allose[139] containing the group



where R = CH_2CH_2Cl (*a*), C_2H_5 (*b*) (for all the above aminodeoxy-sugars), H, CH_3 (*c*), etc. for 6-amino-6-deoxy-D--glucose. Of these compounds, activity against leukaemia 1210 was shown by the derivatives (*b*) for all aminodeoxy--sugars, (*a*) for the ribose and allose, and also by (*c*); in addition, the ribose derivative (*b*) was found to be active against adenocarcinoma 755. Analogous galactose derivatives of the urethane type, containing the $-OCON(CH_2CH_2Cl)_2$ group, have been prepared[273]. American workers have developed a programme for the synthesis of anti-cancer agents based on aminodeoxy-sugars[55].

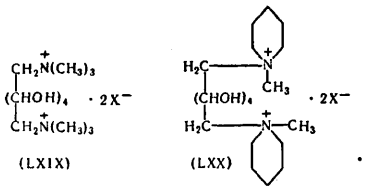
Nucleosides with aminodeoxy-sugars as components of their molecules have been synthesised: the antibiotic puromycin, which exhibits anti-cancer activity, and the possible antimetabolites 3′-amino-2′,3′-dideoxyadenosine and 2′-amino-2′-deoxyadenosine[101].

A number of derivatives of 1,6-dideoxy-1,6-bis(trimethylammonium)-D-sorbitol and -D-mannitol (LXIX) and 1,6-dideoxy-1,6-bis(methylpiperidino)-D-sorbitol (LXX) with *O*-isopropylidene and *O*-acyl substituents have been synthesised as potential drugs[274]. Some of these substances reduce the blood pressure slightly and also exhibit

† *Note added in proof*. Acetobromo-derivatives of 3-amino--3-deoxy- and 6-amino-6-deoxy-D-glucose have been synthesised[296]. The preparation of thioglycosides by the thiolation of 3-amino--3-deoxy-D-mannose has been described[297]. Glucosamine-3--phosphate has been prepared[298]. The kinetics of the alkaline decomposition of D-mannosamine have been studied[299]. Derivatives of 1,6-dithio-D-glucosamine have been synthesised[300]. The infrared spectra of some derivatives of 6-amino-6-deoxy-D-galactose and 5-amino-5-deoxy-D-xylose have been studied[301].

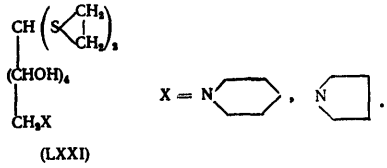
‡ *Note added in proof*. The 1,6-bis-di-*N*-(β-chloroethyl) derivative of L-sorbose was also found to be unsuitable for therapeutic purposes[302].

a weak antispasmodic, cholinergic, and curare-like action; the sorbital derivatives are more active than the mannitol derivatives.



(LXIX) (LXX)

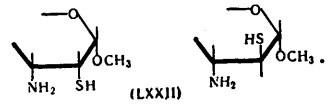
Hydrazides of *N*-acylglucosaminylisonicotinic acid, which are anti-tuberculosis agents, have been prepared[275]. A number of derivatives of the ethylene thioacetal of 6-amino-6-deoxyglucose (LXXI) have been synthesised in the search for anti-fungal materials. The 6-piperidino- and 6-pyrrolidino-derivatives were found to be active against the very resistant forms *Cryptococcus neoformanes* and *Aspergillus niger*:



(LXXI)

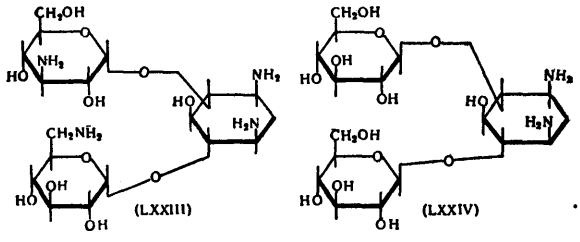
The importance of the nitrogen-containing residue is confirmed by the fact that the corresponding thioacetal of D-glucose is inactive[51].

2-Thiol derivatives of 3-amino-3-deoxy-D-allose[53] and -D-altrose (LXXII)[56] have been synthesised in the search for anti-radiation agents:



(LXXII)

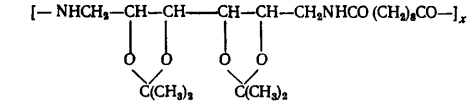
To investigate the influence of aminodeoxy-sugars on the activity of antibiotics, Umesawa and Ito[276] synthesised the anomer of kanamycin (LXXIII) without amino-groups in the glucose residue, 4,6-di(β-D-glucopyranosyl)-deoxystreptamine (LXXIV), which was found to be biologically inactive:



(LXXIII) (LXXIV)

The 1-alkylamino-derivatives of hexahydric alcohols[277], which are used as surface-active agents, are aminodeoxy--sugar alcohols which have been known for a long time. The corresponding aminodeoxy-sugar derivatives may be of interest as cationic surface-active agents.

The preparation of macromolecular compounds of the polyamide type from α,ω-diamino-sugar alcohols and derivatives of dibasic acids has been described. 1,6-Diamino--1,6-dideoxy-2,3:4,5-di-*O*-isopropylidenedulcitol with sebacoyl chloride gives a polymer (LXXV) which is insoluble in water and soluble in alcohol; after removal of the isopropylidene groups it is converted into an insoluble infusible product[278]:



(LXXV)

A large number of polyamides have been prepared by condensing 1,6-diamino-1,6-dideoxy-2,3:4,5-dimethylenedulcitol, -D-mannitol, -D-sorbitol, -L-iditol and the analogous benzylidene derivatives with various dihydrochlorides, including the dihydrochlorides of dimethylenesaccharic acids[279,280].

Another type of polymer has been prepared from aminodeoxy-sugar alcohols acylated with unsaturated acids. 1-Acrylamido-1-deoxy- and 1-methacrylamido-1-deoxy--D-sorbitol have been polymerised with varius polymerisation initiators and also under the influence of ^{60}Co radiation. Water-soluble polymers and polymers assumed to have a "cross-linked" structure have been prepared. The above amides have been copolymerised with other vinyl derivatives[281]. Monomers of possible interest include the *N*-methacryl derivatives of 1-amino-1-deoxyxylitol and 2-amino-2-deoxyxylitan[30].

The present intensive study of aminodeoxy-sugars must lead to the production of valuable biologically active substances, polymers, surface-active agents, etc.

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THE CATALYTIC SYNTHESIS OF CARBOXYLIC ACIDS AND THEIR ESTERS FROM CARBON MONOXIDE, ALKENES, AND ALCOHOLS

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1. INTRODUCTION

More than 100 years have passed since Berthelot's discovery[1] of the reaction between carbon monoxide and caustic alkali to give formates:

$$CO+KOH \rightarrow HCOOK.$$

This process formed the basis of the modern industrial preparation of formic acid. Subsequently, during the first quarter of the 20th century, a number of new reactions of carbon monoxide were discovered, and these have played an important part in the development of organic synthesis. In these reactions, carbon monoxide and hydrogen in the presence of heterogeneous catalysts give either hydrocarbons — methane[2] or a mixture of higher aliphatic hydrocarbons of the synthine type[3] — or oxygen-containing compounds — methanol and its homologues[4] or mixtures of