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Chemical Transformations of Aminoglycoside Antibiotics

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Aminoglycoside antibiotics belong to the class of pseudo-oligosaccharides, which is a chemotherapeutically important group of antibiotics with a broad spectrum of antimicrobial activity. The review surveys and gives a systematic account of the literature data relevant to the chemical properties of aminoglycosides. Particular attention has been devoted to the chemical transformations of natural antibiotics.
The bibliography includes 323 references.

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I. INTRODUCTION

Aminoglycoside antibiotics have changed in recent years from a very narrow and specific group of preparations into a large family with many members, including antibiotics such as streptomycin, neomycin, kanamycins, gentamicins, etc. This class of antibiotics has aroused interest of representatives of a wide variety of disciplines—experts in therapy, selection [of drugs ?], chemical synthesis, and biochemists: the broad search for Actinomycite strains producing aminoglycosides and the vigorous development of biosynthesis is due to the chemotherapeutic properties of the aminoglycoside antibiotics used to fight the most dangerous types of infection.

At the same time the appearance of new antibiotics is accompanied by an increase of the number of bacterial strains with multiple resistance to therapeutic agents. One of the main forms of bacterial resistance to aminoglycosides consists in their inactivation by enzymes produced by micro-organisms. Chemists were faced with the acute problem of specific modification of aminoglycosides in order to create preparations active in relation to multiply resistant forms of bacteria. The determination of the mechanisms of the enzymatic inactivation of aminoglycoside antibiotics, the study of the mechanisms of their action, and the elucidation of the dependence of the biological activity of a compound on its structure made it possible to establish promising trends in chemical transformations. Progress in the study of chemical properties was achieved with the aid of the latest techniques in physicochemical methods of research such as NMR, infrared spectroscopy, mass spectrometry, X-ray diffraction analysis, gas–liquid chromatography, high-pressure liquid chromatography, and electrophoresis.

Natural aminoglycoside antibiotics have become the richest source of a wide variety of monosaccharides, have enriched carbohydrate chemistry in unusual previously unknown aminosugars, and have exerted a significant influence on its development.

The present review surveys and gives a systematic account of the literature data relevant solely to the chemical properties of aminoglycosides, since examination of important problems such as biosynthetic pathways, methods for the determination of structures, the mechanism of action, the dependence of biological properties on structure, etc., would have greatly increased the size of the review. Particular attention is devoted to methods for the specific chemical transformations of natural antibiotics.

The stereochemistry of aminoglycosides has been examined in detail in Umezawa[1,2] and Daniels'[3] reviews. The methods for the determination of the structures of the products of the enzymatic inactivation of aminoglycoside antibiotics have been discussed in Umezawa's reviews[4,5]. †

II. CLASSIFICATION OF AMINOGLYCOSIDE ANTIBIOTICS

Chemically, aminoglycoside antibiotics are pseudo-oligosaccharides. Their molecules consist of two fundamentally different components. One component is a carbohydrate containing at least one amino-group, and the other is the aglycone. The aminosugar is linked to the aglycone by the glycosidic $C_{(1)}$–O bond. The number of carbohydrate rings in the molecule varies from one to four and at least two carbohydrate substituents are linked to the aglycone. The aglycone is a cyclitol or an aminocyclitol. Antibiotics with the most valuable antibacterial properties contain aminocyclitols, mainly streptidine or deoxystreptamine. Thus, aminoglycoside antibiotics belong to the class of aminoglycosidic aminocyclitols.

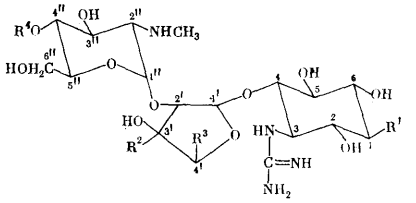
Since aminoglycoside antibiotics are pharmaceutical preparations, it is quite natural that their classification should be based on molecular properties which have the greatest influence on their biological activity. Analysis of the literature data has shown that the biological activity of aminoglycosides depends significantly on their structure (the number, nature, and relative positions of the carbohydrate rings linked to the aglycone and the nature of the

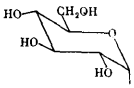
† The problems of biosynthesis have been analysed by Rhinehart and Stroshane[310].

aglycone), functional groups, and molecular configuration and conformation. It is most useful to base the classification on the structural properties of aminoglycoside molecules.

Depending on the nature of the aglycone, aminoglycosides are divided into two important subclasses: one of them includes antibiotics containing streptidine and the other includes those containing deoxystreptamine. The subclass of aminoglycosides containing streptamine has very few members, but includes therapeutically important antibiotics—streptomycin, dihydrostreptomycin, and mannosidostreptomycin. Bleunsomycin, differing from the other streptomycin antibiotics by the structure of the aglycone, has come to be included in the same subclass.

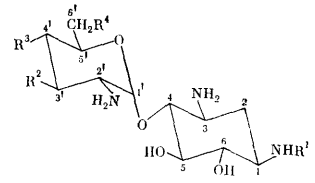
Aminoglycosides containing deoxystreptamine are distinguished by their wide variety, and their characteristic feature is the large number of members of each antibiotic family. Thus two neomycins, four hybrimycins, two lividomycins, four butirosins, the isomeric ribostamycin and xylostasin, seven kanamycins, at least fifteen gentamicins, and several antibiotics of the type of sisomicin are known at the present time. The deoxystreptamine antibiotics can be subdivided into several groups depending on the nature and number of carbohydrate substituents in the molecule and their distribution relative to the carbon atoms of the deoxystreptamine ring.



	R^1	R^2	R^3	R^4
Streptomycin	$-NHC(=NH)NH_2$	CHO	CH_3	H
Dihydrostreptomycin	$-NHC(=NH)NH_2$	CH_2OH	CH_3	H
Mannosidostreptomycin	$-NHC(=NH)NH_2$	CHO	CH_3	
Oxystreptomycin	$-NHC(=NH)NH_2$	CHO	CH_2OH	H
Bluensomycin	$-OCONH_2$	CHO	CH_3	H

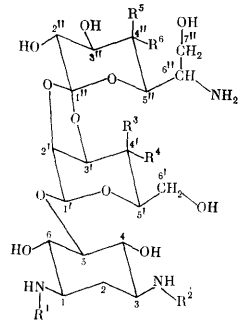
Depending on the number of substituents in the aglycone, aminoglycoside antibiotics containing deoxystreptamine can be divided into two types. The first includes antibiotics in which deoxystreptamine has one carbohydrate substituent, and the second includes those which have two carbohydrate substituents in the deoxystreptamine ring. In aminoglycosides which are monosubstituted 2-deoxystreptamines, the pyranosyl substituent is attached to the carbon atom either in the 4- or 5-position.

Neamine[6], paromamine[9,11], and their semisynthetic derivatives such as 4′-deoxyneamine[12], 3′,4′-dideoxyneamine[13,14], 3′,4′,5,6-tetradeoxyneamine[15], 1-*N*-[(*s*)-4-amino-2-hydroxybutyryl]neamine[16,17], 1-*N*-[(*s*)-4-amino-2-hydroxybutyryl]-4′-deoxyneamine[12], and 1-*N*-[(*s*)-4-amino-2-hydroxybutyryl]-3′,4′-dideoxyneamine[18–21] form a group of antibiotics which are pseudodisaccharides, in which the 2-deoxystreptamine ring has a pyranosyl substituent at the carbon atom in the 4-position:



	R^1	R^2	R^3	R^4
Neamin	H	OH	OH	NH_2
Paromamine	H	OH	OH	OH
3′,4′-Dideoxyneamine	H	H	H	NH_2
1-*N*-[(*s*)-4-Amino-2-hydroxybutyryl]neamine	$-CO-CH(OH)-CH_2-CH_2-NH_2$	OH	OH	NH_2
1-*N*-[(*s*)-4-Amino-2-hydroxybutyryl]-3′,4′-dideoxyneamine	$-CO-CH(OH)-CH_2-CH_2-NH_2$	H	H	NH_2

The antibiotics characterised by the presence of only one substituent in the aglycone also include antibiotics of the destomycin series. In contrast to neamine and paromamine, the carbohydrate substituent in the molecules of these antibiotics is at the $C_{(5)}$ carbon atoms of the deoxystreptamine ring and the pyranose ring also has a substituent—destomic acid. This group includes hygromycin B,[22–25] the antibiotic A-396-1 (SS-56-D),[26,27] destomycins A, B, and C,[28–33] and the antibiotics SS-56-C,[27] and A-16316-C.[34]

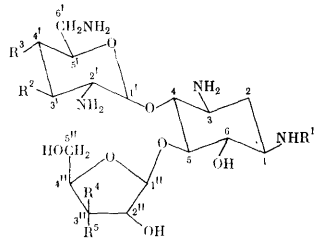


	R^1	R^2	R^3	R^4	R^5	R^6
Destomycin A	CH_3	H	CH_3	H	OH	H
Destomycin B	CH_3	CH_3	H	OH	H	OH
Destomycin C	CH_3	CH_3	OH	H	OH	H
Hygromycin B	H	CH_3	OH	H	OH	H
A-396-1	H	H	OH	H	OH	H
A-16316-C‡	CH_3	CH_3	H	OH	OH	H

A characteristic feature of the aminoglycosides belonging to the group of disubstituted 2-deoxystreptamines is the presence of a pyranosyl substituent at $C_{(4)}$. The second substituent is either at $C_{(5)}$ or $C_{(6)}$. A pyranosyl substituent is located at $C_{(6)}$, while only the furanosyl substituent is at $C_{(5)}$ in all known instances. Accordingly, aminoglycoside antibiotics of this type can be subdivided into two varieties. The first includes aminoglycosides whose deoxystreptamine ring has pyranosyl and furanosyl substituents at the carbon atoms in the 4- and 5-positions respectively, while the second variety combines antibiotics having paranosyl substituents at $C_{(4)}$ and $C_{(6)}$.

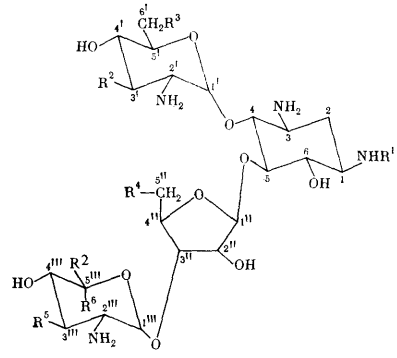
‡ The structure of this antibiotic has not been established exactly.

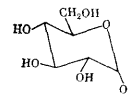
Aminoglycosides containing a furanosyl substituent (D-ribose or D-xylose) can be divided in their turn into two groups. The first includes antibiotics containing unsubstituted D-ribose or D-xylose. Its representatives are ribostamycin[16,35-38], xylostasin[16,37,39], butirosins A and B[16,37,40-47], and the antibiotics Bu-1709 E_1 and E_2 [46] as well as their semisynthetic derivatives 3′-deoxyribostamycin[48], 4′-deoxyxylostasin[12], 3′,4′-dideoxyribostamycin[20,49], 3′,4′,5″-trideoxyribostamycin[20,49], 1-*N*-methylribostamycin[50], 4′-deoxybutirosins A and B,[12,37] 3′,4′-dideoxybutirosin B,[51] and 5″-amino-5″-deoxybutirosin[52].

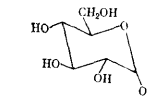
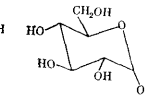


	R^1	R^3	R^3	R^4	R^5
Ribostamycin	H	OH	OH	H	OH
Xylostasin	H	OH	OH	OH	H
Butirosin A	—CO—CH(OH)—CH_2—CH_2—NH_2	OH	OH	OH	H
Butirosin B	—CO—CH(OH)—CH_2—CH_2—NH_2	OH	OH	H	OH
3′,4′-dideoxyribostamycin	H	H	H	H	OH
3′,4′-dideoxybutirosin B	—CO—CH(OH)—CH_2—CH_2—NH_2	H	H	H	OH

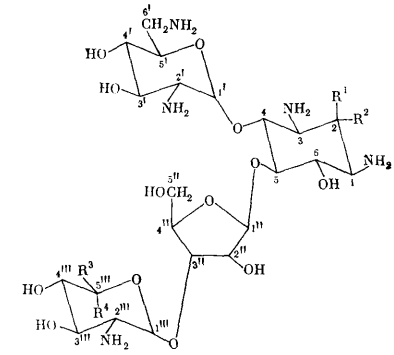
The second group includes antibiotics having an additional pyranosyl substituent at the $C_{(3'')}$ atom of the D-ribose ring: neomycins B and C,[6,53] paromomycins I and II,[54-56], and lividomycin B.[57] Lividomycin A[58-62] and mannosylparomomycin[63], which are 4″-C-mannosyl derivatives of lividomycin B and paromomycin respectively, can be usefully combined into a separate subgroup together with 5″-deoxylividomycin A [64] and 1-*N*-[(*s*)-4-amino-2-hydroxybutyryl]-lividomycin A.[65] A characteristic feature of these antibiotics is the presence of four carbohydrate rings in the molecule.



	R^1	R^2	R^3	R^4	R^5	R^6	R^7
Neomycin B	H	OH	NH_2	OH	OH	CH_2NH_2	H
Neomycin C	H	OH	NH_2	OH	OH	H	CH_2NH_2
Paromomycin I	H	OH	OH	OH	OH	CH_2NH_2	H
Paromomycin II	H	OH	OH	OH	OH	H	CH_2NH_2
Lividomycin B	H	H	OH	OH	OH	CH_2NH_2	H
Lividomycin A	H	H	OH	OH		CH_2NH_2	H

5″-Deoxylividomycin A	H	H	OH	H		CH_2NH_2	H
1-*N*-[(*s*)-4-amino-2-hydroxybutyryl]-lividomycin A	—CO—CH(OH)—CH_2—CH_2—NH_2	H	OH	OH		CH_2NH_2	H

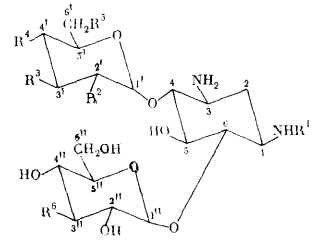
The neomycin group of antibiotics also includes hybrimycins A1, A2, B1, and B2,[66,67] in which the aglycones are streptamine (hybrimycins A) and epistreptamine (hybrimycins B).



	R^1	R^2	R^3	R^4
Hybrimycin A1	H	OH	H	CH_2NH_2
Hybrimycin A2	H	OH	CH_2NH_2	H
Hybrimycin B1	OH	H	H	CH_2NH_2
Hybrimycin B2	OH	H	CH_2NH_2	H

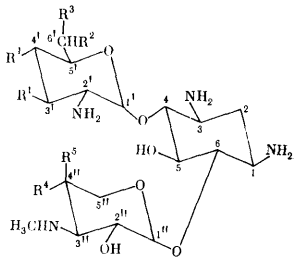
The aminoglycoside antibiotics whose deoxystreptamine ring has two pyranosyl substituents at the $C_{(4)}$ and $C_{(6)}$ atoms are the most important chemotherapeutically. Depending on the nature of the carbohydrate substituent at the $C_{(6)}$ atoms, they can be divided into two groups with numerous members. The first comprises the family of kanamycin antibiotics, a characteristic feature of which is the presence of 3-amino-3-deoxy-α-D-glucose at the $C_{(6)}$ atom of the deoxystreptamine ring. The second group consists of the gentamicin antibiotics, whose deoxystreptamine ring has either garosamine[68] or 3-methyl-amino-3-deoxypentapyranose at the $C_{(6)}$ atom.

The family of kanamycin antibiotics includes kanamycins A, B, and C,[69-74] the antibiotics NK-1001, NK-1012-1, NK-1013-1, and NK-1013-2,[75] tobramycin (nebramycin, factor 6),[76-82] nebramycins, and factors 2,4,5, and 5′,[76,80-83] as well as their semisynthetic derivatives 3′-deoxykanamycin A,[84] 4′-deoxykanamycin A,[85] 6″-deoxykanamycin A,[86-88] 6′-*N*-methylkanamycin B,[89] 3′,4′-dideoxykanamycin B,[90-91] 3′,4′-dideoxy-6′-*N*-methylkanamycin B,[89] amikacin (BB-K8),[92-94] 1-*N*-[(*s*)-4-amino-2-hydroxybutyryl]kanamycin B,[95] 1-*N*-[(*s*)-4-amino-2-hydroxybutyryl]-3′,4′-dideoxykanamycin B,[95] etc.



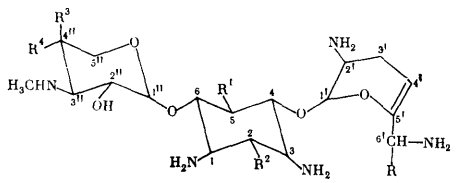
	R^1	R^2	R^3	R^4	R^5	R^6
Kanamycin A	H	OH	OH	OH	NH_2	NH_2
Kanamycin B (nebramycin, factor 5)	H	NH_2	OH	OH	NH_2	NH_2
Kanamycin C	H	NH_2	OH	OH	OH	NH_2
NK-1001	H	OH	OH	OH	NH_2	OH
NK-1012-1	H	NH_2	OH	OH	NH_2	OH
3'-Deoxykanamycin A	H	OH	H	OH	NH_2	NH_2
4'-Deoxykanamycin A	H	OH	OH	H	NH_2	NH_2
Tobramycin (Nebramycin, factor 6)	H	NH_2	H	OH	NH_2	NH_2
3',4'-Dideoxykanamycin B	H	NH_2	H	H	NH_2	NH_2
6'-*N*-Methylkanamycin A	H	OH	OH	OH	$NHCH_3$	NH_2
3',4'-Dideoxy-6'-*N*-methylkanamycin B	H	NH_2	H	H	$NHCH_3$	NH_2
Amikacin	—CO—CH(OH)—CH_2—CH_2—NH_2	OH	OH	OH	NH_2	NH_2
1-*N*-[(*s*)-4-amino-2-hydroxybutyryl]kanamycin B	—CO—CH(OH)—CH_2—CH_2—NH_2	NH_2	OH	OH	NH_2	NH_2
1-*N*-[(*s*)-4-amino-2-hydroxybutyryl]-3',4'-dideoxykanamycin B	—CO—CH(OH)—CH_2—CH_2—NH_2	NH_2	H	H	NH_2	NH_2

The family of gentamicin antibiotics includes the gentamicin complex C [3,68] (the gentamicins C_1, C_2, and C_{1a} [96-110]), the gentamicins, A, [111-113] A_1, [113] A_2, [113] X_2, [113-118], B (the antibiotic Sch 14 342), [113-118] and B_1, [113] the antibiotics JI-20 A and JI-20 B, [113] G-418, [113,119-121], and sagamicin [122-125].



	R^1	R^2	R^3	R^4	R^5
Gentamicin C_{1a}	H	NH_2	H	CH_3	OH
Gentamicin C_1	H	$NHCH_3$	CH_3	CH_3	OH
Gentamicin C_2	H	NH_2	CH_3	CH_3	OH
Gentamicin A	OH	H	OH	OH	H
Sagamicin	H	$NHCH_3$	H	CH_3	OH

The gentamicin antibiotics also comprise sisomicin [126-134], mutamicins [135], verdamicin [113,136], and the antibiotics 66-40B and 66-40D. [113,137] A characteristic feature of these antibiotics is the presence of an unsaturated carbohydrate substituent (dehydropurpurosamine) at the $C_{(4)}$ carbon atom of the deoxystreptamine ring §.



	R	R^1	R^2	R^3	R^4
Sisomicin	H	OH	H	OH	CH_3
Mutamicin-1	H	OH	OH	OH	CH_3
Mutamicin-2	H	H	H	OH	CH_3
Verdamicin	CH_3	OH	H	OH	CH_3
66-40B	H	OH	H	H	OH
66-40D	H	OH	H	OH	H

The following principles have been adopted in the numbering of the carbon atoms of different fragments of the molecules of aminoglycoside antibiotics.

1. Each cyclic fragment of the molecule (carbohydrate, aminocyclitol) has its own independent numbering of the carbon atoms.
2. The numbering in aminocyclitol begins with the carbon atom linked to the amino-group; the numbering proceeds in the direction such that the second amino-group is attached to the carbon atom with the smallest number.
3. The numbering of the carbon atoms in the carbohydrate substituents corresponds to the numbering adopted in carbohydrate chemistry: it begins with the carbon atom linked to the hemiacetal hydroxyl.
4. The carbon atoms of the carbohydrate substituent at the $C_{(4)}$ atom of the aminocyclitol are designated by primed numbers.
5. The carbon atoms of the carbohydrate substituent at the $C_{(5)}$ or $C_{(6)}$ carbon atom of the aminocyclitol are designated by doubly primed numbers.
6. The carbon atoms in the carbohydrate rings attached to the carbohydrate substituents of the aminocyclitol are designated by triply primed numbers.

III. THE MAIN PHYSICOCHEMICAL PROPERTIES OF AMINOGLYCOSIDES

Since aminoglycoside antibiotics are pseudo-oligosaccharides, it follows naturally that they possess many physicochemical properties and undergo many of the reactions characteristic of oligosaccharides. For example, aminoglycosides do not absorb between 220 and 360 nm in the ultraviolet. In most cases, their infrared spectra have no characteristic absorption bands and resemble those of oligosaccharides.

It has been shown for kanamycin monosulphate [73,74] and streptomycin [138] that the wavelengths corresponding to the bonds in the aminoglycoside antibiotics have values characteristic of ordinary covalent bonds. The interatomic distances in kanamycin are as follows: 1.48 Å for S = O (four bonds), 1.55 Å for C–C (sixteen bonds), 1.45 Å for C–N (four bonds), and 1.45 Å for C–O (fifteen bonds). The lengths of the intramolecular hydrogen bonds in the kanamycin molecule show that the oxygen of the hydroxy-groups at the $C_{(5)}$ atom of the deoxystreptamine ring is linked by a strong hydrogen bond to the hydroxy-group at the $C_{(2)}$ atom of the 6-amino-6-deoxy-α-D-glucose ring, i.e. the stereochemical structure of the 4-O-[6'-amino-6'-deoxy-α-D-glucopyranosyl]-2-deoxystreptamine molecule is rigid and determines the stability of the compound even in aqueous solutions.

The ^{1}H NMR spectra of aminoglycoside antibiotics are extremely complex and require the use of model compounds for their interpretation [313]. The ^{13}C NMR spectroscopy has come to be widely used in the study of the stereochemistry of aminoglycosides in recent years [23,38,314-317]. The employment of ^{13}C NMR spectroscopy made it possible to elucidate the nature of α- and β-streptomycins [318]. ^{13}N NMR spectroscopy has been used in the study of nebramycin antibiotics [319].

Crystalline aminoglycosides strongly retain water and carbon dioxide [103]. The gentamicin antibiotics retain water so tenaciously that it cannot be removed completely even on heating the specimens *in vacuo* for seven days at 50°C. [109]

Aminoglycoside antibiotics are readily adsorbed by cellulose, celite, and other filter materials [139], and the total initial amount of the antibiotic cannot be recovered even on acidification.

Aminoglycosides are extremely stable on prolonged storage in both powdered and crystalline state as well as in

§ Reports of the isolation of new antibiotics of the sisomicin series have appeared recently [311,312].

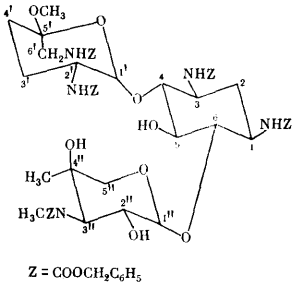
aqueous solutions[140,141,301]. There is no change in the activity of aqueous kanamycin solutions when they are heated in an autoclave for 30 min at 120°C in the pH range 2–9.[141] The gentamicin complex C also withstands heating in an autoclave for 20 min.[142]

IV. REACTIONS INVOLVING GLYCOSIDIC LINKAGES. HYDROLYSIS OF AMINOGLYCOSIDES

Aminoglycoside antibiotics are as a rule stable in solution at pH ≥ 7.0, but are relatively readily hydrolysed in acidic media. An exception is streptomycin, which is unstable in alkaline solutions; at pH 8.5, rapid inactivation takes place[143,144]. Kanamycin is more stable in the pH range 6–8 than at pH 2.0.[71,145] The gentamicin complex C is stable in the pH range between 2.0 and 14.[142]

Hydrolysis of aminoglycoside antibiotics by hydrochloric acid solutions under various conditions leads to the rupture of the glycosidic linkages and the formation of compounds which correspond to fragments of the aminoglycoside molecules in different combinations[146]. It has been shown for kanamycin that hydrolysis involves initially the glycosidic linkage between 6-amino-6-deoxy-α-D-glucose and 2-deoxystreptamine[147–149]. The acid hydrolysis of antibiotics of the gentamicin and sisomicin series does not entail the rupture of the glycosidic linkage between the purpurosamine rings and garamine, which is evidently due to the presence of the 2′-*C*-NH_2 group[302]. The main hydrolysis product is gentamine. On the other hand, *N*-substituted sisomicins are extremely sensitive to hydrolysis [they can be hydrolysed by treatment with the Amberlite IR-120 (H^+) resin]. The main hydrolysis product is garamine[303] and further hydrolysis of the latter is not observed.

It should also be noted that the methanolysis of pentakis-*N*-benzyloxycarbonyl-sisomicin results in the formation, together with garamine, of a methanol adduct having the following structure:



Z = $COOCH_2C_6H_5$

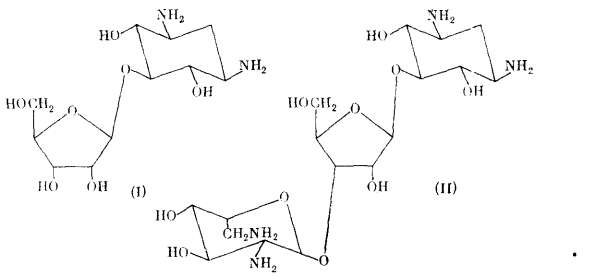
Acid hydrolysis of aminoglycoside antibiotics combined with the periodate oxidation of the *N*-acylated hydrolysis products is the basis of studies designed to determine their structure. For example, the method has been used successfully for kanamycins A,[150–155] B[156] and C,[7,10] lividomycin A,[58,60] and the antibiotic G-418. Analysis of the products of the mild acid hydrolysis of destomycin A and hygromycin B showed that these antibiotics differ in the structure of the main glycoside, but also have a component in common—destomic acid[23,28–31].

However, it is better to use acid methanolysis in the determination of the structures of antibiotics. The combination of acid methanolysis with the periodate oxidation of the hydrolysis products and the simultaneous acid hydrolysis of per-*N*-acetyl-per-*O*-methyl derivatives makes it possible to determine the detailed structure of the aminoglycoside. The method has been used in the determination of the structures of kanamycin[157–164], gentamicin[180,112,165,166], sisomicin[167], ribostamycin[36], Bu-1975 C_1 and C_2,[12] and many other aminoglycoside antibiotics. Methanolysis of the gentamicin complex C yields gentamicin and an anomeric mixture of methylgarosamides. The degradation of purpurosamine under these conditions is not observed, since the rupture of the glycosidic linkage is apparently prevented by the protonation of the 2′-*C*-amino group.

The rupture of the glycosidic linkage in acid hydrolysis has been used successfully not only for the determination of the structures of new antibiotics, but also for synthetic purposes. For example, in the synthesis of 1-*N*-[(*S*)-4-amino-2-hydroxybutyryl]neamine, the furanosyl linkage in butirosins A and B is hydrolysed by a solution of hydrochloric acid in methanol[16,19,20]. It is noteworthy that the amide bond between the aminoacyl group and the 1-*C*-amino-group in the deoxystreptamine ring is retained on acid hydrolysis. The rupture of the amide bond is observed during moderate alkaline hydrolysis. Ribostamycin is then formed from butirosin B,[16] while the alkaline hydrolysis of 4′-deoxybutirosin yields the corresponding 4′-deoxyribostamycin[19].

The selective cleavage of the glycosidic linkage in the elimination of the mannose component in the synthesis of lividomycin B from the lividomycin A is achieved by Barry's method (treatment with sodium periodate in the dark with subsequent removal of iodate, hydrolysis, and treatment with phenylhydrazine)[61,168].

The periodate oxidation of per-*N*-benzyloxycarbonyl derivatives of paromomycin and neomycin leads to the elimination of one or two diaminosugar rings, depending on the reaction conditions. After the removal of protecting groups, either a pseudodisaccharide (I) or a pseudotrisaccharide (II) is obtained[169]:

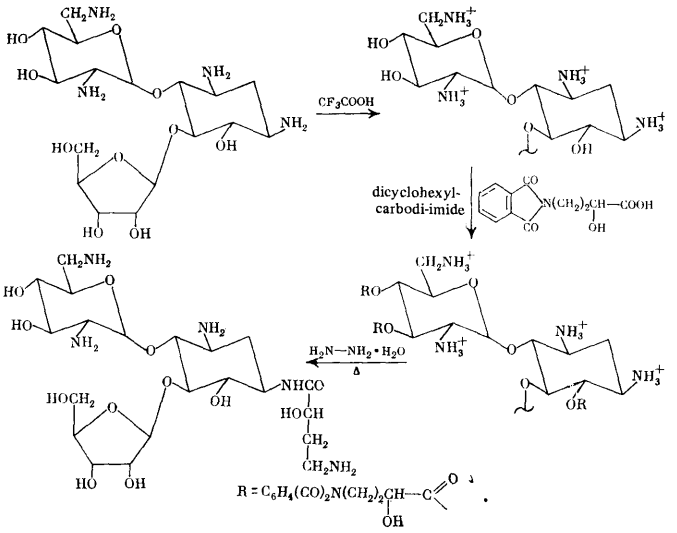


In conclusion one should note the possibility of the acid hydrolysis of paromomycin (I), neomycin, and kanamycin with the aid of ion-exchange resins[170].

V. REACTIONS INVOLVING AMINO-GROUPS

Aminoglycoside antibiotics readily form salts with inorganic acids. The ability of aminoglycosides to form salts has been used for the selective protection of the amino-groups in an elegant synthesis of butirosin B from ribostamycin[171]. The amino-groups of ribostamycin were

protected by preliminary treatment with trifluoroacetic acid. The scheme of the synthesis is presented below.



Aminoglycoside antibiotics readily form Schiff bases with aldehydes in aqueous alcoholic media[69,172-175]. Streptomycin, which contains the formyl group, forms Schiff bases on reaction with amines[176]. In contrast to other aminoglycosides, when gentamicin antibiotics give rise to Schiff bases, a cyclic oxazolidine is formed via the NH_2 group at the $C_{(3'')}$ atom and the OH group at the $C_{(4'')}$ atom in the garosamine component of the molecule[175,177].

Salicylidene derivatives of aminoglycosides are used in mass-spectrometric studies[178-180] and in the investigation of the dispersion of the optical rotation of aminoglycoside aminocyclitols[181].

The reduction of the Schiff bases with sodium tetrahydroborate leads to the formation of *N*-alkyl- and *N*-aryl-kanamycins and other basic antibiotics[174,176,182-184]. It is interesting to note that the possibility of obtaining monoalkylate products has been demonstrated for neomycins and paromomycin[182]. *N*-Alkyl derivatives of aminoglycosides can be obtained also without the preliminary synthesis of the corresponding Schiff bases—by reductive alkylation[174]. The ability of 1-fluoro-2,4-dinitrobenzene to partially dinitrophenylate kanamycin, neomycin, and paromomycin constitutes a method for the determination of the number of free amino-groups and the molecular weights of basic antibiotics[185].

The antibiotics react with formaldehyde to form products corresponding to different degrees of substitution, depending on the reaction conditions[183,186]. It has been shown that the hydrogenolysis of kanamycin in water in the presence of formaldehyde leads to the formation of *N*-octamethylkanamycin. On the other hand, when the reaction is carried out in an acidic medium (acetic acid), the formation of *N*-tetramethylkanamycin is promoted[187]. Various methods for the synthesis of *N*-methanesulphonate and *N*-methanesulphinate derivatives of aminoglycoside antibiotics have been developed[188]. The corresponding "Mannich bases" have been obtained from kanamycin and tetracycline[189-191].

The kanamycin Schiff bases react with carbon disulphide in an alkaline alcoholic medium, forming compounds having the general formula $KM(CSSA)_n$, where KM is kanamycin and A is an alkali metal atom[192]. In an aqueous alkaline solution, kanamycin reacts with trichloromethanesulphenyl chloride, forming *N*-trichloromethylthiokanamycin. Other basic antibiotics behave similarly[193,194]. Derivatives of basic antibiotics having antibacterial properties can be obtained by the reaction of the aminoglycoside bases with trichloromethanesulphenyl chloride and 2-amino-1-(*p*-nitrophenyl)propane-1,3-diol[193].

The aminoacid derivatives of aminoglycosides formed via the NH_2 group at the $C_{(1)}$ atom of the deoxystreptamine ring have continuously attracted the attention of chemists, biochemists, and specialists in chemotherapy in recent years. This interest was aroused by the antibacterial properties of the derivatives, particularly by their high activity against species of micro-organisms exhibiting multiple drug resistance. The problem of the synthesis of aminoacid derivatives reduces intrinsically to the problem of the selective protection of the amino-groups exhibiting a higher reactivity than the 1-*C*-amino-group.

The amino-groups of aminoglycoside antibiotics are known to be located in molecular fragments of different types and have different environments; nevertheless, in most cases they are hardly distinguishable as regards their reactivity, and the chemical reaction involves all the groups simultaneously. For example, the amino-groups are readily acetylated by acetic anhydride in methanol at room temperature[111,142,148,172,195-197] and react with ethyl[198] and benzyl[88,199] chlorocarbonate esters and dimedone[200]. Differences between the reactivities of the amino-groups can be detected in reactions of aminoglycosides with mild acylating agents such as *N*-benzyloxycarbonylhydroxysuccinimide or benzyl *p*-nitrophenyl carbonate and t-butoxycarbonyl azide.

In a series of studies devoted to the synthesis of amikacin (BB-K8) and its positional isomers and analogues, *N*-benzyloxycarbonylhydroxysuccinimide was used successfully for the selective protection of the amino-groups[92,93,201]. Aminoacid derivatives of tobramycin were obtained using a similar scheme[202]. The sequence in which the positional isomers of amikacin are synthesised and their structures make it possible to arrange the kanamycin amino-groups in order of their decreasing activity in the acylation reaction (sequence based on the positions in the molecule):

$$C(6') > C(1) > C(3) > C(3'').$$

It is interesting to note that, in the series of gentamicin antibiotics, the selectivity in the mode of acylation depends on the pH of the medium and the mode of reaction changes almost completely if the amino-groups of the antibiotics are protonated. Under these conditions, the 1-*C*-NH_2 group is the most reactive in relation to acylating agents, while the primary $-CH_2NH_2$ group exhibits the lowest reactivity. This phenomenon, noticed for the first time by Wright[304], has been used to obtain 1-*N*-acyl derivatives of gentamicin C_{1a}, sisomicin, and verdamicin[305]. The acylation of kanamycin is usually carried out with *N*-substituted aminoacids subjected to preliminary activation with *N*-hydroxysuccinimide[16,93,203].

It has been shown in relation to the synthesis of amikacin and 1-*N*-[(*S*)-4-amino-2-hydroxybutyryl]kamamycin B that benzyloxycarbonyl chloride can also be recommended for the selective blocking of the NH_2 group at $C_{(6)}$.[204] Evidently, t-butoxycarbonyl azide[205] is the most suitable agent for the selective protection of the NH_2 group at the $C_{(2')}$ atom in the synthesis of aminoacid derivatives of kanamycin B and 3′,4′-dideoxykanamycin B.[95,206,207] The t-butoxycarbonyl protecting group has valuable advantages over

other types of protecting groups—it can be removed selectively in the presence of *N*-benzyloxycarbonyl groups by means of trifluoroacetic acid, which permits the subsequent modification of only one amino-group. 6′-*N*-Alkyl derivatives of amikacin have been obtained by this method[184].

The NH_2 groups at the $C_{(2')}$ and $C_{(3)}$ atoms have been successfully protected with the trifluoroacetyl group in the synthesis of 1-*N*-[(*S*)-4-amino-2-hydroxybutyryl]- and 1-*N*-[(*S*)-3-amino-2-hydroxypropionyl]-gentamicins C_1 by treating the gentamicin with an equivalent amount of ethyl trifluorothioacetate in methanol solution[208,209]. The sequence in which the trifluoroacetyl protecting group is introduced makes it possible to arrange the amino-groups of gentamicin C_1 in the following sequence in terms of their activity with respect to this reagent (sequence based on the positions in the molecule):

$$C(2') > C(3) > C(1) > C(6') > C(3').$$

It is noteworthy that the selective acylation of the NH_2 group at the $C_{(1)}$ atom of gentamicin $C_{(1)}$ by γ-amino-α-hydroxybutyric acid can be carried out also without the preliminary blocking of the 2′-*C*- and 3-*C*- amino groups[210].

In the synthesis of the isomers of the aminoacid derivatives of butirosin from natural butirosin, it was necessary to select for the protection of the free amino-group a substituent having extremely specific properties: its bond with the amino-group must be stable in an alkaline medium and must be readily ruptured under conditions ensuring the retention of the amide linkage. It was shown that the most suitable protecting group is produced by forming a conjugated enamine in the reaction with dimedone[200]. The advantages of the products thus obtained are their high solubility, intense absorption in the ultraviolet, and ready purification by ion-exchange chromatography. The dimedone groups are removed with the aid of gaseous chlorine.

A new approach to the selective protection of the amino-groups, based on the formation of a cyclic carbamate or oxazolidone via the NH_2 group at the $C_{(1)}$ atom and the OH group at the $C_{(6)}$ atom of the deoxystreptamine ring, was introduced into the chemistry of aminosugars and aminocyclitols by Umezawa and coworkers[211]. This approach has been employed successfully in synthesis of butirosin B,[47,212] 3′-deoxybutirosin B,[213] and the aminoacid derivatives of 3′,4′-dideoxyneamine[18,21], 3′,4′-dideoxyribostamycin[212], lividomycin A,[65,214] and 6′-amino-6′-deoxylividomycin A.[215]

Carbamates or oxazolidinones are usually obtained by treating *N*-per(benzyloxycarbonyl)aminoglycosides with sodium hydride in dimethylformamide at room temperature. The formation of the cyclic carbamate can be explained by the initial attack by sodium hydride on the OH group at $C_{(6)}$ with subsequent anchimeric attack by the resulting alkoxide ion on the urethane carbonyl at $C_{(1)}$. The use of cyclic carbamates for the protection of groups in the *trans*-positions has been described for the first time in connection with the synthesis of *D*-glucopyranosido[2,3 : 4,5]-2′-oxazolidinones[216] with the aid of *NN*′-carbonyldi-imidazole. When the resulting carbamate is heated with barium hydroxide in aqueous dioxan, selective hydrolysis with liberation of the NH_2 group at $C_{(1)}$ and the OH group at $C_{(6)}$ takes place. Subsequent acylation at the amino-group and elimination of all the protecting groups lead to the aminoacid derivatives of aminoglycosides formed via the NH_2 group at $C_{(1)}$.

Weinstein and coworkers[177] showed in relation to the gentamicin complex C that simultaneous selective protection of the amino- and hydroxy-groups of the garosamine ring can be achieved as a result of the formation of oxazolidine when the gentamicin complex reacts with aldehydes in ethanol.

It has been shown for the synthesis of butirosin that the aminoacid derivatives of aminoglycoside antibiotics having a free hydroxy-group at the $C_{(6)}$ atom of the deoxystreptamine ring can be obtained by the elegant reaction involving the O→N acyl migration of the aminoacid group from the $C_{(6)}$ atom to the amino group at $C_{(1)}$[171] (see the reaction scheme at the beginning of this Section).

N-Benzyloxycarbonyl derivatives of aminoglycoside antibiotics are reduced to the corresponding *N*-methylaminoglycosides on heating with lithium tetrahydroaluminate in tetrahydrofuran. The reaction has been used in the preparative synthesis of 6′-*N*-methylkanamycin and 3′,4′-dideoxy-6′-*N*-methylkanamycin B.[89] The selective 6′-*N*-benzyloxycarbonylation of aminoglycosides has been carried out successfully with the aid of benzyl *p*-nitrophenyl carbonate[217] in aqueous dioxan at 0–5°C.

N-Glycoside derivatives of aminoglycoside antibiotics, exhibiting antibacterial activity, are obtained by Pan's enzymatic transglycosylation reaction[218–221].

VI. REACTION INVOLVING HYDROXY-GROUPS

The most characteristic reactions of the hydroxy-groups of aminoglycoside antibiotics are those involving the formation of esters[222–225] and ethers[14,88,155,198,226]. They are used widely in the protection of hydroxy-groups in the synthesis of various derivatives of antibiotics.

Like the amino-groups, the hydroxy-groups of aminoglycosides have different reactivities. The primary alcoholic OH groups at $C_{(6'')}$ and $C_{(6')}$ are chemically the most reactive, the hydroxy-groups and $C_{(2')}$ and $C_{(2'')}$ are somewhat less reactive, and the hydroxy-group at the $C_{(5)}$ atom of the deoxystreptamine ring is least reactive. The reactivities of the remaining hydroxy-groups are virtually the same. The only known instance of reaction involving the hydroxy-group at $C_{(5)}$ is the synthesis of esters of gentamicin C_{1a}.[227]

The interaction of kanamycin with concentrated sulphuric acid at a reduced temperature leads to the formation of kanamycin sulphonate esters, the number of ester groups corresponding to the number of hydroxy-groups in the molecule of the antibiotic. This property of basic antibiotics has been used to develop a method for the determination of the number of free hydroxy-groups in biological preparations[222]. Kanamycin Schiff bases are readily *O*-acylated by benzoyl chloride, benzoic acid anhydride, and benzoate esters with formation of the corresponding *O*-benzoate esters after acid hydrolysis[223]. Kanamycin esters having the general formula $(RCO_2)_nC_{18}H_{21}O_4(OH)_{7-n}(NH_2)_4$, where R is an alkyl group, an alkoxy-group, a *p*-substituted phenyl group, an aryl group, etc, are formed by the reaction of sodium alkoxides derived from the kanamycin Schiff bases with acid chlorides[224].

On reaction with alkane- and arene-sulphonyl chlorides, aminoglycosides readily form sulphonates, which are used to introduce various functional groups into the molecule of the antibiotic (halogen, H, N_3, COOH, NH_2, etc,) via an exchange reaction of the sulphonyloxy-groups with a particular nucleophile. Trifluorophenyl derivatives of aminoglycosides can also be used for such purposes instead of the sulphonate derivatives[88,198].

O-Methyl derivatives are usually obtained by treating aminoglycosides with dimethyl sulphate in the presence of alkali by the method of West and Holden[228] modified by Umezawa et al.[155] This reaction has been used in the synthesis of 3′- and 4′-*O*-methylneamines[14,226]. Diazomethane has been used a methylating agent in the synthesis of 4′,6′-*O*-methyl-lividomycin A;[215] the reaction was catalysed by boron trifluoride etherate.

The differences between the reactivities of the hydroxy-groups have been used in the synthesis of many derivatives of aminoglycosides formed via the most reactive OH group at the $C_{(6'')}$ or $C_{(6')}$ atom; the syntheses are based on the exchange reactions of aminoglycos-6″-*O*-ylalkane(arene)-sulphonates with nucleophiles. 6″-Deoxykanamycin[86-88,229], kanamycin-6″-uronic acid, its methyl ester and amide[198], 6″-hydrazinokanamycin[230,231], 6″-halogenokanamycins[88,231], kanamycin-6″-phosphate[232,233], and 6′-amino-6′-deoxygentamicin A[234] have been obtained in accordance with this scheme. Among aminoglycoside antibiotics containing a furanosyl substituent, the most reactive hydroxy-group is at the $C_{(5'')}$ atom. The following derivatives of these antibiotics have been obtained: ribostamycin-5″-uronic acid, its methyl ester and hydrazide[235], lividomycin A-5″-phosphate and 5″-deoxylividomycins B[236,237] and A,[64] 6′-amino-5″,6′-dideoxylividomycin A,[64] 5″-amino-5″-deoxybutirosin[52], and 5″-amino-3′,4′,5″-trideoxybutirosin[238]. Apart from the OH groups at the $C_{(5'')}$ atom, lividomycins A and B have a further hydroxy-group with a high reactivity—the groups at the $C_{(6')}$ atom. A number of derivatives have also been obtained via this hydroxy-group: 6′-amino-6′-deoxylividomycins A[215] and B[239] and 6′-deoxy-6′-methylamino- and 6′-deoxy-6′-(2-hydroxyethylamino)lividomycins B.[239]

Derivatives of aminoglycoside antibiotics readily epimerise at the 2″-*C*-hydroxy-group in solutions in the presence of bases or simply on heating in dimethylformamide. Thus, such treatment of kanamycin derivatives leads to the formation of the corresponding mannosyl derivatives[240-243]. It has been shown for gentamicin C_1 that epimerisation is also observed on solvolysis of the 2″-C-methanesulphonate in 10% aqueous dimethylformamide[244]. The epimerisation of paromamine in the 3′-*C*-position has been achieved by reduction with sodium tetrahydroborate of the corresponding glycos-3′-yl derivative obtained by oxidising tri-*N*-(benzyloxycarbonyl)-di-4′,6′-*O*-isopropylideneparomamine in the methyl sulphoxide–acetic anhydride system in the dark at room temperature for three days[245]. The epimerisation at the 2′-*C*-hydroxy-group has been observed in the synthesis of 3′-amino-3′-deoxykanamycin via a mechanism which is based on the cyclisation of the dialdehyde obtained by the periodate oxidation of tetra-*N*-acetylkanamycin with nitromethane followed by the reduction and hydrazinolysis[242]. Direct treatment of the intermediate 3′-deoxy-3′-nitro-derivative with hydrazine leads to the decomposition of the nitrosugar component of the compound.

In contrast to the modification of amonoglycosides via the chemically most reactive hydroxy-group at $C_{(6'')}$, the problem of transformations via the 3′-*C*- and 4′-*C*-hydroxy-groups is much more complex, since such reactions necessitate the blocking of all the hydroxy-groups of the antibiotics except those at $C_{(3')}$ and $C_{(4')}$. This is very difficult to achieve in view of the virtually identical reactivities of the hydroxy-groups (except those at $C_{(6'')}$ or $C_{(5'')}$). On the other hand, the synthesis of 3′- and 4′-deoxy and 3′,4′-dideoxy-derivatives of aminoglycosides in one of the tasks of primary importance, since these semisynthetic antibiotics are in fact highly active in relation to bacterial strains inactivating aminoglycosides via the commonest mechanism of enzymatic inactivation—*O*-phosphorylation at $C_{(3')}$. This task can be carried out readily only when there exists a simple method for the selective protection of the functional groups of the antibiotic. At the present time such a method has not been developed yet, and, for example, 3′-deoxykanamycin A has not so far been obtained from the natural antibiotic. The situation is simpler in the case of aminoglycosides incorporating a non-amino-fragment. Nevertheless, the synthesis of 3′- and 4′-deoxy-derivatives of these antibiotics are extremely complex multistage processes, with very low yields of the required product.

Antibiotics containing a non-amino-component give rise to a 3′-deoxy derivative as a result of the selective tosylation of the OH group at $C_{(3')}$ with subsequent exchange for the halogen atom and reduction. A typical scheme for the synthesis of 3′-deoxykanamycin B[79] is as follows. After protecting the amino-groups, the hydroxy-groups at $C_{(3')}$, $C_{(4')}$, $C_{(4'')}$, and $C_{(6'')}$ are blocked with the aid of the isopropylidene or cyclohexylidene groups and the 2″-*C*-hydroxy-group is benzolated; the protecting groups are removed from the 3′- and 4′-*C* positions under mild conditions, the toluenesulphonate group is introduced selectively at $C_{(3')}$ and is exchanged for the halogen atom, and 3′-deoxykanamycin B is obtained after reduction and elimination of protecting groups. A virtually similar scheme constitutes the basis of the synthesis of 3′-deoxy-derivatives of ribostamycin[48] and butirosin B.[213] It has been shown for the synthesis of 3′-deoxybutirosin B that the 2-nitrobenzene-1-sulphonate group is exchanged for a halogen atom more readily than the tosyl group[213].

In the synthesis of 3′,4′-dideoxy-derivatives of aminoglycosides, after the methanesulphonation of the hydroxy-groups at $C_{(3')}$ and $C_{(4')}$ a double bond is introduced by the Tipson–Cohen method[246,247] and hydrogenated, and, after the removal of the blocking groups, the required compound is obtained. This scheme is the basis of the synthesis of aminoglycoside derivatives such as 3′,4′-dideoxykanamycin B,[51,90,91,248] 3′,4′-dideoxy- and 3′,4′,5″-trideoxy-ribostamycin[20], 3′,4′-dideoxybutirosins B[51,212] and A,[249] 5″-amino-3′,4′,5″-trideoxybutirosin A,[238,250] 3′,4′-dideoxyneamine[13], and 1-*N*-[(*s*)-4-amino-2-hydroxybutyryl]-3′,4′-dideoxyneamine[19].

An unexpected synthesis of 4′-deoxykanamycin A of kanamycin A has been discovered. It has been shown that the hydrogenolysis of nona-*NO*-acetyl-6′-*N*-benzyloxycarbonylkanamycin A over palladium on charcoal at room temperature results in the migration of the *O*-acetyl group from the 4′-*C*-position to the 6′-*C*-amino-group. Thus a simple method has been found for protecting all the amino- and hydroxy-groups except the hydroxy-group at $C_{(4')}$.[251] In this synthesis, the 4′-*C*-hydroxy-group is removed by exchanging the methanesulphonyl group for the thioloacetate group with subsequent reduction over Raney nickel at atmospheric pressure.

A second method for the synthesis of 4′-deoxykanamycin, based on the formation of a 4′,6′-cyclic carbamate by the reaction of the tri-*N*-ethoxycarbonyl derivative of kanamycin with phenyl chloroformate[211], was described at the same time[251]. However, this method is complex, it is sufficient to say that it consists of thirteen stages.

The synthesis of deoxy-derivatives of gentamicin is complicated by a series of cyclisations and rearrangements in the garosamine ring[244]. The attempt to obtain 2″-deoxygentamicin C_1 was unsuccessful owing to epimerisation. The 2″-*C*-hydroxy-group was removed from gentamicin C_2. Methanesulphonation of the pentabenzylidene derivative of gentamicin C_2 led to the formation of the 2″-*O*-methanesulphonyl derivative, which cyclises to an epimine after the removal of the benzylidene groups. The

epimine was acetylated with acetic anhydride in methanol and the acetyl derivative was reduced over Raney nickel at 140°C and 176 atm in 30 h. After the removal of the protecting groups, two products were obtained—2″-deoxygentamicin C_2 and its rearrangement product—2″-deoxy-3″-desmethylamino-2″-methylaminogentamicin C_2, the second substance being the main reaction product.

The reduction of penta-*N*-benzyloxycarbonylper-*O*-acetylgentamicin C_1 with sodium in liquid ammonia leads to 4″-deoxygentamicin C_1.[252] It has been shown for garamine that the reaction cannot be extended to the synthesis of 2″-deoxyderivatives by reducing the 2″-acetyl- or 2″-thiobenzoyl-garamine[252].

VII. COMPLEXES OF AMINOGLYCOSIDES

Owing to the large number of their hydroxy- and amino-groups, aminoglycoside antibiotics readily form complexes with heavy metal salts. The formation of aminoglycoside complexes with water-soluble inorganic copper, nickel, cobalt, zinc, magnesium, and iron salts has been described[253-258]. The metal content in the complex varies in the range 0.5–3.0 atoms per mole of the antibiotic[320].

The study of the infrared spectra of chelates of kanamycin, deoxystreptamine, and ethylenediamine with copper(I) chloride, led Yamabe[255] to the conclusion that kanamycin forms a chelate with Cu^{2+} via the propylidenediamine component of deoxystreptamycin. On the other hand, comparison of the polarograms of the chelates of kanamycin and deoxystreptamine shows that these complexes are of different types[255] Thus the problem of the particular amino-groups of kanamycin involved in the formation of chelates with heavy metal ions remains open. The structure of the chelates must undoubtedly depend on the nature of the amino-groups participating in the formation of the complex and on their reactivity.

It has been shown that Ca^{2+} and Mg^{2+} salts decrease the degree of binding of gentamicin and other deoxystreptamine-containing antibiotics to bacterial and blood serum proteins. The maximum binding (70%) is observed in the absence of metal cations, the degree of binding decreasing with increase of the metal ion concentration[259]. There is no doubt that this phenomenon is based on the ability of the aminoglycoside antibiotics to form complexes with metal salts. Under conditions involving competition between the binding of aminoglycosides by metal salts or proteins, the preferred process is apparently the formation of complexes of metal ions.

The capacity of aminoglycoside antibiotics for complex formation is used in the analysis of drugs[260,261]. Kanamycin forms anisotropic monoaxial crystals with the Reinecke salt[262]. The reaction makes it possible to determine kanamycin in solutions at the minimum concentration of 1 : 100 000.

The most important application of the ability of aminoglycosides to form complexes of the Reeves cuprammonium method for the determination of structures[263]. The method has been used to determine the structures of virtually all aminoglycoside antibiotics[54,264-268].

Aminoglycoside antibiotics are known to form carbonates readily by reaction with carbon dioxide. However, the study of the ^{13}C NMR spectra of the products resulting from the absorption of carbon dioxide by gentamicins C_1, C_2, and C_{1a} showed that carbon dioxide is bound by these substances without the formation of carbonates. The structure of the resulting complexes is unknown[103].

VIII. THE FORMATION OF *O*-GLYCOSIDIC LINKAGES. DIRECT SYNTHESIS OF AMINOGLYCOSIDES

The so called "total" synthesis of aminoglycosides, involving the condensation of mono- and pseudodi-saccharides by the Koenigs–Knorr reaction, is very important in the chemistry of aminoglycoside antibiotics. Despite its complexity, the method retains its importance, because it makes it possible to decide finally the validity of the determination of the structure of the aminoglycoside antibiotic and also to obtain derivatives of aminoglycosides which cannot so far be synthesised by the transformation of existing antibiotics.

After the preliminary synthesis of the initial monosaccharides and aminocyclitols[269-281], the method has been used to synthesise streptomycin[282], dihydrostreptomycin[283,321], kanamycins A,[284-287] B,[288,289] and C,[290-292] ribostamycin[293,294,322], xylostasin[39], 3′-*O*-methylkanamycin A,[295] 3-amino-2,3-dideoxy-α-arabinohexapyranosylgentamine C_1,[296] the isomeric di-*O*-(α-D-glucopyranosyl)-2-deoxystreptamines[297], as well as a number of glycosides containing 6′-amino-6′-deoxy-α-D-glucopyranosyl-2-deoxystreptamine[271], etc.,[323].

It is noteworthy that the classical method of glycoside synthesis (the Koenigs–Knorr reaction) is unsuitable on an industrial scale not only because of the low yields of the final product, but also because of the formation of large amounts of the β-isomer. A new method of synthesis of α-D-glucopyranosyldeoxystreptamines, developed by the Lemieux–Nagabhushan group and based on the reaction of dimeric tri-*O*-acetyl-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride with alcohols[298-306], is therefore of definite interest. The Lemieux–Nagabhushan reaction has been used successfully to obtain various derivatives of gentamicin X_2,[307] gentamicin B,[308] and pentosyl derivatives of garamine[309].

In conclusion one should note that, in the absence of a suitable method for the selective protection of hydroxy-groups, the method of "total" synthesis is so far the only available procedure for obtaining 3′-deoxykanamycin[84,299,300]. The method is also important for the synthesis of various isomers of aminoglycosides required for the elucidation of the role of the structural components of the aminoglycoside molecules in their antibacterial activity.

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