The Aminoglycoside Antibiotics: A Guide To Therapy

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PREFACE

The aminoglycoside antibiotics have had a prominent role in the treatment of bacterial infections since streptomycin became available for clinical use in 1947. The continued interest in the application of these antibiotics has provided the stimulus for preparation of this Uniscience volume. Over the years, a prodigious number of scientific publications have appeared in the world's literature pertaining to one aspect or another of the aminoglycoside antibiotics. Much of the pertinent literature that is appropriate to the needs of the clinician and laboratory scientist is scattered throughout a vast array of scientific journals, books, and other publications.

In an effort to compile a concise overview of topics consistent with the objectives of the editors and in order to provide an adequate bibliography for those readers requiring more detailed information, the following topics have been included: the chemistry and structural relationships, mechanisms of action and resistance, pharmacokinetics, therapeutic uses, toxicity, problems of susceptibility testing, and available serum assay methodologies. Because the most frequently utilized aminoglycosides are gentamicin, tobramycin, and amikacin, most of the material included pertains to these three antibiotics. It has not been the intent to provide a complete encyclopedic treatise on all individual topics due to space limitations of a publication this size.

The editors are indebted to the diligent efforts of all the contributors. Their cooperation in sharing their ideas, expertise, and valuable time has been instrumental in the successful completion of this work.

It is our hope that the readers will find *The Aminoglycoside Antibiotics: A Guide to Therapy* of value in providing a better understanding of the role of these agents in the treatment of infectious diseases and to further provide a means for eliminating or preventing potential problems that may occur with their therapeutic use.

W. G. Barnes
G. R. Hodges

THE EDITORS

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Dr. Barnes received the B.A. degree in 1950 from the University of Kansas, M.A. degree from the University of Kansas City in 1960 and the Ph.D. from the University of Kansas in 1968. He served as an Assistant Professor at the University of Missouri at Kansas City, School of Dentistry from 1966 to 1968, and at the University of Missouri at Kansas City, School of Medicine from 1968 to 1974 during his appointment as Chief Microbiologist at the General Hospital, Kansas City, Missouri. He assumed his current position as Director of Microbiology at the V.A. Medical Center in 1974 and has served as an Associate Professor in the Department of Pathology and Oncology, College of Health Sciences, Kansas City, Kansas since 1979.

Dr. Barnes is a member of the American Society for Microbiology, Medical Mycological Society of the Americas, South Central Association for Clinical Microbiology, Southwestern Association for Clinical Microbiology, and Sigma Xi. He is a Fellow of the American Academy of Microbiology and is a Certified Specialist in Public Health and Medical Laboratory Microbiology by the National Registry of Microbiologists. In 1968, he was awarded the C. Herrick Award in Parasitology by Eli Lilly, the Gold Award in 1972 by the American Society of Clinical Pathology and the Special Award in 1971 by the American Academy of Dermatology. He presently is serving on the Board of Directors and as Editor-in-Chief of the Southwestern Association for Clinical Microbiology.

Dr. Barnes is the author or coauthor of more than 50 publications. His major research interests are in the area of clinical microbiology and host parasite relationships.

Glenn R. Hodges, M.D., M.S., is Chief of the Infectious Disease Section at the V.A. Medical Center at Kansas City, Missouri and Associate Professor of Medicine at the College of Health Sciences, University of Kansas, Kansas City, Kansas.

Dr. Hodges received his B.A. in chemistry at Muskingum College, New Concord, Ohio in 1963; his M.D. from the University of Chicago, in 1967; and his M.S. in medical microbiology at Ohio State University in 1972. After his postdoctoral training in internal medicine and infectious diseases at Ohio State University, he served two years in the U.S. Navy as an infectious disease specialist at the Naval Regional Medical Center, Great Lakes, Illinois. Since 1974, Dr. Hodges has been associated with the V.A. Medical Center, Kansas City, Missouri and the College of Health Sciences, University of Kansas, Kansas City, Kansas.

Dr. Hodges is certified by the American Board of Internal Medicine in both internal medicine and infectious disease. He is a fellow of the American College of Physicians and the Infectious Diseases Society of America. He is a member of the American Federation for Clinical Research, the American Public Health Association, the American Society for Microbiology, the Association for Practitioners in Infection Control, and the Central Society for Clinical Research.

Dr. Hodges has authored or coauthored more than 60 articles in the field of infectious diseases. His major interests are treatment of central nervous system infections, hospital infection control, proper use of antimicrobial agents, and the immunologic response to infection.

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Chapter 1

CHEMISTRY OF THE AMINOGLYCOSIDES: STRUCTURE/FUNCTION RELATIONSHIPS

William J. Rost

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I. AMINOGLYCOSIDE ANTIBIOTICS

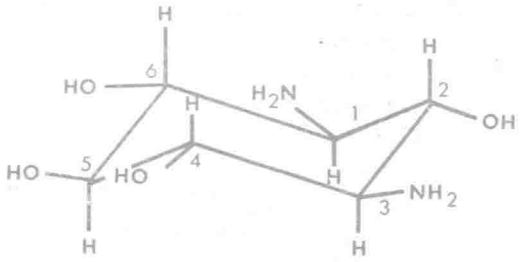
A. Definition

Aminoglycoside antibiotics are a group of closely related basic carbohydrates. They consist of an aminocyclitol ring connected in glycosidic linkage to one or more aminosugars. The amine groups that are present can form crystalline salts with acids.

B. General Structural Units

1. Aminocyclitol

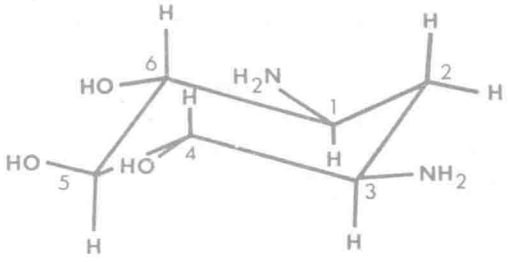
The aminoglycoside antibiotics are characterized by the inclusion of an aminocyclitol group in their structure. An aminocyclitol group may be defined as a saturated ring with amine and hydroxyl substitutions. In fact, Rinehart[1] has suggested that the term aminocyclitol be used to describe this group of antibiotics rather than the less precise term, aminoglycoside. While many variations are possible, the basic aminocyclitol group found in the clinically useful antibiotics is streptamine.



Streptamine

FIGURE 1.

The particular streptamine that is usually included in the structures of these antibiotics is actually 2-deoxystreptamine.

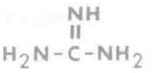


2-Deoxystreptamine

FIGURE 2.

This compound possesses two *cis* amino groups at positions 1 and 3. The 2-deoxy portion of the name indicates the absence of a hydroxyl group at position 2.

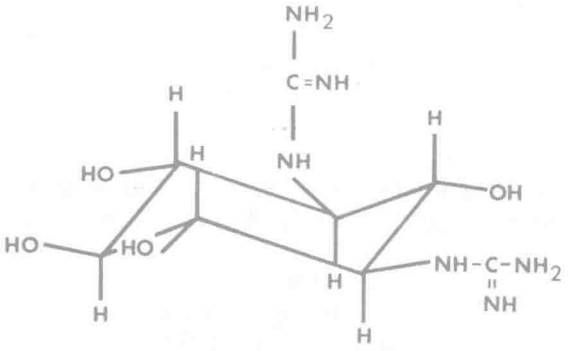
Guanidine has the following structure:



Guanidine

FIGURE 3.

If the amine functions of the streptamines are part of a guanidine group, the molecule is referred to as a streptidine.



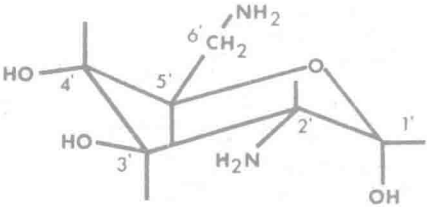
Streptidine

FIGURE 4.

Streptomycin is the only antibiotic of clinical importance that contains the streptidine group.

2. Aminosugars

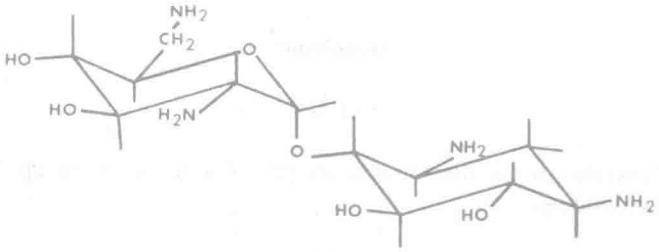
Aminoglycoside antibiotics are also characterized by aminosugars attached to the aminocyclitol ring in glycosidic linkage. The aminocyclitol, 2-deoxystreptamine, contains three hydroxyl groups at C_4, C_5, and C_6. These are available for combination with a sugar in glycosidic linkage. Aminosugars are particularly important in this regard. An example of such a sugar may be found in 2,6-diaminoglucose.



2,6 Diaminoglucose

FIGURE 5.

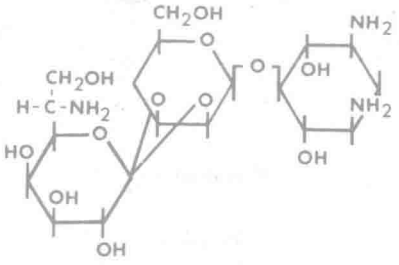
If we combine this sugar with 2-deoxystreptamine in glycosidic linkage, the following product results:



Neamine (Neomycin A)

FIGURE 6.

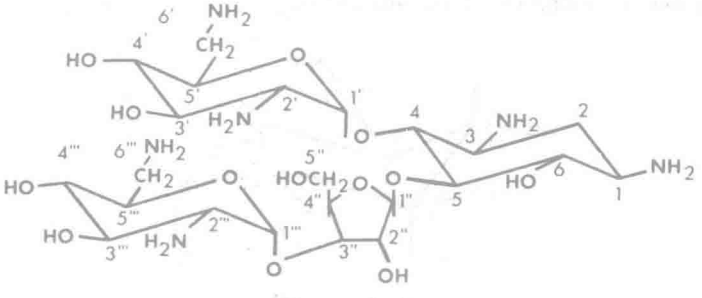
The above substance is called neamine or neomycin A. A glycoside can also be formed at C_5 of the 2-deoxystreptamine ring. Destomycin A is an example of such a compound.



Destomycin A

FIGURE 7.

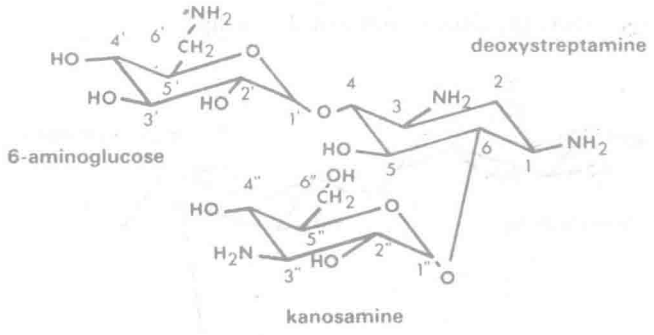
A very large and important group of aminoglycoside antibiotics are the 4,5-disubstituted 2-deoxystreptamine derivatives. Neomycin C is an example of this group.



Neomycin C

FIGURE 8.

Another very important group is the 4,6-disubstituted 2-deoxystreptamine derivatives. Kanamycin A is an example of this group.



Kanamycin A

FIGURE 9.

Before further discussion of specific drugs, a word about nomenclature is in order. The basic group of the aminoglycoside antibiotics is the 2-deoxystreptamine ring. It is numbered as shown in Figure 2. The aminosugars are numbered in the customary manner. In the case of the aminoglycoside antibiotics, the sugar attached to the C_4 of the aminocyclitol ring is numbered with numbers designated as prime numbers. This is illustrated in Figure 5. The second sugar that is attached to the aminocyclitol ring is numbered with double prime numbers. A third sugar that occurs in the molecule is numbered with triple prime numbers. Please refer to neomycin C (see Figure 8) for a specific example of numbering the aminoglycoside antibiotics.

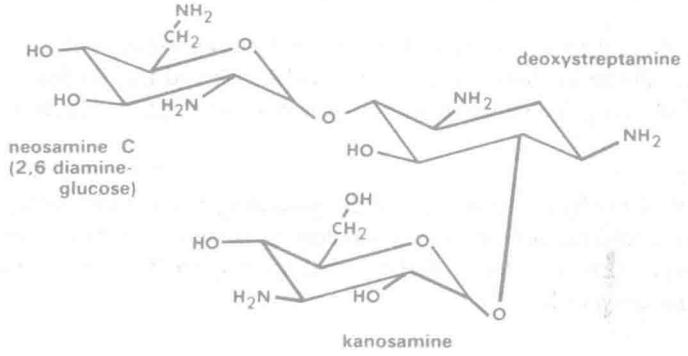
C. Specific Aminoglycoside Antibiotics

1. 4,6-Disubstituted Aminocyclitols

a. Kanamycin

Kanamycin is an example of a 4,6-disubstituted aminocyclitol. It contains two sugars which are attached to positions 4 and 6 of a typical 2-deoxystreptamine ring. The aminosugar attached to position 6 is kanosamine (3-glucosamine). The aminosugar attached to position 4 may vary. This gives rise to three kanamycins which are called kanamycin A, kanamycin B, and kanamycin C. The official product is kanamycin A (see Figure 9).

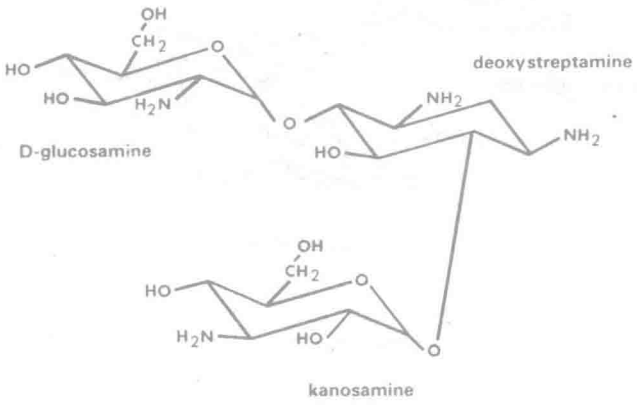
Kanamycin B is one of the kanamycins.



Kanamycin B

FIGURE 10.

Kanamycin C represents the third member of the group.



Kanamycin C

FIGURE 11.

Kanamycin B has in its structure a neosamine (2,6-diaminoglucose). It is about twice as potent as kanamycin A, which is a 6-aminoglucose derivative. Kanamycin A, in turn, is two to four times more potent than kanamycin C. Kanamycin C is the glucosamine (2-aminoglucose) analogue.

Substitutions on the amines which decrease the basicity of the amines decrease the antibiotic activity. For example, if the amines are acetylated and their basicity is destroyed, the activity is reduced or eliminated. If kanamycin A is acetylated at $C_{6'}$ the product is inactive. The basicity of the ring has been destroyed. If kanamycin B is acetylated at $C_{6'}$ the product retains a reasonable amount of activity. The basicity of the ring has not been destroyed because there is still an amino group at $C_{2'}$. The activity is similar to that exhibited by kanamycin C, which has its basic amine at $C_{2'}$.[2]

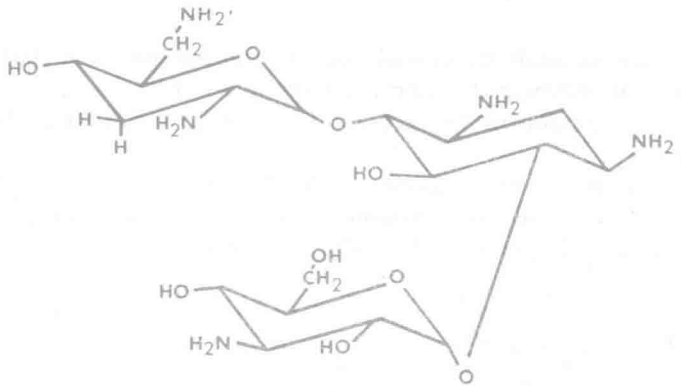
It may be concluded that the sugar at the 4 position of the aminocyclitol must have at least one amino group to be biologically active. The derivatives may be listed as follows in the decreasing order of potency:

2′,6′-diamino > 6′-amino > 2′-amino > hydroxyl

These kanamycin derivatives are metabolized by phosphorylation at $C_{3'}$ and adenylation at $C_{4'}$. Removal of the hydroxyl groups at $C_{3'}$ and $C_{4'}$ should lead to derivatives that resist such chemical changes. Tobramycin and dibekacin are examples of such modifications.

b. Tobramycin

Replacement of the hydroxyl groups on the aminosugar ring with hydrogen atoms leads to an increased antibiotic potency in the kanamycin B series.[3] Tobramycin is an example of such a change. It is a 3′-deoxy derivative of kanamycin B, and it shows an increased potency over kanamycin B.

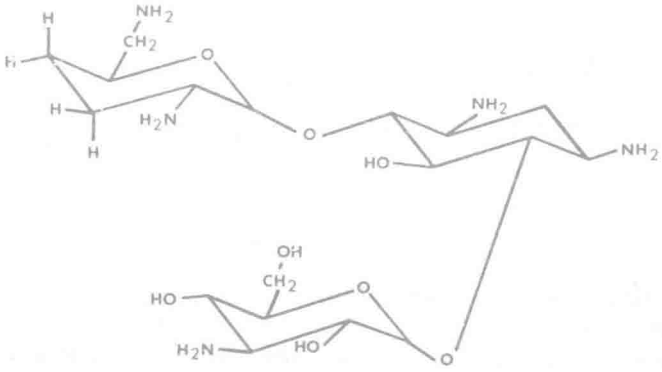


Tobramycin

FIGURE 12.

c. Dibekacin

Replacement of both the 3′- and 4′-hydroxyl groups of kanamycin B gives another more active compound called dibekacin. It is also referred to as dideoxykanamycin B or DKB.



Dibekacin
DKB

FIGURE 13.

These compounds are examples of the increased antibiotic activity when the hydroxyl groups at 3′ and 4′ are replaced with a hydrogen substitution. The same effect is seen in the kanamycin A series. Increased potency is observed with the 3′-deoxy and the 4′-deoxy derivatives of kanamycin A.[4,5]

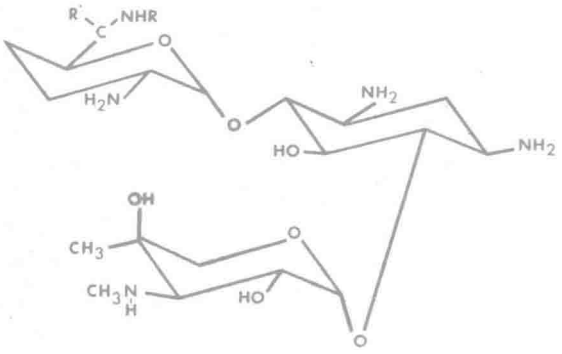
However, some modifications decrease the antibiotic activity in this series. Replacement of the 3′- and 4′-hydroxyl groups with a methoxyl or amino group caused a lessening of activity.[6-8] Unsaturation of the aminosugar ring has a variable effect. Replacement of the 3′,4′ hydroxyl groups with a double bond decreases the activity. However, a double bond between carbons 4′ and 5′ increases the activity. This might be due to the alteration of the ring's conformation due to the double bonds.[9]

Modification of the kanosamine ring of kanamycin A has little or no effect. The $C_{6'}$ chloro kanosamine and the $C_{6'}$ deoxy kanosamine have essentially the same activity as the parent kanamycin A.[10,11]

d. Gentamicin

Gentamicin is also an antibiotic complex of the 4,6-disubstituted aminocyclitol series. Various species of *Streptomyces* have provided almost all of the antibiotics in this series, with the notable exception of the gentamicins which are produced by species of *Micromonospora*.

Gentamicins have three main components. These components are referred to as gentamicins C_1, C_2, and C_{1A}. Thirteen other gentamicins have also been reported. The gentamicin components C_1, C_2, and C_{1A} have the following structural relationships:



	R'	R
Gentamicin C_1	CH_3	CH_3
Gentamicin C_2	CH_3	H
Gentamicin C_{1A}	H	H

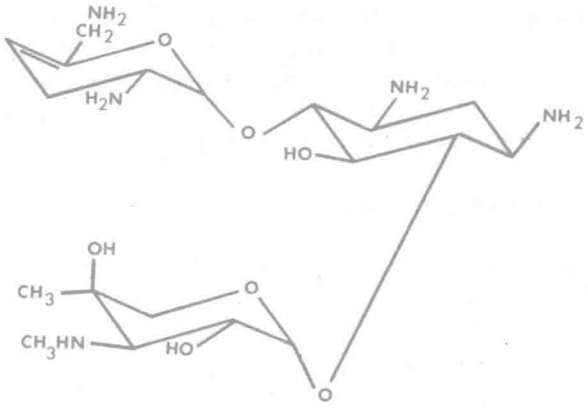
FIGURE 14.

The gentamicins are similar to the kanamycins in two respects. They are derivatives of a 4,6-disubstituted aminocyclitol. The substitutions at positions 4 and 6 are aminosugars. They are different from the kanamycins in the nature of the sugar residues that are substituted. The aminosugar at C_4 is a 2,6-diamine derivative. There are no hydroxyl groups at $C_{3'}$ and $C_{4'}$. In the kanamycin series, kanamycin B is the most active, and it has a 2,6-diaminosugar. Replacement of the hydroxyl groups at $C_{3'}$ and $C_{4'}$ gives tobramycin and dideoxy-kanamycin B, both of which have increased activity over the parent kanamycin. In this series of gentamicins, the $C_{6'}$ and the amine group on the $C_{6'}$ carbon is substituted with a methyl group with the retention of good activity.

The sugar at C_6 of the aminocyclitol ring contains a hydroxyl group at $C_{2''}$. If this group is removed or methylated, the activity is decreased. Activity is retained if this hydroxyl group is replaced with an amino group.[12] The $C_{3''}$ amino group is a secondary amine. The primary amine analogue is also active. The hydroxyl group at $C_{4''}$ can be methylated with the retention of activity. The $C_{6''}$ deoxy and the $C_{6''}$ chloro derivatives also are active.[10,11]

e. Sisomicin

Sisomicin is another example of changes in the aminosugar portion of the molecule.



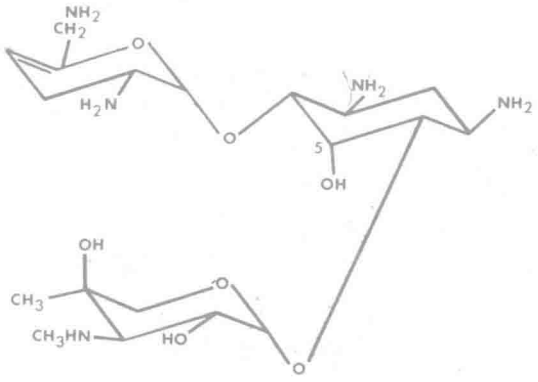
Sisomicin

FIGURE 15.

These modifications are made in the antibiotics of the gentamicin series. The aminosugar in sisomicin is an unsaturated diaminosugar. The amines are at $C_{2'}$ and $C_{6'}$ of the sugar. This combination seems to be very favorable in the kanamycin series (q.v.). In addition, the hydroxyl groups at $C_{3'}$ and $C_{4'}$ have been removed. This was seen to be very beneficial in the debekacin series (q.v.). Introduction of a double bond between the $C_{4'}$ and $C_{5'}$ positions has previously been stated to increase the activity. This combination of changes increases the activity over gentamicin.[13]

f. 5-Episisomicin

A further change in the molecule of sisomicin gives the isomer called 5-episisomicin. This product is a semisynthetic variation of sisomicin where the C_5 hydroxyl group has been epimerized.



5-Episisomicin
Sch 22591

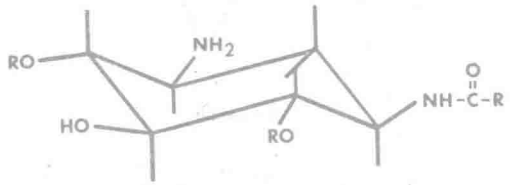
FIGURE 16.

The resulting product has a spectrum and potency similar to gentamicin with an increased potency against certain species of organisms. Epimerization of the sisomicin hydroxyl at C_5 produces a molecule that is resistant to enzymatic inactivation. Even though the hydroxyl group at C_5 is not a site of enzymatic attack, the change in the orientation of this hydroxyl group protects the molecule against enzymatic attack upon other sites in the molecule.[14]

2. Derivatives of 4,6-Disubstituted Aminocyclitols

a. Amikacin

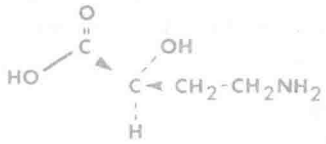
The most important modification that has been made on the aminocyclitol ring is the substitution on the amine on the C_1 carbon atom.



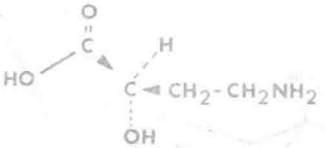
Acylated Aminocyclitol

FIGURE 17.

Amikacin is basically a kanamycin A structure (see Figure 9) that has been synthetically modified by acylation of the amine at C_1 with 2-hydroxy-4-aminobutyric acid (HABA). This increases the activity markedly. It has been proposed that this amine group at C_1 is active in the binding of the antibiotic to inactivating enzymes, and the HABA hinders this binding.[15] In addition, the stereochemistry of this acid (HABA) is quite important. Acylation of the aminocyclitol with the S isomer of HABA gives a product that is four times more potent than acylation with the R isomer.



S Isomer of HABA



R Isomer of HABA

Absolute Configurations of HABA

FIGURE 18.