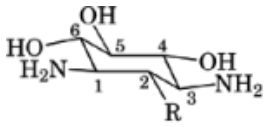
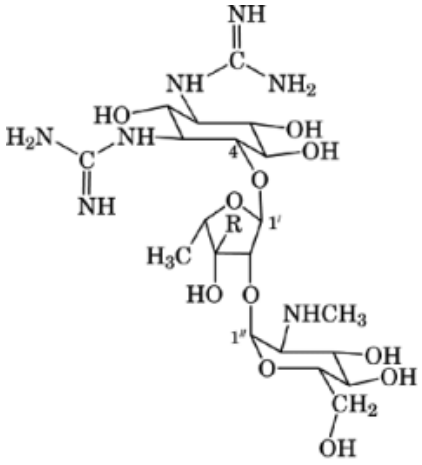
*Kirk-Othmer Encyclopedia of Chemical Technology.*


## AMINOGLYCOSIDES

The term *aminoglycoside* is commonly used to refer to members of the class of antibacterial antibiotics, the structures of which are derived from D-streptamine [488-52-8] $C_6H_{14}N_2O_4$ (**1**, R = OH), D-2-deoxystreptamine [2037-48-1] $C_6H_{14}N_2O_3$ (**1**, R = H), or closely related compounds. The terms *aminocyclitol* and *aminoglycoside-aminocyclitol* are also sometimes used to identify this group of compounds.



(**1**)



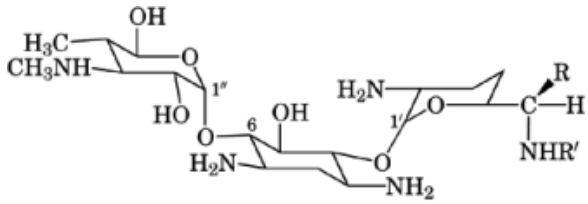
(**2**)

Historically, the first example of an aminoglycoside antibiotic is generally considered to be streptomycin [57-92-1] $C_2H_{39}N_7O_{12}$ (**2**, R = CHO), or streptomycin sulfate [3810-74-0] (chemical name: *O*-2-deoxy-2-(methylamino)-$\alpha$-L-glucopyranosyl-(1→2)-*O*-5-deoxy-3-*C*-formyl-$\alpha$-L-lyxofuranosyl-(1→4)-*N,N′*-bis(aminoiminomethyl)-L-streptamine) isolated in 1944 from a strain of *Streptomyces griseus* (1–4). This discovery, a milestone in the history of antibacterial chemotherapy (5), was the starting point for research and development activities that continue to be important in the management of bacterial infectious disease.

## 1. Aminoglycosides in Medical Usage

In 1991 the following aminoglycosides were most important in medical practice. Clinical experience is most extensive for the first four.

(1) Gentamicin [1403-66-3] or gentamicin sulfate [1405-41-0], is a mixture of gentamicin $C_1$ [25876-10-2] $C_{21}H_{43}N_5O_7$ (**3**, R = R′ = $CH_3$), gentamicin $C_2$ [25876-11-3] $C_{20}H_{41}N_5O_7$ (**3**, R = $CH_3$, R′ = H), and gentamicin $C_{1a}$ [26098-04-4] $C_{19}H_{39}N_5O_7$ (**3**, R = R′ = H) isolated from *Micromonospora purpurea* and related species (6–9). Note that compounds obtained from *Micromonospora* species are given names ending in -micin; those isolated from *Streptomyces* end in -mycin. The chemical name for gentamicin $C_{1a}$ is *O*-3-deoxy-4-*C*-methyl-3-(methylamino)-$\beta$-L-arabinopyranosyl-(1→6)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy-$\alpha$-D-*erthryo*-hexopyranosyl-(1→4)]-2-deoxy-D-streptamine.



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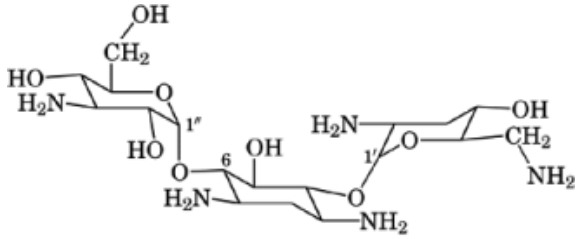
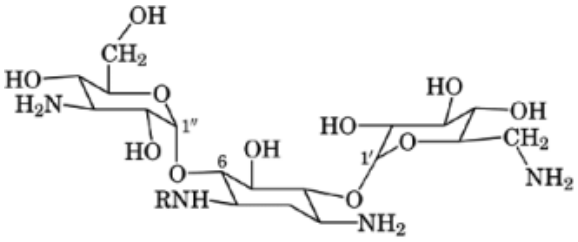


(**4**)

(2) Tobramycin [32986-56-4] $C_{18}H_{37}N_5O_9$, or tobramycin sulfate [79645-27-5], also called nebramycin factor 6, (**4**) (10–16), was isolated from *Streptomyces tenebrarius* and has the chemical name *O*-3-amino-3-deoxy-$\alpha$-D-glucopyranosyl-(1→6)-*O*-[2,6-diamino-2,3,6-trideoxy-$\alpha$-D-*ribo*-hexopyranosyl-(1→4)]-2-deoxy-D-streptamine.

(3) Amikacin [37517-28-5] $C_{22}H_{43}N_5O_{13}$, or amikacin sulfate [39831-55-5] (**5**, R = (*S*)-$COCHOHCH_2CH_2NH_2$) is a semisynthetic derivative (17) of kanamycin A [59-01-8] $C_{18}H_{36}N_4O_{11}$ (**5**, R = H) which is produced by *Streptomyces kanamyceticus* (18–22). Amikacin has the chemical name (*S*)-*O*-3-amino-3-deoxy-$\alpha$-D-glucopyranosyl-(1→6)-*O*-[6-amino-6-deoxy-$\alpha$-D-glucopyranosyl-(1→4)-$N^1$-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-D-streptamine.



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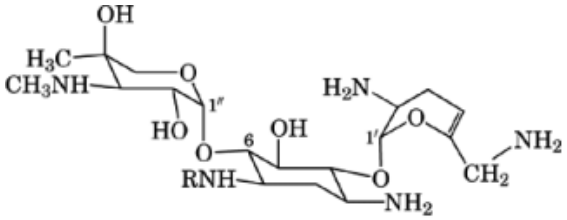
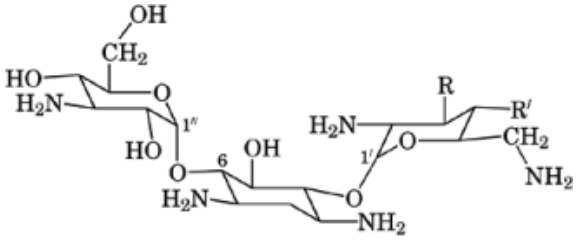


(**6**)

(4) Netilmicin [56391-56-1] $C_{21}H_{41}N_5O_7$, or netilimicin sulfate [56391-57-2], (**6**, R = $CH_2CH_3$) is a semisynthetic derivative (23) of sisomicin [32385-11-8] $C_{19}H_{37}N_5O_7$, (**6**, R = H). Sisomicin is produced by *Micromonospora inyoesis* (24–26). Netilmicin has the chemical name *O*-3-deoxy-4-*C*-methyl-3-(methylamino)-$\beta$-L-arabinopyranosyl-(1→6)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy-$\alpha$-D-*glycero*-hex-4-enopyranosyl-(1→4)]-2-deoxy-$N^1$-ethyl-D-streptamine.

(5) Dibekacin [34493-98-6], $C_{18}H_{37}N_5O_8$, (**7**, R = R′ = H), chemical name *O*-3-amino-3-deoxy-$\alpha$-D-glucopyranosyl-(1→6)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy-$\alpha$-D-*erythro*-hexopyranosyl-(1→4)]-2-deoxy-D-streptamine, is a semisynthetic derivative (27, 28) of kanamycin B [4696-78-8] $C_{18}H_{37}N_5O_{10}$ (**7**, R = R′ = OH) (*O*-3-amino-3-deoxy-$\alpha$-D-glucopyranosyl-(1→6)-*O*-[2,6-diamino-2,6-dideoxy-$\alpha$-D-glucopyranosyl-(1→4)]-2-deoxy-D-streptamine) (29, 30).



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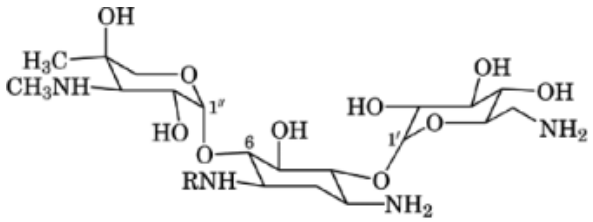
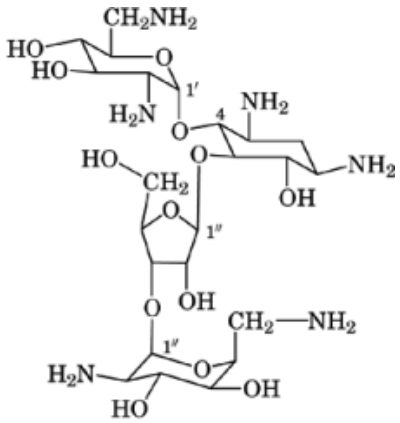


(**8**)

(6) Isepamicin [58152-03-7], $C_{22}H_{43}N_5O_{12}$, (**8**, R = (*S*)-$COCHOHCH_2NH_2$)) ((*S*)-*O*-6-amino-6-deoxy-$\alpha$-D-glucopyranosyl-(1→4)-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-$\beta$-L-arabinopyranosyl-(1→6)]-$N^1$-(3-amino-2-hydroxy-1-oxopropyl)-2-deoxy-D-streptamine), which was introduced in 1988, is a semisynthetic derivative (31) of gentamicin B [36889-15-3] $C_{19}H_{38}N_4O_{10}$ (**8**, R = H) (32).

(7) Neomycin [1404-04-1] (33) or neomycin sulfate [1405-10-3], isolated from *Streptomyces fradiae* (34–36), is sometimes used for gut sterilization and other nonsystemic applications. Neomycin is a mixture of neomycin B [119-04-0] $C_{23}H_{46}N_6O_{13}$ (**9**) (*O*-2,6-diamino-2,6-dideoxy-$\alpha$-D-glucopyranosyl-(1→4)-*O*-[*O*-2,6-diamino-2,6-dideoxy-$\beta$-L-idopyranosyl-(1→3)-$\beta$-D-ribofuranosyl-(1→5)]-2-deoxy-D-streptamine) and neomycin C [66-86-4] $C_{23}H_{46}N_6O_{13}$. Neomycin C is 5‴-epi-neomycin B. Neomycin B is the main component.



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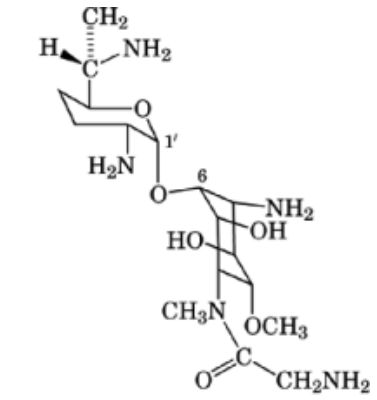

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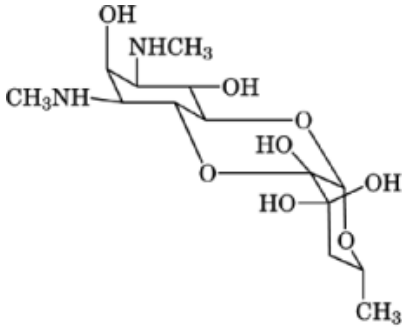


(**11**)

(8) Astromicin [55779-06-1], $C_{17}H_{35}N_5O_6$, (**10**) (4-amino-1-[(aminoacetyl)methylamino]-1,4-dideoxy-3-*O*-(2,6-diamino-2,3,4,6,7-pentadeoxy-$\beta$-L-*lyxo*-heptopyranosyl)-6-*O*-methyl-L-*chiro*-inositol), also known as fortimicin A, is a member of a complex isolated from *Micromonospora olivoasterospora* (37–40). Although astromicin has a structure that is considerably different from those of the other aminoglycosides listed in this section, it is still an aminocyclitol joined to an aminosugar via a glycosidic linkage. Astromicin was introduced in limited markets in 1987.

(9) Spectinomycin [21736-83-4], $C_{14}H_{24}N_2O_7$, or spectinomycin pentahydrate [22189-32-8] (**11**) (decahydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methyl-amino)-4*H*-pyrano[2,3-b][1,4]benzodioxin-4-one) is not strictly an aminoglycoside, but its structure does contain a modified streptamine moiety. The ketone group on position 4 exists as the hydrate. Spectinomycin was isolated from *Streptomyces spectabilis* (41–43). Although it has a fairly broad antibacterial spectrum, medical usage is confined to the treatment of *Neisseria gonorrhoea* infections and it is the agent of choice for resistant strains of that species.

Among the older aminoglycoside derivatives, kanamycin A and sisomicin were, at one time, a significant part of medical practice, but have now been largely replaced by the compounds listed in Table 1. Streptomycin is still used in a few restricted situations.

**Table 1. Annual Worldwide Estimated Sales of Aminoglycosides**

| Aminoglycoside | | | Annual worldwide estimated sales, U.S.$ × $10^6$ | | |
|---|---|---|---|---|---|
| Generic name | Trade name | Company | 1988 | 1989 | 1990 |
| gentamicin | Garamycin and others[a] | Schering-Plough and others[a] | 120 | 130 | 140 |
| tobramycin | Nebcin | Lilly | 170 | 150 | 150 |
| amikacin | Amikin | Bristol-Myers Squibb | 190 | 190 | 200 |
| netilmicin | Netromycin | Schering-Plough | 130 | 130 | 130 |
| dibekacin | Panimycin | Meiji Seika | 60 | 50 | 50 |
| isepamicin | Isepacin | Schering-Plough | 20 | 45 | 45 |
| | Exacin | Toyo Jozo | | | |
| Other aminoglycosides | | | 120 | 95 | 85 |
| *Total* | | | *810* | *790* | *800* |

[a] Gentamicin is off patent, and is currently marketed by several companies.

## 2. Medical and Biological Properties

### 2.1. General Antibacterial Properties

In the clinical control of bacterial infectious disease, the aminoglycosides gentamicin, tobramycin, amikacin, netilmicin, and to a lesser extent, dibekacin and isepamicin are most commonly used for the treatment of serious infections involving aerobic or facultative gram-negative bacilli, especially in the compromised host. This usage is discussed in the literature (44–51).

Overall, these aminoglycosides are approximately equally effective for the clinical treatment of infections involving susceptible strains of *Eschericia coli*, *Klebsiella sp.*, *Enterobacter sp.*, *Citrobacter sp.*, *Serratia sp.*, *Proteus mirabilis*, *Morganella morganii*, *Proteus vulgaris*, *Proteus rettgeri*, *Providencia stuartii*, *Pseudomonas aeruginosa*, and the gram-positive species *Staphylococcus aureus*. Other gram-positive bacteria, such as *Streptococcus sp.*, and anaerobes are not generally susceptible to aminoglycosides (52–56). There are some differences in the *in vitro* activities of the various aminoglycosides against these species. Tobramycin (**4**) tends to have better *in vitro* activity against *P. aeruginosa* than gentamicin (**3**), but it has been difficult to show that these differences are reflected in clinical performance. There are also differences in potency. Amikacin (**5**, R = (*S*)-$COCHOHCH_2CH_2NH_2$), for example, is generally less potent than the others, but a decreased toxicity allows the dose to be adjusted for comparable efficacy. Thus, especially in the case of the four aminoglycosides for which there is the greatest amount of clinical experience, ie, gentamicin, tobramycin, amikacin, and netilmicin (**6**, R = $CH_2CH_3$), there does not appear to be a significant difference in the outcome of treatment of infections (57) due to sensitive strains of these bacteria.

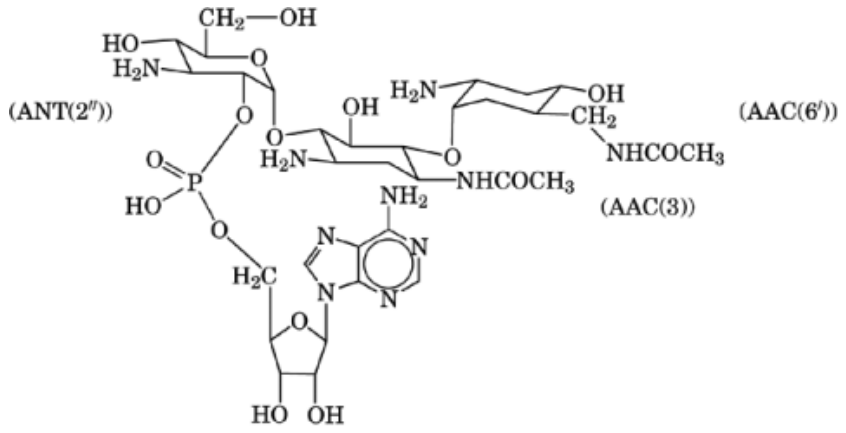
Particular advantages of the aminoglycosides are that, in general, the bactericidal concentration is not significantly different from the growth inhibitory concentration and, furthermore, the bactericidal effect is rapid and concentration dependent (58). In very serious infections such as occur in febrile neutropenic patients or in enterococcal endocarditis, a combination of an aminoglycoside with a $\beta$-lactam antibiotic (see Antibiotics, $\beta$-lactams) or vancomycin (see Antibiotics, glycopeptides) is often used. In addition to extending the spectrum of coverage, such combinations are often found to be synergistic. They have a greater inhibitory effect than would be predicted from additivity alone (59–61). However, under sufficiently concentrated conditions, $\beta$-lactams and aminoglycosides can inactivate each other by acylation of one of the amino groups (62).

### 2.2. Bacterial Resistance Mechanisms

The occurrence of antibiotic resistant bacterial strains is an important medical problem. This is especially true for nosocomial infections (63–65). The incidence and type of resistance are highly variable phenomena that can change with time and location. In some cases, these strains can arise in response to the environmental pressure of aminoglycoside usage. However, the incidence of aminoglycoside resistance overall has remained relatively stable throughout the 1980s and into the 1990s (51). Of the aminoglycosides in current use, amikacin and isepamicin (**8**, R = (*S*)-$COCHOHCH_2NH_2$) are least susceptible to the bacterial resistance mechanisms, netilmicin and dibekacin (**7**, R = R′ = H) are intermediate, and gentamicin and tobramycin are most susceptible (66). Resistance to streptomycin is widespread, and its use is currently confined primarily to infections caused by *Mycobacterium tuberculosis*, *Yersinia pestis*, and *Francisella tularensis*.

Resistance to the antibacterial action of aminoglycosides is mediated primarily by three mechanisms: (*1*) Changes in the bacterial ribosome such that the affinity for the antibiotic is significantly decreased. This mechanism appears to be relatively rare except for streptomycin (67). (*2*) Significant reduction in the rate at which the aminoglycoside passes through the cell wall and cell membrane into the cytoplasm. This phenomenon is presumably responsible for the intrinsic resistance of *Streptococcus sp.* and anaerobic bacteria to the action of aminoglycosides. It may also be an important component of acquired resistance (68). (*3*) Inactivation of the aminoglycoside by plasmid-borne enzymes which catalyze acetylation, phosphorylation, or adenylylation reactions. This is the most common of the resistance mechanisms, and is a significant clinical problem. A large number of aminoglycoside acetyltransferase (AAC), aminoglycoside phosphotransferase (APH), and aminoglycoside nucleotidyltransferase (ANT), also referred to as aminoglycoside adenylyltransferase (AAD), enzymes and related isozymes have been found. These enzymes differ in the substrates on which they operate, their catalytic efficiency, and in the product produced (68–73).

The most clinically significant of the aminoglycoside inactivating enzymes seem to be (74): ANT(2″), an enzyme that catalyzes the transfer of an adenylyl group to the 2″-hydroxy of gentamicin, tobramycin, dibekacin, and kanamycins A and B; AAC(6′)-(various isozymes), enzymes that catalyze the transfer of an acetyl group to the 6′-amino of gentamicin, tobramycin, amikacin, isepamicin, netilmicin, kanamycins A and B, sisomicin, dibekacin, and neomycin; and AAC(3)-(various isozymes), enzymes that catalyze the acetylation of the 3-amino moiety of gentamicin, tobramycin, netilmicin, kanamycins A and B, dibekacin, neomycin, and astromicin. If all three of these enzymes were to operate on tobramycin (**4**), the result would be structure (**12**) (20).




(**12**)

Other enzymes that may play a role clinically are AAC(2′), important in some *Providencia* and *Proteus* species, APH(3′), and APH(3″) (71). Others that have been observed include APH(2″), APH(5″), APH(6), ANT(4′), ANT(3″), and ANT(6). It has been suggested that, for effective resistance, an organism must have both impaired aminoglycoside transport and levels of aminoglycoside inactivating enzymes such that the rate of inactivation in the cytoplasm is greater than the rate of influx (68).

### 2.3. Pharmacokinetics

The aminoglycosides are not reliably absorbed following oral dosing, so they are administered primarily by intravenous infusion or intramuscular injection (75–77). Distribution throughout the vascular and interstitial space occurs fairly rapidly. Because these antibiotics are polycationic and relatively large, biological membranes are not readily crossed, unless transport mechanisms exist as in the kidney proximal tubule cells, and intracellular levels are generally low. Levels in the cerebrospinal fluid (CSF), bronchial secretions, and saliva are also low. Aminoglycoside excretion takes place almost entirely via the kidneys. Most of the compound is eliminated unmetabolized in a relatively rapid beta phase having a half-life of 2–3 h. A small portion, however, is excreted in a slow gamma phase, half-life 35–200 h. Because of the relatively short beta-phase half-life, dosing is usually two or three times per day. Efficient clearance is dependent on glomerular function and, when glomerular filtration rate is reduced because of age or kidney disease, particular care in dosing must be exercised to prevent accumulation of toxic aminoglycoside levels (78). Some studies have shown that, for certain clinical applications, an aminoglycoside can be administered once a day and efficacy is unchanged while toxicity is decreased (79–82). A possible contributor to the success of this strategy is the observation of a post-antibiotic effect (83), in which growth inhibition of some bacterial species continues for a period of time after the serum concentration of the aminoglycoside drops below the presumed inhibitory level.

A novel approach to the modification of aminoglycoside pharmacokinetics is under investigation (84). Administration of gentamicin encapsulated in egg phosphatidylcholine liposomes has been found to lead to a longer half-life and much higher spleen and liver levels for the gentamicin component. This formulation is undergoing clinical study (85).

### 2.4. Toxicology

A primary limiting factor in the clinical use of the aminoglycosides is the potential toxicity. This toxicity prevents the use of significantly increased doses to cover difficult infections. Also, serum aminoglycoside concentrations can reach toxic levels even when normal doses are used because of variation in glomerular filtration efficiency. All the aminoglycosides in medical practice are capable of causing these adverse reactions (51, 57, 77, 86).

The principal aminoglycoside toxicities are neuromuscular paralysis, ototoxicity, and nephrotoxicity. Neuromuscular paralysis is a relatively rare complication resulting from high aminoglycoside concentrations at the neuromuscular junctions following, for example, rapid bolus intravenous injection or peritoneal instillation, rather than the normal intravenous infusion. The mechanism apparently involves an inhibition of both the presynaptic release of acetylcholine and the acetylcholine postsynaptic receptors (51).

Both auditory (cochlear) (high frequency hearing loss), and vestibular (nausea, vertigo) dysfunctions are experienced (87). Whereas the ototoxic responses are not life-threatening, these effects are especially significant because they are often irreversible and cumulative. The incidence is estimated at from 0.5 to 25%. The wide range is partially a reflection of the difficulty in measuring this kind of toxic effect (51). The mechanisms involved in these reactions are not fully understood, but they apparently involve damage to hair cells in the organ of Corti and ampullar cristae, neither of which can regenerate. All of the commonly used aminoglycosides can cause both cochlear and vestibular effects, but amikacin is more likely to cause the cochlear type of toxicity (88, 89) and particularly severe auditory dysfunction has led to the restriction of neomycin use to topical applications. Overall, however, the incidence of clinical ototoxicity seems to be comparable for each of the

different aminoglycosides (51, 57), with the possible exception of a reduced incidence for netilmicin (86, 89, 90). In a comparative study using a guinea pig model, the increasing order of cochlear toxicity was found to be netilmicin, dibekacin, amikacin, tobramycin, gentamicin; the order of vestibular toxicity was amikacin, netilmicin, tobramycin, dibekacin, gentamicin (90).

Estimates of the incidence of nephrotoxicity range from 5 to 25%. In most cases, the observed effects are a mild-to-moderate decrease in glomerular filtration rate accompanied by the urinary excretion of renal tubular enzymes. The effects are usually reversible, and their likelihood is reduced by monitoring serum levels and glomerular filtration rate and adjusting the dosing accordingly. However, the possibility of a serious reaction, particularly in the compromised patient, represents a significant deterrent to aminoglycoside usage. It has been estimated that nephrotoxic reactions add an average of $183 in hospital costs for each patient who receives an aminoglycoside (91). Overall, gentamicin and tobramycin may be somewhat more likely to be nephrotoxic than amikacin and netilmicin (51, 89), but the differences are generally not significant (92). Preliminary experimental evidence in animal models indicate that isepamicin may be less nephrotoxic (93, 94), but clinical evidence is not yet available. Spectinomycin does not have the nephrotoxic and ototoxic liabilities of the aminoglycosides nor does it have the breadth of antibacterial spectrum typical of the aminoglycosides.

Significant progress has been made in recent years toward understanding the mechanisms involved in the nephrotoxic effects of the aminoglycosides (52, 77). The scheme which has evolved can be outlined as follows: (*1*) aminoglycoside in the serum is filtered through the glomerulus into the lumen of the kidney tubule; (*2*) an initial charge–mediated binding of the aminoglycoside to the brush border membrane of the kidney proximal tubule cells is followed by a pinocytotic uptake into those cells, possibly utilizing the basic amino acid transport system (95); (*3*) after uptake, the pinocytotic vesicles fuse with preexisting lysosomes, leading to a rapid and substantial accumulation of aminoglycoside in the lysosomes (96); (*4*) in the lysosome, the aminoglycoside appears to inhibit phospholipases, resulting in the accumulation of phospholipids in the form of myeloid bodies (phosphlipidosis) (97, 98). Extralysosomal effects are also observed, particularly with respect to mitochondrial function (99–101); (*5*) in a step the mechanism of which is unclear, phospholipidosis and the other effects are followed by cell necrosis, then regeneration (102). This may involve destabilization of the lysosomal membrane or interference with membrane recycling processes. The extent of kidney damage can be viewed as a result of competitive rates of cell necrosis and regeneration (97).

A novel approach to the problem of aminoglycoside nephrotoxicity has been to search for compounds that can inhibit toxicity without compromising efficacy. A number of agents have been reported to reduce aminoglycoside toxicity in animal models; the most extensively studied of these is sodium polyaspartate (103–107).

### 2.5. Mechanism of Antibacterial Action

In spite of the fact that the antibacterial activity of the aminoglycosides has been known since the 1940s, the mechanisms involved are still incompletely understood. Numerous reviews have appeared (eg, 108–113) and the sequence of events seems to be as outlined below.

First, the cationic aminoglycoside binds to anionic groups on the bacterial cell surface. This step is both energy-independent and nonspecific. Then, the molecule passes through the cell wall via porins or self-promoted defects in the wall, traverses the periplasmic space, and arrives at the cell membrane. The next step has been termed the energy-dependent phase I and can be inhibited by compounds that block electron transport. According to one model, the aminoglycoside binds to a transporter molecule and, once a threshold electrical potential is reached, is translocated into the cytoplasm with the involvement of the electron-transport chain. Uptake, to the extent that it occurs during this phase, is small. In the energy-dependent phase II, there is an accelerated and irreversible aminoglycoside uptake into the cytoplasm. This step can be inhibited by inhibitors of both electron transport and protein synthesis, and is dependent on an interaction of the aminoglycoside with the ribosomes. One of the several suggested models for this step envisages a cell membrane that becomes

increasing leaky because of the incorporation of faulty proteins resulting from aminoglycoside-induced errors in translation (114, 115). In the cytoplasm, the aminoglycoside binds to the ribosome leading to a misreading of the genetic code (116), and the consequent production of abnormal proteins, and, at higher concentrations, an inhibition of protein synthesis. Cell death, the cause of which is uncertain, follows.

### 2.6. Aminoglycoside Biosynthesis

The biosynthesis of the aminoglycosides has been extensively studied and reviewed (117–119). Perhaps the most interesting aspect is the biosynthesis of 2-deoxystreptamine (**1**, R = H), in which the C-1 and C-6 of a D-glucose molecule become the C-1 and C-2 of 2-deoxystreptamine by way of the intermediate 2-deoxy-*scyllo*-inosose. The details of this conversion are still unclear.

## 3. Structure-Activity Relationships Among Aminoglycoside Derivatives

The aminoglycosides possess properties that make them valuable for the control of bacterial infectious disease, but they also have distinct limitations, especially in the areas of toxicity and susceptibility to bacterial resistance mechanisms. Thus there has been a large amount of research aimed at reducing the limitations while maintaining the advantages generally by introducing modifications into the basic aminoglycoside molecular structure. In general, three approaches have been used to generate novel aminoglycoside structures. (*1*) Search for microorganisms that produce novel structures directly. This approach has resulted in gentamicin and tobramycin. (*2*) Chemically modify structures of molecules available from microorganisms ie, undertake semisynthesis. Netilmicin, amikacin, dibekacin, and isepamicin have resulted from this approach. (*3*) Generate microorganism mutants that require a modifiable exogenous substrate for the biosynthesis of the aminoglycoside. Because of the difficulty of the chemistry, total synthesis (120, 121) has not yet been a major contributor of modified aminoglycosides.

The number of aminoglycoside derivatives reported over the years is very large. Much of the work has been summarized in reviews (120, 122–125). Only the structural subclasses and representative derivatives are discussed here. Some of the structures are given in Table 2.

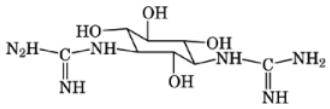
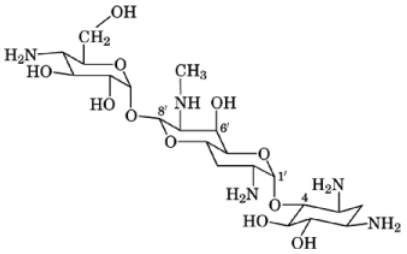
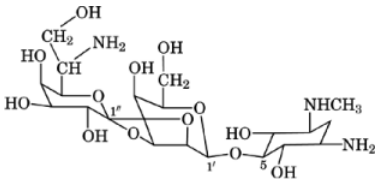
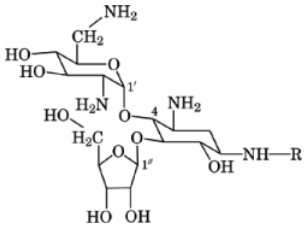
### 3.1. Derivatives of Streptidine

The first aminoglycoside to be isolated was streptomycin (**2**, R = CHO), which is a derivative of streptidine (**13**) shown in Table 2. A number of derivatives have been prepared (126), the most interesting of which was dihydrostreptomycin [128-46-1] $C_{21}H_{41}N_7O_{12}$ (**2**, R = $CH_2OH$), which retained the antimicrobial spectrum of its precursor. This derivative was removed from clinical usage because of a high incidence of ototoxicity. Even minimal modification of the guanidine groups in dihydrostreptomycin led to loss of activity, although a single methyl on the 1-guanidino was tolerated (127). The 3″-deoxy- and 3″-epidihydrostreptomycin derivatives were quite active and resistant to some inactivating reactions (128).

### 3.2. Derivatives Containing a 4-Monosubstituted-2-deoxystreptamine Moiety

Many of these compounds can be viewed as fragments derived from the removal of the *X*-substituent from a 4,*X*-disubstituted-2-deoxystreptamine aminoglycoside, eg, neamine [3947-65-7] $C_{12}H_{26}N_4O_6$ which is derived from neomycin B (**9**) by hydrolysis at the 5-position, paromamine [534-47-4], $C_{12}H_{25}N_3O_7$ derived from paromomycin I or II (discussed below) by hydrolysis at the 5-position, tobramine [34051-04-2] $C_{12}H_{26}N_4O_5$ (nebramine) derived from tobramycin (**4**) by hydrolysis at the 6-position, and gentamine $C_{1a}$ [35025-95-7], $C_{12}H_{26}N_4O_4$, derived from gentamicin $C_{1a}$ (**3**, R = R′ = H) by hydrolysis at the 6-position. Some of these compounds are

**Table 2. Structures Relating to Aminoglycoside Derivatives**

| Name | CAS Registry Number | Molecular formula | Structure number | Structure |
|---|---|---|---|---|
| streptidine | [85-17-6] | $C_8H_{18}N_6O_4$ | (**13**) |  |
| apramycin[a] | [37321-09-8] | $C_{21}H_{41}N_5O_{11}$ | (**14**) |  |
| hygromicin B | [31282-04-9] | $C_{20}H_{37}N_3O_{13}$ | (**15**) |  |
| ribostamycinbutirosin B | [25546-65-0]<br>[34291-03-7] | $C_{17}H_{34}N_4O_{10}$<br>$C_{21}H_{41}N_5O_{12}$ | (**16**, R = H)(**16**, R = (*S*)-$COCHOHCH_2CH_2NH_2$) |  |

[a] Also known as nebramycin factor 2.

found as fermentation products; alternatively, they can be obtained by chemical hydrolysis of the parent antibiotic. In general, however, the antibacterial activity is poor. An exception is apramycin (**14**), isolated from *Streptomyces tenebrarius*, which has respectable antibacterial activity and is resistant to the actions of some aminoglycoside-inactivating enzymes (129, 130). For more details concerning this subclass of derivatives, see references 122 and 125.

### 3.3. Derivatives Containing a 5-Monosubstituted-2-deoxystreptamine Moiety

Few derivatives of this type are known. One is hygromycin B (**15**) isolated from *Streptomyces hygroscopicus* and *Streptomyces eurocidicus* (131–133). The antibacterial activity is poor, but hygromycin B is reported to have anthelmintic activity (see Antiparasitic agents, anthelmintics).

### 3.4. Derivatives Containing a 4,5-Disubstituted-2-deoxystreptamine Moiety

The first of this subclass to be isolated were the neomycins (B (**9**) and C), followed by paromomycin I [7542-37-2] $C_{23}H_{45}N_5O_{14}$, and paromomycin II [51795-47-2] $C_{23}H_{45}N_5O_{14}$. The paromomycins are produced by a *Streptomyces rimosus* strain and have the same structures as neomycins B and C, respectively, except that the 6′-substituent is a hydroxy instead of an amino group (33, 134–136). A closely related compound is lividomycin B [37636-51-4] $C_{23}H_{45}N_5O_{13}$, which has the structure of neomycin B but the 3′-position is unsubstituted, instead of having a hydroxy group, and the 6′-substituent is a hydroxy (137–139). All these derivatives have significant antibacterial activity, but potency is lower than that of gentamicin and all are inactivated by AAC(3). The paromomycins are inactive against *P. aeruginosa* strains.

A related series of aminoglycosides have a structure similar to neomycin B, except that the sugar residue attached to the ribofuranosyl ring at 3″ is missing. The parent compound ribostamycin (**16**, R = H) was isolated from *Streptomyces ribosidificus* (140, 141). A modified version of this molecule, butirosin B (**16**, R = (*S*)-$COCHOHCH_2CH_2NH_2$) was isolated from *Bacillus circulans*. Butirosin B was the first aminoglycoside isolated from a bacterium (142–145) and it was found that, by virtue of the (*S*)-4-amino-2-hydroxybutyryl substituent on the 1-amino group, an expanded antibacterial spectrum and resistance to the inactivating enzymes AAC(3) and APH(3′) had been obtained. This observation indicated that a modification at the 1-position on the molecule could influence enzyme-catalyzed events occurring at the 3- and 3′-positions and ultimately led to the preparation of amikacin. The (*S*)-3-amino-2-hydroxypropionyl substituent was found to have a similar effect, resulting in isepamicin. This work showed that structure manipulation could affect the biological properties of an aminoglycoside in a significantly favorable way, and thus was an important impetus to further structural modifications within the 4,5-disubstituted-2-deoxystreptamine class (122, 125).

### 3.5. Derivatives Containing a 4,6-Disubstituted-2-deoxystreptamine Moiety

Examples of this class are the kanamycin complex, consisting primarily of A (**5**, R = H), B (**7**, R = R′ = OH), and C. Kanamycin C has the same structure as B except that hydroxy replaces the 6′-amino group (146). The members of the nebramycin complex are closely related structurally to the kanamycins (125). The most important are nebramycin factor 6, which is tobramycin (**4**), and nebramycin factor 5, which is kanamycin B (**7**, R = R′ = OH). Kanamycin A was introduced into medical practice and still sees limited use, even though resistance to it is widespread and activity against *P. aeruginosa* strains is poor. Structural modifications of the kanamycins have been extensively investigated (120) and the most notable outcome of this work were the discoveries of amikacin (**5**, R = (*S*)-$COCHOHCH_2CH_2NH_2$) and dibekacin (**7**, R = R′ = H). Many qualitative structure–activity correlations were found from these studies (120, 122, 123).

In general, acylation of any of the 3-, 2′, 6′-, or 3″-amino groups greatly reduces antibacterial activity (147). However, acylation of the 1-amino group with one of a very limited number (148, 149) of acyl groups, most notably, (*S*)-4-amino-2-hydroxybutyryl and (*S*)-3-amino-2-hydroxypropionyl, confers greatly improved resistance to bacterial inactivation reactions catalyzed by APH(3′), ANT(2″), and AAC(3), but not to others such as those of some isozymes of AAC(6′) and ANT(4′). The 1-*N*-(2-aminoethanesulfonyl) derivatives have also been reported to have similar properties (150). Resistance to AAC(6′) was improved somewhat in the formimidoyl and acetimidoyl derivatives of amikacin, but at a cost in potency (151). Interestingly, the

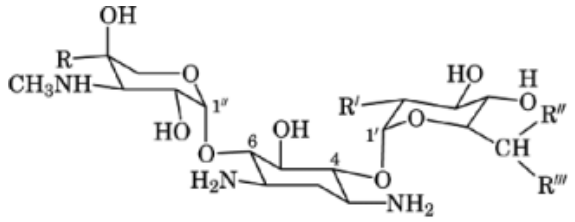
1-*N*-palmitoyl-3″-trifluoroacetyl derivatives of several aminoglycosides have been reported to have antiviral activity (152).

Monoalkylation using small alkyl groups of the 1-, 2′- and 3″-amines tends to reduce potency somewhat, whereas alkylation of the 3-amino group reduces activity considerably (147). 1-*N*-Alkylation, as in the case of 1-*N*-acylation, can lead to resistance to some bacterial resistance reactions, eg, 1-*N*-ethyl kanamycin A (153) has some resistance to APH(3′), ANT(2″), and AAC(3). Butakacin [59733-86-7] $C_{22}H_{45}N_5O_{12}$, the 1-*N*-(*S*)-2-hydroxy-4-aminobutyl derivative of kanamycin A (154), has antimicrobial properties similar to amikacin. A similar effect was seen with the 1-*N*-(1,3-dihydroxy-2-propyl) derivative of kanamycin B, propikacin [66887-96-5] $C_{21}H_{43}N_5O_{12}$ (155). Methylation of the 6′-amine reduces susceptibility to AAC(6′) (156).

Removal of the hydroxyl groups from the 3′-, 4′-, 5-, or 6″-positions does not severely compromise antibacterial activity (157) and, in the case of 3′ and 4′, can protect from the action of APH(3′) and ANT(4′). This type of modification is incorporated naturally in tobramycin (**4**) and semisynthetically in dibekacin (**7**, R = R′ = H), resulting in significantly improved activity against *P. aeruginosa*. Perhaps surprisingly, 5,2′,3′,4′,4″,6″-hexadeoxykanamycin A is fully active, and even the 5,2′,3′,4′,2″,4″,6″-heptadeoxy derivative retains some activity (158). The 2″-hydroxy appears to be the most important for activity (159, 160). Removal of the 6′-hydroxy from kanamycin C, however, is detrimental (161) and the introduction of a 3′-fluoro in place of the 3′-hydroxy increases activity somewhat (162). Removal or epimerization of the 5-hydroxy of kanamycin B reduces antibacterial potency somewhat (163). When the 6″-hydroxy of kanamycin B has a carbamoyl group, the resulting derivative is the naturally occurring (*S. tenebrarius*) nebramycin factor 4 which has significant activity (164). In amikacin, replacement of the 6″-hydroxy with a fluorine decreases activity somewhat (165).

The 1-epi analogue of tobramycin (**4**) was slightly less active than the parent, but the 3-epi was almost inactive (166). Epimerization at the 1-position had a more detrimental effect with kanamycin A (166, 167).

Four members of the gentamicin complex have been mentioned: B (**8**, R = H), $C_1$ (**3**, R = R′ = $CH_3$), $C_{1a}$ (**3**, R = R′ = H), and $C_2$ (**3**, R = $CH_3$, R′ = H). Gentamicin A [13291-74-2] $C_{18}H_{36}N_4O_{10}$ (**17**, R = R″ = H, R′ = $NH_2$, R‴ = OH), gentamicin $X_2$ [36889-17-5] (**17**, R = $CH_3$, R′ = $NH_2$, R″ = H, R‴ = OH), and gentamicin $B_1$ [36889-16-4] $C_{20}H_{40}N_4O_{10}$ (**17**, R = R″ = $CH_3$, R′ = OH, R‴ = $NH_2$) are representative of other members that have been isolated (168).




(**17**)

In addition to being antibacterial agents, although not as good as the $C_1 + C_{1a} + C_2$ combination, these compounds are reported to have antiprotozoal and anthelmintic activity. Many structure–activity correlations can be made within the gentamicin series (120, 122, 123).

1-*N*-Monoalkylation of members of the gentamicin–sisomicin group has been productive. This modification provides resistance to ANT(2″) and AAC(3) (123). Netilmicin (**6**, R = $CH_2CH_3$), which is 1-*N*-ethyl-sisomicin, is the most noteworthy example. Methylation of the 6′-amine confers resistance to some AAC(6′) isozymes, eg, micronomicin [52093-21-7] $C_{20}H_{41}N_5O_7$ (sagamicin, gentamicin $C_{2b}$), the naturally occurring 6′-*N*-methyl derivative of gentamicin $C_{1a}$. The addition of a methyl group to the 6′-carbon, as in verdamicin, has a similar effect. Also, alkylation of the 2′-amino group can provide resistance to AAC(6′) (123).

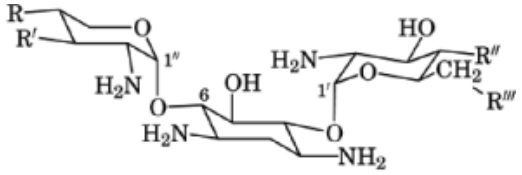
As in the kanamycin series, an $\alpha$-hydroxy-$\omega$-aminoacyl group on the 1-amino moiety of a number of gentamicin–sisomicin analogues confers activity against resistant bacterial strains (169). Isepamicin (**8**, R = (*S*)-$COCHOHCH_2NH_2$) is the primary example of this type of modification. In contrast to the kanamycins, 1-*N*-acetyl sisomicin was resistant to inactivation by AAC(3) and ANT(2″) (170). Other active 1-*N*-acylated derivatives have also been described (171, 172). The naturally occurring 2′-*N*-formylsisomicin is considerably less active overall than sisomicin itself (173). Guanylation of the 1-, 3-, 2′-, or 6′-amines of gentamicin C components generally reduced potency (174); 2′-*N*-guanylgentamicin $C_1$ was less nephrotoxic in rats than gentamicin (175).

Considerable variation at the 2′, 3′, 4′, 5′ and 6′ positions can be tolerated. For example, sisomicin (**6**, R = H) can be considered to be a 4′,5′-dehydro derivative of gentamicin $C_{1a}$, and the related verdamicin [49863-48-1] $C_{20}H_{39}N_5O_7$, isolated from *Micromonospora grisea* (176), is the 4′,5′-dehydro derivative of gentamicin $C_2$ (**3**, R = $CH_3$, R′ = H). The 2′-position can be H, OH, or $NH_2$, as indicated by gentamicins $C_2$ and $B_1$ (169), the 3′-position can be H or OH, the 4′-position can be H or OH, and the 6′-position can carry an OH, $NH_2$, or $NHCH_3$, and may or may not have a C-methyl.

The 3″-methylamino in gentamicin $C_2$ can be changed to amino, ethylamino, *n*-propylamino, or *n*-butylamino with little change in antibacterial activity (177).

1-Deamino- and 1-deamino-1-hydroxy- analogues in the gentamicin series have been obtained by isolation and synthesis (178–180). These derivatives have weak antibacterial activity, although the 1-epi analogues of gentamicin $C_1$, netilmicin, and sisomicin are highly active (180).

The seldomycin complex, represented by seldomycin factor 1 [56276-04-1] $C_{17}H_{34}N_4O_{10}$ (**18**, R = R′ = R″ = R‴ = OH), seldomycin factor 3 [56276-05-2] $C_{17}H_{35}N_5O_9$ (**18**, R = R′ = R″ = OH, R‴ = $NH_2$), and seldomycin factor 5 [56276-26-7] $C_{18}H_{38}N_6O_7$ (**18**, R = $OCH_3$, R′ = R‴ = $NH_2$, R″ = H), were isolated from *Streptomyces hofunensis* (181, 182). Of these, factor 5 has the best antibacterial activity, and is comparable in potency to kanamycin A (**5**, R = H). 3′-Deoxyseldomycin factor 5 (183) was found to be more active than the parent compound, while the 3′-epi analogue was less active (184).

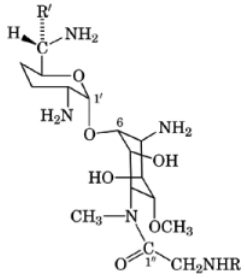
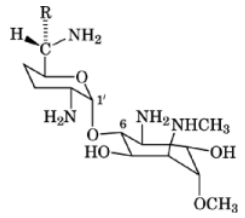



(**18**)

### 3.6. Derivatives Containing a Modified 4,6-Disubstituted-2-deoxystreptamine Moiety

Mutasynthesis is the term used to refer to the process of employing mutated intermediate-requiring organisms to prepare derivatives that would be difficult to obtain by synthetic or semisynthetic means (117, 185–188). Whereas this approach has been used to obtain aminoglycoside analogues, the primary contribution has been as a means to vary the 2-deoxystreptamine portion of the molecule. The most significant compound found by this approach is 5-episisomicin, which is produced by a 2-deoxystreptamine-requiring mutant of *M. inyoensis* (189) when the medium is supplemented by 2-deoxy-5-epistreptamine. Compared to the parent sisomicin (**6**, R = H), this analogue has comparable potency, and is resistant to the effects of ANT(2″), some AAC(3), AAC(2′), and some AAC(6′) (190–193). Other mutasynthetically-produced sisomicin analogues include the 2-hydroxy analogue (from streptamine) and the 5-deoxy analogue (from 2,5-dideoxystreptamine). Similar analogues were obtained in the gentamicin series from a mutated *M. purpurea* strain.

**Table 3. Fortimicin Analogues**

| Name | CAS Registry Number | Molecular formula | Structure number | R | R′ | Structure |
|---|---|---|---|---|---|---|
| fortimicin<br>Afortimicin<br>Cfortimicin<br>Ddactimicin | [62874-51-5]<br>[67330-20-5]<br>[73196-97-1]<br>0.0pt1,67.14478pt | $C_{18}H_{36}N_6O_7$<br>$C_{16}H_{33}N_5O_6$<br>$C_{18}H_{36}N_6O_6$ | (**19**)(**19**)(**19**)<br>0.0pt1,71.6211pt | $CONH_2H$<br>CHNH | $CH_3H$<br>$CH_3$ |  |
| fortimicin<br>Bfortimicin<br>KE | [54783-95-8]<br>[67330-21-6] | $C_{15}H_{32}N_4O_5$<br>$C_{14}H_{30}N_4O_5$ | (**20**)(**20**)<br>0.0pt1,71.6211pt | $CH_3H$ | |  |

### 3.7. Structural Modifications in the Fortimicin Series

The most recent class of aminoglycosides to undergo significant structural modification studies are the fortimicins and related compounds (120, 125, 185). Fortimicin A, astromicin (**10**), has been introduced into medical practice. Its overall antibacterial activity against sensitive strains of susceptible bacteria is similar to that of kanamycin A (**5**, R = H), ie, active against most Enterobacteriaceae and *S. aureus*, but not *P. aeruginosa*. However, fortimicin is resistant to most of the bacterial inactivating enzymes with the exception of some AAC(3) and AAC(6′) isozymes. The 1-amino group is acetylated by AAC(3) (194), and the 6′-amino by AAC(6′) (195). A number of fortimicin analogues have been isolated (196), and some of these are shown in Table 3. The presence of a glycyl residue or a proton on the 4-amino group apparently causes a change in the ring conformation (197).

Fortimicins B and KE show only weak antibacterial activity, and C is somewhat less active than A or D. Other members of the fortimicin complex are described in the literature (198, 199). Two closely related naturally occurring complexes, the istamycins, istamycin A [72503-79-8] $C_{17}H_{35}N_5O_5$, is 2-deoxy-6′-*N*-methylfortimicin D, istamycin B [72523-64-9], $C_{17}H_{35}N_5O_5$, is 1-epi-istamycin A (200, 201), and sporaricins, sporaricin A [68743-79-3], $C_{17}H_{35}N_5O_5$, is 1-epi-2-de-oxyfortimicin A (202), indicate that the 1-epi, 2-deoxy (203–205), and 6′-$NHCH_3$ (206) modifications are consistent with significant antibacterial activity.

Dactimicin (4-amino-1,4-dideoxy-3-*O*-(2,6-diamino-2,3,4,6,7-pentadeoxy-$\beta$-L-*lyxo*-heptopyranosyl)-1-[[[(iminomethyl)amino]acetyl]methylamino]-6-*O*-methyl-L-*chiro*-inositol) and dactimicin sulfate [73245-91-7] were isolated from *Dactylo-sporangium matsuzakiense* (207–209), and have received additional study. The overall antibacterial activity is similar to that of astromicin (**10**) except that dactimicin is less susceptible to the effects of AAC(3) (210–215). Compared to amikacin (**5**, R = (*S*)-$COCHOHCH_2CH_2NH_2$), it is similar except

for being more active against *Serratia* species and less active versus *P. aeruginosa*. There is experimental evidence for a relatively low degree of ototoxicity (211) and nephrotoxicity (216–219).

The biosynthesis of the fortimicins has received some initial study (220–222) and a significant amount of semisynthetic modification has been carried out in this series. 3-*O*-Demethylfortimicin A (223, 224) was found to be significantly more potent than the parent fortmicin A, especially against *P. aeruginosa*, 3-*O*-Demethyl-2-epi-, 2,3-di-epi-, and 3-*O*-demethyl-2,3-di-epi-fortimicin A are somewhat less active than fortimicin A, but the 3-*O*-demethyl-3-epi- analogue is devoid of activity (225, 226). 3-Epi-fortimicin D is poorly active (227), but 3-*O*-demethyl-3-epi-istamycin B is reported to be fully active (228). The 3-amino-3-demethoxy derivative was comparable to the parent (229). In the sporaricin A series, the 3-demethoxy-3-fluoro- and 3-demethoxy-3,3-difluoro- analogues have similar activity to that of the parent (230), as does the 3-*O*-demethyl-3-*O*-(3-amino-2-hydroxy-propyl) derivative (231).

The glycyl, or formimidoylglycyl, residue on the 4-methylamino group is important for good antibacterial potency in the fortimicin series. In a series of acyl and alkyl variations of this residue, only the sarcosyl and $\beta$-alanyl acyl groups (232) and the (*S*)-$CH_2CHOHCH_2CH_2NH_2$ and (*S*)-$CH_2CHOHCH_2CH_2$-$NHCH_3$ alkyl groups were able to come close to the activity of fortimicin A (233). Replacement of the glycyl with a 2-aminoethanesulfonyl residue led to loss of antibacterial activity (234). Furthermore, the methyl group appears to be critical to antibacterial activity; replacement by a hydrogen or an ethyl group eliminated activity (235).

Whereas 2-deoxy-fortimicin A has full antibacterial activity (205), and the 2-deoxy-3-demethoxy- derivative is even more active than fortimicin A (236), the 2,5-dideoxy derivative has poor activity, as do the 2-deoxy-2-chloro and the 2,5-dideoxy-4,5-dehydro derivatives. The 2-amino-3-*O*-demethyl-2-deoxy analogue has quite good activity (229).

The addition of a 3-hydroxypropyl group to the 7′-position of fortimicin A caused a significant reduction in antibacterial activity (237).

## 4. Economic Aspects

Estimated worldwide sales are given in Table 1 for the aminoglycoside derivatives most commonly used in medicine. Although amikacin has somewhat higher sales, gentamicin is by far the most widely used in terms of number of courses of treatment.

Members of the aminoglycoside class of antibacterial antibiotics retain an important role in the control of bacterial infectious disease, especially in the treatment of gram-negative infections in the compromised patient. Semisynthetic modifications of naturally occurring compounds have yielded derivatives with greatly enhanced resistance to bacterial inactivation mechanisms without altering the basic antimicrobial spectrum. The principal factors limiting aminoglycoside usage are nephrotoxicity and ototoxicity. To date, structural modification has not been able to completely dissociate toxicity from antibacterial activity. Current research in the aminoglycoside field is focused on the reduction of toxicity through less frequent dosing, liposomal formulations, and coadministration of toxicity inhibitors.

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