2.7. Units

The production, isolation, and processing of commercial products require careful control for all pharmaceuticals. Because of the extremely high sensitivity and the danger of diminished activity, this consideration has always been particularly important.

The Oxford unit (O. U.) is defined as the amount of penicillin that just prevents the growth of a certain *Staphylococcus aureus* species. Very pure crystalline penicillin salts generally have constant biological activities and the Oxford unit has been replaced by the international unit: 1 mg of pure benzylpenicillin sodium contains 1670 O. U.; the O. U. specific to this salt was declared to be the international unit (I. U., usually abbreviated U). Conversely, 0.6 μg of benzylpenicillin sodium has the activity of 1 I. U. Because the biological activity comes from the penicillin nucleus, the change to another cation leads to a change in activity proportional to the molecular mass. This change can be calculated. The activities of the chief penicillin salts are:

benzylpenicillin sodium	1670 U/mg
benzylpenicillin potassium	1598 U/mg
benzylpenicillin procaine	1011 U/mg
penicillin-2-hydroxyprocaine	1008 U/mg
penicillin-*N*,*N*'-dibenzyl-ethylenediamine	1213 U/mg
penicillin-*N*-ethylpiperidine	1328 U/mg

The mass of 1 U, for benzylpenicillin sodium, 0.6 μg, is extremely small. The following larger units of mass are used in production and trade:

1 Mega U	$= 1 \times 10^6$ I. U.
	= 600 mg benzylpenicillin sodium
	= ca. 1 g benzylpenicillin procaine
1 Mio Mega U	$= 1 \times 10^{12}$ I. U.
	= 600 kg benzylpenicillin sodium
	= ca. 1 t benzylpenicillin procaine

The activities of some older penicillins are given in I. U.

phenoxymethyl-penicillin:	1 mg free acid	1699 U
phenethicillin:	1 mg D-potassium salt	1476 U
	1 mg L-potassium salt	1470 U
penicillin O:	1 mg potassium salt	1612 U

All other penicillins that are used therapeutically can be made very pure and the preparations are dosed and traded in mass units (μg, mg, g, kg).

2.8. Analysis

The practical determination of active substances in penicillins and other antibiotics can be divided among three types of methods [25]:

1) Microbiological testing (see Chap. 7).
2) Determination of the contents by chemical or enzymatic conversion followed by a physical method, such as colorimetry.
3) Purely physical methods, such as UV or IR absorption.

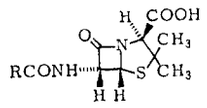
3. Classification of Antibiotics

3.1. β-Lactams

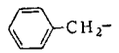
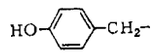
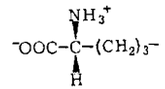
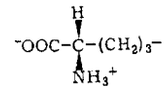
The β-lactam group includes natural penicillins, semisynthetic penicillins, natural cephalosporins, semisyntheric cephalosporins, cephamycins, 1-oxacephems, clavulanic acids, penems, carbapenems, nocardicins, and monobactams.

3.1.1. Natural Penicillins

Penicillin was discovered in 1929 by FLEMING [22]. At first it was obtained as a mixture of several similar compounds, but these were later separated from each other. The β-lactam structure of penicillin was proposed by ABRAHAM and CHAIN and supported by WOODWARD, but it was opposed by those who believed in the alternative thiazolidine-oxazole structure [33]. The β-lactam structure was finally established by an X-ray crystallographic analysis performed by HODGKIN and LOW [34]. Penicillins G, F, K, X, and N, dihydropenicillin F, and isopenicillin N have been isolated from the fermentation broths of *Penicillium notatum* or *P. chrysogenum*. These compounds differ only in the R moiety of structure **1**.



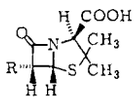
1

Name	R
Penicillin G (Benzylpenicillin) [61-33-6]	
Penicillin F [118-53-6]	$CH_3CH_2CH{=}CHCH_2-$
Dihydropenicillin F [4493-18-9]	$CH_3(CH_2)_4-$
Penicillin K [525-97-3]	$CH_3(CH_2)_6-$
Penicillin X [525-91-7]	
Penicillin N [525-94-0]	
Isopenicillin [58678-43-6]	

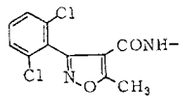
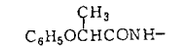
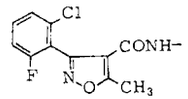
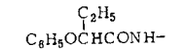
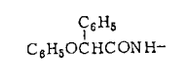
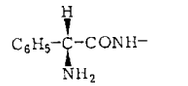
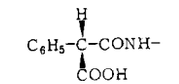
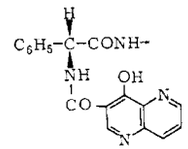
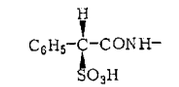
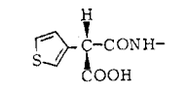
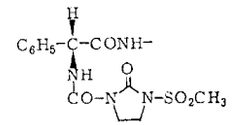
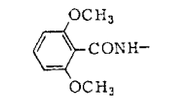
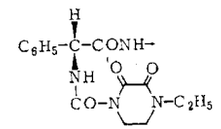
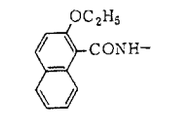
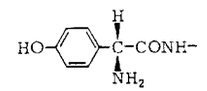
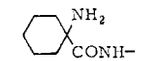
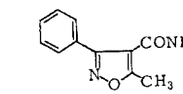
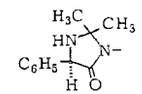
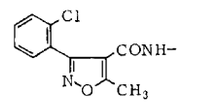
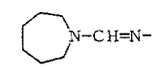
Of these, penicillin G shows good stability, activity, and rate of production by microorganisms. Total synthesis of penicillin V was achieved by SHEEHAN and HENERY-LOGAN in 1957 [35]. Biogenic syntheses of penicillin – cephalosporin antibiotics also have been reported [36], [37].

3.1.2. Semisynthetic Penicillins

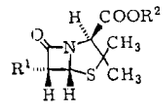
Several limitations have become apparent concerning the antibiotic activity of benzylpenicillin. This drug is not very active against gram-negative bacteria; it is inactivated by penicillinase produced by resistant organisms, and it is not suitable for oral administration because it breaks down under acidic conditions. Penicillins having different side chains have been made by adding appropriate precursors to the fermentation [33]. Various penicillins have been obtained biosynthetically. Among these is phenoxy-methylpenicillin, the first used by oral administration. In contrast, 6-aminopenicillanic acid (6-APA, **2**, R is NH_2) can be prepared by either enzymatic or chemical means. Penicillin amidase or penicillin acylase cleaves the side chain of penicillin to produce 6-APA. The amide bond of the side chain is also efficiently cleaved by treatment with phosphorus pentachloride [25, p. 27]. Penicillins with modified side chains (**2**) have been synthesized from 6-APA via the acyl chloride method, the ethyl or isobutyl chloroformate method, or the dicyclohexylcarbodiimide method in order to improve the antibacterial spectra and increase the stability against penicillinase [33, p. 59]. Ampicillin is active against gram-negative bacteria, and carbenicillin and sulbenicillin are effective against *Pseudomonas*. Ampicillin and amoxicillin are suitable for oral administration. Methicillin, oxacillin, cloxacillin, dicloxacillin, flucloxacillin, and nafcillin are resistant to β-lactamase. Mecillinam has an unusual amidino side chain and is relatively stable and effective against gram-negative bacteria.



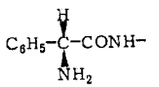
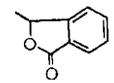
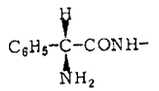
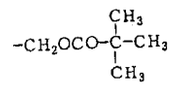
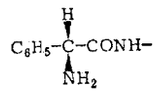
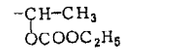
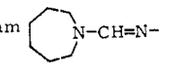
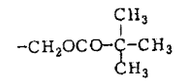
2

Name	R	Name	R
Penicillin V (Phenoxymethylpenicillin) [87-08-1]	$C_6H_5OCH_2CONH-$ (biosynthetic)	Dicloxacillin [3116-76-5]	
Penicillin O [87-09-2]	$CH_2=CHCH_2SCH_2CONH-$		
Phenethicillin [147-55-7]		Flucloxacillin [5250-39-5]	
Propicillin [551-27-9]			
Phenbenicillin [1926-48-3]		Ampicillin [69-53-4]	
Carbenicillin [4697-36-3]		Apalcillin [63469-19-2]	
Sulbenicillin [41744-40-5]			
Ticarcillin [34787-01-4]		Mezlocillin [51481-65-3]	
Methicillin [61-32-5]		Piperacillin [61477-96-1]	
Nafcillin [147-52-4]		Amoxicillin [26787-78-0]	
		Cyclacillin [3485-14-1]	
Oxacillin [66-79-5]		Hetacillin [3511-16-8]	
Cloxacillin [61-72-3]		Mecillinam [32887-01-7]	

Modification of the carboxyl group has been found to be effective for the purpose of oral administration, and penicillin esters (**3**) have been developed [33, p. 59]. These are absorbed and hydrolyzed by the small intestine to release free acids of the parent penicillins.

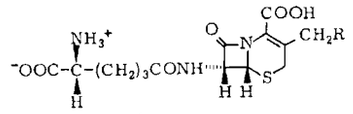


3

Name	R^1	R^2
Talampicillin [47747-56-8]		
Pivampicillin [33817-20-8]		
Bacampicillin [50972-17-3]		
Pivmecillinam [32886-97-8]		

3.1.3. Natural Cephalosporins

The fermentation broth of *Cephalosporium* spp. isolated by BROTZU contained several antibiotics: cephalosporin P, penicillin N, and cephalosporin C. Cephalosporin P was shown to be an acidic steroidal substance. Cephalosporin C was active against gram-negative bacteria, resistant to β-lactamase, and much less toxic than penicillin. The chemical structure of cephalosporin C was determined by ABRAHAM and NEWTON [25]. It consists of 7-aminocephalosporanic acid (7-ACA) and D-α-aminoadipic acid (see **4**). Treatment of cephalosporin C with acetyl esterase yields deacetylcephalosporin C, which exhibits about 20% of the antibacterial activity of cephalosporin C. The allylic acetoxy group of cephalosporin C can be hydrogenated in the presence of palladium–charcoal catalyst to yield deacetoxycephalosporin C, which shows 10% of the activity of the parent cephalosporin C [25]. WOODWARD and his co-workers synthesized cephalosporin C in a fully stereospecific manner [38].



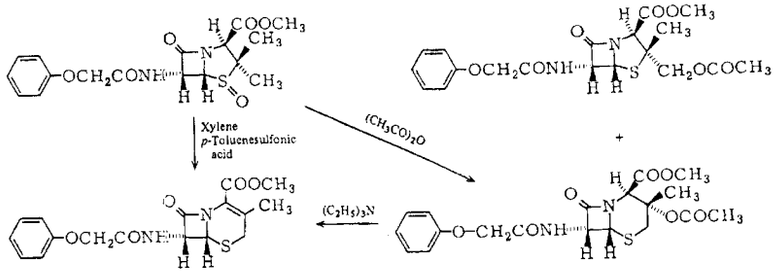
4

Name	R
Cephalosporin C *[61-24-5]*	$OCOCH_3$
Deacetylcephalosporin C *[1476-46-6]*	OH
Deacetoxycephalosporin C *[26924-74-3]*	H

3.1.4. Semisynthetic Cephalosporins

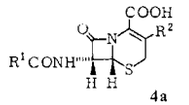
Because the antibacterial activity of cephalosporin C itself is relatively low, the development of a more active derivative is desirable. The phosphorus pentachloride method has been applied to the cephalosporin system to produce 7-aminocephalosporanic acid (7-ACA) in high yield [25, p. 27]. The 3′-acetoxy group of cephalosporin is easily replaced by various nucleophiles [25, p. 134]. Modification of the 7-amino group and the 3′ group make possible the various cephalosporin derivatives **4a** [33, p. 59]. Cephaloridine, cefazolin, and cefamandole are active against gram-negative bacteria. Cefuroxime, cefotaxime, and ceftizoxime have a methoxyimino group and a 2-aminothiazole ring in common and are resistant to β-lactamase. Cefoperazone is particularly active against *Pseudomonas*. All of these are used by injection. On the other hand, several cephalosporins are used only by oral administration. These include cephalexin, cephaloglycin, cefradine, cefadroxil, cefaclor, cefroxadine, and cefatrizine.

Cephalosporins are also obtainable via the ring expansion reaction of penicillin sulfoxide first devised by MORIN [25, p. 183]. Thus, cephalexin is produced by chemical conversion of phenoxymethylpenicillin or benzylpenicillin.

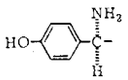
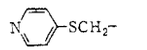
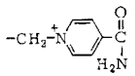
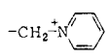
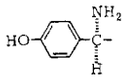
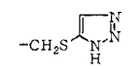


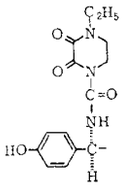
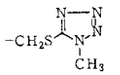
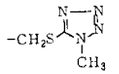
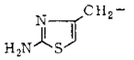
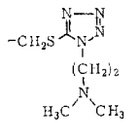
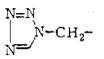
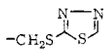
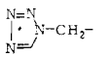
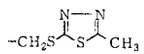
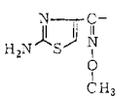
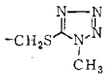
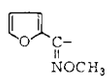
3.1.5. Cephamycins

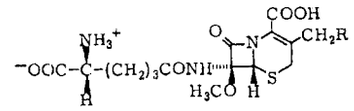
Substances similar to cephalosporin C were found among the products of various streptomycetes and were characterized by the presence of a 7α-methoxy group. They are named cephamycins after their cephem skeleton (see **5**) and their production by streptomycetes [39], [29, vol. 1, p. 199]. They are strongly resistant to β-lactamase and effective against gram-negative bacteria and bacteria that have acquired resistance to penicillins and cephalosporins. Semisynthetic cephamycins (**5a**) with improved activities are obtained by chemical transformations.



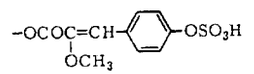
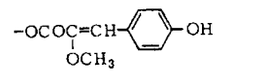
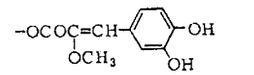
4a

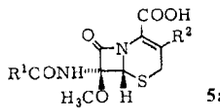
Name	R^1	R^2
Cephalexin [15686-71-2]		$-CH_3$
Cefaclor [53994-73-3]	"	$-Cl$
Cephaloglycin [3577-01-3]	"	$-CH_2OCOCH_3$
Cephradine [38821-53-3]		$-CH_3$
Cefroxadine [51762-05-1]	"	$-OCH_3$
Cefadroxil [50370-12-2]		$-CH_3$
Cephapirin [21593-23-7]		$-CH_2OCOCH_3$
Cephalothin [153-61-7]		$-CH_2OCOCH_3$
Cephacetrile [10206-21-0]	$N{\equiv}CCH_2-$	$-CH_2OCOCH_3$
Cefsulodin [62587-73-9]		
Cephaloridine [50-59-9]		
Cefatrizine [51627-14-6]		

Name	R^1	R^2
Cefoperazone [62893-19-0]		
Cefamandole [34444-01-4]		
Cefotiam [61622-34-2]		
Ceftezole [26973-24-0]		
Cefazolin [25953-19-9]		
Cefmenoxime [65085-01-0]		
Ceftizoxime [68401-81-0]	"	$-H$
Cefotaxime [63527-52-6]	"	$-CH_2OCOCH_3$
Cefuroxime [55268-75-2]		$-CH_2OCONH_2$

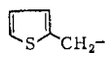
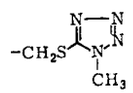
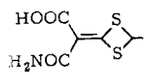
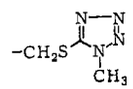


5

Name	R	Producing organism
7 α-Methoxy-cephalosporin C [32178-82-8]	$-OCOCH_3$	*Streptomyces lipmannii* *St. lactamdurans*
Cephamycin C [34279-51-1]	$-OCONH_2$	*St. clavuligerus* *St. lactamdurans* *St. jumonjiensis*
Cephamycin A [34279-78-2]		*St. griseus* *St. chartreusis* *St. cinnamonensis* *St. fimbriatus*
Cephamycin B [34279-77-1]		*St. halstedii* *St. rochei* *St. viridochromogenes*
C-2801X [62851-50-7]		*St. heteromorphous* *St. panagensis*

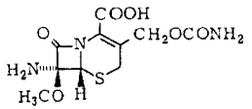


5a

Name	R^1	R^2
Cefoxitin [35607-66-0]		$-CH_2OCONH_2$
Cefmetazole [56796-20-4]	$N{\equiv}CCH_2SCH_2-$	
Cefotetan [69712-56-7]		

Cefoxitin, synthesized from cephamycin C, is particularly active against various gram-negative bacteria and stable to β-lactamase. Cefmetazole, produced from 7-ACA, has almost the same antibacterial spectrum as cefoxitin and maintains its high concentration in blood. Cefotetan, recently under development, is reported to be more active than cefoxitin against gram-negative bacteria (for structures see p. 1034).

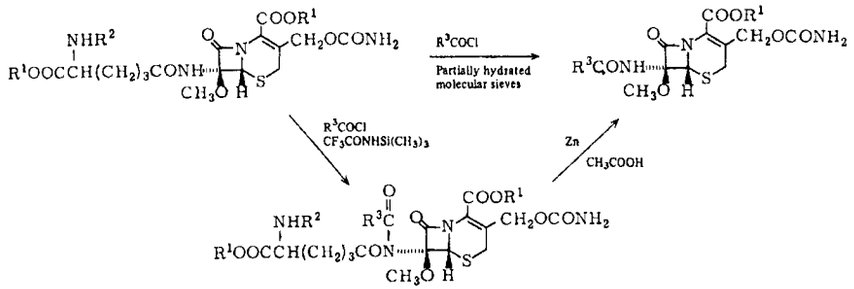
Chemical modification of cephamycins requires special devices for the following reasons. 7-Aminocephamycinoic acid (7-ACMA; **6**), which corresponds to the 7-ACA of cephalosporins, is not easily isolated because of its instability.



6

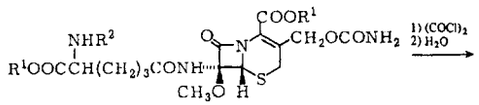
7-Aminocephamycinoic acid
(7-ACMA)
[*62041-14-9*]

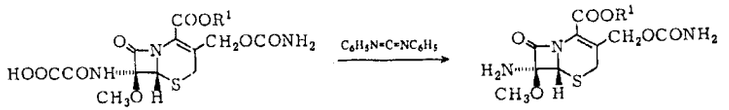
It has methoxy and amino groups on the same carbon atom of the β-lactam ring and the elimination of the protonated amino group is quite facile, because of the electron-donating nature of the methoxy group. Moreover, the usual phosphorus pentachloride method cannot be applied to the side chain cleavage of cephamycin C because a strong N–P bond is formed by the reaction of the carbamate moiety of cephamycin C with phosphorus pentachloride [40]. Instead, exchange of the α-aminoadipoyl side chain for another acyl group is achieved by treating the fully protected cephamycin C with the appropriate acyl chloride in the presence of a neutral acid scavenger. This is followed by the simultaneous removal of the amino protective group and the α-aminoadipoyl group [41]. The side chain transformation is also effected using an acyl chloride and partially hydrated molecular sieves [42].



where R^1 = $-CH_2OCH_3$, $-CH(C_6H_5)_2$
R^2 = $-CO_2CH_2CCl_3$, $-SO_2C_6H_4CH_3$
R^3 = $-CH_2-C_6H_5$, $-CH_2S-C_6H_5$, $-CH_2-$thienyl, $-CH_2-$furyl

Chemical conversion of cephamycin into 7-ACMA ester has been reported [43].

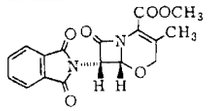
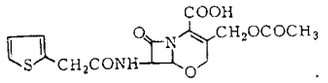
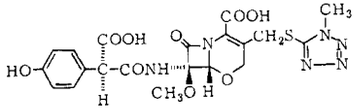


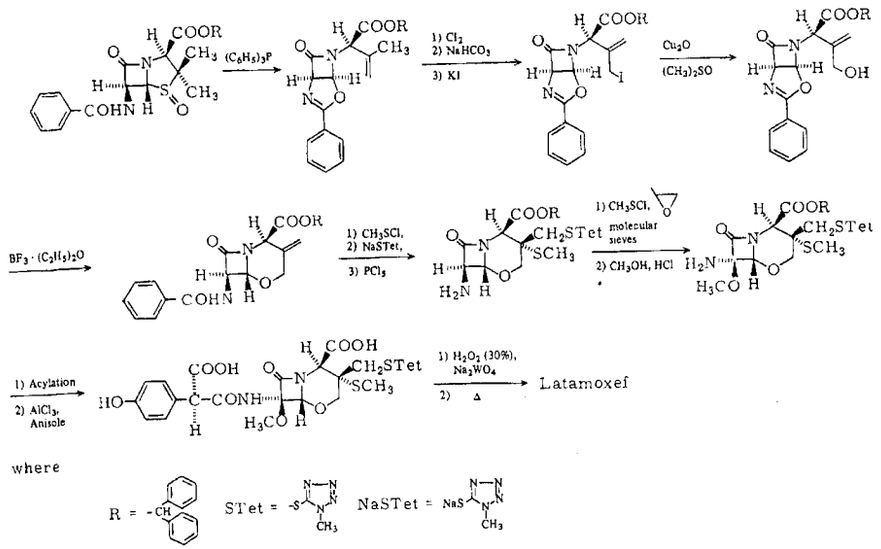


where R^1 = $-CH(C_6H_5)_2$
R^2 = $-COOCH_2CCl_3$

3.1.6. 1-Oxacephems

In addition to the modification of the side chains of natural β-lactam antibiotics, totally or partially synthetic nuclear analogs of penicillins and cephalosporins have been explored extensively [28], [33, p. 59]. In 1974 WOLFE reported the first 1-oxacephem (**7**) derived from penicillin, but its antibacterial activity remains unknown because the amino and carboxy protective groups have not been removed. Racemic 1-oxacephalothin (**8**), synthesized by CHRISTENSEN and his co-workers in the same year, was found to be antibacterially active, suggesting that the sulfur atom is not always necessary for the expression of antibiotic activity. Racemic 1-oxacefamandole is twice as active as cefamandole and the activity of optically active 1-oxacephalothin (**8**) is four to eight times as high as that of cephalothin. NAGATA and his co-workers discovered latamoxef (**9**) (moxalactam, 6059-S), which exhibits strong activity against pathogenic anaerobes, such as *Bacteroides fragilis*, as well as gram-negative bacteria, including *Pseudomonas* [29, vol. 2, p. 1]. It is completely stable against various β-lactamases and has low toxicity. A high plasma-peak level and long duration are maintained. Latamoxef is a nuclear analog of cephamycin that has a 2-(4-hydroxyphenyl)malonylamino side chain and a 1-methyltetrazolylthio moiety; it is produced on an industrial scale by a totally chemical process starting with *epi*-penicillin *S*-oxide [44], [45] .

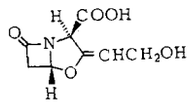
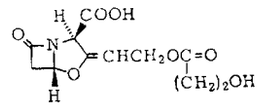
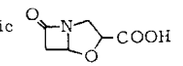
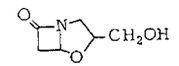
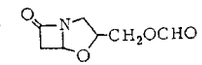
Name	Structure
Methyl (6*S*,7*S*)-3-methyl-8-oxo-7-phthalimido-5-oxa-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate [*54997-17-0*]	 **7**
1-Oxacephalothin [*54214-83-4*]	 **8**
Latamoxef (Moxalactam, 6059-S) [*64952-97-2*]	 **9**



3.1.7. Clavulanic Acids

In the course of screening the substances inhibiting β-lactamase, which is responsible for bacterial resistance to penicillins and cephalosporins, a potent β-lactamase inhibitor, clavulanic acid, was isolated from *Streptomyces clavuligerus* [46]. The antibiotic activity of clavulanic acid is not strong, but it has a broad antibacterial spectrum. Instead, it is effective synergistically when used with β-lactamase-sensitive penicillins and cephalosporins against β-lactamase-producing organisms. Clavulanic acid is characterized by its 1-oxadethiapenam ring system and lack of the side chain at position 6.

Several congeners of clavulanic acid have been isolated [27], [29, vol. 2, p. 361], [47]. Clavam-2-carboxylic acid, 2-hydroxymethylclavam, and 2-formyloxymethylclavam exhibit antifungal activity [48].

Name	Structure
Clavulanic acid [*58001-44-8*]	
ß-Hydroxypropionyl clavulanic acid [*64675-12-3*]	
Clavam-2-carboxylic acid [*71657-61-9*]	
2-Hydroxymethyl-clavam [*66036-39-3*]	
2-Formyloxymethyl-clavam [*66036-40-6*]	

3.1.8. Penems

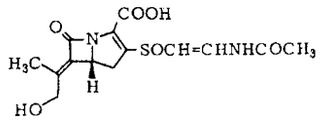
The penem ring system has not been found in nature; it has been designed artificially by WOODWARD [26, p. 167], [28], [29, vol. 2, p. 315]. That the antibacterial activity of β-lactam antibiotics is based on their ability to acylate enzymes is widely accepted. In penicillins, the rigid, nonplanar bicyclic system enhances the reactivity of the β-lactam ring by diminishing the delocalization of the unshared electron pair of the amide nitrogen onto the adjacent carbonyl group. On the other hand, in cephalosporins, where the β-lactam nitrogen is bonded almost planar, the double bond of the six-membered ring interacts with the unshared electrons of the β-lactam nitrogen, diminishing the delocalization to the amide carbonyl. Therefore, the β-lactam ring of cephalosporins is cleaved easily. Penems combine the two structural elements, the five-membered ring and the double bond. 6-Acylaminopenem-3-carboxylic acids (**10**), 6-unsubstituted penem-3-carboxylic acids (**11**), and 6-alkylpenem-3-carboxylic acids (**12**) have been synthesized. The β-lactam moiety with two asymmetric centers derives from penicillin, and the five-membered ring fused with it is formed by the intramolecular Wittig reaction [29, vol. 2, p. 315]. Various 2-substituents, such as H, CH_3, C_2H_5, $CH_2C_6H_5$, and $SCH_2CH_2NHCOCH_3$, have been introduced. Although the

activity of compound **10** with R = CH_3 was disappointing, presumably because of its low stability, 6-unsubstituted penems (**11**) exhibit powerful antibiotic activity [49]. 6-Monoalkylpenems (**12**) show interesting activity in general. The penems having bulky substituents at C-6 are biologically inactive because of the low reactivity of their β-lactam rings.

Name	Structure
6-Acylaminopenem-3-carboxylic acid	 **10**
Penem-3-carboxylic acid	 **11**
6-Alkylpenem-3-carboxylic acid	**12**

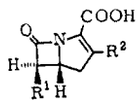
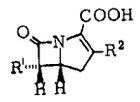
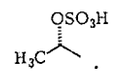
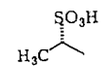
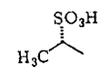
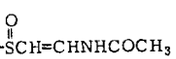
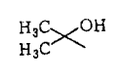
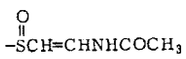
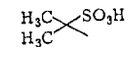
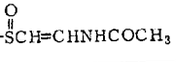
3.1.9. Carbapenems

Cabapenems are a family of antibiotics having the 1-azabicyclo[3.2.0]hept-2-ene system [27], [29, vol. 2, p. 227]. The first carbapenem antibiotic, thienamycin, was discovered at Merck in 1976 among the fermentation products of *Streptomyces cattleya* [50]. Antibiotics of this type have been isolated one after another in the search for inhibitors of bacterial cell wall synthesis and β-lactamase. From the fermentation broth of *Streptomyces olivaceus*, the Beecham group isolated olivanic acids MM4550, MM13902, MM17880, MM22380, MM22381, MM22382, and MM22383 [51]–[54]. Epithienamycin A, B, C, D, E, and F were found by the Merck group [55]–[58]. Some of olivanic acids and epithienamycins are identical. Olivanic acid MM4550 is identical to MC696-SY2-A found by UMEZAWA as a product of *Streptomyces fulvoviridis* [59]. The antibiotics designated PS-5, –6, and –7 were isolated by Sanraku-Ocean in collaboration with Panlabs from *Streptomyces cremeus*, subsp. *auratilis* A271 [60]–[63]. Carpetimycin A and B, reported by the Kowa Company, are products of *Streptomyces* spp. [64], [65]. Asparenomycin A was isolated by the Shionogi research group from *Streptomyces tokunonensis* and *Streptomyces argenteolus* [66].



Asparenomycin
[76466-24-5]

Carbapenems are classified into three classes according to the mode of substitution on the β-lactam ring, that is, *trans*-carbapenems (thienamycin, epithienamycins C and D, PS-5, F-6, and F-7), *cis*-carbapenems (epithienamycin A, B, E, and F, MC696-SY2-A, carpetimycin A and B), and ene-carbapenems (asparenomycin A, B, and C). The 5*R* configuration seems significant for biological activity. The instability of the carbapenems and low broth titer cause difficulties in the determination of the structure.

Structure	Name	R^1	R^2
	Thienamycin [59995-64-1]		$-SCH_2CH_2NH_2$
	Epithienamycin C Olivanic acid MM 22381 [63599-16-6]		$-SCH_2CH_2NHCOCH_3$
	Epithienamycin D Olivanic acid MM 22383 [65322-98-7]		$-SCH{=}CHNHCOCH_3$
	PS-5 [78856-77-6]	CH_3CH_2-	$-SCH_2CH_2NHCOCH_3$
	PS-6 [72615-19-1]	$(CH_3)_2CH-$	$-SCH_2CH_2NHCOCH_3$
	PS-7 [72615-18-0]	CH_3CH_2-	$-SCH{=}CHNHCOCH_3$
	Epithienamycin A Olivanic acid MM 22380 [63582-78-5]		$-SCH_2CH_2NHCOCH_3$
	Epithienamycin B Olivanic acid MM 22382 [65376-20-7]		$-SCH{=}CHNHCOCH_3$
	Epithienamycin E Olivanic acid MM 13902 [79057-46-8]		$-SCH{=}CHNHCOCH_3$
	Epithienamycin F Olivanic acid MM 17880 [79057-45-7]		$-SCH_2CH_2NHCOCH_3$
	Olivanic acid MM 4550 MC696-SY2-A [76985-32-5]		
	Carpetimycin A [76025-73-5]		
	Carpetimycin B [76094-36-5]		

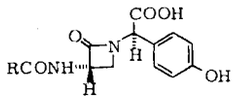
Thienamycin is active against a wide range of gram-positive and gram-negative bacteria, including the ones resistant to conventional β-lactam antibiotics. Carpetimycins and asparenomycin are also effective against resistant bacteria.

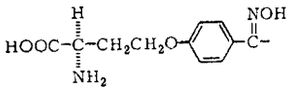
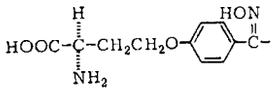
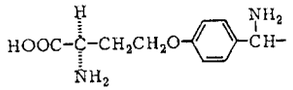
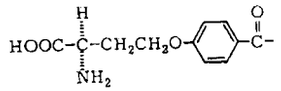
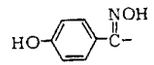
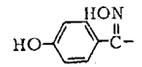
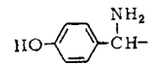
Chemical modifications and a great deal of synthetic study of carbapenems have been undertaken to improve the stability of the carbapenem skeleton and compensate for the low productivity of the microbes. This is one of the most important fields of antibiotics [67]–[80], [69, p. 1142].

Naturally occurring carbapenems have several functional groups that have been subjected to chemical modifications to improve their stability and antibacterial potency [54]. The aminoethylthio side chain plays an important role in extending the antibiotic activity, especially the antipseudomonal activity, and is also thought to be a cause of the instability of carbapenems, presumably by intramolecular aminolysis of the β-lactam ring. Derivatives of the aminoethylthio group, carboxyl group, and hydroxyethyl side chain are being sought.

3.1.10. Nocardicins

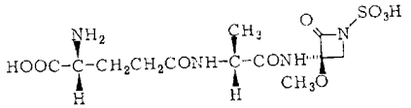
A mutant strain of *Escherichia coli* showing specific supersensitivity to β-lactam antibiotics has been developed at the Fujisawa Research Laboratories and used to isolate nocardicins from *Nocardia uniformis* by a screening procedure [81]. The nocardicin structure has been elucidated by spectroscopic analysis and chemical degradation. The noncardicins are monocyclic β-lactam antibiotics [27], [29, vol. 2, p. 165], [47, p. 281]. Several congeners differing in the side chains have been isolated. Among them, significant activity is exhibited only by nocardicin A, which is active against gram-negative bacteria, especially *Pseudomonas aeruginosa*, *Proteus*, and *Neisseria*, but inactive against gram-positive bacteria.



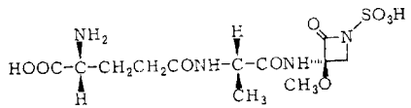
Name	R
Nocardicin A [39391-39-4]	
Nocardicin B [60134-71-6]	
Nocardicin C [59511-12-5]	
Nocardicin D [61425-17-0]	
Nocardicin E [63555-59-9]	
Nocardicin F [63598-46-9]	
Nocardicin G [65309-11-7]	

3.1.11. Monobactams

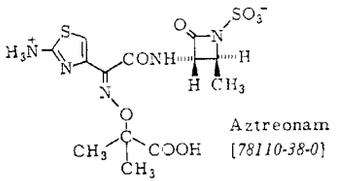
Sulfazecin was isolated in 1981 by the Takeda group as a product of *Pseudomonas acidophila* by screening using organisms highly sensitive to β-lactams [82]. The structure was shown to be a monocyclic β-lactam. *Isosulfazecin*, a diastereomer of sulfazecin, also was isolated by the same group. In the same year, the Squibb group reported on a group of monocyclic β-lactams produced by *Agrobacterium*, *Chromobacterium*, and *Gluconobacter* [83]. A compound (SQ 26 445) identical to sulfazecin was included. Sykes proposed the name "monobactam" for compounds characterized by the 3-acylamino-2-oxoazetidine-1-sulfonic acid group. In monobactams, the β-lactam ring presumably is activated by the electronic effect of the sulfonate moiety alone, in contrast to the case of penicillins and cephalosporins. Because the antibacterial activity of sulfazecin is not satisfactory, many derivatives have been synthesized chemically [29, vol. 3, p. 339]. Among them *aztreonam* (SQ 26 776), synthesized from threonine, has been found highly effective [84].



Sulfazecin [77912-79-9]



Isosulfazecin [77900-75-5]



Aztreonam [78110-38-0]

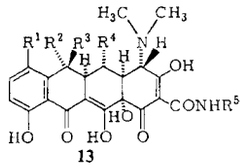
3.2. Tetracyclines

The discovery of the tetracyclines, the first being aureomycin (7-chlorotetracycline), was one of the great successes of the worldwide screenings, i.e., testing of media samples and other materials, for the presence of antibiotic-producing microorganisms. This search began during the early 1940s and continues today.

The first patents and publications of Lederle Laboratories [85], marked the beginning of an extensive stream of publications and patents that reflect the medical, industrial, and economic importance of the tetracyclines [86], [87].

3.2.1. Structure and Properties

The linear four-ring-system skeleton is characteristic of the tetracyclines (**13**) and has given the whole group its name. The strongly conjugated system of keto and enol groups is of particular significance for the biological activity. The structures of the first tetracyclines were elucidated and proved by synthetic work, e.g., that of Muxfeldt et al., shortly after their discovery and parallel to their clinical testing and industrial development. The chief tetracyclines are listed under structure **13**.



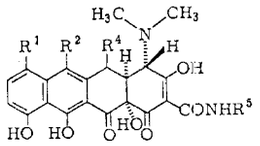
13

Name	Production	R^1	R^2	R^3	R^4	R^5
Tetracycline [6416-04-2]	*Streptomyces aureofaciens*	H	CH_3	OH	H	H
Chlortetracycline (aureomycin) [57-62-5]	*Streptomyces aureofaciens*	Cl	CH_3	OH	H	H
Demethylchlortetracycline (demeclocycline) [127-33-3]	*S. aureofaciens* *S. viridifaciens*	Cl	H	OH	H	H
Oxytetracycline [79-57-2]	*S. rimosus*	H	CH_3	OH	OH	H
Methacycline [914-00-1]	Semisynthetic	H	$=CH_2$		OH	H
Doxycycline [564-25-0]	Semisynthetic	H	CH_3	H	OH	H
Rolitetracycline [751-97-3]	Semisynthetic	H	CH_3	OH	H	CH_2N
Minocycline [10118-90-8]	Synthetic	$N(CH_3)_2$	H	H	H	H

The tetracyclines are bright yellow compounds, amphoteric, and with the exception of rolitetracycline and similarly constructed derivates insoluble in water at the isoelectric point. Their salts, e.g., hydrochlorides, are soluble in water and can be administered either parenterally or orally, although the low pH of the solution causes some problems in the latter instance.

3.2.2. Anhydrotetracyclines

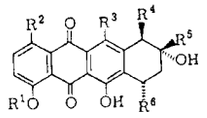
Tetracyclines are aromatized in ring C by dehydration with concentrated acids, e.g., aqueous hydrochloric acid or anhydrous hydrogen chloride in acetone, to form anhydrotetracyclines (**14**, wherein R^1-R^5 are similar to those of **13**) [88]–[90]. These compounds have less biological activity than the starting compounds. Their formation, like that of the *epi*-anhydrotetracyclines, must be avoided because they are toxic to the kidneys. An interesting fact is that antibiotics with the anhydrotetracycline structure also are formed in nature and can be isolated from cultures of microorganisms, e.g., chelocardin from *Nocardia sulfurea* [91].



14

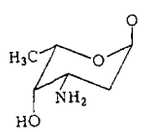
3.2.3. Anthracyclines

Structurally these antibiotics belong to the tetracyclines. They are characterized by the *p*-quinone structure of ring C in addition to the aromatic nuclei B and D (see **15**). Here R^1-R^5 are simple substituents, such as H, OH, or CH_3. Only R^6 is a sugar or similarly complex group. Although anthracyclines show antibacterial activity, they have not been used as antibiotics because of their relatively high toxicity and strong side effects. The antitumor activity of rhodomycin was discovered by ARCAMONE et al. in 1961 [92], and various antitumor anthracyclines were subsequently isolated [93]. The most important anthracyclines are listed under structure **15**. Daunorubicin and doxorubicin are representative anthracyclines. Aclarubicin was found by UMEZAWA during a search for anthracyclines that might have lower cardiac toxicity than doxorubicin. Anthracyclines exert their effect by interacting with DNA, the primary cellular receptor [94].

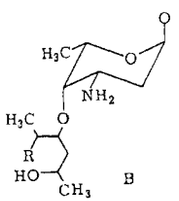


15

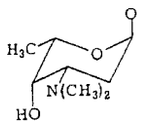
Name	R^1	R^2	R^3	R^4	R^5	R^6
Daunorubicin [20830-81-3]	CH_3	H	OH	H	$COCH_3$	A
Doxorubicin [23214-92-8]	CH_3	H	OH	H	$COCH_2OH$	A
Carminomycin I [50935-04-1]	H	H	OH	H	$COCH_3$	A
Baumycin A_2 [64253-71-0]	CH_3	H	OH	H	$COCH_3$	B ($R = CH_2OH$)
Baumycin B_2 [64312-53-4]	CH_3	H	OH	H	$COCH_3$	B ($R = COOH$)
Rhodomycin A [1404-50-8]	H	H	OH	C	CH_2CH_3	C
Rhodomycin B [1404-52-0]	H	H	OH	OH	CH_2CH_3	C
Aklavin [60504-57-6]	H	H	H	$COOCH_3$	CH_2CH_3	C
Cinerubin [34044-10-5]	H	OH	H	$COOCH_3$	CH_2CH_3	D
Aclarubicin [57576-44-0]	H	H	H	$COOCH_3$	CH_2CH_3	D



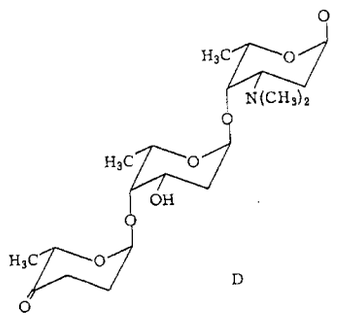
A



B



C



D

3.3. Aminoglycosides

WAKSMAN initiated the screening of antibiotics and, after finding actinomycin and streptothricin, he discovered the first useful aminoglycoside, streptomycin, in 1944 [95]–[99]. After wide use of penicillin, streptomycin, chloramphenicol, and tetracycline, resistant organisms appeared in hospital patients. In 1957, staphylococci and gram-negative organisms resistant to all the known antibiotic drugs caused serious infections; kanamycin was discovered at that time by UMEZAWA and was introduced clinically. However, in 1965, kanamycin-resistant strains appeared. In 1967, the enzymatic mechanism of resistance to aminoglycoside antibiotics was elucidated. UMEZAWA suggested that 3′-phosphotransferase and 6′-acetyltransferase, which transferred the terminal phosphate of ATP to the 3′-hydroxyl group of kanamycin, neomycin, and paromomycin or the acetyl group of acetyl-CoA to the 6′-amino group, were involved in the mechanism of resistance [100], [101]. In order to prove this enzymatic mechanism of resistance conclusively, 3′-deoxykanamycin A and 3′,4′-dideoxykanamycin B were synthesized and used to demonstrate the inhibition of the growth of resistant strains [102]. This conclusively demonstrated the enzymatic mechanism of resistance. Effective derivatives were obtained not only by deoxygenation but also by modification of the 1-amino group, which was involved in binding to the enzymes.

More than 150 naturally occurring aminoglycosides have been isolated from culture filtrates of *Streptomyces, Streptoverticillium, Nocardia, Micromonospora, Streptoalloteichus, Dactylosporangium, Saccharopolyspora,* and other bacterial strains. They can be devided into:

1) **Noncyclitol aminoglycosides**
   a) Monosaccharide derivatives
   3-amino-3-deoxy-D-glucose, nojirimycin, *N*-carbamoyl-D-glucosamine, streptozotocin, prumycin
   b) Disaccharides (trehalosamines)
   trehalosamine, mannosyl glucosaminide, 4-amino-4-deoxytrehalose
   c) Diaminosorbitol aminoglycosides (sorbistins)
   sorbistins A_1, A_2, B, D
   d) Glycocinnamoylspermidines
   LL-BM123β, γ_1, γ_2, glysperins A, B, C
2) **Aminoglycosides containing neutral cyclitols and monoaminocyclitols**
   kasugamycin, myomycins A, B, C, LL-BM782α_1, α_{1a}, α_2, minosaminomycin, LL-BM123α, validamycins A, B, C, D, E, F
3) **Aminoglycosides containing streptamine and related aminocyclitols**
   a) Streptidine aminoglycosides (streptomycins)
   streptomycin, mannosidostreptomycin, dihydrostreptomycin, hydroxystreptomycin (reticulin), *N*-demethylstreptomycin, mannosidohydroxystreptomycin, glebomycin (bluensomycin)

b) Actinamine aminoglycosides (spectinomycins)
spectinomycin (actinospectacin), dihydrospectinomycin
c) 4-Substituted deoxystreptamine aminoglycosides (neamines)
neamine, paromamine, nebramine (nebramycin 8), lividamine, NK-1003, seldomycin factor 2, gentamines C_1, $C_{1\alpha}$, C_2, apramycin (nebramycin 2), oxyapramycin (nebramycin 7)
d) 5-Substituted deoxystreptamine aminoglycosides (destomycins)
hygromycin B, destomycins A, B, C, A-396–1, SS-56-C, A16316-C
e) 4,5-Disubstituted deoxystreptamine aminoglycosides (neomycins)
neomycins B, C, LP-B, LP-C, paromomycins I, II, lividomycins A, B, mannosyl paromomycin, ribostamycin, xylostasin, ribosyl paramamine (LL-BM408α), butirosins A, B, BU-1709E_1, E_2, BU-1975C_1, C_2
f) 4,6-Disubstituted deoxystreptamine aminoglycosides (kanamycins)
kanamycins A, B, C, NK-1001, NK-1012–1, NK-1013–1, NK-1013–2, tobramycin (nebramycin 6), 6″-*O*-carbamoylkanamycin B (nebramycin 4), 6″-*O*-carbamoyltobramycin (nebramycin 5′), 2′-*N*-carbamoyltobramycin (nebramycin 11), 3″-deamino-3″-hydroxytobramycin (nebramycin 12), 6′-*N*-carbamoyltobramycin (nebramycin 13), gentamicins A, A_1, A_2, A_3, A_4, B, B_1, C_1, C_{1a}, C_2, C_{2a}, C_{2b} (sagamicin), X_2, JI-20A, JI-20B, G-418, I-1, 6′-*C*-methylgentamicin A (II-2), 6′-*C*-methylgentamicin A (III-1), VII-1, VII-3, VII-5, seldomycin factors 1, 3, 5, sisomicin, verdamicin, G-52, 66–40B, 66–40C, 66–40D, 3″-*N*-demethylsisomicin (66–40G)

4) **Aminoglycosides containing 1,4-diaminocyclitols**
a) Fortamine aminoglycosides (fortimicins)
fortimicins A, C, D, KG_3, 3-*O*-demethylfortimicin A, sporaricin A, 2″-*N*-carbamoylsporaricin A, 2″-*N*-formylsporaricin A, istamycins A (sannamycin A), A_1, A_2, B, B_1, C, C_1, dactimicin (SF-2052), 2″-*N*-formylfortimicin A
b) Non-glycine fortamine aminoglycosides
fortimicins B, E (AE, KH), AH, AI, AK (KI), AL, AM, AO, AP, AQ, AS, KE, KF, KG, KG_1, KG_2, KO_1, KQ, sporaricin B (KA-6606 II), KA-6606 V, VI, sannamycins B (KA-7038 II, istamycin A_0), C(KA-7038 VI), KA-7038 III, IV, V, VII, istamycin B_0, C_0

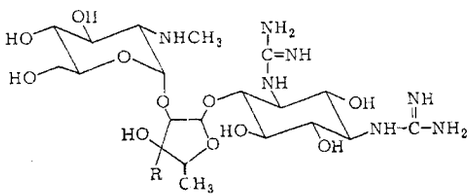
Kanamycins are produced by *Streptomyces kanamyceticus*, gentamicins by *Micromonospora purpurea*, and butirosins by *Bacillus circulans*. Many compounds analogous to aminoglycoside antibiotics are produced by the same strain. For example, more than 20 compounds structurally analogous to gentamicin have been isolated from a culture filtrate of a *Micromonospora* strain [103], [104].

Most aminoglycoside antibiotics that are important for chemotherapy contain 1,3- or 1,4-diaminocyclitols named actinamine, 2-deoxystreptamine, fortamine, or streptidine. Among these naturally occurring aminoglycosides, dihydrostreptomycin, kanamycin A, kanamycin B, lividomycin A, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, a mixture of gentamicins C_1, C_2, and C_{1a}, a mixture of neomycins B and C, and a mixture of paromomycins I and II are commercially available as chemotherapeutic agents useful in treating infections. Hygromycin B and destomycin A are used as animal anthelmintics. Kasugamycin and validamycin A are used for the prevention of plant diseases. Among resistant bacteria of clinical origin, the most important mechanism of resistance to aminoglycoside antibiotics is the inactivation by O-phosphorylation, O-nucleotidylation, or N-acetylation of specific sites of the antibiotic. The gene for these enzymes is located on a plasmid. Organisms with resistance resulting from permeability barriers to drugs have been isolated, but ribosomal resistance to aminoglycosides is very rare in organisms isolated clinically. Studies of the enzymatic mechanism of resistance to aminoglycosides have been reviewed extensively [105] – [108].

Semisynthetic Aminoglycosides have been made. Based on the enzymatic mechanism of resistance, studies of the chemical synthesis of derivatives that inhibit the growth of resistant strains have been initiated. 3′-Deoxykanamycin A has been synthesized and used to inhibit the growth of resistant strains having aminoglycoside-3′-phosphotransferase enzymes. Dibekacin (3′,4′-dideoxykanamycin B), synthesized from kanamycin B, shows a strong activity not only against resistant staphylococci and gram-negative organisms but also against *Pseudomonas* [102]. These results prove the enzymatic mechanism of resistance.

Streptomycin, the first aminoglycoside antibiotic, was discovered by WAKSMAN. This drug is produced by *Streptomyces griseus* and extracted from the culture filtrate by adsorption on a column of Amberlite IRC-50 resin. The hydrogen chloride – calcium chloride ($3\,HCl \cdot 1/2\,CaCl_2$) complex salt of streptomycin is easily crystallized from an anhydrous methanol solution. Streptomycin is also produced by several other strains: *Streptomyces bikiniensis, Streptomyces olivaceus, Streptomyces poonensis, Streptomyces mashuensis, Streptomyces galbus, Streptomyces rameus,* and *Streptomyces erythrochromogenes* subsp. *narutoensis.*

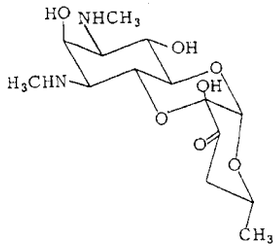
The early structural studies have been reviewed [109]. The two anomeric configurations were found to be α-L by application of Hudson's rules of isorotation and NMR spectral analysis. The absolute structure of streptomycin has been confirmed by X-ray analysis of its oxime selenate [110]. Streptomycin has been synthesized by oxidation of dihydrostreptomycin [111].



Streptomycin
[57-92-1]
R = CHO

Dihydrostreptomycin
[128-46-1]
R = CH_2OH

Spectinomycin (Actinospectacin, M-141) is produced by *Streptomyces spectabilis* and *Streptomyces flavopersicus*. It is also produced by *Streptomyces hygroscopicus* subsp. *sagamiensis*. Spectinomycin hexahydrate is crystallized from an aqueous acetone solution. This antibiotic is labile, especially in acidic solution.



Spectinomycin (**16**)
[*1695-77-8*]

The structure of spectinomycin (**16**) was revealed by chemical studies, and its stereochemistry was determined by X-ray analysis of its dihydrobromide pentahydrate crystal [112]. Total synthesis of spectinomycin has been accomplished [113], [114].

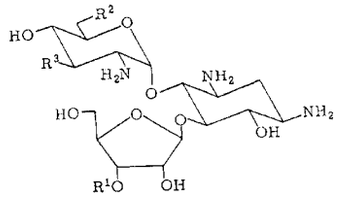
Neomycin (Fradiomycin), a mixture of *Neomycins B and C*, is produced by *Streptomyces fradiae* and by *Streptomyces albogriseolus*. It is marketed as a mixture that contains 85–90% neomycin B [115]. Neomycins B and C are extremely stable in neutral or alkaline aqueous solution.

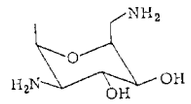
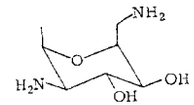
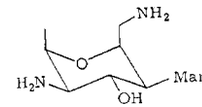
The final structure and stereochemistry of neomycins B and C were established in 1962. Neomycin C has also been synthesized also [116].

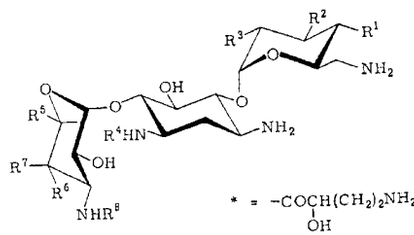
Paromomycin (Catenulin, Aminosidin, Hydroxymycin, Zygomycin A) is produced by *Streptomyces rimosus* subsp. *paromomycinus*; the structures of two isomers, paromomycins I and II, have been proposed. Paromomycin I is the main component of paromomycin preparations.

Catenulin, produced by *Streptomyces catenulae;* amminosidin, produced by *Streptomyces chrestomyceticus;* hydroxymycin, produced by *Streptomyces paucisporogenes;* and zygomycin A, produced by *Streptomyces pulveraceus,* are identical with paromomycin. Zygomycin A_1 is identical with paromomycin I and zygomycin A_2 is identical with paromomycin II.

The absolute configurations of the paromomycins have been determined along with those of other deoxystreptamine-containing aminoglycosides and dihydrostreptomycin [117], [118].



Name	R^1	R^2	R^3
Ribostamycin [*25546-65-0*]	H	NH_2	OH
Neomycin B [*119-04-0*]		NH_2	OH
Paromomycin I [*7542-37-2*]		OH	OH
Lividomycin A [*36441-41-5*]	 Mannose	OH	H



* = $-COCH(CH_2)_2NH_2$ (OH)

Name	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
Kanamycin [*59-01-8*]	OH	OH	OH	H	CH_2OH	OH	H	H
Bekanamycin [*4696-76-8*]	OH	OH	NH_2	H	CH_2OH	OH	H	H
Tobramycin [*32986-56-4*]	OH	H	NH_2	H	CH_2OH	OH	H	H
Gentamicin C_{1a} [*26098-04-4*]	H	H	NH_2	H	H	CH_3	OH	CH_3
Dibekacin [*34493-98-6*]	H	H	NH_2	H	CH_2OH	OH	H	H
Amikacin [*37517-28-5*]	OH	OH	OH	*	CH_2OH	OH	H	H

Ribostamycin (SF-733) is produced by *Streptomyces ribosidificus*. The free base is crystallized from methanol solution. The structure has been determined by chemical methods and total synthesis has been undertaken [119].

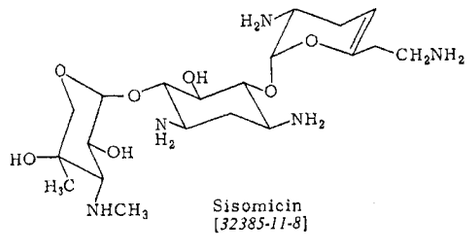
Kanamycin A is produced by *Streptomyces kanamyceticus*. The monosulfate monohydrate and the free base are crystallized from aqueous methanol. Kanamycin A is extremely stable in neutral or alkaline aqueous solutions.

The stereochemical structure of kanamycin A has been confirmed by X-ray analysis of its monosulfate monohydrate and monoselenate monohydrate crystals [120]. Total synthesis of kanamycin A has been achieved [121].

Kanamycin B (Bekanamycin, Aminodeoxykanamycin) is one of the two minor components that have been isolated from the culture filtrate of kanamycin-producing *Streptomyces kanamyceticus*. Kanamycin B has a retention factor (R_f) of 0.37, whereas kanamycin A, the major component, shows R_f 0.21 – 0.26. (R_f is a measure of the relative mobilities of substance and solvent in a chromatographic system.) The free base kanamycin B is crystallized from aqueous *N,N*-dimethylformamide.

Gentamicin (Gentamicin C Complex), a mixture of *Gentamicins C_1, C_{1a}, and C_2*, is the antibiotic complex produced by *Micromonospora purpurea* and *Micromonospora echinospora*. Gentamicins C_1 and C_2 are the principal products, and C_1 is itself a mixture of two major components designated C_1 and C_{1a}. Gentamicin C complex, which consists of the mixture of C_1 and C_{1a} (60 – 80%) and of C_2 (20 – 40%), has been used as a chemotherapeutic agent. The structures and the stereochemistry of the gentamicin C components have been reported [122].

Sisomicin (66 – 40, Rickamicin) is the major antibiotic produced by *Micromonospora inyoensis*. Its structure has been elucidated [123].



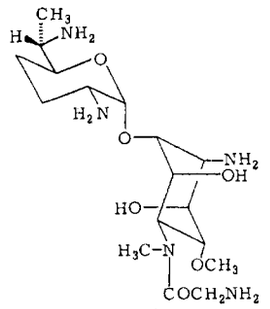
Sisomicin
[32385-11-8]

Dibekacin (3',4'-Dideoxykanamycin B, DKB) was the first drug developed on the basis of the enzymatic mechanism of resistance to aminoglycosides. Dibekacin is synthesized from kanamycin B by the application of the Tipson-Cohen deoxygenation method after selective N- and O-protections [102]. A modified synthetic route via the 3',4'-epoxy compound has given a high yield of more than 40% on an industrial scale [124].

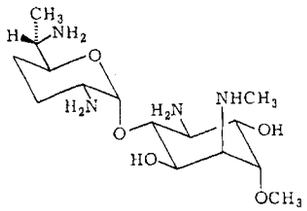
Amikacin (1-*N*-[(S-)-4-Amino-2-hydroxy-butyryl]kanamycin, BB-K_8) is synthesized in 22% yield from the 6'-N-protected kanamycin by selective 1-N-acylation with N-protected (S)-4-amino-2-hydroxybutyric acid using the active ester method [125]. The most important point of this synthesis is the selective protection of all of the amino groups except the 1-amino group. The 3,6'-di-N-protected kanamycin has been obtained in 95% yield by selective N-protection using chelation with Co^{2+}, Ni^{2+}, and Cu^{2+} [126]. A new 3,6',3''-tri-N-protection method using the selective 3''-Ntrifluoroacetylation of the 3,6'-di-N-protected kanamycin with ethyl trifluoroacetate has been developed and the synthesis via 3,6'-di-N(benzyloxycarbonyl)–3''-N-(trifluoroacetyl)kanamycin gives amikacin in a yield of more than 60% [127].

The Fortimicin Group is a new type of deoxyaminoglycoside antibiotics, each consisting of glycine and a pseudodisaccharide, that have been found by screening. Fortimicin is produced by a *Micromonospora* species, sporaricin by *Saccharopolyspora hirsuta* subsp. *kobensis*, istamycin by *Streptomyces tenjimariensis*, sannamycin by *Streptomyces sannanensis*, and dactimicin by *Dactylosporangium matsuzakiense* [128] – [131], [128, p. 1061]. The structures of the fortimicin antibiotics are shown. These antibiotics strongly inhibit the growth of gram-positive and gram-negative bacteria but most *Pseudomonas* strains are resistant to them.

The axial amino group at C-1 in fortimicin A and istamycin A can be acetylated by aminoglycoside acetyltransferase(3)-I, but the equatorial amino group at C-1 in sporaricin A and istamycin B is scarcely acetylated. Other aminoglycoside-modifying enzymes that participate in the resistance to deoxystreptamine-containing aminoglycosides do not inactivate fortimicin-group antibiotics.



Fortimicin A
[55779-06-1]



Fortimicin B
[54783-95-8]

3-*O*-Demethyl derivatives of sporaricin A and istamycin B exhibit good activity not only against gram-positive and gram-negative bacteria but also against most *Pseudomonas* strains. These derivatives will be developed as valuable chemotherapeutic agents in the near future.

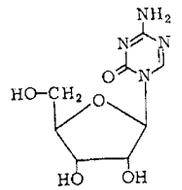
3.4. Nucleosides

The biological effects associated with metabolic processes and specific enzyme control mechanisms are diverse in naturally occurring nucleosides and their synthetic analogs. Nucleosides exhibit several biological effects, including antibiotic, anticancer, and antiviral activities. They possess antimitotic and immunosuppressive activities and cardiovascular and other effects [132] – [134]. Moreover, it should be kept in mind that nucleoside analogs can assume other functional roles not as yet recognized, and that further therapeutic applications can be expected in the future. These analogs are obtained predominantly from microbial sources.

The nucleoside antibiotics consist of a heterocyclic base aglycone and a carbohydrate or a carbocyclic ring linked by a carbon – nitrogen (N-nucleoside) or a carbon – carbon bond (C-nucleoside). The nucleoside antibiotics fall somewhat outside the normal field of antibiotics with respect to their activity spectra and hence to their use. They are important for use against fungi, viruses, and certain types of cancer cells. Some typical nucleoside antibiotics are mentioned here.

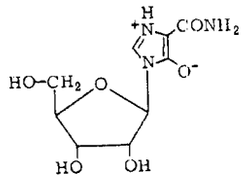
3.4.1. N-Nucleosides

5-Azacytidine (**17**), a triazine analog of cytidine produced by *Streptoverticillium ladakanus*. It is active against some bacterial strains, Ehrlich ascitic tumor, leukemia L1210, and certain other leukemias. 5-Azacytidine also inhibits the DNA synthesis of bacteriophage T4 [135].



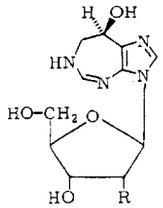
17
5-Azacytidine
[320-67-2]

Bredinin (**18**), produced by *Eupenicillium brefeldianum*, shows marked immunosuppressive activity in mice, interferes with replication of *Vaccinia* virus in vitro, and inhibits leukemia L 5178 cells and *Candida albicans* [136].



18
Bredinin
[50924-49-7]

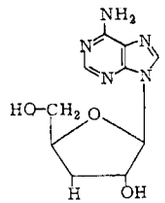
Coformycin (**19a**) is isolated from *Nocardia interforma* along with formycin. Coformycin shows a synergistic effect with formycin on Yoshida rat sarcoma cells because of its strong inhibition of adenosine deaminase, which inactivates formycin. Coformycin, having a characteristic seven-membered ring base moiety, is thought to be a typical example of a "transition-state analog" in the adenosine deaminase reaction. 2′-Deoxycoformycin (**19b**) has also been isolated also [137] – [139].



19a: R = OH
Coformycin
[*11033-22-0*]

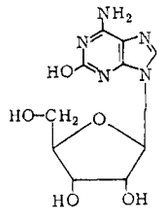
19b: R = H
2'-Deoxycoformycin
[*53910-25-1*]

Cordycepin (**20**), 3'-deoxyadenosine, was one of the first nucleoside antibiotics isolated from *Cordyceps militaris*. It inhibits *Bacillus subtilis, Mycobacterium tuberculosis*, KB cell cultures, and Ehrlich ascites tumor cells.



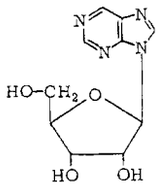
20
Cordycepin
[*73-03-0*]

Crotonoside (**21**), isolated from *Croton tiglium* seeds, acts as a vasopressor [140].



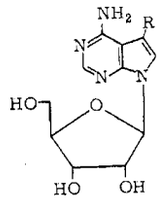
21
Crotonoside
[*1818-71-9*]

Nebularine (**22**), produced by the mushroom *Agaricus* (*Clitocybe*) *nebularis*, inhibits the growth of *Mycobacterium tuberculosis* and *Brucella abortus*, and is markedly cytotoxic to mammalian cells, whereas the purine base is relatively nontoxic. Nebularine is toxic to Sarcoma 180 cells [141], [142].



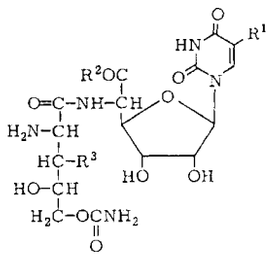
22
Nebularine
[*550-33-4*]

Toyocamycin (**23a**), produced by *Streptomyces toyocaensis*, strongly inhibits *Candida albicans, Trichophyton interdigitale*, and *Mycobacterium tuberculosis* and is also active against NF-sarcoma cells [143]. *Tubercidin* (**23b**) and *sangivamycin* (**23c**) also belong to this class [144].

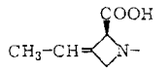
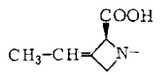
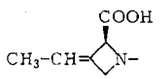
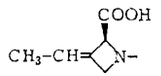


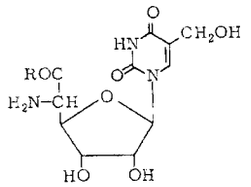
23a: R = CN Toyocamycin [*606-58-6*]
23b: R = H Tubercidin [*69-33-0*]
23c: R = $CONH_2$ Sangivamycin [*18417-89-5*]

Polyoxins A–O (**24**, **25**, **26**) are peptide nucleosides produced by *Streptomyces cacaoi*. They possess various heterocycles, e.g., uracil, thymine, 5-hydroxymethyluracil, uracil-5-carboxylic acid, or formylimidazolone. The compounds **24** and **26** are particularly active against sheath-blight in rice, *Pellicularia sasakii*, and are widely used as agricultural drugs [145]–[147].



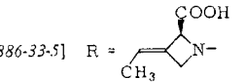
24

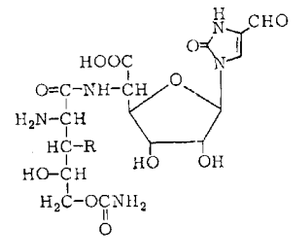
Name	R^1	R^2	R^3
Polyoxin A *[19396-03-3]*	CH_2OH		OH
Polyoxin B *[19396-06-6]*	CH_2OH	HO	OH
Polyoxin D *[22976-86-9]*	COOH	HO	OH
Polyoxin E *[22976-87-0]*	COOH	HO	H
Polyoxin F *[23116-76-9]*	COOH		OH
Polyoxin G *[22976-88-1]*	CH_2OH	HO	H
Polyoxin H *[24695-54-3]*	CH_3		OH
Polyoxin J *[22976-89-2]*	CH_3	HO	OH
Polyoxin K *[22886-46-0]*	H		OH
Polyoxin L *[22976-90-5]*	H	HO	OH
Polyoxin M *[34718-88-2]*	H	HO	H



25

Polyoxin C *[21027-33-8]* R = OH

Polyoxin I *[22886-33-5]* R = 



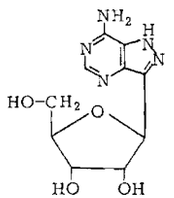
26

Polyoxin N *[37362-29-1]* R = OH

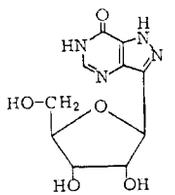
Polyoxin O *[37362-28-0]* R = H

3.4.2. C-Nucleosides

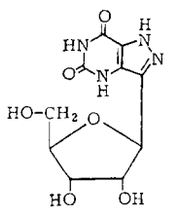
Formycin (27) (**Formycin A**) is isolated from *Nocardia interforma* and from *Streptomyces lavendulae* [148], [149]. The antibiotic is effective against *Xanthomonas oryzae* and *Pellicularia filamentosa*. Its activity against Yoshida rat sarcoma cell is enhanced by coformycin. *Formycin B* (**28**) inhibits *Xanthomonas oryzae* and interferes with multiplication of influenza A virus in the cells of chick chorioallantoic membrane [150]. *Oxoformycin B* (**29**) shows no activity against *Xanthomonas oryzae* [151].



27
Formycin
[6742-12-7]

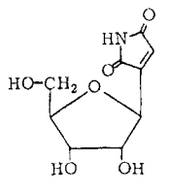


28
Formycin B
[13877-76-4]

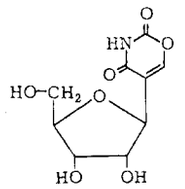


29
Oxoformycin B
[19246-88-9]

Showdomycin (**30**), isolated from *Streptomyces showdoensis*, is very active against *Streptococcus hemolyticus*. It is moderately active against other gram-positive and gram-negative bacteria and also effective against Ehrlich ascites tumor in mice and HeLa cells [152]. *Oxazinomycin* (**31**) belongs to this class of nucleosides [153].



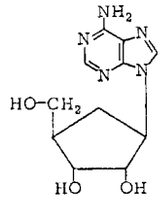
30
Showdomycin
[16755-07-0]



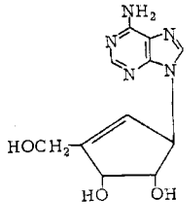
31
Oxazinomycin
[32388-21-9]

3.4.3. Carbocyclic Nucleosides

Since the pioneering synthesis of the racemic carbocyclic analog of adenosine by SHEALY and CLAYTON and the subsequent isolation of *aristeromycin* (**32**) from *Streptomyces citricolor*, the interest in this class of compounds has been renewed by the isolation of a new carbocyclic nucleoside, *neplanocin A* (**33**). The latter exhibits remarkable antitumor activity against L 1210 leukemia in mice, and its synthetic analogs are now being studied extensively [154]–[156].



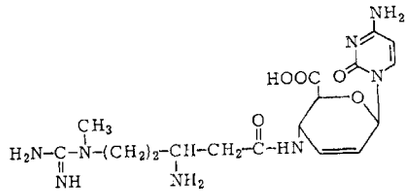
32
Aristeromycin
[19186-33-5]



33
Neplanocin A
[72877-50-0]

3.4.4. An Exceptional Nucleoside

Blasticidin S (**34**) has a pyran ring as the sugar moiety and inhibits various gram-positive and gram-negative bacteria. It is particularly effective against *Pericularia oryzae* and is now used as an agricultural drug [157].



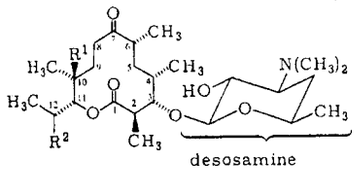
34
Blasticidin S
[2079-00-7]

3.5. Macrolides

This group of antibiotics is characterized by excellent antibacterial activity, particularly against gram-positive bacteria. Macrolides can be defined and distinguished from the other groups of antibiotics by the unique feature of their chemical structure. They are polyfunctional macrocyclic lactones and the majority of them contain at least one amino sugar moiety, which is the cause of the basicity of the molecules. Neutral macrolides containing only a neutral sugar moiety are also known. Recently these antibiotics have become targets in the aldol strategy of organic synthesis to construct their polyhydroxy functions stereoselectively [158], [159]. The antibiotics are classified as either 12-, 14-, or 16-membered ring macrolides according to the ring size of the aglycone.

3.5.1. 12-Membered Ring Macrolides

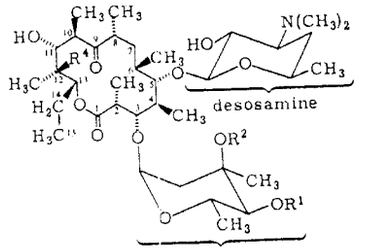
Methymycin (**35**), produced by *Streptomyces venezuelae*, was first shown to be a 12-membered lactone, comprising the aglycone or methynolide and D-desosamine [160], [161]. *Neomethymycin* (**36**) has an isomeric structure.



Methymycin (**35**) R^1 = OH, R^2 = H
[*497-72-3*]
Neomethymycin (**36**) R^1 = H, R^2 = OH
[*497-73-4*]

3.5.2. 14-Membered Ring Macrolides

The erythromycins, produced by *Streptomyces erythreus*, are clinically important macrolides and are the most widely investigated 14-membered ring macrolides [162]. Extensive chemical and X-ray crystallographic studies of *erythromycin A* (**37**) have established its structure as well as those of its minor components, *erythromycin B* (**38**), *erythromycin C* (**39**), and *erythromycin D* (**40**). Erythromycin is effective against streptococcal and pneumococcal infections. Derivatives of erythromycin, modified in the cladinose ring, the desosamine ring, and the aglycone moiety (especially at C-9 of the aglycone), have been described. Their characterization contributed greatly to understanding the chemistry and structure – activity relationships of the macrolide antibiotics [163].



cladinose: R^1 = H, R^2 = CH_3
mycarose: R^1 = R^2 = H

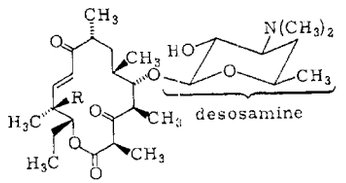
Erythromycin A (**37**) [*114-07-8*]
R^1 = R^3 = H, R^2 = CH_3, R^4 = OH

Erythromycin B (**38**) [*527-75-3*]
R^1 = R^3 = R^4 = H, R^2 = CH_3

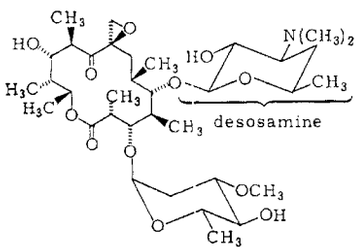
Erythromycin C (**39**) [*1675-02-1*]
R^1 = R^2 = R^3 = H, R^4 = OH

Erythromycin D (**40**) [*33442-56-7*]
R^1 = R^2 = R^3 = R^4 = H

Picromycin (**41**), narbomycin (**42**), and oleandomycin (**43**) belong to the 14-membered lactones.



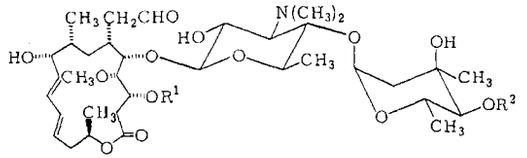
Picromycin (**41**) [*19721-56-3*] R = OH
Narbomycin (**42**) R = H



Oleandomycin (**43**) [*3922-90-5*]

3.5.3. 16-Membered Ring Macrolides

Stereochemical structures of carbomycins, leucomycins, spiramycins, and other macrolides have been disclosed by extensive chemical studies [164], [165]. These compounds have a formylmethyl group at C-6 and two conjugated double bonds in the 16-membered lactone ring. They differ only in the nature of the acyl substituents at C-3 and C-4. For instance, the leucomycin complex (kitasamycin), produced by *Streptomyces kitasatoensis* [166] is a mixture of ten similar components. These are *leucomycin A_1* (**44**, *turimycin H_5*), *leucomycin A_3* (**45**, josamycin, YL-704A_3 or platenomycin A_3), *leucomycin A_4* (**46**), *leucomycin A_5* (**47**), *leucomycin A_6* (**48**, YL-704B_3 or platenomycin B_3), *leucomycin A_7* (**49**), *leucomycin A_8* (**50**), *leucomycin A_9* (**51**), *leucomycin U* (**52**), and *leucomycin V* (**53**) [164], [167].



Leucomycin A_1 (Turimycin H_5) (**44**) R^1 = H, R^2 = $COCH_2CH(CH_3)_2$
[*16846-34-7*]

Leucomycin A_3 (Josamycin, YL-704 A_3 Turimycin A_5) (**45**) R^1 = $COCH_3$, R^2 = $COCH_2CH(CH_3)_2$
[*16846-24-5*]

Leucomycin A_4 (**46**) R^1 = $COCH_3$, R^2 = $COCH_2CH_2CH_3$
[*18361-46-1*]

Leucomycin A_5 (**47**) R^1 = H, R^2 = $COCH_2CH_2CH_3$
[*18361-45-0*]

Leucomycin A_6 (YL-704 B_3) (**48**) R^1 = $COCH_3$, R^2 = $COCH_2CH_3$
[*18361-48-3*]

Leucomycin A_7 (**49**) R^1 = H, R^2 = $COCH_2CH_3$
[*18361-47-2*]

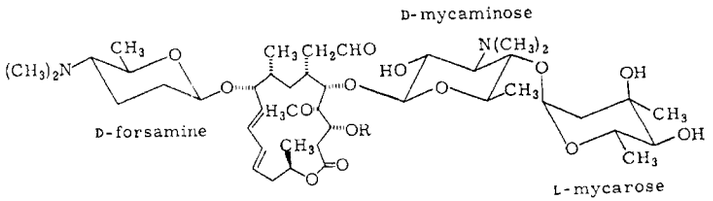
Leucomycin A_8 (**50**) R^1 = $COCH_3$, R^2 = $COCH_3$
[*18361-50-7*]

Leucomycin A_9 (**51**) R^1 = H, R^2 = $COCH_3$
[*18361-49-4*]

Leucomycin U (**52**) R^1 = $COCH_3$, R^2 = H
[*31642-61-2*]

Leucomycin V (**53**) R^1 = H, R^2 = H
[*22875-15-6*]

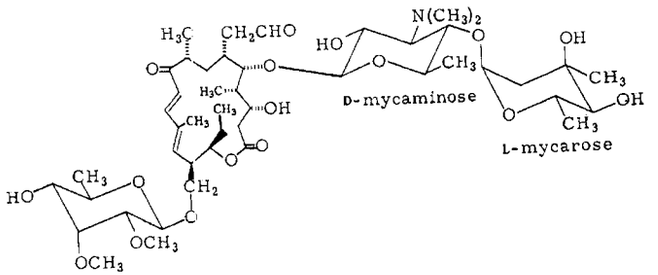
The spiramycins (foromacidins) produced by *Streptomyces ambofaciens* [168] have been separated into three components, namely *spiramycin I* (**54**), *spiramycin II* (**55**), and *spiramycin III* (**56**).



Spiramycin I (Foromacidin A) (**54**): R = H
[*24916-50-5*]

Spiramycin II (Foromacidin B) (**55**): R = $COCH_3$
[*24916-51-6*]

Spiramycin III (Foromacidin C) (**56**): R = $COCH_2CH_3$
[*24916-52-7*]



Tylosin (**57**)
[*1401-69-0*]

Many other macrolides, such as *rosamicin* [169], [170], *cirvamycin A_1* [171], [172], *juvenimicin A_2*, *juvenimicin A_4* [173], [174], *deltamycin* [175], *carbomycin* [176], [177], *angolamycin* [178], *tylosin* (**57**) [179]–[181], and the *mycinamicins* [182], [183], belong to this class.

Since 1950, the structures of more than 90 macrolides have been elucidated, and this knowledge has had a great impact on modern organic synthesis. The classification of the above-mentioned macrolides according to ring size is useful, but very schematic. There is a marked change in the antibiotic activity spectrum corresponding to changes in the ring size, even though many of the substituents and the degree of unsaturation differ considerably.

Macrolides with ca. 10–16 ring members are very strongly antibacterial, as are the smaller lactones. Because there is no cross-resistance among these macrolides, they are mainly used to treat bacterial infections that are resistant to other antibiotics.

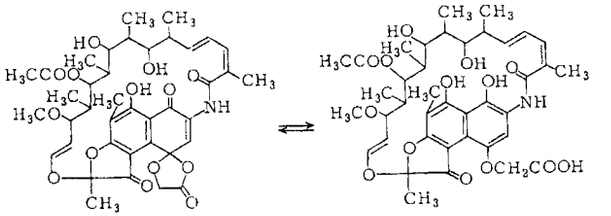
Macrolides with ca. 16–40 ring members show very little activity against bacteria, often none at all, but they are highly effective against fungi, yeasts, etc.

The very large macrolides are highly effective against not only fungi, but also viruses and tumors.

3.6. Ansamycins

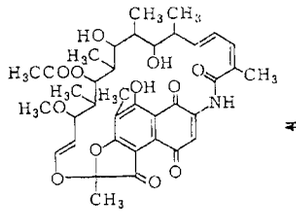
The ansamycins are a clinically important class of antibiotics with a characteristic structure. They have an aliphatic "ansa" bridge that connects two nonadjacent positions of an aromatic system [184]. The name "ansamycin" is based on the term "ansa compounds" [185]. Ansamycins are classified into two groups based on the nature of the aromatic moiety, i.e., benzoquinoid and naphthoquinoid ansamycins. Geldanamycin and maytansinoids belong to the benzoquinoid ansamycins and are studied as potential antitumor agents. The naphthoquinoid ansamycins include rifamycins, tolypomycins, streptovaricins, halomicins, and naphthomycin. The naphthoquinoid ansamycins are the major group of known ansamycins.

The rifamycins, produced by *Nocardia mediterranei,* have great therapeutic value [186], [188]. Their chemistry is very similar to that of the macrolides. After many attempts to separate, isolate, and purify the naturally occurring rifamycins, *rifamycin B* (**58**), *rifamycin O* (**59**), and *rifamycin S* (**60**) were found among the fermentation products. Rifamycin B was moderately effective against gram-positive bacteria. The oxidation of rifamycin B gave rifamycin O, which can be hydrolyzed to the more active rifamycin S. The latter can be reduced to *rifamycin SV* (**61**) using ascorbic acid. Rifamycin SV is converted, through its formyl derivative (**62**), to the therapeutically important *rifampicin* (**63**). In order to obtain an antibiotic with a broader spectrum and good oral absorption characteristics, thousands of derivatives of rifampicin have been prepared. Rifamycins B, O, and S all are used as starting materials for the modifications. The rifampicins have strong biological activity against gram-positive microorganisms and mycobacteria, particularly *Mycobacterium tuberculosis* [189]–[191]. Most of the ansamycins are weakly active against viruses, and certain derivatives, such as *3-formylrifamycin S* (**62**), have been found to be active against certain tumors. No cross-resistance of the ansamycins to most of the other antibiotics has been observed.

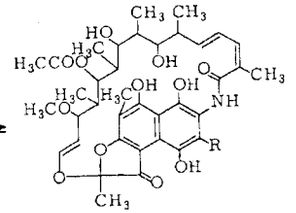


Rifamycin O (**59**)
[*14487-05-9*]

Rifamycin B (**58**)
[*13929-35-6*]



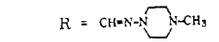
Rifamycin S (**60**)
[*13553-79-2*]



Rifamycin SV (**61**)
[*6998-60-3*]
R = H

3-Formylrifamycin S (**62**)
[*13292-22-3*]
R = CHO

Rifampicin (**63**)
[*13292-46-1*]



3.7. Peptides

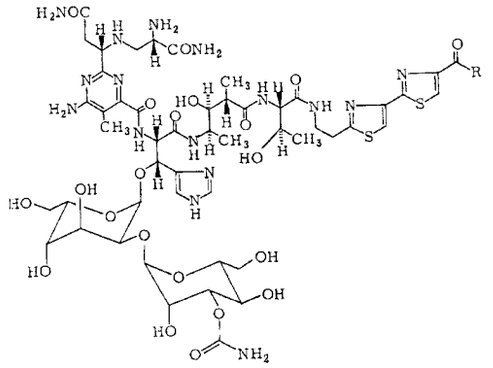
The various important functions of the living organism are frequently mediated by oligopeptides and proteins, which exist in the most diverse structures. It is therefore not surprising that a large number of low molecular mass peptides, oligopeptides, and protein-like substances are found among the antibiotics of microbial origin. Although peptide antibiotics consist of amino acids linked by peptide bonds, they differ from the proteins and peptides of higher animals and plants in many respects [192]. The following characteristics frequently are found in the peptide antibiotics:

1) Molecular masses of the antibiotics are smaller (in the range of 500–1500) than those of peptide hormones, which are frequently much larger.
2) The antibiotics contain some uncommon amino acids that are not found in proteins and peptide hormones of animal or plant origin. The usual amino acids are infrequently detected or are found in modified forms.

3) Lipids and other moieties not of amino acid character are found in many peptide antibiotics.
4) The peptide antibiotics frequently contain D-amino acid residues, whereas peptides of plant and animal origin consist solely of L-amino acid residues.
5) Virtually all of the peptide antibiotics resist hydrolysis by proteolytic enzymes, which are otherwise effective in hydrolyzing peptides of plant and animal origin.
6) The antibiotics are often cyclic peptides.
7) Families of closely related peptide antibiotics are frequently produced by the same microorganism.

3.7.1. The Bleomycin Group

The bleomycins, a group of glycopeptide antibiotics produced by *Streptomyces verticillus* [193], make up one of the most widely used groups of antitumor antibiotics, effective against squamous cell carcinoma and malignant lymphoma. Extensive degradation studies have shown the main structural features to be a peptide containing unusual amino acid residues and a disaccharide of uncommon sugars. The complete structure has been elucidated by chemical studies and X-ray crystallographic analysis of P-3A, a biosynthetic intermediate structurally related to bleomycin [194], [195]. This structure has been verified by the total synthesis of *bleomycin A_2* (**64**). The naturally occurring bleomycins are obtained in copper-chelated form as a mixture of congeners that differ only in the substituents at the C terminus of *bleomycinic acid* (**65**), the common structural unit. Among these are *bleomycin A_1* (**66**), *demethylbleomycin A_2* (**67**), *bleomycin A_2* (**64**), *bleomycin A_2' [a]* (**68**), *bleomycin A_2' [b]* (**69**), *bleomycin A_2' [c]* (**70**), *bleomycin A_5* (**71**), *bleomycin A_6* (**72**), *bleomycin B_1* (**73**), *bleomycin B_2* (**74**), and *bleomycin B_4* (**75**). Metal-free bleomycin can be prepared by treatment with hydrogen sulfide. A mixture of metal-free bleomycins consisting mainly of A_2 (55–70%) and B_2 (25–32%) has been used for clinical treatment because the mixture has an effect superior to that of A_2 alone on human squamous cell carcinoma. The copper ion in bleomycin is replaced by iron after penetration into cells. A bleomycin–iron complex that exerts antitumor activity is formed. More than 300 bleomycin analogs have been prepared by chemical modifications or fermentations. *Pepleomycin* (**76**), *possessing improved properties, has recently been brought into clinical use [196] and the tallysomycins A and B*, **77** and **78**, respectively, are similar glycopeptides [197], [198].



Bleomycinic acid (**64**) [*37364-66-2*]: R = OH

Bleomycin A_1 (**65**) [*58995-26-9*]: R = $NH(CH_2)_3SCH_3$
Bleomycin demethyl A_2 (**66**) [*41089-03-6*]: R = $NH(CH_2)_3SCH_3$
Bleomycin A_2 (**67**) [*11116-31-7*]: R = $NH(CH_2)_3S^+(CH_3)_2$, X^-
Bleomycin A_2' -a (**68**) [*73666-81-6*]: R = $NH(CH_2)_4NH_2$
Bleomycin A_2' -b (**69**) [*41138-53-8*]: R = $NH(CH_2)_3NH_2$

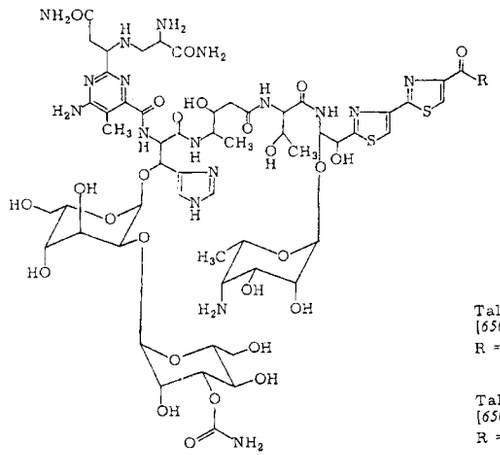
Bleomycin A_2' -c (**70**) [*62960-69-4*]: R = $NH(CH_2)_2$-(imidazole)

Bleomycin A_5 (**71**) [*11116-32-8*]: R = $NH(CH_2)_3NH(CH_2)_4NH_2$
Bleomycin A_6 (**72**) [*37293-17-7*]: R = $NH(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$
Bleomycin B_1 (**73**) [*41138-54-9*]: R = NH_2

Bleomycin B_2 (**74**) [*9060-10-0*]: R = $NH(CH_2)_4NHC(=NH)-NH_2$

Bleomycin B_4 (**75**) [*9060-11-1*]: R = $NH(CH_2)_4NHC(=NH)NH(CH_2)_4NHC(=NH)-NH_2$

Pepleomycin (**76**) [*68247-85-8*]: R = $NH(CH_2)_3NH-CH(CH_3)-C_5H_5$



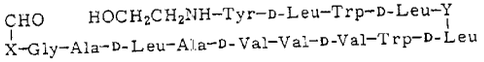
Tallysomycin A (**77**)
[*65057-90-1*]
R = $NH(CH_2)_3CH(NH_2)CH_2CONH(CH_2)_3NH(CH_2)_4NH_2$

Tallysomycin B (**78**)
[*65057-91-2*]
R = $NH(CH_2)_3NH(CH_2)_4NH_2$

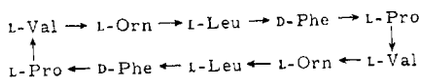
3.7.2. The Gramicidin Group

Generally speaking, peptide antibiotics with simple straight-chain structures play a minor role and are mentioned here only for review purposes. However, peptide antibiotics with cyclic structures, which often contain D-amino acids, are of considerable importance. The usual nomenclature is used here for the constituents of the amino acids: Ala = alanine; Asp = asparagine; Cys = cysteine; Dab = α,γ-diaminobutyric acid; Glu = glutamic acid; Gly = glycine; His = histidine; Ileu = isoleucine; Leu = leucine; Lys = lysine; Orn = ornithine; Phe = phenylalanine; Pro = proline; Thr = threonine; Trp = tryptophan; Tyr = tyrosine; Val = valine; Meval = *N*-methylvaline; Sar = sarcosine; Ser = serine; MOA = 6-methyloctanoic acid; IOA = isooctanoic acid. The arrow indicates the direction of the amide bond between the amino acids. Thus, the arrow begins where the carbonyl group attaches and ends where the amino group attaches (–CO–NH →).

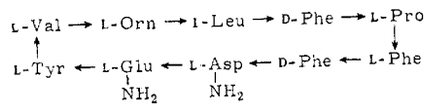
The gramicidin group consists of a series of open chain peptides and a series of cyclic peptides. Clinically important *gramicidin S* (**79**) was isolated from a strain of *Bacillus brevis* [199].



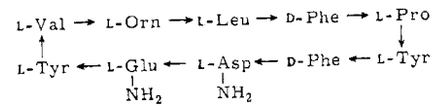
	X	Y
Valine-gramicidin A	Val	Trp
Isoleucine-gramicidin A	Ile	Trp
Valine-gramicidin B	Val	Phe
Isoleucine-gramicidin B	Ile	Phe
Valine-gramicidin C	Val	Tyr
Isoleucine-gramicidin C	Ile	Tyr



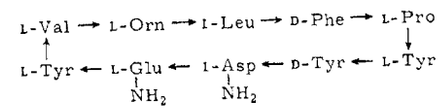
Gramicidin S (**79**)
[*113-73-5*]



Tyrocidine A
[*1481-70-5*]



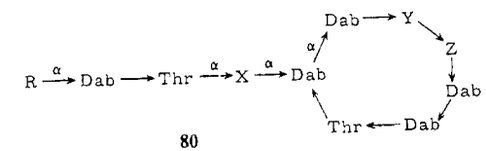
Tyrocidine B
[*865-28-1*]



Tyrocidine C
[*3252-29-7*]

3.7.3. The Polymyxins

Among the polymyxins, *polymyxins B, D, and E* are of particular importance. The *colistins A and B* correspond to *polymyxins* E_1 *and* E_2, respectively, as shown in **80** [200]. These are active only against gram-negative bacteria.



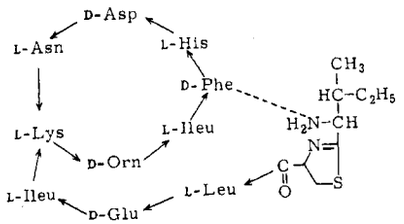
3.7.4. The Bacitracins

Bacitracin, produced by *Bacillus subtilis* [201] and *Bacillus licheniformis* [202], is active against gram-positive bacteria.

	R	X	Y	Z
Polymyxin A_1 (M1) [*65454-50-4*]	MOA	D-Dab	D-Leu	Thr
Polymyxin A_2 (M2) [*65454-51-5*]	IOA	D-Dab	D-Leu	Thr
Polymyxin B_1 [*4135-11-9*]	MOA	Dab	D-Phe	Leu
Polymyxin B_2 [*34503-87-2*]	IOA	Dab	D-Phe	Leu
Polymyxin D_1 [*10072-50-1*]	MOA	D-Ser	D-Leu	Thr
Polymyxin D_2 [*34167-45-8*]	IOA	D-Ser	D-Leu	Thr
Polymyxin E_1 (colistin A) [*7722-44-3*]	MOA	Dab	D-Leu	Leu
Polymyxin E_2 (colistin B) [*7239-48-7*]	IOA	Dab	D-Leu	Leu

Dab = α,γ-diaminobutyric acid; MOA = (+)-6-methyloctanoic acid; IOA = isooctanoic acid

After extensive study on the chemistry of bacitracins, a revised structure was proposed for *bacitracin A* (**81**) [203].



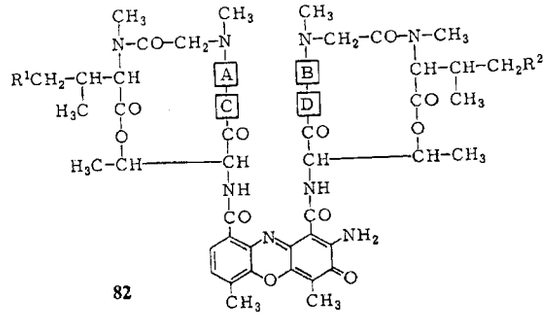
Bacitracin A (**81**)
[*1402-99-9*]

3.7.5. Large-Ring Peptide Antibiotics Containing Lactone Linkages

This important group can be classified with macrolide antibiotics because it contains a lactone moiety, but it is more properly regarded as a group of cyclic peptides. These peptides generally contain about 16- to 19-membered rings, including many amide bonds and lactone linkages. There are no C – C double bonds in the ring.

3.7.6. The Actinomycin Group

These cyclic peptide antibiotics are also known as chromopeptide antibiotics. The *actinomycins* (**82**), first isolated by WAKSMAN in 1940 from *Streptomyces antibioticus*, are of interest because they have found use in therapy of tumors, particularly Wilm's tumor.



82

Name	A	B	C	D	R^1	R^2
Actinomycin C_2 [*2612-14-8*]	L-Pro	L-Pro	D-Val	D-allo-Ile	H	H
Actinomycin C_{2a} (VI) [*17914-41-9*]	L-Pro	L-Pro	D-allo-Ile	D-Val	H	H
Actinomycin C_3 (VII) [*6156-47-4*]	L-Pro	L-Pro	D-all-Ile	D-allo-Ile	H	H
Actinomycin D (C_1, IV) [*50-76-0*]	L-Pro	L-Pro	D-Val	D-Val	H	H
Actinomycin E_1 [*1402-41-1*]	L-Pro	L-Pro	D-allo-Ile	D-allo-Ile	H	CH_3
Actinomycin E_2 [*1402-42-2*]	L-Pro	L-Pro	D-allo-Ile	D-allo-Ile	CH_3	CH_3
Actinomycin F_3 [*1402-46-6*]	Sar	Sar	D-allo-Ile	D-allo-Ile	H	H
Actinomycin F_8 (II, A_{II}) [*32934-48-8*]	Sar	Sar	D-Val	D-Val	H	H
Actinomycin F_9 (III, A_{III}) [*60469-11-8*]	L-Pro	Sar	D-Val	D-Val	H	H
Actinomycin $X_{0\beta}$ (I) [*1402-60-4*]	L-Pro	Pro(4-OH)	D-Val	D-Val	H	H
Actinomycin X_2 (V, A_V, B_V) [*1402-61-5*]	L-Pro	Pro(4-O)	D-Val	D-Val	H	H

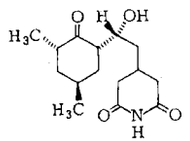
They are also used as a biochemical tool because of their specific inhibition of DNA-primed RNA synthesis. Structurally they have two pentapeptide lactone rings attached to a phenoxazinone chromophore. Several of the actinomycins isolated were found to be identical and the nomenclature is confusing. For example, actinomycin D and actinomycin C_3 are also known as dactinomycin and cactinomycin, respectively [204].

3.7.7. Other Peptide Antibiotics

There are many peptide antibiotics derived from *Streptomyces* species. Among these are amphomycin, capreomycin, distamycin, the enduracidins, mikamycin, neocarzinostatin (antitumor), stendomycin, viomycin, and virginiamycin.

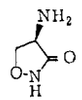
3.8. Other Important Antibiotics and Intermediates

Cycloheximide (83) is produced by *Streptomyces griseus* [205]. It is highly effective against fungi and is therefore used mainly for plant protection. The analogs streptovitacin, naramycin B, and streptimidone have also been isolated, and also are called glutarimide antibiotics because of their common structural moiety.



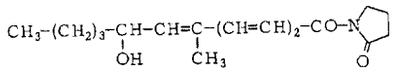
Cycloheximide (83)
[66-81-9]

Cycloserine (84) (*oxymycin, seromycin, orientomycin*) is the simplest antibiotic, D-4-amino-3-isoxazolidine, isolated from many *Streptomyces* species [206]. Cycloserine is now produced only synthetically and used particularly for tuberculosis of the lungs and for leprosy with *p*-aminosalicylic acid (PAS) or isonicotinic acid hydrazide (INH).



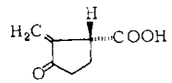
Cycloserine (84)
[68-41-7]

Variotin (85) (*pecilocin*) is produced by *Paecilomyces varioti* [207]. It is an oily, ester-like substance with an aromatic odor and is particularly active against fungi. Variotin is used against trichophytes.



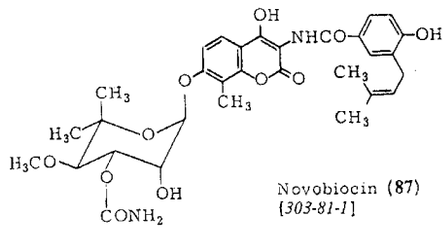
Variotin (85)
[19504-77-9]

Sarkomycin A (86) is produced by *Streptomyces erythrochromogenes* [208]. It is active not only as an antibiotic but also as an antitumor agent.



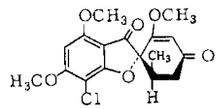
Sarkomycin (86)
[489-21-4]

Novobiocin, isolated from a culture filtrate of *Streptomyces nieveus,* has the structure **87**, consisting of the aglycone, novobiocic acid, and 3-*O*-carbamoylnoviose. The monosodium or calcium salt is used in therapy and is active mainly against gram-positive bacteria [209].



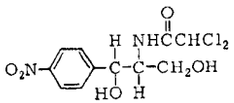
Novobiocin (87)
[303-81-1]

Griseofulvin (88) is produced by *Penicillium griseofulvum, P. janczewskii,* and *Nigrospora oryzae.* It is unique in possessing the spirocarbon moiety [210], [211]. Griseofulvin is very active against fungi, and it is used orally to treat fungal infections of human skin.



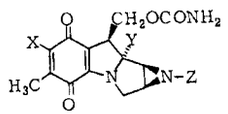
Griseofulvin (88)
[126-07-8]

Chloramphenicol (89), the first of the so-called broad-spectrum medicinal antibiotics, was originally obtained from *Streptomyces venezuelae* in 1947 [212]. It is now manufactured by a chemical process, and the parent compound and its esters are commercially available. Chloramphenicol is active against rickettsia, chlamydiae, and mycoplasmas, as well as a wide range of gram-positive and gram-negative bacteria. However, use is limited by the risk of bone marrow damage or aplastic anemia at too high or too prolonged an application [213].



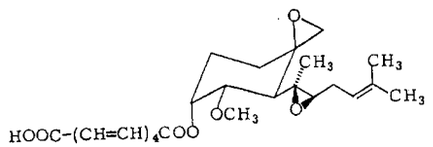
Chloramphenicol (**89**)
[*56-75-7*]

Mitomycins ((**90**)–(**93**)) are a group of unique chemical structures in which three different carcinostatic functions — aziridine, carbamate, and quinone — are arranged around a pyrro[1,2-*a*]indole nucleus [214]. The first mitomycins were discovered in 1956 by HATA in a culture filtrate of *Streptomyces caespitosus*. These compounds, designated mitomycins A and B, show highly potent antibacterial activity and moderate antitumor activity, but they are quite toxic in mice. In 1958, mitomycin C, an extremely valuable antitumor drug, was isolated from *Streptomyces caespitosus* [215], [216]. In 1960, another mitomycin, porfiromycin (**93**), was isolated from *Streptomyces ardus*.



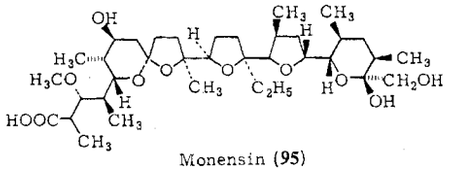
Name	X	Y	Z
Mitomycin A (**90**) [*4055-39-4*]	OCH_3	OCH_3	H
Mitomycin B (**91**) [*4055-40-7*]	OCH_3	OH	CH_3
Mitomycin C (**92**) [*50-07-7*]	NH_2	OCH_3	H
Porfiromycin (**93**) [*801-52-5*]	NH_2	OCH_3	CH_3

Fumagillin (**94**) is a useful polyene antibiotic; feeding it to honeybees with natural *Nosema apis* infections suppressed the disease and led to considerably increased honey production [217].



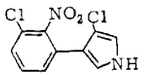
Fumagillin (**94**)
[*23110-15-8*]

Monensins (**95**) are useful polyether antibiotics that control infections of *Coccidia*. They are particularly important to the poultry industry [218].



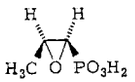
Monensin (**95**)
[*17090-79-8*]

Pyrrolnitrin (**96**), isolated from *Pseudomonas* species, is highly active against fungi, particularly trichophyte species.



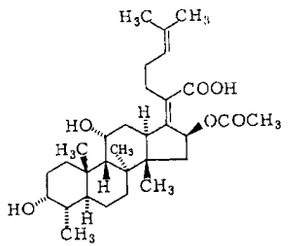
Pyrrolnitrin (**96**)
[*1018-71-9*]

Fosfomycin (**97**) is unique in possessing a simple epoxide ring and has a broad activity spectrum against gram-positive and gram-negative bacteria [219].



Fosfomycin (**97**)
[*23155-02-4*]

Fusidic acid (**98**) has a steroidal skeleton, but it is markedly different from the usual steroid hormones in biological activity. Fusidic acid has been isolated from *Fusidium coccineum* and is particularly active against *Staphylococcus, Clostridium, Neisserias, Corynebacterium diphtheriae*, and *Mycobacterium tuberculosis* [220].



Fusidic acid (**98**)
[*6990-06-3*]

D-(*p*-Hydroxyphenyl)glycine (D-HPG) is widely used in large amounts as an important intermediate for the synthesis of amoxicillin and several other semisynthetic β-lactam antibiotics.

Industrially, D-HPG has been produced by resolving the racemic DL-HPG obtained by the usual nonenzymatic synthesis. The optical resolution by means of fractional crystallization of the corresponding diastereomeric salt or by the predominant crystallization of the corresponding aromatic sulfonic acid salt are typical methods. However,