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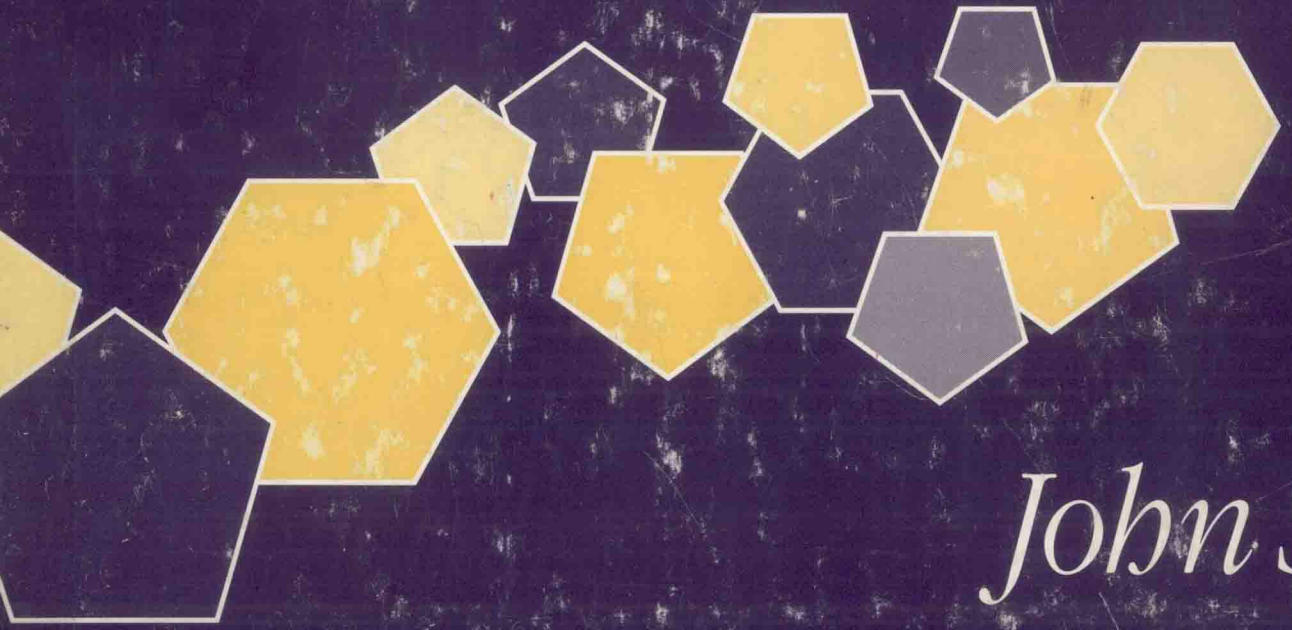
THIRD EDITION



John S. Glasby

Encyclopedia of Antibiotics

3rd edition

John S. Glasby

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Preface

Since the second edition of this Encyclopedia 12 years ago, the number of new antibiotics which have been discovered has increased enormously, particularly those derived from new and mutant strains of known organisms. In order to keep the present volume to a reasonable size, a number of changes have been made to the previous format. Where several related antibiotics have structures differing only in a few substituents, these have been grouped together and the substituents are given in the text under a single chemical structure.

As before, the author wishes to thank all those who have provided important chemical and medical data on these compounds and, in particular, the library staff of the University of Lancaster for access to scientific journals.

Heysham, Lancashire

J. S. Glasby

A

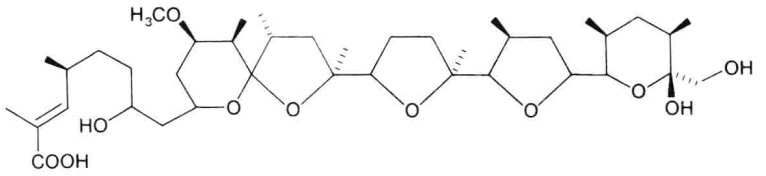
AABOMYCIN

$C_{39-40}H_{65-68}O_{11}N$
M.p. 144–145°C
$[\alpha]_D^{26}$ +93·5° (c 1·0, $CHCl_3$)
This is an antibiotic elaborated by *Streptomyces hygroscopicus* var. *aabomyceticus* cultivated on a medium of glucose, dried beer yeast, defatted soybean flour, meat extract and NaCl at 26–27°C and pH 7·0 for 4 days. Aabomycin forms colourless needles from aqueous EtOH, $CHCl_3$–C_6H_6 or C_6H_6–EtOAc. It is not active against bacteria but is effective against *Piricularia oryzae* and *Trichophyton rubrum*. Mice tolerate a dose of 100 mg/kg given intravenously.

Aizawa *et al.*, *J. Antibiotics* (Japan), **22**, 457 (1969)
Yamaguchi *et al.*, *ibid*, **22**, 463 (1969)
Misato *et al.*, *Japanese Patent*, 71 21,794 (1971)

ABIERIXIN

$C_{40}H_{68}O_{11}$
M.p. 83–85°C
$[\alpha]_D^{25}$ +45° (c 0·03, MeOH)

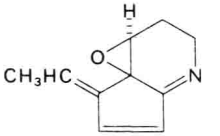


A polyether antibiotic isolated from cultures of *Streptomyces albus*, abierixin is a white amorphous powder when precipitated from H_2O. It is weakly active against gram-positive bacteria.

David *et al.*, *J. Antibiotics* (Japan), **38**, 1655 (1985)

ABIKOVIROMYCIN

$C_{10}H_{11}ON$



Produced by *Streptomyces abikoensis* and *S. rubescens*, this antibiotic has not been obtained pure. It polymerizes rapidly even at −50°C. The sulphate, decomposing at 140–141°C with $[\alpha]_D$ +24° (c 1·0, H_2O), and the picrate, decomposing at 137–140°C, are both stable. Abikoviromycin is active against both Eastern and Western equine encephalomyelitis when dilutions of 1:8,000,000 are mixed with the virus suspensions and administered intracerebrally into mice. It is not effective against the Venezuelan-type virus. The antibiotic is only slightly active against bacteria and fungi. The LD_{50} is 1·0 mg (subcutaneous) and 0·1 mg (intravenous) per 12 g mouse. It has a limited use in medicine as an antimicrobial agent.

Umezawa *et al.*, *Japan. Med. J.*, **4**, 331 (1951)
Umezawa *et al.*, *Japanese Patent*, 6200 (1952)
Identity with latumcidin
Sakagami *et al.*, *J. Antibiotics* (Japan), **11A**, 231 (1958)
See also
Gurevitch *et al.*, *Dokl. Akad. Nauk. USSR*, **182**, 828 (1968)

ABKHAZOMYCIN

An antibiotic isolated from cultures of *Streptomyces badiocolor* var. *abkhasus*, this compound has only weak activity against bacteria and yeasts but is effective against a range of fungi.

Barashkova *et al.*, *Antibiotiki*, **20**, 195 (1975)

ABLASTMYCIN

$C_{18}H_{34}O_{10}N_2$
M.p. Indefinite
Produced by *Streptomyces aburaviensis* var. *ablastmyceticus* freshly isolated from soil and cultivated in a common nutrient medium at 28°C for 3 days,

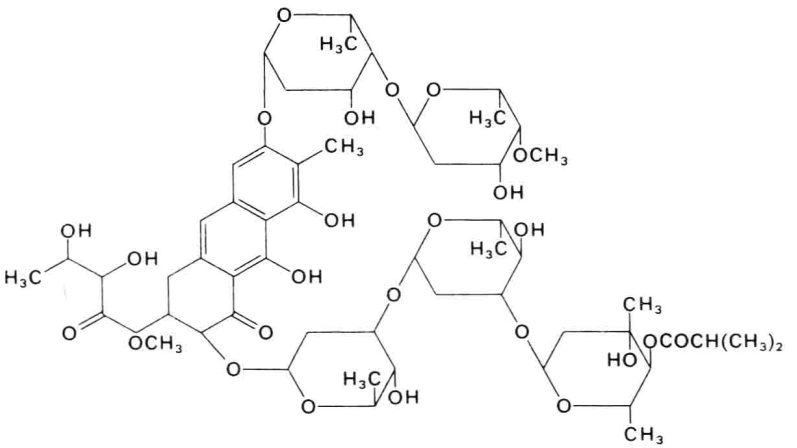
ablastmycin is a basic white powder, insoluble in most organic solvents but soluble in H_2O. It is inactive against bacteria but highly effective against *Piricularia oryzae* and *Helminthosporium oryzae* in the presence of rice juice. It has found some use in the treatment of rice blast.

Umezawa *et al.*, *Japanese Patent*, 72 07,059 (1972)

ABURAMYCIN A
See Chromomycin A_2

ABURAMYCIN B
See Chromomycin A_3

ABURAMYCIN C
$C_{57}H_{84}O_{25}$
M.p. Indefinite
$[\alpha]_D$ −17° (c 1·0, EtOH)

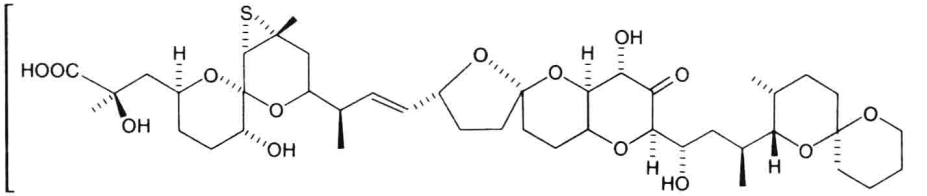


An unclassified *Streptomyces* species yields this antibiotic as an amorphous yellowish powder. The UV spectrum has absorption maxima at 228, 282, 318, 351 and 415 nm ($CHCl_3$). The peracetate has m.p. 219–221°C and $[\alpha]_D$ −18° ($CHCl_3$). It has found some use as a cancerostatic agent.

Berlin *et al.*, *Nature*, **218**, 193 (1968)

ABURAMYCIN D
See Chromomycin A_4

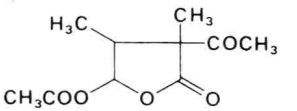
ACANTHIFOLICIN
$C_{44}H_{68}O_{13}S$
M.p. 167–168°C
$[\alpha]_D$ +25·3° (c 0·8, $CHCl_3$)



Pandaros acanthifolium yields this polyether antibiotic which forms colourless crystals from EtOH and has the structure shown above. It possesses antitumour and cytotoxic properties.

Schmitz *et al.*, *J. Am. Chem. Soc.*, **103**, 2467 (1981)

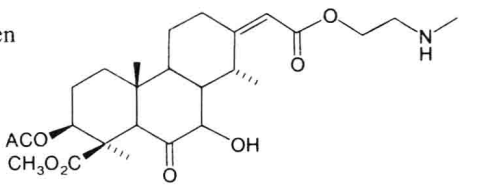
ACETOMYCIN
$C_{10}H_{14}O_5$
M.p. 115°C (subl. 70°C)
$[\alpha]_D$ −167° (EtOH)



A simple antibiotic produced by *Streptomyces ramulosus*, this compound forms colourless rods and is active against a range of gram-positive bacteria.

Ettlinger *et al.*, *Helv. Chim. Acta*, **41**, 316 (1958)

3β-ACETOXYNORERYTHROSUAMINE
$C_{26}H_{39}O_8N$
M.p. Not given

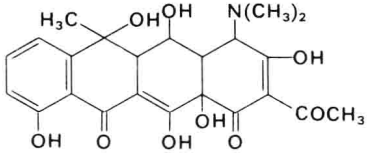


The bark of *Erythrophleum chlorostachys* yields this alkaloidal antibiotic which has been characterized as the hydrochloride, m.p. 173–175°C. It has the structure shown above and possesses pronounced cytotoxic properties.

Loder, Nearn, *Tetrahedron Lett.*, 2497 (1975)

2-ACETYL-2-DECARBOXYAMIDO-OXYTETRACYCLINE (*Terramycin X*)

$C_{23}H_{25}O_9N$

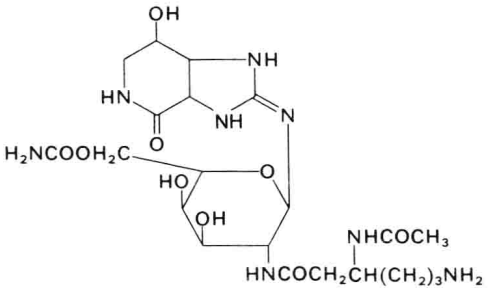


A tetracycline antibiotic produced by *Streptomyces rimosus*, this compound is normally obtained as the crystalline hydrochloride, m.p. 201–203°C, $[\alpha]_D^{25}$ −46·6° (c 0·9, 0·1 N HCl). It is a broad spectrum antibiotic, active against gram-positive and gram-negative bacteria.

Hochstein *et al.*, *J. Am. Chem. Soc.*, **82**, 5934 (1960)
Frolova *et al.*, *Antibiotiki*, **16**, 687 (1971)

β-N-ACETYLRACEMOMYCIN

$C_{21}H_{36}N_8O_9$



An acetyl derivative of racemomycin (q.v.), this antibiotic has been prepared by a series of selective chemical reactions. The minimim inhibitory concentration for *Staphyloccus aureus* is 400 μg/ml compared with 10 μg/ml for the parent antibiotic. From this it has been concluded that the β-amino group of the β-lysine side chain in racemomycin is of significant importance as a site for antimicrobial activity.

Sawada, Taniyama, *Yakugaku Zasshi*, **94**, 264 (1974)

ACHROMYCIN

See Puromycin

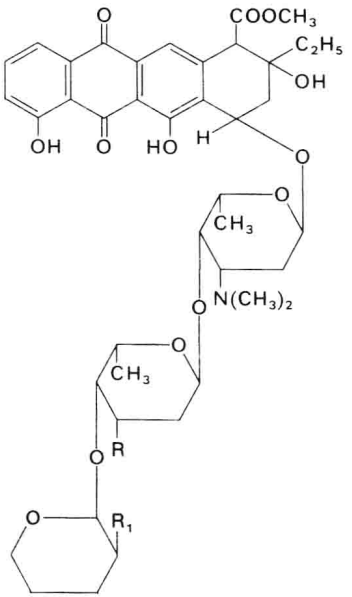
ACIDOPHILIN

An antiobiotic substance obtained from *Lactobacillus acidophilus* by fermentation in a medium containing sterilized skimmed milk, it is normally employed as an aqueous suspension and is active against gram-positive bacteria.

Shahani *et al.*, *U.S. Patent*, 3,689,640 (1972)

ACLACINOMYCIN A

$C_{42}H_{53}NO_{15}$
R = OH, R_1 = H



ACLACINOMYCIN B

$C_{42}H_{51}NO_{15}$
R, R_1 = O
Glycosidic antibiotics isolated from an unclassified microorganism, these compounds form amorphous white powders and are separated chromatographically. They are broad spectrum antibiotics possessing bacteriostatic, fungistatic, antiviral and antileukaemic activity.

Oki *et al.*, *J. Antibiotics* (Japan), **28**, 830 (1975)

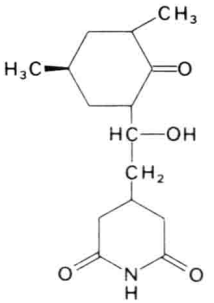
ACRYLAMIDINE

This is an unstable antibiotic produced by an unclassified species of *Streptomyces* allied to *S. eurythermus*. Normally isolated as the crystalline hydrochloride, this compound has no activity against bacteria but is weakly active against species of *Candida*.

Yagishita *et al.*, *J. Antibiotics* (Japan), **21**, 444 (1968)

ACTIDIONE (*Cycloheximide, Naramycin A*)

$C_{15}H_{23}O_4N$
M.p. 115–116·5°C (119·5–121°C)
$[\alpha]_D^{25}$ −2·8° (c 9·6, MeOH)



An antibiotic formed by streptomycin-producing strains of *Streptomyces griseus*, this compound is not active against bacteria but is highly active against several yeasts. It forms colourless plates from amyl acetate or H_2O containing a little MeOH, the latter having the higher melting point. It yields a number of crystalline derivatives: acetate, m.p. 150–152°, $[\alpha]_D^{25}$ +24·6° (c 3·7, MeOH); semicarbazone, m.p. 215–220°C (*dec.*); and the *p*-nitrobenzoyl derivative, m.p. 72–75°C.

When tested against representative bacteria it fails to inhibit even at concentrations up to 1 mg/ml but even in concentrations as low as 0·002 mg/ml it inhibits *Cryptococcus neoformans*, a pathogenic fungus causing cryptococcosis, a rare but normally fatal disease. The LD_{50} is approximately 150 mg/kg (intravenous) in mice.

Whiffen *et al.*, *J. Bacteriol*, **52**, 610 (1946)
Leach *et al.*, *J. Am. Chem. Soc.*, **69**, 474 (1947)
Kornfield *et al.*, *ibid.*, **71**, 150 (1949)
Okuda, *Chem. Pharm. Bull.*, **7**, 659 (1959)
Evans, Smith, *J. Biol. Chem.*, **246**, 6144 (1971)
Verbin *et al.*, *Cancer Res.*, **33**, 2086 (1973)
Szabo *et al.*, *Hung. Teljes*, HU 7931 (1974)
Absolute configuration
Sharkovsky, Johnson, *Tetrahedron Lett.*, 919 (1964)
Total synthesis
Johnson *et al.*, *J. Am. Chem. Soc.*, **86**, 118 (1964)

ACTILIN

See Neomycin (A–F)

ACTINOBOLIN

$C_{13}H_{20}O_6N_2$
M.p. Indefinite
Streptomyces griseoviridis var. *atrofaciens* yields this antibiotic as an amorphous, hygroscopic powder. The UV spectrum has a single absorption maximum at 263 nm (EtOH). Acid hydrolysis furnishes actinobolamine, whereas alkalis yield L-alanine, 1-(2,5-dihydroxyphenyl)-propan-2-ol, ammonia and carbon dioxide. The sulphate has $[\alpha]_D^{22}$ +54·5° (c 1·0, H_2O); the acetate partially melts at 130°C followed by resolidification and decomposition at 263–266°C; the *N*-acetyl derivative has m.p. 254–255°C (*dec.*), $[\alpha]_D^{26}$ +30° (c 3·8, H_2O).

Actinobolin finds some use in medicine, principally as a broad spectrum antimicrobial agent.

Haskell, Bartz, *Antibiotics Annual*, 505 (1958–59)
Haskell *et al.*, *U.S. Patent*, 3,043,830 (1962)
Struck *et al.*, *Tetrahedron Lett.*, 1589 (1967)
Monk *et al.*, *J. Am. Chem. Soc.*, **90**, 1087 (1968)

ACTINOCARCIN

A complex antibiotic, actinocarcin is produced by *Streptomyces cinnamomeus* when grown on a common nutrient medium. Acid hydrolysis with 1N HCl for 20 hours at 110°C furnishes arginine, aspartic acid, histidine, isoleucine, leucine, lysine, phenylalanine, serine, threonine and tyrosine. Actinocarcin is inactive against bacteria, fungi and yeasts, but injections with a dose of 1 mg/kg/day for 6 days prolonged the survival period of mice inoculated with cells of Ehrlich sarcoma. The LD_{50} for mice is approximately 40–50 mg/kg given for 6 days.

Kihora *et al.*, *J. Antibiotics* (Japan), **27**, 994 (1974)

ACTINOFLAVIN

See Actinomycin J_1

ACTINOMYCELIN

An antibiotic produced by a *Streptomyces* species related to *S. antibioticus*, this compound forms yellow-green crystals soluble in EtOH or H_2O with an intense green fluorescence. It is most stable in neutral solution. Actinomycelin is active against gram-positive bacteria but not against mycobacteria or fungi. The LD_{50} in rats is 25 mg/kg (subcutaneous).

Cercos, *Publ. Tech. Fitotecnia* (Buenos Aires), **16**, 147 (1948)

ACTINOMYCES LYSOZYME

This antibiotic substance has been obtained from *Streptomyces violaceus* and classified as a lysozyme.

Kriss, *Mikrobiologiya* (USSR), **9**, 32 (1940)

ACTINOMYCETIN

Produced by *Streptomyces albus* cultures in beef-bouillon, this lytic substance is said to be a protein. The structure is not known but it is said to consist of an enzyme, actinozyme, and a lipoid antibacterial fatty acid. Strong acids and UV light below 300 nm destroy the antibiotic. Electronmicrographs show it to consist of particles with a diameter of about 4 millimicrons.

Actinomycetin dissolves such organisms as *Staphylococcus aureus* in aqueous suspension and also dead gram-negative organisms. Dissolution of dead gram-positive organisms takes place too but with more difficulty. No data on its toxicity have been reported.

Gratia, Alexander, *C. R. Soc. Biol.*, **91**, 1442 (1924)
Gratia, *Bull. Mem. Acad. Chir.*, **56**, 344 (1930)
Welsch, *J. Bacteriol.*, **42**, 801 (1941)
Ghuysen, *Belgian Patents*, 517,191 and 521,114 (1953)
See also
Hoogerheide, Welsch, *Bot. Rev.*, **10**, 599 (1944)
Hoogerheide, Welsch, *J. Bacteriol.*, **53**, 101 (1947)

ACTINOMYCIN A (*Actinomycin B, Actinomycin X*)

This antibiotic has been obtained and described under various synonyms —actinomycin A (Waksman and Woodruff), actinomycin B (Lehr and Berger) and actinomycin X (Linge). Since the last worker has demonstrated that the substance can be fractionated into at least two closely related components, actinomycins X_1 and X_2, these are described below in more detail.

ACTINOMYCIN A_{II}

See Actinomycin F_8

ACTINOMYCIN A_{III}

See Actinomycin F_9

ACTINOMYCIN A_V

See Actinomycin X_2

ACTINOMYCIN B

See Actinomycin A

ACTINOMYCIN B_V

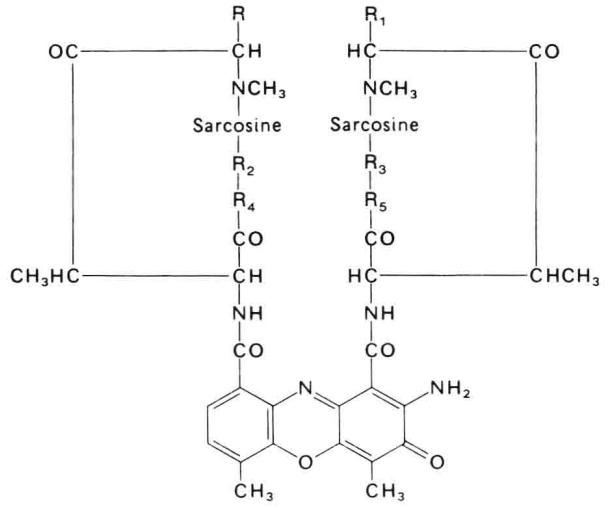
See Actinomycin X_2

ACTINOMYCIN C_1

See Actinomycin D

ACTINOMYCIN C_2 (*Actinomycin I_2, VI*)

$C_{63}H_{88}O_{16}N_{12}$
$R = R_1 = CH(CH_3)_2$; $R_2 = R_3$ = L-proline; R_4 = D-valine; R_5 = D-*allo*-isoleucine
M.p. 237–239°C
$[\alpha]_D$ $-325° \pm 10°$ (MeOH)



Streptomyces antibioticus and *S. chrysomallus* yield this antibiotic which is separated from the accompanying components by countercurrent distribution methods. It forms red needles or bipyramids from C_6H_6 or EtOH. Actinomycin C_2 is an anisoactinomycin in that the two peptide chains are different (cf. actinomycin C_3). The biological activity and toxicity are virtually identical to those given for actinomycin D (q.v.). Reisch and his colleagues give the concentration required to inhibit the growth of *Bacillus subtilis* as 0·25 μg/ml. The activity against *B. subtilis* diminishes with any change in the chromophore, e.g. 7-hydroxyactinomycin C_2 had only about 0·2 per cent of the activity of actinomycin C_3 (taken as the standard).

Brockmann, Pfennig, *Naturwiss.*, **39**, 429 (1952)
Brockmann, Grone, *Chem. Ber.*, **87**, 1036 (1954)
Brockmann, *Angew. Chem.*, **72**, 944 (1960)
Brockmann *et al.*, *Naturwiss.*, **47**, 62 (1960)
Brockmann, Petras, *ibid.*, **48**, 218 (1961)
Brockmann, Boldt, *ibid.*, **50**, 19 (1963)

Structure

Brockmann *et al.*, *Chem. Ber.*, **99**, 3672 (1966)

Synthesis

Brockmann, Lackner, *Tetrahedron Lett.*, 3517 (1964)

Biological activity

Brockmann *et al.*, *Tetrahedron Lett.*, 3531 (1966)

ACTINOMYCIN C_{2a} (*Actinomycin i-C_2*)

$C_{63}H_{86}O_{16}N_{12}$
$R = R_1 = CH(CH_3)_2$; $R_2 = R_3$ = L-proline; R_4 = D-*allo*-isoleucine; R_5 = D-valine
M.p. 233–235°C
$[\alpha]_D^{18}$ −297° (c 0·267, MeOH)
A component of the actinomycin C complex produced by *Streptomyces chrysomallus*, this antibiotic forms red needles from EtOH and is isomeric with the preceding antibiotic. The toxicity and biological activity are similar to those of actinomycin D.

Brockmann, Frank, *Naturwiss.*, **47**, 15 (1960)

Synthesis

Brockmann, Lackner, *Tetrahedron Lett.*, 3517 (1964)

ACTINOMYCIN i-C_2

See Actinomycin C_{2a}

ACTINOMYCIN C_3 (*Actinomycin VII*)

$C_{64}H_{90}O_{16}N_{12}$
$R = R_1 = CH(CH_3)_2$; $R_2 = R_3$ = L-proline; $R_4 = R_5$ = D-*allo*-isoleucine
M.p. 234°C
$[\alpha]_D^{20}$ −357° (C_6H_6)
An antibiotic produced by *Streptomyces antibioticus* and *S. chrysomallus*, this compound forms reddish crystals preferably from EtOAc on addition of CS_2. It is an isoactinomycin since both peptide chains are identical. The first synthesis of an actinomycin was based upon the observation by Sunderkotter that actinomycin C_3 is hydrolytically cleaved between sarcosine and L-*N*-methylvaline to yield bis-(seco-actinomycin C_3), the latter being synthesized through oxidative coupling which brings about dimerization. The bis-(seco-actinomycin C_3) readily reforms the natural antibiotic.

X-ray studies have shown that actinomycin C_3 may have a pseudo-twofold axis of symmetry in the plane of the phenoxazine ring. Solutions in organic solvents contain only monomers but in aqueous solutions dimers predominate between concentrations of 10^{-5} and 10^{-3} molar. At higher concentrations oligomers are formed.

Actinomycin C_3 is active against gram-positive bacteria and inhibits the growth of *Bacillus subtilis* at a concentration of 0·25 μg/ml. It is highly

effective against rhabdomyosarcoma, Wilm's tumour and trophoblastic tumours. Clinical use, however, is limited by its high toxicity; 50 mg/kg being lethal to mice when given orally. The antibiotic complexes with DNA and inhibits the synthesis of RNA although it does not complex with the latter. There is little doubt that this antibiotic acts in the same manner as actinomycin D (q.v.) and a small angle X-ray scattering study on the interaction between actinomycin C_3 and calf thymus DNA has been reported.

Brockmann *et al.*, *Naturwiss.*, **47**, 230 (1960)
Brockmann, Lackner, *ibid.*, **48**, 555 (1961)
Brockmann, Boldt, *ibid.*, **50**, 19 (1963)
Synthesis
Brockmann, Sunderkotter, *Naturwiss.*, **47**, 229 (1960)
X-ray studies
Perutz, *Nature*, **201**, 814 (1964)
Marsh Jnr, Goodman, *Can. J. Chem.*, **44**, 799 (1966)
Solution studies
Berg, *J. Electroanal. Chem.*, **10**, 371 (1965)
Muller, Ennie, *Z. Naturforsch.*, **20B**, 835 (1965)
Gellert *et al.*, *J. Mol. Biol.*, **11**, 445 (1965)
Crothers *et al.*, *Biochemistry*, **7**, 1817 (1968)
Complexes with nucleic acids
Muller, Spatz, *Z. Naturforsch.*, **20B**, 842 (1965)
Crothers, Ratner, *Biochemistry*, **7**, 1823 (1968)
Schara, Muller, *Eur. J. Biochem.*, **29**, 210 (1972)
Complex with calf thymus DNA
Zipper *et al.*, *Fed. Eur. Biochem. Soc. Lett.*, **25**, 123 (1972)

ACTINOMYCIN D (*Actinomycin C_1, D_{IV}, I, IV, X, Dactinomycin*)

$C_{62}H_{86}O_{16}N_{12}$
$R = R_1 = CH(CH_3)_2$; $R_2 = R_3$ = L-proline; $R_4 = R_5$ = D-valine
M.p. 235·5–236·5°C (*dec.*)
$[\alpha]_D^{23}$ −262° (c 0·25, EtOH aq.)

The most important of the actinomycins produced by *Streptomyces antibioticus* and *S. chrysomallus*, this compound forms red crystals from C_6H_6. The UV spectrum has an absorption maximum at 242 nm (EtOH) with negative Cotton effects centred at 269 and 213 nm. X-ray studies do not differentiate between a decapeptide dilactone and a bis-pentapeptide lactone structure but Brockmann has proved the latter structure both by degradation and synthesis.

Actinomycin D is active against gram-positive bacteria but has only a limited activity against gram-negative organisms. The minimum inhibitory concentration against *Bacillus subtilis* has been given as 0·02 μg/ml. Like all actinomycins, this antibiotic is highly toxic. A dose of 5 mg/kg intraperitoneally, or 50 mg/kg orally, is lethal to mice. Nevertheless, it possesses marked antineoplastic effects in non-toxic doses and is a highly effective chemotherapeutic agent in the treatment of carcinoma, particularly of the lymphatic system, and has a use in treating Hodgkin's disease, rhabdomyosarcoma, trophoblastic tumours and Wilm's tumour. The cytostatic properties are due to its complexing with DNA and the consequential inhibition of RNA synthesis.

Molecular models for the actinomycin D–DNA complex have been put forward; two in which the chromophore of the antibiotic is intercalated between two successive base pairs and two in which the antibiotic is bound to the outside of the double-stranded DNA helix. A model described by Sobell and Jain explains most of the observed data, this model combining the specificity of the guanine 2-amino group of the two 'outside-bound' models with the intercalative feature of the 'inner-bound' models.

Studies with numerous synthetic actinomycins have shown that the efficiency of actinomycin D requires a precise and unique fit between the antibiotic and DNA. Even a small change in the actinomycin D molecule interferes with the structural geometry of the complex and renders the system less active.

Waksman, Woodruff, *Proc. Soc. Exp. Biol. Med.*, **45**, 609 (1940)
Waksman, Tishler, *J. Biol. Chem.*, **142**, 519 (1942)
Johnson, *Chem. Soc. Spec. Publ.*, No. 5, 82 (1956)
Roussos, Vining, *J. Chem. Soc.*, 2469 (1956)
Brockmann *et al.*, *Naturwiss.*, **47**, 62 (1960)
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Katz, Weissbach, *J. Biol. Chem.*, **237**, 882 (1962)
Weissbach *et al.*, *ibid.*, **240**, 4377 (1965)
Katz, *Antibiotics II, Biosynthesis*, Ed. Gottlieb, Shaw, p. 276, Springer-Verlag, New York (1967)
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Brockmann, Petras, *Naturwiss.*, **48**, 218 (1961)
Woodward *et al.*, *J. Am. Chem. Soc.*, **83**, 1010 (1961)
Staab, *Angew. Chem.*, **74**, 407 (1962)
Brockmann *et al.*, *Naturwiss.*, **51**, 382, 384, 407 (1964)
Brockmann *et al.*, *Chem. Ber.*, **99**, 3672 (1966)

Meienhofer, *J. Am. Chem. Soc.*, **92**, 3771 (1970)
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Palmer *et al.*, *Nature*, **202**, 1052 (1964)
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Victor *et al.*, *Tetrahedron Lett.*, 4721 (1969)
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Arison, Hoogsteen, *Biochemistry*, **9**, 3976 (1970)
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Meienhofer, *Experientia*, **24**, 776 (1968)
Meienhofer, *J. Am. Chem. Soc.*, **92**, 3771 (1970)
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Goldberg *et al.*, *Proc. Natl. Acad. Sci. USA*, **48**, 2094 (1962)
Reich, Goldberg, *Proc. Nucleic Acid Res.*, **3**, 183 (1964)
Wells, Larson, *J. Mol. Biol.*, **49**, 319 (1970)
Sobell, *Prog. Nucleic Acid Res. Mol. Biol.*, **13**, 153 (1973)
Models of actinomycin D–DNA complex
Hamilton *et al.*, *Nature*, **198**, 538 (1963)
Muller, Crothers, *J. Mol. Biol.*, **35**, 251 (1968)
Gurskii, *Mol. Biol.*, **3**, 749 (1969)
Sobell, Jain, *J. Mol. Biol.*, **68**, 21 (1972)

ACTINOMYCIN D_0

An antibiotic described by Russian workers, this compound differs from previously known actinomycins in that one of the sarcosine units is replaced by glycine.

Devan *et al.*, *Antibiotiki*, **19**, 107 (1974)

ACTINOMYCIN D_{IV}

See Actinomycin D

ACTINOMYCIN E_1

$C_{64}H_{96}O_{16}N_{12}$
$R = CH(CH_3)_2$; $R_1 = CH(CH_3)C_2H_5$; $R_2 = R_3$ = L-proline;
$R_4 = R_5$ = D-*allo*-isoleucine

ACTINOMYCIN E_2

$C_{65}H_{98}O_{16}N_{12}$
$R = R_1 = CH(CH_3)C_2H_5$; $R_2 = R_3$ = L-proline;
$R_4 = R_5$ = D-*allo*-isoleucine
Two similar antibiotics are produced when *Streptomyces antibioticus* is grown on a medium containing DL-isoleucine. Both form red crystals from C_6H_6 and possess similar biological activity to that of actinomycin C_3.

Gunther, Schmidt-Kastner, *Naturwiss.*, **43**, 131 (1956)
Brockmann, *Angew. Chem.*, **72**, 945 (1960)

ACTINOMYCIN F_1 (*Actinomycin KS4 : KS4*)

$C_{58}H_{88}O_{16}N_{12}$
$R = R_1 = CH(CH_3)_2$; $R_2 = R_3$ = sarcosine; R_4 = D-valine;
R_5 = D-*allo*-isoleucine

ACTINOMYCIN F_2

$C_{60}H_{90}O_{16}N_{12}$
$R = R_1 = CH(CH_3)_2$; R_2 = L-proline; R_3 = sarcosine; R_4 = D-valine;
R_5 = D-*allo*-isoleucine

ACTINOMYCIN F_3

$C_{59}H_{90}O_{16}N_{12}$
$R = R_1 = CH(CH_3)_2$; $R_2 = R_3$ = sarcosine; $R_4 = R_5$ = D-*allo*-isoleucine

ACTINOMYCIN F_4

$C_{61}H_{92}O_{16}N_{12}$
$R = R_1 = CH(CH_3)_2$; R_2 = L-proline; R_3 = sarcosine;
$R_4 = R_5$ = D-*allo*-isoleucine
Streptomyces chrysomallus and *S.* BOP 476 (NRRL 2580) produce these four structurally similar antibiotics which have been separated by countercurrent distribution methods. All form reddish crystals from C_6H_6 and have a biological activity similar to that of actinomycin C_3.

Gunther, Schmidt-Kastner, *Naturwiss.*, **43**, 131 (1956)
Brockmann, *Angew. Chem.*, **72**, 939 (1960)

ACTINOMYCIN F_8 (*Actinomycin II, A_{II}*)

$C_{57}H_{86}O_{16}N_{12}$
$R = R_1 = CH(CH_3)_2$; $R_2 = R_3$ = sarcosine; $R_4 = R_5$ = D-valine
M.p. 215–218°C
$[\alpha]_D^{17}$ −157° (c 0·24, $CHCl_3$)

ACTINOMYCIN F_9 (*Actinomycin III, A_{III}, X_0*)
$C_{60}H_{84}O_{16}N_{12}$
$R = R_1 = CH(CH_3)_2$; R_2 = L-proline; R_3 = sarcosine; $R_4 = R_5$ = D-valine
M.p. 237–238°C
$[\alpha]_D^{19}$ −205° (c 0·22, $CHCl_3$)
Two antibiotics produced by *Streptomyces antibioticus*, actinomycin F_8 forms red plates from Me_2CO–CS_2 and actinomycin F_9 furnishes red prisms from Me_2CO. Both are active against gram-positive organisms and possess antineoplastic properties.

Johnson, Mauger, *Biochem. J.*, **73**, 535 (1959)
Brockmann, *Angew. Chem.*, **72**, 939 (1960)
Goss, Katz, *Antibiot. Chemother.*, **10**, 221 (1960)
Brockmann, Manegold, *Chem. Ber.*, **95**, 1081 (1962)

ACTINOMYCIN KS4:KS4
See Actinomycin F_1

ACTINOMYCIN J_1 (*Actinoflavin*)
An antibiotic isolated from *Streptomyces flavus*, this compound is closely related to actinomycin C_1 if not identical to it. It forms red crystals from Me_2CO or Et_2O and has the same biological activity as actinomycin C_1. The toxicity is very high and it has found no use in medicine.

Umezawa *et al.*, *J. Antibiotics* (Japan), **1**, 129 (1947)
Hirata, Nakanishi, *ibid.*, **2**, 181 (1948)
Hirata, Nakanishi, *Bull. Soc. Chem. Japan*, **22**, 121 (1949)

ACTINOMYCIN J_2
The antibiotic described as actinomycin J_2 has been shown to be a mixture of actinomycin J_1 and duodecyl 5-ketostearate, the latter compound having no antibiotic activity whatsoever.

Hirata, Nakanishi, *Bull. Soc. Chem. Japan*, **22**, 121 (1949)

ACTINOMYCIN Pip 1_α
$R = R_1 = CH(CH_3)_2$; R_2 = pipecolic acid; R_3 = 4-oxopipecolic acid;
$R_4 = R_5$ = D-valine

ACTINOMYCIN Pip 1_β
$R = R_1 = CH(CH_3)_2$; R_2 = pipecolic acid; R_3 = L-proline;
$R_4 = R_5$ = D-valine

ACTINOMYCIN Pip 2
$R = R_1 = CH(CH_3)_2$; $R_2 = R_3$ = pipecolic acid; $R_4 = R_5$ = D-valine
Three structurally similar antibiotics are produced when *Streptomyces antibioticus* is grown in a medium containing pipecolic acid. All form red crystals from C_6H_6 and are active against gram-positive bacteria. The minimum inhibitory concentrations against *Bacillus subtilis* are 0·25 μg/ml, 0·02 μg/ml and 0·1 μg/ml respectively.

Formica, *Diss. Abstr.*, **28B**, 3398 (1967)
Formica, Shatkin, Katz, *J. Bacteriol.*, **95**, 2139 (1968)
Formica, Katz, *J. Biol. Chem.*, **248**, 2066 (1973)

ACTINOMYCIN X
See Actinomycin A

ACTINOMYCIN $X_{0\alpha}$
$C_{60}H_{84}O_{17}N_{12}$
$R = R_1 = CH(CH_3)_2$; R_2 = sarcosine; R_3 = hydroxyproline;
$R_4 = R_5$ = D-valine
An antibiotic produced by *Streptomyces antibioticus*, this compound forms reddish crystals from C_6H_6. It has not yet been established in which chain the hydroxyproline moiety is located. The antibiotic inhibits the growth of *Bacillus subtilis* at a concentration of only 0·15 that of actinomycin C_3, taking the latter as the standard.

Brockmann *et al.*, *Naturwiss.*, **40**, 224 (1953)
Brockmann, Manegold, *Chem. Ber.*, **95**, 1081 (1962)

ACTINOMYCIN $X_{0\beta}$
$C_{62}H_{86}O_{17}N_{12}$
$R = R_1 = CH(CH_3)_2$; R_2 = L-proline; R_3 = hydroxyproline;
$R_4 = R_5$ = D-valine
M.p. 244–245°C
$[\alpha]_D^{22}$ −265° (c 0·2, Me_2CO)
A number of *Streptomyces* species elaborate this antibiotic which furnishes reddish crystals from $CHCl_3$–light petroleum. The monoacetate has m.p. 242–243°C, $[\alpha]_D^{22}$ −265° (c 0·2, Me_2CO), and the monopalmitate, m.p. 200–201°C, $[\alpha]_D^{22}$ −238° ± 5° (c 0·2, MeOH). The minimum inhibitory concentration against *Bacillus subtilis* is 0·25 times that of actinomycin C_3.

Brockmann *et al.*, *Naturwiss.*, **40**, 224 (1953)
Brockmann, Grone, *Chem. Ber.*, **87**, 1036 (1954)

Brockmann, Pampus, *Angew. Chem.*, **67**, 419 (1955)
Brockmann *et al.*, *Chem. Ber.*, **92**, 1249 (1959)
Brockmann, Manegold, *ibid.*, **93**, 2971 (1960)
Brockmann *et al.*, *Naturwiss.*, **47**, 62 (1960)
Brockmann, Manegold, *Chem. Ber.*, **95**, 1081 (1962)

ACTINOMYCIN $X_{0\gamma}$
See Actinomycin F_9

ACTINOMYCIN $X_{0\delta}$
$C_{62}H_{86}O_{17}N_{12}$
$R = R_1 = CH(CH_3)_2$; R_2 = hydroxyproline; R_3 = L-proline;
$R_4 = R_5$ = D-valine
M.p. 245–246°C
$[\alpha]_D^{20}$ −297° (c 0·2, MeOH)
A synthetic antibiotic produced by reduction of actinomycin X_1 with aluminium isopropoxide, this compound furnishes red prisms from $CHCl_3$–light petroleum. The monoacetate has m.p. 249–250°C, $[\alpha]_D^{18}$ −310° (c 0·2, MeOH), and the monopalmitate, m.p. 200–201°C, $[\alpha]_D^{21}$ −256° (c 0·2, MeOH). It is highly toxic and the minimum inhibitory concentration against *Bacillus subtilis* is 0·4 times that of actinomycin C_3.

Brockmann, Manegold, *Chem. Ber.*, **93**, 2971 (1960)
Brockmann, Manegold, *ibid.*, **95**, 1081 (1962)

ACTINOMYCIN X_1
$C_{60}H_{82}O_{17}N_{12}$
$R = R_1 = CH(CH_3)_2$; R_2 = sarcosine; R_3 = L-oxoproline;
$R_4 = R_5$ = D-valine
A minor antibiotic obtained from *Streptomyces* species, this compound forms red crystals from $CHCl_3$–light petroleum. The minimum inhibitory concentration against *Bacillus subtilis* is 0·7 times that of actinomycin C_3.

Brockmann, Grone, *Chem. Ber.*, **87**, 1036 (1954)
Brockmann, Manegold, *ibid.*, **93**, 2971 (1960)
Brockmann, Manegold, *ibid.*, **95**, 1081 (1962)

ACTINOMYCIN X_2 (*Actinomycin V*, A_V, B_V)
$C_{62}H_{84}O_{17}N_{12}$
$R = R_1 = CH(CH_3)_2$; R_2 = L-proline; R_3 = L-oxoproline;
$R_4 = R_5$ = D-valine
M.p. 249·5–250·5°C
$[\alpha]_D^{24}$ −359° (c 0·2, MeOH)
This antibiotic, produced by several *Streptomyces* species, forms red crystals from light petroleum. Reduction with aluminium isopropoxide furnishes actinomycin D and actinomycin X_0. The minimum inhibitory concentration against *Bacillus subtilis* is 1·5 times that of actinomycin C_3.

Brockmann, Linge, Grone, *Naturwiss.*, **40**, 224 (1953)
Brockmann, Grone, *Chem. Ber.*, **87**, 1036 (1954)
Brockmann, Manegold, *ibid.*, **93**, 2971 (1960)
Brockmann *et al.*, *Naturwiss.*, **47**, 62 (1960)
Brockmann, Manegold, *Chem. Ber.*, **95**, 1081 (1962)

ACTINOMYCIN Z
An actinomycin produced by *Streptomyces antibioticus*, this antibiotic contains 3-hydroxy-4-oxo-5-methylproline in the molecule.

Brockmann, Staehler, *Tetrahedron Lett.*, 3685 (1973)

ACTINOMYCIN Z_1
The structure of this actinomycin has not yet been fully established. It contains L-threonine, sarcosine, D-valine, L-*N*-methylalanine, L-*N*-methylvaline, 5-methyl(?)-4-L-α-oxoproline and a hydroxyamino acid yet to be identified. The minimum inhibitory concentration against *Bacillus subtilis* is 50 times that of actinomycin C_3.

Brockmann, Staehler, *Naturwiss.*, **52**, 391 (1965)
Brockmann, Staehler, *Hoppe-Seyler's Z. Phys. Chem.*, **343**, 86 (1966)

ACTINOMYCIN Z_5
A further actinomycin produced by *Streptomyces antibioticus*, this antibiotic contains L-*N*-methylproline, L-4-oxo-5-methylproline and L-*N*-methylalanine in the peptide chains. The L-*N*-methylproline has been shown to possess the *cis*-configuration.

Brockmann, Staehler, *Tetrahedron Lett.*, 2567 (1973)
Katz *et al.*, *Biochem. Biophys. Res. Commun.*, **52**, 819 (1973)

ACTINOMYCIN I
See Actinomycin X_0

ACTINOMYCIN I_2
See Actinomycin C_2

ACTINOMYCIN II
See Actinomycin F_8

ACTINOMYCIN III
See Actinomycin F_9

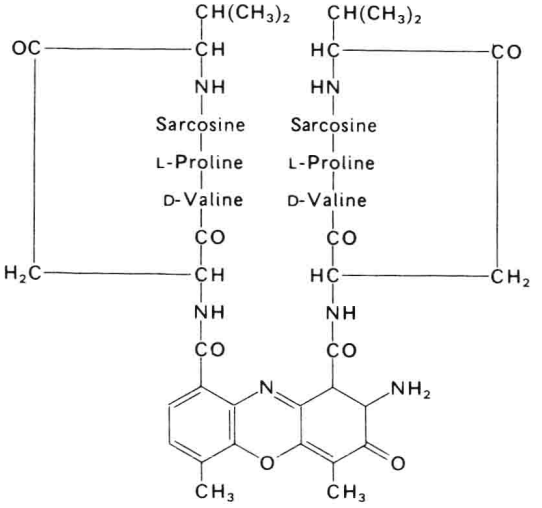
ACTINOMYCIN IV
See Actinomycin D

ACTINOMYCIN V
See Actinomycin X_2

ACTINOMYCIN VI
See Actinomycin C_2

ACTINOMYCIN VII
See Actinomycin C_3

ACTINOMYCIN (Ser-Val-Pro-Sar-MeVal)
$C_{60}H_{82}O_{16}N_{12}$
M.p. 269–273°C (*dec.*)
$[\alpha]_D^{21}$ −435° (c 0·25, MeOH)



A synthetic actinomycin, this compound forms deep red crystals from EtOAc–hexane. The UV spectrum has a single absorption maximum at 450 nm (EtOH). It has a minimum inhibitory concentration against *Bacillus subtilis* eight times that of actinomycin C_3.

Brockmann, Lackner, *Tetrahedron Lett.*, 3523 (1964)

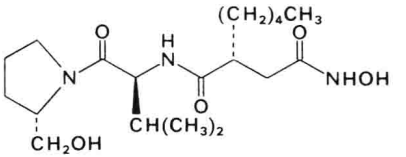
ACTINONE A
This antibiotic is the Et_2O-soluble component of actinone, isolated from a species of *Streptomyces* related to *S. antibioticus*. It is soluble in $CHCl_3$ and active against *Saccharomyces* and *Trichophyton* species. It is inactive against other fungi and bacteria. The LD_{50} in mice is 1000 mg/kg (intravenous).

Ikeda *et al.*, *J. Antibiotics* (Japan), **3**, 724 (1950)

ACTINONE B
Also obtained from a *Streptomyces* species allied to *S. antibioticus*, this antibiotic is insoluble in both Et_2O and $CHCl_3$. Its biological activity and toxicity are similar to those of the preceding compound.

Ikeda *et al.*, *J. Antibiotics* (Japan), **3**, 724 (1950)

ACTINONIN
$C_{19}H_{35}O_5N_3$
M.p. 148–149°C



An antibiotic produced by *Streptomyces* strain Cutter c/2 (NCIB 8845), this compound forms fine white needles or colourless rods from EtOH–Et_2O. It is soluble in H_2O and the lower alcohols and pyridine, stable in cold alkalis and not readily affected by cold dilute acids. Actinonin is active against both gram-positive and gram-negative bacteria, including *Bacillus anthracis*, *Klebsiella pneumoniae*, *Mycobacterium phlei*, *M. smegmatis*, *Salmonella enteritidis*, *S. typhosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*. It also inhibits the phages of a number of strains of *Staphylococcus aureus* at concentrations down to 0·25 μg/ml. It shows no apparent toxicity in mice at

doses up to 400 mg/kg. Activity *in vivo* is comparatively low, possibly due to cleavage of the antibiotic into inactive components.

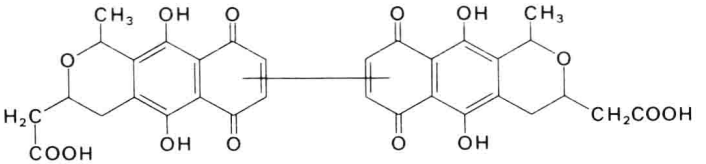
Gordon *et al.*, *Nature*, **195**, 701 (1962)
Broughton *et al.*, *J. Chem. Soc., Perkin I*, 857 (1975)

Synthesis

Anderson *et al.*, *J. Chem. Soc., Chem. Commun.*, 420 (1974)
Devlin *et al.*, *ibid.*, 421 (1974)

ACTINORHODINE

$C_{32}H_{36}O_{14}$
Decomp. 270°C



An antibiotic pigment isolated from *Streptomyces coelicolor* discovered in woods near Gottingen in Germany, this compound crystallizes as bright red needles from dioxan. In this solvent the antibiotic gives a visible spectrum consisting of absorption peaks at 523 and 560 nm. Actinorhodine inhibits *Staphylococcus aureus* at a concentration of 1:100,000.

Plotho *et al.*, *Naturwiss.*, **34**, 190 (1947)
Brockmann *et al.*, *Chem. Ber.*, **83**, 161 (1950)

Structure

Brockmann, Hieronymus, *Chem. Ber.*, **88**, 1379 (1955)
Brockmann *et al.*, *Naturwiss.*, **49**, 131 (1962)
Brockmann, *Angew. Chem.*, **76**, 863 (1964)
Brockmann *et al.*, *Annalen*, **698**, 209 (1966)

ACTINORUBIN

$C_6H_{14}O_3N_2$ ($C_9H_{22}O_4N_5$)
M.p. Indefinite

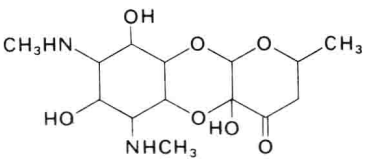
A species of *Actinomyces* produces this antibiotic which is a basic polypeptide. The crude antibiotic is a brownish hygroscopic powder, characterized as the helianthate which forms clusters of small reddish-orange needles, m.p. 206–214°C (*dec.*). It is active against gram-positive, gram-negative and acid-fast bacteria and has some activity against certain fungi. It has only a limited activity against *Bacillus cereus-mycoides* and streptococci.

Typical inhibition concentrations (units/ml) *in vitro* are: *Aerobacter aerogenes* (0·25); *Bacillus anthracis* (2·0–4·0); *B. cereus* (32); *Brucella abortus* (4·0); *B. suis* (16); *Diplococcus pneumoniae* (132); *Escherichia coli* (1·05); *Gaffkya tetragena* (0·03); *Klebsiella pneumoniae* (0·125); *Micrococcus aurantiacus* (0·007); *Mycobacterium tuberculosis bovis* (8·0); *Proteus vulgaris* (1·0); *Staphylococcus aureus* (0·06); *Streptococcus pyogenes* (128); and *Vibrio comma* (0·6). When given to mice intraperitoneally, 0·2 per *E. coli* unit gives complete protection against experimental infection with *Klebsiella pneumoniae*. The LD_{50} in mice is 0·68 mg/kg (intraperitoneal). Following such administration, the antibiotic has been detected in the blood whereas it is not so detected following oral administration.

Kelner *et al.*, *J. Bacteriol.*, **51**, 591 (1946)
Kelner, Morton, *ibid.*, **53**, 695 (1947)
Morton, *Proc. Soc. Exp. Biol. Med.*, **64**, 327 (1947)
Junowicz-Kocholaty, Kocholaty, *J. Biol. Chem.*, **168**, 868 (1947)

ACTINOSPECTACIN (*Spectinomycin*)

$C_{14}H_{24}O_7N_2$
M.p. 65–72°C ($6H_2O$)
$[\alpha]_D^{25}$ +7·6° (c 1·0, H_2O)



Actinospectacin was first isolated from cultures of *Streptomyces spectabilis* and subsequently from *S. flavopersicus* and *S. hygroscopicus* var. *sagamiensis* ATCC 21,703. When anhydrous it is an amorphous white powder which can be crystallized as the hexahydrate from Me_2CO–H_2O. The sulphate has m.p. 185°C (*dec.*), $[\alpha]_D^{25}$ +17° (c 1·0, H_2O). Actinospectacin is active against both gram-positive and gram-negative bacteria, being inhibitory against most strains of *Enterobacter*, *Escherichia coli*, *Klebsiella* and *Staphylococcus epidermidis*. The minimum inhibitory concentration against *Klebsiella pneumoniae* is 2·6 μg/ml. When administered to healthy human volunteers at a dose of 0·5–8·0 g intravenously per day for 5 days, no indications of hepatotoxicity, nephrotoxicity, ototoxicity or local intolerance were observed. In veterinary medicine it has found some use in the treatment of bacterial enteritis and coccidiosis of dogs.

Mason *et al.*, *Antibiot. Chemother.*, **11**, 118 (1961)
Bergy *et al.*, *ibid.*, **11**, 661 (1961)
Chapman *et al.*, *Proc. Natl. Acad. Sci. USA*, **48**, 1108, 1693 (1962)
Nara *et al.*, *German Patent*, 2,233,555 (1973)
Novak *et al.*, *J. Clin. Pharmacol.*, **14**, 442 (1974)
Novak *et al.*, *J. Infect. Dis.*, **130**, 50 (1974)

Structure
Hoeksema *et al.*, *J. Am. Chem. Soc.*, **84**, 3212 (1962)
Hoeksema *et al.*, *ibid.*, **85**, 2652 (1963)

Biosynthesis
Mitscher *et al.*, *J. Chem. Soc., D*, 1541 (1971)

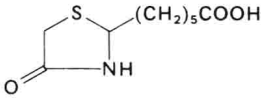
ACTINOTIOCIN

M.p. 247–249°C
$[\alpha]_D^{20}$ +164° (c 0·77, dioxan)
Actinomadura pusilla produces this antibiotic which forms colourless columnar crystals, stable in neutral and alkaline solutions but unstable in acids. It is active against gram-positive bacteria and mycoplasma but not against gram-negative bacteria, *Candida*, *Trichophyton* or *Trichomonas*. It is also active *in vivo*, affording 70 per cent and 100 per cent protection to mice infected with *Staphylococcus aureus* and *Diplococcus pneumoniae* respectively when given at 100 mg/kg intraperitoneally. A dose of 1 g/kg given to mice either orally or intraperitoneally produced no adverse effects.

Tamura *et al.*, *J. Antibiotics* (Japan), **26**, 343 (1973)
Tamura *et al.*, *Japanese Patent*, 73 28,692 (1973)

ACTITHIAZIC ACID (*Mycobacidin*)

$C_9H_{15}O_3NS$
M.p. 139–140°C
$[\alpha]_D^{25}$ −60·5° (EtOH)



An antibiotic elaborated by *Streptomyces lavendulae* and *S. virginiae*, this compound furnishes colourless crystals from BuOH. It is soluble in alkaline solutions and the lower alcohols but insoluble in H_2O, C_6H_6 and $CHCl_3$. Actithiazic acid is active against mycobacteria at a level of 0·02–0·5 g/ml but has only a limited activity against other bacteria. The development of resistance is slow while the toxicity in mice, both intravenous and subcutaneous, is 1·5 g/kg. It has found no application in medicine, being inactive *in vivo*.

Grundy *et al.*, *Antibiot. Chemother.*, **2**, 399 (1952)
Schenck, DeRose, *Arch. Biochem. Biophys.*, **40**, 263 (1952)
Clark, Schenck, *ibid.*, **40**, 270 (1952)
Hwang, *Antiobiot. Chemother.*, **2**, 453 (1952)
Sobin, *J. Am. Chem. Soc.*, **74**, 2247 (1952)
McLamore *et al.*, *ibid.*, **74**, 2246 (1952)
Tejera *et al.*, *Antibiot. Chemother.*, **2**, 233 (1952)

ACULEACINS

Aspergillus aculeatus M 4217 (FERM-P 2324) yields an antibiotic complex when cultured aerobically at 26°C and pH 6·5 for 96 hours on a medium containing peptone, sucrose, dextrose and inorganic salts. Aculeacin is a pale brown powder which yields aculeacins B, C, D, E, F and G by fractionation on a silica gel column. Molecular weight determinations of these peptides give values of 1145–1300. These antibiotics are effective against fungi and yeasts but show little activity against bacteria.

Mizuno *et al.*, *Japanese Patent*, 76 98,387 (1976)

ACUMYCIN

$C_{37}H_{59}O_{12}N$
M.p. 233–237°C (*dec.*)
$[\alpha]_D^{25}$ −92° (c 1·0, $CHCl_3$)
An antibiotic produced by *Streptomyces griseoflavus*, this compound furnishes colourless crystals from EtOAc. The UV spectrum has a single absorption maximum at 241 nm (EtOH). It is active against gram-positive bacteria.

Bicket *et al.*, *Helv. Chim. Acta*, **45**, 1396 (1962)

Structure
Clardy *et al.*, *Tetrahedron*, Suppl. No. 9, **37**, 91 (1981)

ADCILLIN

See Penicillin N

ADRIAMYCIN (*Doxorubicin, 14-Hydroxydaunomycin*)

$C_{27}H_{29}O_{11}N$