

Encyclopaedia
of
Antibiotics

Second Edition

JOHN S. GLASBY

Encyclopaedia
of
Antibiotics
Second Edition

D93-6
4

JOHN S. GLASBY

*ICI (Organics) Limited,
Hexagon House, Blackley,
Manchester*

A Wiley-Interscience Publication

JOHN WILEY & SONS *Chichester • New York • Brisbane • Toronto*

Copyright © 1979, by John Wiley & Sons Ltd.

All rights reserved.

No part of this book may be reproduced by any means, nor transmitted, nor translated into a machine language without the written permission of the publisher.

Library of Congress Cataloging in Publication Data:

Glasby, John Stephen.

Encyclopaedia of antibiotics.

'A Wiley-Interscience publication.'

1. Antibiotics—Dictionaries. I. Title.

RS161.G56 1979 615'.329 78-13356

ISBN 0 471 99722 6

Printed and bound at
William Clowes & Sons Limited
Beccles and London

Preface

Since the first edition of this encyclopaedia two years ago a large number of new antibiotics have been described in the scientific and patent literature and these have been included in the present volume. In addition the structures of several of the antibiotics previously described have been elucidated and others have been revised in the light of further examination.

The author also wishes to thank those research chemists and medical consultants who have provided him with additional data on the antibiotic activity of several important members of this class of compounds, particularly on their present use in human medicine.

Woodhouses, Manchester,
May, 1978

J. S. GLASBY

AABOMYCIN

$C_{39-40}H_{65-68}O_{11}N$
M.p. 144-145°C

This antibiotic is elaborated by *Streptomyces hygroscopicus* var. *aabomyceticus* when cultivated on a medium consisting of glucose, dried beer yeast, defatted soybean flour, meat extract and sodium chloride at 26-27°C and pH 7.0 for 4 days. The compound is isolated by extraction of the culture filtrate with AcOEt and purified by chromatography on an alumina column. Aabomycin forms colourless needles when crystallized from a variety of solvent systems including EtOH-H₂O, (CH₃)₂CO-H₂O, CHCl₃-C₆H₆ and C₆H₆-AcOEt. It is dextrorotatory with a specific rotation of $[\alpha]_D^{20} + 93.5^\circ$ (c 1.0, CHCl₃) and gives an ultraviolet spectrum in EtOH consisting of a single absorption maximum at 280 nm. The antibiotic is weakly acidic and soluble in EtOH but insoluble in H₂O. It is not active against bacteria but is effective against *Piricularia oryzae* and *Trichophyton rubrum*. Mice tolerate a dose of 100 mg/kg when administered intravenously.

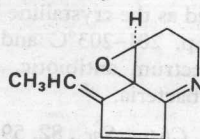
Aizawa *et al.*, *J. Antibiotics* (Japan), **22**, 457 (1969)

Yamaguchi *et al.*, *ibid.*, **22**, 463 (1969)

Misato *et al.*, *Japanese Patent*, 7,121,794 (1971)

ABIKOVIROMYCIN (*Latumcidin*)

$C_{10}H_{11}ON$



Both *Streptomyces abikoensis* and *S. rubescens* produce this antibiotic possessing antiviral properties. The compound is isolated from the broth culture by chromatography on an alumina column. So far, it has not been obtained in the pure state since it is highly unstable and, even at temperatures as low as -50°C, it rapidly polymerizes. Some difficulty is experienced when freeze-drying the antibiotic since it sublimes readily even under these extreme conditions. Dilute solutions are, however, reasonably stable and the substance may be conveniently handled in this form. The ultraviolet

spectrum in 0.1 N-KOH or EtOH exhibits two absorption maxima at 218 and 244 nm and a pronounced shoulder at 289 nm, while that in 0.1 N-HCl has absorption maxima at 236 and 341 nm. The sulphate is stable but decomposes at 140-141°C. This salt is dextrorotatory with a specific rotation of $[\alpha]_D + 24^\circ$ (c 1.0, H₂O). The picrate is also stable and crystalline, decomposing at 137-140°C. Reduction of the antibiotic with LiAlH₄ or NaBH₄ furnishes the dihydro derivative, m.p. 60-61°C.

Abikoviromycin has been shown to be active against both Eastern and Western equine encephalomyelitis viruses when dilutions of 1:8,000,000 are mixed with the virus suspensions and administered intracerebrally into mice. It is not, however, effective against the Venezuelan type virus. The antibiotic has only a slight activity against bacteria or fungi. The LD₅₀ is 1.0 mg (subcutaneous) and 0.1 mg (intravenous) per 12 g mouse. It has a limited use in medicine as an antimicrobial.

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 SSSR*, **182**, 828 (1968)

ABKHAZOMYCIN

Russian workers have described this antibiotic which has been obtained from cultures of *Streptomyces badiocolor* var. *abkhasus*. The antibiotic has been isolated by extraction of the mycelium followed by column chromatography. Abkhazomycin has only weak activity against bacteria and yeasts but is effective against a number of fungi.

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

ABLASTMYCIN

$C_{18}H_{33}O_{10}N_2$

M.p. Indefinite

When *Streptomyces aburaviensis* var. *ablastmyceticus* is freshly isolated from soil and cultivated in a common nutrient medium at 28°C for 3 days,

Aburamycin A

this antibiotic may be obtained by extraction of the culture filtrate with an organic solvent and purified by treatment with an ion exchange resin. Ablastmycin is a basic compound, soluble in H_2O but virtually insoluble in most organic solvents. It gives a negative ninhydrin reaction and has no activity against bacteria but is highly active against both *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*, 7,207,059 (1972)

ABURAMYCIN A

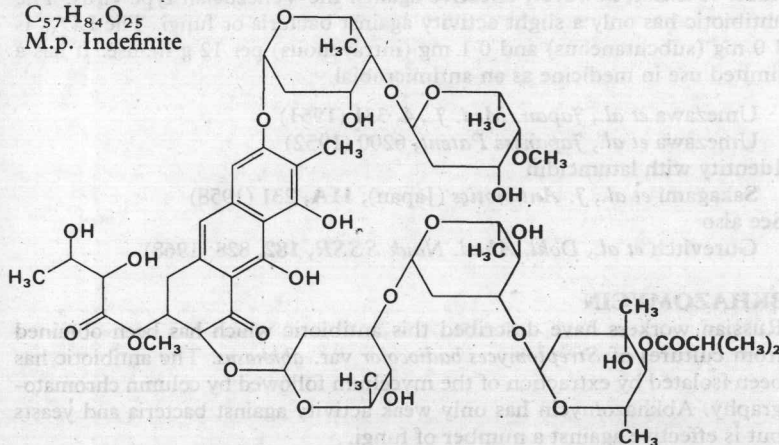
See Chromomycin A_2

ABURAMYCIN B

See Chromomycin A_3

ABURAMYCIN C

$C_{57}H_{84}O_{25}$
M.p. Indefinite



One of the large number of antibiotics elaborated by *Streptomyces* species, this compound is an amorphous powder, yellowish in colour, with no definite melting point. It has a specific rotation of $[\alpha]_D - 17^\circ$ (c 1.0, EtOH) and gives a complex ultraviolet spectrum having absorption maxima at 228, 282, 318, 351 and 415 nm. When treated with Ac_2O it gives a peracetate, m.p. 219–221°C and $[\alpha]_D - 18^\circ$ ($CHCl_3$). Aburamycin C has shown some promise as a cancerostatic agent.

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

2

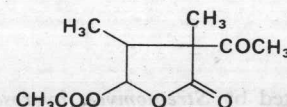
β -N-Acetylracemomycin

ABURAMYCIN D

See Chromomycin A_4

ACETOMYCIN

$C_{10}H_{14}O_5$
M.p. 115°C

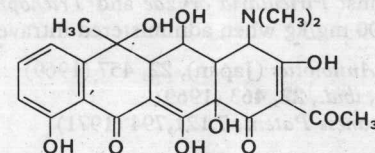


A simple antibiotic produced by *Streptomyces ramulosus*, this substance forms colourless rods and sublimes at 70°C. It is laevorotatory with a specific rotation of $[\alpha]_D - 167^\circ$ (c 1.0, EtOH). Acetomycin is active against gram-positive bacteria.

Ettlinger *et al.*, *Helv. Chim. Acta*, **41**, 216 (1958)

2-ACETYL-2-DECARBOXAMIDO-OXYTETRACYCLINE (Terramycin X)

$C_{23}H_{25}O_9N$



A tetracycline antibiotic, this compound is produced by *Streptomyces rimosus*. It is usually obtained as the crystalline hydrochloride which forms yellow crystals and has m.p. 201–203°C and $[\alpha]_D^{25} - 46.6^\circ$ (c 0.9, 0.1 N-HCl). It is a broad spectrum antibiotic, active against both gram-positive and gram-negative bacteria.

Hochstein *et al.*, *J. Amer. Chem. Soc.*, **82**, 5934 (1960)

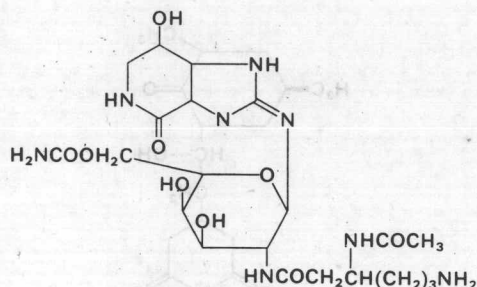
Frolova, Rozenfel'd, Listvinova, *Antibiotiki*, **16**, 687 (1971)

β -N-ACETYLRACEMOMYCIN

$C_{21}H_{36}O_9N_8$

An acetyl derivative of racemomycin (q.v.); this antibiotic substance has been prepared by Japanese workers by a series of selective chemical reactions. The minimum inhibitory concentration of the antibiotic for *Staphylococcus aureus* is given as 400 μ g/ml compared with only 10 μ g/ml for the parent antibiotic. From this observation it has been concluded

Acidophilin



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)

ACIDOPHILIN

This antibiotic substance has been obtained from *Lactobacillus acidophilus* by fermentation in a medium containing sterilized skim milk. The antibiotic is isolated by extraction of the culture filtrate with EtOH, evaporation under reduced pressure, extraction of the residue with $(\text{CH}_3)_2\text{CO}$, evaporation and chromatography. It is normally employed as an aqueous suspension and is active against gram-positive bacteria.

Shahani, Vakil, Chandan, *U.S. Patent*, 3,689,640 (1972) .

ACHROMYCIN

See Puromycin

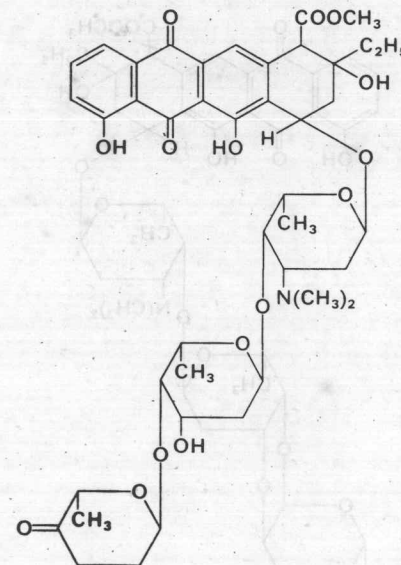
ACLACINOMYCIN A

$$\text{C}_{42}\text{H}_{53}\text{NO}_{15}$$

One of two structurally similar glycosidic antibiotics isolated from an unclassified microorganism, this substance has been separated from the accompanying aclacinomycin B by chromatographic methods. It is a broad spectrum antibiotic possessing bacteriostatic, fungistatic, antiviral and antileukemic properties. The structure has been elucidated from chemical and spectroscopic examination.

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

Aclacinomycin B

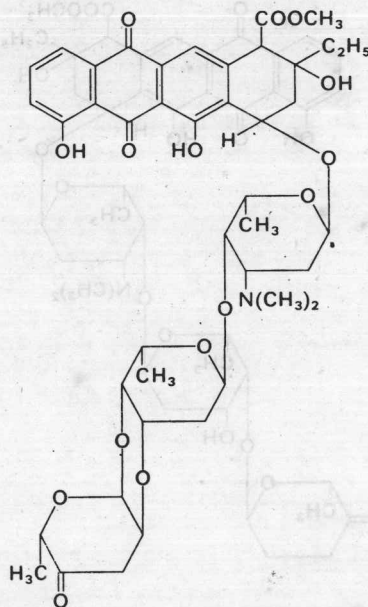


ACLACINOMYCIN B

$$\text{C}_{42}\text{H}_{51}\text{NO}_{15}$$

A second antibiotic isolated by Oki and his colleagues from an unclassified microorganism, this compound possesses similar properties to the preceding antibiotic. It has been assigned the structure shown above on the basis of chemical degradations, hydrolysis experiments and a study of the infrared, NMR and mass spectra.

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



ACRYLAMIDINE

An unstable antibiotic, acrylamidine is produced by a species of *Streptomyces* allied to *S. eurythermus*. It has a maximum stability in neutral solution and is normally isolated as the hydrochloride which forms colourless crystals from H₂O. Acrylamidine has no activity against bacteria but is weakly active against species of *Candida*.

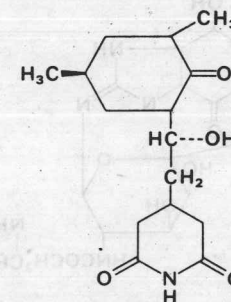
Yagishita *et al.*, *J. Antibiotics* (Japan), **21**, 444 (1968)

ACTIDIONE (Cycloheximide, Naramycin A)

C₁₅H₂₃O₄N

M.p. 115–116.5°C (119.5–121°C)

Streptomycin-producing strains of *Streptomyces griseus* have been found to yield a second antibiotic which, although not active against bacteria, is highly effective against several yeasts. Crude actidione is purified by countercurrent distribution between C₆H₆ and H₂O and, when recrystallized from amyl acetate, gives colourless plates, m.p. 115–116.5°C. When



crystallized from H₂O containing a little CH₃OH it has the higher melting point given above. The substance is laevorotatory having the following specific rotations: $[\alpha]_D^{25} - 2.8^\circ$ (c 9.6, CH₃OH) and $[\alpha]_D^{29} - 3.38^\circ$ (c 9.47, EtOH). The antibiotic forms a number of crystalline derivatives including the biologically inactive acetate, m.p. 150–152°C; $[\alpha]_D^{25} + 24.6^\circ$ (c 3.7, CH₃OH); the semicarbazone monohydrate, m.p. 187–188°C (*dry*) and the *p*-nitrobenzoyl derivative, m.p. 215–220°C (*dec.*). Catalytic reduction with PtO₂ in AcOH furnishes dihydroactidione, m.p. 137–139°C, the latter characterized as the diacetate, m.p. 72–5°C and the N-methyl derivative, m.p. 129–132°C. Oxidation of the antibiotic with CrO₃ in glacial AcOH yields dihydroactidione as colourless crystals, m.p. 177–180°C. Determination of the absolute configuration of actidione has shown that it possesses the (R)(–) configuration.

When tested against a number of 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 which is the cause of cryptococcosis, a rare but normally fatal disease. This high activity suggests its usefulness in the treatment of this disease. Actidione has a toxicity, given intravenously in mice, of LD₅₀ of approximately 150 mg/kg.

Whiffen, Bohonos, Emerson, *J. Bact.*, **52**, 610 (1946)

Leach, Ford, Whiffen, *J. Amer. Chem. Soc.*, **69**, 474 (1947)

Ford, Leach, *ibid.*, **70**, 1223 (1948)

Kornfield, Jones, *Science*, **108**, 437 (1948)

Kornfield, Jones, Parks, *J. Amer. Chem. Soc.*, **71**, 150 (1949)

Okuda, *Chem. Pharm. Bull.*, **7**, 659 (1959)

Hawkins, Hainton, *Exp. Cell. Res.*, **65**, 258 (1971)

Evans, Smith, *J. Biol. Chem.*, **246**, 6144 (1971)

Actilin

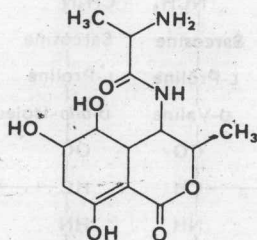
- Cho, *Han'guk Saenghwahakhoe Chi*, **5**, 1 (1972)
Oddoux, Porte, Shaw, *Bull. Trav. Soc. Pharm. Lyon*, **16**, 153 (1972)
Muromtsev, Davydova, Klyagina, *Soviet Patent*, 378,409 (1973)
Verbin, Diluios, Farber, *Cancer Res.*, **33**, 2086 (1973)
Szabo *et al.*, *Hung. Teljes*, 7931 (1974)
Absolute configuration
Sharkovsky, Johnson, *Tetrahedron Lett.*, 919 (1964)
Total synthesis
Johnson *et al.*, *J. Amer. Chem. Soc.*, **86**, 118 (1964)

ACTILIN

See Neomycin B

ACTINOBOLIN

$C_{13}H_{20}O_6N_2$
M.p. Indefinite



This antibiotic has been isolated from *Streptomyces griseoviridis* var. *atrofaciens* and forms a fluffy amorphous powder with no definite melting point. It is hygroscopic and very soluble in H_2O in which it is amphoteric with a weakly acidic pK_a of 8.8 and a basic function pK_a of 7.5. In a phosphate buffer of pH 7.0 it gives an ultraviolet spectrum with a single absorption maximum of 263 nm.

Acid hydrolysis furnishes actinobolamine whereas hydrolysis with alkalis yields L-alanine, 1-(2:5-dihydroxyphenyl)propan-2-ol, ammonia and carbon dioxide. The sulphate forms colourless crystals from aqueous EtOH with $[\alpha]_D^{22} + 54.5^\circ$ (c 1.0, H_2O), the ultraviolet spectrum at pH 7.0 having an absorption peak at 264 nm. The acetate furnishes colourless needles from EtOH, partially melting at $130^\circ C$ followed by resolidification and decomposition at $263-266^\circ C$. This salt is also dextrorotatory with $[\alpha]_D^{26} + 58^\circ$ (c 1.0, H_2O) and its ultraviolet spectrum is virtually identical with that of the sulphate. It is readily soluble in warm CH_3OH , EtOH and $(CH_3)_2CO$ but only sparingly soluble in AcOEt. The N-acetyl derivative,

Actinomyces Lysozyme

formed as white needles from EtOH, has m.p. $254-255^\circ C$ (dec.) and $[\alpha]_D^{26} + 30^\circ$ (c 3.8, H_2O). The ultraviolet spectra of the antibiotic have been extensively studied. In H_2O there is a single absorption maximum at 261 nm; in 0.1 N-NaOH this is shifted to 288 nm, while in 0.1 N-HCl it is at 262 nm.

The antibiotic has found some use in medicine, principally as a broad spectrum antimicrobial.

- Haskell, Bartz, *Antibiotics Annual*, 505 (1958-1959)
Haskell *et al.*, *U.S. Patent*, 3,043,830 (1962)
Struck *et al.*, *Tetrahedron Lett.*, 1589 (1967)
Monk *et al.*, *J. Amer. Chem. Soc.*, **90**, 1087 (1968)

ACTINOCARCIN

A complex antibiotic, actinocarcin is produced by *Streptomyces cinnameus* when grown on a common nutrient medium. Acid hydrolysis with N HCl for 20 hours at $110^\circ C$ 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 six days it prolonged the survival period of mice inoculated with cells of Ehrlich sarcoma. The LD_{50} for mice was approximately 40-50 mg/kg given for six days.

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

ACTINOFLAVIN

See Actinomycin J₁

ACTINOMYCELIN

This antibiotic is produced by a culture which is related to *Streptomyces antibioticus*. It forms yellowish-green crystals which are soluble in H_2O and EtOH with an intense green fluorescence, somewhat less soluble in $CHCl_3$ and $(CH_3)_2CO$. The antibiotic is most stable at neutral reaction, less so under acid or alkaline conditions. It has been shown to be active against gram-positive bacteria but not against mycobacteria or fungi. The toxicity in rats is LD_{50} of 25 mg/kg when administered subcutaneously.

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

ACTINOMYCES LYSOZYME

This substance has been described by Kriss who obtained it from *Streptomyces violaceus* and classified it as a lysozyme.

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

Actinomycetin

ACTINOMYCETIN

Produced by *Streptomyces albus* cultures in beef-bouillon, this lytic substance is stated to be protein-like in nature. The structure is not yet known although it is said to consist of an enzyme, actinoyzyme, and a lipoid antibacterial fatty acid fraction. The compound is soluble in H_2O from which it is precipitated by various protein precipitants such as $(CH_3)_2CO$, EtOH and ammonium sulphate. Strong acid destroys the substance and it is also rapidly deactivated by heating to 60–70°C. It is appreciably more stable at pH 10.0 than at pH 4.0. Ultraviolet light below 300 nm destroys the antibiotic. Electromicrographs show it to be composed of particles with a diameter of about 4 millimicrons.

In its action, 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 has been reported.

Gratia, Alexander, *Compt. Rend. Soc. Biol.*, **91**, 1442 (1924)

Gratia, *Bull. Mem. Acad. Chir.*, **56**, 344 (1930)

Welsch, *J. Bact.*, **42**, 801 (1941)

Ghuysen, *Belgian Patents*, 517,191 and 521,114 (1953)

See also

Hoogerheide, Welsch, *Botan. Rev.*, **10**, 599 (1944)

Hoogerheide, Welsch, *J. Bact.*, **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 compounds, Actinomycins X_1 and X_2 , these are described below in more detail. See Actinomycins X_1 and X_2 .

ACTINOMYCIN A_{II}

See Actinomycin F₈

ACTINOMYCIN A_{III}

See Actinomycin F₉

ACTINOMYCIN A_V

See Actinomycin X₇

ACTINOMYCIN B

See Actinomycin A

ACTINOMYCIN B_V

See Actinomycin X₂

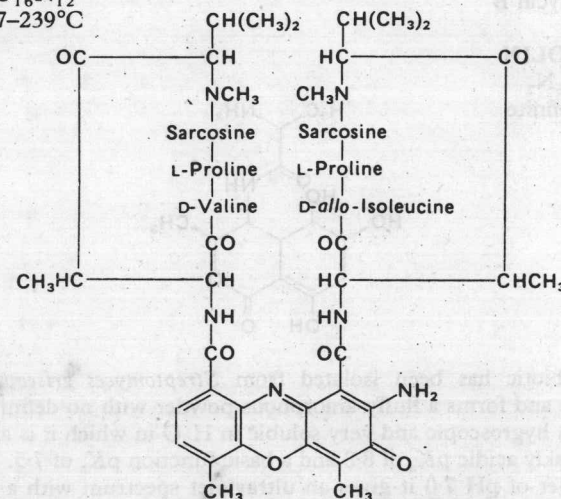
ACTINOMYCIN C₁

See Actinomycin D

ACTINOMYCIN C₂ (*Actinomycin I₂*, VI)

$C_{63}H_{88}O_{16}N_{12}$

M.p. 237–239°C



This antibiotic from *Streptomyces antibioticus* and *S. chrysomallus* is separated from the accompanying components by countercurrent distribution methods, having a higher R_f value than actinomycin D (q.v.). When purified by recrystallization from C_6H_6 or EtOH, the antibiotic forms red needles or bipyramids. It is laevorotatory with a specific rotation of $[\alpha]_D - 325^\circ \pm 10^\circ$ (CH_3OH). The structure is similar to that of actinomycin D, which may be regarded as the basic structure of the actinomycins, but with D-valine in the β -peptide chain replaced by D-allo-isoleucine. It is therefore usually referred to as an anisoactinomycin since the pentapeptide residues are different. This antibiotic has been synthesized, but in order to obtain it free of the isomeric actinomycin C_{2a} (q.v.), separation of the intermediate

actinomycinic acid monolactones must be carried out prior to the final cyclization of the second peptide ring.

The biological activity and toxicity of actinomycin C₂ are virtually identical to those given for actinomycin D (q.v.). The concentration required to inhibit the growth of *Bacillus subtilis* has been given as 0.25 µg/ml by Reich and his colleagues. The activity against *B. subtilis* diminishes with any change in the chromophore, e.g. 7-hydroxyactinomycin C₂ has only about 0.2 per cent of the activity of actinomycin C₃ (taken as the standard), 7-aminoactinomycin C₂ has <1.0 per cent and 7-nitroactinomycin C₂ has 40 per cent relative activity.

Brockmann, Pfennig, *Naturwiss.*, **39**, 429 (1952)

Brockmann, Grone, *Chem. Ber.*, **87**, 1036 (1954)

Brockmann, *Angew. Chem.*, **72**, 944 (1960)

Brockmann, Boldt, Petras, *Naturwiss.*, **47**, 62 (1960)

Brockmann, Petras, *ibid*, **48**, 218 (1961)

Brockmann, Boldt, *ibid*, **50**, 19 (1963)

Structure

Brockmann, Petras, *Naturwiss.*, **48**, 218 (1961)

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

Synthesis

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

Biological activity

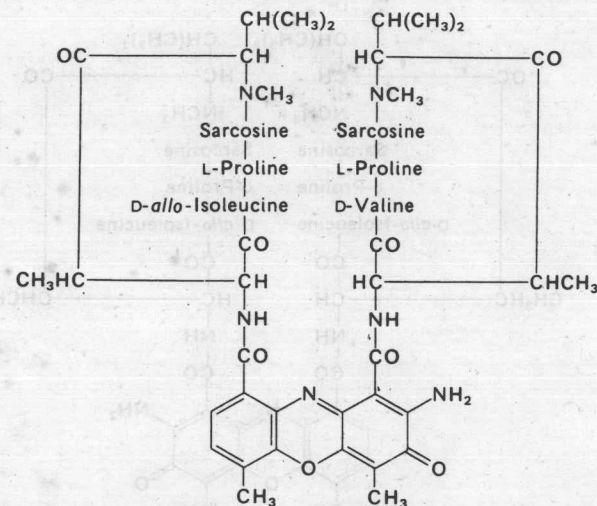
Brockmann, Muller, Peterssen-Borstel, *Tetrahedron Lett.*, 3531 (1966)

ACTINOMYCIN C_{2a} (Actinomycin i-C₂)

C₆₃H₈₈O₁₆N₁₂

M.p. 233–235°C

When separated chromatographically from the actinomycin C mixture isolated from *Streptomyces chrysomallus*, this component has an *R_f* value intermediate between actinomycins C₂ and C₃. The antibiotic forms red crystals from EtOH and is laevorotatory having a specific rotation of $[\alpha]_D^{18} - 297^\circ$ (c 0.267, CH₃OH). It is an anisoactinomycin, isomeric with actinomycin C₂, the structure being the same but with the D-allo-isoleucine and D-valine aminoacids being transposed. In the first attempts to synthesize actinomycin C₂, this isomer was present in the final product and the two compounds cannot be separated. A pure product can only be obtained by separating the intermediate monolactones prior to the final cyclization. This antibiotic has not been studied in as much detail as either actinomycin C₃ or D but the toxicity and biological activity appear to be similar to those of these two compounds.



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

Synthesis

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

ACTINOMYCIN i-C₂

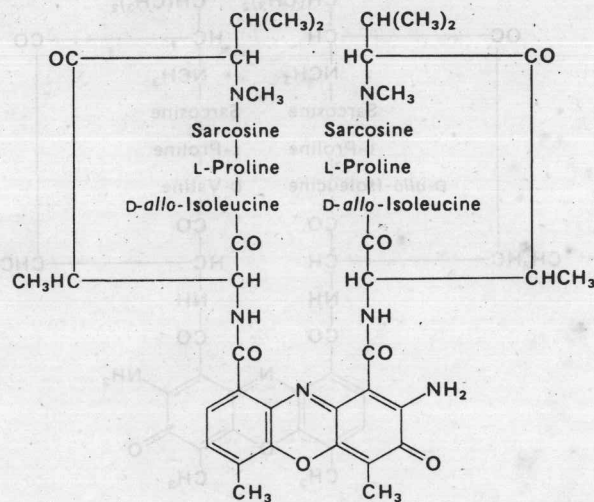
See Actinomycin C_{2a}

ACTINOMYCIN C₃ (Actinomycin VII)

C₆₄H₉₀O₁₆N₁₂

M.p. 234°C

This component of the actinomycin C mixture obtained from *Streptomyces chrysomallus* and *S. antibioticus* forms reddish crystals from C₆H₆. It is, however, more readily obtained in the crystalline form from AcOEt on addition of CS₂. The antibiotic is laevorotatory with $[\alpha]_D^{20} - 357^\circ$ (C₆H₆). Structurally, actinomycin C₃ is an isoactinomycin, both the α- and β-peptide chains consisting of the aminoacids L-threonine, D-allo-isoleucine, L-proline, sarcosine and L-N-methylvaline. The first synthesis of an actinomycin was based upon the observation by Sunderkotter that actinomycin C₃ is hydrolytically cleaved between sarcosine and L-N-methylvaline to yield bis-(seco-actinomycin C₃), the latter being synthesized through oxidative coupling which brings about dimerization. The bis-(seco-actinomycin C₃) readily reforms the natural antibiotic.



X-ray studies have shown that actinomycin C₃ may have a pseudo-two-fold axis of symmetry in the plane of the phenoxazine ring. Solutions in organic solvents contain only monomers, but in aqueous solution molecular weight determinations found by sedimentation equilibrium show that dimers predominate between concentrations of 10^{-5} and 10^{-3} molar. At higher concentrations oligomers are formed. It is now generally accepted that the presence of the nonpolar aminoacids in the molecule produces a hydrophobic effect which explains the stability of the dimers in water.

Actinomycin C₃ is active against gram-positive bacteria and inhibits the growth of *Bacillus subtilis* at a concentration of 0.25 µg/ml. It is also, like actinomycin D, 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. Investigation has shown that the antibiotic complexes with DNA and inhibits the synthesis of RNA although it does not complex with the latter. Several complexes of actinomycin C₃ with various purine bases have been investigated and compared with that formed with DNA. The entropy change for the former is not favourable for interaction and these complexes are about 1000 times weaker than that with DNA where the entropy change is both large and positive. There is now little doubt that this antibiotic acts in the same manner as actinomycin D (q.v.) and recently a small angle X-ray scattering

study on the interaction between actinomycin C₃ and calf thymus DNA has been reported by Zipper and his co-workers.

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

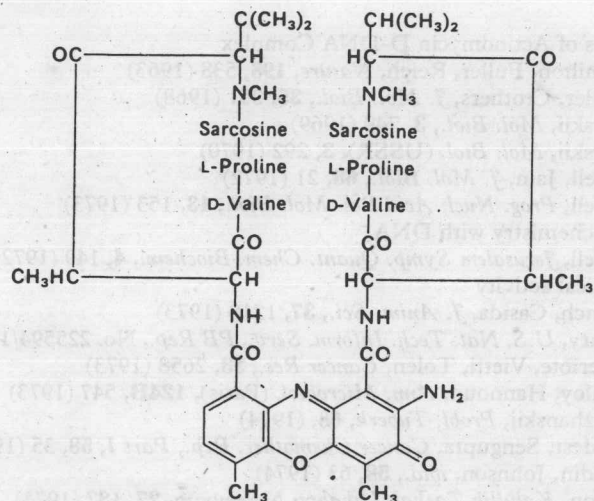
Zipper *et al.*, *Fed. Eur. Biochem. Soc. Lett.*, **25**, 123 (1972)

ACTINOMYCIN D (Actinomycin C₁, D_{IV}, I, IV, X, Dactinomycin)

C₆₂H₈₆O₁₆N₁₂

M.p. 235.5–236.5°C (dec.)

Extraction of the dry mycelium of various species of *Streptomyces*, particularly *S. antibioticus* and *S. chrysomallus*, with C₆H₆ yields an antibiotic substance, actinomycin C, which has been shown by countercurrent distribution and chromatography to consist of a number of components. These have been designated actinomycins C₁ (actinomycin D), C₂, C_{2a} and C₃ where the subscript refers to an increasing R_f value. Actinomycin D forms red crystals which are freely soluble in C₆H₆, (CH₃)₂CO and CHCl₃, less so in EtOH and only slightly soluble in H₂O. The antibiotic is laevorotatory with $[\alpha]_D^{25} = -262^\circ$ (c 0.25, 95 per cent EtOH) and gives an ultraviolet spectrum with an absorption maximum at 242 nm and negative Cotton effects centered at 269 and 213 nm. The visible spectrum in H₂O exhibits an absorption at 441 nm, while in less polar solvents such as C₆H₆, CH₃OH and AcOEt, there are two absorptions at 425 and 445 nm. X-ray studies do not completely differentiate between a decapeptide dilactone and a bis-



pentapeptide lactone structure, but Brockmann has proved the latter structure both by degradation and synthesis.

Like the accompanying components, 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* of pure actinomycin D has been given by Formica and his colleagues as 0.02 µg/ml. Like all of the actinomycins, this antibiotic is highly toxic. When given at a dosage of 5 mg/kg intraperitoneally, or 50 mg/kg orally, mice die within 24 hours. Nevertheless it possesses a marked antineoplastic effect in non-toxic doses and, like actinomycin C₃ (q.v.), is highly effective as a chemotherapeutic in the treatment of carcinoma, particularly of the lymphatic system. It therefore has a use in treating Hodgkin's disease, rhabdomyosarcoma, trophoblastic tumours and Wilm's tumour.

Actinomycin D is one of the most effective antitumour agents known at the present time, but owing to its high toxicity it finds only limited clinical use. The cytostatic properties of the antibiotic are due to its complexing with DNA and the consequential inhibition of RNA synthesis. Actinomycin D also interferes with those reactions in which DNA is modified, e.g. by methylation. Four 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.

Support for all four models comes from a wide variety of physical and spectroscopic measurements, but the model described by Sobell and Jain explains most of the data pertaining to the binding of the antibiotic with DNA and is most widely accepted at the present time. This model combines the specificity of the guanine 2-amino group of the two 'outside-bound' models with the intercalative feature of the 'inner-bound' models.

Although numerous synthetic actinomycins have been prepared in the hope of improving the chemotherapeutic index and increasing the biological activity, it is now apparent 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. Most experimental work is now directed towards improving the chemotherapeutic index which is related to the difference in permeability in the cell wall of the normal and malignant cell.

Waksman, Woodruff, *Proc. Soc. Exp. Biol. Med.*, **45**, 609 (1940)

Waksman, Tishler, *J. Biol. Chem.*, **142**, 519 (1942)

Vining, Waksman, *Science*, **120**, 389 (1954)

Johnson, *Chem. Soc. Spec. Publ.*, No. 5, 82 (1956)

Roussos, Vining, *J. Chem. Soc.*, 2469 (1956)

Bullock, Johnson, *ibid.*, 3280 (1957)

Brockmann, Boldt, Petras, *Naturwiss.*, **47**, 62 (1960)

Biosynthesis

Katz, Weissbach, *J. Biol. Chem.*, **237**, 882 (1962)

Weissbach *et al.*, *ibid.*, **240**, 4377 (1965)

Weissbach *et al.*, *Biochem. Biophys. Res. Commun.*, **19**, 524 (1965)

Katz, Weissbach, *Develop. Ind. Microbiol.*, **8**, 67 (1967)

Katz, *Antibiotics II*, Biosynthesis, Ed. Gottlieb, Shaw, p. 276, Springer-Verlag, New York (1967)

Katz, *Actinomycin*, Ed. Waksman, Chap. 4, Wiley, New York (1968)

Synthesis

Brockmann, Petras, *Naturwiss.*, **48**, 218 (1961)

Woodward, Olofson, Mayer, *J. Amer. Chem. Soc.*, **83**, 1010 (1961)

Staab, *Angew. Chem.*, **74**, 407 (1962)

Brockmann, Mangegold, *Naturwiss.*, **51**, 382 (1964)

Brockmann, Lackner, *ibid.*, **51**, 384, 407 (1964)

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

Brockmann, Lackner, *ibid.*, **101**, 1312 (1968)

Meienhofer, *Experientia*, **24**, 776 (1968)

Meienhofer, *J. Amer. Chem. Soc.*, **92**, 3771 (1970)

CR/ORD Studies

- Courtois, Guschibauer, Fromageot, *Eur. J. Biochem.*, **6**, 106 (1968)
 Crothers *et al.*, *Biochemistry*, **7**, 1817 (1968)
 Ascoli *et al.*, *Nature*, **227**, 1237 (1970)
 Ascoli *et al.*, *Biopolymers*, **11**, 1173 (1972)

X-ray Studies

- Palmer, Palmer, Dickerson, *Nature*, **202**, 1052 (1964)
 Marsh Jnr, Goodman, *Can. J. Chem.*, **44**, 799 (1966)
 Ponnuswamy, McGuire, Scheraga, *Int. J. Peptide Protein Res.*, **5**, 73 (1973)

NMR Studies

- Victor *et al.*, *Tetrahedron Lett.*, 4721 (1969)
 Victor *et al.*, *Nature*, **223**, 302 (1969)
 Lackner, *Tetrahedron Lett.*, 2807 (1970)
 Danyluk, Victor, *Jerusalem Symp. Quant. Chem. Biochem.*, **2**, 394 (1970)
 Arison, Hoogsteen, *Biochemistry*, **9**, 3976 (1970)
 Conti, de Santis, *Nature*, **227**, 1239 (1970)
 Lackner, *Tetrahedron Lett.*, 2221 (1971)
 Lackner, *Proc. of 3rd Amer. Peptide Symp.*, p. 147, Ann Arbor, Mich. (1972)

Conformation

- De Santis, *Jerusalem Symp. Quant. Chem. Biochem.*, **5**, 493 (1973)

Biological Activity

- Meienhofer, *Experientia*, **24**, 776 (1968)
 Meienhofer, *J. Amer. Chem. Soc.*, **92**, 3771 (1970)
 Sobell, *Proc. Nucl. Acid Res. Mol. Biol.*, **13**, 153 (1973)
Cancer Chemother. Rep., Part I, **58**, 1 (1974)

Complex with DNA

- Goldberg, Rabinowitz, Reich, *Proc. Nat. Acad. Sci. U.S.*, **48**, 2094 (1962)
 Reich, Goldberg, *Proc. Nucl. Acid. Res.*, **3**, 183 (1964)
 Reich, *Symp. Soc. Study Develop. Growth*, **23**, 73 (1964)
 Cerami *et al.*, *Proc. Nat. Acad. Sci. U.S.*, **57**, 1030 (1967)
 Hartman *et al.*, *Angew. Chem. Int. Ed. Eng.*, **7**, 693 (1968)
 Wells, Larson, *J. Mol. Biol.*, **49**, 319 (1970)
 Hyman, Davidson, *ibid.*, **50**, 421 (1970)
 Goldberg, Friedman, *Ann. Rev. Biochem.*, **40**, 772 (1971)
 Goldberg, Friedman, *Pure. Appl. Chem.*, **28**, 499 (1971)
 Gale *et al.*, *The Molecular Basis of Antibiotic Action*, p. 220, Wiley, New York (1972)
 Sobell, *Prog. Nucl. Acid Res. Mol. Biol.*, **13**, 153 (1973)

Models of Actinomycin D-DNA Complex

- Hamilton, Fuller, Reich, *Nature*, **198**, 538 (1963)
 Muller, Crothers, *J. Mol. Biol.*, **35**, 251 (1968)
 Gurskii, *Mol. Biol.*, **3**, 749 (1969)
 Gurskii, *Mol. Biol. (USSR)*, **3**, 292 (1970)
 Sobell, Jain, *J. Mol. Biol.*, **68**, 21 (1972)
 Sobell, *Prog. Nucl. Acid Res. Mol. Biol.*, **13**, 153 (1973)

Stereochemistry with DNA

- Sobell, *Jerusalem Symp. Quant. Chem. Biochem.*, **4**, 149 (1972)

Biological activity

- French, Casida, *J. Anim. Sci.*, **37**, 1218 (1973)
 Henry, *U.S. Nat. Tech. Inform. Serv., PB Rep.*, No. 225594/1GA (1973)
 Valeriote, Vietti, Tolen, *Cancer Res.*, **33**, 2658 (1973)
 Bouloy, Hannoun, *Ann. Microbiol. (Paris)*, **124B**, 547 (1973)
 Dolzhanskii, *Probl. Tuberk.*, **68**, (1974)
 Modest, Sengupta, *Cancer Chemother. Rep., Part I*, **58**, 35 (1974)
 Goldin, Johnson, *ibid.*, **58**, 63 (1974)
 Kwon, *Kalullik Taehak Uihakpu Nonmunjip*, **27**, 187 (1974)
 Stephan-Dubois, Biver, *C.R. Seances Soc. Biol. Ses Fil.*, **168**, 1068 (1974)
 De Azevedo e Silva *et al.*, *Mem. Inst. Biocienc., Univ. Fed. Pernambuco*, **1**, 37 (1974)
 Bader *et al.*, *Acta Biol. Med. Ger.*, **32**, 91 (1974)
 Finn, Downie, *J. Endocrinol.*, **65**, 259 (1975)
 Henry, Roesler, DiDomenico, *Cancer Chemother. Rep., Part I*, **59**, 447 (1975)
 Tattersall *et al.*, *Clin. Pharmacol. Ther.*, **17**, 701 (1975)
 See also.
 Hollstein, *Chem. Rev.*, **74** (6), 625 (1974)

ACTINOMYCIN D₀

This new actinomycin has recently been described by Russian workers. It differs from the previously known actinomycins in that one of the sarcosine units is replaced by glycine.

Devan, Orlova, Silaev, *Antibiotiki*, **19**, 107 (1974)

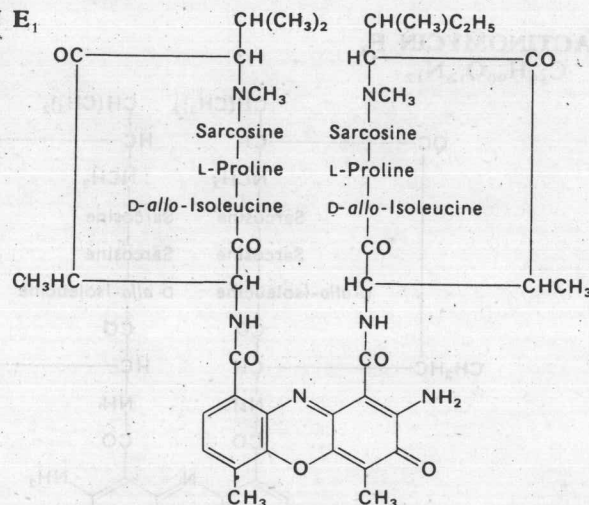
ACTINOMYCIN D_{IV}

See Actinomycin D

Actinomycin E₁

ACTINOMYCIN E₁

C₆₄H₉₆O₁₆N₁₂



One method of predetermining the structure of an antibiotic is controlled biosynthesis. Here, specific chemical precursors are fed to the particular microorganism in the culture medium and these compete with the endogenously synthesized amino acid and are incorporated into the peptide chain. When DL-isoleucine is included in the medium in which *Streptomyces antibioticus* is grown, two new actinomycins are formed designated E₁ and E₂. This particular antibiotic has the same structure as actinomycin C₃ but with one of the L-N-methylvaline groups replaced by L-methyl-*allo*-isoleucine.

Gunther, Schmidt-Kastner, *Naturwiss.*, **43**, 131 (1956)

Brockmann, *Angew. Chem.*, **72**, 945 (1960)

ACTINOMYCIN E₂

C₆₅H₉₈O₁₆N₁₂

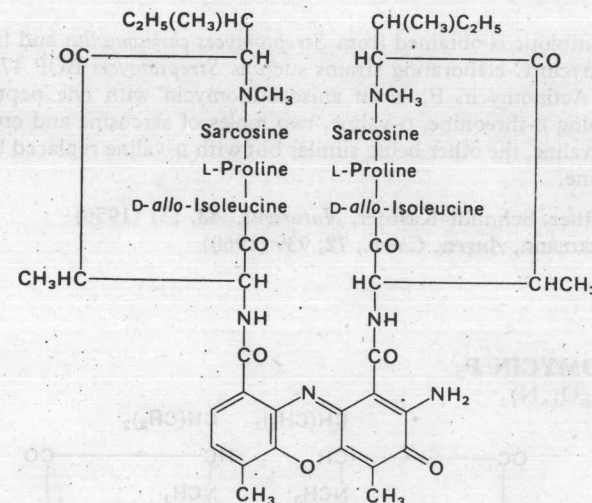
Also isolated in small amounts from cultures of *Streptomyces antibioticus* and *S. chrysomallus* when DL-isoleucine is added to the culture medium, this antibiotic belongs to the isoactinomycin class, both the α - and β -chain consisting of the amino acids L-threonine, D-*allo*-isoleucine, L-proline and L-methyl-*allo*-isoleucine. It forms reddish crystals when crystallized from C₆H₆.

Gunther, Schmidt-Kastner, *Naturwiss.*, **43**, 131 (1956)

Brockmann, *Angew. Chem.*, **72**, 945 (1960)

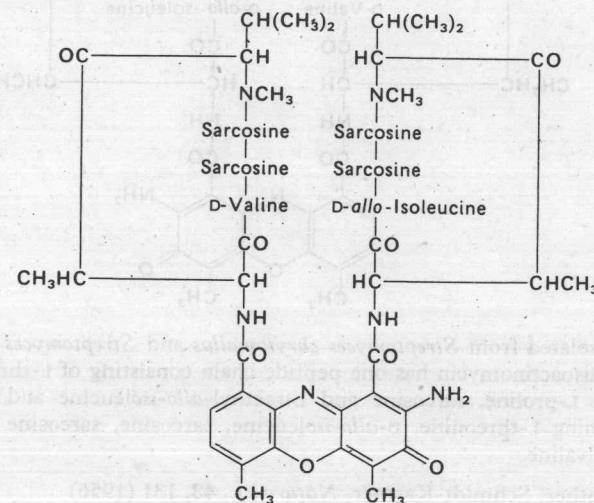
11

Actinomycin F₁



ACTINOMYCIN F₁ (*Actinomycin KS4:KS4*)

C₅₈H₈₈O₁₆N₁₂



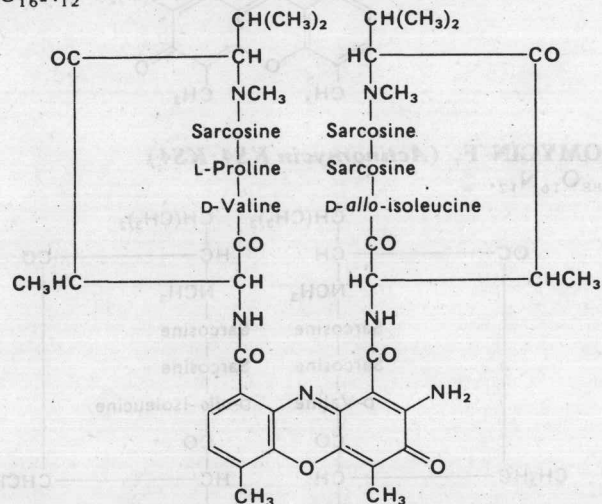
Actinomycin F₂

This antibiotic is obtained from *Streptomyces chrysomallus* and from other actinomycin C-elaborating strains such as *Streptomyces* BOP 476 (NRRL 2580). Actinomycin F₁ is an anisoactinomycin with one peptide chain containing L-threonine, D-valine, two moles of sarcosine and one of L-N-methylvaline, the other being similar but with D-valine replaced by D-allo-isoleucine.

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

ACTINOMYCIN F₂

C₆₀H₉₀O₁₆N₁₂



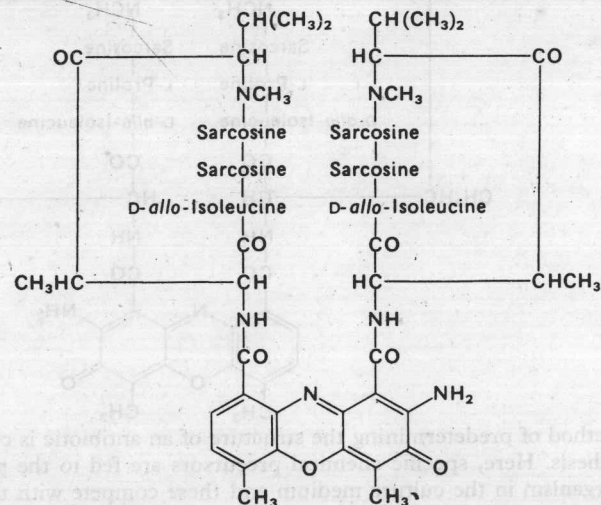
Also isolated from *Streptomyces chrysomallus* and *Streptomyces* BOP 476, this anisoactinomycin has one peptide chain consisting of L-threonine, D-valine, L-proline, sarcosine and L-methyl-allo-isoleucine and the other containing L-threonine, D-allo-isoleucine, sarcosine, sarcosine and L-N-methylvaline.

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

Actinomycin F₄

ACTINOMYCIN F₃

C₅₉H₉₀O₁₆N₁₂



An isoactinomycin isolated from *Streptomyces chrysomallus* and *Streptomyces* BOP 476, the peptide chains in this compound consist of L-threonine, D-allo-isoleucine, sarcosine, sarcosine and L-N-methylvaline.

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

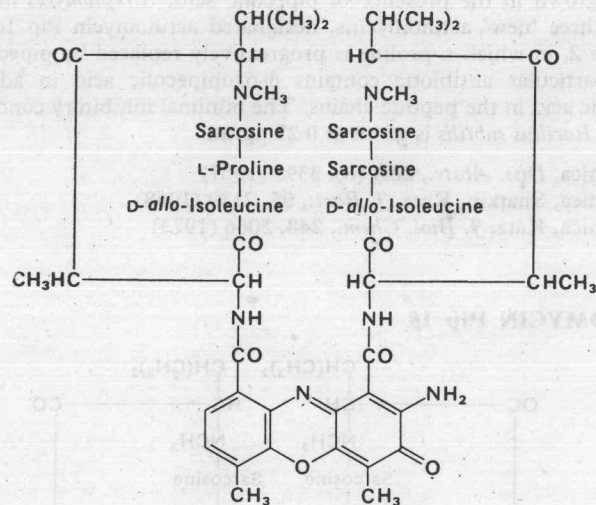
ACTINOMYCIN F₄

C₆₁H₉₂O₁₆N₁₂

A fourth component of the antibiotic mixture obtained from *Streptomyces chrysomallus* and *Streptomyces* BOP 476, the structure of this compound is identical with that of actinomycin E₂ but with one of the sarcosine groups replaced by L-proline.

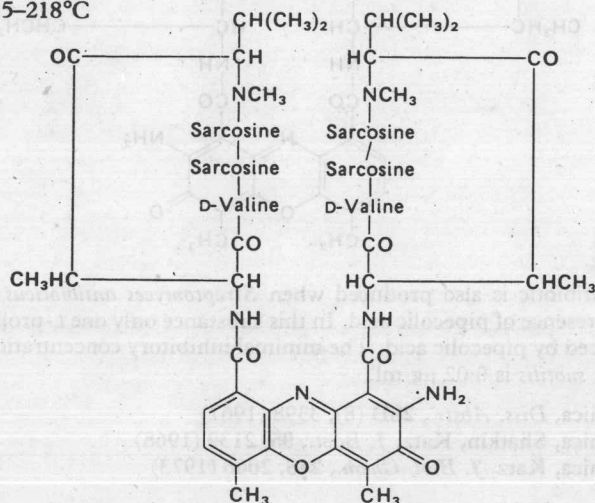
Gunther, Schmidt-Kastner, *Naturwiss.*, **43**, 131 (1956)
Brockmann, *Angew. Chem.*, **72**, 939 (1960)

Actinomycin₈



ACTINOMYCIN F₈ (Actinomycin II, A_{II})

C₅₇H₈₆O₁₆N₁₂
M.p. 215–218°C



13

Actinomycin F₉

An antibiotic produced by *Streptomyces antibioticus*, this substance forms red plates when crystallized from (CH₃)₂CO—CS₂. It is laevorotatory having a specific rotation of $[\alpha]_D^{17} - 157^\circ$ (c 0.24, CHCl₃). The antibiotic is an isoactinomycin, each peptide chain consisting of L-threonine, D-valine, sarcosine, sarcosine and L-N-methylvaline.

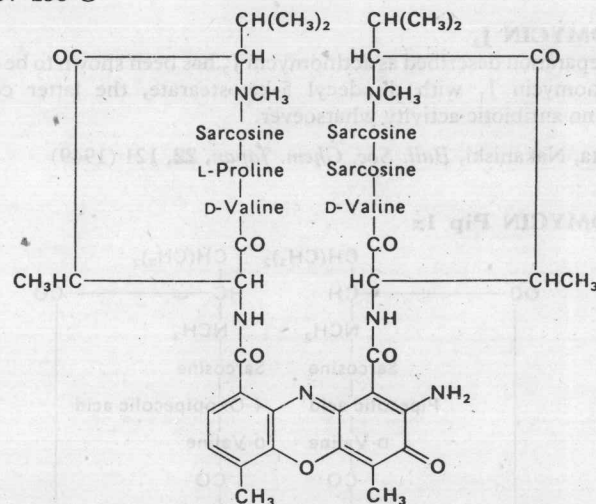
Johnson, Mauger, *Biochem. J.*, **73**, 335 (1959)

Brockmann, *Angew. Chem.*, **72**, 939 (1960)

Goss, Katz., *Antibiotics & Chemotherapy*, **10**, 221 (1960)

ACTINOMYCIN F₉ (Actinomycin III, A_{III})

C₆₀H₈₄O₁₆N₁₂
M.p. 237–238°C



Also formed by *Streptomyces antibioticus*, this antibiotic crystallizes from (CH₃)₂CO as red prisms. It has a specific rotation of $[\alpha]_D^{19} - 205^\circ$ (c 0.22, CHCl₃). The minimal inhibitory concentration against *Bacillus subtilis* is given by Brockmann and Manegold as 0.7 times that of actinomycin C₃, the latter being taken as the standard. It has also been shown that this antibiotic is identical with actinomycin X₀₇.

Johnson, Mauger, *Biochem. J.*, **73**, 535 (1959)

Brockmann, *Angew. Chem.*, **72**, 939 (1960)

Brockmann, Manegold, *Chem. Ber.*, **95**, 1081 (1962)