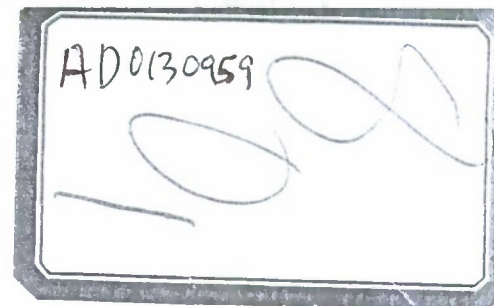


Clauser

TR-01-274



WADC TECHNICAL REPORT 55-16
VOLUME II
ASTIA DOCUMENT No. AD 130959

HANDBOOK OF TOXICOLOGY

20090507 246

WILLIAM S. SPECTOR
EDITOR

VOLUME II
ANTIBIOTICS

THE COMMITTEE ON THE HANDBOOK
OF BIOLOGICAL DATA

DIVISION OF BIOLOGY AND AGRICULTURE
THE NATIONAL ACADEMY OF SCIENCES
THE NATIONAL RESEARCH COUNCIL

JUNE 1957

WRIGHT AIR DEVELOPMENT CENTER

NOTICES

When Government drawings, specifications, or other data are used for any purpose other than in connection with a definitely related Government procurement operation, the United States Government thereby incurs no responsibility nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data, is not to be regarded by implication or otherwise as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

Qualified requesters may obtain copies of this report from the ASTIA Document Service Center, Knott Building, Dayton 2, Ohio.

This report has been published under the same title by the W. B. Saunders Company, Philadelphia, from whom it may be purchased by the general public.

Copies of WADC Technical Reports and Technical Notes should not be returned to the Wright Air Development Center unless return is required by security considerations, contractual obligations, or notice on a specific document.

AD-130959

WADC TECHNICAL REPORT 55-16
VOLUME II
ASTIA DOCUMENT No. AD 130959

HANDBOOK OF TOXICOLOGY

WILLIAM S. SPECTOR
EDITOR

Volume II
ANTIBIOTICS

Compiled from the Literature by
JOHN N. PORTER and GILBERT C. DE MELLO

Prepared under the Direction of the Committee
on the Handbook of Biological Data

DIVISION OF BIOLOGY AND AGRICULTURE
THE NATIONAL ACADEMY OF SCIENCES
THE NATIONAL RESEARCH COUNCIL

JUNE 1957

AERO MEDICAL LABORATORY
CONTRACT NO. AF 33(616)-2873
PROJECT No. 7159-71802

WRIGHT AIR DEVELOPMENT CENTER
AIR RESEARCH AND DEVELOPMENT COMMAND
UNITED STATES AIR FORCE
WRIGHT-PATTERSON AIR FORCE BASE, OHIO

Foreword

This compilation of data on antibiotics--their physical, chemical, biological and toxicological properties--comprises Volume 11 of the Handbook of Toxicology. The Handbook was prepared under Aero Medical Laboratory Contract No. AF 33(616)-2875 between The National Academy of Sciences and the Wright Air Development Center, United States Air Force. Under the same contract additional volumes are scheduled for publication in the coming year. The contract was administered under the direction of the Aero Medical Laboratory, Directorate of Research, Wright Air Development Center, Dr. George Kitzes acting as Project Director, Project No. 7159, "Health Hazards of Air Force Materials." The United States Army Chemical Center has also generously assisted in support of this contract.

Data for all volumes were contributed by experts in various areas of the fields represented. The material was reconciled, assembled, compiled, and edited by the Handbook Staff and reviewed and authenticated by specialists in the subjects covered. The work was carried out under the direction of the Committee on the Handbook of Biological Data, operating under the Division of Biology and Agriculture of The National Academy of Sciences-National Research Council.

Acknowledgment is made, on behalf of the Committee, to the Wright Air Development Center for the foresight and scientific judgment inherent in the commission to prepare this Handbook; to the Army Chemical Center for its generous support and cooperation; to Dr. John N. Porter and Mr. Gilbert C. de Mello of the Research Division, American Cyanamid Company, who compiled the data appearing in this volume and who served as guides and advisors in its preparation; to The National Research Council Committee on Toxicology, under the chairmanship of Dr. Harold C. Hodge, for encouragement and advice in planning the contents of the Handbook of Toxicology; to Mrs. Dorothy Dittmer for her tireless editorial efforts, without which this volume never would have reached the stage of publication; to Miss Florence Lochrie for her meticulous proofing of the manuscript; to Mr. John F. Sobrofski and Mr. John P. Henner for their excellent performance in the most tedious job of layout and drafting the entire volume; to the many biologists and toxicologists who served as contributors and reviewers for the Handbook; and finally to all the Handbook staff members who so willingly shared the multitude of tasks inherent in the preparation of the book.

May 28, 1957

W. S. Spector

Abstract

This report presents data on the physical, chemical, biological and toxicological properties of 340 antibiotics, compiled from more than 2500 literature references. The material is as up-to-date as possible at the time of publication. To enhance reliability, and consequently usefulness, each page of data has been exhaustively reviewed and authenticated by the contributors.

The compilation is unusually complete, not only with respect to the selection of antibiotic compounds, but also with the coverage of each. Wherever possible, data are presented on the source, nature, structure and formula, physical and chemical properties, biological activity (both in vivo and in vitro), toxicity, and utilization for each compound. A huge bibliography at the back of the book is divided into sets of references and literature citations, with one set for each antibiotic, in the same sequence as the compounds appear in the volume.

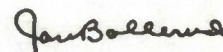
Two appendices supplement the text. One is an antibiotic efficacy listing by organism, and the other is a compendium of antibiotic-source microorganisms. The book also contains a cross index of synonyms, proprietary names, and official designations for the compounds involved.

An informative introduction explains some of the problems encountered in compiling data on the biological and toxicological properties of antibiotics and the reasons for wide variations in such data even within a single species. The introduction points out that although the information given in this volume is as authentic and reliable as could be procured, the book is still, nevertheless, a survey, and the values presented herein should be considered as "yardsticks" of activity rather than as absolute and definitive. The compilers recognize that all data, and particularly those in the fields of toxicology and antibiotics, are subject to continuing revision as investigators standardize techniques and make more measurements.

Publication Review

This report has been reviewed and is approved.

FOR THE COMMANDER



JACK BOLLERUD
Colonel, USAF (MC)
Chief, Aero Medical Laboratory
Directorate of Research

THE COMMITTEE ON THE HANDBOOK
OF BIOLOGICAL DATA

Theodore C. Byerly, *Chairman*

J. W. Heim, *Project Director*

William S. Spector, *Executive Secretary*

Frank H. Babers
Detlev W. Bronk*
David B. Dill
Wallace O. Fenn
A. P. Gagge
David R. Goddard
Charles M. Goss
William W. Greulich
Frank G. Hall

John A. Hilcken
Paul E. Howe
E. Morton Jellinek
Paul J. Kramer
Milton O. Lee
Daniel L. Leedy
Dale R. Lindsay
W. D. McElroy
L. A. Maynard*

Orr E. Reynolds
Charles H. Roadman
Royal Shanks
Charles W. Shilling
Ralph W. Stacy
Oswald Tippo
Lionel A. Walford
Paul A. Weiss
Raymund L. Zwemer

* ex officio

HANDBOOK STAFF

William S. Spector, *Editor*

Dorothy S. Dittmer, *Assistant Editor*

Rudolph M. Grebe, *Assistant Editor*

RESEARCH

Philip L. Altman
Everett F. Davis
John F. Gibson
Lucy C. Lee
William O. Negherbon
Barbara L. Tuma
Charles C. Wang

Gloria R. Alonso
Nellie F. Brown
Helen D. Carmack
Viola A. Crowder
Doris R. Folen
John P. Henner

EDITORIAL

Martha H. Lewis
S. W. Lipsman
Florence M. Lochrie
Francys E. Richardson
Laura B. Sheridan
John F. Sobrofski
Olga G. Stanczak

Contributors and Reviewers

Volume II

PRINCIPAL CONTRIBUTORS

JOHN N. PORTER, Ph.D.
Group Leader, Biochemical Research Section
Research Division
American Cyanamid Company
Pearl River, New York

and

GILBERT C. DE MELLO
Biologist, Experimental Therapeutics Research Section
Research Division
American Cyanamid Company
Pearl River, New York

with the technical assistance of
DOROTHY S. DITTMER
Assistant Editor
The Handbook of Biological Data



OTHER CONTRIBUTORS

CLARENCE DE BOER
Department of Microbiology
The Upjohn Company
Kalamazoo, Michigan

JAMES D. DUTCHER, Ph.D.
The Squibb Institute for Medical Research
New Brunswick, New Jersey

ARTHUR R. ENGLISH, Ph.D.
Pfizer Therapeutic Institute
Maywood, New Jersey

J. A. FOX
Department of Microbiology
The Upjohn Company
Kalamazoo, Michigan

STANLEY GREEN, M.D.
Arlington, Virginia

GEORGE GEE JACKSON, M.D.
Graduate College of Medicine
University of Illinois
Chicago, Illinois

A. F. LANGLYKKE, Ph.D.
The Squibb Institute for Medical Research
New Brunswick, New Jersey

C. N. LEWIS, M.D.
Division of Antibiotics
Food and Drug Administration
Washington, D. C.

JOHN E. LITTLE, Ph.D.
Department of Agricultural Biochemistry
University of Vermont
Burlington, Vermont

MACK H. McCORMICK, Ph.D.
The Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana

YOSHIRO OKAMI, Ph.D.
Japan Antibiotics Research Association
National Institute of Health of Japan
Tokyo, Japan

JOSEPH F. PAGANO, Ph.D.
The Squibb Institute for Medical Research
New Brunswick, New Jersey

WILLIAM A. RANDALL
Division of Antibiotics
Food and Drug Administration
Washington, D. C.

A. RAVINA, M.D.
Hôpital Beaujon
Paris, France

S. J. SHANE, M.D.
Sidney Point Hospital
Sidney, Nova Scotia

H. WALLICK
Chemical Division
Merck and Company, Inc.
Rahway, New Jersey

EUGENE D. WEINBERG, Ph.D.
Department of Bacteriology
Indiana University
Bloomington, Indiana

G. B. WHITFIELD, Jr., Ph.D.
Department of Microbiology
The Upjohn Company
Kalamazoo, Michigan

Contents

Volume II

| <u>Subject</u> | <u>Page</u> |
|---|-------------|
| Introduction | 1 |
| 1. Abikoviromycin | 3 |
| 2. Achromoviromycin | 3 |
| 3. Actiduins | 3 |
| 4. Actinoleukin | 3 |
| 5. Actinomyceline | 4 |
| 6. Actinomycetin | 4 |
| 7. Actinomycins | 4 |
| 8. Actinone | 7 |
| 9. Actinorhodin | 7 |
| 10. Actinorubin | 8 |
| 11. Actithiazic acid | 8 |
| 12. Agrocybin | 9 |
| 13. Albidin | 10 |
| 14. Albomycetin | 10 |
| 15. Albomycin | 11 |
| 16. Alternaric acid | 11 |
| 17. Alternarine | 12 |
| 18. Alternariol | 12 |
| 19. Alvein | 13 |
| 20. Amaromycin | 13 |
| 21. Amicetin | 14 |
| 22. <i>p</i> -4-Amino-3-isoxazolidone | 15 |
| 23. Amphomycin | 16 |
| 24. Amphotericins | 17 |
| 25. Angolamycin | 18 |
| 26. Angustmycin | 18 |
| 27. Anisomycin | 19 |
| 28. Antimycin A | 20 |
| 29. Argomycin | 20 |
| 30. Ascosin | 21 |
| 31. Aspergillic acid | 21 |
| 32. Aurantidin | 22 |
| 33. Aurantiogliocladin | 22 |
| 34. Aureolic acid | 23 |
| 35. Aureothricin | 23 |
| 36. Azaserine | 24 |
| 37. Azomycin | 25 |
| 38. Baccatine A | 26 |
| 39. Bacilipins | 26 |
| 40. Bacillin | 26 |
| 41. Bacillomycin | 26 |
| 42. Bacillomycin B | 27 |
| 43. Bacillomycin C | 27 |
| 44. Bacilysin | 28 |
| 45. Bacitracins | 28 |
| 46. Biformynes | 30 |
| 47. Biocerin | 31 |
| 48. Borrelidin | 31 |
| 49. Bostrycoidin | 31 |
| 50. Brevin | 32 |
| 51. Brevolin | 32 |
| 52. Bromotetracycline | 32 |
| 53. Bryamycin | 33 |
| 54. Cacaomycetin | 34 |
| 55. Camphomycin | 34 |
| 56. Candicidins | 34 |
| 57. Candidins | 35 |
| 58. Candidulin | 35 |
| 59. Canescin | 36 |
| 60. Carbomycin | 36 |

| | | |
|------|---------------------------------------|----|
| 61. | Carbomycin B | 38 |
| 62. | Cardicin | 38 |
| 63. | Carneolutescin | 39 |
| 64. | Carzinocidin | 39 |
| 65. | Carzinophilin | 39 |
| 66. | Carzinophilin A | 40 |
| 67. | Catenulin | 40 |
| 68. | Celesticetin | 41 |
| 69. | Cephalosporin C | 42 |
| 70. | Cephalosporin N | 42 |
| 71. | Cephalosporin P series | 43 |
| 72. | Cephalothecin | 44 |
| 73. | Cereviocidin | 44 |
| 74. | Chartreusin | 44 |
| 75. | Chartreusin-like antibiotic | 45 |
| 76. | Chetomin | 45 |
| 77. | Chlamydosporin | 46 |
| 78. | Chloramphenicol | 46 |
| 79. | Chlororaphin | 48 |
| 80. | Chlortetracycline | 49 |
| 81. | Chromin | 53 |
| 82. | Chrysomycin | 53 |
| 83. | Cinnamycin | 54 |
| 84. | Circulin | 54 |
| 85. | Citrinin | 55 |
| 86. | Citromycetin | 56 |
| 87. | Clitocybins | 56 |
| 88. | Coelicolorin | 57 |
| 89. | Colicines | 57 |
| 90. | Coliformin | 58 |
| 91. | Colistatin | 58 |
| 92. | Collinomycin | 58 |
| 93. | Comirin | 58 |
| 94. | Congocidin | 59 |
| 95. | Cordycepin | 59 |
| 96. | Cycloheximide | 60 |
| 97. | Cyclopaldic acid | 61 |
| 98. | Dechlorogriseofulvin | 62 |
| 99. | Dextromycin | 62 |
| 100. | Diatretynes | 62 |
| 101. | Diplococcin | 63 |
| 102. | Drosophilins | 63 |
| 103. | Ehrlichin | 64 |
| 104. | Elaiomycin | 64 |
| 105. | Endomycin | 65 |
| 106. | Enniatin A | 65 |
| 107. | Enniatin B | 66 |
| 108. | Erythromycin | 67 |
| 109. | Erythromycin B | 69 |
| 110. | Esperin | 70 |
| 111. | Estin | 70 |
| 112. | Etamycin | 70 |
| 113. | Eulicin | 71 |
| 114. | Eumycetin | 72 |
| 115. | Eumycin | 72 |
| 116. | Eurocidin | 72 |
| 117. | Exfoliatin | 73 |
| 118. | Fermicidin | 73 |
| 119. | Filipin | 73 |
| 120. | Flavacid | 74 |
| 121. | Flaveolin | 75 |
| 122. | Fluvomycin | 75 |
| 123. | Fomecin A | 76 |
| 124. | Foromacidins | 76 |
| 125. | Fradicin | 77 |
| 126. | Framycetin | 77 |
| 127. | Frequentin | 78 |

| | | |
|------|---------------------------------|-----|
| 128. | Fumagillin | 78 |
| 129. | Fumigatin | 79 |
| 130. | Fungichromin | 80 |
| 131. | Fungistatin | 80 |
| 132. | Fusaric acid | 81 |
| 133. | Fuscin | 81 |
| 134. | Fuscomycin | 82 |
| 135. | Gentisyl alcohol | 82 |
| 136. | Geodin | 82 |
| 137. | Geomycins | 83 |
| 138. | Gladiolic acid | 83 |
| 139. | Gliorosein | 84 |
| 140. | Gliotoxin | 84 |
| 141. | Globicin | 85 |
| 142. | Glutinosin | 85 |
| 143. | Glyco-lipide | 86 |
| 144. | Gramicidin | 86 |
| 145. | Gramicidin J | 87 |
| 146. | Gramicidin S | 88 |
| 147. | Granegillin | 88 |
| 148. | Grasseriomycin | 88 |
| 149. | Grifolin | 89 |
| 150. | Grisamine | 89 |
| 151. | Grisein | 90 |
| 152. | Griseoflavin | 90 |
| 153. | Griseofulvin | 91 |
| 154. | Griseoluteins | 91 |
| 155. | Griseomycin | 92 |
| 156. | Griseoviridin | 93 |
| 157. | Helenine | 93 |
| 158. | Helixin | 94 |
| 159. | Helvolic acid | 94 |
| 160. | Hemipyocyanine | 95 |
| 161. | Herquein | 95 |
| 162. | Hirsutic acids | 96 |
| 163. | Homomycin | 96 |
| 164. | Humicolin | 97 |
| 165. | Hydroxystreptomycin | 97 |
| 166. | Hygromycin | 97 |
| 167. | Hygroscopins | 98 |
| 168. | Illudins | 99 |
| 169. | Inolomin | 99 |
| 170. | Iodin | 100 |
| 171. | Isorhodomycins | 100 |
| 172. | Iturins | 101 |
| 173. | Javanicin | 101 |
| 174. | Kojic acid | 102 |
| 175. | Lactaroviolin | 102 |
| 176. | Lateritiin group | 103 |
| 177. | Laterosporins | 104 |
| 178. | Lavendulin | 104 |
| 179. | Lenzitin | 104 |
| 180. | Leucomycin | 105 |
| 181. | Levomycin | 105 |
| 182. | Licheniformins | 106 |
| 183. | Litmocidin | 107 |
| 184. | Luteomycin | 107 |
| 185. | Mannosidostreptomycin | 107 |
| 186. | Marasmic acid | 108 |
| 187. | Marcesin | 109 |
| 188. | Mediocidin | 109 |
| 189. | Mellein | 109 |
| 190. | Mesenterin | 110 |

| | | |
|------|---------------------------------------|-----|
| 191. | 5-Methoxy-p-toluquinone | 110 |
| 192. | 6-Methyl-1,4-naphthaquinone | 111 |
| 193. | Methymycin | 111 |
| 194. | Microcins | 112 |
| 195. | Micrococcin | 112 |
| 196. | Micromonosporin | 113 |
| 197. | Moldin | 113 |
| 198. | Musarin | 113 |
| 199. | Mycelianamide | 114 |
| 200. | Mycelin | 114 |
| 201. | Mycocidin | 115 |
| 202. | Mycolutein | 115 |
| 203. | Mycomycin | 115 |
| 204. | Mycophenolic acid | 116 |
| 205. | Mycosubtilin | 116 |
| 206. | Mycoticin | 117 |
| 207. | Narbomycin | 117 |
| 208. | Nebularine | 118 |
| 209. | Nemotin | 119 |
| 210. | Nemotinic acid | 119 |
| 211. | Neocidin | 119 |
| 212. | Neomycins | 120 |
| 213. | Neonocardin | 122 |
| 214. | Netropsin | 122 |
| 215. | Nidulin and Nor-nidulin | 123 |
| 216. | Nigericin | 123 |
| 217. | Nisins | 124 |
| 218. | Nitrosporin | 124 |
| 219. | Nocardamin | 125 |
| 220. | Nocardianin | 125 |
| 221. | Nocardorubin | 126 |
| 222. | Noformicin | 126 |
| 223. | Notatin | 127 |
| 224. | Novobiocin | 127 |
| 225. | Nudic acids | 129 |
| 226. | Nybomycin | 130 |
| 227. | Nystatin | 130 |
| 228. | Oleandomycin | 132 |
| 229. | Oligomycin | 132 |
| 230. | Oregonensin | 133 |
| 231. | Oryzasazine | 133 |
| 232. | Oxytetracycline | 133 |
| 233. | Antibiotics PA-114 | 137 |
| 234. | Palitantin | 138 |
| 235. | Patulin | 138 |
| 236. | Penicillic acid | 139 |
| 237. | Penicillins | 140 |
| 238. | Phaeofacin | 141 |
| 239. | Phagolessin A-58 | 142 |
| 240. | Phalamycin | 142 |
| 241. | Phenicin | 142 |
| 242. | Phthiocol | 143 |
| 243. | Phthiomycin | 143 |
| 244. | Picromycin | 143 |
| 245. | Pleocidin | 144 |
| 246. | Pleomycin | 145 |
| 247. | Pleuromutilin | 145 |
| 248. | Pleurotin | 146 |
| 249. | Polymyxins | 146 |
| 250. | Polypeptin | 148 |
| 251. | Polyporenic acid C | 149 |
| 252. | Polyporin | 149 |
| 253. | Primycin | 150 |
| 254. | Proactinomycins | 150 |
| 255. | Prodigiosin | 151 |
| 256. | Puberulic acid | 152 |
| 257. | Puberulonic acid | 152 |

| | | |
|------|--|-----|
| 258. | Pumilin | 153 |
| 259. | Puromycin | 153 |
| 260. | Pyo compounds | 155 |
| 261. | Pyocyanine | 156 |
| 262. | Pyolipic acid | 156 |
| 263. | Pyridomycin | 156 |
| | | |
| 264. | Quadrifidins | 157 |
| 265. | Quatrimycin | 157 |
| | | |
| 266. | Ractinomycins | 158 |
| 267. | Raisnomycin | 159 |
| 268. | Ramnacin | 159 |
| 269. | Resistomycin | 159 |
| 270. | Rhodocidin | 159 |
| 271. | Rhodomycetin | 160 |
| 272. | Rhodomycins | 160 |
| 273. | Rimocidin | 161 |
| 274. | Rosein II | 161 |
| 275. | Roseomycin | 162 |
| 276. | Roseothricin | 162 |
| 277. | Rotaventin | 162 |
| 278. | Rubidin | 163 |
| 279. | Rubrogliaocladin | 163 |
| 280. | Rubromycin | 163 |
| 281. | Rugulosin | 164 |
| 282. | Ruticin | 164 |
| | | |
| 283. | Sarcidin | 165 |
| 284. | Sarkomycin | 165 |
| 285. | Seligocidin | 166 |
| 286. | Simplexin | 166 |
| 287. | Sistomycosin | 166 |
| 288. | Spinulosin | 167 |
| 289. | Spiramycin | 167 |
| 290. | Streptocardin | 168 |
| 291. | Streptocin | 168 |
| 292. | Streptogramin | 169 |
| 293. | Streptogramin-like antibiotic | 169 |
| 294. | Streptolins | 170 |
| 295. | Streptolydigin | 170 |
| 296. | Streptomycin and Dihydrostreptomycin | 171 |
| 297. | Streptothricin | 173 |
| 298. | Streptothricin type 3 | 174 |
| 299. | Subtenolin | 174 |
| 300. | Subtilin | 175 |
| 301. | Sulfactin | 176 |
| 302. | Synnematins | 176 |
| | | |
| 303. | Tardin | 177 |
| 304. | Terrecin | 177 |
| 305. | Terreic acid | 178 |
| 306. | Tertiomycin A | 178 |
| 307. | Tertiomycin B | 179 |
| 308. | Tetaine | 179 |
| 309. | Tetracycline | 179 |
| 310. | Thermophilin | 182 |
| 311. | Thermoviridin | 182 |
| 312. | Thioaurin | 183 |
| 313. | Thiolutin | 183 |
| 314. | Thiomycin | 184 |
| 315. | Thiostrepton | 184 |
| 316. | Toximycin | 185 |
| 317. | Toyocamycin | 185 |
| 318. | Trichomycin | 186 |
| 319. | Trichothecin | 187 |
| 320. | Tyrocidine | 187 |
| 321. | Tyrothricin | 188 |
| | | |
| 322. | Ungulinic acid | 189 |

| | | |
|------|--------------------------|-----|
| 323. | Usnic acid | 190 |
| 324. | Ustilagic acid | 191 |
| 325. | Valinomycin | 191 |
| 326. | Vancomycin | 192 |
| 327. | Vinacetin | 192 |
| 328. | Violacein | 193 |
| 329. | Violacetin | 193 |
| 330. | Viomycin | 194 |
| 331. | Viridicatin | 195 |
| 332. | Viridins | 196 |
| 333. | Viscosin | 196 |
| 334. | Whitmorin | 197 |
| 335. | Xanthellin | 197 |
| 336. | Xanthocillin | 197 |
| 337. | Xanthomycins | 198 |
| 338. | Xanthothricin | 198 |
| 339. | Xerosin | 199 |
| 340. | Zaomycin | 199 |
| | Bibliography | 201 |
| | Appendix | 247 |
| | Index | 259 |

Introduction

This volume presents data on the physical, chemical, biological, and toxicological properties of 340 antibiotics. The word "antibiotic" is used in the strictest sense, i.e., "a chemical substance produced by microorganisms which has the capacity, in dilute solutions, to inhibit the growth of, or to destroy, bacteria and other microorganisms." Other anti-infectives and chemotherapeutic agents have not been listed in this book.* The data herein are recorded as accurately as possible from the literature and are current as the book goes to press. Because the field of antibiotics is tremendously fast-moving, it is by no means beyond possibility that some of the biological and toxicological information may be out of date by the time the volume appears in print--or that some of the facts may be contradicted by more recent reports.

The guiding principles in selection of material have been that it be of basic importance and from reliable literature sources. Some data of value have had to be omitted either because they were not on hand for publication or because time has not permitted the necessary preparatory steps for printing. The fact that certain data have been compiled and are already in print, or available in other form, has not been regarded as a reason for excluding them from this Handbook. Every page of this volume has been examined for accuracy by the contributors.

In the compilation of this information, one of the chief objectives has been clarity of presentation. To attain this clarity, only the most fundamental data appear in the body of the text. In several instances footnotes have been used to supply additional facts and preserve the conciseness of the text. Other pertinent material prohibited by limitations of space is to be found in the literature, and for this reason the bibliography is presented in sets of references, with a set for each antibiotic listed. Chemical nomenclature has been kept exactly as contributed and is, in every case, identical with that commonly found in the literature. However, a cross index at the back of the book contains numerous synonyms and proprietary names to facilitate location of any compound listed.

In an attempt to increase the usefulness of the volume, two appendices have been added. The first of these is an antibiotic efficacy listing in which organisms are compiled alphabetically and each is followed by the code numbers of all antibiotics showing moderate to high activity against it. The second appendix is a source list of antibiotics, alphabetized by the source organism.

It must be emphasized that the data presented in these tables, particularly those values concerned with toxicology, are by no means absolute and should be interpreted only as a "yardstick" of activity for the compounds listed. Again, the literature reference, in most cases, will reveal the number of determinations, the number of animals in each determination, and conditions under which determinations were made. Some of the conditions which influence toxicity or biological effect of any given compound are as follows:

- a. Dose: Generally, the larger the dose the more rapid the action.
- b. Rate of absorption: The faster this rate, the quicker the action of the drug. With oral administration the lethal dose may be considerably influenced by the condition of the gastrointestinal tract, especially by the amount of food and fecal material in the stomach and intestine.
- c. Route of administration: For the most part, toxicity or efficacy is greatest by the route that carries the active substance to the bloodstream most rapidly. In descending order of speed of action, routes for most drugs are: intravenous, inhalation, interperitoneal, intramuscular, subcutaneous, oral, and cutaneous. Food in the alimentary canal may delay or decrease activity; digestive enzymes may destroy or alter the compounds with resultant changes in the effectiveness thereof. Certain compounds are harmless if taken orally and lethal when introduced parenterally; in some cases the converse is true. The efficacy of the drug may also vary considerably with the form in which it is administered, i.e., solid, in suspension, or in solution. In the last instance the activity again may be influenced by the solvent and the concentration.
- d. Site of injection: With subcutaneous injections, toxicity may be affected by the density of the subcutaneous tissue. With intravenous administration, whether the injection is made into the femoral or jugular vein may be of importance, but in any case the rate of injection, or the amount of toxic material injected per minute, will considerably influence the value of the toxic dose.
- e. Other important influences: Idiosyncrasy, disease, environmental temperature, habit and tolerance, diet, season of the year (especially with hibernating animals) may all affect the activity or toxicity of an antibiotic. These properties will also vary with the species of animals used, and sometimes with different strains of the same species and within the same strain they may differ with age, weight, sex, and the general condition of the animals.

With all of the above variables exerting their individual or collective influences, it is important that the activity be delineated with reference to the time of death, the period of time for which fatalities are counted, or whatever other end-point is employed.

Unfortunately, only in rare instances are all these factors considered and specified in the literature on toxicity determinations. This renders the duplication of such data by different investigators extremely difficult if not impossible. At the present time, attempts are being made to put toxicity data on a quantitative basis. The older literature often refers simply to "lethal doses" (LD) or "minimal lethal doses" (MLD), meaning doses which will be

*Data on these compounds will be presented in a forthcoming volume entitled "Anti-infectives."

fatal or the smallest dose which will kill a limited number of animals. By using a larger number of animals of comparative weight and sex for each level tested, attempts are now being made to determine more precisely the dose which will kill 50 per cent (LD₅₀). These values can be further certified by the application of various statistical methods, by stating the degree of deviation of single values from the mean or the slope of the toxicity curve.

The data in this Handbook are, in the judgment of the contributors, as authentic as can be procured under the conditions as they exist. It is recognized, however, that all data, and particularly those in the fields of toxicology and antibiotics, are subject to continuing revision as investigators standardize techniques and make more measurements. The user of the volume is warned against attributing significance to small differences from species to species. He is invited to submit any data he feels should be given consideration.



TOXICITY CLASSES

The toxicological data presented in this Handbook are the result of extensive tests on laboratory animals. Frequently, toxicologists, industrial hygienists, industrial physicians, etc., are asked to translate these data into terminology that will readily describe the hazards associated with their use. Consequently, classes have been established to define the toxicity of a chemical material, in common terms, with reference to data obtained by specified animal tests. The following tabulation of toxicity classes is useful only for those data which are applicable.

COMBINED TABULATION OF TOXICITY CLASSES*

| Various Routes of Administration | | | | | |
|----------------------------------|-----------------------|--|---|-------------------------------|------------------------------|
| Toxicity Rating | Commonly Used Term | LD ₅₀ Single Oral** Dose Rats | Inhalation 4-hr Vapor Exposure Mortality 2/6-4/6 Rats | LD ₅₀ Skin Rabbits | Probable Lethal Dose for Man |
| 1 | Extremely toxic | 1 mg or less/kg | <10 ppm | 5 mg or less/kg | A taste, 1 grain |
| 2 | Highly toxic | 1-50 mg | 10-100 | 5-43 mg | 1 teaspoon, 4 cc |
| 3 | Moderately toxic | 50-500 mg | 100-1000 | 44-340 mg | 1 ounce, 30 g |
| 4 | Slightly toxic | 0.5-5 g | 1000-10,000 | 0.35-2.81 g/kg | 1 pint, 250 g |
| 5 | Practically non-toxic | 5-15 g | 10,000-100,000 | 2.82-22.59 g/kg | 1 quart |
| 6 | Relatively harmless | 15 g and more | >100,000 | 22.6 or more g/kg | >1 quart |

* Hodge, H. C., and Sterner, J. H., American Industrial Hygiene Association Quarterly, 10:4, 93, Dec. 1943.

** Standards for intravenous LD₅₀ for rats and rabbits may be obtained approximately by dividing the oral toxicity standards for rats by 10.

Antibiotics

1. ABIKOVIROMYCIN

SOURCE *Streptomyces rubescens*, n. sp. and *S. abikoensum*, n. sp [1].

STABILITY Unstable to heat, acid, exposure in dry state [1].

OTHER REACTIONS Red color on heating 5 minutes at 100°C in 1% phosphate buffer at pH 7; positive Molisch, Tollens, Ag mirror; sublimes during freeze drying. [1]

BIOLOGICAL ACTIVITY In vitro. Weak antibacterial and antifungal activity. Inhibits, at 62.5-250 µg/ml, *Shigella dysenteriae*, *Salmonella paratyphi*, *S. typhimurium*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Bacillus anthracis*, *Mycobacterium phlei*, and *Candida albicans*. *Brucella melitensis*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Micrococcus pyogenes* var. *aureus* are not sensitive, requiring 500 µg/ml or more. Inhibits western and eastern equine encephalitis virus in dilution of 1:8,000,000. No activity against Venezuelan equine encephalitis and Japanese encephalitis viruses.[2] Poliomyelitis virus rendered non-infective to mice when mixed with crude filtrates. Partially purified product exhibited antiviral activity in dilution of 1:25,000.[3]

ACUTE TOXICITY LD₅₀ in mice, approximately 6.6 mg/kg, i.v., and 66 mg/kg, s.c. [1].

2. ACHROMOVIROMYCIN

SOURCE *Streptomyces achromogenes*, n. sp [1].

REACTIONS Extractable with ethyl acetate at pH 2; related to, but not identical with, abikoviromycin and sarcidin [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits only *Sarcina lutea*, no other bacteria or fungi. Crude preparation inhibited Japanese B encephalitis virus in mice in dilution of 1:16,000 [1].

ACUTE TOXICITY Mice tolerated s.c. doses of approximately 100 mg/kg [1].

3. ACTIDUINS

SOURCE *Streptomyces* sp [1].

COLOR Yellow to reddish substances [1].

MELTING POINT (°C) None definite; darken at approximately 280, but no melting at 350.[1]

SOLUBILITY s. strong mineral acids; sl. s. butanol, ethanol, pyridine, acetic acid, cyclohexanone, dimethylformamide; i. water, ether¹. [1]

STABILITY Stable at acid and neutral pH; unstable at alkaline pH [1].

OTHER REACTIONS Yellowish fluorescence in organic solvents, less so in aqueous solvents; activity may be obscured in beers by faster diffusing substances; contain C, H, N, S, and one contains Cl; precipitated by dilution after dissolving in strong acids; crystalline reneckates soluble in acetone. Infrared peaks: actiduin II, 6.04, 6.54, 6.86, 7.05, 7.27, 7.47, 7.67, 8.1, 8.3, 8.6, 8.73, 9-9.14, 9.45, 9.87, 10.91, 11.9, 12.2, 12.7, 13.33 µ; actiduin III, 6.04, 6.41, 6.86, 7.04, 7.27, 8.1, 8.3, 8.61, 8.71, 9-9.14, 9.45, 10.91, 11.9, 12.2, 12.7, 13.33, 13.91, 14.37 µ; actiduin VI, 6.04, 6.54, 6.86, 7.28, 7.48, 7.67, 8.05, 8.3, 8.58, 9-9.14, 9.4, 9.85, 10.1, 10.9, 12.67, 13.3, 13.9 µ. On hydrolysis they yield both a ninhydrin positive and a fluorescent, somewhat acidic material, the former separating into acidic and neutral fractions on paper ionophoresis.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*² [1].

BIOLOGICAL ACTIVITY Actiduids II, III, IV, VI inhibit *M. pyogenes* var. *aureus* in dilution of 1:60,000,000-1:360,000,000. Also highly active against *Streptococcus pyogenes*, *Diplococcus pneumoniae*, *Corynebacterium xerose*. No activity against Gram-negative bacteria and *Mycobacterium tuberculosis*. [1]

4. ACTINOLEUKIN

SOURCE A strain of *Streptomyces aureus* [1].

MOLECULAR FORMULA (C₉H₁₂N₂O₃)_n [1].

CRYSTAL FORM AND COLOR White platelets or needles [1].

MELTING POINT (°C) 191-192 (d.)³ [1].

/1/ Different actiduids, however, are soluble in acetone, methanol, or chloroform, and can be separated on this basis. /2/ Preferably using serial tube dilution. /3/ After repeated crystallization.

4. ACTINOLEUKIN (Concluded)

UV ABSORPTION MAXIMA 243, 312 m μ [1].

SOLUBILITY s. methanol, ethanol, butanol, acetone, ethyl acetate, butyl acetate, dioxane; sl. s. benzene, chloroform; i. ether, petroleum ether, water. [1]

OTHER REACTIONS Positive FeCl₃; negative ninhydrin, biuret, Tollens, Fehling; purple ring in Molisch test. Analysis: C, 55.53, 55.68; H, 6.05, 5.98; N, 14.05, 14.01. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus*, *Sarcina lutea*, *Bacillus anthracis*, *B. subtilis* at 0.005-0.04 μ g/ml. Gram-negative bacteria not susceptible.

In vivo. Slight inhibition of Ehrlich carcinoma in mice when 6 μ g daily were injected, i.p., for 9 days. [1, 2]

ACUTE TOXICITY LD₅₀ in mice, 1 mg/kg, i.v. [1].

5. ACTINOMYCELINE

SOURCE *Streptomyces* sp related to *S. antibioticus* [1].

NATURE Neutral, yellowish-green pigment [1].

SOLUBILITY s. water, ethanol, methyl acetate; less s. acetone; sl. s. amyl acetate, chloroform; i. ether, benzene. [1]

STABILITY Thermolabile; stable at pH 7, less stable at pH 2.0; destroyed in 0.1 N NaOH in 24 hours. [1]

OTHER REACTIONS Intense fluorescence in ethanol [1].

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive bacteria; no activity against fungi and mycobacteria. [1]

ACUTE TOXICITY Rats tolerated s.c. doses of 25 mg/kg [1].

6. ACTINOMYCETIN

SOURCE *Streptomyces albus* [3].

NATURE Probably polypeptide enzyme [1].

SOLUBILITY s. water; i. ether, ethanol. [1]

STABILITY Thermo- and acid labile [1]. Inactivated by UV shorter than 300 m μ [2].

OTHER REACTIONS Precipitated by acetone, ethanol, (NH₄)₂SO₄; repeated precipitation with (NH₄)₂SO₄ yields 10-fold increase in activity. [1, 4]

BIOLOGICAL ACTIVITY Contains a lytic substance, "actinozyme," which dissolves dead and, to a lesser extent, living bacteria, e.g., *Micrococcus pyogenes* var. *aureus*, *Streptococcus pyogenes*, *Diplococcus pneumoniae*, *Bacillus megatherium* [4].

7. ACTINOMYCINS¹

SOURCE *Streptomyces antibioticus*, *S. chrysomallus* [12, 14, 21].

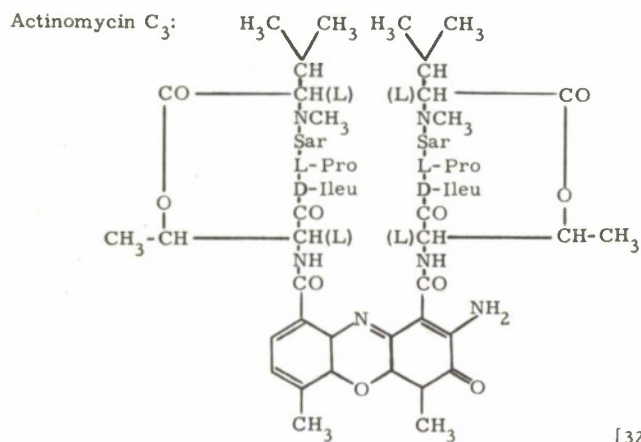
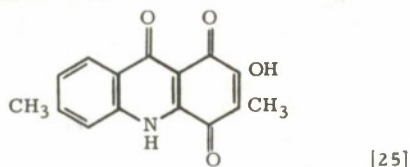
NATURE Weakly basic chromopeptides, quinonoid [4, 7, 12].

MOLECULAR FORMULA AND WEIGHT

Actinomycin A: C₄₁H₅₈N₈O₁₁ [4]; 1000 \pm (Rast); 768-780, 813 (cryo.); 716 \pm 15 (cryst.). [1, 2, 6]
B: C₆₁H₈₈N₁₂O₁₆ or C₆₅H₈₈N₁₂O₂₀; 1240 \pm 20 (found); 1245, 1356 (calc.). [7, 9]
C: C₆₂H₈₉N₁₁O₁₇ or C₆₀H₈₃O₁₆N₁₁; 915 (Beckman); 876-944 (Barger-Rast); 1260.4, 1214 (calc.). [5]
C₂: 1296 \pm 35 [26].
C₃: C₆₄H₉₀O₁₆N₁₂ [32]; 1307 \pm 35. [26]
D: C₆₀H₇₆O₁₅N₁₂·3H₂O (proposed); approximately 1200 (by analogy). [23]
J₁: 1305 \pm 35.
X₁: 1320 \pm 35.
X₂: 1307 \pm 35.
X₀₈: 1393 \pm 35. [26]

/1/ Actinomycin C also known as actinochrysin, Sanamycin.

STRUCTURE Actinomycins appear to have a common chromophore but differ in peptides. Peptide-free chromophore (actinomycinol) postulated to be:



CRYSTAL FORM AND COLOR

- Actinomycin A: red-vermilion platelets¹ [1, 2].
 B: red plates², orange needles³ [8].
 C₁, C₂, C₃, I₀, I₁, X₁: hexagonal bipyramids, six-angled prisms or needles⁴ [10, 11, 13].
 D: bright red rhomboid prisms [23].
 X₂: rhombic plates⁵ [10, 11, 13].
 X_{0β}: yellow needles [31].

MELTING POINT (°C)

- Actinomycin A: 250, 252 (d.) [1-3].
 B: 250-252 (d., corr.) [8].
 C₁: 241-243 (d.)⁶ [10, 13].
 C₂: 237-239 (d.)⁶ [10, 13].
 C₃: 232-235 (d.)⁶ [10, 13].
 D: 241.5, 243 (d.) [23].
 I₀: 242-243 (d.)⁶ [10, 13].
 I₁: 240.5-242 (d.)⁶ [10, 13].
 X₁: 240-242 (d.)⁶ [10, 11, 13].
 X₂: 244-246 (d.)⁶ [10, 11, 13].
 X_{0β}: 245-247 [31].

OPTICAL ACTIVITY

- Actinomycin A: $[\alpha]_D^{25} = -320^\circ \pm 5^2$ [1].
 B: $[\alpha]_D^{31} = -332^\circ, -340^\circ$ [3, 8].
 C₁: $[\alpha]_D^{20} = -349^\circ \pm 10$ [10, 13].
 C₂: $[\alpha]_D^{19} = -325^\circ \pm 10$ [10, 13].
 C₃: $[\alpha]_D^{19} = -321^\circ \pm 10$ [10, 13].
 D: $[\alpha]_D^{28} = -315^\circ \pm 10^7$ [23].
 I₀: $[\alpha]_D^{20} = -314^\circ \pm 10$ [10, 13].
 I₁: $[\alpha]_D^{20} = -353^\circ \pm 10$ [10, 13].
 X₁: $[\alpha]_D^{20} = -309^\circ \pm 10$ [10, 13].
 X₂: $[\alpha]_D^{19} = -341^\circ \pm 10$ [10, 13].
 X_{0β}: $[\alpha]_D^{20} = -261^\circ \pm 10^8$ [31].

/1/ From ether-acetone or ethyl acetate. /2/ Ethanol. /3/ Butanol. /4/ Ethyl acetate, methanol, benzene.
 /5/ Ethyl acetate. /6/ Koffler-Block MP determinations. /7/ c, 0.25 methanol. /8/ c, 0.22 acetone.

7. ACTINOMYCINS (Continued)

SPECIFIC EXTINCTION¹ AND R_{c2} VALUES²

| | | |
|-------------------------------|------|--------------------------|
| Actinomycin C _{0a} : | | 0.13, 0.10 [13]. |
| C ₀ : | | 0.13, 0.10 [13]. |
| C ₁ : | 20.5 | 0.72, 0.56 [10, 13]. |
| C ₂ : | 19.9 | 1.00, 1.00 [10, 13]. |
| C ₃ : | 18.8 | 1.39, 1.61 [10, 13]. |
| I _{0a} : | | -, 0.12 [13]. |
| I ₀ : | 20.5 | 0.49, 0.27 [10, 13]. |
| I ₁ : | 20.7 | 0.74, 0.63 [10, 13]. |
| I ₂ : | | 1.00, 0.97 [13]. |
| I ₃ : | | -, 1.34 [13]. |
| X _{0a} : | | 0.14, 0.17 [13]. |
| X ₀ : | | 0.14, 0.39 [13]. |
| X ₁ : | 17.3 | 0.48, 0.56 [10, 11, 13]. |
| X _{1a} : | | -, 0.71 [13]. |
| X ₂ : | 18.6 | 0.72, 0.98 [10, 11, 13]. |
| X ₃ : | | 0.93, 1.49 [13]. |
| X ₄ : | | 1.11, 1.90 [13]. |

UV ABSORPTION MAXIMA

| | |
|----------------|---|
| Actinomycin A: | 230-250, 450 m μ ³ [1, 2]. |
| B: | 240, 447 m μ ³ [8]. |
| D: | 240-242, 422 m μ [23]. |

SOLUBILITY Actinomycin A, B: s. chloroform, benzene, ethanol, acetone, hot ethyl acetate, 10% HCl; sl. s. water, ether; i. petroleum ether, dilute mineral acids, dilute alkali.[1, 2, 8, 12]

C: s. benzene, chloroform, acetone; less s. ethanol, glacial acetic acid; sl. s. water, carbon disulfide.[5]

STABILITY Thermostable except in alkali and strong acid [1, 2, 12].

AMINO ACID CONTENT Actinomycin A, B, C₁, I₀, I₁, X₁, X₂: threonine, sarcosine, proline, valine, n-methyl-valine [1, 4, 7, 10, 13].

C₂: threonine, sarcosine, proline, valine, n-methyl-valine, allo-iso-leucine [13].

C₃: threonine, sarcosine, proline, n-methyl-valine, allo-iso-leucine [10, 13].

OTHER REACTIONS Actinomycin A: Transient purple color with concentrated NaOH; negative color reaction with alcoholic FeCl₃; reduced by sodium hydrosulfite, stannous chloride or hydrogen over platinum oxide to pale yellow, reversed by exposure to air; no reaction with sodium bisulfite.[1, 12]

C: Negative ninhydrin; gray-brown precipitate with Nessler, yellow-green fluorescence in methanol or glacial acetic acid.[5]

E₁, E₂: Produced biosynthetically from a C-producing Streptomyces strain by use of DL-isoleucine in medium [33].

F₀-F₅: Produced by same strain as above when sarcosine is the precursor [33].

I: Identical with A [13].

J: May be identical with A [39].

X mixture: Identical with B [13].

X_{0b}: Can be acetylated; has higher threonine content than other actinomycins and contains an amino acid not present in the others; with acetic anhydride-pyridine produces a crystalline yellow acetate, MP 229°C.[31]

QUANTITATIVE DETERMINATION Microbiological: Bacillus subtilis, Micrococcus pyogenes var. aureus [1].

BIOLOGICAL ACTIVITY in vitro. Actinomycin A: Inhibits (μ g/ml) Streptococcus sp. and Diplococcus pneumoniae at 1; B. subtilis and Sarcina lutea at 0.01-0.02; Aerobacter aerogenes and Escherichia coli, 200 [14]. Inhibited certain fungi at 20-100 μ g/ml: Aspergillus niger, Fusarium sp, Penicillium sp, and Trichoderma sp. Slight activity against Candida albicans, Trichophyton mentagrophytes, and Cryptococcus neoformans.[14, 17]

B: A mixture of A and biologically inactive substances; shows low biological activity.

C: Inhibited (μ g/ml) M. pyogenes var. aureus at 0.05, B. subtilis at 0.01, E. coli at 100.[21, 22]

In vivo. Actinomycin A: Inactive against Str. pyogenes and D. pneumoniae infections in mice; slight protection afforded in infections with Trypanosoma equiperdum.[16] Showed no activity in chicks infected with Plasmodium gallinaceum [34].

C: Shows cytostatic activity against malignant tumors. Daily i.p. doses of 75-100 mg/kg for 7 days inhibited sarcoma 180 in mice; 25-75 mg/kg/da suppressed RC carcinoma and prolonged survival time in mice with leukemia L-4946.[35] In rats with Walker carcinoma, oral, i.v. or s.c. treatment with 50 μ g/kg considerably suppressed tumor development [18]. No antitumor activity observed in chick embryos.[24] Intracardiac injections, in doses of 10 μ g, delayed deaths from anaphylactic shock in guinea pigs [27]. No activity in mice infected with viruses of influenza (PR-8) and rabies [24].

/1/ At 446 m μ in cyclohexane. /2/ First column: butanol, n-dibutyl ether (2:3)/10% sodium-m-creosotinate; 2nd column: butyl acetate, n-dibutyl ether (3:1)/10% sodium-m-creosotinate. /3/ Ethanol.

7. ACTINOMYCINS (Concluded)

D: Showed a low therapeutic index in experimental tumors in mice, with activity following dosages of 0.5-0.75 mg/kg. The most sensitive neoplasms were a glioblastoma, a C₃H adenocarcinoma and S-91 melanoma, with moderate tumoristatic activity against sarcoma 180 and 6C₃HED lymphosarcoma. Failed to prolong life in mice bearing L-1210 leukemia.[36] Daily doses of 0.025 mg/kg in mice and rats had a marked suppressive effect on Ridgeway osteogenic sarcoma and ascites tumor, and little or no effect on solid tumors.[37, 38]

J: Single doses of 5 µg or 0.03-0.5 µg/da, i.p., inhibited Ehrlich ascites carcinoma in mice; the suppression was only slight when therapy was delayed for 24 hours or longer. Daily doses of 0.125-1.0 µg inhibited subcutaneous solid tumor of Ehrlich carcinoma and Yoshida rat sarcoma. Also active against Usubuchi rat sarcoma and Takeda rat liver sarcoma.[39] Daily doses of 0.025 mg/kg in mice and rats had a marked inhibitory effect on Ridgeway osteogenic sarcoma and ascites tumor and little or no effect on solid tumors.[37, 38]

CLINICAL Actinomycin C: Encouraging results in a few patients with lymphogranulomatosis (Hodgkin's disease); total doses of 1900-4350 µg per patient were used, with no toxic reactions observed.[19] In another series of 30 patients with lymphogranulomatosis, given daily i.v. doses of 50-400 µg, some objective as well as subjective improvement described [28]. Favorable clinical responses reported in patients with malignant conjunctival tumors following intravenous therapy with 0.2 mg/kg/da, increasing to 0.4-0.6 mg/kg [40]. In further preliminary observations, inconclusive results obtained in patients with a variety of inoperable malignant conditions, following daily i.v. doses of 200 µg for 25 days. These doses appeared to be well tolerated.[24] Daily i.v. injections of 40-150 µg appeared to exert beneficial effect in several cases of bronchial asthma [27].

D: Daily i.v. doses of 25-400 µg, over periods of 9-30 days, failed to alter significantly the course of Hodgkin's disease in 3 patients [29].

ACUTE TOXICITY Actinomycin A: LD₁₀₀ in mice, 1-2 mg/kg, i.v.; 0.5-5.0 mg/kg, s.c. [14-16] Following 0.125 mg/kg doses in mice, 10-20% excreted in urine in 6 hours [16]. Liver damage, altered kidney function, and eventual death in rats given daily doses of 0.025-0.1 mg/kg, i.p.[15].

C: LD₁₀₀ in mice, 5 mg/kg, i.p.; 50 mg/kg, oral doses.[20, 22] Injection of 30 µg in mice produces a marked diminution in spleen size within 3 days [27]. In vitro. Bone marrow cells in tissue culture were unaffected by concentrations of 0.025 µg/ml, but proliferation was retarded by concentrations of 0.25-2.5 µg/ml. No hemolysis of rabbit erythrocytes in concentrations of 500 µg/100 ml.[30]

D: LD₅₀ in mice, 0.67-0.74 mg/kg, i.v. Marked reduction in size of spleen in mice following i.v. dose of 0.5 mg/kg.[23]

J: LD₅₀ in mice, 0.8 mg/kg, i.v. or i.p.; 1.37 mg/kg, s.c. LD₅₀ in rats, 0.58 mg/kg, i.v.; 0.53 mg/kg, i.p. Five daily i.v. doses of 16 µg/kg lethal in dogs, 2-4 µg/kg tolerated, 8 µg/kg nephrotoxic. Three daily doses of 2 µg/kg in rabbits had no adverse effect on the blood picture.[39]

CHRONIC TOXICITY Actinomycin C: In man, following intravenous therapy, thrombocytopenia, stomatitis and brown pigmentation of the skin have been reported after dosages totaling 7-10 mg over long periods [43]. I.v. doses in excess of 400 µg may also produce nausea, diarrhea, pharyngitis, alopecia and vaginitis. Intravenous injection is the route of choice in view of localized reactions following intramuscular or subcutaneous use.[40, 42]

Daily i.v. doses of 20 µg/kg for 60 days were well tolerated in rabbits; 40 µg/kg induced anemia which persisted until antibiotic was discontinued. Doses of 80 µg/kg produced bone marrow changes and reduction in size of lymph glands, but had no appreciable effect on spleen size.[30]

ABSORPTION AND EXCRETION Actinomycin C: Rapidly eliminated in urine following i.v. therapy in man [40].

MODE OF ACTION In microbiologic systems using a variety of organisms, a competitive inhibition of pantothenate by actinomycin D was demonstrated. In addition to excess pantothenate, the inhibition could be reversed non-competitively by certain amino acids, dicarboxylic acids, orotic acid, or adenine.[41]

8. ACTINONE

SOURCE *Streptomyces* sp related to *S. antibioticus* [1].

SOLUBILITY s. ether, butyl acetate; less s. benzene, petroleum ether, ethyl acetate; i. chloroform.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Saccharomyces* sp and *Trichophyton* sp in dilutions of 1:1,000,000-1:1,500,000. Inactive against other fungi and bacteria.[1]

ACUTE TOXICITY Low toxicity; mice tolerated i.v. and s.c. doses of 1000 mg/kg [1].

9. ACTINORHODIN

SOURCE *Streptomyces coelicolor*¹ [3].

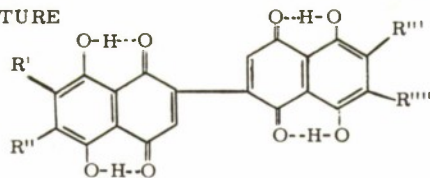
NATURE Red pigment [2]; acidic [4].

/1/ From mycelium.

9. ACTINORHODIN (Concluded)

MOLECULAR FORMULA AND WEIGHT $C_{32}H_{30}O_{14}$, $C_{32}H_{26}O_{14}$ or $C_{32}H_{28}O_{14}$; 566, 587 (found).[4]

STRUCTURE



R', R'', R''', R''''
2-CO₂H, 2-CH₃, C₈H₁₆O₂ [4]

CRYSTAL FORM AND COLOR Fine red needles [1]; microscopic prisms [3].

MELTING POINT (°C) 270 (d.) [2].

ABSORPTION MAXIMA 531, 571 mμ¹ [1].

SOLUBILITY s. pyridine, tetrahydrofuran, dioxane, alkali; sl. s. water, alcohol, acetone; i. ether, petroleum ether.[1]

STABILITY Rapidly changed in weak alkaline solution, but stable in n-alkali; partially destroyed on heating in tetrahydrofuran or dioxane.[3]

OTHER REACTIONS Blue color in alkaline solution; deep blue solution in H₂SO₄, becoming red-violet on addition of boric acid; red solution in acetone, changing to violet-blue with red fluorescence on heating with boric-acetic anhydride.[1,2] Cultures, made weakly acid and extracted with acetone, yield proto-actinorhodin² which oxidizes to actinorhodin on treatment with alkali in air [3].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus* in dilution of 1:100,000 [1].

10. ACTINORUBIN

SOURCE *Streptomyces* sp [1].

NATURE Basic [1,2].

CRYSTAL FORM AND COLOR Round, reddish orange clusters³ [1].

MELTING POINT (°C) 206-214³ (d., corr.) [1].

STABILITY Thermostable when neutral [1].

OTHER REACTIONS Base: positive biuret; reduces Fehling, KMnO₄; negative Sakaguchi, Molisch; dialyzes through cellophane; related to streptothricin.[1]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli* [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits, at 0.004-8.0 units/ml, *Bacillus subtilis*, *B. anthracis*, *Micrococcus pyogenes* var. *aureus*, *Corynebacterium xerose*, *C. diphtheriae*, *E. coli*, *Aerobacter aerogenes*, *Salmonella* spp, *Shigella* spp, *Brucella abortus*, *Br. melitensis*, *Alcaligenes faecalis*, *Vibrio comma*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis* [2,3]. *Streptococci* and *Diplococcus pneumoniae* are resistant [2].

In vivo. Good protection against infection with *K. pneumoniae* in mice treated with very low doses (14-30 μg) [2].

ACUTE TOXICITY LD₅₀ in mice, 34 mg/kg, i.p. Blood levels detectable following i.p., but not oral, doses of 3 to 4 mg. Mice surviving higher sublethal doses showed renal and liver damage.[2]

11. ACTITHIAZIC ACID (Acidomycin, Mycobacidin)

SOURCE *Streptomyces virginiae*, n. sp, and *S. lavendulae* [3,4]; by synthesis [9].

/1/ Butanol. /2/ Carmen-red, blue-fluorescing dioxane extract yields rose-colored microscopic prisms which lose their red color at 270° and decompose at 335°. /3/ Helianthate.

11. ACTITHIAZIC ACID (Concluded)

NATURE Monobasic acid [1, 4, 5].

MOLECULAR FORMULA AND WEIGHT $C_9H_{15}NO_3S$ [1, 4-6]; 212 (neut. equiv.); 217 (calc.).[4]

STRUCTURE
[1-3]

CRYSTAL FORM Fine needles [4-6].

MELTING POINT ($^{\circ}C$) 140-141 [1]; 138-139 [4]; 139-140 [5]; 137 [6].

OPTICAL ACTIVITY $[\alpha]_D^{25} = -60.5^{\circ 1}$ [1], $-57^{\circ 1}$ [4]; $[\alpha]_D^{23} = -54^{\circ 2}$ [5]; $[\alpha]_D^{15} = -46.2^{\circ}$ [6].

UV ABSORPTION No characteristic spectrum [5].

SOLUBILITY s. dilute NaOH, lower alcohols; i. water, benzene, chloroform.[1]

STABILITY Stable at room temperature over wide pH range [5].

OTHER REACTIONS Action reversed by addition of biotin [1, 3]; blue fluorescence in UV; negative Tollens, 2, 4-dinitrophenylhydrazine, ninhydrin; Br absorbed evolving HBr in glacial acetic acid or CCl_4 ; permanganate quickly decolorized in aqueous solution; NH_3 evolved and slight darkening on heating a strongly alkaline solution in presence of Pb acetate; white precipitate with $HgCl_2$; no reaction with HgO . [5]

QUANTITATIVE DETERMINATION Microbiological: Mycobacterium 607 [1, 4, 6].

BIOLOGICAL ACTIVITY In vitro. Inhibits Myco. tuberculosis at 1.25-2.5 $\mu g/ml$. Slightly active (1000 $\mu g/ml$) against Aerobacter aerogenes, Serratia marcescens, Bacillus subtilis, Saccharomyces pastorianus, and Oospora lactis.[3, 4, 7] The amide and lower alkyl esters are also active against mycobacteria [2]. Inhibition of Myco. tuberculosis in vitro is reversed by low levels of biotin (0.008 $\mu g/ml$). Has been suggested that activity against Myco. tuberculosis may be caused by interference with biotin synthesis within this organism.[3, 7] In vitro resistance of mycobacteria to actithiazic acid not readily acquired. Only 2-fold increase in sensitivity (0.125-0.25 $\mu g/ml$), following 25 serial transfers on antibiotic-containing media.[3]

In vivo. Inactive against infections with Myco. tuberculosis in mice. Suggested that this may be from in-activation by biotin in vivo [8]. No antitumor activity against Yoshida sarcoma and Ehrlich carcinoma in mice [10].

ACUTE TOXICITY Mice tolerated i.v. and s.c. doses of 1500 mg/kg [8]. LD_{50} in mice, 2500 mg/kg, i.p. [10].

CHRONIC TOXICITY No side effects or histopathology noted in mice following daily s.c. doses of 1250 mg/kg daily for 4 weeks [8].

ABSORPTION Fairly high blood levels obtained in mice following s.c. or oral administration [8].

12. AGROCYBIN

SOURCE Agrocybe dura [1].

NATURE Neutral or weakly acidic, acetylenic [1, 2].

MOLECULAR FORMULA $C_8H_5O_2N$ [4].

STRUCTURE $CH_2OHC\equiv CC\equiv CC\equiv CONH_2$ [4].

CRYSTAL FORM AND COLOR White crystals [1].

MELTING POINT ($^{\circ}C$) 130-140 (d. explosively in air) [3]; approximately 90 (d. explosively in vacuo) [1].

OPTICAL ACTIVITY Inactive [1].

UV ABSORPTION MAXIMA 216, 224, 269, 286, 304, 325 $m\mu^3$ [1-3].

SOLUBILITY s. alcohol, acetone, ether, chloroform, methyl-iso-butyl ketone; sl. s. water; i. hexane.[1]

STABILITY Thermolabile above pH 8.5 [1].

/1/ c, 1 absolute ethanol. /2/ c, 1 methanol. /3/ 95% ethanol.

12. AGROCYBIN (Concluded)

OTHER REACTIONS Crystals turn black after exposure to air; optical density increases 10-fold during 30-minute treatment with 1% KOH in ethanol.[1, 3]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*. Antiluminescence.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits, at 1 µg or less per ml, *Bacillus mycoides*, *B. subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Mycobacterium smegmatis*, *Myco. phlei*, *M. pyogenes* var. *aureus*. Also inhibits fungi: *Aspergillus niger*, *Chaetomium globosum*, *Trichophyton mentagrophytes*.[1]

ACUTE TOXICITY Highly toxic to mice; LD₅₀, <6 mg/kg, i.v.
In man, caused a dermatitis.[1]

13. ALBIDIN

SOURCE *Penicillium albidum* [2].

NATURE Red pigment [1].

MOLECULAR FORMULA C₅H₄O₂ (probable) [1].

CRYSTAL FORM AND COLOR Glistening red needles [1].

MELTING POINT (°C) No melting at 380 [1].

SOLUBILITY s. hot ethanol; sl. s. cold ethanol, benzene, pyridine, glacial acetic acid; 1,4 dioxane.[1]

STABILITY Very unstable, especially above pH 3 [1, 2].

OTHER REACTIONS Color changes with decomposition on standing: orange → brown at alkaline pH, orange → colorless → pale brown at acid pH; concentrated H₂SO₄, green; concentrated HNO₃, orange; concentrated HCl, crimson.[1, 2]

QUANTITATIVE DETERMINATION Microbiological: Inhibition of germination of *Botrytis allii* spores [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi (µg/ml): *Fusarium graminearum*, *Thamnidium elegans*, 0.04; *B. allii*, 0.2; *F. caeruleum*, *Penicillium brevi-compactum*, *P. expansum*, *P. gladioli*, 0.4; *Aspergillus terreus*, 0.8; *A. niger*, *Myrothecium verrucaria*, *Absidia glauca*, 1.6, *Trichoderma viride*, 3.1. Some antibacterial activity; inhibits *Micrococcus pyogenes* var. *aureus* and *Salmonella typhosa* at concentrations of approximately 25 µg/ml.[2]

14. ALBOMYCETIN

SOURCE *Streptomyces albus* [1].

NATURE Basic [1].

MOLECULAR FORMULA AND WEIGHT C₃₂H₅₄O₉N (proposed); 596.4 (Rast). [1]

CRYSTAL FORM AND COLOR Hexagonal; colorless [1].

MELTING POINT (°C) 166-167 [1].

SOLUBILITY s. xylene, benzene, ethylene dichloride, methanol, ethanol, acetone, ethyl acetate, dioxane, butanol, tetralin, acid water; sl. s. ether, carbon bisulfide; i. distilled water, petroleum ether.[1]

STABILITY Thermostable at pH 2-9, 10 minutes. At 100°C for 20 minutes: 20% loss at pH 2, 50% at pH 8, no loss at pH 5.[1]

OTHER REACTIONS Precipitated by ammonium reineckate and picric acid, but not by flavianic acid and methyl orange; positive Fehling, Tollens; cherry color with Elson-Morgan; negative FeCl₃, Molisch, Millon, Sakaguchi, pentose with phloroglucinol. Infrared: 2.89, 3.1-4.0, 5.74, 5.90, 6.14, 7.47, 7.68, 7.79, 7.89, 8.44, 8.61, 9.01, 9.23, 9.42, 9.88, 10.3, 10.59, 10.97, 11.21, 12.08 µ.[1]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* PCI 219¹ [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (µg/ml) *Corynebacterium diphtheriae*, 0.1; *Streptococcus viridans*, 0.4;

/1/ More active at alkaline pH.

14. ALBOMYCETIN (Concluded)

Micrococcus citreus, *B. agri*, 0.8; *B. anthracis*, *B. subtilis*, *Gaffkya tetragena*, 1.6; *Diplococcus pneumoniae*, 3.1; *M. pyogenes* var. *aureus*, 3.1-6.3; *Str. pyogenes*, *Clostridium histolyticum*, 6.3; *Cl. perfringens*, *Cl. sporogenes*, 12.5; *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, 800. *Leptospira icterohemorrhagiae* inhibited by 0.4 µg/ml. Fungi: *Trichophyton mentagrophytes*, *Aspergillus niger*, *Saccharomyces cerevisiae*, *Candida albicans* not sensitive to 500 µg/ml. No activity against *E. coli* bacteriophage C or against viruses of influenza A or Japanese B encephalitis.[1]

In vivo. Doses of 62 mg/kg, i.p., protected mice infected with *Borrelia duttoni* [1].

TOXICITY LD₅₀ in mice, 166 mg/kg, i.v.; approximately 332 mg/kg, i.p.; 58 mg/kg, intracerebral. LD₀, 250 mg/kg, i.p.[1]

15. ALBOMYCIN

SOURCE *Streptomyces subtropicus*, n. sp [1,2].

NATURE Basic; cyclic polypeptide containing Fe.[1,2]

MOLECULAR WEIGHT >1300 [1,2].

FORM AND COLOR Sulfate: amorphous red powder [1,2].

UV ABSORPTION MAXIMA Approximately 290, 420 mµ [1,2].

SOLUBILITY s. water; sl. s. methanol; i. other organic solvents [1,2].

OTHER REACTIONS About 4% of pure substance by weight is Fe; removal of Fe by treatment with acetone, with mineral acids or hydroxyquinoline, gives color loss and decline in antibiotic activity, but addition of FeCl₃ restores both; negative Sakaguchi, Millon, Pauly, Molisch, Seliwanoff, orcinol, phloroglucinol, ninhydrin; contains ornithine, serine, glutamic acid, alanine, glycine, proline, plus one unidentified amino acid.[1,2]

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive and Gram-negative bacteria. Inhibits *Escherichia coli* and *Micrococcus pyogenes* var. *aureus* at 0.0014-0.14 µg/ml.[3] Strains of the latter which are resistant to penicillin, streptomycin, erythromycin, and the tetracycline antibiotics, are sensitive to albomycin. *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Shigella dysenteriae*, *Diplococcus pneumoniae*, *Bacillus subtilis*, *Sarcina subflava*, and some strains of *Streptococcus pyogenes*, are also sensitive; *Neisseria meningitidis* and *Hemophilus pertussis* inhibited by higher concentrations. *Listeria* sp, *B. mycoides*, and *Mycobacterium tuberculosis* not sensitive.

Growth inhibition occurred only under aerobic conditions. Activity reduced in presence of blood serum because of a partial, but reversible, binding by serum protein. The antimicrobial activity is "masked" in vitro, but is demonstrable in vivo by mouse protection tests.[2]

In vivo. Described as more active, on a weight basis, than penicillin against *D. pneumoniae* and *Spirochaeta sogdianum*. Single s.c. doses of 750,000 units/kg¹ protected mice against *D. pneumoniae*; 150,000 units daily by the same route cleared guinea pigs of *S. sogdianum*. A single s.c. dose of 25,000-100,000 units/kg protected mice against *K. pneumoniae*. The antibiotic also protected mice against *M. pyogenes* var. *aureus*, *Str. pyogenes*, and *Sh. dysenteriae*, but was ineffective against *Listeria* sp, *Salmonella* sp, *Myco. tuberculosis* and *rickettsiae*.[2]

CLINICAL Good clinical responses following treatment of various pathogenic cocci infections (including those caused by penicillin-resistant strains) and in septic complications of dysentery and measles. Intrathecal injection of 100,000-200,000 units in children effectively controlled meningitis caused by penicillin-resistant strains of *D. pneumoniae*; these doses were well tolerated. In adults, 3 million units b.i.d., administered i.m. for 7-12 days, effectively treated relapsing fever caused by *Spirochaeta sogdianum*. Good results have also been reported in peritonitis and other surgical infections, prostatitis, and in urethritis from penicillin-resistant *N. gonorrhoeae* [2].

PHARMACOLOGY The very low toxicity resembles that of penicillin. In mice, the highest levels tested (50 million units/kg), i.v. and s.c., were well tolerated. The antibiotic was also well tolerated as high doses in rabbits, cats, and, unlike penicillin, in guinea pigs. I.v. injections of large doses had no effect on the heart rate, blood pressure or respiration in animals. No histopathology observed in animals given large parenteral doses daily for 30-day periods. No side effects in man treated with daily doses of 6 million units for variable periods. Following s.c. injections in rabbits of 100,000 units/kg, blood concentrations of 240 units/ml were produced in 30 minutes, decreasing to 150 units in 4 hours and 100 units at the end of 24 hours, with about 70-80% of the total dose not bound by serum proteins excreted in the urine for 6-8 hours after administration. The protein-bound fraction was slowly excreted for 2-3 days. Wide distribution demonstrated in the various organs and tissues, with no penetration into the cerebrospinal fluid.[2]

16. ALTERNARIC ACID

SOURCE *Alternaria solani* [2].

/1/ One unit equivalent to approximately 0.02 Oxford unit of penicillin [2].

16. ALTERNARIC ACID (Concluded)

NATURE Unsaturated dibasic acid [1].

MOLECULAR FORMULA AND WEIGHT $C_{21}H_{30}O_8$; 408 (Rast); 410 (calc.).[1]

CRYSTAL FORM AND COLOR Colorless, thin rectangular plates or elongated prisms [1].

MELTING POINT ($^{\circ}C$) 138 [1].

OPTICAL ACTIVITY Inactive [1].

UV ABSORPTION MAXIMUM 273 $m\mu$ [1].

SOLUBILITY s. ethanol, methanol, pyridine, chloroform, benzene, ether, carbon tetrachloride; sl. s. cold water; i. petroleum ether.[1]

STABILITY Thermostable [1].

OTHER REACTIONS Positive hydroxamic, $FeCl_3$; no reduction of Fehling, Schiff; reduced warm ammoniacal $AgNO_3$; decolorized Br water or $KMnO_4$ in acetone.[1]

QUANTITATIVE DETERMINATION Microbiological: Stunting of germ tubes of *Botrytis allii* or *Myrothecium verrucaria* [1].

BIOLOGICAL ACTIVITY *In vitro*. Antifungal activity (plant pathogens). Inhibits ($\mu g/ml$) spore germination of *Absidia glauca* and *M. verrucaria* at concentrations of 0.1-1.0; *B. allii* at 10.[2] No antibacterial activity [3].

TOXICITY Toxic to radish, cabbage, carrot and tomato seedlings in concentrations of 1-10 $\mu g/ml$ [1]. May be the chemical agent which is directly responsible for the disease effects of early blight of potatoes [4]. A crystalline toxin isolated from *Alternaria solani* filtrates, apparently identical with alternaric acid, produced wilting, epinasty and necrosis in tomato cuttings within a few hours, in dilutions as high as 1:50,000,000 [5].

17. ALTERNARINE

SOURCE *Alternaria solani* [1].

CRYSTAL FORM AND COLOR White needles [1].

MELTING POINT ($^{\circ}C$) 230 [1].

BIOLOGICAL ACTIVITY *In vitro*. Active against a number of bacteria and fungi including *Pseudomonas medicaginis*, *Ps. mori*, *Xanthomonas phaseoli*, *X. malvacearum*, *X. campestris*, *Agrobacterium tumefaciens*, *Penicillium claviforme*, *P. chrysogenum* and *Botrytis allii*. Also active against *Micrococcus pyogenes* var. *aureus*, *Bacillus mesentericus*, *B. alvei*, *B. mycoides*, *Sarcina lutea*, *Streptococcus pyogenes*, *Proteus vulgaris*, *Escherichia coli*, *Mycobacterium sp* and *Myco. phlei*. [1]

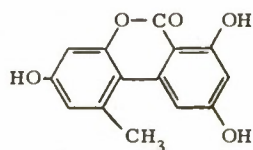
18. ALTERNARIOL

SOURCE *Alternaria tenuis* [1].

NATURE Substituted dibenzo- α -pyrone [1].

MOLECULAR FORMULA $C_{14}H_{10}O_5$ [1].

STRUCTURE



CRYSTAL FORM AND COLOR Colorless needles [1].

MELTING POINT ($^{\circ}C$) 350 (d.) [1].

SOLUBILITY s. cold aqueous Na_2CO_3 or $NaOH$, ethanol, cold concentrated H_2SO_4 , methanol, acetone, ether; i. aqueous $NaHCO_3$, benzene, petroleum ether.[1]

18. ALTERNARIOL (Concluded)

OTHER REACTIONS Sublimes without decomposing at 250°C in high vacuum; yellow-green in alkaline solution, becoming orange-red overnight; ethanolic solution gives intense purple color with ethanolic FeCl₃; reduces Fehling; bright cherry-red color in aqueous layer when boiled in aqueous NaOH with an equivalent volume of CHCl₃; yellow solution with strong blue-green fluorescence in cold concentrated H₂SO₄; no precipitation with Brady.

Alternariol methyl ether (C₁₅H₁₂O₅), MP 267°C (d.), is formed concurrently in fermentation; sublimes at 180-200°C in high vacuum; no optical activity; other properties very similar to alternariol. Demethylation, by heating at 140°C with concentrated HI, yields alternariol almost quantitatively.[1]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *Micrococcus pyogenes* var. *aureus* in dilution of 1:40,000; *Escherichia coli*, 1:20,000 [1].

19. ALVEIN

SOURCE *Bacillus alvei* [1].

NATURE Probably strong basic polypeptide [1].

SOLUBILITY Base: s. ethanol, butanol; decreasing solubility above pH 7 in water. HCl: s. ethanol, water; i. acetone, chloroform, ether. [1]

STABILITY Thermostable at acid pH; less so at alkaline. [1]

OTHER REACTIONS Positive reaction for arginine, negative for tyrosine and tryptophan; positive ninhydrin after hydrolysis; presence of other amino acids indicated; inactivated by trypsin.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *Mycobacterium tuberculosis* in dilution of 1:100,000; *Myc. phlei*, 1:32,000,000; *Bacillus anthracis*, *M. pyogenes* var. *aureus*, 1:512,000; *Streptococcus pyogenes*, *Corynebacterium diphtheriae*, 1:128,000.[1]

TOXICITY Hemolyzes red blood cells [1].

20. AMAROMYCIN

SOURCE *Streptomyces flavochromogenes* [1].

NATURE Basic [1].

MOLECULAR FORMULA C₂₅H₃₉O₇N (proposed) [1].

CRYSTAL FORM AND COLOR White prisms [1].

MELTING POINT (°C) 164.5-165 [1].

OPTICAL ACTIVITY [α]_D²⁵ = + 6.19° [1].

UV ABSORPTION MAXIMUM 220 mμ² [1].

SOLUBILITY s. ether, chloroform, methanol, benzene, toluene, ethyl acetate, butanol, carbon tetrachloride, ethanol, warm carbon disulfide; sl. s. cold carbon disulfide, petroleum ether, water. HCl: s. water.[1]

OTHER REACTIONS Free base analysis: C, 63.66; H, 8.73; N, 3.0. Infrared: 2.9, 3.4, 5.7, 6.10, 6.85, 7.2, 7.45, 7.85, 8.38, 8.60, 9.0, 9.25, 10.15, 10.60, 11.3 μ. Bitter taste; yellow color when concentrated H₂SO₄ is added to aqueous solution; positive Fehling, Tollens; negative FeCl₃, Schiff, Sakaguchi, xanthoproteic, biuret, ninhydrin, Molisch; precipitated from aqueous solution by picric acid, reinecke salt.[1]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* PCI 219³ [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits (μg/ml) *Streptococcus pyogenes*, *B. agri*, 0.2; *Hemophilus pertussis*, 0.4-50; *Sarcina lutea*, 0.05; *Diplococcus pneumoniae*, 0.78-1.56; *Corynebacterium diphtheriae*, 0.78; *Micrococcus pyogenes* var. *aureus*, 0.78-3.2; *B. subtilis*, 3.2; *Brucella abortus*, 1.56; *Br. melitensis*, *Br. suis*, 6.25; *Proteus vulgaris*, 12.5; *Mycobacterium avium*, *Myc. phlei*, 25; *Myc. smegmatis*, *Saccharomyces cerevisiae*, 50. *Myc. tuberculosis*, *Escherichia coli*, *Vibrio comma*, *Shigella dysenteriae*, *Salmonella enteritidis*, *Nocardia asteroides*, *Candida albicans* and *Trichophyton mentagrophytes* not sensitive to 50 μg/ml.[1]

ACUTE TOXICITY I.v. doses of 150-232 mg/kg toxic to mice [1].

/1/ 1% in ethanol. /2/ With broad peak. /3/ Increased zones on alkaline pH agar.

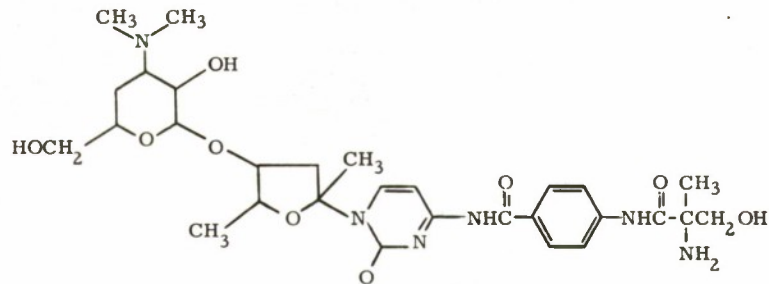
21. AMICETIN
(Allomycin, Sacromycin)

SOURCE *Streptomyces fasciculatus* [1] ; *S. sindenensis* [9] ; *S. vinaceus-drappus* [10] .

NATURE Amphoteric [4] .

MOLECULAR FORMULA AND WEIGHT Free base: $C_{29}H_{44}N_6O_9$ [1-4] ; 620.7 (calc.) [4] .

STRUCTURE Partial:



CRYSTAL FORM AND COLOR Colorless needles [6] .

MELTING POINT ($^{\circ}C$) Free base: 160-165; 165-169 [1-4, 6] . Granular form: 243-245 [1-4] .

OPTICAL ACTIVITY $[\alpha]_D^{24} = +116.5^{\circ I}$ [3] ; $[\alpha]_D^{16} = +107.7^{\circ} \pm 4^I$ [6] .

UV ABSORPTION MAXIMA 305², 316³, 302⁴, 322⁵, 318 $m\mu$ ⁶ [1-3] .

SOLUBILITY s. water⁷, aqueous mineral acid and alkali, n-butanol saturated with water; sl. s. organic solvents. [3, 4, 6]

STABILITY Most stable at pH 5; especially unstable above 8.5.[4]

OTHER REACTIONS pK 7 and 10.4; apparently 2 antibiotics in beers.[1-4] Positive ninhydrin; negative biuret, Sakaguchi, Fehling, Ag mirror, $FeCl_3$. [6]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*; *Mycobacterium avium*. [2, 3]

BIOLOGICAL ACTIVITY *In vitro*. Active against Gram-positive bacteria, particularly mycobacteria. Inhibits ($\mu g/ml$) *Myco. tuberculosis*, 0.5-1.0; *Myco. avium*, *Myco. smegmatis*, *Leuconostoc citrovorum*, *Corynebacterium diphtheriae*, 1.6; *Myco. phlei*, 0.2; *M. pyogenes* var. *aureus*, 2.0; *Bacillus subtilis*, 4.0; *M. flavus*, 0.4; *Klebsiella pneumoniae* and *Escherichia coli*, >20. [1, 2] The following sensitivity levels ($\mu g/ml$) appear in another report: *C. diphtheriae*, *Gaffkya tetragena*, 0.4; *M. citreus*, *Clostridium tetani*, 0.8; *B. subtilis*, *Hemophilus pertussis*, *Salmonella enteritidis*, *Vibrio comma*, *Myco. tuberculosis* var. *hominis* (including streptomycin-resistant strains), 1.6; *M. pyogenes* var. *aureus*, 1.6-3.2; *Myco. avium*, 3.2; *B. anthracis*, *Streptococcus pyogenes*, *Cl. perfringens*, *Cl. botulinum*, 6.3; *Str. mitis*, *Diplococcus pneumoniae*, 12.5; *B. agri*, 50; *Shigella dysenteriae*, *Proteus vulgaris*, 100. Resistant to 100 $\mu g/ml$: *Salmonella typhosa*, *S. paratyphi*, *S. schottmuelleri*, *Sh. boydii*, *Sh. sonnei*, *Pseudomonas aeruginosa*, yeasts and filamentous fungi. [6] Antibacterial activity antagonized by a number of antifungal and antiprotozoal antibiotics, including trichomycin, eurocidin, aureofacin, and seligocidin, but not by antibacterial agents (chlortetracycline, chloramphenicol, dextromycin, acidomycin, streptomycin). Activity was not impaired by a variety of amino acids, pyrimidine compounds and vitamins. [8]

In vivo. Some protection against *Myco. tuberculosis* in mice [1] . Activity against one strain of mouse leukemia following multiple doses of 200 mg/kg, i.p., or 2000 mg/kg, oral [5] .

ACUTE TOXICITY LD_{50} in mice, 90 mg/kg, i.v.; 600-700 mg/kg, s.c.⁸ Toxic for guinea pigs. LD_{50} in rats, 200 mg/kg, i.v.; 600 mg/kg, s.c. [2] In another report, mice tolerated doses of 100 mg/kg, i.v.; 400 mg/kg, i.p.; 500 mg/kg, s.c.; and 2000 mg/kg, orally. Daily intramuscular doses of 200 mg/kg for 2 weeks were well tolerated. [6]

RESISTANCE Strains of *B. megatherium* readily developed a high degree of resistance [7] . A strain of *M. pyogenes* var. *aureus* developed 150-fold resistance after 9 passages in the antibiotic. The resistance development pattern resembled that characteristic of streptomycin. [6]

/1/ c, 0.5 in 0.1 N HCl. /2/ Neutral aqueous solution. /3/ 0.1 N HCl. /4/ HCl at pH 2.5. /5/ 0.1 N NaOH. /6/ NaOH at pH 11.4. /7/ 1-2 mg/ml. /8/ Citrate complex.

21. AMICETIN (Concluded)

MODE OF ACTION Essentially bacteriostatic; high concentration (500 $\mu\text{g/ml}$) was bactericidal to *M. pyogenes* var. aureus in 12 hours [6].

22. D-4-AMINO-3-ISOXAZOLIDONE
(PA-94)

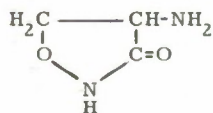
Trademarks for D-4-amino-3-isoxazolidone are Cycloserine (Commercial Solvents Corporation), Seromycin (Eli Lilly & Company), and Oxamycin (Merck & Co., Inc.).

SOURCE *Streptomyces garyphalus*, n. sp [1], *S. orchidaceus*, n. sp [2], *S. lavendulae* [9], and by synthesis [10].

NATURE Weakly acidic [2]; amphoteric [8, 9].

MOLECULAR FORMULA AND WEIGHT $\text{C}_3\text{H}_6\text{N}_2\text{O}_2$ [2, 3]; 102 (calc.) [5]; 101 (cryo.) [4]; 101-102 (equiv. wt., titr.) [4]; 104 (equiv. wt., pot. titr.) [2]; 110-130 (Rast) [8].

STRUCTURE



[2-5]

CRYSTAL FORM AND COLOR Colorless crystals [4]; fine white needles¹ [5].

MELTING POINT ($^{\circ}\text{C}$) 154-155 [4]; 156 [2]; 153 [8]; 140-150 (d.) [9].

OPTICAL ACTIVITY $[\alpha]_D^{25} = +116^{\circ 2}$ [4], $+112^{\circ 3}$ [5], $+64^{\circ 4}$ [9]; $[\alpha]_D^{24} = +121^{\circ 5}$ [8].

UV ABSORPTION MAXIMUM 226 $\text{m}\mu$ [4].

SOLUBILITY v.s. water; s. methanol; sl. s. most organic solvents [8, 9].

STABILITY Stable to alkali [4]; thermostable [9].

OTHER REACTIONS Positive ninhydrin; one-half of the N exists as a primary amino group; D(-)serine and hydroxylamine isolated from hydrolysates; Ag salt, $\text{C}_3\text{H}_5\text{N}_2\text{O}_2 \text{ Ag}$, prepared; Ca salt, MP 215-220 $^{\circ}$ (d.), $[\alpha]_D^{25} = 73.7^{\circ}$ (c, 1 water), more stable than ionic form; pKa 4.4, 7.3-7.4; dimerizes in solution. Infrared: No band in region of 2.5-3.4 μ ; broad hydrogen bonded NH-OH stretching frequencies in the region 3.6-4.7 μ ; maxima at 6.12, 6.20, 6.28, 6.43, 6.52 μ . [2, 4, 5] Yellow-brown with ninhydrin, red with FeCl_3 ; poorly adsorbed except on strong cation and anion exchange resins; addition of p-toluenesulfonic, or other strong organic acids, facilitates extraction with higher alcohols. [8, 9]

QUANTITATIVE DETERMINATION Colorimetric [14]. Microbiological: *Micrococcus pyogenes* var. aureus [1]; *Bacillus subtilis*, *Escherichia coli* [9].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Mycobacterium tuberculosis* (including strains resistant to isoniazid, pyrazinamide, and p-aminosalicylic acid), 2.5-10; *Corynebacterium diphtheriae*, *M. pyogenes* var. aureus, 6.25-50; *C. pseudodiphtheriticum*, 6.25-62.5; *C. renale*, *C. xerose*, 12.5; *Myc. phlei*, 20-125; *Klebsiella pneumoniae*, 25-500; *Streptococcus* (group D) 50-100; *C. pyogenes*, *Pasteurella multocida*, *Str. pyogenes*, *Str. viridans*, *Diplococcus pneumoniae*, *Salmonella gallinarum*, *S. pullorum*, *S. schottmuelleri*, *Shigella dysenteriae*, *Sh. paradysenteriae*, *Sh. sonnei*, *E. coli*, *M. conglomeratus*, *Neisseria meningitidis*, 100; *Pseudomonas aeruginosa*, 100-1000; *Proteus* spp, 125-500; *Str. faecalis*, 200; *Alcaligenes faecalis*, *S. typhimurium*, 400. Fungi: *Candida albicans*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Trichophyton mentagrophytes*, *Microsporium audouini*, *Epidermophyton floccosum* not inhibited by 100 $\mu\text{g/ml}$ [1-3, 6]. Combinations of this antibiotic with streptomycin, penicillin, or oxytetracycline show synergistic effect against Gram-positive (including *Myc. tuberculosis*) and Gram-negative bacteria *in vitro* and *in vivo* [1, 3].

In vivo. Relatively inactive against *Myc. tuberculosis* infection in mice treated with oral or s.c. doses of 10 mg/da, but when combined with dihydrostreptomycin the therapeutic effect is greater than that of the latter alone [3]. Good protection in mice infected with *M. pyogenes* var. aureus and *K. pneumoniae* following s.c. or oral doses of 1.1-2.5 mg, or *S. schottmuelleri* after mouse doses of 5.2 mg. Also effective in mouse infections with *E. coli*, *Ps. aeruginosa*, *Str. pyogenes*, *D. pneumoniae*, and penicillin-resistant strains of *M. pyogenes* var. aureus. In chick embryos, 1-5 mg suppressed *Rickettsia mooseri* (murine typhus); on a weight basis the antibiotic was approximately 1/10 as active as chlortetracycline. In mice, single s.c. or oral doses of 330 mg/kg gave protection against *R. mooseri*, and on a weight basis was approximately 1/50 as active as chlortetracycline. Slight suppression of feline pneumonitis virus in embryonated eggs; no activity against viruses of SK encephalomyelitis and swine influenza. In mouse infections with *Borrelia novyi*, the organisms were completely eliminated following treatment,

/1/ From aqueous alcohol. /2/ c, 1.17 water. /3/ c, 5 in 2 N NaOH. /4/ Methanol. /5/ c, 2.53 water.

but the antibiotic was only approximately 1/10 as active as penicillin on a weight basis. Slight activity against *Entamoeba histolytica* in rats and *Plasmodium gallinaceum* in chicks. No effect on cecal coccidiosis (*Eimeria tenella*) in chicks, enterohepatitis (*Histomonas meleagridis*) in turkeys, or experimental trypanosomiasis (*Trypanosoma brucei*) in mice. No anthelmintic activity against *Schistosoma mansoni* or mouse oxyurids.[3] No activity against psittacosis virus in chick embryos [15]. Little or no protection in guinea pigs with experimental tuberculosis [16].

CLINICAL Favorable responses reported in preliminary trials in advanced pulmonary tuberculosis refractory to treatment with other antitubercular agents, following oral doses of 1-1.5 g/da for 6 weeks-4 months [7, 17]. Good clinical response in urinary tract infections in which *Proteus*, *Pseudomonas*, *Aerobacter aerogenes*, and *Escherichia coli* were predominating organisms [6]; also good response in bacterial pneumonia and chronic upper respiratory infections [18, 19]. Preliminary trials showed good results in herpetic infections [18], and in donovanosis [21]. Was ineffectual in treatment of gonorrhea and lymphogranuloma venereum [19, 20].

PHARMACOLOGY In man, side effects were rare following daily oral doses of 1-4 g; some patients showed headache, vertigo, and drowsiness during therapy; anorexia and neurological symptoms in isolated cases.[6, 7] Readily absorbed from gastrointestinal tract. Following oral doses of 0.5-1.0 g, blood levels of 6-15 µg/ml produced in 4 hours, dropping to 2-7.5 µg/ml in 24 hours; urine concentrations of 52-190 µg/ml observed in 8 hours with continuous excretion for 48 hours, but no significant levels in the feces. Very high blood concentrations observed following oral amounts of 2-3 g/da in divided doses. Preliminary studies indicate high levels obtained in cerebrospinal and pleural fluids.[6, 11] After oral doses, the concentrations in spinal fluid and in milk approximated those in plasma. The antibiotic was well distributed in the body tissues. Single oral, or intramuscular, doses penetrated the placental barrier. Following intramuscular injection of 250 mg, 26% of the administered dose was excreted into the urine during the following 24 hours at concentrations of approximately 54 µg/ml. Neurological symptoms, both excitatory and depressant, appeared in several cases of tuberculosis during treatment. Grand mal seizures, twitchings and psychoses have been observed.[17, 21-23, 25]

In mice, the LD₅₀ was reported as 1810 mg/kg, i.v.; 2870 mg/kg, i.p.; 2800 mg/kg, s.c.; 5290 mg/kg, oral. LD₅₀ in rats, >3000 mg/kg, s.c.; >5000 mg/kg, oral; in guinea pigs, >1000 mg/kg, s.c.; >2000 mg/kg, oral; in dogs, >2000 mg/kg, oral. High doses (50 mg/kg, i.v.) resulted in a transient depressor action in the anesthetized dog, with no significant effect on the heart or intestinal motility. The renal clearance in dogs approximated the glomerular filtration rate. Daily i.v. doses of 50-100 mg/kg in dogs over a one-year period, and multiple oral doses of 100-300 mg/kg/da in monkeys, produced no visceral or hemopoietic changes.[26] In guinea pigs treated with a single i.m. dose of 65-70 mg/kg, the average plasma level was 95 µg/ml in 1-1/2 hours, dropping to 10 µg/ml at 7 hours [27]. In monkeys, dogs, and rabbits, the antibiotic was rapidly absorbed from the stomach and intestines, with high levels in plasma, urine, lymph, amniotic fluid and fetal blood [26].

MODE OF ACTION In vitro. Activity against *Myco. tuberculosis* is bacteriostatic rather than bactericidal. The antibiotic does not appear to arrest immediately metabolism of *Myco. tuberculosis*, since exposure to 20 µg/ml had no effect on oxygen consumption during the first six hours.[24] Unlike isoniazid, there was no significant tuberculocidal effect in the presence of glucose [12]. Action against *Myco. paratuberculosis* is reversed by increasing concentrations of mycobactin, a growth factor prepared from *Myco. phlei*. Since *Myco. paratuberculosis* is unable to synthesize mycobactin, it appears that the antibiotic competes directly with this factor.[13]

23. AMPHOMYCIN

SOURCE *Streptomyces canus* [1].

NATURE Amphoteric; acidic polypeptide.[1, 3]

OPTICAL ACTIVITY $[\alpha]_D^{25} = +7.5^0 \pm 0.5^1$ [1, 3].

UV ABSORPTION MAXIMA Only end adsorption [1, 3].

SOLUBILITY s. water², lower alcohols; i. non-polar solvents.[1, 3]

STABILITY Stable in aqueous solution 1 month at pH 7, room temperature [1, 3].

OTHER REACTIONS Negative ninhydrin (positive after acid hydrolysis), Sakaguchi, Molisch, Ehrlich-Pauly; positive biuret [1, 3].

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis*³ [1, 3].

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive bacteria; no activity against Gram-negative bacteria and *Candida albicans*. Inhibits (µg/ml) *Corynebacterium xerosis*, 0.25; *B. anthracis*, *B. cereus*, *Lactobacillus leichmannii*, 0.5; *Streptococcus agalactiae*, *Str. dysgalactiae*, 1.25; *Str. pyogenes*, *Str. uberis*, *Diplococcus pneumoniae*, *Micrococcus pyogenes* var. *aureus*, 2.5; *B. subtilis*, *L. casei* and *Gaffkya tetragena*, 5; *L. acidophilus*, 10.

/1/ c, 1 water pH 6. /2/ Minimum solubility at pH 3-4 [3]. /3/ ATCC 6633.

23. AMPHOMYCIN (Concluded)

Resistant, >100 µg/ml: *Salmonella typhosa*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Shigella sonnei*, *Candida albicans*. [1]

In vivo. Doses of 0.5 mg/kg, i.p., gave good protection against infections with *D. pneumoniae* in mice; much larger oral doses were required. [1]

ACUTE TOXICITY LD₅₀ in mice, (Na salt) 178 mg/kg, i.v.; (Ca salt) 120 mg/kg, i.v. LD₅₀ in dogs (Na salt), 100 mg/kg, i.v.; >500 mg/kg, oral. Single i.m. doses of 60 mg/kg tolerated by rats, rabbits, and dogs with some irritation at injection site. [2]

CHRONIC TOXICITY Mice tolerated 100 mg/kg/da, i.p., for 20 days. Repeated injections in dogs of 15-50 mg/kg/da, i.v., or 20-40 mg/kg, i.m., did not alter blood chemistry or cell counts; a slight proteinuria noted. Doses >50 mg/kg produced some renal and cardiovascular damage. Repeated daily topical applications of 1-2.5% to rabbit eye were non-irritating; higher concentrations induced mild reactions. [2] In vitro. Partial hemolysis of red blood cells [1].

ABSORPTION Rapidly absorbed following i.m. administration in dogs and rabbits; poor absorption after oral doses. I.m. injection of 20-40 mg/kg gave very high serum concentrations which were maintained between 1-5 hours, with approximately 37% of the total dose excreted in urine within 24 hours. [2]

24. AMPHOTERICINS

SOURCE *Streptomyces* sp [1].

NATURE Amphoteric [2]. Neutral equivalent, A: 915; B: 929. [1]

STRUCTURE

Amphotericin A: conjugated tetraene.
B: conjugated heptaene. [2]

OPTICAL ACTIVITY

Amphotericin A: $[\alpha]_D^{23.5} = -9.9^{\circ 1}, +32^{\circ 2}$.
B: $[\alpha]_D^{23.5} = -33.6^{\circ 1}, +333^{\circ 2}$. [2]

UV ABSORPTION MAXIMA

Amphotericin A: 291, 305, 320 mµ^{3,4}.
B: 364, 383, 408 mµ³; 363, 382, 406 mµ⁴ [1].

SOLUBILITY s. aqueous lower alcohols at pH 10.5. Amphotericin A more soluble than B in methanol-CaCl₂, N, N-dimethylformamide; i. anhydrous alcohols, esters, ethers, benzene, toluene, H₂O at neutral pH. [2]

STABILITY Dry solids stable for long periods at moderate temperature.

Amphotericin A: Stable at pH 6 and 7 at 30°C.
B: Undergoes decomposition at all pH values between pH 4 and 10. [2]

OTHER REACTIONS Analysis: Amphotericin A: C, 60.32; H, 8.39; N, 1.72; B: C, 60.40; H, 8.38; N, 1.62. Both negative FeCl₃; both positive Molisch; decolorize KMnO₄ or Br₂-CCl₄; yield volatile bases when treated with concentrated NaOH. Amphotericin A forms water-soluble Na salt with methanolic NaOH, B does not; A forms methanol-soluble CaCl₂ complex, B does not [2].

QUANTITATIVE DETERMINATION Microbiological: *Saccharomyces cerevisiae*⁵ [1].

BIOLOGICAL ACTIVITY In vitro. Primarily active against yeasts and fungi.

Amphotericin A: Inhibits (µg/ml) *Histoplasma capsulatum*, *Rhodotorula glutinis*, 0.8; *Candida tropicalis*, *C. pseudotropicalis*, *Rh. mucilaginosa*, *Sac. cerevisiae*, *Sporotrichum schenckii* (yeast phase), *Microsporium audouini*, *Trichophyton megnini*, *Epidermophyton floccosum*, *Phialophora verrucosa*, *Blastomyces brasiliensis*, 1.2-1.8; *C. albicans*, *T. rubrum*, *T. gallinae*, *Monosporium apiospermum*, *Cryptococcus neoformans*, *Fusarium bulbigenum*, 2.4; *Candida parakrusei*, *T. tonsurans*, *T. mentagrophytes*, *Aspergillus fumigatus*, 3.1-3.9; *Microsporium canis*, *Cladosporium werneckii*, *Fonsecaea pedrosoi*, *F. compactum*, *Geotrichum* sp, 4.0-4.7; *Candida parapsilosis*, 5.5; *Cephalosporium recifei*, 5.9; *Cladosporium carrioni*, 6.3; *Microsporium gypseum*, 9.4; *S. schenckii* (mycelial phase), 18.8. Bacteria and *Nocardia* spp not sensitive to 50 µg/ml. [1]

B: Inhibits (µg/ml) *S. schenckii* (yeast phase), <0.07; *H. capsulatum*, 0.04; *Cr. neoformans*, *Ep. floccosum*, *Bl. brasiliensis*, 0.2; *Candida albicans*, *Rh. glutinis*, *Rh. mucilaginosa*, *Sac. cerevisiae*, 0.5-0.6; *C. pseudotropicalis*, *C. parakrusei*, *Microsporium audouini*, *T. megnini*, *Monosporium apiospermum*, 0.9-1.1; *A. fumigatus*, 1.9; *T. mentagrophytes*, 2.4; *C. tropicalis*, 3.7; *T. tonsurans*, 4.9; *Microsporium canis*, *T. rubrum*, *T. gallinae*, *Fusarium bulbigenum*, 14.7. The following were not sensitive to 40 µg/ml: *C. parapsilosis*, *S. schenckii* (mycelial

/1/ 0.1 N methyl-hydroxide-HCl. /2/ Acid dimethylformamide. /3/ 70% propanol. /4/ Methanol. /5/ Squibb culture No. 1600.

24. AMPHOTERICINS (Concluded)

phase), *Cephalosporium recifei*, *Cladosporium carrioni*, *C. wernecki*, *Fonsecaea pedrosoi*, *F. compactum*, *Phialophora verrucosa*, *Geotrichum* sp; also Gram-positive and Gram-negative bacteria and *Nocardia* spp.[1]

In vivo. Amphotericin A: Median protective dose against intravenously-injected *Candida albicans* in mice, >17.6 mg/kg/da, s.c.; in *H. capsulatum* infection, 20 mg/kg/da; against *Cr. neoformans*, 25.5 mg/kg/da.[4]

B: Daily doses of 10-25 mg/kg, i.p., or 600 mg/kg, orally, gave good protection in mice infected with *Coccidioides immitis*. Daily i.p. doses of 10-25 mg/kg controlled *Candida albicans* infection induced by the same route.[3] Median protective dose in mice, infected with *C. albicans* by i.v. or intracerebral routes, was <0.32 mg/kg, s.c., or 0.55 mg/kg, per os; against *H. capsulatum*, 10.2 mg/kg/da, s.c., for 6 days; and against *Cr. neoformans*, 2 daily doses of 5.1 mg/kg, s.c. Experimental skin infections with *T. mentagrophytes* in guinea pigs were successfully treated with 2% antibiotic ointment.[4]

PHARMACOLOGY Amphotericin A (Na salt): LD₅₀ in mice, 450 mg/kg, i.p. Daily oral doses of 80 mg/kg tolerated.

B: LD₅₀ in mice, 25 mg/kg, i.v.; 280 mg/kg and >1200 mg/kg, i.p. Daily doses of 100 mg/kg, i.p., and 600 mg/kg, oral, tolerated.[3, 4] Following daily oral doses of 40 mg/kg in mice, B appeared to cross the blood-brain barrier [4].

25. ANGOLAMYCIN

SOURCE *Streptomyces eurythermus*, n. sp [1].

NATURE Basic [1].

MOLECULAR FORMULA AND WEIGHT C₄₉₋₅₀H₈₇₋₉₁O₁₈N [1]. 1020 (equiv. wt. found); 992.2±14 (calc.).[1]

CRYSTAL FORM AND COLOR Colorless crystals¹; colorless needles². [1]

MELTING POINT (°C) 133-136¹; 165-168² [1].

OPTICAL ACTIVITY [α]_D²¹ = -64°³ [1].

UV ABSORPTION MAXIMUM 240 mμ⁴ [1].

OTHER REACTIONS Infrared: In 6μ range bands at 1715, 1686, 1623 (recip. cm); upon hydrogenation with palladium, takes up 1 mole H, and, with platinum oxide in acetic acid, 3 moles of H; very similar to carbomycin, but differs from carbomycin and erythromycin in color reactions and paper chromatography; at least 2 sugar components are obtained by acid hydrolysis, but neither is identical with desosamine (C₈H₁₇O₃N) [1].

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis*, *B. megatherium* [1].

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive bacteria and protozoa. Inhibits (μg/ml) *B. megatherium*, 0.1-1.0; *Streptococcus pyogenes*, 10; *Micrococcus pyogenes* var. *aureus* (including a penicillin-resistant strain), *Entamoeba histolytica*, 10-100; *Corynebacterium diphtheriae*, 100. The following were not sensitive to 100 μg/ml: *Str. mitis*, *Str. faecalis*, *Escherichia coli*, *Salmonella* sp, *Shigella sonnei*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Pasteurella pestis*, *Vibrio comma*, *Mycobacterium tuberculosis*, *Candida albicans*, and *C. tropicalis*. [1]

In vivo. Doses of 50 mg/kg, s.c., protected mice against infection with *Str. pyogenes* [1].

ACUTE TOXICITY Mice tolerated 500 mg/kg, s.c.; 1000 mg/kg s.c. doses were lethal.[1]

26. ANGUSTMYCIN

SOURCE *Streptomyces hygroscopicus* [2].

NATURE Neutral or weak base [1].

MOLECULAR FORMULA C₁₄H₁₄O₅N₆ or C₁₄H₁₆O₅N₆ (proposed)⁵; C₁₄H₁₆O₆N₆ or C₁₄H₁₈O₆N₆ (proposed)⁶. [1]

CRYSTAL FORM AND COLOR Colorless needles [1].

MELTING POINT (°C) Anhydride: 169.5 (d.). Hydrate: 128-131 (d. at 164.5).[1]

OPTICAL ACTIVITY [α]_D¹⁸ = +48.3°⁷ [1].

UV ABSORPTION MAXIMUM 260 mμ⁸ [1].

/1/ From benzol-ether. /2/ From diisopropyl ether. /3/ c, 1.30 chloroform. /4/ Alcohol. /5/ Crystals from ethanol (anhydride). /6/ Crystals from water (hydrate). /7/ c, 1.5 water. /8/ Methanol.

26. ANGSTMYCIN (Concluded)

SOLUBILITY sl. s. water, ethanol, methanol, aqueous acetone; i. other organic solvents.[1]

STABILITY Thermostable at neutral and alkaline pH [1] .

OTHER REACTIONS Positive Schiff, Tollens, FeCl_3 , ninhydrin, Sakaguchi, Molisch, indole; negative Fehling. Anhydride analysis: C, 48.27; H, 4.74; N, 24.23; hydrate: C, 45.28; H, 4.46; N, 23.85.[1]

QUANTITATIVE DETERMINATION Microbiological: Mycobacterium 607 [1] .

BIOLOGICAL ACTIVITY In vitro. Inhibits Myco. 607 and Myco. phlei at 25 $\mu\text{g/ml}$. Inactive against a variety of Gram-positive and Gram-negative bacteria and fungi (Bacillus subtilis, Micrococcus pyogenes var. aureus, Escherichia coli, Aspergillus sp).[1]

ACUTE TOXICITY Very low; mice tolerated doses of 2500 mg/kg, i.p.[1]

27. ANISOMYCIN

The trademark of Chas. Pfizer & Co., Inc., for anisomycin is Flagecidin.

SOURCE Streptomyces spp, including S. griseolus [1, 5] .

NATURE Basic [4, 5] .

MOLECULAR FORMULA $\text{C}_{14}\text{H}_{19}\text{NO}_4$ [1, 4, 5]

CRYSTAL FORM AND COLOR Long white needles [1, 4, 5] .

MELTING POINT ($^{\circ}\text{C}$) 140-141 [1, 4, 5] .

OPTICAL ACTIVITY $[\alpha]_D^{23} = -30^{\circ}1$ [1, 4] ; $[\alpha]_D^{25} = -45^{\circ} \pm 3^2$ [1, 4, 5] .

UV ABSORPTION MAXIMA 224, 277, 283 $\text{m}\mu^3$ [1, 4, 5] .

SOLUBILITY s. dilute aqueous acids, methanol, ethanol, acetone, dioxane, chloroform; less s. water; i. hexane, cyclohexane, carbon tetrachloride, ether.[4, 5]

STABILITY Stable at room temperature; thermolabile at acid pH.[4, 5]

OTHER REACTIONS Infrared: 3545, 3450, 3320, 2890, 2800, 1725, 1610, 1582, 1515, 1470, 1447, 1380, 1320, 1302, 1242, 1178, 1036, 962 (recip. cm) [4, 5] .

BIOLOGICAL ACTIVITY In vitro. Little or no antibacterial activity. Inhibits certain fungi ($\mu\text{g/ml}$): Candida albicans, 1.25-12.5; Microsporium canis, M. audouini, Histoplasma capsulatum, Cryptococcus neoformans, 100; Trichophyton sulfureum, Phialophora verrucosa, 500. The following were resistant, $>500 \mu\text{g/ml}$: Blastomyces dermatitidis, Bl. brasiliensis, Sporotrichum schenckii, Trichophyton violaceum, Hormodendrum compactum.[2, 5] Antiprotozoan activity: Inhibits Entamoeba histolytica, Trichomonas foetus, T. vaginalis at 1.5-3.1 $\mu\text{g/ml}$. [2, 5] Concentrations of 3.12 $\mu\text{g/ml}$ were lethal to T. vaginalis [9] .

In vivo. Active in experimental T. foetus infection in mice. 25 mg/kg doses administered s.c. for 1-5 days cleared 70-94% of these animals of infection [3] . S.c. doses of 25-100 mg/kg effective in mice infected s.c. with T. vaginalis [10] . Daily oral doses of 25-50 mg/kg in guinea pigs protected 55-86% of the animals against E. histolytica [6] . Effective clearance of E. histolytica obtained with oral doses of 20 mg/kg in rats and 50-100 mg/kg in guinea pigs [12] .

CLINICAL Favorable results reported in human infections with T. vaginalis following topical use for several days of 1 mg tablets or powder containing 1 mg antibiotic per g powder base. No local irritation resulted from intravaginal therapy.[7, 8]

ACUTE TOXICITY LD_{50} in mice, 140 mg/kg, i.v.; 400 mg/kg, i.p.; 600 mg/kg, s.c.; 148 mg/kg, oral. LD_{50} in rats, 167 mg/kg, i.v.; 345 mg/kg, i.p.; 230 mg/kg, s.c.; 72 mg/kg, oral. LD_{50} in guinea pigs, $>300 \text{mg/kg}$, i.m.; $>400 \text{mg/kg}$, oral. Oral LD_{50} in rabbits, $>200 \text{mg/kg}$. In cats and dogs, parenteral or oral doses as low as 0.1 mg/kg induced emesis. Dogs tolerated 100 mg/kg, i.v. or i.m.[11]

CHRONIC TOXICITY Rats fed on diet containing 50 ppm for periods of 33 weeks showed no ill effects or histopathologic changes. Daily oral doses of 1-64 mg/kg over periods of more than 6 months were well tolerated in monkeys, with occasional emesis and diarrhea in groups receiving the higher doses.[11]

MISCELLANEOUS Some molluscicidal activity; concentrations of 6.25 $\mu\text{g/ml}$ lethal to snail (Australorbis

/1/ c, 1 methanol. /2/ c, 1 chloroform. /3/ 3.34 mg in 25 ml methanol.

27. ANISOMYCIN (Concluded)

glabratus) in 48 hours.[13]

28. ANTIMYCIN A (Virosin, Antipiricullin)

SOURCE *Streptomyces* sp [13]; *S. kitazawaensis*, n. sp [17].

NATURE Weakly acid [2].

MOLECULAR FORMULA AND WEIGHT $C_{28}H_{40}O_9N_2$ (proposed) [2, 4, 5]; 493, 506 (Rast); 548.6 (calc.).[2]

CRYSTAL FORM AND COLOR Colorless crystals [2, 4-6].

MELTING POINT ($^{\circ}C$) 139-140 [2]; 149.8-150.2 [3]; 148-149.5 [6]; 141-142 [17].

OPTICAL ACTIVITY $[\alpha]_D^{25} = +64.8^{\circ}$ [2, 5], $77.2^{\circ} \pm 1.0^{\circ}$ [17].

UV ABSORPTION MAXIMA 230, 320 $m\mu$ [2]; 245, 347 $m\mu$ [5]; 225, 320 $m\mu$ [6].

SOLUBILITY s. ether, lower alcohols, ethylene glycol, propylene glycol, amyl acetate, methyl acetate, pyridine, acetone, chloroform; sl. s. petroleum ether, benzene, toluene, carbon tetrachloride; i. water, dilute aqueous HCl, sodium carbonate or bicarbonate.[1, 2, 4-6]

STABILITY Thermolabile; stable at room temperature, less so at alkaline pH.[1, 2, 6]

OTHER REACTIONS Positive $FeCl_3$, Gibbs phenol, Folin, diazobenzene-sulfonic acid, xanthoproteic; negative Molisch, ninhydrin, anthrone, Benedict, Hopkins-Cole, Millon, biuret, Ehrlich, fuchsin aldehyde, 2, 4-dinitrophenylhydrazine, concentrated H_2SO_4 ; disintegration of crystals and loss of activity in aqueous NaOH forming milky suspension; non-dialyzable; yields antimycic acid ($C_{11}H_{14}O_5N_2$) and a neutral fragment on mild alkaline hydrolysis; 4 active components common to antimycin A-35 and A-102; A-35 contains a fifth.[1, 2, 4-6]

QUANTITATIVE DETERMINATION Microbiological: *Glomerella cingulata*, *Saccharomyces cerevisiae* [1, 3, 5, 17].

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi ($\mu g/ml$): *Colletotrichum* spp, 0.8-12.5; *Nigrospora sphaerica*, 0.2; *Phoma lingam*, 0.4; *Chalara quercina*, 0.8; *Sclerotinia fructicola*, 0.4-1.6; *Venturia inaequalis*, 0.4-0.8; *Stemphylium sarcinaeforme*, 1.6.[1, 2, 7] *Torula utilis* sensitive to 0.1 $\mu g/ml$; *Alternaria kikuchiana*, *G. cingulata*, *Gibberella saubinetii*, *Ceratostomella fimbriata*, *Sclerotinia arachidis*, *Colletotrichum lindemuthianum*, *Gloeosporium kaki*, <1.0; *Piricularia oryzae*, <1.0-10; *Cladosporium fulvum*, 10. *Candida albicans*, *Aspergillus oryzae*, *A. niger*, *Trichophyton* sp, and phytopathogenic bacteria were not sensitive to 100 $\mu g/ml$. [15] Inhibits other fungi and yeasts (*Sac. cerevisiae*), but there is little or no activity against bacteria [1, 2, 7]. Low concentrations (0.013 $\mu g/ml$) inhibited propagation of PR-8 influenza virus, but did not destroy preformed virus. Experimental evidence suggested that the antibiotic acted by interfering with synthetic mechanisms which permit the reproduction of virus in infected tissue.[14]

TOXICITY Oral doses of 12 mg/kg in methyl laurate were tolerated in rats; 30 mg/kg were fatal.[7] LD_{50} in rats, 0.81 mg/kg, i.p. [12]. LD_{50} in mice, 0.9 mg/kg, i.v.; 7.6 mg/kg, i.p.; 21.2 mg/kg, s.c.[17]

PHYTOTOXICITY Low toxicity when tested in a wide variety of plants [6].

UTILIZATION Was effective in control of certain *Helminthosporium* diseases of oats and barley [8]. Complete control of apple scab and early blight of tomato with crude and crystalline preparations [9, 13]. Has insecticidal and miticidal properties; was effective against Coleoptera and inactive against Lepidoptera. Very effective in low concentrations against Mexican bean beetle larvae. Gave good fabric protection against the black carpet beetle at 1/100 the necessary concentration of sodium aluminum silicofluoride which is widely used for protection of fabric against insects.[10] Topical application of 20 $\mu g/ml$ solutions lethal to houseflies within 24 hours. Under greenhouse conditions, infection with *Piricularia oryzae* was prevented in rice plants when solutions containing 18 $\mu g/ml$ were sprayed on the leaves.[15]

MODE OF ACTION As a metabolic inhibitor it resembles sodium malonate in its capacity to inhibit the renal tubular excretion of p-aminohippurate in rats [16]. Acts as a pseudo-irreversible inhibitor of succinoxidase. This was demonstrated both in vitro and in vivo.[11, 12]

29. ARGOMYCIN

SOURCE *Streptomyces griseolus* [1].

/1/ c, 10 chloroform. /2/ c, 3.57 chloroform.

29. ARGOMYCIN (Concluded)

MOLECULAR FORMULA AND WEIGHT $C_{25}H_{43}O_7N$ [1].

MELTING POINT ($^{\circ}C$) 164-164.5 [1].

OPTICAL ACTIVITY $[\alpha]_D^{25} = +8.2^{\circ}$ [1].

SOLUBILITY sl. s. carbon disulfide [1].

OTHER REACTIONS Infrared: Includes bands at 7.38, 7.65, 7.98, 8.2, 9.8, 9.95, 10.48 μ [1].

BIOLOGICAL ACTIVITY No antitumor activity against Yoshida sarcoma and Ehrlich carcinoma in mice [2].

TOXICITY LD_{50} in mice, 172 mg/kg, i.v.[2]

30. ASCOSIN

SOURCE *Streptomyces canescens* [1].

NATURE Probably a polyene [2, 5].

UV ABSORPTION MAXIMA 234, 288, 340, 357, 376, 398 $m\mu^2$ [5].

SOLUBILITY Crude preparations: s. aqueous pyridine and other N-containing heterocyclic solvents; sl. s. dry pyridine, most other organic solvents, water.[1, 5]

STABILITY Thermo-, acid, and alkali labile [1].

OTHER REACTIONS Negative Molisch, Tollens, Ehrlich, $FeCl_3$, ninhydrin, Benedict, Sakaguchi; activity antagonized by unsaturated fatty acids, Tween 80, and less by yeast, liver extracts; some resemblance to fungicidin.[1, 2] Soluble in but inactivated by phosphoric acid, dipropyl hydrogen phosphate, dibutyl hydrogen phosphate and aromatic sulfonic acids; aqueous brucine yields an amorphous precipitate while methanolic brucine yields no precipitate; intense, unstable blue color when methanolic solution of ascosin is added to 35% or more concentration of phosphoric acid in presence of air; green color with HCl. Infrared: Includes bands at 3.0, 6.4, 8.7, 9.5, 10.1, 12.0 13.2 μ . [5]

QUANTITATIVE DETERMINATION Microbiological: *Saccharomyces cerevisiae* [1, 5].

BIOLOGICAL ACTIVITY In vitro. Inhibits yeasts and filamentous fungi ($\mu g/ml$): *Candida albicans*, 0.2; *C. krusei*, *Torula utilis*, 0.4; *Willia sp.*, 0.8; *Aspergillus niger*, *Sac. cerevisiae*, 1.6; *Absidia orchidis*, *Botrytis sp.*, 6.2 μg ; *Trichophyton interdigitale*, 25 μg ; *Mucor pusilis*, 50 $\mu g/ml$. [6] Also inhibits *Mycoderma*, *Cryptococcus*, *Histoplasma capsulatum*, *Penicillium spinulosum*, *Rhizopus nigricans*. No activity against bacteria. [1]

In vivo. Some protection against *Cryptococcus neoformans* in mice [4]. Prolonged survival time in mice infected with *H. capsulatum*. The i.p. therapeutic dose approached toxicity level. [3]

ACUTE TOXICITY LD_{50} in mice, 12.5 mg/kg, i.v.; 8.6 mg/kg, i.p.; 168 mg/kg, s.c.; >500 mg/kg, oral. [1]

ABSORPTION No significant blood levels obtained in rabbits following i.p. or s.c. administration. Detectable concentrations in blood of mice after i.p. administration. [1]

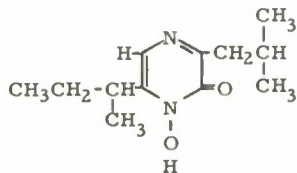
31. ASPERGILLIC ACID

SOURCE *Aspergillus flavus* [1].

NATURE Monobasic acid [3].

MOLECULAR FORMULA AND WEIGHT $C_{12}H_{20}O_2N_2$ [1-3]; 220, 222 (found); 224.3 (calc.). [1, 2]

STRUCTURE



[7]

/1/ Ethanol. /2/ Methanol.

31. ASPERGILLIC ACID (Concluded)

CRYSTAL FORM AND COLOR Radial clusters of yellow needles [8] .

MELTING POINT (°C) 97-99. HCl: 178.[2, 8]

OPTICAL ACTIVITY $[\alpha]_D^{24} = +13.4^{\circ 1}, +18.5^{\circ 2}$ [2] .

UV ABSORPTION MAXIMA 234, 328 m μ [8] .

SOLUBILITY s. hot water, excess acid, most organic solvents; i. cold water, dilute acid, petroleum ether.[1, 2]

STABILITY Very thermo-, acid and alkali stable [1, 2] .

OTHER REACTIONS Hydroxyaspergillic acid, C₁₂H₂₀N₂O₃, produced under some fermentation conditions; negative Millon, xanthoproteic, Molisch, biuret, ninhydrin, dinitrophenylhydrazine, Fehling, nitrous acid, KMnO₄, Br in CCl₄ or glacial acetic acid; vigorous reaction with aqueous Br; intense red color with FeCl₃ in alcohol; green precipitate with CuSO₄, orange with CoCl₂; precipitate with phosphotungstic acid; crystalline precipitate with AgNO₃ and Hg(C₂H₃O₂)₂, but not with HgCl₂. [1, 3, 9]

QUANTITATIVE DETERMINATION Microbiological: Several organisms, including Mycobacterium tuberculosis; antiluminescence with Photobacterium fischeri [4-6] . UV absorption spectrum [4] .

BIOLOGICAL ACTIVITY In vitro. Inhibits (μ g/ml) Streptococcus pyogenes, 2; Diplococcus pneumoniae, 4; Klebsiella pneumoniae, 8; Micrococcus pyogenes var. aureus, 10; Salmonella enteritidis, Escherichia coli, 30; Clostridium spp, 20-60.[5] Inhibits Myco. tuberculosis in dilution of 1:10,000 [12] . Treponema pallidum immobilized in dilution of 1:2500 [10] .

In vivo. No activity in mouse infections with Str. pyogenes, D. pneumoniae, and M. pyogenes when given i.p. [5] .

ACUTE TOXICITY LD₁₀₀ in mice, 150 mg/kg, i.p.; 250 mg/kg, oral.[1] Antibacterial activity enhanced by bismuth [11] .

32. AURANTIDIN

SOURCE Aspergillus parasiticus, or closely related sp [1] .

FORM AND COLOR Orange-red; resinous [1] .

SOLUBILITY s. most organic solvents and 50% ethanol; i. water.[1]

STABILITY Thermostable [1] .

OTHER REACTIONS Derived from medium and mycelium; has a chloramphenicol-type antimicrobial spectrum [1] .

BIOLOGICAL ACTIVITY In vitro. Active against Escherichia coli. Also contains a factor active against Gram-positive bacteria.[1]

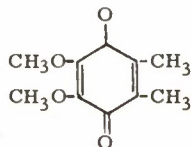
33. AURANTIOLIOCLADIN

SOURCE Gliocladium roseum [1] ; by synthesis [3] .

NATURE p-Benzoquinone [2, 3] .

MOLECULAR FORMULA C₁₀H₁₂O₄ [1] .

STRUCTURE



[2, 3]

CRYSTAL FORM AND COLOR Large orange leaflets [1] .

MELTING POINT (°C) 63 [1] .

/1/ c, 0.85 ethanol. /2/ c, 1.05 1 N NaOH.

33. AURANTIOGLIOCLADIN (Concluded)

UV ABSORPTION MAXIMA 275, 407 m μ [1, 2].

OTHER REACTIONS Deep violet in concentrated H₂SO₄; reduced to a hydroquinone by SO₂ in aqueous solution; monodinitrophenylhydrazone produced with 2, 4-dinitrophenylhydrazine [1]. Closely related to spinulosin and fumigatin [2].

QUANTITATIVE DETERMINATION Microbiological: Bacillus subtilis; inhibition of germination of Botrytis allii spores.[1]

BIOLOGICAL ACTIVITY Low activity in vitro. Inhibits (μ g/ml) B. allii at 50, Bacillus subtilis at 200, Escherichia coli at 400.[1]

34. AUREOLIC ACID

SOURCE Streptomyces sp [1].

NATURE Weakly acidic [2].

MOLECULAR FORMULA AND WEIGHT Mg salt: (C₅₆₋₆₀H₉₆₋₁₀₄O₂₉₋₃₁)₂ Mg; approximately 1350 (neut. equiv.).[2]

CRYSTAL FORM AND COLOR Yellow crystals [2].

OPTICAL ACTIVITY [α]_D = + 68⁰ [2].

SOLUBILITY s. lower alcohols, acetone; moderately s. water, ethyl acetate, ether.[2]

OTHER REACTIONS Negative Fehling, anthrone; positive tyrosine reagent, FeCl₃ (green); not decolorized by sodium hydrosulfite [2].

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. aureus [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits Gram-positive bacteria at 0.16-0.63 μ g/ml: M. pyogenes var. aureus, Streptococcus pyogenes, Sarcina lutea, Bacillus subtilis, B. cereus. Little or no activity against Str. faecalis, mycobacteria and Gram-negative organisms. Slightly active against Trichomonas vaginalis.[1]

In vivo. Limited protection in mice infected with Str. pyogenes following i.m. doses of 1-2 mg/kg [1].

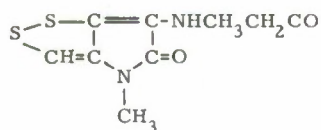
ACUTE TOXICITY Highly toxic parenterally. LD₅₀ in mice, 2.5-5.0 mg/kg, i.v. I.v. doses of 0.25 mg/kg lethal in rabbits and dogs. Mice tolerated 500 mg/kg by oral route.[1]

35. AUREOTHRICIN

SOURCE Streptomyces celluloflavus, n. sp [1].

MOLECULAR FORMULA C₉H₁₀N₂O₂S₂ [1].

STRUCTURE



[4, 5]

CRYSTAL FORM AND COLOR Golden-yellow needles [1].

MELTING POINT (⁰C) 256-257 (d.) [1].

OPTICAL ACTIVITY Inactive [2].

UV ABSORPTION MAXIMA 248, 312, 388 m μ [2].

SOLUBILITY sl. s. organic solvents; more s. chloroform; i. water.[1]

STABILITY Very thermo- and acid stable [1].

OTHER REACTIONS Similar to thiolutin; acid hydrolysis yields an amine, C₆H₆N₂OS₂, identical with one so obtained from thiolutin.[2]

/1/ c, 1 methanol.

35. AUREOTHRICIN (Concluded)

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* PCI 219¹ [1].

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive and Gram-negative bacteria, and fungi. Inhibits (dilution units x 10,000) *B. subtilis*, 100; *Vibrio comma*, 75-150; *Corynebacterium diphtheriae*, 75; *Micrococcus pyogenes* var. *aureus*, 40-45; *Streptococcus pyogenes*, *Diplococcus pneumoniae*, *Salmonella typhosa*, *S. paratyphi*, *Shigella dysenteriae*, *Sh. paradysenteriae*, *Escherichia coli*, *B. anthracis*, 25-50; *Mycobacterium phlei*, 40; *Myco. tuberculosis*, 32; *Myco. smegmatis*, *Salmonella schottmuelleri*, 15; *Myco. avium*, 5; *Klebsiella pneumoniae*, 1. Fungi: *Mucor javanicus*, 32; *Phytophthora* sp., 64; *Saccharomyces saké*, 8; *Aspergillus niger*, 2; *Botrytis cinerea*, *Rhizopus japonicus*, 4.[1]

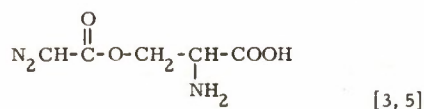
In vivo. Promoted growth of chicks when given in concentration of 15 mg/kg of ration, but diet was refused when concentrations of 45 mg/kg were used [3]. Daily i.p. doses of 30 µg had no effect on Ehrlich ascites tumor in mice [6].

36. AZASERINE
(O-Diazoacetyl-L-serine)

SOURCE *Streptomyces fragilis* [1]; by synthesis [22].

MOLECULAR FORMULA AND WEIGHT C₅H₇N₃O₄; 173.13 (calc.).[3, 5]

STRUCTURE



CRYSTAL FORM AND COLOR Light yellow-green needles [3, 4].

MELTING POINT (°C) 142-162 (d. before melting) [3, 4].

OPTICAL ACTIVITY $[\alpha]_D^{27.5} = -0.50^2$; $[\alpha]_D^{28} = +9.70^3$. [3, 4]

UV ABSORPTION MAXIMA 250.5 mµ⁴; 252 mµ⁵. [3, 4]

SOLUBILITY s. water, warm aqueous methanol, ethanol, acetone; sl. s. absolute methanol, ethanol, acetone.[3, 4]

OTHER REACTIONS Pronounced infrared peak at 4.66 µ; acidification at pH 2 results in vigorous evolution of N₂ and loss of biological activity.[3, 4]

QUANTITATIVE DETERMINATION Microbiological: *Kloeckera brevis* [1, 2, 4, 14].

BIOLOGICAL ACTIVITY In vitro. Inhibits bacteria at 50 µg/ml or less: *Acetobacter aceti*, *Bacillus cereus*, *B. megatherium*, *Clostridium* spp, *Escherichia coli*, *Hemophilus influenzae*, *Neisseria catarrhalis*, *N. meningitidis*, *Pasteurella multocida*, *Salmonella typhosa*, *S. schottmuelleri*, *Vibrio comma*, *Mycobacterium tuberculosis*[2, 6]. Fungi inhibited at 250 µg/ml or less: species of *Alternaria*, *Armillaria*, *Aspergillus*, *Candida*, *Cercospora*, *Helminthosporium*, *Nematospora*, *Polyporus* and *Poria* [2, 6, 9]. Protozoa (µg/ml): *Entamoeba histolytica*, 250; *Trichomonas foetus*, 100. No activity against 3 species of trypanosomes.[6] The antibiotic is a potent mutagen for *Escherichia coli* [15].

In vivo. Activity in chicks infected with *Plasmodium lophurae* (0.1% drug in diet). Inactive against *Entamoeba histolytica* in rats. Active against meningopneumonitis virus and *Rickettsia prowazekii* in chick embryos in doses of 0.2-1.0 mg. No activity demonstrated with viruses of influenza, yellow fever, vaccinia, St. Louis encephalitis, rabies and poliomyelitis.[6] In mice, azaserine inhibited development of a strain of mouse leukemia [7]. Retarded growth in mice of Crocker mouse sarcoma 180. Good correlation noted between this antitumor activity and the in vitro inhibition of the yeast, *K. brevis*. [2] Retarded growth of Murphy-Sturm lymphosarcoma and Walker carcinoma 256 in rats; also adenocarcinoma E-0771, Patterson lymphosarcoma and several ascites tumors in mice. Daily i.p. doses of 0.8-3.2 mg had a slight suppressive effect on Ehrlich ascites carcinoma in mice; higher dose levels were too toxic to evaluate [16]. Daily i.p. doses of 2-5 mg/kg in mice or rats inhibited Flexner-Jobling carcinoma, Mecca lymphosarcoma, and mammary carcinoma 755, and were ineffective against certain other experimental neoplasms [24, 25]. Tumoristatic activity observed following oral as well as parenteral dosage [26]. Other carcinomas and lymphosarcomas of mice and rats arrested with i.p. doses of 5 mg/kg, provided treatment was initiated one day later. Sarcoma 180 was the only experimental tumor inhibited by therapy started 7 days later.[13] A marked potentiation of activity against sarcoma 180 in mice was observed when combined with 6-mercaptopurine [15]. No protection in mice infected with *Myco. tuberculosis* [9].

CLINICAL Trial in 56 patients with various forms of neoplastic disease, with total i.v. or oral doses of 50-200 mg

/1/ Zones increased at acid, decreased at alkaline pH. /2/ c, 8.46 water pH 5.18. /3/ In 2 N HCl, final value preceded by constant change. /4/ pH 7. /5/ 0.1 N NaOH; little or no absorption with 0, 1 N HCl.

36. AZASERINE (Concluded)

over periods of 5-20 days, gave rather indifferent results with brief periods of objective improvement observed in a few cases [17].

PHARMACOLOGY S.c. doses of 50 mg/kg/da for 14 days were toxic in tuberculosis-infected mice [9]. Single parenteral doses of 100-200 mg/kg in rats induced necroses in the pancreas, liver and kidneys, within 24 hours [10]. Azaserine rapidly disappeared from the blood and was excreted in the urine within 2 hours after i.v. injection in animals. Only 1% or less of i.v. or oral dose was recovered in the urine during 24-hour period. The antibiotic appeared to be destroyed by an enzyme (probably a deaminase) present in the liver, kidneys and spleen. [11] Antimicrobial and antitumor activity were destroyed by extracts prepared from mouse liver [8].

In man, toxic effects which appeared after 5-20 days of medication, with total i.v. or oral doses of 50-200 mg, mainly involved the digestive tract with nausea and vomiting. Redness of tongue and buccal mucosa, which occasionally became ulcerated, also were noted. [17]

PHYTOTOXICITY Repressed root growth of cucumber, barley, and flax seedlings in low concentrations (0.7-2.6 µg/ml) [12].

MODE OF ACTION In *Saccharomyces cerevisiae*, the antibiotic inhibits glucose fermentation, stimulates uptake of inorganic phosphate, and is utilized by the yeast with a parallel release of serine into the culture medium. All of these actions are reversed by leucine. [27] Concentrations as low as 0.1 µg/ml in vitro caused a 50% inhibition of the biosynthesis of ribosidic derivatives of both 5-amino-imidazole and 5-amino-4-imidazole carboxamide by resting cells of mutant strains of *Escherichia coli*; inhibition of the latter compound was reversed by amino acids. [28]. In relatively small doses, the antibiotic affected de novo purine synthesis in ascites cell tumors by inhibiting utilization of glycine. The utilization of adenine was enhanced. A single dose caused a reduction in the mitotic index and gross damage to the tumor cells during the 12-hour period in which it was effective. [20]

MISCELLANEOUS The antibiotic appears to interfere with synthesis of aromatic amines by *E. coli* [18]. When injected into tumor-bearing animals prior to administration of labelled compounds, azaserine inhibits incorporation of formate and glycine into nucleic acids of sarcoma 180, adenocarcinoma E-0771, intestine and liver [19]. It induced rapid formation of greatly elongated non-septate filaments in *E. coli* [21]. Concentrations as low as 0.1 µg/ml in a salts-glucose medium induced formation of active bacteriophage (lambda) in the lysogenic *E. coli* strain K-12 [23]. Azaserine produces characteristic developmental abnormalities in chick embryos which are prevented by adenine, adenosine, hypoxanthine, and inosine, but not by guanine, xanthine, uric acid, glutamine, serine or histidine [29].

37. AZOMYCIN

SOURCE *Nocardia* sp resembling *N. mesenterica* [2].

NATURE 2-Nitro-imidazole [3].

MOLECULAR FORMULA $C_3H_3N_3O_2$ [3].

CRYSTAL FORM AND COLOR White needles [4].

MELTING POINT (°C) 283 (d.) [1]; 281-282 (d.) [4].

OPTICAL ACTIVITY Inactive¹ [1].

UV ABSORPTION MAXIMA 313 mµ² [1]; 314 mµ [4].

SOLUBILITY s. methanol, ethanol, acetone, ethyl acetate, butyl acetate, alkali, dioxane; i. ether, petroleum ether, chloroform, carbon tetrachloride, benzene, acid water. [1, 4]

STABILITY 50% loss at 100°C at pH 2-8 in 30 minutes [4].

OTHER REACTIONS Analysis: C, 32.0, 31.89; H, 2.65, 2.67; N, 36.67, 36.75, 36.56. [1] Nitro group confirmed by infrared and by catalytic hydrogenation; hydrogenated product gives positive Pauly; reductive acetylation gives crystalline compound ($C_5H_7N_3O$); negative $FeCl_3$, ninhydrin, biuret, Fehling, Molisch, Millon. [3, 4]

BIOLOGICAL ACTIVITY *In vitro*. Active against Gram-positive and Gram-negative bacteria. Inhibits (µg/ml) *Salmonella paratyphi*, *Shigella dysenteriae*, 3; *Salmonella typhosa*, 5; *Bacillus subtilis*, 6; *Micrococcus pyogenes* var. *aureus*, *Shigella paradysenteriae*, 12; *Mycobacterium phlei*, 2; *Mycobacterium* sp, 50; *Escherichia coli*, 25. Fungi are not susceptible. [1]

In vivo. Daily i.p. doses of 0.5 mg showed slight activity against Ehrlich carcinoma in mice, with slight inhibition of ascites production but no prolongation of survival time [5].

/1/ c, 0.5 methanol. /2/ Ethanol.

37. AZOMYCIN (Concluded)

ACUTE TOXICITY LD_{50} in mice, 80 mg/kg, i.v. [1].

38. BACCATINE A

SOURCE *Gibberella baccata*.

MOLECULAR FORMULA AND WEIGHT $C_{26}H_{48}O_6N_2$ (probable); 480 (Rast).[1]

CRYSTAL FORM AND COLOR Colorless crystals [1].

MELTING POINT ($^{\circ}C$) 135 [1].

SOLUBILITY s. ether, methanol, ethanol, other organic solvents; sl. s. water.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi (phytopathogens). Marked fungistatic activity against *Leptosphaeria acuta*, and *Sclerotinia sclerotiorum*. Weaker activity against *L. culmifraga*, *L. culmorum*, *Ophiobolus herpotrichus* and *Wojnowicia graminis* (agents of cereal foot rots). Inhibits growth of *Micrococcus pyogenes* var. *aureus* but not *Escherichia coli*. [1]

39. BACILIPINS

SOURCE *Bacillus subtilis* [1].

NATURE Acids [1].

SOLUBILITY s. amyl acetate, benzene, chloroform, ether; sl. s. water; i. petroleum ether.[1]

STABILITY Salts: thermolabile; stable at room temperature in solutions of pH 2-10. Acids: unstable; unstable to drying.[1]

OTHER REACTIONS Negative Molisch, 2,4-dinitrophenylhydrazine, ammoniacal $AgNO_3$; readily catalytically hydrogenated; unaffected by serum or trypsin. Analysis: Ba salt of A: C, 42.6; H, 6.3; N, 2.5; Ba 24.6. Ba salt of B: C, 52.5; H, 6.75; N, 2.09; Ba 21.6.[1]

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium phlei*, *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibit *Myco. phlei* in dilution of 1:100,000, *M. pyogenes* var. *aureus* in 1:10,000. Weaker activity against *Corynebacterium diphtheriae*, *Bacillus anthracis*, *Salmonella typhosa*, and *Escherichia coli*. [1]

40. BACILLIN

SOURCE *Bacillus subtilis* [3].

SOLUBILITY i. organic solvents [2].

STABILITY Thermostable [1, 2].

OTHER REACTIONS Inactivated by blood, some media, H_2S [1-3].

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (in dilution of 1:80-1:960) *Streptococcus* sp, *Diplococcus pneumoniae*, *Pasteurella* sp, *E. coli*, *Salmonella typhosa*, *S. schottmuelleri*, *Micrococcus pyogenes* var. *aureus*, *Mycobacterium tuberculosis*. [1]

In vivo. Inactive in mouse infections with *M. pyogenes* var. *aureus* and *D. pneumoniae*, following doses of 1,000 mg/kg [1].

ACUTE TOXICITY LD_0 in mice, 1000 mg/kg, i.p. [1].

41. BACILLOMYCIN (Fungocin, Bacillomycin R)

SOURCE *Bacillus subtilis* [1, 6].

NATURE Polypeptide with titratable acid function [3-5].

MOLECULAR WEIGHT Approximately 1000 (acid equiv. wt.) [4, 5]; at least 960 [9].

41. BACILLOMYCIN (Concluded)

CRYSTAL FORM AND COLOR Colorless, microscopic needles or rosettes [3].

OPTICAL ACTIVITY Inactive¹ [3].

UV ABSORPTION MAXIMA 277 m μ ²; 296 m μ ³. [9]

SOLUBILITY s. methanol, ethanol, n-butanol, acetone, concentrated acids; i. ether, hydrocarbons, dilute acids below pH 4-4.5. [2, 3, 5]

STABILITY Thermostable [1-3].

OTHER REACTIONS Similar to, or same as, eumycin; precipitated by concentrated ammonium sulfate; non-dialyzable through cellophane; unaffected by pepsin, trypsin; contains glutamic acid, aspartic acid, tyrosine, serine, threonine; positive biuret, xanthoproteic; negative Molisch, pK 5.5. [1-5] Analysis: C, 52.69; H, 7.20; N, 12.29; O, 27.82 (by diff.). [9]

| Analysis for Amino Acids ⁴ | | |
|---------------------------------------|-------------|----------------|
| Amino acid | Molar ratio | % Bacillomycin |
| Asp | 4.19 | 19.0 |
| Thr | 1.00 | 4.0 |
| Ser | 3.94 | 13.7 |
| Glu | 2.03 | 10.4 |
| Tyr | 1.98 | 12.7 |
| | | 59.8 |

[9]

QUANTITATIVE DETERMINATION Microbiological: Trichophyton mentagrophytes [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi (μ g/ml): Blastomyces dermatitidis, Rhizoctonia solani, Botrytis cinerea, Sclerotinia spp at 2.5-10; Histoplasma capsulatum, Bl. brasiliensis, Epidermophyton floccosum, Ep. inguinale, Microsporum audouinii, M. gypseum, Monosporium apiospermum, T. rubrum, T. schoenleinii, T. violaceum, Sporotrichum schenckii, Aspergillus niger, Penicillium notatum, P. roqueforti at 25-50; Rhizopus nigricans at 50-100; T. mentagrophytes, Candida albicans at 25->100. Nocardia asteroides, Hormodendrum pedrosoi and species of Colletotrichum, Phytophthora and Pythium are resistant. [1, 5, 6] Bacteria: Klebsiella pneumoniae at 25-50 μ g/ml; Clostridium perfringens, Cl. histolyticum, Corynebacterium diphtheriae and Micrococcus spp are sensitive to higher concentrations. In general, Gram-negative bacteria are resistant. [6, 7]

ACUTE TOXICITY LD₅₀ in mice, 75 mg/kg, i.p. [2]. Hemolytic to red blood cells in vitro in concentration of 100 μ g/ml [5].

UTILIZATION Was effective in control of diseases of grain incited by Puccinia graminis tritici, Helminthosporium sativum and H. teres [8].

42. BACILLOMYCIN B

SOURCE Bacillus subtilis [1].

NATURE Polypeptide [1].

FORM AND COLOR Yellow, amorphous substance [1].

SOLUBILITY s. alkali, ethanol, methanol, butanol, ethyl acetate; sl. s. acetone; i. benzene, xylene, ether. [1]

STABILITY Thermostable at pH 2.6-8.2 [1].

OTHER REACTIONS Isoelectric point, pH 4.3-4.5; no S or halogen; positive biuret, xanthoproteic, Millon, Liebermann; negative ninhydrin, FeCl₃, Molisch; red-brown in concentrated H₂SO₄ and red on heating; no reduction of Fehling, Tollens; non-dialyzable; contains glutamic acid, aspartic acid, tyrosine, leucine, proline. [1]

QUANTITATIVE DETERMINATION Microbiological: Aspergillus niger [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits Aspergillus niger and other fungi [1].

43. BACILLOMYCIN C

NATURE Polypeptide [1].

/1/ Alcohol. /2/ In n-butanol-water-acetic acid-95% ethanol. /3/ In alcoholic NaOH. /4/ Ion-exchange chromatography.

43. BACILLOMYCIN C (Concluded)

SOLUBILITY s. ethanol, methanol, butanol, ethyl acetate, acetone, alkali; i. benzene, toluene, ether, petroleum ether, chloroform, hydrogen sulfide, carbon tetrachloride, water.[1]

STABILITY Fairly thermostable [1].

OTHER REACTIONS Isoelectric point, pH 4.2; positive biuret, xanthoproteic, Millon, Liebermann; negative ninhydrin, FeCl₃, Molisch, Fehling, Tollens; red color in hot concentrated H₂SO₄; contains glutamic acid, aspartic acid, tyrosine, leucine, valine, but no threonine, serine or proline.[1]

44. BACILYSIN

SOURCE *Bacillus subtilis* [1].

NATURE Neutral peptide containing S [1].

SOLUBILITY s. water, methanol; i. dry organic solvents except methanol [1].

STABILITY Thermostable except at low pH [1].

OTHER REACTIONS Not precipitated by ammonium sulfate, basic lead acetate or picric, phosphotungstic and trichloroacetic acids; negative Molisch; positive ninhydrin, Pauly; inactivated by enzymes, H₂S.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. aureus [1].

BIOLOGICAL ACTIVITY In vitro. *M. pyogenes* var. aureus, *Corynebacterium xerose* and to a lesser extent *Mycobacterium phlei* are sensitive. Action is mainly bactericidal. Resistance appeared to develop fairly readily.[1]

TOXICITY Mice tolerated i.v. doses of 450 mg/kg. Appeared to be inactivated *in vivo* since no activity was detected in urine, blood or liver 5 hours after administration of these doses in mice.[2]

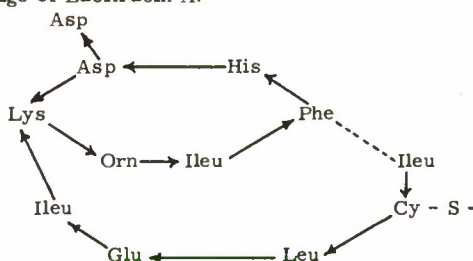
45. BACITRACINS [8, 9] (Ayiviv)

SOURCE *Bacillus subtilis*, *B. licheniformis* [1].

NATURE Polypeptides; weakly basic [3, 5, 6].

MOLECULAR FORMULA AND WEIGHT Bacitracin A: C₆₆H₁₀₃O₁₆N₁₇S (proposed) [15]; 1470±10% (found); 1411 (calc.). [11, 17]

STRUCTURE Probable amino acid linkage of Bacitracin A:



FORM AND COLOR White, highly hygroscopic, amorphous powder [5].

OPTICAL ACTIVITY $[\alpha]_D^{23} = +5^{\circ} \pm 2.5^{\circ}$ [2].

UV ABSORPTION MAXIMA Bacitracin A, B, D, E: 253 m μ .

C, G: 250, 268 m μ .

F₁, F₂, F₃: 253, 288, m μ . [8]

SOLUBILITY s. methanol, ethanol, water; sl. s. acetone, cyclohexanone, propanols, butanols, pyridine; i. ether, chloroform, benzene, ethyl acetate, petroleum ether.[1, 2, 6, 7]

STABILITY Relatively thermostable, especially at pH 4-5; unstable above pH 9; aqueous solution unstable after storage at room temperature.[1, 2, 6, 7]

/1/ c, 1 0.02 N HCl.

OTHER REACTIONS Precipitated by heavy metal salts, trichloroacetic, tannic, azobenzene-p-sulfonic, molybdic, and fuoric acids, concentrated NaCl, acetone, ammonium rhodanilate, Reinecke's salt; positive ninhydrin; negative FeCl_3 , alkaline nitroprusside, Sakaguchi, Adamkiewicz, biuret, Folin-Marenzi; not inactivated by proteolytic enzymes; inactivated by Cu, H_2O_2 and partially by BAL, sodium thiosulfate.[2, 3, 5-7]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* and other Gram-positive organisms [1, 4, 7].

BIOLOGICAL ACTIVITY *In vitro*. In general, active against Gram-positive bacteria with little or no activity against Gram-negative organisms. Inhibition concentrations for most strains of the following microorganisms average 0.002-5.0 units/ml¹: *Actinomyces israeli*, *Corynebacterium diphtheriae*, *C. xerose*, *Diplococcus pneumoniae*, *M. pyogenes* var. *aureus*, *Streptococcus pyogenes*, *Str. viridans*, *Str. uberis*, *Str. agalactiae*, *Sarcina lutea*, *Clostridium* spp, *Hemophilus influenzae*, *H. pertussis*, *Neisseria gonorrhoeae*, *Bacillus anthracis*, *Treponema pallidum*. Strains of most of the following are generally resistant, 50 units/ml or more: *Aerobacter aerogenes*, *Vibrio comma*, *Alcaligenes* sp, *Klebsiella pneumoniae*, *Pasteurella multocida*, *Past. pestis*, *Past. tularensis*, *Proteus* spp, *Salmonella* spp, *Shigella* spp, *Escherichia coli*, *N. meningitidis*, *B. subtilis*. Fungi are not sensitive.[1, 18, 19] *In vitro* activity is enhanced by cationic and decreased by anionic surface active agents [20]. Reported to enhance growth of *Trichomonas foetus*, hence it has been suggested that bacitracin may be a metabolite for this protozoan [21].

In vivo, i. p. doses of 50-100 units/kg protected mice infected with clostridia, *Str. pyogenes* and *M. pyogenes* var. *aureus* [1, 22]. Activity against *Treponema pallidum* in rabbits at 1200-2000 units/kg/da [23], and in mice infected with *Borrelia duttoni* [61]. In experimental meningitis induced with *M. pyogenes* var. *aureus*, good protection was obtained in dogs treated by intracisternal and i.m. routes [24]. Inhibited vaccinia virus in mice and *Plasmodium lophurae* in chicks dosed with 400-500 units/kg/da [25]. No activity in chicks infected with *P. gallinaceum* after daily i.p. doses of 400 units/kg [60]. Very effective against pinworm infestation in mice treated with a single oral dose of 100,000 units/kg [26, 27]. Daily i.p. doses of 100 mg/kg had no inhibitory effect on RC carcinoma in mice [66].

CLINICAL In general, systemic use of bacitracin is indicated only in infections resistant to penicillin and other antibiotics. Solutions containing 500 units/ml administered by local infiltration, or as wet dressing, have been effective in therapy of superficial and deep abscesses, ulcers, infected operative wounds and in various surgical infections.[28, 46] Favorable clinical response reported in a wide variety of surgical infections following i.m. doses of 2,000-20,000 units to adults every 6-8 hours [28, 29]. Topical application of bacitracin, or of this antibiotic in combination with polymyxin or other drug in an ointment base, was highly effective in control and prophylaxis of various skin infections [30, 31]. Topical therapy useful in ocular infections [32]; also in aural and pharyngeal infections from susceptible microorganisms [33]. Intracranial and intrathecal injection of 5,000-10,000 units has been used in purulent infections of the central nervous system and in neurosurgical wounds [37, 38]. Oral administration reported of value in chronic bacillary dysentery [34]. A high cure rate obtained following oral therapy with daily doses of approximately 60,000 units for 5-20 days in cases of acute amebic dysentery [35, 36]. Oral therapy was of value in eliminating pinworms (*Enterobius vermicularis*) [27].

VETERINARY Intramammary infusions effective in bovine mastitis caused by *Str. agalactiae* [39]. Ointments and wet dressings for topical application gave favorable results in animals with superficial abscesses, cellulitis, suppurating surgical and traumatic wounds, and skin infections [40]. Because of little or no absorption from intestines, oral bacitracin offers a wide margin of safety for treating enteric infections in animals [41]. Favorable results have been obtained in swine enteritis [42].

TISSUE CULTURE Low toxicity in tissue cultures. Growth inhibition of skin tissue required concentrations of 5-10 mg/ml; no inhibition of spleen tissue at 20 mg/ml.[49]

ACUTE TOXICITY LD₅₀ in mice, 360 mg/kg (approximately 7500 units), i.v.; 200-650 mg/kg (approximately 7,500-15,000 units), i.p.; 1300-2500 mg/kg (31,000-52,000 units), s.c. Oral doses of 3750 mg/kg (131,000 units) tolerated. In rats the LD₅₀ is 190 mg/kg (6700 units), i.p. Oral doses of 50,000 units/kg tolerated by rabbits; >400,000 units/kg by dogs.[41, 43, 44] I.v. lethal dose in mice for bacitracin A: 342 mg/kg; bacitracin B: 500 mg/kg; bacitracin C: 75 mg/kg.[45]

CHRONIC TOXICITY No evidence of toxicity in mice given daily oral doses of 125,000 units/kg for 30 days [41]. Prolonged daily i.m. administration of 1000-1500 units/kg well tolerated by dogs and monkeys. Damage to renal tubules noted in mice, but not in dogs, following prolonged i.m. administration.[44]

In man, nephrotoxicity, as reflected by abnormal urine findings, noted after 10 daily i.m. doses of 40,000-80,000 units [46]. Parenteral administration of 1500 units/kg on 2 successive days resulted in proteinuria, glycosuria and depressed the glomerular filtration rate for approximately 2 months [47]. Gastrointestinal disturbances have been occasionally reported. Skin sensitivity following topical use is rare, hence this advantage over penicillin [48].

/1/ Average lots of bacitracin have a potency of approximately 40 units per mg. Further purification beyond 45 units/mg generally results in decreasing stability. More recently, however, parenteral bacitracin possesses a minimum potency of 50 units per mg, and preparations of higher potency (63-71 units/mg) have shown the same thermal stability as those of lower unitage.[65]

45. BACITRACINS (Concluded)

RESISTANCE In general, bacteria sensitive to bacitracin do not develop resistance to it in vivo with any facility, although it is possible to demonstrate this in vitro with strains of *Str. pyogenes*; these strains, however, rapidly lost resistance.[58]

ABSORPTION AND EXCRETION In animals after parenteral administration, antibiotic was detected in the blood, urine, feces, bile, kidney, liver, spleen, lung, heart, and skeletal muscle, with very low concentrations in the brain and cerebrospinal fluid. Highest blood concentrations occurred 1-4 hours after injection. In dogs, blood levels of 1.5-3.0 units/ml followed i.m. or s.c. doses of 3000 units/kg.[50, 51]

In man, after single i.m. dose of 50,000 units, serum concentrations of approximately 0.3 unit/ml appeared in 2 hours, declining to 0.03 unit at the 6th hour. Levels of 1-3 units/ml noted following repeated injections at 6-hour intervals. A daily urinary excretion of 10-31% of the administered dosage was observed. Following oral doses, the greater part of the total dose was recovered in the feces, and little or no measurable blood concentrations were noted.[52]

MODE OF ACTION Bactericidal as well as bacteriostatic. Reiter strain of *T. pallidum* inhibited by 0.004 unit in vitro, and concentrations of 0.025 unit/ml were lethal. The rate of treponemicidal activity increased with concentration up to the highest level tested (64 units/ml).[68] Bacitracin inhibits glutamic acid uptake in *M. pyogenes* var. *aureus* in a similar way to penicillin [69].

ANIMAL NUTRITION Injections of bacitracin stimulated growth of chicks although it did not alter their fecal microbial flora [53]; incorporation of 5 mg/lb ration also enhanced growth [54] and increased egg production and fertility [59]. Growth of pigs promoted when antibiotic was incorporated in diet or implanted s.c. These growth responses were generally smaller than those obtained with other antibiotics.[55, 56] Subcutaneous implantation of pellets had little or no effect on weight curve of range lambs and calves [70].

PLANT NUTRITION Plant growth was markedly stimulated by 5-10 ppm of bacitracin in sterile tissue cultures using duckweed (*Lemna minor*) as the test subject [57]. Growth of wheat roots in distilled water was stimulated by addition of 0.1-0.32 ppm of antibiotic [67].

MISCELLANEOUS Concentrations of 100 ppm in autoclave-sterilized media useful in laboratory for controlling bacterial contamination in cultures of sunflower-callus tissues [62]. Relatively high concentrations of bacitracin (300-500 mg per 14 lb of wheat) and certain other antibiotics were lethal to several varieties of coleopterous stored-grain insects within 30-60 days [63]. The median lethal dose, by injection, in the German cockroach, *Blattella germanica*, was 100-235 μg [64].

46. BIFORMYNES (Biformin, Biforminic Acid)

SOURCE *Polyporus biforminis* [1].

NATURE Polyacetylene¹ [2].

UV ABSORPTION MAXIMA Biformyne 1: 259, 274, 291, 310 $\text{m}\mu$ [2, 3].
Biformyne 2: 263, 274, 290, 310 $\text{m}\mu$ ² [3].

SOLUBILITY s. water, ether, chloroform, methyl isobutyl ketone, alcohol [1].

STABILITY Thermostable in dilute solution; unstable in concentrated aqueous solution.[1]

OTHER REACTIONS Destroyed by drying; no color with KCN; no I from cold HI; negative FeCl_3 ; biformyne 1 extractable with organic solvents, but 2 is extractable only after culture liquid is boiled; 2 can be reduced catalytically to a compound of molecular formula $\text{C}_{10}\text{H}_{20}\text{O}_2$. [1-3]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY *In vitro*. Biformyne 1: Inhibits ($\mu\text{g}/\text{ml}$) *Bacillus subtilis*, *M. pyogenes* var. *aureus*, *Mycobacterium tuberculosis*, *Myc. smegmatis*, *Myc. phlei*, *Escherichia coli*, *Klebsiella pneumoniae* at 0.04-3.5; *Pseudomonas aeruginosa*, *B. mycoides* at 32-63. Inhibits fungi at 0.25-4.0 $\mu\text{g}/\text{ml}$: *Stemphylium consortiale*, *Trichophyton mentagrophytes*, *Memnoniella echinata*, *Chaetomium globosum*, *Saccharomyces cerevisiae*, *Aspergillus niger*, and *Penicillium notatum*. *Myrothecium verrucaria* required 32-63 $\mu\text{g}/\text{ml}$. Resistance by *M. pyogenes* var. *aureus* did not develop.

Biformyne 2: *In vitro* activity similar to that of biformyne 1 [1].

In vivo. Inactive when administered i.p. or s.c. to mice infected with *M. pyogenes* var. *aureus* and *Myc. tuberculosis* [1, 2].

/1/ Biformyne 1 appears to be an unsaturated 9-carbon glycol with 2 ethylenic and 2 acetylenic bonds. /2/ On treatment with alkali, both show a slow UV shift complete after 8-9 days at pH 10, 37°C; new maxima at 278, 291 $\text{m}\mu$.

46. BIFORMYNES (Concluded)

ACUTE TOXICITY LD₁₀₀ in mice, 18.8 mg/kg, i.v.; 37.5 mg/kg, i.p. Contact with human skin produced a severe dermatitis.[1]

47. BIOCERIN

SOURCE *Bacillus cereus* [1].

SOLUBILITY s. acetone, ether, chloroform, 95% ethanol; i. water.[1]

OTHER REACTIONS Activity decreased in presence of rabbit serum [1].

BIOLOGICAL ACTIVITY In vitro. Crude preparations inhibited ($\mu\text{g/ml}$) *Micrococcus pyogenes* var. aureus and var. albus at 50; *Corynebacterium diphtheriae*, *B. anthracis*, *B. subtilis*, *Brucella suis*, *Escherichia coli*, *Aerobacter aerogenes* at 500.[1]

ACUTE TOXICITY Mice tolerated i.p. doses of 1000 mg/kg [1].

48. BORRELIDIN

SOURCE *Streptomyces rochei* [1].

NATURE Acidic [1].

MOLECULAR FORMULA C₂₈H₄₃O₆N (proposed) [1].

MELTING POINT (°C) 145-146 [1].

OPTICAL ACTIVITY $[\alpha]_D^{27} = -28^{\circ 1}$ [1].

UV ABSORPTION MAXIMUM 256 m μ [1].

SOLUBILITY s. ether, benzene, butanol, butyl acetate, methanol, isopropanol [1].

QUANTITATIVE DETERMINATION Microbiological: *Borrelia* spp, *Sarcina lutea* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *S. lutea* and micrococci [1].

In vivo. Active in mice infected with *B. novyi*, following s.c. doses of 3.25 mg/kg. No protection afforded in experimental rabbit syphilis. Enhances activity of penicillin in vivo in experimental infections.[2]

ACUTE TOXICITY Fairly toxic to mice, rats, rabbits and chicks. LD₅₀ in mice, 39 mg/kg, i.v.; 75 mg/kg, s.c.; rats, 1.8 mg/kg, s.c.[3]. Toxicity (growth stunting of rats) can be counteracted by oral doses of niacin or tryptophan [4]. Irritating to human skin [3].

49. BOSTRYCOIDIN

SOURCE *Fusarium bostrycoides* [1].

NATURE Pigment, substituted naphthaquinone [1, 2].

MOLECULAR FORMULA AND WEIGHT C₁₈H₁₄O₇ (probable); 342 (calc.).[2]

CRYSTAL FORM AND COLOR Brown or red laths in clusters [2].

MELTING POINT (°C) 243-244 [2].

UV ABSORPTION MAXIMA 251, 320 m μ [2].

SOLUBILITY s. strong acids, alkalies; less s. 1,4-dioxane, benzene, ethanol, chloroform, carbon tetrachloride, acetone; i. water. [2]

OTHER REACTIONS Similar to javanicin; sublimes in vacuo; orange-red in acid, deep purple in alkaline solution. [1, 2]

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium tuberculosis* var. *hominis* [1].

/1/ Ethanol.

49. BOSTRYCOIDIN (Concluded)

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Myco. tuberculosis* at 10-20; *Micrococcus pyogenes* var. *aureus*, *Streptococcus pyogenes*, *Bacillus subtilis*, *Brucella abortus*, *Corynebacterium hoffmani*, *Pseudomonas aeruginosa* at 2-10.[1]

PHARMACOLOGY Mice tolerated 250 mg/kg doses, i.p., s.c., or per os, for 2-21 days. Rapidly excreted in the urine following i.p. or oral administration.[1]

50. BREVIN

SOURCE *Bacillus brevis* [1].

NATURE Polypeptide [1].

SOLUBILITY sl. s. water, aqueous ethanol; i. absolute ethanol.[1]

OTHER REACTIONS Contains aspartic acid, glycine, tyrosine, serine, and an unidentified basic substance [1].

QUANTITATIVE DETERMINATION Microbiological: *Corynebacterium xerose*, *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *M. pyogenes* var. *aureus*, *C. xerose*, *C. diphtheriae*, *Mycobacterium tuberculosis* in dilutions of 1:20,000-1:160,000. No inhibition of *Streptococcus pyogenes* and Gram-negative rods. [1]

51. BREVOLIN

SOURCE *Bacillus brevis* [1].

FORM AND COLOR HCl: yellowish-white; amorphous [1].

OPTICAL ACTIVITY $[\alpha]_D^{26} = -18.9^{\circ 1}$ [1].

UV ABSORPTION MAXIMUM $272.5 \mu\text{m}^2$ [1].

SOLUBILITY s. water, acid methanol, methanol; sl. s. ethanol; i. acetone, ether, butanol, ethyl acetate, chloroform, benzol, petroleum ether, ligroin.[1]

OTHER REACTIONS Positive ninhydrin, biuret, Millon, Sakaguchi, xanthoproteic, Molisch, Elson-Morgan.[1]

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium avium*, *Bacillus subtilis* PCI 219 [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Myco. tuberculosis*, 0.8-1.6; *Myco. avium*, 3-5; *Myco. phlei*, *B. subtilis*, *Brucella abortus*, 0.3; *Micrococcus pyogenes* var. *aureus*, *Escherichia coli*, 5; *Shigella dysenteriae*, 2.5; *Salmonella typhosa*, 20. No activity against *Pseudomonas* sp and fungi.[1]

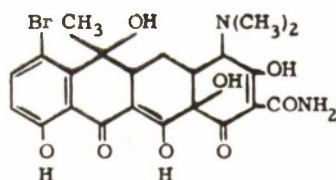
ACUTE TOXICITY LD_{50} in mice, 37.5 mg/kg, i.v.[1].

52. BROMOTETRACYCLINE

SOURCE Chlorotetracycline-producing *Streptomyces* strains [1].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{22}\text{H}_{23}\text{O}_8\text{N}_2 \text{Br}$; 523.45 (calc.).[1]

STRUCTURE



MELTING POINT ($^{\circ}\text{C}$) HCl: 235-240 (d.)[1]; browns at 218 (d. at 235)[3]. Free base: 170-172 [1].

OPTICAL ACTIVITY $[\alpha]_D^{20} = -196^{\circ 3}$ [1]; $[\alpha]_D = -205^{\circ 4}$ [3].

/1/ c, 1, methanol. /2/ 99% methanol. /3/ In 0.1 N HCl. /4/ 0.5% in 0.03 N aqueous HCl.

52. BROMOTETRACYCLINE (Concluded)

UV ABSORPTION MAXIMA 227, 260, 370 $m\mu$ ¹; 225, 255, 285, 345 $m\mu$ ². [1]

SOLUBILITY In water, 1.36%³; in dry n-butanol, 0.038%³. [3]

STABILITY Stable at acid pH; decreasing stability above pH 7.0 at 37°C. [2]

QUANTITATIVE DETERMINATION Hydrochloride in terms of chlortetracycline HCl: Turbidimetric: *Micrococcus pyogenes* var. *aureus*, 95%; *Escherichia coli*, 90%. Fluorometric: 26%. Hiscox: 45%. Spectrophotometric: 77%⁴. [3]

BIOLOGICAL ACTIVITY *In vitro*. Antibacterial spectrum resembles that of chlortetracycline. Inhibits (μ g/ml) *Bacillus anthracis* at 0.03; *Sarcina lutea*, 0.15; *M. pyogenes* var. *aureus*, *Streptococcus pyogenes*, *Str. faecalis*, *Klebsiella pneumoniae*, *B. subtilis*, *Clostridium perfringens*, *Mycobacterium phlei*, *Myco. ranae*, 0.3; *Diplococcus pneumoniae*, 0.5; *M. flavus*, *Myco. minetti*, 0.6; *E. coli*, 1.0; *Brucella abortus*, 1.2; *Salmonella typhosa*, *Bacillus cereus*, 1.5; *Proteus vulgaris*, 2; *Shigella sonnei*, 3; *Myco. tuberculosis* var. *hominis*, 10; *Pseudomonas aeruginosa*, 20. Fungi not sensitive to 100 μ g/ml. [2]

In vivo. Complete protection in mice infected with *Str. pyogenes* following daily oral doses of 200 mg/kg, and 30-60% protection with 50-100 mg/kg. Good protection against *K. pneumoniae* with 250-500 mg/kg/da, orally. High doses (500 mg/kg) gave slight protection against *Myco. tuberculosis* var. *hominis* in mice. [2]

PHARMACOLOGY LD₅₀ in mice, 89 mg/kg, i.v. (HCl). Action on isolated organs and blood pressure of guinea pigs similar to that of chlortetracycline [2].

RESISTANCE Complete cross resistance with tetracycline, chlortetracycline and oxytetracycline. No cross resistance with streptomycin and neomycin. Some *E. coli* strains rendered resistant to chloramphenicol showed increased resistance to bromotetracycline [2].

MODE OF ACTION Primarily bacteriostatic; high concentrations may be bactericidal. Like other tetracyclines, bromotetracycline is active against multiplying bacterial cells. [2]

53. BRYAMYCIN

SOURCE *Streptomyces hawaiiensis*, n. sp [1].

NATURE Polypeptide [1].

MOLECULAR WEIGHT 1600-1750⁵ [1].

MELTING POINT (°C) 223-235 (d.) [1].

OPTICAL ACTIVITY $[\alpha]_D^{27} = -68.50^6$ [1].

UV ABSORPTION MAXIMA 310 $m\mu$; strong end absorption below 250 $m\mu$ ⁷ [1].

SOLUBILITY s. pyridine, glacial acetic acid, 2-methylol tetrahydropyran, tetrahydrofurfuryl alcohol; less s. (20 mg/ml) chloroform, ethylene glycol, monomethyl ether, dioxane, 2 N HCl; i. water, ethanol, acetone, benzene, ethyl acetate, dimethoxyethane. [1]

OTHER REACTIONS Infrared peaks or shoulders at 3.1, 5.8, 6.04, 6.15, 6.6 (S), 8.33, 8.83, 9.48 (S), 10.73, 11.26, 12.4 and 15.0 (S) μ in a liquid petrolatum mull suspension; hydrolysis yields ninhydrin-positive hydrolysates which contain glycine, α -alanine, threonine, cystine, isoleucine, and several unidentified substances. [1]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis*⁸ [1].

BIOLOGICAL ACTIVITY Active primarily against Gram-positive bacteria.

In vitro. Inhibits (μ g/ml) *Streptococcus agalactiae*, *Str. dysgalactiae*, *Diplococcus pneumoniae*, *Lactobacillus acidophilus*, *Corynebacterium xerose*, 0.002-0.003; *Micrococcus pyogenes* var. *aureus*, *M. tetragena*, *L. casei*, *Clostridium perfringens*, *Cl. sporogenes*, 0.02-0.03; *B. anthracis*, 0.05; *Str. pyogenes*, 0.5. The following Gram-negative bacteria were insensitive to 10 μ g/ml: *Salmonella typhosa*, *Shigella sonnei*, *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa*. [1]

In vivo. Activity in mice infected with *D. pneumoniae* with CD₅₀ of 0.004 mg/kg, i.p.; 5 mg/kg, i.m.; and 62 mg/kg by oral route. Median curative dose against *Str. pyogenes* infection was 0.13 mg/kg, i.p., and 30 mg/kg, i.m. [1]

/1/ In 0.1 N HCl. /2/ In 0.25 N NaOH. /3/ 25°C. /4/ 368 $m\mu$ in 0.1 N H₂SO₄. /5/ Signer. /6/ c, I chloroform. /7/ In 6 N H₂SO₄. /8/ ATCC 6633.

53. BRYAMYCIN (Concluded)

PHARMACOLOGY Acute toxicity in mice; LD₅₀, >750 mg/kg, i.v.; >1000 mg/kg by i.p. or oral routes.[1] Slight irritation following i.m. injection in rats and rabbits. Absorbed very slowly from intramuscular site of injection; could be recovered therefrom up to 10 days later.[1]

54. CACAOMYCETIN

SOURCE *Streptomyces* sp, resembling *S. cacaoi* [1].

SOLUBILITY s. water, many organic solvents including carbon tetrachloride [1].

STABILITY Stable at neutral and acid pH; unstable at alkaline pH [1].

OTHER REACTIONS Paper chromatography indicates 4 antibiotics [1].

BIOLOGICAL ACTIVITY In vitro. Activity against a number of saprophytic phycomycetes and ascomycetes. Inhibits ($\mu\text{g/ml}$) *Monascus* spp, 0.2-0.5; *Aspergillus* spp, 0.1-0.5; *Ceratostomella fimbriata*, 5; *Helminthosporium oryzae*, 20; *Alternaria* sp, 100. *Trichophyton purpureum*, *Mucor* spp, *Penicillium chrysogenum*, and *Torula utilis* are resistant, >200. Bacteria: *Micrococcus pyogenes* var. *aureus*, *Bacillus subtilis*, and *Mycobacterium avium* were sensitive to 50 $\mu\text{g/ml}$; *Escherichia coli* resistant, >200.[1]

55. CAMPHOMYCIN (Canphomycin)

SOURCE *Streptomyces rutgersensis* var. *castelarensis*, n. var. [1].

NATURE Possibly a quaternary ammonium base [1].

FORM AND COLOR White to yellowish-white powder [2].

MELTING POINT ($^{\circ}\text{C}$) 20-22 [2].

UV ABSORPTION No peaks or crests; progressively diminishes from 210 to 450 $\text{m}\mu$. [2]

OTHER REACTIONS Positive Nessler; Tollens; liberates NH_3 on action of NaOH; alcoholic solution, treated with hot concentrated HCl or H_2SO_4 , turns green, then orange, and finally reddish; hot NaOH gives a red color which clears on cooling; this color disappears on oxidation with chlorine; has reductive properties.[1,2]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Micrococcus pyogenes* var. *aureus*, *M. pyogenes* var. *albus*, *Bacillus subtilis*, *B. mycoides*, *B. anthracis*, 5; *Chromobacterium violaceum*, 10; *Escherichia coli*, 50; *Xanthomonas campestris*, 100; *Mycobacterium smegmatis*, *Myco. avium*, *Sarcina lutea*, *Klebsiella pneumoniae*, *Salmonella paratyphi*, *S. typhimurium*, *S. pullorum*, *Serratia marcescens*, *Erwinia carotovora*, >100. Fungi ($\mu\text{g/ml}$): *Helminthosporium sativum*, *Neurospora crassa*, 5; *Botrytis cinerea*, *Rhizoctonia solani*, *Penicillium roseum*, *Fusarium* spp, *Rhizopus nigricans*, *Aspergillus niger*, *Piricularia oryzae*, *Absidia glauca*, *Saccharomyces* spp, >100.[1,2]

In vivo. No activity against *Trypanosoma equiperdum* in mice treated with doses of 5 mg [2].

TOXICITY Mice tolerated 550 mg/kg, i.v. or by oral route [1]. Concentrations of 1-10 ppm toxic to a variety of plants including maize, oat, barley, wheat, alfalfa, cabbage, tomato, carrot [2].

56. CANDICIDINS

SOURCE *Streptomyces griseus* and other *Streptomyces* spp [1].

UV ABSORPTION MAXIMA Candicidin A: 360, 380, 403 $\text{m}\mu$.
B: 362, 381, 404 $\text{m}\mu$.
C: 358, 379, 402 $\text{m}\mu$. [1]

SOLUBILITY s. higher alcohols; i. benzene, petroleum ether, carbon tetrachloride, xylene, carbon disulfide, ethylene dichloride, ether, ethyl acetate. Only Candicidin A s. water.[1]

STABILITY Concentrated solution more stable than dilute; A and B stable at neutrality for 10 minutes at 60 $^{\circ}\text{C}$ and 1 week at 4 $^{\circ}$; activity gradually lost at room temperature.[1]

OTHER REACTIONS Crude candicidin non-dialyzable [1].

QUANTITATIVE DETERMINATION Microbiological: *Candida albicans*¹ [1].

/1/ Assays on streak plates because of poor diffusion; values increase with NaCl or higher pH.

56. CANDICIDINS (Concluded)

BIOLOGICAL ACTIVITY *In vitro*. Candicidin A, B: Antifungal activity; inhibit, at 0.5-10 $\mu\text{g}/\text{ml}$, *C. albicans*, *C. stellatoidea*, *C. tropicalis*, *C. pseudotropicalis*, *C. krusei*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Cryptococcus neoformans*, *Geotrichum* spp, and *Hormodendrum pedrosoi*. *Candida parakrusei* inhibited at 25-50 $\mu\text{g}/\text{ml}$. Less sensitive, 200-500 $\mu\text{g}/\text{ml}$: *Coccidioides immitis*, *Sporotrichum schenckii*, *Nocardia asteroides*, *Trichophyton* spp, *Microsporum canis*, *M. audouini*, *Epidermophyton floccosum*. Also inhibit species of *Aspergillus*, *Cercospora*, *Botrytis*, *Pullularia*, *Trichoderma*, and other phytopathogens.[1, 2]

C: Relatively inactive.

In vivo. Candicidin A, B: Protected mice against infections with *Candida albicans*, *Bl. dermatitidis*, and *S. schenckii*. Little or no activity against *Coccidioides immitis* and *H. capsulatum* following i.p. doses of 37.5 mg/kg/da for 10 days.[2, 4, 5]

CLINICAL Topical use of 1% solution and daily administration of suppository containing 1 g of candicidin was effective in the treatment of an isolated case of vulvovaginitis caused by *Candida albicans* [6]. Four patients with intertriginous moniliasis showed favorable response after topical treatment with 1% solution candicidin B. Candicidin A failed to benefit 3 cases of paronychia moniliasis [3].

PHYTOPATHOLOGY Crude preparations decreased powdery mildew infection in young bean plants sprayed once weekly with 660 $\mu\text{g}/\text{ml}$ solution. No toxic effect on bean plants at 660 $\mu\text{g}/\text{ml}$ or on germination of pea seeds at 125 $\mu\text{g}/\text{ml}$. [1] A single spray application of 1:5000 of antibiotic, 3 days before inoculation of Pinto beans with *Uromyces phaseoli*, reduced infection by 90% [7]. Concentration of 1:16,000 is excellent protective dip against brown rot infection of peach fruit [8]. Failed to control effectively stem rust of wheat when used as a preinoculation spray under greenhouse conditions [9].

TOXICITY *In vitro*. In tissue cultures, concentrations of 100-200 $\mu\text{g}/\text{ml}$ inhibited explants of chick embryonic heart, and 80-165 $\mu\text{g}/\text{ml}$ inhibited human skin tissue [10].

ACUTE TOXICITY Considerable variation between lots. Candicidin A: LD₅₀ in mice, 277 mg/kg, s.c., and 47-65 mg/kg, i.p.

B: LD₅₀ in mice, 159 mg/kg, s.c., and 53 mg/kg, i.p. Necrosis developed at site of s.c. injection of 25 mg/kg.[2]

57. CANDIDINS

SOURCE *Streptomyces viridoflavus*, n. sp [1].

UV ABSORPTION MAXIMA Na salt: 234, 282, 345, 360, 383, 405 $\text{m}\mu$ ¹ [1].

SOLUBILITY s. water at neutral and alkaline pH. Free acid: s. ethanol, methanol, glacial acetic acid, ethylene glycol, monomethyl ether, pyridine, other basic solvents. Free acid (Na salt): i. or sl. s. ether, chloroform, acetone, benzene, non-polar solvents.[1]

OTHER REACTIONS Precipitated by dilute acetic or mineral acids; contain N, but negative ninhydrin after hydrolysis; negative Molisch, Benedict, Fehling, Tollens, Schiff, pine splint, FeCl_3 , deep blue with H_2SO_4 ; decolorize Br in CHCl_3 and 1% KMnO_4 ; positive tests for ketones with NaHSO_4 , semicarbazide, 2,4-dinitrophenylhydrazine; resemble candicidin, ascocin, trichomycin. Separates by solvent extraction into 2 fractions; ethanol-soluble is candicidin A, insoluble is B, but A is probably an artifact.[1, 2]

QUANTITATIVE DETERMINATION Microbiological: *Candida albicans*² [1].

BIOLOGICAL ACTIVITY *In vitro*. Antifungal activity; inhibit *C. albicans*, *Trichophyton mentagrophytes*, *Blastomyces dermatitidis*, and *Sporotrichum schenckii* at 0.2-4.1 $\mu\text{g}/\text{ml}$. [1]

In vivo. Candidin B: Daily oral doses of 100 mg/kg resulted in complete suppression of fungi with a concomitant 1000-fold increase in bacterial fecal flora of mice [2].

ACUTE TOXICITY LD₅₀ of crude preparations in mice, 7-36 mg/kg, i.p. [1].

Candidin B: LD₅₀ in mice, 1.5 mg/kg, i.v.; 30 mg/kg, s.c., with necrosis at site of injection after single doses of 10-40 mg/kg.

CHRONIC TOXICITY Daily oral doses of 100 mg/kg for 6 days were well tolerated, but mice showed a reduction in spleen size [2].

58. CANDIDULIN

SOURCE *Aspergillus candidus* [1].

NATURE Neutral, non-aromatic [1].

/1/ Aqueous solutions; free acid lacks 345 $\text{m}\mu$ peak. /2/ By streak plate.

58. CANDIDULIN (Concluded)

MOLECULAR FORMULA AND WEIGHT $C_{11}H_{15}NO_3$ (proposed); 209.13 (calc.).[1]

CRYSTAL FORM AND COLOR Long, white needles [1].

MELTING POINT ($^{\circ}C$) 88-89 (uncorr.) [1].

OPTICAL ACTIVITY $[\alpha]_D^{24} = +15^{\circ} \pm 2^1$ [1].

UV ABSORPTION No characteristic spectrum [1].

SOLUBILITY s. methanol, ethanol, acetone, ether; less s. chloroform, benzene, carbon tetrachloride, water; sl. s. n-hexane.[1]

STABILITY Thermostable; alkali labile [1].

OTHER REACTIONS Negative $FeCl_3$, ninhydrin, 2,4-dinitrophenylhydrazine, 3,5-dinitrobenzylchloride, xanthidrol, HgO ; inactivated by Br in CCl_4 . [1]

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium ranae* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu g/ml$) *Myco. tuberculosis*, 0.06-0.1; *Myco. ranae*, 0.4-2.5; *Myco. smegmatis*, 2.5; *Mycobacterium sp.*, 1.25; *Bacillus subtilis*, *Klebsiella pneumoniae*, 10; *Brucella abortus*, 20; *Escherichia coli*, 160; *Streptococcus hemolyticus*, 160; *Micrococcus pyogenes var. aureus*, *Sarcina lutea*, 320. Fungi: *Aspergillus fumigatus*, 80; *Penicillium puberulum*, 40.[1] Inhibits *Saccharomyces cerevisiae*, *Torula utilis*, *Absidia orchidis*, *Aspergillus niger*, 6.2; *Willia sp.*, *Candida krusei*, *Mucor pusilis*, *Botrytis sp.*, 12.5; *Trichophyton interdigitale*, 50.[2] Inactivated in vitro by whole blood [1].

In vivo. No protection against *Myco. tuberculosis* in mice given 12 daily s.c. injections of doses up to 200 mg/kg [1].

ACUTE TOXICITY LD_{50} in mice, approximately 250 mg/kg, s.c. [1].

59. CANESCIN

SOURCE *Penicillium canescens* (Sopp.) [1].

NATURE Monobasic acid [1].

MOLECULAR FORMULA AND WEIGHT $C_{15}H_{14}O_7$; 282 (found); 306 (calc.). [1]

CRYSTAL FORM AND COLOR Colorless needles² [1].

MELTING POINT ($^{\circ}C$) 201-202 (d.) [1].

SOLUBILITY s. cold sodium bicarbonate; sl. s. water, organic solvents.[1]

STABILITY Very unstable, especially at pH 6 and above [1].

OTHER REACTIONS Dissolves in cold $NaHCO_3$ with effervescence, giving a red color, later orange; purple color with $FeCl_3$ added to ethanol solution; negative Fehling.[1]

BIOLOGICAL ACTIVITY In vitro. Low antibacterial activity; inhibits *Bacillus subtilis* and *Micrococcus pyogenes var. aureus* at 100 $\mu g/ml$. Inhibits fungi at 12.5-25 $\mu g/ml$: *Botrytis allii*, *Penicillium brevi-compactum*, *P. stoloniferum*, *Stachybotrys atra*, *Fusarium caeruleum*, *F. graminearum*, *Thamnidium elegans*. At 50-100 $\mu g/ml$: *P. digitatum*, *P. expansum* and *Stemphylium sp.*[1]

60. CARBOMYCIN

The trademark of Chas. Pfizer & Co., Inc., for carbomycin is Magnamycin.

SOURCE *Streptomyces halstedii* [1].

NATURE Monobasic [1-4].

MOLECULAR FORMULA AND WEIGHT $C_{40-42}H_{67-71}NO_{16}$ [2]; $C_{41-42}H_{67-69}NO_{16}$ [3,4]; 830, 840, 860, 864 (neut. equiv.).[2,4]

/1/ c, 1 chloroform. /2/ From ethanol.

CRYSTAL FORM AND COLOR Slender, white, blunt-ended, needle-shaped crystals [1]; colorless laths¹ [3]; rectangular plates² [4].

MELTING POINT (°C) 210-218 (d.) [2-4].

OPTICAL ACTIVITY $[\alpha]_D^{25} = -58.6 \cdot 10^3$ [1], $-56.1 \cdot 10^3$ [4], $-54 \cdot 10^3 \pm 2^4$ [2], -56 ± 2^5 , $-55.2 \cdot 10^3$ [2].

UV ABSORPTION MAXIMA 238, 327 $m\mu$ ⁶ [3, 4].

SOLUBILITY s. water (acid salts), most organic solvents; i. water (base), hexane.[1, 3]

STABILITY Most stable at pH 5-7⁷; stable for several months in dark at room temperature; unstable below pH 3 and above pH 9.[2-4]

OTHER REACTIONS Negative ninhydrin, Van Slyke, FeCl₃; positive Fehling, Tollens, 2, 4-dinitrophenylhydrazine, Baeyer permanganate, ceric nitrate; decolorizes Br; unaltered by serum; violet color at room temperature with 40% H₂SO₄ or 4 N HCl; intense yellow color with methanolic KOH solution; water-insoluble precipitate with trichloroacetic acid.[2-4] Acid hydrolysis yields 2 sugars: mycarose (C₇H₁₄O₄) and mycaminose (C₈H₁₇NO₄) from both carbomycin and carbomycin B [32, 33].

QUANTITATIVE DETERMINATION Microbiological: Bacillus subtilis [4]. Colorimetric [5].

BIOLOGICAL ACTIVITY In vitro. Active mainly against Gram-positive and a few Gram-negative bacteria, large viruses, rickettsiae, and certain protozoa. Fungi are insensitive. Inhibits ($\mu\text{g/ml}$) B. subtilis, B. anthracis, and B. mycoides, 0.2-1.5; Diplococcus pneumoniae, 0.01-0.15; Gaffkya tetragena, 0.3; Micrococcus pyogenes var. aureus, 0.2->25; Streptococcus pyogenes, 0.01-2.5; Str. faecalis, 0.2-12.5; Str. lactis, 0.16; Str. mitis, 0.04-1.25; Streptococcus spp, 0.1-12.0; Corynebacterium diphtheriae and C. bovis, 0.04-0.8; Clostridium tetani and Cl. botulinum, 0.4-1.5; Cl. perfringens, 6.2; Clostridium spp, 1.5-3.0; Erysipelothrix rhusiopathiae, 0.25; Listeria monocytogenes, H. pertussis, 3.1; Neisseria gonorrhoeae, 0.1-3.1; Mycobacterium spp, 0.4->25; N. catarrhalis, 0.02-0.8; N. meningitidis, 0.2-2.5; Hemophilus influenzae, 0.02-6.2; Pasteurella multocida, 6.25; Brucella bronchiseptica, 6.25-12.5; Escherichia coli, 3.2->100; pleuropneumonia-like organisms, <1.0. Generally resistant, 50 μg or more: Aerobacter aerogenes, Klebsiella pneumoniae, Proteus spp, Pseudomonas spp, Salmonella spp, Shigella spp, and Candida albicans.[6, 7] Protozoa ($\mu\text{g/ml}$): Trypanosoma cruzi and Leishmania donovani sensitive to 32-62; T. rhodesiensis, 125; Trichomonas vaginalis, T. foetus, 250; Entamoeba histolytica, 32-125. Spermatozoa in man immobilized by 1000 $\mu\text{g/ml}$ in 95 minutes.[8] Concentrations of 2 mg/ml had no effect on the virus of herpes simplex [34].

In vivo. Good protection afforded against M. pyogenes var. aureus, Str. pyogenes, and D. pneumoniae infections in mice, with total doses of 5-50 mg/kg administered i.p. or s.c. [9]. Doses of 10 mg/kg, i.p., gave good protection against Past. multocida in mice; 65 mg/kg highly active in fowl typhoid infection (Salmonella gallinarum) in chicks; no protection against mouse infections with B. anthracis and Myco. tuberculosis.[30] High activity (in chick embryos, mice, guinea pigs, or cotton rats) against Rickettsia prowazeki, R. typhi, R. akari, R. tsutsugamushi, R. rickettsi, R. conori, North Queensland tick typhus, and Coxiella burnetii; also against viruses of psittacosis, ornithosis, lymphogranuloma venereum, human pneumonitis, feline pneumonitis, and sporadic encephalomyelitis. [10, 25] Oral doses of 100 mg/kg ineffective in guinea pigs infected with Entamoeba histolytica [29]. Daily intramuscular doses of 20 mg/kg for 10 days cured experimental syphilitic orchitis in rabbits [35]. In rats, oral doses of 337-665 mg/kg/da effectively controlled experimental intestinal amebiasis [37].

CLINICAL On basis of preliminary trials, carbomycin appears useful in therapy of infections, particularly those caused by Gram-positive organisms which are resistant to penicillin and other antibiotics. Favorable response has been reported in infections with Str. pyogenes treated with 1-2 g daily in divided oral doses.[11] Doses of 100-125 mg/kg for approximately 9 days were effective in children for control of infections caused by M. pyogenes var. aureus (pyoderma, deep abscesses, and pneumonia)[12]. Good response in pneumonia caused by D. pneumoniae and Str. pyogenes [22]; in chronic urinary tract infections caused by enterococci [24] and in gonorrhoea [26]. In a limited series of patients with primary or secondary syphilis, daily oral doses of 2-3 g promptly cleared lesions of Treponema pallidum [31, 36]. Preliminary trials suggest value in granuloma inguinale (donovanosis) [13]; also indicate value in clinical amebiasis [38] and in tsutsugamushi disease [39]. Daily doses of approximately 1.5 g for 10 days gave good clinical response in amebic dysentery [14, 15].

VETERINARY Daily oral doses of 25 mg/kg had a suppressive effect on experimental Neorickettsia helmintheca infection ("salmon poisoning") in dogs, but the infection was not completely eliminated [40]. In preliminary trials antibiotic appeared valuable in treating distemper complex in dogs [27].

ACUTE TOXICITY LD₅₀ in mice, 550 mg/kg, i.v.; 2950 mg/kg, s.c.; 1000 mg/kg, i.m.; >3500 mg/kg, per os. LD₅₀ in rabbits, 700 mg/kg, i.v.; >5000 mg/kg, per os.[16]

/1/ From ethanol. /2/ From ethanol-water. /3/ c, 1 chloroform. /4/ c, 1 methanol. /5/ c, 7 chloroform. /6/ Absolute ethanol. /7/ 11 days at 25°C.

60. CARBOMYCIN (Concluded)

CHRONIC TOXICITY Five daily i.v. injections of 200 mg/kg, or same dose administered orally or i.m., for 20 weeks were well tolerated. No evidence of eighth cranial nerve damage in cats given daily i.m. doses of 200 mg/kg for 9 weeks.[16]

In man, daily oral doses of 2 g well tolerated [17, 23]; nausea with occasional vomiting and diarrhea reported following daily oral doses of 2.5 g [18].

ABSORPTION AND EXCRETION Wide variations in blood levels noted in animals and man after oral or parenteral administration; these levels are generally low. In rabbits, 100 mg/kg, i.v., gave serum levels of 10 µg/ml in 30 minutes which dropped to 2.2 µg/ml after 3 hours; following oral administration of 200 mg/kg, low levels of approximately 0.75 µg appeared in 2 hours and 0.1 µg at the fourth hour, with usually less than 1% of the total i.m. or oral dose recovered in the urine. However, wide distribution in tissues, exudates, or organ contents, equal to or exceeding the serum concentration, was noted. Little or no diffusion through blood-brain barrier.[19, 20] In man, following i.m. injection of 3.3-8.0 mg/kg, or oral doses of 12-18 mg/kg, peak serum concentrations of approximately 0.7 µg/ml declined to 0.1-0.3 µg in 3-4 hours [17, 19].

RESISTANCE Certain test bacteria acquired resistance in vitro in a slow stepwise pattern similar to that exhibited by penicillin [1]. Cross resistance of streptococci and micrococci exhibited between carbomycin and erythromycin [21].

ANIMAL NUTRITION Stimulated growth of chicks when incorporated in ration in concentration of 2 g per ton, and of baby pigs in concentration of 40 g/ton [28].

61. CARBOMYCIN B (Magnamycin B)

SOURCE *Streptomyces halstedii* [1].

NATURE Weak base [1].

MOLECULAR FORMULA C₄₁₋₄₂H₆₇₋₆₉NO₁₅ (proposed) [1].

CRYSTAL FORM AND COLOR Colorless anisotropic plates, frequently hexagonal¹. HCl: fine needles.[1]

MELTING POINT (°C) 141-144 (d.). HCl: 164-166 (d.).[1]

OPTICAL ACTIVITY [α]_D²⁵ = -35⁰² [1].

UV ABSORPTION MAXIMUM 278 mµ³ [1].

SOLUBILITY s. ethanol⁴; less s. water⁵. [1]

STABILITY Stable 3 months at pH 5; relatively unstable at pH 3 and 10⁶. [1]

OTHER REACTIONS May be isomeric with carbomycin; contains a single methoxyl group, a dimethylamino nitrogen group, and a volatile acid; yields methylmycarose isovalerate on hydration in methanolic HCl; vigorous acid hydrolysis yields C₈H₁₇NO₄; mono-acetyl, tetrahydro, and mono-acetyltetrahydro are biologically active derivatives. [1]

BIOLOGICAL ACTIVITY In vitro. Same antimicrobial spectrum as carbomycin [1].

ACUTE TOXICITY LD₅₀ in mice, by oral, i.p., and s.c. routes, comparable to that of carbomycin. Slightly higher toxicity by i.v. route. LD₅₀, 300 mg/kg.[1]

ABSORPTION AND EXCRETION In man, preliminary trials indicated that oral doses gave higher blood concentrations than those usually obtained with carbomycin. Following doses of 500 mg every 12 hours, serum levels of 0.3-0.6 µg/ml were maintained for 1-3 hours, with high concentrations in the urine and feces in 6-24 hours. No detectable levels in cerebrospinal fluid.[2]

62. CARDICIN

SOURCE *Nocardia* sp [1].

NATURE Acidic [1].

CRYSTAL COLOR White [1].

/1/ From acetone. /2/ c, 2 chloroform. /3/ Absolute ethanol. /4/ 450 mg/ml at 25⁰. /5/ 0.1-0.2 mg/ml.
/6/ Half-life, 10 days.

62. CARDICIN (Concluded)

SOLUBILITY Free acid: s. methanol, ethanol, aqueous butanol; i. water, saline, ether, acetone. Na salt: s. water, ethanol, aqueous butanol; i. ether, cold anhydrous butanol.[1]

STABILITY Fairly stable at wide temperature and pH range; stable at 5°C.[1]

QUANTITATIVE DETERMINATION Microbiological: Antiviral in eggs; *Bacillus subtilis*. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *B. subtilis*, *Saccharomyces cerevisiae*, <1; *Mycobacterium* sp. 2.5; *Aspergillus niger*, 5. Inactive against *Escherichia coli*, *Proteus vulgaris*, *Salmonella typhosa*. Inhibits bacteriophages. In chick embryo, antibiotic is active against strains PR-8 and FM-1 influenza virus.[1]

ACUTE TOXICITY LD₁₀₀ in mice, 8.25 mg/kg, i.p. and s.c.[1].

63. CARNEOLUTESCIN

SOURCE *Penicillium carneo-lutescens* [1].

NATURE Oil containing C, H, O [1].

SOLUBILITY s. ether, benzene, ethanol; sl. s. water. [1]

STABILITY Stable at room temperature at acid pH; less stable at higher pH.[1]

OTHER REACTIONS Negative FeCl₃, Fehling; activity greatly reduced by serum.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *M. pyogenes* var. *aureus* at 1:1, 600,000 dilution, *Streptococcus pyogenes* at 1:800,000, *Salmonella enteritidis* at 1:100,000, *Bacillus anthracis* at 1:6, 400,000.[1]

64. CARZINOCIDIN

SOURCE *Streptomyces* sp [1], *S. kitazawaensis* [3].

FORM AND COLOR Brownish black powder [1].

UV ABSORPTION MAXIMA None specific [1].

SOLUBILITY s. alkaline water; i. organic solvents. [1]

STABILITY Unstable to heat, particularly at alkaline pH; stable at 5°C for 10 days.[1]

OTHER REACTIONS Positive xanthoproteic, Pauly; negative Millon, biuret, Adamkiewicz, Liebermann, ninhydrin, Neubauer-Rhode, diphenylamine, cysteine-H₂SO₄, nitroprusside, Folin, anthrone; culture also produces antimycin A.[1]

BIOLOGICAL ACTIVITY In vitro. Slight activity against *Candida albicans*, *Torula utilis*, and *Saccharomyces cerevisiae*. Bacteria are not sensitive.[1]

In vivo. Crude preparations showed antitumor activity. Daily i.p. doses of 10-20 mg/kg inhibited Ehrlich ascites carcinoma in mice; also active against Yoshida rat sarcoma and subcutaneous solid tumor induced by Ehrlich carcinoma.[2]

TOXICITY LD₅₀ in mice, 4.7 mg/kg, i.v.; 43.5 mg/kg, i.p.[1] LD₀ in mice, 20 mg/kg, s.c. These animals tolerated daily doses of 10 mg/kg, i.p., for 7 days, and 40 mg/kg for 2 days. There was no necrosis at site of inoculation following 20 mg/kg/da, s.c., for 10 days.[2]

In vitro. Concentrations of 1 mg/ml did not hemolyze erythrocytes [2].

65. CARZINOPHILIN

SOURCE *Streptomyces sahachiroi*, n. sp [1].

UV ABSORPTION MAXIMA 217, 290 m μ ¹; 285-290 m μ ². [1]

SOLUBILITY s. water, alcohols, acetone, butyl acetate, chloroform, benzol; i. petroleum ether.[1]

STABILITY Most stable at pH 7; relatively stable at pH 6-9; unstable below pH 5; thermolabile; unstable in air at acid pH; stable in H₂ gas.[1]

/1/ Water. /2/ 30 minutes in 0.1 N HCl or NaOH.

65. CARZINOPHILIN (Concluded)

OTHER REACTIONS Positive xanthoproteic; negative Molisch, Sakaguchi, Fehling, Benedict, ninhydrin, Schiff, FeCl_3 , Tollens; no hemolysis; antibacterial activity highest at pH 6-7; serum, KCN, $\text{Na}_2\text{S}_2\text{O}_3$, $\text{CS}(\text{NH}_2)_2$ inhibit activity; glucose, cysteine enhance activity.[1]

QUANTITATIVE DETERMINATION Microbiological: *Sarcina lutea* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Mycobacterium smegmatis*, *Myco. avium*, *Myco. phlei*, *Micrococcus pyogenes* var. *aureus*, *Bacillus subtilis*, *B. anthracis*, *Diplococcus pneumoniae*, *Streptococcus pyogenes*, *Brucella abortus*, *Br. melitensis*, 2.5-10; *Vibrio comma*, 25; *Proteus vulgaris*, 50; *Pseudomonas aeruginosa*, 100. *Nocardia asteroides* is sensitive to 10 $\mu\text{g/ml}$. Resistant, >100 $\mu\text{g/ml}$: *Salmonella* spp, *Shigella* spp, *Candida*, *Trichophyton interdigitale* and other fungi.[1]

In vivo. Antitumor activity in rats against Yoshida sarcoma, Ehrlich carcinoma and ascitic hepatoma following single i.p. doses of approximately 1 mg/kg [1]. Daily i.p. doses of 2500 units/kg in mice had marked inhibitory effect on the following ascites tumors: Sarcoma 180, Ehrlich carcinoma, Krebs 2 carcinoma; there was little or no effect on solid tumors.[3]

CLINICAL Trials in 36 cases of malignant tumor described in which slight clinical improvement was noted in certain instances. The antibiotic was administered mainly by the i.v. route.[2]

ACUTE TOXICITY Mice tolerated only 2-3 mg/kg doses by i.v., i.p. or s.c. routes [1].

66. CARZINOPHILIN A

SOURCE *Streptomyces sahachiroi*, n. sp [1].

MOLECULAR WEIGHT 900-1200¹; 800-1200². [1]

CRYSTAL FORM AND COLOR Colorless needles [1].

MELTING POINT ($^{\circ}\text{C}$) 217-222 (d.) [1].

OPTICAL ACTIVITY $[\alpha]_D^{28} = +57.8^{03}$ [1].

UV ABSORPTION MAXIMA 2% NaHCO_3 , 218, 250, 283 μm ; 0.1 N NaOH , 230, 283 μm ; 0.1 N HCl , 216, 250 μm ; methanol, 218, 250, 283 μm ; ethanol, 219, 251, 290 μm ; ether, 219, 252 μm ; acetone, 210, 330 μm ; chloroform, 270 μm ; dioxane, 250 μm ; benzene, 282 μm ; ethyl acetate, 255 μm ; carbon tetrachloride, 262 μm ; carbon disulfide, 242, 378 μm ; ethylene dichloride, 255 μm . [1]

SOLUBILITY s. acetone, chloroform, ethyl acetate, butyl acetate, benzene, dioxane, dilute alkaline water; sl. s., or i., methanol, ethanol, ether, carbon tetrachloride, petroleum ether, water.[1]

STABILITY Stable in dry crystalline state; very unstable in aqueous state, especially at non-neutral pH; also rapidly destroyed by thiourea, thioglycollic acid, cysteine, thioglycerin, methionine, hydroquinone, anthraquinone, vitamin B₂, chlorophyllin, hydrogen peroxide, formalin; destroyed in aqueous solution by UV.[1]

OTHER REACTIONS Positive Baeyer, xanthoproteic, ninhydrin, Br absorption, 2,4-dinitrophenylhydrazine, Neubauer-Rhode, Na 1,2-naphthoquinone-4-sulfonate, sodium nitroprusside, diphenylamine, anthrone. Infrared (in CHCl_3): 2.78, 2.90, 3.03, 3.30-3.45, 5.80-5.85, 6.10-6.26, 6.45, 6.68, 6.85, 7.10, 7.20, 7.33, 7.50-7.60, 7.82, 7.95-8.20, 8.47, 8.58, 8.89, 9.13-9.30, 9.35, 9.60, 10.44, 10.80, 11.10, 11.30, 11.75, 12.40, 13.2, 13.5 μ . [1]

BIOLOGICAL ACTIVITY In vivo. Single i.p. doses of 1-3 $\mu\text{g/kg}$ in rats inhibited Yoshida sarcoma [1].

TOXICITY LD_{50} in mice, 0.15 mg/kg, i.v.; LD_0 , approximately 0.025-0.050 mg/kg.[1]

67. CATENULIN

SOURCE *Streptomyces* sp [1].

NATURE Resembles neomycin B [1].

OPTICAL ACTIVITY $[\alpha]_D^{25} = +33^{04}$ [1].

UV ABSORPTION End absorption only [1].

STABILITY Stable in aqueous solution at pH 1.5-10 [1].

1/ Rast. 2/ Electroconduction. 3/ In chloroform. 4/ c, 1 methanol.

67. CATENULIN (Concluded)

OTHER REACTIONS Acid hydrolysis yields active fragment identified as neamine. Analysis of benzene sulfonate salt: C, 50.24, 50.24; H, 5.29, 5.26; N, 10.01, 10.16; S, 8.00, 7.8.[1]

BIOLOGICAL ACTIVITY In vitro. Active against *Mycobacterium tuberculosis* (including streptomycin-resistant strains) [1]. Inhibited *Myco. ranae* at 2 µg/ml [3].

ACUTE TOXICITY LD₅₀ in mice, 125 mg/kg, i.v. Neurotoxicity in cats following repeated daily doses of 100 mg/kg.[1]

PHYTOTOXICITY Highly toxic to duckweed plant (*Lemna minor*) at 1 ppm in tissue culture [2].

MISCELLANEOUS Growth of wheat roots in tap water (but not in distilled water) was stimulated by addition of 0.1 ppm of antibiotic [4].

68. CELESTICETIN

SOURCE *Streptomyces caelestis*, n. sp, resembling *S. glaucous* [1].

NATURE Basic [2].

MOLECULAR FORMULA AND WEIGHT C₂₄H₃₆₋₄₀O₉N₂S (suggested); 517 ± 20 (equiv. wt. found; 490-537¹).[2]

CRYSTAL FORM AND COLOR Oxalate: white needles. Free base: amorphous, hygroscopic white glass.[2]

MELTING POINT (°C) Oxalate: 147-152. Salicylate: 139.[2]

OPTICAL ACTIVITY Oxalate: $[\alpha]_D^{24} = +106.6^{\circ 2}, +105.8^{\circ 3}$. Salicylate: $[\alpha]_D^{24} = +90.2^{\circ 2}, +99.0^{\circ 3}$. Free base: $[\alpha]_D^{24} = +126.6^{\circ 4}$.[2]

UV ABSORPTION MAXIMA 248, 341 mµ⁵; 240, 310 mµ⁶.[2]

SOLUBILITY s. acidic, strongly basic solutions, more polar organic solvents; i. water at pH 7-10, ether, light hydrocarbons.[2]

STABILITY Stable at room temperature in aqueous solution at pH 5-7; unstable above pH 9; more stable in acid than in base, but unstable in 1 N HCl at 100°C.[2]

OTHER REACTIONS Infrared (in CHCl₃): 1670, 1645, 1614, 1584, 1517, 1486, 1462, 1390, 1324, 1300, 1250, 1210, 1157, 1136, 1085, 1046, 985, 957, 924, 900, 859, 850 (recip. cm); pK_a¹ 7.7, 9.8; positive FeCl₃, Molisch, Ekkert; white precipitates with Br water, Millon, HgCl₂; not precipitated by AgNO₃, lead acetate; negative Benedict, ninhydrin, iodoform; negative nitroprusside becoming positive after several days in 6 N HCl; no reaction with Br in CCl₄.[2]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* [1].

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive bacteria. Inhibits (µg/ml) *Streptococcus hemolyticus*, 0.2-3.1; *Str. agalactiae*, 0.8-1.5; *Str. dysgalactiae*, 0.8; *Str. viridans*, 1.5-12.5; *Str. faecalis*, 2.5-6.2; *Diplococcus pneumoniae*, 0.2-3.9; *Micrococcus pyogenes* var. *aureus*, 0.2-12.5; *Clostridium novyi*, 0.4; *Cl. sporogenes*, *Str. mitis*, 6.2. Inactive, >100 µg/ml: *Hemophilus influenzae*, *Neisseria meningitidis*, *Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Salmonella* spp, *Shigella* spp, and *Mycobacterium tuberculosis*. Phytopathogens (µg/ml): *Bacterium stewartii*, *Phytomonas fascians*, and *Xanthomonas pruni* sensitive to 0.5. *Erwinia carotovora*, *Agrobacterium tumefaciens* not inhibited by 50 µg/ml. Inhibits *Nocardia asteroides* at 500 µg/ml. Fungi are resistant, >1000 µg/ml: *Blastomyces dermatitidis*, *Coccidioides immitis*, *Hormodendrum compactum*, *Histoplasma capsulatum*, *Microsporium audouini*, *Candida albicans*, *Saccharomyces cerevisiae*. In vitro action bacteriostatic; bactericidal at higher concentrations. Sensitivity increased with increasing pH. Activity not affected by serum, cysteine, methionine, or penicillinase.[1] Resistance did not develop readily but followed a stepwise pattern. No cross resistance with other antibiotics with the exception of erythromycin.

In vivo. Good protection in mice infected with *Str. pyogenes* and *M. pyogenes* var. *aureus*; slight activity against *D. pneumoniae*. No activity in infections with *Salmonella typhosa*, *S. paratyphi*, *K. pneumoniae* and *Myco. tuberculosis*. Inactive against viruses of Newcastle disease and influenza in ovo.[1]

PHYTOTOXICITY Concentrations of 1000 ppm non-toxic to foliage of apple, pear, and cherry trees [1].

/1/ Calculated from rotation in HCl. /2/ Water. /3/ 1 N HCl. /4/ Chloroform, c, 0.5 in all. /5/ In 0.01 N alcoholic KOH. /6/ In 0.01 N alcoholic H₂SO₄.

70. CEPHALOSPORIN N (Concluded)

QUANTITATIVE DETERMINATION Chemical: CO₂; hydroxylamine; iodine. Penicillinase.[4]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits Gram-positive and Gram-negative bacteria at 5-10 µg/ml: Streptococcus pyogenes, Salmonella typhosa, S. typhimurium, S. enteritidis, S. schottmuelleri, Klebsiella pneumoniae, Bacillus subtilis, Vibrio comma, Corynebacterium ovis, Listeria monocytogenes, Brucella abortus, Micrococcus pyogenes var. aureus, Sarcina lutea, Str. viridans, Diplococcus pneumoniae, Neisseria meningitidis, N. gonorrhoeae, Pasteurella multocida, Hemophilus pertussis, Clostridium perfringens, Cl. tetani, Cl. septicum. At >40 µg/ml: penicillin-resistant M. pyogenes var. aureus, Mycobacterium tuberculosis. Action is essentially bactericidal. Cross resistance between this antibiotic and penicillin demonstrated with M. pyogenes var. aureus.[6]

PHARMACOLOGY Mice tolerated i.v. doses of 2000 mg/kg. Toxicity for mice, i.v., or rabbits, intracisternally, was less than that of penicillin. General behavior is like that of penicillin, but cephalosporin N is more slowly absorbed from the intestine and excreted at a lower rate. Following i.v. doses in rabbits, serum levels were higher than those obtained with an equimolar dose of penicillin. Cephalosporin N is destroyed like penicillin in the stomach by gastric juice and in the intestine by penicillinase-producing bacteria.[6]

71. CEPHALOSPORIN P SERIES

SOURCE Cephalosporium sp [2].

NATURE Acidic substances [2].

MOLECULAR WEIGHT Cephalosporin P₁: 580 (equiv. wt.) [2]; 601 ± 16 (X ray) [4].

STRUCTURE Cephalosporin P₁: Has a polycyclic hydroaromatic structure [2].

CRYSTAL FORM AND COLOR Cephalosporin P₁: needles.

P₃: white, greasy amorphous solid.

P₄: light fawn-colored crystals.[2]

MELTING POINT (°C) Cephalosporin P₁: 147.

P₂: 151.

P₄: 220-230.[2]

OPTICAL ACTIVITY Cephalosporin P₁: [α]_D = +28° [2].

UV ABSORPTION MAXIMUM 211 mµ [4].

SOLUBILITY Cephalosporin P₁: s. most organic solvents; sl. s. petroleum ether, water.

P₂: s. ethanol, acetone, butyl acetate; less s. diisopropyl ether, benzene.

P₃: s. most organic solvents; sl. s. water.

P₄: s. acetone; sl. s. water, ether.[2]

STABILITY All thermolabile.

Cephalosporin P₁: Unstable at alkaline pH.

P₃: Less stable than P₁ and P₂; inactivated in air.

P₄: Stable at room temperature.[1, 2]

OTHER REACTIONS Inactivated by an impurity associated with penicillinase; not inactivated by heavy metals or cysteine; some resemblance to helvolic acid; associated with cephalosporin N.

Cephalosporin P₁ analysis: C, 65.8; H, 9.0; C-CH₃, 12.1; acetyl, 16.8; active H, 0.6. Yellow color with tetranitromethane in chloroform; positive Liebermann-Burchard, Salkowski; negative FeCl₃, Tollens, Legal, Rosenheim, Tortelli-Jaffé.[2, 4]

P₂ analysis: C, 65.25; H, 8.5; C-CH₃, 9.4; OCH₃, 5.8; acetyl, 18.8; active H, 0.8.[2]

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. albus, or var. aureus [1, 2].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits Corynebacterium xerose, Mycobacterium phlei, M. pyogenes var. aureus, Streptococcus sp, Bacillus anthracis, B. mesentericus, Sarcina sp, Str. lactis, Pasteurella sp, Salmonella spp. Inactive against Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli.[1] Activity of P₁ almost twice that of helvolic acid against M. pyogenes var. aureus. M. pyogenes var. aureus developed cross resistance to cephalosporin P₁ and helvolic acid.[2]

In vivo. Cephalosporin P₁: Inactive against mouse infections with M. pyogenes var. aureus. Substantial blood concentrations noted in mice following s.c. administration.[3]

TOXICITY Cephalosporin P₁: Toxic at approximately 500 mg/kg, i.v., in mice [3].

72. CEPHALOTHECIN

SOURCE *Cephalothecium* sp [1].

MELTING POINT (°C) 124-126 (d.) [1].

SOLUBILITY s. alcohols, acetone-ether, chloroform; sl. s. water. [1]

STABILITY Thermostable [1].

OTHER REACTIONS No halogen, S, N, P [1].

BIOLOGICAL ACTIVITY Antifungal activity in vitro [1].

PHYTOPATHOLOGY Rice plants treated with the antibiotic resisted infection with *Piricularia oryzae*, the agent of rice blast. The addition of cephalothecin inhibited growth of the fungus and the absorption of ammonium ions from the culture solution, suggesting a relation between these two phenomena.[2]

73. CEREVIOCIDIN

SOURCE *Streptomyces* sp resembling *S. cacaoi* [1].

MOLECULAR FORMULA AND WEIGHT $C_{22}H_{39}N_5O_4$; 420 (Rast); 437 (calc.) [1].

CRYSTAL FORM AND COLOR Colorless needles [1].

MELTING POINT (°C) 249-250 (d.) [1].

UV ABSORPTION MAXIMA None [1].

SOLUBILITY s. methanol; sl. s. water; i. ethanol, acetone, ethyl acetate, ether, chloroform, benzene [1].

OTHER REACTIONS Sublimes at 217-218°, but sublimate is decomposition product; positive Janovsky; negative Tollens, biuret, Fehling, ninhydrin, Sakaguchi, maltol, glucosamine; another component also active only against yeasts is obtained in culture fluids in greater quantity, but only thus far purified as a syrup [1].

QUANTITATIVE DETERMINATION Microbiological: yeasts [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits yeasts ($\mu\text{g/ml}$): *Saccharomyces cerevisiae*, *Sac. fragilis*, *Sac. pastorianus*, *Sac. saké*, *Zygosaccharomyces major*, *Hansenula anomala*, *Torula utilis*, 3; *Schizosaccharomyces pomb*, 25. *Candida albicans*, *Aspergillus niger*, and bacteria (*Micrococcus pyogenes* var. *aureus*, *Escherichia coli*, and *Mycobacterium tuberculosis*) not sensitive to 10 $\mu\text{g/ml}$. [1]

74. CHARTREUSIN

SOURCE *Streptomyces chartreusis*, n. sp [1].

MOLECULAR FORMULA AND WEIGHT $C_{18}H_{18}O_8 \cdot 2H_2O$ (proposed); 357 (Rast); 362.32 (calc.) [1]

CRYSTAL FORM AND COLOR Greenish-yellow crystals. Na salt: golden-colored needles or plates. [1]

MELTING POINT (°C) 180 [1].

SOLUBILITY s. organic solvents [1].

STABILITY Stable at pH 2-10; unstable at pH 2 or 10 with prolonged heating. [1]

OTHER REACTIONS Na salt soluble in water (20 mg/ml) at pH 9.5, but acid precipitates below pH 9 or on exposure to CO_2 ; crystals fluoresce. [1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* phage¹ [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Corynebacterium fascians*, 0.1; *Hemophilus pertussis*, 0.25; *Xanthomonas campestris*, 0.5; *Streptococcus pyogenes*, 1; *Mycobacterium tuberculosis*, 1.7-2.0; *Myco. avium*, 1-2.5; *Bacillus brevis*, *Myco. phlei*, *Myco. ranae*, *Sarcina lutea*, *M. pyogenes* var. *albus*, 2.5; *C. diphtheroides*, *Erysipelothrix rhusiopathiae*, *Myco. smegmatis*, *Neisseria catarrhalis*, 5; *B. cereus*, *B. subtilis*, *Lactobacillus casei*, *M. pyogenes* var. *aureus*, *Str. viridans*, 10; *X. pruni*, 25; *Str. lactis*, *Klebsiella pneumoniae*, 100; *Aerobacter aerogenes*, *Agrobacterium tumefaciens*, *Erwinia carotovora*, *Brucella bronchiseptica*, *Escherichia coli*, *Proteus*

/1/ Fumagillin method.

74. CHARTREUSIN (Concluded)

vulgaris, Pseudomonas spp, Serratia marcescens, Shigella sonnei, Salmonella spp, >100. Nocardia asteroides inhibited by 10 µg/ml. Geotrichum sp, Hormodendrum compactum, Cryptococcus neoformans, Sporotrichum schenckii, and Candida albicans not sensitive to 1000 µg/ml. Active against bacteriophages of Escherichia coli, Bacillus cereus, M. pyogenes var. aureus.[1, 2]

ACUTE TOXICITY Mice tolerated 2500 mg/kg, s.c. LD₅₀ in mice (Na salt), 250 mg/kg, i.v.[1]

75. CHARTREUSIN-LIKE ANTIBIOTIC

SOURCE Streptomyces sp [1].

NATURE Glucoside; weakly acidic.[1]

MOLECULAR FORMULA C₃₂H₃₄O₁₄ [1].

MELTING POINT (°C) 186-187 [1].

UV ABSORPTION MAXIMA 236, 266, 334, 381, 401, 424 mµ [1].

SOLUBILITY Slowly s. in saturated NaHCO₃ solution; more s. in dilute acid than in water.[1]

STABILITY Rapidly inactivated at room temperature [1].

OTHER REACTIONS Yellow-green color with alcoholic FeCl₃ solution; on heating above the melting point, it undergoes decomposition and separates into aglycone needle-like crystals; not reduced by hydrogen in presence of Pt at room temperature and normal pressure; no reaction with ketones; sublimes at about 260°C; negative test for flavonols; acid hydrolysate gives positive Molisch and reduces ammoniacal AgNO₃. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits Gram-positive bacteria, including mycobacteria [1].

76. CHETOMIN
(Chaetomin)

SOURCE Chaetomiium cochlioides [1].

NATURE Probably neutral [2].

MOLECULAR FORMULA AND WEIGHT C₁₆H₁₇O₄N₃S₂ (proposed); 310 (ethylene bromide).[2]

FORM AND COLOR White, non-crystalline powder [2].

MELTING POINT (°C) 215, 218-220 (d.) [1, 2].

OPTICAL ACTIVITY [α]_D²² = +360° [2].

UV ABSORPTION MAXIMUM 287 mµ [2].

SOLUBILITY s. acetone, ethyl acetate, chloroform, benzene, dioxane, pyridine; less s. ether, methanol, ethanol; i. water, petroleum ether.[1]

STABILITY Thermostable; stable to dilute acid but not alkalis.[1]

OTHER REACTIONS Not precipitated by picric acid, HgCl₂; no amino N; positive indole, Hopkins-Cole; negative biuret, Millon; inactivated by oxidizing agents, alkalis, hot acids; forms lead sulfide with sodium plumbite.[1, 2]

QUANTITATIVE DETERMINATION Microbiological: Bacillus subtilis, Micrococcus pyogenes var. aureus [1].

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive bacteria. Inhibits Micrococcus spp, Sarcina lutea, Bacillus spp, including B. subtilis in dilution of 1:30,000-1:200,000. M. pyogenes var. aureus very sensitive, inhibited by 0.002 µg/ml. Mycobacterium tuberculosis sensitive to 1:3000; Myco. phlei, 1:20,000; Phytomonas michiganensis, P. pruni, and P. phaseoli, 1:200,000.[1, 3] No activity against fungi and Gram-negative bacteria [4].
In vivo. Inactive [3].

TOXICITY Low toxicity in animals [2].

/1/ c, 1 chloroform.

77. CHLAMYDOSPORIN

SOURCE *Fusarium* sp [1] .

BIOLOGICAL ACTIVITY In vitro. Active against phytopathogens ($\mu\text{g/ml}$): *Agrobacterium tumefaciens* at 50; *Xanthomonas malvacearum*, 0.8. Active against human and animal pathogens ($\mu\text{g/ml}$): *Bacillus anthracis*, *B. mesentericus*, 0.2; *B. mycoides*, 0.4; *Brucella abortus*, 5.0; *Br. suis*, 0.9; *Micrococcus pyogenes* var. *aureus*, 0.3; *Corynebacterium diphtheriae*, *Sarcina lutea*, *Mycobacterium tuberculosis*, 7.5-10; *Neisseria meningitidis*, *Streptococcus lactis*, 4; *N. gonorrhoeae*, 10; *N. catarrhalis*, *Clostridium septicum*, *Cl. perfringens*, *Cl. sporogenes*, *Str. hemolyticus*, 2.[1]

78. CHLORAMPHENICOL

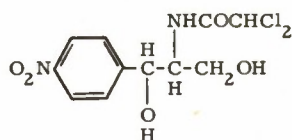
The trademark of Parke, Davis & Company for chloramphenicol is Chloromycetin.

SOURCE *Streptomyces venezuelae* [1] ; by synthesis [99,100] .

NATURE Neutral [1, 4, 5, 8] .

MOLECULAR FORMULA AND WEIGHT $\text{C}_{11}\text{H}_{12}\text{O}_5\text{N}_2\text{Cl}_2$ [3, 4] ; 310 (Rast); 323 (calc.).[4]

STRUCTURE



[4, 5]

CRYSTAL FORM AND COLOR Colorless, elongated plates or fine needles [1, 2, 8] .

MELTING POINT ($^{\circ}\text{C}$) 149.7-150.7 (corr.) [1-4, 8] .

OPTICAL ACTIVITY $[\alpha]_D^{25} = -25.5^{\circ}$ [1, 4, 8] , $+19^{\circ}$ [4] .

UV ABSORPTION MAXIMUM 278 $\text{m}\mu$ [2, 4, 8] .

SOLUBILITY s. propylene glycol, methanol, ethanol, butanol, ethyl acetate, acetone, diethyl ether; sl. s. chloroform, water, alkali; i. acid, benzene, petroleum ether, vegetable oils.[1, 2, 4, 5, 8]

STABILITY Thermostable; alkali labile.[1-3, 8]

OTHER REACTIONS Chlorine non-ionic; negative FeCl_3 , Sakaguchi, Pauly, Molisch, biuret, Benedict; not hydrolyzed by papaine, trypsin, chymotrypsin, pepsin; hydrolyzed by some bacterial enzymes.[2, 3, 6, 8]

QUANTITATIVE DETERMINATION Microbiological: *Shigella* spp, *Bacillus subtilis* [2, 3, 7, 8] . Colorimetric [9] .

BIOLOGICAL ACTIVITY A broad spectrum antibiotic active against Gram-positive and Gram-negative bacteria, rickettsiae and larger viruses; no activity gainst fungi. In vitro. In general, most strains of the following bacteria are sensitive to 0.06-6.0 $\mu\text{g/ml}$: *Aerobacter aerogenes*, *Alcaligenes faecalis*, *B. subtilis*, *B. mycoides*, *B. anthracis*, *Brucella abortus*, *Br. bronchiseptica*, *Br. suis*, *Br. melitensis*, *Corynebacterium diphtheriae*, *C. pyogenes*, *Diplococcus pneumoniae*, *Escherichia coli*, *Gaffkya tetragena*, *Hemophilus influenzae*, *H. pertussis*, *Klebsiella pneumoniae*, *Micrococcus pyogenes* var. *aureus*, *Mycobacterium leprae*, *Neisseria catarrhalis*, *N. meningitidis*, *N. gonorrhoeae*, *Pasteurella multocida*, *Salmonella typhosa*, *Salmonella* spp, *Sh. dysenteriae*, *Shigella* spp, *Streptococcus pyogenes*, *Stretococcus* spp, *Vibrio comma*. Most strains of the following are generally less sensitive or resistant, 10-25 $\mu\text{g/ml}$ or more: *Proteus vulgaris*, *Proteus* spp, *Clostridium* spp, *Pseudomonas aeruginosa*, *Malleomyces mallei*, *Myc. tuberculosis*, *Mycobacterium* spp, pleuropneumonia-like organisms. Inhibition ($\mu\text{g/ml}$) of *Actinomyces bovis*, 5; *Nocardia asteroides*, 20. Spirochetes and protozoa: *Borrelia recurrentis*, 2.5-10; *B. novyi*, 10-50; *Entamoeba histolytica*, 125-1500; *Trichomonas foetus*, 2000.[10-18] Concentrations of 2 mg/ml had no effect on the virus of herpes simplex [69] . Inhibited *H. aegyptius* (a cause of conjunctivitis in man) at 0.2-1.6 $\mu\text{g/ml}$; also active against this agent in chick embryo [70] .

In vivo. S. c. treatment protected mice infected with *K. pneumoniae* and *Sh. paradysenteriae*; no protection against *D. pneumoniae*, *Str. pyogenes* and *Str. viridans* except slight activity with higher doses of >80 mg/kg . [19, 20] Relatively low doses showed high activity in mice infected with *Past. pestis* and *Past. multocida*; no activity displayed against infections with *B. anthracis*, *Listeria monocytogenes* and *Erysipelothrix rhusiopathiae*. [28, 31] High protection in chicks treated with 30 mg/kg/da i.p. doses against *Salmonella gallinarum* [31] , but relatively low activity in mice infected with *S. typhosa* [32] . Good protection against *Borrelia novyi* and *V. comma* following i.p. or drug-diet

/1/ Ethyl acetate. /2/ Ethanol.

treatment [21, 22]. A transient suppressive action against *Entamoeba histolytica* noted in dogs, but larger doses of 700-1000 mg/kg/da in the diet were ineffective in cecal amebiasis in rats [23]. Prolonged survival time in mouse infections with *Toxoplasma gondii* when 1-2% was incorporated in the diet [24]. Little or no effect in experimental animals infected with *Myc. tuberculosis*, *Leptospira icterohemorrhagiae*, and a limited protection against *Treponema pallidum* in rabbits [10, 19, 25, 33]. Active against *Plasmodium berghei* in mice, *P. gallinaceum* and *Borrelia anserina* in chicks when relatively large doses were administered [26, 27]. In mice or in embryonated eggs, antibiotic was highly active against rickettsiae of epidemic, murine and scrub typhus, rickettsialpox, Rocky Mt. spotted fever, Q fever, and against the viruses of lymphogranuloma venereum and psittacosis. The following viruses were not affected: vaccinia, variola, St. Louis encephalitis, Japanese encephalitis, rabies, mumps, poliomyelitis, influenza A and B, lymphocytic choriomeningitis, eastern and western equine encephalitis, distemper, fowl laryngotracheitis, Newcastle disease and Theiler's intestinal virus.[10, 19, 29] Showed an adverse effect on experimental pinworm infestation; daily oral doses of 500 mg/kg in mice increased the worm burden approximately 2-fold [38]. Daily i.p. doses of 500 mg/kg had little or no inhibitory effect on several ascites and solid tumors in mice [78, 79]. An antitumor effect was observed when 3% chloramphenicol was added to sarcoma I or sarcoma 180 suspension immediately before inoculation (a dose of 4.5 mg of antibiotic per animal), or when a 30-mg pellet was implanted subcutaneously one day after inoculation of the tumor into mice via the same route; under these conditions the growth rate of tumors was reduced and survival time of animals was prolonged.[80] Daily doses of 0.4-1 mg/ml in drinking water effectively controlled experimental air-borne mouse pneumonitis virus infections in mice [71].

CLINICAL This broad spectrum antibiotic has established clinical usefulness in a wide variety of infections caused by susceptible microorganisms, and is especially valuable against Gram-negative infections, and the rickettsioses. Initial oral doses of 50-75 mg/kg, followed by 0.25 g every 2-3 hours, are usually recommended with larger doses (0.5 g) in severe infections.[30] Oral therapy with doses of 25-150 mg/kg/da, or parenteral administration in variable dosages, gave favorable results in typhoid fever, bacillary dysentery, cholera, gonorrhoea, chancroid, lymphogranuloma venereum, granuloma inguinale, urinary and intestinal tract infections caused by susceptible organisms, various surgical infections, bacterial pneumonia, epidemic and scrub typhus, Rocky Mt. spotted fever, Q fever, psittacosis, brucellosis, tularemia [34-37, 49]. Favorable results have also been reported in primary atypical pneumonia [39], syphilis [40], relapsing fever [41], Carrion's disease (bartonellosis) [42], non-specific urethritis [43], smallpox [44], yaws and tropical ulcer [56]. Oral, plus i.v., medication has been beneficial in meningitis caused by *N. meningitidis*, *H. influenzae* and *D. pneumoniae* [45]. Total oral doses of 2.5-24.75 g over periods of 2-7 days were effective in the treatment of cases of anthrax infection in man [84]. Oral therapy with this or other broad spectrum antibiotics did not influence the course of herpes simplex, plantar warts, lichen planus, dermatitis herpetiformis, or discoid eczema [73].

Topical use of 0.5-1% in ointment base was effective in the treatment of trachoma [72]. Topical therapy has given good clinical response in ocular infections caused by susceptible microorganisms [34]. In experimental chancroid induced in human volunteers by intradermal injection of cultures of *H. ducreyi*, the topical application of 1% chloramphenicol rapidly sterilized lesions which had developed and was also effective in prophylaxis of these lesions, in contrast to penicillin and chlortetracycline which were ineffective [82]. Valuable in prophylaxis and therapy of septic peritonitis and in prevention of infections which may develop in other parts of the body, e.g., complications of colon surgery [96]. Like other antibiotics, chloramphenicol was of no value in the treatment of Reiter's syndrome [98]. The antibiotic has been injected intrathecally with good results in cases of staphylococcal meningitis resistant to penicillin and streptomycin [97]. Despite a number of favorable reports, the direct value of this and other broad-spectrum antibiotics in pertussis, infectious mononucleosis, herpes zoster, and leptospirosis has been questioned [46]. Chloramphenicol is considered the antibiotic of choice in typhoid fever [30, 35, 47].

VETERINARY Intramuscular therapy with 1 g/da for 2-3 days in calves was beneficial in control of shipping fever (hemorrhagic septicemia) [92]. Oral doses of 500 mg daily for 4 days prevented "scours complex" associated with *Salmonella bredenyi* infection in calves [93]. Intramuscular doses of 25-35 mg/kg daily for 3 days successfully controlled virus pneumonia in pigs [94]. Useful in a wide variety of infections, e.g., diarrhea of calves, colts, and lambs, and conjunctivitis, keratitis, and gastroenteritis in dogs. Variable results in distemper complex [48]. Preliminary trial with 0.25-0.5% in feed suggests value in infectious sinusitis of turkeys [50]. 1-2 g/lb of feed gave excellent protection against artificially-induced fowl typhoid (*S. gallinarum*) in chickens [74]. 10% solutions in propylene glycol or methanol highly effective when topically used in foot rot in sheep [75]. Preliminary trials indicate oral medication of value in controlling contagious pleuropneumonia in goats [76].

PHYTOPATHOLOGY Levels of 4-125 µg/ml inhibited development of crown gall disease in tomato plants induced with *Agrobacterium tumefaciens* [89]. Concentrations of 25-50 µg/ml increased resistance of wheat seedlings to infection with *Xanthomonas translucens* [90].

TISSUE CULTURE Proliferation of fibroblasts and epithelial cells retarded by concentrations of 10 µg/ml; completely inhibited by 1000 µg/ml. [57] Growth of skin tissue inhibited by 550-830 µg/ml, spleen tissue by 1665-3330 µg/ml [58].

ACUTE TOXICITY LD₅₀ in mice, 245 mg/kg, i.v.; 1320 mg/kg, i.p.; 2640 mg/kg, oral. LD₅₀ in rats, 171-278 mg/kg, i.v.; in rabbits, 117 mg/kg, i.v. LD₅₀ in dogs, 150 mg/kg, i.v.; >101 mg/kg, i.m.; >300 mg/kg, oral. [5, 19]

78. CHLORAMPHENICOL (Concluded)

In vitro. Concentrations of $1.0-6.1 \times 10^{-3}$ molar significantly inhibited respiration of human leukocytes; similar concentrations of penicillin, streptomycin, and the tetracycline antibiotics, had little or no effect on oxygen uptake.[81]

CHRONIC TOXICITY Mice tolerated for 2 weeks 385 mg/kg/da in diet, 100 mg/kg, s.c., and 250 mg/kg, i.p. Dogs tolerated daily oral doses of >200 mg/kg for over 4 months, or daily i.v. doses of 25-50 mg/kg. No cumulative toxic effect observed on hemopoiesis, liver and kidney function or visceral tissues.[5]

In man, oral doses of 1-2 g/da for 10 days or more were well tolerated. Side reactions, e.g., nausea, headache, skin eruptions and enteric symptoms, have been relatively rare and relatively minor.[51-53] In rare instances, certain disorders of the hemopoietic system, including aplastic anemia, have been ascribed to medication with this antibiotic, particularly after prolonged dosage [54, 55]. An occasional side effect, also occurring with other orally administered antibiotics, is stomatitis; secondary infections with yeast-like organisms have occurred, particularly in the peri-anal region and on the mucous surfaces of the vagina and lower rectum.[30] Continued topical use of dermatological preparations containing 1% of the antibiotic, is associated with a relatively low index of sensitization in contrast to penicillin, streptomycin, and the sulfonamide drugs [83].

ABSORPTION AND EXCRETION Readily absorbed following parenteral and oral administration and found in blood, urine, bile, and cerebrospinal fluid 2 hours after dosage in animals; disappeared within 4-6 hours after i.v., and 12-16 hours after oral, administration. S.c. doses of 100 mg/kg given twice daily produced blood concentrations of 11 μ g/ml and 60 μ g/ml urine levels in mice. Urinary excretion persisted for over a 24-hour period, with a recovery of 3.5-8.7% of the total dosage.[5, 19] In man, initial oral doses of 2.0 g, followed by 0.5 g 8 hours later, produced blood levels of 9-13 μ g/ml in 2 hours, levelling off to 5 μ g/ml at 8 hours, with subtherapeutic concentrations thereafter. About 10% of the oral dose of the antibiotic was recovered as such in the urine during the first 24 hours; the bulk of the antibiotic is excreted as inactive nitro compounds.[59, 60] Following oral administration, it diffuses into the spinal fluid and also through the placenta. Chloramphenicol is absorbed into the circulation following rectal administration in infants.[61]

RESISTANCE Resistant variants do not develop readily. Some Gram-negative bacteria developed 2 to 50-fold resistance after 7-12 subcultures in antibiotic-containing media. Thus far, no resistant strains of rickettsiae have been developed.[10, 29] Relatively few strains of bacteria show developed cross resistance between chloramphenicol and other antibiotics [62].

MODE OF ACTION Bacteriostatic levels (1-5 μ g/ml) inhibited protein synthesis in *M. pyogenes* var. aureus, but fermentation, respiration, free glutamic acid accumulation, and nucleic acid synthesis were depressed only by much higher concentrations of the antibiotic [85]. Growth inhibitory activity of 1 μ g/ml concentrations against *Escherichia coli* was completely reversed by addition of 500 μ g/ml of phenylalanine to culture medium, but this reversal did not occur with higher concentrations (2 μ g/ml) of the antibiotic. Similar results were obtained with tryptophan and tyrosine.[86] Several species of bacteria which are sensitive to the antibiotic reduce the nitro group of chloramphenicol to the corresponding arylamine which is devoid of antimicrobial activity [87]. The antibiotic inhibits oxidation of succinate, fumarate, malate, and α -ketoglutarate by intact and crushed cells of *Pseudomonas fluorescens*, but not of oxalacetate, pyruvate, lactate, aspartate, and citrate [95]. Inhibits bacterial esterases of *E. coli* [65]. Has been suggested that a mode of action may be that of interference with bacterial synthesis of indole from anthranilic acid [66]. Addition of antibiotic to growing cultures of *E. coli* abruptly interrupts synthesis of proteins, but not that of nucleic acids [67]. When fed to rats, chloramphenicol decreases xanthine oxidase of liver, but has no effect on intestinal xanthine oxidase [68].

ANIMAL NUTRITION Of slight or questionable value in the growth promotion of pigs [63]. Little or no effect on growth of chicks as compared with marked effect of other antibiotics [64].

MISCELLANEOUS Following exposure to 2 mg/ml of antibiotic, the kappa particles were eliminated from the cytoplasm of "killer" strains of *Paramecium aurelia* [77]. Relatively high levels of chloramphenicol (300-500 mg per 14 lb of wheat) and certain other antibiotics were lethal to several varieties of coleopterous stored-grain insects within 30-60 days [88]. Like streptomycin and penicillic acid, the antibiotic inhibits carotenoid synthesis in the non-photosynthetic organism, *Phycomyces blakesleeanus* [91].

79. CHLORORAPHIN

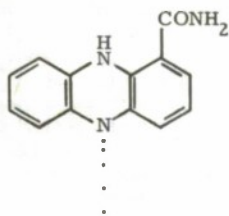
SOURCE *Chromobacterium* sp [1].

NATURE Green pigment [2].

MOLECULAR FORMULA $C_{28}H_{20}O_2N_6$ or $C_{13}H_{10}ON_3$ [1-3].

79. CHLORORAPHIN (Concluded)

STRUCTURE



Probable [3].

CRYSTAL COLOR Green crystals [3].

MELTING POINT (°C) 225-230 (d.) [2].

SOLUBILITY sl. s. alcohol; i. chloroform, benzene, petroleum ether, aqueous acids and alkalis.[3]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits hemolytic streptococcus at 100 µg/ml. Inactive against *Micrococcus pyogenes* var. *aureus* and Gram-negative bacteria (>100 µg/ml).[1]

80. CHLORTETRACYCLINE

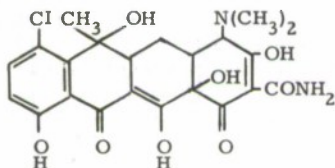
The trademark of Lederle Laboratories Division, American Cyanamid Company, for chlortetracycline is Aureomycin.

SOURCE *Streptomyces aureofaciens*, n. sp [9].

NATURE Amphoteric [1, 2].

MOLECULAR FORMULA $C_{22}H_{23}ClN_2O_8$ [4, 176].

STRUCTURE



[4, 176]

CRYSTAL FORM AND COLOR Base: acicular to bladed, small. HCl: rhomboid; clear vitreous lemon-yellow.[2]

MELTING POINT (°C) Base: 168-169 (uncorr.) [1]. HCl: d. above 210 [2].

OPTICAL ACTIVITY Base: $[\alpha]_D^{23} = -274.9^{01}$. HCl: $[\alpha]_D^{23} = -295.9^{01}$, -227.9^{02} . [1, 2]UV ABSORPTION MAXIMA HCl: 365, 264, 226 $\mu\mu^3$; 370, 265, 251, 229 $\mu\mu^4$; 276, 248, 240, 223 $\mu\mu^5$. [2]

SOLUBILITY Base: s. dilute acids, alkali, "Cellosolve," "Carbitol," dioxane, pyridine; less s. methanol, ethanol, butanol, acetone, ethyl acetate, benzene; i. ether, petroleum ether. HCl: s. water, methanol; sl. s. ethanol.[1, 2]

STABILITY Thermolabile in strong acids, alkalis; stable at pH 2.5, unstable at pH 7.0 and above at 25°C.[3]

OTHER REACTIONS In alcoholic $FeCl_3$ greenish-brown color by reflected light, reddish color by transmitted light; precipitates with picric acid, Reinecke's acid, ammonium molybdate; UV shifts in acids, alkali; fluoresces in basic solution. Infrared bands of free base (recip. cm): 3420, 3050, 1643, 1609, 1580, 1523, 1302, 1231, 1209, 1121, 1080, 1050, 969, 943, 867, 844, 825, 805, 794, 788, 733, 713.[1, 2, 7, 8]QUANTITATIVE DETERMINATION Microbiological: Especially *Micrococcus pyogenes* var. *aureus* [2, 3]. Fluorometric [8]. Colorimetric [5, 6, 8]. UV [7].BIOLOGICAL ACTIVITY Active against Gram-positive and Gram-negative bacteria, rickettsiae and larger viruses, and certain protozoa. No activity against fungi. *In vitro*. Most strains of the following bacteria are sensitive to 0.002-7.5 µg/ml: *Actinomyces bovis*, *Alcaligenes* spp, *Bacillus anthracis*, *B. cereus*, *B. subtilis*, *Brucella abortus*, *Br. bronchiseptica*, *Br. melitensis*, *Br. suis*, *Clostridium botulinum*, *Cl. fesceri*, *Cl. histolyticum*, *Cl. novyi*, *Cl. perfringens*, *Cl. septicum*, *Cl. sordellii*, *Cl. tetani*, *Corynebacterium diphtheriae*, *C. renale*, *C. pyogenes*, *C. xerosis*, *Diplococcus pneumoniae*, *Erysipelothrix rhusiopathiae*, *Hemophilus ducreyi*, *H. influenzae*, *H. pertussis*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *M. pyogenes* var. *aureus*, *Mycobacterium tuberculosis*, *Myc. leprae*, *Neisseria catarrhalis*, *N. gonorrhoeae*, *N. meningitidis*, *Nocardia asteroides*, *Paracolonobacterium* spp./1/ Methanol. /2/ Water. /3/ 0.1 M phosphoric acid. /4/ 0.1 M KH_2PO_4 pH 4.3. /5/ 0.1 M K_2HPO_4 pH 8.9.

Pasteurella multocida, *Past. hemolytica*, *Past. pestis*, *Past. tularensis*, pleuropneumonia-like organisms, *Salmonella typhosa*, *S. paratyphi*, *S. enteritidis*, *S. schottmuelleri*, *Salmonella* spp, *Shigella dysenteriae*, *Shigella* spp, *Streptococcus pyogenes*, *Str. agalactiae*, *Str. dysgalactiae*, *Str. faecalis*, *Str. viridans*, *Vibrio comma*, *V. foetus*. Inhibited *Hemophilus aegyptius* (causes a conjunctivitis in man) at 0.4-3.2 µg/ml; also active against the same agent in ovo [125]. Less sensitive (10-25 µg/ml), or resistant (>50 µg/ml): *Aerobacter aerogenes*, *Escherichia coli*, *Mycobacterium smegmatis*, *Proteus vulgaris*, *Proteus* spp, *Pseudomonas aeruginosa*. Spirochetes and protozoa (µg/ml): *Borrelia recurrentis*, 1-25; *Trichomonas foetus*, 25-100; *Trypanosoma cruzi*, >1000; *Entamoeba histolytica*, 2->200. [10-28] Rous sarcoma virus inactivated by exposure to antibiotic, as evidenced by failure to develop tumors in chickens [27].

In vivo. In general, there was good protection in mice with parenteral doses of 5-30 mg/kg, or with higher oral doses in infections with *Str. pyogenes*, *Salmonella typhosa*, *Ery. rhusiopathiae*, *Past. multocida*, *D. pneumoniae*, *B. anthracis*, *Listeria monocytogenes*, *H. influenzae* B, *Proteus vulgaris*, *Escherichia coli*, *V. comma*, *K. pneumoniae*, and several species of clostridia [29-36, 45]. No effect on *Mycobacterium tuberculosis* in guinea pigs and mice [36, 67]. High activity against fowl cholera (*Past. multocida*) and fowl typhoid (*S. gallinarum*) in chicks [36, 38]. Survival time was prolonged in experimental tularemia in mice [39]. Active in low doses in experimental leptospirosis in hamsters and guinea pigs [40], and in experimental plague (*Past. pestis*) in mice and monkeys [41]. Successful control of experimental toxoplasmosis in mice, but did not prevent carrier state [42]. Active against *Bartonella muris* infection in rats [43], and was the most effective of several antibiotics tested against experimental toxoplasmosis in mice [44]. Three parenteral injections of 30 mg/kg effective against experimental rat-bite fever induced with *Spirillum minus* in mice and guinea pigs [130]. Good protection in mice against *Borrelia duttoni* and *B. novyi* [46]; also against rabbit syphilis, but less active on a weight basis than penicillin [47]. In experimental relapsing fever in rats treated with heavy doses of the antibiotic, the organism (*B. duttoni*) was still present in the central nervous system 29 days later [131]. Suppressive effect on *Brucella melitensis* infection in mice [48], and on *Br. abortus* in guinea pigs [49]. Good protection elicited against *Plasmodium gallinaceum* in chicks treated with high oral doses of 150-300 mg/kg/da [50]. Oral therapy with 100 mg/kg afforded high protection, but failed to be curative in infant rabbits infected intra-intestinally with *V. comma* [139]. Active in embryonated eggs against pleuropneumonia-like organisms isolated from chronic respiratory disease of poultry [134]. Daily i.p. doses of 50 mg/kg in mice and rats had no inhibitory effect on 21 varieties of transplantable solid tumors and 3 ascites tumors [132, 133].

S.c. doses of 7-70 mg/kg/da gave 100% protection in mice infected with the viruses of psittacosis and lymphogranuloma venereum and with the rickettsiae of murine typhus, scrub typhus and rickettsialpox. Daily s.c. injections of 5-6 mg/kg gave high protection in guinea pigs against the rickettsiae of epidemic typhus, Q fever, and Rocky Mt. spotted fever. In embryonated eggs, single doses of 1 mg highly active against the same agents and also against the rickettsiae of boutonniere fever, South African tick-bite fever and North Queensland tick typhus. The viruses of mouse pneumonitis, SF strain of human pneumonitis, feline pneumonitis and meningopneumonitis were also sensitive in ovo. [51, 59] Excellent protection in mice against feline pneumonitis [53] and gray lung virus infection [54]. Doses of 0.1-1.0 mg/ml in drinking water effectively controlled air-borne mouse pneumonitis virus infections in mice [126]. Completely inhibited development of pulmonary consolidation in cotton rats infected with Eaton's atypical pneumonia virus following daily i.p. doses of 14 mg/kg; the same strain of this virus was also inhibited in ovo. [55] Cleared lice of *Rickettsia prowazeki* [59]. No activity against the viruses of influenza B, canine distemper, rabies, Newcastle disease, Venezuelan equine encephalitis, poliomyelitis (MEF-1 strain), mumps, herpes simplex and foot and mouth disease [51, 56, 58]. Oral medication with 500 mg/kg/da suppressed pinworms (*Aspicularis tetraptera*) in mice [60]. I.p. doses of 100 mg/kg had an adverse effect on *Candida albicans*, enhancing infections in mice [52, 64].

CLINICAL. This broad spectrum antibiotic has established value in a wide variety of Gram-positive and Gram-negative bacterial infections, rickettsioses and infections with the larger viruses. The minimum daily oral dose recommended for adults is 1 g divided into 250 mg doses; children should receive proportionately less, e.g., a 44-lb (approximately 20 kg) child may be given 50 mg 4 or 5 times daily. Total oral dosages of 4.5-20.5 g, over periods of 1-8 days, effectively controlled anthrax infection in man [135]. In seven cases of tick-borne relapsing fever in East Africa treated with 4 oral doses of 500 mg in 2 days, there was prompt clinical response, rapid disappearance of parasitemia, and no recorded relapse [136]. In children with cystic fibrosis of the pancreas, associated pulmonary infections were controlled by oral chlortetracycline, and there was a marked improvement in the nutritional status [165]. Oral therapy with this and other broad spectrum antibiotics did not influence the course of herpes simplex, plantar warts, lichen planus, pityriasis, dermatitis herpetiformis, or discoid eczema [127].

For i.v. use, buffered antibiotic is usually administered in daily doses of 20-25 mg/kg divided into 2-4 injections administered at intervals of 12, 8, or 6 hours. These regimens, and oral therapy, have given good clinical responses in bacillary infections caused by *E. coli*, *Aerobacter aerogenes*, *K. pneumoniae*, *Shigella* spp, *N. gonorrhoeae* (including acute gonorrhoeal ophthalmia); also in chancroid, granuloma inguinale, brucellosis, tularemia, streptococcal and *D. pneumoniae* infections, and subacute bacterial endocarditis caused by Gram-positive and Gram-negative organisms. Clinical efficacy has been established in rickettsial infections and diseases induced by certain of the larger viruses: Rocky Mt. spotted fever, epidemic typhus, murine typhus, scrub typhus, Q fever, Brill's disease, lymphogranuloma venereum and psittacosis. It is useful in acute extra-intestinal amebic infection, including amebic hepatitis and (with surgery) amebic abscess. It is also effective in urinary tract infections caused by susceptible Gram-positive and Gram-negative organisms, and in acute bronchitis, anthrax and otitis media. The antibiotic has found wide usage in the prophylaxis and treatment of surgical infections. Topical therapy is effective in ocular infections and dermatoses [10, 63, 78-81].

In experimental chancroid in human volunteers, induced with intradermal injection of cultures of *H. ducreyi*, topical application of 3% calcium chlortetracycline ointment, or penicillin, 24 hours later had no effect in preventing development of infected lesions, in contrast to erythromycin and chloramphenicol which were effective [137]. In preliminary clinical trials the application of the antibiotic (3% in ointment base) to the axilla was effective in controlling the odor from apocrine sweat [128].

The value of this antibiotic in primary atypical pneumonia is established [82]. Chlortetracycline and oxytetracycline are the antibiotics of choice in psittacosis [83] and for topical use in trachoma [84]. Good clinical responses have been reported in non-specific urethritis [85], cervicofacial actinomycosis [86], and in infections with *Balantidium coli* [89]. Total oral doses of 70 g, over a period of 12 days, appeared as effective as penicillin in the secondary stage of syphilis [87]; excellent results have been noted in yaws and tropical ulcer [62, 88]. Local therapy is of value in vaginitis caused by *Trichomonas vaginalis* [90]. There is little or no evidence that chlortetracycline (and other antibiotics are of direct value in the therapy of measles, mumps, common cold, acute viral hepatitis, infectious mononucleosis, varicella, smallpox, viral encephalitides, lymphocytic choriomeningitis and influenza. Despite a number of favorable reports, the direct activity in pertussis, herpes zoster and leptospirosis is not well established. [78, 81, 91] The antibiotic is of little or no value in paratyphoid fever and certain other salmonellosis, or in infections caused by *Proteus* or *Pseudomonas* spp [78]. Chlortetracycline, like other antibiotics, was of no value in the treatment of Reiter's syndrome [164].

VETERINARY Of value in a wide variety of infections caused by susceptible organisms, including bovine infections (calf scours, pneumonia, foot rot, vibriosis, chronic bloat, heartwater, mastitis from micrococci or *Str. agalactiae*), equine infections (strangles, septicemia), and swine infections (dysentery, salmonellosis, baby pig diarrhea and pneumonia). In experimental anaplasmosis in splenectomized calves, the number of *Anaplasma marginale* in red cells was depressed following therapy [140]. Incorporation of 50-200 g per ton of feed resulted in increased weight gains and reduced mortality in swine affected with atrophic rhinitis, a disease of undetermined etiology [144]. In smaller animals successful treatment has been described in leptospirosis, coccidiosis, gastrointestinal infection, canine rickettsiosis, feline distemper, fowl typhoid, and topically in the therapy of skin, eye and ear infections [92-99]. Medication with 1 g per gallon drinking water controlled an epidemic of *Erysipelothrix rhusiopathiae* infection in mink [143]. A field outbreak of chronic respiratory disease in poultry was successfully reduced by therapeutic doses of 400 ppm in the diet for 14 days, followed by 100 ppm for 8 weeks [141]. According to another report, the use of 200 g per ton of feed failed to alter markedly the course of this disease (associated with pleuropneumonia-like organisms) in chickens [142]. Supplementation of diet with 36-100 g per ton of feed, or use of 250 ppm in drinking water, controlled outbreaks of blue comb disease in fowls ("pullet disease," avian monocytosis), a disease of undetermined cause [145, 163]. For systemic infections, the antibiotic is usually administered i.v. in daily doses of approximately 5 mg/lb of body weight (11 mg/kg), or as the initial dose with 2.5 mg/lb thereafter, or orally in initial doses of 25 mg/lb followed by 12.5 mg/lb every 12 hours. In mastitis, intramammary infusion of ointment has been used, containing 100-400 mg in 7 g ointment base, and for topical use in small animals 25 mg antibiotic per g of ointment base. [92, 94]

PHYTOPATHOLOGY Concentrations up to 115 µg/ml were non-toxic to tomato plants [157]. Highly effective in control of crown gall tumor of tomato and other plants in concentrations of 10-20 µg/ml [114, 115]. Effective in other bacterial diseases of plants, e.g., black rot of crucifers [124]. Accelerated photosynthesis and induced an abnormal increase in sucrose in the alga *Scenedesmus* [120].

ACUTE TOXICITY LD₅₀ in mice, 134 mg/kg, i.v.; approximately 3500 mg/kg, s.c. LD₀, >200 mg/kg, i.p.; 1500 mg/kg, orally. LD₅₀ in rats, 118 mg/kg, i.v.; LD₀, 200 mg/kg, i.p.; 3000 mg/kg, oral. Dogs, rabbits and guinea pigs tolerated i.v. and oral doses of 50 mg/kg. [31, 61]

In vitro. Proliferation of epithelial cells and fibroblasts retarded in tissue cultures containing 10 µg/ml; complete inhibition with 1000 µg/ml [67]. Using roller tube method, concentrations as high as 2500 µg/ml were required partially to inhibit human skin transplant. in tissue cultures [146]. Outgrowths of skin tissue inhibited at 830-1250 µg/ml; spleen tissue not affected by highest test level of 5000 µg/ml [68]. High concentrations (1000 µg/ml) inhibited phagocytosis of *M. pyogenes* var. *albus* by polynuclear leukocytes [69]. In high concentrations antibiotic was non-toxic to human spermatozoa [70].

CHRONIC TOXICITY Dogs tolerated multiple i.v. doses of 20 mg/kg; daily oral doses of 100-200 mg/kg for 12 weeks were well tolerated by mice, rats, and dogs; repeated i.m. or s.c. doses of 20-50 mg/kg non-toxic to rabbits, rats, and dogs. [31, 61]

In man, daily oral doses of 15-30 mg/kg are usually well tolerated although nausea, vomiting, and diarrhea were noted in some patients, especially following doses of >500 mg [63]. An occasional side effect (also occurring with other orally administered antibiotics) is stomatitis; secondary infections with yeast-like organisms have occurred, particularly in the peri-anal region and on the mucous membrane of the vagina and lower rectum. Allergic reactions after topical use and other side effects have occasionally been reported [65, 66, 77]. Continued topical use of dermatological preparations containing 3% chlortetracycline is associated with a relatively low index of sensitization, in contrast to penicillin, streptomycin, and the sulfonamides [138]. Side reactions were few in a group of 300 children receiving continuous oral therapy of 10-20 mg/kg/da over prolonged periods of 1-5 years [165].

RESISTANCE Resistant variants of bacteria did not develop readily in vitro; resistance increased in some Gram-negative and Gram-positive organisms following 14-60 transfers in antibiotic-containing media. [29, 100] A con-

siderable number of resistant strains of *M. pyogenes* var. *aureus* have emerged; in clinical experience this has not been a problem with other bacteria, e.g., streptococci, *D. pneumoniae*, *N. meningitidis* and *N. gonorrhoeae*. Organisms developing resistance to chlortetracycline generally show cross resistance with the other tetracycline antibiotics.[23,101,102] Occasional strains of *Str. pyogenes* have developed resistance to the tetracycline antibiotics in burned patients treated with oral chlortetracycline. These resistant forms were atypical in that they lost the capacity to propagate under aerobic conditions, except in media containing concentrated (4%) agar, and required anaerobiosis.[147]

ABSORPTION AND EXCRETION Readily absorbed following oral or parenteral administration, with good distribution in tissues and body fluids. In rabbits and dogs, an i.m. dose of 20-40 mg/kg produced serum levels of 0.3-1.25 µg/ml in 15-30 minutes. Three i.v. doses of 20 mg/kg at 2-hour intervals in dogs produced serum concentrations of 40 µg/ml and cerebrospinal fluid levels of 0.8 µg/ml within 2 hours, with rapid excretion in the urine during the first 2 hours.[61] In mice, a single i.m. dose of 150 mg/kg produced prolonged blood levels of 1 µg in 1-4 hours, leveling to 0.2 µg for as long as 72 hours; oral doses of 250 mg/kg gave a peak of 2.5-3.0 µg in 1-4 hours, with no detectable blood concentrations at 24 hours.[71] Serum levels in rats after oral administration were markedly increased (as high as 10-fold) by simultaneous administration of citric acid, malic acid, tartaric acid [72], but this increase was not observed in man [73].

In man, following a single oral dose of 500 mg, serum levels of 0.7-1.1 µg/ml appeared in 3-6 hours, declining to 0.2 µg in 12 hours, with detectable quantities (0.07 µg) in 24 hours. After doses of 0.5-1.0 g every 6-8 hours, serum concentrations of 2-6 µg/ml are noted with urine levels as high as 260 µg/ml. The antibiotic readily passes into the peritoneal fluid, cerebrospinal fluid, bile and milk and crosses the placental barrier.[63,74,75] Was detectable in significant amount (0.2-0.5 µg) in human brain tissue following oral or i.v. medication administered prior to prefrontal lobotomy [76].

MODE OF ACTION Action primarily bacteriostatic; very high concentrations required for bactericidal activity.[29] Acts primarily on actively multiplying bacteria; electron microscopy reveals marked morphological changes in these cells, with little or no effect on fully grown organisms.[107] Concentrations of 150-200 µg blocked aerobic phosphorylation in mitochondria of tissue cells without interfering with respiration; in this respect the antibiotic resembled dinitrophenol and gramicidin.[103] In the absence of citrate, respiration of liver homogenates was suppressed; the antibiotic appears to block some part of the Krebs cycle.[104] Mn⁺⁺ reverses antibiotic inhibition of the bacterial cell-free nitroreductase [105]. Concentrations of 100-300 µg/ml inhibit oxidation of glutamate and thus the respiration of murine and epidemic typhus rickettsiae in vitro [106]. Riboflavin reversed, in vitro, antibacterial activity of this antibiotic against *E. coli* [113]. Inhibition of oxidative phosphorylation in rat liver mitochondria occurred in the presence of magnesium, phosphate, and adenosinetriphosphate; addition of magnesium ion in higher concentrations caused reversal of this inhibition [148]. Bacteriostatic concentrations interfere with protein synthesis in bacteria [149]. Low levels inhibited synthesis of both pentose and desoxyribose nucleic acids in *Lactobacillus casei*; addition of folic acid and higher concentrations of vitamin B₁₂ reversed this effect.[150] The hydroxylation of aniline to p-aminophenol by resting cells of mycobacteria was inhibited by small amounts of the antibiotic; this inhibition was partially reversed by a metabolite of p-aminobenzoic acid which appeared to function as a cofactor or cosubstrate in the hydroxylation reaction.[151] Very low concentrations of the antibiotic (1.0 x 10⁻⁶ molar) prevented the production of streptolysin S by resting cells of *Str. pyogenes*. Much higher concentrations of other antibiotics (penicillin, streptomycin, chloramphenicol) were required to inhibit development of this hemolysin. [152] Chlortetracycline (and penicillin) inhibited in vitro the deaminases of the intestinal microflora and prevented liberation of ammonia [153].

ANIMAL NUTRITION Wide usage as a nutritional supplement for the growth stimulation of animals; generally low levels of approximately 9-20 g are incorporated in a ton of feed. Good growth responses in swine, young calves, lambs, poultry and experimental animals (rats, mice, rabbits and dogs, but not in guinea pigs which poorly tolerate this antibiotic).[108-112] An improvement in the growth curve is not observed in ruminants such as cattle; some observers have reported that incorporation of antibiotics at the usual levels in diets of these animals has a deleterious effect on the weight curve. This effect may be related to alterations in the rumen microflora.[108,170,171] Supplemental feeding of chlortetracycline enhanced growth of rats which had been made chronically diabetic with alloxan [154]. The response of rachitic rats to graded doses of vitamin D, as measured by the line test, was increased by adding the antibiotic to the rachitogenic diet [155]. When fed at levels ordinarily recommended for other species of animals, no growth improvement was observed in young rabbits fed a pelleted natural ration [156]. The experimental massive liver necrosis produced in rats fed on a necrogenic diet was prevented by addition of chlortetracycline to the diet. This inhibitory effect was attributed to elimination of intestinal bacteria which may utilize protective constituents of food.[172] The antibiotic had a highly protective effect in rats on experimental dietary hepatic cirrhosis and its sequelae, such as ascites and renal injury [173]. Anti-anemic effects have been described; dietary antibiotic had a beneficial effect on rats which had developed a macrocytic anemia following the surgical formation of an intestinal diverticulum [174]. It has been shown that these dietary antibiotics have a sparing effect on folic acid, B₁₂, and other B vitamins in animals on diets which were restricted with respect to these vitamins [166-169].

The mechanism of growth stimulation by this and other antibiotics is poorly understood; may involve its therapeutic activity, increased bacterial synthesis of essential or stimulatory growth factors, inhibition of bacteria competing with host for essential nutrients, or inhibition of organisms which are deleterious because they produce toxic substances or are damaging to intestinal tissues. In this regard it is noteworthy that chlortetracycline and other antibiotics show no growth-stimulation effect in the developing chick embryo and in germ-free animals. Growth effects also reported in premature infants and young children.[108-112]

80. CHLORTETRACYCLINE (Concluded)

MISCELLANEOUS Concentrations of 16-32 $\mu\text{g}/\text{ml}$ lethal to tadpoles; 4-10 $\mu\text{g}/\text{ml}$ inhibited metamorphosis, but had no effect on the regenerative processes or longevity [158]. Supplemental feeding of high levels (equivalent to 20% of the weight of added food) caused a marked inhibition of somatic development and growth, but did not affect gonadal development in the tropical fish, *Lebistes reticularis*, more commonly known as the guppy [159]. Solutions containing 1 mg/ml were lethal to viviparous fishes within 10-30 minutes [160]. Relatively high levels of chlortetracycline (300-500 mg/14 lb of wheat) were lethal to several varieties of coleopterous stored-grain insects within 30-60 days [161]. The antibiotic displayed an ACTH-like activity by stimulating the adrenal cortex in rats; following a single i.v. injection of 50-100 mg/kg there was a decrease in adrenal cholesterol, a reduction in circulating eosinophils, increased weight of adrenals and liver, and a marked rise in the urinary levels of unconjugated gonadal hormones [162]. The neurological deterioration resulting from oral doses of methionine in humans with liver disease was prevented by oral doses of chlortetracycline [175].

Was the most effective antibiotic (of 12 tested) for preservation of fish. Concentrations of 0.5-2.0 $\mu\text{g}/\text{g}$ incorporated in minced fish markedly inhibited bacterial spoilage; concentrations of approximately 2 ppm effective as meat preservative. [116, 117] Immersion in 3-40 ppm increased the shelf life of poultry stored under refrigeration [118, 119]. Yeasts for fermentation have been prepared by utilizing chlortetracycline and other broad spectrum antibiotics to inhibit growth of bacteria during the yeast propagation or storage period [121]. Effective in concentrations of 2-10 $\mu\text{g}/\text{ml}$ for controlling bacterial contaminants characteristic of grain alcohol fermentation [122]. Silkworms fed on a diet containing this antibiotic and amino acids produced 8-14% more silk [123]. The antibiotic does not inhibit the curative action of thiamine on the polyneuritic pigeon; even larger doses had no effect on the *in vivo* action of thiamine or cocarboxylase [129].

81. CHROMIN

SOURCE *Streptomyces* sp resembling *S. antibioticus* [1].

CRYSTAL FORM AND COLOR Fine white needles [2].

UV ABSORPTION MAXIMA 281, 292.5, 305, 320 $\text{m}\mu$ [2].

SOLUBILITY Crude: s. methanol, aqueous butanol, chloroform, water (especially alkaline), acetone, acetonitrile, ethyl acetate. Crystals: i. most organic solvents, water. [1, 2]

STABILITY Thermo-, acid, and alkali labile [1, 2].

OTHER REACTIONS Tollens questionable; reduces Fehling; negative ninhydrin, Molisch, biuret, FeCl_3 , Sakaguchi, Millon. Analysis: C, 58.19; H, 7.81; N, 2.29; no S, halogen. Infrared: 10.9, 9.9, 9.2, 8.8, 8.5, 7.7, 7.1, 6.4, 5.9 μ . [2]

QUANTITATIVE DETERMINATION Microbiological: *Aspergillus niger* [1].

BIOLOGICAL ACTIVITY *In vitro*. Active against certain yeasts and filamentous fungi. *Candida albicans* strains sensitive to 0.16-2.5 $\mu\text{g}/\text{ml}$. Inhibits, at 0.8-6.0 $\mu\text{g}/\text{ml}$, *Absidia orchidis*, *Monascus* spp, *Helminthosporium oryzae*, *Botrytis cinerea*, *Glomerella cingulata*, *Penicillium italicum*, *P. chrysogenum*, *Ustilago zeae*, *Rhizopus nigricans*, *Aspergillus niger*, *Mucor* spp, and *Saccharomyces sake*. Inhibits, at 6-12 $\mu\text{g}/\text{ml}$, *Trichophyton interdigitale*, *T. purpureum*. Bacteria are insensitive: *Bacillus subtilis*, *Micrococcus pyogenes* var. *aureus*, *Escherichia coli*, *Mycobacterium avium*, >1000 μg . [1] Some inactivation by serum [2].

ACUTE TOXICITY LD_{50} in mice, 36 mg/kg, i.p. [2].

82. CHRYSOMYCIN

SOURCE *Streptomyces* sp [1].

NATURE Neutral [1].

MOLECULAR FORMULA AND WEIGHT Chrysomycin: $\text{C}_{22}\text{H}_{20}\text{O}_7$ (proposed). Reduction product: $\text{C}_{22}\text{H}_{28}\text{O}_7$; 360 (found); 404 (calc.). [1]

CRYSTAL FORM AND COLOR Slender, greenish-yellow needles or rods [1].

MELTING POINT ($^{\circ}\text{C}$) 255-260 (d.)¹ [1].

OPTICAL ACTIVITY $[\alpha]_D^{22} = +16^{\circ}$ [1].

UV ABSORPTION MAXIMA 247, 287, 390-400 $\text{m}\mu$ [1].

/1/ Micro-block, no sharp melting. /2/ c, 1 acetic acid.

82. CHRYSOMYCIN (Concluded)

SOLUBILITY s. concentrated HCl, pyridine, glacial acetic acid, dioxane; sl. s. methanol, higher alcohols, ethyl acetate; i. water, petroleum ether.[1]

STABILITY Solutions thermostable at pH 3-7 [1].

OTHER REACTIONS Sublimes at 240°C without loss of activity; diffuses well in agar; dry crystals are photosensitive and turn brown on exposure to light; dissolves slowly on treatment with dilute alkali giving biologically inactive red solution that shows only end UV absorption; on hydrogenation with platinum oxide as a catalyst, 4 moles of H are taken up (colorless reduction product, MP 208°C, UV maxima 240, 355 m μ , biologically inactive).[1]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus cereus* phage [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits (μ g/ml) *B. subtilis*, *B. cereus*, 0.1; *Micrococcus pyogenes* var. *aureus*, 0.2; *Mycobacterium smegmatis*, 0.6; *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, 25; *Escherichia coli*, 50. The following fungi inhibited by 50-100 μ g/ml: *Aspergillus niger*, *Chaetomium globosum*, *Gliomastix convoluta*, *Memnoniella echinata*, *Myrothecium verrucaria*, *Penicillium notatum*, *Phycomyces blakesleeana*, *Stemphylium consortiale*, *Trichophyton mentagrophytes*, *Saccharomyces cerevisiae*. Bacteriophages (μ g/ml): *B. cereus* phage, 0.01; staphylophage, 0.04; *B. subtilis* phage, cholera phage, 0.4; *E. coli* phage T₂, 10.[1]

PHARMACOLOGY Doses of 250 mg/kg, i.p., were relatively toxic to mice but were sublethal; 100 mg/kg, i.p., well tolerated. Detectable blood levels after i.p. administration. Slowly eliminated in feces, with detectable amounts after 9 days. None detected in the urine.[1]

83. CINNAMYCIN

SOURCE *Streptomyces cinnamoneus* [3].

NATURE Polypeptide [1].

OPTICAL ACTIVITY Levorotatory [1,3].

UV ABSORPTION MAXIMUM End absorption: 230 m μ ¹ [1,2].

SOLUBILITY s. water, 50% aqueous ethanol, 80% methanol, water-saturated n-butanol, glacial acetic acid; i. ether.[1,3]

STABILITY Thermo- and acid stable²; unstable to alkali [1].

OTHER REACTIONS HCl: positive Sakaguchi, biuret, azide-iodine; negative nitroprusside, ninhydrin, FeCl₃, Molisch, maltol, Tollens, reducing sugars; not inactivated by pepsin, trypsin, light. Amino acids tentatively identified: mesolanthionine, aspartic acid, arginine, glutamic acid, proline, phenylalanine, valine, β -methyl-lanthionine.[1-3]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* [2,3].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits Gram-positive bacteria, including clostridia and mycobacteria. *B. cereus*, *B. circulans*, *B. megatherium*, *B. subtilis*, *Mycobacterium phlei*, *Myco. smegmatis* and *Myco. tuberculosis* are sensitive to 16 μ g/ml or less. Inactive against streptococci, micrococci, Gram-negative bacteria and yeasts. [3]

ACUTE TOXICITY LD₅₀ in mice: acetate, 5-10 mg/kg; HCl, 8-12 mg/kg, i.p. LD₀: HCl, 400 mg/kg, s.c. Marked hyperemia of ears and forefeet following i.p. administration of doses of 25 mg/kg or more.[4]

RESISTANCE Some strains of *B. megatherium* readily developed a high degree of resistance *in vitro* [5].

84. CIRCULIN

SOURCE *Bacillus circulans* [1].

NATURE Basic polypeptide [2,3].

MOLECULAR FORMULA AND WEIGHT (C₃₉H₇₄O₉N₁₂)_n [2,3]; 1200 (ionic sulfate) [3].

FORM AND COLOR Sulfate: white, amorphous solid [2].

MELTING POINT (°C) Sulfate: 226-228 [2,3]. HCl: 232-236 (d.) [3].

/1/ With shoulder at 250-260 m μ not in pure compound. /2/ 30 minutes at 94°C, pH 2.0-5.4.

84. CIRCULIN (Concluded)

OPTICAL ACTIVITY Sulfate: $[\alpha]_D^{25} = -61.6^{01}$ [2, 3]. HCl: $[\alpha]_D^{25} = -60.1^{02}$ [3].

UV ABSORPTION MAXIMA None significant [3].

SOLUBILITY s. water; less s. lower alcohols; i. hydrocarbons, chlorinated hydrocarbons, acetone, ether, glacial acetic acid.[1]

STABILITY Thermo- and acid stable; unstable above pH 7 in aqueous solution.[1-3]

OTHER REACTIONS Positive biuret, Van Slyke, formalin, 2,4-dinitrofluorobenzene; negative ninhydrin, xanthoproteic; Knoop; inactivated by crude trypsin and in presence of lipase, but not pepsin; forms HCl, reineckate and helianthate salts; contains β -leucine, L-threonine, L- α - γ -diaminobutyric acid, and an optically active isomer of pelargonic acid.[1-3]

QUANTITATIVE DETERMINATION Microbiological: *Salmonella typhosa*, *Escherichia coli* [1]. Release of cellular contents [12].

BIOLOGICAL ACTIVITY In vitro. Primarily active against Gram-negative bacteria. Inhibits ($\mu\text{g}/\text{ml}$) *Salmonella* spp, 0.4-6.2; *Brucella abortus*, 0.3; *Br. bronchiseptica*, 0.8; *Shigella dysenteriae*, 0.4; *E. coli*, *Klebsiella pneumoniae*, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Neisseria catarrhalis*, 3.1; *Serratia marcescens*, *Mycobacterium tuberculosis*, 30; *Proteus vulgaris*, 67; *Bacillus anthracis*, *B. subtilis*, *Micrococcus pyogenes* var. *aureus*, *Myco. avium*, 100; *Streptococcus faecalis*, 10. [1] Inhibited *Trichomonas vaginalis* by direct tests at 200 $\mu\text{g}/\text{ml}$ [10]. Phytopathogens: *Xanthomonas phaseoli*, *X. campestris*, *X. beticola*, *Erwinia amylovora*, *E. carotovora* sensitive to 0.4-3.1 $\mu\text{g}/\text{ml}$. [14]

In vivo. Doses of 10-16 mg/kg, administered s.c. or i.p., protected mice against infections with *Salmonella typhosa*, *K. pneumoniae*, *Vibrio comma*, and *Hemophilus influenzae* (type B). Ineffective as intestinal antiseptic in dogs.[4, 5, 7, 8]

TOXICITY LD₅₀ in mice, 10 mg/kg, i.v.; 77 mg/kg, s.c. No evidence of chronic toxicity in mice and guinea pigs after repeated doses.[6] In dogs, toxicity shown by mucosal hyperemia; larger doses caused hemorrhages in the bowel.[4] Detectable blood levels in dogs, but not in rats, after oral administration [4, 6]. Low toxicity in tissue cultures: 3000-5000 μg required to inhibit growth of skin tissue, and >20,000 μg for spleen tissue [9].

PHYTOTOXICITY Highly toxic to onion root tips [11].

MODE OF ACTION Bacterial cells exposed to circulin exhibit a leakage of cellular constituents and a loss of viability. Experimental evidence suggests that the lethal effects of the antibiotic are exerted in or near the bacterial cell walls. [13]

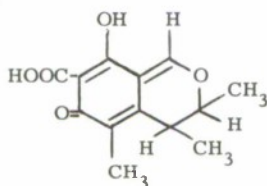
85. CITRININ

SOURCE *Penicillium citrinum* and other *Penicillium* spp, as well as *Aspergillus* spp [1, 9].

NATURE Monobasic acid [1].

MOLECULAR FORMULA AND WEIGHT C₁₃H₁₄O₅ [1, 2]; 259 (found); 250 (by analysis).[8]

STRUCTURE



[6, 7]

CRYSTAL FORM AND COLOR Golden prismatic needles or serrate plates from alcohol [5, 8].

MELTING POINT (°C) 170, 175 (d.) [1, 2, 7, 8].

OPTICAL ACTIVITY $[\alpha]_{5461}^{23} = -43.1^{03}$ [8]; $[\alpha]_D^{18} = -37.4^{04}$ [7].

SOLUBILITY s. hot ethanol, ethyl acetate, benzene, acetone, chloroform; sl. s. ether, petroleum ether, ethanol; i. water.[5]

STABILITY Thermostable; less stable at alkaline pH.[1]

/1/ c, 1.25 water. /2/ c, 2.094 water. /3/ c, 0.92 absolute ethanol. /4/ c, 1.15 ethanol.

85. CITRININ (Concluded)

OTHER REACTIONS Positive Tauber, FeCl_3 ; destroyed by cysteine; greenish-yellow fluorescence in UV; colorless in NaHCO_3 solution; orange-yellow in aqueous NaOH , later orange-red; bright lemon yellow in aqueous solution below pH 4.6, changing to orange-pink at pH 5.6-5.8 and to cherry red above 9.9.[2, 3, 8]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*, *Escherichia coli* [4].

BIOLOGICAL ACTIVITY *In vitro*. Active against Gram-positive bacteria. Inhibits (in dilutions of 1:10,000-1:200,000) *M. pyogenes*, *Streptococcus pyogenes*, *Bacillus subtilis*, *B. mycoides*, *Vibrio comma*, *Salmonella enteritidis*, *E. coli*, *Shigella dysenteriae*. *Salmonella typhimurium*, *S. paratyphi*, *Pseudomonas aeruginosa*, *Str. viridans*, *Mycobacterium phlei* and *Myco. smegmatis* are less susceptible.[10, 13]

In vivo. No activity in mice infected with *M. pyogenes* var. *aureus* [12].

ACUTE TOXICITY LD_{50} in mice, 35 mg/kg, s.c. or i.p. LD_{50} in rabbits, 19 mg/kg, i.v. Kidney damage followed repeated sublethal doses in rabbits. Depressed blood pressure in dogs. Dry citrinin very irritating to cornea and nasal mucosa of handlers.[11]

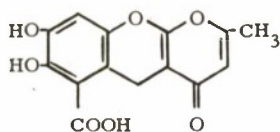
86. CITROMYCETIN (Frequentin Acid)

SOURCE Strain of *Penicillium frequentans* [2].

NATURE Dibasic acid [3].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{14}\text{H}_{10}\text{O}_7 \cdot 2\text{H}_2\text{O}$ [1, 3]; 324 (found); 326 (calc.).[3]

STRUCTURE



[4]

CRYSTAL FORM AND COLOR Yellow crystals [2, 3].

MELTING POINT ($^{\circ}\text{C}$) 290-300 (d.) [3].

OPTICAL ACTIVITY Inactive [2].

SOLUBILITY s. ethanol, aqueous sodium carbonate; sl. s. chloroform, water; i. benzene, hexane.[2]

STABILITY Thermostable [2].

OTHER REACTIONS Deep green color with FeCl_3 ; orange solution with green fluorescence with concentrated H_2SO_4 ; reduces ammoniacal AgNO_3 ; converts to citromycin when boiled with 2 N H_2SO_4 ; decomposes when boiled with 3 N NaOH . [1, 3]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [3].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *Micrococcus pyogenes* var. *aureus* at 1:8,000 dilution. Slight activity against *Salmonella enteritidis* (1:500 dilution). Activity reduced approximately 50% by serum.[2]

TOXICITY Na salt: Mice tolerated doses of 1200 mg/kg, i.v., and 2250 mg/kg, i.p. Evidence of kidney damage following multiple doses. Small amounts excreted in urine following large parenteral doses.[2]

87. CLITOCYBINS

SOURCE *Clitocybe candida* [1].

CRYSTAL FORM AND COLOR Long, colorless, orthorhombic [2].

MELTING POINT ($^{\circ}\text{C}$) 77 [2].

SOLUBILITY s. water, ethanol, acetone, chloroform, amyl acetate, sulfuric ether [1, 2].

STABILITY Thermolabile [1].

87. CLITOCYBINS (Concluded)

OTHER REACTIONS Readily diffusible; not a protein.[2]

BIOLOGICAL ACTIVITY In vitro. Inhibit *Bacillus anthracis*, *Streptococcus pyogenes*, *Micrococcus pyogenes* var. *aureus*, *Erysipelothrix rhusiopathiae*, *Malleomyces mallei*, *Pasteurella multocida*, *Salmonella typhosa*, *S. paratyphi*, *Escherichia coli*, *Brucella abortus* and *Mycobacterium tuberculosis* in dilution of 1:300,000-1:800,000 [3].

In vivo. Slight protection against *Myco. tuberculosis* in guinea pigs. No activity in experimental infections with streptococci, or *Past. multocida*. [1] Claimed to have some effect in delaying the development of foot and mouth disease virus [5].

TOXICITY Guinea pigs tolerated 20 mg doses. Higher s.c. doses induced necrosis at the site of injection and were lethal.[2, 4]

88. COELICOLORIN

SOURCE *Streptomyces coelicolor* [1].

FORM AND COLOR Purplish-red powder [1].

MELTING POINT (°C) 142-146 [1].

SOLUBILITY s. water at pH 8 and above, acetone, ethyl acetate, chloroform, benzene, ethanol, methanol, ether; sl. s. water at pH 6-7; i. water at pH 5, petroleum ether.[1]

OTHER REACTIONS Red at pH 5, purple at pH 6-7, green at pH 8 and above [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus* in dilution of 1:1,000,000; *Bacillus subtilis*, 1:400,000; *Escherichia coli*, *Shigella dysenteriae*, *Salmonella typhosa*, *S. paratyphi*, and *S. schottmuelleri*, 1:10,000.[1]

ACUTE TOXICITY LD₅₀ in mice, 500 mg/kg, i.p. [1].

89. COLICINES

SOURCE *Escherichia coli* and other members of *Enterobacteriaceae* [1].

NATURE Polypeptides; proteic.

COLOR COLICINE K: colorless [4].

SOLUBILITY s. water, acetic acid; sl. s. pyridine, aqueous phenol; i. other organic solvents.[1, 2, 4]

STABILITY Thermostable when acid or neutral; unstable to alkali¹. [1, 2, 4]

OTHER REACTIONS Dialyze through cellophane; destroyed by pepsin, trypsin, mouse kidney or liver tissue; precipitated from aqueous solution by neutral salts.[1, 2]

Colicine K: Free of nucleic acid; contains N, 6.5; P, 1.6; appears to have but 1 electrophoretic component in Tiselius apparatus; composed of carbohydrate, protein, lipid; destroyed by trypsin, chymotrypsin, contact with 1% formalin.[4]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli* [1].

BIOLOGICAL ACTIVITY In vitro. Active against *Shigella dysenteriae*, *Sh. sonnei*, *Pseudomonas aeruginosa*, *Salmonella* spp, *Vibrio comma*, *Corynebacterium xerosis*, *Mycobacterium phlei* [1, 3]. Action is bactericidal; activity is enhanced by small amounts of serum.[1]

Purified colicine K: In concentrations of 1 µg/ml, inhibits *E. coli* [4].

PHARMACOLOGY Lots vary in toxicity. LD₀ in mice, 900 mg/kg, i.v. Appear to be destroyed in the body; mice injected i.v. with 18.5 mg excreted less than 5% in urine.[1]

Purified colicine K: Toxic in mice and rabbits [4].

MISCELLANEOUS Colicines resemble bacteriophages, but differ in that they are not transmitted by serial passage. Suggested that they may be precursors of phages [5], although more recent evidence does not support this view [4].

Purified colicine K is highly antigenic in rabbits, producing an antibody which precipitates the colicine, neutralizes its antimicrobial activity and agglutinates the strain of *E. coli* from which it is derived. Colicine K was shown to be chemically and immunologically unrelated to *E. coli* phage T6.[4]

/1/ Strain C₃: 13% loss at 100°C in 30 minutes, 22% in 1 hour.

90. COLIFORMIN

SOURCE A bacterium of *Escherichia coli*-*Aerobacter aerogenes* group [1].

NATURE Polypeptide [1].

MOLECULAR WEIGHT 4000 ± 400 (found) [1].

UV ABSORPTION MAXIMUM $272 \text{ m}\mu^1$ [1].

STABILITY Thermostable at acid and neutral pH; unstable at alkaline pH.[1]

OTHER REACTIONS HCl analysis: C, 47.6; H, 8.22; Cl, 3.31; S, 0.23; P, 0.47; O, 33.15 (by difference); positive ninhydrin (after hydrolysis); Molisch; contains alanine, glycine, serine, glutamic acid, aspartic acid, lysine, valine, leucine.[1]

QUANTITATIVE DETERMINATION Microbiological: *Pullularia pullulans* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits yeasts and fungi ($\mu\text{g/ml}$): *Candida albicans* 0.6-3.0; *C. krusei*, *Cryptococcus neoformans*, 0.6; *Candida tropicalis*, *Hormodendrum pedrosoi*, *Microsporium gypseum*, *Trichophyton mentagrophytes*, *T. tonsurans*, 3.[1] A wide variety of phytopathogenic fungi also sensitive [2]. Also active against fungi causing damage to wood, textiles, leather, and wood pulp [3].

91. COLISTATIN

SOURCE An aerobic sporulating bacillus [1].

SOLUBILITY Crude preparation: s. acid methanol and ethanol; i. butanol.[1]

STABILITY Thermostable [1].

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Escherichia coli*, *Proteus* sp, *Salmonella schottmuelleri*, *Shigella dysenteriae*, *Salmonella typhosa*, *M. pyogenes* var. *aureus*, *Diplococcus pneumoniae* [1].

In vivo. In mice, doses of 30,000 units/kg cleared *Borrelia sogdianum* from the blood within 24 hours [1].

ACUTE TOXICITY Mice tolerated 100,000 units/kg by s.c., i.m., or i.v. routes [1].

92. COLLINOMYCIN

SOURCE Mycelium of *Streptomyces collinus* [1].

CRYSTAL FORM AND COLOR Orange prisms² [1].

MELTING POINT ($^{\circ}\text{C}$) 280-282 (uncorr.) [1].

ABSORPTION MAXIMA 535, 575 $\text{m}\mu^3$; 480, 525 $\text{m}\mu^4$. [1]

SOLUBILITY s. chloroform, acetone, dioxane; sl. s. ether, lower alcohols; i. water, petroleum ether, sodium bicarbonate.[1]

OTHER REACTIONS Sodium salt precipitates as violet precipitate at interface when yellow ether solution is shaken with 2 N Na_2CO_3 , the aqueous phase being colored a weak violet; in pyridine-methanol and titanium trichloride, solution is first olive-green, then red; orange color (also fluoresces orange) in acetic anhydride, but becomes carmine red on addition of pyroboracetate, and after short heating has absorption maxima at 608, 555 and 515 $\text{m}\mu$; yellow-red dioxane solution becomes pale yellow when sodium hyposulfite is added, but original color returns after standing in air.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus* at 1:2,000,000 dilution [1].

93. COMIRIN

SOURCE Bacterium antimyceticum, n. sp, resembling *Pseudomonas fluorescens* [1]; *Ps. antimycetica* [2].

NATURE Peptide containing an ether-soluble moiety [1,2].

FORM AND COLOR Whitish, amorphous powder [1].

/1/ Broad band. /2/ From chloroform-methanol. /3/ 2 N NaOH. /4/ Concentrated H_2SO_4 .

93. COMIRIN (Concluded)

MELTING POINT (°C) 230-235 (d.)¹ [2].

SOLUBILITY s. organic bases and acids; less s. aqueous alcohols; sl. s. water; i. neutral organic solvents. [1, 2]

STABILITY Thermostable except in alkali² [1, 2].

OTHER REACTIONS Precipitated by 50% (NH₄)₂SO₄ and protein precipitants; negative ninhydrin, glyoxylic acid, Molisch; positive Millon-Cole, Pauly, Sakaguchi, xanthoproteic, biuret. No free amino acid groups; dialyzes slowly through cellophane; acid hydrolysis yields mainly serine, glycine, aspartic acid; dinitrophenyl derivatives readily formed with 2, 4-dinitrofluorobenzene. Other amino acids present: leucine, isoleucine, tyrosine, arginine, lysine, α, γ-diaminobutyric acid.[1, 2]

QUANTITATIVE DETERMINATION Microbiological: *Aspergillus flavus* [1, 2].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits the following yeasts and fungi in dilution of 1:25,000 or more: *Candida albicans*, *C. reukauffii*, *C. tropicalis*, *Torulopsis neoformans*, *Trichosporon* sp, *Zygosaccharomyces saulsus*, *Debaryomyces matruchoti*, *Mycoderma valida*, *Saccharomyces cerevisiae*, *Saccharomyces* spp, *Schizosaccharomyces* spp, *Torulopsis utilis*, *Zygosaccharomyces* spp, *Epidermophyton* sp, *Hormodendrum* sp, *Sporotrichum schenckii*, *Trichophyton mentagrophytes*, *Trichosporium rubrum*, *Aspergillus* spp, *Cladosporium herbarum*, *Fusarium oxysporum*, *Mucor mucedo*, *Neurospora sitophila*, *Oidium lactis*, *Penicillium notatum*, *P. chrysogenum*, *Rhizoctonia solani*, *Rhizopus* sp, *Sclerotium rolfsii*, *Trichoderma viride*, *Verticillium* spp, *Botrytis allii*, *B. cinerea*. No activity against bacteria.[1]

UTILIZATION Marked hemolytic properties preclude parenteral use. Topical use (1:10,000-1:30,000 in ointment base) suggested for mycotic infections of skin and ear. Usefulness as a fungicidal spray for plants also indicated. [1].

94. CONGOCIDIN

SOURCE *Streptomyces ambofaciens*, n. sp [1].

NATURE Basic [1, 2].

MOLECULAR FORMULA C₁₀H₂₁O₃N₅·HCl [1]; C₁₇H₂₅O₂N₉·2HCl [2].

CRYSTAL FORM AND COLOR Almost colorless needles [1].

MELTING POINT (°C) 205-210 (d.) [1, 2].

OPTICAL ACTIVITY Inactive [1, 2].

UV ABSORPTION MAXIMA 296, 235 mμ [2].

STABILITY Stable in the crystalline state [2].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits Gram-positive (including mycobacteria) and Gram-negative bacteria, with the exception of *Pseudomonas aeruginosa* and *Brucella bronchiseptica* [1].

In vivo. Little or no activity in mice infected with *Micrococcus pyogenes* var. *aureus*, and *Klebsiella pneumoniae*. Slight activity in rats infected with *Entamoeba histolytica* following s.c. doses of 25 mg/kg/da. Single s.c. doses of 75-150 mg/kg suppressed infections with *Trypanosoma congolense* in mice; also *T. brucei* (including strains resistant to arsenicals).[1, 2]

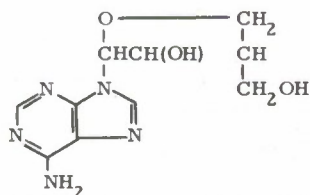
TOXICITY LD₅₀ in mice, 75 mg/kg, i.v.; 200 mg/kg, s.c.; 5000 mg/kg, oral.[2]

95. CORDYCEPIN

SOURCE *Cordyceps militaris* (Link) [1].

MOLECULAR FORMULA AND WEIGHT C₁₀H₁₃O₃N₅ [1]; 247 ± 10 (found); 251 (calc.).[1]

STRUCTURE



[2]

/1/ Depends on rate of heating. /2/ Heating in acid results in apparent increase in activity, possibly because of strong surface-active and colloidal properties in aqueous solution.

95. CORDYCEPIN (Concluded)

CRYSTAL FORM AND COLOR Colorless needles or plates¹ [1].

MELTING POINT (°C) 225-226 [1].

OPTICAL ACTIVITY $[\alpha]_D^{20} = -47^{02}$ [1].

UV ABSORPTION MAXIMUM 260 $m\mu^3$ [1].

SOLUBILITY s. warm dilute mineral acids [2].

OTHER REACTIONS Forms the picrate and picrolonate [1].

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *B. subtilis* at 10-100, *Mycobacterium avium* at 100. No activity against *Micrococcus pyogenes* var. *aureus*, *Sarcina lutea*, *Escherichia coli*, *Clostridium perfringens*, *Proteus* sp, and streptococci.[1]

In vivo. Daily i.p. doses of 100 mg/kg for 7 days in mice had no inhibitory effect on RC carcinoma [3].

TOXICITY Of low order [2].

96. CYCLOHEXIMIDE

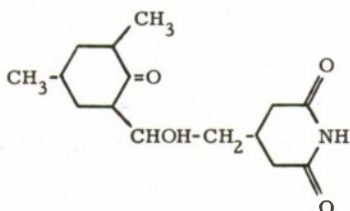
The trademark of The Upjohn Company for cycloheximide is Actidione.

SOURCE Certain strains of *Streptomyces griseus* [1]; *S. noursei* [33].

NATURE Weakly acidic [4].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{15}\text{H}_{23}\text{NO}_4$ [2-4]; 254 (Rast); 281 (calc.).[2]

STRUCTURE



[3, 4]

CRYSTAL FORM AND COLOR Colorless plates [5].

MELTING POINT (°C) 115-116.5 [2, 5].

OPTICAL ACTIVITY $[\alpha]_D^{25} = -2.8^{04}$ [5], -6.8^{05} [2].

SOLUBILITY s. water, all organic solvents except saturated hydrocarbons [1, 2].

STABILITY Thermostable [1].

OTHER REACTIONS Inactivated at room temperature by acetic anhydride, sodium acetate, dilute alkali [5].

Nonactin ($\text{C}_{30}\text{H}_{48}\text{O}_9$, a neutral, colorless crystalline compound, having very weak antibiotic properties) is found in cycloheximide-producing beers of *Streptomyces viridochromogenes* or *S. olivochromogenes* [37].

QUANTITATIVE DETERMINATION Microbiological: *Saccharomyces pastorianus* [5, 6].

BIOLOGICAL ACTIVITY In vitro. Little or no effect on bacteria. Antifungal activity; inhibits, at 0.2-50 $\mu\text{g/ml}$: *Cryptococcus neoformans*, *Aspergillus niger*, *Sac. cerevisiae* and other yeasts. In general, most fungal animal pathogens are not susceptible ($>1000 \mu\text{g/ml}$): *Candida albicans*, *Epidermophyton floccosum*, *Blastomyces dermatitidis*, *Nocardia asteroides*, *Hormodendrum pedrosoi*, *Trichophyton* spp.[1, 6, 12] Many phytopathogenic fungi are sensitive. Inhibited by 5 $\mu\text{g/ml}$ or less: *Sclerotinia fructicola*, *Diplocarpon rosae*, *Physalospora tucumanensis*, *Diaporthe citri*, *Endothia parasitica*, *Venturia inequalis*, *Ustilago tritici*, *U. zeae*, *Heterosporium iridis*, *Cladosporium fulvum*, *Diplodia zeae*, *Colletotrichum lagenarium*, *Sclerotium rolfsii*. [8] Protozoa: *Tetrahymena geleii* and *Euglena gracilis* are sensitive to 1-5 $\mu\text{g/ml}$ [9]. *Sac. pastorianus* developed a 68-fold increase in resistance in vitro (0.06-4.08 $\mu\text{g/ml}$) following 3 transfers in media containing the antibiotic [4].

/1/ Transparent needles from ethanol and n-propanol, lustrous needles or plates from n-butanol, dull matted needles from water. /2/ Water. /3/ Ethanol. /4/ c, 9.6 methanol. /5/ c, 2 water.

96. CYCLOHEXIMIDE (Concluded)

In vivo. Daily i.p. doses of 1 mg suppressed production of ascites in mice injected with Ehrlich carcinoma, but failed to prolong survival time of the animals [24]. Was effective in control of experimental amebiasis (*Entamoeba histolytica*) in monkeys [10]. Intraperitoneal administration of 100 mg/kg/da had slight retarding effect on growth of a mouse tumor (Crocker sarcoma 180) [11]. Daily parenteral doses in mice had little or no inhibitory effect on sarcoma 180 [34].

CLINICAL Good clinical response reported in a single patient with meningitis caused by *Coccidioides immitis* [12], and in a case of *Cryptococcus neoformans* meningitis following i.m. and i.v. administration [13]. Another report describes intravenous therapy as unsuccessful in three cases of cryptococcosis [28]. The antibiotic was toxic when administered intrathecally [13].

PHARMACOLOGY LD₅₀ in mice, 150 mg/kg, i.v.; in rats, 2.5 mg/kg, i.v., and 2.7 mg/kg, s.c.[7] Oral doses as low as 1 mg/kg were fatal to rats; rabbits tolerated approximately 4.5 mg/kg, per os.[14] Crude preparations were highly irritating to the skin [1]. Detectable blood levels in rats, guinea pigs and dogs following i.p. administration [7].

MISCELLANEOUS In view of inactivity against bacteria and dermatophytes, antibiotic has been recommended for use in laboratory culture media in concentrations of approximately 100 µg/ml for the isolation of microorganisms from mixed cultures containing saprophytic fungi, e.g., aspergilli, penicillia [22, 23]. Incorporation of 40 µg/ml in agar media useful in laboratory isolation of actinomycetes in presence of contaminating fungi [29]. Liquid spray, containing 50-100 ppm antibiotic, provided good protection against brown rot fungus (*Sclerotinia fructicola*) on cling peach fruits [30]. Spraying with 25-50 ppm in casco summer oil prevented development of red cedar rust; no foliage injury observed as a result of this treatment.[31] In greenhouse and field tests, cycloheximide was the most effective of six antibiotics tested as spray in concentrations of 25-100 ppm for the control of stem rust of wheat [35]. Concentrations of 20-25 ppm sprayed on seedling plants effective in control of wheat stem rust [25]. The antibiotic did not increase the resistance of wheat seedlings to infection with *Xanthomonas translucens* [36]. Concentrations of approximately 10 ppm resulted in good control against powdery mildew of apple, onion, bean, and rose; also effective against cherry leaf spot, mint rust, and turf diseases.[15-19] 10-50 ppm inhibited *Ascochyta pisi* infection in peas, but was toxic to pea seeds [20]. Phytotoxicity of cycloheximide (e.g., to peach, tomato, bean, geranium) limits its use as agricultural fungicide on some crops [21]. Concentrations of 100 µg/ml induced specific aberrations in mitotic behavior in the cells of onion root [26]. At pH 6.0, cycloheximide markedly inhibited endogenous respiration of *Tetrahymena pyriformis* S, as well as its utilization of mono- and disaccharides, organic acids and amino acids [27]. Cycloheximide induced formation of gametangia in *Allomyces arbuscula*, thus transforming a sporophytic plant into a gametophytic plant [32]. Was effective as a rat repellent; paperboards when treated with 50 mg/sq inch reduced gnawing attacks [14].

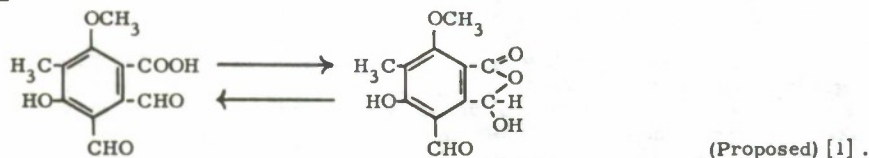
97. CYCLOPALDIC ACID

SOURCE *Penicillium cyclopium* (Westling).[1]

NATURE Dibasic acid [1].

MOLECULAR FORMULA AND WEIGHT C₁₁H₁₀O₆; 119 (equiv.).[1]

STRUCTURE



CRYSTAL FORM AND COLOR Long fluffy colorless needles¹ [1].

MELTING POINT (°C) 224-225 [1].

SOLUBILITY Moderately s. ethanol, methanol, ethyl acetate; sl. s. ether, chloroform, hot benzene, boiling petroleum ether.[1]

OTHER REACTIONS Slowly soluble in cold aqueous NaHCO₃, yellow solution, effervescence; yellow solution in NaOH, deepens on warming; aqueous or ethanolic solution, ruby-red with FeCl₃; gelatinous orange precipitate with Brady; negative Fehling; Br water added to dilute aqueous solution gives transient buff color with no precipitate; trace exposed to NH₃ vapor turns brown, and if then dissolved in aqueous NH₃ gives purple color, fading after 2-3 hours to orange with yellow fluorescence; green fluorescence in methanolic solution in UV; transient pale yellow with bleaching powder; in pH 9.2 buffer and treated with aqueous suspension of 2,6-dichloroquinone chloroimide,

/1/ From water.

97. CYCLOPALDIC ACID (Concluded)

forms a green color in 2 minutes, then blue-green in 10 minutes, reddish-brown after 3 days; sublimes readily in high vacuum at 170°. [1]

QUANTITATIVE DETERMINATION Microbiological: Inhibition of germination of *Botrytis allii* spores [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits germination of *B. allii* spores at 2.5 µg/ml. (Cyclopolic acid is inactive; no inhibition of *B. allii* at 320 µg/ml.) [2]

98. DECHLOROGRISEOFULVIN

SOURCE *Penicillium janczewski* and *P. griseofulvum* (Dieckx).

NATURE Neutral [1].

MOLECULAR FORMULA AND WEIGHT $C_{17}H_{18}O_6$ [1]; 306 (Rast)[2].

STRUCTURE Dechloro-analogue of griseofulvin [1, 2]. (See also griseofulvin.)

CRYSTAL FORM Needles [2].

MELTING POINT (°C) 179-181 [1, 2].

OPTICAL ACTIVITY $[\alpha]_D^{19} = +390^{\circ}$ [1, 2].

UV ABSORPTION MAXIMA 250, 286, 325 mµ [2].

OTHER REACTIONS Dechlorogriseofulvin gives intense blue-violet color with HNO_3 at room temperature, griseofulvin giving a pale yellow color under same conditions (sensitive to 1 µg in a solid mixture). [1]

QUANTITATIVE DETERMINATION Microbiological: *Botrytis allii* response [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *B. allii* at 6.25 µg/ml, in contrast to griseofulvin which inhibits this organism at 0.5 µg/ml.

99. DEXTROMYCIN

SOURCE *Streptomyces* sp resembling *S. fradiae*.

NATURE Base [1].

MELTING POINT (°C) Helianthate: 227-228° [1].

OPTICAL ACTIVITY HCl: $[\alpha]_D^{25} = +61.0^{\circ}$ [1].

OTHER REACTIONS Resembles neomycin; recovered by same methods used with streptothricin and streptomycin; no maltol on alkaline hydrolysis; negative Sakaguchi; diffuses slowly through agar. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits (µg/ml) *Bacillus subtilis*, *Sarcina lutea*, 0.1-0.2; *Corynebacterium diphtheriae*, 0.125; *Klebsiella pneumoniae*, 0.25; *Micrococcus pyogenes* var. *aureus*, 0.4-0.5; *Mycobacterium avium*, 0.5; *Proteus vulgaris*, *Escherichia coli*, 1.0-1.25; *Vibrio comma*, 2-8; *Hemophilus pertussis*, 4; *Salmonella typhosa*, 4-8; *Shigella dysenteriae*, 4-16; *Myco. tuberculosis* var. *hominis*, 5; *Salmonella enteritidis*, 8; *Pseudomonas aeruginosa*, 64; *Streptococcus pyogenes*, 125-250. Resistance did not develop readily in vitro. Fungi are not sensitive, >20,000 µg/ml: *Aspergillus oryzae*, *A. niger*, *Penicillium* spp. [1, 2]

In vivo. S. c. doses protected mice against *S. typhosa*; slight activity against *H. pertussis* infection. No activity in rats with transplanted Yoshida sarcoma. [2]

ACUTE TOXICITY LD_{50} in mice, 50 mg/kg, i.v.; 750-1000 mg/kg, s.c.; 1250 mg/kg, oral [1, 2].

100. DIATRETYNES

SOURCE *Clitocybe diatreta* [1].

NATURE Polyacetylene [1-3].

MOLECULAR FORMULA AND WEIGHT Diatretyne 1: $C_8H_5NO_3$ [2]; 159 (ebull.); 163 (calc.). [2]
Diatretyne 2: $C_8H_3NO_2$; 145.11 (calc.). [4]

/1/ c, 1 acetone.

100. DIATRETYNES (Concluded)

STRUCTURE Diatretyne 1: $\text{HOOCCH}=\text{CHC}\equiv\text{CC}=\text{CCONH}_2$ [3].

Diatretyne 2: $\text{HOOC}-\text{CH}=\text{CH}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{C}\equiv\text{N}$ [4].

MELTING POINT ($^{\circ}\text{C}$) 198 (uncorr.)¹ [2].

UV ABSORPTION MAXIMA Diatretyne 1: 225, 260, 275, 291, 310 $\text{m}\mu^2$ [1].

Diatretyne 2: 230, 240, 270, 285, 303, 323 $\text{m}\mu^2$ [1].

STABILITY Diatretyne 1: Very unstable [1, 2].

OTHER REACTIONS Diatretyne 1: pK 3.3; catalytic reduction product $\text{C}_8\text{H}_{15}\text{NO}_3$ is a colorless, crystalline solid, MP 144-145 $^{\circ}\text{C}$ (uncorr.) [2, 3]

BIOLOGICAL ACTIVITY In vitro. Diatretyne 1: Inhibits *Micrococcus pyogenes* var. *aureus* at concentration of 0.1 $\mu\text{g}/\text{ml}$ [4].

Diatretyne 2: Apparently no antibacterial activity; no inhibition of *Micrococcus pyogenes* var. *aureus* at 1000 $\mu\text{g}/\text{ml}$. Antimicrobial activity, originally attributed to diatretyne 2, caused by contamination with diatretyne 1 [4]

101. DIPLOCOCCIN

SOURCE *Streptococcus lactis* [2]

NATURE Protein-like [1].

OPTICAL ACTIVITY Levorotatory [1].

SOLUBILITY s. water; i. absolute ethanol [1]

STABILITY Thermostable in acid; unstable in alkaline solution [1]

OTHER REACTIONS Positive protein tests with the exception of Millon, Heller; negative Molisch; precipitated by half-saturated $(\text{NH}_4)_2\text{SO}_4$, tannic acid; slow diffusion through collodion; positive arginine, tyrosine, tryptophan [1]

QUANTITATIVE DETERMINATION Microbiological: *Streptococcus cremoris* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Str. cremoris*, *Str. hemolyticus*, *Str. lactis*, and *Micrococcus pyogenes* var. *aureus* in dilution of 1:10,000-1:200,000 [1].

102. DROSOPHILINS

SOURCE *Drosophila substrata* [1].

NATURE Drosophilin A: p-methoxytetrachlorophenol.
C: polyacetylene [2, 3]

MOLECULAR FORMULA AND WEIGHT Drosophilin A: $\text{C}_7\text{H}_4\text{O}_2\text{Cl}_4$ [2]; 249 (found); 262 (calc.) [1].

CRYSTAL FORM AND COLOR Drosophilin A: white crystals [1].

MELTING POINT ($^{\circ}\text{C}$) Drosophilin A: 118 (corr.) [1].

OPTICAL ACTIVITY Drosophilin A: inactive [1].

UV ABSORPTION MAXIMA Drosophilin A: 301 $\text{m}\mu$.

C: 238, 251, 265, 280 $\text{m}\mu^3$ [3]⁴
D: 217, 259, 274, 290, 309 $\text{m}\mu^4$ [1].

SOLUBILITY s. most organic solvents; sl. s. water. [1]

OTHER REACTIONS Drosophilin B is identical with pleuromutilin; C and D, but not A, precipitated from aqueous solution by AgNO_3 . A: positive FeCl_3 , negative 2,4-dinitrophenylhydrazine, reduces alkaline permanganate and alkaline AgNO_3 . UV of alkaline conversion product of C: 233, 243, 264, 273, 279, 290, 309, 330 $\text{m}\mu^5$; 230, 241, 264, 273, 279, 289, 308, 329⁶; of D: 233, 244, 257, 273, 290, 309, 330 $\text{m}\mu^5$ [1, 2]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

/1/ Explodes, no melting. /2/ 95% ethanol. /3/ Ether. /4/ Ethanol. /5/ Borate buffer, pH 10. /6/ Phosphate buffer, pH 2.

102. DROSOPHILINS (Concluded)

BIOLOGICAL ACTIVITY In vitro. Drosophilin A: Inhibits *M. pyogenes* var. aureus, 16; *Bacillus subtilis*, 31; *B. mycoides* and *Mycobacterium smegmatis*, 63; *Escherichia coli*, 125; *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, 250 µg. [1, 5] Fungi (µg/ml): *Chaetomium globosum*, *Memnoniella echinata*, *Trichophyton mentagrophytes*, 2; *Gliomastix convoluta*, *Penicillium notatum*, 8; *Aspergillus niger*, *Myrothecium verrucaria*, *Stemphylium consortiale*, 16; *Saccharomyces cerevisiae*, 31. High activity against phages of *Micrococcus pyogenes* and *Vibrio comma*. [5] In tissue cultures, partially inhibited Y-SK strain of poliomyelitis virus in concentration of 4-8 mg/ml. Concentrations >8 mg/ml are toxic. [4]

B: (See pleuromutilin.)

C: In vitro. Inhibition of *M. pyogenes* var. aureus, *B. subtilis*, *E. coli*, *Ps. aeruginosa*, *Myco. smegmatis*, and *K. pneumoniae* at 0.03-32.0 µg/ml [1].

D: Active only against *M. pyogenes* var. aureus and *B. subtilis* at 2-4 µg/ml [1].

TOXICITY Drosophilin A: Mice tolerated single i.v. doses of 50 mg/kg [5].

MISCELLANEOUS Drosophilin A: Ineffective as spray in control of early blight of tomato plants; toxic to tomato plants at 200-400 ppm. [5] Some molluscicide activity; 10 ppm lethal for snail (*Australorbis glabratus*) in 24 hours. [5]

103. EHRLICHIN

SOURCE *Streptomyces* sp resembling *S. lavendulae* [1].

STABILITY Thermostable; less stable in fermented broths; acid labile¹. [1]

OTHER REACTIONS Dialyzes without loss of activity; resists tryptic digestion. [1]

QUANTITATIVE DETERMINATION Microbiological: Influenza B virus [1].

BIOLOGICAL ACTIVITY In vitro. Antiviral activity; no effect on bacteria, fungi and bacteriophages. Inhibits influenza A and B viruses. [1]

In vivo. Active against influenza B virus (suppressive effect on pulmonary consolidation in mice and in chick embryos). No activity against influenza A virus. [1]

ACUTE TOXICITY Mice tolerated 100 mg/kg, i.p.; 300 mg/kg, s.c. Necrosis developed at site of s.c. injection of 100 mg/kg doses. [1]

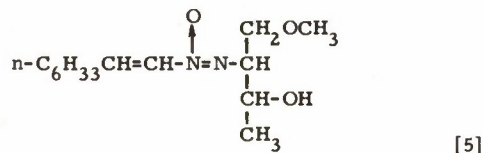
104. ELAIOMYCIN

SOURCE *Streptomyces hepaticus* [2, 3]; *S. gelaticus* [4].

NATURE A neutral oil [1-3].

MOLECULAR FORMULA AND WEIGHT C₁₃H₂₆N₂O₃ (proposed); 244 (found); 258 (calc.). [2, 3]

STRUCTURE



COLOR Light yellow [2, 3].

OPTICAL ACTIVITY $[\alpha]_D^{26} = +38.4^{\circ 2}$ [2, 3].

UV ABSORPTION MAXIMUM 237.5 mµ [2, 3].

SOLUBILITY s. organic solvents; sl. s. water [2, 3].

STABILITY Thermo- and acid stable; alkali labile [3].

OTHER REACTIONS Negative FeCl₃, periodic acid, xanthate, hydroxamate, Benedict, sodium nitroprusside, ninhydrin, Sakaguchi, Ehrlich; decomposes in 0.1 N NaOH into a yellow product. [2] Infrared: pronounced peaks at 2.88, 3.41, 6.83, 7.29, 8.93 µ; less pronounced at 7.68, 8.37, 10.39, 10.83, 10.96, 12.70 µ; peaks of minimal absorption at 6.05, 11.82, 13.78 µ; deep purple when placed in light at 256 mµ. [3]

/1/ 100°C for 5 minutes. /2/ c, 2.8 absolute ethanol.

104. ELAIOMYCIN (Concluded)

BIOLOGICAL ACTIVITY In vitro. Inhibits human and bovine strains of *Mycobacterium tuberculosis* at 0.3-5.0 $\mu\text{g/ml}$. Other bacteria (including mycobacteria) resistant. Some inhibition of fungi, e.g., *Candida* spp.[1]
In vivo. No activity against *Myco. tuberculosis* in mice [1].

ACUTE TOXICITY LD_{50} in mice, 43.7 mg/kg, i.v.; 62.5 mg/kg, s.c.[1]

105. ENDOMYCIN

SOURCE *Streptomyces* sp related to *S. albus* [1]; *S. endus*, n. sp [8].

NATURE Acidic [1].

MOLECULAR WEIGHT: 1450 (pot. titr.); 1300 (cryo-).[2, 8]

UV ABSORPTION MAXIMA 226, 232 $\text{m}\mu$ [8].

SOLUBILITY s. alcohols, methyl cellosolve, water above pH7 and at pH 2 or below¹; sl. s. dioxane; i. ether, chloroform, benzene, ethyl acetate.[1, 2, 8]

STABILITY Thermostable at pH 7-10 [1, 2, 8].

OTHER REACTIONS Infrared: 3.0, 3.56, 5.82, 6.04, 6.87, 7.28, 8.81, 9.45, 10.15, 10.97, 11.71, 11.91, 13.90 μ [2, 8].

QUANTITATIVE DETERMINATION Microbiological: *Torula utilis*, *Candida albicans* [1, 2, 8].

BIOLOGICAL ACTIVITY In vitro. Active against yeasts, fungi, Gram-positive bacteria and protozoa (trypanosomes). No effect on Gram-negative bacteria. Fungi inhibited at 1-25 units/ml: species of *Sclerotinia*, *Torula*, *Endomyces*, *Mycoderma*, *Candida*, *Trichophyton*, *Microsporum*, *Rhizoctonia*, *Glomerella*, *Blastomyces*, *Coccidioides*, *Geotrichum*, *Cryptococcus*, *Histoplasma*, and *Sporotrichum*. [1] Most strains of *Candida albicans* inhibited by 8-18 $\mu\text{g/ml}$; *C. tropicalis* by 6-225 [7]. Concentrations of 25-50 $\mu\text{g/ml}$ suppressed growth of *C. albicans* in tissue cultures, but even much higher levels were not monilicidal [9]. Inhibited ($\mu\text{g/ml}$) *Microsporum canis*, *Epidermophyton floccosum*, 1; *M. audouini*, *Trichophyton rubrum*, *T. schoenleinii*, *T. acuminatum*, *T. crateriforme*, *T. tonsurans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, 6; *T. mentagrophytes*, *M. fulvum*, 14-16; *Sporotrichum schenckii*, >22.[7] Bacteria inhibited at 1-10 units/ml: *Micrococcus pyogenes* var. *aureus*, *Bacillus cereus*, *B. subtilis*, *Brucella abortus*, *Corynebacterium xerose*. The following required 10->100 units for growth inhibition: *Streptococcus faecalis*, *Aerobacter aerogenes*, *Escherichia coli*, *Pseudomonas aeruginosa*. [1] Inhibited *Trypanosoma cruzi* in dilution of 1:12,800 [3]. Was the most active of 11 antibiotics tested against *Trichomonas vaginalis* in vitro. In direct tests, *T. vaginalis* was lysed by concentrations of 50-100 $\mu\text{g/ml}$. [5]

In vivo. Very slight suppression of *Trypanosoma cruzi* in mice treated i.p. with injections of 5-10 mg/kg [3].

ACUTE TOXICITY Mice tolerated doses of 500 mg/kg; 1000 mg/kg were lethal.[1] Inhibited ($\mu\text{g/ml}$) outgrowth of skin tissue in tissue culture at 250-500, and spleen tissue at 2500-5000 [4]. Chick embryonic heart tissue cultures inhibited by 625-1250 $\mu\text{g/ml}$ [8]. Using roller tube tissue culture method, there was no inhibition of human skin explants by concentrations of 1250 $\mu\text{g/ml}$ [10].

PHYTOTOXICITY Of low order. Non-toxic when sprayed in concentrations of 10,000 ppm on wheat, beans, and tomatoes under greenhouse conditions. [5]

RESISTANCE Strains of *Candida albicans* readily developed resistance in vitro (6 to >45-fold increase when sub-cultured 11-15 times in presence of antibiotic)[7].

MISCELLANEOUS Leaf rust of wheat was readily prevented by 100-1000 ppm as spray [6]. Under greenhouse conditions, antibiotic failed to control stem rust of wheat when used as a pre-inoculation spray [11].

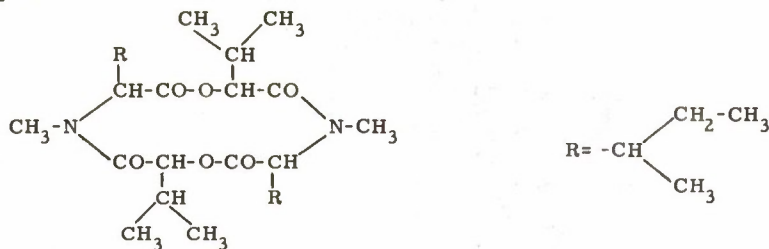
106. ENNIATIN A

SOURCE *Fusarium orthoceras* var. *enniatinum* [1].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{24}\text{H}_{42}\text{O}_6\text{N}_2$ (proposed) [1-3]; 413-446 (found); 454, 459 (analysis). [1, 3]

/1/ Solubility in water at pH 7 reduced by NaCl , Ca^{++} or Mg^{++} .

STRUCTURE



CRYSTAL FORM AND COLOR Long colorless needles [1-3].

MELTING POINT ($^{\circ}\text{C}$) 121-122 [3].

OPTICAL ACTIVITY $[\alpha]_{\text{D}}$ = -90 to $-92^{\circ 1}$ [1, 3].

UV ABSORPTION MAXIMA None characteristic [2, 3].

SOLUBILITY s. organic solvents; less s. water.[2]

STABILITY Thermostable; alkali inactivated [1-3].

OTHER REACTIONS Probably identical with lateritiin I; sublimes in vacuo without loss of activity [1-3].

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium paratuberculosis* [1, 3].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *Myco. tuberculosis*, 1:100,000-1:500,000 dilution; *Myco. paratuberculosis*, 1:1,000,000; *Myco. phlei*, 1:310,000; *Bacillus subtilis*, 1:320,000; *B. cereus*, 1:300,000; *B. megatherium*, *Micrococcus pyogenes* var. *albus*, 1:100,000; *M. pyogenes* var. *aureus*, 1:160,000; *M. citreus*, 1:400,000; *Serratia marcescens*, 1:80,000. *Pseudomonas aeruginosa*, *Escherichia coli*, and *Salmonella* spp are relatively resistant (<1:1000).[1, 5] Inhibits phytopathogenic fungi ($\mu\text{g/ml}$): *Merulius domesticus*, 5; *Calonectria nivalis*, *Helminthosporium gramineum*, *Coniophora cerebella*, *Rhizoctonia crocorum*, 10; *Clasterosporium carphophilum*, *Lenzites abietina*, *Polystictus versicolor*, *Venturia inaequalis*, *Ophiobolus graminis*, *Armillaria mellea*, 20-50. Activity is decreased by 5-50% in the presence of serum.[5]

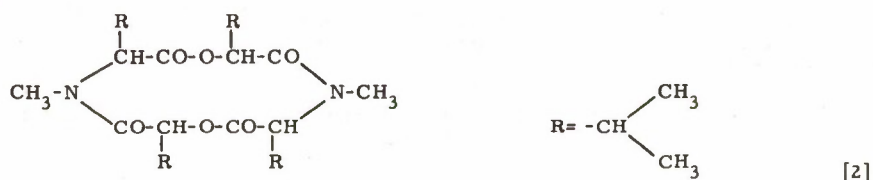
TOXICITY Low toxicity in animals (low solubility precluded high test doses) [5].

107. ENNIATIN B

SOURCE Same as Enniatin A.

MOLECULAR FORMULA $\text{C}_{22}\text{H}_{38}\text{O}_6\text{N}_2$ (proposed) [1, 3].

STRUCTURE



MELTING POINT ($^{\circ}\text{C}$) 173-176 [1, 3].

OPTICAL ACTIVITY $[\alpha]_{\text{D}}$ = -106 to $-108^{\circ 2}$ [1, 3].

SOLUBILITY s. most organic solvents; sl. s. water, petroleum ether.[3]

OTHER REACTIONS Sublimes in high vacuum [3].

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium paratuberculosis* [3].

/1/ c, about 1 chloroform. /2/ c, 0.63-1.2 chloroform.

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Myc. phlei* at 3, *Myc. paratuberculosis* at 5. Activity against bacteria and phytopathogenic fungi weaker than that of Enniatin A.[2]

108. ERYTHROMYCIN

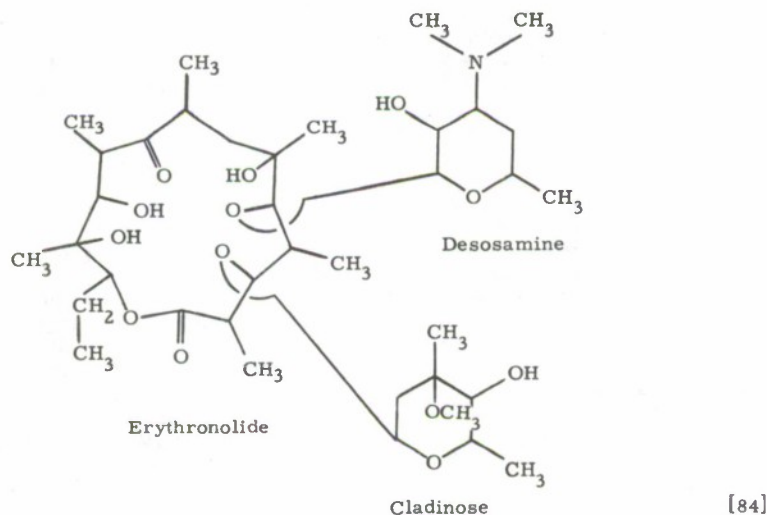
The trademarks for erythromycin are Ilotycin (Eli Lilly & Company) and Erythrocin (Abbott Laboratories).

SOURCE *Streptomyces erythreus* [1].

NATURE Basic [1].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{37}\text{H}_{67-69}\text{NO}_{13}$; 733.9-735.9 (calc.).[5]

STRUCTURE



CRYSTAL FORM AND COLOR White needles [3, 5].

MELTING POINT ($^{\circ}\text{C}$) Base: 136-140¹ [3, 5]. HCl: 170-173. Complex: 82-83.5 (uncorr.) [3].

OPTICAL ACTIVITY Base: $[\alpha]_D^{25} = -78^{\circ 2}$ [1, 3]. Complex: $[\alpha]_D^{25} = -47^{\circ 3}$ [3].

UV ABSORPTION MAXIMA Base: 278 $\text{m}\mu$ [5]. Complex: 274 $\text{m}\mu$ [3].

SOLUBILITY s. alcohols, acetone, chloroform, acetonitrile, ethyl acetate; less s. ether, ethylene dichloride, amyl acetate, water. HCl: very s. water, lower alcohols [1, 3, 5].

STABILITY Stable at -25 to $+4^{\circ}\text{C}$; stable 4 days at 37°C ; unstable to 60 or 100°C . [9]

OTHER REACTIONS One titratable group with pK_a 8.6; activity not reduced by serum. Two basic degradation products: amine A ($\text{C}_8\text{H}_{17}\text{NO}_3$) and amine B ($\text{C}_7\text{H}_{15}\text{NO}_2$), the latter obtained by oxidation of amine A. Two acid degradation products: a neutral oil ($\text{C}_8\text{H}_{16}\text{O}_4$) and a crystalline base ($\text{C}_{29}\text{H}_{49}\text{NO}_8$). [1-3, 5] Reduction of erythromycin with sodium trimethoxyborohydride gives dihydro-erythromycin, the infrared spectrum having only 1 carbonyl band at 5.84μ , with the 5.90μ infrared and 278 $\text{m}\mu$ UV bands of erythromycin being lost [49].

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*, *Streptococcus pyogenes* [1, 8]. Spectrophotometric [10]. Infrared absorption [4]. Colorimetric [6, 7].

BIOLOGICAL ACTIVITY Active primarily against Gram-positive bacteria; a few Gram-negative organisms, certain rickettsiae and larger viruses are also susceptible.

In vitro. Inhibits most strains of the following at concentrations of 0.003-0.1 $\mu\text{g/ml}$: *Bacillus circulans*, *B. polymyxa*, *B. subtilis*, *Corynebacterium diphtheriae*, *C. xerosis*, *Lactobacillus casei*, *Lactobacillus* spp, *Leuconostoc citrovorum*, *Mycobacterium avium*, *Myc. phlei*, *Sarcina lutea*, *Streptococcus mitis*, *Diplococcus pneumoniae*. Most strains of the following are sensitive to 0.1-6.2 $\mu\text{g/ml}$: *Actinomyces israeli*, *B. anthracis*, *B. brevis*, *B. cereus*,

/1/ If slow rate of heating continues, it partially resolidifies and then melts at $190-193^{\circ}\text{C}$. /2/ c, 1.99 alcohol.
/3/ c, 2 ethanol.

Brucella bronchiseptica, *Br. melitensis*, *Br. suis*, *Hemophilus influenzae*, *H. pertussis*, *Listeria monocytogenes*, *Erysipelothrix rhusiopathiae*, *Clostridium* spp, *Lactobacillus arabinosus*, *M. pyogenes* var. *aureus*, *Myc. smegmatis*, *Neisseria catarrhalis*, *N. gonorrhoeae*, *N. meningitidis*, *Str. pyogenes*, *Str. faecalis*, *Streptococcus* spp, *Gaffkya tetragena*, *Pasteurella multocida*, *Vibrio comma*. Generally resistant, >50 µg/ml: most strains of *Aerobacter* spp, *Klebsiella pneumoniae*, *Serratia marcescens*, *Pseudomonas* spp, *Salmonella* spp, *Shigella* spp, *Proteus* spp, *Escherichia coli*, yeasts and fungi.[1, 9, 11-16] *Entamoeba histolytica* was inhibited by dilution of 1:8000 [11]. *Leptospira icterohemorrhagiae* sensitive to 0.001-0.01 µg/ml [50]. Concentrations of 2 mg/ml failed to inactivate the virus of herpes simplex [51]. Active against avian and goat strains of pleuropneumonia-like organisms; strains isolated from sheep were less sensitive.[63]

In vivo. In mice, good protection against infections with *Str. pyogenes* and *D. pneumoniae* afforded by 66 mg/kg, s.c., or 133 mg/kg, oral doses; moderate protection against intranasal infections with *H. pertussis*. [11, 16] Some activity noted in experimental tuberculosis in mice [1, 16]. Daily i.p. doses of 80 mg/kg gave moderate protection in mouse infections with *M. pyogenes* var. *aureus* and *Listeria monocytogenes*, and were ineffective against *Ery. rhusiopathiae*, *B. anthracis* and *K. pneumoniae*; no activity in chicks with experimental fowl typhoid (*Salmonella gallinarum*) infection.[16] In guinea pigs, s.c. doses as low as 2 mg/kg/da were highly effective against *Corynebacterium diphtheriae* [15]. High activity in experimental rabbit syphilis, but less active, on a weight basis, than penicillin [17]. Ten daily i.m. doses of 20 mg/kg cured experimental syphilitic orchitis in rabbits [65]. Single i.p. doses in mice of 125 mg/kg, or oral doses of 125-250 mg/kg, gave high protection against *Borrelia novyi*, moderate protection in experimental toxoplasmosis [1, 18]. Median protective dose against experimental tetanus infection in mice was 11.6 mg/kg/da, given i.p. for 5 days [64]. High oral doses of 200 mg/kg effective in mouse infections with *Trypanosoma equiperdum*, but inactive against *T. cruzi* and *T. gambiense*. Highly effective in clearing rats infected with *Entamoeba histolytica*; some activity against *Trichomonas vaginalis*; also suppressed pinworm (*Syphacia obvelata*) in mice.[1, 18] Daily i.p. doses of 100 mg/kg in mice for 7 days gave 100% protection in infections with psittacosis virus; lower oral doses suppressed infections with lymphogranuloma venereum and meningopneumonitis viruses. High activity against *Rickettsia prowazeki* in embryonated eggs [11]. Active against *R. rickettsii*, *R. typhi*, and *R. akari* in chick embryos; maximum tolerated doses slightly suppressed *Coxiella burnetii* [52]. Concentrations of 0.1-0.5 mg/ml in drinking water protected mice against experimental air-borne mouse pneumonitis virus infection [53]. Oral dosage initiated within 2 days of infection protected 80% of guinea pigs against *Leptospira icterohemorrhagiae*. Renal carriers of this organism were reduced to 10% by continuing medication for 6 days. Similar results were obtained in hamsters.[50] No activity against smaller viruses (rabies, poliomyelitis, lymphocytic choriomeningitis, influenza, Semliki Forest) in mice or guinea pigs [11].

CLINICAL Because of its high order of activity against Gram-positive bacteria, erythromycin is useful in infections caused by these organisms and particularly when strains (e.g., *M. pyogenes* var. *aureus*) are resistant to penicillin and the tetracycline antibiotics. Optimal oral dosage not finally established. The average effective dose for adults ranges from 0.2-0.5 g every 6 hours; for children, 6-8 mg/kg doses every 6 hours has been suggested. Pneumonia from *D. pneumoniae* has responded to initial doses of 0.2 g, with 0.1 g every 3 hours thereafter. In severe infections, doses up to 0.5 g have been repeated every 6 hours [19, 20]. The antibiotic (erythromycin glucoheptonate) may also be administered by the intravenous route [39]. Good results have been obtained in micrococcic enteritis and septicemia caused by strains of *M. pyogenes* resistant to penicillin and the tetracycline antibiotics [21, 22]. Excellent clinical responses in pneumonia caused by *D. pneumoniae* and in micrococci and streptococci infections, including pharyngitis, tonsillitis, scarlet fever and cellulitis [9, 23, 24, 33], and has been used with success prophylactically in patients convalescing from rheumatic fever [25]. Favorable, as well as indifferent, results have been reported in preliminary trials in gonorrhoea, lymphogranuloma venereum, chancroid and donovanosis [26-30]. In experimental chancroid induced in human volunteers by intradermal injection of cultures of *H. ducreyi*, topical application of 1% erythromycin ointment 24 hours later prevented the development of lesions [71]. In a small series of patients with primary or secondary syphilis, 200 mg administered 4 times daily rapidly cleared treponemes and reduced the serologic titer [27]. Gonorrhoeal urethritis successfully treated with single intramuscular doses of 100 or 200 mg [66]. Was of value in therapy of non-gonococcal urethritis; total oral doses of 6.0 g were given over a 5-day period.[69] Good responses in scrub typhus [70]. Favorable results obtained following i.v. therapy in meningitis caused by *N. meningitidis* and *H. influenzae* [67]. Total oral doses of 3.2-5.6 g over periods of 4-7 days effectively treated cases of anthrax infection in man [68]. Favorable results in intestinal infections caused by *Entamoeba histolytica* [37, 54]. Topical use of ophthalmic ointment containing 5 mg/g valuable in the treatment of ocular infections caused by susceptible bacteria [74]. Good clinical responses in trachoma [31], and the antibiotic proved useful in the treatment and prophylaxis of surgical infections [32]. Topical therapy useful in cases of acute pyoderma [34, 35] and in acne vulgaris [36]. Antibiotic therapy failed to influence viral infections of the respiratory tract, including influenza [72, 73]. Little or no effect on the clinical course of pertussis demonstrated in children treated orally with 50 mg/kg/da in divided doses over periods of 4-21 days [55]. Preliminary trials indicate oral medication is effective in actinomycosis [56] and gave good clinical responses in acute and chronic brucellosis [57]. Erythromycin stearate in daily doses of 15 mg/kg for 10-14 days cleared 14 of 15 patients with hepatic amebiasis [58].

VETERINARY Oral medication, or i.v. doses of 50-150 mg, effective in the control of a variety of canine infections, including pneumonia, bronchitis, pyogenic surgical infections, otitis media and early cases of distemper [43, 59-61]. Useful in urinary tract infections of small animals, with usual doses in dogs of approximately 300-1200 mg/da, administered orally in divided doses [59, 60].

108. ERYTHROMYCIN (Concluded)

ACUTE TOXICITY LD₀ in mice, 1000 mg/kg, s.c.; 2000 mg/kg, oral. LD₅₀, approximately 1800 mg/kg, s.c. Doses of 250 mg/kg, s.c. or i.p., were irritating. Oral doses of >100 mg/kg non-toxic to dogs.[1, 15] When administered intratracheally in doses of 5-20 mg/kg in dogs, or in doses of 10-20 mg as an aerosol to guinea pigs, caused bronchopneumonic inflammations which, however, were less severe than those caused by tetracycline antibiotics [75].

In vitro. In tissue cultures, erythromycin inhibited outgrowth of skin tissue at concentrations of 345-690 µg/ml and spleen tissue at 520-1040 µg/ml [38].

CHRONIC TOXICITY 5% antibiotic in diet well tolerated in mice, as were daily oral doses of 1.0 g for 2 weeks in dogs. No chronic toxicity in mice receiving daily i.p. or s.c. doses of 700 mg/kg, or in dogs given oral doses of 250 mg/kg/da for 14 weeks.[1, 15, 42] Oral doses for 3-6 days poorly tolerated in guinea pigs and hamsters, with development of diarrhea and anorexia [50].

In man, toxic symptoms not generally observed with oral doses up to 300-500 mg. Higher doses may cause gastric distress; this was not uncommon in patients receiving 2.0 g every 6 hours [15, 20, 40]. Continued topical use of dermatological preparations, containing 1% of the antibiotic, is associated with a low index of skin sensitization, in contrast to the sulfonamides, penicillin and streptomycin [76].

RESISTANCE Some strains of *M. pyogenes* var. *aureus* developed resistance in vitro with facility; less readily developed by *Str. pyogenes*. [15, 45] No significant cross-resistance between erythromycin and penicillin or most other antibiotics, with the exception of carbomycin [15, 46-48]. In another series, a high percentage of *M. pyogenes* var. *aureus* strains which were resistant to carbomycin were found sensitive to erythromycin [79]. The incidence of infections caused by *M. pyogenes* var. *aureus* strains resistant to erythromycin, as well as to other established antibiotics, is increasing [80-82].

ABSORPTION AND EXCRETION Peak blood levels noted 1 hour after single oral doses in dogs; readily detectable levels in the urine, feces and cerebrospinal fluid.[1] In man, single and multiple oral administration of 0.3-0.5 g produced serum levels of 0.12-2.0 µg/ml in 1 hour, with concentrations as high as 8-16 µg in 3 hours dropping to 0.5-4.0 µg in 9 hours. Therapeutically effective concentrations (0.12 µg) were detected in cerebrospinal fluid, ascitic fluid, and bile, with prolonged excretion at high levels in the urine. The antibiotic traversed the placental barrier.[15] Intravenous preparations administered in single 300 mg doses produced serum levels of 21-82 µg/ml in a few minutes, falling to 2.5 µg in 2 hours and approximately 0.3 µg at the 6th hour. Low spinal fluid concentrations (0.04-0.08 µg) were maintained 2-6 hours after injection. About 15% of the original i.v. dose was excreted in the urine during the first 24 hours.[41] Single or repeated doses of 1% erythromycin lactobionate, injected intrapleurally, were well tolerated in man. A single dose of 250 mg gave high concentrations in pleural fluid and adequate levels in blood for at least 3 days.[62]

MODE OF ACTION Action is bacteriostatic or bactericidal, depending on concentration of the antibiotic and sensitivity of the organism. Active primarily against rapidly multiplying bacteria.[44] Inhibition of *C. diphtheriae* markedly antagonized by addition to culture medium of β-alanine, calcium pantothenate, or L-carnosine; these substances permitted growth in 30-70 times the original minimal inhibitory concentrations of the antibiotic.[77] In non-bactericidal concentrations, erythromycin, like chloramphenicol and the tetracyclines, inhibited oxidation of glutamic acid in *Escherichia coli* [78].

MISCELLANEOUS Solutions containing 1 mg/ml were tolerated for 24 hours by viviparous tropical fish (guppies) [83].

109. ERYTHROMYCIN B

SOURCE Same as erythromycin [1].

NATURE Basic [1].

MOLECULAR FORMULA AND WEIGHT C₃₇H₇₁NO₁₂; equiv. wt. 708, 720 (found) [3]; 736 ± 36 (titr.) [1].

MELTING POINT (°C) 191-195 [1]; 202-203 [3]. HCl: 149-150; SO₄: 154-156; hydriodide: 167-169; benzoate: 102-104; ethyl carbonate ester: 117-118; p-(p-hydroxyphenylazo) benzene sulfonate: 165-167; stearate: 54-57.[3]

OPTICAL ACTIVITY [α]_D²⁵ = -78° [1]; [α]_D = -98° ± 1 [3].

UV ABSORPTION MAXIMUM 286 mµ [1].

SOLUBILITY s. ether, acetone, chloroform, ethyl acetate; i. water. Acid salts: s. water. [1]

STABILITY More stable to acid than erythromycin² [3].

/1/ c, 2 ethanol. /2/ Treatment at pH 1.5 of extracted mixture destroys erythromycin and leaves B unchanged.

109. ERYTHROMYCIN B (Concluded)

OTHER REACTIONS Properties very similar to erythromycin from which it can be separated in Craig distribution apparatus [1]. Methoxyl, N-methyl, C-methyl tests positive; on mild acid hydrolysis, cladinose ($C_8H_{16}O_4$) and 2 bases, ($C_{29}H_{55}NO_9$) and ($C_{29}H_{51}NO_8$), are isolated, the former on strong acid hydrolysis yielding desosamine HCl and possibly an α , β unsaturated aldehyde or ketone.[3]

BIOLOGICAL ACTIVITY In vitro. Antimicrobial spectrum similar to that of erythromycin, but B is only approximately 75-85% as active [1].

In vivo. Activity resembles that of erythromycin [4].

TOXICITY Approximately twice as toxic to animals as erythromycin [2].

RESISTANCE *Micrococcus pyogenes* var. *aureus* developed resistance to product B somewhat more readily than to erythromycin [4].

ABSORPTION Following oral doses in man, blood levels obtained were approximately twice as high as those following similar doses of erythromycin. After oral doses of 300 mg of erythromycin B, blood concentrations of approximately 5 μ g/ml appeared in 2 hours and 0.8 μ g in 8 hours.[2]

110. ESPERIN

SOURCE *Bacillus mesentericus* [1].

CRYSTAL FORM Na salt: needles [2].

MELTING POINT ($^{\circ}$ C) Na salt: 268-269 (d.). Free acid: 195.[1,2]

SOLUBILITY s. dilute alkali, acetone, chloroform, benzene, acetic acid; i. water.[3]

OTHER REACTIONS Contains DL-leucine, L-aspartic acid, L-valine, and a probable fatty acid, C_{14-16} [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Mycobacterium tuberculosis* in dilution of 1:160,000 [1].

111. ESTIN

SOURCE *Penicillium paxilli* var. *echinulatum* [1].

MOLECULAR FORMULA $C_{16}H_{14}O_6Cl_2$ [1].

MELTING POINT ($^{\circ}$ C) 223-225 [1].

OTHER REACTIONS Contains 2 MeO groups; impure materials contain a second substance, nordin: $C_{18}H_{16}O_8Cl_2$, needles, MP 134-136 $^{\circ}$ C.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus* (in dilution of 1:700,000), *Sarcina lutea* (1:400,000), and *Mycobacterium tuberculosis* (1:20,000-1:40,000) [1].

112. ETAMYCIN
(Viridogrisein)

SOURCE *Streptomyces* sp, *S. griseus* [1,2]; *S. griseoviridis* [7].

NATURE Amphoteric; weakly basic polypeptide [1,3].

MOLECULAR FORMULA AND WEIGHT $C_{42-43}H_{62-64}N_8O_{11}$ (suggested) [3]; 550 ± 10^1 [1]; 530 ± 10^2 [1]; 816-865, 982 (neut. equiv. found) [3].

CRYSTAL FORM AND COLOR White crystals [1]; white amorphous solid [2].

MELTING POINT ($^{\circ}$ C) HCl: 163-170 (some decomposition) [1,3].

OPTICAL ACTIVITY $[\alpha]_D^{25} = +7.7^{03}$ [1], $+28^{04}$, $+59^{05}$ [2], -10^{06} [2].

UV ABSORPTION MAXIMA 304 $m\mu^7$, 333-335 $m\mu^8$ [1,2]. Strong end absorption below 250 $m\mu$ [1].

SOLUBILITY Base: s. lower alcohols and ketones, chloroform, carbon tetrachloride, carbon disulfide, ethyl acetate, peanut oil, ether, 1 N HCl, 1 N NaOH; sl. s. water⁹; i. petroleum ether. HCl: s. water¹⁰, methanol,

/1/ Cryoscopic in benzene. /2/ Cryoscopic in dioxane. /3/ c, 2 methanol. /4/ c, 5 absolute ethanol. /5/ c, 5 chloroform. /6/ c, 5 in 50% aqueous ethanol. /7/ Ethanolic or methanolic HCl. /8/ NaOH. /9/ 1 mg/ml. /10/ 4 mg/ml.

112. ETAMYCIN (Concluded)

ethanol, formamide; sl. s. acetone, ethyl acetate, less polar solvents.[1, 2]

STABILITY Very stable at acid and neutral pH; unstable at alkaline.[3]

OTHER REACTIONS C, 60.6, 60.3; H, 7.28, 7.22; N, 12.4, 12.8 [1]. Infrared: Strong bands at 6.05, 6.60, 6.87 μ ; moderate bands at 2.93, 3.30, 5.70, 9.5 μ ; weak bands at 12.40, 14.35 μ . Brownish-red with FeCl_3 ; weakly positive Folin-Ciocalteu, Baeyer; negative ninhydrin, Sakaguchi; doubtful biuret; acid hydrolysate gives strong ninhydrin; contains threonine, hydroxyproline, alanine, one or more of the leucines; resembles pyridomycin.[1-3]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus mycoides*, *Micrococcus pyogenes* var. *aureus* [1]; *Streptococcus infrequens* [4].

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive and some Gram-negative bacteria; slight activity against certain protozoa, rickettsiae and larger viruses; no activity against fungi. Inhibits ($\mu\text{g/ml}$) *Actinomyces bovis*, *B. anthracis*, *B. cereus*, *Clostridium feresi*, *Cl. hemolyticum*, *Cl. novyi*, *Cl. perfringens*, *Cl. septicum*, *Cl. sporogenes*, *Cl. tetani*, *Corynebacterium acnes*, *C. diphtheriae*, *C. xerosis*, *Erysipelothrix rhusiopathiae*, *Diplococcus pneumoniae*, *Lactobacillus acidophilus*, *M. pyogenes* var. *aureus*, *Moraxella bovis*, *Gaffkya tetragena*, *Streptococcus agalactiae*, *Str. dysgalactiae*, *Str. uberis* at 0.04-1.25; *Streptococcus* sp., *Str. pyogenes*, *B. subtilis*, *L. casei*, 0.63-2.5; *Neisseria meningitidis*, 1-5; *N. gonorrhoeae*, *Listeria monocytogenes*, 5; *N. catarrhalis*, 2.5; *Hemophilus pertussis*, 5-10; *H. influenzae*, 10-50; *Mycobacterium tuberculosis*, 0.8-6.2; *Shigella sonnei*, *Klebsiella pneumoniae*, *Proteus vulgaris*, 200; *Brucella suis*, *Br. bronchiseptica*, *Escherichia coli*, *Malleomyces mallei*, *Paracolobactrum* spp, *Salmonella schottmuelleri*, *S. typhosa*, *Pseudomonas aeruginosa*, *Candida albicans*, >10->200; pleuropneumonia-like organisms, 6.25; *Leptospira icterohemorrhagiae*, 33. Protozoa ($\mu\text{g/ml}$): *Entamoeba histolytica*, 667; *Trichomonas foetus*, 2000; *Trypanosoma rhodesiense* partially inhibited at 250; *T. cruzi* resistant.[1, 4]

In vivo. Mice protected against *D. pneumoniae* with i.p. doses of 90 mg/kg, or daily oral doses of 125-400 mg/kg, b.i.d.[1, 4]. Good activity with 200-400 mg/kg oral doses in infections with *Str. pyogenes* and *M. pyogenes* var. *aureus*. Slightly active in mouse infections with *H. pertussis*, viruses of meningopneumonitis and psittacosis, and in embryonated eggs against *Rickettsia prowazeki*. Inactive against small viruses and *Schistosoma mansoni* in mice. Some protection afforded in chicks infected with *Plasmodium lophurae*. [4] In rats and dogs oral doses of 45-168 mg/kg/da were effective in experimental intestinal amebiasis [6].

VETERINARY Effective in acute bovine mastitis caused by micrococci or streptococci (some of these cases had not responded to penicillin or streptomycin therapy), following instillation of 250 mg per udder quarter. In preliminary trials, favorable results noted in infectious bronchitis of chickens treated with single oral dose of 250 mg; the same doses also gave good results in kittens with pan-leukemia.[4]

ACUTE TOXICITY LD_{50} in mice, 25-39 mg/kg, i.v.; 125 mg/kg, or >2000 mg/kg, s.c.; >3000 mg/kg, oral. Dogs tolerated single oral doses of 1000 mg/kg; higher doses induced marked leukopenia. Oral LD_{50} in rabbits, >4000 mg/kg.[4, 5]

CHRONIC TOXICITY Mice tolerated 2 daily doses of 100 mg/kg, s.c., for 20 days, or oral doses of 1000 mg/kg/da for 4 days. Hamsters and guinea pigs did not tolerate antibiotic as well as did mice and dogs.[4] Repeated daily oral doses of >250 mg/kg in dogs and cats, but not in rabbits and mice, induced marked leukopenia which subsided soon after drug was withdrawn [5]. Instillation of 250-1000 mg per quarter into bovine udder gave no signs of irritation [4].

ABSORPTION AND EXCRETION Oral doses of 250-500 mg/kg in mice produced blood levels of 45-50 $\mu\text{g/ml}$ in 1 hour, with no detectable concentration at 3 hours. Peak urine concentrations of 142-830 $\mu\text{g/ml}$ within 2 hours. In dogs, 800 mg/kg oral doses were poorly absorbed.[4] Oral doses of 1000 mg/kg gave blood concentrations of 1-10 $\mu\text{g/ml}$ in 5 hours, with variable distribution in tissues and body fluids; no detectable concentration in cerebrospinal fluid [5].

113. EULICIN

SOURCE *Streptomyces* sp resembling *S. parvus* [1].

CRYSTAL FORM AND COLOR Helianthate: rosettes. HCl: colorless.[1]

MELTING POINT ($^{\circ}\text{C}$) Helianthate: 139 [1].

SOLUBILITY HCl: s. water [1].

STABILITY HCl: Stable to autoclaving 1 hour at 120°C [1].

OTHER REACTIONS An actinomycin and a basic substance also produced in culture fluids [1].

QUANTITATIVE DETERMINATION Microbiological: *Aspergillus niger* [1].

113. EULICIN (Concluded)

BIOLOGICAL ACTIVITY *In vitro*. Primarily active against fungi. Inhibits ($\mu\text{g/ml}$) *A. niger* at 0.005; *Blastomyces dermatitidis*, 0.018-0.037; *Alternaria solani*, <0.074; *Monosporium apiospermum*, *Histoplasma capsulatum*, *Cladosporium werneckii*, *Cryptococcus neoformans*, 0.074; *Hormodendrum pedrosoi*, 0.14; *H. compacti*, *Phialophora verrucosa*, 0.28; *Bl. brasiliensis*, 0.59; *Epidermophyton floccosum*, 1.2; *Trichophyton mentagrophytes*, 2.3; *Microsporium gypseum*, 9.5; *Saccharomyces cerevisiae*, 35-38.3; *Candida stellatoidea*, 60.4; *C. albicans*, *C. krusei*, 121; *Fusarium oxysporum*, >38. Bacteria and actinomycetes ($\mu\text{g/ml}$): *Mycobacterium tuberculosis* var. *hominis*, 0.7; *Bacillus subtilis*, 8.7; *Micrococcus pyogenes* var. *aureus*, 17.4; *Nocardia asteroides*, 2.3. [1,2] Gram-negative bacteria not sensitive to 25 $\mu\text{g/ml}$: *Escherichia coli*, *Proteus vulgaris*, *Salmonella typhosa*, *Pseudomonas aeruginosa* [1].

In vivo. Active in mice against intraperitoneal infection with *Bl. dermatitidis*, with median protective daily doses (administered for 10 days) of 0.04 mg/kg, i.p., 0.42 mg/kg, i.m., and 28.6 mg/kg, oral [2].

PHARMACOLOGY LD₅₀ in mice, 3 mg/kg, i.v.; 17 mg/kg, i.p.; 12 mg/kg, i.m.; 46 mg/kg, s.c. [1] Ten daily doses of 8.6 mg/kg, i.p., or 10.1 mg/kg, were toxic in mice (LD₅₀). Preliminary tests in mice indicate that the antibiotic rapidly disappears from the blood within one hour following single i.v. injection [2].

MODE OF ACTION Fungicidal to *Cryptococcus neoformans* in vitro in low concentration of 0.25 $\mu\text{g/ml}$; this was only approximately three times the fungistatic level. [2]

114. EUMYCETIN

SOURCE *Streptomyces* sp resembling *S. purpeochromogenus* [1].

CRYSTAL FORM AND COLOR Colorless fine needles [1].

MELTING POINT ($^{\circ}\text{C}$) 148-150 [1].

UV ABSORPTION MAXIMUM 302 $\text{m}\mu$ ¹ [1].

SOLUBILITY s. organic solvents; i. or sl. s. water, 10% HCl, 10% NaOH. [1]

OTHER REACTIONS Positive FeCl₃, diazo; negative biuret, ninhydrin, Millon, Molisch, Liebermann-Burchard, Sakaguchi, Rosenheim, Fehling; no color with concentrated H₂SO₄, HCl. [1]

QUANTITATIVE DETERMINATION Microbiological: *Candida albicans* [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits fungi ($\mu\text{g/ml}$): *Mycoderma* sp, *Penicillium chrysogenum*, <0.05; *Trichophyton interdigitale*, 0.15; *Aspergillus oryzae*, 0.32; *Willia anomala*, 0.5; *Oidium lactis*, *Saccharomyces saké*, 1; *Rhizopus nigricans*, *Mucor mucedo*, *Candida albicans*, 10. Actinomycetes: *Nocardia mexicana*, *Streptomyces griseus*, <0.05; *S. roseoflavus*, 0.1; *N. asteroides*, 1; *S. scabies*, 5. Bacteria: *Mycobacterium tuberculosis*, 100; *Bacillus subtilis*, *Micrococcus pyogenes* var. *aureus*, *Escherichia coli*, >100. [1]

TOXICITY Very toxic in mice; LD₅₀, 2.2 mg/kg, i.p.; 3.0 mg/kg, s.c. [1]

115. EUMYCIN

SOURCE *Bacillus subtilis* [1].

SOLUBILITY s. butanol, ethanol, acetone; i. ether, amyl acetate. [1]

STABILITY Thermostable below pH 8 [1].

OTHER REACTIONS Similar to bacillomycin [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Corynebacterium diphtheriae* at 5; *Mycobacterium tuberculosis* and *Myc. avium* at 100-300. Slight activity against *Micrococcus pyogenes* var. *aureus*. No activity against *Escherichia coli*, *Salmonella* spp. Inhibits fungi, 100-300 $\mu\text{g/ml}$: *Trichophyton mentagrophytes*, *Epidermophyton floccosum* and *Microsporium gypseum*. No activity against *Candida* and *Cryptococcus* spp. [1]

In vivo. Inconclusive results in guinea pigs infected with *Myc. tuberculosis* [2].

ACUTE TOXICITY Mice tolerated i.v. doses of 250 mg/kg [2].

116. EUROCIDIN

SOURCE *Streptomyces albireticuli*, n. sp [2].

UV ABSORPTION MAXIMA 318, 333, 350 $\text{m}\mu$ [1].

/1/ In methanol.

116. EUROCIDIN (Concluded)

SOLUBILITY s. alkali; i. water.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi, 3.1-6.3 µg/ml: *Cryptococcus neoformans*, *Penicillium chrysogenum*, *Trichosporon beigei* III, *T. utilis*, *Candida tropicalis*, *Saccharomyces sake*. Growth inhibition of *C. albicans*, *Sporotrichum beurmanni*, and *Aspergillus niger* at 12.5; *Trichophyton mentagrophytes*, *T. rubrum*, 25. Inactive against bacteria: *Bacillus subtilis*, *Escherichia coli*, *Micrococcus pyogenes* var. *aureus*, *Nocardia asteroides*. [1] Other investigators report *C. albicans*, *Sac. cerevisiae*, and *A. niger* sensitive to 1.6 µg/ml; *Absidia orchidis*, 0.4; *C. krusei*, 3.1; *Mucor pusillus*, 6.2; *Trichophyton interdigitale*, 12.5. [3]

ACUTE TOXICITY LD₅₀, i.p. in mice, 22 mg/kg [2], 36 mg/kg [1].

117. EXFOLIATIN

SOURCE *Streptomyces exfoliatus* [1].

MOLECULAR FORMULA C₂₇H₄₀O₁₆Cl·H₂O [1].

CRYSTAL FORM AND COLOR Colorless needles [1].

MELTING POINT (°C) 172 [1].

SOLUBILITY s. ethanol, acetone, chloroform, ethyl acetate; sl. s. petroleum ether, ether, water. [1]

OTHER REACTIONS Positive Molisch, FeCl₃; negative Fehling, Tollens, Liebermann-Burchard. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus*, *Diplococcus pneumoniae*, *Streptococcus pyogenes*, *Bacillus subtilis*, *B. anthracis*, *Corynebacterium diphtheriae* and *Hemophilus pertussis* at 0.3-5.0 µg/ml. With the exception of *H. pertussis*, Gram-negative bacteria are not sensitive. [1, 2]

ACUTE TOXICITY LD₅₀ in mice, 500 mg/kg, s.c. [2]

118. FERMICIDIN

SOURCE *Streptomyces* sp resembling *S. griseolus* [1].

MOLECULAR FORMULA C₁₄H₂₁NO₄ [1].

CRYSTAL FORM AND COLOR Colorless needles [1].

MELTING POINT (°C) 96-97 [1].

UV ABSORPTION MAXIMUM 290 mµ [1].

OPTICAL ACTIVITY [α]_D¹⁸ = +52.3° ± 1.5° [1].

QUANTITATIVE DETERMINATION *Saccharomyces cerevisiae* [1].

BIOLOGICAL ACTIVITY In vitro. Active against fungi and protozoa (*Trichomonas vaginalis*). Inhibits (µg/ml) *Sac. formosensis*, 0.04; *Sac. pastorianus*, 0.05; *Sac. cerevisiae*, 0.4; *Torula rubra*, 0.2; *Candida krusei*, 0.5; *C. tropicalis*, 10; *Alternaria kikuchiana*, *Colletotrichum atramentarium*, *Phytophthora infestans*, 20; *Ustilago zaeae*, 50. Resistant, >100 µg/ml: *Aspergillus* spp, *Penicillium chrysogenum*, *Mucor mucedo*, *Trichophyton* spp. Protozoa: *Trichomonas vaginalis* inhibited at 0.2 µg/ml. [1] In other reports, *Willia* sp sensitive to 0.1; *Torula utilis*, 0.2; *Botrytis* sp, 0.8; *Aspergillus niger*, 1.6; *Absidia orchidis*, 3.1; *Candida albicans*, 50; *Trichophyton interdigitale*, 100. [2]

VETERINARY Daily intravenous doses of 15-25 µg/kg ineffective in the treatment of chronic infectious (viral) anemia in horses [3].

ACUTE TOXICITY LD₅₀ in mice, 180 mg/kg, i.v.; in rats, 2 mg/kg, i.v. [1]

119. FILIPIN

SOURCE *Streptomyces filipinensis*, n. sp [2, 3].

NATURE Conjugated polyene; neutral [2].

MOLECULAR FORMULA AND WEIGHT C₃₀H₅₀O₁₀; 571 (calc.). [2]

/1/ c, 0.65 water.

CRYSTAL FORM AND COLOR Fine feathery needles [2].

OPTICAL ACTIVITY $[\alpha]_D^{22} = -148.3^{\circ 1}$ [2].

UV ABSORPTION MAXIMA 355, 338, 322 $m\mu^2$ [2, 3].

SOLUBILITY v.s. dimethylformamide, pyridine; s. 95% ethanol, methanol, n-butanol, isopropyl alcohol, tert.-butyl alcohol, glacial acetic acid, ether, ethyl acetate, amyl acetate; i. water, chloroform, 50% ethanol, methylene chloride, Skellysolve B.[2, 3]

STABILITY Thermolabile; susceptible to autoxidation, especially in light; stable in dark in air at refrigerated conditions; stable in dilute ethanolic solution (50 $\mu\text{g}/\text{ml}$), but unstable at 10 mg/ml under all conditions; deteriorates slowly in methanolic solution at pH 2 and 11.[2]

OTHER REACTIONS Resembles fungichromin; at 147 $^{\circ}$ changes to a second form which melts at 195-205 $^{\circ}$ (d.); indication of partial degradation in higher form. Infrared (Nujol): bands at 3580, 3360, 1715, 1177, 1137, 1085, 1040, 1005, 840 (recip. cm). Infrared (5% solution in dimethylformamide): bands at 1303, 1160, 1005, 958, 846 (recip. cm). Positive Molisch; negative ninhydrin, Benedict, biuret, Tollens, anthrone, FeCl_3 , 2,4-dinitrophenylhydrazine. Degrades in 2 ways, (1) where biological activity and UV maxima disappear simultaneously, and (2) when concentrated methanolic or ethanolic solutions stand at 4 $^{\circ}\text{C}$. In the latter case, a white crystalline substance, without antifungal activity but still a polyene, is formed (probable empirical formula, $\text{C}_{30}\text{H}_{50}\text{O}_{11}$). Deep blue color in concentrated HCl or H_2SO_4 , but not in HNO_3 . [1, 3]

QUANTITATIVE DETERMINATION Microbiological: *Saccharomyces pastorianus* ATCC 2360 [2]. *Penicillium oxalicum* [2, 3]. UV [2, 3].

BIOLOGICAL ACTIVITY In vitro. Active against fungi. Inhibits ($\mu\text{g}/\text{ml}$) *Cryptococcus neoformans*, 0.95; *Candida albicans*, *Histoplasma capsulatum*, *Microsporium audouini*, *Monosporium apiospermum*, *Sporotrichum schenckii*, *Trichophyton rubrum*, 7.7; *Coccidioides immitis*, *Homodendrum compactum*, *Phialophora verrucosa*, 15.5; *Geotrichum* sp, *Blastomyces dermatitidis*, *Nocardia asteroides*, 31. Saprophytes and plant pathogens ($\mu\text{g}/\text{ml}$): *Gnomonia fragariae*, 0.95; *Colletotrichum lindemuthianum*, *Endothia parasitica*, 1.9; *Aspergillus niger*, *P. digitatum*, *Phoma betae*, *Phomopsis* sp, *Thielaviopsis* sp, 3.9; *Dendrophoma obscurans*, *Fusarium oxysporum* dianthi, *Helminthosporium sativum*, *Sclerotinia sclerotiorum*, 7.8; *Diplodia* sp, *Penicillium notatum*, 31; *Rhizoctonia solani*, 500. Yeasts: *Sac. pastorianus*, *Zygosaccharomyces prioranus*, 5 $\mu\text{g}/\text{ml}$. Protozoa: *Trichomonas foetus* sensitive to 25-50 $\mu\text{g}/\text{ml}$. Bacteria not sensitive to 1000 $\mu\text{g}/\text{ml}$: *Micrococcus pyogenes* var. aureus, *Streptococcus pyogenes*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella typhosa*, *Proteus vulgaris*, *Pseudomonas aeruginosa*. [3]

PHYTOTOXICITY Concentrations of 100 $\mu\text{g}/\text{ml}$ had no toxic effect upon germination of pea and tomato seeds [3].

PHYTOPATHOLOGY Sprays with crude filipin partially protected young tomato plants from gray leaf spot caused by *Stemphylium solani* [3]. Immersion of pea seeds in the antibiotic prevented development of fungus rot [1].

MODE OF ACTION Action against *Candida albicans* is primarily fungicidal; these cells were non-viable when exposed to concentrations of 10 $\mu\text{g}/\text{ml}$ for 7-24 hours or to 50 $\mu\text{g}/\text{ml}$ for 2 hours. A greater concentration, or longer exposure period, was required to kill *Penicillium oxalicum*. [4]

120. FLAVACID

SOURCE *Streptomyces* sp resembling *S. flavus* [1].

NATURE Weakly acidic [1].

CRYSTAL FORM AND COLOR Yellowish cryst. powder [1].

MELTING POINT ($^{\circ}\text{C}$) 102-105 (d.) [1].

UV ABSORPTION MAXIMA 340, 360, 380 $m\mu$ [3].

SOLUBILITY s. water, butanol, acetone. Na salt: s. methanol, aqueous acetone, water, ethanol; less s. acetone, butanol; i. ether, ethyl acetate, chloroform, benzene. [1]

STABILITY Unstable at acid and alkaline pH [1].

/1/ c, 0.89 methanol. /2/ Shoulder at 305 $m\mu$; in methanol, but does not change in 0.1 N KOH or HCl.

120. FLAVACID (Concluded)

OTHER REACTIONS Serum inactivated; yellowish at neutral pH, green at acid, red at alkaline; precipitates as Ba, Ca, Pb, Zn, or procaine crystalline salts; negative ninhydrin, FeCl_3 ; resembles fungicidin.[1]

QUANTITATIVE DETERMINATION Microbiological: *Saccharomyces cerevisiae* [1].

BIOLOGICAL ACTIVITY In vitro. Active against yeasts, fungi, a few bacteria, and also *Trichomonas vaginalis*. Inhibits ($\mu\text{g/ml}$) *Aspergillus* spp, 3-12; *Mucor* spp, 3; *Torula utilis*, 1.2; *Trichophyton* spp, *Candida albicans*, 0.6-2.5. *Bacillus subtilis*, *B. anthracis* and *Micrococcus pyogenes* var. *aureus* are sensitive to 3-6 $\mu\text{g/ml}$. [1] According to another report, *Sac. cerevisiae* inhibited by 3.1 $\mu\text{g/ml}$; *C. krusei*, *Botrytis* sp, 12.5; *Torula utilis*, *Willia* sp, *A. niger*, 25; *Absidia orchidis*, *Mucor pusilis*, 50; *Trichophyton interdigitale*, 100.[2]

In vivo. Activity against *C. albicans* infection in guinea pigs. Oral doses of 10 mg cleared the feces of *C. albicans*. [1]

CLINICAL Was of some value when applied topically in patients with trichophyton infections. Favorable results obtained with tamponades containing 20 mg in *Trichomonas vaginalis* vaginitis. [1]

ACUTE TOXICITY LD_{50} in mice, 50 mg/kg, i.p. [1]

121. FLAVEOLIN

SOURCE *Streptomyces* sp [1].

NATURE Basic [1].

MELTING POINT ($^{\circ}\text{C}$) Picrate: 126-128 (d.). Reineckate: 147-150 (d.). [1]

SOLUBILITY HCl: s. water, methanol, ethanol, propanol; sl. s. acetone, benzene, butanol, chloroform; i. ether, petroleum ether, ethyl acetate. Free base: s. butanol, chloroform, iso-amyl alcohol. [1]

STABILITY Fairly stable at pH 2; unstable at alkaline pH at 100 $^{\circ}\text{C}$. [1]

OTHER REACTIONS HCl lemon yellow at acid pH, reddish-brown at alkaline; greenish-blue with Cu acetate in alcohol; positive Liebermann, Pauly; negative Millon, biuret, Sakaguchi, ninhydrin; black color but no precipitate with Fehling; HCl more active at pH 6 than 8; no reduction in activity by glucose, NaCl, serum. [1]

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive and Gram-negative bacteria, yeasts, and fungi. Inhibits ($\mu\text{g/ml}$) *Micrococcus pyogenes* var. *aureus*, *Bacillus anthracis*, *B. subtilis*, *Streptococcus pyogenes*, *Diplococcus pneumoniae* at 0.025-0.5; *Salmonella typhosa*, *Proteus vulgaris*, *Shigella dysenteriae*, *Neisseria meningitidis*, *Vibrio comma*, and *Brucella melitensis*, 0.05-2.5; *Mycobacterium phlei*, *Myc. smegmatis* and *Myc. avium* at 0.8. Fungi: *Aspergillus niger*, *Mycotorula* sp, and *Monilia* sp inhibited by 3.1-12.5 $\mu\text{g/ml}$. [1]

ACUTE TOXICITY LD_{50} in mice, 20 mg/kg, i.v. (HCl) [1].

122. FLUVOMYCIN

SOURCE A strain of *Bacillus subtilis* [1].

NATURE Probably a polypeptide; weakly acidic. [1]

FORM AND COLOR White amorphous powder [1].

SOLUBILITY s. water, aqueous methanol, aqueous ethanol; i. acetone, ether, chloroform, amyl acetate. [1]

STABILITY Stable 2 years at pH 5.5 at 5 $^{\circ}\text{C}$, 1 month at room temperature, 3+ days at pH 2 and 9; destroyed by autoclaving. [1]

OTHER REACTIONS Stable to proteolytic enzymes; readily dialyzable; not precipitated by acids, alkalies. [1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* 209; *Candida albicans* ATCC 10231.

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *M. pyogenes* var. *aureus*, *Proteus vulgaris*, *C. albicans* and *Torulopsis rotundata* at 0.5-1.0; *Escherichia coli* and *Trichophyton mentagrophytes* at 33-90. Growth inhibition of other bacteria and fungi at higher concentration. [1]

In vivo. Apparently inactive [1].

PHARMACOLOGY LD_{50} in mice, 1300 mg/kg, i.v.; 1250 mg/kg, s.c.; 750 mg/kg, i.m. Could not be detected in the blood or urine of dogs and rabbits after i.v. injection. [1]

123. FOMECIN A

SOURCE *Fomes juniperinus* [1].

NATURE Weakly acidic [1].

MOLECULAR FORMULA AND WEIGHT $C_8H_8O_5$; 173, 189 (found); 184 (calc.).[1]

CRYSTAL FORM AND COLOR Depends on solvent [1].

MELTING POINT ($^{\circ}C$) Chars above 160 [1].

OPTICAL ACTIVITY Inactive [1].

UV ABSORPTION MAXIMA 241, 305 $m\mu$ [1].

SOLUBILITY Somewhat s. water, ethanol, acetone, ethyl acetate, chloroform; sl. s. benzene.[1]

STABILITY Thermostable at acid and neutral pH; alkali labile.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. aureus [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu g/ml$) *M. pyogenes* var. aureus, 8-16; *Bacillus subtilis*, 31-63; *Klebsiella pneumoniae*, 63; *Escherichia coli*, *Pseudomonas aeruginosa*, 125; *B. mycoides*, 250; *Mycobacterium smegmatis*, 250-500. Slight antifungal activity; inhibits *Trichophyton mentagrophytes*, but no other fungi tested. Possessed antiphage activity.[1] Antiviral activity: Virucidal against influenza virus A in concentration of 500 $\mu g/ml$. No activity against strain SK poliomyelitis and eastern equine encephalitis viruses.[2]

ACUTE TOXICITY Mice tolerated doses of >50 mg/kg, i.v. [1].

124. FOROMACIDINS

SOURCE *Streptomyces* sp¹ [1].

NATURE Basic.

MOLECULAR FORMULA AND WEIGHT

Foromacidin A: $C_{54}H_{78}O_{15}N_2$; equiv. wt. 458 (found); MW 887.09 (calc.).
 B: $C_{47}H_{80}O_{16}N_2$; equiv. wt. 462, 472 (found); MW 929.13 (calc.).
 C: $C_{48}H_{82}O_{16}N_2$; equiv. wt. 478 (found); MW 943.15 (calc.).
 D: Equiv. wt. 452 (found).[1]

CRYSTAL FORM AND COLOR Colorless microcrystalline powders [1].

MELTING POINT ($^{\circ}C$) Foromacidin A: 134-138.

B: 130-132.
 C: 124-128.
 D: 135-140.[1]

OPTICAL ACITIVITY Foromacidin A: $[\alpha]_D = -81^{02}, -56^{03}$.

B: $[\alpha]_D = -83^{04}, -61^{05}$.
 C: $[\alpha]_D = -79^{06}, -62^{07}$.
 D: $[\alpha]_D = -75^{08}$. [1]

UV ABSORPTION MAXIMA Foromacidin A, B, C, D: 231 $m\mu$ [1].

SOLUBILITY s. most organic solvents [1].

OTHER REACTIONS Infrared maxima include, foromacidin A: 3500, 1725; B: 3500, 1733, 1245; C: 3500, 1733, 1190; D: 3500, 1725, 1245 (recip. cm). Mild acid hydrolysis of A, B, or C yields mycarose, plus forocidin A, B or C; alkaline hydrolysis of foromacidin B and forocidin B yields 1 mole of acetic acid, and foromacidin C and forocidin C 1 mole of propionic acid. An antibiotic active against Gram-negative organisms is also produced in culture fluids.[1]

BIOLOGICAL ACTIVITY In vitro. Foromacidin A: Inhibits ($\mu g/ml$) *Bacillus megatherium*, 0.1; *Streptococcus mitis*, *Str. faecalis*, 1.0; *Corynebacterium diphtheriae*, *Str. pyogenes*, *Micrococcus pyogenes* var. aureus, 10.

/1/ Resembles *S. ambofaciens*. /2/ c, 0.34 methanol. /3/ c, 0.52 chloroform. /4/ c, 0.82 ethanol. /5/ c, 0.93 chloroform. /6/ c, 1.19 ethanol. /7/ c, 0.90 chloroform. /8/ c, 0.81 ethanol.

124. FOROMACIDINS (Concluded)

B: Inhibits ($\mu\text{g/ml}$) *Str. mitis*, 0.1; *Str. faecalis*, *C. diphtheriae*, *Str. pyogenes*, 1.0; *B. megatherium*, *M. pyogenes* var. *aureus*, 10.

C: Inhibits ($\mu\text{g/ml}$) *Str. mitis*, *C. diphtheriae*, 0.1; *Str. faecalis*, *Str. pyogenes*, *B. megatherium*, 1.0; *M. pyogenes* var. *aureus*, 10.

A, B, C: Required 1000 $\mu\text{g/ml}$ or greater for inhibition of *Escherichia coli*, *Salmonella typhosa*, *S. schottmuelleri*, *Klebsiella pneumoniae*, *Vibrio comma*, *Pasteurella pestis*, *Shigella sonnei*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis* var. *hominis*, *Candida albicans*, and *C. tropicalis*.

D: Shows about 10% of activity of A, B, C.[1]

In vivo. Five s.c. doses of 1-10 mg/kg gave 50-100% protection against *Str. pyogenes* in mice; oral doses were also effective. In vivo activity was also demonstrated against infections with *M. pyogenes* var. *aureus*, *Diplococcus pneumoniae*, *Pasteurella* sp, *Borrelia recurrentis*, *Entamoeba histolytica*, and *Plasmodium berghei*. [1]

TOXICITY Mice tolerated doses of 250 mg/kg, i.v.; 500 mg/kg, s.c.[1]

RESISTANCE Penicillin-resistant organisms were sensitive to foromacidin. Picromycin-resistant strains of *M. pyogenes* var. *aureus* showed some cross-resistance to foromacidin.[1]

125. FRADICIN

SOURCE *Streptomyces fradiae* [1].

NATURE Weak base [2].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_4$ (proposed); 500 (Barger); 514.6 (calc.).[2]

CRYSTAL COLOR Light greenish-yellow [2].

MELTING POINT ($^{\circ}\text{C}$) 180-300¹ [2].

OPTICAL ACTIVITY $[\alpha]_D^{25} = +65^{\circ}2$ [2].

UV ABSORPTION MAXIMUM 290-295 $\text{m}\mu^3$ [2].

SOLUBILITY s. dioxane, chlorinated hydrocarbons, propylene glycol; sl. s. methanol, ethanol, water; i. petroleum ether, cyclohexane, xylene.[1,2]

STABILITY Thermostable at neutral pH; unstable at acid pH at room temperature.[1]

OTHER REACTIONS From alkali fusion: volatile product giving positive pine splint and Ehrlich's tests for a pyrrol [2].

QUANTITATIVE DETERMINATION Microbiological: *Penicillium notatum* [1].

BIOLOGICAL ACTIVITY In vitro. Active against fungi and protozoa (*Entamoeba histolytica*). Inhibits *Aspergillus niger*, *Penicillium notatum*, *Candida albicans*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Fusarium* spp, *Trichoderma* spp, *Trichophyton mentagrophytes* at 0.12-2.4 $\mu\text{g/ml}$. [1] Inhibits growth of *Entamoeba histolytica* at 1 $\mu\text{g/ml}$. *Trypanosoma cruzi* inhibited in dilution of 1:100,000 [1,2]. In vitro activity reversed by reducing agents [3], and by certain unsaturated fatty acids and Tween 80, but not by saturated, straight-chain fatty acids [4]. Action essentially fungistatic, only weakly fungicidal [3].

In vivo. No activity against *T. cruzi* infections in mice [5].

TOXICITY LD₅₀ in mice, 4 mg/kg, i.p., or oral [2]. Renal ischemia observed in mice following sublethal doses. Very irritating to rabbit skin when topically applied in ointment containing 500 $\mu\text{g/g}$. [2]

126. FRAMYCETIN
(Actiline)

The trademark of Laboratoires Roussel for framycetin is Soframycine.

SOURCE *Streptomyces* sp resembling *S. lavendulae* [2].

MOLECULAR WEIGHT 1400-1500 (found) [1].

FORM AND COLOR Chlorhydrate: white, amorphous powder [1].

MELTING POINT ($^{\circ}\text{C}$) Picrate: 189 (d., corr.) [1].

/1/ Darkens without melting. /2/ c. 1.0 1,4-dioxane. /3/ Ethanol.

126. FRAMYCETIN (Concluded)

OPTICAL ACTIVITY Picrate: $[\alpha]_D = -32^{01}$. Chlorhydrate: $[\alpha]_D = +57^{02}$ [1].

SOLUBILITY Chlorhydrate: s. water, aqueous methanol; i. acetone, ether, most organic solvents.[1]

OTHER REACTIONS No guanidinic grouping; all N as primary amine; forms picrate, reineckate, and p-(p'hydroxyphenylazo) benzene sulfonate. Hydrolysis yields 3 fractions: neamine, a diaminohexose, and a pentose. Resembles streptomycin and neomycin, but differs from both.[1]

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive (including mycobacteria) and Gram-negative bacteria. Low activity against fungi. Inhibits *Bacillus subtilis*, *B. anthracis*, *Micrococcus pyogenes* var. *aureus*, *Salmonella typhosa*, *S. paratyphi*, *S. schottmuelleri*, *Shigella* sp, *Pasteurella* sp, *Escherichia coli*. [2] Inhibits ($\mu\text{g/ml}$) strains of *M. pyogenes* var. *aureus* resistant to other antibiotics at 0.5-1.0; *Proteus* spp, *Pseudomonas* spp, 2-20 [7]; *Pr. morgani*, *Pr. rettgeri*, 1-40; *Pr. mirabilis*, 1-100; *Pr. vulgaris*, 6-20; *Malleomyces pseudomallei*, 12.5-25.[4, 5] A majority of 115 strains of *Ps. aeruginosa* were sensitive to 1-10 $\mu\text{g/ml}$ [6]. Active against strains of *Mycobacterium tuberculosis* var. *hominis* which were resistant to streptomycin and isoniazid [8].

CLINICAL Treatment with framycetin in aerosol form gave good results in a majority of patients with a variety of bronchopneumonopathies, e.g., bronchial asthma, pulmonary abscess, acute bronchitis, and suppurative bronchiectasis [9]. Daily oral doses of 2.0 g had a marked suppressive effect (70-99%) on the enteric bacteria, suggesting value as in intestinal antiseptic [7]. Good response noted in patients with staphylococcal infections who received topical applications of framycetin [3].

ACUTE TOXICITY LD_{50} in mice, 65 mg/kg, i.v. Multiple doses of culture filtrate were non-toxic to rabbits, dogs and guinea pigs.[2] In man, total daily oral doses of 0.75-2.0 g were well tolerated [7].

ABSORPTION AND EXCRETION Poorly absorbed from gastrointestinal tract in man [7].

MODE OF ACTION Bacteriostatic and bactericidal [8].

MISCELLANEOUS Exposure to solutions, containing 1 mg/ml, for 8-24 hours was lethal to viviparous tropical fish (guppies) [10].

127. FREQUENTIN

SOURCE Certain strains of *Penicillium frequentans* [3].

NATURE Aldehyde [1, 3].

MOLECULAR FORMULA $\text{C}_{14}\text{H}_{20}\text{O}_4$ [1].

CRYSTAL FORM AND COLOR Colorless needles [1, 3].

MELTING POINT ($^{\circ}\text{C}$) 134.5 (d.) [1, 3].

OPTICAL ACTIVITY $[\alpha]_D^{24} = +82^{03}$ [1].

SOLUBILITY s. acetone, dioxane, chloroform, ethanol, benzene; sl. s. carbon tetrachloride, water.[3]

OTHER REACTIONS Closely related to palitantin; reddish-purple with FeCl_3 in aqueous or alcoholic solution; yields a precipitate with Brady; reduces ammoniacal silver oxide; positive Schiff; no CO_2 from NaHCO_3 . [1-3]

QUANTITATIVE DETERMINATION Microbiological: Inhibition of germination of *Botrytis allii* spores [3].

BIOLOGICAL ACTIVITY In vitro. Activity against fungi; only very slight activity against bacteria. Prevents germination of spores of *B. allii*, *Stachybotrys atra*, *Penicillium gladioli*, and *Mucor mucedo* at 2.5 $\mu\text{g/ml}$; *Absidia glauca* and *Aspergillus niger* at 25-50 $\mu\text{g/ml}$. [3]

128. FUMAGILLIN

(Phagopedin sigma)

The trademark for fumagillin is Fumidil (Abbott Laboratories), and Fugillin (The Upjohn Company).

SOURCE *Aspergillus fumigatus* [8].

NATURE Weak monobasic acid [1, 7], or monoester of decatetraenedioic acid [3].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{26-27}\text{H}_{34-36}\text{O}_7$ [3]; 436-488 (found); 472 (calc.). [1, 7]

/1/ c, 0.5 methanol. /2/ c, 1 water. /3/ Chloroform.

128. FUMAGILLIN (Concluded)

STRUCTURE $[C_{16-17}H_{25-27}O_3] - O - CO - (CH=CH)_4 COOH$ [3].

CRYSTAL FORM AND COLOR Colorless or light yellow crystals [1, 2, 7].

MELTING POINT ($^{\circ}C$) 189-194 (d.) [1, 2, 7].

OPTICAL ACTIVITY $[\alpha]_D^{25} = -26.6^{\circ 1}$ [1, 7], $-24^{\circ 2}$ [2].

UV ABSORPTION MAXIMA 239, 304, 322, 336, 351 $m\mu$ [1, 2, 7].

SOLUBILITY s. most organic solvents, $NaHCO_3$, dilute alkali; i. saturated hydrocarbons, water, dilute acid.[1]

STABILITY Thermolabile [6].

OTHER REACTIONS Becomes yellow and properties change on exposure to air for one week; activity loss correlated with loss of spectrophotometric absorptivity at 351 $m\mu$; the tetraenedioic chromophore is destroyed by photolysis of the crystal form in the presence or absence of air; negative $FeCl_3$, Millon, Hopkins-Cole, Fehling, Molisch, Liebermann-Burchard, Legal; forms a methyl ester (MP, 145-147 $^{\circ}C$), an octabromide (MP, 118-122 $^{\circ}C$), an amide (chars at 160 $^{\circ}C$), a dinitrophenylhydrazone (MP, 123-126 $^{\circ}C$).[1, 4-7]

QUANTITATIVE DETERMINATION Microbiological: Antiphage activity [1, 2].

BIOLOGICAL ACTIVITY Little or no activity against bacteria and fungi; active against certain protozoa and viruses. In vitro. Inhibits *Entamoeba histolytica* in dilution of 1:131,000,000 [9], and *Trichomonas vaginalis* at 25 $\mu g/ml$ [10]. Active against bacteriophages [8]. In tissue cultures, antibiotic is virucidal to eastern and western equine encephalitis and slightly active against influenza PR-8 viruses at concentrations of 2.5 mg/ml ; inhibition of poliomyelitis (Lansing strain) at 0.5 mg/ml . [11]

In vivo. High activity in experimental amebiasis in monkeys, rats and rabbits. Rats cleared of *E. histolytica* when treated with oral doses of 11 mg/kg in divided doses for 2 days; in rabbits, complete clearance was obtained with total doses of 100 mg/kg . [9, 12] Slight activity in experimental acute toxoplasmosis (prolonged survival time) in mice [13]. Inactive against mouse infections with *Trypanosoma equiperdum*, *T. gambiense*, *T. cruzi*, or *Borrelia novyi* [9, 14]. No antiviral activity in mice infected with poliomyelitis (MM strain), influenza A, or swine influenza viruses; inactive in ovo against viruses of herpes simplex or influenza PR-8. [8, 11] Active against noseema disease of bees, arresting the infection during the intracellular phase [15]. Oral doses of 0.02 mg (approximately 0.5 mg/kg) protected chicks against infection with *Plasmodium gallinaceum* [24]. Daily i.p. doses of 25 mg/kg for 7 days had no inhibitory effect on Ehrlich carcinoma, sarcoma 180, and Krebs-2 carcinoma in mice [27]. Doses of 200 $mg/kg/da$ for 7 days had no effect on RC carcinoma in mice [28]. Single i.p. doses of 50 mg/kg had a slight suppressive effect on Yoshida sarcoma in rats [21].

CLINICAL Total oral dosages of 50-100 mg , in divided doses over a period of approximately 12 days, cleared majority of human *E. histolytica* cyst passers [16, 17]. Generally favorable results in extended studies of chronic intestinal amebiasis with optimal oral doses of 10 mg , b.i.d., for approximately 10 days [12, 18]. In other trials, oral regimens of 50-200 mg/da for periods of 9-14 days were reported to be highly effective in intestinal amebiasis, with disappearance of trophozoites and healing of ulcers in all cases [22]. A combined course of fumagillin with tetracycline or erythromycin gave good clinical responses in ulcerative amebiasis, with prompt clearance of *E. histolytica* [25].

ACUTE TOXICITY LD_{50} in mice, 800 mg/kg , s.c.; oral doses of 2000 mg/kg tolerated.[1] Chicks tolerated oral doses of 0.3 mg (7.5 mg/kg) [24]. In vitro. Low concentrations (0.012 $\mu g/ml$) were toxic to human spermatozoa [19].

In man, oral doses of 5-10 mg/da for 10-12 days were well tolerated. Following larger doses, abdominal pain and skin rash were frequently noted.[12, 18] A side effect, noted in 2 of 3 patients treated with daily doses of 30-60 mg , was peeling of skin of the palms and soles [23].

MISCELLANEOUS In concentrations of 1 $\mu g/ml$ which did not interfere with growth of host *Micrococcus pyogenes* var. *aureus*, fumagillin prevented multiplication of staphylophage. There was no action on free phage, but when antibiotic was added during first 15 minutes after the start of the latent period, it prevented phage growth.[26] Feeding of fumagillin to bees increased honey production over 25% [20].

129. FUMIGATIN

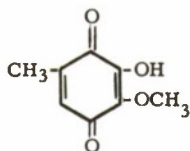
SOURCE *Aspergillus fumigatus* [1].

NATURE Pigmented quinone [1].

MOLECULAR FORMULA AND WEIGHT $C_8H_8O_4$ [1, 2]; 161 (cryo.); 168 (calc.).[1]

/1/ c, 0.25 methanol. /2/ c, 5 chloroform.

STRUCTURE



[1]

CRYSTAL FORM AND COLOR Maroon-colored needles [1, 2].

MELTING POINT (°C) 116 [1] [2].

SOLUBILITY s. acetone, ether, chloroform, benzene, ethyl acetate, alcohol, water; sl. s. petroleum ether. [1]

STABILITY Unstable in aqueous solution, especially alkaline [3].

OTHER REACTIONS Can be converted into spinulosin; intense purple-black color in absolute ethanol with one drop of FeCl₃; brown changing to cherry red after 2 minutes with cold concentrated H₂SO₄; I from acidified KI; sublimes at high vacuum without decomposition, no reaction with o-phenylenediamine. [1-3]

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. aureus [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits Vibrio comma and Sarcina lutea in dilutions of 1:100,000; M. pyogenes var. aureus, 1:1,200-1:200,000; M. pyogenes var. albus, 1:20,000-1:33,000; Bacillus anthracis, 1:33,000-1:50,000; B. subtilis, 1:40,000; Streptococcus viridans, Escherichia coli, 1:1,200-1:12,000. [2, 3]

130. FUNGICHROMIN

SOURCE Streptomyces cellulosa [1].

NATURE Polyene [1].

MOLECULAR FORMULA AND WEIGHT C₃₅H₆₀O₁₃; 688.8 (calc.). [1]

CRYSTAL COLOR Pale yellow crystals [1].

MELTING POINT (°C) 205-210 (uncorr.) [1]

UV ABSORPTION MAXIMA 322.5, 338.5, 356.5 mμ [1].

SOLUBILITY s. methanol, ethanol, butanol, acetone, pyridine, dimethylformamide; i. water, aliphatic hydrocarbons. [1]

OTHER REACTIONS Culture also produces actinomycin; related fungichromatin has similar properties but differs in UV; C, 60.93; H, 8.65; O, 30.42; alkoxy, <0.1; C-methyl, 8.2; violet changing to blue in concentrated H₂SO₄; slowly reduces Tollens; decolorizes KMnO₄ and Br; white waxy solid on hydrogenation; reduced compound inactive biologically and loses characteristic UV. Infrared: 2.36, 3.06, 3.42, 3.54, 5.85, 6.10, 6.30, 6.85, 7.28, 7.48, 8.10, 8.50, 8.79, 9.01, 9.19, 9.39, 9.62, 9.90, 10.25, 11.17, 11.82, 12.42, 13.10, 13.83 μ. [1]

QUANTITATIVE DETERMINATION Microbiological: Aspergillus niger [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi (μg/ml): Blastomyces dermatitidis, 0.8; A. niger, 3.2; Candida albicans, Microsporium audouini, 6.3; Trichophyton mentagrophytes, 12.4. The following phytopathogenic fungi are sensitive to 10 μg/ml: Ascochyta lincicola, Botryosphaeria ribis, Fusarium oxysporum, Alternaria solani. Fungichromatin, produced by Streptomyces sp, has the same in vitro antimicrobial spectrum as fungichromin. [1]ACUTE TOXICITY LD₁₀₀ in mice, 16.4 mg/kg, i.p. Oral doses of 1000 mg/kg non-toxic. [1]131. FUNGISTATIN
(Antibiotic XG)

SOURCE Bacillus sp [2].

NATURE Amphoteric polypeptide [2].

MOLECULAR WEIGHT Approximately 2400 [1].

131. FUNGISTATIN (Concluded)

SOLUBILITY s. methanol, ethanol; i. ether, chloroform, ethyl acetate, dry acetone.[2]

STABILITY Thermostable at acid and neutral pH [2] .

OTHER REACTIONS Gels on standing in water, becoming reversibly inactive; contains lysine, serine, aspartic acid, proline, threonine, alanine, tyrosine, tryptophan, valine, isoleucine, and other amino acids.[1, 2]

QUANTITATIVE DETERMINATION Microbiological: Trichophyton gypseum [2] .

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi: Candida albicans, Microsporum canis, Cryptococcus neoformans, Rhodotorula sp, Trichophyton sp, Epidermophyton sp at 0.7-11.2 units/ml [2] .

TOXICITY LD₅₀ of crude preparations in mice, 50-90 mg/kg, i.v. In vitro. Hemolytic to red blood cells.[2]

UTILIZATION Of 5 antibiotics tested, fungistatin was the most effective in controlling Ascochyta pisi infection (leaf and pod spot) of pea plant; concentration of 25 ppm effective.[3]

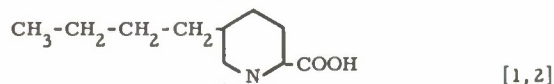
132. FUSARIC ACID
(5-n-Butylpyridine-2-carboxylic acid)

SOURCE Gibberella fujikuroi [1] .

NATURE An acid related to nicotinic acid [1] .

MOLECULAR FORMULA C₁₀H₁₃NO₂ [1, 2] .

STRUCTURE



CRYSTAL FORM AND COLOR Colorless plates [2] .

MELTING POINT (°C) 108-109 [2] .

OTHER REACTIONS Forms a Cu salt with light-violet plates; oxidized to isocinchomeric acid and propionic acid by KMnO₄; distillation of fusaric acid with CaO gives fusarin; oxidation of fusarin with KMnO₄ gives nicotinic acid. [2]

BIOLOGICAL ACTIVITY In vitro. Weakly bacteriostatic; inhibits Micrococcus pyogenes var. aureus Salmonella typhosa, Escherichia coli in dilution of 1:2000.[1]

MISCELLANEOUS Preliminary experimental data suggest that fusaric acid may be a vivotoxin implicated in Fusarium wilt of cotton plants [3] .

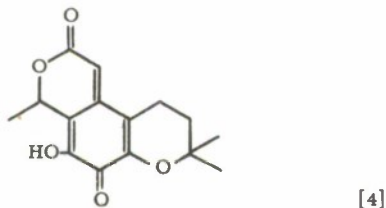
133. FUSCIN

SOURCE Oidiodendron fuscum [1] .

NATURE Quinonoid pigment [1] .

MOLECULAR FORMULA AND WEIGHT C₁₅H₁₆O₅ (proposed); 276 (calc.).[2]

STRUCTURE



CRYSTAL FORM AND COLOR Orange, diamond-shaped plates [1, 2] .

133. FUSCIN (Concluded)

MELTING POINT (°C) 230 [1, 2].

OPTICAL ACTIVITY Inactive [1, 2].

SOLUBILITY s. chloroform, acetone, hot ethanol, ethyl acetate, acetic acid, ether, benzene; sl. s. cold ethanol; i. petroleum ether, water.[1, 2]

OTHER REACTIONS Purple color in alkali and aqueous pyridine; red-purple with FeCl₃; dihydrofusicin (C₁₅H₁₈O₅, MP 206, colorless rhombic crystals) occurs in fusicin filtrates; a stable, active crystalline compound (C₁₇H₂₂O₈) is formed with thioglycollic acid.[1, 2]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY Primarily active against Gram-positive bacteria. In vitro. Inhibits (in dilution x 1000) *M. pyogenes* var. *aureus*, 80-1280; *M. citreus*, 1280; *Streptococcus pyogenes*, *Str. viridans*, 640; *Bacillus anthracis*, 320-1280; *Corynebacterium diphtheriae*, 160-320; *B. subtilis*, *Vibrio comma*, 80; *Mycobacterium smegmatis*, 20; *Myco. phlei*, *Shigella dysenteriae*, 10; *Proteus vulgaris*, *Salmonella typhosa*, *Escherichia coli*, 5; *Shigella paradysenteriae*, *Sh. sonnei*, *Salmonella enteritidis*, *S. paratyphi*, <5.[3]

134. FUSCOMYCIN

SOURCE *Streptomyces fuscus* [1].

MELTING POINT (°C) HCl: 180 (d.) [1].

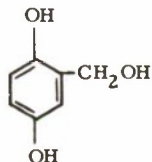
BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus* [1].

135. GENTISYL ALCOHOL

SOURCE *Penicillium patulum* (Bainier), and other *Penicillium* spp [1].

MOLECULAR FORMULA C₇H₈O₃ [1, 2].

STRUCTURE



CRYSTAL FORM AND COLOR Colorless needles [1, 2]

MELTING POINT (°C) 100-101 [1, 2].

SOLUBILITY s. water, ethanol, ether; sl. s. benzene, chloroform; i. petroleum ether.[1]

OTHER REACTIONS Decolorizes permanganate; reduces AgNO₃; blue color with aqueous FeCl₃ changing to yellow; reacts with aqueous I; yellow color with 2 N NaOH, darkening to reddish brown; white amorphous precipitate when heated with 2 N H₂SO₄; sublimes in high vacuum.[1, 2]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

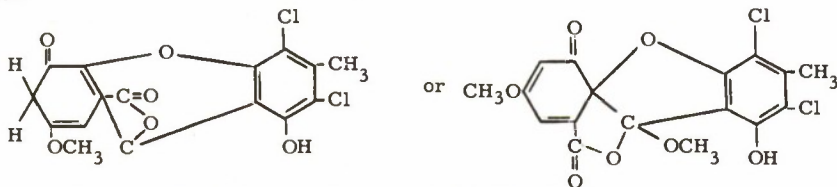
BIOLOGICAL ACTIVITY In vitro. Low activity against *M. pyogenes* var. *aureus*: inhibited at 2 mg/ml [1].

136. GEODIN

SOURCE *Aspergillus terreus* [1].

MOLECULAR FORMULA AND WEIGHT C₁₇H₁₂O₇Cl₂ [1-4]; 380 (cryo.).[4]

STRUCTURE



136. GEODIN (Concluded)

CRYSTAL FORM AND COLOR Brown or yellow needles [2].

MELTING POINT ($^{\circ}\text{C}$) 227-230; 235 (d.).[3, 4]

OPTICAL ACTIVITY $[\alpha]_{5461}^{20} = +179^{\circ 1}$; $[\alpha]_{5790}^{20} = +149^{\circ 1}$. [4]

SOLUBILITY s. alcohol, ethyl acetate, chloroform, acetone, dioxane, sodium bicarbonate; sl. s. benzene, ether; i. water, petroleum ether.[4]

OTHER REACTIONS Green to brown color in alcoholic solution with FeCl_3 ; brown-gray precipitate with FeCl_3 and neutral Na salt.[4]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [3].

BIOLOGICAL ACTIVITY In vitro. Inhibited (in dilution x 1000) *M. pyogenes* var. *aureus*, 8-2000; *Bacillus subtilis*, 32-1000; *M. citreus*, *Streptococcus pyogenes*, 128; *B. anthracis*, 32-128; *Corynebacterium diphtheriae*, 23-128; *Escherichia coli*, 40; *Pseudomonas fluorescens*, 20; *Str. viridans*, *M. pyogenes* var. *albus*, 8; *Mycobacterium smegmatis*, 4-20; *Vibrio comma*, 2; *Shigella dysenteriae*, 1.[5]

137. GEOMYCINS

SOURCE *Streptomyces xanthophaeus*, n. sp [1].

NATURE Basic [1, 2].

MOLECULAR FORMULA AND WEIGHT $(\text{C}_6\text{H}_{12}\text{O}_2\text{N}_2)_{8-10}$ (proposed). HCl: 1650 ± 165 . Free base: equiv. wt. 147 ± 3 (found); 144.2 (calc.).[1, 2]

CRYSTAL FORM AND COLOR Helianthate: red platelets². HCl: amorphous, hygroscopic.[2]

MELTING POINT ($^{\circ}\text{C}$) Helianthate: 205-215 (d.).[2]

OPTICAL ACTIVITY HCl: $[\alpha]_{\text{D}}^{20} = +16.0^{\circ} \pm 0.4^3$ [2].

SOLUBILITY HCl: s. water, methanol; less s. ethanol; i. acetone, ethyl acetate, ether, petroleum ether.[2]

OTHER REACTIONS Positive ninhydrin, Elson-Morgan, nitroprusside-ferricyanide; biuret bright blue; weakly positive Sakaguchi; negative maltol, FeCl_3 ; no change with 2, 4-dinitrophenylhydrazine; both *L*- β -lysine and a new amino acid (geamine, $\text{C}_6\text{H}_{12}\text{O}_3\text{N}_4$) obtained on acid destruction.[1, 3]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*, *Escherichia coli* [2].

BIOLOGICAL ACTIVITY In vitro. Inhibit *M. pyogenes* var. *aureus* in dilution of 1:1,000,000-1:3,000,000, *E. coli* in 1:210,000-1:500,000. *Proteus* sp, *Klebsiella pneumoniae*, *Aerobacter aerogenes*, *Alcaligenes faecalis*, *Salmonella typhosa*, *S. paratyphi*, and *Hemophilus influenzae* are also sensitive to a lesser extent. *Diplococcus pneumoniae* and *Streptococcus viridans* are not susceptible.[1]

In vivo. Some activity displayed in experimental amebiasis (*Entamoeba histolytica*) in rats.[1]

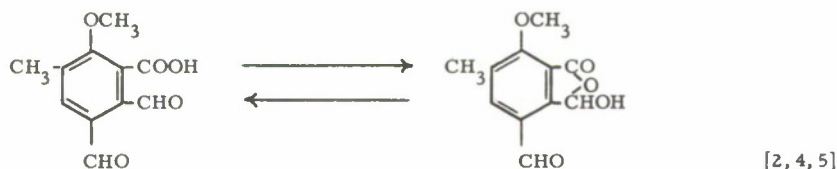
138. GLADIOLIC ACID

SOURCE *Penicillium gladioli* [1]; by synthesis [7].

NATURE Monobasic carboxylic acid [1, 2].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{11}\text{H}_{10}\text{O}_5$ [1-4]; 212 (Rast); 222.1 (anal.).[1, 2]

STRUCTURE



CRYSTAL FORM AND COLOR Long, colorless, silky needles [1].

/1/ c, 0.8 chloroform. /2/ From dilute methanol. /3/ c, 3.25 water.

MELTING POINT ($^{\circ}\text{C}$) 160 [1, 2].

OPTICAL ACTIVITY Inactive [2].

UV ABSORPTION MAXIMA 275, 343 $\text{m}\mu^1$ [2, 3]; 267, 305 $\text{m}\mu^2$ [5].

SOLUBILITY s. water [5].

STABILITY Stable at 25°C , pH 3-8; stable to hydrolysis by dilute mineral acids.[1, 2]

OTHER REACTIONS pK_a 4.45 at 18° ; negative FeCl_3 , Fehling, Schiff; ammoniacal AgNO_3 immediately reduced in cold; intense green color with ammonia solution; no iodoform reaction; readily converted to the slightly active dihydrogladiolic acid.[2, 4]

QUANTITATIVE DETERMINATION Microbiological: Inhibition of germination of *Botrytis allii* conidia [1, 5].

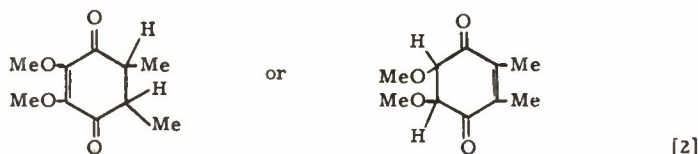
BIOLOGICAL ACTIVITY *In vitro*. Inhibits spore germination of the following phytopathogenic fungi at 1.9-15.6 $\mu\text{g}/\text{ml}$: *Absidia glauca*, *Fusarium graminearum*, *F. caeruleum*, *Penicillium janczewski*, *P. notatum*, *P. digitatum*, *P. expansum*, *Mucor erectus*, *Byssochlamys fulva*, *Verticillium alboatrum*, *Botrytis allii*, and *Cephalosporium longisporum*. Inhibited, at 62.5-250 $\mu\text{g}/\text{ml}$, *Aspergillus flavus*, *A. niger*, *Myrothecium verrucaria*, *Stemphylium* sp, *Thamnidium elegans*, *Trichoderma viride*, *Trichothecium roseum* [1, 6]. Bacteria: *Micrococcus pyogenes* var. *aureus* inhibited by 250 $\mu\text{g}/\text{ml}$; *Escherichia coli* and *Salmonella typhosa* not susceptible to 500.[1]

139. GLIOROSEIN

SOURCE *Gliocladium roseum* [1].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{10}\text{H}_{14}\text{O}_4$ [1, 2]; 188 (Rast); 198 (calc.) [2].

STRUCTURE



CRYSTAL FORM AND COLOR Colorless needles [1].

MELTING POINT ($^{\circ}\text{C}$) 48 [1].

UV ABSORPTION MAXIMUM 289 $\text{m}\mu$ [1].

OTHER REACTIONS No reaction with ketonic reagents; negative FeCl_3 ; does not decolorize Br in glacial acetic acid; reduces Fehling; color produced with tetranitromethane; does not form a quinhydrone.[1, 2]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* [1].

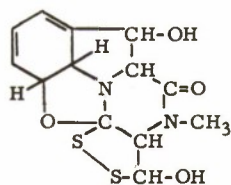
BIOLOGICAL ACTIVITY *In vitro*. Low activity. Inhibits ($\mu\text{g}/\text{ml}$) *B. subtilis*, 200; *Escherichia coli*, 400. The phytopathogenic fungus, *Botrytis allii*, not sensitive to 400 $\mu\text{g}/\text{ml}$. [1]

140. GLIOTOXIN
(Aspergillin)

SOURCE *Aspergillus fumigatus* [2], and several unrelated species of fungi [5, 9, 15].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{13}\text{H}_{14}\text{N}_2\text{S}_2\text{O}_4$ [1-3, 5]; 314 (cryo.); 326 (calc.).[1, 2, 5]

STRUCTURE³



(Proposed) [6].

/1/ 0.1 N NaOH. /2/ Lactol form. /3/ Replacing S atoms with H gives dethiogliotoxin.

140. GLIOTOXIN (Concluded)

CRYSTAL FORM AND COLOR Colorless, elongated plates or needles [1, 3].

MELTING POINT ($^{\circ}\text{C}$) 195 (d.) [1-3].

OPTICAL ACTIVITY $[\alpha]_D = -239$ to -256^{01} [2]; $[\alpha]_D^{25} = -290^{\circ} \pm 10^2$ [5].

UV ABSORPTION MAXIMUM 270 $\text{m}\mu$ [2].

SOLUBILITY s. acetic acid, acetone, acetonitrile, tert.-butanol, carbon tetrachloride, chloroform, dioxane, dimethylformamide, ethyl acetate, ethyl bromide, HCl, methanol, pyridine; sl. s. water, benzene, ethanol.[5]

STABILITY Acid stable, alkali unstable; unstable to light.[1]

OTHER REACTIONS Readily oxidized with S, forming sulfates; yields H_2S when reduced; black precipitate with lead acetate in boiling alkali; in alkaline solution decolorizes KMnO_4 , giving a green color.[4]

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. aureus; Rhizoctonia solani; inhibition of germination of Botrytis allii spores.[1, 2, 4]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g}/\text{ml}$) M. pyogenes var. aureus, M. pyogenes var. albus, Streptococcus viridans, Hemophilus pertussis, Neisseria catarrhalis, Salmonella typhosa, S. paratyphi, 0.2-5.0; S. schottmuelleri, Escherichia coli, 10.[5] Corynebacterium diphtheriae, N. meningitidis, Str. pyogenes, and Diplococcus pneumoniae also sensitive to low concentrations; Proteus vulgaris and Pseudomonas aeruginosa are resistant.[1, 3] Human and bovine strains of Mycobacterium tuberculosis sensitive to 0.02-0.06 $\mu\text{g}/\text{ml}$ [7]. Fungi: Inhibited (in dilution of 1:250,000-1:1,000,000) Trichophyton rubrum, T. purpureum, Microsporium canis, Epidermophyton floccosum, Candida stellatoidea. T. tonsurans, T. gypseum, M. audouini, C. albicans, C. krusei, C. tropicalis inhibited by 1:20,000-1:100,000 [5, 8, 12]; Blastomyces dermatitidis at 1:2000-1:8000 [5]. Phytopathogenic fungi: Ascochyta pisi, Botrytis allii, Rhizoctonia solani, Sclerotinia americana inhibited by 1:300,000-1:450,000; Ceratostomella ulmi by 1:12,000.[9-11, 16] Inactivation of Gardner lymphosarcoma and various transplantable carcinomas of mice and rabbits by exposure to 1-25 $\mu\text{g}/\text{ml}$ [7]. Sarcoma 180 implants rendered almost completely innocuous in mice by exposure to 1 mg/ml [13].

In vivo. No protection in mice against infection with Str. pyogenes [1]. Daily oral doses up to 6.2 mg/kg gave no protection in experimental mouse tuberculosis [7]. Daily i.p. doses up to 3 mg/kg had no inhibitory effect on RC carcinoma or sarcoma 180 in mice [17, 18]. Post-treatment in mice failed to suppress implants of sarcoma 180 [13].

TOXICITY LD_{100} in mice, 45-65 mg/kg , i.p., s.c., or oral; in rabbits, 45-65 mg/kg , i.v. [1, 5].

PHYTOPATHOLOGY Good control in covered smut of barley and bunt of wheat when used as seed protective [11]. Failed to control stem rust of wheat when used as pre-inoculation spray under greenhouse conditions [19]. High protective action against infections with the fungus Cercospora nicotinae in tobacco leaves, with low toxicity to these plants [14].

141. GLOBICIN

SOURCE Strain of Bacillus subtilis [1].

SOLUBILITY s. water at neutral and alkaline pH; i. water at acid pH, organic solvents.[1]

STABILITY Thermostable at pH 2.0-8.5³ [1].

OTHER REACTIONS Precipitates with $(\text{NH}_4)_2\text{SO}_4$; adsorbed on asbestos-pad filters; no hemolysis; activity decreased in presence of Albumin V (Armour); contains tryptophan and loosely bound S, but no tyrosine; no blue color with FeCl_3 . [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits Micrococcus pyogenes var. aureus, B. subtilis, B. cereus, Mycobacterium avium, and Myco. phlei at 10 $\mu\text{g}/\text{ml}$ or less. Gram-negative organisms resistant.[1]

142. GLUTINOSIN

SOURCE Metarrhizium glutinosum [1].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{48}\text{H}_{60}\text{O}_{16}$ (proposed); 920, 755 (Rast); 892.7 (calc.).[1]

CRYSTAL FORM AND COLOR Thin colorless plates [1].

/1/ Chloroform. /2/ c, 0.078 ethanol. /3/ 120 $^{\circ}\text{C}$ for at least 30 minutes.

142. GLUTINOSIN (Concluded)

MELTING POINT ($^{\circ}\text{C}$) Darkens but does not melt at 300 [1].

OPTICAL ACTIVITY $[\alpha]_{\text{D}}^{20} = \text{approximately } +54^{\circ}1$ [1].

SOLUBILITY s. chloroform, ether, n-butanol, petroleum ether, ethanol, cyclohexane, benzene; sl. s. water. [1,2]

STABILITY Thermostable at acid pH; less so above pH 7 [1,2].

QUANTITATIVE DETERMINATION Microbiological: *Botrytis allii* spore germination [1,2].

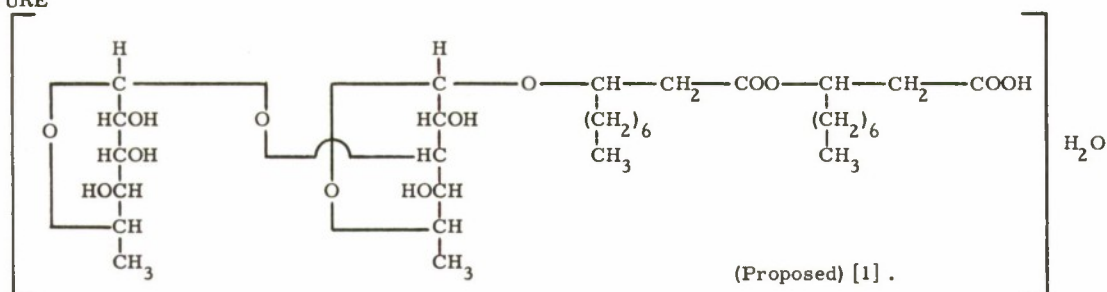
BIOLOGICAL ACTIVITY In vitro. Inhibits phytopathogenic fungi: *B. allii*, *Penicillium digitatum*, *Phoma betae*, *Phytophthora palmivora*, *Mucor mucedo*, *Thamnidium elegans*, *Byssochlamys fulva*, 1-25 $\mu\text{g/ml}$. *M. erectus*, *Chaetomium globosum*, *Gibberella saubinetii*, *Fusarium coeruleum* insensitive to 100 $\mu\text{g/ml}$. [2]

143. GLYCO-LIPIDE
(1- β -Hydroxydecanoic acid)

SOURCE *Pseudomonas aeruginosa* [1].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{32}\text{H}_{60}\text{O}_{14}$; 665 (neut. equiv.); 650 (Rast). [1]

STRUCTURE



CRYSTAL FORM AND COLOR Thin, colorless rectangular platelets [1].

MELTING POINT ($^{\circ}\text{C}$) 86 [1].

OPTICAL ACTIVITY $[\alpha]_{\text{D}} = -84^{\circ}2$ [1].

SOLUBILITY s. ether, ethyl acetate, acetone, dioxane, dilute NaHCO_3 ; i. water, petroleum ether. [1]

OTHER REACTIONS Positive Molisch; negative Fehling; undergoes acid hydrolysis; a loss of weight equivalent to 1 water molecule per mole of acid occurs upon heating under reduced pressure to 60° for 24 hours. [1]

QUANTITATIVE DETERMINATION Spectrophotometric [2].

BIOLOGICAL ACTIVITY In vitro. Strains of *Mycobacterium tuberculosis* var. *hominis* inhibited by concentration of 500 $\mu\text{g/ml}$ [1].

ACUTE TOXICITY 1.p. doses of 250 mg/kg lethal to mice [1].

144. GRAMICIDIN
A component of tyrothricin (q.v.).

SOURCE *Bacillus brevis* [1].

NATURE Neutral polypeptide [1, 8].

MOLECULAR FORMULA AND WEIGHT Possibly $\text{C}_{148}\text{H}_{210}\text{O}_{26}\text{N}_{30}$ [8]; 1000-3000 (found); 2826 (calc.). [1, 6, 8]

CRYSTAL FORM AND COLOR Colorless platelets with pointed or rectangular ends [1, 3, 8].

MELTING POINT ($^{\circ}\text{C}$) 228-231 [1-3, 8].

/1/ c, 0.2 benzene. /2/ c, 3 chloroform.

OPTICAL ACTIVITY $[\alpha]_D^{20} = +3.0^1$ [9].

UV ABSORPTION MAXIMA 281.5, 290.5, 271 $m\mu$ [8].

SOLUBILITY s. lower alcohols, acetic acid, pyridine, wet acetone, dioxane; sl. s. absolute acetone; i. water, ether, hydrocarbons, chlorinated hydrocarbons. [1, 3, 8]

STABILITY Thermostable [1].

OTHER REACTIONS Composed of 3 closely related substances: A fraction contains L-tryptophan, D-leucine, L-alanine, DL-valine, glycine; B fraction same plus phenylalanine; C fraction same as A plus tyrosine; negative Millon; positive to most common protein tests; hydrolyzed by acid; not digested by enzymes; forms a gel with picric acid. [2, 3, 7, 8]

Treatment of gramicidin with HCHO yields argicillin (hydroxymethyl gramicidin), MP 265; soluble in water (2.6 mg/100 ml), ethanol, acetone, glycols; thermostable [25].

QUANTITATIVE DETERMINATION Microbiological: Streptococcus spp, Micrococcus conglomeratus [2, 4, 9]; Str. faecalis ATCC 10541 [26]. Colorimetric (for tyrothricin) [5].

BIOLOGICAL ACTIVITY Primarily active against Gram-positive bacteria. In vitro. Inhibits ($\mu\text{g/ml}$) Diplococcus pneumoniae, 0.1-20; Str. pyogenes, 1-50; Group D streptococci, 0.2; Str. faecalis, 40-200; M. pyogenes var. aureus, 5-5000; M. lysodeikticus, 0.03; Sarcina lutea, 3; Gaffkya tetragena, 0.6; Lactobacillus spp, Corynebacterium spp, 50-500; Clostridium spp, 20-500; Mycobacterium tuberculosis, 20-50; Neisseria catarrhalis, 20; N. gonorrhoeae, 20-10,000; N. meningitidis, 40-10,000; Brucella abortus, 100. Escherichia coli, Salmonella typhosa, Salmonella spp, Shigella spp, Aerobacter aerogenes, Bacillus anthracis, B. mycoides, B. mysentericus, >300; Actinomyces spp, 300. [8, 11] Protozoa: Leishmania tropica, Trypanosoma cruzi, and T. lewisi insensitive to 1 $\mu\text{g/ml}$ [12]. Argicillin inhibits ($\mu\text{g/ml}$) D. pneumoniae, 0.012-0.05; M. pyogenes var. aureus, 0.4-0.6; Str. pyogenes, 10-15; N. catarrhalis, 15-20; E. coli, 200. [25]

In vivo. Single i.p. doses of 8-16 μg protected mice against infections with Str. pyogenes [13], and doses as low as 2 μg gave high protection against D. pneumoniae [1, 10]. Active against mouse infections with B. anthracis, M. pyogenes var. aureus, and Cl. perfringens [13, 14], and in chicks infected with Plasmodium gallinaceum [15]. Little or no protection when injected by s.c., i.m., i.v., or oral routes [8].

CLINICAL Reports of clinical and veterinary usage deal mainly with tyrothricin (q.v.). Parenteral toxicity of gramicidin (or tyrothricin) precludes use in systemic infections. Beneficial effect of gramicidin reported in minor oral disorders when combined with bacitracin in troches for topical administration. [16]

VETERINARY Intramammary instillation of purified preparations of value in therapy of bovine mastitis [8, 22].

ACUTE TOXICITY LD₁₀₀ in mice, 2.5-5.0 mg/kg, i.v.; 60 mg/kg, i.p. Oral doses as high as 1000 mg/kg non-toxic to mice and rats. [8, 17] Marked induration at site of s.c. injection of 200 μg in rabbits [20]. In vitro. Hemolytic activity less than that of tyrocidin, but low concentrations (0.5-1.0 $\mu\text{g/ml}$) slowly lysed red blood cells; this was counteracted by high concentrations (2 mg/ml) of glucose. [10] In tissue cultures, concentrations of 100 $\mu\text{g/ml}$ non-toxic to leukocytes [19]; no inhibition of phagocytic activity of leukocytes at 2000 $\mu\text{g/ml}$ [20]. Cattle spermatozoa immobilized by 10 $\mu\text{g/ml}$ [18].

Argicillin: 0.1 mg/kg, i.v., lethal to mice. In vitro. Hemolytic activity of argicillin against rabbit erythrocytes is approximately 1/4 that of gramicidin [25].

CHRONIC TOXICITY Daily i.v. doses of approximately 2 mg/kg were lethal to mice, rabbits and dogs. Sublethal doses induced progressive anemia, hematuria, ascites and severe degenerative changes in the viscera. [17, 20]

RESISTANCE Many strains of M. pyogenes var. aureus readily acquired resistance in vitro [23].

MODE OF ACTION Primarily bacteriostatic, but low concentrations may be bactericidal; activity is depressed by phospholipids of the cephalin type [10], and cationic detergents [24]. Gramicidin resembles the latter in its effect upon surface tension and also in precipitation of proteins [3]. Sub-bacteriostatic concentrations of 40 $\mu\text{g/ml}$ inhibit production of capsular material (polysaccharide) by Klebsiella pneumoniae [21]. Prevents uptake of phosphate but not O₂ by M. pyogenes; this failed to occur in yeast cells [8].

145. GRAMICIDIN J

SOURCE Bacillus brevis [1].

NATURE Cyclic heptapeptide [1].

MOLECULAR WEIGHT Approximately 800 [1].

/1/ c, 0.17 95% ethanol.

145. GRAMICIDIN J (Concluded)

OTHER REACTIONS Contains 1 D-phenylalanine, 1 L-phenylalanine, 1 D-leucine, 1 L-ornithine, 1 D-ornithine, 1 L-valine, 1 L-proline [1].

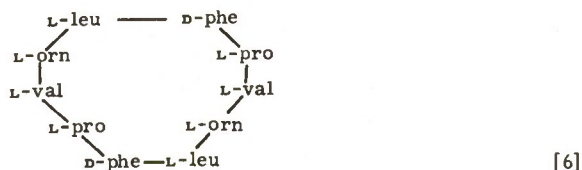
146. GRAMICIDIN S

SOURCE *Bacillus* sp, similar to *B. brevis* [1].

NATURE Cyclic decapeptide [6].

MOLECULAR WEIGHT 1060-1340 [2, 3]; 1,248 (X ray) [5].

STRUCTURE



CRYSTAL FORM AND COLOR Thin colorless needles [1].

MELTING POINT (°C) 268-270 [2].

OPTICAL ACTIVITY $[\alpha]_D^{18} = -292^{\circ 1}$; $[\alpha]_D^{20} = -295^{\circ 1}$. [4, 5]

SOLUBILITY s. aqueous ethanol, chloroform, acetone; less s. absolute ethanol; i. water, acids, alkalies. [2]

STABILITY Thermo- and acid stable [1].

OTHER REACTIONS Positive ninhydrin (deep blue color but no evolution of CO₂), biuret; negative xanthoproteic, Millon, Pauly, Voisenet, Sakaguchi. [2] Some copolymers are antibioticly active [9].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Micrococcus pyogenes* var. *aureus*, *Streptococcus* spp, *Diplococcus pneumoniae*, 10; *Clostridium perfringens*, *Cl. histolyticum*, 7. Also active against Gram-negative bacteria ($\mu\text{g/ml}$): *Shigella dysenteriae*, 12; *Vibrio comma*, *Escherichia coli*, 25; *Salmonella paratyphi*, *Salmonella* spp, 50; *Proteus vulgaris*, 100. [7]

In vivo. Doses of 400 μg gave good protection in guinea pigs infected with *Cl. perfringens* [7].

CLINICAL Used topically (400 $\mu\text{g/ml}$ solution) in skin infections, empyema, osteomyelitis and peritonitis with favorable results [8].

TOXICITY LD₅₀ in rats, 17 mg/kg [1]. In man, solutions of 400-800 $\mu\text{g/ml}$ were non-toxic when topically applied to the skin [7].

147. GRANEGILLIN

SOURCE *Aspergillus* sp resembling *A. flavus* [1].

NATURE Resembles aspergillic acid [1].

MOLECULAR FORMULA C₁₂H₂₀N₂O₂ [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Shigella* spp, and *Salmonella* spp; *Proteus vulgaris*, *Pseudomonas aeruginosa* and Gram-positive bacteria are less sensitive. [1]

In vivo. Protection observed in mice infected with *Salmonella typhosa* and *Klebsiella pneumoniae* [1].

ACUTE TOXICITY LD₅₀ in mice, 100-150 mg/kg, i.p.; 280-320 mg/kg, oral. [1]

148. GRASSERIOMYCIN

SOURCE *Streptomyces lavendulae* [1].

COLOR HCl: faint yellow [1].

MELTING POINT (°C) Helianthate: 215-225 (d.). Reineckate: 187-190 (d.). [1]

/1/ c, 1.5 ethanol.

148. GRASSERIOMYCIN (Concluded)

SOLUBILITY HCl: s. water, methanol; i. most organic solvents.[1]

OTHER REACTIONS Resembles streptothricin in most reactions, but differs in a few. Reactions of 10 mg/ml, aqueous HCl solution: positive Molisch, Fehling, Tollens, ninhydrin; negative biuret, Sakaguchi, xanthoproteic, Millon, Adamkiewicz, Liebermann, Neubauer, FeCl₃. [1]

QUANTITATIVE DETERMINATION Microbiological: Virus of silkworm jaundice in silkworms [1].

BIOLOGICAL ACTIVITY In vitro. Active against Mycobacterium tuberculosis, Myco. phlei, Bacillus subtilis, Micrococcus pyogenes var. aureus, Pseudomonas fluorescens, Escherichia coli, Aspergillus oryzae, A. niger, Penicillium chrysogenum, and Saccharomyces cerevisiae. Trichophyton interdigitale, Torula utilis and Candida albicans are not sensitive. Strains of E. coli resistant to streptothricin, neomycin and grisein were not sensitive to grasseriomycin.[1]

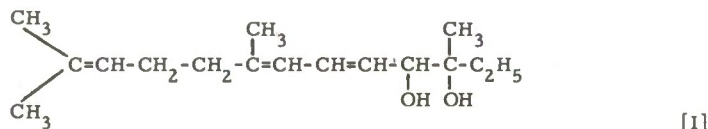
In vivo. Active against the virus of silkworm jaundice. When injected s.c., protection was afforded in artificially infected silkworm pupae.[1]

149. GRIFOLIN

SOURCE Grifola confluens [1].

MOLECULAR FORMULA AND WEIGHT C₁₆H₂₈O₂; 250 (found); 252 (calc.).[1]

STRUCTURE



CRYSTAL FORM AND COLOR Fine colorless crystals [1].

MELTING POINT (°C) 40 [1].

UV ABSORPTION MAXIMUM 275 mμ¹ [1].

SOLUBILITY s. most organic solvents; i. water. [1]

STABILITY Thermostable; fairly stable to acid and alkali [1].

OTHER REACTIONS In increasing alkaline concentration, a purple-red color; resinifies when heated in 10% alkaline solution.[1]

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. aureus, Bacillus subtilis [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits M. pyogenes var. aureus in dilution of 1:200,000; B. subtilis, 1:180,000; B. anthracis, Salmonella typhimurium, Shigella dysenteriae, 1:10,000; Mycobacterium avium, Myco. phlei, 1:5000.[1]

TOXICITY LD₁₀₀ in mice, 1600 mg/kg [1].

150. GRISAMINE

SOURCE Streptomyces sp resembling S. griseoflavus [1].

MOLECULAR FORMULA AND WEIGHT C₂₈H₃₈N₆O₁₀; 603.24 (calc.); 604.546 (Rast); or C₂₀H₃₀N₄O₇. [1]

CRYSTAL FORM Needles [1].

MELTING POINT (°C) Free grisamine: 165-170. SO₄: 175-180.[1]

UV ABSORPTION MAXIMA 255, 320 mμ² [1].

SOLUBILITY s. water, ethyl acetate, butanol, chloroform; sl. s. ether; i. petroleum ether, benzene, toluene, ligroin.[1]

/1/ Complete transmission above 300 mμ. /2/ Water.

150. GRISAMINE (Concluded)

OTHER REACTIONS Negative ninhydrin, biuret, Fehling, Sakaguchi, FeCl_3 ; weakly positive p-dimethylamino-benzaldehyde, sodium nitroprusside.[1]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Mycobacterium tuberculosis* var. *hominis*, 4-13; *Myc. phlei*, 8; *B. subtilis*, 30; *Micrococcus pyogenes* var. *aureus*, 70. Not sensitive: *Escherichia coli*, *Pseudomonas aeruginosa*, yeasts and fungi.[1]

ACUTE TOXICITY Mice tolerated 150 mg/kg, i.v.; 160 mg/kg caused delayed deaths.[1]

151. GRISEIN

SOURCE Certain strains of *Streptomyces griseus* [1].

NATURE Weak acid [3].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{40}\text{H}_{61}\text{O}_{20}\text{N}_{10}\text{SFe}$; 1034 (found); 1090 (calc.).[3]

CRYSTAL FORM AND COLOR Red amorphous powder [3].

ABSORPTION MAXIMA 265, 420 $\text{m}\mu$ [3].

SOLUBILITY s. water, phenol; sl. s. acetone, 95% ethanol; i. ether, chloroform, absolute ethanol, absolute ether.[1-3]

STABILITY Stable at 100°C for 10 minutes; inactivated by methanolic HCl [1-3].

OTHER REACTIONS Not affected by cysteine, sodium thioglycollate, hydrazine, hydroxylamine, semicarbazide; forms amorphous picrate, but no helianthate or reineckate, negative Brady, Fehling, Tollens, Liebermann phenol; no formation of furfural; no free C=S or =CSH groups; Fe may be removed from and re-added to molecule.[2, 3]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli* (especially streptomycin-resistant strains) [1, 2].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Bacillus subtilis*, *Micrococcus pyogenes* var. *aureus*, *Sarcina lutea*, *Mycobacterium tuberculosis*, *Myc. phlei*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Salmonella pullorum*, *Shigella* spp, *E. coli*, *Salmonella* spp. Streptomycin-resistant strains of *E. coli* were sensitive to grisein. Fungi not sensitive.[1, 2] In vitro resistance was readily developed by some organisms [1].

In vivo. Protection afforded mice infected with *M. pyogenes* var. *aureus* and *Salmonella schottmuelleri* [2].

TOXICITY Parenteral doses of 500,000 units/kg tolerated by experimental animals [2]. Mice tolerated parenteral doses of 500 mg/kg [4].

152. GRISEOFLAVIN

SOURCE *Streptomyces griseoflavus* [1].

CRYSTAL FORM AND COLOR Colorless needles [1].

MELTING POINT (°C) 210-215 (d.) [1].

SOLUBILITY s. methanol, ethanol, propanol, phenol, acetic acid, hot acetone, alkaline water; sl. s. water, ethyl acetate, butyl acetate; i. ether, petroleum ether, benzene, trichloroethylene, chloroform. [1]

OTHER REACTIONS Not precipitated with picric acid, flavianic acid, methyl orange; negative biuret, ninhydrin, Millon, Sakaguchi, Molisch, glucosamine, AgNO_3 reduction, Fehling, FeCl_3 , triphenylmethane; more active at acid pH.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*, *Bacillus subtilis* PCI-219 [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *M. pyogenes* var. *aureus*, 0.2-3.1; *B. anthracis*, 3.1; *Vibrio comma*, 0.8; *Mycobacterium tuberculosis*, 2.0; *B. subtilis*, 25; *Shigella sonnei*, 50; *Diplococcus pneumoniae*, 25-50; *Neisseria meningitidis*, 100; *Mycobacterium* spp, 25-400.[1]

TOXICITY LD_{50} in mice, >250 mg/kg, i.p. [1].

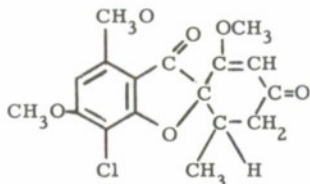
153. GRISEOFULVIN

SOURCE *Penicillium griseofulvum* [1], and other *Penicillium* spp [8]; *P. urticae* (Bain), *P. nigricans* [12]; *P. raistrickii* [13].

NATURE Neutral [1].

MOLECULAR FORMULA AND WEIGHT $C_{17}H_{17}O_6Cl$ [1, 4, 6]; 309-398 (found); 352.5 (calc.). [1, 3]

STRUCTURE



[5, 6]

CRYSTAL FORM AND COLOR Massive colorless rhombic or octahedral crystals [1, 3].

MELTING POINT ($^{\circ}C$) 218-221 [1, 3, 4, 6].

OPTICAL ACTIVITY $[\alpha]_{5790}^{19} = +354^{\circ 1}$ [1]; $[\alpha]_D^{17} = +370^{\circ 2}$ [3]; $[\alpha]_{5461}^{19} = +417^{\circ 1}$ [1]; $[\alpha]_D^{21} = +337^{\circ 3}$ [4].

UV ABSORPTION MAXIMA 286, 325 $m\mu$ [6].

SOLUBILITY s. NN'-dimethylformamide 12-14% at room temperature [11], acetic acid, dioxane, benzene, ether, ethanol; sl. s. chloroform, ethyl acetate, toluene, acetone, ligroin; i. water, petroleum ether. [1, 3]

STABILITY Thermostable [2].

OTHER REACTIONS Negative $FeCl_3$, HBr, alkaline sodium nitroprusside, pyridine; yellow color with H_2SO_4 or HNO_3 ; reacted with phenylhydrazine and 2, 4-dinitrophenylhydrazine, but not with diazomethane or semicarbazide; bromo-analogue can be made by replacing KCl in culture medium with KBr. [1, 7] Can be precipitated with water from concentrated solutions of dimethylformamide to yield fine dispersions; solutions in above solvent up to 1% can be diluted with water without precipitating. [11]

QUANTITATIVE DETERMINATION Microbiological: Curling of hyphae and stunting of germ tubes of *Botrytis allii* [2]. Spectrophotometric [11, 14]. Isotope dilution [11, 15]. Polarimetric [11].

BIOLOGICAL ACTIVITY In vitro. Shows antifungal activity. Inhibits numerous species of zygomycetes, ascomycetes (except *Saccharomyces cerevisiae*), basidiomycetes, and Fungi imperfecti at 20 $\mu g/ml$ or less. [8]

PHYTOTOXICITY In general, toxic to angiosperm seeds at 25 $\mu g/ml$; low toxicity in wheat, clover, and mustard seedlings. [8, 10] Concentrations of 5 $\mu g/ml$ toxic to wheat plants and tended to accumulate in the leaves [17].

PHYTOPATHOLOGY Did not increase the resistance of wheat seedlings to infection with *Xanthomonas translucens*. The antibiotic is readily taken up by the roots and translocated in wheat seedlings. [16] Protection in plants against several phytopathogenic fungi, e.g., *B. cinerea* infection of lettuce when grown in water culture containing 10 μg antibiotic per ml [9].

MODE OF ACTION Griseofulvin prevented penetration of cell membranes by *B. tulipae* in tulip stems, and rendered onion epithelium impermeable to *B. allii* [18].

154. GRISEOLUTEINS

SOURCE *Streptomyces griseoluteus*, n. sp [1].

NATURE Acidic [1].

MOLECULAR FORMULA Possibly $(C_{8,6}H_{7,6}NO_3)_n$ [1].

CRYSTAL FORM AND COLOR Griseolutein A: reddish-yellow needles⁴ [1, 2].
B: light yellow crystals [2].

MELTING POINT ($^{\circ}C$) Griseolutein A: 193 (d.) [1, 2].
B: Darkens approximately 150 (d. >220) [2].

/1/ c, 1.0127 acetone. /2/ c, 2 chloroform. /3/ c, 1 acetone. /4/ Recrystallized from ethyl acetate.

154. GRISEOLUTEINS (Concluded)

UV ABSORPTION MAXIMA Griseolutein A: 267, 368 m μ .

B: 281, 342 m μ . [2]

SOLUBILITY s. NaHCO₃; sl. s. ethyl acetate, alcohol; i. water, ether, benzene.

STABILITY Most stable at acid, least at alkaline pH [1].

BIOLOGICAL ACTIVITY In vitro. Griseolutein A: Inhibits (μ g/ml) *Micrococcus pyogenes* var. *aureus*, 0.2-0.8; *Bacillus subtilis*, 0.1-0.2; *B. anthracis*, 0.4; *Escherichia coli*, 5-6; *Salmonella typhosa*, 3.1-5.0; *S. paratyphi*, 3.1; *S. typhimurium*, 25; *Shigella dysenteriae*, 1.6-5.0; *Proteus vulgaris*, 0.2-0.4; *Brucella melitensis*, 0.2; *Pseudomonas aeruginosa*, 12.5. Weak activity against mycobacteria. [1, 2]

B: Inhibits (μ g/ml) *Micrococcus pyogenes* var. *aureus*, *B. anthracis*, *B. subtilis*, *Salmonella paratyphi*, *Shigella dysenteriae*, *Sh. paradysenteriae*, 0.2-4.0; *Salmonella typhosa*, *Escherichia coli*, 5-10; *Streptococcus* sp, *Salmonella typhimurium*, *Diplococcus pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, 25-50. [2, 4]

In vivo. Griseolutein B: S.c. doses of 1-2.5 mg protected mice against infection with *M. pyogenes* var. *aureus* [4].

TOXICITY Griseolutein A: S.c. doses of 2000 mg/kg were sublethal to mice, but induced kidney damage [1, 3].

B: LD₅₀ in mice, 240 mg/kg, i.v.; 450 mg/kg, s.c.; 800 mg/kg, oral. [4]

ABSORPTION Griseolutein B: S.c. doses of 100 mg/kg, and oral doses of 50 mg/kg, in rabbits produced blood concentrations of approximately 50 μ g/ml after 5 hours [4].

155. GRISEOMYCIN
(Lomycin)

SOURCE *Streptomyces griseolus* [1].

NATURE Basic [1].

MOLECULAR FORMULA C₂₅H₄₆NO₈Cl [2].

CRYSTAL FORM AND COLOR White plates [1].

MELTING POINT (°C) 76-80 (d.); HCl, 120 [1].

OPTICAL ACTIVITY [α]_D²⁵ = +32⁰¹ [1].

SOLUBILITY s. most organic solvents; sl.s. H₂O. HCl: s. water, methanol, ethanol, chloroform; sl.s. most other organic solvents. [1]

STABILITY Thermolabile; less stable at alkaline pH; stable at pH 2-9 at room temperature. [1]

OTHER REACTIONS Bitter taste; HCl precipitates from aqueous solution by picric acid, Reinecke salt, Br water, iodopotassium iodide; slightly positive Mandelin, Margin, Wasicky. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits (μ g/ml) *Corynebacterium diphtheriae*, *C. pseudodiphtheriae*, *Bacillus cereus*, *B. mycoides*, *B. subtilis*, *Mycobacterium lacticola*, *Streptococcus pyogenes*, 0.2-0.5; *B. mesentericus*, 1.3; *Neisseria* sp, 5; *Myc. smegmatis*, 15; *Myc. tuberculosis*, 187. No inhibition at 1000 μ g/ml of *Pseudomonas aeruginosa*, *Escherichia coli*, *Serratia marcescens*, *Salmonella typhosa*, *Shigella* spp, and *Candida albicans*. [1]

TOXICITY LD₅₀ in mice, 210 mg/kg, i.p.; 1330 mg/kg, s.c.; oral doses of 2100 mg/kg tolerated. Lethal doses induced symptoms of neurotoxicity. Repeated daily s.c. doses of 110 mg/kg were non-toxic. [1]

RESISTANCE *M. pyogenes* var. *aureus* rapidly developed resistance in vitro; 400-fold increase (0.5-200 μ g/ml) following 5 transfers in media containing antibiotic. This antibiotic shows very marked cross resistance with erythromycin and carbomycin. [1]

ABSORPTION AND EXCRETION In guinea pigs, 200 mg/kg, i.m., produced peak blood concentrations of 10 μ g/ml in 35 minutes, dropping to 5 μ g in 1 hour and 1.5 μ g in 10 hours. High levels in urine and bile, and in lungs, spleen and kidneys; no detectable concentrations in the liver and brain. Following oral doses, highest blood levels were noted in 3 hours. In man, there was good absorption from the gastrointestinal tract following oral doses; antibiotic was excreted in the urine in concentrations up to 125 μ g/ml. [3]

/1/ c, 1 chloroform.

156. GRISEOVIRIDIN

SOURCE *Streptomyces griseoviridus*, n. sp. and *S. griseus* [1, 3].

NATURE Neutral compound [1].

MOLECULAR FORMULA AND WEIGHT $C_{22}H_{29}O_7N_3S$ (proposed); 485-490.[4]

CRYSTAL FORM AND COLOR Colorless crystals [1].

MELTING POINT ($^{\circ}C$) (All corr.) 158-166; 194-200; 230-240¹. [1] 228-230²; 160³. [4]

OPTICAL ACTIVITY $[\alpha]_D^{27} = -237^{\circ 4}$ [1, 4].

UV ABSORPTION MAXIMA 221 $m\mu$ ⁵ [1]; 220.5 $m\mu$ [4].

SOLUBILITY s. pyridine, lower alcohols; s.l.s. water, non-polar solvents.[1]

STABILITY Stable at pH 2-9 for 24 hours at room temperature⁶ [1].

OTHER REACTIONS Positive Baeyer; negative $FeCl_3$, Folin-Ciocalteu, Sakaguchi, Jacobs-Hoffman. Infrared absolute maxima depend on crystal form. Analysis: C, 55.2; H, 6.2; O, 23.0; N, 8.6; S, 6.4.[1] Crystallizes from methanol in 2 forms: A is obtained above 30 $^{\circ}$ and B below; form B loses solvent in air, yielding A. In water, antibiotic gives a light blue color in 1½-2 hours in the chromate-nitric acid test for primary and secondary alcohol groups.[4]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli* [2].

BIOLOGICAL ACTIVITY Active against Gram-positive and Gram-negative bacteria; no activity against fungi and protozoa. In vitro. Inhibits ($\mu g/ml$) *Actinomyces bovis*, *Clostridium hemolyticum*, *Corynebacterium diphtheriae*, *Hemophilus pertussis*, *Moraxella bovis*, *Neisseria gonorrhoeae*, 0.1-0.5; *N. meningitidis*, 0.5->10; *N. catarrhalis*, 0.25-1.0; *Streptococcus pyogenes*, 0.5-1.0; *Str. agalactiae*, 0.8; *Streptococcus spp.*, 0.25->10; *Micrococcus pyogenes var. aureus*, 1.0->100; *Brucella suis*, 5-25; *Br. abortus*, 50-100; *Diplococcus pneumoniae*, *Erysipelothrix rhusiopathiae*, 10->10; *Hemophilus influenzae*, 1; *Mycobacterium tuberculosis*, 25-300; *Vibrio comma*, 25; *Salmonella typhosa*, 50->100; *Shigella paradysenteriae*, 2.5-10. The following were not sensitive to 10 $\mu g/ml$: *Bacillus anthracis*, *Br. bronchiseptica*, *Escherichia coli*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Malleomyces mallei*, *Paracolobactrum spp.*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Salmonella schottmuelleri*, *Clostridium perfringens*, *Cl. novyi*, *Str. salivarius*, *Leptospira icterohemorrhagiae*, and *Nocardia asteroides*. Fungi are not susceptible at 200 $\mu g/ml$. *Entamoeba histolytica*, *Trichomonas foetus*, and trypanosomes were not sensitive to 250-500 $\mu g/ml$. [1]

In vivo. Daily i.p. doses of 250 mg/kg protected mice infected with *H. pertussis*; oral doses of 250-500 mg/kg were less effective. Some protection afforded in mouse infections with meningopneumonitis and psittacosis viruses. Activity against *Rickettsia prowazeki* in chick embryo. No activity against *Myco. tuberculosis* and *Schistosoma mansoni* in mice; inactive against smaller viruses.[1]

VETERINARY In limited trials in chronic bovine mastitis caused by *M. pyogenes* or *E. coli*, single infusions of 250 mg in ointment base to each udder quarter effectively eliminated these organisms. Preliminary trials indicated chickens with infectious sinusitis rendered asymptomatic following single oral dose of 250 mg.[1]

TOXICITY LD₅₀ in mice, 75 mg/kg, i.v.; >100 mg/kg, i.p. or s.c. Mice tolerated 100 mg/kg, i.p. or s.c., twice daily for 10 days without evidence of toxicity. Dogs tolerated oral doses of 100-200 mg/kg/da for 10 days. Instillation of 250-1000 mg in ointment into bovine teat canal was well tolerated; no irritation when instilled into the conjunctival sac of dogs.[1]

157. HELENINE

May be identical with antibiotic 8450 of Powell and Culbertson. [3-5]

SOURCE *Penicillium funiculosum* [1].

STABILITY Stable when frozen; thermolabile.[2]

OTHER REACTIONS Precipitable from 50% acetone; filterable through a Seitz pad but non-dialyzable; large amounts of polysaccharide found with crude active preparations.[1, 2]

BIOLOGICAL ACTIVITY In vivo. Good protection in mice infected with Columbia SK encephalomyelitis and Semliki Forest viruses following i.p. doses of approximately 5 mg, b.i.d.[1, 2]. Increased survival rates of mice infected with western equine encephalomyelitis virus [6]. Daily i.p. doses of 5 ml per kg for 4 days protected monkeys

/1/ Depending on crystal modification. /2/ From pyridine. /3/ From methanol. /4/ c, 0.5 methanol. /5/ In methanol. /6/ In culture filtrate.

157. HELENINE (Concluded)

infected orally with Mahoney strain of type I poliomyelitis virus and reduced amount of virus recoverable in feces. No protection when antibiotic was administered orally. [7]

158. HELIXIN

SOURCE *Streptomyces* sp [1].

SOLUBILITY s. ethanol, methanol, methyl cellosolve, pyridine, 0.01 M phosphate buffer at pH 8.5, glacial acetic acid, n-butanol, acetone; sl. s. chloroform; i. ether, petroleum ether, benzene, ethyl acetate, carbon tetrachloride.[1]

STABILITY Thermolabile at pH 3; more stable at alkaline pH.[1]

OTHER REACTIONS Negative Molisch, ninhydrin, Hopkins-Cole, xanthoproteic, Millon, FeCl₃; deep red in ethanol solution; amorphous precipitate in aqueous solution below pH 4-5; components A, B, C, D present; B is identical with a component of endomycin.[1, 2]

QUANTITATIVE DETERMINATION Microbiological: *Glomerella cingulata* [1].

BIOLOGICAL ACTIVITY Active against fungi and certain bacteria. In vitro. Inhibits *Candida albicans*, *Saccharomyces cerevisiae*, *Trichophyton mentagrophytes*; also *Bacillus subtilis* and *Micrococcus pyogenes* var. *aureus* at 22.5 µg/ml or less. Phytopathogenic fungi: *Alternaria solani*, *Botrytis allii*, *Colletotrichum* sp, *Helminthosporium* sp, and *Verticillium* sp inhibited at 7.5 µg/ml or less. [1, 2]

PHYTOPATHOLOGY Sprays (45 µg/ml solution) protected tomato leaves against *Alternaria solani* [3]. Was effective in control of certain *Helminthosporium* diseases of oats and barley and 3 covered smuts of small grain [4]. Failed to control stem rust of wheat when used as pre-inoculation spray under greenhouse conditions [5].

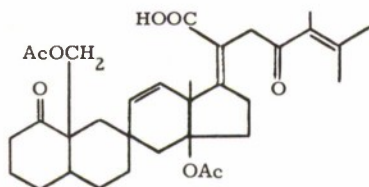
159. HELVOLIC ACID
(Fumigacin)

SOURCE *Aspergillus fumigatus* [1, 2].

NATURE Monobasic acid [7].

MOLECULAR FORMULA AND WEIGHT C₃₂H₄₂O₈; 555 (calc.); 585 (found for methyl ester).[13]

STRUCTURE



[12]

CRYSTAL FORM AND COLOR Fine, long, white needles [1-3, 6, 13].

MELTING POINT (°C) 220-226 [4]; 211.3-212.1 (d.).[13]

OPTICAL ACTIVITY $[\alpha]_D^{23} = -113^{\circ 1}$, $-117^{\circ 2, 3}$ [8]; $[\alpha]_D^{25} = -124^{\circ 4}$ [13].

UV ABSORPTION MAXIMA 230, 234 mµ [5, 6]; 231, 322 mµ [13]. Methyl helvolate: 218, 232 mµ [11].

SOLUBILITY s. chloroform, acetone, ethyl acetate, benzene, pyridine, glacial acetic acid, dioxane, ether, warm ethanol; sl. s. cold ethanol and methanol, petroleum ether, water.[1]

STABILITY Thermostable at acid pH; unstable at alkaline.[1]

OTHER REACTIONS Yellow precipitate with FeCl₃; strong red color in Liebermann-Burchard; orange color in Zimmerman; yellow color with tetranitromethane; positive bile acid; negative Fehling, ammoniacal AgNO₃, fuchsin, sulfurous acid, Tollens, Molisch, Rosenheim, cholic acid, Jaffé-Tortelli; digitonin fails to consume periodate; fumigacin is helvolic acid plus gliotoxin.[1, 6, 8, 11-13]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1, 3, 4, 6].

/1/ c, 3.1 chloroform. /2/ c, 2.6 chloroform. /3/ Higher rotations obtained by early investigators may have been caused by contamination with gliotoxin. /4/ c, 1 chloroform.

159. HELVOLIC ACID (Concluded)

BIOLOGICAL ACTIVITY *In vitro*. Inhibited (in dilution x 1000) *M. pyogenes* var. *aureus*, 1280; *Streptococcus pyogenes*, 160-640; *Corynebacterium diphtheriae*, 640; *Diplococcus pneumoniae*, *Str. viridans*, 160; *Bacillus anthracis*, *Clostridium perfringens*, *Cl. novyi*, 320; *Salmonella enteritidis*, *Cl. septicum*, *Neisseria meningitidis*, 25-80; *S. typhosa*, *Proteus* sp, *Pseudomonas aeruginosa*, *Escherichia coli*, 0.5; *Mycobacterium tuberculosis*, 20. [1, 2] **Phytopathogens** (in dilution x 1000): *Corynebacterium sepeidonicum*, 160; *C. michiganense*, *Bacterium stewartii*, *Pseudomonas glycinea*, 30; *Agrobacterium tumefaciens*, >90; *Ps. syringae*, *Xanthomonas campestris*, 40; *X. pruni*, 60; *Ps. marginalis*, *X. malvacearum*, 20. No activity against phytopathogenic fungi.[9, 10]

TOXICITY Mice tolerated doses of 250 mg/kg, i.v. or s.c.; oral doses of 1000 mg/kg.[1] LD₅₀, 400 mg/kg by i.p. route [11]. Repeated i.v. or s.c. doses of 100 mg/kg produced fatty changes in liver [1].

RESISTANCE *M. pyogenes* and *Str. pyogenes* showed 250-fold increase in resistance after 26 transplants in antibiotic-containing media [1]. *In vivo*. Slight activity in mice infected with *M. pyogenes* and *Str. pyogenes* [1, 6].

ABSORPTION Serum levels obtained after s.c., i.m., and oral doses in mice; no detectable concentration in cerebrospinal fluid.[1]

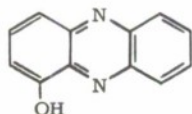
160. HEMIPYOCYANINE
(α -Hydroxyphenazine)

SOURCE *Pseudomonas aeruginosa* [2, 3].

NATURE A pigment [1].

MOLECULAR FORMULA C₁₂H₈ON₂ [1].

STRUCTURE



[1]

CRYSTAL FORM AND COLOR Yellow needles [1].

MELTING POINT (°C) 158 [1].

SOLUBILITY s. alkali [1].

OTHER REACTIONS Red-violet in alkaline solution, yellow when neutralized [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits (in dilutions of 1:10,000-1:1,000,000) *Bacillus anthracis*, *Brucella abortus*, *Clostridium perfringens*, *Cl. fesceri*, *Cl. tetani*, *Cl. septicum*, *Corynebacterium pyogenes*, *Escherichia coli*, *Micrococcus pyogenes* var. *aureus*, *Pasteurella multocida*, *Salmonella choleraesuis*, *Streptococcus agalactiae*, *Str. dysgalactiae*, *Vibrio comma*, *V. foetus* [2, 4]. **Fungi:** *Candida albicans* and *Trichophyton schoenleinii* inhibited by 1:100,000, *Microsporium gypseum* and *Trichophyton mentagrophytes* by 1:20,000-1:60,000.[5]

In vivo. Some protection against *Br. abortus* infection in guinea pigs. Infusions of 0.5-1.0 g failed to eliminate *Br. abortus* from bovine udder.[4]

CLINICAL Limited value when topically used in dermatophytosis [6].

TOXICITY I.p. doses of 500 mg/kg sublethal to mice. [2]

161. HERQUEIN

SOURCE *Penicillium herquei* [1].

MOLECULAR FORMULA C₁₉H₂₀O₈ (proposed) [1].

FORM AND COLOR Yellow-brown crystals [1].

MELTING POINT (°C) 129 (d.) [1].

SOLUBILITY s. ethanol, chloroform, ether, carbon tetrachloride; sl.s. water, benzene; i. petroleum ether.[1]

OTHER REACTIONS Precipitated by lead acetate; yellow solution in water which exhibits a bottle-green fluorescence on addition of alkali.[1]

161. HERQUEIN (Concluded)

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *Micrococcus pyogenes* var. *aureus* and *Vibrio comma* in dilution of 1:2500. *Pseudomonas aeruginosa*, *Shigella dysenteriae*, *Streptococcus pyogenes*, and *Mycobacterium phlei* also sensitive.[1]

162. HIRSUTIC ACIDS

SOURCE *Stereum hirsutum* [1].

NATURE Several active and inactive acids [1].

MOLECULAR FORMULA AND WEIGHT Hirsutic acid C: $C_{15}H_{20}O_4$ (proposed); 260-264 (titr.); 264 (calc.).[1]

CRYSTAL FORM AND COLOR Hirsutic acid C: large, colorless prisms.
N: transparent, colorless, non-crystalline solid.[1]

MELTING POINT ($^{\circ}C$) Hirsutic acid C: 179.5 (uncorr.) [1].

OPTICAL ACTIVITY $[\alpha]_D^{20} = +11.9^{\circ}$ [1].

UV ABSORPTION MAXIMA Hirsutic acid C: No UV spectrum [1].

SOLUBILITY Hirsutic acid C: s. most organic solvents; sl. s. water; i. hexane, CCl_4 .
N: s. alkali and most organic solvents; sl.s. hot water; i. cold water, hexane, CCl_4 . [1]

STABILITY Hirsutic acid N: Stable as free acid solid; less stable in water, especially at alkaline pH.[1]

OTHER REACTIONS Group of active and inactive acids of which C is an inactive precursor, while A, N and some other derivatives are active; negative Fehling, ammoniacal $AgNO_3$, 2,4-dinitrophenylhydrazine, acidified KI; decolorized $KMnO_4$; white precipitate with Br water; faint brown color with $FeCl_3$; C titrates as a monobasic acid, pK_a 4.6.[1]

QUANTITATIVE DETERMINATION: Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY *In vitro*. Hirsutic acid A: Inhibits *M. pyogenes* var. *aureus* at 1:8000; *Streptococcus pyogenes* less sensitive; no activity against *Salmonella enteritidis* and *Escherichia coli*. [1]

N: Inhibits *Corynebacterium diphtheriae* and *Neisseria meningitidis* in dilution of 1:40,000; *M. pyogenes* var. *aureus* and *Str. pyogenes* at 1:10,000. *M. lysodeikticus*, *Sarcina lutea*, *Bacillus anthracis*, *B. subtilis*, and *Vibrio comma* less sensitive; no activity against *S. enteritidis* and *E. coli*.

TOXICITY Hirsutic acid A: LD_{100} , 15-20 mg, i.v.

C: Atoxic to mice in high doses.[1]

N: LD_{100} in mice, 1-2 mg, i.v.; oral doses of 20 mg tolerated.

A, N: *In vitro*, both are toxic to leukocytes in dilution of 1:16,000.

163. HOMOMYCIN

SOURCE *Streptomyces noboritoensis*, n. sp [1].

FORM AND COLOR White powder [1].

MELTING POINT ($^{\circ}C$) 105-109² [1].

UV ABSORPTION MAXIMA 270-272 $m\mu$ [1].

SOLUBILITY s. water, lower alcohols; sl. s. other organic solvents.[1]

OTHER REACTIONS Some resemblance to hygromycin; positive diazo, Nessler, Fehling, Tollens, indole, carbazole; negative ninhydrin, $FeCl_3$, biuret. Analysis: C, 53.60; H, 6.85; N, 2.70.[1]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu g/ml$) *Mycobacterium tuberculosis* var. *hominis* and *Myco. tuberculosis* var. *bovis* at 5; *Micrococcus flavus*, *M. pyogenes* var. *aureus*, 25; *Bacillus agri*, 100; *Myco. phlei*, 250; *B. subtilis*, *Escherichia coli*, 500. A streptomycin-resistant strain of *E. coli* was sensitive to 50 $\mu g/ml$ of homomycin.[1]

TOXICITY Mice tolerated i.v. doses of >2000 mg/kg [1].

/1/ Free acid in absolute alcohol. /2/ Decomposes gradually above 160 $^{\circ}C$.

164. HUMICOLIN

SOURCE *Aspergillus humicola* [2].

NATURE Weakly acidic [2].

FORM AND COLOR Yellow oil [1, 2].

SOLUBILITY s. most organic solvents; sl. s. water; i. petroleum ether. [1]

STABILITY Relatively stable at pH 3.5-4.5, unstable above. [1, 2]

OTHER REACTIONS Brown color with $FeCl_3$ in alcoholic solution; inactivated by UV in sodium bicarbonate solution. [2]

QUANTITATIVE DETERMINATION Microbiological: *Botrytis allii* spore germination [1, 2].

BIOLOGICAL ACTIVITY In vitro: Inhibits fungi ($\mu g/ml$): *Aspergillus niger*, *A. terreus*, *Fusarium caeruleum*, *Mucor mucedo*, *Myrothecium verrucaria*, *Penicillium expansum*, 0.8-6.2; *B. allii*, 1; *Trichoderma viride*, 12.5-25.0. [2]

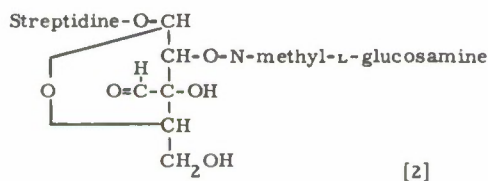
165. HYDROXYSTREPTOMYCIN
Identical with reticulof of Hosoya, et al. [5]

SOURCE *Streptomyces griseo-carneus*, n. sp [1].

NATURE Basic [1].

MOLECULAR FORMULA $C_{21}H_{39}N_7O_{13}$ [1, 2].

STRUCTURE



CRYSTAL COLOR Helianthate: reddish-brown crystals. Trihydrochloride: white. [2]

MELTING POINT ($^{\circ}C$) Helianthate: Darkens at 220; chars without melting. [2]

OPTICAL ACTIVITY Trihydrochloride: $[\alpha]_D^{28} = -91^{01}$ [2].

OTHER REACTIONS X-ray diffraction pattern like that of streptomycin; more stable to acid hydrolysis than is streptomycin.

| | % Activity Remaining (in 2N HCl at 20 $^{\circ}C$) | | | |
|---------------------|---|--------|--------|---------|
| | 1 day | 2 days | 7 days | 21 days |
| Streptomycin | 50 | 19 | <1 | |
| Hydroxystreptomycin | 93 | 85 | 58 | 20 |

[2, 3]

BIOLOGICAL ACTIVITY Antimicrobial spectrum same as that of streptomycin (q.v.) [1, 4].

TOXICITY About the same as streptomycin and dihydrostreptomycin. Marked ototoxicity in cats. LD_{50} in mice, 865 mg/kg, s.c. [4]; LD_0 , 550 mg/kg, i.v.; 440 mg/kg, i.p. [5]

166. HYGROMYCIN

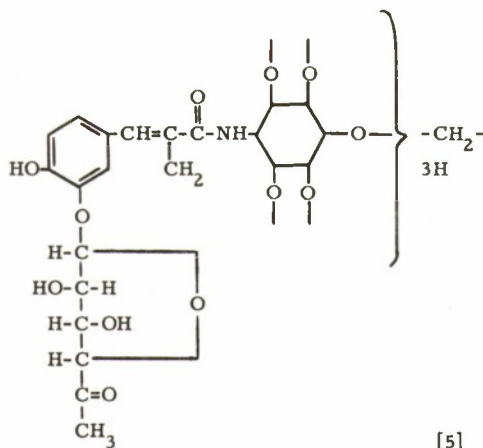
SOURCE *Streptomyces hygroscopicus* (Jensen) [1].

NATURE Weakly acidic [2].

MOLECULAR FORMULA AND WEIGHT $C_{23}H_{29}NO_{12}$ [5]; 536 ± 25 (titr.). [2]

/1/ c, 1 water.

STRUCTURE



CRYSTAL FORM Not crystallized [2].

OPTICAL ACTIVITY $[\alpha]_D^{25} = -126^{\circ 1}$ [2].

UV ABSORPTION MAXIMA 272, 214² [2, 5]; 254, 286, 323 $m\mu^3$ [5].

SOLUBILITY s. water, alcohol; i. less polar solvents.[2]

STABILITY Thermostable at pH 3 to 7; unstable above 9.[1]

OTHER REACTIONS Not greatly affected by pH of assay medium; positive Folin-Ciocalteu, Benedict, Fehling; negative $FeCl_3$, anthrone, Molisch, maltol. Infrared: Strong absorption bands at 3.0, 5.84, 6.08, 6.22, and 6.62 μ .[2, 5]

QUANTITATIVE DETERMINATION Microbiological: *Klebsiella pneumoniae* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu g/ml$) *Micrococcus sphaeroides*, *Hemophilus ducreyi*, 0.2; *Mycobacterium tuberculosis*, 1-2; *Lactobacillus lactis*, 1.6; *Bacillus brevis*, *B. polymyxa*, *Streptococcus pyogenes*, *Str. mitis*, 3.1; *Corynebacterium diphtheriae*, *Sarcina lutea*, *Shigella paradysenteriae*, 6.2; *Aerobacter aerogenes*, *K. pneumoniae*, *Proteus vulgaris*, *Micrococcus flavus*, *M. lysodeikticus*, 12.5; *M. pyogenes* var. *aureus*, 12.5-50; *Lactobacillus* spp, *Leuconostoc citrovorum*, *Str. faecalis*, *Str. lactis*, *Str. salivarius*, *Streptococcus* spp, 25->25; *Salmonella ambigua*, *S. enteritidis*, *Myco. avium*, *Myco. phlei*, 50. *B. cereus*, *B. macerans*, *B. subtilis*, *Brucella bronchiseptica*, *Escherichia coli*, *Neisseria catarrhalis*, *Pseudomonas aeruginosa*, *S. gallinarum*, *S. paratyphi*, 100 $\mu g/ml$ or greater. Actinomycetes ($\mu g/ml$): *Nocardia coeliaca*, 12.5; *Streptomyces lavendulae*, 6.2; *N. gardneri*, *S. diastaticus*, *S. griseus*, 50; *S. venezuelae*, 100. Fungi: *Trichophyton rubrum*, *Candida albicans*, *Saccharomyces pastorianus*, 100 $\mu g/ml$ or greater.[1, 3, 4]

In vivo. Good protection in mice infected with *Myco. tuberculosis*, *Str. pyogenes*, and *Borrelia novyi*; moderate activity against *K. pneumoniae*.[1, 3] Activity demonstrated in mice infected with meningopneumonitis virus; no effect on smaller viruses, e.g., poliomyelitis "MM" and Semliki Forest viruses.[1, 3]

TOXICITY I.v. doses of 1000 mg/kg tolerated in mice.

RESISTANCE *K. pneumoniae* acquired 1600-fold resistance following six transfers in antibiotic-containing media; strains of *Str. pyogenes*, *M. pyogenes* var. *aureus* and *Mycobacterium* sp did not readily develop resistance in vitro. Bacteria, made resistant to hygromycin, showed increased resistance to chlortetracycline, oxytetracycline, and, in some instances, erythromycin.[3]

MODE OF ACTION Although relatively high concentrations are required for bacteriostasis in vitro, the same or lower levels show marked bactericidal effect. Activity depressed by cysteine, thiamine, biotin and ascorbic acid in vitro.[3]

167. HYGROSCOPINS

SOURCE *Streptomyces hygrosopicus* [11].

NATURE Oils [2].

/1/ c, 1 water. /2/ Dilute HCl. /3/ Dilute alkali.

167. HYGROSCOPINS (Concluded)

MOLECULAR FORMULA AND WEIGHT Hygroscofin A: $C_{13}H_{24}O_3N_2$.
 B: $C_{15}H_{28}O_3N_2$. [2]

OPTICAL ACTIVITY Hygroscofin A: $[\alpha]_D^{14} = +84.7^{\circ 1}$.
 B: $[\alpha]_D^{14} = -38.8^{\circ 1}$. [2]

UV ABSORPTION MAXIMA Hygroscofin A: $235 m\mu^2$.
 B: $233 m\mu^2$. [2]

OTHER REACTIONS Three fractions from carbon chromatography and distillation.

Hygroscofin A: refractive index $n_D^{13} = 1.4830$, BP $0.003 64^{\circ}$.
 B: refractive index $n_D^{14} = 1.4935$, BP $0.008 70^{\circ}$. [2]

BIOLOGICAL ACTIVITY In vitro. Active against phytopathogenic fungi [1].

Hygroscofin A: Inhibits Mycobacterium tuberculosis var. hominis at $10 \mu\text{g/ml}$. Influenza virus inhibited in tissue cultures by concentration of $10 \mu\text{g/ml}$.

B: Inactive against Myco. tuberculosis. Influenza virus inhibited by $10 \mu\text{g/ml}$ tissue culture. [2]

In vivo. Hygroscofin A, B: Doses of 1 mg/kg retarded development of Yoshida sarcoma in animals [2].

ACUTE TOXICITY Hygroscofin A: LD_{50} in mice, 8.8 mg/kg , i.p.
 B: LD_{50} in mice, 19.3 mg/kg , i.p. [2]

168. ILLUDINS

SOURCE Clitocybe illudens [1].

NATURE Neutral [1].

MOLECULAR FORMULA AND WEIGHT Illudin M: $C_{15}H_{20}O_3$; 241 (found); 248 (calc.). [1]
 S: $C_{15}H_{22}O_4$; 264 (found); 266 (calc.). [1]

MELTING POINT ($^{\circ}\text{C}$) Illudin M: 130-131 (uncorr.).
 S: 124-125 (uncorr.). [1]

OPTICAL ACTIVITY Illudin M: $[\alpha]_D^{20} = -126^{\circ 3}$.
 S: $[\alpha]_D^{20} = -165^{\circ 3}$. [1]

UV ABSORPTION MAXIMA Illudin M: 230, $320 m\mu^2$.
 S: 255, $328 m\mu^2$. [1]

SOLUBILITY s. organic solvents; less s. water. [1]

STABILITY Relatively stable [1].

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. aureus, Mycobacterium smegmatis [1].

BIOLOGICAL ACTIVITY In vitro. Illudin M: Inhibits ($\mu\text{g/ml}$) Myco. tuberculosis, Myco. smegmatis, Myco. ranae, 1; Klebsiella pneumoniae, 16; Bacillus subtilis, 500. Weak antifungal activity.

S: Inhibits ($\mu\text{g/ml}$) Myco. tuberculosis, 6; Myco. ranae, 5; Myco. smegmatis, K. pneumoniae, M. pyogenes var. aureus, 4; B. subtilis, 31. No antifungal activity. [1, 2]

In vivo. Daily i.p. doses of 0.8 mg/kg of illudin M for 7 days had no inhibitory effect on RC carcinoma in mice [5]. Illudin M and S active in chicks infected with Plasmodium gallinaceum, but active dosages ($2-5 \text{ mg/kg/da}$) were fairly toxic [3]. Slight retardation of growth of Crocker sarcoma 180 following i.p. administration of $0.6-0.8 \text{ mg/kg/da}$ in mice [4].

RESISTANCE Strains of B. megatherium and Myco. ranae showed complete cross resistance in vitro between illudin M and S [6].

169. INOLOMIN

SOURCE Inoloma traganum [1].

FORM AND COLOR Yellow, glassy, hygroscopic, amorphous [1].

SOLUBILITY s. water, pH 7 phosphate buffer [1].

/1/ Methanol. /2/ Ethanol. /3/ Absolute ethanol.

169. INOLOMIN (Concluded)

STABILITY Thermolabile; stable at room temperature [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits Micrococcus sp and Corynebacterium pseudodiphtheriticum [1].

TOXICITY Mice tolerated i.v. doses of 5000 mg/kg [1].

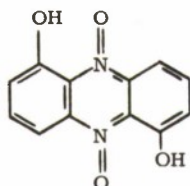
170. IODININ

SOURCE Chromobacterium iodinum [1].

NATURE Bacterial pigment [1].

MOLECULAR FORMULA $C_{12}H_8O_4N_2$ [1].

STRUCTURE



[4]

CRYSTAL FORM AND COLOR Purple crystals with a coppery glint [1].

MELTING POINT (°C) 236 (d.) [1].

SOLUBILITY s. benzene, toluene, xylene, chloroform, carbon disulfide, ethyl acetate; sl. s. hot alcohol; i. ether, cold alcohol, acetic acid, petroleum ether, amyl alcohol [4].

STABILITY Acid stable, alkali unstable [1].

OTHER REACTIONS pK about 12.5; blue-green, water-soluble salt with alkali; decomposed by heat to a gray colloidal substance, reformed by acidification and addition of benzene; activity antagonized by anthraquinone and naphthaquinone derivatives.[1-4]

QUANTITATIVE DETERMINATION Microbiological: Escherichia coli, Streptococcus pyogenes [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits (μg/ml) Str. pyogenes, 0.4-2.0; Micrococcus pyogenes var. aureus, 8-43.[1, 2]

171. ISORHODOMYCINS

SOURCE Streptomyces purpurascens [1].

MOLECULAR FORMULA AND WEIGHT Isorhodomyacin A HCl: $C_{20}H_{29}O_8N$. HCl: 447.9 (calc.); or $C_{21}H_{31}O_8N$. HCl: 461.9 (calc.).[1]

CRYSTAL FORM AND COLOR Isorhodomyacin A HCl: dark red prisms [1].
A perchlorate: thin, red needles [1].

MELTING POINT (°C) Isorhodomyacin A HCl: 220 [1].
A perchlorate: 177 [1].

OPTICAL ACTIVITY Isorhodomyacin A HCl: $[\alpha]_{D}^{18} = +268^{\circ} \pm 30^{\circ}$ [1].

ABSORPTION MAXIMA: Isorhodomyacin A HCl: 610, 563, 551 $m\mu^2$ [1].

SOLUBILITY Isorhodomyacin A HCl: s. water, lower alcohols; sl. s. benzene, chloroform; i. ether, petroleum ether.[1]

OTHER REACTIONS Compound B recognized by paper chromatography; isorhodomyacin A HCl crimson red in solution; intense red fluorescence under UV lamp; occurs with rhodomyacin A, both on mild hydrolysis giving a water-insoluble N-free chromophore, and a water-soluble N-containing fraction.[1]

/1/ c, 0.1 methanol. /2/ Methanol.

171. ISORHODOMYCINS (Concluded)

BIOLOGICAL ACTIVITY In vitro. Isorhodomyacin A: Inhibits *Micrococcus pyogenes* var. *aureus* in dilution of 1:30,000,000.[1]

172. ITURINS

SOURCE *Bacillus subtilis* [1].

NATURE Iturin L: protein [2].

CRYSTAL FORM AND COLOR Iturin L: gray powder.

N: yellow powder.

O: brown substance.[1]

UV ABSORPTION MAXIMA Iturin L: 278 m μ .

N: 270 m μ .

O: 260 m μ .

SOLUBILITY Iturin L: s. water, methanol, ethanol, propanol, pyridine; i. amyl acetate, ether, carbon disulfide, cyclohexanol, dioxane, petroleum ether, acetone.[2]

N: i. benzene.

O: s. benzene.[1]

STABILITY Stable at 100°C, but loss on autoclaving [1].

OTHER REACTIONS Iturin L: Non-dialyzable; stable in UV after 30 minutes; precipitates with many agents; positive biuret, xanthoproteic, Millon; negative Liebermann; Raspail, Sakaguchi, Adamkiewicz; not inactivated by trypsin, pepsin, papain, H₂S; inactivated by H₂O₂, HCHO; contains several amino acids.

Iturin N: Dialyzable; inactivated by UV in 10 minutes.

O: Dialyzable; stable in UV 20-25 minutes.[2]

QUANTITATIVE DETERMINATION Microbiological: Iturin L: *Penicillium notatum* [2].

BIOLOGICAL ACTIVITY In vitro. Inhibit *Sarcina lutea*, *Bacillus subtilis*, *B. megatherium*, *Micrococcus pyogenes* var. *aureus*, and *P. notatum* [1].

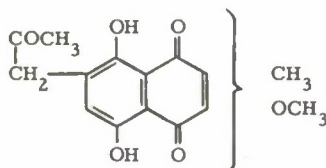
173. JAVANICIN

SOURCE *Fusarium javanicum* [1].

NATURE Weak monobasic acid [1].

MOLECULAR FORMULA C₁₅H₁₄O₆ [1, 3].

STRUCTURE



[2, 3]

CRYSTAL FORM AND COLOR Red laths with coppery luster [1, 3].

MELTING POINT (°C) 207.5-208 (d.) [1, 3].

OPTICAL ACTIVITY Inactive [1].

ABSORPTION MAXIMA 303, 505 m μ ¹ [1].

SOLUBILITY s. water, organic solvents; sl. s. petroleum ether.[1]

STABILITY Thermo-, acid, and alkali stable [1, 3].

OTHER REACTIONS Deep violet color with 10% NaOH, purple with ammonia or sodium carbonate, violet with lead acetate in methanol; no color with sodium bicarbonate; decolorized by Br water or aqueous sodium bisulfite; active derivatives; oxyjavanicin (C₁₅H₁₄O₇, MP 212°C) also occurs in culture filtrates.[1, 3]

/1/ Ethanol.

173. JAVANICIN (Concluded)

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [3] .

BIOLOGICAL ACTIVITY In vitro. Inhibits *M. pyogenes* var. *aureus*, *Streptococcus pyogenes*, *Clostridium perfringens*, *Mycobacterium tuberculosis*, *Myco. phlei*, *Bacillus subtilis* in dilution of 1,40,000-1:200,000. *Pseudomonas aeruginosa*, *Escherichia coli* not sensitive to 1:10,000.[2]

In vivo. No activity in guinea pigs infected with *Myco. tuberculosis* [2] .

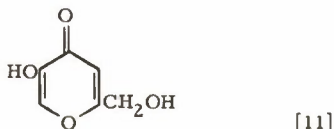
TOXICITY Mice tolerated i.p. doses of 500 mg/kg [2] .

174. KOJIC ACID

SOURCE *Aspergillus* spp¹, *Penicillium daleae*, *Acetobacter* spp [1,4,10] .

MOLECULAR FORMULA C₆H₆O₄ [1] ; 142 (cryo., calc.) [10] .

STRUCTURE



CRYSTAL FORM AND COLOR Colorless prisms [3,10] .

MELTING POINT (°C) 158 [3] ; 151-154 [10] .

OPTICAL ACTIVITY Inactive [3] .

SOLUBILITY s. water, alcohol, acetone; sl. s. ether, chloroform, pyridine, ethyl acetate; i. benzene.[3,10]

STABILITY Thermostable at pH 3-7.5 [3] .

OTHER REACTIONS Red color with FeCl₃; reduces Fehling; slowly inactivated by dilute alkali; reacts nearly quantitatively with KCN.[3,9]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*, *Escherichia coli* [2] . Colorimetric with FeCl₃. Isolation of Cu salt.[3]

BIOLOGICAL ACTIVITY In vitro. Low activity against a variety of Gram-positive and Gram-negative bacteria. Inhibits *Pseudomonas aeruginosa*, 1:3200-1:6400; *M. pyogenes* var. *aureus*, *E. coli*, *Proteus* spp, *Salmonella typhosa*, *S. enteritidis* and other bacteria at 1:800-1:4000.[2,3] Microorganisms responsible for spoilage of Japanese saké inhibited by 2-4 mg/ml [5] . *Leptospira canicola* inhibited by 1:1,000,000; *L. icterohemorrhagiae*, 1:100,000.[3]

In vivo. No activity against viruses of poliomyelitis and St. Louis encephalitis in mice [6] . No protection in chicks infected with *Plasmodium gallinaceum* [7] .

CLINICAL Topical use in wounds infected with *Pseudomonas aeruginosa* gave indifferent results [4] .

TOXICITY Doses of 250 mg/kg, administered s.c., i.p., or i.v., produced toxic symptoms in mice; 1500 mg/kg lethal. Oral doses of 1000 mg/kg were tolerated and 2000 mg/kg were toxic.[2,3] i.v. doses of 1000 mg/kg were lethal to rabbits, rats, and dogs; 150 mg/kg, i.v., toxic to dogs.[8]

In vitro. 1:400 dilution non-toxic to leukocytes; 1:100 was lethal.[2]

175. LACTAROVIOLIN

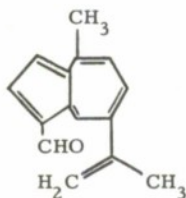
SOURCE *Lactarius deliciosus* [1] .

NATURE Violet-red pigment; an azulenealdehyde.[1-3]

MOLECULAR FORMULA C₁₅H₁₄O [1] .

/1/ Especially strains of the *A. tamaris-oryzae* group.

STRUCTURE



[2, 3]

MELTING POINT (°C) 53 [1].

ABSORPTION MAXIMA Cyclohexane: 541, 390, 311, 241 m μ . Alcohol: 527, 398, 315, 242 m μ . Formic acid: 455, 407, 331, 286 m μ . 50% H₂SO₄: 430, 391, 323, 270, 237, 228 m μ . [3]

SOLUBILITY s. organic solvents; i. water [1].

OTHER REACTIONS Reacts with carbonyl reagents [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibited a strain of *Mycobacterium tuberculosis* var. *hominis* in dilution of 1:16,000. The azulylacrylic acid derivative showed similar activity. [1]

176. LATERITIIN GROUP

SOURCE *Fusarium* spp [1].

NATURE Neutral compounds [3].

MOLECULAR FORMULA AND WEIGHT Lateritiin I: C₂₆H₄₆O₇N₂; 523 (cryo.); 498 (calc.).Lacteritiin II: C₂₆H₄₆O₇N₂.Avenacein: C₂₅H₄₄O₇N₂; 489-494 (cryo.); 484 (calc.).Fructigenin: C₂₆H₄₄₋₄₆O₇N₂.Sambucinin: C₂₄H₄₂O₇N₂. [3]

CRYSTAL FORM AND COLOR Colorless plates or tetrahedra [3].

MELTING POINT (°C) Lateritiin I: 121-122.

Lateritiin II: 125.

Avenacein: 139.

Fructigenin: 129.

Sambucinin: 86-87. [3]

OPTICAL ACTIVITY Lateritiin I: $[\alpha]_D^{20} = -95.6^\circ \pm 2.0^1$.Lateritiin II: $[\alpha]_D^{19} = -92.0^\circ \pm 1.6^2$.Avenacein: $[\alpha]_D^{19} = -101^\circ \pm 2.0^1$.Fructigenin: $[\alpha]_D^{18} = -103^\circ \pm 2.0^1$.Sambucinin: $[\alpha]_D^{21} = -83.2^\circ \pm 2.0^1$. [3]UV ABSORPTION Absorption only below 219 m μ [3].

SOLUBILITY s. organic solvents; sl. s. water. [3]

STABILITY Thermo- and acid stable; alkali unstable. [3]

OTHER REACTIONS HCl or HBr degradation yields nitrogen base and α -hydroxyisovaleric acid; lateritiin I and enniatin A probably identical. [2, 3]

BIOLOGICAL ACTIVITY *In vitro* (inhibition dilution x 1000). Lateritiin I: *Mycobacterium phlei*, 200-320; *Micrococcus pyogenes* var. *aureus*, 50; *Streptococcus pyogenes*, 40; *Bacillus subtilis*, 80. (See enniatin A.) [1]

Lateritiin II: *Myc. phlei*, 160-320; *M. pyogenes* var. *aureus*, 40; *Str. pyogenes*, 25; *B. subtilis*, 30.Avenacein: *Myc. phlei*, 160; *M. pyogenes* var. *aureus*, *Str. pyogenes*, 10; *B. subtilis*, 5.Fructigenin: *Myc. phlei*, 200-300; *M. pyogenes* var. *aureus*, 20; *Str. pyogenes*, 50; *B. subtilis*, 10.Sambucinin: *Myc. phlei*, 40-200; *M. pyogenes* var. *aureus*, 40; *Str. pyogenes*, 20; *B. subtilis*, 10.

/1/ c, 1 ethanol. /2/ c, 1.2 ethanol.

176. LATERITIIN GROUP (Concluded)

TOXICITY Low i.p. toxicity in mice [1].

177. LATEROSPORINS

SOURCE *Bacillus laterosporus* [1].

NATURE Peptides [1].

SOLUBILITY s. acid water; i. ether, chloroform, amyl acetate.

Laterosporin A: s. absolute ethanol.

B: i. absolute ethanol.[1]

STABILITY Thermostable at pH 2-8 [1].

OTHER REACTIONS Dialyze through cellophane [1].

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. aureus [1].

BIOLOGICAL ACTIVITY In vitro. Laterosporin A, B: Inhibit ($\mu\text{g/ml}$) *M. pyogenes* var. aureus, 0.01; *Streptococcus pyogenes*, 0.03-0.12; *Corynebacterium xerose*, 0.003-0.005; *C. diphtheriae*, 0.12; *Escherichia coli*, 0.6; *Mycobacterium phlei*, 0.004-0.008; *Myco. smegmatis*, 10; *Myco. tuberculosis*, 1; *Pseudomonas aeruginosa*, 5-10; *Salmonella enteritidis*, 1.2-2.5; *S. typhosa*, 0.6; *Clostridium botulinum*, 0.02.[1,2] In vitro activity lowered by serum [1].

178. LAVENDULIN

SOURCE *Streptomyces* sp resembling *S. lavendulae* [1].

NATURE Basic [2].

MOLECULAR FORMULA Helianthate: probably $\text{C}_{49}\text{H}_{63}\text{O}_{18}\text{N}_{13}\text{S}_3$; less probable, $\text{C}_{33}\text{H}_{42}\text{O}_{12}\text{N}_8\text{S}_2$ or $\text{C}_{16}\text{H}_{20}\text{O}_6\text{N}_4\text{S}$. [2]

CRYSTAL FORM AND COLOR Helianthate: orange needles or irregular triangular blades [2].

MELTING POINT ($^{\circ}\text{C}$) Helianthate: 212-220 (d., corr.) [2].

SOLUBILITY s. methanol, water; i. ether, ethanol. [2]

STABILITY Thermostable at neutral pH [2].

OTHER REACTIONS Free base: positive biuret, Fehling, KMnO_4 ; negative Sakaguchi, Molisch; dialyzes through cellophane; NaCl reduces activity.[2]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli* [1, 2].

BIOLOGICAL ACTIVITY In vitro. Inhibits, in concentration of 6 $\mu\text{g/ml}$ or less, *Aerobacter aerogenes*, *Bacillus anthracis*, *B. subtilis*, *B. mesentericus*, *Corynebacterium diphtheriae*, *C. xerose*, *Brucella melitensis*, *E. coli*, *Mycobacterium tuberculosis*, *Myco. smegmatis*, *Micrococcus pyogenes* var. aureus, *Neisseria catarrhalis*, *Salmonella* spp, *S. typhosa*, *Shigella dysenteriae*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Vibrio comma*. The following bacteria were not sensitive to 100 $\mu\text{g/ml}$: *Diplococcus pneumoniae*, *Streptococcus pyogenes*, *Str. viridans*, *Pseudomonas aeruginosa*. [1]

In vivo. I.p. doses of 25 μg (0.125 mg/kg) gave good protection against *K. pneumoniae* infection in mice [3].

TOXICITY LD_{100} in mice, 25 mg/kg, i.p. Sublethal doses induced liver damage. [3]

179. LENZITIN

SOURCE *Lenzites sepiaria* (Wulf) [1].

CRYSTAL FORM AND COLOR Thin, colorless needles [1].

MELTING POINT ($^{\circ}\text{C}$) 166-168 [1].

SOLUBILITY s. chloroform, benzene, dioxane, amyl acetate, acetone; s.l.s. alcohol, ether, water.[1]

STABILITY Thermostable [1].

179. LENZITIN (Concluded)

OTHER REACTIONS Dissolves in alkali upon heating, with partial loss of activity; violet color with FeCl_3 ; KMnO_4 reduced in alcoholic and aqueous solution; no halogens, N or S.[1]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *Micrococcus pyogenes* var. *aureus*, *Shigella dysenteriae*, *Sh. paradysenteriae*, *Salmonella typhosa*, *S. paratyphi*, *S. schottmuelleri*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Corynebacterium diphtheriae*, *Streptococcus pyogenes*, *Str. viridans*, *Bacillus subtilis*, *B. mycoides*, *B. mesentericus*. No activity against *Pseudomonas aeruginosa*, *Ps. fluorescens*, *Serratia marcescens*. [1]

TOXICITY Irritating to conjunctiva and mucous membranes of nasopharynx [1].

180. LEUCOMYCIN

SOURCE *Streptomyces kitasatoensis*, n. sp [1].

NATURE Basic [1, 3].

MOLECULAR FORMULA $\text{C}_{33-38}\text{H}_{54-66}\text{NO}_{11-13}$ [3].

MELTING POINT ($^{\circ}\text{C}$) 124-125.5 [2].

OPTICAL ACTIVITY $[\alpha]_D^{25} = -60.42^{\circ 1}$ [1]; $[\alpha]_D^{20} = -67.1^{\circ 2}$ [2, 3].

UV ABSORPTION MAXIMA 230-232, 285 $\text{m}\mu^3$ [1-3].

SOLUBILITY Free Base: s. alcohols, acetone, ethyl acetate, butyl acetate, chloroform, ether, benzene [1, 3]; sl.s. water [1, 4]; i. petroleum ether, hexane [1, 3]. Tartrate: s. water [1, 4].

STABILITY Thermostable, acid labile [1, 3].

OTHER REACTIONS PK 7.5; resembles erythromycin and carbomycin; negative Fehling, Benedict, biuret, ninhydrin, Sakaguchi, glucosamine, xanthoproteic, FeCl_3 , maltol; weakly positive Tollens, Seliwanoff, Molisch. [1-3] Characteristic deep violet color slowly fading to reddish brown in concentrated mineral acid [4, 5].

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* 209-P [3]. Colorimetric [5].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *M. pyogenes* var. *aureus*, *Streptococcus* sp, *Clostridium* sp, *Hemophilus pertussis*, *Neisseria gonorrhoeae*, *Klebsiella pneumoniae*, and *Leptospira icterohemorrhagiae* at 0.04-12.5 $\mu\text{g/ml}$. *Salmonella* spp, *Proteus* spp, *Pseudomonas* spp, and fungi not sensitive. [1] *Cl. perfringens*, *Cl. novyi*, *Cl. septicum*, *Cl. histolyticum*, and *Cl. tetani* sensitive to 0.05-1.5 $\mu\text{g/ml}$ [6].

In vivo. Daily doses of 50 mg/kg gave high protection in mice against *Diplococcus pneumoniae*, *Borrelia recurrentis*, and *Rickettsia tsutsugamushi*, and against *R. prowazeki* in chick embryos [4]. Good protection against *Cl. perfringens* when guinea pigs were injected with 50 mg/kg immediately after infection but no protection when treatment was delayed 2 hours [6]. No protection in mice infected with rabies virus or with *Trypanosoma evansi* [4].

TOXICITY LD_{50} in mice, 650 mg/kg, i.v.; >800 mg/kg, s.c.; >2000 mg/kg (tartaric salt), oral. [1]

RESISTANCE *M. pyogenes* var. *aureus* developed resistance after 14 transfers in media containing antibiotic. The strain showed cross resistance to carbomycin, but not to erythromycin. [2]

MISCELLANEOUS After darkening one cotyledon of a cucumber seedling, there is increased growth of that side of the hypocotyl; addition of leucomycin or oxytetracycline to the soil markedly increased the resulting curvature of the seedling. [7]

181. LEVOMYCIN

SOURCE *Streptomyces* sp [1].

NATURE Peptide with an aromatic group [1].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{27}\text{H}_{38}\text{N}_6\text{O}_{10}$ (proposed); 550-660 (Rast); 606.6 (calc.). [1]

CRYSTAL FORM AND COLOR White or colorless prisms [1].

MELTING POINT ($^{\circ}\text{C}$) 213-215⁴; 218-220⁵; 222-224⁶. [1]

/1/ c, 2 ethanol. /2/ c, 1 ethanol. /3/ Ethanol. /4/ From hot isopropanol. /5/ From cold chloroform/methanol. /6/ From chromatography.

181. LEVOMYCIN (Concluded)

OPTICAL ACTIVITY $[\alpha]_D^{25} = -290^{\circ 1}$, $-323^{\circ 2}$. [1]

UV ABSORPTION MAXIMA 318, 243 $m\mu$ [1].

SOLUBILITY s. chloroform, pyridine; less s. carbon tetrachloride, ethyl acetate, hot alcohols; sl. s. ether, benzene, cold alcohols, acetone, dioxane; i. water, petroleum ether, 5% aqueous HCl and NaOH. [1]

OTHER REACTIONS Soluble in cold 6 N HCl, but decomposes slowly; negative ninhydrin, biuret, Millon, Hopkins-Cole, Pauly, Sakaguchi, maltol, Benedict, Tollens, 2,4-dinitrophenylhydrazine, Br water, bromine (CCl₄), KMnO₄, periodate, methanolic FeCl₃, Molisch, Zn-NH₄Cl, Zeisel alkoxy, hydroxamic acid; positive pine splint; converted to an acid (designated levomycic) when treated with cold dilute methanolic NaOH. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Listeria monocytogenes*, *Spirillum serpens*, and *Mycobacterium phlei*, <1.0; *Pasteurella multocida*, *Micrococcus pyogenes* var. *aureus*, 5; *Myco. ranae*, *Bacillus subtilis*, 10; *Myco. tuberculosis*, *Myco. avium*, *Corynebacterium diphtheriae*, *Klebsiella pneumoniae*, 20; *Escherichia coli*, *Salmonella gallinarum*, 40-80; *Streptococcus faecalis*, *Pseudomonas aeruginosa*, >80. [1]

TOXICITY LD₁₀₀ of crude preparations in mice, 44 mg/kg, i.v. [1]

182. LICHENIFORMINS

SOURCE *Bacillus licheniformis* [1].

NATURE Peptides [2].

MOLECULAR WEIGHT Licheniformin A: 4400 (found).
B: 3800 (found).
C: 4800 (found). [2]

FORM AND COLOR HCl: white, amorphous powder [1, 2].

MELTING POINT (°C) No melting point; char on strong heating. [1]

OPTICAL ACTIVITY Licheniformin A HCl: $[\alpha]_D^{20} = -37.4^{\circ}$; $[\alpha]_{5461}^{20} = -45.2^{\circ}$.
B HCl: $[\alpha]_D^{20} = -37.7^{\circ}$; $[\alpha]_{5461}^{20} = -48.2^{\circ}$.
C HCl: $[\alpha]_D^{20} = -36.8^{\circ}$; $[\alpha]_{5461}^{20} = -44.9^{\circ}$. [2]

UV ABSORPTION Below 250 $m\mu^3$ [1, 2].

SOLUBILITY HCl: s. water, methanol; sl. s. ethanol; i. dry n-butanol, acetone, non-polar organic solvents. [1]

STABILITY Thermostable; unstable to concentrated acid, alkali. [1]

OTHER REACTIONS Unstable to light after long exposure; slow dialysis; positive biuret, Sakaguchi; negative ninhydrin, Molisch, glucosamine; precipitate with sodium hypochlorite.

Licheniformin A, B: Contain aspartic acid, glycine, serine, proline, arginine, phenylalanine, valine, lysine. [1, 2]

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium phlei* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibit (in dilution x 100,000) *Corynebacterium renale*, 400; *C. diphtheriae*, 12.5-100; *Myco. phlei*, 25-50; *Myco. tuberculosis*, 1.6-6.4; *Micrococcus pyogenes* var. *aureus*, 12.5-50; *Streptococcus* spp, 0.8-12.5; *Pasteurella multocida*, 0.05-6.4; *Brucella abortus*, 3.2; *Bacillus anthracis*, 2.0; *Shigella paradysenteriae*, 0.4-1.6; *Diplococcus pneumoniae*, 0.2-1.6; *Escherichia coli*, 0.1-0.8; *Pseudomonas aeruginosa*, 0.4; *Vibrio comma*, *Salmonella schottmuelleri*, *Str. viridans*, 0.05-0.2; *Myco. ranae*, 7.5. [1, 3] Licheniformin A inhibited *Myco. phlei*, 50. B inhibited the same organism in 100. C, the same organism in 3.2. [2]

In vivo. Slight protection afforded in mice against infections with *Str. pyogenes*, *B. anthracis*, and *Myco. tuberculosis* var. *bovis*, after 25-450 mg/kg doses [1].

Licheniformin A: Showed some activity in experimental mouse tuberculosis following s.c. doses of 150-300 mg/kg/da [2].

PHARMACOLOGY LD₅₀ in mice, 250 mg/kg, i.v.; 375 mg/kg, i.p.; 1000 mg/kg, s.c. Crude preparations administered s.c. daily to mice in doses of 300 mg/kg induced renal damage. Readily absorbed following s.c. injection, with maximum blood levels in 1-2 hours. [1] Product A less toxic than B or C in mice; C is the most toxic. Slight kidney damage following 14 daily s.c. doses of A; renal changes severe with same doses of B and C. [2] Injection of licheniformin into experimental animals causes rapid release of histamine from tissues [4].

/1/ c, 2 acetone. /2/ c, 1 chloroform. /3/ UV data inconclusive because of the possible effect of impurities.

183. LITMOCIDIN

SOURCE *Proactinomyces cyaneus* var. *antibioticus*, n. sp [1].

NATURE Pigment [1, 2].

MELTING POINT (°C) 144-146 (d.) [2].

SOLUBILITY Acid form: s. alcohols, acetone, ether, amyl acetate; sl. s. water. Alkali form: s. water [2].

STABILITY Acid stable, alkali unstable [2].

OTHER REACTIONS Red in acid, violet in neutral, blue in alkaline solution; blue sediment with lead acetate; decolorized by Zn dust, restored by exposure to air; decolorized by bisulfite.[2]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *M. pyogenes* var. *aureus*, hemolytic streptococci, and *Vibrio comma* in dilutions of 1:400,000-1:4,000,000; *Shigella dysenteriae*, *Sh. paradysenteriae*, 1:10,000; *Salmonella typhosa*, *S. paratyphi*, *S. schottmuelleri*, *Escherichia coli*, 1:1000.[1]

In vivo. No activity against *M. pyogenes* var. *aureus* in mice [1].

TOXICITY LD₅₀ in mice, approximately 50 mg/kg, i.p. [1].

184. LUTEOMYCIN
(Antibiotic 289)

SOURCE *Streptomyces tanashiensis*, related to *S. antibioticus* [1]; *S. flaveolus* [6].

NATURE Basic [2].

MOLECULAR FORMULA C₂₆H₃₃NO₁₂ (proposed) [3].

CRYSTAL FORM AND COLOR HCl: orange-yellow, rhomboid [1].

MELTING POINT (°C) HCl: 199 (d.) [1].

UV ABSORPTION MAXIMA 215, 255-257, 430 mμ [2, 3].

SOLUBILITY HCl: s. water, chloroform, ethanol, methanol, butyl acetate, acetone; i. ether, petroleum ether, carbon disulfide, benzene, amyl alcohol. SO₄: s. water; sl. s. ethanol, acetone.[1, 2]

STABILITY Stable [1].

OTHER REACTIONS Color changes from orange-yellow to purple at pH 7-9; extracted into ethyl or butyl acetate at pH 7-8, back to aqueous layer at pH 2; precipitates as picrate, reineckate, helianthate and, at low temperature, crystalline citrate; positive FeCl₃, quinone-Na₂CO₃, H₂O₂; negative xanthoproteic, biuret, Molisch, Fehling, ninhydrin, Sakaguch [1, 2].

BIOLOGICAL ACTIVITY In vitro. Inhibits (μg/ml) *Micrococcus pyogenes* var. *aureus*, *Hemophilus pertussis*, *H. influenzae*, *Neisseria gonorrhoeae*, *N. meningitidis*, *Bacillus subtilis*, *Brucella abortus*, *Mycobacterium avium*, <1.0; *Br. melitensis*, *Br. suis*, *Diplococcus pneumoniae*, *Streptococcus pyogenes*, *B. anthracis*, *Vibrio comma*, 1-3. *Shigella dysenteriae*, *Salmonella* spp, *Escherichia coli*, *Pseudomonas aeruginosa*, *Myc. tuberculosis* are less sensitive [2, 4]. The *in vitro* action was bacteriostatic, but higher concentrations were bactericidal. Resistance did not develop readily.[4]

In vivo. Total s.c. doses of approximately 3 mg/kg protected mice against *D. pneumoniae*, *Br. melitensis*, and *H. pertussis*; ineffective against *B. anthracis* and *S. paratyphi*. Some activity against influenza virus in mice. [5] Suppressed development of Yoshida sarcoma cells in rats [2].

PHARMACOLOGY LD₀ in mice, 6.25 mg/kg, i.v. or s.c.; LD₁₀₀, 25 mg/kg.[2] Mice tolerated oral doses of 108 mg/kg. Rapidly excreted in urine following oral administration.[5]

185. MANNOSIDOSTREPTOMYCIN
(Streptomycin B)

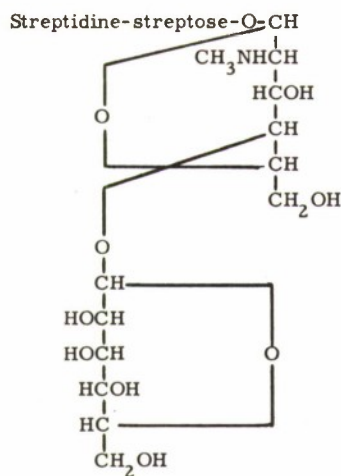
SOURCE *Streptomyces griseus* [1].

NATURE Triacidic base; D-mannoside of streptomycin.[3]

185. MANNOSIDOSTREPTOMYCIN (Concluded)

MOLECULAR FORMULA AND WEIGHT $C_{27}H_{49}O_{17}N_7$ [3, 9]. Tri-HCl: 780, 820 (equiv. wt.) [1, 9].

STRUCTURE



CRYSTAL FORM Reineckate: large thin plates¹ [1]. Tri-HCl: hexagonal isotropic plates [2].

MELTING POINT (°C) Anhydrous reineckate: 178-179 (d., corr.) [1, 9]. Tri-HCl: 190-200 (d.) [9].

OPTICAL ACTIVITY Tri-HCl: $[\alpha]_D^{25} = -47.0^2$ [1, 9]; $[\alpha]_D^{26.6} = -54.10^3$ [2].

QUANTITATIVE DETERMINATION Microbiological: *Klebsiella pneumoniae* [1]. Anthrone test⁴ [5-7]. Carbazole in H_2SO_4 ⁵ [4]. Spectrophotometric [8].

BIOLOGICAL ACTIVITY *In vitro*. Antimicrobial spectrum similar to streptomycin, but approximately 4-8 times less active than streptomycin, on a weight basis, in comparative tests with the same strains. Inhibits ($\mu\text{g/ml}$) *Micrococcus pyogenes* var. *aureus*, 7.8-9.5; *Mycobacterium tuberculosis*, 3.7; *Myco. smegmatis*, 6.8; *K. pneumoniae*, 5.7; *Salmonella typhosa*, 12.2; *S. schottmuelleri*, 13.5.[10]

In vivo. Spectrum in experimental infections similar to streptomycin, but approximately 3 times less active on weight basis. Mouse protection (ED_{50}) with 9 mg/kg against *S. schottmuelleri*, and doses of 155 mg/kg/da afforded 100% protection against *Myco. tuberculosis*. [10]

TOXICITY Similar to streptomycin; LD_{50} in mice, approximately 250 mg/kg, i.v.[10]

186. MARASMIC ACID

SOURCE *Marasmius conigenus* [1].

NATURE Monobasic acid [1].

MOLECULAR FORMULA AND WEIGHT $C_{16}H_{20}O_4$ (proposed); 276 (calc.).[1]

CRYSTAL FORM AND COLOR Long, white needles [1].

MELTING POINT (°C) 174-175 (corr.)⁶ [1].

OPTICAL ACTIVITY $[\alpha]_D^{25} = +176.0^7$ [1].

UV ABSORPTION MAXIMA 240-242, 314-318 $m\mu$ ⁸; 245, 246, 248, 260 $m\mu$ ⁹.

SOLUBILITY s. acetone, ethanol, ether, chloroform, water; i. hexane.[1]

OTHER REACTIONS pK 5.8 in 30% alcohol; reduces Fehling, ammoniacal $AgNO_3$ (when boiled); increased reducing properties at high pH; negative with hydroxylamine HCl, Br in carbon tetrachloride, alcoholic $FeCl_3$; red color with alkaline nitroprusside, changing to pale gray-green on acidification; orange-colored 2,4-dinitrophenylhydrazone, MP 136-138° (corr.).[1]

/1/ With 8.1% water of crystallization. /2/ c, 1.35 water. /3/ c, 1 water. /4/ May be preceded by ion exchange resin separation from streptomycin. /5/ Mannosidostreptomycin=purple-red color, streptomycin=yellow-brown. /6/ In sealed capillary in vacuo. /7/ c, 1.4 acetone. /8/ Ethanol. /9/ Phosphate buffer at pH 1.45-3.52, 5.4, 8.8, 11.0.

186. MARASMIC ACID (Concluded)

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*; antiluminescence with *Photobacterium fischeri*. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *P. fischeri*, 0.016; *Bacillus mycoides*, *B. subtilis*, 1.0; *M. pyogenes* var. *aureus*, 2; *Mycobacterium smegmatis*, 32; *Escherichia coli*, 64; *Klebsiella pneumoniae*, 128; *Pseudomonas aeruginosa*, 250. Fungi: *Trichophyton mentagrophytes*, 4; *Phycomyces blakesleeana*, 16; *Aspergillus niger*, *Saccharomyces cerevisiae*, *Penicillium notatum*, 32; *Chaetomium globosum*, *Memnoniella echinata*, *Myrothecium verrucaria*, 64; *Stemphylium consortiale*, 128; *Gliomastix convoluta*, 250. [1]

In vivo. No activity against *Plasmodium gallinaceum* infection in chicks treated with 20 mg/kg/da, i.p. [2].

TOXICITY LD_{50} in mice, 16 mg/kg, i.v.; LD_{100} , 32 mg/kg, i.v. [1]

187. MARCESIN

SOURCE *Serratia marcescens* [1].

NATURE Polypeptide [1].

UV ABSORPTION MAXIMA 240, 260 $\text{m}\mu$ [1].

SOLUBILITY s. aqueous solvents: ethanol, isopropanol, n-butanol, acetone, dioxane, pyridine, morpholine, diethylamine, acetic acid; i. anhydrous solvents. [1]

STABILITY Thermostable; less stable in alkaline solution. [1]

OTHER REACTIONS Dialyzes through cellophane from acid solution, less readily from ammonium citrate or broth. Precipitated by picric, trichloroacetic, toluenesulfonic and tannic acids, acid dyes, nucleic acid, insulin, heparin; unaffected by pepsin, trypsin; readily lowers surface tension. [1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*, *Escherichia coli* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Corynebacterium diphtheriae*, <0.01; *Pasteurella multocida*, 0.02; *Clostridium perfringens*, 0.03; *Micrococcus pyogenes* var. *aureus*, 0.08-0.2; *Mycobacterium tuberculosis*, 0.7; *Streptococcus pyogenes*, *Str. faecalis*, 0.8-2.0; *Shigella paradysenteriae*, 2.0; *E. coli*, 3.2. [1]

In vivo. No protection in mice infected with *M. pyogenes* var. *aureus*, *Str. pyogenes* or *Past. multocida*. Injection of 1-5 mg into rabbit skin appeared to suppress *M. pyogenes* var. *aureus* local infection. [1]

TOXICITY LD_{50} in mice, 2.5 mg/kg, i.p.; 125 mg/kg, s.c. Intradermal administration of 1-5 mg induced severe necrosis at site of injection. In vitro. Red blood cells hemolyzed. [1]

188. MEDIOCIDIN

SOURCE *Streptomyces mediodicus*, n. sp [1].

FORM AND COLOR Yellow powder [1].

UV ABSORPTION MAXIMA 339-340, 356-357, 377-378 $\text{m}\mu$ [1].

SOLUBILITY s. methanol, ethanol; sl. s. water, acetone; i. benzene, ether, petroleum ether [1].

BIOLOGICAL ACTIVITY Inhibits fungi ($\mu\text{g/ml}$): *Penicillium chrysogenum*, *Sporotrichum beurmanni*, *Cryptococcus neoformans*, 1.6; *Candida albicans*, *C. tropicalis*, 3.1; *Trichophyton* spp, 12.5-50; *Aspergillus niger*, 100. *Nocardia asteroides* inhibited at 100. Bacteria: *Bacillus subtilis*, *Micrococcus pyogenes* var. *aureus*, 25 $\mu\text{g/ml}$. [1]

In vivo. Daily i.p. doses of 10-40 μg in mice showed slight activity against Ehrlich carcinoma by inhibiting production of ascites and by slight prolongation in survival time of the animals [2].

TOXICITY LD_{50} in mice, approximately 2 mg/kg, i.p. [1].

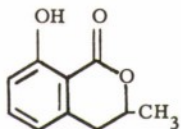
189. MELLEIN
(Ochracin)

SOURCE *Aspergillus melleus* and *A. ochraceus* [3]; by synthesis [5].

NATURE A lactone of 6-hydroxy-2- α -hydroxypropylbenzoic acid [3].

MOLECULAR FORMULA $\text{C}_{10}\text{H}_{10}\text{O}_3$ [1, 2].

STRUCTURE



[4, 5]

CRYSTAL FORM AND COLOR Colorless needles [1].

MELTING POINT (°C) 58 [1, 3]; 56-57 [4].

OPTICAL ACTIVITY $[\alpha]_D^{12} = -108.15^{01}$ [2].UV ABSORPTION MAXIMA 212, 246, 314 $m\mu^2$ [4].

SOLUBILITY s. chloroform, ether, acetone, alcohol; i. water, petroleum ether [1, 2].

OTHER REACTIONS Violet color with $FeCl_3$; yields an acetyl derivative (MP 126°C) and a nitro derivative (MP 160°C); converted to 6-hydroxy-2-methylbenzoic acid by KOH fusion. [1-3]BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus* [1].

190. MESENERIN

SOURCE *Nocardia mesenterica*³ [1].

NATURE Basic [1].

CRYSTAL FORM AND COLOR Colorless needles⁴ [1].

MELTING POINT (°C) 122-126 [1].

UV ABSORPTION Strong end absorption only [1].

SOLUBILITY s. methanol, ethanol, ethyl acetate, butyl acetate, ether, benzene, acid water; sl. s. water; i. petroleum ether. [1]

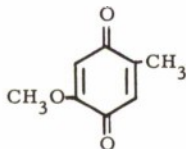
STABILITY At 100°C for 30 minutes, 35% remained at pH 2, 40% at pH 4, 90% at pH 6, 22% at pH 8 [1].

OTHER REACTIONS Analysis: C, 65.82; H, 7.10; N, 8.66, 8.44. Negative ninhydrin, Millon biuret, Tollens, Fehling, $FeCl_3$; positive Molisch. [1]BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu g/ml$) *Sarcina lutea*, *Micrococcus flavus* at concentrations below 0.2; *M. pyogenes* var. *aureus*, 0.8-3.1; *Bacillus subtilis*, 1.6-3.1; *Mycobacterium* sp., 6.3. *Escherichia coli*, *Salmonella paratyphi*, *Proteus vulgaris* not sensitive to 50. [1]TOXICITY LD_{50} in mice, >100 mg/kg, parenterally [1].

191. 5-METHOXY-p-TOLUQUINONE

SOURCE *Coprinus similis* and *Lentinus degener* [1].MOLECULAR FORMULA $C_8H_8O_3$ [1].

STRUCTURE



[1]

CRYSTAL FORM AND COLOR Golden-yellow plates or clusters of short prisms [1].

MELTING POINT (°C) 170-172 [1].

/1/ Chloroform. /2/ Ethanol. /3/ This culture also produces azomycin and antibiotic 446. /4/ From benzene.

191. 5-METHOXY-p-TOLUQUINONE (Concluded)

SOLUBILITY sl. s. water, saline [1].

OTHER REACTIONS Characteristic aromatic odor; bright orange-red in concentrated H₂SO₄; in alkaline solution darkens rapidly to a purplish-brown; reacts with carbonyl reagents; takes up Br in CCl₄; yields purple crystalline derivative with aniline; gives blue-violet color changing to blue-green, and finally reddish-brown with ethyl cyanoacetate and ammoniacal ethanol. (Other reactions and products are reported in reference [1] as typical of this compound.) [1]

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. aureus [1].

BIOLOGICAL ACTIVITY Active against bacteria and fungi. In vitro. Inhibits (μg/ml) M. pyogenes var. aureus, 0.5-1.0; Bacillus subtilis, 2-4; B. mycoides, Klebsiella pneumoniae, 16-64; Mycobacterium smegmatis, 64-128; Escherichia coli, 31-128; Pseudomonas aeruginosa, 128-256. Fungi: Trichophyton mentagrophytes, 4; Aspergillus niger, Chaetomium globosum, 16; Memnoniella echinata, Phycomyces blakesleeanus, 32; Gliomastix convoluta, Myrothecium verrucaria, Stemphylium consortiale, 64; Penicillium notatum, 128. 50% loss of in vitro activity in presence of blood.[1]

TOXICITY LD₅₀ in mice, approximately 25 mg/kg, i.v. [1]

192. 6-METHYL-1,4-NAPHTHAQUINONE

SOURCE Marasmius graminum [1].

MOLECULAR FORMULA C₁₁H₈O₂ [2].

CRYSTAL FORM AND COLOR Golden yellow needles¹ [2].

MELTING POINT (°C) 90-91 [2].

SOLUBILITY sl. s. water [1].

OTHER REACTIONS Yellow aqueous solution, turning violet if alkali is added; at first red needles (MP 87-88°C), recrystallized from petroleum ether, are obtained, then use of acid-washed alumina column gives yellow needles; degradation of red compound gives trimellitic acid.[1,2]

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. aureus [1,2].

BIOLOGICAL ACTIVITY In vitro. Inhibits M. pyogenes var. aureus [1].

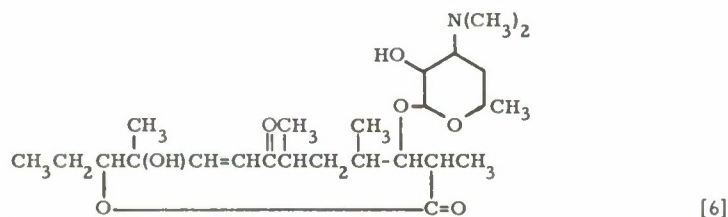
193. METHYMYCIN

SOURCE Streptomyces sp [1].

NATURE Basic [1].

MOLECULAR FORMULA AND WEIGHT C₂₅H₄₃O₇N (proposed); 469 (neut. equiv.); 469.6 (calc.).[1,4]

STRUCTURE



CRYSTAL FORM AND COLOR Colorless prisms²; needles³ [1].

MELTING POINT (°C) 195.5-197⁴ [1,4].

OPTICAL ACTIVITY [α]_D = +61⁰⁵, +74⁰⁶. [1]

UV ABSORPTION MAXIMA 223, 322 mμ⁵ [1].

/1/ Recrystallized from dilute acetic acid. /2/ Purified. /3/ Less pure. /4/ A second MP reported for a polymorphic variation: 203-205°C. /5/ Methanol. /6/ Chloroform.

193. METHYMYCIN (Concluded)

SOLUBILITY Free base: s. methanol, acetone, chloroform, aqueous acid; less s. ethanol, ether; i. water, hexane. Sulfate salts: s. methanol, water. Hydrogen sulfate base: s. acetone.[1]

OTHER REACTIONS Similar to picromycin and the proactinomycins; decolorizes permanganate in acetone solution; absorbs Br in carbon tetrachloride solution; negative Molisch, biuret, ninhydrin, FeCl_3 . [1] Similarity also to narbomycin, carbomycin, and erythromycin [4, 5].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Klebsiella pneumoniae*, 3.2; *Diplococcus pneumoniae*, 6-50; *Corynebacterium diphtheriae*, *Brucella abortus*, *Clostridium septicum*, *Streptococcus pyogenes*, 10-20; *Micrococcus pyogenes* var. aureus, 40. The following required 312-1875 $\mu\text{g/ml}$: *Str. faecalis*, *Shigella sonnei*, *Aerobacter aerogenes*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Salmonella* spp, *Proteus vulgaris*. Fungi not sensitive to 1000 $\mu\text{g/ml}$. [1]

In vivo. No activity in experimental toxoplasmosis in mice treated with 2 mg, s.c. [2].

CLINICAL Used in 4 cases of acute brucellosis (*Br. melitensis*) in man. 1.5-2.0 g/da in 3 divided doses had some suppressive effect on infection, but was not curative. These doses, continued up to 34 days, appeared to be well tolerated. [3]

194. MICROCINS

SOURCE *Micromonospora* sp [1].

NATURE Microcin A: neutral.
B: acidic. [1]

CRYSTAL FORM AND COLOR Microcin A: reddish-purple powder.
B: yellowish-red powder. [1]

SOLUBILITY Microcin A: s. ethyl acetate; i. water.
B: s. ethyl acetate; sl. s. water. [1]

OTHER REACTIONS Negative Molisch, FeCl_3 [1].

BIOLOGICAL ACTIVITY In vitro. Inhibit *Micrococcus pyogenes* var. aureus in dilution of 1:2000; *Bacillus subtilis*, 1:1000; *Escherichia coli*, *Proteus vulgaris*, 1:100; *Mycobacterium avium*, 1:50. Low activity against fungi: *Aspergillus oryzae*, *Penicillium* sp, *Saccharomyces* sp [1].

TOXICITY LD_{50} in mice, 6.25 mg/kg, i.v. [1].

195. MICROCOCCIN

SOURCE *Micrococcus* sp, resembling *M. varians* [1].

MOLECULAR FORMULA AND WEIGHT Possibly $\text{C}_{25}\text{H}_{28}\text{O}_6\text{N}_6\text{S}_3$; 2170-2720 (Barger). [2]

CRYSTAL FORM AND COLOR Fine, long, silky, white needles in fans, sheaves or balls; birefringent. [2]

MELTING POINT ($^{\circ}\text{C}$) 222-228 (sinters) [2].

OPTICAL ACTIVITY $[\alpha]_D^{21} = +116^{\circ} \pm 1^{\circ}$ [2].

UV ABSORPTION MAXIMUM 345 $\text{m}\mu^2$ [2].

SOLUBILITY s. alcohol, acetone, chloroform, propylene glycol, glacial acetic acid, pyridine; sl. s. water; i. ether, benzene, amyl acetate, glycerine, vegetable oils. [1, 2]

STABILITY Thermostable; alkali labile. [1, 2]

OTHER REACTIONS Dialyzes through cellophane; positive ninhydrin only after acid hydrolysis; unaffected by trypsin, pepsin, cysteine, fluorescence and UV absorption reduced by traces of Cu, partly restored by BAL. [1-3]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis*. Fluorescence. UV absorption. [3]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. aureus, *Streptococcus* spp, *B. subtilis*, *B. anthracis*, *Corynebacterium diphtheriae*, *Clostridium* spp, *Mycobacterium tuberculosis*, *Vibrio comma*, 6 $\mu\text{g/ml}$ or less. Gram-negative bacteria not sensitive to 1000 $\mu\text{g/ml}$, e.g., *Pseudomonas aeruginosa*, *Escherichia coli*,

/1/ Ethanol. /2/ With blue or purple fluorescence.

195. MICROCOCCIN (Concluded)

Salmonella typhosa. In vitro action primarily bacteriostatic rather than bactericidal.[1] Slightly retarded growth of intracellular Myco. tuberculosis within rabbit macrophages. Under same test conditions, streptomycin and other antitubercular agents were highly active.[4]

In vivo. Slight protection afforded against *Str. pyogenes* infection in mice [5]. In experimental tuberculosis of guinea pigs and rabbits, i.v. administration delayed but did not prevent lesions in the spleen and liver. The antibiotic did not penetrate tubercles in a significant amount.[6]

PHARMACOLOGY This almost insoluble antibiotic, after i.v. administration, enters and remains in phagocytic cells for many months without apparent cytotoxicity [7]. Immediately following i.v. injection, micrococcin (solubilized in synthetic detergent "Triton") was detected in high concentrations in the lungs and in 2-3 days within the cells of the reticuloendothelial system, especially the spleen and liver. Repeated larger i.v. doses damaged renal glomeruli.[5]

RESISTANCE Myco. tuberculosis, micrococci, streptococci, and *Actinomyces* rapidly developed resistance in vitro [1].

196. MICROMONOSPORIN

SOURCE *Micromonospora* sp [1].

NATURE Pigmented protein [1].

STABILITY Thermolabile; unstable below pH 3 and above pH 9 [1].

OTHER REACTIONS Protein associated with a carbohydrate in culture filtrates; non-dialyzable; positive Molisch; negative phloroglucinol, orcinol, naphthoresorcinol, unaffected by pepsin, trypsin; precipitated by saturated ammonium sulfate.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. aureus, *Bacillus subtilis*, *B. mycoides*, *Sarcina lutea*. Gram-negative bacteria not sensitive.[1]

197. MOLDIN

SOURCE *Streptomyces phaeochromogenus* [1].

UV ABSORPTION MAXIMUM 370 m μ [1].

SOLUBILITY s. ethanol, ethyl acetate; sl. s. petroleum ether, ether, benzol; i. water.[2]

OTHER REACTIONS Can be adsorbed on alumina from ethyl acetate but not eluted; positive Molisch, FeCl₃; negative biuret, ninhydrin, Tollens, Fehling, Sakaguchi.[1,2]

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi (μ g/ml): *Trichophyton* spp, *Histoplasma capsulatum*, *Cryptococcus neoformans*, 0.4-1.5; *Candida* spp, 0.4-50.0. No activity against bacteria.[1,2]

TOXICITY LD₁₀₀ in mice, approximately 10 mg/kg, i.p. [2].

198. MUSARIN

SOURCE *Streptomyces* sp [1].

NATURE An acid [1].

MOLECULAR FORMULA AND WEIGHT (C₃₅H₆₀O₁₄N₂)_n (proposed); approximately 5000.[1]

FORM AND COLOR Light yellow powder [1].

MELTING POINT (°C) 170 (d.) [1].

OPTICAL ACTIVITY $[\alpha]_D^{20} = +35.1^\circ \pm 1.6^1; +38.7^\circ \pm 2.7^2$. [1]

UV ABSORPTION MAXIMA 240, 267 m μ ³ [1].

SOLUBILITY Free acid: s. aqueous acetone and alcohol; i. water, dry acetone. Na or K salt: s. water, methanol, ethanol, butanol; i. ether, acetone.[1]

STABILITY Thermolabile; free acid unstable at room temperature; Na salt more stable.[1]

/1/ c, 1.21 methanol. /2/ c, 0.736 methanol. /3/ Ethanol.

198. MUSARIN (Concluded)

OTHER REACTIONS Precipitated by mineral acids, barium chloride, mercuric chloride, copper acetate; negative Molisch, Millon, biuret, H₂SO₄ in acetic acid or with I, Salkowski, Liebermann, murexide; weak or negative ninhydrin; positive Axenfeld; inactivated product with diazomethane or methanolic HCl.[1]

QUANTITATIVE DETERMINATION Microbiological: *Fusarium oxysporium* var. *cubense* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Streptococcus pyogenes* in dilution of 1:25,000; *Micrococcus pyogenes* var. *aureus*, *Bacillus subtilis*, *Mycobacterium phlei*, 1:100,000-1:500,000. Phytopathogenic fungi: *Botrytis cinerea*; *Verticillium* spp, *Ceratostomella paradoxa*, *Corticium solani*, *Sclerotinia fructigena*, *Melanospora destruens*, *Alternaria* sp, 1:400,000-1:800,000; *Fusarium* spp, *Rhizopus stolonifer*, *Aspergillus niger*, *Penicillium notatum*, 1:50,000-1:100,000.[1]

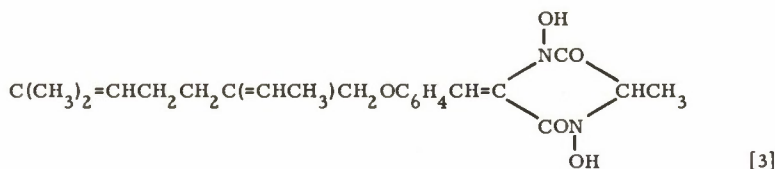
199. MYCELIANAMIDE

SOURCE *Penicillium griseofulvum* [1].

NATURE An amide of *o*-mycelyl-*N*-pyruvyl- β -ketotyrosine [1].

MOLECULAR FORMULA AND WEIGHT C₂₂H₂₈O₅N₂; 400.5 (cryo.); 400 (calc.).[1]

STRUCTURE



CRYSTAL FORM AND COLOR Shiny colorless leaflets [1].

MELTING POINT (°C) 170-172 (d.) [1]; 171 [3].

OPTICAL ACTIVITY $[\alpha]_{5461}^{19} = -217^{01}$; $[\alpha]_{5790}^{19} = -182^{01}$. [1]

SOLUBILITY s. acetone, dioxane, sodium carbonate solution; sl. s. ethanol, chloroform, ether, benzene, glacial acetic acid; i. dilute sodium bicarbonate, barium hydroxide, HCl.[1]

STABILITY Thermostable; acid and alkali unstable.[1]

OTHER REACTIONS In cold dilute NaOH, antibiotic foams and darkens, producing a lavender-like odor; ferric salt reddish-brown, copper salt green, nickel salt yellow-silver turning to black, all being insoluble; negative Millon, murexide, biuret, *p*-dimethylaminobenzaldehyde; no picrate or methiodide; red-brown with dilute FeCl₃ in ethanol or glacial acetic acid.[1] Acid hydrolysis yields alanine [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus*, *M. pyogenes* var. *albus*, *Bacillus anthracis*, *Streptococcus pyogenes* in dilution of 1:20,000-1:50,000. Inactive against Gram-negative bacteria.[1]

200. MYCELIN

SOURCE *Streptomyces roseoflavus* [1].

CRYSTAL FORM Prisms² [2].

MELTING POINT (°C) 260 (blackens); 263 (d., uncorr.).[1]

SOLUBILITY s. chloroform, butanol, methanol, ethanol, amyl alcohol, acetone, benzene; i. water, ether, petroleum ether.[1]

STABILITY Thermostable; stable in acetone at pH 2, 7, and 8.8 for 24 hours.[1]

OTHER REACTIONS Negative Molisch [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi ($\mu\text{g/ml}$): *Penicillium* spp, 0.5-1.0; *Mycoderma* sp, *Aspergillus niger*, 1.25; *Torula rubra*, *Trichophyton interdigitale*, 2.5; *A. oryzae*, *Oidium lactis*, 5; *Mucor mucedo*, *Saccharomyces sake*, *Candida albicans*, 10; *T. purpureum*, 12.5; *Cryptococcus* spp, 5-10. No activity against bacteria.[1, 2]

/1/ c, 0.8688 chloroform. /2/ From acetone.

200. MYCELIN (Concluded)

In vivo. Topical application of 0.005% hydrophilic ointment effective in experimental skin mycoses (T. purpureum) in guinea pigs [2].

201. MYCOCIDIN

SOURCE *Aspergillus* sp [1].

NATURE Acidic [1].

SOLUBILITY Salts: s. water, alkali; i. acid. Acid precipitate: s. ether, chloroform, ethyl acetate; i. water [1].

STABILITY Thermostable [1].

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium tuberculosis* var. *hominis* [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Myco. tuberculosis* var. *hominis*. Exposure of these cultures to mycocidin rendered them non-infective to guinea pigs.[2]

202. MYCOLUTEIN

SOURCE *Streptomyces* sp [1].

MOLECULAR FORMULA AND WEIGHT $C_{22}H_{24}NO_6$ (proposed); 417, 495.[1]

CRYSTAL FORM AND COLOR Bright yellow tablets¹ [1].

MELTING POINT (°C) 157-158 [1].

OPTICAL ACTIVITY $[\alpha]_D^{25} = +54^{\circ 2}$ [1].

UV ABSORPTION MAXIMA 254, 345 m μ [1].

SOLUBILITY s. chloroform, acetone, lower alcohols, benzene, 1,4-dioxane, pyridine, glacial acetic acid; less s. ethyl acetate, carbon tetrachloride, ether, petroleum ether; i. water, dilute HCl, Na_2CO_3 . [1]

STABILITY Decomposed by aqueous NaOH; stable in boiling methanol for at least 10 minutes at pH 5.1-8.2, but decomposed rapidly at higher or lower pH values even in cold.[1]

OTHER REACTIONS Found in mycelium; dissolves in concentrated H_2SO_4 , with an olive color that turns rapidly to dark red; decolorizes $KMnO_4$ in acetone in cold, and a solution of Br in methanol with the evolution of HBr; positive test for aromatic nucleus with anhydrous aluminum chloride and chloroform; negative $FeCl_3$, acetylation with acetic anhydride in pyridine; on standing at room temperature, in equal volumes of concentrated HCl and either methanol or dioxane, the UV peaks disappear and one at 265 m μ appears, one of the degradation products being an acid.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits the following fungi ($\mu g/ml$): *Candida stellatoidea* at 0.2; *C. albicans*, *C. tropicalis*, *Trichophyton mentagrophytes*, 0.4; *C. guillermondii*, *T. rubrum*, *Microsporum gypseum*, 0.7; *Cryptococcus neoformans*, 1.4. Bacteria not sensitive. In vitro antifungal activity diminished in media containing glucose or other sugars.[1]

TOXICITY Mice tolerated 5 mg/kg, i.p.; 25 mg/kg were lethal [1].

203. MYCOMYCIN

SOURCE *Nocardia acidophilus* [4].

NATURE Highly unsaturated carboxylic acid [3].

MOLECULAR FORMULA AND WEIGHT $C_{13}H_{10}O_2$ [1, 2]; 200 (neut. equiv. found); 198 (calc.).[1]

STRUCTURE $HC\equiv C-C\equiv CCH=C-CHCH=CHCH=CHCH_2CO_2H$ [1, 3].

CRYSTAL FORM AND COLOR Colorless needles [1, 2].

MELTING POINT (°C) 75 (d. explosively) [1-3].

OPTICAL ACTIVITY $[\alpha]_D^{25} = -130^{\circ 3}$ [1-3].

/1/ Recrystallized from methanol and benzene. /2/ c, 1 chloroform. /3/ c, 0.4 ethanol.

205. MYCOSUBTILIN (Concluded)

FORM AND COLOR White crystals [1].

MELTING POINT (°C) 256-257 (corr.) [1].

UV ABSORPTION MAXIMUM 277 $m\mu$ ¹ [1].

SOLUBILITY s. pyridine, 70% ethanol, dilute NaOH; i. dilute HCl and NaHCO₃, other solvents.[1]

STABILITY Thermostable [1].

OTHER REACTIONS Analysis: C, 55.31, 55.12; H, 7.61, 7.33; N, 15.15, 15.18. Acid hydrolysis yields several amino acids; negative 2,4-dinitrophenylhydrazine, Fehling, FeCl₃; positive Millon, nitric acid, ninhydrin (acid hydrolysaates).[1]

QUANTITATIVE DETERMINATION Microbiological: Trichophyton sp [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits yeasts and fungi ($\mu\text{g/ml}$): *Torulopsis delbruckii*, *Hansenula anomala*, *Dipodascus uninucleatus*, 3.75; *Torula cremoris*, *Rhodotorula rubra*, *Saccharomyces carlsbergensis*, 7.5; *Debaryomyces gruetzii*, *Candida guilliermondi*, >20; *Trichophyton* sp, *Sclerotinia fructicola*, *Ustilago zaeae* inhibited at 1.5-2.5; *Epidermophyton inguinale*, *Cryptococcus neoformans*, *Achorion schoenleinii*, *Microsporium audouini*, *Nematospora coryli*, 5.0-7.5; *T. mentagrophytes*, *M. lanosum*, 10; *Trichoderma* sp, >20.[1] Also inhibits *Torula utilis*, *Aspergillus niger*, 6.2; *Absidia orchidis*, *Mucor pusilis*, 12.5; *Candida albicans*, *C. krusei*, *Botrytis* sp, *Trichophyton interdigitale*, 100.[2] Relatively inactive against bacteria, but *Micrococcus lysodeikticus* sensitive to 16 $\mu\text{g/ml}$. *In vitro* activity depressed by serum.[1]

TOXICITY LD₀ in mice, 12.5 mg/kg, s.c.; LD₁₀₀, 25-50 mg/kg, s.c.[1]

206. MYCOTICIN

SOURCE *Streptomyces ruber* [1].

MOLECULAR FORMULA C₁₈H₃₀O₅ (proposed) [1].

FORM AND COLOR Yellow crystals [1].

UV ABSORPTION MAXIMA 363, 263, 210 $m\mu$ [1].

SOLUBILITY s. lower alcohols, propylene glycol, diethylene glycol, H₂SO₄, phosphoric acid; partly s. water, benzene, acetone; i. ether, petroleum ether, xylene, chloroform.[1]

STABILITY Thermo- and acid stable; unstable to UV and as crystalline material in dark.[1]

OTHER REACTIONS Infrared: In mineral oil, strong OH band at 3.1 μ , medium bands at 5.94, 6.2, 6.34 μ ; in pyridine, broad bands at 3.2-3.6, 5.9-6.4 μ ; fluoresces in UV; dialyzable; negative Br, KMnO₄; positive Brady; reduces ammoniacal AgNO₃, Fehling; most antifungal activity at alkaline pH.[1]

QUANTITATIVE DETERMINATION: Microbiological: *Sporotrichum schenckii* [1].

BIOLOGICAL ACTIVITY Active against fungi. In vitro. Inhibits ($\mu\text{g/ml}$) *Histoplasma capsulatum*, *S. schenckii*, *Coccidioides immitis*, *Microsporium audouini*, 1-3; *Blastomyces dermatitidis*, 2-4; *Trichophyton rubrum*, 3-5; *M. canis*, 4-7; *T. mentagrophytes*, 5-9; *M. gypseum*, 8-10; *Cryptococcus neoformans*, 6-8; *Hormondendrum pedrosoi*, 7-10; *Candida albicans*, 6-10. Bacteria and protozoa not sensitive to 100 $\mu\text{g/ml}$, e.g., *Escherichia coli*, *Bacillus subtilis*, *Streptococcus pyogenes*, *Salmonella typhosa*, *Entamoeba histolytica*, *Leishmania donovani*. [1]

TOXICITY LD₅₀ in mice, 10-20 mg/kg, i.p.; >100 mg/kg, s.c. Necrosis at site of s.c. injection of 100 mg/kg. Hemolyzes red blood cells in vitro, but no evidence of this in vivo.[1]

207. NARBOMYCIN

SOURCE *Streptomyces narbonensis*, n. sp [1].

MOLECULAR FORMULA AND WEIGHT C₂₈H₄₇O₇N; 502, 514 (found); 509.66 (calc.).[1]

CRYSTAL FORM AND COLOR Colorless crystals [1].

MELTING POINT (°C) 113.5-115 [1].

/1/ Alcohol-water.

OPTICAL ACTIVITY $[\alpha]_D = +68.5^{\circ 1}$ [1].

UV ABSORPTION MAXIMA 225, 286 $m\mu$ [1].

OTHER REACTIONS Infrared: Bands at 1730, 1689, 1629 recip. cm in the 6μ region; on hydrogenation in presence of palladium takes up 1 mole of H forming crystalline dihydro derivative ($\text{C}_{28}\text{H}_{49}\text{O}_7\text{N}$, MP 96-99, $[\alpha]_D = +26^{\circ}$ in chloroform); hydrolysis with 1 N HCl yields a base as a hydrochloride which resembles the desosamine HCl obtained by hydrolysis of picromycin and erythromycin ($\text{C}_8\text{H}_{18}\text{O}_3\text{N Cl}$, MP 185-187 $^{\circ}$); cross resistance of a strain of *Micrococcus pyogenes* var. *aureus* to narbomycin and picromycin; culture fluids produce at least 3 antibiotics extractable with organic solvents.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Streptococcus pyogenes*, 0.1-1.0; *Corynebacterium diphtheriae*, 1; *Str. mitis*, *Bacillus megatherium*, 10; *Micrococcus pyogenes* var. *aureus*, 10-100; *Str. faecalis*, 100. Not sensitive (100 $\mu\text{g/ml}$): *Escherichia coli*, *Salmonella typhosa*, *S. schottmuelleri*, *Shigella sonnei*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Pasteurella pestis*, *Vibrio comma*, *Candida albicans*, *C. tropicalis*. [1]

In vivo. No activity in mice infected with *Str. pyogenes* [1].

ACUTE TOXICITY Mice tolerated s.c. doses of 500 mg/kg [1].

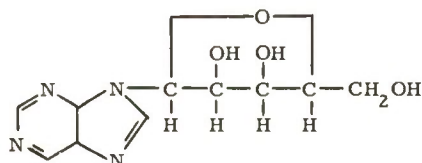
208. NEBULARINE
(9-(β -D-Ribofuranosyl)purine)

SOURCE *Clitocybe nebularis* (Batsch) [1], and by synthesis [2].

NATURE Furanoside; neutral.[1, 4]

MOLECULAR FORMULA $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_4$.

STRUCTURE



[4]

CRYSTAL FORM Long prisms, small rhombohedral crystals [2, 4].

MELTING POINT ($^{\circ}\text{C}$) 181-182 (corr.) [2-4].

OPTICAL ACTIVITY $[\alpha]_D^{25} = -48.6^{\circ 2}$, $-61^{\circ 3}$, $-22^{\circ 4}$; $[\alpha]_D^{20} = -47.5^{\circ 5}$, $-47.3^{\circ 2}$. [2, 4]

UV ABSORPTION MAXIMUM 263 $m\mu$ [2, 4].

SOLUBILITY s. water (8.9%), methanol (0.5%), at 25 $^{\circ}\text{C}$; sl. s. cold ether; i. ether, chloroform, acetone.[1, 4]

STABILITY Thermostable [1, 4].

OTHER REACTIONS Precipitates with Reinecke's salt; positive Molisch; splits into a purine and D-ribose on hydrolysis; fairly stable in dilute ammonia solutions, but less so in aqueous solutions of diethylamine, piperidine, mineral acids.[1, 4]

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium avium* [4].

BIOLOGICAL ACTIVITY Active against mycobacteria. In vitro. Inhibits *Myco. tuberculosis* var. *hominis*, *Myco. tuberculosis* var. *bovis*, *Myco. avium* and *Myco. phlei* in dilution of 1:500,000-1:3,000,000. No activity against *Bacillus subtilis*, *Sarcina lutea*, *Micrococcus pyogenes* var. *aureus*, *Escherichia coli*, *Aerobacter aerogenes*, *Proteus vulgaris*. [4]

In vivo. Daily i.p. doses of 5 mg/kg in mice had a moderate suppressive effect on an ascites tumor (sarcoma 180) [6].

TOXICITY LD_{50} s.c. in mice, 200 mg/kg ; in rats, 220 mg/kg ; in guinea pigs, 15 mg/kg . Mice tolerated single i.v. doses of 200 mg/kg , and guinea pigs 60 mg/kg , i.v.[5] Rabbits tolerated daily i.v. doses of 30 mg for 7 days [4]. In anesthetized dogs, antibiotic caused transient fall in blood pressure; caused reduction in tone of rabbit ileum and spasm of guinea pig uterus [5]. In vitro. Red blood cells hemolyzed by concentrations of 5 mg/ml . Growth of barley seedlings inhibited by dilution of 1:3000; toxic to onion root tips at 1:10,000-1:100,000.[4]

/1/ c, 1.35 chloroform. /2/ c, 1 water. /3/ c, 0.8 0.1 N NaOH. /4/ c, 0.8 0.1 N HCl. /5/ c, 2 water. /6/ Water.

209. NEMOTIN

SOURCE *Poria corticola* and *P. tenuis* [1].

NATURE Acetylenic; neutral.[1,2]

OPTICAL ACTIVITY $[\alpha]_D^{23} = +202^{\circ 1}$ [1].

UV ABSORPTION MAXIMA 207, 236, 248, 262, 276 $m\mu^2$ [2].

SOLUBILITY s. ether, chloroform, acetone, methyl isobutyl ketone; sl. s. water, hexane [1].

STABILITY Stable in acid aqueous solution [1].

OTHER REACTIONS Drying produces a brown inactive product; changes to active nemotin A above pH 6. UV of nemotin A in phosphate buffer at pH 7: 231, 242, 257.8, 272, 289, 307, 328 $m\mu$. [1,2]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Bacillus subtilis*, 0.1; *Mycobacterium smegmatis*, 1.0; *Myc. tuberculosis*, 7; *M. pyogenes* var. *aureus*, 2; *Escherichia coli*, *Klebsiella pneumoniae*, 32; *Pseudomonas aeruginosa*, 250. Fungi (0.03-4.0 $\mu\text{g/ml}$): *Penicillium notatum*, *Phycomyces blakesleeana*, *Memnoniella echinata*, *Myrothecium verrucaria*, *Aspergillus niger*, *Chaetomium globosum*, *Saccharomyces cerevisiae*, *Trichophyton mentagrophytes*. Nemotin A, in general, is less active on a weight basis.[1]

TOXICITY LD_{50} in mice, approximately 125 mg/kg, i.v. [1].

210. NEMOTINIC ACID

SOURCE Same as nemotin [1].

NATURE Acetylenic; monobasic acid [1,2].

MOLECULAR WEIGHT 205 (equiv. wt.) [1].

OPTICAL ACTIVITY $[\alpha]_D^{23} = +270^{\circ 3}$ [1].

UV ABSORPTION MAXIMA 208, 237, 249, 263, 277 $m\mu^2$ [2].

SOLUBILITY s. ether, chloroform, acetone, methyl isobutyl ketone; sl. s. water, hexane.[1]

STABILITY Stable at room temperature for 1 hour at pH 3.6-9.4 [1].

OTHER REACTIONS Inactive when dried in air at room temperature; major change at pH 12.6.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Same antibacterial spectrum as nemotin, but less active against fungi [1].

211. NEOCIDIN

SOURCE Certain strains of *Bacillus subtilis* [1].

FORM AND COLOR Light yellow powder [1].

SOLUBILITY s. methanol, water; sl. s. ethanol; i. acetone, n-butanol, ether, petroleum ether, amyl acetate.[1]

STABILITY Thermolabile; most stable at pH 5.0-6.4.[1]

OTHER REACTIONS 1% aqueous solution faintly opalescent; negative biuret, Ehrlich aldehyde; larger diffusion zones at pH 8 than at 7; light-sensitive.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus* in dilution of 1:64,000-1:256,000; *Vibrio comma*, 1:64,000; *Bacillus anthracis*, 1:128,000; *Mycobacterium avium*, 1:32,000; *Salmonella* spp, 1:4000-1:8000.[1]

TOXICITY LD_0 in mice, 660 mg/kg, i.v.; 1900 mg/kg, s.c. [1]

/1/ c, 1.2 ethanol. /2/ Water. /3/ c, 0.44 ethanol.

212. NEOMYCINS

(Flavomycin)

The trademark of The Upjohn Company for neomycin is Mycifradin.

SOURCE *Streptomyces fradiae* [1], and other *Streptomyces* spp [62].

NATURE Basic [1, 2, 5].

MOLECULAR FORMULA AND WEIGHT Neomycin A: $C_{12}H_{26}N_4O_6$ [11].B, C: $C_{23}H_{46}N_6O_{12}$ or $C_{23}H_{48}N_6O_{13}$ [64]; 507-669 (ebull. in methanol); 616.7 (calc.).[64]

FORM AND COLOR Neomycin A HCl: white, amorphous powder. Base: white.[4, 11]

MELTING POINT (°C) Neomycin A: 256 (d.) [10].

OPTICAL ACTIVITY Neomycin A base: $[\alpha]_D^{25} = +112.8^{01}$, or 123.5^0 [11]. HCl: $[\alpha]_D^{25} = +83^{01}$ [4, 9].B base: $[\alpha]_D^{25} = +71^{02}$, $+83^{03}$. [64] HCl: $[\alpha]_D^{25} = +63^{04}$ [64], $+54^{05}$ [9]. Sulfate: $[\alpha]_D^{25} = +56^{06}$ [64].C base: $[\alpha]_D^{25} = +110^{02}$, $+121^{06}$ [64]. HCl: $[\alpha]_D^{25} = +88^{04}$ [64], $+80^{05}$ [9]. Sulfate: $[\alpha]_D^{25} = +82^{06}$ [64].

UV ABSORPTION MAXIMUM End absorption only [4].

SOLUBILITY s. water; sl. s. methanol; i. other organic solvents.[1, 3]

STABILITY Thermo-, acid, and alkali stable [1, 3].

OTHER REACTIONS Neamine and neomycin A are identical; positive ninhydrin, Molisch, carbazole; negative glucosamine, Tollens, Elson-Morgan; crystalline salts with p-hydroxyazobenzene-p'-sulfonic acid, ammonium reineckate; amorphous hydrochloride and sulfate salts; cysteine slightly reduces activity; yields furfural on acid hydrolysis; all N present as primary amino groups.[1-5, 9, 12] B and C yield equimolar amounts of neamine and the respective methyl neobiosaminides on methanolysis [64]. Streptothricin BII identical with Neomycin B, and streptothricin BI with neomycin C [63].

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli*, *Bacillus subtilis* [5-9]. Colorimetric [4, 7].

BIOLOGICAL ACTIVITY Active primarily against Gram-negative and Gram-positive bacteria (including mycobacteria) and actinomycetes; little or no activity against yeasts, filamentous fungi, viruses or protozoa. Wide variation in sensitivity between strains of same species of bacteria. In vitro. In general, most strains of the following inhibited by 0.2-10.0 $\mu\text{g/ml}$: *Aerobacter aerogenes*, *B. anthracis*, *B. subtilis*, *B. cereus*, *B. mycoides*, *Brucella abortus*, *Br. melitensis*, *Br. suis*, *Corynebacterium diphtheriae*, *Corynebacterium* spp, *E. coli*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Micrococcus pyogenes* var. *aureus*, *M. lysodeikticus*, *Mycobacterium avium*, *Myco. leprae*, *Myco. phlei*, *Myco. ranae*, *Myco. tuberculosis*, *Pasteurella multocida*, *Pseudomonas aeruginosa*, *Salmonella schottmuelleri*, *Shigella dysenteriae*, *Sh. paradysenteriae*, *Sh. sonnei*, *Sarcina lutea*, *Serratia marcescens*. Generally inhibited by 10-50 $\mu\text{g/ml}$: *Diplococcus pneumoniae*, *Hemophilus pertussis*, *Proteus vulgaris*, *Salmonella typhosa*, *Streptococcus pyogenes*, *Str. viridans*, *Neisseria gonorrhoeae*, *N. meningitidis*. *H. influenzae*, *Malleomyces mallei*, *Clostridium perfringens*, *Clostridium* spp, *Salmonella paratyphi*, *Vibrio comma*, >50 $\mu\text{g/ml}$. Actinomycetes: *Streptomyces antibioticus*, *S. coelicolor*, *S. fradiae*, *S. lavendulae* inhibited by <3 $\mu\text{g/ml}$. Spirochetes and protozoa ($\mu\text{g/ml}$): *Borrelia recurrentis*, *Leptospira icterohemorrhagiae*, 2.5; *Entamoeba histolytica*, 42-165; *Leishmania donovani*, *Trypanosoma cruzi*, 3000; *Trichomonas vaginalis*, >300.[12-18] Concentration of 25 $\mu\text{g/ml}$ in vitro bacteriostatic to *Myco. tuberculosis* within rabbit macrophages [19]. Inhibits bovine strains of *Cryptococcus neoformans* at 25 $\mu\text{g/ml}$ [65]. *Trichomonas foetus* and *T. gallinae* are not sensitive [66]. Neomycin A (neamine), a degradation product and not a true member of neomycin complex, has only 1/100 to 1/2 antibacterial activity of neomycin [20]. Commercial preparations of neomycin contain >90% neomycin B.

In vivo. Good protection in experimental murine tuberculosis with s.c. doses of approximately 20-35 mg/kg/da [21], and in guinea pigs infected with streptomycin-resistant strains of *Myco. tuberculosis* [22]. On a weight basis, this antibiotic was approximately 1/5 as active as streptomycin in experimental tuberculosis [23]. In mice, single s.c. dosages as low as 5 μg (0.025 mg/kg) gave high protection against *M. pyogenes* var. *aureus*, and 0.5-1.0 mg/kg was effective in infections with *Salmonella typhosa* and *S. schottmuelleri* [1, 24]. Low doses also suppressed experimental mouse infections with *Pr. vulgaris*, *S. choleraesuis*, *S. typhimurium*, *Klebsiella pneumoniae*, and *H. influenzae* [12, 14, 25]. High activity in mice infected with *Vibrio comma*, *Past. multocida*, *B. anthracis* and in chicks with *S. gallinarum* [26, 35]. In mice with experimental bubonic and pneumonic plague (*Past. pestis*), neomycin was the most effective of 8 antibiotics tested [27]. Active against *S. pullorum* and *H. pertussis* in embryonated eggs [1, 28]. Little or no activity in experimental infections with *D. pneumoniae*, *Str. pyogenes*, *Listeria monocytogenes*, *Erysipelothrix rhusiopathiae* [14, 25, 26]. Inactive in *Borrelia anserina* infection (spirochetosis) in chicks [29], *Plasmodium gallinaceum* in canaries, and *Pl. berghei* in mice [30]. No effect in experimental infections with *Leishmania donovani*, *Trypanosoma brucei* and *T. cruzi* [31, 49]. Showed an adverse effect

/1/ c, 1 water. /2/ 0.02 N NaOH. /3/ 0.2 N H_2SO_4 and 0.2 N HCl. /4/ Water. /5/ c, 0.5 water. /6/ 0.2 N H_2SO_4 .

on pinworm infestation in mice; following daily oral dose of 50 mg/kg, mice harbored nearly twice as many worms (*Aspicularis tetraptera*) as untreated controls; a similar effect observed with dihydrostreptomycin and chloramphenicol.[32] However, another report indicates neomycin had suppressive effect on mouse oxyurid (*Syphacia obvelata*) after 500 mg/kg doses [58]. Some activity against experimental rickettsialpox and amebiasis [15].

CLINICAL Neomycin sulfate has established clinical usefulness as intestinal antiseptic when administered orally prior to bowel surgery. In general, doses of 1 g are administered every 4 hours for 1-3 days. In view of the damage to the kidneys and 8th cranial nerve following systemic use, parenteral administration and prolonged oral medication have not been recommended [8, 33, 34, 40]. Oral doses of approximately 50 mg/kg/da of value in bacillary dysentery, amebiasis, and in epidemic infantile diarrhea [12, 36, 37, 41]. Topical application (solutions containing 5 mg/ml of antibiotic in ointment base) has given favorable results in a variety of infections of the skin [38, 39] and in ocular infections [42], singly or in combination with other antibiotics. Combination with hydrocortisone in suspension was effective in external otitis [48]. Instillation of solution has given favorable clinical response in cervicitis and vaginitis caused by *Proteus* spp [43], and in non-gonococcal urethritis [44]. Patients with peritonitis were successfully treated with daily doses of 1-2 g for 1-3 days, administered by the intraperitoneal route without toxic effects [45]. In tuberculosis, beneficial results were observed, but the attendant nephrotoxicity and ototoxicity, following prolonged parenteral administration, limits its usefulness in the therapy of this disease [12] [36].

Urinary tract infections responded to intramuscular therapy with 0.5-1.0 g daily for periods up to 5 days [69]. Aerosol treatment with dosages of 42-53 mg of neomycin base/kg/da for one week was beneficial in certain cases of pulmonary complications associated with cystic fibrosis of the pancreas in children [70]. The antibiotic had no therapeutic value in amebic dysentery [71]. In experimental chancroid in human volunteers, induced by intradermal injection of cultures of *Hemophilus ducreyi*, topical application of 0.5% neomycin sulfate failed to prevent development of infected lesions, in contrast to chloramphenicol and erythromycin which were effective [72]. Daily oral doses of 12 g reduced the elevated blood ammonia levels and prevented coma in patients with hepatic cirrhosis; this effect was attributed to alterations in the intestinal bacterial flora.[73]

VETERINARY Preliminary trials indicated value in bovine mastitis caused by *Str. agalactiae*, *M. pyogenes*, *Pseudomonas* spp, and coliform organisms, following infusion of 0.5 g into each infected udder quarter [12]. A variety of gastrointestinal infections in domestic animals respond to oral therapy [68]. Highly effective in calf scours caused by *Salmonella dublin* when administered orally in doses of 0.5-1.0 g/da for 7 days [46]. Oral therapy with doses of 0.5 g was effective in calves with enteritis presumably caused by *Paracolobactrum* sp [74]. Chronic cellulitis and streptococcal septicemia in dogs successfully treated with daily intramuscular doses of 5 mg/lb body weight [75]. Topical application with solutions or ointment gave favorable results in a wide variety of skin and ocular infections of domestic animals [47, 68]. Topical therapy of value in foot-rot in cattle and sheep [67]. The antibiotic powder, topically applied, is a useful adjunct in a variety of veterinary surgical procedures [76].

ACUTE TOXICITY LD₅₀ in mice, 15-53 mg/kg, i.v.; 116-133 mg/kg, i.p.; 265-353 mg/kg, s.c.; >2880 mg/kg, oral. S.c. LD₅₀ of neomycin B, 220 mg/kg; neomycin C, 290 mg/kg. Rats tolerated higher doses.[1, 12] Preliminary results in experimental animals suggest that the pantothenate of neomycin is less toxic (with particular reference to ototoxicity) than the sulfate [77].

In vitro. Low toxicity in tissue cultures; 4.1-6.2 mg/ml required to inhibit outgrowths of skin tissue and 250-500 mg/ml for spleen tissue [50]. When tested by roller tube tissue culture method, concentrations as high as 20 mg/ml were non-toxic to human skin explants [78].

CHRONIC TOXICITY Mice tolerated 15-30 mg/kg/da, s.c., in divided doses for 30 days. In dogs, s.c. doses of 33-66 mg/kg/da induced renal tubular degeneration and damage to glomeruli. Daily oral doses of 100 mg/kg were well tolerated in dogs.[12]

In man, ototoxicity and nephrotoxicity, following parenteral administration [12, 33, 36, 51, 52], precludes general systemic use in infections. Total oral doses of 6-10 g, over periods of 1-3 days, were well tolerated [33, 53]. Continued topical use of dermatological preparations is associated with a relatively low index of sensitization, in contrast to penicillin, streptomycin, and the sulfonamides [79].

RESISTANCE A high degree of resistance could be developed in vitro only in short steps; this pattern resembles that of penicillin rather than streptomycin. No appreciable cross resistance between neomycin and streptomycin or other antibiotics.[2, 55, 56, 59] Some cross resistance, in varying but not marked degrees, between neomycin and streptomycin has been described. Bacteria, rendered resistant by repeated subculture, in the presence of neomycin display no increased resistance to chloramphenicol or the tetracyclines, but may become more resistant to streptomycin than the original strain. This cross resistance is more effectively induced by neomycin than by streptomycin.[80-82]

ABSORPTION AND EXCRETION Very limited absorption after oral administration. In dogs, peak blood levels of 1.0-2.2 µg/ml noted within 1 hour after oral administration of various dosages 3 times daily for 3 days, with a total urinary excretion of approximately 3-8%. In mice, 30 mg/kg oral doses produced no appreciable blood or urine concentrations. Following i.m. doses of 6.5 mg/kg every 6 hours for 8 days, substantial blood levels were continuously maintained throughout this period.[12]

In man, following oral administration, the small fraction absorbed is rapidly excreted in the urine, with the remainder eliminated unchanged in the feces [33]. A single i.m. injection of 1.2 mg/kg produced blood concentration of 4-5 µg/ml, maintained between 1-4 hours after administration, and urine levels of 72 µg/ml in 2 hours [54].

212. NEOMYCINS (Concluded)

MODE OF ACTION Primarily bactericidal in action; bactericidal concentrations approximate the bacteriostatic titers, e.g., lethal to broth culture of *E. coli* within 4 hours.[57,59] In vitro antimicrobial activity antagonized by nucleic acids [12], and by a heat-stable substance present in culture filtrates of *Ps. aeruginosa* [60].

MISCELLANEOUS As compared with certain other antibiotics, neomycin is of little value as a food supplement for the growth stimulation of domestic animals [61]. Topical application of cream or lotion, containing 3.5 mg neomycin per g of vehicle, to the axilla in man was effective in controlling the odor from apocrine sweat [83]. The antibiotic failed to increase the resistance of wheat seedlings to infection with *Xanthomonas translucens* [84]. The median lethal dose, by injection, in the German cockroach (*Blattella germanica*) was 27-60 µg [85]. Concentrations of 10 µg neomycin sulfate, in combination with 20 units of nystatin per ml, have been recommended for routine prevention of bacterial and fungal contaminations in tissue cultures [86].

213. NEONOCARDIN

SOURCE *Nocardia kuroishi*, n. sp [2].

FORM AND COLOR Crude HCl: grayish-white [1].

SOLUBILITY s. water, methanol, ethanol; sl. s. amyl alcohol, benzene; i. ether, petroleum ether, toluene, amyl acetate, xylene.[1]

STABILITY Thermostable¹ [1].

OTHER REACTIONS Slow diffusion through agar [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. aureus, *Escherichia coli*, *Bacillus anthracis*. Low activity against *B. subtilis*, *Pseudomonas aeruginosa*. [1]

TOXICITY LD₀ of crude preparations in mice, 100 mg/kg, i.p. [1].

214. NETROPSIN
(IA 887)

SOURCE *Streptomyces netropsis* [1]; *S. chromogenus*, n. sp, resembling *S. netropsis* [6].

NATURE Tetra-acidic base [1]; diacidic base [7].

MOLECULAR FORMULA AND WEIGHT C₃₂H₄₈O₄N₁₈ (proposed) [1]; C₁₈H₂₆N₁₀O₃ [7]. Sulfate: 945 (calc.) [2].

CRYSTAL FORM AND COLOR HCl: long, thin, colorless hydrated prisms [1]. Sulfate: long, colorless needles [2]. Picrate: sheaves of yellow needles [2,6].

MELTING POINT (°C) HCl: 167-172 (d.) [1,6]. Sulfate: 224-225 [2]. Picrate: 232 (d.) [7], 205 (d., uncorr.) [6].

OPTICAL ACTIVITY Inactive [1].

UV ABSORPTION MAXIMA 238, 295 mµ [2]; 236, 297 mµ [6,7].

SOLUBILITY s. water; i. organic solvents.[2]

STABILITY Thermostable at acid pH; alkali labile.[2,6]

OTHER REACTIONS Positive Sakaguchi, Ehrlich; negative ninhydrin, biuret, Tollens, Fehling, fuchsin-aldehyde, murexide, FeCl₃, aminoantipyrine, 2,4-dinitrophenylhydrazine; anhydrous HCl hygroscopic.[1,6] Converted by hydrolysis to 1 mole each of ammonia, guanidinoacetic acid and netropsinine (C₁₅H₂₀N₆O₃) [7].

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. aureus, *M. pyogenes* var. albus, *B. subtilis*, *Mycobacterium ranae*, *Salmonella typhosa*, *S. pullorum*, *S. schottmuelleri*, *Klebsiella pneumoniae*, *Aerobacter aerogenes*, *Shigella paradysenteriae*, 5-10 µg/ml. *Pseudomonas aeruginosa*, *Proteus* spp not sensitive. [1,3] Protozoa: *Trichomonas vaginalis* inhibited by 12.5 µg/ml [4]. Phagocidal to a number of bacteriophages [8].

In vivo. Slight protection (prolonged survival time) in mice infected with *S. typhosa* and *Ps. aeruginosa* [1]. Showed antiviral activity in mice infected intracerebrally with "WR" strain of vaccinia virus [5]. Daily i.p. doses of 30 mg/kg for 5 days protected mice against vaccinia virus introduced by intranasal or intracerebral routes [9].

/1/ No loss at 100°C for 10-30 minutes; 90% loss for 60 minutes.

214. NETROPSIN (Concluded)

No activity in mice against viruses of feline pneumonitis, influenza, poliomyelitis, or western equine encephalitis [5]. Seven daily i.p. doses of 25 mg/kg inhibited Mecca lymphosarcoma in mice [10]. Little or no suppressive effect on a variety of other experimental neoplasms [11]. Had insecticidal properties; active against clothes moth larvae and black carpet beetle.[1]

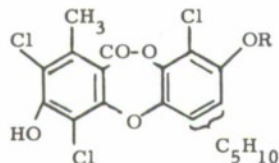
TOXICITY LD₅₀ in mice, 17 mg/kg, i.v.; 70 mg/kg, s.c.; >300 mg/kg, oral.[1] LD₅₀ in chick embryo, 0.03 mg per egg injected into yolk sac of 4-day old embryo [12].

215. NIDULIN and NOR-NIDULIN
Nor-nidulin formerly called ustin.

SOURCE *Aspergillus nidulans* [1].

MOLECULAR FORMULA AND WEIGHT Nidulin: C₂₀H₁₇O₅Cl₃; 463 (micro-Rast); 443.7 (calc.).[4, 5]
Nor-nidulin: C₁₉H₁₅O₅Cl₃; 214 (neut. equiv.).[3, 5]

STRUCTURE



Nidulin: R = CH₃

Nor-nidulin: R = H

[4]

CRYSTAL FORM AND COLOR Nidulin: colorless rhombs¹; slender shining rods². [4, 5]
Nor-nidulin: heavy square plates³; rosettes of fine needles⁴; hexagonal plates or prisms². [2, 5]

MELTING POINT (°C) Nidulin: 180 [4, 5].
Nor-nidulin: 185-187³; 214-216⁴. [2, 5]

OPTICAL ACTIVITY Inactive⁵ [4, 5].

UV ABSORPTION MAXIMUM Nidulin: 267 mμ⁶.
Nor-nidulin: 266 mμ⁶. [5]

SOLUBILITY s. aqueous NaOH⁷, NaHCO₃, chloroform; sl. s. 95% ethanol, benzene, petroleum ether; i. water. [4, 5]

STABILITY Thermostable; inactivated by heat in alkali.[1]

OTHER REACTIONS Monomethyl, dimethyl and acetyl derivatives; increased activity at lower pH; decreased activity by serum albumin, lipids, components of complex media.[3] Nidulin is monomethyl ester of nor-nidulin [4]. Nidulin isolated from mycelium, nor-nidulin from culture fluids. Nidulin: negative FeCl₃, Fehling, aqueous methanolic 2, 4-dinitrophenylhydrazine sulfate.[5]

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium tuberculosis* [1, 4].

BIOLOGICAL ACTIVITY In vitro. Nidulin: Inhibits *Myco. tuberculosis* at 1:5000-1:10,000; little or no activity against other bacteria. Fungi: *Trichophyton tonsurans*, *Microsporum audouini* sensitive to 1:1000.[4]
Nor-nidulin: Inhibits *Micrococcus pyogenes* var. *aureus*, *Streptococcus* sp at 1:500,000; *Myco. tuberculosis*, 1:200,000-1:500,000; *Myco. ranae*, 1:300,000.[1-3]

TOXICITY Mice tolerated 300-400 mg/kg i.p. doses of crude nor-nidulin [1].

216. NIGERICIN

SOURCE *Streptomyces* sp related to *S. violaceoniger* [1].

NATURE Monobasic acid [1].

MOLECULAR FORMULA AND WEIGHT C₃₉H₆₉O₁₁; 728 (found); 713.55 (calc.).[1]

CRYSTAL FORM AND COLOR Colorless needles⁸ [1].

MELTING POINT (°C) 246-254 (uncorr.)⁸ [1].

/1/ From ethanol. /2/ From petroleum ether. /3/ Fraction I. /4/ Fraction II. /5/ c, 4 chloroform.
/6/ Inflection at 323 mμ. /7/ Crude nidulin soluble in aqueous NaOH, crystalline nidulin insoluble. /8/ Sodium salt.

216. NIGERICIN (Concluded)

SOLUBILITY s. most organic solvents; sl. s. water.[1]

STABILITY Thermostable at neutral pH [1] .

QUANTITATIVE DETERMINATION Microbiological: *Sarcina lutea* [1] .

BIOLOGICAL ACTIVITY Active against Gram-positive bacteria, including mycobacteria and certain fungi. In vitro. Inhibits ($\mu\text{g/ml}$) *Bacillus subtilis*, *B. mycoides*, *Micrococcus pyogenes* var. *aureus*, *M. flavus*, *S. lutea*, *Mycobacterium ranae*, 0.12-0.5; *Myc. smegmatis*, *Mycobacterium sp.*, 4.0; *Brucella bronchiseptica*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, 64. *Candida albicans* inhibited by 2 $\mu\text{g/ml}$; *Trichophyton mentagrophytes* by 16.[1] High activity in concentration of 0.2 ppm, in accelerating death of spores of *Clostridium botulinum*, suggests its usefulness as food preservative [2] .

TOXICITY LD_{50} in mice, 2.5 mg/kg, i.p. [1] .

217. NISINS

SOURCE *Streptococcus cremoris* [4] .

NATURE Polypeptide or low molecular weight protein [2] .

CRYSTAL FORM AND COLOR Almost white needles [2] .

UV ABSORPTION MAXIMUM 275 $\text{m}\mu$ [3] .

SOLUBILITY s. ethanol, formamide, acids; s. but activity destroyed in glacial acetic acid, benzyl alcohol, other organic solvents.[2]

STABILITY Thermostable at acid pH, not at alkaline [2] .

OTHER REACTIONS Dialyze; precipitate from solution at neutrality; negative Ehrlich.

Nisin A, B, C: Contain leucine and/or isoleucine, valine, alanine, glycine, proline, aspartic acid, histidine, lysine, methionine, lanthionine, and a structural isomer of cystathionine.

D: Contains glutamic acid, no valine or methionine; resemblance to subtilin; S-containing amino acids may also be present in cinnamycin.[1, 3]

QUANTITATIVE DETERMINATION Microbiological: *Streptococcus agalactiae*, *Mycobacterium phlei* [1, 2] .

BIOLOGICAL ACTIVITY In vitro. Crude nisin preparations inhibited (units/ml) hemolytic streptococci, 0.25-4.0; *Diplococcus pneumoniae*, 0.25-100; *Clostridium spp.*, 0.25-80.0; *Neisseria spp.*, 2-50; *Corynebacterium spp.*, 4-120; *Erysipelothrix rhusiopathiae*, 2; *Micrococcus pyogenes* var. *aureus*, 100; *Myc. tuberculosis*, 100-500; *Actinomyces spp.*, 1-10.[6] Fractions A, B, C, D displayed activity similar to crude nisin in inhibition of *Myc. tuberculosis* in dilution of 1:100,000-1:800,000 [1] . Nisin failed to inhibit intracellular *Myc. tuberculosis* within rabbit macrophages in vitro in concentration of 50 $\mu\text{g/ml}$; streptomycin and other antitubercular agents were effective in lower concentration under same test conditions.[8] Inhibited growth of anaerobic spore formers responsible for spoilage of European fondu cheeses at 50-100 units/g cheese [11, 13] , and prevented growth of *Cl. botulinum* at 5 ppm [12] , suggesting value as food preservative.

In vivo. Protection afforded in mice against infections with *Str. agalactiae* [5] , *Str. pyogenes*, *M. pyogenes* var. *aureus* [1, 7] , and *Cl. septicum* [6] . No activity in experimental mouse tuberculosis [7] , although preliminary experiments had suggested slight activity in guinea pigs with same infection [6] .

VETERINARY Intramammary instillation of 2.5-5 million units per quarter in bovine udder was of some value in mastitis caused by *Str. agalactiae*. During treatment a depression in milk yield was noted.[9, 10]

PHARMACOLOGY LD_0 in mice, 400 mg/kg, i.v. Repeated daily doses of 50 mg/kg, i.v., or 250 mg/kg, s.c., were well tolerated in mice and guinea pigs. Following i.m. doses of 200,000 units in rabbits, blood concentration of 4 units/ml in 6 hours was noted, with high levels excreted in the urine [6] ; in mice, antibiotic detectable in blood, tissues and urine several hours after i.v. injection of 50 mg/kg [1] . Substantial blood concentrations noted in rabbits after s.c. injection of nisin at 12-hour intervals [5] .

218. NITROSPORIN

SOURCE *Streptomyces nitrosporeus* [1] .

NATURE Basic [1] .

MOLECULAR FORMULA $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_6$ [1] .

218. NITROSPORIN (Concluded)

CRYSTAL FORM AND COLOR White crystals [1].

MELTING POINT (°C) 130-140 (d.)¹ [1].

UV ABSORPTION MAXIMA 250, 320 mμ [1].

SOLUBILITY s. alcohol, ethyl acetate, acid water; sl.s. ether, benzene, ethylene dichloride; i. water [1].

OTHER REACTIONS White crystals turn light-brown on exposure to air [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (μg/ml) Micrococcus pyogenes var. aureus, 0.2-0.4; Bacillus subtilis, 0.2; Diplococcus pneumoniae, Streptococcus pyogenes, 0.1-0.4; Escherichia coli, 25; Salmonella typhosa, 12.5; S. paratyphi, 100; Shigella dysenteriae, Hemophilus pertussis, 50; Proteus vulgaris, B. anthracis, Corynebacterium diphtheriae, Mycobacterium spp.; S. schottmuelleri, >100. No activity against fungi.[1]

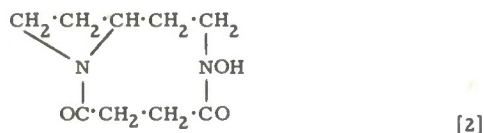
TOXICITY LD₅₀ in mice, approximately 16 mg/kg, i.v. [1].

219. NOCARDAMIN

SOURCE Nocardia sp related to N. flavescens [1].

MOLECULAR FORMULA C₉H₁₄O₃N₂ [1, 2].

STRUCTURE



CRYSTAL FORM Needles in clusters [1, 2].

MELTING POINT (°C) 183-184 (corr.) [1, 2].

OPTICAL ACTIVITY Inactive [1, 2].

OTHER REACTIONS Red-brown with FeCl₃; yellow, then Ag mirror with ammoniacal Ag solution; green with copper chloride; reduced Fehling.[1]

QUANTITATIVE DETERMINATION Microbiological: Mycobacterium phlei [1].

BIOLOGICAL ACTIVITY In vitro. Bactericidal to Myco. phlei in dilution of 1:1000. No activity against other bacteria at 1:1000 dilution: Micrococcus pyogenes var. aureus, Streptococcus pyogenes, Escherichia coli, Salmonella typhosa, Shigella dysenteriae, and fungi.[1, 2] In vitro activity reduced by serum [1].

220. NOCARDIANIN

SOURCE Nocardia sp [1].

MOLECULAR FORMULA AND WEIGHT C₆₅₋₆₇H₉₆₋₁₀₄O₁₅N₁₈; 1375 (found).[1]

CRYSTAL FORM AND COLOR Red prisms [1].

MELTING POINT (°C) 228-235 (d.) [1].

OPTICAL ACTIVITY [α]_D²⁵ = -223° [1].

UV ABSORPTION MAXIMUM 440 mμ [1].

SOLUBILITY s. chloroform, glacial acetic acid, pyridine, acetone, methanol, dilute acids; sl. s. ether, water; i. petroleum ether, carbon disulfide, carbon tetrachloride.[1]

OTHER REACTIONS Negative xanthine, Liebermann, Millon, Duke, Schiff, Ehrlich, fluorescein chloride, biuret, hydroxamic, ninhydrin [1].

/1/ Browns at 115-120°C. /2/ c, 0.3 methanol.

220. NOCARDIANIN (Concluded)

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits Gram-positive bacteria. No activity against mycobacteria or Gram-negatives.[1]

221. NOCARDORUBIN

SOURCE *Nocardia* sp [1].

NATURE Pigment [1].

STRUCTURE Possible quinoid structure [1].

MELTING POINT (°C) Blackens at 180; no melting at 250.[1]

SOLUBILITY Alkaline form: sl. s. dioxane, ethyl acetate, chloroform, propylene glycol; i. most organic solvents, water. Acid form: s. most organic solvents, water [1].

STABILITY Stable at neutral and alkaline pH; unstable at pH 2.0.[1]

OTHER REACTIONS Red in alkali, yellow in acid; negative Fehling; not decolorized by Zn dust; activity unaffected by NaCl, dextrose.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* 209-P [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Corynebacterium diphtheriae*, 0.001; *Bacillus subtilis*, 0.05-0.5; *B. mesentericus*, 0.1; *Diplococcus pneumoniae*, 0.2-0.5; *M. pyogenes* var. *aureus*, *M. pyogenes* var. *albus*, 0.5; *Streptococcus pyogenes*, *Str. viridans*, 1.0; *Mycobacterium avium*, 1.2; *Myco. phlei*, 1.6; *Myco. tuberculosis* var. *hominis*, 1-5; *Str. faecalis*, *Hemophilus pertussis*, 5; *Escherichia coli*, *Proteus vulgaris*, *Shigella dysenteriae*, *Salmonella typhosa*, *S. paratyphi*, *S. schottmuelleri*, 10-20. Also inhibits *Streptomyces griseus*, 5; *Aspergillus niger*, 20; *Saccharomyces sake*, >100. Micrococci and mycobacteria did not readily develop resistance in vitro.[1]

In vivo. Single s.c. doses of 5 mg protected mice against *D. pneumoniae* [1].

TOXICITY LD₀ of crude extracts in mice, 154 mg/kg, i.p. [1].

222. NOFORMICIN

SOURCE *Nocardia formica* [1].

MOLECULAR FORMULA Cryst. sulfate: C₁₇H₃₄N₁₀-O₅(SO₄)₂ [1].

MELTING POINT (°C) HCl: 265 (d.)¹ [1].

SOLUBILITY s. water [1].

STABILITY Stable in solution up to pH 8 [1].

OTHER REACTIONS Dialyzable; ammonia and glutamic acid are among the hydrolysis products; two other ninhydrin-active, non-amino acid materials are present; approximately 70% of the N remains unaccounted for; no phenolic groups; non-reducing.[1]

QUANTITATIVE DETERMINATION Microbiological: Increase in survival time of mice infected intranasally with swine influenza virus [1].

BIOLOGICAL ACTIVITY In vitro. Slight activity against *Diplococcus pneumoniae*, *Corynebacterium pseudodiphtheriticum*. Protozoa: *Trichomonas foetus*, *T. vaginalis* inhibited by 1:40-1:80 dilution. Failed to inactivate viruses in vitro.[1]

In vivo. Administration by i.v., oral, or s.c. route protected mice infected intranasally with viruses of influenza A and B and swine influenza. No activity against Columbia-SK encephalomyelitis virus in mice, hog cholera in swine, hepatitis in dogs, enteritis virus in mink, or Newcastle disease virus in mice or chickens. Suppressed mumps virus and Newcastle disease virus in embryonated eggs.[1-3]

TOXICITY Mice tolerated 10 mg/kg, s.c., in single doses, multiple s.c. or i.v. daily doses of 5 mg/kg, or oral doses of 12.5 mg/kg. Mice receiving these doses developed alopecia.[2] Concentrations of 100 $\mu\text{g/ml}$ were toxic to tobacco plant [4].

/1/ 99.8% pure.

222. NOFORMICIN (Concluded)

PHYTOPATHOLOGY No *in vitro* inactivation of tobacco mosaic virus or southern bean mosaic virus when exposed to 250 ppm noformicin HCl for 24 hours at 28°C, or 81 hours at 6°C. In systemic infections, antibiotics suppressed development of lesions by southern bean mosaic virus in intact Pinto bean plant, and by tobacco mosaic virus in tobacco plant, following spray of 50-220 ppm pure antibiotic at 1, 24 and 48 hours after inoculation with virus suspension. Antibiotic absorbed by roots; was translocated from base of leaf toward tip and in the reverse direction to a lesser extent. Antiviral activity similar to, but not as lasting as, thiouracil.[5]

223. NOTATIN
(Penatin, Penicillin B)

SOURCE *Penicillium notatum* and other *Penicillium* spp [1, 4, 5].

NATURE Flavoprotein, glucose-oxidase enzyme [3, 4, 6, 7].

MOLECULAR WEIGHT 152,000 (ultracentrifuge) [8].

FORM AND COLOR Yellow- or buff-colored powder [1, 5, 7].

OPTICAL ACTIVITY $[\alpha]_D^{22} = -4.8^{01}$ [4].

ABSORPTION MAXIMA 270-280, 375-380, 450-460 m μ [4].

SOLUBILITY s. water; i. organic solvents [1, 2, 5].

STABILITY Heat labile; unstable except at pH 2-8 [1, 2, 4, 5].

OTHER REACTIONS Non-dialyzable; positive protein reactions; precipitated by tannic, tungstic, phosphotungstic, phosphomolybdic, trichloroacetic, flavianic, rufianic acids; green fluorescence with acetic acid; inactivated by alcohol; by nature requires dextrose to be effective.[1, 2, 4, 5]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*, *Escherichia coli* [2, 4, 5].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits (in dilution $\times 10^6$) *Streptococcus pyogenes*, *Streptococcus* spp, *Salmonella typhosa*, *Proteus vulgaris*, *Vibrio comma*, 10-1000; *Neisseria catarrhalis*, *Sarcina lutea*, *Gaffkya tetragena*, 250; *Diplococcus pneumoniae*, 12.5-100; *M. pyogenes* var. *aureus*, 42-125; *Salmonella paratyphi*, 25-100; *Shigella paradyserteriae*, 100; *Brucella abortus*, *Br. melitensis*, *Bacillus anthracis*, *B. subtilis*, *B. mycoides*, *Corynebacterium diphtheriae*, *Aerobacter aerogenes*, *Clostridium histolyticum*, *Salmonella enteritidis*, *S. schottmuelleri*, *S. typhimurium*, 10-50; *Sh. sonnei*, *E. coli*, 1-10; *Klebsiella pneumoniae*, 0.1-1.0.[4, 5, 9]

In vivo. No activity in mice infected with *M. pyogenes* var. *aureus*, *Str. pyogenes* or *Salmonella* sp [10].

TOXICITY LD₅₀ in mice, 3 mg/kg, i.p.; 4.5 mg, s.c.[5] Rabbits tolerated oral doses of 300 mg/kg. In rats, antibiotic produced methemoglobinemia; no marked chronic toxicity.[10]

224. NOVOBIOCIN
(Antibiotic PA-93, Streptonivicin)

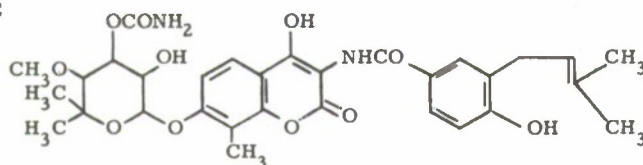
Trademarks for novobiocin are Albamycin (The Upjohn Company), Cathomycin (Merck & Co., Inc.) and Cardelmycin (Chas. Pfizer & Co., Inc.).²

SOURCE *Streptomyces niveus* [1, 2], and *S. spheroides* [3, 4].

NATURE Dibasic acid [1, 3, 5].

MOLECULAR FORMULA AND WEIGHT C₃₁H₃₆N₂O₁₁ [6]; 592 ± 25 (ebull.); 610 (Rast); 618 (X ray).[1, 3, 5]

STRUCTURE



[7]

CRYSTAL FORM AND COLOR Pale yellow; 2 crystalline forms.[1, 3-5]

MELTING POINT (°C) 152-154, 152-156 (d.), and 170-172, 174-178 (d.) [1, 3-5, 8].

/1/ c, 0.012 water. /2/ Cathocin was formerly a trademark of Merck & Co., Inc., for novobiocin, but both this name and streptonivicin have been eliminated.

OPTICAL ACTIVITY $[\alpha]_D^{25} = -27.0^1 [3, 4]$, $-44.0^2 [3, 4]$; $[\alpha]_D^{24} = -63.0^3 [1, 5]$; $[\alpha]_D^{28} = -34.0^2 [8]$; $[\alpha]_D^{26} = -35.2^2 [8]$.

UV ABSORPTION MAXIMA 304 m μ in pH 7 phosphate buffer; 248, 308 m μ in 0.01N ethanolic phosphate buffer pH 7.5; 307 m μ in 0.1N NaOH; 311 m μ in 0.01N ethanolic KOH; 324 m μ in 0.1 HCl-methanol; 334 m μ in 0.01N ethanolic H₂SO₄. 238, 250 (shoulder), 290 (shoulder), 304 m μ in 1% phosphate buffer pH 6; 290 (shoulder), 326 m μ in 0.1 N HCl and 95% methanol; 230 (shoulder), 307 m μ in 0.1 N NaOH.[1, 3, 5, 8]

SOLUBILITY s. in aqueous solution above pH 7.5; i. below. Acid form: s. acetone, ethyl acetate, amyl acetate, methanol, ethanol, pyridine.[5, 8]

STABILITY Dry material of both forms stable at 24°C in absence of light; dilute aqueous solution stable at pH 2 at 24°C; half-life, 60 days at pH 7-10.[5]

OTHER REACTIONS pK'a 4.3 and 9.1 in water; catalytic hydrogenation with Raney nickel yields dihydrostreptovivincin, MP 163-165°C; hydrolysis with 4N HCl in 60% ethanol yields an optically inactive acid. Infrared of Form I (MP 174°): 3500, 3445, 3395, 1744, 1738, 1694, 1642, 1607, 1542, 1500, 1374, 1360, 1320, 1294, 1280, 1252, 1235, 1219, 1162, 1138, 1124, 1103, 1091, 1080, 1062, 1029, 1000, 969, 930, 904, 879, 846, 800, 789, 770, 755, 739, 716 (recip. cm); Form II (MP 152°): 3480, 3360, 3280, 1715, 1690, 1635, 1610, 1586, 1534, 1507, 1374, 1344, 1315, 1293, 1259, 1186, 1157, 1121, 1084, 1064, 1022, 998, 972, 934, 919, 837, 818, 809, 789, 781, 761, 753, 741 (recip. cm); both crystalline forms are isotropic with a mean refractive index of 1.595 \pm 0.003.[1, 5, 8]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*; *Klebsiella pneumoniae*⁴. [2, 9] Streptothricin-resistant strain of *M. pyogenes* var. *aureus* [32]. Colorimetric [33].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits (μ g/ml) *M. pyogenes* var. *aureus* (including strains resistant to penicillin, streptomycin, erythromycin, chloramphenicol, and the tetracycline antibiotics) at 0.02-25; *Corynebacterium diphtheriae*, 0.04-0.78; *Hemophilus pertussis*, 0.06; *Neisseria meningitidis*, 0.09-3.1; *M. pyogenes* var. *albus*, *Sarcina lutea*, 0.19; *Diplococcus pneumoniae*, 0.19-12.5; *Streptococcus agalactiae*, *C. renale*, *H. influenzae*, 0.2-0.8; *N. gonorrhoeae*, 0.4-6.3; *Str. pyogenes*, 0.78-200; *Pasteurella multocida*, 0.78-12.5; *Str. viridans*, 0.78-50; *C. pseudotuberculosis*, *Erysipelothrix rhusiopathiae*, 0.8-25; *Proteus vulgaris*, 1.0->400; *Leuconostoc mesenteroides*, *L. citrovorum*, 2.5; *Mycobacterium tuberculosis* var. *hominis*, 2.5-62; *X. pruni*, 3.0; *Str. uberis*, 6.2; *K. pneumoniae*, *Pr. rettgeri*, 6.2->200; *Aerobacter aerogenes*, 12.5->400; *Clostridium novyi*, 12.5-25; *Salmonella typhosa*, 12.5-1000; *S. paratyphi*, *S. schottmuelleri*, *Shigella dysenteriae*, *Pseudomonas aeruginosa*, 12.5->1000; *Cl. sporogenes*, *Serratia marcescens*, 25; *Pr. mirabilis*, 25-100; *Brucella abortus*, 31.2; *Proteus* spp, 12.5-400; *Corynebacterium pseudodiphtheriticum*, 50; *Escherichia coli*, *Pr. morgani*, 50->400; *Salmonella pullorum*, 50->1000; *S. typhimurium*, *Erwinia amylovora*, 100; *Sh. sonnei*, 100->100. *Nocardia asteroides* sensitive to 10-100 μ g/ml. *Blastomyces dermatitidis* inhibited by 15 μ g/ml; *Monosporium apiospermum*, 100-1000. *Trichophyton mentagrophytes*, *Microsporum audouini*, *Aspergillus niger*, *Cryptococcus neoformans*, and *Candida albicans* not sensitive to 100 μ g/ml. *Trichomonas vaginalis* inhibited by 125 μ g/ml.[2, 10, 11, 17, 18, 22] *In vitro* activity is reduced in presence of serum [12-14].

In vivo. Single mouse doses of 0.3-1.8 mg, s.c., protected 50% of mice against infection with *Micrococcus pyogenes* var. *aureus*, *D. pneumoniae*, *Proteus* sp, *Pr. vulgaris*, and *Past. multocida*. The median effective dose in *Str. pyogenes* infection was 7.0 mg/mouse. Dosages of this order by oral or other routes gave comparable results. Dietary levels of 100 mg/kg controlled an experimental chronic *M. pyogenes* var. *aureus* infection. Seven i.p. doses of 1.5 mg protected mice against intranasal infection with *H. pertussis*. No *in vivo* activity demonstrated against *K. pneumoniae*, *Escherichia coli*, *Ps. aeruginosa*, *S. typhosa*, *S. schottmuelleri*, *Shigella dysenteriae* and *Myc. tuberculosis* in mice. No protection afforded against murine infection with *Rickettsia mooseri*, *Columbia-SK encephalomyelitis virus*, or with *Trypanosoma brucei* and *Trichomonas foetus*. In chick embryos there was no demonstrable activity against influenza B (Lee strain) or Newcastle disease virus. Activity against *Plasmodium gallinaceum* in chicks was approximately 1/10 that of quinine sulfate.[10, 11, 17, 19]

CLINICAL Generally good clinical responses have been reported in a variety of infections caused by susceptible bacteria (including pneumococcal and Friedländer pneumonia, acute pharyngitis, sinusitis, otitis media, panophthalmitis, urinary tract infections, scarlet fever, cutaneous anthrax, breast abscess, acute tracheobronchitis, bacteremia, osteomyelitis) and in wound infections. Oral therapy with 1.5-2.0 g per day in divided doses in adults, or 5 mg/kg every 6 hours in infants and children, has been employed. Intravenous and intramuscular therapy has also been described.[16, 26-30] Successfully used in conjunction with surgery in cases of soft tissue infection [25]. Oral therapy gave excellent results in pyodermic infections caused by *M. pyogenes* var. *aureus*, and *Str. pyogenes* [15]. In preliminary trials in amebiasis, oral doses of 1.5 g daily for 10 days gave indifferent results [20].

TOXICITY LD₅₀ in mice, 407 mg/kg, i.v.; 262-300 mg/kg, i.p.; 962->1000 mg/kg, oral. LD₅₀ in guinea pigs, 11.5 mg/kg, i.p.; 27.8 mg/kg, s.c.[21] Poor weight gains in guinea pigs treated with daily s.c. doses of 5-12.5 mg/kg for 3 weeks. In rats, 385 mg/kg/da in the diet for 8 weeks were well tolerated, with no evidence of pathologic changes. The antibiotic was moderately irritating to rabbit skeletal muscle. In dogs, daily i.v. doses of 50-100 mg/kg for 5 days produced no evidence of systemic toxicity; 300 mg/kg for 2-4 days induced rapid emesis and prostration -- at necropsy these animals showed severe hepatic and renal changes, gastrointestinal hemorrhages and severe vascular irritation. Pharmacodynamic studies in barbital-anesthetized dogs disclosed no alarming properties.[21]

/1/ c, 1 in 1 N NaOH. /2/ c, 1 in pyridine. /3/ c, 1 in ethanol. /4/ PCI 602, ATCC 10031.

In man, daily oral doses of 1.5-2.0 g, 500 mg intravenously at 12-hour intervals, or 250 mg intramuscularly, were well tolerated. Allergic dermatitis appeared to be a fairly common reaction to the oral doses; other side effects were minimal.[20, 26-30] Drug rash was almost completely absent in a group of 208 adults given 0.5 g twice daily for a total dosage of 10 g over a 12-day period [31].

RESISTANCE Strains of *M. pyogenes* var. *aureus* developed resistance fairly rapidly (13-15 subcultures in anti-biotic) *in vitro*. This development appeared to be intermediate between the rapid one-step pattern characteristic of streptomycin and the stepwise penicillin-type. Initially the rate was rapid, with a levelling off followed by a stepwise development.[12-14, 17] No cross resistance shown between this antibiotic and penicillin, streptomycin, chloramphenicol, erythromycin, carbomycin, tetracyclines, bacitracin, polymyxin, or spiramycin [10, 22].

ABSORPTION AND EXCRETION There is a high degree of binding by serum albumin [14, 18]. Unusually high and well-maintained blood levels obtained with peak concentrations in 2-4 hours after oral administration in dogs and man. Oral doses of 40 mg/kg in dogs produced peak levels of 128 µg/ml. Approximately 1/3 of the oral dose was excreted in the feces, with only approximately 1% detected in the urine within 24-48 hours. The antibiotic was widely distributed in the tissues as well as in body fluids. In mice, the serum levels were relatively lower, with highest concentrations within one hour.[9]

In man, single oral doses of 10 mg/kg produced peak serum levels of 57 µg/ml in 2 hours. Initial oral doses of 2.0 g promptly produced high serum levels (126 µg/ml), and subsequent therapy with 500 mg at 12-hour intervals tended to maintain levels in the range of 20 µg/ml or greater. Urinary excretion was quite low and approximated 2.7-3.3% of the administered dose. Distributed in pleural and ascitic fluids and in thyroid tissue; excreted in bile, urine, and feces. No detectable concentrations in cerebrospinal fluid.[9, 13, 14, 19, 23, 24] Following single intramuscular doses of 250 mg, serum levels up to 12.8 µg/ml noted in 1-2 hours and 1.6-6.4 µg/ml in 4 hours [18, 23].

MODE OF ACTION Bacteriostatic; also significantly bactericidal *in vitro*. Concentrations of 11.7 µg/ml lethal to *D. pneumoniae* within 4 hours.[11] A strain of *M. pyogenes* var. *aureus*, for which 0.1 µg/ml was bacteriostatic, was rendered non-viable by 1.0 µg/ml in 48 hours, 10 µg/ml in 24 hours, and 100-1000 µg/ml in 7 hours [17].

225. NUDIC ACIDS

SOURCE *Tricholoma nudum* [1].

MOLECULAR FORMULA AND WEIGHT Nudic acid A: $C_{14}H_{20}O_3$ (proposed).
B: $C_8H_4O_3$ (proposed); 135-140 (found); 148 (calc.).[1]

CRYSTAL FORM AND COLOR Nudic acid A: colorless needles or plates.
B: small, colorless needles [1].

MELTING POINT (°C) Nudic acid A: 123.5 (uncorr.).
B: 150 (darkens, sublimes) [1].

OPTICAL ACTIVITY Active¹ [1].

SOLUBILITY s. most organic solvents; sl. s. hot water; i. cold water, hexane, dilute acids.
Nudic acid A: s. sodium carbonate.
B: sl. s. sodium carbonate.[1]

STABILITY Nudic acid A: Thermostable.
B: Thermostable only at acid and neutral pH [1].

OTHER REACTIONS Negative Fehling, ammoniacal $AgNO_3$, KI; decolorized aqueous $KMnO_4$.
Nudic acid A: Decolorizes Br water; amorphous precipitate with 2,4-dinitrophenylhydrazine.
B: No decolorization of Br water; no precipitate with 2,4-dinitrophenylhydrazine; loses activity in pyridine; crystals darken after 2-hour exposure to sunlight.[1]

BIOLOGICAL ACTIVITY *In vitro*. Nudic acid A: Inhibits *Escherichia coli*, *Micrococcus pyogenes* var. *aureus*, *Streptococcus pyogenes*, *Bacillus anthracis*, *Salmonella enteritidis*, *Corynebacterium xerosis* in dilution of 1:2000-1:8000.

B: More active; inhibits *M. pyogenes* var. *aureus*, *B. anthracis*, *Proteus* sp, *S. typhosa* in dilution of 1:8000-1:640,000.[1]

TOXICITY Nudic acid A: LD_{50} in mice, 25 mg/kg, i.v.
B: LD_{50} , approximately 6.2 mg/kg, i.v.[1]

/1/ Alcohol.

SOURCE *Streptomyces* sp [1].

MOLECULAR FORMULA AND WEIGHT $C_8H_7O_2N$; 164 (ebull. in acetic acid); 149 (calc.).[1]

CRYSTAL FORM AND COLOR Small, colorless, thin needles, rods, or rhomboid forms¹ [1].

MELTING POINT (°C) Darkens at 330 without melting [1].

UV ABSORPTION MAXIMA 266, 285 $m\mu^2$ [1].

SOLUBILITY s. concentrated HCl; less s. boiling acetic acid, boiling lower alcohols; sl. s. cold water, alkali, organic solvents.[1]

OTHER REACTIONS Sublimes in vacuo at 250°C without change in UV or loss of biological activity; negative $FeCl_3$, biuret, ninhydrin.[1]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus cereus* phage [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu g/ml$) *Klebsiella pneumoniae*, 0.003-0.08; *B. subtilis*, 0.025-0.25; *Mycobacterium smegmatis*, 0.2; *B. mycoides*, 0.8; *B. cereus*, 2; *Escherichia coli*, 0.08->50; *Micrococcus pyogenes* var. *aureus*, 1.0->50; *Pseudomonas aeruginosa*, >50. Active against a variety of phages, including those of *E. coli*, *B. subtilis*, *Salmonella*, *Shigella*, *Pseudomonas*, *Vibrio comma*, *Streptococcus*, *Enterococcus*, and *M. pyogenes* var. *aureus*. [1]

TOXICITY Mice tolerated 250 mg/kg (in peanut oil), i.p. Following this dose, detectable concentrations were observed in the feces within 24 hours and in the urine after 3 days.[1]

227. NYSTATIN

(Fungicidin)

The trademark of E. R. Squibb and Sons, Division of Olin Mathieson Chemical Corp., for nystatin is Mycostatin.

SOURCE *Streptomyces noursei* [1].

NATURE Amphoteric [2].

MOLECULAR FORMULA AND WEIGHT $C_{46}H_{83}NO_{18}$ (proposed); 922, 956 (neut. equiv.); 939 (calc.).[2]

FORM AND COLOR Yellow powder [1].

MELTING POINT (°C) Gradual decomposition above 160 without melting at 250 [2].

OPTICAL ACTIVITY $[\alpha]_D^{25} = +10^{03}$, $+21^{04}$, $+12^{05}$, -7^{06} . [2]

UV ABSORPTION MAXIMA 280, 291, 304, 318 $m\mu$ [2].

SOLUBILITY sl. s. methanol, ethanol, butanol, dioxane; i. water, pyridine, dimethylformamide, glacial acetic acid, 0.05 N methanolic HCl or NaOH.[1, 2]

STABILITY No loss in cold; unstable at pH 2 or 9.[1, 2]

OTHER REACTIONS Negative $FeCl_3$, Millon; positive Molisch, carbazole; decolorizes $KMnO_4$, $Br-CCl_4$; in concentrated H_2SO_4 , color changes from violet to blue to black; strong blue color with $FeCl_3-K_3Fe(CN)_6$; no reduction of Fehling or Tollens; slow positive Schiff aldehyde test.[2]

QUANTITATIVE DETERMINATION Microbiological: *Cryptococcus neoformans*, *Candida albicans*, *Saccharomyces cerevisiae* [1, 3].

BIOLOGICAL ACTIVITY In vitro. Active against fungi. Inhibits, in concentrations of 1.25-6.25 $\mu g/ml$, *Blastomyces brasiliensis*, *Bl. dermatitidis*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Epidermophyton floccosum*, *Histoplasma capsulatum*, *Microsporium audouini*, *M. canis*, *Trichophyton mentagrophytes*, *T. rosaceum* and *T. rubrum*. [1] Strains of *Candida albicans* and *Geotrichum* spp inhibited by 1.25-12.5 $\mu g/ml$ [1, 10]. Concentrations of 575 units/ml (250 $\mu g/ml$) inhibited *Entamoeba histolytica*. Enhancement of amebicidal activity observed when combined with fumagillin, bacitracin, polymyxin, or the tetracycline antibiotics.[16] Antifungal activity enhanced by alcohols; activity depressed by glucose and other sugars, and unsaturated fatty acids.[36, 40]

In vivo. S. c. doses of 25-150 mg/kg protected mice against infections with *C. albicans* [4, 7], *H. capsulatum* [6], *Coccidioides immitis* [5, 8], *Cryptococcus neoformans* [8], and *Sporotrichum schenckii* [8]. In mice infected

/1/ Depending on solvent. /2/ Ethanol. /3/ Glacial acetic acid. /4/ Pyridine. /5/ Dimethylformamide.
/6/ 0.1 N HCl in methanol.

i.v. with *Candida albicans*, there was a high protection rate following oral doses of 4 mg [11]. In rabbits infected with *C. albicans*, doses of 40 mg/kg, s.c. or i.v., reduced mortality from 100% to 62% [28]. Doses of 6000 units/egg sterilized 60% of embryonated eggs infected with *C. albicans* [38]. Median protective dose against *Bl. dermatitidis* in mice was 0.8 mg/kg/da, i.p., for 10 days [33]. Daily i.p. doses of 20 mg/kg had no inhibitory effect on Ehrlich ascites tumor in mice [34].

CLINICAL Daily oral doses of 1 g reduced the number of *Candida albicans* in fecal flora in man [7]. The increase in yeast flora in the gastrointestinal tract accompanying oral tetracycline therapy was counteracted by simultaneous oral administration of 250,000 unit doses of nystatin [9]. Incidence of side effects occasionally associated with oral tetracycline therapy appeared to be reduced when this antibiotic was combined with nystatin for antibacterial therapy. The combination was well tolerated.[22-24] Despite data indicating poor absorption of nystatin from the gastrointestinal tract, a report describes the successful use in systemic moniliasis in which skin and urinary tract infections cleared after 5 days of oral therapy [14]. Monilial infections of the skin responded to topical therapy with fungicidin in a drying lotion base [13]. Favorable responses noted in a variety of monilial infections in patients treated with oral doses of 0.25-1.0 g/da for 1-5 days [10]. Good clinical responses observed in several cases of monilial vulvovaginitis following oral therapy [30]. Further clinical trials have confirmed the value of topical therapy in oral, vulvovaginal, and cutaneous moniliasis [18-21]. Topical application (in propylene glycol or in ointment base) appeared effective in anogenital and vaginal moniliasis [12]. Topical therapy in dermatophytosis gave poor to fair responses [35]. Improvement noted in three cases of disseminated coccidioidomycosis following intravenous therapy; no clinical response in two cases with meningeal involvement.[17] In preliminary trials, total oral doses of 45 million units over a 10-day period cleared the stools of *E. histolytica* in five cases of amebiasis [16].

ACUTE TOXICITY LD₅₀ in mice, 29,430-50,040 units/kg, i.p.; oral doses of 8.1-12.5 million units tolerated¹. LD₅₀ in rats, 85,068-93,440 units/kg, i.p.; oral doses of 7.68 million units/kg non-toxic.[16] In vitro. Concentrations of 30 units/ml did not interfere with phagocytic activity of human leukocytes [40]. In tissue cultures, using the roller tube method, 1250-2500 units/ml (approximately 625-1250 µg/ml) were required for partial inhibition of human skin explants [29]. Concentrations of 250 units/ml toxic to HeLa (carcinoma) cells; 500 units/ml toxic to "L" cells of Earle and to chick embryo fibroblasts. Concentrations up to 100 units/ml did not interfere with the production of Mahoney (type 1) strain of poliomyelitis virus in HeLa cells. In view of the low toxicity, antibiotic appears to be a useful agent for control of mold and yeast contaminations when employed in concentrations of 30 units/ml.[26]

CHRONIC TOXICITY Toxic manifestations were observed in rats receiving daily oral doses of 810,000 units/kg over a 3-month period. No histopathologic changes in dogs receiving 90,000-450,000 units/kg orally for 185-217 days, or i.v. doses of 3200 units/kg/da for 35-37 days.[25] Daily subcutaneous doses of 1250 units (0.5 mg), over periods of 58 days, were well tolerated in hamsters initially weighing 25-30 g, but single doses of 80 mg/kg were toxic [31]. Mice tolerated repeated daily i.p. doses of 24 mg/kg [5], or 50 mg/kg, s.c., for 10 days [8]. Repeated oral administration of 300 mg/kg in rats and 1000 mg/kg in dogs non-toxic [7].

In man, there was no evidence of toxicity following 400,000-800,000 units per day, orally, for 22 days [16]. Daily oral doses up to 1.25 g for 30 days were well tolerated without significant side effects [8].

ABSORPTION AND EXCRETION Poorly absorbed from the gastrointestinal tract of animals and man after oral administration. In dogs, plasma level was 0.9-1.1 units/ml within 2-4 hours after single oral dose of 450,000 units/kg. Following oral dosages of 150,000-260,000 units/kg for 31 weeks, concentrations of 35-150 units/g were noted in the liver and 75 units/g in the kidneys, with no detectable levels in the lungs and spleen.[25]

In man, in a case of coccidioidomycosis treated with 70,000-1,400,000 units per day orally, the plasma level reached 9 units/ml. Following an oral dose of 15 million units, the blood concentration was 9 units/ml four hours later. Intravenous doses of 200,000 units twice daily, followed by four times daily, produced plasma levels of 54 units/ml.[25] No detectable concentrations in the cerebrospinal fluid after intravenous or oral therapy [17].

RESISTANCE Resistance in *C. albicans* failed to develop in vitro, or was of very low order following repeated transfers in the antibiotic. Reciprocal cross-resistance of low magnitude displayed between nystatin and other polyene-type antibiotics (rimocidin, candicidin, ascocin, trichomycin, candidin B), but not with non-polyene types (gliotoxin, comirin, aspergillidic acid, streptothricin).[27]

MODE OF ACTION Action is fungicidal as well as fungistatic. A strain of *C. albicans*, which was inhibited by 8 units/ml in vitro, was rendered non-viable within 6 hours when exposed to 32 units/ml.[36] A suspension, containing 3.0×10^9 living *C. albicans* cells per ml, was killed by a concentration of 1 mg/ml of the antibiotic [28]. In vitro concentrations of 3 µg inhibited aerobic and anaerobic utilization of glucose, maltose, or fructose by yeast, and also eliminated endogenous uptake. Higher concentrations had no effect on glucose utilization by *Escherichia coli* and *Streptococcus faecalis* which are not sensitive to fungicidin.[39]

MISCELLANEOUS Yeast contaminations were controlled by incorporating 20-80 units of fungicidin per ml in cultures examined for foot-and-mouth disease virus. The following species of yeast were inhibited: *Endomycopsis*, *Saccharomyces*, *Sporobolomyces*, *Kloeckera*, *Trichosporon*, *Rhodotorula*. [15] Concentrations of 20 µg/ml useful

/1/ Most preparations assay 2.3-2.5 units/µg.

227. NYSTATIN (Concluded)

for controlling fungal contaminations in fecal, sewage, and polluted water samples in laboratory examinations for isolation of enteric viruses [37]. Nystatin shows molluscicidal activity; concentrations of 15.6 µg/ml were lethal to snails (*Australorbis glabratus*) in one hour [32].

228. OLEANDOMYCIN
(Antibiotic PA-105, Amimycin)

Trademark of Chas. Pfizer & Co., Inc., for oleandomycin is Matromycin.

SOURCE *Streptomyces antibioticus* [1].

NATURE Basic [1].

MOLECULAR FORMULA $C_{37}H_{67}NO_{13} \cdot HCl$ (possible) [1].

MELTING POINT (°C) Dihydrate: 134-135. Anhydrous HCl: 125-128 [1].

OPTICAL ACTIVITY Dihydrate: $[\alpha]_D^{25} = -54.0^1$ [1].

UV ABSORPTION MAXIMUM 286-289 mµ [1].

STABILITY Stable at room temperature at pH 2-9 in aqueous solution [1].

OTHER REACTIONS Found: C, 57.63; H, 8.73; N, 1.87; Cl, 4.30 (ionic). Reduces Fehling slowly; positive Tollens; negative $FeCl_3$; ninhydrin.[1]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits (µg/ml) *Streptococcus pyogenes*, *Hemophilus pertussis*, 0.08; *Erysipelothrix rhusiopathiae*, 0.2-0.4; *Bacillus subtilis*, 0.4; *Micrococcus pyogenes* var. *aureus*, *Diplococcus pneumoniae*, 0.2-1.6; *Clostridium tetani*, 0.8; *Corynebacterium diphtheriae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Mycobacterium phlei*, *Mycobacterium smegmatis*, *Mycobacterium* sp, 1.6; *N. gonorrhoeae*, *N. catarrhalis*, 3.2; *Cl. sporogenes*, *Brucella bronchiseptica*, 6.2. Most Gram-negative bacteria, e.g., *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus vulgaris* not sensitive to 100 µg/ml.[1]

In vivo. S.c. doses of 15-30 mg/kg protected mice against infections with *Str. pyogenes* and *M. pyogenes* var. *aureus* [1].

CLINICAL Favorable responses in 20 cases of bacterial pneumonia and in 13 cases of possible staphylococcal enteritis in children treated with 40 mg/kg daily in 6-hour divided oral doses for 5-7 days. Little or no response in cases of enteritis caused by *Salmonella* sp. or *Shigella paradysenteriae*. [2]

PHARMACOLOGY LD₅₀ in mice, 550 mg/kg, i.v. Following oral administration of 200 mg/kg in rabbits, peak blood concentration of 3.8 µg/ml in 1 hour noted, with 0.2-0.4 µg in 5-7 hours.[1] Daily oral doses of 40 mg/kg for 5-8 days appeared to be well tolerated in children [2].

RESISTANCE Cross resistance with erythromycin and carbomycin has been described [1]. In another report, 22 erythromycin-resistant strains of *M. pyogenes* var. *aureus* were all sensitive to oleandomycin.[2]

229. OLIGOMYCIN

SOURCE *Streptomyces* sp [1].

MOLECULAR FORMULA AND WEIGHT $C_{25}H_{40-42}O_7$ (proposed); 408, 439 (Rast); 454 (calc.).[1]

CRYSTAL FORM AND COLOR Colorless, hexagonal crystals [1].

MELTING POINT (°C) 135.8-136.3 (uncorr.) [1].

OPTICAL ACTIVITY $[\alpha]_D^{25.8} = -51.0^2$ [1].

UV ABSORPTION MAXIMA 225, 232 mµ¹ [1].

SOLUBILITY s. most organic solvents; sl. s. petroleum ether, cyclohexane, water [1].

STABILITY Thermo-, acid, and alkali stable [1].

OTHER REACTIONS Br in CCl_4 and $KMnO_4$ in acetone slowly decolorized; negative phenolic, $FeCl_3$, digitonin; positive 2, 4-dinitrophenylhydrazine; a second component present at start of purification.[1]

QUANTITATIVE DETERMINATION Microbiological: *Blastomyces dermatitidis* [1].

/1/ Methanol. /2/ c, 3 methanol.

229. OLIGOMYCIN (Concluded)

BIOLOGICAL ACTIVITY Active against filamentous fungi; no activity against bacteria and yeasts. *In vitro*. Inhibits *Aspergillus fumigatus*, *Ascochyta pinodella*, *Bl. dermatitidis*, *Chalara quercina*, *Cladosporium cucumerinum*, *Colletotrichum circinans*, *C. lagenarium*, *C. pisi*, *Glomerella cingulata*, *Histoplasma capsulatum*, *Monilia nigra*, *Penicillium expansum*, *P. notatum*, *Verticillium albo-atrum*, 8.0 µg/ml.[1] Oligomycin was the most effective of 8 antibiotics tested against *Tilletia caries* (wheat smut fungus), causing complete inhibition of flask cultures at concentrations of 0.4 µg/ml [2].

TOXICITY LD₁₀₀ in mice, 2.5 mg/kg, i.v. or i.p. [1]. Sprays containing 3000 ppm of antibiotic were non-toxic in various plants. Seeds treated with 100-150 ppm germinated normally.[3]

PHYTOPATHOLOGY Greenhouse experiments indicate that the antibiotic may be added to the soil without decreasing soil microflora, and is detected in stems of various plants. Under these conditions alfalfa seed was protected against damping off caused by *Pythium sp.*[3]

230. OREGONENSIN

SOURCE *Ganoderma oregonense* [1].

NATURE Neutral [1].

MOLECULAR FORMULA C₂₀H₃₂O₈ (proposed) [1].

CRYSTAL FORM AND COLOR White needles [1].

MELTING POINT (°C) 82 [1].

OPTICAL ACTIVITY Inactive [1].

UV ABSORPTION MAXIMUM 325 mµ [1].

SOLUBILITY s. most organic solvents; sl. s. water; i. petroleum ether.[1]

STABILITY Thermo- and alkali labile [1].

OTHER REACTIONS Positive 2, 4-dinitrophenylhydrazine; negative Tollens.[1]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *Micrococcus pyogenes* var. *aureus* in dilution of 1:800,000; *Mycobacterium phlei*, 1:100,000; *Streptococcus pyogenes*, *Escherichia coli*, 1:50,000. Inactivated *in vitro* in presence of 50% serum.[1]

231. ORYZASIZINE
(Oryzacidine)

SOURCE *Aspergillus oryzae* [2].

MOLECULAR FORMULA C₈H₁₃O₅N [1, 2].

CRYSTAL FORM AND COLOR White needles; hygroscopic [1, 2]. Quinine salt: white tablets [2].

MELTING POINT (°C) 162-163 (d.) [1, 2]. Quinine salt: 210 (d.) [2].

OPTICAL ACTIVITY [α]_D = -138° [1]; [α]_D^{13.5} = -133° [2].

SOLUBILITY s. water, methanol, ethanol, propanol, hot acetone; sl. s. butanol, ethyl acetate; i. ether, acetone, chloroform, carbon tetrachloride.[2]

BIOLOGICAL ACTIVITY *In vitro*. Active against saké putrefying bacteria in dilution of 1:300,000 [2].

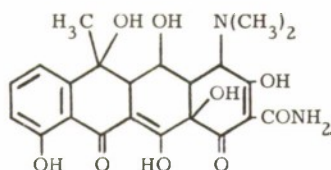
232. OXYTETRACYCLINE
The trademark of Chas. Pfizer & Co., Inc., for oxytetracycline is Terramycin.

SOURCE *Streptomyces rimosus* [1].

NATURE Amphoteric [2, 3].

MOLECULAR FORMULA AND WEIGHT C₂₂H₂₄N₂O₉ [3, 6]; approximately 440 (ebull.); 462.5 ± 5 (X ray).[3, 8]

STRUCTURE



[5, 6]

CRYSTAL FORM AND COLOR Pale yellow needles; thick, hexagonal plates [1-3].

MELTING POINT (°C) Dihydrate: 181-182 (d.). Anhydride: approximately 185 (d.). HCl: 190-194 (d.). [1-3, 6]

OPTICAL ACTIVITY Dihydrate: $[\alpha]_D^{25} = -196.6^{\circ 1}, -2.1^{\circ 2}, +26.5^{\circ 3}$. [2, 3, 6]

UV ABSORPTION MAXIMA 270, 370 $m\mu^4$; 270, 359 $m\mu^5$; 245, 264, 375 $m\mu^6$. Dihydrate: 249, 276, 353 $m\mu^7$; 268, 353 $m\mu^8$. [2, 3, 6]

SOLUBILITY s. acids, alkalies; sl. s. acetone, ethanol, chloroform, water; i. ether. HCl: s. water; i. ether, petroleum ether, benzene. [1-3]

STABILITY Stable at acid pH; decreasing stability at pH 7 and above at 37°C. [1-3]

OTHER REACTIONS Positive $FeCl_3$, Pauly, Friedel-Crafts, Fehling, Molisch; HCl pK'_a 3.49, 7.55, 9.24 in aqueous solution; forms complexes with inorganic salts; Ba-Ca and Ba-Mg salts very insoluble in water and precipitate readily from aqueous solution at pH 8.5-9.5; no infrared bands below 5.9 μ ; dihydrate crystals biaxial negative with parallel extinction, $\alpha = 1.634 \pm 0.004$, $\beta = 1.646 \pm 0.004$, $\gamma = >1.70$. [3, 6, 8]

QUANTITATIVE DETERMINATION Microbiological: *Klebsiella pneumoniae*, *Micrococcus pyogenes* var. *aureus* [2, 3]. Colorimetric [4, 7]. Spectrophotometric [4].

BIOLOGICAL ACTIVITY Active against Gram-positive and Gram-negative bacteria, rickettsiae and larger viruses, and certain protozoa. No activity against fungi. *In vitro*. Most strains of the following actinomycetes or bacteria are sensitive to 0.002-7.5 $\mu g/ml$: *Actinomyces bovis*, *Bacillus anthracis*, *B. mycoides*, *B. subtilis*, *Brucella abortus*, *Br. bronchiseptica*, *Br. melitensis*, *Br. suis*, *Clostridium botulinum*, *Cl. tetani*, *Cl. fesceri*, *Cl. histolyticum*, *Cl. hemolyticum*, *Cl. novyi*, *Cl. perfringens*, *Corynebacterium diphtheriae*, *Corynebacterium* spp, *Diplococcus pneumoniae*, *Erysipelothrix rhusiopathiae*, *Escherichia coli*, *Hemophilus influenzae*, *H. pertussis*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Micrococcus pyogenes* var. *aureus*, *Mycobacterium tuberculosis*, *Myc. smegmatis*, *Myc. avium*, *Myc. phlei*, *Neisseria catarrhalis*, *N. gonorrhoeae*, *N. meningitidis*, *Pasteurella multocida*, *Past. pestis*, *Salmonella typhosa*, *S. paratyphi*, *S. enteritidis*, *S. pullorum*, *Shigella dysenteriae*, *Streptococcus agalactiae*, *Str. dysgalactiae*, *Str. faecalis*, *Str. pyogenes*, *Str. viridans*, *Vibrio comma*. Generally less sensitive (10-50 $\mu g/ml$): *Nocardia asteroides*, *Aerobacter aerogenes*, *Salmonella* spp, *Shigella* spp, *Cl. bifermantans*. Most strains of *Pseudomonas aeruginosa* and *Proteus* spp are resistant, >50 $\mu g/ml$. [9-20] Spirochetes and protozoa ($\mu g/ml$): *Borrelia recurrentis* inhibited by 1.0 [21]; *Trichomonas vaginalis*, 125-250 [22]; *Entamoeba histolytica*, 31.2-250. [23] Inhibits *H. aegyptius*, cause of conjunctivitis in man, at 0.4-6.25 $\mu g/ml$; also active against this agent in chick embryos. [125] Rous sarcoma virus inactivated by exposure to antibiotic as demonstrated by failure to develop tumors in chickens [24]. Penetrated rabbit macrophages and suppressed growth of intracellular *Myc. tuberculosis* [25].

In vivo. S.c. doses of 200-300 mg/kg afforded protection against experimentally induced s.c. infections with *T. vaginalis* in mice [126]. 0.5-1.0 mg/ml in drinking water was effective in mice in controlling experimental air-borne mouse pneumonitis virus infections [127]. In mice, single s.c. doses of 6.5-30 mg/kg, or totals of 0.25-20 mg/kg in divided doses, gave good protection against infection with *Str. pyogenes*, *K. pneumoniae*, *H. influenzae*, *Salmonella typhosa*, *S. choleraesuis*, *S. enteritidis*, *S. typhimurium*, with somewhat higher doses required for *D. pneumoniae*, *Cl. septicum*, *Cl. tetani*. Higher oral doses were also protective. [9, 12] Was the most effective of several antibiotics tested against experimental *Cl. tetani* infection; complete protection obtained with 5 daily parenteral doses of 5 mg/kg in hamsters and with 20 mg/kg in mice and rabbits [133]. Doses of 2.5-10 mg/kg, administered i.p., gave high protection in mice against *Cl. perfringens*, *Cl. histolyticum*, *Cl. bifermantans* and *Cl. novyi* [16]; similar levels were effective against *M. pyogenes* var. *aureus*, *Past. multocida*, *B. anthracis*; higher doses of 20-80 mg/kg required against *Ery. rhusiopathiae* and *L. monocytogenes* in mice or *S. gallinarum* in chicks. [27] Daily oral doses in mice had a suppressive effect on infection with *Br. melitensis* [28]; also highly effective against *V. comma* [20] and *Past. tularensis* [38]. Oral doses of 100 mg/kg afforded high protection, but failed to be curative, in infant rabbits infected intra-intestinally with *V. comma* [132]. High activity in mice or rats infected with *Borrelia novyi*, *B. duttoni* [9, 30], and against *B. anserina* in chicks treated with low doses [31]. Effective in experimental rabbit syphilis, but less active on a weight basis than penicillin [33]; suppressive effect noted in experimental toxoplasmosis in mice [32]. Showed activity in mice and guinea pigs infected with *Myc. tuberculosis*, including strains which were streptomycin-resistant [26, 29]. Active against *Plasmodium* spp in mice, chicks

/1/ c, 1 in 0.1 N HCl. /2/ c, 1 in 0.1 N NaOH. /3/ c, 1 methanol. /4/ Methanol. /5/ 0.01 N methanolic HCl. /6/ 0.01 N methanolic NaOH. /7/ 0.1 M KH_2PO_4 pH 4.5. /8/ Phosphoric acid pH 1.7.

and canaries [34], and Bartonella muris infections in rats [44]. Oral medication highly effective in suppressing pinworm (*Aspicularis tetraoptera*) infestation in mice; little or no effect on hookworm or tapeworm in dogs and cats. [40] High anti-rickettsial activity in chick embryos or mice against rickettsiae of epidemic typhus, murine typhus, scrub typhus, rickettsialpox, Rocky Mt. spotted fever [35-38]. Active in chick embryos against pleuropneumonia-like organisms isolated from chronic respiratory disease of poultry [130]. Doses as low as 0.031 mg protected chick embryos against feline pneumonitis virus [131]. In mice, antibiotic is highly protective against gray lung virus [41] and experimental infection with feline pneumonitis virus [42]. No activity against the viruses of rabies, herpes simplex or influenza A [39, 46]. Daily i.p. doses of 150 mg/kg in mice had a moderate inhibitory effect on sarcoma 180 and carcinoma 1025 [136, 137]. High i.p. doses of 250-350 mg/kg/da slightly retarded development of Crocker sarcoma 180 in mice [43]. Heavy i.p. doses of 150 mg/kg had an adverse effect on *Candida albicans*, enhancing infections in mice [58, 59]. Single i.m. doses of approximately 110 mg/kg had a stimulatory effect on spermatogenesis in rats [60].

CLINICAL This broad-spectrum antibiotic has established usefulness in a variety of infections caused by Gram-positive and Gram-negative bacteria, spirochetes, rickettsiae and the larger viruses of the psittacosis-lymphogranuloma venereum group. The drug may be administered orally, with usual doses for adults of 1 g/da, or 2 g in severe infections; as much as 4 g/da dosages are well absorbed and usually well tolerated. In children with severe infections, total daily oral doses of 25-40 mg/kg are regarded as adequate. [45, 61] Total oral doses of 3-29.5 g, administered over periods of 3-8 days, successfully treated cases of anthrax infection in man [138]. In 7 cases of tick-borne relapsing fever in East Africa, treated with 4 oral daily doses of 500 mg in 2 days, there was prompt response and rapid disappearance of parasitemia; one patient relapsed on the 14th day after treatment. [139] Medication by the i.v. and i.m. routes, as well as by topical application, has frequently been used [45, 61]. Single intramuscular doses of 400 mg were successfully used in the treatment of gonorrhoeal urethritis [140].

Oxytetracycline has proven highly effective in the treatment of infections caused by streptococci, micrococci, bacteroides, brucellae, *D. pneumoniae*, and in urinary tract infections caused by susceptible organisms. It is useful for pre- and postoperative prophylaxis in surgical procedures on the large bowel, and in the treatment of peritonitis and respiratory infections. Highly effective in rickettsioses (Rocky Mt. spotted fever, epidemic typhus, scrub typhus, rickettsialpox and Q fever); it is also of value in lymphogranuloma venereum and granuloma inguinale. [36-38, 45, 61, 62, 124] This drug and chlortetracycline described as antibiotics of choice in psittacosis [52]. Conflicting results have been reported in pertussis, herpes zoster, infectious mononucleosis and leptospirosis; the direct action of this and other antibiotics in these conditions is debatable. [45, 47, 48] Very effective in gonorrhoea; preliminary trials in syphilis gave variable results. [47, 51, 76] Combination with streptomycin in pulmonary tuberculosis described as promising, with the advantage that strains resistant to either antibiotic may not emerge [49, 50]. Favorable clinical response in yaws [53], primary atypical pneumonia [54], *Plasmodium vivax* and *P. falciparum* malaria [55], and in amebic dysentery [56, 57]. Excellent response in pinworm infestation (*Enterobius vermicularis*) following 1-2 g daily oral doses for one week [63, 89]. Favorable results in cervicofacial actinomycosis [64], *Balantidium coli* infection [65], and in non-gonococcal urethritis [66, 67]. Intramuscular preparations in doses of 50-200 mg have given good results in systemic infections [68, 69]; subcutaneous route also employed in infants [70]. Meningitis caused by *H. influenzae* or *N. meningitidis* has responded favorably to i.m. or i.v. administration of the antibiotic, with or without sulfadiazine [71, 72]. Topical therapy is effective in a variety of ocular infections, including trachoma, and in various skin infections [61, 73, 74, 78]; good results also obtained in vaginitis caused by *Trichomonas vaginalis* [75]. Little or no evidence that this (or other) antibiotic is of direct value in measles, mumps, common cold, viral hepatitis, varicella, smallpox, viral encephalitis, influenza, or lymphocytic choriomeningitis [45, 47]. Ineffective in mumps orchitis [77]. Oral medication with this or other broad spectrum antibiotics failed to influence the course of the following dermatoses: herpes simplex, lichen planus, plantar warts, pityriasis dermatitis, herpeticiformis, and discoid eczema [128]. Oral therapy with oxytetracycline or other antibiotics was of no value in Reiter's syndrome [167].

VETERINARY Intramammary infusions of value in bovine mastitis [79, 83]. Useful in control of bovine anaplasmosis [80]; in experimental anaplasmosis in splenectomized calves, the numbers of *Anaplasma marginale* in the red cells were decreased following therapy [144]. Intratracheal and intrathoracic injections of value in treating infectious rhinotracheitis and chronic pneumonia in cattle [145]. Preliminary trials indicate intravenous therapy with 0.5-1.0 g effective in tick-borne fever in bovines [146]. Good clinical responses in strangles and upper respiratory diseases in equines, pneumo-enteritis complex and metritis in cattle, and necrotic enteritis in swine [94]. Intramuscular injection of a single 1 g dose in nursing sows successfully controlled peracute gastroenteritis (scours), characterized by a profuse diarrhea, in their baby pigs. Presumably these doses gave adequate therapeutic levels in the milk. [147] Oxytetracycline or penicillin at levels of 15 mg/lb body weight, failed to protect weanling pigs against swine erysipelas experimentally induced by intradermal injection of cultures of *Erysipelothrix rhusiopathiae* [148]. Oral doses of 50-160 mg/kg were highly effective in prophylaxis of an artificially induced enzootic (virus) pneumonia in pigs [149]. Preliminary trials indicate value of oral therapy in controlling contagious pleuropneumonia in goats [129]. Experimental infections with *Neorickettsia helmintheca* (salmon poisoning) in dogs responded to oral therapy [150]. Favorable results in canine practice in pneumonia and wound infections [91, 92]. Oral medication in cats useful for control of feline pneumonitis and infectious panleucopenia [151]. Useful in control of chronic respiratory disease and infectious sinusitis in poultry [81, 82]. Effectively controlled natural psittacosis and ornithosis in parakeets and pigeons [84], and salmonellosis in poultry [93]. Was the most effective of several antibiotics tested against experimental fowl cholera; a single intramuscular injection of 25 mg/kg was curative when given 6-24 hours after infection of chickens with *Past. multocida*. [141] Experimentally induced infectious synovitis

in chicks, a disease of unknown etiology, was clinically controlled by feeding 200 ppm in feed for 2-3 weeks [135]. Feeding at levels of 200 g per ton of feed for 7-10 weeks did not markedly alter in chickens the clinical course of chronic respiratory disease associated with pleuropneumonia-like organisms [142]. Was ineffective in controlling an outbreak of blue comb disease in turkeys, a disease of undetermined etiology [143].

ACUTE TOXICITY LD₅₀ in mice, 178 mg/kg, i.v.; 650-892 mg/kg, s.c.; 6696-7200 mg/kg, oral. LD₅₀ in rats, 260 mg/kg; in rabbits, approximately 75 mg/kg; in dogs, approximately 150 mg/kg, i.v. Liver and kidney function not affected by these doses. No effect on smooth muscle of isolated intestines or uteri of guinea pigs and rabbits; no effect on blood sugar level. I.v. injection in anesthetized dogs and cats had no effect on blood pressure. Rabbits tolerated intracisternal injection of 2 mg [85-87]. *In vitro*. Oxytetracycline and tetracycline, but not chlortetracycline, in tissue cultures in concentrations of 50 µg/ml had a growth-stimulating action on embryonic cardiac tissues of the chick. All three antibiotics were toxic to the fibroblasts in concentrations over 100 µg/ml. [152] Concentrations of 100-200 µg/ml in tissue cultures inhibited outgrowths of skin tissue [88]. Using the roller tube method of tissue culture, concentrations of 1250 µg/ml were required for partial inhibition of human skin explants [153].

CHRONIC TOXICITY Daily oral doses of 75-200 mg/kg for 6-8 weeks were well tolerated in mice, rats and dogs. In dogs, daily i.m. doses of 75 mg/kg for 77-90 days were non-toxic. [85] When incorporated in the diet at high levels (0.02-0.04% or approximately 20-25 mg/kg/da) and fed continually for 7-11 months, the average life span of rats was decreased by approximately 10% [90]. The antibiotic, like other tetracyclines, is poorly tolerated in guinea pigs and in hamsters. Oral doses of 50 mg/kg/da for 3 days in Syrian hamsters produced a frequently fatal diarrhea with necrosis of intestinal mucosa. This effect was largely prevented by concurrent administration of 125-500 mg/kg of sulfaguanidine. [154]

In man, daily oral doses of 15-30 mg/kg usually were well tolerated, although nausea, vomiting and diarrhea were noted in some patients, especially after higher dosages. Secondary infections with yeast-like organisms have occurred, particularly in the peri-anal region and on the mucous membranes of the vagina and lower rectum after therapy with broad spectrum antibiotics. Allergic reactions following topical use and other side effects have been occasionally reported. [45, 61, 95, 96, 124] Continued topical use of dermatological preparations containing 3% of the antibiotic is associated with a relatively low index of sensitization, in contrast to the sulfonamides, penicillin, and streptomycin [155].

RESISTANCE Resistant variants did not readily develop *in vitro*. Following 40 transfers in antibiotic, a 4 to 64-fold increase developed in some strains. [13] In clinical experience, resistant strains of *M. pyogenes* var. *aureus* have emerged in considerable numbers, although this has not become a problem with other bacteria. Organisms developing resistance generally exhibit cross resistance to other tetracycline antibiotics. [101-103, 113]

ABSORPTION AND EXCRETION Readily absorbed after oral or parenteral administration, with wide distribution in the tissues and body fluids. In rabbits, single oral doses of 500 mg/kg produced substantial levels in blood, skin, liver, kidneys, lungs, spleen, heart, brain, bile, urine and gastrointestinal tract. [97] In mice, antibiotic accumulated in the reticuloendothelial system with high concentrations in the liver and kidney, with lowest concentration in muscular, bone and nervous tissue [104].

In man, following single oral dose of 0.5-1.0 g, oxytetracycline produced serum concentration of 1-3 µg/ml, declining after 6 hours, and with peak urine levels of 300 µg/ml in approximately 4 hours. After 1.0-1.25 g, six hourly, a blood concentration of 4-8 µg was maintained. Antibiotic did not readily traverse the blood-brain barrier, but diffused through the placenta and into the pleural fluid at therapeutic levels. Appeared in the bile in concentrations of approximately 4-8 times that of the blood, and approximately 8% of the total ingested was recovered in active form in the urine in 24 hours. [97, 98, 100] Administration of i.m. preparations provided effective blood levels for approximately 8 hours [99].

MODE OF ACTION Action is primarily bacteriostatic, but may be bactericidal in very high concentrations [9]. Acts primarily on actively multiplying bacteria [105]. Experiments in leucopenic rabbits suggest this drug (also penicillin) may be bactericidal *in vivo* in absence of cellular and humoral defenses of host [112]. Interferes with synthesis or metabolism of protein in *M. pyogenes* var. *aureus* [107, 108]. Inhibits adaptive enzyme formation in *E. coli* growing in medium containing lactose [109]. Acts on phosphorylation systems by inhibiting acid-soluble organic P fraction [110]. Concentrations of 100-300 µg/ml inhibit oxidation of glutamate and thus the respiration of murine and epidemic typhus rickettsiae *in vitro* [106]. Antibacterial activity reversed by Mg⁺⁺ and other multi-valent cations [111].

ANIMAL NUTRITION Animal feeds containing supplements of this or other antibiotics have found wide usage for growth stimulation and improvement of feed efficiency. Good growth responses have been noted in pigs, young calves, lambs and poultry, and also in experimental animals. [114-119] When fed at levels ordinarily recommended for other species of animals, no growth improvement was noted in young rabbits fed a pelleted natural ration containing oxytetracycline or chlortetracycline [156]. (For additional data, see chlortetracycline.)

MISCELLANEOUS Showed stimulatory effect on seed germination of sorrel, cucumber and sweet corn [120]. Accelerated photosynthesis and induced an abnormal increase in sucrose in the alga, *Scenedesmus* [121]. Low concentrations highly effective in control of European foul brood, a bacterial disease of the honey bee, when dusted

232. OXYTETRACYCLINE (Concluded)

over brood frames [122]. Effective in prevention of bacterial spoilage of fish and meat [123]. Addition of approximately 250 mg to 5 gallons of aquarium water of value in treatment of certain diseases of tropical fishes, e.g., columnaris disease, furunculosis, gill disease, fin-rot and tail-rot [157]. Solutions containing 1 mg/ml were well tolerated over 24-hour periods by viviparous fish (guppies) [158]. Relatively high levels (300-500 mg per 14 g of wheat) of oxytetracycline and certain other antibiotics were lethal to several varieties of coleopterous stored-grain insects within 30-60 days [159]. The median lethal dose, by injection, in the German cockroach (*Blattella germanica*) was 90-165 μ g [160]. Oxytetracycline alone, or in combination with dihydrostreptomycin, when fed at levels of 0.2 g (in sugar water) per honeybee colony, effectively controlled European foul brood (probably caused by *Bacillus pluton*). Was less effective against diseased colonies when applied as a spray in a thin mist to the brood frames.[161] Intraperitoneal injection of 1-3 mg per lb body weight in beef cattle, sheep and hogs, 1-4 hours prior to slaughter, assured tissue levels which were adequate for preserving the meat and controlling spoilage [134]. Levels of 20 μ g/ml completely prevented crown gall development in tomato plants induced with *Agrobacterium tumefaciens* [162]. Foliage sprays with the antibiotic, especially in combinations with streptomycin, were highly effective in control of fireblight caused by *Erwinia amylovora* in apple and pear trees [163]. A combination of 1.5% oxytetracycline and 15% streptomycin was effective against a wide variety of plant pathogens and has been effectively used for controlling diseases of potato, tomato, apple, pear, pepper, walnut, and tobacco [164]. After darkening one cotyledon of a cucumber seedling, there is increased growth of that side of the hypocotyl; addition of oxytetracycline or leucomycin to the soil markedly increases the resulting curvature of the seedling.[165] Growth of wheat roots in distilled water was stimulated by addition of 0.1-3.2 ppm of crude oxytetracycline (502 μ g/mg). Injury to roots by higher concentrations of the antibiotic (10-32 ppm) was reduced by addition of calcium ions [166].

233. ANTIBIOTICS PA-114

SOURCE *Streptomyces olivaceus* [1].

NATURE PA-114 A: neutral.
B: weakly acidic [1].

MOLECULAR FORMULA AND WEIGHT PA-114 A: $C_{25}H_{31}N_3O_6$ or $C_{35}H_{42}N_4O_9$; 525 (roentgen ray); 546 (Singer); 469.5, 662.7 (calc.).[1]
B: $C_{52}H_{63}N_9O_{12}$ (proposed); 981 (roentgen ray); 1006 (calc.).[1]

CRYSTAL FORM AND COLOR PA-114 A: colorless, crystalline needles¹.
B: colorless tablets²; feathery needles³. [1]

MELTING POINT (°C) PA-114 A: 200 (d.).
B: 265 (d.).[1]

OPTICAL ACTIVITY PA-114 A: $[\alpha]_D^{25} = -207^\circ$.
B: $[\alpha]_D^{25} = -59.7^\circ$. [1]

UV ABSORPTION MAXIMA PA-114 A: 220-230, 275 $m\mu$ ⁴.
B: 260, 305 $m\mu$ ⁴. [1]

OTHER REACTIONS Synergistic effect when A and B are both present.

PA-114 A: positive $FeCl_3$ (green), neutral permanganate, Br in CCl_4 , Tollens, 2,4-dinitrophenylhydrazine, copper acetate; negative Fehling, Molisch, Millon, ninhydrin.

B: positive $FeCl_3$ (red), neutral permanganate, Br in CCl_4 ; negative Tollens, 2,4-dinitrophenylhydrazine, copper acetate, Fehling, Molisch, Millon, ninhydrin.[1]

BIOLOGICAL ACTIVITY In vitro. When tested individually, products A and B showed lower activity than their combination. The combination is primarily active against Gram-positive bacteria. Inhibits (μ g/ml) *Streptococcus pyogenes*, 0.08; *Erysipelothrix rhusiopathiae*, <0.19-0.39; *Micrococcus pyogenes* var. *aureus* (including strains resistant to penicillin, streptomycin, the tetracyclines, erythromycin, polymyxin, and carbomycin), <0.19-1.56; *Str. faecalis*, *Corynebacterium diphtheriae*, *C. pseudodiphtheriticum*, 0.39; *Diplococcus pneumoniae*, 0.39-6.25; *Bacillus subtilis*, *Clostridium perfringens*, *Cl. tetani*, 0.78; *B. anthracis*, 1.56; *Corynebacterium xerose*, *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *N. catarrhalis*, *N. meningitidis*, *Hemophilus pertussis*, *Mycobacterium smegmatis*, 3.12; *Mycobacterium* sp., 6.25; *Brucella bronchiseptica*, 12.5; *Aerobacter aerogenes*, 50-100; *Escherichia coli*, *Pseudomonas aeruginosa*, 100; *Proteus vulgaris*, *Salmonella typhosa*, *S. paratyphi*, *Klebsiella pneumoniae*, >100. *Candida albicans* and *Trichophyton sulfureum* resistant to 100 μ g/ml. In vitro activity not altered in presence of serum.[2]

In vivo. Good protection afforded in mice by 50 mg/kg, s.c., or 100 mg/kg, oral, against *Str. pyogenes* and *M. pyogenes* var. *aureus*. Less effective against infection with *D. pneumoniae*. When used individually, products A and B were practically inactive against *Str. pyogenes* infection. For in vivo activity, product A was more critical than B; approximately 5% of B in combination with A was required for optimal activity.[2]

/1/ From n-butylethyl ketone. /2/ From methanol. /3/ From toluene. /4/ Methanol.

TOXICITY Mice tolerated s.c. and oral doses of 200 mg/kg.[2]

ABSORPTION AND EXCRETION Poorly absorbed in rabbits, with no detectable plasma levels following oral dosage of 100 mg/kg. Intramuscular dosage of 200 mg/kg produced blood levels of approximately 1 µg/ml in 1-5 hours, dropping to 0.2 µg/ml in 7 hours. In rats, oral doses of 100 mg/kg produced peak blood levels of 0.1 µg/ml in 1-3 hours.[2]

234. PALITANTIN

SOURCE *Penicillium palitans* [1].

NATURE Unsaturated dihydroxyaldehyde [1].

MOLECULAR FORMULA AND WEIGHT $C_{14}H_{22}O_4$ [1, 2]; 256 (cryo.); 254 (calc.).[1]

CRYSTAL FORM AND COLOR Colorless needles [1].

MELTING POINT (°C) 163 [1].

OPTICAL ACTIVITY $[\alpha]_{5461}^{23} = +4.40^1$ [2].

SOLUBILITY s. hot water, alcohol, chloroform; sl. s. cold water, ether.[1]

OTHER REACTIONS Closely associated with, and structurally related to, frequentin; positive Schiff; reduces silver oxide; readily oxidized by potassium mercuriodide to the corresponding acid.[1, 3]

235. PATULIN

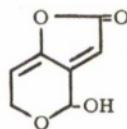
(Clavacin, Clavatin, Claviformin, Expansine, Penicidin)

SOURCE A variety of *Penicillium* spp and *Aspergillus* spp [1-4, 9, 10]; by synthesis [28].

NATURE Neutral [3].

MOLECULAR FORMULA AND WEIGHT $C_7H_6O_4$ [2, 4, 5, 7]; 169 (Rast); 154 (calc.).[2]

STRUCTURE



[8]

CRYSTAL FORM AND COLOR Colorless, rhomboid plates or prisms [1-3, 5].

MELTING POINT (°C) 111-112 [3].

OPTICAL ACTIVITY Inactive [1, 3, 5].

UV ABSORPTION MAXIMUM 276 mµ [2, 7].

SOLUBILITY s. water, alcohol, acetone, chloroform, ether, dilute alkali; i. petroleum ether, benzene.[1, 5]

STABILITY Thermostable; rather alkali labile.[1, 3]

OTHER REACTIONS Negative $FeCl_3$, Schiff; red color with alkali; yellow with dilute ammonia, piperidine, asparagine, amino acids, peptones without loss of activity; loss on repeated crystallization; reduces ammoniacal $AgNO_3$, Fehling, $KMnO_4$; yellow crystals with 2,4-dinitrophenylhydrazine; inhibited by serum, cysteine.[1, 4-6]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli*, *Micrococcus pyogenes* var. *aureus* [2, 5].

BIOLOGICAL ACTIVITY Active against Gram-positive and Gram-negative bacteria, fungi. In vitro. Inhibits *Sarcina lutea* in dilution of 1:500,000; *Salmonella typhosa*, *S. choleraesuis*, *S. paratyphi*, *S. typhimurium*, *Proteus vulgaris*, 1:80,000-1:400,000; *Bacillus cereus*, *B. megatherium*, *B. mycoides*, *B. subtilis*, 1:100,000-1:200,000; *S. enteritidis*, *S. schottmuelleri*, *Shigella dysenteriae*, *Sh. paradysenteriae*, *Pseudomonas aeruginosa*, *Aerobacter aerogenes*, *E. coli*, *Neisseria catarrhalis*, *Diplococcus pneumoniae*, *M. pyogenes* var. *aureus*, *Streptococcus pyogenes*, *Str. viridans*, 1:33,000-1:80,000.[1, 4, 11-13] Fungi: *Trichophyton mentagrophytes*, *Candida albicans*, 1:2500-1:5000 [14]. *Microsporium audouini*, *Epidermophyton cruris*, *Trichophyton* spp, *Microsporium* spp,

/1/ c, 0.8 chloroform.

235. PATULIN (Concluded)

1:40,000-1:160,000 [15]. Phytopathogens: *Pythium ultimum*, 1:800,000; *Phytophthora erythroseptica*, 1:320,000; *Rhizoctonia solani*, *Stereum purpureum*, *Claviceps purpurea*, 1:20,000-1:80,000; *Verticillium dahliae*, *Sclerotinia sclerotiorum*, *Rhizoctonia crocorum*, *Penicillium digitatum*, 1:5000.[16] Dilution of 1:50,000 markedly stimulated cell proliferation, migration of leukocytes, and inhibited carcinoma cells in tissue culture [17]. Solutions of 1 mg/ml destroyed viability of sarcoma 180 and a mouse melanoma, but had little or no effect in vivo [18]. Inactivated tetanus toxin [19]. Dilution of 1:1,000,000 lethal to *Chilomonas paramecium* [2].

In vivo. No activity in mice infected with *Salmonella schottmuelleri* [20]; inactive against experimental infections with *M. pyogenes* var. *aureus*, *Str. pyogenes*, *D. pneumoniae*, *Corynebacterium diphtheriae*, *Clostridium perfringens*, *Salmonella typhimurium*, *Mycobacterium tuberculosis*, *Leptospira icterohemorrhagiae*, and the viruses of vaccinia, influenza and herpes [21]. Daily i.p. doses of 2 mg/kg for 5 days had a suppressive effect on Ehrlich ascites tumor in mice [29]. No activity against *Plasmodium gallinaceum* in chicks [22].

CLINICAL Topical use in common cold gave indifferent results [23]. Ointment of slight value in skin infections [21].

PHYTOPATHOLOGY Solution containing 1:20,000 patulin failed to control *Ustilago tritici* infection of wheat [24].

ACUTE TOXICITY LD₅₀ in mice, approximately 25-35 mg/kg, i.v.; 10-15 mg/kg, s.c.; 35 mg/kg, oral. LD₁₀₀, 5-10 mg/kg, i.p.[1, 4, 11, 23, 25] Marked antidiuretic effect in cats; sublethal doses produced severe pathological changes in viscera and tissues [2, 23, 25]. *In vitro*. Dilution of 1:800,000 toxic to leukocytes [1]. Concentrations as low as 2 µg markedly altered morphology and phagocytic activity of polymorphonuclears and macrophages. This toxic effect was partially inhibited by cysteine HCl.[27]

PHYTOTOXICITY Dilution of 1:20,000 toxic to wheat embryo [24]; highly toxic to various plant cells in concentrations >1:200,000; inhibited growth of maize roots at 1:1,000,000.[26] Concentration of 60 µg/ml lethal to tomato plants [30].

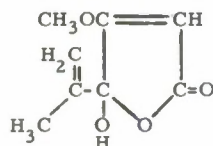
236. PENICILLIC ACID

SOURCE A variety of *Penicillium* spp and *Aspergillus* spp [1, 2, 5-7]; by synthesis [3].

NATURE Monobasic acid [1].

MOLECULAR FORMULA AND WEIGHT C₈H₁₀O₄ [1, 2]; 169-172 (found); 170 (calc.).[1]

STRUCTURE



[4]

CRYSTAL FORM AND COLOR Large, colorless rhombic or hexagonal plates [1].

MELTING POINT (°C) Hydrate 64-65 [1]. Anhydrous: 86-87.[3]

OPTICAL ACTIVITY Inactive [1].

SOLUBILITY s. hot water, alcohol, ether, benzene, chloroform; i. petroleum ether.[1]

STABILITY Stable [2].

OTHER REACTIONS No color with FeCl₃ in cold, orange-brown when heated; reddish-purple with strong ammonia on standing; no color with concentrated H₂SO₄, NaNO₂, Fearon's nitrochromic acid reagent; negative 2,4-dinitrophenylhydrazine; gives iodoform reaction with hypoiodite solution.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*; *Escherichia coli*. [2]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *E. coli* in dilution of 1:500,000; *Shigella dysenteriae*, *Proteus vulgaris*, *Vibrio comma*, *M. pyogenes* var. *aureus*, *Bacillus anthracis*, 1:50,000-1:100,000; *Salmonella enteritidis*, *S. paratyphi*, *S. typhimurium*, *S. typhosa*, 1:33,000. *M. citreus*, *Streptococcus viridans* not sensitive to 1:2000.[2] Plant pathogens: *Xanthomonas malvacearum*, *X. campestris*, 1:280,000-1:320,000; *Erwinia carotovora*, 1:160,000. Phytopathogenic fungi: *Pythium ultimum*, 1:5000; *Alternaria citri*, *Botrytis cinerea*, *Myrothecium roridum* not sensitive to 1:5000.[8]

236. PENICILLIC ACID (Concluded)

TOXICITY LD₅₀ in mice, 110 mg/kg, s.c.; 250 mg/kg, i.v.; 600 mg/kg, oral. In rats, antibiotic had antidiuretic effect, and weak digitalis-like action on heart.[9] 1:2000 free acid (but not 1:1000 neutral salt) lethal to tadpoles [5].

237. PENICILLINS

SOURCE *Penicillium notatum* (Westling) [1]; *Penicillium* spp, *Aspergillus* spp.

NATURE Strong monobasic carboxylic acids.

MOLECULAR FORMULA AND WEIGHT F = C₁₄H₂₀O₄N₂S.

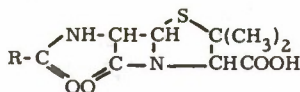
G = C₁₆H₁₈O₄N₂S.

K = C₁₆H₂₆O₄N₂S.

X = C₁₆H₁₈O₅N₂S.

331 (found); 333 (calc. -ion only).

STRUCTURE



F: R = CH₃-CH₂CH=CH-CH₂-

G: R = CH₂-

K: R = CH₃(CH₂)₆-

X: R = HO CH₂-

CRYSTAL FORM AND COLOR Colorless prisms.

MELTING POINT (°C) Penicillin F, Na salt: 204-205 (d.).

G, Na salt: 215 (d.).

X, Na salt: 228-235 (d.).

OPTICAL ACTIVITY Penicillin F: [α]_D²⁰⁻²⁵ = +276° to 316°¹.

G: [α]_D²⁵ = +305°¹, +301°².

K: [α]_D²⁵ = +258°³.

X: [α]_D = +267°⁴.

UV ABSORPTION MAXIMA Penicillin G: 252, 257.5, 264 mμ.

F, K: no characteristic bands.

X: 278 mμ.

V: 268, 274 mμ⁵; 270, 276 mμ⁶. [5]

SOLUBILITY Acids: s. alcohols, ketones, ethers, esters, aromatic hydrocarbons; sl. s. water; i. aliphatic hydrocarbons. Na salts: s. water, methanol, ethanol; sl. s. dry butanol, ketones, ethyl acetate.

STABILITY Stable in aqueous solution when pure, unstable when impure; labile to acids, alkalis, heat, penicillinase. Penicillin V: More stable at acid pH than G [5].

OTHER REACTIONS Free acids hygroscopic, rapidly inactivated unless completely dry; inactivated by heavy metals; precipitated from solution by aliphatic hydrocarbons; Na salts inactivated in glacial acetic acid, primary alcohols.

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*. Colorimetric [2]. Iodometric [3, 6]. Penicillinase [4]. Penicillin V: inactivation at pH 2⁷ [6].

BIOLOGICAL ACTIVITY *In vitro*. In general, penicillin is highly active against Gram-positive bacteria. Although resistant strains are occasionally encountered, most strains of the following genera are sensitive to very low concentrations: *Streptococcus*, *Micrococcus*, *Diplococcus*, *Clostridium*, *Corynebacterium*, *Bacillus*; also *Actinomyces*. Species of *Treponema*, *Borrelia*, and *Leptospira* are highly sensitive. Strains of *Hemophilus* and *Neisseria* are sensitive, but the majority of strains of other Gram-negative bacteria are not: *Aerobacter*, *Escherichia*, *Klebsiella*, *Pasteurella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Shigella* and *Vibrio* spp. Inactive against *Mycobacterium* spp, pleuropneumonia-like organisms, yeasts, fungi, viruses, rickettsiae, and protozoa. A growing increase in penicillin-resistant strains of *M. pyogenes* isolated from hospital patients and personnel; recent surveys indicate the incidence of these resistant strains may be well over 50% of the total isolates.

/1/ c, 0.821 water. /2/ c, 2 water. /3/ c, 0.43 water. /4/ c, 0.525 water. /5/ Water. /6/ Chloroform. /7/ To differentiate V from G, using *Bacillus subtilis* as test organism.

In vivo. Activity in experimental infections in general follows the *in vitro* antimicrobial spectrum.

CLINICAL For systemic treatment, penicillin is administered almost entirely by *i.m.* injection, or, much more rarely, by the oral route. Other methods are seldom used. For highly sensitive organisms, systemic therapy by spray inhalation is practicable. When employed orally, much larger doses are generally administered (usually 5-6 times the average *i.m.* dose) in view of destruction in the digestive tract as well as incomplete absorption. Oral medication is generally regarded as an uncertain therapeutic procedure except when administered in the form of the complex salt, benzathine penicillin G. Penicillin is indicated in a wide variety of infections caused by susceptible organisms. It is also of established value in veterinary practice. (See general references for detailed information on Penicillin F, G, K, O, V, X.)

TOXICITY Crystalline penicillin G is essentially non-toxic in animals, with the exception of guinea pigs. Guinea pigs are peculiarly sensitive to penicillin (and certain other antibiotics); doses as small as 7000 units/kg may produce anorexia, cachexia and finally death within a few days. Doses as high as 9,800,000 units, or 5.93 g/kg, *i.v.*, were tolerated in mice.

In man, tremendous doses of penicillin G are tolerated. One report describes an average daily dose of >86,000,000 units for a 28-day period in an individual, without obvious untoward reactions. Although penicillin G does not produce organic injury, it has considerable capacity in producing sensitization. Sensitivity reactions, varying from mild erythema or hives to severe serum sickness, dermatitis exfoliativa, and even fatal anaphylactic shock, have been reported. Topical application is seldom recommended because this method is most likely to produce sensitization. Penicillin O (allylmercaptomethyl penicillin) is clinically as effective as G and less likely to cause sensitivity or allergic reactions after *i.m.* injection. Approximately 90% of patients sensitive to G will tolerate penicillin O.

RESISTANCE Development of resistance against penicillin has taken on proportions of a serious clinical problem with *Micrococcus pyogenes* only. The clinically isolated resistant strains are generally penicillinase producers, in contrast to the resistance induced *in vitro* by repeated exposure to the antibiotic which is temporary and not associated with penicillinase production.

ABSORPTION AND EXCRETION Penicillin does not enter into brain, nerve, bone and certain other tissues in appreciable amounts. When renal function is normal, approximately 90-100% of crystalline penicillin G appears in the urine a few hours after *i.m.* administration; approximately 40-70% of this is biologically active and the remainder inactive metabolites. It is also excreted in the bile, with small amounts in the feces and little or none in the saliva, milk, sweat or tears. The rapid urinary excretion has necessitated frequent doses of penicillin G in order to maintain effective blood levels. Methods developed for decreasing this excretion rate include the use of *p*-aminobenzoic acid, *p*-aminohippuric acid, carinamide, probenecid and other agents. More widely used method for obtaining sustained blood and urine concentrations has been the injection of small particulate procaine G; because of its low solubility following *i.m.* administration, detectable concentrations are usually found for 8-12 hours in the blood and as long as 72 hours in the urine. Benzathine penicillin (N, N'-dibenzylethylenediamine dipenicillin G), a recently developed complex salt of penicillin, is very poorly soluble and produces therapeutic blood concentrations which are sustained for as long as 3 weeks after a single *i.m.* injection. Because of its limited solubility in the stomach, it is not highly susceptible to destruction by gastric juices. When administered orally in adequate doses of 6-8 hour intervals, it provides effective blood levels. Another recently developed ester, penicillin penethamate hydriodide (diethylaminoethyl ester penicillin G hydriodide), following *i.m.* administration produces fairly high tissue concentrations in the lung and lymph tissues; also gives higher cerebrospinal fluid concentrations than other penicillins. The recently developed penicillin V (phenoxymethylpenicillin) after oral administration produces blood concentrations considerably higher than those obtained with comparable doses of penicillin G, and twice as much penicillin V as penicillin G is excreted in active form. The higher blood levels obtained with product V are attributed to its greater stability than G under acid conditions.[7]

MODE OF ACTION Bacteriostatic and slowly bactericidal. Penicillin inhibits assimilation of glutamic acid and other amino acids by bacterial cells; has been postulated that it interferes with nucleic acid metabolism.

238. PHAEOFACIN

SOURCE *Streptomyces phaeofaciens* [1].

SOLUBILITY *s.* ethyl acetate, ethanol, acetone, benzol; *sl. s.* ether, petroleum ether; *i.* water.[1]

OTHER REACTIONS Positive $FeCl_3$; negative biuret, Millon, ninhydrin, Molisch, Tollens, Sakaguchi.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi: *Trichophyton* spp, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Achorion gypseum*, *Torula utilis*, *Penicillium chrysogenum*, *Trichosporon beigelli*, 0.7-6.0 $\mu g/ml$. *No-cardia asteroides* also sensitive. No activity against bacteria.[1, 2]

TOXICITY LD_{100} in mice, approximately 200 mg/kg, *i.p.* [1, 2].

SOURCE *Streptomyces griseus* [1].

FORM AND COLOR Light yellow, amorphous, hygroscopic powder [1].

SOLUBILITY s. water, methanol, ethanol; i. acetone, ether, benzene, chloroform, petroleum ether.[1]

STABILITY Thermostable at pH 3, less so above [1].

OTHER REACTIONS Negative FeCl_3 , biuret, Millon, ninhydrin, Lassaigne's nitrogen; reacts with picric acid, Reinecke's salt, methyl orange.[1]

QUANTITATIVE DETERMINATION Microbiological: Cholera phage C [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Klebsiella pneumoniae*, 3; *Micrococcus pyogenes* var. aureus, *Escherichia coli*, 12.5; *Bacillus subtilis*, 25; *Mycobacterium smegmatis*, 50; *B. mycoides*, *Pseudomonas aeruginosa*, >1000. High activity against bacteriophages: 37 out of 59 (including phage C of *Vibrio comma*, *Ps. aeruginosa* phage 2A, and phage of *Streptomyces griseus*) inactivated within 15 minutes by concentrations of 10 units/ml.[1] Active in vitro against viruses of vaccinia, herpes simplex, rabies; slight activity against Theiler and Lansing strains of poliomyelitis; no activity against viruses of lymphogranuloma venereum and influenza (PR-8 strain).[3] Concentration of 5 mg/ml inhibited Y-SK poliomyelitis virus in tissue cultures; also inhibited influenza A virus in chick embryo.[2] Spirochetes and protozoa: *Borrelia duttoni*, *Plasmodium berghei*, *Trypanosoma equiperdum* sensitive in vitro [3].

TOXICITY LD_{100} in mice, 31 mg/kg, i.p.; 500 mg/kg, s.c.[1] Toxic when tested in mice infected with poliomyelitis or swine influenza virus [2].

240. PHALAMYCIN

SOURCE A variant of *Streptomyces noursei* [1].

NATURE Neutral [1].

FORM AND COLOR Yellow amorphous powder [1].

SOLUBILITY s. lower aliphatic alcohols, esters, chloroform, acetone; sl. s. benzene, water.[1]

STABILITY Stable at pH 2.5-7 [1].

OTHER REACTIONS Negative biuret, ninhydrin, Sakaguchi, Molisch, Millon, FeCl_3 ; slight reduction of Benedict's solution; decolorizes Br water and KMnO_4 ; produces small amount of Prussian blue with Palet's reagent; slight UV inflection between 2930 and 3160 Å.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Diplococcus pneumoniae*, <0.4-0.8; *Micrococcus pyogenes* var. aureus, *Streptococcus* spp, 0.8-8.9; *Corynebacterium* spp, <0.4-4.4; *Bacillus subtilis*, *Mycobacterium tuberculosis*, *Sarcina lutea*, 0.8; *B. anthracis*, 16. *Nocardia* sp sensitive to 6 $\mu\text{g/ml}$. [1]

In vivo. Crude preparations gave protection against *Str. pyogenes* in mice.[1]

TOXICITY LD_0 in mice, >116 mg/kg, s.c.; >30 mg/kg, i.p.[1]

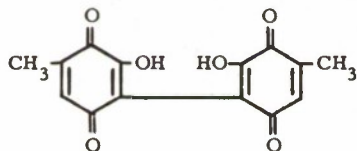
241. PHENICIN
(Phoenicin)

SOURCE *Penicillium phoeniceum* [1]; *P. rubrum* [4].

NATURE Dibasic acid pigment [2].

MOLECULAR FORMULA $\text{C}_{14}\text{H}_{10}\text{O}_6$ [1-3].

STRUCTURE



[3]

CRYSTAL FORM AND COLOR Long, rectangular, yellow-brown tablets [1,2].

241. PHENICIN (Concluded)

MELTING POINT (°C) 229-231 [1, 2].

SOLUBILITY s. chloroform, acetic acid, warm ethanol; sl. s. water.[1, 2]

OTHER REACTIONS Yellow, red or violet color depending on pH; intense violet color in alcoholic solution in presence of FeCl₃; released I from KI; decolorized by sodium hydrosulfite.[1, 2] Closely related to fumigatin and spinulosin [4].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Corynebacterium xerose*, *Micrococcus pyogenes* var. *aureus*, *Mycobacterium phlei* [1].

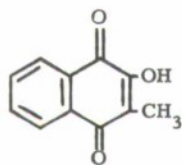
242. PHTHIOLCOL
(3-Hydroxy-2-methyl-1,4-naphthoquinone)

SOURCE *Mycobacterium tuberculosis* [2].

NATURE Pigment [1].

MOLECULAR FORMULA C₁₁H₈O₃ [1].

STRUCTURE



CRYSTAL FORM AND COLOR Bright yellow prisms [1].

MELTING POINT (°C) 173-175 [1].

SOLUBILITY s. organic solvents; i. water, petroleum ether. Salts: s. water, alcohol, acetone.[1]

OTHER REACTIONS An isomer of plumbagin; volatile with steam; deep red salts with alkalis and strong bases; intense red solutions in alkali or bicarbonate.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Streptococcus pyogenes*, *Diplococcus pneumoniae*, *Bacillus anthracis* in dilution of 1:5000; *Micrococcus pyogenes* var. *aureus*, *Str. salivarius*, *Corynebacterium diphtheriae*, *Escherichia coli*, *Shigella paradysenteriae*, 1:2000; *Salmonella typhosa*, *Neisseria catarrhalis*, 1:1000.[2]

243. PHTHIOMYCIN

SOURCE *Streptomyces luteochromogenes*, n. sp [1].

FORM AND COLOR White amorphous powder [1].

UV ABSORPTION MAXIMA 268 mμ¹; 282 mμ². [1, 2]

OTHER REACTIONS Resembles viomycin; positive Sakaguchi, ninhydrin, negative Molisch, maltol, FeCl₃. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits (μg/ml) *Mycobacterium tuberculosis*, 10->50; *Myco. phlei*, 6-10; *Myco. smegmatis*, 10; *Mycobacterium* spp, *Bacillus anthracis*, *B. subtilis*, 25.[1, 2]

In vivo. Daily s.c. doses of 2-6 mg for 29 days reduced morbidity in mice infected with *Myco. tuberculosis* [2].

TOXICITY LD₅₀ in mice, 505-600 mg/kg, i.v. [1, 2].

244. PICROMYCIN

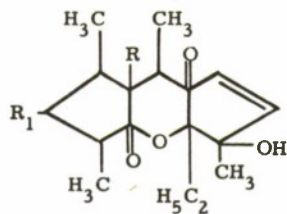
SOURCE *Streptomyces felleus*, n. sp [1].

NATURE Basic [2, 3].

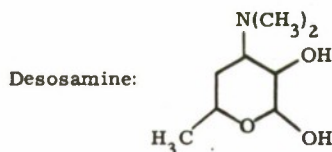
MOLECULAR FORMULA AND WEIGHT C₂₅H₄₃O₇N [1-3]; 458 (Rast); 469 (calc.). [1, 3]

/1/ 0.1 N HCL. /2/ 0.1 N NaOH.

STRUCTURE



R = desosamine group; R₁ = H
 or R₁ = " " ; R = H



[8]

CRYSTAL FORM AND COLOR Colorless; "coffin-cover shaped" [1, 3] ; needles [8] .

MELTING POINT (°C) 169-170 [1, 3] ; 160-162¹ [8] .

OPTICAL ACTIVITY $[\alpha]_D^{24} = -50.2^{\circ 2}$, $+8.2^{\circ 3}$ [1-3] ; $[\alpha]_D^{20} = -33.5^{\circ 4}$ [8] .

UV ABSORPTION 225 m μ [8] .

SOLUBILITY *s.* most organic solvents, dilute acids; *sl. s.* water, petroleum ether, carbon disulfide, alkali.[1, 3]

STABILITY Thermolabile in dilute acid, alkali; thermostable in vacuo.[1, 2]

OTHER REACTIONS Bitter taste; negative ninhydrin, p-nitrophenylhydrazine, semicarbazide; forms amorphous picrate and picrolonate; dissolves in concentrated HCl to produce orange-red color that fades when diluted, forming flocculent precipitate; no methoxy groups present; negative Abderhalden reaction with ninhydrin after boiling with HCl; insoluble inactive degradation product obtained after heating the HCl at pH 8 for 12-14 hours at 60°C. Infrared: 2.93, 3.47, 3.54, 3.65, 5.74, 5.91, 6.12, 6.89, 7.28, 7.48, 7.61, 7.87, 8.41, 8.62, 9.07, 9.19, 9.31, 9.34, 9.44, 9.57, 9.78 μ . [1-3] Mild hydrolysis yields picrocin, C₈H₁₇O₃N₂, and chromycin, C₁₆H₂₄O₄, the lactone of an α -keto acid [7] .

BIOLOGICAL ACTIVITY In vitro. Inhibits (μ g/ml) Streptococcus pyogenes, Str. agalactiae, Str. faecalis, Diplococcus pneumoniae, Corynebacterium pyogenes, Clostridium spp, Mycobacterium tuberculosis, Bacillus anthracis, B. subtilis, Micrococcus pyogenes var. aureus, Pasteurella multocida, 0.1-3.0; Escherichia coli, Aerobacter aerogenes, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella spp, and fungi, 200-1000.[1, 4] Inhibits B. subtilis, 1:3,000,000 dilution; Myco. tuberculosis, 1:20,000; E. coli, 1:2000.[5] In vitro resistance not readily acquired after 10 passages in antibiotic-containing media [4] .

In vivo. No activity against Str. pyogenes, M. pyogenes var. aureus, D. pneumoniae; mouse pneumonitis virus in mice treated by s.c. or oral routes.[4]

CLINICAL Successfully used in topical application for skin infections in 170 cases [6] .

TOXICITY LD₁₀₀ in mice, 100 mg/kg, s.c.; 250 mg/kg, oral.[4] 150 mg/kg, i.v., lethal [1] .

245. PLEOCIDIN

SOURCE Streptomyces sp resembling S. lavendulae [1] .

FORM AND COLOR White hygroscopic powder [1] .

SOLUBILITY *s.* water, methanol, ethanol [1] .

STABILITY Most stable in aqueous solution at pH 4-6 [1] .

OTHER REACTIONS Resembles streptothricin [1] .

/1/ A sample crystallized four times from ethyl acetate had a melting point of 169.5-170. /2/ c, 6.3 chloroform. /3/ c, 3.5 ethanol. /4/ c, 2.071 chloroform.

245. PLEOCIDIN (Concluded)

QUANTITATIVE DETERMINATION Microbiological: *Proteus vulgaris* [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Bacillus subtilis*, *Mycobacterium tuberculosis*, *Salmonella typhosa*, 0.9; *Micrococcus pyogenes* var. *aureus*, *Klebsiella pneumoniae*, 1.9; *Pseudomonas aeruginosa*, 31.2; *Escherichia coli*, 62.5. Inhibits *Saccharomyces cerevisiae*, *Aspergillus niger*, 0.9.[1]

In vivo. No activity in mice infected with *Trypanosoma cruzi* [3].

PHYTOPATHOLOGY Low concentrations inhibited growth of *Tilletia caries* (wheat smut fungus) in vitro [4]. The antibiotic was readily absorbed by leaves of tobacco, tomato, and bean plants when applied as spray. Was transported down out of intermediate treated leaves and up stem to younger leaves, as well as downward to older untreated leaves. In some instances, translocation to roots occurred. The antibiotic caused injury to treated leaves in the form of necrotic spots.[5]

TOXICITY Highly toxic to mice. LD_{50} , 3 mg/kg, i.p.; approximately 120 mg/kg, oral. Repeated topical application irritating to rabbit eye.[1]

246. PLEOMYCIN

SOURCE *Streptomyces pleofaciens*, n. sp [1].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{14}\text{H}_{12}\text{O}_8$; 303 (found).[1]

CRYSTAL FORM AND COLOR Acid form: glistening, colorless rectangular plates [1].

MELTING POINT ($^{\circ}\text{C}$) Acid form: 235 (uncorr.) [1].

UV ABSORPTION MAXIMA 270, 330-340 $\text{m}\mu$ [1].

SOLUBILITY s. methanol, ethanol, ethyl acetate, ether, benzene. Alkaline salts: s. water.[1]

OTHER REACTIONS Sublimes at 200°C or lower in vacuo, but retains biological activity; C, 54.63; H, 3.94; O, 41.43. Infrared: 2.90, 3.23; 3.43, 3.54, 6.29, 6.59, 6.85, 7.08, 7.28, 7.44, 7.80, 7.88, 8.20, 8.48, 8.60, 9.60, 10.16, 12.24, 12.62, 13.80, 15.07 μ . [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Bacillus subtilis*, *Micrococcus pyogenes* var. *aureus*, *Escherichia coli*, *Proteus vulgaris*, *Salmonella typhosa*, *Pseudomonas aeruginosa*, 6.25; *Mycobacterium tuberculosis*, 10-12.5. *Aspergillus niger* inhibited by 100 $\mu\text{g/ml}$. [1]

TOXICITY LD_{50} in mice, 35 mg/kg, i.p. Topical application of 1 mg/ml solution induced corneal opacity in rabbit eye.[1]

247. PLEUROMUTILIN
(Drosophilin B)

SOURCE *Pleurotus mutilus* [2].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{22}\text{H}_{34}\text{O}_5$ [1, 2]; 310 (found); 378 (calc.). [2]

CRYSTAL FORM AND COLOR White crystals [2].

MELTING POINT ($^{\circ}\text{C}$) 170-171 [1].

OPTICAL ACTIVITY $[\alpha]_D^{24} = +20^{\circ}$ [1].

UV ABSORPTION MAXIMA 290 $\text{m}\mu$; end absorption below 230 $\text{m}\mu$. [1, 2]

SOLUBILITY s. alcohol, acetone, chloroform, ether; sl. s. water; i. hexane.[2]

STABILITY Relatively stable [2].

OTHER REACTIONS Reduces Tollens; no reduction of ammoniacal AgNO_3 . [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Klebsiella pneumoniae*, *Mycobacterium smegmatis*, *Diplococcus pneumoniae*, *Streptococcus pyogenes*, *Micrococcus pyogenes* var. *aureus*, *Bacillus subtilis*, 0.5-16.0; *B. mycoides*, *Escherichia coli*, *Pseudomonas aeruginosa*, 125-500. Fungi not sensitive.[3] Active against influenza (PR-8) virus at 2 mg/ml, but inactive in chick embryo. No activity against poliomyelitis virus.[4]

/1/ In 0.13 M phosphate buffer. /2/ c, 3 absolute methanol.

247. PLEUROMUTILIN (Concluded)

In vivo. No activity in mice infected with *Str. pyogenes*; no suppression in development of sarcoma 180 in mice.[2] Daily i.p. doses of 80 mg/kg were ineffective against *Plasmodium gallinaceum* in chicks [5] .

TOXICITY LD₀ in mice, 50 mg/kg, i.v. and i.p. [3] .

248. PLEUROTIN

SOURCE *Pleurotus griseus* [1] .

NATURE Neutral compound [1] .

MOLECULAR FORMULA AND WEIGHT C₂₀H₂₂O₅; 343 (Rast); 342.4 (calc.).[1]

CRYSTAL FORM AND COLOR Orange, amber, yellow needles [1] .

MELTING POINT (°C) 200-215 (d.) [1] .

OPTICAL ACTIVITY [α]_D²³ = -20° [1] .

UV ABSORPTION MAXIMUM 250 mμ [1] .

SOLUBILITY s. acetone; less s. water, ethanol, ether, chloroform; i. or sl. s. dilute acids, dilute sodium carbonate, petroleum ether.[1]

STABILITY Thermolabile, especially at alkaline pH [1] .

OTHER REACTION Inactivated by light; negative FeCl₃; I liberated from acidified KI; blue color with KCN.[1, 2]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1] . Colorimetric [1, 2] . Fluorometric [2] .

BIOLOGICAL ACTIVITY In vitro. Inhibits (μg/ml) *Bacillus subtilis*, 0.2; *M. pyogenes* var. *aureus*, 0.8; *B. mycoides*, 1.6-3.0; *Photobacterium fischeri*, 6; *Mycobacterium smegmatis*, 32; *Myco. phlei*, >32; *Myco. tuberculosis*, >100; *Escherichia coli*, *Klebsiella pneumoniae*, 500->500.[1, 2]

In vivo. Daily i.p. doses of 100 mg/kg gave no protection in chicks infected with *Plasmodium gallinaceum* [4] .

TOXICITY Mice tolerated 24 mg/kg, i.v.; low solubility did not permit higher doses.[1]

249. POLYMYXINS

The trademark of Burroughs Wellcome & Co., Inc., for polymyxin B is Aerosporin.

SOURCE Various strains of *Bacillus polymyxa* [1, 9, 10] .

NATURE Basic polypeptides [2] .

MOLECULAR FORMULA AND WEIGHT Polymyxin B₁·5HCl: C₅₆H₁₀₄O₁₄N₁₆Cl₅; 1150 ± 10% (found).[7]
D·4HCl: C₅₀H₉₇O₁₅N₁₅Cl₄ (proposed); 1150 (found); 1144 (calc.).[5]
A, B, D, E: Average MW, 1250 (found) [8] .

CRYSTAL FORM Birefringent; no definite structure [3] .

MELTING POINT (°C) 228-235 (d.) [4, 5] .

OPTICAL ACTIVITY Polymyxin A HCl: [α]_D²⁰ = -42° [4] .
B HCl: [α]_D²⁵ = -75.7° [6] ; [α]_D²³ = -40° [5] .
B₁·5HCl: [α]_D²⁵ = -85.1° [7] .

UV ABSORPTION MAXIMA None characteristic [4] .

SOLUBILITY s. water, methanol; less s. higher alcohols; i. ether, esters, hydrocarbons, chlorinated solvents. Base: sl. s. water; i. alcohol.[4, 5]

STABILITY Thermo- and acid stable; alkali unstable.[4]

/1/ c, 0.59 chloroform. /2/ Water. /3/ c, I in 75% ethanol. /4/ c, 1.05 water. /5/ c, 2.33 in 75% ethanol.

OTHER REACTIONS Amino acid content:

| | <u>D-Leucine</u> | <u>Phenylalanine</u> | <u>L-Threonine</u> | <u>D-Serine</u> |
|-------------|------------------|----------------------|--------------------|-----------------|
| Polymyxin A | + | - | + | - |
| B | + | + | + | - |
| C | - | + | + | - |
| D | + | - | + | + |

Positive biuret, ninhydrin; negative Molisch, Sakaguchi, Pauly, Hopkins-Cole; precipitate with picric, flavianic, helianthic, Reinecke acids; amorphous materials with acetic, phenylacetic, oxalic, malic, benzoic, phthalic, cinnamic, succinic, naphthalene β -sulfonic acids. Polymyxin B separates by countercurrent distribution into B₁ and B₂; B₁ differs in that it contains isopelargonic acid (both contain α , γ -diaminobutyric acid, and amino acids shown above).[2, 4, 5, 7]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli* and other Gram-negative organisms [1, 3, 50, 52]. Precipitation as phosphotungstate [50].

BIOLOGICAL ACTIVITY Active mainly against Gram-negative bacteria. All polymyxins show essentially similar antibacterial spectra. In vitro. The majority of strains of the following are inhibited by concentrations of 0.02-5.0 $\mu\text{g/ml}$: *Aerobacter aerogenes*, *Alcaligenes* spp, *Brucella abortus*, *Br. bronchiseptica*, *Escherichia coli*, *Hemophilus influenzae*, *H. pertussis*, *Klebsiella pneumoniae*, *Neisseria catarrhalis*, *N. meningitidis*, *Pasteurella multocida*, *Past. pestis*, *Pseudomonas aeruginosa*, *Salmonella typhosa*, *S. paratyphi*, *S. schottmuelleri*, *S. enteritidis*, *Salmonella* spp, *Shigella dysenteriae*, *Sh. paradysenteriae*, *Sh. sonnei*, *Vibrio comma*. In general, the following require 10-50 $\mu\text{g/ml}$ for inhibition: *Clostridium perfringens*, *Corynebacterium diphtheriae*, *Bacillus subtilis*. Generally resistant, >50 $\mu\text{g/ml}$: *N. gonorrhoeae*, *Proteus* spp, *Streptococcus pyogenes*, *Streptococcus* spp, *Diplococcus pneumoniae*, *Micrococcus pyogenes* var. *aureus*, *Mycobacterium tuberculosis*. [11-19] Bovine strains of *Cryptococcus neoformans* sensitive to 25 $\mu\text{g/ml}$ [53]. Little or no activity against fungi, but polymyxins B and E in high concentration (125-250 $\mu\text{g/ml}$) inhibited *Trichophyton mentagrophytes*, *T. purpureum*, *Microsporium audouini*, *M. lanosum*, *Candida albicans*; products A and D less active. [20] Polymyxin B inhibited *Trichomonas vaginalis* at 125 $\mu\text{g/ml}$ [30].

In vivo. Polymyxins A, B, and D administered i.p. or s.c. gave good protection in mice infected with *S. typhosa*, *H. pertussis*, *K. pneumoniae*, and in chicks infected with *Past. multocida* and *S. gallinarum*. [3, 11, 13, 21, 24] A, B, C, D and E were all equally effective against *S. typhosa*, but against *H. pertussis* product D was less active [23]. Good protection in experimental plague (*Past. pestis*) and against *H. influenzae* in mice [34, 42]. Polymyxin B effective in experimental corneal ulcer induced with *Ps. aeruginosa* in rabbits [28]. No protection in mice infected with *S. typhimurium*, *Str. pyogenes*, *Erysipelothrix rhusiopathiae*, *Micrococcus pyogenes* var. *aureus* when treated with product A [21]. Polymyxin D ineffective in mouse infections with *Past. tularensis* and in guinea pigs infected with *Br. suis* [22]. No activity in *Borrelia anserina* infection (spirochetosis) in chicks [27], or in mice infected with *Trypanosoma cruzi* [29].

CLINICAL Early studies indicated that polymyxin D, in i.m. doses of 3-7 mg/kg/da for 3-20 days, gave promising results in *Aerobacter aerogenes* bacteremia, in pertussis, acute brucellosis, *K. pneumoniae* infection; evidence of renal toxicity noted. [25] Lower doses of products A and B were beneficial in pertussis and in infections with *E. coli* and *Ps. aeruginosa* [26]. The nephrotoxicity and neurotoxicity following i.m. administration has limited their general use in systemic infections. Polymyxin B shows least toxicity, and it is probable that impurities present in various lots may partially account for these effects [31]. Purer preparations of B (and more recently polymyxin E) appear to have been safely used for i. n. injection without evidence of nephrotoxicity and other side effects. *Ps. aeruginosa* infections (especially those of the urinary tract), which generally do not respond to therapy with other antibiotics, frequently respond to treatment with polymyxin B. The usual i.m. dosage range is 1.5-2.5 mg/kg/da and should not exceed 2.5 mg/kg/da, or in any case 200 mg/da. [32, 33, 36] Subconjunctival administration of polymyxin E has given good clinical response in ocular infections caused by *Pseudomonas* [35]. Oral therapy is of value in gastrointestinal infections caused by *Shigella* and *Pseudomonas* [37], and is highly effective in clearing carriers of *Sh. paradysenteriae*. No side effects were noted as a result of oral medication. [38] In preliminary trials, favorable results reported in *Ps. aeruginosa* meningitis following intrathecal injection of polymyxin B in doses of approximately 5 mg/da [39, 40]. For topical use, polymyxin B has been combined with oxytetracycline and other antibiotics, with favorable response in a wide variety of skin infections [31, 41]. The antibiotic is also of value when topically applied in corneal ulcers caused by *Ps. aeruginosa* [31].

ACUTE TOXICITY Polymyxin A, B, E: LD₅₀ in mice, 6-9 mg/kg, i.v.; 13-39 mg/kg, i.p.; 68-87 mg/kg, s.c. [21, 23] Polymyxin D: 12-18 mg/kg, i.v.; 24-77 mg/kg, i.p.; 160-230 mg/kg, s.c. [11, 42] Intracisternal injection of 0.6 mg/kg of A lethal to rabbits [24]. Dogs tolerated D in i.v. doses of 15 mg/kg; 25 mg/kg were lethal [42]. Little or no tissue injury at site of i.m. or s.c. injection of product E, as compared with some local reaction with B [23].

In vitro. In tissue cultures, polymyxin B sulfate partially suppressed growth of chick embryonic heart at concentrations of 300 $\mu\text{g/ml}$, with complete inhibition at 2500 $\mu\text{g/ml}$ [54]. The antibiotic has a fragmenting action on rat mast cells in vitro which is comparable to that of certain histamine liberators [55].

CHRONIC TOXICITY Renal toxicity noted in rats after repeated doses of polymyxin A and D; much less with B, least with E. Some protection against kidney damage in rats and dogs afforded by administration of DL-methionine. [23, 24] The protection afforded by methionine and S-methyl-cysteine against the nephrotoxicity induced by polymyxin A appears to be attributable to a replenishment of the supply of labile methyl groups [56].

In man, polymyxins A and D induced renal damage as evidenced by proteinuria, cylindruria and nitrogen retention; nausea and epigastric distress observed in a few patients [24, 39]. Polymyxin B appears to be fairly well tolerated following i.m. dosages of approximately 2.5 mg/kg/da, with minimal nephrotoxicity or other side effects in patients with normal kidneys [32, 33]. Oral doses are well tolerated [37, 38]. Topical use of dermatological preparations of polymyxin B is associated with a low index of skin sensitization, in contrast to penicillin, streptomycin, and the sulfonamides [57].

RESISTANCE In vitro resistance did not readily develop with strains of *E. coli*, *K. pneumoniae*, and *S. pullorum* [3, 11]. Development of resistance to polymyxin B is dependent upon the amino acid content of the culture medium [48].

ABSORPTION AND EXCRETION Polymyxins A, B, E were not absorbed in significant amount after oral administration. Following i.m. dosages in man or animals, measurable blood concentrations were maintained for 3-16 hours. Polymyxin A produced higher levels than B or E. After single parenteral injection, only a small fraction of the dose was excreted in the urine and none was detected in the bile.[23] No polymyxin D detectable in cerebrospinal fluid after i.v. or i.m. injection in dogs, or following i.m. administration in man [25, 39]. Serum concentrations of 1-8 µg/ml were observed in man after 2-4 mg/kg/da of polymyxin B in divided doses administered i.m., with peak levels $\frac{1}{2}$ -2 hours after injections, approximately 0.5-3.0 µg/ml after 6 hours, and detectable concentrations up to 12 hours.[43]

MODE OF ACTION Action essentially bactericidal, e.g., sterilization and partial lysis of cells of *E. coli* within 20 minutes of exposure [11, 12]. Forms water-insoluble products with ribonucleic acids, mononucleotides, certain phosphoamino lipids and related compounds; this may explain the ability of polymyxin to agglutinate certain bacteria.[44] In low concentration, antibiotic inhibits mycobacterial esterases similar to that observed with quaternary ammonium detergents, hence a detergent-like structure has been postulated [45]. Exposure to polymyxin causes release of soluble constituents from sensitive bacterial cells; has been suggested that polymyxin disorganizes structures within cell wall which maintain osmotic equilibrium.[46, 47] In vitro activity of polymyxins antagonized by magnesium ribonucleate, hence it has been suggested that presence of this substance in Gram-positive organisms may be a factor contributing to the selective action of this antibiotic [58]. Inhibition of *Ps. aeruginosa* was reversed when Mg^{++} , Mn^{++} , Ca^{++} , and $Fe^{++(+)}$ were added to the culture medium [59].

MISCELLANEOUS S. c. injection of polymyxin B or E in rats released skin histamine remote from the site of inoculation; when injected i.v. in dogs and cats this effect was much less marked.[51] Relatively high levels (300-500 mg per 14 lb of wheat) of polymyxin B and certain other antibiotics were lethal to several varieties of coleopterous stored-grain insects within 30-60 days [60]. Growth of wheat roots in water was stimulated by addition of 0.32-1.0 ppm of product B [61]. Root growth of young seedlings of barley and other species inhibited by immersion in solutions containing 5-100 ppm of this antibiotic; this inhibition was suppressed by an excess of calcium, probably by preventing absorption of the antibiotic.[62] Highly effective for control of microbial contamination in brewing industry [49].

250. POLYPEPTIN

Formerly named Circulin

SOURCE *Bacillus krzemieniewski*, a variant of *B. circulans* [4].

NATURE Basic polypeptide [1, 2].

MOLECULAR FORMULA AND WEIGHT $C_{56}H_{96}O_{13}N_{12}$ (proposed); 1100-1200 (found); 1145 (calc.).[3]

CRYSTAL FORM Triangular prisms¹ [1, 2].

MELTING POINT (°C) Sulfate: 235 (d.). Acetate: 160. Base: 176.[2]

OPTICAL ACTIVITY Sulfate: $[\alpha]_D^{20} = -93.3^\circ$ [1, 2].

UV ABSORPTION MAXIMA 252, 258, 264 mµ [1, 2].

SOLUBILITY Sulfate: s. ethylene glycol, pyridine, glacial acetic acid, allyl alcohol, phenol; briefly s. methanol, ethanol; i. anhydrous acetone, ether, chloroform, amyl acetate, benzene, carbon disulfide, petroleum ether.[2]

STABILITY Thermostable; less so in alkaline solution; base stable when dry.[1, 2]

/1/ From 65% ethanol; crystal form varies with solvents.

250. POLYPEPTIN (Concluded)

OTHER REACTIONS Positive biuret, ninhydrin; dialyzable; not inactivated by pepsin, trypsin, H_2S , $FeCl_3$; precipitated from water by dilute solution of I in KI; base precipitates in methanol; crystalline sulfate found to be 2 basic polypeptides with identical amino acid spectra (residues isolated: 3 L- α - γ -diaminobutyric acid, 1 L-threonine, 1 D-valine, 1 L-isoleucine; 2 L-leucine; 1 D-phenylalanine plus an unknown acid).[2, 3]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli* [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu g/ml$) *Bacillus subtilis*, 0.75; *Diplococcus pneumoniae*, *Streptococcus pyogenes*, *Clostridium histolyticum*, *Shigella dysenteriae*, 1.5; *Klebsiella pneumoniae*, 1.5-3.0; *E. coli*, *Salmonella typhosa*, *S. paratyphi*, *S. schottmuelleri*, *B. mycoides*, *Cl. perfringens*, *Cl. fallax*, 3; *Mycobacterium tuberculosis*, *S. typhimurium*, 4.5; *Pseudomonas aeruginosa*, 10. Fungi: *Epidermophyton floccosum*, *Blastomyces dermatitidis*, *Sporotrichum schenckii*, *Histoplasma capsulatum*, *Microsporium audouini*, 1.5; *Trichophyton rubrum*, *Candida albicans*, 3.[4]

TOXICITY LD_{50} in mice, 15 mg/kg, i.p. *In vitro*. Hemolytic for red blood cells.[4]

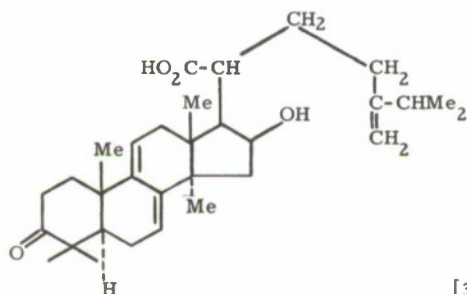
251. POLYPORENIC ACID C

SOURCE *Polyporus betulina* [1].

NATURE Triterpenoid acid [1].

MOLECULAR FORMULA AND WEIGHT $C_{31}H_{46}O_4$ [3]; 480 (equiv. wt. found).[1]

STRUCTURE



[3, 4]

CRYSTAL FORM Microcrystalline aggregates [1].

MELTING POINT ($^{\circ}C$) 285-290 (d.) [1].

OPTICAL ACTIVITY $[\alpha]_{5461}^{20} = +8.19^{\circ}$ [1].

SOLUBILITY s. pyridine, ethanol, hot glacial acetic acid, dioxane, chloroform, nitrobenzene; sl. s. acetone, ethyl acetate.[1]

OTHER REACTIONS Blue-violet with acetic anhydride and H_2SO_4 ; orange lower layer with chloroform and H_2SO_4 . [1]

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium* spp [2].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *Myco. phlei*, *Myco. smegmatis* in dilution of 1:640,000-1:1,280,000. Slight activity against *Micrococcus pyogenes* var. *aureus* and *Escherichia coli*. [2]

252. POLYPORIN

SOURCE *Polystictus sanguineus* [1].

NATURE Acidic [1].

SOLUBILITY s. dry ether, chloroform, ethyl acetate, absolute alcohol, acetone [1].

STABILITY Thermostable except in alkali and acid [1].

/1/ c, 5.1 pyridine.

252. POLYPORIN (Concluded)

OTHER REACTIONS Non-volatile; unaffected by pepsin, gastric juice [1].

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli*, *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *M. pyogenes* var. *aureus*, *Streptococcus pyogenes*, *Str. viridans*, *Salmonella typhosa*, *S. paratyphi*, *S. schottmuelleri*, *Shigella paradysenteriae*, *E. coli*, *Vibrio comma*. Virulent cultures of *S. typhosa* and *V. comma* following exposure to polyporin were rendered non-infective for guinea pigs.[1]

TOXICITY Non-toxic to guinea pigs and rabbits. Non-pyrogenic when administered i.m. in humans. In vitro. No hemolysis of red blood cells.[1]

CLINICAL Appeared beneficial in typhoid and other *Salmonella* infections and in cholera following oral doses of 3 ml every 4 hours for 7-10 days. Topical use gave good response in skin and ocular infections caused by micrococci and streptococci.[1,2]

253. PRIMYCIN

SOURCE An unidentified actinomycete [1].

MOLECULAR FORMULA AND WEIGHT $C_{19}H_{37}O_7N$ (proposed); 329.9 (ebull. in methanol); 391.5 (calc.).[1]

CRYSTAL FORM AND COLOR White microcrystals¹ [1].

MELTING POINT (°C) 166-168 (d.) [1].

UV ABSORPTION MAXIMA None characteristic [1].

SOLUBILITY s. methanol; less s. higher alcohols; sl. s. pyridine, glacial acetic acid, water; i. other solvents.[1]

STABILITY Thermostable [1].

OTHER REACTIONS C, 58.79; H, 9.56; N, 3.63, 3.58; aqueous solution sensitive to electrolytes; strongly surface active and adsorptive; first a yellow than a red color in concentrated H_2SO_4 ; no reduction of Fehling; no reaction with aldehyde reagents; positive Brunner-Pettenkoffer reaction; can be acetylated in pyridine, the product being inactive, but can be reactivated by splitting off acyl groups; partially inactivated by serum; more active in alkali than in acid, optimum pH 7.6-7.8.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *M. pyogenes* var. *aureus* at 0.02-0.06 $\mu g/ml$. Also active against other Gram-positive bacteria, including *Mycobacterium* spp. In vitro activity reduced by approximately 1/4 in presence of serum.[1]

TOXICITY LD_{100} in mice (route not stated), 2.5 mg/kg; in rats, 10 mg/kg. Following i.p. doses of 5 mg/kg in rabbits, detectable levels in serum were noted at 6 hours. In vitro. Non-toxic in tissue cultures [1].

CLINICAL Used topically with good results in superficial infections [1].

254. PROACTINOMYCINS

SOURCE *Nocardia gardneri* [1].

NATURE Basic [1].

MOLECULAR FORMULA AND WEIGHT Proactinomycin A: $C_{27}H_{47}O_8N$ (proposed); 445 (Rast).
B: $C_{28}H_{49}O_8N$ (proposed); 513 (Rast).
C: $C_{24}H_{41}O_6N$ (proposed); 322 (Rast).[2]

CRYSTAL FORM Proactinomycin A: short thick plates or prisms.
B: indefinite crystals.
C: amorphous.[2]

MELTING POINT (°C) Proactinomycin A: 168-169. B: 83-87.[2]

UV ABSORPTION MAXIMA Proactinomycin A: approximately 260 $m\mu^2$.
B: approximately 265 $m\mu^2$.
C: approximately 300 $m\mu^2$.

/1/ From methanol-butanol. /2/ Ether.

254. PROACTINOMYCINS (Concluded)

SOLUBILITY Base: s. ether, amyl acetate, benzene, carbon tetrachloride. Salts: s. water.[1]

STABILITY Thermostable at pH 2-7, not at 10.0 [1].

OTHER REACTIONS Precipitated by picric, picrolonic, Reinecke, flavianic acids [1].

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. aureus [2].

BIOLOGICAL ACTIVITY In vitro. Inhibit (in dilution x 1000) Corynebacterium diphtheriae, 512-2000; Bacillus anthracis, 256-2000; Streptococcus pyogenes, M. pyogenes var. aureus, 160-640; Str. viridans, 256; Diplococcus pneumoniae, 200; Neisseria meningitidis, 800; Salmonella enteritidis, 32-160. Other Gram-negative bacteria, e.g., Salmonella, Proteus, Pseudomonas, Shigella spp, and fungi, not sensitive.[1-3] Proactinomycin B showed slightly lower activity than A and C against bacteria [2].

PHARMACOLOGY Proactinomycin A: LD₁₀₀ in mice, 100 mg/kg, i.v.; 250-500 mg/kg, i.p.; oral doses of 250 mg/kg well tolerated.[3]

B: LD₅₀ in mice, 120 mg/kg. Depressed the blood pressure of decerebrate cats and altered the normal contractions of guinea pig uterus.[2]

C: 80 mg/kg. In mice, oral doses of all three products produced detectable levels in the urine and the gastrointestinal tract, but were not detected in the blood.

In vitro. Decreased motility of human leukocytes.[2]

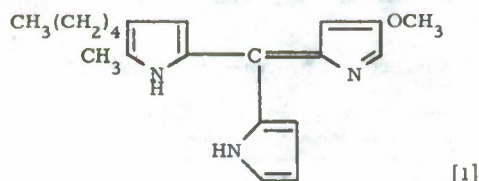
255. PRODIGIOSIN

SOURCE Serratia marcescens [3].

NATURE Red pigment; monoacidic base.[2, 10]

MOLECULAR FORMULA AND WEIGHT C₂₀H₂₅ON₃; 387, 390 (found); 323.2 (calc.).[2, 10]

STRUCTURE



CRYSTAL FORM AND COLOR Vivid green, metallic leaflets [2]. Base: lustrous, square pyramids, dark red with green reflex [10].

MELTING POINT (°C) 70-80 (sinters) [2]. Base: 151-152 [10]. Perchlorate: 227-229 [10].

ABSORPTION MAXIMA 535-540 mμ¹ [1]. Base in ethanol: pH 7.4: 225.5, 288.5, 337, 471, 539 mμ. pH 11: 257, 281, 335.5, 468.5 mμ. pH 2.9: 216, 296, 371, 541 mμ². [10]

SOLUBILITY s. alcohol, ether, chloroform, bromoform, benzene; i. water.[2]

STABILITY Thermostable [5].

OTHER REACTIONS Forms picrate, MP 176°C; salicylate, MP 178°C; benzoate, MP 170°C; perchlorate, MP 228°C (uncorr.).[2] Deep red in acid, orange-yellow in alkaline solution. Infrared: 3270, 3235, 3070, 2895, 2835, 1622, 1578, 1557, 1543, 1458, 1430, 1373, 1360, 1336, 1277, 1253, 1198, 1185, 1144, 1136, 1115, 1078, 1054, 1030, 998, 957, 926, 907, 890, 844, 821, 806, 782, 767, 739, 727 (recip. cm).[10]

BIOLOGICAL ACTIVITY Little or no activity against bacteria; active against certain fungi and protozoa. In vitro. Inhibits protozoa (μg/ml): Entamoeba histolytica, 0.05-15; Trypanosoma cruzi, T. conorrhini, Leishmania donovani, L. tropica, 15 or less.[3, 4] E. coli, Dientamoeba fragilis, Endolimax nana sensitive to 40 μg/ml or less [7]. Inhibited growth of the fungus Coccidioides immitis at 2 μg/ml [5]. Little or no antibacterial activity [3]. In vitro antifungal activity reversed by certain unsaturated fatty acids and Tween 80, but not by saturated straight-chain fatty acids [9].

In vivo. Slight activity in mice infected with Micrococcus pyogenes var. aureus and Diplococcus pneumoniae following i.p. treatment [6]. Oral doses in rodents of 6.5 mg/kg prevented infection with E. histolytica, Trypanosoma brucei and T. equiperdum [3].

/1/ Acid chloroform. /2/ Inflections at 275.0, 382, 510 mμ.

255. PRODIGIOSIN (Concluded)

CLINICAL Encouraging results in 6 of 9 patients with disseminated coccidioidomycosis treated with oral doses of 10-30 mg/da, or i.v. doses of 10-25 mg/da. No kidney or liver damage noted in these cases.[8]

TOXICITY Mice and guinea pigs tolerated i.p. doses of 1 mg/kg.[3]

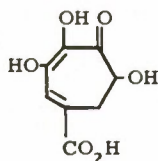
256. PUBERULIC ACID

SOURCE *Penicillium puberulum* and other *Penicillium* spp [1, 2].

NATURE Dibasic acid [1, 2].

MOLECULAR FORMULA AND WEIGHT $C_8H_6O_6$; 95.4 (equiv. found); 99 (equiv. calc.).[1]

STRUCTURE



CRYSTAL FORM AND COLOR Microcrystalline plates; colorless [6].

MELTING POINT (°C) 316-320 (d.) [2, 6].

UV ABSORPTION MAXIMA 270, 350 m μ [6].

SOLUBILITY sl. s. water; i. saturated hydrocarbons.[1, 5]

OTHER REACTIONS Yellow-brown color with dilute $FeCl_3$, amethyst to deep red-brown with excess $FeCl_3$; various derivatives among which the diacetyl compound has colorless crystals, MP 212°C; occurs in culture fluids with puberulonic acid.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [2].

BIOLOGICAL ACTIVITY *in vitro*. Inhibits *Bacillus anthracis*, *M. pyogenes* var. *aureus* in dilution of 1:17,000-1:33,000; *Streptococcus pyogenes*, 1:6000. *Str. viridans*, *Escherichia coli*, *Vibrio comma* less sensitive.[2]

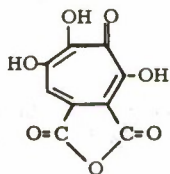
257. PUBERULONIC ACID

SOURCE Same as for puberulic acid [2].

NATURE Dibasic acid [1].

MOLECULAR FORMULA AND WEIGHT $C_9H_4O_7$ [4-6]; 217, 187 (found).[1]

STRUCTURE



CRYSTAL FORM AND COLOR Yellow plates, prisms or needles¹ [1, 2, 6].

MELTING POINT (°C) 296-298 (d.) [1, 2].

UV ABSORPTION MAXIMA 274.5, 317 m μ [6].

SOLUBILITY s. ether, alcohols; sl. s. water; i. saturated hydrocarbons.[5]

OTHER REACTIONS Can be converted into puberulic acid; $FeCl_3$ reactions same as puberulic acid; no esters or acetyl derivatives [1, 2, 4].

/1/ Sodium salt: orange needles.

257. PUBERULONIC ACID

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [2] .

BIOLOGICAL ACTIVITY In vitro. Same antibacterial spectrum as puberulic acid, but approximately 1/4 as active [2] .

258. PUMILIN

SOURCE *Bacillus pumilus* [1] .

NATURE Largely non-peptide [1] .

CRYSTAL FORM AND COLOR Lemon yellow, small hexagonal crystals, average diameter $10 \mu^1$ [1] .

MELTING POINT ($^{\circ}\text{C}$) No melting below 360 [1] .

SOLUBILITY s. pyridine, collidine, morpholine; less s. aqueous acetone (1 mg/ml); sl. s. warm methanol, ethanol.[1]

STABILITY Loses activity in UV light and sunlight, more slowly in diffuse light; inactivated slowly in nutrient broth at 37°C .[1]

OTHER REACTIONS Fluoresces strongly in solution in UV; no diffusion through agar; dissolves in N/20 NaOH without losing activity; infrared shows hydroxyl group; no color with FeCl_3 ; irreversible change to copper-red with slight decrease in activity in 5N HCl at room temperature; activity antagonized by horse serum; unaffected by cysteine.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits (in dilution $\times 10^6$) *Micrococcus pyogenes* var. *aureus*, *Streptococcus pyogenes*, 400-500; *Str. faecalis*, 50-125; *Pasteurella multocida*, 20.[1]

In vivo. No activity when administered i.p. or s.c. in mice infected with *Str. pyogenes* [1] .

ACUTE TOXICITY I.p. doses of 0.75 mg/kg lethal to mice; 50 mg/kg, s.c., tolerated.[1]

259. PUROMYCIN²

(6-Dimethylamino-9[3'-(p-methoxy-L-phenylalanyl-amino)- β -D-ribofuranosyl]-purine)

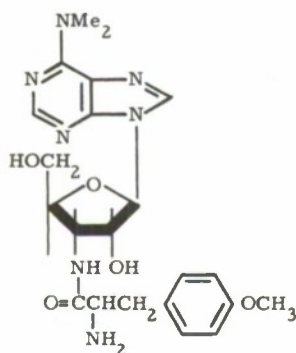
The trademark of Lederle Laboratories Division, American Cyanamid Company, for puromycin is Stylomycin.

SOURCE *Streptomyces albo-niger* [1] ; by synthesis [3] .

NATURE Diacidic base [2] .

MOLECULAR FORMULA $\text{C}_{22}\text{H}_{29}\text{N}_7\text{O}_5$; 471.52 (calc.).[2]

STRUCTURE



[2, 3]

CRYSTAL FORM AND COLOR White crystals [1] .

MELTING POINT ($^{\circ}\text{C}$) Base: 175.5-177 (uncorr.) [1, 2] .

OPTICAL ACTIVITY $[\alpha]_D^{25} = -11^{\circ}3$ [2] .

/1/ From n-butanol. /2/ Originally named Achromycin; the Lederle Laboratories trademark "Achromycin" was transferred to the antibiotic with the generic name tetracycline. /3/ Ethanol.

UV ABSORPTION MAXIMA $275 \mu\text{m}^1$ [3] ; $267.5 \mu\text{m}^2$ [4] .

SOLUBILITY HCl: s. lower alcohols, water; sl. s. ethyl acetate, ethyl methyl ketone; i. petroleum ether, ether, chloroform. Base: s. aqueous alcohols; less s. anhydrous alcohols, most organic solvents; i. water, ether, petroleum ether.[4]

STABILITY Thermo- and pH stable [4] .

OTHER REACTIONS Readily forms a dihydrochloride or monosulfate; negative Brady. Infrared: 3309, 3200, 3125, 1645, 1600, 1560, 1512, 1428, 1403, 1345, 1303, 1248, 1230, 1184, 1158, 1107, 1070, 1040, 998, 968, 930, 871, 820, 791, 758 (recip. cm).[1,2]

BIOLOGICAL ACTIVITY Active against certain bacteria and protozoa. *In vitro*. Inhibits ($\mu\text{g/ml}$) *Bacillus cereus*, *B. subtilis*, *Klebsiella pneumoniae*, *Micrococcus pyogenes* var. *aureus*, *Sarcina lutea*, 2-8; *Mycobacterium* sp, 40; *Alcaligenes* sp, 62; *Salmonella pullorum*, 150; *S. typhosa*, *S. gallinarum*, *Escherichia coli*, *Proteus vulgaris*, 200-400.[1] Protozoa: Inhibited *Trypanosoma cruzi* in dilution of 1:40,000 [5] ; *T. gambiense*, 1:15,000-1:30,000 [6] ; *Tetrahymena pyriformis* (strain W), 2 $\mu\text{g/ml}$ [7] . In tissue cultures, exposure to concentrations of 2-40 $\mu\text{g/ml}$ for 1/2-24 hours caused irreversible damage to several malignant tumor tissues[8]. Mouse mammary (Bittner) tumor and mouse brain tumor 8110 inhibited by 2.5-4.0 $\mu\text{g/ml}$ [9] . Concentrations of 2 mg/ml partially inactivated virus of herpes simplex [23] .

In vivo. Daily i.p. doses of 80 mg/kg for 15 days suppressed *Trypanosoma cruzi* infection in rats [24] . I.p. doses of 10-20 mg/kg/da in mice suppressed infections with *T. cruzi* and *T. equiperdum*; i.v. doses of 20 mg/kg for 7-14 days caused disappearance of well-developed lesions in rabbits.[5,10,11] Good protection in mouse infections with *T. evansi*, *T. equinum*; somewhat less against *T. rhodesiense*, *T. gambiense*; little or no activity against *T. congolense*. [11] Single large i.p. doses of 200-250 mg/kg failed to protect mice against *T. gambiense* and *T. rhodesiense*, but the same infections were controlled with 30-60 mg/kg daily for 10-12 days [25] . Protection afforded against *T. equiperdum* in mice by a number of puromycin analogs following single i.p. or oral doses of 25-50 mg/kg [12] . Oral doses of 6.2-50 mg/kg , b.i.d., for 5 days effective against *Entamoeba histolytica* infection in rats and guinea pigs; certain analogs were less active.[13,14] Prolonged survival time in mice infected with *Toxoplasma gondii* following 0.05-0.4% of drug in the diet, or daily oral doses of 100-200 mg/kg [15,16] . Single oral doses of 100-500 mg/kg were highly effective against mouse oxyurids (*Aspicularis tetraptera* and *Syphacia obvelata*), and partially suppressed tapeworm (*Hymenolepis nana* var. *fraterna*) in mice [17] . Four daily i.p. doses of 90 mg/kg in mice effective against infection with *Babesia rodhaini* (Piroplasmidea), completely clearing the blood of the parasites [31] . Doses of 100 mg/kg/da , i.p., for 7 days failed to suppress RC carcinoma in mice [32]. Carcinolytic activity demonstrated in transplanted leukemia in mice [33] . Active against transplanted mouse mammary adenocarcinoma; slightly effective against mouse sarcoma 180 following i.p. or oral dosage; 100-200 μg partially suppressed development of glioblastoma in chick embryos. No activity against mouse and rat leukemia.[18] A number of amino acid analogs also were effective against mouse mammary adenocarcinoma. Carcinostatic activity closely paralleled trypanostatic property; no correlation with activity against bacteria and the protozoan, *Tetrahymena pyriformis*. [19]

CLINICAL Effectively controlled *T. gambiense* infection in 15 patients treated with daily oral doses of 1-2.25 g for 8-10 days, with excellent clinical response 24-48 hours after initiation of therapy [6,29] . Slight to moderate tumor regression observed in 14 out of 50 patients with disseminated or advanced incurable neoplastic disease [8] . In a series of 24 cases of acute ulcerative amebiasis, there was effective clearance of *E. histolytica* after 10 daily oral doses of 1.5 g, but control of symptoms and healing of ulcers was slow as compared with results following therapy with tetracycline antibiotics [28] . Clinical response poor in patients with amebic liver abscess; good results obtained with puromycin in combination with tetracycline.[34] 60 patients with chronic amebiasis responded favorably to oral treatment of 12.5-25 mg/kg/da for 3 days; *E. histolytica* cleared from stools of 75-98% of patients, and stools were negative one year later. The 12.5 mg/kg doses were well tolerated; 25 mg/kg occasionally produced nausea, asthenia, headache, and diarrhea.[26] No significant response in 5 cases of Chagas' disease (*T. cruzi*) treated with total doses of 4-23 g over periods of 8-29 days [27] .

ACUTE TOXICITY LD_{50} in mice, 335-360 mg/kg , i.v.; 525-580 mg/kg , i.p.; 678-720 mg/kg , oral. LD_{50} in guinea pigs, 202 mg/kg , i.m.; 287 mg/kg , i.p.; and 600 mg/kg , oral.[1,20] Oral or i.v. doses of 50 mg/kg poorly tolerated in dogs; total amounts of 150-200 mg , in divided doses over 2-3 hour period, were well tolerated in anesthetized cats, with little or no effect on blood pressure, cardiac rate, and respiration.[20] Maximum tolerated dosage in mice was 150 mg/kg/da , i.p., for 4 days [31] .

CHRONIC TOXICITY Evidence of renal damage in animals following repeated parenteral administration of 25-100 mg/kg for 1-4 weeks [1] . Repeated oral doses of 100 mg/kg toxic to guinea pigs [13] . Daily i.p. doses of 25 mg/kg in rats over period of 10 days were well tolerated; doses of 100 mg/kg resulted in weight loss and histopathologic changes in the kidneys and bone marrow. Multiple i.m. doses of 10 mg/kg/da for 25 days well tolerated in dogs; 50 mg/kg doses were toxic. Repeated instillations of 0.5% buffered aqueous solutions were non-irritating to rabbit eye [20] .

In man, total oral doses of 9.5-21.0 g over periods of 8-10 days well tolerated; headache and gastrointestinal distress were occasional side effects.[6]

/1/ 0.1 N NaOH. /2/ 0.1 N HCl.

ABSORPTION AND EXCRETION Appears to be readily absorbed from all tissues since effective doses by several routes are within same general range [5, 20]. Probably rapidly changed in the body and excreted by the kidneys in altered form [20, 21]. Only small amounts (5-7%) of the antibiotic appeared to be bound by plasma; the bound portion was almost entirely in the albumin fraction.[30]

MODE OF ACTION Trypanostatic rather than trypanocida [5]. Aminonucleoside is the active antitumor moiety in the puromycin molecule [22]. Trypanostatic activity of puromycin and its aminonucleoside reversed in vivo by adenine sulfate and various substituted purines; has been suggested that the antibiotic is an antimetabolite of adenine or its analogs.[21] Inhibition of strain W of *Tetrahymena pyriformis* reversed by guanylic acid, a metabolite of this organism, hence it has been postulated that the antibiotic interferes with synthesis of nucleic acids or nucleoproteins in these protozoa [7, 21].

260. PYO COMPOUNDS

SOURCE *Pseudomonas aeruginosa* [1, 3].

NATURE Pyo Ib: 2-heptyl-4-quinolinol.
Ic: 2-nonyl-4-quinolinol.
III: 2-(Δ^1 -nonyl)-4-quinolinol.[2]

MOLECULAR FORMULA AND WEIGHT Pyo Ib: $C_{16}H_{21}NO$; 440 (Rast)¹; 243.3 (calc.).
Ic: $C_{18}H_{25}NO$; 486 (found); 271.4 (calc.).
II: $C_{17}H_{23}NO_2$; 546 (found); 273 (calc.).
III: $C_{18}H_{23}NO$; 502 (found); 269.4 (calc.).
IV: $C_{16}H_{23}NO_3$; 280, 285 (found); 277.4 (calc.).[1, 2]

CRYSTAL FORM AND COLOR Pyo Ib, III: colorless crystals.
II: light yellow platelets.
IV: colorless needles.[1]

MELTING POINT ($^{\circ}C$) Pyo Ib: 146.2-147.
Ic: 138.8-139.2.
II: 149-149.5.
III: 151.5-153.5.
IV: 131-132; 139.5-140.[1, 2]

UV ABSORPTION MAXIMA (In $m\mu$) [1, 2]

| | In 95% ethanol | In 0.01 N ethanolic HCl | In 0.009 N ethanolic KOH |
|--------|--------------------|----------------------------|-----------------------------|
| Pyo Ib | 236, 316, 328 | 232, 300 | 242, 314 |
| Ic | 236, 316, 328 | 232, 300 | 244, 314 |
| II | 242, 330 | | |
| III | 258, 266, 307, 338 | 258, 267, 320 | 260, 326 |
| IV | 232, 258, 340 | | |

SOLUBILITY Pyo Ib, Ic, III: s. alcohols, chloroform, benzene, dioxane, acetone, ether.

II: s. aqueous carbonate; sl. s. cold acetone, benzene, methanol; i. petroleum ether, water, 5% sodium bicarbonate.[1, 2]

STABILITY Stable [1].

OTHER REACTIONS Iodinated derivatives of Pyo Ib, Ic, II, and III have greater antibiotic activity than the parent compounds; both types inactivated by serum.

Pyo Ib and Ic: Precipitated from ether by oxalic, flavianic, hydrochloric acids, and occur in $NaHCO_3$ purification fractions.

II: Negative $FeCl_3$, Ag and Ba salts and reacts with diazomethane.

IV: Forms dibenzoate and 2, 4-dinitrophenylhydrazone.[1, 3]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1, 3].

BIOLOGICAL ACTIVITY *In vitro*. Pyo II: Inhibits (units/ml) *M. pyogenes* var. *aureus*, *Corynebacterium diphtheriae*, *C. hoffmanni*, *Bacillus anthracis*, *B. subtilis*, *Diplococcus pneumoniae*, *Streptococcus pyogenes*, I-64. Less sensitive: *Str. viridans*, *Brucella abortus*, *Br. suis*, *Br. melitensis*, *Salmonella typhosa*, *S. enteritidis*, *Serratia marcescens*, *Escherichia coli*, *Proteus vulgaris*, 128-256 units/ml.[1]

/1/ Molecular weights found are approximately twice the calculated because they dimerize in the tribromophenol in which they are determined.

260. PYO COMPOUNDS (Concluded)

Ic: Inhibits *M. pyogenes* var. *aureus*, *Str. pyogenes*, *E. coli*, *C. xerosis* in dilutions of 1:20-1:320 [1].
In vivo. Pyo II: Inactive in experimental infections with *D. pneumoniae* in mice, or *Mycobacterium tuberculosis* in guinea pigs [4].

TOXICITY Pyo II: LD₁₀₀ in mice, approximately 38 mg/kg, i.p. [4].

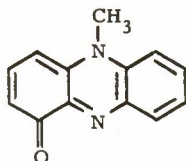
261. PYOCYANINE

SOURCE *Pseudomonas aeruginosa* [1, 2].

NATURE Basic blue pigment [1].

MOLECULAR FORMULA C₁₃H₁₀ON₂ [1].

STRUCTURE



CRYSTAL FORM AND COLOR Dark blue needles [2].

MELTING POINT (°C) 130 (d.) [2].

SOLUBILITY s. hot water, dilute alcohol, chloroform, acetone, ethyl acetate, pyridine; i. ether, benzene, xylene, carbon tetrachloride, petroleum ether, carbon disulfide.[2]

STABILITY Unstable, but salts are stable [2].

OTHER REACTIONS Acts as respiratory enzyme; picrate, MP 194-195°C (d.); perchlorate, MP 221-223°C (d.); salts dark red in color; turns green when treated with nitrous acid in cold; color destroyed by potassium permanganate, ferrous sulfate; unaffected by potassium ferrocyanide.[1, 2]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. *aureus*, *Streptococcus pyogenes*, *Bacillus anthracis*, *Neisseria catarrhalis* and other bacteria in dilution of 1:10,000 or higher. Fungi: *Achorion schoenleinii*, *Microsporium gypseum*, *Trichophyton mentagrophytes*, *Candida albicans* inhibited by 1:2000-1:5000.[3]

TOXICITY LD₁₀₀ in mice, approximately 100 mg/kg, i.p. [4].

262. PYOLIPIC ACID

SOURCE *Pseudomonas aeruginosa* [1].

NATURE Acidic lipid [1].

MOLECULAR FORMULA C₁₁H₂₂O₃ (proposed) [1].

FORM AND COLOR Colorless, odorless, viscous oil [1].

OPTICAL ACTIVITY [α]_D²⁰ = -18.9° [1].

SOLUBILITY s. most fat solvents. Lead salt: s. alcohol, ether; i. water.[1]

OTHER REACTIONS Contains DL-β-hydroxydecanoic acid and a carbohydrate [1].

QUANTITATIVE DETERMINATION Manometric: Oxygen uptake with *Mycobacterium tuberculosis* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibited Myco. tuberculosis in dilution of 1:10,000-1:30,000 [2].

263. PYRIDOMYCIN

SOURCE *Streptomyces albidofuscus*, n. sp [1].

MOLECULAR FORMULA AND WEIGHT C₂₆₋₂₇H₃₂O₈N₄ (proposed); 531 (Rast).[3]

263. PYRIDOMYCIN

CRYSTAL FORM AND COLOR Colorless needles [1, 3].

MELTING POINT (°C) 222 [1]; 218-222 [2]; 214-216.[3]

UV ABSORPTION MAXIMA 303-304 $m\mu^1$; 303 $m\mu^2$; 331 $m\mu^3$. [1-3]

SOLUBILITY s. methanol, ethanol, butanol, ethyl acetate, butyl acetate, benzene, chloroform, acetone, dioxane, cellosolve, tetrahydrofuran; sl. s. ether, petroleum ether, water⁴. [1, 3]

OTHER REACTIONS Negative $FeCl_3$, Fehling, fuchsin, Tollens, ninhydrin, Millon.

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu g/ml$) *Mycobacterium tuberculosis*, *Myc. phlei*, *Proteus vulgaris*, 1.6; *Escherichia coli*, 3.2-25; *Salmonella enteritidis*, 6.3; *S. schottmuelleri*, *S. typhosa*, *Shigella dysenteriae*, 100- >100; *Bacillus anthracis*, 100; *B. subtilis*, *Candida albicans*, >100. [1, 3]

In vivo. Daily i.p. doses of 5 mg slightly inhibited ascites production in Ehrlich carcinoma in mice, but did not prolong the survival time of these animals [4].

TOXICITY LD_{50} in mice, 830 mg/kg, i.p.; 1000 mg/kg, oral. [3]

264. QUADRIFIDINS

SOURCE *Coprinus quadrifidus* [1].

NATURE Quadrifidin A_1 : acidic.
 A_2 , B_2 , B_3 : neutral. [1]

CRYSTAL FORM AND COLOR Quadrifidin B_1 : feathery colorless crystals which rapidly darken.
 B_2 : white crystals turning black.
 B_3 : strongly dichroic white crystals. [1]

UV ABSORPTION MAXIMA Quadrifidin B_2 : 274 $m\mu^5$.
 B_3 : 265, 276, 294, 313 $m\mu^5$. [1]

SOLUBILITY Quadrifidin A_1 , A_2 , A_3 : s. ether, chloroform, ethanol; sl. s. water, hexane.
 B_1 , B_2 , B_3 : s. ether, ethanol; sl. s. water, hexane. [1]

STABILITY Quadrifidin A_1 : thermolabile at acid pH.
 A_2 , A_3 , B_1 , B_2 , B_3 : unstable.
 B_3 : particularly unstable to light. [1]

OTHER REACTIONS A_1 , B_2 , B_3 : reduced ammoniacal $AgNO_3$; positive Schiff, 2,4-dinitrophenylhydrazine.
 B_2 : highly unsaturated; inactivated by silver oxide, cysteine (latter reversible with I).
 B_2 , B_3 : negative $FeCl_3$. [1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Quadrifidin B_2 : Inhibits *Mycobacterium tuberculosis* in dilution of 1:144,000; *M. pyogenes* var. *aureus*, 1:576,000. *Bacillus anthracis* also sensitive.
 B_1 , B_2 : Inhibit *M. pyogenes* var. *aureus*, *Escherichia coli*, *Salmonella typhosa*, *S. enteritidis*, *Shigella paradysenteriae*, *Myc. phlei* and *B. subtilis*. [1]

TOXICITY Quadrifidin B_2 : Mice tolerated 25 mg/kg, i.v. [1].

265. QUATRIMYCIN
(Epitetracycline)⁶

NATURE An isomer of tetracycline [1].

MOLECULAR FORMULA $C_{22}H_{24}N_2O_8$ [2].

/1/ Alcohol. /2/ 0.1 N HCl. /3/ 0.1 N NaOH. /4/ 50 $\mu g/ml$ at room temperature. /5/ Ether. /6/ Corresponding synonyms for related compounds: for chlortetracycline, chlorquatrimecin; for oxytetracycline, oxyquatrimecin; for bromotetracycline, bromoquatrimecin.

STRUCTURE



[2, 3]

MELTING POINT ($^{\circ}\text{C}$) 170-171 (d.) [2].OPTICAL ACTIVITY $[\alpha]_{\text{D}}^{25} = -339^{\text{O}1}$ [2].OTHER REACTIONS Isoelectric point greater than that of tetracycline; less *in vitro* activity than tetracycline; *Escherichia coli* activity is 2-5% that of tetracycline by turbidimetric assay.[1]BIOLOGICAL ACTIVITY In vitro. Antibacterial activity of lower order than that of tetracycline [1].
In vivo. Shows broad activity against experimental bacterial infections [1].

266. RACTINOMYCINS

SOURCE Streptomyces of *S. phaeochromogenus* group [1].MOLECULAR FORMULA AND WEIGHT Ractinomycin A: $\text{C}_{32}\text{H}_{31}\text{N}_3\text{O}_{13}$ or $\text{C}_{64}\text{H}_{60}\text{N}_6\text{O}_{26}$ (proposed) [1].CRYSTAL FORM AND COLOR Ractinomycin A: yellow needles.
B: reddish-orange needles.[1]MELTING POINT ($^{\circ}\text{C}$) Ractinomycin A: 148-150 (d.).
B: 172-175 (d.). [1]UV ABSORPTION MAXIMA Ractinomycin A: 245, 440-450 $\text{m}\mu^2$.
B: 250, 400-450 $\text{m}\mu^2$. [1]SOLUBILITY Ractinomycin A: s. chloroform, acetone, ethyl acetate, butyl acetate; less s. methanol, ethanol, benzene, carbon disulfide; sl. s. ether, carbon tetrachloride; i. water, petroleum ether, 5% NaHCO_3 .
B: Same as A but of lower order.[1]

STABILITY Ractinomycin A, B: thermolabile above pH 7; stable at room temperature at pH 2-10.[1]

OTHER REACTIONS Ractinomycin A: C, 57.80, 57.84; H, 4.55, 4.56; N, 6.25, 6.44; O, 31, 30 (calc.); negative ninhydrin, biuret, Millon; positive FeCl_3 , Tollens; aqueous solution yellow at acid, violet at alkaline pH; in concentrated H_2SO_4 first reddish violet, later blue; in concentrated HCl, first orange than violet on heating; in 10% NaOH, first violet than reddish violet. R_f in 3% NH_4Cl , 0.21; in H_2O -saturated butanol, 0.95; in 15% acetone, 0.4.B: Color reactions differ from A as follows: negative FeCl_3 ; orange yellow at acid, violet at alkaline pH in aqueous acetone; violet in concentrated H_2SO_4 ; insoluble in concentrated HCl and 10% NaOH; brown when suspended in 10% NaOH and heated. R_f in 3% NH_4Cl , 0.04; H_2O -saturated butanol, 0.95; 15% acetone, 0.1.[1]QUANTITATIVE DETERMINATION Microbiological: *Micrococcus flavus*, *Bacillus subtilis* [1].BIOLOGICAL ACTIVITY In vitro. Ractinomycin A: Inhibits ($\mu\text{g}/\text{ml}$) *M. pyogenes* var. aureus, 0.1-0.2; *Sarcina lutea*, *B. anthracis*, 0.2; *M. flavus*, *B. megatherium*, 0.4; *B. subtilis*, 0.4-0.8; *Shigella dysenteriae*, 50; *Proteus vulgaris*, 100; *Mycobacterium tuberculosis*, *Myco. phlei*, 12.5; *Myco. butyricum*, 6.3-12.5. *Penicillium chrysogenum*, *Trichophyton mentagrophytes*, *Saccharomyces cerevisiae*, *Sac. saké*, 25; *Candida albicans*, *Aspergillus niger*, 50. Not sensitive to 100 $\mu\text{g}/\text{ml}$: *Escherichia coli*, *Salmonella paratyphi*, *S. schottmuelleri*, *Pseudomonas aeruginosa*.B: Inhibits ($\mu\text{g}/\text{ml}$) *M. pyogenes* var. aureus, 0.1; *B. anthracis*, 0.2; *M. flavus*, *Sarcina lutea*, 0.8; *B. subtilis*, 0.8-1.6; *E. coli*, *Salmonella paratyphi*, *Sh. dysenteriae*, *Pr. vulgaris*, 50; *S. schottmuelleri*, *Ps. aeruginosa*, 100; *Myco. phlei*, *Myco. butyricum*, 3.1; *Myco. tuberculosis*, 6.3. *C. albicans*, *Sac. cerevisiae*, 0.4-0.8; *P. chrysogenum*, *T. mentagrophytes*, 0.8; *Sac. saké*, 0.8-1.6; *A. niger*, 6.3.[1]In vivo. Ractinomycin A: Daily i.p. doses of 6 μg in mice showed no antitumor activity against Ehrlich carcinoma [1].TOXICITY Ractinomycin A: LD_{50} in mice, approximately 10 mg/kg, i.p.

B: Mice tolerated 25 mg/kg, i.p.[1]

/1/ 0.5% in methanol, 0.1N HCl. /2/ Methanol.

267. RAISNOMYCIN

SOURCE *Streptomyces kentuckensis*, n. sp [1].

NATURE Basic [1].

COLOR Dark yellow [1].

SOLUBILITY s. ethanol, methanol, butanol, isopropanol; i. water, acetone, ether. HCl and $-SO_4$: sl. s. water.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibited by 100 μ g/ml or less: *Micrococcus pyogenes* var. aureus (including tetracycline-resistant strains), *Diplococcus pneumoniae*, *Streptococcus pyogenes*, *Str. faecalis*, *Str. viridans*, *Bacillus subtilis*, *B. anthracis*, *Salmonella typhosa*, *S. pullorum*, *S. schottmuelleri*, *Shigella dysenteriae*, *Sh. paradysenteriae*, *Escherichia coli*, *Aerobacter aerogenes*, *Proteus vulgaris*, *Brucella abortus*, *Pasteurella multocida*. Resistant to 100 μ g/ml: *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Br. bronchiseptica*, *Mycobacterium tuberculosis* var. *hominis*; also *Candida albicans* and *Torula histolytica*. [1]

TOXICITY LD_{50} of crude preparations in rats, 28-35 mg/kg (route not given) [1].

MODE OF ACTION Action is bactericidal as well as bacteriostatic [1].

268. RAMNACIN

SOURCE *Streptomyces* sp [1].

MOLECULAR FORMULA AND WEIGHT $C_{26}H_{43}O_8$ (proposed); 499 (Rast).[1]

MELTING POINT ($^{\circ}C$) 235 [1].

SOLUBILITY s. alcohol, acetic acid, ethyl acetate, chloroform, ether; less s. benzene, petroleum ether (80-100 $^{\circ}C$); sl. s. water [1].

STABILITY Very stable [1].

OTHER REACTIONS Does not decolorize Br in CCl_4 ; positive test for benzenoid structure; paper chromatography on n-butanol/acetic acid/water (4:1:5) gives 1 substance with an R_f value of 0.92; C, 64.51; H, 8.97.[1]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* NCIB 3610 [1].

BIOLOGICAL ACTIVITY In vitro. Activity shown against *B. cereus* var. *mycoides*, *B. subtilis*, *Micrococcus pyogenes* var. aureus, *Streptococcus pyogenes*, *Sarcina lutea*, *Proteus vulgaris*. *Pseudomonas aeruginosa* not sensitive. Also active against *Helminthosporium* sp and *Penicillium* sp. No activity against *P. notatum*, *P. chrysogenum*, *Aspergillus* sp, and various yeasts.[1]

269. RESISTOMYCIN

SOURCE *Streptomyces resistomycificus*, n. sp [1].

NATURE Weakly acidic [1].

MOLECULAR FORMULA AND WEIGHT $C_{23}H_{18}O_6$ [1]; 386 \pm 5 (found); 390.4 (calc.).[2]

CRYSTAL FORM AND COLOR Yellow needles [1, 2].

MELTING POINT ($^{\circ}C$) 315 (d.) [1, 2].

SOLUBILITY s. ether, benzene, ethanol, acetone, glacial acetic acid; sl. s. water. [1]

STABILITY Very thermostable; acid and alkali stable [1, 2].

OTHER REACTIONS Orange-red in NaOH, piperidine, and on heating over 300 $^{\circ}C$; red in pyridine; fluorescence in ethanol, benzene, acetone, H_2SO_4 ; yellow precipitate with original activity after heating with H_2SO_4 ; present in mycelium and too insoluble to detect by agar diffusion tests.[1, 2]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Micrococcus pyogenes* var. aureus, *Bacillus subtilis* in dilution of 1:20,000,000; *Mycobacterium tuberculosis*, 1:500,000-1:1,000,000.[1]

270. RHODOCIDIN

SOURCE *Streptomyces phoenix*, n. sp [1].

270. RHODOCIDIN (Concluded)

SOLUBILITY s. water, organic solvents [1].

STABILITY Rapidly inactivated when aeration of fermentation liquors was discontinued¹; stable in absence of mycelium; inactivated by dilute acid or alkali; stable indefinitely in organic solvents below 5°C; stable in lyophilized form unless moisture present.[1]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* ATCC 6633 [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (units/ml)² *B. subtilis*, 0.02; *Micrococcus pyogenes* var. *aureus*, 0.03; *Streptococcus* sp, 0.25; *Mycobacterium tuberculosis*, 0.45; *Klebsiella* spp, 0.06; *Proteus vulgaris*, 0.11; *Brucella abortus*, 1.2; *Salmonella typhosa*, 4.5; *Pseudomonas aeruginosa*, *Escherichia coli*, 9.0.[1]

In vivo. I.p. doses gave protection in mice infected with *Streptococcus* sp [1].

TOXICITY Highly toxic to mice. LD₅₀, 14,000 units/kg, i.v.; 15,000 units/kg, i.p.; 21,000 units/kg, i.m.[1]

271. RHODOMYCETIN

Name changed from rhodomycin.

SOURCE A mutant of *Streptomyces griseus* [1].

NATURE Red pigment [1].

FORM AND COLOR Dark red powder [1].

MELTING POINT (°C) >300 [1].

ABSORPTION MAXIMA 235, 540, 580 mμ; 520 mμ³. [1]

SOLUBILITY Red form: s. ethylene glycol, monomethyl ether, ethyl ether, acetone, acetic acid, lower alcohols; i. water. Blue form: s. water.[1]

STABILITY Thermolabile, especially in alkali; blue form very unstable in water.[1]

OTHER REACTIONS Resembles actinorhodin. Red in acid, blue in alkaline solution; reddish-violet in concentrated H₂SO₄; amber with FeCl₃ added to alcoholic solution; decolorized by sodium hydrosulfite, not so by sodium bisulfite; decolorized by Zn dust in alcoholic solution when boiled with acid or alkali.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*, *Bacillus subtilis* [1].

BIOLOGICAL ACTIVITY In vitro. Active against Gram-positive bacteria; slight activity against mycobacteria; Gram-negative bacteria not sensitive.[1]

In vivo. No activity in mice infected with *M. pyogenes* var. *aureus* [1].

TOXICITY Mice tolerated 200 mg/kg, s.c.; 25 mg/kg, i.p.[1]

272. RHODOMYCINS

SOURCE *Streptomyces purpurascens*, n. sp [1].

NATURE Amphoteric pigment [1, 3].

MOLECULAR FORMULA AND WEIGHT Rhodomycin A HCl: C₂₀H₂₉O₇N·HCl [3], or C₁₉H₂₉O₇N·HCl [5]; 431.9 (calc.) [3]; 419.9 (calc.) [5].

B HCl: C₁₉H₂₇O₇N·HCl; 417.9 (calc.).[5]

CRYSTAL FORM AND COLOR Rhodomycin A HCl: long, fine dark-red needles [3].

A, B HCl: red prisms [5].

A perchlorate: fine red needles [5].

MELTING POINT (°C) Rhodomycin perchlorate: 198 (d.) [1].

A HCl: 193 (d.) [3]; 205 [5].

A perchlorate: 188 [5].

B HCl: 180 [5].

OPTICAL ACTIVITY Rhodomycin A HCl: $[\alpha]_{606-760}^{18} = +178^{\circ} \pm 10^4$ [5].

B HCl: $[\alpha]_{606-760}^{18} = +174^{\circ} \pm 10^5$ [5].

/1/ 0.03% H₂O₂ added to beer before filtration. /2/ 400-7000 units/mg. /3/ Concentrated H₂SO₄. /4/ c, 0.13 methanol. /5/ c, 0.05 methanol.

272. RHODOMYCINS (Concluded)

ABSORPTION MAXIMA Rhodomycin A HCl: 566, 532, 498 $m\mu^1$; 600, 542, 501 $m\mu^2$; 535, 500 $m\mu^3$; 587, 545, 507 $m\mu^4$. [3] 532, 494 $m\mu^1$ [5].
 B HCl: 530, 496 $m\mu^1$ [5].

SOLUBILITY s. water, methanol, pyridine, acetic acid; sl. s. ether, chloroform, ethyl acetate, benzene, tetrahydrofuran. [3, 5]

STABILITY Thermo-, acid, and alkali labile [1, 2].

OTHER REACTIONS Red in acid, blue in alkaline solution; isoelectric point, 8.6; precipitated from aqueous solution by picric, picrolonic, styphnic, alizarinsulfonic, phosphotungstic, molybdic, chloroplatinic, chloroauric acids, and by $HgCl_2$, helianthin, $SnCl_2$, I_2-KI . Hydrolysis with dilute acid yields the N-free chromophores, rhodomycinone and isorhodomycinone, plus rhodosamine, $C_8H_{17}O_3N$, identified as 2,6-desoxydimethylaminoaldohexose. Rhodomycins A and B and isorhodomycins A and B can be separated by ring chromatograms. [1, 3-5]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1-3].

BIOLOGICAL ACTIVITY In vitro. Inhibit *M. pyogenes* var. *aureus* in dilution of 1:50,000,000 [2].

Rhodomycin A: Inhibits *M. pyogenes* var. *aureus* in dilution of 1:30,000,000.

B: Inhibits the same microorganism in dilution of 1:5,000,000. [5]

273. RIMOCIDIN

SOURCE *Streptomyces rimosus* [1].

NATURE Amphoteric [1].

CRYSTAL FORM Sulfate: large, fragile plates [1].

MELTING POINT ($^{\circ}C$) Sulfate: 151 (d.) [1].

OPTICAL ACTIVITY Sulfate: $[\alpha]_D^{25} = +75.2^{05}$ [1].

UV ABSORPTION MAXIMA 279, 291, 304, 318 $m\mu^1$ [1].

OTHER REACTIONS Analysis: C, 57.65; H, 7.82; N, 1.81; S, 2.03. [1]

BIOLOGICAL ACTIVITY Active against fungi and certain protozoa. In vitro. Inhibits ($\mu g/ml$) *Candida albicans*, *Blastomyces brasiliensis*, *Histoplasma capsulatum*, *Sporotrichum schenckii*, *Hormodendrum compactum*, *Phialophora verrucosa*, *Trichophyton violaceum*, 5; *Bl. dermatitidis*, *T. sulfureum*, *Cryptococcus neoformans*, 10. [1] Protozoa: *Entamoeba histolytica*, 62.5-250; *Leishmania donovani*, *L. tropica*, *Trypanosoma cruzi*, 12.5; *Trichomonas vaginalis*, 25. [2, 3]

In vivo. No activity in mice infected with *Trypanosoma cruzi* [4], or *Candida albicans* [5]; no protection against *Plasmodium cathemerium* in canaries [6].

TOXICITY LD_{50} in mice, 20 mg/kg, i.v. In vitro. Hemolysis of rabbit red blood cells in concentration of 30 $\mu g/ml$. [1] Low levels (0.012 $\mu g/ml$) toxic to human spermatozoa [7].

ANIMAL NUTRITION Stimulated growth of chicks when fed at levels of 10-25 mg/kg [8], but had little or no effect on the growth of pigs [9].

MISCELLANEOUS Concentrations of 25-100 ppm controlled *Ascochyta pisi* infection of pea seeds. Concentrations of 200 ppm were non-toxic to the seeds. [10] Growth of wheat roots in distilled water was slightly stimulated by addition of 1 ppm of antibiotic [11]. Concentrations of 10 $\mu g/ml$ in tissue culture media for cultivation of poliomyelitis virus have been useful for controlling fungal contaminations [12]. Showed molluscicidal activity; concentrations of 3.9 $\mu g/ml$ were lethal to snails (*Australorbis glabrata*) in 24 hours [13].

274. ROSEIN II

SOURCE *Trichothecium roseum* [1].

NATURE $C_{19}H_{28}O_3$; 278, 337 (Rast); 304 (calc.). [1]

CRYSTAL FORM AND COLOR Colorless fibrous needles [1].

MELTING POINT ($^{\circ}C$) 186 [1].

/1/ Methanol. /2/ Pyridine. /3/ Acetic anhydride. /4/ Acetic anhydride and pyroboracetate. /5/ c, 1 methanol.

274. ROSEIN II (Concluded)

OPTICAL ACTIVITY $[\alpha]_D^{23} = +5.90^1$; $[\alpha]_{5461}^{20} = +7.50^2$. [1]

SOLUBILITY s. most organic solvents, hot alkali; sl. s. petroleum ether; i. water, cold alkali. [1]

OTHER REACTIONS Associated with trichothecin and inactive roseins I and III; negative $FeCl_3$, Salkowski, Liebermann-Burchard; deep orange-yellow in concentrated H_2SO_4 ; potassium permanganate oxidation gives a mono-basic acid $C_{16}H_{26}O_5$. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu g/ml$) *Bacillus subtilis*, 4; *Mycobacterium phlei*, 12. Slightly active against *Myco. tuberculosis*. Rosein I and III are devoid of antibacterial activity. [1]

275. ROSEOMYCIN

SOURCE *Streptomyces roseochromogenus* [1].

NATURE Basic [1].

REACTIONS Streptothricin-like; from pure HCl, crystalline helianthate (211-216°C, d.) and crystalline reineckate (114°C, d.) were obtained; positive Fehling, glucosamine, Molisch, Tollens, indole; negative biuret, ninhydrin, xanthoproteic, Adamkiewicz, Liebermann, Neubauer, Sakaguchi, maltol. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Vibrio comma*, *Escherichia coli*, *Pasteurella tularensis*, *Mycobacterium* spp, *Salmonella typhosa* [1, 2, 4].

In vivo. Good protection in mice infected with *V. comma* and *S. typhosa* [2, 3]. Excellent protection against *Past. tularensis* with doses of 1 mg/da [4].

TOXICITY Mice tolerated 1000 mg/kg, i.v. or i.m. [1].

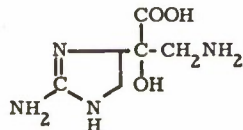
ANIMAL NUTRITION In diet, 15-45 $\mu g/kg$ ration promoted growth in chicks [5].

276. ROSEOTHRICIN

SOURCE *Streptomyces roseochromogenus* [2].

REACTIONS Streptothricin-like. Hydrolysis gave 2 products; β - ϵ -diaminohexanoic acid (also found in streptothricin, viomycin, streptolin), and a new amino acid, roseonine.

Roseonine:



[1]

BIOLOGICAL ACTIVITY In vitro. Low concentrations inhibit varied Gram-negative and Gram-positive bacteria. Spectrum resembles that of streptothricin. [2]

TOXICITY Fairly toxic to mice [2].

277. ROTAVENTIN

SOURCE *Streptomyces reticuli* [2].

CRYSTAL FORM AND COLOR White thin leaves turning yellow at 130°C [1].

MELTING POINT (°C) 170-175 (d.) [1].

SOLUBILITY s. methanol, ethanol, butanol, amyl alcohol, acetone; i. ether, petroleum ether, chloroform, benzene, ethyl acetate, amyl acetate, trichloroethylene, water, 5% aqueous $NaHCO_3$, acid water at pH 2. [1]

OTHER REACTIONS No N or S; not precipitated in methanol or ethanol by adding phosphotungstic acid, flavianic acid, methyl orange, picric acid, lead acetate, or Ca, Hg, or Ba chlorides; red color with concentrated H_2SO_4 . [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Aspergillus flavus*, *A. niger*, *A. oryzae*, *Penicillium glaucum*, *P. chrysogenum*, *Torula rubra*, *Saccharomyces saké*, 6 $\mu g/ml$. Little or no activity against *Mucor mucedo*, *Rhizopus nigricans*, *Trichophyton interdigitale*, *Botrytis bassiana*, *Candida albicans*, and bacteria. [2] Inhibits *Trichomonas vaginalis* in concentration of 100 $\mu g/ml$ [3].

/1/ c, 2 chloroform. /2/ c, 1 ethanol.

277. ROTAVENTIN (Concluded)

TOXICITY Mice tolerated 150 mg/kg, i.p.; 770 mg/kg, s.c.[2]

278. RUBIDIN

SOURCE *Streptomyces* sp [1].

NATURE Quinonoid pigment [1].

FORM AND COLOR Red powder [1].

ABSORPTION MAXIMA 500, 530 m μ ¹; 400, 520 m μ ²; 320, 415 m μ ³; 530 m μ ⁴. [1]

SOLUBILITY s. most organic solvents; sl. s. sodium bicarbonate; i. petroleum ether.[1]

STABILITY Stable at acid, unstable at alkaline pH [1].

OTHER REACTIONS Blue at alkaline, red at acid pH; positive FeCl₃ in ethanolic solution; decolorized at room temperature by Zn dust in presence of HCl or NaOH, the pigment reappearing on aeration; similarly decolorized with sodium bisulfite. Analysis: C, 51.9; H, 5.56; O, 42.54.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Crude preparations inhibited (μ g/ml) *M. pyogenes* var. *aureus* (including strain resistant to streptomycin and penicillin) at 1.5-2.5; *Bacillus subtilis*, *Vibrio comma*, 2.5; *Streptococcus faecalis*, 5; *Mycobacterium phlei*, 15; *Proteus vulgaris*, 20; *Shigella dysenteriae*, *Salmonella typhosa*, *Pseudomonas aeruginosa*, 100. Resistant, >200 μ g/ml: *Escherichia coli*, *Klebsiella pneumoniae*, *Agrobacterium tumefaciens*; also *Aspergillus niger*. [1]

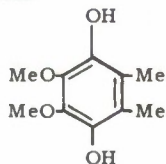
279. RUBROGLIOCLADIN

SOURCE *Gliocladium roseum* [1].

NATURE Quinhydrone [1,2].

MOLECULAR FORMULA C₂₀H₂₆O₈ [1].

STRUCTURE Quinhydrone formed from



[2]

CRYSTAL FORM AND COLOR Dark red needles [1].

MELTING POINT (°C) 74 [1].

UV ABSORPTION MAXIMA 275, 407 m μ [1].

SOLUBILITY s. organic solvents, water [1].

OTHER REACTIONS Monodinitrophenylhydrazone produced when treated with 2,4-dinitrophenylhydrazine [1].

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis*, *Botrytis allii* spores [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (μ g/ml) *B. allii* in concentrations of 50; also inhibits *Bacillus subtilis*, 200, *Escherichia coli*, 400.[1]

280. RUBROMYCIN

SOURCE *Streptomyces collinus*, n. sp [1].

CRYSTAL FORM AND COLOR "Beam-like" thin crystals; pale violet microscopically, red macroscopically.[1]

MELTING POINT (°C) 215 (d.) [1].

/1/ 0.1N HCl. /2/ 0.1N NaOH. /3/ n-Butanol. /4/ Concentrated H₂SO₄.

280. RUBROMYCIN (Concluded)

ABSORPTION MAXIMA 584, 546 $m\mu$ ¹; 518-520 $m\mu$ ². [1]

SOLUBILITY s. acetone, chloroform; less s. ether, lower alcohols; i. water, petroleum ether, sodium bicarbonate solution. [1]

OTHER REACTIONS Red methylene chloride solution + aqueous NaHCO₃ gives red-violet precipitate of Na salt at interface; red color is lost on shaking in aqueous dioxane with sodium hyposulfite (but not with sodium bisulfite), becoming red again on standing in air; blue-green solution in pyridine-methanol with titanium trichloride, becoming red-violet after a short time. Analysis: C, 60.3; H, 4.26; O, 33.91. Acetate crystallizes as yellow needles, MP 193-195°C (uncorr.); resembles rhodomycetin, but differs in being only found in mycelium. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits Streptococcus spp, Corynebacterium diphtheriae, Bacillus subtilis in dilution of 1:800,000; Micrococcus pyogenes var. aureus, Streptococcus group D, 1:100,000; Escherichia coli, Salmonella typhosa, 1:10,000. [1]

281. RUGULOSIN

SOURCE Penicillium rugulosum and P. wortmanni [1].

NATURE Related to polyhydroxyanthraquinones [1].

MOLECULAR FORMULA AND WEIGHT C₃₀H₂₂O₁₀; 413, 420 (cryo. in dioxane); 542 (calc.). [1]

CRYSTAL FORM AND COLOR Yellow cubes or prisms³ [1].

MELTING POINT (°C) 293 (d.) [1].

OPTICAL ACTIVITY $[\alpha]_{5461}^{18} = +605^{\circ 4}$ [1].

SOLUBILITY s. acetone, dioxane, pyridine, ethyl acetate, glacial acetic acid; less s. methanol, ethanol, ether, chloroform, butanol, benzene, 2 N NaOH, 2 N Na₂CO₃, saturated NaHCO₃, NH₄OH; i. water, petroleum ether, concentrated HCl. [1]

OTHER REACTIONS Crystalline forms are very hygroscopic; antibiotic does not sublime on heating in high vacuum; solutions in chloroform and glacial acetic acid bright yellow with slightly green fluorescence; dissolves in concentrated H₂SO₄ giving pure yellow solution with slight fluorescence which changes on heating through brown to a stable purplish crimson color; olive brown color in ethanolic solution with FeCl₃; negative Brady, Schiff; no decolorization of Br in CCl₄ or acid KMnO₄; does not form a semicarbazone, methyl ester, or p-bromophenacyl ester. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits (in dilution x 10³) Micrococcus citreus, M. albus, Mycobacterium phlei, Myco. smegmatis, Escherichia coli, Salmonella typhosa, S. typhimurium, S. schottmuelleri, S. enteritidis, Shigella dysenteriae, Pseudomonas aeruginosa, Ps. fluorescens-2, M. pyogenes var. aureus-2-1024, Vibrio comma-16, Bacillus subtilis-256, Corynebacterium diphtheriae-512-4096, B. anthracis-1024-2048, B. cereus, Streptococcus viridans-2048, Str. pyogenes-2048-4096. Fungi: Inhibits Pythium intermedium in dilution of 1:50,000. [1]

In vivo. I.p. doses of 25 mg/kg protected mice against Str. pyogenes; no protection against Escherichia coli. [1]

282. RUTICIN

SOURCE Streptomyces sp, resembling S. rutgersensis [1].

NATURE Acidic [1].

CRYSTAL FORM AND COLOR Impure crystals: needles and rosettes. Pure crystals: orange needles. [1]

UV ABSORPTION MAXIMA 364, 262 $m\mu$ [1].

SOLUBILITY Acid form: s. methanol, ethanol, ethyl acetate; sl. s. water. Sodium salt: s. water, methanol, ethanol; i. ethyl acetate, less polar solvents. [1]

STABILITY Rapid and irreversible inactivation in culture fluids when aeration is discontinued; addition of H₂O₂ stabilizes filtrates; crystalline antibiotic unstable after a few months at -20°C. [1]

OTHER REACTIONS Second antibiotic produced in complex media [1].

/1/ In 2 N NaOH. /2/ In concentrated H₂SO₄. /3/ From ethanol or acetone. /4/ Dioxane; falls to +222° after exposure to light for periods of 14 days or more.

282. RUTICIN (Concluded)

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Micrococcus pyogenes* var. *aureus*, 0.08; *Bacillus subtilis*, 0.16; *Proteus vulgaris*, 0.64; *Salmonella typhosa*, 5.3.[1]

In vivo. Slight protection in mice infected with *Streptococcus pyogenes* after i.p. treatment; no protection when administered i.v. Appears to be inactivated in vivo.[1]

TOXICITY LD_{50} in mice, approximately 20 mg/kg, i.v. [1].

283. SARCIDIN

SOURCE *Streptomyces achromogenes*, n. sp [1].

MELTING POINT ($^{\circ}\text{C}$) 274-275 (d.) [1].

STABILITY Stable at 60°C for 1 hour at pH 2; 25% loss at pH 4, 75% loss at pH 7, 80% loss at pH 9.[1]

OTHER REACTIONS Analysis: C, 41.89; H, 5.02; N, 21.82; halogen, S.[1]

QUANTITATIVE DETERMINATION Microbiological: *Sarcina lutea* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *S. lutea* at 1.0-1.5 $\mu\text{g/ml}$. Other bacteria or fungi not sensitive.[1]

TOXICITY Mice tolerated 660 mg/kg, i.p. [1].

284. SARKOMYCIN

SOURCE *Streptomyces* sp related to *S. erythrochromogenes* [2].

NATURE Obtained only as an oil [6].

UV ABSORPTION MAXIMUM 230 $\text{m}\mu^1$ [6].

SOLUBILITY Free acid: s. water, methanol, ethanol, butanol, ethyl acetate; sl. s. petroleum ether. Na salt: s. water, methanol, aqueous ethanol. Ca salt: s. water; sl. s. ethanol.[1]

OTHER REACTIONS Negative biuret, xanthoproteic, Sakaguchi, Molisch, Benedict, Fehling, Tollens, Seliwanoff, Foulger, picric acid; doubtful ninhydrin; positive nitroprusside, iodine azide; S present.[1, 2] All samples with antibacterial activity yield reddish pink anthrone test; non-crystalline precipitates obtained with 2,4-dinitrophenylhydrazine, with loss of activity. Infrared bands at 3.4, 5.8, 6.1, 6.9, 7.1, 8, 9.1, 10.5 μ . Hydrogenation destroys antibacterial activity and reaction to anthrone, the hydrogenated product being 2-methyl-3-oxocyclopentane carboxylic acid which does have antitumor activity.[6]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* 209-P² [1-3, 6]. A strain of hemolytic streptococcus. Anthrone test.[5]

BIOLOGICAL ACTIVITY Antitumor activity; some activity against bacteria and certain fungi. In vitro. Inhibits ($\mu\text{g/ml}$) *Bacillus anthracis*, *M. pyogenes* var. *aureus*, 25-50; *Salmonella paratyphi*, *Shigella dysenteriae*, 100; *B. subtilis*, *Escherichia coli*, *Salmonella typhosa*, *S. schottmuelleri*, *Proteus vulgaris*, 500-1000; *Pseudomonas aeruginosa*, *Mycobacterium* spp, >1000 μg . *Nocardia asteroides* inhibited by 63 $\mu\text{g/ml}$. Fungi ($\mu\text{g/ml}$): *Histoplasma capsulatum*, 63; *Trichophyton mentagrophytes*, 500; *Torula utilis*, *Cryptococcus neoformans*, *Saccharomyces saké*, 1000; *Aspergillus niger*, *Penicillium chrysogenum*, >1000.[2, 3] Concentrations of 750 $\mu\text{g/ml}$ inhibited transplantability of Ehrlich ascites carcinoma [7]. Desquamation of HeLa (neoplasm) cells induced with concentrations of 30-60 $\mu\text{g/ml}$; these cells could not be subcultivated. Sulfhydryl compounds did not reverse this activity against HeLa cells.[8]

In vivo. Doses of 50-100 mg/kg, s.c. or i.p., prolonged survival time in rats with Yoshida sarcoma and in mice with Ehrlich carcinoma [2]. In another report activity was demonstrated against Usubuchi sarcoma in rats by prolongation of survival time; no effect on Yoshida and Hirosaki sarcomas.[8] In mice, daily doses of 1 mg, i.v., 2.5 mg, i.p., or 5 mg, orally, retarded development of Ehrlich carcinoma [1]. Little or no activity against Ehrlich carcinoma in mice when treatment was delayed until 2 days after transplantation [7]. Inhibited ascites production and prolonged survival time in mice with transplanted mouse sarcoma 180 [8]; daily i.p. doses of 150-250 mg/kg in mice or rats had a marked inhibitory effect on ascites tumors, but little or no effect on solid tumors except carcinoma 1025 and Harding-Passey melanoma [11, 12].

CLINICAL Clinical improvement in 26 of 78 cases of inoperable carcinoma following total i.v. doses of 5 and up to 114 g over periods of 8-46 days. No serious side effects observed.[4] Subjective and objective improvement observed in 7 of 11 cases of malignant tumor in children treated with i.v. doses of 100 mg up to 4 g per day [9]. Clinical trials in the United States have indicated no carcinostatic effect on various types of cancers [13, 16].

/1/ Water; purest samples only, less pure giving only end absorption. /2/ Parallels antitumor activity.

284. SARKOMYCIN (Concluded)

PHARMACOLOGY Following i.v. administration in humans, approximately 18% of total dose recovered in urine with continuous excretion 3-11 hours after injection [5]. High concentrations (>1:200 or >100 mg/kg) inhibited cardiac action of isolated frog or rabbit heart, dilated rabbit auricular vessels, and had some diuretic action in dogs [10].

TOXICITY LD₅₀ in mice, 1000-1800 mg/kg, i.p. [7]; 800-1600 mg/kg, i.v.; 400-800 mg/kg, s.c.; 4800-6400 mg/kg, oral.[1] Daily intravenous doses of 100 mg/kg were well tolerated in children; side effects were rare.[9]

MODE OF ACTION Cytologic studies with rat sarcoma cells (Hirosaki and Usubuchi types) supply evidence that the antibiotic acts neither as a mitotic poison nor as an antimetabolite, but specifically destroys tumor cells both in the dividing and resting stages [14].

MISCELLANEOUS Antitumor activity depressed by sulfhydryl compounds [2]; BAL, cysteine and serum decreased bacteriostatic activity and mouse toxicity [3]. One report describes the development of a fibrosarcoma in a rat which had received multiple subcutaneous doses of 0.05 mg of sarkomycin over a 5-month period; this tumor developed at the site of injection at the end of one year.[15]

285. SELIGOCIDIN
(Enteromycin)

SOURCE Streptomyces sp, resembling *S. roseochromogenus* [1].

UV ABSORPTION MAXIMUM 304 m μ [1].

SOLUBILITY s. methanol; sl. s. water, ethanol.[1]

OTHER REACTIONS Positive Sakaguchi, ninhydrin; negative biuret.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits (μ g/ml) *Candida albicans*, *C. tropicalis*, *Torula utilis*, *Botrytis bassiana*, *Streptomyces griseus*, 3-6; *Sporotrichum beurmanni*, 0.7; *Aspergillus niger*, *Cryptococcus neoformans*, *Penicillium chrysogenum*, 12-25; *Trichophyton rubrum*, 50; *Trichophyton mentagrophytes*, 12-200. Actinomycetes and bacteria (μ g/ml): *Nocardia asteroides*, 6; *Bacillus anthracis*, *B. subtilis*, *B. agri*, 50. *Mycobacterium* spp and Gram-negative bacteria not sensitive to 200 μ g/ml.[1]

TOXICITY LD₅₀ in mice, 200 mg/kg, i.p. [1].

286. SIMPLEXIN

SOURCE *Bacillus simplex* [1].

SOLUBILITY s. methanol, 95% alcohol; i. chloroform, ether, benzene, ethyl acetate, n-butanol.[2]

STABILITY Acid stable, alkali labile [2].

QUANTITATIVE DETERMINATION Microbiological: *Rhizoctonia solani* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (units/ml) *Pasteurella* sp, *Diplococcus pneumoniae*, 0.13; *Salmonella typhosa*, *Escherichia coli*, 1.0; *Micrococcus pyogenes* var. *aureus*, *S. paratyphi*, >32.[3] Also inhibits *R. solani* [1].

In vivo. No protection in mice infected with *D. pneumoniae* and *M. pyogenes* var. *aureus* [3].

TOXICITY LD₀ in mice, approximately 1000 mg/kg [3].

287. SISTOMYCOSIN

SOURCE *Streptomyces viridosporus*, n. sp [1].

NATURE Neutral [1].

CRYSTAL FORM AND COLOR Buff or light yellow microcrystalline solid [1].

MELTING POINT ($^{\circ}$ C) Approximately 230¹ [1].

UV ABSORPTION MAXIMA 218, 300 m μ ² [1].

SOLUBILITY s. water, methanol; less s. moist acetone, aqueous alcohols; i. chloroform, ether, ethyl acetate, benzene, petroleum ether.[1]

/1/ Turns brown at 130 $^{\circ}$ C. /2/ Latter has 3 peaks: 292.5, 306, 320.5 m μ in water, weak acid or base.

287. SISTOMYCOSIN (Concluded)

STABILITY Unstable to light, acid, alkali; stable in water below 25°C; less than 50% loss in water at 100°C for 1 hour.[1]

OTHER REACTIONS Reduces cold aqueous KMnO_4 and boiling Benedict's solution; positive Molisch; negative Beilstein, FeCl_3 ; deep cherry-red to chocolate color when small amount is added to warm concentrated H_2SO_4 ; no color change when added to warm concentrated HNO_3 or HCl .[1]

QUANTITATIVE DETERMINATION Microbiological: *Candida albicans* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (in concentration of 25 $\mu\text{g}/\text{ml}$ or less) *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Microsporium canis*, *Sporotrichum schenckii*, *Trichophyton rubrum*, *C. albicans*. Little or no activity against *Cryptococcus neoformans*. Bacteria not sensitive.[1]

TOXICITY LD_{50} in mice, 90 mg/kg, i.v.; LD_{01} , 80 mg/kg, i.v.[1]

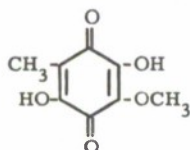
288. SPINULOSIN

(3,6-Dihydroxy-4-methoxy-2,5-toluquinone)

SOURCE *Penicillium spinulosum* [1]; *Aspergillus fumigatus* [4]; by synthesis [3].

MOLECULAR FORMULA AND WEIGHT $\text{C}_8\text{H}_8\text{O}_5$ [1-3, 6]; 184 (Rast); 184 (calc.) [1, 3, 4].

STRUCTURE



[1-3]

CRYSTAL FORM AND COLOR Purplish-bronze or black plates [1, 3, 4, 6].

MELTING POINT (°C) 201-203.5 [1, 3, 6].

OPTICAL ACTIVITY Inactive [1, 3, 4, 6].

SOLUBILITY s. hot water, ether; sl. s. cold water.[1]

STABILITY Thermostable at pH 2.0-9.5 [1].

OTHER REACTIONS Polarographic properties; characteristic quinone odor; intense blue with concentrated H_2SO_4 ; blue-purple with N NaOH ; intense brown in alcohol with FeCl_3 ; reduced by Zn and HCl to a colorless compound which gives a blue-green color with FeCl_3 ; buff to purple to colorless with increasing pH.[3]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [5].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g}/\text{ml}$) *Photobacterium fischeri*, 16; *M. pyogenes* var. *aureus*, 63-170; *Bacillus mycoides*, *B. subtilis*, 125; *B. anthracis*, *Salmonella typhimurium*, *Vibrio comma*, 170; *Escherichia coli*, 100-250; *Klebsiella pneumoniae*, *Mycobacterium phlei*, 250; *Myco. smegmatis*, *Pseudomonas aeruginosa*, 500.[7, 8]

289. SPIRAMYCIN

The trademark of May & Baker, Ltd., for spiramycin is Rovamycin.

SOURCE *Streptomyces ambofaciens*, n. sp.

NATURE Amorphous base [1].

MOLECULAR WEIGHT Approximately 450 (neut. equiv.) [1].

OPTICAL ACTIVITY $[\alpha]_D^{20} = -80^{\circ 1}$ [1].

UV ABSORPTION MAXIMUM 231 $\text{m}\mu$ [1].

SOLUBILITY s. most organic solvents; sl. s. water. Sulfate: s. water, lower aliphatic alcohols.[1]

OTHER REACTIONS Analysis: C, 60.7; H, 9.0; N, 3.2; O, 27.1. Infrared²: 2968, 2930, 1735, 1453, 1375, 1162, 1122, 1085, 1070, 1055, 1017, 995 (recip. cm). Associated in culture liquors with congocidin, but latter does not

/1/ c, 1 methanol. /2/ In carbon tetrachloride solution.

extract with methyl isobutyl-ketone or amyl acetate; 3 components by countercurrent distribution; resemblance to erythromycin and carbomycin.[1]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Diplococcus pneumoniae*, 0.2; *Streptococcus pyogenes*, 0.6; *Gaffkya tetragena*, *Sarcina lutea*, 0.8; *Str. faecalis*, 1.0; *Str. viridans*, 1.3; *Micrococcus pyogenes* var. *aureus* (including strains resistant to penicillin, chlortetracycline and other antibiotics), 1.4-3.5.[1] 114 strains of *M. pyogenes* var. *aureus* resistant to penicillin or erythromycin were sensitive to spiramycin [3]. Inhibits ($\mu\text{g/ml}$) *Neisseria meningitidis*, 3; *N. gonorrhoeae*, 0.7; *Hemophilus influenzae*, 6-25; *Alcaligenes faecalis*, 6-50; *Brucella bronchiseptica*, 25-50; *Pasteurella multocida*, 25; *Pseudomonas aeruginosa*¹, >50.[2] *Bacillus subtilis*, *Corynebacterium pseudodiphtheriticum*, 3; *N. catarrhalis*, 10; *Mycobacterium* sp, 23; *Escherichia coli*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, 31-33. *Proteus vulgaris* resistant to 1500 $\mu\text{g/ml}$. Also active against rickettsiae. [1]

In vivo. Daily i.p. doses of 25 mg/kg for 5 days gave good protection in mice infected with *D. pneumoniae*; protection also afforded against *M. pyogenes* var. *aureus* and *Str. pyogenes* following treatment by i.p., s.c., or oral routes.[1] Daily parenteral doses of 300-400 mg/kg prolonged survival time in rabbits and mice with experimental toxoplasmosis. Appeared to be less effective than oxytetracycline in this experimental infection.[4]

CLINICAL Preliminary trials indicate favorable response in infections with *M. pyogenes* var. *aureus* (furunculosis, osteomyelitis, cardiovascular infections); also in nasopharyngeal, pulmonary, and septicemic infections, following oral doses of approximately 2 g/da. In some cases, total dosage up to 50 g was administered over a period of 20 days. One day of treatment appeared adequate in *N. gonorrhoeae* urethritis.[1] In other reports, infections caused by *Str. pyogenes*, *M. pyogenes* var. *aureus*, and *H. influenzae* responded less favorably to therapy. Good results obtained in bacterial pneumonia; a case of *Klebsiella pneumoniae* failed to respond.[3, 5, 6] Average daily dose recommended for adults is 3 g/da in 3-4 oral doses at regular intervals over a 24-hour period, or 4-5 g/da in severe cases. For children the recommended dosage averages 50-100 mg/kg/da in 3-4 divided doses. Side effects were minimal.[3, 5, 6]

TOXICITY LD₅₀ of sulfate salt in mice, 150-250 mg/kg, i.v.; 1500-2000 mg/kg, s.c. Oral doses of 5000 mg/kg were well tolerated². In dogs, oral doses of 500 mg/kg/da for 4 weeks were non-toxic.[1]

In man, oral doses up to 4 g/da failed to induce side effects.[1]

RESISTANCE Cross resistance between bacterial strains resistant to spiramycin, erythromycin and carbomycin [1, 2].

ABSORPTION AND EXCRETION Following oral doses of 100-200 mg/kg in rabbits, peak blood concentrations of 4.4-14.7 $\mu\text{g/ml}$ were noted in approximately 1 hour, with measurable levels in 8-24 hours. High levels in urine, but percentage of total dosage excreted by this route was low.[1]

In man, following 3 g per day administered orally in divided doses, blood levels averaged 2.7 $\mu\text{g/ml}$ in 1 hour, and 1.6 $\mu\text{g/ml}$ at 6 hours [2]. Peak serum levels of 1.0-6.7 $\mu\text{g/ml}$ were obtained 2-4 hours after oral therapy [3].

290. STREPTOCARDIN

SOURCE *Streptomyces* sp, and *Nocardia* sp [1].

CRYSTAL FORM AND COLOR Brown needles [1].

UV ABSORPTION MAXIMA 365, 242-252 $\text{m}\mu$ ³ [1].

SOLUBILITY Acid form: s. many organic solvents, including alcohol, acetone, ether, ethyl acetate. Alkaline salts: s. water.[1]

QUANTITATIVE DETERMINATION Microbiological: *Proteus vulgaris* ATCC 7829 [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Mycobacterium tuberculosis*, 0.3-3.13; *Bacillus subtilis*, *Pr. vulgaris*, 0.39; *Micrococcus pyogenes* var. *aureus*, 1.56; *Salmonella typhosa*, 3.13; *Escherichia coli*, *Pseudomonas aeruginosa*, 12.5. Fungi: *Aspergillus niger*, *Saccharomyces cerevisiae* not sensitive to 25 $\mu\text{g/ml}$. [1]

TOXICITY Very toxic to mice. LD₅₀ of Na salt, 12.5 mg/kg, i.v.[1]

291. STREPTOCIN

SOURCE *Streptomyces griseus* [1].

CRYSTAL FORM Needle-like crystals in rosettes [1].

UV ABSORPTION None characteristic [1].

/1/ In another report, *Ps. aeruginosa* is resistant to 1500 $\mu\text{g/ml}$. /2/ In another report, LD₅₀ in mice was >5000 mg/kg, orally [5]. /3/ pH 6 phosphate buffer.

291. STREPTOCIN (Concluded)

SOLUBILITY s. water, methanol, ethanol; i. chloroform.[1]

STABILITY Thermostable at pH 2.0-11.0 [1].

OTHER REACTIONS Crystallizable from 1% glacial acetic acid in methanol or from acetone, but not from amyl acetate; forms gel in amyl acetate; crystalline structure lost on standing; sublimable.[1]

QUANTITATIVE DETERMINATION Microbiological: *Trichomonas vaginalis* [1].

BIOLOGICAL ACTIVITY In vitro. High concentrations inhibit *Bacillus subtilis*, *B. mycoides*, *Micrococcus pyogenes* var. *aureus*, *Mycobacterium avium*, *Mycobacterium* sp. Inhibits *T. vaginalis* and *T. foetus* in dilutions of 1:20,000-1:29,000.[1]

TOXICITY LD₀ in mice, >800 mg/kg, i.v. [2].

292. STREPTOGRAMIN

SOURCE *Streptomyces graminofaciens*, n. sp [1].

NATURE Substantially neutral [1].

MOLECULAR FORMULA C₂₆H₃₃N₃O₇ (approximately) [1].

FORM Non-crystalline as yet [1].

SOLUBILITY s. methanol, ethanol, acetone, ethyl acetate; sl. s. water, dilute, acid; i. ligroin.[1]

STABILITY Alkali treatment causes solution and rapid inactivation [1].

OTHER REACTIONS Analysis: C, 62.25; H, 6.62; N, 8.42; S (trace impurity), 0.36; O, 22.35 (by diff.). Infrared: 2.98, 3.4, 5.73, 5.95, 6.14, 6.27, 6.8, 6.95, 7.2, 7.87, 8.12, 8.4, 8.52, 8.89, 9.45, 9.78, 10.21, 10.75, 10.98, 11.22, 11.46, 11.7, 12.25, 13.0, 13.40, 13.9, 14.3 μ.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits (μg/ml) *Streptococcus pyogenes*, 0.02; *Hemophilus pertussis*, 0.06; *Micrococcus pyogenes* var. *aureus*, 0.08; *Bacillus subtilis*, 0.66; *Mycobacterium tuberculosis*, 5.0; *Brucella abortus*, 15; *Proteus vulgaris*, 21; *Escherichia coli*, *Salmonella typhosa*, 85.[2]

In vivo. 50% protection in mice infected with *Str. pyogenes* afforded by 7 doses of 0.1 mg/kg, i.p., 5 mg/kg, i.m., or 44 mg/kg administered orally [2]. Administration by several routes also protected mice against *M. pyogenes* var. *aureus* [3].

TOXICITY LD₅₀ in mice, 450 mg/kg, i.p. [1].

RESISTANCE Induction of resistance in vitro showed a slow stepwise pattern. A strain of *M. pyogenes* var. *aureus* originally sensitive to 0.2 μg/ml required 100 μg/ml for inhibition after 35 transfers in antibiotic-containing medium. No cross-resistance with penicillin.[1]

293. STREPTOGRAMIN-LIKE ANTIBIOTIC
(Antibiotic 899)

SOURCE *Streptomyces* sp resembling *S. virginiae* [1].

NATURE Neutral [1].

FORM AND COLOR Amorphous, reddish-yellow powder [1].

MELTING POINT (°C) 115-120 [1].

SOLUBILITY s. chloroform, methanol, ethanol; less s. methyl isobutyl ketone, benzene, amyl acetate; sl. s. water, ether; i. petroleum ether.[1]

STABILITY Loss after boiling 3 minutes: at pH 7, 10%; at pH 8, 100%; at pH 2, 75%.[1]

OTHER REACTIONS Same infrared and UV as streptogramin, but shows paper chromatographic differences [1].

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (μg/ml) *Corynebacterium pseudotuberculosis*, *Diplococcus pneumoniae*, *Streptococcus pyogenes*, 0.05-0.07; *Sarcina lutea*, 0.1; *M. pyogenes* var. *aureus* (including strains resistant to penicillin, streptomycin, chloramphenicol, erythromycin and the tetracycline antibiotics), 0.2-0.3; *Hemophilus*

293. STREPTOGRAMIN-LIKE ANTIBIOTIC (Concluded)

pertussis, 0.4; *Str. faecalis*, 0.5; *Bacillus subtilis*, 1; *Mycobacterium smegmatis*, *Myco. tuberculosis lacticola*, 7; *Myco. tuberculosis var. hominis* (strain H37RV), 20. *Aerobacter aerogenes* and *Candida albicans* not sensitive to 100.[1]

In vivo. Two i.p. doses of 12.5 mg/kg protected mice against *Str. pyogenes*. No protection against *Salmonella typhimurium* infection.[1]

RESISTANCE Development of resistance follows the slow stepwise pattern characteristic for penicillin. No cross resistance with erythromycin. Complete cross resistance shown between this antibiotic and streptogramin.[1]

294. STREPTOLINS

SOURCE *Streptomyces* sp [1].

NATURE Polyacidic base [1].

MOLECULAR FORMULA Streptolin A: $C_{17}H_{31}N_5O_8$ or $C_{24}H_{45}N_7O_{11}$ ¹ [2, 3].

MELTING POINT (°C) Streptolin A: 206 (d.) [2].

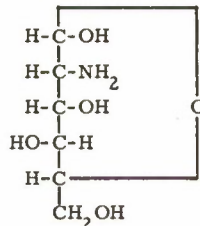
OPTICAL ACTIVITY Streptolin AB HCl: $[\alpha]_D^{28} = -22^{\circ 2}$, $-25^{\circ 3}$. [1]

AB sulfate: $[\alpha]_D^{25} = -20^{\circ 2}$.

A sulfate: $[\alpha]_D^{25} = -20^{\circ 4}$. [2]

STABILITY Most stable at pH 3-3.5 [1].

OTHER REACTIONS Streptolin A and B very similar; precipitated as helianthate and converted to hydrochloride; positive biuret, ninhydrin; reducing properties shown by the Shaffer-Somogyi copper reagent and by the Park and Johnson ferroferricyanide method; negative maltol, phenylhydrazine, 2,4-dinitrophenylhydrazine; <1% arginine; isolysine ($C_6H_{14}N_2O_2$) is an acid hydrolysis product derived from streptolin AB, viomycin and streptothricin⁵. [1, 3, 4] Acid hydrolysis produces (inter alia) CO_2 , NH_3 , L-β-lysine streptolidine, and the following amino sugar, which is also derived from streptothricin:



[6]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli* [1-3].

BIOLOGICAL ACTIVITY In vitro. Inhibit (in units/ml)⁶ *Fusobacterium plauti-vincenti*, *Bacillus megatherium*, 0.1-0.3; *B. polymyxa*, *E. coli*, 1.0; *Aerobacter aerogenes*, *B. cereus*, *Proteus* sp, 3.3; *B. mycoides*, *Pseudomonas aeruginosa*, 10; *Ps. fluorescens*, 33.[1]

TOXICITY LD₁₀₀ in mice, approximately 8-10 mg/kg, i.v. (deaths delayed 4-5 days) [1]. Streptolin A: LD₁₀₀ approximately 6 mg/kg, i.v. [2].

RESISTANCE A number of bacteria show cross resistance to streptolin, streptomycin, streptothricin, and neomycin [5].

295. STREPTOLYDIGIN

The trademark of The Upjohn Company for streptolydigin is Portamycin.

SOURCE *Streptomyces lydicus*, n. sp [1].

NATURE Strong enol acid [2].

MOLECULAR FORMULA AND WEIGHT $C_{32}H_{46}N_2O_9$ or $C_{35}H_{50}N_2O_{10}$; 603, 658 (calc.); 675-685 (equiv. wt. found).[2]

CRYSTAL FORM Orthorhombic, acicular [2].

/1/ Free base minimum formula. /2/ c, 1.8. /3/ c, 2.9. /4/ c, 1.0. /5/ Reactions for AB combination.

/6/ Approximately 33 units per μg.

295. STREPTOLYDIGIN (Concluded)

MELTING POINT (°C) Free acid: 144-150 [2].

OPTICAL ACTIVITY Free acid: $[\alpha]_D^{25} = -65.7^{01}; -93^{02}; -76^{03}$. [2]

UV ABSORPTION MAXIMA 262, 291, 335 $m\mu^4$; 357, 370 $m\mu^5$. [2]

SOLUBILITY Free acid and Ca salt: s. most organic solvents; i. water, hydrocarbons. Na and K salts: s. organic solvents, water; i. hydrocarbons. [2]

STABILITY Alkali stable, acid labile [2].

OTHER REACTIONS Positive $FeCl_3$, iodoform, titanium trichloride; negative reduction of 2, 6-dichlorophenol indophenol, Fehling, Molisch, biuret, ninhydrin; biologically inactive product when reacted with Br in CCl_4 . [2]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu g/ml$) *Clostridium novyi*, 0.04; *Cl. tetanomorphum*, *Cl. perfringens*, *Cl. septicum*, *Diplococcus pneumoniae*, *Streptococcus pyogenes*, 0.1-0.2; *Str. mitis*, 0.39; *Cl. acetobutylicum*, 1.6; *Cl. botulinum*, *Erysipelothrix rhusiopathiae*, *Str. faecalis*, *Str. lactis*, 3.12; *Bacillus cereus*, *Listeria monocytogenes*, *Str. viridans*, *Mycobacterium ranae*, *Pasteurella multocida*, 6.25; *Myc. tuberculosis var. hominis*, 6.25-15; *Myc. phlei*, *Str. agalactiae*, 12.5; *B. subtilis*, *Bacteroides sp.*, *Corynebacterium diphtheriae*, *Myc. smegmatis*, 25; *Micrococcus pyogenes var. aureus*, 25-100; *Neisseria catarrhalis*, 50; *Pseudomonas aeruginosa*, *Salmonella typhosa*, 100. Several species of *Shigella* and *Salmonella* resistant to 100. *Nocardia asteroides* sensitive to 10 $\mu g/ml$. Fungi not sensitive, requiring 1000 μg or more for inhibition. [1]

In vivo. The median protective dosage in mice infected with *Str. pyogenes* was 95 mg/kg, s.c., and 220 mg/kg, in oral doses, daily for 6 days; against *D. pneumoniae*, 260 mg/kg, s.c., and 600 mg/kg, oral; against *Past. multocida*, 130 mg/kg, s.c., and 610 mg/kg, oral. Higher doses were ineffective against infections with *M. pyogenes var. aureus*, *Klebsiella pneumoniae*, *S. typhosa*, *S. schottmuelleri*. [3]

TOXICITY Maximum tolerated dose in mice (Na salt) was 400 mg/kg/da for 6 days by the subcutaneous route. Daily oral doses of 1000 mg/kg of Na salt and 1800 mg/kg/da of the free acid were well tolerated. [3]

RESISTANCE Development of resistance in vitro was rapid, resembling that characteristic of streptomycin rather than the one-step increases characteristic of penicillin. Streptococci showed no cross resistance between streptolydigin and the broad spectrum antibiotics. [3]

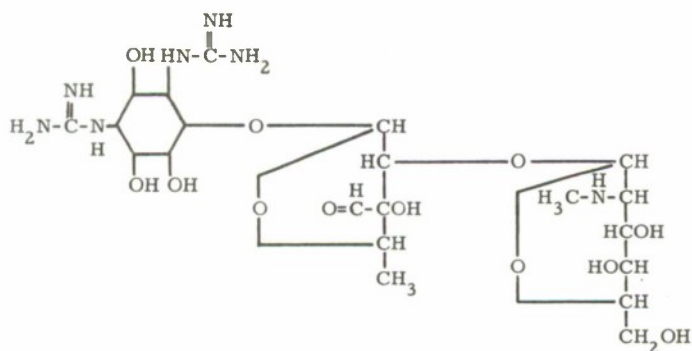
296. STREPTOMYCIN and DIHYDROSTREPTOMYCIN

SOURCE *Streptomyces griseus* [10]; *S. bikiniensis* [11]; *S. mashuensis* [12].

NATURE Strong base [3, 6].

MOLECULAR FORMULA $C_{21}H_{39}O_{12}N_7$ [3, 6].

STRUCTURE



[2]

CRYSTAL FORM AND COLOR Reineckate: thin plates [7]. HCl: white amorphous powder [8]. Tri-HCl: monoclinic prisms [4].

MELTING POINT (°C) Reineckate: 164-165 (d.) [7]. Helianthate: 220-226 (d.) [7].

OPTICAL ACTIVITY HCl: $[\alpha]_D = -84^{06}$ [8]. Tri-HCl: $[\alpha]_D^{26.6} = -86.1^{07}$ [4]. Sulfate: $[\alpha]_D^{25} = -79^{07}$ [1].

UV ABSORPTION End absorption only [8].

/1/ c, 2.28% in 0.005N ethanolic KOH. /2/ c, 1.60% in chloroform. /3/ c, 1.78% in dioxane. /4/ In alkaline ethanol. /5/ In acid. /6/ c, 0.5 water. /7/ c, 1 water.

SOLUBILITY s. water; less s. lower alcohols; i. other organic solvents.[1, 3, 6]

STABILITY Stable at pH 3-7; less stable to heat, acid, alkali.[1, 3, 6]

OTHER REACTIONS Maltol produced by alkaline hydrolysis; inactivated by cysteine, reactivated by iodine; acid hydrolysis yields streptidine, streptobiosamine; positive Sakaguchi; react rapidly with carbonyl group reagents. [1, 3, 5, 6, 8]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli*, *Bacillus subtilis* [1]. Maltol determination [3]. Colorimetric¹ [9].

BIOLOGICAL ACTIVITY Active against Gram-negative and Gram-positive bacteria, including mycobacteria; no activity against fungi, rickettsiae, and viruses. *In vitro*. Microorganisms vary considerably in their susceptibility, not only from one genus or species to another, but from strain to strain. In general, the most sensitive Gram-negative bacteria are species of *Pasteurella*, *Salmonella*, *Klebsiella*, *Shigella*, *Hemophilus*, and *Brucella*; the more susceptible Gram-positive organisms include species of *Streptococcus* and *Micrococcus*, *Diplococcus pneumoniae*, *Corynebacterium diphtheriae*, *Bacillus anthracis*, and *Mycobacterium tuberculosis*. Although freshly isolated cultures of *Mycobacterium tuberculosis* from clinical cases are generally sensitive to low concentrations of the antibiotic, these organisms may rapidly acquire resistance *in vitro*; this also occurs with other bacteria. Dihydrostreptomycin has essentially the same activity as streptomycin, and both antibiotics exhibit reciprocal cross resistance.

In vivo. The activity in general follows the *in vitro* spectrum. Excellent protection is afforded by parenteral administration in a wide variety of experimental infections; these include *Mycobacterium tuberculosis*, *Br. abortus*, *Past. pestis*, *Past. tularensis*, *Neisseria meningitidis*, *B. anthracis*, *D. pneumoniae*, *Str. pyogenes*, *M. pyogenes* var. *aureus*, and species of *Salmonella*, *Shigella*, *Klebsiella*, *Hemophilus*, and *Pseudomonas*.

CLINICAL Streptomycin and dihydrostreptomycin have been used with success in tuberculosis and in a variety of infections caused by Gram-negative and Gram-positive bacteria. The main non-tuberculous conditions which have responded favorably to therapy, include bacteremia, meningitis, and urinary tract infections caused by sensitive bacteria; pneumonia caused by *K. pneumoniae*; empyema and other pulmonary conditions caused by susceptible strains; chancroid, tularemia, plague, glanders, wounds and skin infections caused by *Pr. vulgaris*; peritonitis and enteritis, corneal ulcers caused by *Ps. aeruginosa*; also valuable for prophylaxis in bowel surgery. The emergence of resistant strains has been increasingly noted, e.g., the majority of strains of *Pr. vulgaris*, *Ps. aeruginosa*, *Aerobacter aerogenes*, and *Str. faecalis*, now being clinically isolated, are resistant to these antibiotics. For this reason their use is generally limited to infections in which the responsible agent is shown to be sensitive by laboratory tests. Favorable results have been obtained in systemic infections with streptomycin in combination with other drugs, e.g., with penicillin in mixed infections of the urinary tract, and with one of the tetracyclines and/or sulfadiazine in brucellosis and glanders. In pulmonary and certain other forms of tuberculosis, streptomycin therapy combined with PAS (p-aminosalicylic acid), or with isoniazid (isonicotinic acid hydrazid) and related compounds, has been highly successful. Streptomycin (or dihydrostreptomycin) is generally administered i.m. daily, 1-2 g in divided doses every 6 hours, or in severe infections 2-4 g/da for 2-3 days. In pulmonary tuberculosis, doses of 1 g 2-3 times weekly in conjunction with PAS or isoniazid, for periods of approximately 120 days, have been recommended. In tuberculous meningitis, daily i.m. doses of 2 g or more have been administered, and this has been supplemented with intrathecal doses of approximately 50 mg on alternate days. Streptomycin has been administered intravenously, but this route is seldom recommended and should never be used for dihydrostreptomycin. In view of the ototoxic and neurotoxic capacity of either drug, it has been recommended that audiometric and vestibular function tests be frequently made in patients under therapy. Following oral administration, or inhalation as aerosol, there is practically no absorption and the bulk of the dose is excreted in the feces. Oral doses are well tolerated without side effects, hence this method is useful in the treatment of gastrointestinal infection or in preparation for surgical procedures on the colon. Topical therapy has proved effective in a variety of local infections. Dihydrostreptomycin has been favored for topical use in view of the fairly high incidence of sensitization following local use of streptomycin.

VETERINARY Useful in infections caused by susceptible organisms, e.g., in bovine vibriosis, calf pneumonia, mastitis, navel ill in foals, canine leptospirosis, distemper complex, dysentery and peritonitis, swine enteritis, sinusitis in turkeys, and other conditions.

ACUTE TOXICITY LD₅₀ in mice, approximately 200 mg/kg, i.v.; 900 mg/kg, s.c.; 9000 mg/kg, oral.

In vitro. Low toxicity in tissue cultures; 2200-6600 µg/ml required to inhibit skin, and >300 mg/ml for inhibition of outgrowth of spleen tissue.

CHRONIC TOXICITY Mice tolerate up to 1000 mg/kg/da in divided doses for 6 days by s.c. route, and 1500 mg/kg/da in the diet. Repeated high doses were well tolerated by rats, monkeys, and other animals.

In man, streptomycin and dihydrostreptomycin are of low toxicity, and although untoward reactions are occasionally observed these are rarely severe. Minor effects consist of skin rash, malaise, drug fever and eosinophilia. Incidence of severe renal complications is low. Neurotoxic action on eighth cranial nerve is of particular importance during prolonged therapy, e.g., symptoms of vertigo, tinnitus, ataxia and diminished acuity of hearing are watched for. Recovery from these effects after discontinuation of therapy may be slow and occasionally incomplete. Streptomycin appears to be less toxic to the auditory branch of the 8th cranial nerve, and dihydrostreptomycin less toxic to the vestibular branch of this nerve.

/1/ Assay for dihydrostreptomycin based on reaction between guanido materials and diacetyl, alkali and α-naphthol.

ABSORPTION AND EXCRETION Readily absorbed and excreted following i.m. administration in man, with peak serum concentrations in 1 hour decreasing at a uniform and relatively rapid rate. Approximately 50-75% of the total dose is excreted in the urine within 24-hour period; high levels in the bile. Readily diffuse through the placenta; very little diffusion into cerebrospinal fluid, although therapeutic concentrations are obtained in presence of inflamed meninges. Practically no absorption following oral administration; hence this route is of no value in the treatment of systemic infections, but is useful in gastrointestinal infections.

RESISTANCE Strains of *Myc. tuberculosis* and other organisms may develop resistance to streptomycin (or dihydrostreptomycin) very rapidly. Development in vitro of dependent strains which require the antibiotic for growth has been described; this suggests that these strains may utilize the antibiotic as an essential nutrient. Bacteria may develop resistance either gradually through a series of changes, or in a single step, the result of a single genetic change which produces a resistant variant.

MODE OF ACTION Bacteriostatic and bactericidal. Inhibit oxaloacetate-pyruvate condensation which is essential to oxidation energy processes of *E. coli*. Interfere with the complete oxidation of fatty acid by *Myc. tuberculosis*.

ANIMAL NUTRITION As feed supplement, antibiotic shows growth-promoting effect in chicks and pigs.

PHYTOPATHOLOGY Streptomycin has given good protection in bacterial diseases of plants, e.g., bacterial spot of tomato, fire blight of apple and pear, cucumber leaf spot, wildfire of tobacco, wilt of chrysanthemum; also blue mold disease of tobacco.

297. STREPTOTHRICIN

SOURCE *Streptomyces lavendulae*, and other *Streptomyces* spp [6, 29, 30].

NATURE Basic [2].

MOLECULAR FORMULA $C_{13}H_{25}O_7N_5$ [2], or $C_{20}H_{34}O_9N_8$ (proposed) [4, 5].

CRYSTAL FORM AND COLOR HCl: white powder [1]. Sulfate: white powder [2]. Reineckate: fine platelets in clusters [2].

MELTING POINT (°C) Reineckate: 192-194 (d.) [2]. Helianthate: 220-230 (d.) [1, 3].

OPTICAL ACTIVITY HCl: $[\alpha]_D^{25} = -51.3^{01}$ [1].

UV ABSORPTION End absorption only [2].

SOLUBILITY HCl: s. water, dilute mineral acids; i. ether, petroleum ether, chloroform.[1, 2]

STABILITY Stable at pH 1-8.5; thermolabile in culture filtrate, especially at alkaline pH.[1, 2]

OTHER REACTIONS Destroyed by concentrated acids; not digested by proteolytic enzymes; reduces Tollens, neutral permanganate, boiling Fehling; positive biuret, ninhydrin, Pauly; negative $FeCl_3$, nitroprusside, Molisch, Sakaguchi, Schiff, Hopkins-Cole, Millon; activity unaffected by cysteine; compound A (β - ϵ -diaminocaproic acid) was isolated and also appears in streptolin and viomycin². [1, 5] In common with streptolin, acid hydrolysis yields (inter alia) CO_2 , NH_3 , ϵ - β -lysine, streptolidine, and an amino sugar³ [32].

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis* [1].

BIOLOGICAL ACTIVITY Active against Gram-positive and Gram-negative bacteria and certain fungi. In vitro. Inhibits (units/ml) *Micrococcus lysodeikticus*, *Salmonella typhosa*, *S. gallinarum*, 1; *M. pyogenes* var. *aureus*, *Micrococcus* spp, *S. paratyphi*, *S. schottmuelleri*, *Shigella* spp, *Mycobacterium avium*, *Myc. smegmatis*, 2.5-5.0; *Escherichia coli*, 2.5-20; *Sarcina lutea*, 10; *Diplococcus pneumoniae*, 30; *Myc. tuberculosis*, 1-250. *Aerobacter aerogenes*, *Shigella dysenteriae*, *Sh. paradysenteriae*, *Myc. phlei*, *B. subtilis* are sensitive; *B. cereus*, *B. mycoides*, *Pseudomonas aeruginosa*, *Ps. fluorescens* are resistant.[7-10] Yeasts and fungi: *Coccidioides immitis*, 1; *Dipodascus uninucleatus*, 1.25; *Rhodotorula rubra*, 20; *Saccharomyces cerevisiae*, 80; *Candida albicans*, *C. stellatoidea*, >160; *Blastomyces dermatitidis*, *Rhizopus nigricans*, 10; *Penicillium notatum*, 30; *Trichophyton schoenleinii*, 100; *T. interdigitale*, 300; *T. mentagrophytes*, *Aspergillus flavus*, *Mucor sulfa*, *Neurospora ascospora*, >300.[7] Concentration of 25 μ g/ml inhibits the protozoan, *Trichomonas vaginalis* [26].

In vivo. Active against *Brucella abortus* in chick embryos and guinea pigs [11]. Single or repeated doses of 50-300 units by i.v., i.p., or s.c. routes gave good protection in mice infected with *S. schottmuelleri*, *S. typhosa*, *Sh. dysenteriae*, *E. coli*, and little or no protection against *Proteus vulgaris*, *Ps. aeruginosa*, *Streptococcus pyogenes*, *D. pneumoniae*, and *Pasteurella pestis* [12, 13, 18]. High activity in mice infected with *Past. tularensis* following parenteral injection of 10,000 units/kg/da [27]; no activity in experimental tuberculosis of guinea pigs or hamsters [16, 17]. When included in the diet, 30,000 units/da for 3-4 days reduced number of coliform bacteria in the feces of mice [9]. Suppressed *Bl. dermatitidis* in chick embryos [14]. No activity against viruses of

/1/ c, 1.4 water. /2/ Streptothricin B I [33] is probably neomycin C, and B II [34], neomycin B. /3/ See streptolin for formula.

297. STREPTOTHRICIN (Concluded)

influenza, lymphogranuloma venereum or feline pneumonitis in mice or embryonated eggs, or against the protozoa *Trypanosoma equiperdum* in mice and *Plasmodium gallinaceum* in chicks [9, 12, 15, 19].

ACUTE TOXICITY Wide variations in toxicity of preparations, depending on purity. Purer preparations of 250-530 units/mg were fairly toxic; LD₅₀ in mice, 86,000-131,000 units/kg, i.v. Delayed deaths at higher doses.[20]

CHRONIC TOXICITY Daily s.c. doses up to 5000 units/kg for 1 month were tolerated in mice and rats; repeated doses of 10,000 units induced hematuria, anuria, and were eventually lethal. Daily i.v. amounts of >2500 units/kg for 7 days lethal to dogs; 5000 units/kg/da administered s.c. for 1 month, lethal to guinea pigs [21]. Diets containing 5000 units/100 g food well tolerated in chicks, but levels of 10,000 units were toxic [23]. In mice after i.v. administration, lesions observed in renal tubules, liver and nervous system; also intestinal and cardiovascular changes noted [20]. Severe fatty and necrotic histopathologic changes in the liver have been described [22].

ABSORPTION AND EXCRETION Rapidly excreted in the urine 5-6 hours after parenteral injection in experimental animals, and approximately 10% excreted in the bile. In dogs, 15,000 units/kg/da in divided doses every 3 hours produced peak serum concentrations of 2-5 units/ml.[21] Like streptomycin, this antibiotic was poorly absorbed from the gastrointestinal tract following oral administration [12].

RESISTANCE In vitro. Resistance develops fairly readily [24]. Resistant strains frequently display cross resistance to streptomycin and neomycin [25].

PHYTOPATHOLOGY Effective (superior to penicillin) in control of crown gall disease in plants [28]. When primary older leaves of pinto bean plants were sprayed with streptothricin, the young untreated trifoliolate leaves were protected from blight caused by *Xanthomonas phaseoli*. When sprayed on intermediate leaves of tobacco, tomato, and bean plants, the antibiotic was readily absorbed and transported up stem to young leaves as well as downward to older untreated leaves; in some cases translocation to roots occurred. The antibiotic caused injury to treated leaves in the form of necrotic spots.[31]

298. STREPTOTHRICIN TYPE 3 Related to, but not identical with, neomycin.

SOURCE *Streptomyces* sp resembling *S. flavus* [1].

MELTING POINT (°C) Reineckate: 172-178 (d.) [1]. Helianthate: 208-211 (d.) [1].

STABILITY Thermolabile at alkaline pH, e.g., 95% loss at pH 9 [1].

OTHER REACTIONS Culture also produces flavacid; positive Molisch, glucosamine; negative ninhydrin.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. aureus [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Brucella melitensis*, 0.75; *Bacillus anthracis*, 1.5; *Streptococcus pyogenes*, *Str. viridans*, *Shigella sonnei*, 3; *M. pyogenes* var. aureus, 3-6; *Mycobacterium* spp, 3-12; *Neisseria meningitidis*, *Salmonella typhosa*, *S. paratyphi*, *Klebsiella pneumoniae*, *B. subtilis*, 6; *Diplococcus pneumoniae*, *S. schottmuelleri*, *Vibrio comma*, *Escherichia coli*, 12; *E. coli* (streptomycin-resistant strains), 6-96; *Myco. tuberculosis* var. *hominis*, 30; *Pseudomonas aeruginosa*, >96.[1]

TOXICITY LD₅₀ in mice, approximately 100 mg/kg, i.v. (deaths delayed 3-7 days) [1].

299. SUBTENOLIN

SOURCE *Bacillus subtilis* [1].

FORM AND COLOR Light yellow powder, somewhat hygroscopic [2].

UV ABSORPTION Only end absorption, 270 m μ [2, 3].

SOLUBILITY s. water, ethylene glycol, 95% methanol, some other wet organic solvents; i. acetone, butanone, ether, 95% ethanol, methyl ethyl ketone.[2, 3]

STABILITY Thermostable; loses activity on drying in presence of water.[2]

OTHER REACTIONS Activity destroyed by H₂S but not by trypsin; not precipitated by acids or alkalis; positive peroxidase, Molisch, Benedict; negative biuret, Millon, Hopkins-Cole, trichloroacetic acid, FeCl₃, enol, p-phenylenediamine; slight purple with ninhydrin¹; reduces permanganate; I, Br, ammoniacal AgNO₃, Shaffer-Somogyi sugar reagent; brown solution and rosette crystals with picric acid; dialyzable. Analysis: C, 51.4; H, 7.00; N, 7.88; S, 0.81.[2, 3]

/1/ Reference 2, in contrast, lists positive FeCl₃, enol, ninhydrin.

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) *Pasteurella pestis*, 16; *Pasteurella* sp, 22.5; *M. pyogenes* var. *aureus*, 140-200; *Salmonella typhosa*, 165; *Streptococcus* sp, 375; *Clostridium* spp, 300-600; *Neisseria gonorrhoeae*, *S. schottmuelleri*, 600; *Escherichia coli*, 370-1500; *Str. pyogenes*, 1500. A variety of organisms including *Bacillus subtilis*, *B. anthracis*, *Diplococcus pneumoniae*, *Brucella* spp, *Mycobacterium tuberculosis*, *Klebsiella pneumoniae* and certain strains of *M. pyogenes* var. *aureus*, are highly resistant.[1]

In vivo. No activity in chicks infected with *Plasmodium gallinaceum* following i.p. doses of 200 mg/kg/da [4].

PHARMACOLOGY LD_{50} in mice, 30-60 mg, i.p. Appeared in the urine 15 minutes after injection, with 30-50% of total dose excreted within 10 hours.[1]

300. SUBTILIN

SOURCE *Bacillus subtilis* [1].

NATURE Basic polypeptide [2].

MOLECULAR WEIGHT 3420 (average found); 3188 (calc.).[3]

FORM AND COLOR Amorphous white powder [2].

OPTICAL ACTIVITY $[\alpha]_D^{23} = -29.0$ to -35.0° [2].

SOLUBILITY s. water, water-saturated n-butanol, 0-80% ethanol, methanol, acetic acid; i. anhydrous ethanol, butanol, amyl alcohol, acetone, ether, petroleum ether, chloroform.[2]

STABILITY Stable, especially at pH 2.5; dry preparations relatively unstable at room temperature.[1, 2]

OTHER REACTIONS Incomplete empirical formula: glycine₂ alanine₁ valine₁ leucine₁ isoleucine₁ proline₁-phenylalanine₁ tryptophan₁ lysine₃ asparagine₁ glutamic acid₃ lanthionine₁ ($\text{C}_7\text{H}_{12}\text{O}_3\text{N}_2\text{S}$)₄ (amide)₅ H_2O ; inactivated by light, alkali, pepsin, trypsin, methanol, formaldehyde; blue with FeCl_3 ; dialyzable; solubility in acid solution decreased by salt [2, 3].

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus*. FeCl_3 color reaction². [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *M. pyogenes* var. *aureus*, *M. conglomeratus*, *Streptococcus pyogenes*, *Str. viridans*, *Lactobacillus casei*, *Bacillus anthracis*, *Diplococcus pneumoniae*, *Neisseria gonorrhoeae* [1, 4]. *Mycobacterium tuberculosis* inhibited by dilution of 1:50,000, but only in the presence of surfactant Tween 80 in culture medium [4, 5]. Gram-negative bacteria (except *N. gonorrhoeae*) not susceptible. Yeasts and fungi: *Candida albicans*, *Cryptococcus neoformans*, *Sporotrichum schenckii*, *Trichophyton mentagrophytes* sensitive.[4] Spirochetes and protozoa: Inhibits *Trypanosoma equiperdum* in dilution of 1:2000; *T. cruzi*, 1:200; *Entamoeba histolytica*, 1:400,000; *Borrelia duttoni*, 1:2800; *Treponema pallidum*, 1:300,000-1:500,000; *Leptospira icterohemorrhagiae* and *Leishmania donovani* not sensitive.[6-9, 15] Active against a variety of bacteriophages [10].

In vivo. Active in experimental mouse infections with *Str. pyogenes*, *D. pneumoniae*, *M. pyogenes* var. *aureus*, *B. anthracis*. A modified serum-soluble fraction showed activity in experimental tuberculosis in guinea pigs following s.c. doses of 22 mg/kg/da.[11] Low doses of 0.4 mg/kg suppressed experimental relapsing fever (*Borrelia duttoni*); 2.5-16.0 mg/kg doses sterilized this infection in mice.[12, 15] No effect on *Treponema pallidum* infection in rabbits [6], *Trypanosoma equiperdum* and *T. cruzi* in mice [7, 8], *Leptospira icterohemorrhagiae* in guinea pigs [9], or *Plasmodium gallinaceum* in chicks [16]. Inactivated influenza PR-8 and Newcastle disease virus in embryonated eggs [14]. Rickettsiostatic activity in chick embryos against *Rickettsia tsutsugamushi*; less effective against *R. rickettsii*. [17]

VETERINARY Instillation of amounts up to 0.4 g in each udder quarter in cases of bovine mastitis failed appreciably to eliminate streptococcal infection [30].

TOXICITY LD_{50} in mice, approximately 60 mg/kg, i.v.; 670 mg/kg, s.c. Oral doses of 5000 mg/kg were lethal. [7] Rats fed 0.1% antibiotic in the diet for 220 days showed no untoward effects and no significant histopathologic changes. Subtilin administered parenterally was precipitated in the tissues.[18] In vitro. Partially purified preparations showed low toxicity in embryonic chick heart tissue cultures; exposure to concentrations as high as 0.2% for 10 minutes were required to stop proliferation.[28]

RESISTANCE Strains of *M. pyogenes* var. *aureus*, *Myco. phlei*, and *E. coli* readily developed resistance after serial transfers in medium containing antibiotic [4]; *M. pyogenes* var. *aureus* and *Myco. phlei* developed a 250 to 400-fold resistance after 6-9 serial transfers in increasing concentrations of the antibiotic [31]. A virulent strain of *M. pyogenes* var. *aureus* showed a 50-fold increase in resistance following only 2 serial exposures to subtilin [37].

/1/ c, 1 acetic acid. /2/ May or may not be active molecule.

300. SUBTILIN (Concluded)

ABSORPTION AND EXCRETION Intravenous administration in rabbits produced blood levels of 100-200 ppm which dropped to 10-30 ppm in 2 hours, with no detectable concentrations in 24 hours. As much as 7% of the administered dose was recovered in the urine within 2 hours.[29]

MODE OF ACTION Bactericidal action similar to that of tyrocidin and surfactants; hence suggested this antibiotic be included in the surfactant class of germicidal agents [19]. In relatively high concentrations subtilin lyzed *Trypanosoma equiperdum*, *Treponema pallidum*, and *Borrelia duttoni*. Concentrations in excess of those required for growth inhibition induced changes in morphology and staining properties of *M. pyogenes* var. *aureus*, *Escherichia coli*, and *B. anthracis*. [32] Primarily sporostatic rather than lethal to spores of *B. macerans* which multiplied following inactivation of the antibiotic with trypsin [38].

ANIMAL NUTRITION When used as feed supplement, subtilin gave good growth response in chicks [22].

MISCELLANEOUS Usefulness as food preservative suggested in view of report that spores of *Clostridium botulinum* were less resistant to heat when suspended in food containing small amount of antibiotic [20]. Action on *Cl. botulinum*, types A and B, was sporostatic rather than sporocidal [21]. Subtilin controlled growth of experimentally added micrococci in custard fillings [23], and, when combined with oxytetracycline, also enterococci and salmonella [24]. Good control in experimental infection of barley seedlings with seed pathogen, *Xanthomonas translucens* [13]. Vaccines prepared by inactivation of Newcastle disease virus with this antibiotic were effective in immunization of chicks [25]. Certain derivatives of subtilin were more active in vitro than parent antibiotic against *Myc. tuberculosis*, *Str. faecalis*, and other bacteria [26, 27]. Methyl and hydroxyethyl esters of the antibiotic were more soluble and showed 2-4 times greater in vitro bacteriostatic activity; ethyl and hydroxypropyl esters were as active as the parent antibiotic. [33] In concentrations of 0.01-1.0 ppm, subtilin inhibited lactic streptococci in starter cultures used in cheddar cheese-making [34]. The antibiotic was of no value in preventing development of American foul brood, a bacterial disease of honeybee colonies [35]. High concentrations (100-1000 ppm) delayed, but did not prevent, spoilage in comminuted beef inoculated with 100 or 10,000 spores of a putrefactive anaerobic bacterium [36].

301. SULFACTIN

SOURCE *Streptomyces roseus* [1].

MOLECULAR FORMULA $C_{38}H_{55}O_7N_{11}S_4$ or $C_{27}H_{40}O_5N_8S_3$ (proposed) [1].

CRYSTAL FORM AND COLOR Needles; white double pyramids.[1]

MELTING POINT ($^{\circ}C$) 245-275 (d. corr.) [1].

SOLUBILITY s. chloroform, ethanol, ethyl acetate, dioxane, n-butanol; sl. s. methanol; i. water, ether, petroleum ether, benzene.[1]

STABILITY Stable in boiling alcohol; less stable in boiling neutralized culture filtrates.[1]

OTHER REACTIONS Dialyzable, but loses activity; reduces Fehling, permanganate; negative Sakaguchi, Molisch, biuret, $FeCl_3$; hygroscopic.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (units/ml)¹; *Corynebacterium diphtheriae*, 0.03; *C. xerose*, 0.06; *M. lysodeikticus*, *M. aurantiacus*, 0.25; *Diplococcus pneumoniae*, *Bacillus mesentericus*, *Neisseria sicca*, 0.5; *B. subtilis*, 0.5-4.0; *B. mycoides*, 0.5-16.0; *Gaffkya tetragena*, 0.5-8.0; *M. pyogenes* var. *aureus*, 1.0; *B. circulans*, *B. megatherium*, 2; *Streptococcus pyogenes*, 4; *B. anthracis*, 8-16; *B. cereus*, 16; *Str. viridans*, 32. Gram-negative bacteria not sensitive to 32 units/ml include *Aerobacter aerogenes*, *Brucella* spp, *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria catarrhalis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella* spp, *Shigella* spp. Also resistant to 32 units/ml: *Sarcina lutea*, *Str. faecalis*, *Mycobacterium smegmatis*. Activity reduced by serum.[2]
In vivo. Doses of 1-10 μg , i.p., protected mice against infection with *D. pneumoniae* [2].

TOXICITY LD_{50} in mice, 135 mg/kg, i.p. Liver enlargement noted following doses of 50 mg/kg.[2]

302. SYNNEMATINS

SOURCE *Cephalosporium salmosynnematum* [1].

SOLUBILITY s. water, methanol, aqueous acetone, aqueous ethanol; i. ethanol, acetone, ether.[1, 3]

STABILITY Thermo- and acid labile; stable at 11 months at 5 $^{\circ}C$ dried, but loses activity in 17 months.[1, 3]

OTHER REACTIONS More active at acid pH; activity reduced in presence of serum; by paper chromatography with buffered methanol, component A remains at point of application, B moves.[1-3] Synnematin B may be identical with cephalosporin N.[8, 9]

/1/ 1 unit = approximately 0.025 μg .

302. SYNNEMATINS (Concluded)

QUANTITATIVE DETERMINATION Microbiological: *Salmonella typhimurium* [1-3].

BIOLOGICAL ACTIVITY *In vitro*. Inhibit (units/ml)¹ *Corynebacterium diphtheriae*, 0.25; *S. typhosa*, *S. pullorum*, 0.5; *Brucella melitensis*, *Br. suis*, *Diplococcus pneumoniae*, *Proteus* sp., *S. choleraesuis*, *S. enteritidis*, *S. paratyphi*, *S. schottmuelleri*, *S. typhimurium*, *Micrococcus pyogenes* var. *aureus*, *Mycobacterium phlei*, 1-2; *Streptococcus pyogenes*, 1-32; *Br. abortus*, 2; *Bacillus subtilis*, 8; *Shigella alkalescens*, 4-16; *Sh. paradysenteriae*, 8-64; *Sh. dysenteriae*, 32; *Escherichia coli*, 32->64; *Myco. tuberculosis*, >12; *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, >32. Fungi not sensitive (>32 units/ml).[1]

Synnematin A: Active against *Pr. vulgaris*, *Sarcina lutea*, *Salmonella typhimurium*; low activity against *B. subtilis*, *M. pyogenes* var. *aureus*. [2]

B: Very active against *Pr. vulgaris*, *Sarcina lutea*; no activity against *B. subtilis*, *M. pyogenes* var. *aureus*. [2] Inhibited 40 strains of *Salmonella typhosa* at concentrations of 1.2-5.0 µg/ml [4]. Activity reduced by 50% in presence of serum [1].

In vivo. Single s.c. dose protected mice infected with *D. pneumoniae*; also active against *S. pullorum* in chick embryos.[1]

Synnematin B: Thirty s.c. injections of 25 units eliminated *S. typhimurium* from mice; also effective against infections with *S. typhosa*. [5] S.c. doses of 40-80 mg/kg every 3 or 12 hours protected guinea pigs infected with *Leptospira icterohemorrhagiae* [10]. Chicks freed of *S. pullorum* after total doses of 1500-6000 units; the preparations used in these animal tests assayed 40-100 units/mg [5]. Ineffective against experimental toxoplasmosis in mice treated with s.c. doses of 5 mg every 12 hours [6].

CLINICAL Preliminary trial in 15 patients with typhoid fever showed generally favorable clinical response with 3 relapses. No carrier state during therapy; blood and feces cleared of *S. typhosa*. Preparations used contained approximately 25% pure synnematin B; 80-350 mg/kg/da of whole drug (20-87.5 mg/kg/da pure synnematin B) was administered i.m. for 9-14 days, with no notable untoward reactions.[7]

TOXICITY Mice tolerated 5000 mg/kg (160,000 units/kg), i.p., of synnematin B [1]. Weanling rats tolerated daily parenteral doses of 1000 mg (50,000 units/kg) of B for 21 days; no effect on weight gains and no histopathologic changes noted.[5]

In man, i.m. doses of 20-87.5 mg/kg/da of synnematin B were well tolerated [7].

ABSORPTION AND EXCRETION Detectable blood concentrations in 2 hours after i.m. administration in man. Rapidly excreted in the urine in 4-hour period between injections.[7]

303. TARDIN

SOURCE *Penicillium tardum* [1].

MOLECULAR FORMULA C₁₁H₁₅O₃ (proposed) [1].

FORM AND COLOR Pale yellow oil [1].

OPTICAL ACTIVITY $[\alpha]_D^{20} = -11.4^{\circ}$ [1].

SOLUBILITY s. alcohol, acetone, ether, benzene, amyl acetate; s.l.s. water, warm hexane [1].

STABILITY Stable at pH 2.8, unstable above 8 [1].

OTHER REACTIONS Purple color with FeCl₃, brown on warming; negative 2,4-dinitrophenylhydrazine; yields an acid and neutral fraction on decomposition or acid hydrolysis.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *M. pyogenes* var. *aureus* in dilution of 1:128,000; *Corynebacterium xerosis*, 1:64,000; *C. diphtheriae*, *Streptococcus viridans*, 1:8000; *Salmonella enteritidis*, 1:1000. *Escherichia coli*, *Pseudomonas aeruginosa* not sensitive to 1:1000. Fungi: *Microsporium audouini*, *M. canis*, *Trichophyton equinum* inhibited by 1:5000 dilution.[1]

PHARMACOLOGY Mice tolerated 40 mg/kg, i.v., and 125 mg/kg, s.c. Low solubility precluded higher dosages. Skin over site of s.c. injection sloughed. Isolated guinea pig uterus showed increased contraction, followed by cessation, in 1:25,000 solution. Same concentration perfused through heart produced complete stoppage in 9 minutes. *In vitro*. 1:16,000 showed no effect on human leukocytes; dilution of 1:2000 lethal in 30 minutes.[1]

304. TERRECIN

SOURCE *Aspergillus terreus* [1].

CRYSTAL FORM AND COLOR Light yellow prisms [1].

/1/ Preparations for in vitro tests contained 32 units/mg. /2/ Alcohol.

304. TERRECIN (Concluded)

MELTING POINT (°C) 219-220 [1].

SOLUBILITY s. acetone, ether, alcohol, benzene, Na₂CO₃, NaOH [1].

STABILITY Thermostable 10 minutes, unstable 30 minutes, at 100°C [1].

OTHER REACTIONS Analysis: C, 51.89, H, 3.51; N, 3.8, Cl, 19.1; yellow in solution; precipitated by addition of acid when in alkaline solution; deep violet with FeCl₃; not hygroscopic.[1]

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. aureus 209-P [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (μg/ml) Clostridium tetani, 0.025-0.2; Cl. perfringens, 0.05-0.2; Bacillus anthracis, 1.0; Streptococcus pyogenes, Neisseria gonorrhoeae, 1.25; Diplococcus pneumoniae, 2.5; M. pyogenes var. aureus, 5.0; Salmonella typhosa, 1000; Escherichia coli, >500.[1]

TOXICITY Mice tolerated 1000 mg/kg, i.p. [1].

305. TERREIC ACID

SOURCE Aspergillus terreus [1].

MOLECULAR FORMULA AND WEIGHT C₇H₆O₄ [1,2]; 154, 157 (equiv. wt. found).[2]

CRYSTAL FORM AND COLOR Colorless plates [1]; pale yellow, large, glistening plates [2].

MELTING POINT (°C) 120-121 [1]; 127-127.5 [2].

OPTICAL ACTIVITY [α]_D²² = -16.6⁰¹, -28.6⁰², +74.3⁰³. [2]

UV ABSORPTION MAXIMA 213, 316 mμ [2].

SOLUBILITY s. ether, benzene, alcohol, acetone, hot cyclohexane; sl. s. water, hexane.[1,2]

STABILITY Thermo- and alkali labile; acid stable; thermostable in solid form.[1,2]

OTHER REACTIONS pKa about 4.0-4.5; forms bright yellow salts; deep red color with FeCl₃; reduces Fehling and ammoniacal AgNO₃; precipitate with 2,4-dinitrophenylhydrazine.[1,2]

QUANTITATIVE DETERMINATION Microbiological: Micrococcus pyogenes var. aureus [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits (μg/ml) Proteus vulgaris, 3.1; M. pyogenes var. aureus, Salmonella typhosa, 25; Klebsiella pneumoniae, Escherichia coli, 50.[2] Streptococcus pyogenes and Pseudomonas aeruginosa inhibited by dilutions of 1:5,000-1:10,000 [1]. Candida albicans and Trichophyton mentagrophytes sensitive to 100-400 μg/ml.[2]

In vivo. No activity in mice infected with Diplococcus pneumoniae or K. pneumoniae [2].

TOXICITY LD₅₀ in mice, 71-119 mg/kg, i.v. Inhalation of vapor during sublimation irritating to human nasopharynx.[2]

306. TERTIOMYCIN A
Formerly named Tertiomycin [2].

SOURCE Streptomyces eurocidicus [1].

CRYSTAL FORM AND COLOR White needles [1].

MELTING POINT (°C) 202-204 (d.) [1].

OPTICAL ACTIVITY [α]_D¹⁷ = -44⁰⁴, -49⁰¹. [1]

UV ABSORPTION MAXIMUM 233 mμ⁵ [1].

SOLUBILITY s. methanol, ethanol, butanol, ethyl acetate, butyl acetate, ether, dioxane, ethyl cellosolve, chloroform, acetone; i. water, petroleum ether.[1]

OTHER REACTIONS Analysis: C, 60.10, 60.09, 59.85; H, 8.45, 8.40, 8.18; N, 2.49, 2.79, 2.26, 2.45; negative ninhydrin, biuret, Benedict, Sakaguchi, xanthoproteic, FeCl₃, maltol, Fehling; positive Molisch, Seliwanoff; reddish orange in 40% H₂SO₄; belongs to erythromycin-carbomycin antibiotic group.[1]

/1/ c, 1 chloroform. /2/ c, 1 50% CH₃OH - 50% C₆H₆. /3/ c, 1 phosphate buffer at pH 7. /4/ c, 1 ethanol.
/5/ Ethanol.

306. TERTIOMYCIN A (Concluded)

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Micrococcus flavus*, *Bacillus anthracis*, *B. megatherium*, 0.1; *M. pyogenes* var. *aureus*, *Sarcina lutea*, 0.5; *B. subtilis*, 1.5. Gram-negative bacteria, mycobacteria, and fungi not sensitive to 100 $\mu\text{g/ml}$: *Escherichia coli*, *Shigella dysenteriae*, *Salmonella paratyphi*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, *Myco. phlei*, *Aspergillus niger*, and *Candida albicans*. [1]

TOXICITY Mice tolerated 415 mg/kg, i.p. [1].

307. TERTIOMYCIN B

SOURCE *Streptomyces eurocidicus*¹ [1].

MOLECULAR FORMULA $\text{C}_{43}\text{H}_{71}\text{NO}_{17}$ (proposed) [1].

CRYSTAL FORM AND COLOR White needles² [1].

MELTING POINT ($^{\circ}\text{C}$) 97-99 [1].

OPTICAL ACTIVITY $[\alpha]_{\text{D}}^{22} = -56^{\circ}$ [1].

UV ABSORPTION MAXIMA 231, 278 $\text{m}\mu$ [1].

OTHER REACTIONS Carbomycin type; positive Tollens, Molisch; negative Fehling, ninhydrin, Liebermann, FeCl_3 ; added to 6 N HCl gives no color at room temperature, but turns brownish violet on heating; light reddish brown color with 40% H_2SO_4 . R_f values: 0.08 with citrate buffer at pH 4.6 and benzene, 0.85 with citrate buffer at pH 4.0 and butyl acetate. Analysis: C, 59.1; H, 8.26; N, 1.62. [1]

BIOLOGICAL ACTIVITY *In vitro*. Active against Gram-positive bacteria. Inhibits ($\mu\text{g/ml}$) *Sarcina lutea*, *Micrococcus flavus*, 0.1; *Bacillus anthracis*, *B. megatherium*, 1.0; *B. subtilis*, 1-3; *M. pyogenes* var. *aureus*, 2; *Mycobacterium phlei*, 75. The following were not sensitive to 100 $\mu\text{g/ml}$: *Escherichia coli*, *Shigella dysenteriae*, *Salmonella paratyphi*, *Proteus vulgaris*, *Pseudomonas aeruginosa*; also *Penicillium chrysogenum*, *Aspergillus niger*, *Saccharomyces cerevisiae*, *Candida albicans*. [1]

TOXICITY LD_{50} in mice, approximately 250 mg/kg, i.v. [1].

308. TETAINE

SOURCE *Bacillus pumilus* [2].

FORM AND COLOR Amorphous, colorless powder [1, 2].

SOLUBILITY s. methanol, ethanol, ethylene glycol, water, water-saturated phenol⁴ [1]; i. acetone, chloroform, ether, petroleum ether, benzene, butanol, propanol. [3]

STABILITY Stable in water; unstable to drying. [1, 3]

OTHER REACTIONS Very hygroscopic [3]. Positive ninhydrin; negative COOH, NH_2 tests; dialyzable; not precipitated by protein precipitants. [1, 2]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits a variety of Gram-positive and Gram-negative bacteria. *Shigella dysenteriae* especially sensitive; inhibited by concentration of 8 $\mu\text{g/ml}$. [1, 2] *Micrococcus pyogenes* var. *aureus* and species of *Salmonella*, *Proteus*, and *Klebsiella* are sensitive [3].

TOXICITY Described as slightly toxic. *In vitro*. Non-hemolytic to erythrocytes. [3]

309. TETRACYCLINE

Trademarks for tetracycline are Achromycin (Lederle Laboratories Division, American Cyanamid Company), Panmycin (The Upjohn Company), Polycycline (Bristol Laboratories, Inc.), Steclin (E. R. Squibb and Sons, Division of Olin Mathieson Chemical Corp.), and Tetracyn (Chas. Pfizer & Co., Inc.).

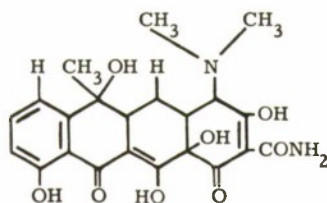
SOURCE *Streptomyces* spp [3], and by catalytic reduction of chlortetracycline [1, 2].

NATURE Amphoteric [4].

MOLECULAR FORMULA AND WEIGHT $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_8$; 227 (equiv. wt. found); 444 (calc.). [2, 4]

/1/ Also produces tertiomycin A, eurocidin, and azomycin. /2/ From benzene. /3/ 1% ethanol. /4/ Reference 2 reports s. water, i. organic solvents.

STRUCTURE



[2]

CRYSTAL FORM Base: orthorhombic¹ [3].

MELTING POINT (°C) Anhydrous form: 170-173 (d.) [1,2]; 170-175 (d.) [4]. HCl: 214 [1,2].

OPTICAL ACTIVITY Base: $[\alpha]_D^{25} = -239.0^2$ [2,4]. HCl: $[\alpha]_D^{25} = -257.9^3$ [1].UV ABSORPTION MAXIMA 220, 268, 355 $m\mu$ ⁴ [1]; 268, 363 $m\mu$ ⁵ [2]; 246, 372 $m\mu$ ⁶ [2].SOLUBILITY Trihydrate: sl. s. water⁷. HCl: s. water⁸. [6]STABILITY Stable in solution of pH 7.0; 50% loss in 12 hours at pH 8.85; no loss in 0.1 N H₂SO₄ in 48 hours, but about 40% after 8 days at room temperature; 40% loss in 3 weeks in pH 4 buffer.[3,5]

OTHER REACTIONS Produced by fermentation or when chlortetracycline is dehalogenated in presence of palladium; pKa 8.3, 10.2⁹; with Ehrlich in dilute aqueous HCl, oxytetracycline gives a bluish-green precipitate after 8 hours and a bluish-green supernatant, chlortetracycline a canary yellow solution, tetracycline an orange-yellow solution (chlortetracycline does not inhibit development of color with oxytetracycline while tetracycline does). With H₂SO₄, oxytetracycline is cherry-red, chlortetracycline purple and later greenish black, tetracycline a stable violet color [1-3]. Like its chloro- and hydroxy- derivatives, tetracycline has a high affinity for divalent cations of heavy metals [80].

QUANTITATIVE DETERMINATION Microbiological: *Klebsiella pneumoniae*¹⁰, *Bacillus subtilis*, *Escherichia coli*, *Sarcina lutea* [3,5,7]. Colorimetric [78,79].

BIOLOGICAL ACTIVITY Antimicrobial spectrum similar to that of its analogues, chlortetracycline and oxytetracycline. In vitro. In general, most strains of the following Gram-positive and Gram-negative bacteria are inhibited by 0.05-5.0 $\mu\text{g/ml}$: *B. anthracis*, *B. subtilis*, *Aerobacter aerogenes*, *Brucella bronchiseptica*, *Clostridium perfringens*, *Cl. tetani*, *Corynebacterium diphtheriae*, *C. xerosis*, *Diplococcus pneumoniae*, *Erysipelothrix rhusiopathiae*, *E. coli*, *Hemophilus ducreyi*, *H. influenzae*, *K. pneumoniae*, *Listeria monocytogenes*, *Micrococcus pyogenes* var. *aureus*, *Mycobacterium tuberculosis*, *Myc. smegmatis*, *Myc. phlei*, *Myc. ranae*, *Neisseria catarrhalis*, *N. gonorrhoeae*, *N. meningitidis*, *Pasteurella multocida*, *Salmonella typhosa*, *S. paratyphi*, *S. schottmuelleri*, *S. gallinarum*, *Sarcina lutea*, *Shigella dysenteriae*, *Sh. sonnei*, *Streptococcus pyogenes*, *Str. viridans*, *Str. faecalis*. Strains of *Pseudomonas aeruginosa* and *Proteus* spp vary widely; majority are resistant to 50 $\mu\text{g/ml}$ or more. Yeasts and fungi not sensitive.[3,7-15] Inhibits *Entamoeba histolytica* in concentrations of 62-250 $\mu\text{g/ml}$ [16]. Concentrations of 2 mg/ml failed to inactivate the virus of herpes simplex [72].

In vivo. Single or multiple s.c. or i.p. doses of 5-25 mg/kg gave good protection in mice infected with *D. pneumoniae*, *Str. pyogenes*, *Str. mitis*, *M. pyogenes* var. *aureus*, *K. pneumoniae* (type A), or *Past. multocida*; higher doses of 40-50 mg/kg required for 100% protection against *Salmonella typhosa* and *K. pneumoniae* (type B).[8,17,18] Some protection afforded in experimental tuberculosis in mice with s.c. doses of 100 mg/kg/da; the order of activity resembled that of oxytetracycline.[18] Daily s.c. doses of 75-125 mg/kg increased survival time in mice infected intracerebrally with *Myc. tuberculosis* var. *hominis*. Oral doses effective in mice infected i.v. with *Myc. tuberculosis* var. *bovis*. [73] The median protective dose against experimental tetanus infection in mice was 14.1 mg/kg, injected i.p. daily for 5 days [81]. Ten daily intramuscular injections of 10 mg/kg in rabbits cured experimental syphilitic orchitis [82]. Doses as low as 0.031 mg per egg were active against feline pneumonitis virus in chick embryos; the action appeared to be virustatic rather than virucidal [84]. Doses of 65 mg/kg/da, administered i.p., prolonged survival time in chicks infected with *S. gallinarum*; did not eradicate the carrier state.[18] Multiple i.p. amounts of 20 mg/kg suppressed *B. anthracis* and *L. monocytogenes* in mice; partial protection against *Ery. rhusiopathiae* with higher doses of 80 mg/kg.[19] The antibiotic failed to protect mice infected with a strain of *M. pyogenes* var. *aureus* which was resistant to chlortetracycline and oxytetracycline [17]. Prolonged survival time in mice with experimental toxoplasmosis, but was less effective, on a weight basis, than chlortetracycline [20,21]. Daily i.p. doses of 10-20 mg/kg suppressed infections with Eaton's atypical pneumonia virus in cotton rats [22]. High i.p. doses of 100-150 mg/kg had an adverse effect on *Candida albicans*, enhancing the infection in mice [23,24]. A number of new tetracycline derivatives were much more active against *Trichomonas vaginalis* in vitro and in vivo in mice than the parent antibiotic; none of these derivatives was active against *Trypanosoma equiperdum* infection.[83]

/1/ Refractive indices: $\alpha = 1.572 \pm 0.005$, $\beta = 1.646 \pm 0.005$, $\gamma = >1.750$. /2/ c, 1 methanol. /3/ c, 0.5 in 0.1 N HCl. /4/ 0.1 N HCl. /5/ 0.01 M methanolic HCl. /6/ 0.01 M methanolic NaOH. /7/ 0.36 mg/ml at 26.5°C. /8/ 132 mg/ml at 26.5°C. /9/ 50% aqueous dimethylformamide. /10/ ATCC 10,031, PCI 602.

CLINICAL This broad-spectrum antibiotic is effective in a wide variety of infections caused by susceptible organisms, including pneumonia, scarlet fever, otitis media, acute pharyngitis, sinusitis, osteomyelitis, laryngotracheobronchitis, meningitis, surgical infections, infections of the urinary tract and soft tissues. The uses and indications are similar to those described for the two analogues, chlortetracycline and oxytetracycline, although tetracycline is not yet as fully evaluated clinically. In general, it is not routinely used as an alternative agent for infections resistant to the analogues since cross resistance to these antibiotics is common although not absolute. Clinical studies have shown that tetracycline may be effective after therapy with its analogues has proved ineffective. The usual dosages are similar to those employed for the analogues. The suggested minimum daily oral dose is 1-2 g divided into 4 equal parts and for children proportionately less, e.g., 20-25 mg/kg/da in 4-5 divided doses. [5, 8, 9, 11, 25-34] Parenteral administration with intramuscular and intravenous preparations has been frequently used [29, 35, 36]. Excellent results have been reported in acute gonorrhoea following single oral doses of 2 g or with the same amount in 8 divided doses administered over a 2-day period [37, 38]. Preliminary trials indicate favorable response in non-gonococcal urethritis following total oral doses of 6 g over a 6-day period [39]. A limited series of patients with acute or chronic brucellosis (probably caused by *Br. melitensis*) showed good clinical response when treated for 8-15 days with 12-50 mg/kg/da [40, 68]. Favorable preliminary results reported in lymphogranuloma venereum, donovanosis, and chancroid [41, 42]; also in a small series of patients with psittacosis [43, 44], exanthematic typhus [45], and Rocky Mt. spotted fever [46]. Oral therapy was generally effective in patients with pustular dermatoses [47], and for prophylaxis and treatment of surgical infections [48]. Preliminary trial suggests the drug is of value in acute amebiasis [49, 69] and in bartonellosis (Carrion's disease) [71]. Good results reported in 26 out of 27 cases of bacillary dysentery caused by *Shigella sonnei* [50]. Variable results noted in a series of 25 patients with typhoid fever treated with oral doses of 50-100 mg/kg/da over periods of 7-12 days [51]. Topical application in ointment base has been successful in the treatment of a variety of skin infections [52], and in trachoma [70]. Appeared to benefit 36 out of 45 patients with infectious hepatitis treated with daily oral doses of 1-1.5 g for 1-12 days. The duration of illness was reduced from 5-8 weeks to 1-2 weeks. [74]. Tsutsugamushi disease successfully controlled with oral therapy [85]. Total oral doses of 10-14 g over periods of 5½-8 days effective in treating human cases of anthrax infection [86]. Beneficial results in pertussis have been described [29]. The antibiotic was of no value in cases of active tuberculosis [5, 87]. Initial intravenous dosage of 7 mg/kg at 8-hour intervals, followed with oral therapy, has been successful in the treatment of *H. influenzae meningitis* [88]. Good results have also been obtained in five cases of leptospiral meningitis [89].

VETERINARY Value of tetracycline in veterinary practice is still under investigation. Preliminary reports indicate it is beneficial in bovine mastitis caused by *Str. agalactiae*. [53] Parenteral administration of 1-2 mg/lb of body weight was effective in cattle with shipping fever complex and pneumonia; also in infectious scours and pneumonia in swine. [54] In limited trials, cases of pneumonia-enteritis complex, mastitis and listeriosis in sheep responded favorably to therapy [55]. Oral medication with doses of 100-250 mg twice daily for 4-5 days was of value in feline distemper [54]; pneumonia, bacillary enteritis and distemper complex in dogs responded to oral or parenteral medication [56]. Highly effective in the treatment of natural psittacosis infection in parakeets; a regimen of 0.4 mg administered i.m. twice daily for 14 days was employed. [57] Intramuscular doses of 2 mg/lb of value in canine and feline infection [75]. One or two doses of 2 mg/lb, i.m., effective in controlling shipping fever complex in cattle, sheep, and pigs [76]. Three i.m. doses protected sheep against experimentally induced anthrax infection [77]. In experimental anaplasmosis in splenectomized calves, single intravenous or intramuscular injection of 3 mg/lb body weight prevented increase in the number of *Anaplasma marginale* in red blood cells [90]. Daily oral doses of 50-160 mg/kg were highly effective in prophylaxis of an artificially induced enzootic (virus) pneumonia in pigs [91]. Daily intravenous medication with 2.5 mg/lb body weight in divided doses recommended for a variety of bacterial infections in dogs and cats, including peritonitis, endometritis, pneumonia, pharyngitis, otitis media, upper respiratory mixed infections, bronchitis, sinusitis, urinary tract infections, wound infections, and feline panleucopenia [92]. Multiple intramuscular doses controlled feline infectious anemia [93]. Topical therapy valuable in a wide variety of eye, ear and skin infections encountered in small animal practice [99].

TOXICITY LD₅₀ in mice, 162-170 mg/kg, i.v.; 190-330 mg/kg, i.p.; 2130->3000 mg/kg, oral. LD₅₀ in rats, 129-220 mg/kg, i.v.; 320 mg/kg, i.p.; >3000 mg/kg, oral. [8, 58] Daily oral amounts of 100 mg/kg in mice and 100-400 mg/kg in rats for periods up to 30 days were well tolerated. In dogs, oral doses of 200-250 mg/kg/da for 12-14 weeks were non-toxic; no pathologic changes noted. [8, 58, 60]. Repeated i.v. doses were well tolerated with no effect on the liver or kidney function; no adverse cardiovascular or respiratory effects observed in anesthetized dogs. [58] Repeated injection of 50 mg/kg/da for 4 weeks, via the i.p. route, produced changes in abdominal viscera of weanling rats, but appeared less irritating than chlortetracycline [59]. Like its chloro- and hydroxy- derivatives, tetracycline is poorly tolerated in guinea pigs and hamsters. Three daily oral doses of 50 mg/kg in hamsters induced a frequently fatal diarrhea, with necrosis of the intestinal mucosa. These adverse effects were largely prevented by concurrent administration of 250 mg/kg/da of sulfaguanidine. [94] In vitro. In tissue cultures, tetracycline and oxytetracycline (but not chlortetracycline), in concentrations of 50 µg/ml, had a growth-stimulating action on embryonic cardiac tissue of the chick. All three antibiotics in concentrations of >100 µg/ml were toxic to fibroblasts. [96]

In man, the antibiotic appears to be well tolerated and although occasional nausea, vomiting, and diarrhea are noted following oral therapy, these side effects appear to be less frequently associated with tetracycline than with its analogues [5, 27-30]. Continued topical use of dermatological preparations containing 3% of the antibiotic is associated with a relatively low index of sensitization, in contrast to penicillin, streptomycin, and the sulfonamides [95].

RESISTANCE In vitro. Resistance develops slowly in a gradual, stepwise manner. Resistant forms of *M. pyogenes*

309. TETRACYCLINE (Concluded)

var. aureus and *E. coli* were developed by 10-12 consecutive transfers in the presence of increasing amounts of the antibiotic. Cross resistance shown by various microorganisms to all three tetracyclines, but not to other antibiotics.[3, 8, 61, 65]

ABSORPTION AND EXCRETION After single or repeated doses of tetracycline, concentrations in the blood appear at somewhat higher levels and are generally better sustained than has been noted for its analogues. It passes the blood-brain barrier more readily, producing higher cerebrospinal fluid concentrations than those usually obtained with either chlortetracycline or oxytetracycline. After oral ingestion, the antibiotic is excreted in the urine, bile and feces in a similar manner and retains its antimicrobial activity in the urine and gastrointestinal contents. In dogs, single oral doses of 6.2-12.5 mg/kg produced appreciable serum levels for at least 8 hours; after 10 mg/kg, i.v., therapeutic levels were maintained for approximately 24 hours; similar results in rabbits.[8, 58]. In chick embryo, application of antibiotic to chorioallantoic membrane is followed by rapid absorption, with peak concentrations in embryo after 2 days, and in the allantoic fluid on the third day. Injection into allantoic fluid resulted in 33% destruction of tetracycline within 48 hours; approximately 15% of active antibiotic remained after 8 days.[98]

In man, following repeated oral doses, peak blood concentrations of 2-8 µg/ml noted, with levels of approximately 320 µg/ml in the urine in 6-12 hours, and detectable concentrations in the spinal fluid, pleural fluid, saliva, abdominal fluid and cord serum [3, 61-63]. Repeated i.v. doses produced high blood concentrations and levels of 1.25-5.0 µg/ml in cerebrospinal fluid [64]. Intramuscular administration of 10 mg/kg every 12 hours gave serum concentrations approximating those generally obtained after oral medication with the usual dosages [35]. Concentrations in thyroid tissue following oral therapy with tetracycline were significantly higher than those obtained with comparable doses of chlor- or oxytetracycline [97].

MODE OF ACTION Essentially bacteriostatic in action, but higher concentrations may be bactericidal [3, 8]. (See also chlortetracycline.)

ANIMAL NUTRITION Preliminary results with chicks and pigs indicate that, like certain other antibiotics, tetracycline may be of value as a feed supplement for stimulating growth in animals [3, 66, 67].

310. THERMOPHILLIN

SOURCE *Lenzites thermophila* [1].

NATURE Quinonoid properties [1].

MOLECULAR FORMULA C₁₈H₁₈O₉ [1].

CRYSTAL FORM AND COLOR Golden plates [1].

SOLUBILITY sl. s. ethanol, ether, chloroform, water; i. most organic solvents.[1]

STABILITY Thermostable at neutral and acid pH; unstable in alkali [1].

OTHER REACTIONS Sublimes at 245°C in air, 260°C in sealed tube; yellow aqueous solution, changing to red in alkali; I from KI; reduced to colorless with sodium hydrosulfite; bright red with concentrated H₂SO₄, becoming brown on heating and yellow upon addition of ethanol.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. aureus [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits *M. pyogenes* var. aureus in dilution of 1:10,000 [1].

311. THERMOVIRIDIN

SOURCE *Thermoactinomyces viridis*, n. sp, resembling *T. monospora* [1].

NATURE Acidic [1].

UV ABSORPTION MAXIMA 268-272 mµ [1].

STABILITY Stable for 21 hours at pH 2-8 at 37°C; at pH 10, 50% loss at 8 hours.[1]

OTHER REACTIONS Negative biuret, ninhydrin, xanthoproteic, Molisch, lead acetate; dialyzable; precipitated with (NH₄)₂SO₄. [1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. aureus 209-P [1].

BIOLOGICAL ACTIVITY In vitro. Preparations containing 64 units per mg inhibited (units/ml) *Clostridium septicum* at 0.03; *Sarcina lutea*, 0.25; *Bacillus subtilis*, 0.5; *M. pyogenes* var. aureus, including strains resistant to penicillin, 1-4; *Cl. tetani*, 2; *Diplococcus pneumoniae*, 4; *Streptococcus pyogenes*, 4-16; *Str. viridans*, *Coryne-*

311. THERMOVIRIDIN (Concluded)

bacterium diphtheriae, 16; Proteus vulgaris, Escherichia coli, Shigella paradysenteriae, Salmonella typhimurium, 64. The following were not sensitive to 26 units/ml: Mycobacterium tuberculosis var. hominis, Myco. phlei; also Nocardia asteroides, Candida albicans, Blastomyces dermatitidis, Aspergillus fumigatus, Histoplasma capsulatum, Trichophyton mentagrophytes. No loss of in vitro activity in the presence of sheep blood.[1]

TOXICITY Mice tolerated i.p. doses of 32 mg of material containing a total of 800 units of antibiotic activity [1].

312. THIOAURIN
(Antibiotic HA-9, Orosomycin)

SOURCE Streptomyces sp related to S. lipmanii [1, 2].

MOLECULAR FORMULA AND WEIGHT $C_7H_6N_2O_2S_2$ [2], or $C_{14}H_{12}O_4N_4S_4$ (proposed) [1]; 226 (Rast); 214 (calc.) [2]; 290-400 (Rast) [1].

CRYSTAL FORM AND COLOR Yellow crystals.

MELTING POINT ($^{\circ}C$) 179-181 [1]; 175-180 [2].

OPTICAL ACTIVITY $[\alpha]_D^{25} = 0^1$ [2].

UV ABSORPTION MAXIMA 232, 370 $m\mu$ [1].

SOLUBILITY Crude: s. methyl isobutyl ketone, ethyl acetate, n-butanol, chloroform, i. or sl. s. benzene, ether. Crystalline: s. methanol; sl. s. ethyl acetate; i. water, chloroform.[2]

OTHER REACTIONS Negative $FeCl_3$; zones greatly enhanced at pH 6; solubility not affected by pH.[2]

QUANTITATIVE DETERMINATION Microbiological: Sarcina lutea [2].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu g/ml$) Salmonella typhosa, 1.1; Micrococcus pyogenes var. aureus, Proteus vulgaris, 4.5; Bacillus subtilis, Aerobacter aerogenes, Klebsiella pneumoniae, S. schottmuelleri, Mycobacterium tuberculosis, 1.6-6.2; Escherichia coli, 9; Pseudomonas aeruginosa, 72-100. Yeasts and fungi ($\mu g/ml$): Saccharomyces cerevisiae, Aspergillus niger, 144; Chaetomium globosum, Myrothecium verrucaria, 100; Candida albicans, Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Microsporium gypseum, Sporotrichum schenckii, Trichophyton mentagrophytes, 1000.[1, 2] *In vitro* activity appears to be enhanced by 25% serum [2].

TOXICITY LD_{50} in mice, 15-16 mg/kg, i.v.; 20 mg/kg, s.c. Poor weight gains in mice receiving s.c. doses of 2 mg/kg/da for 7 days, with ulcerating nodules at site of injection.[1, 2] I.v. doses of 7.8 mg/kg lethal to dogs [2].

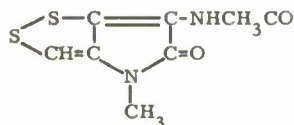
313. THIOLUTIN

SOURCE Certain strains of Streptomyces albus [6].

NATURE Neutral [1, 16].

MOLECULAR FORMULA $C_8H_8O_2N_2S_2$ [3]; 228 (calc.) [16].

STRUCTURE



[5, 16]

CRYSTAL FORM AND COLOR Brilliant yellow needles [1, 2, 16].

MELTING POINT ($^{\circ}C$) 270 (d.) [2, 16].

OPTICAL ACTIVITY Inactive [3, 16].

UV ABSORPTION MAXIMA 245, 315, 365 $m\mu$ [2]; 250, 311, 388 $m\mu$ [4, 16].

SOLUBILITY s. most organic solvents; sl. s. water.[1, 2]

/1/ c, 0.75 glacial acetic acid.

313. THIOLUTIN (Concluded)

STABILITY Acid stable, alkali labile [2] ; thermostable [16] .

OTHER REACTIONS Raney nickel treatment yields "desthiolutin" (MP 130-131°C); acid hydrolysis yielded an amine, $C_6H_6N_2OS_2$, identical to one so obtained from aureothricin.[3,4] Sublimes without decomposition when heated in vacuo. Infrared: Carbonyl bands at 6.00 and 6.12 μ ; NH stretching and bending absorption at 3.12 and 6.45 μ ; strong C=C stretching absorption at 6.25 μ . [16]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits (μ g/ml) *Bacillus subtilis*, 1; *Proteus* sp, *Salmonella typhosa*, 2.5; *S. paratyphi*, *Escherichia coli*, *Mycobacterium* spp, *Micrococcus pyogenes* var. *aureus*, 5; *Aerobacter aerogenes*, 7.5; *Klebsiella pneumoniae*, 10; *Streptococcus faecalis*, 15; *Brucella bronchiseptica*, *Pseudomonas aeruginosa*, 50-200. Fungi: *Histoplasma capsulatum*, 6.2; *Microsporium audouini*, *Trichophyton rubrum*, *Epidermophyton floccosum*, 12.5; *Coccidioides immitis*, *C. brasiliensis*, *Blastomyces dermatitidis*, 50. *Candida albicans* not sensitive. [2] Phytopathogenic fungi: Species of *Pythium*, *Sphaeropsis*, *Sclerotinia* inhibited by 10 ppm; *Colletotrichum*, *Phomopsis*, *Rhizoctonia* by 50-100 ppm.[7] Protozoa: *Trichomonas vaginalis* sensitive to concentration of 0.2 μ g/ml; *Entamoeba histolytica*, *Leishmania tropica*, *L. donovani*, *Trypanosoma cruzi*, 4-7.8 μ g/ml.[2,8] Low levels (0.012 μ g/ml) toxic to human spermatozoa [9] . Of several antibiotics tested, thiolutin was the most active against 4 species of *Leptospira* (*L. mitis*, *L. canicola*, *L. icterohemorrhagiae*, *L. grippityphosa*), with nearly complete immobilization following exposure to concentrations of 60 μ g/ml [17] .

In vivo. Slight suppressive effect in experimental infections with *Trypanosoma cruzi*, but toxic to mice at doses administered (0.25 mg/kg, i.p.) [10] . No activity against *Plasmodium gallinaceum* in chicks following 2 mg/kg/da, i.p. [11] .

TOXICITY LD₅₀ in mice, 25 mg/kg, s.c.; 25 mg/kg, oral.[2]

PHYTOPATHOLOGY Sprays useful in control of fire blight of apple trees (caused by *Erwinia amylovora*) [12] , and late blight of potato [13] . Levels of 10-20 ppm effectively controlled tomato wilt caused by *Bacterium lycopersici* [14] . Use in concentrations up to 1% as dust markedly improved germination of oat grain infected with the fungus *Helminthosporium sativum*. Levels of 100 ppm non-toxic to leaves of young tomato plants, roots of maize, pea, tomato, sunflower, or to seeds of maize, pea or radish.[7]

MISCELLANEOUS Concentration of 1 μ g/ml inhibited secondary yeast growths in unpasteurized beer. Combinations with polymyxin or penicillin very effective in protecting against microbiologic contaminants in finished beer. [15] Growth of wheat roots in distilled water (but not in tap water) was stimulated by addition of 0.32 ppm of thiolutin [18] . The antibiotic was a potent molluscicide; concentrations of 0.06-0.25 μ g/ml were lethal to snails (*Australorbis glabrata*) in 12-24 hours [19] .

314. THIOMYCIN

SOURCE *Streptomyces* sp resembling *S. phaeochromogenus* var. *chloromyceticus* [1] .

CRYSTAL FORM AND COLOR Golden yellow needles¹ [1] .

MELTING POINT (°C) 176-178 (d.) [1] .

SOLUBILITY s. methanol, ethanol, butanol, amyl alcohol, acetone, ethyl acetate, chloroform, benzene; sl. s. water, ether, petroleum ether.[1]

STABILITY Stable at pH 2; unstable to alkali.[1]

OTHER REACTIONS Analysis: C, 49.61; H, 5.50; N, 8.88; S, 16.26. Negative ninhydrin, $FeCl_3$, Fehling; some resemblance to thioaurin.[1]

QUANTITATIVE DETERMINATION Microbiological: *Proteus vulgaris* (OX-19)² [1] .

BIOLOGICAL ACTIVITY *In vitro*. Inhibits (μ g/ml) *Bacillus anthracis*, *Salmonella enteritidis*, *Proteus vulgaris*, 3.2; *Micrococcus pyogenes* var. *aureus*, *B. subtilis*, *Escherichia coli*, *Shigella sonnei*, *Mycobacterium tuberculosis*, 12.5; *Pseudomonas aeruginosa*, 100.[1]

TOXICITY Very toxic in mice; LD₅₀, 10 mg/kg, s.c. [1]

315. THIOSTREPTON

SOURCE *Streptomyces* sp [1] .

MOLECULAR WEIGHT 420 (equiv. wt.) [2] .

MELTING POINT (°C) 246-256 (d.) [2] .

/1/ Ethyl acetate. /2/ More active at pH 6 than at 6.8.

315. THIOSTREPTON (Concluded)

OPTICAL ACTIVITY $[\alpha]_D^{23} = -98.5^{01}, -61^{02}, -20^{03}.$ [2]

UV ABSORPTION MAXIMA None; shoulders at 225, 250, 280 m μ . [2]

SOLUBILITY s. chloroform, dioxane, pyridine, glacial acetic acid, dimethylformamide; i. water, lower alcohols, non-polar organic solvents. [2]

STABILITY Stable 4 days in broth at 37°C; loses 80% of activity in 8 days. [1]

OTHER REACTIONS Analysis: C, 51.3; H, 5.4; N, 14.6; S, 7.4; methoxyl or thiomethyl, 0. Infrared: 3.05, 3.5, 5.7, 6.02, 6.2, 6.6, 7.25, 8.3, numerous from 9-14, and a broad band at 14.5 μ . Tests using dioxane as a solvent give higher values than centrifuged beers; dissolves in methanolic acid or base with inactivation; positive biuret; negative ninhydrin, Sakaguchi; probable amino acids are leucine (or isoleucine), valine, alanine, threonine, proline, lysine, glycine, aspartic acid, glutamic acid, cystine, tryptophan. [1,2]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* 209-P [1].

BIOLOGICAL ACTIVITY *In vitro*. Primarily active against Gram-positive bacteria. Inhibits (μ g/ml) *Streptococcus pyogenes* at 0.003; *M. pyogenes* var. *aureus* (including strains resistant to penicillin, streptomycin, chloramphenicol, carbomycin, erythromycin and the tetracycline antibiotics), 0.024-0.125; *Bacillus subtilis*, *Clostridium septicum*, 0.03; *Str. faecalis*, *Lactobacillus acidophilus*, 0.06; *Neisseria gonorrhoeae*, 0.3; *Mycobacterium tuberculosis* var. *hominis* (strain BCG), 3; *Diplococcus pneumoniae* (type 2), 4-8. The following Gram-negative bacteria were insensitive to 50 μ g/ml: *Escherichia coli*, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Salmonella schottmuelleri*, *Shigella* spp. No activity against fungi. [1]

In vivo. Active in mice infected with an *M. pyogenes* var. *aureus* strain resistant to penicillin and the tetracyclines when injected in doses of 25-50 μ g per mouse, i.v. Two daily doses of 6-10 μ g, i.v., or 50 μ g, s.c., protected mice against *Str. pyogenes*. [3]

PHARMACOLOGY In mice, antibiotic apparently is not absorbed from the gastrointestinal tract following oral doses as high as 250 mg/kg [3].

RESISTANCE No cross resistance shown between thiostrepton and penicillin, streptomycin, erythromycin, carbomycin, tetracycline, neomycin, or gramicidin [1].

MODE OF ACTION Essentially bacteriostatic [1].

316. TOXIMYCIN

SOURCE *Bacillus subtilis* [2].

NATURE Polypeptide or protein [1].

SOLUBILITY s. water at pH 6-10, 80% ethanol, 50% acetone; less s. water at pH 5-6, absolute ethanol, glacial acetic acid; sl. s. dioxane, n-butanol, isopropanol; i. acetone, ether, chloroform, benzene, methyl, ethyl and amyl acetates, water below pH 5. [1]

STABILITY Thermostable in buffer at pH 6.8; thermolabile in water, especially at alkaline pH. [1]

OTHER REACTIONS Positive Millon, xanthoproteic, biuret, ninhydrin; negative Fehling; slowly dialyzable; not inactivated by pepsin or trypsin. [1]

QUANTITATIVE DETERMINATION Microbiological: *Glomerella cingulata* [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits fungi (μ g/ml): *Trichophyton mentagrophytes*, 6.25; *G. cingulata*, 12.5-25; *Gliocladium fimbriatum*, *Alternaria solani*, *Botrytis allii*, *Chalara quercina*, *Penicillium notatum*, 25; *Helminthosporium* spp., *Sclerotinia fructicola*, 25-50; *Saccharomyces cerevisiae*, 50. Bacteria (μ g/ml): *Bacillus cereus*, 25; *Xanthomonas campestris*, 25-50; *Micrococcus pyogenes* var. *aureus*, 50-100; *Corynebacterium* sp., 250. [1]

PHYTOTOXICITY Concentrations of 1.0 mg/ml non-toxic to a variety of plants [1].

PHYTOPATHOLOGY Good protection against *Alternaria solani* on tomato foliage at 45-300 μ g/ml. Inhibited lesion development in leaves of cowpea plants infected with tobacco necrosis virus. [1]

317. TOYOCAMYCIN
(Toyokamycin)

SOURCE *Streptomyces* sp resembling *S. albus* [1].

/1/ c, 1 in glacial acetic acid. /2/ c, 1 in dioxane. /3/ c, 1 in pyridine.

NATURE Weakly basic [1].

CRYSTAL FORM AND COLOR Free base: colorless needles [1].

MELTING POINT (°C) 233-234 [1].

UV ABSORPTION MAXIMA 230, 277 $m\mu$ ¹; 235, 273 $m\mu$ ²; 233, 280 $m\mu$ ³. [1]

SOLUBILITY s. methanol, ethanol, n-butanol, ethyl acetate, acetone; sl. s. water (1 mg/ml); i. benzene, chloroform, ether, petroleum ether. HCl: s. water [1].

STABILITY Relatively stable at pH 5; unstable at pH 2, 7, 9. [1]

OTHER REACTIONS Culture produces 2 other antibiotics; negative Sakaguchi, Fehling, FeCl₃, Molisch, Millon, Ehrlich. Analysis: C, 49.14; H, 4.34; N, 23.77; O, 22.75. [1]

BIOLOGICAL ACTIVITY In vitro. Inhibits (μ g/ml) *Candida albicans* at 1.6; *Saccharomyces cerevisiae*, 6.2; *Willia* sp, 100. The following were not sensitive to 100 μ g/ml: *Aspergillus niger*, *Mucor pusillus*, *Absidia orchidis*, *C. krusei*, *Torula utilis*, *Trichophyton interdigitale*. [2]

318. TRICHOMYCIN

SOURCE *Streptomyces hachijoensis*, n. sp [3].

FORM AND COLOR Yellow amorphous powder [1].

MELTING POINT (°C) 155 (d.) [1].

UV ABSORPTION MAXIMA 286, 346, 364, 384, 405 $m\mu$ [1].

SOLUBILITY s. water, aqueous acetone, aqueous methanol, aqueous ethanol at slightly alkaline pH; less s. butanol, ethanol, methanol, acetone; i. ether, petroleum ether, ethyl acetate, amyl alcohol. [1]

STABILITY Thermostable at pH 7-8.5; unstable at pH 2. [1]

OTHER REACTIONS No N, S, or halogens; color changes from yellow to brick red upon decomposition; blue color becoming violet upon addition of concentrated H₂SO₄ or HCl; negative FeCl₃, ninhydrin, biuret, Fehling, Benedict, Molisch, Tollens, quinone reactions [1]. Precipitated by acridine derivatives (rivanol, acriflavin), sulfonamides, basic antibiotics, enzymes, dyes, metallic salts; rivanol-trichomycin water-insoluble salt especially useful; can be separated into fractions A, B, C by alumina chromatography [9, 10].

QUANTITATIVE DETERMINATION Microbiological: *Candida albicans* [2].

BIOLOGICAL ACTIVITY In vitro. Inhibits spirochetes and protozoa (μ g/ml): *Treponema pallidum* immobilized by concentration of 250 in 9 minutes; *Trichomonas vaginalis*, *T. foetus* immobilized by 0.6; *Trypanosoma gambiense* and *Borrelia duttoni* also sensitive. The yeast-like fungus, *C. albicans*, inhibited by 5 μ g/ml. [1, 4, 19] Inhibited 56 strains of *C. albicans* at 0.05-0.4 units/ml [11]. Most strains of *C. tropicalis*, *C. krusei*, inhibited by 2.5-10 μ g/ml. *C. solani*, *Torulopsis* spp, *Saccharomyces carlsbergensis*, *Hansenula anomala*, and *Rhodotorula mucilaginosa* not sensitive to high concentrations [17]. Active against *Trypanosoma cruzi* [12]. Concentrations of 0.1 μ g/ml immobilized *Leishmania donovani* [13]. Reiter strain of *Treponema pallidum* inhibited by 0.047 μ g/ml [18].

In vivo. No activity against *Trypanosoma gambiense* and *Borrelia duttoni* in mice [4]. I.p. doses of 10-50 μ g gave high protection against *Trichomonas vaginalis* in mice [19]. S.c. doses of 1.8-28 mg/kg effective against s.c. infection with *T. vaginalis* in mice [14]. Four i.v. doses of 20 μ g/da protected mice infected i.v. with *C. albicans* [15]. Daily oral doses of 10,000 *Candida* units for 10-20 days in rabbits were effective against experimental syphilitic orchitis [18].

CLINICAL A case of *trichomonas* vaginitis was successfully treated with daily oral doses of 18,000-27,000 units over a 3-week period [16]. Intravaginal use of tablets containing 50 mg in one or two daily doses for 4-7 days controlled vaginitis caused by *T. vaginalis* and *C. albicans* [5]. Topical administration of solutions containing 1-10 mg/ml effective in otitis media caused by *Candida* spp, and in infections of the external auditory canal caused by *Candida* or *Absidia ramosa*; no response in infections with *Aspergillus* sp. [6]

PHARMACOLOGY LD₅₀ in mice, 160 mg/kg, s.c.; 4.2 mg/kg, i.p. Mice tolerated oral doses of 160 mg/kg, 830 mg/kg were lethal. [7] With preparations of 1900 units/mg, LD₅₀ in mice: 34,000 units/kg, s.c.; 4200 units/kg, i.p., 4300 units/kg, i.v. [8] Small amounts were excreted in the urine of guinea pigs following s.c. or oral doses. [2] Concentration of >1.9 units/ml stimulated isolated frog heart. Respiration inhibited and cessation of cardiac

/1/ Water. /2/ 0.1 N HCl. /3/ 0.1 N NaOH.

318. TRICHOMYCIN (Concluded)

contraction noted in rabbits after doses of 700-750 units/kg; doses of 475 units/kg had no effect on the blood count or liver function. Red blood cells lysed by concentration of 1.2 units/ml.[8]

In man, oral doses of 50 mg were tolerated [2].

RESISTANCE *C. albicans* did not readily develop resistance in vitro; 8 to 23-fold resistance developed in 5 strains following 60 serial subcultures in antibiotic.[11] No in vitro resistance developed by *T. vaginalis* following contact of 30 generations with trichomycin [13].

319. TRICHOHECIN

SOURCE *Trichothecium roseum* (Link) [1].

NATURE Neutral; ester [3].

MOLECULAR FORMULA AND WEIGHT $C_{19}H_{24}O_5$; 312-332 (Rast); 332 (calc.).[3]

CRYSTAL FORM AND COLOR Slender, fibrous, colorless needles [1,2].

MELTING POINT ($^{\circ}C$) 118 (corr.) [1,2].

OPTICAL ACTIVITY $[\alpha]_D^{18} = +44^{\circ}$ [1,2].

UV ABSORPTION MAXIMA 220, 334 μ^2 ; 230, 325 μ^3 . [2]

SOLUBILITY s. chloroform, acetone, benzene, ethanol; sl. s. petroleum ether, water.[1,2]

STABILITY Thermostable; labile at pH 12.[1,2]

OTHER REACTIONS Ester components are isocrotonic acid and trichothecolone (a ketonic alcohol); reduces cold permanganate, but not Br; forms 2,4-dinitrophenylhydrazones; the acetyl, butyryl and crotonyl esters had the same order of activity as trichothecin.[2-4]

QUANTITATIVE DETERMINATION Microbiological: Inhibition of spore germination of *Penicillium digitatum* [1,2].

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi ($\mu g/ml$): *P. digitatum*, 0.04; *Neurospora crassa*, 3.2; *P. melea-grinus*, *P. oxalicum*, *P. spinulosum*, *Aspergillus niger*, *Chaetomium convolutum*, *Fusarium graminearum*, *Thamnidium elegans*, *Saccharomyces carlsbergensis*, 16; *A. fumigatus*, *Helminthosporium sacchari*, *P. citrinum*, *P. expansum*, *P. lilacinum*, *P. roqueforti*, *Mucor erectus*, 80.[5] Animal pathogens ($\mu g/ml$): *Histoplasma capsulatum*, 3.2; *Trichophyton mentagrophytes*, *T. rubrum*, *Microsporium canis*, *Cryptococcus neoformans*, *Candida albicans*, 16; *Blastomyces dermatitidis*, *Geotrichum cutaneum*, *T. interdigitale*, *T. sulfureum*, *Hormodendrum langeroni*, 80; *Coccidioides immitis*, *Sporotrichum tropicale*, *S. schenckii*, *S. beurmanni*, >80. *Nocardia asteroides* and bacteria not sensitive to 80 $\mu g/ml$. [4]

TOXICITY Mice tolerated i.v. doses of 5 mg/kg; 12.5 mg/kg, toxic; 500 mg/kg, lethal. 250 mg/kg, s.c., lethal to rabbits. 1% solution topically applied irritated guinea pig and human skin; same concentration irritated rabbit eye and induced conjunctivitis.[4]

PHYTOPATHOLOGY Preinoculation spray with 500 ppm successfully prevented stem rust of wheat (caused by *Puccinia graminis*) under greenhouse conditions [7]. When sprayed on leaves 1 day after inoculation, trichothecin inhibited infection by tobacco mosaic, tobacco necrosis, and tomato bushy stunt viruses, but was ineffective when applied 2 days before. Direct antiviral activity questionable; has been suggested that antibiotic may have altered metabolism of host leaf cells so that virus particles could not multiply.[6]

320. TYROCIDINE

A component of tyrothricin, q.v.

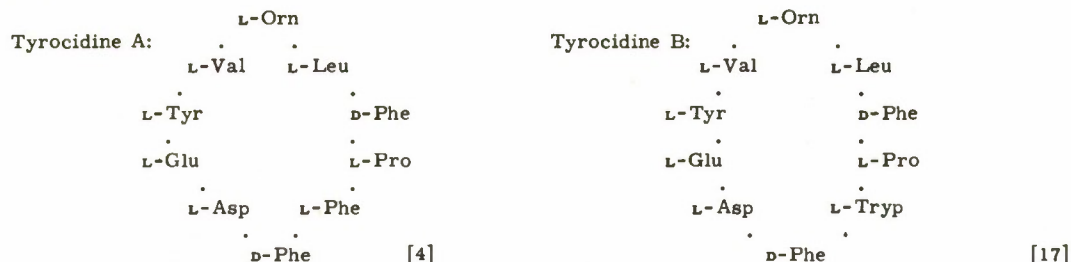
SOURCE *Bacillus brevis* [1].

NATURE Mixture of basic polypeptides [2-5].

MOLECULAR FORMULA AND WEIGHT Mixture: $C_{127}H_{166}N_{26}O_{26} \cdot 2HCl$ (possible); 1000-3000 (found); 2546 (calc.). [3] Tyrocidine A⁴: $C_{66}H_{86}O_{13}N_{13}$ [4]; 1270 (found).[6] B: $C_{68}H_{88}O_{13}N_{14}$; 1346 (calc.). Mono-DNP derivative: 1660 (found); 1512 (calc.). Di-DNP derivative: 1890 (found); 1678 (calc.).[16]

/1/ c, 1.0 chloroform. /2/ Chloroform or hexane. /3/ Ethanol. /4/ Tyrocidine A is one of polypeptides present in the mixture called "tyrothricin."

STRUCTURE



CRYSTAL FORM AND COLOR HCl: fine colorless needles or rods [1, 3, 5].

MELTING POINT (°C) Mixture: 237-239 (uncorr.) [2]; 240 (corr., d.) [1, 3]. Tyrocidine A: 240-242 (d.) [5].

OPTICAL ACTIVITY Mixture: $[\alpha]_D^{25} = -101^{\circ}$, $-102^{\circ 1}$ [2, 3]. Tyrocidine A: $[\alpha]_D^{25} = -111^{\circ 2}$ [5].

UV ABSORPTION MAXIMUM Tyrocidine A: 290 m μ [5].

SOLUBILITY s. methanol, ethanol, acetic acid, pyridine (especially in presence of water); sl. s. water, dry acetone, dioxane; i. ether, hydrocarbons, chloroform, electrolytes. [1, 3, 5]

STABILITY Thermostable [3].

OTHER REACTIONS Polypeptide component of tyrothricin; positive ninhydrin, p-dimethylaminobenzaldehyde, Millon; red color with diazobenzenesulfonic acid; precipitate with phosphotungstic acid; not digested by enzymes. [1, 3]

QUANTITATIVE DETERMINATION Microbiological: Streptococcus spp, Micrococcus conglomeratus [7-9]. Colorimetric³ [10].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) M. lysodeikticus, Bacillus subtilis, 1; M. conglomeratus, 7; M. pyogenes var. aureus, 15-150; B. mycoides, Sarcina lutea, 3; Clostridium tetani, 2; Cl. perfringens, Actinomyces spp, 10; Diplococcus pneumoniae, 2-5; Str. pyogenes, 3-10; Neisseria gonorrhoeae, N. meningitidis, 40; Salmonella typhosa, 800; Escherichia coli, Aerobacter aerogenes, >300. Protozoa: Inhibits Trypanosoma cruzi at 100-200 $\mu\text{g/ml}$. [11]

In vivo. Little or no effect on M. pyogenes var. aureus or Cl. perfringens infections in mice [12]. No activity against T. cruzi in mice treated i.p. with doses of 5-10 mg/kg [13].

TOXICITY LD₅₀ in mice, 15 mg/kg, i.v.; 40 mg/kg, i.p. Oral doses of 1000 mg/kg tolerated. [14, 15] Depressed respiration in anesthetized animals [14]. In vitro. Rapid lysis of red blood cells by concentrations of 50-100 $\mu\text{g/ml}$. Low concentrations toxic to leukocytes and to frog embryos. [3]

321. TYROTHRICIN

SOURCE Bacillus brevis [1].

COMPOSITION Consists mainly of approximately 20% gramicidin, and approximately 80% tyrocidine (q.v.), the latter usually present as the hydrochloride. Gramicidin (q.v.) is the more active component; tyrocidine, despite its high in vitro activity, loses much of this activity in vivo. [2]

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) Diplococcus pneumoniae, 0.006-3.0; Streptococcus pyogenes, 0.2-10; Str. salivarius, 1-5; Str. faecalis, 1-20; Corynebacterium diphtheriae, 1; Micrococcus lysodeikticus, 0.1; M. pyogenes var. aureus, 1-200; M. conglomeratus, 5; Clostridium perfringens, 0.1-10; Cl. tetani, 2; Bacillus subtilis, Lactobacillus acidophilus, 3; Sarcina lutea, B. mycoides, 10; Neisseria meningitidis, 10->50; N. catarrhalis, 600; Escherichia coli, 800->800; Salmonella paratyphi, 800. In general, most Gram-negative bacteria are not sensitive. Fungi: Trichophyton schoenleinii, 50; T. mentagrophytes, Microsporium gypseum, 100; Candida albicans, 200. [2, 15] Spirochetes and protozoa ($\mu\text{g/ml}$): Borrelia vincentii, 5-20; Treponema pallidum, 1000; Trichomonas vaginalis, 50; Trypanosoma cruzi, 250. [3-6]

In vivo. Small i.p. doses protected mice infected with D. pneumoniae, Str. pyogenes (including strains resistant to sulfonamide drugs), and B. anthracis [7-10]. Prolonged survival time in mouse infections caused by M. pyogenes var. aureus and Cl. perfringens [8]. Experimental empyemata, induced with Str. pyogenes in rabbits, were sterilized after intrapleural administration of the antibiotic; similar infections with M. pyogenes var. aureus were more resistant to treatment. [11] Str. pyogenes eliminated from nasopharynx of monkeys and from knee joints of rabbits after local treatment [11, 12]. Tyrothricin protected chickens against infection with Plasmodium gallinaceum when given i.v. in doses of 2 mg/kg/da, but was inactive against P. lophurae in turkeys [13, 14]. Slight suppression of Trypanosoma cruzi in mice although the i.p. doses of 2.5-5.0 mg/kg were toxic [5]. No activity in experimental rabbit syphilis at maximum tolerated doses [6]. Local treatment failed to protect mice with Cl. perfringens

/1/ c, 1 in 95% alcohol. /2/ c, 1.37 in 50% ethanol. /3/ For tyrothricin.

infection [16].

CLINICAL The toxicity of tyrothricin is such as to preclude its parenteral use; it is ineffective orally and dangerous when administered i.v. The antibiotic may be employed with caution in body cavities provided there is no direct connection with the vascular system. It has been successfully used topically in superficial indolent ulcers, mastoiditis, empyema and wound infections when the predominating organisms are susceptible Gram-positive bacteria. Since it is effective only when in direct contact with microorganisms, it is of little or no value in deep-seated infections. Body fluids (e.g., saliva, urine, and serum) slightly depress its activity, and substances produced by Gram-negative bacteria markedly inhibit its action. The antibiotic is generally employed for topical application in solutions containing 0.5 mg/ml, or in ointment base. Indiscriminate use in irrigation of paranasal sinuses or other cavities close to subarachnoid spaces following surgery should be avoided in view of the danger of chemical meningitis. Local application of solution or ointment in infections caused by *Streptococcus* spp, *D. pneumoniae*, and *M. pyogenes* var. *aureus* has been successful, and the antibiotic is effective in tonsillitis, otitis, dermatoses, infected ulcers and burns, and in infections of the eye and conjunctiva.[17-22] Inhalation of 2 ml tyrothricin aerosol, 2-3 times daily, was beneficial in various forms of bronchitis; also in rhinopharyngitis and allergic rhinitis.[23,27] Favorable results reported in patients with puerperal mastitis caused by *M. pyogenes* var. *aureus* when instilled immediately after surgical incision and administered topically thereafter [24]. Local use of the antibiotic in combination with phenylmercuric acetate gave generally favorable results in vaginitis caused by *Trichomonas vaginalis* [25,26]. Solutions of 1 mg/ml in 70% alcohol effective in treatment of dermatomycoses caused by *Microsporum canis*, *Trichophyton mentagrophytes*, *T. violaceum*, but were ineffective in pityriasis versicolor caused by *Malessezia furfur* [28]. Dentifrices containing 0.2-0.5% antibiotic in powder base of value for controlling oral lactobacilli [29]. Although investigations in the United States indicate tyrothricin is very toxic when administered parenterally, a recent report from Hungary describes the successful i.v. administration of total doses of 25 mg which gave favorable results in *D. pneumoniae* pneumonia in 29 patients; also in cases of cholecystitis, and malaria. The response in malaria treated by the same route was striking; blood was cleared of plasmodia after the first injection.[30]

VETERINARY The antibiotic is of value in acute and chronic bovine mastitis; streptococci are eliminated from the udder, but *M. pyogenes* var. *aureus* is generally more resistant to treatment by intramammary instillation [2, 31-33]. Tyrothricin, in alcoholic or aqueous solution or in ointment base, has been effective in topical treatment of infected wounds, canine dermatoses and sarcoptic mange; also against ear mites of dogs, cats, and rabbits, and in scaly leg mange of birds.[33-35]

TOXICITY LD₅₀ in mice and rats, 3.7 mg/kg, i.v.; 20-45 mg/kg, i.p. Oral doses as high as 1000 mg/kg were tolerated. Death apparently caused by respiratory failure since heart continued to beat for some time after cessation of respiration. Lethal doses in dogs caused anemia, and a fall in blood pressure and body temperature. Animals showed marked changes in lungs and abdominal viscera; histopathological examination revealed fatty degeneration of the liver and severe renal lesions. In rabbits or dogs, 0.3 mg/kg/da, i.v., produced ascites and liver damage. Consolidation in lungs noted when 5 mg were injected into the trachea of rabbits; 10 mg doses occasionally fatal.[2, 36-38] in vitro, Hemolysis of red blood cells and toxicity to leukocytes attributed mainly to tryocidine component [2]; spermatozoa immobilized by concentration of 10 µg/ml [39].

In man, parenteral use contraindicated because of toxicity. Olfactory disturbances occasionally observed following topical use as nose drops.[40] Chemical meningitis reported in 2 surgical patients following irrigation of sinus cavities in close proximity to subarachnoid spaces [41]. Topical use of dermatological preparations of tyrothricin is associated with a relatively low index of skin sensitization, in contrast to penicillin, streptomycin, and the sulfonamides [46].

RESISTANCE Strains of *M. pyogenes* var. *aureus* developed resistance both in vitro and during therapy [42].

MODE OF ACTION Bacteriostatic and bactericidal in low concentrations; produces lysis in certain bacteria. Resistance of Gram-negative bacteria may be caused by their phospholipid content. Inhibitory effect of serum on tyrothricin probably attributable to serum lipids.[2] In *Cl. sporogenes*, antibiotic causes slowing of processes of glucose phosphorylation because of rapid lytic action of tyrocidine on bacterial cells and liberation of phosphoric acid and adenosine triphosphate in supernatant fluid [43]. Gramicidin resembles cationic detergents in its effect upon surface tension and also in precipitation of proteins [2, 44]. (See also gramicidin.)

MISCELLANEOUS Useful in laboratory for selective isolation of anaerobic Gram-negative bacteria from heavily contaminated sources when used in concentration of 2 µg/ml in culture media [45].

322. UNGULINIC ACID

SOURCE *Polyporus betulina* [1].

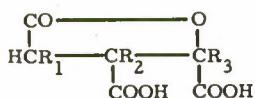
NATURE Potentially tribasic [1].

MOLECULAR FORMULA C₂₂H₃₈O₆ [1].

322. UNGULINIC ACID (Concluded)

STRUCTURE

(Tentative)



- I R₁ = C₁₆H₃₃, R₂ = R₃ = H
 II R₂ = C₁₆H₃₃, R₁ = R₃ = H
 III R₃ = C₁₆H₃₃, R₁ = R₂ = H

[1]

CRYSTAL FORM Microcrystalline needles [1].

MELTING POINT (°C) 78-80 [1].

OPTICAL ACTIVITY Inactive [1].

SOLUBILITY s. organic solvents.

STABILITY Relatively unstable [1].

OTHER REACTIONS The anhydride (C₂₂H₃₆O₅, MP 53-54°C, MW 358 cryo., 380.5 calc.) is more soluble in organic solvents and more stable; pink color when warmed with acetic anhydride at 100°C, giving green fluorescence upon addition of acetone; affords stearic, oxalic and acetic acids on KOH fusion.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [2].

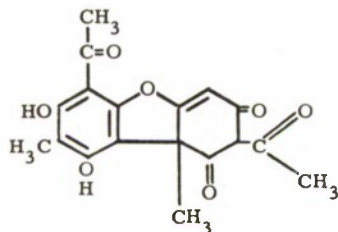
BIOLOGICAL ACTIVITY In vitro. *M. pyogenes* var. *aureus* was the only sensitive microorganism [2].

323. USNIC ACID
(Usinic acid, Usnein)

SOURCE Various species of lichens [3, 7]; also a fungal symbiont of a lichen [8].

MOLECULAR FORMULA AND WEIGHT C₁₈H₁₆O₇ [4]; 298-312 (neut. equiv.) [1].

STRUCTURE



[2]

CRYSTAL FORM AND COLOR Yellow orthorhombic needles or tablets [5].

MELTING POINT (°C) 193-204 [1]. (±) usnic acid, 195-196; (±) usnic acid diacetate, 205-207.[14]

OPTICAL ACTIVITY L-isomer: [α]_D²⁰ = -445 to -478⁰¹. D-isomer: [α]_D²⁰ = +445 to +515⁰². [1, 4, 6]

UV ABSORPTION MAXIMA 226-230, 284 mμ [1].

SOLUBILITY s. acetone, hot ethanol, hot propylene glycol, ether; sl. s. petroleum ether, cold ethanol, cold propylene glycol; i. water, HCl.[1, 4]

QUANTITATIVE DETERMINATION Microbiological: *Bacillus subtilis*, *Sarcina lutea* [3].

BIOLOGICAL ACTIVITY In vitro. Inhibits (μg/ml) *Mycobacterium tuberculosis* var. *hominis*, 1-50; *Mycobacterium tuberculosis* var. *bovis*, 1.5-50; *Mycobacterium avium*, 3-50; *Mycobacterium phlei*, *Mycobacterium smegmatis*, 5-50; *Streptococcus pyogenes*, 8-50; *Diplococcus pneumoniae*, 10-20; *Micrococcus pyogenes* var. *aureus*, 10-50; *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, 50.[1, 9] *Neisseria meningitidis*, *Corynebacterium diphtheriae*, *Clostridium tetani*, and *Clostridium perfringens* are also sensitive [18]. Fungi: *Trichophyton mentagrophytes*, *Torula utilis*, *Saccharomyces cerevisiae*, *Candida albicans* are sensitive [10].

In vivo. Daily s.c. doses of 10-20 mg showed slight activity in guinea pigs infected with *Mycobacterium tuberculosis* (development of lesions delayed) [1]. According to another report, daily s.c. doses for 21 days in guinea pigs arrested development of tubercular lesions when treatment was begun on day of infection. When treatment was delayed, s.c. doses of 4-8 mg were less effective. Little or no activity when administered orally.[15] In still another

/1/ c, 2.0-3.08 chloroform. /2/ c, 2.0-3.19 chloroform.

323. USNIC ACID (Concluded)

report, no activity against *Myco. tuberculosis* could be demonstrated in guinea pigs [16]. No activity in mice infected with *D. pneumoniae* [1]. No activity against mice infected with Lansing strain of poliomyelitis virus, or A-2 strain of Coxsackie virus [18]. No effect in chicks experimentally infected with *Plasmodium gallinaceum* [19].

CLINICAL Preliminary trials in human pulmonary tuberculosis showed inconclusive results [11,17]. When combined with streptomycin, antibiotic showed some promise in cutaneous tuberculosis [12].

TOXICITY S.c. doses of 75 mg/kg lethal to mice. Guinea pigs tolerated 15-20 mg/da, s.c., for 3 weeks.[1] Rabbits tolerated daily oral doses of 460 mg/kg [18]. Maximum tolerated oral doses in 7-da-old chicks, 0.2 mg [19].

MODE OF ACTION Actively bactericidal [9]. Inhibits oxidative phosphorylation and depresses orthophosphate which is normally associated with oxidation of various substrates by rat liver homogenates. In this respect the biological activity resembles that of atabrin, gramicidin, and chlortetracycline.[13]

324. USTILAGIC ACID

SOURCE *Ustilago zeae* [1].

NATURE A mixture of closely related, partially acylated *D*-glucolipids [3].

MOLECULAR FORMULA AND WEIGHT $C_{37}H_{62-66}O_{17}$; 777 ± 7 (neut. equiv.); 760 (found); 779-783 (calc.).[1]

CRYSTAL FORM AND COLOR Colorless, needle-like crystals [1].

MELTING POINT (°C) 144-147 [1].

OPTICAL ACTIVITY $[\alpha]_D^{23} = +7.0^1$ [1].

SOLUBILITY s. methanol, pyridine, 2,3-butanediol, 1,2-propanediol; sl. s. ethanol, butanol, acetone; i. water, glycerol, ethyl acetate, ether, benzene, petroleum ether.[1]

OTHER REACTIONS Saponification equivalent, 384; 42% glucose liberated on hydrolysis. C, 56.8; H, 8.2; terminal methyl as % acetyl, 11.9.[1] Alkaline hydrolysis yields amorphous gluco-ustilic acid, the removal of glucose residues from which yield ustilic acid; ustilic acid is a mixture of A and B, A being 15,16-dihydroxyhexadecanoic acid, and B being 2,15,16-trihydroxyhexadecanoic acid.[3,4]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits fungi (μ g/ml): *Ascochyta* sp, *Claviceps purpurea*, *Neurospora sitophila*, 3.1-12.5; *Chaetomium* sp, *Pleospora* sp, *Rhizoctonia solani*, *Aspergillus niger*, 12.5-25.0; *Helminthosporium sativum*, *Penicillium* sp, *Stachybotrys* sp, *Verticillium* sp, 25-50; *Alternaria tenuis*, *Armillaria mellea*, *Gliocladium roseum*, *Polyporus circinatus*, >50; *Cryptococcus neoformans*, 10-15; *Candida albicans*, 15-20; *Microsporum audouini*, *M. canis*, *Trichophyton mentagrophytes*, *T. rubrum*, >50. Actinomycetes: *Streptomyces griseus*, *Streptomyces* sp, 3.1-12.5 μ g/ml. Bacteria (μ g/ml): *Micrococcus pyogenes* var. *aureus*, *Xanthomonas campestris*, *X. translucens*, 5-10; *Bacillus subtilis*, *Corynebacterium flaccumfaciens*, 10-20; *Brucella bronchiseptica*, 20-30; *Mycobacterium butyricum*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Aerobacter aerogenes*, >50.[2]

TOXICITY Mice tolerate 1500 mg/kg, i.p., or 1% antibiotic in diet for 2 weeks. Rats tolerate 5% in diet for 3 weeks [2].

325. VALINOMYCIN

SOURCE *Streptomyces fulvissimus* [1].

MOLECULAR FORMULA AND WEIGHT $C_{36}H_{60}O_{12}N_4$; 713², 735³ (found); 740.9 (calc.).[1]

CRYSTAL FORM AND COLOR Colorless, shining, rectangular platelets [1].

MELTING POINT (°C) 190⁴ [1].

OPTICAL ACTIVITY $[\alpha]_D^{20} = +31.0^{05}$ [1].

UV ABSORPTION MAXIMUM Approximately 282 $m\mu$ ⁶ [1].

SOLUBILITY s. petroleum ether, ether, benzol, chloroform, glacial acetic acid, butyl acetate, acetone, concentrated H_2SO_4 (colorless); i. water, 2 N HCl, 2 N aqueous alkali.[1]

/1/ c, 1 pyridine. /2/ Beckmann in glacial acetic acid. /3/ Phenol. /4/ Berl-Block. /5/ c, 1.6 benzol. /6/ n-Hexane, small broad peak.

325. VALINOMYCIN (Concluded)

OTHER REACTIONS 5 active H atoms; 4 C-methyl groups; no acetyl, methoxy, N-methyl or carboxy groups; all N accounted for as valine; negative ninhydrin.[1]

BIOLOGICAL ACTIVITY In vitro. Inhibits *Mycobacterium tuberculosis* in dilution of 1:900,000; *Micrococcus pyogenes* var. *aureus*, *Bacillus subtilis*, 1:20,000-1:30,000.[1]

In vivo. S.c. doses protected mice against *Trypanosoma brucei* infection [1].

326. VANCOMYCIN

The trademark of Eli Lilly & Company for vancomycin is Vancocin.

SOURCE *Streptomyces orientalis*, n. sp [1, 4].

NATURE Amphoteric [1].

MOLECULAR WEIGHT 3200-3500 ± 200 (titr.) [1].

FORM AND COLOR HCl: white solid [1].

UV ABSORPTION MAXIMA HCl: 282 m μ ¹ [1].

SOLUBILITY HCl: s. water; less s. aqueous methanol; i. higher alcohols, acetone, ether. Solubility increased in neutral aqueous solution by low concentrations of urea [1].

OTHER REACTIONS Precipitated from aqueous solution with phosphomolybdic acid, phosphotungstic acid, heavy metals; precipitated from acidic solutions with (NH₄)₂SO₄, NaCl.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. *aureus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits (μ g/ml) *Streptococcus pyogenes* at 0.15-2.5; *M. pyogenes* var. *aureus*, 0.15->10 (strains resistant to penicillin, streptomycin, or erythromycin inhibited by 0.4-1.6); *Bacillus megatherium*, 0.2; *Diplococcus pneumoniae*, 0.29; *Str. faecalis*, 0.31-2.5; *Str. viridans*, 0.31->10; *B. polymyxa*, *B. subtilis*, *Corynebacterium flaccumfaciens*, *C. sepedonicum*, 0.4; *Sarcina lutea*, 0.4-1.6; *B. licheniformis*, *C. diphtheriae*, *C. michiganense*, *Salmonella enteritidis*, 0.8; *Leptospira pomona*, 1.0; *Aerobacter aerogenes*, 1.25->100; *M. albus*, 1.6; *Neisseria catarrhalis*, 2.5->10; *B. brevis*, *B. cereus*, *Mycobacterium phlei*, *Myc. smegmatis*, 3.1; *Myc. avium*, *Flavobacterium* sp, 100. Organisms insensitive to 100 μ g/ml include *Myc. tuberculosis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Shigella* and *Salmonella* spp, *Proteus vulgaris*, *Achromobacter fischeri*; also yeasts and filamentous fungi.[1, 3]

In vivo. Parenteral doses protected mice against infections with *M. pyogenes* var. *aureus*, *Str. pyogenes*, and *D. pneumoniae*. Active against *Borrelia novyi* infection when administered orally or parenterally.[1]

CLINICAL Preliminary trials showed good clinical response in cases of pneumococcal pneumonia, streptococcal pharyngitis, and erysipelas, treated intravenously with 50-100 mg doses every 6-8 hours [2].

TOXICITY LD₅₀ in mice, between 400 and 500 mg/kg, i.v. Daily oral doses of 1000 mg/kg for one week, and 100 mg/kg, s.c., for 14 days, were tolerated in mice. Little or no tissue irritation following intramuscular injection in dogs and rabbits.[1] In man, intravenous doses of 50-100 mg every 6-8 hours for periods up to 7 days were well tolerated [2].

ABSORPTION AND EXCRETION In man, intravenous doses of 50-100 mg gave serum levels of 0.5-2.0 μ g/ml in 2-6 hours, with high concentrations in the urine at 24 hours [2].

RESISTANCE Strains of *M. pyogenes* var. *aureus* developed resistance very slowly. Only an 8-fold increase in resistance developed after 25 transfers in the antibiotic.[3]

MODE OF ACTION Rapidly bactericidal to *M. pyogenes* var. *aureus* and *Str. pyogenes* in low concentrations (0.67-2.0 μ g/ml). Like many other antibiotics, vancomycin is active only against multiplying bacteria. No lethal effect on either resting cells or respiring cells; no inhibition of oxidation of glucose by washed cells of *M. pyogenes* var. *aureus*.

327. VINACETIN

SOURCE *Streptomyces* sp [1].

STRUCTURE Probably quinoid [1].

CRYSTAL FORM AND COLOR Yellow platelets [1].

/1/ In water.

327. VINACETIN (Concluded)

MELTING POINT (°C) 157-158 [1].

SOLUBILITY s. ethyl acetate, butyl acetate, methanol, acetone; sl. s. water, trichloroethylene; i. ether, petroleum ether.[1]

STABILITY Most stable at pH 5; very unstable at alkaline pH.[1]

OTHER REACTIONS Violet color at alkaline pH; activity greatest at pH 5; almost inactive at alkaline pH; negative ninhydrin, Sakaguchi, Millon; positive Molisch (violet), FeCl_3 (brown), Liebermann, Fehling, Ag mirror; decolorized by H_2O_2 in Na_2CO_3 medium.[1]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus citreus* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g}/\text{ml}$) *M. citreus*, 0.1-0.8; *Corynebacterium diphtheriae*, 0.8; *Mycobacterium tuberculosis var. hominis*, 5; *Streptococcus pyogenes*, 6; *Str. viridans*, 25; *M. pyogenes var. aureus*, 25-200; *Myc. phlei*, *Myc. avium*, 32; *Proteus vulgaris*, *Neisseria meningitidis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Shigella sonnei*, 100-500.[1]

TOXICITY Mice tolerated 330 mg/kg, i.v. or i.p.; 660 mg/kg lethal by either route.[1]

328. VIOLACEIN

SOURCE *Chromobacterium violaceum* [1].

NATURE Violet pigment [1].

MOLECULAR FORMULA $\text{C}_{42}\text{H}_{35}\text{O}_6\text{N}_5$ [1], or $\text{C}_{42}\text{H}_{28}\text{O}_7\text{N}_6$ [5].

CRYSTAL FORM AND COLOR Violet-black microcrystals; thick needles; elongated, rectangular crystals.[3]

MELTING POINT (°C) >350 (d.) [1].

SOLUBILITY sl. s. ethanol, dioxane [2].

OTHER REACTIONS Deep violet in ethanolic, purple-red in dioxane solution; acetate forms red-brown needles, MP >300°C (d.); forms stable addition compounds with aniline, chloroaniline, pyridine, chloropyridine; contains a β -hydroxypprrylmethene.[2, 5, 6]

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes var. aureus* [4].

BIOLOGICAL ACTIVITY In vitro. Inhibits *Bacillus subtilis*, *Neisseria meningitidis* in dilution of 1:200,000; *Streptococcus pyogenes*, *Str. viridans*, 1:100,000; *M. pyogenes var. aureus*, *B. anthracis*, *B. megatherium*, *B. mesentericus*, 1:50,000; *Diplococcus pneumoniae*; *Corynebacterium diphtheriae*, 1:20,000-1:30,000. Little or no inhibition, <1:3000: *Escherichia coli*, *Proteus vulgaris*, *Hemophilus pertussis*, *Neisseria catarrhalis*, *Salmonella typhosa*. Fungi: *Saccharomyces cerevisiae* sensitive to 1:200,000; *Blastomyces dermatitidis*, 1:100,000; *Trichophyton rubrum*, 1:10,000.[2] Protozoa: Inhibits flagellates, ciliates, and soil amebas [7].

In vivo. Very slight protection against *Diplococcus pneumoniae* in mice [4].

TOXICITY Mice tolerated 100 mg/kg, i.p.[4]

329. VIOLACETIN

SOURCE *Streptomyces* sp resembling *S. purpeochromogenus* [1].

NATURE Basic [1].

CRYSTAL FORM AND COLOR Light yellow, fine needles¹ [1].

MELTING POINT (°C) HCl: >210 [1].

UV ABSORPTION MAXIMUM 293 $\text{m}\mu^2$ [1].

SOLUBILITY HCl. s. water, methanol, ethanol; i. or sl. s. butanol, ether, petroleum ether, benzene, ethyl acetate, chloroform, acetone, dioxane.[1]

STABILITY Thermostable in aqueous acid, not in alkali [1].

/1/ 500-950 $\mu\text{g}/\text{mg}$. /2/ Water.

OTHER REACTIONS Analysis of HCl: H, 6.74; C, 38.26; N, 24.71; Cl, 9.33. Precipitated from aqueous solution by picric, Reinecke and phosphotungstic acids; negative FeCl_3 , Fehling, biuret, Sakaguchi, glucosamine, xanthoproteic, Millon, maltol; positive diazo, ninhydrin.[1]

QUANTITATIVE DETERMINATION Microbiological: *Escherichia coli*, *Bacillus subtilis* PCI 219 [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Micrococcus citreus*, *M. flavus*, *E. coli*, *Salmonella typhosa*, *Brucella abortus*, 0.3-0.6; *M. pyogenes* var. *aureus*, *M. albus*, *Bacillus subtilis*, *Corynebacterium diphtheriae*, *S. schottmuelleri*, *S. hirschfeldii*, *S. enteritidis*, *Shigella dysenteriae*, 1.26; *Sh. paradysenteriae*, 1.25-2.5; *Diplococcus pneumoniae*, 1.26-10; *M. freudenrichii*, *Streptococcus faecalis*, *B. mesentericus*, *Salmonella paratyphi*, *S. typhimurium*, *Neisseria meningitidis*, *Hemophilus influenzae*, 2.5; *Serratia marcescens*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis* var. *hominis*, 5; *Clostridium botulinum*, Cl. *butyricum*, Cl. *sporogenes*, 12-24; *Proteus vulgaris*, 20; *Pseudomonas aeruginosa*, 40. Fungi: *Cryptococcus parvulus*, *Torula rubra*, *Candida krusei*, 50; *C. albicans*, 50-75; *Aspergillus niger*, 75; *Trichophyton interdigitale*, *Saccharomyces sake*, *Willia anomala*, 100.[1]

In vivo. Doses of 22-37.5 mg/kg, i.v. or i.p., gave good protection in mice infected with *D. pneumoniae* and *Salmonella enteritidis*. Single oral doses of 150 mg/kg afforded little or no protection. Three daily i.p. doses of 45 mg/kg protected mice against infection with ornithosis virus.[1]

PHARMACOLOGY Doses of 45 mg/kg, i.p.; 75 mg/kg, s.c.; 37.5 mg/kg, i.v.; and 375 mg/kg orally well tolerated. Following i.m. administration in rabbits, maximum plasma levels were produced in 20-60 minutes with rapid excretion thereafter.[1]

330. VIOMYCIN (Vinactin A)

Trademarks for viomycin are Vinactane (Ciba Pharmaceutical Products, Inc.), and Viocin (Chas. Pfizer & Co., Inc.).

SOURCE *Streptomyces floridiae*, n. sp, and other *Streptomyces* spp [2, 3, 5].

NATURE Strongly basic polypeptide [1].

MOLECULAR FORMULA $\text{C}_{17-18}\text{H}_{31-35}\text{O}_8\text{N}_9$ [1, 25].

MELTING POINT ($^{\circ}\text{C}$) Hydrated sulfate: 280 (d.) [2]. Anhydrous sulfate: 252 (d.) [3].

OPTICAL ACTIVITY Sulfate: $[\alpha]_D = -32.0^1$ [2], -39.8^0 [3].

UV ABSORPTION MAXIMA $268 \mu\text{m}^3$; $268.5 \mu\text{m}^4$; $282.5 \mu\text{m}^5$. [3]

SOLUBILITY Sulfate and HCl: s. water; i. most organic solvents.[2, 3]

STABILITY Very stable in acid; less stable in alkaline solution.[3]

OTHER REACTIONS Positive Sakaguchi, biuret, Fehling, ninhydrin; negative maltol, Molisch, Benedict; contains L-serine, α, β -diaminopropionic acid, a basic amino acid isomeric with lysine, and a guanidino compound; forms neutral salts. Infrared: 3.06, 3.40, 5.97, 6.06, 6.16, 6.43, 6.51, 6.60, 6.65, 6.71 (s), 6.87, 7.30, 7.49, 7.61 (s), 8.15, 8.65 (s), 9.23, 13.85 μ^6 . [1-3]

QUANTITATIVE DETERMINATION Microbiological: *Klebsiella pneumoniae*; *mycobacteria*. [2] Colorimetric [4].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Mycobacterium tuberculosis* (including strains resistant to streptomycin and neomycin), 0.78-12.5; *K. pneumoniae*, 1-20; *Corynebacterium diphtheriae*, 1-25; *Neisseria catarrhalis*, *N. meningitidis*, 2.5-25; *Escherichia coli*, 2.5-100; *Salmonella typhosa*, 2.5->636; *Myco. phlei*, *Myco. ranae*, *Myco. smegmatis*, 10; *S. schottmuelleri*, *Shigella paradysenteriae*, 10-100; *Hemophilus influenzae*, 12; *Bacillus subtilis*, 20-25; *Micrococcus pyogenes* var. *aureus*, 25->100; *Aerobacter aerogenes* 25-40; *Brucella abortus*, *Br. suis*, *H. pertussis*, 50; *Br. bronchiseptica*, *Salmonella paratyphi*, 80; *Streptococcus pyogenes*, 80->100; *Str. viridans*, *Pasteurella* sp, *Proteus* sp, *Pseudomonas aeruginosa*, *Vibrio comma*, >100. *Acintomyces bovis*, *Nocardia asteroides* inhibited by 25 $\mu\text{g/ml}$. [2, 3, 6-8] Inhibited 8 strains of *Shigella paradysenteriae* at 0.3-10 $\mu\text{g/ml}$ [24]. Inhibition ($\mu\text{g/ml}$) of *B. anthracis* by 1.56-25; *Serratia marcescens* and *B. subtilis*, 50-100; *Erysipelothrix rhusiopathiae*, >100. [26] Fungi not sensitive to 250 $\mu\text{g/ml}$: *Aspergillus fumigatus*, *Blastomyces dermatitidis*, *Candida albicans*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Sporotrichum schenckii*, *Trichophyton mentagrophytes* [6]. Protozoa: *Entamoeba histolytica*, *Trichomonas foetus*, *Trypanosoma cruzi* not inhibited by 2000 $\mu\text{g/ml}$ [6, 11]. Bacteriostatic for intracellular *Myco. tuberculosis* within rabbit macrophages *in vitro* at concentrations of 100 $\mu\text{g/ml}$; under same test conditions streptomycin, neomycin, and oxytetracycline were 4-10 times more active on a weight basis. [12]

In vivo. In mice infected with *Myco. tuberculosis* by the i.v. or intracerebral route, daily s.c. doses of 25-175 mg/kg gave good protection [2, 7, 8, 25]. In guinea pigs, 20-80 mg/kg/da, administered i.m., suppressed experimental tuberculosis; on a weight basis, the antibiotic was approximately 1/4 as active as streptomycin. Infections induced with either streptomycin-sensitive or streptomycin-resistant strains of *Myco. tuberculosis*

/1/ c, 1 water. /2/ c, 1 water at pH 6.0; rotation varies with pH. /3/ 0.1 N HCl. /4/ pH 7. /5/ 0.1 N NaOH. /6/ In Nujol mull, s=shoulder on a stronger band.

were equally responsive to viomycin treatment.[9, 13] Marked therapeutic effect in guinea pig tuberculosis when treatment was delayed until the disease had progressed extensively [10]. Multiple s.c. or i.p. doses of approximately 12-40 mg/kg protected mice against infections with *K. pneumoniae*, *Salmonella typhosa*, *Proteus vulgaris* and *Past. multocida*; higher oral dosages also effective.[7, 14] In chicks, i.p. doses of 18 mg/kg had suppressive effect on *S. gallinarum* [14]. Higher doses of 80 mg/kg, i.p., were required to protect mice against *B. anthracis*; little or no activity in infections with *Str. pyogenes*, *Diplococcus pneumoniae*, *M. pyogenes* var. *aureus*, *Listeria monocytogenes*, *Ery. rhusiopathiae* or *Ps. aeruginosa*. [7, 14] The antibiotic showed activity in infections with mouse leprosy bacilli (*Myc. lepraemurium*) [15]. In embryonated eggs, viomycin suppressed *Rickettsia typhi* [5], and was without effect against a variety of small viruses in mice or chick embryos [6]. No activity against *Trypanosoma cruzi* infection in mice treated with i.p. doses of 500 mg/kg [11].

CLINICAL Viomycin is an effective antibiotic for the treatment of tuberculosis, but its usefulness is limited inasmuch as its activity is less impressive than that of streptomycin or isoniazid and because of its toxic potentialities. Earlier reports of clinical studies described toxic effects from disturbances of electrolyte balance and neurotoxic action on the eighth cranial nerve.[16] These hazards have been substantially reduced by the introduction of intermittent therapy with lower doses, e.g., regimens of 2 g administered i.m. twice weekly, preferably in combination with another tuberculostatic drug. The companion drug generally selected is isoniazid or para-aminosalicylic acid (PAS), but not streptomycin since streptomycin and viomycin have such similar neurotoxic potentialities that an additive toxic effect might be expected. Favorable responses in pulmonary and extrapulmonary tuberculosis have been reported after the use of such regimens, but the therapeutic efficiency of viomycin remains to be evaluated.[17-21]

PHARMACOLOGY LD₅₀ in mice, 165-240 mg/kg, i.v.; 1381 mg/kg, s.c. LD₀ in mice, 120-176 mg/kg, i.v.; oral doses of 7500 mg/kg well tolerated. Doses of 120-210 mg/kg, s.c., once or twice daily for 5 days were tolerated.[2, 7, 22] Daily i.m. doses of 150 mg/kg non-toxic in guinea pigs [9]. In rats or dogs, 100 mg/kg/da, administered s.c. over periods of 5-6 weeks, appeared to be well tolerated with no significant effect on the blood count or liver and kidney function. Cats injected i.m. with 50-100 mg/kg/da for 25-40 days, developed disturbances in posture and gait. In anesthetized cats or dogs, 100 mg/kg, i.v., did not affect blood pressure or respiration. Repeated injection of 10% solution by several routes caused no signs of irritation in animals. Solutions containing 0.5 mg/ml had no effect on contractility or rhythmicity of isolated intestines or uteri.[22]

In man, renal and neural toxicity were observed in patients with advanced pulmonary tuberculosis, treated with daily i.m. doses of 30-75 mg/kg over periods of 14-182 days. Toxicity evidenced by renal irritation, slight elevation of blood urea N, abnormalities of serum electrolytes, vestibular and auditory disturbances, eosinophilia, and skin eruptions.[16, 23] Later reports indicate reduced incidence of these side effects by employing intermittent therapy and lower doses of 2.0 g every third day, especially in combination with PAS or isoniazid [17-19]. Preliminary tests in animals indicate the antibiotic is readily absorbed following parenteral or oral administration [7]. Preliminary results in experimental animals indicate a detoxication of the antibiotic by pantothenic acid; the pantothenate of viomycin was less toxic than the sulfate.[27] *In vitro*. Low toxicity in tissue cultures; complete inhibition of chick embryo heart explants required concentrations as high as 30 mg/ml or more [28].

RESISTANCE *Myc. tuberculosis* may develop resistance *in vitro* and in patients during therapy. Resembles streptomycin in the pattern in which resistance develops although this resistance appears somewhat more slowly than with streptomycin. Strains of *Myc. tuberculosis* resistant to streptomycin or neomycin do not show cross resistance to viomycin.[6, 7, 9, 23]

331. VIRIDICATIN

SOURCE *Penicillium viridicatum* [1]; *P. cyclopium* (Westling) [2].

MOLECULAR FORMULA C₁₅H₁₁O₂N [1].

CRYSTAL FORM AND COLOR Colorless crystals; lustrous needles¹; prisms². [1]

MELTING POINT (°C) 269 [1].

OPTICAL ACTIVITY No rotation [1].

SOLUBILITY s. boiling concentrated HCl; sl. s. cold organic solvents, dilute mineral acids.[1]

OTHER REACTIONS Infrared bands include 3.0, 6.08, 6.16, 6.34, 6.40, 6.68 μ; carbonyl derivative could not be prepared; monobenzoate formed when reacted with benzoyl chloride in pyridine; Na salt formed when treated with dilute or concentrated aqueous NaOH; Na salt deposits crystals of viridicatin on exposure to air; Na salt reacts with p-phenylphenacyl bromide and gives deep red color when reacted with diazotized sulfanilic acid; intense permanent green color with neutral aqueous FeCl₃. [1]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits *Mycobacterium tuberculosis* in dilution of 1:15,000. No activity against other bacteria tested (*Escherichia coli*, *Bacillus subtilis*, *Micrococcus pyogenes* var. *aureus*) or protozoa (*Entamoeba histolytica*). [1]

/1/ From ethanol. /2/ From acetone, glacial acetic acid, ethylene glycol, monomethyl ether.

SOURCE *Trichoderma viride* [1].

MOLECULAR FORMULA AND WEIGHT $C_{19}H_{16}O_6$ [3]; 331 (found); 340 (calc.).[2, 3]

CRYSTAL FORM AND COLOR Colorless, rod-like prisms [1, 2].

α -Viridin: fine colorless needles [3].

β -Viridin: fine needles [3].

MELTING POINT ($^{\circ}C$) 217-223 (d.) [1, 2].

α -Viridin: 208-217 (d.) [3].

β -Viridin: 140 (d.) [3].

OPTICAL ACTIVITY $[\alpha]_D^{19} = -222.0^1$ [1, 2].

α -Viridin: $[\alpha]_D^{20} = -213.4^{02}$ [3].

β -Viridin: $[\alpha]_D^{20} = -50.7^{02}$ [3].

UV ABSORPTION MAXIMA α -Viridin: 241.3, 304.5 $m\mu^3$.

β -Viridin: 241.5, 304 $m\mu^3$.

SOLUBILITY s. chloroform, bromoform; sl. s. carbon disulfide, carbon tetrachloride; i. ether, camphor.[2]

STABILITY Stable in acid; very unstable in alkaline solution.[1]

OTHER REACTIONS α and β -viridin are isomeric; negative $FeCl_3$, Schiff, 1,4-dihydroxynaphthalene, iodoform; does not decolorize Br in cold; deep red-violet with phloroglucinol and HCl; reacts with hydrazine, phenylhydrazine, 2,4-dinitrophenylhydrazine; reduces Fehling, Tollens; red color with concentrated H_2SO_4 , cold caustic soda.[1-3]

QUANTITATIVE DETERMINATION Microbiological: Inhibition of spore germination of *Botrytis allii* [3].

BIOLOGICAL ACTIVITY In vitro. Inhibits fungi ($\mu g/ml$): *Colletotrichum lini*, *Fusarium caeruleum*, 0.003; *B. allii*, 0.006; *Trichothecium roseum*, 0.05; *Fusarium culmorum*, *Cladosporium herbarum*, *Penicillium notatum*, *Stemphylium sp.*, 0.2; *Cephalosporium sp.*, 0.8; *Aspergillus niger*, 3.1⁴; *P. expansum*, *Stachybotrys atra*, 6.25; *Trichoderma viride*, 50->50.[1, 4] Also inhibits ($\mu g/ml$) *Candida albicans*, *Saccharomyces cerevisiae*, *Torula orlitis*, and *Trichophyton interdigitale* at 6.2; *Botrytis sp.*, *Mucor pusillis*, 12.5; *C. krusei*, *Willia sp.*, 25; *Absidia orchidis*, 50.[7] *Ascochyta pisi* sensitive to low concentrations. These levels were fungistatic; concentrations approximately 1000 times greater were required for fungicidal effect. No activity against bacteria.[1, 4] Protozoa: Inhibits *Trypanosoma cruzi* in dilutions of 1:800-1:1600 [5].

In vivo. Slight suppressive effect on *T. cruzi* infection in mice treated with 0.5-5.0 mg/kg, i.p. [5].

TOXICITY I.p. doses of 5 mg/kg toxic to mice [5]. Dilution of 1:10,000 lethal to *Allium cepa* in tissue cultures [6].

333. VISCOSIN

SOURCE *Pseudomonas viscosa* [1].

NATURE Acidic polypeptide [1-3].

MOLECULAR WEIGHT 700-900 (Rast); 1100 (titr.).[3]

MELTING POINT ($^{\circ}C$) 269 (d.) [3].

OPTICAL ACTIVITY $[\alpha]_D^{20} = -162.2^{\circ}$ [3].

SOLUBILITY s. ethanol, methanol, ether, acetone, alkaline phosphate buffer; i. distilled water.[1, 2]

STABILITY Thermostable [1, 2].

OTHER REACTIONS A monocarboxylic acid with pK' of 6.10; acid hydrolysis yields a fatty acid mixture and glycine, alanine, valine, leucine, threonine; 2 fatty acids: volatile 2-decenoic acid ($C_{10}H_{18}O_2$) and non-volatile (-)-3-hydroxycapric acid ($C_{10}H_{20}O_3$).[3]

QUANTITATIVE DETERMINATION Microbiological: *Mycobacterium 607* [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu g/ml$) *Myco. tuberculosis* (including strains resistant to streptomycin and neomycin) in concentration of 10-20. No activity against other Gram-positive or Gram-negative bacteria.[2]

/1/ c, 1 chloroform. /2/ Chloroform. /3/ Alcohol. /4/ In another report, *A. niger* inhibited by 12.5 μg [7].

333. VISCOSIN (Concluded)

In vivo. Slightly suppressed Myco. tuberculosis infection in guinea pigs. Slight activity in mice infected with influenza A (PR-8) virus following s.c. doses of 250 mg/kg/da for 3 days. In chick embryos, marked inhibition of infectious bronchitis virus of fowls, slight suppression of influenza and Newcastle disease viruses, but no activity against viruses of vaccinia or feline pneumonitis.[1]

TOXICITY Mice tolerated 50 mg/kg, i.p.; >250 mg/kg, s.c. Doses of 50 mg/kg or more produced necrosis at site of injection.[1]

334. WHITMORIN

SOURCE Pfeifferella whitmori [1].

SOLUBILITY sl. s. chloroform; i. ether, benzene, nitrobenzene, xylene.[1]

STABILITY Stable in cold; unstable at 37°C (55% loss in 3 days); thermolabile.[1]

QUANTITATIVE DETERMINATION Microbiological: Corynebacterium diphtheriae mitis [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits Corynebacterium spp, Bacillus subtilis, Streptococcus pyogenes, Micrococcus pyogenes var. aureus, Diplococcus pneumoniae, Mycobacterium tuberculosis var. hominis, Neisseria meningitidis, N. gonorrhoeae. Very slight activity against enteric bacteria.[1]

In vivo. Very slight activity in guinea pigs infected with C. diphtheriae [1].

335. XANTHELLIN

SOURCE Bacillus subtilis [1].

NATURE Acidic [1].

FORM AND COLOR Sodium salt: pale yellow, non-hygroscopic, amorphous solid [1].

SOLUBILITY Sodium salt: s. water, methanol, ethanol, butanol, acetone; i. ether, chloroform, benzene, petroleum ether. Free acid: s. organic solvents; i. water.[1]

STABILITY Thermolabile; unstable at room temperature except at neutrality.[1]

OTHER REACTIONS Dialyzable; precipitates on acidification of aqueous solution.[1]

QUANTITATIVE DETERMINATION Microbiological: Bacillus cereus [1].

BIOLOGICAL ACTIVITY In vitro. Inhibits ($\mu\text{g/ml}$) Sarcina lutea, 10; Brucella suis, 11; Bacillus cereus, 15; B. polymyxa, Micrococcus pyogenes var. aureus, Mycobacterium tuberculosis, 50; B. subtilis, 75; Myco. smegmatis, 150; Aerobacter aerogenes, Br. bronchiseptica, Escherichia coli, Klebsiella pneumoniae, Salmonella paratyphi, S. pullorum, S. typhosa, 100-380. In vitro activity decreased by serum.[1]

TOXICITY LD₅₀ in mice, approximately 900 mg/kg, i.p. [1].

336. XANTHOCILLIN

SOURCE Penicillium notatum [1].

MOLECULAR FORMULA $\text{C}_{18}\text{H}_{14}\text{O}_2\text{N}_2$ [1].

CRYSTAL FORM AND COLOR Yellow clusters of needles¹; yellow, rhombic prisms². [2]

MELTING POINT (°C) None; chars at 200.[1, 2]

SOLUBILITY sl. s. alcohol, ether, NaOH; i. water, benzene, chloroform. Dipotassium salt: s. water.[1]

STABILITY Thermo- and chemical stable.[1]

OTHER REACTIONS Contains 2 substances, X and Y, in ratio of 4:1; benzene ring and 2 phenol groups in molecule. Analysis: C, 72.93; H, 4.83; N, 8.64.[1, 2]

BIOLOGICAL ACTIVITY In vitro. Inhibits Micrococcus pyogenes var. aureus, Streptococcus spp, and Corynebacterium diphtheriae in low concentrations. Bacillus anthracis, Clostridium perfringens, Cl. tetani, Mycobacterium tuberculosis, Escherichia coli, Proteus spp, and Pseudomonas aeruginosa are also sensitive. In vitro. Bactericidal in low concentrations. Resistance did not develop readily. No cross resistance with penicillin or streptomycin [3]; activity antagonized by streptomycin [4].

/1/ From alcohol. /2/ From ethyl acetate.

336. XANTHOCILLIN (Concluded)

CLINICAL Local therapy with doses of 10-20 mg was of value in prophylaxis and the treatment of peritonitis. Larger amounts (350 mg) effective when inserted in large infected wound cavities, with no untoward reactions noted. Also topically used in infections of skin, eyes, and nasopharynx.[3]

PHARMACOLOGY Not readily absorbed; very low blood levels following oral and parenteral doses in animals [3].

337. XANTHOMYCINS

SOURCE *Streptomyces* sp [1].

NATURE Basic [1-3].

MOLECULAR FORMULA $C_{23}H_{29-31}N_3O_7 \cdot 2HCl$ [3].

CRYSTAL FORM AND COLOR HCl: bright orange-yellow, rectangular plates [3]. Free base: deep orange-red, amorphous solid [3]. Reineckate: long, orange needles [1].

MELTING POINT ($^{\circ}C$) Reineckate: 165-170 (d.) [1].

OPTICAL ACTIVITY HCl: $[\alpha]_D^{25} = +115^{01}$ [3].

UV ABSORPTION MAXIMA HCl: 265, 345 $m\mu$ ². Free base: 288, 460 $m\mu$ ³. [3]

SOLUBILITY s. water, methanol, chloroform, butanol, acetone⁴; less s. ethyl acetate, amyl acetate, ether; i. cold water.[1, 2]

STABILITY Stable in acid solution; unstable at pH 6 and above; thermolabile, especially at pH 6 and above.[1, 2]

OTHER REACTIONS Continual change in aqueous phase to other active components of differing solubility; bitter taste; bright yellow in acid, deep reddish pink in dilute alkali; evanescent purple color with sodium ethoxide; positive Benedict, Br in CCl_4 , $KMnO_4$, $AgNO_3$, acidified KI, sodium hydrosulfite, periodic acid; slight precipitate with 2, 4-dinitrophenylhydrazine and with dimedone; deep red with hydroxylamine; negative Sakaguchi, Molisch, ninhydrin, $FeCl_3$, nitroprusside, acidified stannous chloride, fuchsin, cysteine⁵; loss of color and activity with Adams platinum oxide catalyst; no loss of color with Thiele acetylation nor with chemical reductive acetylation; colorless crystalline product with catalytic reduction in acetic acid-acetic anhydride.[1-3] Hydrolysis with HCl yields ethanolamine, ammonia, methylamine, and a humin-like substance; oxidation of methyltetrahydroxanthomycin, a derivative, yields xanthomycinic acid I ($C_7H_{11}N_3O_{10}$), and II as the benzylisothiuronium salt ($C_4H_3O_3 \cdot C_8H_{10}N_2S$).[4] The hydrochloride of this salt has an optical rotation of $[\alpha]_D^{20} = +100$ (water), and an equivalent weight of 540 [5].

QUANTITATIVE DETERMINATION Microbiological: *Micrococcus pyogenes* var. aureus (strain H) [1, 3].

BIOLOGICAL ACTIVITY *In vitro*. Xanthomycin A picrate: Inhibits (dilution x 1,000,000) *M. pyogenes* var. aureus, 300; *Bacillus subtilis*, 240; *B. niger*, 200; *Sarcina lutea*, *Alcaligenes viscosa*, 40; *B. mycoides*, 28; *B. vulgatus*, 20; *B. mesentericus*, *B. brevis*, *B. megatherium*, *Serratia marcescens*, *Aerobacter aerogenes*, 4; *Escherichia coli*, *Proteus vulgaris*, *Salmonella gallinarum*, *B. cereus*, 2.4. *Mycobacterium* spp are insensitive.

Xanthomycin B picrate: Has similar antibacterial spectrum.[1]

Other preparations of xanthomycin inhibited ($\mu g/ml$) *Klebsiella pneumoniae*, 0.05; *Shigella sonnei*, 0.07; *Salmonella schottmuelleri*, 0.12; *E. coli*, 0.18; *M. pyogenes* var. aureus, 0.003.[2]

TOXICITY Xanthomycin A HCl: LD_{50} in mice, 0.1-0.16 mg/kg, i.v. LD_0 in mice, 0.06 mg/kg, i.v.

Xanthomycin B: equally toxic.[1, 2]

338. XANTHOTHRICIN

SOURCE *Streptomyces* sp resembling *S. albus* [1].

CRYSTAL FORM AND COLOR Yellow needles [1].

MELTING POINT ($^{\circ}C$) 165 [1].

UV ABSORPTION MAXIMA 257.5, 390-402 $m\mu$ [1].

SOLUBILITY s. water, chloroform, ethyl acetate, ethanol [1].

OTHER REACTIONS Best extraction chloroform at pH 6.5; loss of yellow color at pH 10.5.[1]

/1/ c, 0.4 water. /2/ 0.1 N HCl. /3/ Absolute ethanol. /4/ Insoluble at acid pH. /5/ Cysteine stabilized activity.

338. XANTHOTHRICIN (Concluded)

QUANTITATIVE DETERMINATION *Bacillus subtilis* ATCC 6633 [1].

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Salmonella typhosa*, 1.56; *Mycobacterium tuberculosis*, 1.75-3.13; *Escherichia coli*, 3.1; *Proteus vulgaris*, 6.2; *B. subtilis*, *Micrococcus pyogenes* var. *aureus*, 12.5. Little or no activity against *Pseudomonas aeruginosa* and fungi.[1]

TOXICITY LD_{50} in mice, 1.7 mg/kg, i.v.; 8.4 mg/kg, oral.[1]

339. XEROSIN

Originally described as Antibiotic APM.

SOURCE *Achromobacter xerosis*, n. sp [2].

UV ABSORPTION MAXIMUM 255-260 $\text{m}\mu$ ¹ [1].

STABILITY Stable at pH 9 for 45 minutes at 120°C [1].

OTHER REACTIONS Analysis: N, 9.7-12.1; P, 2.1-2.7; positive biuret, anthrone; negative Fehling, Molisch, Millon, nitroprusside, ninhydrin, iodine; not destroyed by dialysis against running tap water for 24 hours nor by serial extraction with n-butanol and other organic solvents.[1]

BIOLOGICAL ACTIVITY No antibacterial activity *in vitro* or antiviral activity in chick embryos [2]. Inactive against type 1 poliomyelitis virus in tissue cultures [1]. No inhibition of influenza virus hemagglutination *in vitro* [2]. The antibiotic failed to protect HeLa cells in tissue cultures against cytotoxic effects of influenza A and B viruses [5].

In vivo. Showed activity in mice infected with influenza A and B viruses, Newcastle disease, and mouse pneumonitis [1, 2]. Enhanced therapeutic effectiveness of chlortetracycline, oxytetracycline, and chloramphenicol in mice previously infected with mouse pneumonitis virus [1]. S. c. injection of xerosin produced delay in onset of tonic convulsions in mice previously infected intracerebrally with toxic amounts of influenza virus, but not when this virus was administered i.v. Neurotoxic action of influenza virus neutralized when small doses of antibiotic were administered by intracerebral route 1-3 days before, but not following, inoculation of virus by the same route.[4] No activity against Newcastle disease virus in chick embryos [6]. Intramuscular injection in chicks suppressed and modified the grossly invasive character of virus-induced Rous sarcoma. The inhibitory effect was slight when larger doses of virus were used to initiate the tumor.[7]

TOXICITY LD_0 in mice, 200 mg/kg, i.v.; 400 mg/kg, i.p.; 800 mg/kg, s.c. [1] Daily s.c. doses of 25-50 mg/kg poorly tolerated in guinea pigs [8]. Three daily injections of 2 mg into yolk sac were non-toxic in chick embryos [6].

MODE OF ACTION Not only suppressed pneumonitis in mice initiated with viruses, but also inhibited development of lung lesions produced by chemical agents. Experimental evidence suggests that xerosin does not reduce damage to host cells by the virus, but rather inhibits host reactions of exudation, edema, and hemorrhage to this initial injury.[3] Pulmonary consolidation produced in mice by intranasal inoculation with capsular polysaccharide of *Klebsiella pneumoniae* (type B), or with xerosin itself, was inhibited by daily s.c. injection of 2 mg of the antibiotic. Subcutaneous injections of xerosin did not prevent the lethal effect of Newcastle disease virus upon Ehrlich ascites tumor cells in peritoneal cavity of mice. There was no evidence that the inhibitory action upon influenzal viral pneumonia in mice was related to a possible cortisone-like activity.[6] Parenteral injection of the antibiotic suppressed a pneumonia produced in mice by intranasal instillation of *Escherichia coli* endotoxin, as well as that produced with the toxic factor of Newcastle disease virus [9]. Xerosin possesses anti-inflammatory properties. Daily s.c. doses of 20 mg in guinea pigs reduced the tuberculin reaction, the reversed passive Arthus reaction and the inflammatory response to turpentine and urease, but did not modify the histamine wheal [8].

340. ZAOMYCIN

SOURCE *Streptomyces zaomyceticus*, n. sp.

MELTING POINT (°C) 242-246 (d.) [1].

SOLUBILITY s. methanol, ethanol, dilute alkali, acid; sl. s. water; i. most organic solvents.[1]

STABILITY Unstable dry, accompanied by a change of color to dark violet; unstable in water, but more stable at pH 7-8.[1]

OTHER REACTIONS Resembles amphomycin; positive ninhydrin, Millon, biuret, FeCl_3 (reddish-brown); negative Fehling, Liebermann; brown precipitate on addition of concentrated H_2SO_4 . [1]

BIOLOGICAL ACTIVITY *In vitro*. Inhibits ($\mu\text{g/ml}$) *Bacillus subtilis*, *B. agri*, *Mycobacterium smegmatis*, 0.8; *B. anthracis*, *Gaffkya tetragena*, 1.5; *Micrococcus pyogenes* var. *aureus*, *Streptococcus pyogenes*, *Diplococcus*

/1/ Aqueous solution.

340. ZAOMYCIN (Concluded)

pneumoniae, 3.0. Mycobacteria, Gram-negative bacteria, and fungi not sensitive to 100 $\mu\text{g/ml}$. Protozoa: *Trichomonas foetus* inhibited by 60 $\mu\text{g/ml}$. [1]

TOXICITY LD_0 in mice, 0.3 mg/kg, i.v. [1]

BIBLIOGRAPHY

REFERENCES

1. ABIKOVIROMYCIN

- [1] Umezawa, H., Tazaki, T., and Fukuyama, S., *Jap. M. J.* 4:331, 1951. [2] Umezawa, H., Tazaki, T., and Fukuyama, S., *J. Antibiot., Tokyo* 5:469, 1952. [3] Umezawa, H., et al, *Jap. Pat.* 6200, Sept. 27, 1954; *Chem. Abstr.* 50:2929, 1956.

2. ACHROMOVIROMYCIN

- [1] Umezawa, H., Takeuchi, T., Okami, Y., Oikawa, K., and Tazaki, T., *J. Antibiot., Tokyo, Ser. A* 6:38, 1953.

3. ACTIDUINS

- [1] Burton, H. S., *Chemistry and Industry* 1955:442.

4. ACTINOLEUKIN

- [1] Ueda, M., Tanigawa, Y., Okami, Y., and Umezawa, H., *J. Antibiot., Tokyo, Ser. A* 7:125, 1954. [2] Nitta, K., Takeuchi, T., Yamamoto, T., and Umezawa, H., *ibid* 8:120, 1955.

5. ACTINOMYCELINE

- [1] Cercós, A. P., *Inst. Fitotecnica, Pub. Tecnica No. 16*, p 147, 1948.

6. ACTINOMYCETIN

- [1] Waksman, S. A., "Microbial Antagonisms and Antibiotic Substances," *Commonwealth Fund*, 1945.
[2] Hoogerheide, J. C., *Botan. Rev.* 10:599, 1944. [3] Welsch, M., *J. Bact., Balt.* 42:801, 1941. [4] Welsch, M., *ibid* 53:101, 1947.

7. ACTINOMYCINS

- [1] Waksman, S. A., and Tishler, M., *J. Biol. Chem.* 142:519, 1942. [2] Tishler, M., *U. S. Pat.* 2,378,449, 1945.
[3] Dalglish, C. E., and Todd, A. R., *Nature* 164:830, 1949. [4] Dalglish, C. E., Johnson, A. W., Todd, A. R., and Vining, L. C., *J. Chem. Soc.* 1950:2946. [5] Brockmann, H., Grubhofer, N., Kass, W., and Kalbe, H., *Chem. Ber.* 84:260, 1951. [6] Sarlet, H., Toussaint, J., and Brasseur, H., *Nature* 168:469, 1951. [7] Johnson, A. W., Todd, A. R., and Vining, L. C., *J. Chem. Soc.* 1952:2672. [8] Lehr, H., and Berger, J., *Arch. Biochem.* 23:503, 1949. [9] Sarlet, H., *Biochim. biophys. acta* 13:143, 1954. [10] Brockmann, H., and Gröne, H., *Naturwissenschaften* 41:65, 1954. [11] Brockmann, H., Linge, H., and Gröne, H., *ibid* 40:224, 1953. [12] Waksman, S. A., *Antibiotics and Chemotherapy* 4:502, 1954. [13] Brockmann, H., and Gröne, H., *Chem. Ber.* 87:1036, 1954.
[14] Waksman, S. A., and Woodruff, H. B., *J. Bact., Balt.* 42:23, 1941. [15] Robinson, H. J., and Waksman, S. A., *J. Pharm. Exp. Ther.* 74:25, 1942. [16] Waksman, S. A., Robinson, H. J., Metzger, H. J., and Woodruff, H. B., *Proc. Soc. Exp. Biol.* 47:261, 1941. [17] Reilly, H. C., Schatz, A., and Waksman, S. A., *J. Bact., Balt.* 49:585, 1945. [18] Hackman, C., *Zschr. Krebsforsch.* 58:607, 1952. [19] Schulte, G., and Linge, H., *Strahlentherapie* 90:301, 1945. [20] Brockmann, H., and Grubhofer, N., *Naturwissenschaften* 39:429, 1952. [21] Brockmann, H., and Grubhofer, N., *ibid* 37:494, 1950. [22] Brockmann, H., et al, *Chem. Ber.* 84:284, 1951. [23] Manaker, R. A., Gregory, F. J., Vining, L. C., and Waksman, S. A., "Antibiotics Annual, 1954-55," p 853, New York: Medical Encyclopedia, Inc. [24] Field, J. B., Costa, F., Borycza, A., and Sekely, L. I., *ibid*, p 842. [25] Angyal, S. J., Bullock, E., Hanger, W. G., and Johnson, A. W., *Chemistry and Industry* 1955:1295. [26] Brockmann, H., and Vohwinkel, K., *Angew. Chem.* 67:618, 1955. [27] Businco, L., *Acta alerg., Kbh.* 9:13, 1955. [28] Schmidt, V. H., Loosen, H., and Heinen, W., *Deut. med. Wschr.* 80:140, 1955. [29] Korst, D. R., and Meyer, O. O., *Antibiot. M.* 1:476, 1955. [30] Freiderici, L., *Zschr. Krebsforsch.* 60:553, 1955. [31] Brockmann, H., and Pampus, G., *Angew. Chem.* 67:519, 1955. [32] Brockmann, H., et al, *ibid* 68:70, 1956. [33] Schmidt-Kastner, G., *Naturwissenschaften* 43:131, 1956.
[34] Coatney, G. R., Cooper, W. C., Eddy, N. B., and Greenberg, J., "Survey of Antimalarial Agents," *Public Health Mono. No. 9*, p 250, Federal Security Agency, Washington, D. C., 1953. [35] Field, J. B., Filler, D. A., Bascoy, L. T., Costa, F., and Borycza, A., *Fed. Proc.* 15:250, 1956. [36] Fantini, A., Moser, L., Will, L., Partridge, R., and Halliday, S. L., *Proc. Am. Ass. Cancer Res.* 2:108, 1956. [37] Sugiura, K., *Ann. N. York Acad. Sc.* 63:692, 1956. [38] Sugiura, K., and Schmid, M. S., *Proc. Am. Ass. Cancer Res.* 2:151, 1956. [39] Nishibori, A., *J. Antibiot., Tokyo, Ser. A* 9:31, 1956. [40] Ravina, A., Pestel, M., Eloy, P., and Thielen, R., "Antibiotics Annual, 1955-56," p 604, New York: Medical Encyclopedia, Inc. [41] Foley, G. E., *ibid*, p 432. [42] Schwarz, K., and Rolph, G. S., *Pharm. J.* 176:215, 1956. [43] Trounce, J. R., Wayte, A. B., and Robson, J. M., *Brit. M. J.* 2:1418, 1955.

8. ACTINONE

- [1] Ikeda, Y., Hirai, T., and Nishimaki, T., *J. Antibiot., Tokyo* 3:726, 1950.

REFERENCES (Continued)

9. ACTINORHODIN

- [1] Plotho, O. V., Brockmann, H., and Pini, H., *Naturwissenschaften* 34:190, 1947. [2] Brockmann, H., Pini, H., and Plotho, O. V., *Chem. Ber.* 83:161, 1950. [3] Brockmann, H., and Loeschcke, V., *ibid* 88:778, 1955. [4] Brockmann, H., and Hieronymus, E., *ibid* 88:1379, 1955.

10. ACTINORUBIN

- [1] Junowicz-Kocholaty, R., and Kocholaty, W., *J. Biol. Chem.* 168:757, 1947. [2] Morton, H. E., *Proc. Soc. Exp. Biol.* 64:327, 1947. [3] Kelner, A., and Morton, H. E., *J. Bact., Balt.* 53:695, 1947.

11. ACTITHIAZIC ACID

- [1] Schenck, J. R., and DeRose, A. F., *Arch. Biochem.* 40:263, 1952. [2] Clark, R. K., Jr., and Schenck, J. R., *ibid* 40:270, 1952. [3] Grundy, W. E., et al, *Antibiotics and Chemotherapy* 2:399, 1952. [4] Tejera, E., et al, *ibid* 2:333, 1952. [5] Sobin, B. A., *J. Am. Chem. Soc.* 74:2947, 1952. [6] Ogata, K., et al, *Jap. Pat.* 5799, 1953. [7] Hamada, Y., Kawashima, M., Miyake, A., and Okamoto, K., *J. Antibiot., Tokyo* 6:158, 1953. [8] Hwang, K., *Antibiotics and Chemotherapy* 2:453, 1952. [9] McLamore, W. M., et al, *J. Am. Chem. Soc.* 75:105, 1953.

12. AGROCYBIN

- [1] Kavanagh, F., Hervey, A., and Robbins, W. J., *Proc. Nat. Acad. Sc. U. S.* 36:102, 1950. [2] Anchel, M., *J. Am. Chem. Soc.* 74:1588, 1952. [3] Jones, E. R., and Bu'lock, J. D., *J. Chem. Soc.* 1953:3719. [4] Bu'lock, J. D., Jones, E. R., Mansfield, G. H., Thompson, J. W., and Whiting, M. C., *Chemistry and Industry* 1954:990.

13. ALBIDIN

- [1] Curtis, P. J., and Grove, J. F., *Nature* 160:574, 1947. [2] Curtis, P. J., Hemming, H. G., and Unwin, C. H., *Brit. Mycol. Soc. Trans.* 34:332, 1951.

14. ALBOMYCETIN

- [1] Takahashi, B., *J. Antibiot., Tokyo, Ser. A* 7:149, 1954.

15. ALBOMYCIN

- [1] Brazhnikova, M. G., Lomakina, N. N., and Murav'eva, L. I., *Doklady Akad. nauk SSSR* 99:827, 1954; *Chem. Abstr.* 49:5573, 1955. [2] Gause, G. F., *Brit. M. J.* 2:1177, 1955. [3] Sazykin, Y. O., *Mikrobiologia, Moskva* 24:75, 1955; *Chem. Abstr.* 49:11780, 1955.

16. ALTERNARIC ACID

- [1] Grove, J. F., *J. Chem. Soc.* 1952:4056. [2] Brian, P. W., Curtis, P. J., Hemming, H. G., Unwin, C. H., and Wright, J. M., *Nature* 164:534, 1949. [3] Brian, P. W., et al, *J. Gen. Microb., Lond.* 5:619, 1951. [4] Anderson, H. W., and Gottlieb, D., *Econ. Botany* 6:294, 1952. [5] Pound, G. S., and Stahmann, M. A., *Phytopathology* 41:1104, 1951.

17. ALTERNARINE

- [1] Darpoux, H., Faivre-Amiot, A., and Roux, L., *C. rend. Acad. sc.* 230:993, 1950.

18. ALTERNARIOL

- [1] Raistrick, H., Stickings, C. E., and Thomas, R., *Biochem. J., Lond.* 55:421, 1953.

19. ALVEIN

- [1] Gilliver, K., Holmes, A. M., and Abraham, E. P., *Brit. J. Exp. Path.* 30:209, 1949.

20. AMAROMYCIN

- [1] Hata, T., et al, *J. Antibiot., Tokyo, Ser. A* 8:9, 1955.

21. AMICETIN

- [1] DeBoer, C., Caron, E. L., and Hinman, J. W., *J. Am. Chem. Soc.* 75:499, 1953. [2] McCormick, M. H., and Hoehn, M. M., *Antibiotics and Chemotherapy* 3:718, 1953. [3] Hinman, J. W., Caron, E. L., and DeBoer, C., *J. Am. Chem. Soc.* 75:5864, 1953. [4] Flynn, E. H., Hinman, J. W., Caron, E. L., and Woolf, D. O., Jr., *ibid* 75:5867, 1953. [5] Burchenal, J. H., Yuceoglu, M., Dagg, M. K., and Stock, C. C., *Proc. Soc. Exp. Biol.* 86:891, 1954.

REFERENCES (Continued)

21. AMICETIN (Concluded)

- [6] Hinuma, Y., et al, *J. Antibiot.*, Tokyo, Ser. A 8:148, 1955. [7] Szybalski, W., *Appl. Microbiol.* 2:57, 1954. [8] Tatsuoka, S., et al, *J. Pharm. Soc. Japan* 75:1276, 1955. [9] Tatsuoka, S., Inoue, M., Hamada, Y., and Fugii, S., *Ann. Repts. Takeda Research Lab.* 13:41, 1954. [10] Hinman, J. W., Caron, E. L., and DeBoer, C., *J. Am. Chem. Soc.* 75:5864, 1953.

22. D-4-AMINO-3-ISOXAZOLIDONE

- [1] Harris, D. A., et al, *Antibiotics and Chemotherapy* 5:183, 1955. [2] Harned, R. L., Hidy, P. H., and LaBaw, E. K., *ibid* 5:204, 1955. [3] Cuckler, A. C., Frost, B. M., McClelland, L., and Solotorovsky, M., *ibid* 5:191, 1955. [4] Kuehl, F. A., Jr., et al, *J. Am. Chem. Soc.* 77:2344, 1955. [5] Hidy, P. H., et al, *ibid* 77:2345, 1955. [6] Welch, H. Putnam, L. E., and Randall, W. A., *Antibiotic M.* 1:72, 1955. [7] Epstein, I. G., Nair, K. B., and Boyd, L. J., *ibid* 1:80, 1955. [8] Schull, G. M., and Sardinas, J. L., *Antibiotics and Chemotherapy* 5:398, 1955. [9] *Brit. Pat.* 715,362, 1954. [10] Stammer, C. H., Wilson, A. N., Holly, F. W., and Folkers, K., *J. Am. Chem. Soc.* 77:2344, 1955. [11] Robinson, H. J., Morgan, C., Richards, D. W., Frost, B. M., and Alpert, E., *Antibiotic M.* 1:351, 1955. [12] Hudgins, P. C., Patnode, R. A., and Cummings, M. M., *Am. Rev. Tuberc.* 72:685, 1955. [13] Sutton, W. B., and Stanfield, L., *Antibiotics and Chemotherapy* 5:582, 1955. [14] Jones, L. R., *Anal. Chem.* 28:39, 1956. [15] Roth, E. E., and Delaplane, J. P., *Southwest. Veterinarian* 8:154, 1955. [16] Patnode, R. A., Hudgins, P. C., and Cummings, M. M., *Am. Rev. Tuberc.* 72:856, 1955. [17] Epstein, I. G., Nair, K. G., and Boyd, L. J., *Dis. Chest* 29:241, 1956. [18] Lillick, L., Strang, R., Boyd, L. J., Schwimmer, M., and Mulinos, M. G., "Antibiotics Annual, 1955-56," p 158, New York: Medical Encyclopedia, Inc. [19] Herrold, R. D., Boand, A. V., and Kamp, M., *ibid*, p 165. [20] Marmell, M., and Prigot, A., *ibid*, p 153. [21] Epstein, I. G., Nair, K. G., and Boyd, L. J., *ibid*, p 141. [22] Nair, K. G., Epstein, I. G., Baron, H., and Mulinos, M. G., *ibid*, p 136. [23] Morton, R. F., McKenna, M. H., and Charles, E., *ibid*, p 169. [24] Barclay, W. R., and Russe, H., *Am. Rev. Tuberc.* 72:236, 1955. [25] Katz, S., *M. Ann. District of Columbia* 25:129, 1956. [26] Anderson, R. C., Worth, H. M., Welles, J. H., Harris, P. N., and Chen, K. K., *Antibiotics and Chemotherapy* 6:360, 1956. [27] Steenken, W., Jr., and Wolinsky, E., *Am. Rev. Tuberc.* 73:539, 1956.

23. AMPHOMYCIN

- [1] Heinemann, B., Kaplan, M. A., Muir, R. D., and Hooper, I. R., *Antibiotics and Chemotherapy* 3:1239, 1953. [2] Tisch, D. E., Hoekstra, J. B., Fisher, D. S., and Dickison, H. L., "Antibiotics Annual, 1954-55," p 1011, New York: Medical Encyclopedia, Inc. [3] *Brit. Pat.* 736,325, 1955.

24. AMPHOTERICINS

- [1] Gold, W., Stout, H. A., Pagano, J. F., and Donovan, R., "Antibiotics Annual, 1955-56," p 579, New York: Medical Encyclopedia, Inc. [2] Vandeputte, J., Wachtel, J. L., and Stiller, E. T., *ibid*, p 587. [3] Sternberg, T. H., Wright, E. T., and Oura, M., *ibid*, p 566. [4] Steinberg, B. A., Jambor, W. P., and Suydam, L. O., *ibid*, p 574.

25. ANGOLAMYCIN

- [1] Corbaz, R., et al, *Helvet. chim. acta* 38:1202, 1955.

26. ANGUSTMYCIN

- [1] Yüntsen, H., Yonehara, H., and Ui, H., *J. Antibiot.*, Tokyo, Ser. A 7:113, 1954. [2] Sakai, H., Yüntsen, H., and Ishikawa, F., *ibid* 7:116, 1954.

27. ANISOMYCIN

- [1] Sobin, B. A., and Tanner, F. W., Jr., *J. Am. Chem. Soc.* 76:4053, 1954. [2] Lynch, J. E., English, A. R., Bauck, H., and Deligianis, H., *Antibiotics and Chemotherapy* 4:844, 1954. [3] Lynch, J. E., English, A. R., Morrison, J., and Maven, I., *ibid* 4:899, 1954. [4] Tanner, F. W., Jr., Lynch, J. E., and Routin, J. B., *U. S. Pat.* 2,691,618, 1954. [5] Tanner, F. W., Jr., Sobin, B. A., and Gardocki, J. F., "Antibiotics Annual, 1954-55," p 809, New York: Medical Encyclopedia, Inc. [6] Lynch, J. E., English, A. R., Bamforth, B. J., and Goeckeritz, D., *ibid*, p 813. [7] Frye, W. W., Mule, J. G., and Swartzelder, C., *ibid*, p 820. [8] Armstrong, T., and Maria, O. S., *ibid*, p 824. [9] Lynch, J. E., Holley, E. C., and Salmirs, A. M., *Antibiotics and Chemotherapy* 5:300, 1955. [10] Lynch, J. E., Holley, E. C., and Margison, J. E., *ibid* 5:508, 1955. [11] Gardocki, J. F., Timmens, E. K., Wilson, L. B., Sodergren, J. O., Hettlinger, B. R., and P'an, S. Y., *ibid* 5:490, 1955. [12] Lynch, J. E., Bamforth, B. J., and Goeckeritz, D., *ibid* 6:330, 1956. [13] Seneca, H., and Bergendahl, E., *ibid* 5:737, 1955.

28. ANTIMYCIN A

- [1] Leben, C., and Keitt, G. W., *Phytopathology* 38:899, 1948. [2] Dunshee, B. R., Leben, C., Keitt, G. W., and Strong, F. M., *J. Am. Chem. Soc.* 71:2436, 1949. [3] Schneider, H. G., Tener, G. M., and Strong, F. M., *Arch. Biochem.* 37:147, 1952. [4] Tener, G. M., Bumpus, F. M., Dunshee, B. R., and Strong, F. M., *J. Am. Chem. Soc.* 75:1100, 1953. [5] Keitt, G. W., Leben, C., and Strong, F. M., *U. S. Pat.* 2,657,170, 1953. [6] Lockwood, J. L.,

REFERENCES (Continued)

28. ANTIMYCIN A (Concluded)

- Leben, C., and Keitt, G. W., *Phytopathology* 44:438, 1954. [7] Ahmad, K., Schneider, H. G., and Strong, F. M., *Arch. Biochem.* 28:281, 1950. [8] Leben, C., Army, D. C., and Keitt, G. W., *Phytopathology* 44:704, 1954. [9] Leben, C., and Keitt, G. W., *ibid* 39:529, 1949. [10] Kido, G. S., and Spyhalski, E., *Science* 112:172, 1950. [11] Potter, V. R., and Reif, A. E., *J. Biol. Chem.* 194:287, 1952. [12] Reif, A. E., and Potter, V. R., *Cancer Res.* 13:49, 1953. [13] Leben, C., and Keitt, G. W., *Phytopathology* 38:16, 1948. [14] Ackermann, W. W., *J. Biol. Chem.* 189:421, 1951. [15] Sakagami, Y., et al, *J. Antibiot., Tokyo, Ser. A* 9:1, 1956. [16] Dominguez, A. M., and Shideman, F. E., *Proc. Soc. Exp. Biol.* 90:329, 1955. [17] Nakayama, K., Okamoto, F., and Harada, Y., *J. Antibiot., Tokyo, Ser. A* 9:63, 1956.

29. ARGOMYCIN

- [1] Hata, T., et al, *J. Antibiot., Tokyo, Ser. A* 8:9, 1955. [2] Aramaki, Y., et al, *Ann. Repts. Takeda Research Lab.* 14:60, 1955.

30. ASCOSIN

- [1] Hickey, R. J., et al, *Antibiotics and Chemotherapy* 2:472, 1952. [2] Hickey, R. J., *Arch. Biochem.* 46:331, 1953. [3] Emmons, C. W., and Haberman, R. T., *Antibiotics and Chemotherapy* 3:1204, 1953. [4] Bachman, M. C., (quoted by Hickey, et al), *ibid* 2:472, 1952. [5] Cohen, I. R., *U. S. Pat.* 2,723,216, 1955. [6] Yajima, T., *J. Antibiot., Tokyo, Ser. A* 8:189, 1955.

31. ASPERGILLIC ACID

- [1] White, E. C., and Hill, H. H., *J. Bact., Balt.* 45:433, 1943. [2] Dutcher, J. D., *J. Biol. Chem.* 171:321, 1947. [3] Dutcher, J. D., and Wintersteiner, O., *ibid* 155:359, 1944. [4] Woodward, C. R., Jr., *J. Bact., Balt.* 54:375, 1947. [5] Jones, H., Rake, G., and Hamre, D. M., *ibid* 45:461, 1943. [6] Rake, G., McKee, C. M., and Jones, H., *Proc. Soc. Exp. Biol.* 51:273, 1942. [7] Newbold, G. T., Sharp, W., and Spring, F. S., *Chemistry and Industry* 1951:651. [8] Dunn, G., Gallagher, J. J., Newbold, G. T., and Spring, F. S., *J. Chem. Soc.* 1949:S 126. [9] Dutcher, J. D., Wintersteiner, O., and Menzel, A. E., *Fed. Proc.* 7:152, 1948. [10] Dunham, W. G., Hamre, D. M., McKee, C. M., and Rake, G., *Proc. Soc. Exp. Biol.* 55:158, 1944. [11] Goth, A., *Science* 104:330, 1946. [12] Goth, A., *J. Laborat. Clin. M.* 30:899, 1945.

32. AURANTIDIN

- [1] Tsuda, Y., *Arch. Antibiot., Tokyo* 4:95, 1951.

33. AURANTIOGLOCLADIN

- [1] Brian, P. W., Curtis, P. J., Howland, S. R., Jefferys, E. G., and Raudnitz, H., *Experientia, Basel* 7:266, 1951. [2] Vischer, E. B., *J. Chem. Soc.* 1953:815. [3] Baker, W., McOmie, J. F., and Miles, D., *ibid* 1953:820.

34. AUREOLIC ACID

- [1] Grundy, W. E., et al, *Antibiotics and Chemotherapy* 3:1215, 1953. [2] Philip, J. E., and Schenck, J. R., *ibid* 3:1218, 1953.

35. AUREOTHRICIN

- [1] Nishimura, H., Kimura, T., and Kuroya, M., *J. Antibiot., Tokyo, Ser. A* 6:57, 1953. [2] Celmer, W. D., and Solomons, I. A., "Antibiotics Annual, 1953-54," p 622, New York: Medical Encyclopedia, Inc. [3] Takahashi, T., Matsunaga, M., and Uematsu, K., *J. Antibiot., Tokyo, Ser. B* 6:452, 1953. [4] Celmer, W. D., and Solomons, I. A., abstr. of papers, 126th Meet. Am. Chem. Soc., p 15N, 1954. [5] Celmer, W. D., and Solomons, I. A., *J. Am. Chem. Soc.* 77:2861, 1955. [6] Nitta, K., Takeuchi, T., Yamamoto, T., and Umezawa, H., *J. Antibiot., Tokyo, Ser. A* 8:120, 1955.

36. AZASERINE

- [1] Stock, C. C., et al, *Nature* 173:71, 1954. [2] Ehrlich, J., et al, *ibid* 173:72, 1954. [3] Bartz, Q. R., et al, *ibid* 173:72, 1954. [4] Fusari, S. A., et al, *J. Am. Chem. Soc.* 76:2878, 1954. [5] Fusari, S. A., Haskell, T. H., Frohardt, R. P., and Bartz, Q. R., *ibid* 76:2881, 1954. [6] Coffey, G. L., Hillegas, A. B., Knudsen, M. P., Koepsell, H. J., Oyaas, J. E., and Ehrlich, J., *Antibiotics and Chemotherapy* 4:775, 1954. [7] Burchenal, J. H., Yucooglu, M., Dagg, M. K., and Stock, C. C., *Proc. Soc. Exp. Biol.* 86:891, 1954. [8] Reilly, H. C., *Fed. Proc.* 13:279, 1954. [9] Ehrlich, J., et al, *ibid* 13:444, 1954. [10] Sternberg, S. S., Philips, F. S., and Clarke, D. A., *ibid* 13:444, 1954. [11] Reilly, H. C., *Soc. Am. Bact. Bact. Proc.*, p 79, 1954. [12] Norman, A. G., *Science* 121:213, 1955. [13] Sugiura, K., and Stock, C. C., *Proc. Soc. Exp. Biol.* 88:127, 1955. [14] Kohberger, D. L., Reilly, H. C., Coffey, G. L., Hillegas, A. B., and Ehrlich, J., *Antibiotics and Chemotherapy* 5:59, 1955. [15] Stock, C. C.,

REFERENCES (Continued)

36. AZASERINE (Concluded)

- Reilly, H. C., Buckley, S. M., Clarke, D. A., and Rhoads, C. P., *Acta Unio Intern. contra Cancrum* 11:186, 1955. [16] Nitta, K., Takeuchi, T., Yamamoto, T., and Umezawa, H., *J. Antibiot.*, Tokyo, Ser. A 8:120, 1955. [17] Ellison, R. R., Karnofsky, D. A., Sternberg, S. S., Murphy, M. L., and Burchenal, J. H., *Cancer* 7:801, 1954. [18] Kaplan, L., and Stock, C. C., *Fed. Proc.* 13:239, 1954. [19] Skipper, H. E., Bennett, L., Jr., and Schabel, F. M., Jr., *ibid* 13:298, 1954. [20] Fernandes, J. F., LePage, G. A., and Lindner, A., *Cancer Res.* 16:154, 1956. [21] Maxwell, R. E., and Nickel, V. S., *Science* 120:270, 1954. [22] Nicolaides, E. D., Westland, R. D., and Wittle, E. L., *J. Am. Chem. Soc.* 76:2887, 1954. [23] Gots, J. S., Bird, T. J., and Mudd, S., *Biochem. biophys. acta* 17:449, 1955. [24] Sugiura, K., *Cancer Res., Sup.* 3:18, 1955. [25] Gellhorn, A., and Hirschberg, E., *ibid* 3:1, 1955. [26] Clarke, D. A., Reilly, H. C., and Stock, C. C., *Proc. Am. Soc. Cancer Res.* 2:100, 1956. [27] Halvorson, H., *Antibiotics and Chemotherapy* 4:948, 1954. [28] Gots, J. S., and Gollub, E. G., *Proc. Am. Soc. Cancer Res.* 2:111, 1956. [29] Dagg, C. P., and Karnofsky, D. A., *Fed. Proc.* 15:238, 1956.

37. AZOMYCIN

- [1] Maeda, K., Osato, T., and Umezawa, H., *J. Antibiot.*, Tokyo, Ser. A 6:182, 1953. [2] Okami, Y., Maeda, K., and Umezawa, H., *ibid* 7:53, 1954. [3] Nakamura, S., and Umezawa, H., *ibid* 8:66, 1955. [4] Osato, T., et al, *J. Antibiot.*, Tokyo 8:105, 1955. [5] Nitta, K., Takeuchi, T., Yamamoto, T., and Umezawa, H., *ibid*, Ser. A 8:120, 1955.

38. BACCATINE A

- [1] Guérillot-Vinet, M., and Mme. J., Guyot, L., Montegut, J., and Roux, L., *C. rend. Acad. sc.* 230:1424, 1950.

39. BACILIPINS

- [1] Newton, G. G., *Brit. J. Exp. Path.* 30:306, 1949.

40. BACILLIN

- [1] Foster, J. W., and Woodruff, H. B., *J. Bact.*, Balt. 51:363, 1946. [2] Rudert, F. S., and Foter, M. S., *ibid* 54:793, 1947. [3] Woodruff, H. B., and Foster, J. W., *ibid* 51:371, 1946.

41. BACILLOMYCIN

- [1] Landy, M., Rosenman, S. B., and Warren, G. H., *J. Bact.*, Balt. 54:24, 1947. [2] Landy, M., Warren, G. H., Rosenman, S. B., and Colio, L. G., *Proc. Soc. Exp. Biol.* 67:539, 1948. [3] Tint, H., and Reiss, W., *J. Biol. Chem.* 190:133, 1951. [4] Babad, J., Pinsky, A., Turner-Graff, R., and Sharon, N., *Nature* 170:618, 1952. [5] Sharon, N., Pinsky, A., Turner-Graff, R., Babad, J., and Cercós, A. P., *ibid* 174:1190, 1954. [6] Cercós, A. P., *Rev. de Invest. Ag.* 4:3, 1950. [7] Cercós, A. P., and Castro-Novo, A., *An. Soc. cient. argent.* 152:68, 1951; *Biol. Abstr.* 26:15612, 1952. [8] Cercós, A. P., *Rev. de Invest. Ag.* 4:325, 1950. [9] Turner, R. A., *Arch. Biochem.* 60:364, 1956.

42. BACILLOMYCIN B

- [1] Shibasaki, I., and Terui, G., *J. Fermentation Technol.*, Japan 31:339, 1953.

43. BACILLOMYCIN C

- [1] Shibasaki, I., and Terui, G., *J. Fermentation Technol.*, Japan 32:115, 1954.

44. BACILYSIN

- [1] Newton, G. G., *Brit. J. Exp. Path.* 30:306, 1949. [2] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949.

45. BACITRACINS

- [1] Johnson, B. A., Anker, H. S., and Meloney, F. L., *Science* 102:376, 1945. [2] Anker, H. S., Johnson, B. A., Goldberg, J., and Meloney, F. L., *J. Bact.*, Balt. 55:249, 1948. [3] Craig, L. C., Gregory, J. D., and Barry, G. T., *J. Clin. Invest.* 28:1014, 1949. [4] Darker, G. D., et al, *J. Am. Pharm. Ass.* 37:156, 1948. [5] Barry, G. T., Gregory, J. D., and Craig, L. C., *J. Biol. Chem.* 175:485, 1948. [6] Sharp, V. E., Arriagada, A., Newton, G. G., and Abraham, E. P., *Brit. J. Exp. Path.* 30:444, 1949. [7] Bennett, R. E., Dudley, J. F., and Shepard, M. W., *Indust. Engin. Chem.* 43:1488, 1951. [8] Newton, G. G., and Abraham, E. P., *Biochem. J.* 53:597, 1953. [9] Newton, G. G., and Abraham, E. P., *ibid* 53:604, 1953. [10] Porath, J., *Nature* 172:871, 1953. [11] Craig, L. C., Hausmann, W., and Weisiger, J. R., *J. Biol. Chem.* 200:765, 1953. [12] Lockhart, I. M., Newton, G. G., and Abraham, E. P., *Nature* 173:536, 1954. [13] Craig, L. C., Hausmann, W., and Weisiger, J. R., *J. Am. Chem. Soc.* 76:2839, 1954. [14] Lockhart, I. M., and Abraham, E. P., *Biochem. J.* 58:633, 1954. [15] Hausmann, W., Weisiger,

REFERENCES (Continued)

45. BACITRACINS (Concluded)

- J. R., and Craig, L. C., *J. Am. Chem. Soc.* 77:721, 1955. [16] Hausmann, W., Weisiger, J. R., and Craig, L. C., *ibid* 77:723, 1955. [17] Porath, J., *Acta chem. scand.* 6:1237, 1952. [18] Welch, H., "Principles and Practice of Antibiotic Therapy," New York: Blakiston Co., 1954. [19] Meleney, F. L., and Johnson, B. A., *Am. J. M.* 7:794, 1949. [20] Bruce, C. B., and Mitchell, L., *J. Am. Pharm. Ass. (Sci. Ed.)* 41:654, 1952. [21] Cole, B. A., *Proc. Helminth. Soc. Washington* 17:65, 1950. [22] Arriagada, A., Florey, H. W., Jennings, M. A., and Wallmark, I. G., *Brit. J. Exp. Path.* 30:458, 1949. [23] Eagle, H., and Fleischman, R., *J. Bact., Balt.* 55:341, 1948. [24] Meleney, F. L., and Teng, P., *J. Clin. Invest.* 28:1054, 1949. [25] Felsenfeld, O., Volini, I. F., Young, V. M., and Ishihara, S. J., *Am. J. Trop. M.* 30:499, 1950. [26] Wells, H. S., *J. Infect. Dis.* 90:110, 1952. [27] Brown, H. W., *Ann. N. York Acad. Sc.* 55:1133, 1952. [28] Meleney, F. L., and Johnson, B. A., *J. Am. M. Ass.* 133:675, 1947. [29] Longacre, A. B., Waters, R. M., and Evans, F., *J. Clin. Invest.* 28:1054, 1949. [30] Miller, J. L., Slatkin, M. H., and Johnson, B. A., *Arch. Derm. Syph., Chic.* 60:106, 1949. [31] Kile, R. L., Rockwell, E., and Schwarz, J., *ibid* 68:296, 1953. [32] Leopold, I. H., *Arch. Ophth., Chic.* 44:300, 1950. [33] Coyle, J. E., Collins, K., and Nungester, W. J., *Arch. Otolar., Chic.* 50:284, 1949. [34] Silverman, D. N., *Gastroenterology* 19:320, 1951. [35] Most, H., Miller, J. W., Grossman, E. B., and Conan, N., Jr., *J. Am. M. Ass.* 143:792, 1950. [36] Shookhoff, H. B., and Sterman, M. M., *Ann. N. York Acad. Sc.* 55:1125, 1952. [37] Teng, P., *Surgery* 33:321, 1953. [38] Teng, P., Cohen, I., and Meleney, F. L., *Surg. Gyn. Obst.* 92:53, 1951. [39] Benson, D. V., *J. Am. Vet. M. Ass.* 112:160, 1948. [40] Rose, H. T., *ibid* 117:306, 1950. [41] Payne, H. G., Spencer, J. N., and Schultz, F. H. Jr., *Antibiotics and Chemotherapy* 1:387, 1951. [42] Rossoff, I. S., and Abel, W., *Vet. M., Chic.* 43:369, 1953. [43] Scudi, J. V., and Antopol, W., *Proc. Soc. Exp. Biol.* 64:503, 1947. [44] Scudi, J. V., Coret, I. A., and Antopol, W., *ibid* 66:558, 1947. [45] Newton, G. G., Abraham, E. P., Florey, H. W., and Smith, N., *Brit. J. Pharm.* 6:417, 1951. [46] Pulaski, E. J., and Connell, J. F., Jr., *Bull. U. S. Army M. Dep.* 9:141, 1949. [47] Miller, J. H., McDonald, R. K., and Shock, N. W., *J. Clin. Invest.* 29:389, 1950. [48] Kutscher, A. H., Lane, S. L., and Segall, R., *J. Allergy* 25:135, 1954. [49] Pomerat, C. M., and Leake, C. D., *Ann. N. York Acad. Sc.* 58:1110, 1954. [50] Teng, P., Levin, F. S., and Meleney, F. L., *Proc. Soc. Exp. Biol.* 72:244, 1949. [51] Scudi, J. V., Clift, M. E., and Kruger, R. A., *ibid* 65:9, 1947. [52] Zintel, H. A., Ma, R. A., Nichols, A. C., and Ellis, H., *Am. J. M. Sc.* 218:439, 1949. [53] Elam, J. F., Gee, L. L., and Couch, J. R., *Proc. Soc. Exp. Biol.* 78:832, 1951. [54] Elam, J. F., et al, *J. Nutrit.* 49:307, 1953. [55] Braude, R., Wallace, H. D., and Cunha, T. J., *Antibiotics and Chemotherapy* 3:273, 1953. [56] Noland, P. R., Tucker, D. L., and Stephenson, E. L., *Arkansas Agr. Exp. Sta. Rept., Ser. No. 34*, 1952. [57] Nickell, L. G., and Finlay, A. C., *J. Agr. Food Chem.* 2:178, 1954. [58] Gezon, H. M., Fasan, D. M., and Collins, G. R., *Proc. Soc. Exp. Biol.* 74:505, 1950. [59] Jacobs, R. L., Elam, J. F., Tidwell, W. L., Fowler, J., and Couch, J. R., "Antibiotics Annual, 1954-55," p 525, New York: Medical Encyclopedia, Inc. [60] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952. [61] Schuhardt, V. T., *ibid* 55:1209, 1952. [62] Rier, J. P., Jr., and Henderson, J. H., *J. Nat. Cancer Inst.* 16:981, 1956. [63] Steinhaus, E. A., and Bell, C. R., *J. Econom. Entom.* 46:582, 1953. [64] Liles, J. N., and Fisk, F. W., *ibid* 48:217, 1955. [65] Gross, H. M., *J. Am. Pharm. Ass. (Sci. Ed.)* 44:704, 1955. [66] Tarnowski, G. S., *Cancer Res. Sup.* 2:333, 1955. [67] Barton, L. V., and MacNab, J., *Contrib. Boyce Thompson Inst.* 17:419, 1954. [68] Eagle, H., Musselman, A. D., and Fleishman, R., *J. Bact., Balt.* 55:347, 1948. [69] Paine, T. F., Jr., *ibid* 61:259, 1951. [70] Robertstad, G. W., Sullivan, R., Tucker, O., and Glenn, M. W., *Vet. M., Chic.* 50:142, 1955.

46. BIFORMYNES

- [1] Robbins, W. J., Kavanagh, F., and Hervey, A., *Proc. Nat. Acad. Sc. U. S.* 33:176, 1947. [2] Anchel, M., and Cohen, M. P., *J. Biol. Chem.* 208:319, 1954. [3] Anchel, M., *Tr. N. York Acad. Sc.* 16:337, 1954.

47. BIOCERIN

- [1] Johnson, C. W., West, H. D., Jones, H. L., and Long, C. J., *J. Bact., Balt.* 57:63, 1949.

48. BORRELIDIN

- [1] Berger, J., Jampolsky, L. M., and Goldberg, M. W., *Arch. Biochem.* 22:476, 1949. [2] Buck, M., Farr, A. C., and Schnitzer, R. J., *Tr. N. York Acad. Sc.* 11:207, 1949. [3] Schnitzer, R. J., Buck, M., and Farr, A. C., *J. Clin. Invest.* 28:1047, 1949. [4] Cooperman, J. M., Rubin, S. H., and Tabenkin, B., *Proc. Soc. Exp. Biol.* 76:18, 1951.

49. BOSTRYCOIDIN

- [1] Hamilton, M. A., Khorr, M. S., and Cajori, F. A., *Antibiotics and Chemotherapy* 3:853, 1953. [2] Cajori, F. A., Otani, T. T., and Hamilton, M. A., *J. Biol. Chem.* 208:107, 1954.

50. BREVIN

- [1] Barnes, E. M., and Newton, G. G., *Antibiotics and Chemotherapy* 3:866, 1953.

51. BREVOLIN

- [1] Kawamata, J., and Motomura, Y., *J. Antibiot., Tokyo, Ser. A* 7:25, 1954.

REFERENCES (Continued)

52. BROMOTETRACYCLINE

- [1] Sensi, P., DeFerrari, G. A., Gallo, G. G., and Rolland, G., *Il Farm. sci. e tec.*, Pavia, Ed. sci. 10:337, 1955.
 [2] Rolland, G., Timbal, M. T., Maffii, G., and Sensi, P., *ibid* 10:346, 1955. [3] Doerschuk, A. P., et al, *J. Am. Chem. Soc.* 78:1508, 1956.

53. BRYAMYCIN

- [1] Cron, M. J., Whitehead, D. F., Hooper, I. R., Heinemann, B., and Lein, J., *Antibiotics and Chemotherapy* 6:63, 1956.

54. CACAOMYCETIN

- [1] Wakaki, S., *J. Antibiot.*, Tokyo 5:24, 1952.

55. CAMPHOMYCIN

- [1] Cercos, A. P., *Rev. Argentina de Agron.* 20:53, 1953. [2] Cercós, A. P., *Rev. de Invest. Ag.* 8:263, 1954.

56. CANDICIDINS

- [1] Lechevalier, H. A., Acker, R. F., Corke, C. T., Haenseler, C. M., and Waksman, S. A., *Mycologia, Lanc.* 45:155, 1953. [2] Kligman, A. M., and Lewis, F. S., *Proc. Soc. Exp. Biol.* 82:399, 1953. [3] Franks, A. G., Taschdjian, C. L., and Thorpe, G. A., *J. Invest. Derm.* 23:75, 1954. [4] Solotorovsky, M., Ironson, E. J., Gregory, F. J., and Winsten, S., *Antibiotics and Chemotherapy* 4:165, 1954. [5] De Mello, G. C., and Kiser, J. S., "Antibiotics Annual, 1954-55," p 678, New York: Medical Encyclopedia, Inc. [6] Fox, J. L., *Antibiotic M.* 1:349, 1955. [7] Alcorn, S. M., and Ark, P. A., *Plant Disease Repr.* 38:705, 1954. [8] Alcorn, S. M., and Ark, P. A., *ibid* 39:210, 1955. [9] Wallen, V. R., *ibid* 39:124, 1955. [10] Hu, F., Livingood, C. S., Johnson, P., and Pomerat, C. M., *Arch. Derm. Syph.*, Chic. 70:1, 1954.

57. CANDIDINS

- [1] Taber, W. A., Vining, L. C., and Waksman, S. A., *Antibiotics and Chemotherapy* 4:455, 1954. [2] Vining, L. C., Taber, W. A., and Gregory, F. J., "Antibiotics Annual, 1954-55," p 980, New York: Medical Encyclopedia, Inc.

58. CANDIDULIN

- [1] Stansly, P. G., and Ananenko, N. H., *Arch. Biochem.* 23:256, 1949. [2] Yajima, T., *J. Antibiot.*, Tokyo, Ser. A 8:189, 1955.

59. CANESCIN

- [1] Brian, P. W., Hemming, H. G., Moffatt, J. S., and Unwin, C. H., *Brit. Mycol. Soc. Trans.* 36:243, 1953.

60. CARBOMYCIN

- [1] Tanner, F. W., Jr., English, A. R., Lees, T. M., and Routien, J. B., *Antibiotics and Chemotherapy* 2:441, 1952. [2] Dutcher, J. D., Vandeputte, J., Fox, S., and Heuser, L. J., *ibid* 3:910, 1953. [3] Wagner, R. L., Hochstein, F. A., Murai, K., Messina, N., and Regna, P. P., *J. Am. Chem. Soc.* 75:4684, 1953. [4] Finlay, A. C., and Regna, P. P., 6th Internat. Congr. Microb. 4:58, 1953. [5] Perlman, D., *Science* 118:628, 1953. [6] English, A. R., Field, M. F., Szendy, S. R., Tagliani, N. J., and Fitts, R. A., *Antibiotics and Chemotherapy* 2:678, 1952. [7] Welch, H., Randall, W. A., Reedy, R. J., and Kramer, J., *ibid* 2:693, 1952. [8] Seneca, H., and Ides, D., *ibid* 3:117, 1953. [9] English, A. R., Mullady, H. E., and Fitts, R. A., *ibid* 3:94, 1953. [10] Wong, S. C., James, C. G., and Finlay, A. C., *ibid* 3:741, 1953. [11] Manning, P. R., Jones, P. N., and Bigham, R. S., *N. England J. M.* 249:758, 1953. [12] Gauvreau, L., Lapointe, D., and Jacobs, N., *Laval méd.* 19:731, 1954. [13] Robinson, H. M., Jr., and Cohen, M. M., *J. Invest. Derm.* 22:263, 1954. [14] Sodeman, W. A., *J. Louisiana State M. Soc.* 105:171, 1953. [15] Crosnier, R., et al, *Bull. Soc. path. exot., Par.* 47:52, 1954. [16] Gardocki, J. F., P'an, S. Y., Rapuzzi, A. L., Fanelli, G. M., and Timmens, E. K., *Antibiotics and Chemotherapy* 3:55, 1952. [17] Hewitt, W. L., and Wood, J. P., *N. England J. M.* 249:261, 1953. [18] Finland, M., et al, *ibid* 249:310, 1953. [19] English, A. R., Field, M. F., Reilly, J., McNierny, J., and P'an, S. Y., *Antibiotics and Chemotherapy* 3:309, 1953. [20] English, A. R., Rapuzzi, A. L., Field, M. F., McNierny, J., and P'an, S. Y., *ibid* 4:561, 1954. [21] Finland, M., Wilcox, C., Wright, S. S., and Purcell, E. M., *Proc. Soc. Exp. Biol.* 81:725, 1952. [22] Field, W. W., and Taylor, G., *Antibiotics and Chemotherapy* 4:65, 1954. [23] Kutscher, A. H., et al, *ibid* 3:1194, 1953. [24] Trafton, H. M., et al, *N. England J. M.* 248:379, 1953. [25] Eaton, M. D., "Antibiotics Annual, 1954-55," p 1046, New York: Medical Encyclopedia, Inc. [26] Gable, G. R., Romansky, M. J., and Taggart, S. R., *ibid*, p 578. [27] Hawley, G. E., and Downing, H. E., *ibid*, p 336. [28] Reynolds, W. M., Warden, W. K., Pendergrass, G. P., and Luther, H. G., *ibid*, p 510. [29] Taylor, D. J., Bond, H. W., and Sherman, J. F., *ibid*, p 745. [30] Kiser, J. S., and De Mello, G. C., *Proc. 58th Annual Meet., Nov. 1954, U. S. Livestock Sanitary Ass.*, p 81, 1955. [31] Buckinger, R. H., Hookings, C. E.,

REFERENCES (Continued)

60. CARBOMYCIN (Concluded)

and Garson, W., *Antibiotic M.* 1:100, 1955. [32] Regna, P. P., Hochstein, F. A., Wagner, R. L., and Woodward, R. B., *J. Am. Chem. Soc.* 75:4625, 1953. [33] Hochstein, F. A., and Regna, P. P., *ibid* 77:3353, 1955. [34] MacKneson, R. G., and Ormsby, H. L., *Am. J. Ophth.* 39:689, 1955. [35] Kolmer, J. A., "Antibiotics Annual, 1955-56," p 592, New York: Medical Encyclopedia, Inc. [36] Hookings, C. E., and Graves, L. M., *ibid*, p 217. [37] Thompson, P. E., McCarthy, D. A., Bayles, A., Reinertson, J. W., and Cook, A. R., *Antibiotics and Chemotherapy* 6:337, 1956. [38] El-Din, G. N., *Am. J. Trop. M. Hyg.* 5:72, 1956. [39] Hara, Y., and Abe, T., *ibid* 5:218, 1956. [40] Ott, R. L., Gorham, J. R., *North Am. Vet.* 36:574, 1955.

61. CARBOMYCIN B

[1] Hochstein, F. A., and Murai, K., *J. Am. Chem. Soc.* 76:5080, 1954. [2] Whitaker, J. C., Prigot, A., and Morgan, E. G., "Antibiotics Annual, 1953-54," p 527, New York: Medical Encyclopedia, Inc.

62. CARDICIN

[1] Machlowitz, R. A., et al, *Antibiotics and Chemotherapy* 3:966, 1953.

63. CARNEOLUTESCIN

[1] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949.

64. CARZINOCIDIN

[1] Harada, Y., Nara, T., and Okamoto, F., *J. Antibiot., Tokyo, Ser. A* 9:6, 1956. [2] Harada, Y., Nubo, S., and Itagaki, S., *ibid* 9:9, 1956. [3] Harada, Y., and Tanaka, S., *ibid* 9:113, 1956.

65. CARZINOPHILIN

[1] Hata, T., et al, *J. Antibiot., Tokyo, Ser. A* 7:107, 1954. [2] Shimada, N., et al, *ibid* 8:67, 1955. [3] Sugiura, K., *Ann. N. York Acad. Sc.* 63:962, 1956.

66. CARZINOPHILIN A

[1] Kamada, H., et al, *J. Antibiot., Tokyo, Ser. A* 8:187, 1955.

67. CATENULIN

[1] Davisson, J. W., Solomons, I. A., and Lees, T. M., *Antibiotics and Chemotherapy* 2:460, 1952. [2] Nickell, L. G., and Finlay, A. C., *J. Agr. Food Chem.* 2:178, 1954. [3] Szybalski, W., and Bryson, V., *Am. Rev. Tuberc.* 69:267, 1954. [4] Barton, L. V., and MacNab, J., *Contrib. Boyce Thompson Inst.* 17:419, 1954.

68. CELESTICETIN

[1] De Boer, C., Dietz, A., Wilkins, J. R., Lewis, C. N., and Savage, G. M., "Antibiotics Annual, 1954-55," p 831, New York: Medical Encyclopedia, Inc. [2] Hoeksema, H., Crum, G. F., and DeVries, W. H., *ibid*, p 837.

69. CEPHALOSPORIN C

[1] Newton, G. G., and Abraham, E. P., *Nature* 175:548, 1955. [2] Florey, H. W., *Ann. Int. M.* 43:480, 1955. [3] Newton, G. G., and Abraham, E. P., *Biochem. J., Lond.* 62:651, 1956. [4] Abraham, E. P., and Newton, G. G., *ibid* 62:658, 1956.

70. CEPHALOSPORIN N

[1] Abraham, E. P., Newton, G. G., Crawford, K., Burton, H. S., and Hale, C. W., *Nature* 171:343, 1953. [2] Newton, G. G., and Abraham, E. P., *ibid* 172:395, 1953. [3] Hale, C. W., Miller, G. A., and Kelly, B. K., *ibid* 172:545, 1953. [4] Abraham, E. P., Newton, G. G., and Hale, C. W., *Biochem. J., Lond.* 58:94, 1954. [5] Newton, G. G., and Abraham, E. P., *ibid* 58:103, 1954. [6] Heatley, N. G., and Florey, H. W., *Brit. J. Pharm.* 8:252, 1953. [7] Abraham, E. P., et al, *Nature* 176:551, 1955.

71. CEPHALOSPORIN P SERIES

[1] Crawford, K., et al, *J. Gen. Microb., Lond.* 6:47, 1952. [2] Burton, H. S., and Abraham, E. P., *Biochem. J., Lond.* 50:168, 1951. [3] Ritchie, E. C., Smith, N., and Florey, H. W., *Brit. J. Pharm.* 6:430, 1951. [4] Burton, H. S., Abraham, E. P., and Cardwell, H. M., *Biochem. J., Lond.* 62:171, 1956.

72. CEPHALOTHECIN

[1] Yoshii, H., *Ann. Phytopath. Soc., Japan* 14:84, 1950; *Chem. Abstr.* 47:11366, 1953. [2] Yoshii, H., *ibid* 18:9, 17, 1953; (abstr.) *Rev. Appl. Mycol.* 35:39, 1956.

REFERENCES (Continued)

73. CEREVIOCCIDIN

- [1] Yamashita, A., et al, *J. Antibiot.*, Tokyo, Ser. A 8:42, 1955.

74. CHARTREUSIN

- [1] Leach, B. E., Calhoun, K. M., Johnson, L. E., Teeters, C. M., and Jackson, W. G., *J. Am. Chem. Soc.* 75:4011, 1953. [2] Calhoun, K. M., and Johnson, L. E., *Antibiotics and Chemotherapy* 6:294, 1956.

75. CHARTREUSIN-LIKE ANTIBIOTIC

- [1] Arcamone, F., Bizioli, F., and Scotti, T., *Antibiotics and Chemotherapy* 6:283, 1956.

76. CHETOMIN

- [1] Geiger, W. B., Conn, J. E., and Waksman, S. A., *J. Bact.*, Balt. 48:531, 1944. [2] Geiger, W. B., *Arch. Biochem.* 21:125, 1949. [3] Waksman, S. A., and Bugie, E., *J. Bact.*, Balt. 48:527, 1944. [4] Reilly, H. C., Schatz, A., and Waksman, S. A., *ibid* 49:585, 1945.

77. CHLAMYDOSPORIN

- [1] Faivre-Amiot, A., Darpoux, H., and Roux, L., *C. rend. Acad. sc.* 235:912, 1952.

78. CHLORAMPHENICOL

- [1] Ehrlich, J., Bartz, Q. R., Smith, R. M., and Joslyn, D. A., *Science* 106:417, 1947. [2] Gottlieb, D., Bhattacharyya, P. K., Anderson, H. W., and Carter, H. E., *J. Bact.*, Balt. 55:409, 1948. [3] Bartz, Q. R., *J. Clin. Invest.* 28:1051, 1949. [4] Rebstock, M. C., Crooks, H. M., Jr., Controulis, J., and Bartz, Q. R., *J. Am. Chem. Soc.* 71:2458, 1949. [5] Gruhzit, O. M., Fischen, R. A., Reutner, T. F., and Martino, E., *J. Clin. Invest.* 28:943, 1949. [6] Smith, G. N., Worrel, C. S., and Lilligren, B. L., *Science* 110:297, 1949. [7] Joslyn, D. A., Ehrlich, J., and Schwab, J. L., *J. Clin. Invest.* 28:1051, 1949. [8] Bartz, Q. R., *J. Biol. Chem.* 172:445, 1948. [9] Glazko, A. J., Dill, W. A., and Wolf, L. M., *J. Clin. Invest.* 28:1051, 1949. [10] McLean, I. W., Jr., Schwab, J. L., Hillegas, A. B., and Schlingman, A. S., *ibid* 28:953, 1949. [11] Finland, M., and Wilcox, C., *Am. J. Clin. Path.* 20:335, 1950. [12] Frank, P. F., Wilcox, C., and Finland, M., *J. Laborat. Clin. M.* 35:188, 1950. [13] Wells, E. B., Shih-Man, C., Jackson, G. G., and Finland, M., *J. Pediat.*, St. Louis 36:752, 1950. [14] Gocke, T. M., Wilcox, C., and Finland, M., *Am. J. Syph.* 34:265, 1950. [15] Frank, P. F., Wilcox, C., and Finland, M., *J. Laborat. Clin. M.* 35:205, 1950. [16] Kiser, J. S., De Mello, G. C., Reichard, D. H., and Williams, J. H., *J. Infect. Dis.* 90:76, 1952. [17] Welch, H., Randall, W. A., Reedy, R. J., and Kramer, J., *Antibiotics and Chemotherapy* 2:693, 1952. [18] Potee, K. G., Wright, S. S., and Finland, M., *J. Laborat. Clin. M.* 44:463, 1954. [19] Smith, R. M., et al, *J. Bact.*, Balt. 55:425, 1948. [20] Bliss, E. A., and Todd, P., *J. Clin. Invest.* 28:1044, 1948. [21] Thompson, P. E., Dunn, M. C., and Winder, C. V., *J. Infect. Dis.* 86:110, 1950. [22] Gauld, R. L., et al, *J. Bact.*, Balt. 57:349, 1949. [23] Thompson, P. E., Dunn, M. C., Bayles, A., and Reinertson, J. W., *Am. J. Trop. M.* 30:203, 1950. [24] Eyles, D. E., and Coleman, N., *Am. J. Trop. M. Hyg.* 2:64, 1953. [25] Dunn, M. C., and Thompson, P. E., *J. Infect. Dis.* 92:33, 1953. [26] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952. [27] Hsiang, C. M., and Pakchianian, A., *Texas Repts. Biol. M.* 9:34, 1951. [28] Meyer, K. F., Quan, S. F., McCrumb, F. R., and Larson, A., *Ann. N. York Acad. Sc.* 55:1228, 1952. [29] Smadel, J. E., Jackson, E. B., and Cruise, A. B., *J. Immun.*, Balt. 62:49, 1949. [30] Am. M. Ass. Council on Pharmacy and Chemistry, "New and Nonofficial Remedies," Philadelphia: J. B. Lippincott Co., 1956. [31] Kiser, J. S., and De Mello, G. C., *Proc. 58th Meet.*, Nov. 1954, U.S. Livestock Sanitary Ass., p 81, 1955. [32] Welch, H., Reedy, R. J., and Wolfson, S. W., *J. Laborat. Clin. M.* 35:663, 1950. [33] Youmans, G. P., Youmans, A. S., and Osborne, R. R., *Proc. Soc. Exp. Biol.* 67:426, 1948. [34] Welch, H., et al, "Principles and Practice of Antibiotic Therapy," New York: Medical Encyclopedia, Inc., 1954. [35] Kirsner, J. B., Levin, E., and Palmer, W. L., *Arch. Int. M.* 90:677, 1952. [36] Pratt, R., and Dufrenoy, J., "Antibiotics," 2nd ed., Philadelphia: J. B. Lippincott Co., 1953. [37] Brown, H. W., et al, Monograph, "Use of Antibiotics in Tropical Diseases," *Ann. N. York Acad. Sc.* 55:967-1284, 1952. [38] Wells, H. S., *J. Infect. Dis.* 90:34, 1952. [39] James, D. G., *J. Am. M. Ass.* 151:810, 1954. [40] Mazzini, M. A., and Blasi, A. A., *Am. J. Syph.* 38:341, 1954. [41] Hirschboeck, M. M., *Am. J. Trop. M. Hyg.* 3:712, 1954. [42] Payne, E. H., and Urteaga, O., *Antibiotics and Chemotherapy* 1:92, 1951. [43] Willcox, R. R., *Brit. J. Vener. Dis.* 29:225, 1953. [44] Payne, E. H., Capriolo, C. E., and Salmon, J. G., *Gac. méd.*, Guayaquil 6:195, 1951. [45] Parker, R. T., et al, "Antibiotics Annual, 1954-55," p 26, New York: Medical Encyclopedia, Inc. [46] Kirby, W. M., *Annual Rev. Microb.* 6:387, 1952. [47] Woodward, T. E., Smadel, J. E., Parker, R. T., and Wissemann, C. L., Jr., *Ann. N. York Acad. Sc.* 55:1228, 1952. [48] Eastman, J. W., et al, *J. Am. Vet. M. Ass.* 120:28, 1952. [49] McCrumb, F. R., et al, *Am. J. M.* 14:284, 1953. [50] Grumbles, L. C., and Boney, W. A., Jr., *J. Am. Vet. M. Ass.* 119:384, 1951. [51] Ley, H. L., Jr., Smadel, J. E., and Crocker, T. T., *Proc. Soc. Exp. Biol.* 68:9, 1948. [52] Kutscher, A. H., Lane, S. L., and Segall, R., *J. Allergy* 25:135, 1954. [53] Meyler, L., "Side Effects of Drugs," New York: Elsevier Pub. Co., 1952. [54] Smiley, R. K., Cartwright, G. E., and Wintrobe, M. M., *J. Am. M. Ass.* 149:914, 1952. [55] Welch, H., Lewis, C. N., and Kerlan, I., *Antibiotics and Chemotherapy* 4:607, 1954. [56] Payne, E. H., Bellerive, A., and Jean, L., *ibid* 1:88, 1951. [57] Lépine, P., Barski, G., and Maurin, J., *Proc. Soc. Exp. Biol.* 73:252, 1950. [58] Pomerat, C. M., and Leake, C. D., *Ann. N. York Acad. Sc.* 58:1110, 1954. [59] Woodward, T. E., Smadel, J. E., and Ley, H. L., Jr., *J. Clin. Invest.* 29:87, 1950. [60] Glazko, A. J., Wolf, L. M., Dill, W. A., and Bratton,

78. CHLORAMPHENICOL (Concluded)

- A. C., Jr., *J. Pharm. Exp. Ther.* **96**:445, 1949. [61] Ross, S., Bischoff, H., Preisser, W., and Orr, W., *J. Clin. Invest.* **28**:1050, 1949. [62] Gocke, T. M., and Finland, M., *J. Laborat. Clin. M.* **38**:719, 1951. [63] Braude, R., Kon, S. K., and Porter, J. W., *Nutrit. Abstr.*, Aberdeen **23**:473, 1953. [64] Whitehill, A. R., Oleson, J. J., and Hutchings, B. L., *Proc. Soc. Exp. Biol.* **74**:11, 1950. [65] Smith, G. N., Worrel, C. S., and Swanson, A. L., *J. Bact.*, Balt. **58**:803, 1949. [66] Bergmann, E. D., and Sicher, S., *Nature* **170**:931, 1952. [67] Wisseman, C. L., Jr., Smadel, J. E., Hahn, F. E., and Hopps, H. E., *J. Bact.*, Balt. **67**:662, 1954. [68] Swendseid, M. E., Swanson, A. L., and Bethell, F. H., *J. Biol. Chem.* **201**:811, 1953. [69] MacKneson, R. G., and Ormsby, H. L., *Am. J. Ophth.* **39**:689, 1955. [70] Davis, D. J., Pittman, M., Vogel, J. E., and Ottinger, B., *Antibiotics and Chemotherapy* **5**:363, 1955. [71] Loosli, C. G., Hamre, D., Ritter, G., and Berlin, B. S., "Antibiotics Annual, 1954-55," p 474, New York: Medical Encyclopedia, Inc. [72] Mikuni, M., and Tsuchiya, A., *Acta Med. et Biol.* **2**:755, 1954; (abstr.) *J. Am. M. Ass.* **159**:229, 1955. [73] Medical Research Council, *Brit. M. J.* **1**:856, 1954. [74] Glantz, P. J., and Gordeuk, S., Jr., *Poultry Sc.* **34**:880, 1955. [75] Stewart, D. F., *Austral. Vet. J.* **30**:209, 1954. [76] Manjrekar, S. L., *Ind. Vet. J.* **31**:417, 1955. [77] Brown, C. H., *Nature* **166**:527, 1950. [78] Skipper, H. E., and Thomson, J. R., *Cancer Res.*, Sup. **2**:147, 1955. [79] Sugiura, K., *Ann. N. York Acad. Sc.* **63**:962, 1956. [80] Bernfeld, P., and Inglis, N. R., *Proc. Am. Ass. Cancer Res.* **2**:94, 1956. [81] Follette, J. H., Shugarman, P. M., Reynolds, J., Valentine, W. N., and Lawrence, J. S., *Blood*, N. Y. **11**:234, 1956. [82] Deacon, W. E., Olansky, S., Albritton, D. C., and Kaplans, W., *Antibiotic M.* **2**:143, 1956. [83] *Am. M. Ass. Council on Pharmacy and Chemistry*, *J. Am. M. Ass.* **159**:1634, 1955. [84] Gold, H., *Arch. Int. M.* **96**:387, 1955. [85] Gale, E. F., and Folkes, J. P., *Biochem. J.*, Lond. **53**:493, 1953. [86] Wooley, D. W., *J. Biol. Chem.* **185**:293, 1950. [87] Smith, G. N., and Worrel, C. S., *J. Bact.*, Balt. **65**:313, 1953. [88] Steinhaus, E. A., and Bell, C. R., *J. Econom. Entom.* **46**:582, 1953. [89] Klemmer, H. W., Riker, A. J., and Allen, O. N., *Phytopathology* **45**:618, 1955. [90] Hagborg, W. A., *Canad. J. Microbiol.* **2**:80, 1956. [91] Goodwin, T. W., Griffiths, L. A., and Modi, V. V., *Biochem. J.*, Lond. **62**:259, 1956. [92] Barnes, R. W., *North Am. Vet.* **36**:1017, 1955. [93] Howarth, J. A., Cordy, D. R., and Bittle, J., *J. Am. Vet. M. Ass.* **124**:43, 1954. [94] Penny, R. H., *Vet. Rec.*, Lond. **66**:730, 1954. [95] Kushner, D. K., *Arch. Biochem. and Biophys.* **52**:332, 1955. [96] Boling, E., and Finch, H., *Am. Surgeon* **18**:903, 1952. [97] Anderson, K. F., and Ellis, F. G., *Brit. M. J.* **2**:1067, 1951. [98] Fowler, W., and Knight, G. H., *Brit. J. Vener. Dis.* **32**:2, 1956. [99] Controulis, J., Rebstock, M. C., and Crooks, H. M., Jr., *J. Am. Chem. Soc.* **71**:2463, 1949. [100] Long, L. M., and Troutman, H. D., *ibid* **71**:2469, 1949.

79. CHLORORAPHIN

- [1] McIlwain, H., *Nature* **148**:628, 1941. [2] Richter, V., "The Chemistry of the Carbon Compounds," (translated by Taylor, T. W., Jr., and Millidge, A. F.), vol. 2, p 474, New York: Nordemann, 1939. [3] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press. 1949.

80. CHLOROTETRACYCLINE

- [1] Broschard, R. W., et al, *Science* **109**:199, 1949. [2] Duggar, B. M., U. S. Pat. 2,482,055, 1949. [3] Dornbush, A. C., and Pelcak, E. J., *Ann. N. York Acad. Sc.* **51**:218, 1948. [4] Stephens, C. R., et al, *J. Am. Chem. Soc.* **74**:4976, 1952. [5] Perlman, D., *Science* **118**:628, 1953. [6] Oxford, A. E., *Nature* **172**:395, 1953. [7] Hiscox, D. J., *J. Am. Pharm. Ass., Sci. Ed.* **40**:237, 1951. [8] Levine, J., Garlock, E. A., Jr., and Fischbach, H., *ibid* **38**:473, 1949. [9] Duggar, B. M., *Ann. N. York Acad. Sc.* **51**:177, 1948. [10] Duggar, B. M., et al, Monograph, "Aureomycin, a New Antibiotic," *Ann. N. York Acad. Sc.* **51**:175-342, 1948. [11] Pelcak, E. J., Metzger, W. I., and Dornbush, A. C., *Harlem (N. Y.) Hosp. Bull.* **2**:47, 1949. [12] Frank, P. F., Wilcox, C., and Finland, M., *J. Laborat. Clin. M.* **35**:188, 1950. [13] Frank, P. F., Wilcox, C., and Finland, M., *ibid* **35**:205, 1950. [14] Wells, E. B., Shih-Man, C., Jackson, G. G., and Finland, M., *J. Pediat.*, St. Louis **36**:752, 1950. [15] Finland, M., Frank, P. F., and Wilcox, C., *Am. J. Clin. Path.* **20**:209, 1950. [16] Finland, M., Frank, P. F., and Wilcox, C., *ibid* **20**:325, 1950. [17] Finland, M., and Wilcox, C., *ibid* **20**:335, 1950. [18] Hewitt, R., Wallace, W. S., and White, E., *Science* **112**:144, 1950. [19] Balamuth, W., *Ann. N. York Acad. Sc.* **55**:1093, 1952. [20] Welch, H., Randall, W. A., Reedy, R. J., and Kramer, J., *Antibiotics and Chemotherapy* **2**:693, 1952. [21] Bliss, E. A., and Chandler, C. A., *Proc. Soc. Exp. Biol.* **69**:467, 1948. [22] Steenzen, W., and Wolinsky, E., *Am. Rev. Tuberc.* **59**:221, 1949. [23] Finland, M., "Antibiotics Annual, 1954-55," p 35, New York: Medical Encyclopedia, Inc. [24] De Mello, G. C., and Kiser, J. S., unpublished. [25] Yow, E. M., and Spink, W. W., *J. Clin. Invest.* **28**:871, 1949. [26] Bliss, E. A., Warth, P. T., and Chandler, C. A., *Ann. N. York Acad. Sc.* **53**:277, 1950. [27] Chinn, B. D., *Proc. Soc. Exp. Biol.* **80**:35, 1952. [28] Wright, S. S., Potee, K. G., and Finland, M., *Am. J. Clin. Path.* **24**:1121, 1954. [29] Price, C. W., Randall, W. A., and Welch, H., *Ann. N. York Acad. Sc.* **51**:211, 1948. [30] Little, P. A., *ibid* **51**:246, 1948. [31] Bryer, M. S., Schoenbach, E. B., Bliss, E. A., and Chandler, C. A., *ibid* **51**:254, 1948. [32] Kanegis, L. A., et al, *Vet. M.*, Chic. **45**:313, 1950. [33] Kiser, J. S., De Mello, G. C., Reichard, D. H., and Williams, J. H., *J. Infect. Dis.* **90**:76, 1952. [34] Zink, A., De Mello, G. C., and Burkhardt, R. L., *Am. J. Vet. Res.* **12**:194, 1951. [35] Chandler, C. A., and Hodes, H. L., *Pediatrics*, Springf. **5**:267, 1950. [36] Kiser, J. S., et al, "Antibiotics Annual, 1953-54," p56, New York: Medical Encyclopedia, Inc. [37] Perry, T. L., *Proc. Soc. Exp. Biol.* **72**:45, 1951. [38] Prier, J. E., *Vet. M.*, Chic. **45**:243, 1950. [39] Woodward, T. E., et al, *J. Am. M. Ass.* **139**:830, 1949. [40] Heilman, F. R., *Proc. Staff Meet. Mayo Clin.* **23**:569, 1948. [41] Meyer, K. F., Quan, S. F., McCrumb, F. R., and Larson, A., *Ann. N. York Acad. Sc.* **55**:1228, 1952. [42] Steen, E., *Acta path. microb. scand.* **27**:844, 1950. [43] Stanton, M. F., Laskowski, L., and Pinkerton, H., *Proc. Soc. Exp. Biol.* **74**:705, 1950. [44] Eyles, D. E., *Am. J. Trop. M. Hyg.* **2**:429, 1953. [45] Felsenfeld, O., and Soman, D. W., *Ann. N. York Acad. Sc.* **55**:1059, 1952. [46] Carminati, G. M.,

80. CHLORTETRACYCLINE (Continued)

- and Ercoli, N., *Boll. Ist. sieroter. milan.* 30 :97, 1951. [47] Turner, T. B., and Schaeffer, K., *Am. J. Syph.* 38:81, 1954. [48] Knight, V., *Ann. N. York Acad. Sc.* 53:332, 1950. [49] Holm, L. W., and Moore, W. G., *Am. J. Vet. Res.* 11:211, 1950. [50] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952. [51] Wong, S. C., and Cox, H. R., *ibid* 51:290, 1948. [52] Seligmann, E., *Proc. Soc. Exp. Biol.* 74:481, 1952. [53] Kneeland, Y., Jr. and Mills, K., *J. Immun., Balt.* 65:653, 1950. [54] Andrewes, C. H., and Niven, J. F., *Brit. J. Exp. Path.* 31:767, 1950. [55] Eaton, M. D., *Proc. Soc. Exp. Biol.* 73:24, 1950. [56] Baldridge, G. D., and Blank, H., *ibid* 72:560, 1949. [57] Przesmycki, F., Wojciechowski, E., and Mikolasczyk, E., *Canad. J. Comp. M.* 14:325, 1950. [58] Levaditi, C., and Vaisman, A., *C. rend. Acad. Sc.* 230:1221, 1950. [59] Anigstein, L., Whitney, D. M., and Beninson, J., *Ann. N. York Acad. Sc.* 51:306, 1948. [60] Wells, H. S., *J. Infect. Dis.* 90:110, 1952. [61] Harned, B. K., et al, *Ann. N. York Acad. Sc.* 51:182, 1948. [62] Hill, K. R., *Bull. World Health Org.*, N. Y. 7:108, 1953. [63] Welch, H., et al, "Principles and Practice of Antibiotic Therapy," New York: Medical Encyclopedia, Inc., 1954. [64] De Mello, G. C., and Kiser, J. S., "Antibiotics Annual, 1954-55," p 678, New York: Medical Encyclopedia, Inc. [65] Von Oettingen, W. F., *ibid*, p 361. [66] Kutscher, A. H., Lane, S. L., and Segall, R., *J. Allergy* 25:135, 1954. [67] Lépine, P., Barski, G., and Maurin, J., *Proc. Soc. Exp. Biol.* 73:252, 1950. [68] Pomerat, C. M., and Leake, C. D., *Ann. N. York Acad. Sc.* 58:1110, 1954. [69] Munoz, J., and Geister, R., *Proc. Soc. Exp. Biol.* 75:367, 1950. [70] Seneca, H., and Ides, D., *J. Urol., Balt.* 70:947, 1953. [71] Klein, M., Schorr, S. E., Tashman, S., and Hunt, A. D., Jr., *J. Bact., Balt.* 60:159, 1950. [72] Eisner, H. J., Stirn, F. E., Dornbush, A. C., and Oleson, J. J., *J. Pharm. Exp. Ther.* 108:442, 1953. [73] Hall, B., *Ann. Int. M.* 40:743, 1954. [74] Herrell, W. E., and Heilman, F. R., *Proc. Staff Meet. Mayo Clin.* 24:157, 1949. [75] Finland, M., Collins, H. S., and Paine, T. F., Jr., *J. Am. M. Ass.* 138:946, 1948. [76] Wellman, W. E., Dodge, H. W., Jr., Heilman, F. R., and Petersen, M. C., *J. Laborat. Clin. M.* 43:275, 1954. [77] Meyler, L., "Side Effects of Drugs," New York: Elsevier Pub. Co., 1952. [78] *Am. M. Ass. Council on Pharmacy and Chemistry*, "New and Nonofficial Remedies," Philadelphia: J. B. Lippincott Co., 1956. [79] Long, P. H., *Pennsylvania M. J.* 53:209, 1950. [80] Brown, H. W., et al, Monograph, "Use of Antibiotics in Tropical Diseases," *Ann. N. York Acad. Sc.* 55:967-1284, 1952. [81] Kirby, W. M., *Annual Rev. Microb.* 6:387, 1952. [82] James, D. G., *J. Am. M. Ass.* 151:810, 1953. [83] Perlman, L., and Milzer, A., *Arch. Int. M.* 94:82, 1954. [84] Expert Committee on Trachoma, World Health Org., *Rev. internat. trachome* 29:285, 1952. [85] Jensen, T., *Am. J. Syph.* 38:125, 1954. [86] McVay, L. V., Jr., and Sprunt, D. H., *Ann. Int. M.* 38:955, 1953. [87] Rodriguez, J., et al, *Arch. Derm. Syph., Chic.* 66:59, 1952. [88] Ampofo, O., and Finlay, G. M., *Nature* 165:398, 1950. [89] Burrows, W. B., and Jannes, W. G., *Am. J. Trop. M. Hyg.* 1:626, 1952. [90] Lang, W. R., Rakoff, A. E., and Sholes, D. M., Jr., *Obst. Gyn.* 2:527, 1953. [91] Hall, H. E., et al, *Ann. Int. M.* 35:988, 1951. [92] Scheidy, S. F., *J. Am. Vet. M. Ass.* 118:213, 1951. [93] McCulloch, E. C., Kiser, J. S., and Migaki, H., *Vet. M., Chic.* 44:253, 1949. [94] Harms, H. F., Harms, H. F., Jr., and Harms, G. R., *J. Am. Vet. M. Ass.* 117:462, 1950. [95] Easterbrooks, H. L., *ibid* 116:48, 1950. [96] Burkhardt, R. L., and Black, J., *Vet. M., Chic.* 45:338, 1950. [97] Sheetz, H. O., *ibid* 46:38, 1951. [98] Easterbrooks, H. L., and Plastringer, W. N., *J. Am. Vet. M. Ass.* 117:388, 1950. [99] Coles, J. D., *Ann. N. York Acad. Sc.* 55:1139, 1952. [100] Paine, T. F., Jr., Collins, H. S., and Finland, M., *J. Bact., Balt.* 56:488, 1948. [101] Gocke, T. M., and Finland, M., *J. Laborat. Clin. M.* 38:719, 1951. [102] Welch, H., Randall, W. A., Reedy, R. J., and Oswald, E. J., *Antibiotics and Chemotherapy* 4:741, 1954. [103] Loomis, W. F., *Science* 111:474, 1950. [104] Van Meter, J. C., and Oleson, J. J., *ibid* 113:273, 1951. [105] Saz, A. K., and Slie, R. B., *J. Am. Chem. Soc.* 75:4626, 1953. [106] Karp, A., and Snyder, J. C., *Proc. Soc. Exp. Biol.* 79:216, 1952. [107] Ruziczka, A., and Orth, E., *Umschau Wiss. u. Tech.* 51:432, 1951. [108] Braude, R., Kon, S. K., and Porter, J. W., *Nutrit. Abstr., Aberdeen* 23:473, 1953. [109] Stokstad, E. L., *Physiol. Rev.* 34:25, 1954. [110] Knodt, C. B., *Antibiotics and Chemotherapy* 3:442, 1953. [111] Jukes, T. H., and Williams, W. L., *Pharm. Rev., Balt.* 5:381, 1953. [112] Reid, J. T., Warner, R. G., and Loosli, J. K., *J. Agr. Food Chem.* 2:186, 1954. [113] Foster, J. W., and Pittillo, R. F., *J. Bact., Balt.* 66:478, 1953. [114] De Ropp, R. S., *Phytopathology* 39:822, 1949. [115] Blanchard, F. A., *ibid* 41:954, 1951. [116] Weiser, H. H., Goldberg, H. S., Cahill, V. R., Kunkle, L. E., and Deatherage, F. E., *Food Technol.* 7:495, 1953. [117] Tarr, H. L., Southcott, B. A., Bissett, H. M., *ibid* 6:363, 1952. [118] Ziegler, F., and Stadelman, W. J., *ibid* 9:107, 1955. [119] Kohler, R. A., Broquitt, H. P., and Miller, W. H., *ibid* 8:19, 1954. [120] Havinga, E., Lynch, V., Norris, L., and Calvin, M., *Rec. Trav. chim.* 72:597, 1953. [121] Hesseltine, C. W., and Bohonos, N., *Abstr. of Appl.* 229, 226, *Offic. Gaz. U. S. Pat. Office*, p 1368, Sept. 29, 1953. [122] Day, W. H., Serjak, W. C., Stratton, J. R., and Stone, L. R., *J. Agr. Food Chem.* 2:252, 1954. [123] Murthy, M. R., and Sreenivasaya, M., *Nature* 172:684, 1953. [124] Zaumeyer, W. J., *J. Agr. Food Chem.* 3:112, 1955. [125] Davis, D. J., Pittman, M., Vogel, J. E., and Ottinger, B., *Antibiotics and Chemotherapy* 5:363, 1955. [126] Loosli, C. G., Hamre, D., Ritter, G., and Berlin, B. S., "Antibiotics Annual, 1954-55," p 474, New York: Medical Encyclopedia, Inc. [127] Medical Research Council, *Brit. M. J.* 1:856, 1954. [128] Ferguson, E. H., *J. Invest. Derm.* 24:567, 1955. [129] Malaguzzi-Valeri, C., and Orabona, M. L., *Internat. Zschr. Vitaminforsch.*, Bern 25:402, 1955. [130] Wada, H., and Fujino, T., *M. J. Osaka Univ.* 6:97, 1955; *Biol. Abstr.*, Balt. 30:8127, 1956. [131] Heisch, R. B., and Harvey, A. E. (cited by Cherry, J. K.), *Tr. R. Soc. Trop. M. Hyg., Lond.* 49:563, 1955. [132] Tarnowski, G. S., *Cancer Res., Sup.* 2:333, 1955. [133] Sugiura, K., *Ann. N. York Acad. Sc.* 63:962, 1956. [134] Gross, W. B., and Johnson, E. P., *Poultry Sc.* 32:260, 1953. [135] Gold, H., *Arch. Int. M.* 96:387, 1955. [136] Cherry, J. K., *Tr. R. Soc. Trop. M. Hyg., Lond.* 49:563, 1955. [137] Deacon, W. E., Olansky, S., Albritton, D. C., and Kaplans, W., *Antibiotic M.* 2:143, 1956. [138] *Am. M. Ass. Council on Pharmacy and Chemistry*, *J. Am. M. Ass.* 159:1634, 1955. [139] Dutta, N. K., and Habbu, M. K., *Brit. J. Pharm.* 10:153, 1955. [140] Miller, J. G., Levy, H. E., Torbert, B. J., and Oglesby, W. T., *Proc. 89th Annual Meet.*, 1952, *Am. Vet. M. Ass.*, p 160, 1953. [141] White-Stevens, R., and Zeibel, H. G., *Poultry Sc.* 33:1164, 1954. [142] Fahey, J. E., and Crawley, J. F., *Canad. J. Comp. M.* 19:281, 1955. [143] Burkhardt, R. L., and Allen, G., *Vet. M., Chic.* 49:451, 1954. [144] Gouge, H. E., Bolton, R., and Alson, M. C., "Antibiotics Annual, 1955-56," p 768, New York: Medical Encyclopedia, Inc.

REFERENCES (Continued)

80. CHLORTETRACYCLINE (Concluded)

- [145] McKay, W. M., and Pelly, A. V., *Brit. Vet. J.* **112**:76, 1956. [146] Hu, F., Livingood, C. S., and Hildebrand, J. F., *J. Invest. Derm.* **26**:23, 1956. [147] Lowbury, E. J., and Hurst, L., *J. Clin. Path., Lond.* **9**:59, 1956. [148] Van Meter, J. C., Spector, A., Oleson, J. J., and Williams, J. H., *Proc. Soc. Exp. Biol.* **81**:215, 1952. [149] Eagle, H., *J. Exp. M.* **100**:117, 1954. [150] Rege, D. V., and Sreenivasan, A., *Nature* **173**:728, 1954. [151] Sloane, N. H., *J. Am. Chem. Soc.* **75**:6352, 1953. [152] Younathan, E. S., and Barkulis, S. S., *Soc. Am. Bact. Bact. Proc.*, p 119, 1956. [153] Francois, A. C., and Michel, M., *C. rend. Acad. sc.* **240**:124, 1955. [154] Cohen, A. M., and Rachmilewitz, M., *Proc. Soc. Exp. Biol.* **83**:50, 1953. [155] Murray, T. K., and Campbell, J. A., *Canad. J. Biochem. Physiol.* **33**:797, 1955. [156] Huang, T. C., Ulrich, H. E., and McCay, C. M., *J. Nutrit.* **54**:621, 1954. [157] Klemmer, H. W., Riker, A. J., and Allen, O. N., *Phytopathology* **45**:618, 1955. [158] Sanfilippo, G., *Boll. Soc. ital. biol. Sper.* **29**:1339, 1953. [159] Berke, P., Silver, A. M., and Kupperman, H. S., *Proc. Soc. Exp. Biol.* **84**:32, 1953. [160] Hagemann, G., Teillon, J., and Velu, H., *Ann. pharm. fr.* **12**:210, 1953. [161] Steinhaus, E. A., and Bell, C. R., *J. Econom. Entom.* **46**:582, 1953. [162] Trams, E. G., Kashiwa, H. K., Cornman, I., and Klopp, C. T., *Antibiotic M.* **1**:677, 1955. [163] Sieburth, J. McN., and Pomeroy, B. S., *J. Am. Vet. M. Ass.* **128**:509, 1956. [164] Fowler, W., and Knight, G. H., *Brit. J. Vener. Dis.* **32**:2, 1956. [165] Schwachman, H., and Schuster, A., "Pediatric Clinics of North America," p 295, Philadelphia: W. B. Saunders Co., 1956. [166] Oleson, J. J., Hutchings, B. L., and Whitehill, A. R., *Arch. Biochem.*, N. Y. **29**:334, 1950. [167] Stokstad, E. L., and Jukes, T. H., *Proc. Soc. Exp. Biol.* **76**:73, 1951. [168] Cravioto-Munoz, J., Poucher, H. G., and Waisman, H. A., *ibid* **77**:18, 1951. [169] Biely, J., and March, B., *Science* **114**:330, 1951. [170] Bell, M. C., Whitehair, C. K., and Gallup, W. D., *Proc. Soc. Biol.* **76**:284, 1951. [171] Jukes, T. H., "Antibiotics in Nutrition," Antibiotics Monographs No. 4, New York: Medical Encyclopedia, Inc., 1955. [172] György, P., *Am. J. Digest. Dis.* **19**:392, 1952. [173] György, P., *Ann. N. York Acad. Sc.* **57**:925, 1954. [174] Watson, G. M., and Witts, L. J., *J. Path. Bact., Lond.* **64**:232, 1952. [175] Phear, E. A., Ruebner, B., Sherblock, S., and Summerskill, W. H., *Clinical Sc., Lond.* **15**:93, 1956. [176] Waller, C. W., et al, *J. Am. Chem. Soc.* **74**:4981, 1952.

81. CHROMIN

- [1] Wakaki, S., Akanabe, S., Hamada, K., and Asahina, T., *J. Antibiot., Tokyo* **5**:677, 1952. [2] Wakaki, S., Hamada, K., Akanabe, S., and Asahina, T., *ibid*, Ser. B **6**:247, 1953.

82. CHRYSOMYCIN

- [1] Strelitz, F., Flon, H., and Asheshov, I. N., *J. Bact., Balt.* **69**:280, 1955.

83. CINNAMYCIN

- [1] Benedict, R. G., *Botan. Rev.* **19**:229, 1953. [2] Dvonch, W., Shotwell, O. L., Benedict, R. G., Pridham, T. G., and Lindenfelser, L. A., *Antibiotics and Chemotherapy* **4**:1135, 1954. [3] Benedict, R. G., Dvonch, W., Shotwell, O. L., Pridham, T. G., and Lindenfelser, L. A., *ibid* **2**:591, 1952. [4] Ambrose, A. M., *ibid* **4**:1242, 1954. [5] Szybalski, W., *Appl. Microbiol.* **2**:57, 1954.

84. CIRCULIN

- [1] Murray, F. J., Tetrault, P. A., Kaufmann, O. W., and Koffler, H., *J. Bact., Balt.* **57**:305, 1949. [2] Peterson, D. H., and Reineke, L. M., *J. Biol. Chem.* **181**:95, 1949. [3] Tetrault, P. A., U. S. Pat. 2,676,133, 1954. [4] Finegold, S. M., *Texas Repts. Biol. M.* **9**:432, 1951. [5] Tetrault, P. A., Koffler, H., Kaufmann, O. W., and Quinn, L. Y., *J. Clin. Invest.* **28**:1053, 1949. [6] Brook, M. J., and Richmond, M. T., *ibid* **28**:1032, 1949. [7] Bliss, E. A., and Todd, P., *J. Bact., Balt.* **58**:61, 1949. [8] Chandler, C. A., and Hodes, H. L., *Pediatrics*, Springf. **5**:267, 1950. [9] Pomerat, C. M., and Leake, C. D., *Ann. N. York Acad. Sc.* **58**:1110, 1954. [10] Wilkins, J. R., and Henshaw, C. T., *Exp. Parasitol.* **3**:417, 1954. [11] Wilson, G. B., and Bowen, C. C., *J. Hered.* **42**:251, 1951. [12] Colasito, D. J., Koffler, H., Tetrault, P. A., and Reitz, H. C., *Canad. J. Microbiol.* **1**:685, 1955. [13] Colasito, D. J., Koffler, H., Reitz, H. C., and Tetrault, P. A., *Soc. Am. Bact. Bact. Proc.* p 72, 1956. [14] Colasito, D. J., Koffler, H., Tetrault, P. A., and Reitz, H. C., *Proc. Soc. Exp. Biol.* **77**:107, 1951.

85. CITRININ

- [1] Hetherington, A. C., and Raistrick, H., *Trans. Roy. Soc., London B* **220**:269, 1931. [2] Hirschy, H. W., and Rouff, P. M., *J. Am. Chem. Soc.* **64**:1490, 1942. [3] Tauber, H., Laufer, S., and Goll, M., *ibid* **64**:2228, 1942. [4] Heatley, N. G., and Philpot, F. J., *J. Gen. Microb., Lond.* **1**:232, 1947. [5] Ambrose, A. M., and De Eds, F., *J. Pharm. Exp. Ther.* **88**:173, 1946. [6] Brown, J. P., Cartwright, N. J., Robertson, A., and Whalley, W. B., *Nature* **162**:72, 1948. [7] Cartwright, N. J., Robertson, A., and Whalley, W. B., *ibid* **163**:94, 1949. [8] Raistrick, H., and Smith, G., *Biochem. J., Lond.* **29**:606, 1935. [9] Baron, A. L., "Handbook of Antibiotics," New York: Reinhold Pub. Corp., 1950. [10] Oxford, A. E., *Chemistry and Industry* **20**:48, 1942. [11] Ambrose, A. M., and De Eds, F., *Fed. Proc.* **5**:162, 1946. [12] Chu, W. C., *J. Laborat. Clin. M.* **31**:72, 1946. [13] Kavanagh, F., *J. Bact., Balt.* **54**:761, 1947.

REFERENCES (Continued)

86. CITROMYCETIN

- [1] Hetherington, A. C., and Raistrick, H., *Trans. Roy. Soc., London B* 220:269, 1931. [2] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949. [3] Grove, J. F., and Brian, P. W., *Nature* 167:995, 1951. [4] Robertson, A., and Whalley, W. B., *J. Chem. Soc.* 1949:848.

87. CLITOCYBINS

- [1] Hollande, A. C., *C. rend. Acad. sc.* 221:361, 1945. [2] Hollande, A. C., *ibid* 228:1758, 1949. [3] Rivière, C., Salomon, L., Thély, M., and Gautron, G., *Ann. Inst. Pasteur, Par.* 74:118, 1948. [4] Rivière, C., Thély, M., and Gautron, G., *C. rend. Acad. sc.* 224:1856, 1947. [5] Rivière, C., Thély, M., and Gautron, G., *Bull. Soc. chim. biol., Par.* 29:857, 1947.

88. COELICOLORIN

- [1] Hatsuta, Y., *J. Antibiot., Tokyo* 2:276, 1949.

89. COLICINES

- [1] Heatley, N. G., and Florey, H. W., *Brit. J. Exp. Path.* 27:378, 1946. [2] Depoux, R., and Chabbert, Y., *Ann. Inst. Pasteur, Par.* 84:798, 1953. [3] Gratia, A., Joiris, E., and Weerts, E., *Repts. Proc. 4th Internat. Congr. Microbiol.* p 141, 1947. [4] Goebel, W. F., Barry, G. T., Jesaitis, M. A., and Miller, E. M., *Nature* 176:700, 1955. [5] Fredericq, P., *Ann. Inst. Pasteur, Par.* 84:294, 1953.

90. COLIFORMIN

- [1] Freyschuss, S. K., Pehrson, S. O., and Steenberg, B., *Antibiotics and Chemotherapy* 5:218, 1955. [2] Johansson, N. O., *Växtskyddsnotiser, Stockholm* 16:17, 1952. [3] Pehrson, S. O., *Svensk Botan. Tidskr.* 41:354, 1947.

91. COLISTATIN

- [1] Gause, G. F., *Science* 104:289, 1946.

92. COLLINOMYCIN

- [1] Brockmann, H., and Renneberg, K., *Naturwissenschaften* 40:166, 1953.

93. COMIRIN

- [1] *Brit. Pat.* 714,427, 1954. [2] Forsyth, W. G., *Biochem. J., Lond.* 59:500, 1955.

94. CONGOCIDIN

- [1] Cosar, C., Ninet, L., Pinnert-Sindico, S., and Preud'homme, J., *C. rend. Acad. sc.* 234:1498, 1952. [2] Despois, R., and Ninet, L., *Proc. 6th. Internat. Congr. Microbiol.,* p 241, 1953.

95. CORDYCEPIN

- [1] Cunningham, K. G., Hutchinson, S. A., Manson, W., and Spring, F. S., *J. Chem. Soc.* 1951:2299. [2] Bentley, H. R., Cunningham, K. G., and Spring, F. S., *ibid* 1951:2301. [3] Tarnowski, G. S., *Cancer Res., Sup.* 2:333, 1955.

96. CYCLOHEXIMIDE

- [1] Whiffen, A. J., Bohonos, N., and Emerson, R. L., *J. Bact., Balt.* 52:610, 1946. [2] Ford, J. H., and Leach, B. E., *J. Am. Chem. Soc.* 70:1223, 1948. [3] Kornfeld, E. C., and Jones, R. G., *Science* 108:437, 1948. [4] Kornfeld, E. C., Jones, R. G., and Parke, T. V., *J. Am. Chem. Soc.* 71:150, 1949. [5] Leach, B. E., Ford, J. H., and Whiffen, A. J., *ibid* 69:474, 1947. [6] Whiffen, A. J., *J. Bact., Balt.* 56:283, 1948. [7] Goth, A., and Robinson, F. J., *J. Clin. Invest.* 28:1044, 1949. [8] Whiffen, A. J., *Mycologia, Lanc.* 42:253, 1950. [9] Loefer, J. B., and Matney, T. S., *Physiol. Zool.* 25:272, 1952. [10] Anderson, H. H., and Anderson, J. V., *Am. J. Trop. M.* 30:193, 1950. [11] Reilly, H. C., Stock, C. C., Buckley, S. M., and Clark, D. A., *Cancer Res.* 13:684, 1953. [12] Wilson, H. M., and Duryea, A. W., *Arch. Neur. Psychiat., Chic.* 66:470, 1951. [13] Jenkins, V. E., and Postlewaite, J. C., *Ann. Int. M.* 35:1068, 1951. [14] Traub, R., De Witt, J. B., Welch, J. F., and Newman, D., *J. Am. Pharm. Ass. (Sci. Ed.)* 39:552, 1950. [15] Felber, I. M., and Hamner, C. L., *Botan. Gaz.* 110:324, 1948. [16] Vaughn, J. R., et al, *Mich. Agr. Exp. Sta. Bull.* 31:456, 1951. [17] Petersen, D., and Cation, D., *Plant Disease Repr.* 34:5, 1950. [18] Nelson, R., *Phytopathology* 41:27, 1951. [19] McClure, T. T., and Cation, D., *Plant Disease Repr.* 35:393, 1951. [20] Wallen, V. R., and Skolko, A. J., *Canad. J. Botany* 29:316, 1951. [21] Anderson, H. W., and Gottlieb, D., *Econ. Botany* 6:294, 1952. [22] Phillips, G. B., and Hanel, E., Jr., *J. Bact., Balt.* 60:104, 1950. [23] Georg, E. K., Ajello, L., and Gordon, M. A., *Science* 114:387, 1951. [24] Nitta, K., Takeuchi, T., Yamamoto, T., and Umezawa, H., *J. Antibiot., Tokyo, Ser. A* 8:120, 1955. [25] Silverman, W. B., and Hart, H., *Phytopathology* 44:506, 1954. [26] Wilson, G. B., *J. Hered.* 41:227, 1950. [27] Mefferd, R. B., Jr., and Loefer, J. B., *Physiol. Zool.*

REFERENCES (Continued)

96. CYCLOHEXIMIDE (Concluded)

- 27:115, 1954. [28] Boshes, L. D., et al, Arch. Neur. Psychiat., Chic. 75:175, 1956. [29] Corke, C. T., and Chase, F. E., Canad. J. Microbiol. 2:12, 1956. [30] Ogawa, J. M., and Vergara, C., Phytopathology 45:695, 1955. [31] Strong, F. C., and Klomparens, W., Plant Disease Repr. 39:569, 1955. [32] Whiffen, A. J., Mycologia, Lanc. 43:635, 1951. [33] Brown, R., and Hazen, E. L., "Antibiotics Annual, 1955-56," p 245, New York: Medical Encyclopedia, Inc. [34] Field, J. B., Filler, D. A., Bascosy, L. T., Costa, F., and Borycza, A., Fed. Proc. 15:250, 1956. [35] Wallen, V. R., Plant Disease Repr. 39:124, 1955. [36] Aytoun, R. S., Ann. Botany, London 20:297, 1956. [37] Corbaz, R., et al, Helvet. chim. acta 38:1445, 1955.

97. CYCLOPALDIC ACID

- [1] Birkinshaw, J. H., Raistrick, H., Ross, D. J., and Stickings, C. E., Biochem. J., Lond. 50:610, 1952. [2] Smith, G., *ibid* 50:629, 1952.

98. DECHLOROGRISOFULVIN

- [1] MacMillan, J., Chemistry and Industry 1951:719. [2] MacMillan, J., J. Chem. Soc. 1953:1697.

99. DEXTROMYCIN

- [1] Ogata, K., J. Antibiot., Tokyo 3:440, 1950. [2] Araki, T., et al, Ann. Repts. Takeda Research Lab. 13:1, 1954.

100. DIATRETYNES

- [1] Anchel, M., J. Am. Chem. Soc. 74:1588, 1952. [2] Anchel, M., *ibid* 75:4621, 1953. [3] Anchel, M., Tr. N. York Acad. Sc. 16:337, 1954. [4] Anchel, M., Science 121:607, 1955.

101. DIPLOCOCCIN

- [1] Oxford, A. E., Biochem. J., Lond. 38:178, 1944. [2] Whitehead, H. R., *ibid* 27:1793, 1933.

102. DROSOPHILINS

- [1] Kavanagh, F., Hervey, A., and Robbins, W. J., Proc. Nat. Acad. Sc. U. S. 38:555, 1952. [2] Anchel, M., J. Am. Chem. Soc. 74:2943, 1952. [3] Anchel, M., Arch. Biochem., N. Y. 43:127, 1953. [4] Asheshov, I. N., Strelitz, F., Hall, E. A., and Flon, H., Antibiotics and Chemotherapy 4:380, 1954. [5] Anchel, M., Hervey, A., and Robbins, W. J., Mycologia, Lanc. 47:30, 1955.

103. EHRLICHIN

- [1] Groupé, V., Frankel, J. W., Lechevalier, M. P., and Waksman, S. A., J. Immun., Balt. 67:471, 1951.

104. ELAIOMYCIN

- [1] Ehrlich, J., et al, Antibiotics and Chemotherapy 4:338, 1954. [2] Haskell, T. H., Ryder, A., and Bartz, Q. R., *ibid* 4:141, 1954. [3] Brit. Pat. 730,341, 1955. [4] Anderson, L. E., Ehrlich, J., Huang, Sun, S., and Burkholder, P. R., Antibiotics and Chemotherapy 6:100, 1956. [5] Stevens, C. L., Gillis, B. T., French, J. C., and Haskell, T. H., J. Am. Chem. Soc. 78:3229, 1956.

105. ENDOMYCIN

- [1] Gottlieb, D., Bhattacharyya, P. K., Carter, H. E., and Anderson, H. W., Phytopathology 41:393, 1951. [2] Brit. Pat. 705,622, 1954. [3] Packchianian, A., Am. J. Trop. M. Hyg. 2:243, 1953. [4] Pomerat, C. M., and Leake, C. D., Ann. N. York Acad. Sc. 58:1110, 1954. [5] Wilkins, J. R., and Henshaw, C. T., Exp. Parasitol. 3:417, 1954. [6] Anderson, H. W., and Gottlieb, D., Econ. Botany 6:294, 1952. [7] Perry, H. O., J. Invest. Derm. 24:623, 1955. [8] Gottlieb, D., and Carter, H. E., U. S. Pat. 2,746,902, 1956. [9] Hu, F., Livingood, C. S., Johnson, P., and Pomerat, C. M., Arch. Derm. Syph., Chic. 70:1, 1954. [10] Hu, F., Livingood, C. S., and Hildebrand, J. F., J. Invest. Derm. 26:23, 1956. [11] Wallen, V. R., Plant Disease Repr. 39:124, 1955.

106. ENNIATIN A

- [1] Gaeumann, E., Roth, S., Ettlinger, L., Plattner, P. A., and Nager, U., Experientia, Basel 3:202, 1947. [2] Plattner, P. A., and Nager, U., *ibid* 3:325, 1947. [3] Plattner, P. A., Nager, U., and Boller, A., Helvet. chim. acta 31:594, 1948. [4] Plattner, P. A., and Nager, U., *ibid* 31:2192, 1948. [5] Gaeumann, E., Roth, S., and Ettlinger, L., Phytopathol. Zschr. 16:289, 1950; Biol. Abstr., Balt. 25:18514, 1951.

107. ENNIATIN B

- [1] Plattner, P. A., Nager, U., and Boller, A., *Helvet. chim. acta* 31:594, 1948. [2] Plattner, P. A., and Nager, U., *ibid* 31:665, 1948. [3] Plattner, P. A., and Nager, U., *Experientia*, Basel 3:325, 1947.

108. ERYTHROMYCIN

- [1] McGuire, J. M., et al, *Antibiotics and Chemotherapy* 2:281, 1952. [2] Clark, R. K., Jr., *ibid* 3:663, 1953. [3] Bunch, R. L., and McGuire, J. M., U. S. Pat. 2,653,899, 1953. [4] Washburn, W. H., *J. Am. Pharm. Ass., Sci. Ed.* 43:48, 1954. [5] Flynn, E. H., Sigal, M. V., Jr., Wiley, P. F., and Gerzon, K., *J. Am. Chem. Soc.* 76:3121, 1954. [6] Perlman, D., *Science* 118:628, 1953. [7] Ford, J. H., Prescott, G. C., Hinman, J. W., and Caron, E. L., *Anal. Chem.* 25:1195, 1953. [8] Higgins, C. E., Pittenger, R. C., and McGuire, J. M., *Antibiotics and Chemotherapy* 3:50, 1953. [9] Haight, T. H., and Finland, M., *N. England J. M.* 247:227, 1952. [10] Kuzel, N. R., Woodside, J. M., Comer, J. P., and Kennedy, E. E., *Antibiotics and Chemotherapy* 4:1234, 1954. [11] Powell, H. M., Boniece, W. S., Pittenger, R. C., Stone, R. L., and Culbertson, C. G., *ibid* 3:165, 1953. [12] Welch, H., Randall, W. A., Reedy, R. J., and Kramer, J., *ibid* 2:693, 1952. [13] Potee, K. G., Wright, S. S., and Finland, M., *J. Laborat. Clin. M.* 44:463, 1954. [14] Wright, S. S., Potee, K. G., and Finland, M., *Am. J. Clin. Path.* 24:1121, 1954. [15] Heilman, F. R., Herrell, W. E., Wellman, W. E., and Geraci, J. E., *Proc. Staff Meet. Mayo Clin.* 27:285, 1952. [16] Kiser, J. S., and De Mello, G. C., *Proc. 58th Annual Meet.*, Nov. 1954, U. S. Livestock Sanitary Ass., p 81, 1955. [17] Turner, T. B., and Schaeffer, K., *Am. J. Syph.* 38:81, 1954. [18] McCowen, M. C., Callender, M. E., Lawlis, J. F., Jr., and Brandt, M. C., *Am. J. Trop. M. Hyg.* 2:212, 1953. [19] Am. M. Ass. Council on Pharmacy and Chemistry, "New and Nonofficial Remedies," Philadelphia: J. B. Lippincott, 1956. [20] Welch, H., et al, "Principles and Practice of Antibiotic Therapy," New York: Medical Encyclopedia, Inc., 1954. [21] Dearing, W. H., and Heilman, F. R., *Proc. Staff Meet. Mayo Clin.* 28:121, 1953. [22] Martin, W. J., Nichols, D. R., and Geraci, J. E., *ibid* 28:609, 1953. [23] Gibson, C. D., Jr., Nuchan, H., and Anderson, D. N., *Ann. Int. M.* 41:112, 1954. [24] Moulton, B., Blatt, N. H., and Lepper, M. H., "Antibiotics Annual, 1954-55," p 229, New York: Medical Encyclopedia, Inc. [25] Healey, C. E., and Simon, A. J., *ibid*, p 242. [26] David, N. A., *ibid*, p 699. [27] Alexander, L. J., and Schoch, A. G., *Am. J. Syph.* 38:107, 1954. [28] Shoemaker, E. H., and Yow, E. M., "Antibiotics Annual, 1953-54," p 460, New York: Medical Encyclopedia, Inc. [29] Banov, L., Jr., and Goldberg, J., *ibid*, p 475. [30] Cordice, J. W., Jr., et al, *ibid*, p 480. [31] Agarwal, L. P., and Saxena, R. P., *Brit. J. Ophth.* 38:690, 1954. [32] Pulaski, E. J., and Weslowski, S. A., *Surg. Gyn. Obst.* 98:55, 1954. [33] Gattman, G. B., and Rosenbaum, I., *J. Pediat.*, S. Louis 44:547, 1954. [34] Robinson, H. M., Jr., and Cohen, M. M., *J. Invest. Derm.* 20:407, 1953. [35] Laing, C. R., and Scott, R. B., *Antibiotics and Chemotherapy* 4:641, 1953. [36] Van de Erve, J., Jr., *J. Invest. Derm.* 23:67, 1954. [37] Nelson, T. L., Anderson, H. H., and Roh, J., "Antibiotics Annual, 1954-55," p 250, New York: Medical Encyclopedia, Inc. [38] Pomerat, C. M., and Leake, C. D., *Ann. N. York Acad. Sc.* 58:1110, 1954. [39] Geraci, J. E., Martin, W. J., Nichols, D. R., and Larson, L. W., *Proc. Staff Meet. Mayo Clin.* 29:536, 1954. [40] Kutscher, A. H., Lane, S. L., and Segall, R., *J. Allergy* 25:135, 1954. [41] Griffith, R. S., Johnstone, D. M., and Smith, J. W., "Antibiotics Annual, 1953-54," p 496, New York: Medical Encyclopedia, Inc. [42] Nelson, A. A., and Radomski, J. L., *Antibiotics and Chemotherapy* 4:1174, 1954. [43] Campbell, K. C., *Vet. M., Chic.* 49:333, 1954. [44] Haight, T. H., and Finland, M., *Proc. Soc. Exp. Biol.* 81:188, 1952. [45] Haight, T. H., and Finland, M., *ibid* 81:183, 1952. [46] Finland, M., Wilcox, C., Wright, S. S., and Purcell, E. M., *ibid* 81:725, 1952. [47] Kutscher, A. H., et al, *Antibiotics and Chemotherapy* 4:1023, 1954. [48] Fusillo, M. H., Noyes, H. E., Pulaski, E. J., and Tom, J. Y., *ibid* 3:581, 1953. [49] Wiley, P. F., et al, *J. Am. Chem. Soc.* 77:3676, 1955. [50] Faine, S., and Kaipainen, W. J., *J. Infect. Dis.* 97:146, 1955. [51] MacKneson, R. G., and Ormsby, H. L., *Am. J. Ophth.* 39:689, 1955. [52] Ormsbee, R., Parker, H., and Pickens, E. G., *J. Infect. Dis.* 96:162, 1955. [53] Loosli, C. G., Hamre, D., Ritter, G., and Berlin, B. S., "Antibiotics Annual, 1954-55," p 474, New York: Medical Encyclopedia, Inc. [54] Villarejos, V. M., *Am. J. Trop. M. Hyg.* 4:699, 1955. [55] Brem, J., and Kaibilling, T. R., *Antibiotic M.* 1:276, 1955. [56] Herrell, W. E., Balows, A., and Dailey, J. S., *ibid* 1:507, 1955. [57] Urteaga, O. B., Larrea, P. R., and Calderon, J. M., *ibid* 1:513, 1955. [58] Anderson, H. H., Nelson, T. L., Carbono, C., and Diaz, J., *Am. J. Trop. M. Hyg.* 4:693, 1955. [59] Nesperke, E. I., *J. Am. Vet. M. Ass.* 123:42, 1953. [60] Haas, K. B., *Vet. M. Chic.* 50:460, 1955. [61] Campbell, K. C., *ibid* 49:333, 1954. [62] Takimura, Y., Lopez-Belio, M., and Sher, B. C., *Antibiotic M.* 1:210, 1955. [63] Adler, H. E., Yamamoto, R., and Cordy, D. R., *Cornell Vet.* 46:206, 1956. [64] Anwar, A. A., and Turner, T. B., *Bull. Johns Hopkins Hosp.* 98:85, 1956. [65] Kolmer, J. A., "Antibiotics Annual, 1955-56," p 592, New York: Medical Encyclopedia, Inc. [66] Haight, T. H., *ibid*, p 648. [67] Romansky, M. J., Nasov, J. P., Davis, D. S., and Ritts, R. E., Jr., *ibid*, p 48. [68] Gold, H., *Arch. Int. M.* 96:387, 1955. [69] Willcox, R. R., *Brit. J. Vener. Dis.* 31:186, 1955. [70] Hara, Y., and Abe, T., *Am. J. Trop. M. Hyg.* 5:218, 1956. [71] Deacon, W. E., Olansky, S., Albritton, D. C., and Kaplans, W., *Antibiotic M.* 2:143, 1956. [72] Haight, T. H., U. S. Armed Forces M. J. 5:1405, 1954. [73] Cronk, C. A., and Naumann, D. E., *N. York State J. M.* 54:373, 1954. [74] Am. M. Ass. Council on Pharmacy and Chemistry, *J. Am. M. Ass.* 159:1635, 1955. [75] Serembe, M., and Visentini, P., *Arch. ital. sc. farm.* 4:334, 1954. [76] Am. M. Ass. Council on Pharmacy and Chemistry, *J. Am. M. Ass.* 159:1634, 1955. [77] Brown, R. G., and Emerson, G. A., *Fed. Proc.* 12:304, 1953. [78] Parro, A., and Soncin, E., *Arch. internat. pharm. dyn.*, Par. 99:481, 1954. [79] Johnston, B., Solomon, S., and Vogel, J. M., *N. York State J. M.* 55:3457, 1955. [80] Finland, M., *N. England J. M.* 353:909, 1955. [81] Martin, W. J., Nichols, D. R., Wellman, W. E., and Geraci, J. E., *Proc. Staff Meet. Mayo Clin.* 29:379, 1954. [82] Thomson, E. F., Rountree, P. M., and Freeman, B. M., "Antibiotics Annual, 1955-56," p 63, New York: Medical Encyclopedia, Inc. [83] Hagemann, G., Teillon, J., and Velu, H., *Ann. pharm. fr.* 12:210, 1954. [84] Anon., *Chem. Eng. News* 34:5138, 1956.

REFERENCES (Continued)

109. ERYTHROMYCIN B

- [1] Pettinga, C. W., Stark, W. M., and Van Abeele, F. R., *J. Am. Chem. Soc.* **76**:569, 1954. [2] Sylvester, J. C., and Josselyn, L. E., "Antibiotics Annual, 1954-55," p 283, New York: Medical Encyclopedia, Inc. [3] Clark, R. K., Jr., and Taterka, M., *Antibiotics and Chemotherapy* **5**:206, 1955. [4] Grundy, W. E., Alford, E. F., Rickher, C. J., Bower, R. R., Rdzok, E. J., and Sylvester, J. C., *ibid* **5**:212, 1955.

110. ESPERIN

- [1] Ogawa, H., and Ito, T., *J. Agr. Chem. Soc. Japan* **24**:191, 1950; *Chem Abstr.* **47**:1335, 1953. [2] Kochi, M., et al, *Jap. Pat.* 2497, 1951; *Chem. Abstr.* **47**:690, 1953. [3] Kochi, M., *Jap. Pat.* 1145, 1951; *Chem. Abstr.* **46**:11596, 1952.

111. ESTIN

- [1] Komatsu, E., *Jap. Pat.* 4799, 1953; *Chem. Abstr.* **48**:11010, 1954.

112. ETAMYCIN

- [1] Heinemann, B., et al, "Antibiotics Annual, 1954-55," p 728, New York: Medical Encyclopedia, Inc. [2] Bartz, Q. R., et al, *ibid*, p 777. [3] Haskell, T. H., Marezki, A., and Bartz, Q. R., *ibid*, p 784. [4] Ehrlich, J., et al, *ibid*, p 790. [5] Dickison, H. L., Cull, K. M., and Tisch, D. E., *ibid*, p 733. [6] Thompson, P. E., McCarthy, D. A., Bayles, A., Reinertson, J. W., and Cook, A. R., *Antibiotics and Chemotherapy* **6**:337, 1956. [7] Anderson, L. E., Ehrlich, J., Huang Sun, S. H., and Burkholder, P. R., *ibid* **6**:100, 1956.

113. EULICIN

- [1] Charney, J., et al, "Antibiotics Annual, 1955-56," p 228, New York: Medical Encyclopedia, Inc. [2] West, M. K., Verwey, W. F., and Miller, A. K., *ibid*, p 231.

114. EUMYCETIN

- [1] Arai, T., and Takamizawa, Y., *J. Antibiot., Tokyo, Ser. A* **7**:165, 1954.

115. EUMYCIN

- [1] Johnson, E. A., and Burdon, K. L., *J. Bact., Balt.* **51**:591, 1946. [2] Burdon, K. L., and Johnson, E. A., paper presented at Conf. on Antibiotic Research, Washington, D. C., Jan. 31, 1947.

116. EUROCIDIN

- [1] Utahara, R., Okami, Y., Nakamura, S., and Umezawa, H., *J. Antibiot., Tokyo, Ser. A* **7**:120, 1954. [2] Nazawa, K., et al, 1953 (quoted by Utahara, R., et al), *ibid* **7**:120, 1954. [3] Yajima, T., *ibid* **8**:189, 1955.

117. EXFOLIATIN

- [1] Umezawa, H., Takahashi, S., Takeuchi, T., Maeda, K., and Okami, Y., *J. Antibiot., Tokyo* **5**:466, 1952. [2] Umezawa, H., et al, *Japan. J. Med. Sci. Biol.* **5**:311, 1952; *Chem. Abstr.* **47**:4949, 1953.

118. FERMICIDIN

- [1] Igarasi, S., and Wada, S., *J. Antibiot., Tokyo, Ser. B* **7**:221, 1954. [2] Yajima, T., *ibid, Ser. A* **8**:189, 1955. [3] Nakamura, R., et al, *Jap. J. Vet. Res.* **3**:113, 1955; *abstr. in Vet. Bull., Lond.* **26**:328, 1956.

119. FILIPIN

- [1] Gottlieb, D., Ammann, A., and Carter, H. E., *Plant Disease Repr.* **39**:219, 1955. [2] Whitfield, G. B., Brock, T. D., Ammann, A., Gottlieb, D., and Carter, H. E., *J. Am. Chem. Soc.* **77**:4799, 1955. [3] Ammann, A., Gottlieb, D., Brock, T. D., Carter, H. E., and Whitfield, G. B., *Phytopathology* **45**:559, 1955. [4] Gottlieb, D., in "Therapy of Fungus Diseases" (edited by Sternberg, T. H., and Newcomer, V. D.), p 142, Boston: Little, Brown and Co., 1955.

120. FLAVACID

- [1] Takahashi, I., *J. Antibiot., Tokyo, Ser. A* **6**:117, 1953. [2] Yajima, T., *ibid* **8**:189, 1955. [3] Kuroya, M., *Jap. Pat.* 8547, 1954; *Chem. Abstr.* **50**:9696, 1956.

REFERENCES (Continued)

121. FLAVEOLIN

- [1] Takahashi, B., *J. Antibiot.*, Tokyo, Ser. A 6:11, 1953.

122. FLUVOMYCIN

- [1] Carvajal, F., *Antibiotics and Chemotherapy* 3:765, 1953.

123. FOMECIN A

- [1] Anchel, M., Hervey, A., and Robbins, W. J., *Proc. Nat. Acad. Sc. U. S.* 38:655, 1952. [2] Asheshov, I. N., Strelitz, F., Hall, E. A., and Flon, H., *Antibiotics and Chemotherapy* 4:380, 1953.

124. FOROMACIDINS

- [1] Corbaz, R., et al, *Helvet. chim. acta* 39:304, 1956.

125. FRADICIN

- [1] Swart, E. A., Romano, A. H., and Waksman, S. A., *Proc. Soc. Biol.* 73:376, 1950. [2] Hickey, R. J., and Hidy, P. H., *Science* 113:361, 1951. [3] Waksman, S. A., Romano, A. H., Lechevalier, H. A., and Raubitschek, F., *Bull. World Health Org.*, N. Y. 6:163, 1952. [4] Hickey, R. J., *Arch. Biochem. and Biophys.* 46:331, 1953. [5] Packchianian A., *Am. J. Trop. M. Hyg.* 2:243, 1953.

126. FRAMYCETIN

- [1] Janot, M. M., Penau, H., Van Stolk, D., Hagemann, G., and Penasse, L., *Bull. Soc. chim. biol.*, Par. 1954:1458. [2] Decaris, L. J., *Ann. pharm. fr.* 11:44, 1953. [3] Lutz, A., *C. rend. Acad. sc.* 236:157, 1953. [4] Lutz, A., and Hofferer, M. J., *Rev. immunol.* 19:69, 1955. [5] Chambon, L., *Ann. Inst. Pasteur, Par.* 88:466, 1955. [6] Lutz, A., Grooten, O., and Witz, M. A., *Strasbourg méd.* 4:431, 1953; abstr. in *Excerpta Med.*, Sect. IV 7:1060, 1954. [7] Shidlovsky, B. A., Marmell, M., and Prigot, A., "Antibiotics Annual, 1955-56," p118, New York: Medical Encyclopedia, Inc. [8] Lutz, A., and Witz, M. A., *C. rend. Soc. biol.* 149:1467, 1955. [9] Biron, A., *Presse méd.* 63:551, 1955. [10] Hagemann, G., Teillon, J., and Velu, H., *Ann. pharm. fr.* 12:210, 1954.

127. FREQUENTIN

- [1] Birkinshaw, J. H., *Biochem. J.*, Lond. 51:271, 1952. [2] Curtis, P. J., and Duncanson, L. A., *ibid* 51:276, 1952. [3] Curtis, P. J., Hemming, H. G., and Smith, W. K., *Nature* 167:557, 1951.

128. FUMAGILLIN

- [1] Eble, T. E., and Hanson, F. R., *Antibiotics and Chemotherapy* 1:54, 1951. [2] Asheshov, I. N., Strelitz, F., and Hall, E. A., *ibid* 2:361, 1952. [3] Schenck, J. R., Hargie, M. P., Tarbell, D. S., and Hoffman, P., *J. Am. Chem. Soc.* 75:2274, 1953. [4] Garrett, E. R., and Eble, T. E., *J. Am. Pharm. Ass., Sci. Ed.* 43:385, 1954. [5] Eble, T. E., and Garrett, E. R., *ibid* 43:536, 1954. [6] Garrett, E. R., *ibid* 43:539, 1954. [7] Hanson, F. R., and Eble, T. E., *U. S. Pat.* 2,652,356, 1953. [8] Hanson, F. R., and Eble, T. E., *J. Bact.*, Balt. 57:453, 1949. [9] McCowen, M. C., Callender, M. E., and Lawlis, J. F., Jr., *Science* 113:202, 1951. [10] Seneca, H., and Ides, D., *Am. J. Trop. M. Hyg.* 2:1045, 1953. [11] Asheshov, I. N., Strelitz, F., Hall, E. A., and Flon, H., *Antibiotics and Chemotherapy* 4:380, 1953. [12] Anderson, H. H., *Ann. N. York Acad. Sc.* 55:1118, 1952. [13] Eyles, D. E., and Coleman, N., *Am. J. Trop. M. Hyg.* 2:64, 1953. [14] Armleder, N. H., and Jarpa, A. G., *Bol. inform. Parasit. chile.* 7:38, 1952. [15] Bailey, L., *Nature* 171:212, 1953. [16] Anderson, H. H., Hrenoff, A. K., Anderson, J. V., Nakamura, M., and Contopoulos, A. N., *Am. J. Trop. M. Hyg.* 1:552, 1952. [17] Frye, W. W., Brooke, M. M., and Weinstein, P., *Ann. N. York Acad. Sc.* 55:1104, 1952. [18] MacQuiddy, E. L., *Antibiotics and Chemotherapy* 4:178, 1954. [19] Seneca, H., and Ides, D., *J. Urol.*, Balt. 70:947, 1953. [20] Anon., *Chem. Eng. News* 32:4640, 1954. [21] Koga, F., *J. Antibiot.*, Tokyo, Ser. A 7:176, 1954. [22] Portilla, R. H., Becerra, E., and Ruiloba, J., *Gastroenterology* 27:93, 1954. [23] Schindel, L., *J. Am. M. Ass.* 155:903, 1954. [24] Coatney, G. R., Cooper, W. C., Eddy, N. B., and Greenberg, J., "Survey of Antimalarial Agents," *Public Health Monograph No. 9*, p 250, Washington: Fed. Security Agency, 1953. [25] Shafei, A. Z., *Antibiotic M.* 1:496, 1955. [26] Mills, R. F., *J. Gen. Microb.*, Lond. 13:39, 1955. [27] Sugiura, K., *Ann. N. York Acad. Sc.* 63:962, 1956. [28] Field, J. B., et al, *Fed. Proc.* 15:250, 1956.

129. FUMIGATIN

- [1] Anslow, W. K., and Raistrick, H., *Biochem. J.*, Lond. 32:687, 1938. [2] Waksman, S. A., and Geiger, W. B., *J. Bact.*, Balt. 47:391, 1944. [3] Oxford, A. E., and Raistrick, H., *Chemistry and Industry* 61:128, 1942.

130. FUNGICHRONIN

- [1] Tytell, A. A., McCarthy, F. J., Fisher, W. P., Bolhofer, W. A., and Charney, J., "Antibiotics Annual, 1954-55," p 716, New York: Medical Encyclopedia, Inc. [2] McCarthy, F. J., Fisher, W. P., Charney, J., and Tytell, A. A., *ibid* p 719.

REFERENCES (Continued)

131. FUNGISTATIN

- [1] Peck, R. L., and Lyons, J. E., *Annual Rev. Biochem.* **20**:367, 1951. [2] Hobby, G. L., et al, *J. Clin. Invest.* **28**:927, 1949. [3] Wallen, V. R., and Skolko, A. J., *Canad. J. Res., Ser. C* **28**:623, 1950.

132. FUSARIC ACID

- [1] Yasue, Y., *J. Antibiot., Tokyo*, **2**:255, 1949. [2] Yabuta, T., Kambe, K., and Hayashi, T., *J. Agr. Chem. Soc. Japan* **10**:1059, 1934; *Chem. Abstr.* **29**:1132, 1935. [3] Lakshminarayanan, K., and Subramanian, D., *Nature* **176**:697, 1955.

133. FUSCIN

- [1] Michael, S. E., *Biochem. J., Lond.* **42**:x1, 1948. [2] Michael, S. E., *ibid* **43**:528, 1948. [3] Marcus, S., *ibid* **43**:532, 1948. [4] Barton, D. H., and Hendrickson, J. B., *J. Chem. Soc.* **1956**:1028.

134. FUSCOMYCIN

- [1] Hata, F., and Sano, K., *Jap. Pat.* 5046, 1953.

135. GENTISYL ALCOHOL

- [1] Birkinshaw, J. H., Bracken, A., and Raistrick, H., *Biochem. J., Lond.* **37**:726, 1943. [2] Brack, A., *Helvet. chim. acta* **30**:1, 1947.

136. GEODIN

- [1] Clutterbuck, P. W., Koerber, W., and Raistrick, H., *Biochem. J., Lond.* **31**:1089, 1937. [2] Calam, C. T., Clutterbuck, P. W., Oxford, A. E., and Raistrick, H., *ibid* **41**:458, 1947. [3] Rinderknecht, H., Ward, J. L., Bergel, F., and Morrison, A. L., *ibid* **41**:463, 1947. [4] Raistrick, H., and Smith, G., *ibid* **30**:1315, 1936. [5] Marcus, S., *ibid* **41**:462, 1947.

137. GEOMYCINS

- [1] Brockmann, H., and Musso, H., *Naturwissenschaften* **41**:451, 1954. [2] Brockmann, H., and Musso, H., *Chem. Ber.* **87**:1779, 1954. [3] Brockmann, H., and Musso, H., *ibid* **88**:648, 1955.

138. GLADIOLIC ACID

- [1] Brian, P. W., Curtis, P. J., Grove, J. F., Hemming, H. G., and McGowan, J. C., *Nature* **157**:698, 1946. [2] Grove, J. F., *Biochem. J., Lond.* **50**:648, 1952. [3] Grove, J. F., *J. Chem. Soc.* **1952**:3345. [4] Raistrick, H., and Ross, D. J., *Biochem. J., Lond.* **50**:635, 1952. [5] Grove, J. F., *ibid* **54**:664, 1953. [6] Brian, P. W., Curtis, P. J., and Hemming, H. G., *J. Gen. Microb., Lond.* **2**:341, 1948. [7] Brown, J. J., and Newbold, G. T., *Chemistry and Industry* **1953**:1151.

139. GLIOROSEIN

- [1] Brian, P. W., Curtis, P. J., Howland, S. R., Jefferys, E. G., and Raudnitz, H., *Experientia, Basel* **7**:266, 1951. [2] Vischer, E. B., *J. Chem. Soc.* **1953**:815.

140. GLIOTOXIN

- [1] Stanley, N. F., and Mills, J. A., *Austral. J. Exp. Biol.* **24**:133, 1946. [2] Menzel, A. E., Wintersteiner, O., and Hoogerheide, J. C., *J. Biol. Chem.* **152**:419, 1944. [3] Waksman, S. A., and Geiger, W. B., *J. Bact., Balt.* **47**:391, 1944. [4] Weindling, R., and Emerson, O. H., *Phytopathology* **26**:1068, 1936. [5] Johnson, J. R., Bruce, W. F., and Dutcher, J. D., *J. Am. Chem. Soc.* **65**:2005, 1943. [6] Johnson, J. R., and Buchanan, J. B., *ibid* **75**:2103, 1953. [7] Tompsett, R., McDermott, W., and Kidd, J. G., *J. Immun., Balt.* **65**:59, 1950. [8] Kenner, B. A., and Murray, F. J., *Antibiotics and Chemotherapy* **1**:509, 1951. [9] Weindling, R., *Phytopathology* **31**:991, 1941. [10] Waksman, S. A., and Bugie, E., *Proc. Soc. Exp. Biol.* **54**:79, 1943. [11] Brian, P. W., and Hemming, H. G., *Ann. Appl. Biol.* **32**:214, 1945. [12] Herrick, J. A., *Ohio J. Sc.* **45**:45, 1945. [13] Stock, C. C., *Am. J. M.* **8**:658, 1950. [14] Van der Laan, P. A., *Tijdschr. PlZiekt.* **53**:180, 1947; *Rev. Appl. Mycol.* **27**:202, 1948. [15] Weindling, R., *Phytopathology* **22**:837, 1932. [16] Wallen, V. R., and Skolko, A. J., *Canad. J. Bot.* **29**:316, 1951. [17] Tarnowski, G. S., *Cancer Res., Sup.* **2**:333, 1955. [18] Skipper, H. E., and Thomson, J. R., *ibid* **2**:147, 1955. [19] Wallen, V. R., *Plant Disease Repr.* **39**:124, 1955.

141. GLOBICIN

- [1] Quinn, L., *Antibiotics and Chemotherapy* **2**:221, 1952.

REFERENCES (Continued)

142. GLUTINOSIN

- [1] Brian, P. W., and McGowan, J. C., *Nature* 157:334, 1946. [2] Brian, P. W., Curtis, P. J., and Hemming, H. G., *Proc. R. Soc., Lond., B* 135:106, 1947.

143. GLYCO-LIPIDE

- [1] Jarvis, F. G., and Johnson, M. J., *J. Am. Chem. Soc.* 71:4124, 1949. [2] Hauser, G., and Karnovsky, M. L., *J. Bact., Balt.* 68:645, 1954.

144. GRAMICIDIN

- [1] Hotchkiss, R. D., and Dubos, R. J., *J. Biol. Chem.* 132:791, 1940. [2] Tishler, M., Stokes, J. L., Trenner, N. R., and Conn, J. B., *ibid* 141:197, 1941. [3] Hotchkiss, R. D., and Dubos, R. J., *ibid* 141:155, 1941. [4] Stokes, J. L., and Woodward, C. R., Jr., *J. Bact., Balt.* 46:83, 1943. [5] Rittenberg, S. C., Sternberg, H. E., and Bywater, W. G., *J. Biol. Chem.* 168:183, 1947. [6] Polson, A. J., *Phys. Colloid Chem.* 54:649, 1950. [7] Craig, L. C., Gregory, J. D., and Barry, G. T., *Cold Spring Harbor Symposia* 14:24, 1949. [8] Hotchkiss, R. D., *Advance. Enzymol., N. Y.* 4:153, 1944. [9] James, A. T., and Syngé, R. L., *Biochem. J., Lond.* 50:109, 1951. [10] Dubos, R. J., and Hotchkiss, R. D., *J. Exp. M.* 73:629, 1941. [11] Henderson, J., *J. Am. Pharm. Ass., Sci. Ed.* 35:141, 1946. [12] Weinman, D., *Proc. Soc. Exp. Biol.* 54:38, 1943. [13] Robinson, H. J., and Graessle, O. E., *J. Pharm., Lond.* 76:316, 1942. [14] Hoogerheide, J. C., *J. Franklin Inst.* 229:677, 1940. [15] Geiling, E. M., and Taliaferro, W. H., "A Survey of Antimalarial Drugs, 1941-45," *Ann Arbor: J. W. Edwards*, 1946. [16] Kutscher, A. H., Budowsky, J., and Chilton, N. W., *J. Allergy* 25:46, 1954. [17] Robinson, H. J., and Molitor, H., *J. Pharm., Lond.* 74:75, 1942. [18] Henle, G., and Zittle, C. A., *Proc. Soc. Exp. Biol.* 47:193, 1941. [19] Herrell, W. E., and Heilman, D. J., *Clin. Invest.* 20:583, 1941. [20] Rammelkamp, C. H., and Weinstein, L., *J. Infect. Dis.* 71:166, 1942. [21] McDonald, E., *J. Franklin Inst.* 229:805, 1940. [22] Little, R. B., Dubos, R. J., and Hotchkiss, R. D., *J. Am. Vet. M. Ass.* 98:189, 1941. [23] Phillips, R. L., and Barnes, L. H., *J. Franklin Inst.* 233:396, 1942. [24] Herrell, W. E., and Heilman, D., *Am. J. M. Sc.* 206:221, 1943. [25] Quevauvillier, A., Desvignes, A., and Garcet, S., *Presse méd.* 62:1268, 1954; *Chem. Abstr.* 49:13367, 1955. [26] Kramer, J., and Kirshbaum, A., *Antibiotics and Chemotherapy* 5:561, 1955.

145. GRAMICIDIN J

- [1] Otani, S., and Saito, Y., *Proc. Jap. Acad.* 30:991, 1954; *Chem. Abstr.* 49:13362, 1955.

146. GRAMICIDIN S

- [1] Gause, G. F., Brazhnikova, M. G., and Lissovskaya, N. P., *Am. Rev. Soviet M.* 2:134, 1944-45. [2] Belozersky, A. N., and Passhina, T. S., *Lancet, Lond.* 247:716, 1944. [3] Battersby, A. R., and Craig, L. C., *J. Am. Chem. Soc.* 73:1887, 1951. [4] Syngé, R. L., *Biochem. J., Lond.* 39:363, 1945. [5] Hodgkin, D. C., *Cold Spring Harbor Symposia* 14:65, 1949. [6] Erlanger, B. F., and Goode, L., *Nature* 174:840, 1954. [7] Gause, G. F., and Brazhnikova, M. G., *Lancet, Lond.* 247:715, 1944. [8] Sergiev, P. G., *ibid* 247:717, 1944. [9] Katchalski, E., Berger, A., Bichowski-Slomnicki, L., and Kurtz, J., *Nature* 176:118, 1955.

147. GRANEGILLIN

- [1] Csillag, A., *Acta Microbiologica, Budapest* 1:321, 1954; *abstr. in Bull. Hyg.*, 30:159, 1955.

148. GRASSERIOMYCIN

- [1] Ueda, K., Okimoto, Y., Sakai, H., and Arima, K., *J. Antibiot., Tokyo, Ser. A* 8:91, 1955.

149. GRIFOLIN

- [1] Hirata, Y., and Nakanishi, K., *J. Biol. Chem.* 184:135, 1950.

150. GRISAMINE

- [1] Sawazaki, T., et al, *J. Antibiot., Tokyo, Ser. A* 8:39, 1955.

151. GRISEIN

- [1] Reynolds, D. M., Schatz, A., and Waksman, S. A., *Proc. Soc. Exp. Biol.* 64:50, 1947. [2] Reynolds, D. M., and Waksman, S. A., *J. Bact., Balt.* 55:739, 1948. [3] Kuehl, F. A., Jr., et al, *J. Am. Chem. Soc.* 73:1770, 1951. [4] Umezawa, H., Hayano, S., and Ogata, Y., *Jap. M. J.* 2:79, 1949; *Chem. Abstr.* 46:7165, 1952.

152. GRISEOFLOVIN

- [1] Waga, Y., *J. Antibiot., Tokyo, Ser. A* 6:66, 1953.

REFERENCES (Continued)

153. GRISEOFULVIN

- [1] Oxford, A. E., Raistrick, H., and Simonart, P., *Biochem. J.*, Lond. **33**:240, 1939. [2] Brian, P. W., Curtis, P. J., and Hemming, H. G., *Brit. Mycol. Soc. Trans.* **29**:173, 1946. [3] McGowan, J. C., *ibid* **29**:188, 1946. [4] Grove, J. F., MacMillan, J., Mulholland, T. P., and Rogers, M. A., *J. Chem. Soc.* **1952**:3949. [5] Grove, J. F., MacMillan, J., Mulholland, T. P., and Rogers, M. A., *ibid* **1952**:3977. [6] Grove, J. F., Tsmay, D., MacMillan, J., Mulholland, T. P., and Rogers, M. A., *Chemistry and Industry* **1951**:219. [7] MacMillan, J., *J. Chem. Soc.* **1954**:2585. [8] Brian, P. W., *Ann. Botany*, Lond. **13**:59, 1949. [9] Brian, P. W., and Wright, J. M., *Nature* **167**:347, 1951. [10] Wright, J. M., *Ann. Botany*, Lond. **15**:493, 1951. [11] Ashton, G. C., and Rhodes, A., *Chemistry and Industry* **1955**:1183. [12] Jefferys, E. G., Brian, P. W., Hemming, H. G., and Lowe, D., *J. Gen. Microb.*, Lond. **9**:314, 1953. [13] Brian, P. W., Curtis, P. J., and Hemming, H. G., *Brit. Mycol. Soc. Trans.* **38**:305, 1955. [14] Ashton, G. C., and Brown, A. P., *Analyst* **81**:220, 1956. [15] Ashton, G. C., *ibid* **81**:228, 1956. [16] Hagborg, W. A., *Canad. J. Microbiol.* **2**:80, 1956. [17] Stokes, A., *Plant and Soil* **5**:132, 1954; *abstr. in Rev. Appl. Mycol.* **34**:802, 1955. [18] Aytoun, R. S., *Ann. Botany*, Lond. **20**:297, 1956.

154. GRISEOLUTEINS

- [1] Umezawa, H., et al, *J. Antibiot.*, Tokyo **4**:34, 1951. [2] Osato, T., Maeda, K., and Umezawa, H., *ibid*, Ser. A **7**:15, 1954. [3] Ogata, Y., *Jap. M. J.* **3**:213, 1950. [4] Ogata, Y., Nitta, K., Yamazaki, S., Taya, O., Takeuchi, T., and Umezawa, H., *J. Antibiot.*, Tokyo, Ser. A **6**:139, 1953.

155. GRISEOMYCIN

- [1] Van Dijck, P. J., Van de Voorde, H. P., and De Somer, P., *Antibiotics and Chemotherapy* **3**:1243, 1953. [2] Belgian, Pat. 522,647, 1954; *Chem. Abstr.* **48**:7855, 1954. [3] De Somer, P., Van Dijck, P. J., and Van de Voorde, H. P., *Antibiotics and Chemotherapy* **4**:546, 1954.

156. GRISEOVIRIDIN

- [1] Bartz, Q. R., et al, "Antibiotics Annual, 1954-55," p 777, New York: Medical Encyclopedia, Inc. [2] Ehrlich, J. et al, *ibid*, p 790. [3] Anderson, L. E., Ehrlich, J., Huang Sun, S., and Burkholder, P. R., *Antibiotics and Chemotherapy* **6**:100, 1956. [4] Ames, D. E., Bowman, R. E., Cavalla, J. F., and Evans, D. D., *J. Chem. Soc.* **1955**:4260.

157. HELENINE

- [1] Shope, R. E., *J. Exp. M.* **97**:601, 1953. [2] Shope, R. E., *ibid* **97**:639, 1953. [3] Powell, H. M., Culbertson, C. G., McGuire, J. M., Hoehn, M. M., and Baker, L. A., *Antibiotics and Chemotherapy* **2**:432, 1952. [4] Powell, H. M., and Culbertson, C. G., *Proc. Soc. Exp. Biol.* **83**:161, 1953. [5] Cochran, K. W., Brown, G. C., and Francis, T., Jr., *ibid* **85**:104, 1954. [6] Schabel, F. M., Jr., and Skipper, H. E., *Cancer Res. Sup.* **3**:52, 1955. [7] Cochran, K. W., Chu, L. W., and Francis, T. Jr., *Fed. Proc.* **15**:584, 1956.

158. HELIXIN

- [1] Leben, C., Stessel, G. J., and Keitt, G. W., *Mycologia*, Lanc. **44**:159, 1952. [2] Smeby, R. R., Leben, C., Keitt, G. W., and Strong, F. M., *Phytopathology* **42**:506, 1952. [3] Leben, C., and Keitt, G. W., *ibid* **42**:168, 1952. [4] Leben, C., Arny, D. C., and Keitt, G. W., *ibid* **43**:391, 1953. [5] Wallen, V. R., *Plant Disease Reprtr.* **39**:124, 1955.

159. HELVOLIC ACID

- [1] Chain, E., Florey, H. W., Jennings, M. A., and Williams, T. I., *Brit. J. Exp. Path.* **24**:108, 1943. [2] Waksman, S. A., Horning, E. S., and Spencer, E. L., *J. Bact.*, Balt. **45**:233, 1943. [3] Waksman, S. A., and Geiger, W. B., *ibid* **47**:391, 1944. [4] Birkinshaw, J. H., Bracken, A., and Raistrick, H., *Biochem. J.*, Lond. **39**:70, 1945. [5] Elliott, W. H., Katzman, P. A., Thayer, S. A., and Doisy, E. A., *Fed. Proc.* **6**:250, 1947. [6] Menzel, A. E., Wintersteiner, O., and Hoogerheide, J. C., *J. Biol. Chem.* **152**:419, 1944. [7] Crowfoot, D. M., and Low, B. W., *Brit. J. Exp. Path.* **24**:120, 1943. [8] Williams, T. I., *Biochem. J.*, Lond. **51**:538, 1952. [9] Waksman, S. A., Bugie, E., and Reilly, H. C., *Bull. Torrey Bot. Club* **71**:107, 1944. [10] Gilliver, K., *Ann. Botany*, Lond. **10**:271, 1946. [11] Burton, H. S., Abraham, E. P., and Cardwell, H. M., *Biochem. J.*, Lond. **62**:171, 1956. [12] Allinger, N. L., *J. Org. Chem.* **21**:1180, 1956. [13] Cram, D. J., and Allinger, N. L., *J. Am. Chem. Soc.* **78**:5275, 1956.

160. HEMIPYOCYANINE

- [1] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949. [2] Schoental, R., *Brit. J. Exp. Path.* **22**:137, 1941. [3] Hays, E. E., et al, *J. Biol. Chem.* **159**:725, 1945. [4] Zweig, J., *Vet. J.* **102**:55, 1946. [5] Stokes, J. L., Peck, R. L., and Woodward, C. R., Jr., *Proc. Soc. Exp. Biol.* **51**:126, 1942. [6] Hopkins, J. G., et al, *J. Invest. Derm.* **7**:239, 1946.

REFERENCES (Continued)

161. HERQUEIN

- [1] Burton, H. S., *Brit. J. Exp. Path.* 30:151, 1949.

162. HIRSUTIC ACIDS

- [1] Heatley, N. G., Jennings, M. A., and Florey, H. W., *Brit. J. Exp. Path.* 28:35, 1947.

163. HOMOMYCIN

- [1] Sumiki, Y., et al, *J. Antibiot., Tokyo, Ser. A* 8:170, 1955.

164. HUMICOLIN

- [1] Brian, P. W., *Botan. Rev.* 17:357, 1951. [2] Curtis, P. J., Hemming, H. G., and Jefferys, E. G., *Brit. Mycol. Soc. Trans.* 35:263, 1952.

165. HYDROXYSTREPTOMYCIN

- [1] Benedict, R. G., Stodola, F. H., Shotwell, O. L., Borud, A. M., and Lindenfelser, L. A., *Science* 112:77, 1950. [2] Stodola, F. H., Shotwell, O. L., Borud, A. M., Benedict, R. G., and Riley, A. C., Jr., *J. Am. Chem. Soc.* 73:2290, 1951. [3] Hooper, I. R., and Kaplan, M. A., *ibid* 75:6055, 1953. [4] Ambrose, A. M., *Proc. Soc. Exp. Biol.* 76:466, 1951. [5] Hosoya, S., Soeda, M., Komatsu, N., and Sonoda, Y., *Jap. J. Exp. M.* 20:327, 1949.

166. HYGROMYCIN

- [1] Pittenger, R. C., et al, *Antibiotics and Chemotherapy* 3:1268, 1953. [2] Mann, R. L., Gale, R. M., and Van Abeele, F. R., *ibid* 3:1279, 1953. [3] Pittenger, R. C., Wolfe, R. N., Hoehn, M. M., Marks, P. N., Daily, W. A., and McGuire, J. M., "Antibiotics Annual, 1953-54," p 157, New York: Medical Encyclopedia, Inc. [4] Thayer, J. D., Field, F. W., and Perry, M. I., *Antibiotics and Chemotherapy* 5:132, 1955. [5] Mann, R. L., and Woolf, D. O., *J. Am. Chem. Soc.* 79:120, 1957.

167. HYGROSCOPINS

- [1] Nakazawa, K., et al, *J. Agr. Chem. Soc. Japan* 28:296, 1954. [2] Tatsuoka, S., et al, *J. Antibiot., Tokyo, Ser. B* 7:329, 1954.

168. ILLUDINS

- [1] Anchel, M., Hervey, A., and Robbins, W. J., *Proc. Nat. Acad. Sc. U. S.* 36:300, 1950. [2] Szybalski, W., and Bryson, V., *Am. Rev. Tuberc.* 69:267, 1954. [3] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952. [4] Reilly, H. C., Stock, C. C., Buckley, S. M., and Clark, D. A., *Cancer Res.* 13:684, 1953. [5] Tarnowski, G. S., *ibid*, Sup. 2:333, 1955. [6] Szybalski, W., *Appl. Microbiol.* 2:57, 1954.

169. INOLOMIN

- [1] Fagner, P., *Experientia, Basel* 5:167, 1949.

170. IODININ

- [1] Clemo, G. R., and McIlwain, H., *J. Chem. Soc.* 1938:479. [2] McIlwain, H., *Nature* 148:628, 1941. [3] McIlwain, H., *Biochem. J., Lond.* 37:265, 1943. [4] Clemo, G. R., and Daghish, A. F., *J. Chem. Soc.* 1950:1481.

171. ISO-RHODOMYCINS

- [1] Brockmann, H., and Patt, P., *Chem. Ber.* 88:1455, 1955.

172. ITURINS

- [1] Delcambe, L., *C. rend. Soc. biol.* 146:789, 1952. [2] Delcambe, L., *ibid* 146:1808, 1952.

173. JAVANICIN

- [1] Arnstein, H. R., Cook, A. H., and Lacey, M. S., *Nature* 157:333, 1946. [2] Arnstein, H. R., Cook, A. H., and Lacey, M. S., *Brit. J. Exp. Path.* 27:349, 1946. [3] Arnstein, H. R., and Cook, A. H., *J. Chem. Soc.* 189:1021, 1947.

REFERENCES (Continued)

174. KOJIC ACID

- [1] Prescott, S. C., and Dunn, C. G., "Industrial Microbiology," 2nd ed., New York: McGraw-Hill, Book Company, 1949. [2] Jennings, M. A., and Williams, T. I., *Nature* 155:302, 1945. [3] Morton, H. E., Kocholaty, W., Junowicz-Kocholaty, R., and Kelner, A., *J. Bact., Balt.* 50:579, 1945. [4] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949. [5] Teramoto, S., Inomoto, Y., and Yamamoto, A., *J. Fermentation Technol., Japan* 28:253, 1950. [6] Kramer, S. D., Greer, H. A., and Szobel, D. A., *J. Immun., Balt.* 49:273, 1944. [7] Coggeshall, L. T., and Porter, R. J., "A Survey of Antimalarial Drugs, 1941-45," Ann Arbor: J. W. Edwards, 1946. [8] Friedmann, T. E., *Science* 80:34, 1934. [9] Woods, L. L., *J. Am. Chem. Soc.* 77:1702, 1955. [10] Bečlik, A., *Advance. in Carbohydrate Chem.* 11:145, 1956. [11] Yabuta, T., *J. Chem. Soc.* 125:575, 1924.

175. LACTAROVIOLIN

- [1] Willstaedt, H., and Zetterberg, B., *Svensk Kem. Tidskr.* 58:306, 1946. [2] Plattner, P. A., Heilbronner, E., Schmid, R. W., Sandrin, R., and Fürst, A., *Chemistry and Industry* 1954:1202. [3] Heilbronner, E., and Schmid, R. W., *Helvet, chim. acta.* 37:2018, 1954.

176. LATERITIIN GROUP

- [1] Cook, A. H., Cox, S. F., Farmer, T. H., and Lacey, M. S., *Nature* 160:31, 1947. [2] Cook, A. H., Cox, S. F., and Farmer, T. H., *ibid* 162:61, 1948. [3] Cook, A. H., Cox, S. F., and Farmer, T. H., *J. Chem. Soc.* 1949:1022.

177. LATEROSPORINS

- [1] Barnes, E. M., *Brit. J. Exp. Path.* 30:100, 1949. [2] Anderson, A. A., Michener, H. D., and Olcott, H. S., *Antibiotics and Chemotherapy* 3:521, 1953.

178. LAVENDULIN

- [1] Kelner, A., and Morton, H. E., *J. Bact., Balt.* 53:695, 1947. [2] Junowicz-Kocholaty, R., and Kocholaty, W., *J. Biol. Chem.* 168:757, 1947. [3] Morton, H. E., *Proc. Soc. Exp. Biol.* 64:327, 1947.

179. LENZITIN

- [1] Litvinov, M. A., and Moiseeva, E. N., *Priroda* 1:60, 1951.

180. LEUCOMYCIN

- [1] Hata, T., et al, *J. Antibiot., Tokyo, Ser. A* 6:87, 1953. [2] Sano, Y., Hoshi, T., and Hata, T., *ibid* 7:88, 1954. [3] Sano, Y., *ibid* 7:93, 1954. [4] Hata, T., et al, *ibid* 6:163, 1953. [5] Mitsuishi, N., and Nagata, A., *ibid* 8:15, 1955. [6] Okazaki, S., *Jap. J. Bact.* 10:49, 1955; *Biol. Abstr., Balt.* 29:2911, 1955. [7] Kribben, F. J., *Naturwissenschaften* 41:144, 1954.

181. LEVOMYCIN

- [1] Carter, H. E., Schaffner, C. P., and Gottlieb, D., *Arch. Biochem. and Biophys.* 53:282, 1954.

182. LICHENIFORMINS

- [1] Callow, R. K., Glover, R. E., Hart, P. D., and Hills, G. M., *Brit. J. Exp. Path.* 28:418, 1947. [2] Callow, R. K., and Work, T. S., *Biochem. J., Lond.* 51:558, 1952. [3] Szybalski, W., and Bryson, V., *Am. Rev. Tuberc.* 69:267, 1954. [4] Paton, W. D., *Internat. Arch. Allergy, Basel* 6:203, 1955.

183. LITMOCIDIN

- [1] Gause, G. F., *J. Bact., Balt.* 51:649, 1946. [2] Brazhnikova, M. G., *ibid* 51:655, 1946.

184. LUTEOMYCIN

- [1] Hata, T., et al, *Kitasato Arch.* 22:229, 1949; *Chem. Abstr.* 45:713, 1951. [2] Umezawa, H., et al, *J. Antibiot., Tokyo, Ser. A* 6:45, 1953. [3] Osato, T., et al, *ibid* 6:52, 1953. [4] Hata, T., Higuchi, T., Sano, Y., and Sawachika, K., *J. Antibiot., Tokyo* 3:313, 1950. [5] Nakase, Y., and Hata, T., *ibid* 5:542, 1952. [6] Govorčín, B., *Tehnički Pregled, Zagreb* 8:43, 1956; *Chem. Abstr.* 51:2953, 1957.

185. MANNOSIDOSTREPTOMYCIN

- [1] Fried, J., and Titus, E., *J. Biol. Chem.* 168:391, 1947. [2] Heuser, L. J., Dolliver, M. A., and Stiller, E. T., *J. Am. Chem. Soc.* 70:2833, 1948. [3] Stavely, H. E., and Fried, J., *ibid* 71:135, 1949. [4] Perlman, D., *J. Biol. Chem.* 179:1147, 1949. [5] Emery, W. B., and Walker, A. D., *Analyst* 74:455, 1949. [6] Kowald, J. A., and McCormack, R. B., *Anal. Chem.* 21:1383, 1949. [7] St. John, C. V., Flick, D. E., and Tepe, J. B., *ibid* 23:1289,

REFERENCES (Continued)

185. MANNOSIDOSTREPTOMYCIN (Concluded)

1951. [8] Levine, J., Selzer, G., and Wright, W. W., *ibid* 25:671, 1953. [9] Fried, J., and Titus, E., *J. Am. Chem. Soc.* 70:3615, 1948. [10] Rake, G., McKee, C. M., Pansy, F. E., and Donovick, R., *Proc. Soc. Exp. Biol.* 65:107, 1947.

186. MARASMIC ACID

[1] Kavanagh, F., Hervey, A., and Robbins, W. J., *Proc. Nat. Acad. Sc. U. S.* 35:343, 1949. [2] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952.

187. MARCESIN

[1] Fuller, A. T., and Horton, J. M., *J. Gen. Microb., Lond.* 4:417, 1950.

188. MEDIOCIDIN

[1] Utahara, R., Okami, Y., Nakamura, S., and Umezawa, H., *J. Antibiot., Tokyo, Ser. A* 7:120, 1954. [2] Nitta, K., Takeuchi, T., Yamamoto, T., and Umezawa, H., *ibid* 8:120, 1955.

189. MELLEIN

[1] Burton, H. S., *Nature* 165:274, 1950. [2] Nishikawa, E., *Chem. Abstr.* 28:2751, 1934. [3] Birkinshaw, J. H., *Biol. Rev. Cambridge Philos. Soc.* 12:357, 1937. [4] Blair, J., and Newbold, G. T., *J. Chem. Soc.* 1955:2871. [5] Blair, J., and Newbold, G. T., *Chemistry and Industry* 1955:93.

190. MESENERIN

[1] Ueda, M., and Umezawa, H., *J. Antibiot., Tokyo, Ser. A* 8:164, 1955.

191. 5-METHOXY-p-TOLUQUINONE

[1] Anchel, M., Hervey, A., Kavanagh, F., Polatnick, J., and Robbins, W. J., *Proc. Nat. Acad. Sc. U. S.* 34:498, 1948.

192. 6-METHYL-1,4-NAPHTHAQUINONE

[1] Bendz, G., *Acta chem. scand.* 2:192, 1948. [2] Bendz, G., *ibid* 5:489, 1951.

193. METHMYCIN

[1] Donin, M. N., Pagano, J., Dutcher, J. D., and McKee, C. M., "Antibiotics Annual, 1953-54," p 179, New York: Medical Encyclopedia, Inc. [2] Palencia, L., Gonzalez, R., and Varela, G., *Rev. Inst. salub. enferm. trop., Méx.* 14:113, 1954. [3] Chavez Max, G., and Mendez, D., *Antibiotics and Chemotherapy* 4:83, 1954. [4] Djerassi, C., Bowers, A., and Khastgir, H. N., *J. Am. Chem. Soc.* 78:1729, 1956. [5] Djerassi, C., Bowers, A., Hodges, R., and Riniker, B., *ibid* 78:1733, 1956. [6] Djerassi, C., and Zderic, J. A., *ibid* 78:2907, 1956.

194. MICROCINS

[1] Taira, T., and Fujii, S., *J. Antibiot., Tokyo* 5:185, 1952.

195. MICROCOCCIN

[1] Su, T. L., *Brit. J. Exp. Path.* 29:473, 1948. [2] Heatley, N. G., and Doery, H. M., *Biochem. J., Lond.* 50:247, 1951. [3] Heatley, N. G., Kelly, B. K., and Smith, N., *J. Gen. Microb., Lond.* 6:30, 1952. [4] Mackaness, G. B., *J. Path. Bact., Lond.* 64:429, 1952. [5] Heatley, N. G., Gowans, J. L., Florey, H. W., and Sanders, A. G., *Brit. J. Exp. Path.* 33:105, 1952. [6] Markham, N. P., Wells, A. Q., Heatley, N. G., and Florey, H. W., *ibid* 32:353, 1951. [7] Markham, N. P., Heatley, N. G., Sanders, A. G., and Florey, H. W., *ibid* 32:136, 1951.

196. MICROMONOSPORIN

[1] Waksman, S. A., Geiger, W. B., and Bugie, E., *J. Bact., Balt.* 53:355, 1947.

197. MOLDIN

[1] Maeda, K., Okami, Y., Taya, O., and Umezawa, H., *Jap. J. M. Sc. Biol.* 5:327, 1952; *Chem. Abstr.* 47:5986, 1953. [2] Maeda, K., Okami, Y., Taya, O., and Umezawa, H., *J. Antibiot., Tokyo* 5:465, 1952.

REFERENCES (Continued)

198. MUSARIN

- [1] Arnstein, H. R., Cook, A. H., and Lacey, M. S., *J. Gen. Microb.*, Lond. 2:111, 1948.

199. MYCELIANAMIDE

- [1] Oxford, A. E., and Raistrick, H., *Biochem. J.*, Lond. 42:323, 1948. [2] Birch, A. J., Massy-Westropp, R. A., and Rickards, R. W., *Chemistry and Industry* 1955:1599. [3] Birch, A. J., Massy-Westropp, R. A., and Rickards, R. W., *J. Chem. Soc.* 1956:3717.

200. MYCELIN

- [1] Aiso, K., et al, *J. Antibiot.*, Tokyo 5:217, 1952. [2] Aiso, K., et al, *ibid* 5:488, 1952.

201. MYCOCIDIN

- [1] Gerber, I. E., and Gross, M., *Science* 101:616, 1945. [2] Gerber, I. E., and Gross, M., *ibid* 103:167, 1946.

202. MYCOLUTEIN

- [1] Schmitz, H., and Woodside, R., *Antibiotics and Chemotherapy* 5:652, 1955.

203. MYCOMYCIN

- [1] Celmer, W. D., and Solomons, I. A., *J. Am. Chem. Soc.* 74:1870, 1952. [2] Celmer, W. D., and Solomons, I. A., *ibid* 74:2245, 1952. [3] Celmer, W. D., and Solomons, I. A., *ibid* 75:1372, 1953. [4] Johnson, E. A., and Burdon, K. L., *J. Bact.*, Balt. 54:281, 1947. [5] Jenkins, D. E., *Trans. 9th Conf. on Chemotherapy of Tuberculosis*, p 179, April, 1950. [6] Jenkins, D. E., *Trans. 11th Conf. on Chemotherapy of Tuberculosis*, p 309, Jan., 1952. [7] Hobby, G. L., *ibid*, p 311.

204. MYCOPHENOLIC ACID

- [1] Florey, H. W., Gilliver, K., Jennings, M. A., and Sanders, A. G., *Lancet* 250:46, 1946. [2] Clutterbuck, P. W., Oxford, A. E., Raistrick, H., and Smith, G., *Biochem. J.*, Lond. 26:1441, 1932. [3] Clutterbuck, P. W., and Raistrick, H., *ibid* 27:654, 1933. [4] Birkinshaw, J. H., Bracken, A., and Morgan, E. N., *ibid* 42:xxxix, 1948. [5] Burton, H. S., *Brit. J. Exp. Path.* 30:151, 1949. [6] Birkinshaw, J. H., Raistrick, H., and Ross, D. J., *Biochem. J.*, Lond. 50:630, 1952. [7] Gilliver, K., *Ann. Botany*, Lond. 10:271, 1946.

205. MYCOSUBTILIN

- [1] Walton, R. B., and Woodruff, H. B., *J. Clin. Invest.* 28:924, 1949. [2] Yajima, T., *J. Antibiot.*, Tokyo, Ser. A 8:189, 1955.

206. MYCOTICIN

- [1] Burke, R. C., Swartz, J. H., Chapman, S. S., and Huang, W., *J. Invest. Derm.* 23:163, 1954.

207. NARBOMYCIN

- [1] Corbaz, R., et al, *Helvet. chim. acta* 38:935, 1955.

208. NEBULARINE

- [1] Löfgren, N., Takman, B., and Hedström, H., *Svensk Farm. Tidskr.* 53:321, 1949. [2] Brown, G. B., and Weliky, V. S., *J. Biol. Chem.* 204:1019, 1953. [3] Löfgren, N., and Luning, B., *Acta chem. scand.* 7:225, 1953. [4] Löfgren, N., Luning, B., and Hedström, H., *ibid* 8:670, 1954. [5] Truant, A. P., and D'Amato, H. E., *Fed. Proc.* 14:391, 1955. [6] Sugiura, K., *Ann. N. York Acad. Sc.* 63:962, 1956.

209. NEMOTIN

- [1] Kavanagh, F., *Proc. Nat. Acad. Sc. U. S.* 36:1, 1950. [2] Anchel, M., *J. Am. Chem. Soc.* 74:1588, 1952.

210. NEMOTINIC ACID

- [1] Kavanagh, F., *Proc. Nat. Acad. Sc. U. S.* 36:1, 1950. [2] Anchel, M., *J. Am. Chem. Soc.* 74:1588, 1952.

211. NEOCIDIN

- [1] Tsukamura, M., *J. Antibiot.*, Tokyo 3:499, 1950.

212. NEOMYCINS

- [1] Waksman, S. A., and Lechevalier, H. A., *Science* **109**:305, 1949. [2] Waksman, S. A., Lechevalier, H. A., and Harris, D. A., *J. Clin. Invest.* **28**:934, 1949. [3] Swart, E. A., Waksman, S. A., and Hutchinson, D., *ibid* **28**:1045, 1949. [4] Peck, R. L., Hoffhine, C. E., Jr., Gale, P., and Folkers, K., *J. Am. Chem. Soc.* **71**:2590, 1949. [5] Leach, B. E., et al, *ibid* **73**:2797, 1951. [6] Swart, E. A., Hutchinson, D., and Waksman, S. A., *Arch. Biochem.*, N. Y. **24**:92, 1949. [7] Hamre, D. M., et al, *Antibiotics and Chemotherapy* **2**:135, 1952. [8] Regna, P. P., and Murphy, F. X., *J. Am. Chem. Soc.* **72**:1045, 1950. [9] Dutcher, J. D., Hosansky, N., Donin, M. N., and Wintersteiner, O., *ibid* **73**:1384, 1951. [10] Leach, B. E., and Teeters, C. M., *ibid* **74**:3187, 1952. [11] Peck, R. L., Hoffhine, C. E., Jr., Gale, P. H., and Folkers, K., *ibid* **75**:1018, 1953. [12] Waksman, S. A., "Neomycin: Nature, Formation, Isolation, and Practical Application," *New Brunswick: Rutgers Univ. Press.* 1953. [13] Clancy, C. F., *J. Bact.*, Balt. **61**:715, 1951. [14] Warth, P. T., Chandler, C. A., and Bliss, E. A., *Bull. Johns Hopkins Hosp.* **86**:179, 1950. [15] Felsenfeld, O., Volini, I. F., Ishihara, S. J., Bachman, M. C., and Young, V. M., *J. Laborat. Clin. M.* **35**:428, 1950. [16] Gocke, T. M., Wilcox, C., and Finland, M., *Am. J. Syph.* **34**:265, 1950. [17] Poth, E. J., Fromm, S. M., Wise, R. I., and Hsiang, C. M., *Texas Repts. Biol. M.* **8**:353, 1950. [18] Jackson, G. G., Gocke, T. M., Collins, H. S., and Finland, M., *J. Infect. Dis.* **87**:63, 1950. [19] Mackaness, G. B., *J. Path. Bact.*, Lond. **64**:429, 1952. [20] Leach, B. E., and Teeters, C. M., *J. Am. Chem. Soc.* **73**:2794, 1951. [21] Rake, G., *Ann. N. York Acad. Sc.* **52**:765, 1949. [22] Karlson, A. G., Gainer, J. H., and Feldman, W. H., *Am. Rev. Tuberc.* **62**:345, 1950. [23] Grumbich, F., and Rist, N., *Ann. Inst. Pasteur, Par.* **81**:320, 1951. [24] Waksman, S. A., Frankel, J., and Graessle, O. E., *J. Bact.*, Balt. **58**:229, 1949. [25] Hobby, G. L., Lenert, T. F., and Dougherty, N., *Ann. N. York Acad. Sc.* **52**:775, 1950. [26] Kiser, J. S., and De Mello, G. C., *Proc. 58th Annual Meet.*, Nov. 1954, U. S. Livestock Sanitary Ass., p 81, 1955. [27] Meyer, K. F., Quan, S. F., McCrumb, F. R., and Larson, A., *Ann. N. York Acad. Sc.* **55**:1228, 1952. [28] Jackson, G. G., Barnes, M. W., and Finland, M., *J. Immun.*, Balt. **65**:419, 1950. [29] Hsiang, C. M., and Packchianian, A., *Texas Repts. Biol. M.* **9**:34, 1951. [30] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* **55**:1075, 1952. [31] Felsenfeld, O., Volini, I. F., Young, V. M., and Ishihara, S. J., *Am. J. Trop. M.* **30**:499, 1950. [32] Brown, H. W., *Ann. N. York Acad. Sc.* **55**:1133, 1952. [33] *Am. M. Ass. Council on Pharmacy and Chemistry*, "New and Nonofficial Remedies," Philadelphia: J. B. Lippincott, 1956. [34] Milberg, M. B., Kamens, E. A., Ripstein, C. B., and Banowitch, M. M., "Antibiotics Annual, 1954-55," p 462, New York: Medical Encyclopedia, Inc. [35] Felsenfeld, O., and Soman, D. W., *Ann. N. York Acad. Sc.* **55**:1059, 1952. [36] Welch, H., et al, "Principles and Practice of Antibiotic Therapy," New York: Medical Encyclopedia, Inc., 1954. [37] Wheeler, W. E., and Wainerman, B., *Pediatrics*, Springf. **14**:357, 1954. [38] Kile, R. L., Rockwell, E. M., and Schwarz, J., *J. Am. M. Ass.* **148**:339, 1952. [39] Livingood, C. S., Nilasena, S., King, W. S., Stevenson, R. A., and Mullins, J. F., *ibid* **148**:334, 1952. [40] Riddell, M. I., *Am. J. M. Sc.* **223**:301, 1952. [41] Kirsner, J. B., Levin, E., and Palmer, W. L., *Arch. Int. M.* **90**:677, 1952. [42] Lopez, S. P., *Antibiotics and Chemotherapy* **4**:1189, 1954. [43] Weinberg, W., *South Afr. M. J.* **29**:14, 1955. [44] Ferguson, C., and Carron, J., *Mil. Surgeon* **115**:176, 1954. [45] Schatten, W. E., De Sanctis, A. L., and Abbott, W. E., "Antibiotics Annual, 1954-55," p 691, New York: Medical Encyclopedia, Inc. [46] Dickson, R. S., *Vet. M.*, Chic. **49**:421, 1954. [47] Davidson, J. L., *ibid* **47**:239, 1952. [48] Harris, H. E., and Loza, E. P., *Cleveland Clin. Q.* **22**:10, 1955. [49] Packchianian, A., *Am. J. Trop. M. Hyg.* **2**:243, 1953. [50] Pomerat, C. M., and Leake, C. D., *Ann. N. York Acad. Sc.* **58**:1110, 1954. [51] Waisbren, B. A., and Spink, W. W., *Ann. Int. M.* **33**:1099, 1950. [52] Kutscher, A. H., Lane, S. L., and Segall, R., *J. Allergy* **25**:135, 1954. [53] Poth, E. J., *South. M. J.* **44**:226, 1951. [54] Felsenfeld, O., Volini, I. F., Kadison, E. R., Zimmerman, E., and Ishihara, S., *Am. J. Clin. Path.* **20**:670, 1950. [55] Gocke, T. M., and Finland, M., *J. Laborat. Clin. M.* **38**:719, 1951. [56] Gorzynski, E. A., and Neter, E., *Antibiotics and Chemotherapy* **3**:798, 1953. [57] Waisbren, B. A., and Spink, W. W., *Proc. Soc. Exp. Biol.* **74**:35, 1950. [58] Chan, K. F., *Am. J. Hyg.* **56**:22, 1952. [59] Weiss, D., and Waksman, S. A., *Proc. Nat. Acad. Sc. U. S.* **36**:293, 1950. [60] Bergman, S., Grubb, R., Bergstrom, S., and Rosch, H., *Antibiotics and Chemotherapy* **4**:493, 1954. [61] Braude, R., Kon, S. K., and Porter, J. W., *Nutrit. Abstr.*, Aberdeen **23**:473, 1953. [62] Aiso, K., Miyaki, K., Yanagisawa, F., Arai, T., and Hayashi, M., *J. Antibiot.*, Tokyo **3**:87, 1950. [63] Maeda, K., *ibid* **5**:343, 1952. [64] Ford, J. H., et al, *J. Am. Chem. Soc.* **77**:5311, 1955. [65] Simon, J., *Am. J. Vet. Res.* **16**:394, 1955. [66] Deom, J., and Mortelmans, J., *Am. Inst. Pasteur, Par.* **88**:521, 1955. [67] Haas, K. B., *Vet. M.*, Chic. **50**:460, 1955. [68] Konde, W. N., and Monroe, W. P., *ibid* **50**:231, 1955. [69] Roantree, R. J., and Rantz, L. A., *Antibiotic M.* **2**:103, 1956. [70] Gibbs, G. E., and Raskin, J., *ibid* **2**:332, 1956. [71] El-Din, G. N., *Am. J. Trop. M. Hyg.* **5**:68, 1956. [72] Deacon, W. E., Olansky, S., Albritton, D. C., and Kaplans, W., *Antibiotic M.* **2**:143, 1956. [73] Fisher, C. J., and Faloon, W. W., *Clin. Res. Proc.* **4**:147, 1956 (abstr.). [74] Dickson, E., *Vet. M.*, Chic. **50**:143, 1955. [75] Todd, L. K., and Wright, H. L., *ibid* **50**:363, 1955. [76] Kitchen, H. B., and Waksman, S., *J. Am. Vet. M. Ass.* **127**:260, 1955. [77] Keller, H., Krüpe, W., Sous, H., and Mückter, H., "Antibiotics Annual, 1955-56," p 35, New York: Medical Encyclopedia, Inc. [78] Hu, F., Livingood, C. S., and Hildebrand, J. F., *J. Invest. Derm.* **26**:23, 1956. [79] *Am. M. Ass. Council on Pharmacy and Chemistry*, *J. Am. M. Ass.* **159**:1634, 1955. [80] Gocke, T. M., and Finland, M., *J. Laborat. Clin. M.* **38**:719, 1951. [81] Gezon, H. M., and Fasan, D. M., *Science* **114**:422, 1951. [82] Finland, M., *N. England J. M.* **353**:909, 1955. [83] Shelley, W. B., and Cahn, M. M., *J. Am. M. Ass.* **159**:1736, 1955. [84] Hagborg, W. A., *Canad. J. Microbiol.* **2**:80, 1956. [85] Liles, J. N., and Fisk, F. W., *J. Econom. Entom.* **48**:217, 1955. [86] Heseltine, W. W., *Pharm. J.* **176**:62, 1956.

213. NEONOCARDIN

- [1] Ueda, S., and Uesaka, I., *J. Antibiot.*, Tokyo **5**:170, 1952. [2] Uesaka, I., *ibid* **5**:75, 1952.

REFERENCES (Continued)

214. NETROPSIN

- [1] Finlay, A. C., Hochstein, F. A., Sobin, B. A., and Murphy, F. X., *J. Am. Chem. Soc.* 73:341, 1951. [2] Finlay, A. C., and Sobin, B. A., *U. S. Pat.* 2,586,762, 1952. [3] Szybalski, W., and Bryson, V., *Am. Rev. Tuberc.* 69:267, 1954. [4] Seneca, H., and Ides, D., *Am. J. Trop. M. Hyg.* 2:1045, 1953. [5] Schabel, F. M., Jr., Laster, W. R., Jr., Brockman, R. W., and Skipper, H. E., *Proc. Soc. Exp. Biol.* 83:1, 1953. [6] Isono, K., et al, *J. Antibiot.*, Tokyo, Ser. A 8:19, 1955. [7] Van Tamelen, E. E., White, D. M., Kogon, I. C., and Powell, A. D., *J. Am. Chem. Soc.* 78:2157, 1956. [8] Asheshov, I. N., Hall, E. A., and Flon, H., *Cancer Res. Sup.* 3:57, 1955. [9] Schabel, F. M., Jr., and Skipper, H. E., *ibid*, p 52. [10] Sugiura, K., *ibid*, p 18. [11] Gellhorn, A., and Hirschberg, E., *ibid*, p 1. [12] Karnofsky, D. A., *ibid*, p 83.

215. NIDULIN and NOR-NIDULIN

- [1] Kurung, J. M., *Science* 102:11, 1945. [2] Hogeboom, G. H., and Craig, L. C., *J. Biol. Chem.* 162:363, 1946. [3] Doering, W. E., Dubos, R. J., Noyce, D. S., and Dreyfus, R., *J. Am. Chem. Soc.* 68:725, 1946. [4] Dean, F. M., Robertson, A., Roberts, J. C., and Raper, K. B., *Nature* 172:344, 1953. [5] Dean, F. M., Roberts, J. C., and Robertson, A., *J. Chem. Soc.* 1954:1432.

216. NIGERICIN

- [1] Harned, R. L., et al, *Antibiotics and Chemotherapy* 1:594, 1951. [2] Lewis, J. C., Michener, H. D., Stumbo, C. R., and Titus, D. S., *J. Agr. Food Chem.* 2:298, 1954.

217. NISINS

- [1] Gowans, J. L., Smith, N., and Florey, H. W., *Brit. J. Pharm.* 7:438, 1952. [2] Berridge, N. J., *Biochem. J.*, Lond. 45:486, 1949. [3] Newton, G. G., and Abraham, E. P., *Nature* 171:606, 1953. [4] Mattick, A. T., Hirsch, A., *ibid* 154:551, 1944. [5] Hirsch, A., and Mattick, A. T., *Lancet*, Lond. 257:190, 1949. [6] Mattick, A. T., and Hirsch, A., *ibid* 253:5, 1947. [7] Bavin, E. M., Beach, A. S., Falconer, R., and Friedmann, R., *ibid* 262:127, 1952. [8] Mackaness, G. B., *J. Path. Bact.*, Lond. 64:429, 1952. [9] Hulse, E. C., and Lancaster, J. E., *Vet. Rec.*, Lond. 63:477, 1951. [10] Taylor, J. I., Hirsch, A., and Mattick, A. T., *ibid* 61:197, 1949. [11] McClintock, M., et al, *J. Dairy Res.* 1952:187. [12] Anderson, A. A., Michener, H. D., and Olcott, H. S., *Antibiotics and Chemotherapy* 3:521, 1953. [13] Berridge, N. J., *Chemistry and Industry* 1953:1158.

218. NITROSPORIN

- [1] Umezawa, H., and Takeuchi, T., *J. Antibiot.*, Tokyo 5:270, 1952.

219. NOCARDAMIN

- [1] Stoll, A., Brack, A., and Renz, J., *Schweiz. Zschr. Path. Bakt.* 14:225, 1951. [2] Stoll, A., Renz, J., and Brack, A., *Helvet. chim. acta.* 34:862, 1951.

220. NOCARDIANIN

- [1] Bick, I. R., Gregory, J. J., and Cram, D. J., *Antibiotics and Chemotherapy* 2:255, 1952.

221. NOCARDORUBIN

- [1] Aiso, K., Arai, T., Shidara, I., and Ogi, K., *J. Antibiot.*, Tokyo, Ser. A 7:1, 1954.

222. NOFORMICIN

- [1] Harris, D. A., and Woodruff, H. B., "Antibiotics Annual, 1953-54," p 609, New York: Medical Encyclopedia, Inc. [2] McClelland, L., *ibid*, p 615. [3] Woodruff, H. B., *Proc. 6th Internat. Congr. Microbiology*, p 326, Sept., 1953. [4] Schlegel, D. E., and Rawlins, T. E., *Phytopathology* 44:328, 1954. [5] Gray, R. A., *ibid* 45:281, 1955.

223. NOTATIN

- [1] Coulthard, C. E., et al, *Nature* 150:634, 1942. [2] Roberts, E. C., et al, *J. Biol. Chem.* 147:47, 1943. [3] Birkinshaw, J. H., and Raistrick, H., *ibid* 148:459, 1943. [4] Coulthard, C. E., et al, *Biochem. J.*, Lond. 39:24, 1945. [5] Kocholaty, W., *Arch. Biochem.*, N. Y. 2:73, 1943. [6] Schales, O., *ibid* 2:487, 1943. [7] Keilin, D., and Hartree, E. F., *Biochem. J.*, Lond. 42:221, 1948. [8] Cecil, R., and Ogston, A. G., *ibid* 42:229, 1948. [9] Kocholaty, W., *Science* 97:186, 1943. [10] Broom, W. A., Coulthard, C. E., Gurd, M. R., and Sharpe, M. E., *Brit. J. Pharm.* 1:225, 1946.

224. NOVOBIOCIN

- [1] Hoeksema, H., Johnson, J. L., and Hinman, J. W., *J. Am. Chem. Soc.* 77:6711, 1955. [2] Smith, C. G., Dietz, A., Sokolski, W. T., and Savage, G. M., *Antibiotics and Chemotherapy* 6:135, 1956. [3] Kaczka, E. A., Wolf, F. J.,

224. NOVOBIOCIN (Concluded)

- Rathe, F. P., and Folkers, K., *J. Am. Chem. Soc.* 77:6404, 1955. [4] Wallick, H., et al, "Antibiotics Annual, 1955-1956," p 909, New York: Medical Encyclopedia, Inc. [5] Hoeksema, H., et al, *Antibiotics and Chemotherapy* 6:143, 1956. [6] Hinman, J. W., Hoeksema, H., Caron, E. L., and Jackson, W. G., *J. Am. Chem. Soc.* 78:1072, 1956. [7] Hoeksema, H., Caron, E. L., and Hinman, J. W., *ibid* 78:2019, 1956. [8] Welch, H., and Wright, W. W., *Antibiotics and Chemotherapy* 5:670, 1955. [9] Taylor, R. M., Sokolski, W. T., Savage, G. M., and Van der Brook, M. J., *ibid* 6:157, 1956. [10] Frost, B. M., Valiant, M. E., McClelland, L., Solotorovsky, M., and Cuckler, A. C., "Antibiotics Annual, 1955-1956," p 918, New York: Medical Encyclopedia, Inc. [11] Verwey, W. F., Miller, A. K., and West, M. K., *ibid*, p 924. [12] Finland, M., *ibid*, p 929. [13] Lin, F-K., and Coriell, L. L., *ibid*, p 634. [14] Martin, W. J., Heilman, F. R., Nichols, D. R., Wellman, W. E., and Geraci, J. E., *Proc. Staff Meet. Mayo Clin.* 30:540, 1955. [15] Mullins, J. F., and Wilson, C. J., *Antibiotic M.* 2:201, 1956. [16] Limson, B. M., and Romansky, M. J., *ibid* 2:277, 1956. [17] Wilkins, J. R., Lewis, C., and Barbiers, A. R., *Antibiotics and Chemotherapy* 6:149, 1956. [18] Lubash, G., Van der Meulen, J., Bernsten, C., Jr., and Tompsett, R., *Antibiotic M.* 2:233, 1956. [19] Simon, H. J., McCune, R. M., Dineen, P. A., and Rogers, D. E., *ibid* 2:205, 1956. [20] McHardy, G., McHardy, R., Ward, S., and Cradic, H., *ibid* 2:230, 1956. [21] Larson, E. J., et al, *Antibiotics and Chemotherapy* 6:226, 1956. [22] Jones, W. F., Jr., Nichols, R. L., and Finland, M., *J. Laborat. Clin. M.* 47:783, 1956. [23] Wright, W. W., Putnam, L. E., and Welch, H., *Antibiotic M.* 2:311, 1956. [24] Bayne, G. M., Strickland, S. C., Gylfe, J. M., and Boger, W. P., *ibid* 2:166, 1956. [25] Morton, R. F., Prigot, A., and Maynard, A. De L., *ibid* 2:282, 1956. [26] David, N. A., and B rgner, P. R., *ibid* 2:219, 1956. [27] Nichols, R. L., and Finland, M., *ibid* 2:241, 1956. [28] Martin, W. J., Heilman, F. R., Nichols, D. R., Wellman, W. E., and Geraci, J. E., *ibid* 2:258, 1956. [29] Lin, F-K., and Coriell, L. L., *ibid* 2:268, 1956. [30] Milberg, M. B., Schwartz, R. D., and Silverstein, J. N., *ibid* 2:286, 1956. [31] Welch, H., Lewis, C. N., Putnam, L. E., and Randall, W. A., *Antibiotic M.* 3:27, 1956. [32] Frost, B. M., and Valiant, M. E., *Antibiotics and Chemotherapy* 6:648, 1956. [33] Boxer, G. E., and Shonk, C. E., *ibid* 6:589, 1956.

225. NUDIC ACIDS

- [1] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949.

226. NYBOMYCIN

- [1] Strelitz, F., Flon, H., and Asheshov, I. N., *Proc. Nat. Acad. Sc. U. S.* 41:620, 1955.

227. NYSTATIN

- [1] Hazen, E. L., and Brown, R., *Proc. Soc. Exp. Biol.* 76:93, 1951. [2] Dutcher, J. D., Boyack, G., and Fox, S., "Antibiotics Annual, 1953-54," p 191, New York: Medical Encyclopedia, Inc. [3] Gold, W., Stander, H., and Pansy, F. E., *ibid*, p 195. [4] Brown, R., Hazen, E. L., and Mason, A., *Science* 117:609, 1953. [5] Newcomer, V. D., Wright, E. T., Leeb, A. J., Tarbet, J. E., and Sternberg, T. H., *J. Invest. Derm.* 22:431, 1954. [6] Campbell, C. C., Hodges, E. P., and Hill, G. B., "Antibiotics Annual, 1953-54," p 210, New York: Medical Encyclopedia, Inc. [7] Sternberg, T. H., et al, *ibid*, p 199. [8] Campbell, C. C., O'Dell, E. T., and Hill, G. B., "Antibiotics Annual, 1954-55," p 858, New York: Medical Encyclopedia, Inc. [9] Newcomer, V. D., Wright, E. T., and Sternberg, T. H., *ibid*, p 686. [10] Drouhet, E., *Ann. Inst. Pasteur, Par.* 88:298, 1955. [11] Millberger, H., and Blank, E., *Naturwissenschaften* 41:503, 1954. [12] Sloane, M. B., *J. Invest. Derm.* 24:569, 1955. [13] Osbourne, R. A., *Arch. Derm. Syph., Chic.* 72:371, 1955. [14] Robinson, R. C., *J. Invest. Derm.* 24:375, 1955. [15] Wigmore, J. O., and Henderson, W. M., *Nature* 176:516, 1955. [16] Seneca, H., "Antibiotics Annual, 1955-56," p 697, New York: Medical Encyclopedia, Inc. [17] Newcomer, V. D., *ibid*, p 831. [18] Huang, N. N., Kendall, N., Lamberti, A. J., and High, R. H., *ibid*, p 711. [19] Wright, E. T., Graham, J. H., Newcomer, V. D., and Sternberg, T. H., *ibid*, p 846. [20] Robinson, R. C., *ibid*, p 851. [21] Weiss, W., Eisenberg, G. M., Sass, D. K., Kayser, H. L., and Flippin, H. E., *ibid*, p 842. [22] Kimble, A. I., Shea, J. G., and Katz, S., *ibid*, p 676. [23] Stone, M. L., and Mersheimer, W. L., *ibid*, p 862. [24] Hewitt, W. L., Finegold, S. M., and Sutter, V. L., *ibid*, p 856. [25] Strade, H. A. (quoted by Seneca, H.), *ibid*, p 697. [26] McLimans, W. F., Bonissol, C., Davis, E. V., and Rake, G., *ibid*, p 690. [27] Stout, H. A., and Pagano, J. F., *ibid*, p 704. [28] Drouhet, E., *Presse m d.* 63:620, 1955. [29] Hu, F., Livingood, C. S., and Hildebrand, J. F., *J. Invest. Derm.* 26:23, 1956. [30] Sarewitz, A. B., *Ann. Int. M.* 42:1187, 1955. [31] Drouhet, E., Schwarz, J., and Bingham, E., *Antibiotics and Chemotherapy* 6:23, 1956. [32] Seneca, H., and Bergendahl, E., *ibid* 5:737, 1955. [33] West, M. K., Verwey, W. F., and Miller, A. K., "Antibiotics Annual, 1955-56," p 231, New York: Medical Encyclopedia, Inc. [34] Lettr , H., *Cancer Res. Sup.* 2:125, 1955. [35] Graham, J. H., Wright, E. T., Newcomer, V. D., and Sternberg, T. H., "Therapy of Fungous Diseases" (edited by Sternberg, T. H., and Newcomer, V. D.), p 220, Boston: Little, Brown and Co., 1955. [36] Donovan, R., et al, *ibid*, p 176. [37] Brown, R., and Hazen, E. L., *ibid*, p 164. [38] Steinberg, B. A., and Jambor, W. P., *ibid*, p 195. [39] Lampen, J. O., Morgan, E. R., and Slocum, A. C., *Fed. Proc.* 15:295, 1956. [40] Stewart, G. T., *Brit. M. J.* 1:658, 1956.

228. OLEANDOMYCIN

- [1] Sobin, B. A., English, A. R., and Celmer, W. D., "Antibiotics Annual, 1954-55," p 827, New York: Medical Encyclopedia, Inc. [2] Ross, S., "Antibiotics Annual, 1955-56," p 600, New York: Medical Encyclopedia, Inc.

REFERENCES (Continued)

229. OLIGOMYCIN

- [1] Smith, R. M., Peterson, W. H., and McCoy, E., *Antibiotics and Chemotherapy* 4:962, 1954. [2] Newburgh, R. W., and Cheldelin, V. H., *Plant Disease Repr.* 39:684, 1955. [3] McCoy, E. (quoted by Zaumeyer, W. J.), *Proc. 1st Internat. Conference on the Use of Antibiotics in Agriculture*, National Academy of Sciences-National Research Council, Washington, D. C., Publication 397, p 171, 1956.

230. OREGONENSIN

- [1] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press. 1949.

231. ORYZASIZINE

- [1] Shimoda, C., *Jap. Pat.* 1594, 1952; *Chem. Abstr.* 47:6097, 1953. [2] Shimoda, C., *J. Agr. Chem. Soc. Japan* 25:254, 1951; *Chem. Abstr.* 46:10284, 1952.

232. OXYTETRACYCLINE

- [1] Finlay, A. C., et al, *Science* 111:85, 1950. [2] Sobin, B. A., Finlay, A. C., and Kane, J. H., *U. S. Pat.* 2,516,080, 1950. [3] Regna, P. P., et al, *J. Am. Chem. Soc.* 73:4211, 1951. [4] Monastero, F., et al, *J. Am. Pharm. Ass., Sci. Ed.* 40:241, 1951. [5] Stephens, C. R., et al, *J. Am. Chem. Soc.* 74:4976, 1952. [6] Hochstein, F. A., et al, *ibid* 75:5455, 1953. [7] Perlman, D., *Science* 118:628, 1953. [8] Robertson, J., Robertson, I., Eiland, P. F., and Pepinsky, R., *J. Am. Chem. Soc.* 74:841, 1952. [9] Hobby, G. L., Dougherty, N., Lenert, T. F., Hudders, E., and Kiseluk, M., *Proc. Soc. Exp. Biol.* 73:503, 1950. [10] Welch, H., Hendricks, F. D., Price, C. W., and Randall, W. A., *J. Am. Pharm. Ass., Sci. Ed.* 39:185, 1950. [11] Welch, H., Randall, W. A., Reedy, R. J., and Kramer, J., *Antibiotics and Chemotherapy* 2:693, 1952. [12] Bliss, E. A., Warth, P. T., and Chandler, C. A., *Ann. N. York Acad. Sc.* 53:277, 1950. [13] Gocke, T. M., Jackson, G. G., Wilcox, C., and Finland, M., *ibid* 53:297, 1950. [14] Dowling, H. F., Lepper, M. H., Caldwell, E. R., and Spies, H. W., *ibid* 53:433, 1950. [15] Runyon, E., *J. Laborat. Clin. M.* 37:713, 1951. [16] Kiser, J. S., De Mello, G. C., Reichard, D. H., and Williams, J. H., *J. Infect. Dis.* 90:76, 1952. [17] Meyer, K. F., Quan, S. F., McCrumb, F. R., and Larson, A., *Ann. N. York Acad. Sc.* 55:1228, 1952. [18] Bohonos, N., Dornbush, A. C., Feldman, L. I., Martin, J. H., Pelcak, E., and Williams, J. H., "Antibiotics Annual, 1953-54," p 49, New York: Medical Encyclopedia, Inc. [19] English, A. R., P'an, S. Y., McBride, T. J., Gardocki, J. F., Van Halsema, G., and Wright, W. A., *ibid*, p 70. [20] Felsenfeld, O., and Soman, D. W., *Ann. N. York Acad. Sc.* 55:1059, 1952. [21] Schuhardt, V. T., *ibid* 55:1209, 1952. [22] Seneca, H., and Ides, D., *Am. J. Trop. M. Hyg.* 2:1045, 1953. [23] Seneca, H., and Bergendahl, E., *Am. J. M. Sc.* 228:16, 1954. [24] Chinn, B. D., *Proc. Soc. Exp. Biol.* 80:359, 1952. [25] MacKanes, G. B., *J. Path. Bact., Lond.* 64:429, 1952. [26] Steenken, W., Jr., and Wolinsky, E., *Ann. N. York Acad. Sc.* 53:309, 1950. [27] Kiser, J. S., and De Mello, G. C., *Proc. 58th Annual Meet., Nov. 1954, U. S. Livestock Sanitary Ass.*, p 81, 1955. [28] Knight, V., *Ann. N. York Acad. Sc.* 53:332, 1950. [29] Hobby, G. L., Lenert, T. F., Donikian, M., and Pikula, D., *Am. Rev. Tuberc.* 63:434, 1951. [30] Berks, G., and Goodwin, L. G., *Nature* 167:447, 1951. [31] Hsiang, C., and Packchianian, A., *Texas Repts. Biol. M.* 9:34, 1951. [32] Eyles, D. E., *Am. J. Trop. M. Hyg.* 2:429, 1953. [33] Turner, T. B., and Schaeffer, K., *Am. J. Syph.* 38:81, 1954. [34] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952. [35] Snyder, J. C., Fagan, R., Wells, E. B., Wick, H. C., and Miller, J. C., *ibid* 53:362, 1950. [36] Smadel, J. E., Jackson, E. B., and Ley, H. L., Jr., *ibid* 53:375, 1950. [37] Rose, H. M., *ibid* 53:385, 1950. [38] Bauer, R. E., et al, *ibid* 53:395, 1950. [39] Quilligan, J. J., Jr., *ibid* 53:407, 1950. [40] Brown, H. W., *ibid* 55:1133, 1952. [41] Andrewes, C. H., and Niven, J. F., *Brit. J. Exp. Path.* 31:767, 1950. [42] Kneeland, Y., Jr., and Mills, K., *J. Immun., Balt.* 65:653, 1950. [43] Reilly, H. C., Stock, C. C., Buckley, S. M., and Clarke, D. A., *Cancer Res.* 13:684, 1953. [44] Stanton, M. F., Laskowski, L., and Pinkerton, H., *Proc. Soc. Exp. Biol.* 74:705, 1950. [45] Am. M. Ass. Council on Pharmacy and Chemistry, "New and Nonofficial Remedies," Philadelphia: J. B. Lippincott Co., 1956. [46] Kass, E. H., Barnes, M. W., and Finland, M., *Ann. N. York Acad. Sc.* 53:412, 1950. [47] Kirby, W. M., *Annual Rev. Microb.* 6:387, 1952. [48] Hall, H. E., et al, *Ann. Int. M.* 35:988, 1951. [49] Miller, F. L., et al, *Am. Rev. Tuberc.* 66:534, 1952. [50] King, D. S., *N. England J. M.* 252:135, 1955. [51] Dunlop, E. M., and Robinson, R. C., *Am. J. Syph.* 38:24, 1954. [52] Perlman, L., and Milzer, A., *Arch. Int. M.* 94:82, 1954. [53] Hill, K. R., *Bull. World Health Org., N. Y.* 7:108, 1953. [54] James, D. G., *J. Am. M. Ass.* 151:810, 1953. [55] Ruiz Sanchez, F., et al, *Antibiotics and Chemotherapy* 2:51, 1952. [56] Martin, G. A., et al, *J. Am. M. Ass.* 151:1055, 1953. [57] McHardy, G., and Frye, W. W., *ibid* 154:646, 1954. [58] Seligmann, E., *Proc. Soc. Exp. Biol.* 83:778, 1953. [59] De Mello, G. C., and Kiser, J. S., "Antibiotics Annual, 1954-55," p 678, New York: Medical Encyclopedia, Inc. [60] Seneca, H., and Ides, D., *J. Urolo., Balt.* 70:947, 1953. [61] Welch, H., et al, "Principles and Practice of Antibiotic Therapy," New York: Medical Encyclopedia, Inc., 1954. [62] Greenblatt, R. B., *Ann. N. York Acad. Sc.* 55:1082, 1952. [63] Loughlin, E. H., and Mullin, W. G., *Antibiotic M.* 1:145, 1955. [64] Lane, S. L., et al, *J. Am. M. Ass.* 151:986, 1953. [65] Hoekenga, M. T., *Am. J. Trop. M. Hyg.* 2:271, 1953. [66] Wilcox, R. R., *Antibiotics and Chemotherapy* 4:173, 1954. [67] Ambrose, S. G., *J. M. Ass. Georgia* 43:950, 1954. [68] Montmorency, F. A., Caffery, E. L., and Musselman, M. M., *Antibiotics and Chemotherapy* 4:313, 1954. [69] Waddington, W. S., Smart, T. B., and Kirby, W. M., *ibid* 4:1037, 1954. [70] Kagan, B. M., Mendelsohn, R. S., Miller, R. A., and Elegant, L. D., *ibid* 4:308, 1954. [71] Moll, F. C., and Stamm, S., "Antibiotics Annual, 1954-55," p 900, New York: Medical Encyclopedia, Inc. [72] Koch, R., *ibid*, p 908. [73] Appel, B., *ibid*, p 949. [74] Expert Committee on Trachoma, *World Health Org., Rev. Internat. trachome* 29:295, 1952. [75] Kistner, R. W., and Duncan, C. J., *Obst. Gyn.* 4:155, 1954. [76] Wright, L. T., Prigot, A., Di Lorenzo, J. C., Whitaker, J. C., and Marmell, M., *Am. J. Syph.* 35:490, 1951. [77] Sutcliffe, W. D., and Barnes, Z. B., *Arch. Int. M.* 91:68, 1953. [78] Wright, C. S., and Tschan, D. N.,

232. OXYTETRACYCLINE (Concluded)

- Arch. Derm. Syph., Chic. 67:125, 1953. [79] Tableman, H. G., Vet. M., Chic. 46:373, 1951. [80] Miller, J. W., Southwest. Veterinarian 6:346, 1953. [81] Peterson, E. H., Vet. M., Chic. 48:311, 1953. [82] Gross, W. B., Poultry Sc. 32:364, 1953. [83] Hawley, G. E., et al, "Antibiotics Annual, 1954-55," p 329, New York: Medical Encyclopedia, Inc. [84] Meyer, K. F., and Eddie, B., *ibid*, p 544. [85] P'an, S. Y., Scaduto, L., and Cullen, M., Ann. N. York Acad. Sc. 53:238, 1950. [86] Schoenbach, E. B., Bryer, M. S., and Long, P. H., *ibid* 53:245, 1950. [87] P'an, S. Y., et al, J. Pharm. Exp. Ther. 99:234, 1950. [88] Pomerat, C. M., and Leake, C. D., Ann. N. York Acad. Sc. 58:1110, 1954. [89] Kendig, E. L., Jr., and Arnold, G. G., Antibiotics and Chemotherapy 4:1111, 1954. [90] French, C. E., Uram, J. A., Ingram, R. H., and Swift, R. W., J. Nutrit. 54:75, 1954. [91] Antelyes, J., J. Am. Vet. M. Ass. 119:299, 1951. [92] Lutz, H. H., *ibid* 119:302, 1951. [93] Lukas, G. N., and Bradford, D. R., *ibid* 125:215, 1954. [94] Farquaharson, H., Delehanty, D. D., and Milne, F. T., *ibid* 122:176, 1953. [95] Von Oettingen, W. F., "Antibiotics Annual, 1954-55," p 361, New York: Medical Encyclopedia, Inc. [96] Kutscher, A. H., Lane, S. L., and Segall, R., J. Allergy 25:135, 1954. [97] Welch, H., Ann. N. York Acad. Sc. 53:253, 1950. [98] Herrell, W. E., Heilman, F. R., and Wellman, W. E., *ibid* 53:448, 1950. [99] Wright, W. A., P'an, S. Y., and Carlozzi, M., "Antibiotics Annual, 1953-54," p 137, New York: Medical Encyclopedia, Inc. [100] Werner, C. A., Knight, V., and McDermott, W., Proc. Soc. Exp. Biol. 74:261, 1950. [101] Gocke, T. M., and Finland, M., J. Laborat. Clin. M. 38:719, 1951. [102] Finland, M., "Antibiotics Annual, 1954-55," p 35, New York: Medical Encyclopedia, Inc. [103] Fusillo, M. H., and Ramansky, M. J., Antibiotics and Chemotherapy 1:107, 1951. [104] Helander, S., and Böttiger, L. E., Acta med. scand. 147:71, 1953. [105] Wyss, O., Smith, G. N., Hobby, G. L., Oginsky, E. L., and Pratt, R., Bact. Rev., Balt. 17:17, 1953. [106] Karp, A., and Snyder, J. C., Proc. Soc. Exp. Biol. 79:216, 1952. [107] Gale, E. F., and Paine, T. F., Biochem. J., Lond. 48:298, 1951. [108] Pratt, R., and Dufrenoy, J., Texas Repts. Biol. M. 9:76, 1951. [109] Hahn, F. E., and Wissemann, C. L., Jr., Proc. Soc. Exp. Biol. 78:690, 1951. [110] Miura, Y., Nakamura, Y., Matsudaira, H., and Komeiji, T., Antibiotics and Chemotherapy 2:152, 1952. [111] Weinberg, E. D., J. Infect. Dis. 95:291, 1954. [112] Gowans, J. L., Brit. J. Exp. Path. 34:35, 1953. [113] Szybalski, W., and Bryson, V., J. Bact., Balt. 64:489, 1952. [114] Weber, E. M., Luther, H. G., and Reynolds, W. M., Bull. World Health Org., N. Y. 6:149, 1952. [115] Knodt, C. B., Antibiotics and Chemotherapy 3:442, 1953. [116] Stokstad, E. L., Physiol. Rev. 34:25, 1954. [117] Braude, R., Kon, S. K., and Porter, J. W., Nutrit. Abstr., Aberdeen 23:473, 1953. [118] Jukes, T. H., and Williams, W. L., Pharmacol. Rev., Balt. 5:381, 1954. [119] Reid, J. T., Warner, R. G., and Loosli, J. K., J. Agr. Food Chem. 2:186, 1954. [120] Nickell, L. G., Antibiotics and Chemotherapy 3:449, 1953. [121] Havinga, E., Lynch, V., Morris, L., and Calvin, M., Rec. Trav. chim. 72:597, 1953. [122] Moffett, J. O., Colorado Agr. Exp. Sta. Tech. Bull. No. 53, April, 1954. [123] Tarr, H. L., Southcott, B. A., and Bissett, H. M., Food Technol. 6:363, 1952. [124] Finland, M., Grigsby, M. E., and Haight, T. H., Arch. Int. M. 93:23, 1954. [125] Davis, D. J., Pittman, M., Vogel, J. E., and Ottinger, B., Antibiotics and Chemotherapy 5:363, 1955. [126] Lynch, J. E., Holley, E. C., and Margison, J. E., *ibid* 5:508, 1955. [127] Loosli, C. G., Hamre, D., Ritter, G., and Berlin, B. S., "Antibiotics Annual, 1954-55," p 474, New York: Medical Encyclopedia, Inc. [128] Medical Research Council, Brit. M. J. 1:856, 1954. [129] Manjrekar, S. L., Ind. Vet. J. 31:417, 1955. [130] Wong, S. C., and James, C. G., Poultry Sc. 32:260, 1953. [131] Katz, E., J. Infect. Dis. 98:177, 1956. [132] Dutta, N. K., and Habbu, M. K., Brit. J. Pharm. 10:153, 1955. [133] Anwar, A. A., and Turner, T. B., "Antibiotics Annual, 1955-56," p 422, New York: Medical Encyclopedia, Inc. [134] McMahan, J. R., et al, *ibid*, p 727-739. [135] Peterson, E. H., Chalquest, R., and Luther, H. G., *ibid*, p 313. [136] Sugiura, K., Ann. N. York Acad. Sc. 63:962, 1956. [137] Sugiura, K., and Sugiura, M., Proc. Am. Ass. Cancer Res. 2:151, 1956 (abstr.). [138] Gold, H., Arch. Int. M. 96:387, 1955. [139] Cherry, J. K., Tr. R. Soc. Trop. M. Hyg., Lond. 49:563, 1955. [140] Braff, E., Perkins, H., Koch, R., Gara, G., and Stephens, W., Antibiotic M. 2:110, 1956. [141] Smith, H. W., J. Comp. Path., Lond. 65:309, 1955. [142] Fahey, J. E., and Crawley, J. F., Canad. J. Comp. M. 19:281, 1955. [143] Sieburth, J. McN., and Pomeroy, B. S., J. Am. Vet. M. Ass. 128:509, 1956. [144] Miller, J. G., Levy, H. E., Torbert, B. J., and Oglesby, W. T., Proc. 89th Annual Meet., 1952. Am. Vet. M. Ass. p 160, 1953. [145] Hawley, G. E., Sacchi, E. M., and Bunn, C., Vet. M., Chic. 51:56, 1956. [146] Venn, J. A., and Woodford, M. H., Vet. Rec., Lond. 68:132, 1956. [147] Schipper, I. A., Buchanan, M. L., and Eveleth, D. F., J. Am. Vet. M. Ass. 128:92, 1956. [148] Schneider, B. H., Spencer, G. R., and Ensminger, M. E., J. Animal Sc. 14:1140, 1955. [149] Lannek, N., and Börnfors, S., Vet. Rec., Lond. 68:53, 1956. [150] Ott, R. L., and Gorham, J. R., North Am. Vet. 36:574, 1955. [151] Riser, W. H., J. Am. Vet. M. Ass. 125:238, 1954. [152] De Armijo Valenzuela, M., and Wattenberg, J. M., Arch. inst. farmacol. exptl., Madrid 6:77, 1954; Chem. Abstr. 49:15070, 1955. [153] Hu, F., Livingood, C. S., and Hildebrand, J. F., J. Invest. Derm. 26:23, 1956. [154] Cosar, C., and Kolsky, M., C. rend. Soc. biol. 149:1163, 1955. [155] Am. M. Ass. Council on Pharmacy and Chemistry, J. Am. M. Ass. 159:1634, 1955. [156] Huang, T. C., Ulrich, H. E., and McCay, C. M., J. Nutrit. 54:621, 1954. [157] Axelrod, H. R., "Diseases of Tropical Fishes," New York: T. F. H. Publications, Inc., 1954. [158] Hagemann, G., Teillon, J., and Velu, H., Ann. pharm. fr. 12:210, 1954. [159] Steinhaus, E. A., and Bell, C. R., J. Econom. Entom. 46:582, 1953. [160] Liles, J. N., and Fisk, F. W., *ibid* 48:217, 1955. [161] Moffett, J. O., *ibid* 46:879, 1953. [162] Klemmer, H. W., Riker, A. J., and Allen, O. N., Phytopathology 45:618, 1955. [163] Winter, H. F., and Young, H. C., J. Agr. Food Chem. 3:623, 1955. [164] Dunegan, J. C., *ibid* 2:1020, 1954. [165] Kribben, F. J., Naturwissenschaften 41:144, 1954. [166] Barton, L. V., and MacNab, J., Contrib. Boyce Thompson Inst. 17:419, 1954. [167] Fowler, W., and Knight, G. H., Brit. J. Vener. Dis. 32:2, 1956.

233. ANTIBIOTICS PA-114

- [1] Celmer, W. D., and Sobin, B. A., "Antibiotics Annual, 1955-56," p 437, New York: Medical Encyclopedia, Inc.
 [2] English, A. R., McBride, T. J., and Van Halsema, G., *ibid*, p 442.

REFERENCES (Continued)

234. PALITANTIN

- [1] Birkinshaw, J. H., and Raistrick, H., *Biochem. J.*, Lond. 30:801, 1936. [2] Birkinshaw, J. H., *ibid* 51:271, 1952. [3] Curtis, P. J., and Duncanson, L. A., *ibid* 51:276, 1952.

235. PATULIN

- [1] Chain, E., Florey, H. W., Jennings, M. A., and Callow, D., *Brit. J. Exp. Path.*, 23:202, 1942. [2] Katzman, P. A., et al, *J. Biol. Chem.* 154:475, 1944. [3] Birkinshaw, J. H., and Michael, S. E., U. S. Pat. 2,417,584, 1947. [4] Lochhead, A. G., Chase, F. E., and Landerkin, G. B., *Canad. J. Res.* 24E:1, 1946. [5] Raistrick, H., et al, *Lancet*, Lond. 245:625, 1943. [6] Cavallito, C. J., and Bailey, J. H., *Science* 100:390, 1944. [7] Bergel, F., Morrison, A. L., Moss, A. R., and Rinderknecht, H., *J. Chem. Soc.* 1944:415. [8] Woodward, R. B., and Singh, G., *J. Am. Chem. Soc.* 71:758, 1949. [9] Waksman, S. A., Horning, E. S., and Spencer, E. L., *Science* 96:202, 1942. [10] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949. [11] Hopkins, W. A., *Lancet*, Lond. 245:631, 1943. [12] Waksman, S. A., Horning, E. S., and Spencer, E. L., *J. Bact.*, Balt. 45:233, 1943. [13] Umezawa, H., Mizukara, Y., Vekane, R., and Hagikara, M., *J. Penicillin*, Tokyo 1:6, 1947. [14] Herrick, J. A., *Proc. Soc. Exp. Biol.* 59:41, 1945. [15] Sanders, A. G., *Lancet*, Lond. 250:44, 1946. [16] Gilliver, K., *Ann. Botany*, London 10:271, 1946. [17] Vollmar, H., *Zschr. Hyg.* 127:316, 1947. [18] Stock, C. C., *Am. J. M.* 8:658, 1950. [19] Neter, E., *J. Infect. Dis.* 76:20, 1945. [20] Karow, E. O., and Foster, J. W., *Science* 99:265, 1944. [21] De Wit, J. J., "Modern Developments of Chemotherapy," Monographs on the Progress of Research in Holland, No. 4, New York: Elsevier Pub. Co., 1946. [22] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952. [23] Stansfield, J. M., Francis, A. E., and Stuart-Harris, C. H., *Lancet*, Lond. 247:370, 1944. [24] Timonin, M. I., *Sc. Agr.* 26:358, 1946. [25] Broom, W. A., et al, *Brit. J. Exp. Path.* 25:195, 1944. [26] Wang, F. H., *Bot. Bull. Acad. sinica* 2:265, 1948; abstr. in *Rev. Appl. Mycol.* 28:26, 1949. [27] Delaunay, A., Daniel, P., DeRoquefeuil, C., and Hénon, M., *Ann. Inst. Pasteur, Par.* 88:699, 1955. [28] Woodward, R. B., and Singh, G., *J. Am. Chem. Soc.* 72:1428, 5352, 1950. [29] Lettré, H., *Cancer Res. Sup.* 2:125, 1955. [30] Klemmer, H. W., Riker, A. J., and Allen, O. N., *Phytopathology* 45:618, 1955.

236. PENICILLIC ACID

- [1] Birkinshaw, J. H., Oxford, A. E., and Raistrick, H., *Biochem. J.*, Lond. 30:394, 1936. [2] Oxford, A. E., Raistrick, H., and Smith, G., *Chemistry and Industry* 61:22, 1942. [3] Raphael, R. A., *Nature* 160:261, 1947. [4] Ford, J. H., Johnson, A. R., and Hinman, J. W., *J. Am. Chem. Soc.* 72:4529, 1950. [5] Alsberg, C. L., and Black, O. F., U. S. Dept. Agr. Bur. Plant Indust. Bull. No. 270, 1913. [6] Karow, E. O., Woodruff, H. B., and Foster, J. W., *Arch. Biochem.*, N. Y. 5:279, 1944. [7] Burton, H. S., *Nature* 165:274, 1950. [8] Gilliver, K., *Ann. Botany*, Lond. 10:271, 1946. [9] Murnaghan, M. F., *J. Pharm. Exp. Ther.* 88:119, 1946.

237. PENICILLINS

- [1] Fleming, A., *Brit. J. Exp. Path.* 10:226, 1929. [2] Boxer, G. E., and Everett, P. M., *Anal. Chem.* 21:670, 1949. [3] Alicino, J. F., *Indust. Engin. Chem. (Anal. Ed.)* 18:619, 1946. [4] Royce, A., Bowler, C., and Sykes, G., *J. Pharm.*, Lond. 4:904, 1952. [5] Parker, G., Cox, R. J., and Richards, D., *ibid* 7:683, 1955. [6] Goodey, R., Reed, K. N., and Stephens, J., *ibid* 7:692, 1955. [7] Wright, W. W., Kirshbaum, A., Arret, B., Putnam, L. E., and Welch, H., *Antibiotic M.* 1:490, 1945.

General References

Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949. Clarke, H. T., Johnson, J. R., and Robinson, R., "The Chemistry of Penicillin," Princeton: Princeton Univ. Press, 1949. Council of the Pharmaceutical Soc. of Gt. Britain, "Antibiotics, a Survey of Their Properties and Uses," London: Pharmaceutical Press, 1952. Florey, M. E., "The Clinical Application of Antibiotics; Pencillin," London: Oxford Univ. Press, 1952. Fleming, A., "Penicillin, its Practical Application," Philadelphia: P. Blakiston and Sons, 1946. Welch, H., et al, "Principles and Practice of Antibiotic Therapy," New York: Medical Encyclopedia, Inc., 1954. Am. M. Ass. Council on Pharmacy and Chemistry, "New and Nonofficial Remedies," Philadelphia: J. B. Lippincott, 1956. Valentine, F. C., and Shooter, R. A., "Recent Advances in Chemotherapy, vol. III, Antibiotics," New York: Blakiston Co., 1954. Smith, L. W., and Walker, A. D., "Pencillin Decade: 1941-51, Sensitizations and Toxicities," Washington: Arundel Press, Inc., 1951. Finlan, M., *N. England J. M.* 353:909, 1955. Cooper, P. D., *Bact. Rev.*, Balt. 20:28, 1956. Welch, H., *Antibiotic M.* 2:11, 1956.

238. PHAEOFACIN

- [1] Maeda, K., Okami, Y., Taya, O., and Umezawa, H., *J. Antibiot.*, Tokyo 5:465, 1952. [2] Maeda, K., et al, *Jap. J. M. Sc. Biol.* 5:327, 1952.

239. PHAGOLESSIN A-58

- [1] Asheshov, I. N., Strelitz, F., and Hall, E. A., *Antibiotics and Chemotherapy* 2:366, 1952. [2] Asheshov, I. N., Strelitz, F., Hall, E. A., and Flon, H., *ibid* 4:380, 1954. [3] Levaditi, C., Gueli, A., and Vaisman, A., *Rev. immunol.* 17:21, 1953.

240. PHALAMYCIN

- [1] Brown, R., and Hazen, E. L., *Antibiotics and Chemotherapy* 3:818, 1953.

241. PHENICIN

- [1] Burton, H. S., *Brit. J. Exp. Path.* 30:151, 1949. [2] Posternak, T., *Helvet. chim. acta* 21:1326, 1938.
 [3] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949. [4] Raistrick, H., *Annual Rev. Biochem.* 9:571, 1940.

242. PHTHIOLCOL

- [1] Tarbell, D. S., Scott, G. P., and Kemp, A. D., *J. Am. Chem. Soc.* 72:379, 1950. [2] Lichstein, H. C., and Van de Sand, V. F., *J. Bact., Balt.* 52:145, 1946.

243. PHTHIOMYCIN

- [1] Maeda, K., Okami, Y., Utahara, R., Kosaka, H., and Umezawa, H., *J. Antibiot., Tokyo, Ser. A* 6:183, 1953.
 [2] Miyamoto, V., and Maeda, K., *ibid* 7:17, 1954.

244. PICROMYCIN

- [1] Brockmann, H., and Henkel, W., *Chem. Ber.* 84:284, 1951. [2] Brockmann, H., and Henkel, W., *Naturwissenschaften* 37:138, 1950. [3] Brockmann, H., and Bohne, A., *U. S. Pat.* 2,693,433, 1954. [4] Brodersen, R., Bunch-Christensen, K., and Tybring, L., *Acta pharm. tox., Kbh.* 9:255, 1953. [5] Brockmann, H., Genth, H., and Strufe, R., *Chem. Ber.* 85:426, 1952. [6] Suhren, O., *Med. Klin., Berl.* 46:722, 1951. [7] Brockmann, H., and Oster, R., *Naturwissenschaften* 42:154, 1955. [8] Anliker, R., and Gubler, K., *Helvet. chim. acta* 40:119, 1957.

245. PLEOCIDIN

- [1] Charney, J., Roberts, W. S., and Fisher, W. P., *Antibiotics and Chemotherapy* 2:307, 1952. [2] Fisher, W. P., and Charney, J., *ibid* 2:311, 1952. [3] Packchanian, A., *Am. J. Trop. M. Hyg.* 2:243, 1953. [4] Newburgh, R. W., and Cheldelin, V. H., *Plant Disease Repr.* 39:684, 1955. [5] Gray, R. A., *Sup. to Proc. of 6th Plant Physiol. Meet., Plant Physiol.* 30:vi, 1955.

246. PLEOMYCIN

- [1] Machlowitz, R. A., Charney, J., Tytell, A. A., and Fisher, W. P., "Antibiotics Annual, 1954-55," p 806, New York: Medical Encyclopedia, Inc.

247. PLEUROMUTILIN

- [1] Anchel, M., *J. Biol. Chem.* 199:133, 1952. [2] Kavanagh, F., Hervey, A., and Robbins, W. J., *Proc. Nat. Acad. Sc. U. S.* 37:570, 1951. [3] Kavanagh, F., Hervey, A., and Robbins, W. J., *ibid* 38:555, 1952. [4] Asheshov, I. N., Strelitz, F., Hall, E. A., and Flon, H., *Antibiotics and Chemotherapy* 4:380, 1954. [5] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952.

248. PLEUROTIN

- [1] Robbins, W. J., Kavanagh, F., and Hervey, A., *Proc. Nat. Acad. Sc. U. S.* 33:171, 1947. [2] Kavanagh, F., *Arch. Biochem., N. Y.* 15:95, 1947. [3] Kavanagh, F., *J. Bact., Balt.* 54:761, 1947. [4] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952.

249. POLYMYXINS

- [1] Ainsworth, G. C., Brown, A. M., and Brownlee, G., *Nature* 160:263, 1947. [2] Brownlee, G., *Ann. N. York Acad. Sc.* 51:875, 1949. [3] Porter, J. N., Broschard, R., Krupka, G., Little, P., and Zellat, J. S., *ibid* 51:857, 1949. [4] Catch, J. R., Jones, T. S., and Wilkinson, S., *ibid* 51:917, 1949. [5] Bell, P. H., et al, *ibid* 51:897, 1949. [6] Regna, P. P., Solomons, I. A., Forscher, B. K., and Timreck, A. E., *J. Clin. Invest.* 28:1022, 1949. [7] Hausmann, W., and Craig, L. C., *J. Am. Chem. Soc.* 76:4892, 1954. [8] Few, A. V., and Schulman, J. H., *Biochem. J., Lond.* 54:171, 1953. [9] Benedict, R. G., and Langlykke, A. F., *J. Bact., Balt.* 54:24, 1947. [10] Stansly, P. G., Shepherd, R. G., and White, H. J., *Bull. Johns Hopkins Hosp.* 81:43, 1947. [11] White, H. J., Alverson, C. M., Baker, M. J., and Jackson, E. R., *Ann. N. York Acad. Sc.* 51:879, 1949. [12] Bliss, E. A., Chandler, C. A., and Schoenbach, E. B., *ibid* 51:944, 1949. [13] Brownlee, G., Bushby, S. R., and Short, E. I., *ibid* 51:891, 1949. [14] Finland, M., and Wilcox, C., *Am. J. Clin. Path.* 20:335, 1950. [15] Frank, P. F., Wilcox, C., and Finland, M., *J. Laborat. Clin. M.* 35:188, 1950. [16] Wells, E. B., Shih-Man, C., Jackson, G. G., and Finland, M., *J. Pediat., St. Louis* 36:752, 1950. [17] Gocke, T. M., Wilcox, C., and Finland, M., *Am. J. Syph.* 34:1, 1950. [18] Frank, P. F., Wilcox, C., and Finland, M., *J. Laborat. Clin. M.* 35:205, 1950. [19] Wright, S. S., Potee, K. G., and Finland, M., *Am. J. Clin. Path.* 24:1121, 1954. [20] Florestano, H. J., and Bahler, M. E., *Proc. Soc. Exp. Biol.* 79:141, 1952. [21] Brownlee, G., and Bushby, S. R., *Lancet, Lond.* 254:127, 1948. [22] Larson, C. L., Carle, B. N., and Verder, A. E., *Ann. N. York Acad. Sc.* 51:982, 1949. [23] Brownlee, G., Bushby, S. R., and Short, E. I., *Brit. J. Pharm.* 7:170, 1952. [24] Brownlee, G., Bushby, S. R., and Short, E. I., *Ann. N. York Acad. Sc.* 51:952, 1949. [25] Schoenbach, E. B., Bryer, M. S., and Long, P. H., *ibid* 51:987, 1949. [26] Brownlee, G., *ibid* 51:998, 1949.

REFERENCES (Continued)

249. POLYMYXINS (Concluded)

- [27] Hsiang, C. M., and Packchianian, A., *Texas Repts. Biol. M.* 9:34, 1951. [28] Williams, R. K., Hench, M. E., and Guerry, D., *Am. J. Ophth.* 37:538, 1954. [29] Packchianian, A., *Am. J. Trop. M. Hyg.* 2:243, 1953. [30] Seneca, H., and Ides, D., *ibid* 2:1045, 1953. [31] Welch, H., et al, "Principles and Practice of Antibiotic Therapy," New York: Medical Encyclopedia, Inc., 1954. [32] Jawetz, E., *Arch. Int. M.* 89:90, 1952. [33] Yow, E. M., and Moyer, J. H., *ibid* 92:248, 1953. [34] Meyer, K. F., Quan, S. F., McCrumb, F. R., and Larson, A., *Ann. N. York Acad. Sc.* 55:1228, 1952. [35] Ainslee, D., *Brit. J. Ophth.* 37:336, 1953. [36] Pulaski, E. J., and Rosenberg, M. L., *J. Urol., Balt.* 62:564, 1949. [37] Kagan, B. M., Krevsky, D., Milzer, A., and Locke, M., *J. Laborat. Clin. M.* 37:402, 1951. [38] Lieberman, D., and Jawetz, E., *Pediatrics*, Springf. 8:249, 1951. [39] Schoenbach, E. B., *J. Mount Sinai Hosp. N. York* 16:71, 1949. [40] Trapnell, D. H., *Lancet*, Lond. 265:759, 1954. [41] Appel, B., *Antibiotics and Chemotherapy* 3:1258, 1953. [42] Bryer, M. S., Schoenbach, E. B., and Bliss, E. A., *Ann. N. York Acad. Sc.* 51:935, 1949. [43] Pulaski, E. J., Baker, H. J., Rosenberg, M. L., and Connell, J. F., Jr., *J. Clin. Invest.* 28:1028, 1949. [44] Latterade, C., and Macheboeuf, M., *Ann. Inst. Pasteur, Par.* 78:753, 1950. [45] Cohen, S., Purdy, C. V., and Kushnick, J. B., *Antibiotics and Chemotherapy* 4:18, 1954. [46] Few, A. V., and Shulman, J. H., *J. Gen. Microb., Lond.* 9:454, 1953. [47] Newton, B. A., *ibid* 10:491, 1954. [48] Haas, G. J., and Sevag, M. G., *Arch. Biochem. and Biophys* 43:11, 1953. [49] Strandkov, F. B., and Bockelmann, J. B., *J. Agr. Food Chem.* 1:1219, 1953. [50] Drey, R. E., Foster, G. E., and Stewart, G. A., *J. Pharm., Lond.* 7:706, 1955. [51] Bushby, S. R., and Green, A. F., *Brit. J. Pharm.* 10:215, 1955. [52] Arret, B., and Kirshbaum, A., *Antibiotics and Chemotherapy* 6:95, 1956. [53] Simon, J., *Am. J. Vet. Res.* 16:394, 1955. [54] Metzger, J. F., Fusillo, M. H., and Kuhns, D. M., *Antibiotics and Chemotherapy* 2:227, 1952. [55] Norton, S., and DeBeer, E. J., *Arch. internat. pharm. dyn., Par.* 102:352, 1955. [56] Short, E. I., *Brit. J. Pharm.* 7:248, 1952. [57] Am. M. Ass. Council on Pharmacy and Chemistry, *J. Am. M. Ass.* 159:1634, 1955. [58] Rhodes, R. E., Vila, O. A., and Ferlauto, R. J., *Antibiotics and Chemotherapy* 3:509, 1953. [59] Newton, B. A., *Nature* 172:160, 1953. [60] Steinhau, E. A., and Bell, C. R., *J. Econom. Entom.* 46:582, 1953. [61] Barton, L. V., and MacNab, J., *Contrib. Boyce Thompson Inst.* 17:419, 1954. [62] Norman, A. G., *Arch. Biochem. and Biophys.* 58:461, 1955.

250. POLYPEPTIN

- [1] Howell, S. F., *Fed. Proc.* 8:208, 1949. [2] Howell, S. F., *J. Biol. Chem.* 186:863, 1950. [3] Hausmann, W., and Craig, L. C., *ibid* 198:405, 1952. [4] McLeod, C., *J. Bact., Balt.* 56:749, 1948.

251. POLYPORENIC ACID C

- [1] Birkinshaw, J. H., Morgan, E. N., and Findlay, W. P., *Biochem. J., Lond.* 50:509, 1952. [2] Marcus, S., *ibid* 50:516, 1952. [3] Bowers, A., Halsall, T. G., Jones, E. R., and Lemin, A. J., *J. Chem. Soc.* 1953:2548. [4] Bowers, A., Halsall, T. G., and Sayer, G. C., *ibid* 1954:3070.

252. POLYPORIN

- [1] Bose, S. R., *Nature* 158:292, 1946. [2] Bose, S. R., *Bull. Bot. Soc. Bengal* 1:71, 1947; *Biol. Abstr., Balt.* 24:19543, 1950.

253. PRIMYCIN

- [1] Vályi-Nagy, T., Úri, J., and Szilágyi, I., *Nature* 174:1105, 1954.

254. PROACTINOMYCINS

- [1] Gardner, A. D., and Chain, E., *Brit. J. Exp. Path.* 23:123, 1942. [2] Marston, R. Q., *ibid* 30:398, 1949. [3] Florey, H. W., Jennings, M. A., and Sanders, A. G., *ibid* 26:337, 1945.

255. PRODIGIOSIN

- [1] Hubbard, R., and Rimington, C., *Biochem. J., Lond.* 46:220, 1950. [2] Wrede, F., and Hettche, O., *Chem. Ber.* 62:2678, 1929. [3] Felsenfeld, O., Mast, G. W., and Ishihara, J., *J. Parasit., Lanc. Sup.* 36:25, 1950. [4] Balamuth, W., and Brent, M. M., *Proc. Soc. Exp. Biol.* 75:374, 1950. [5] Lack, A., *ibid* 72:656, 1949. [6] Mose, J. R., and Pötsch, A., *Arch. Hyg., Münch.* 138:52, 1954. [7] Balamuth, W., *Ann. N. York Acad. Sc.* 55:1093, 1952. [8] Wier, R., Egberg, R. O., Lack, A. R., and Leiby, G. M., *Am. J. M. Sc.* 224:70, 1952. [9] Hickey, R. J., *Arch. Biochem. and Biophys.* 46:331, 1953. [10] Morgan, E. N., and Tanner, E. M., *J. Chem. Soc.* 1955:3305.

256. PUBERULIC ACID

- [1] Birkinshaw, J. H., and Raistrick, H., *Biochem. J., Lond.* 26:441, 1932. [2] Oxford, A. E., Raistrick, H., and Smith, G., *Chemistry and Industry* 61:485, 1942. [3] Johnson, A. W., Sheppard, N., and Todd, A. R., *J. Chem. Soc.* 1951:1139. [4] Corbett, R. E., Johnson, A. W., and Todd, A. R., *ibid* 1950:6. [5] Aulin-Erdtman, G., *Acta chem. scand.* 5:301, 1951. [6] Corbett, R. E., Hassal, C. H., Johnson, A. W., and Todd, A. R., *J. Chem. Soc.* 1950:1.

REFERENCES (Continued)

257. PUBERULONIC ACID

- [1] Birkinshaw, J. H., and Raistrick, H., *Biochem. J.*, Lond. 26:441, 1932. [2] Oxford, A. E., Raistrick, H., and Smith, G., *Chemistry and Industry* 61:485, 1942. [3] Johnson, A. W., Sheppard, N., and Todd, A. R., *J. Chem. Soc.* 1951:1139. [4] Corbett, R. E., Johnson, A. W., and Todd, A. R., *ibid* 1950:6. [5] Aulin Erdtman, G., *Acta chem. scand.* 5:301, 1951. [6] Corbett, R. E., Hassall, C. H., Johnson, A. W., and Todd, A. R., *J. Chem. Soc.* 1950:1.

258. PUMILIN

- [1] Bhate, D. S., *Nature* 175:816, 1955.

259. PUROMYCIN

- [1] Porter, J. N., et al, *Antibiotics and Chemotherapy* 2:409, 1952. [2] Waller, C. W., Fryth, P. W., Hutchings, B. L., and Williams, J. H., *J. Am. Chem. Soc.* 75:2025, 1953. [3] Baker, B. R., Schaub, R. E., Joseph, J. P., and Williams, J. H., *ibid* 77:12, 1955. [4] Lowery, J. A., and Porter, J. N., unpublished. [5] Hewitt, R., Wallace, W. S., Gumble, A. R., Gill, E. R., and Williams, J. H., *Am. J. Trop. M. Hyg.* 2:254, 1953. [6] Trincão, C., Franco, A., Nogueira, A., Pinto, A. R., and Mühlpfordt, H., *ibid* 4:13, 1955. [7] Bortle, L., and Oleson, J. J., "Antibiotics Annual, 1954-55," p 770, New York: Medical Encyclopedia, Inc. [8] Wright, J. C., Dolgop, V. B., Logan, M., Prigot, A., and Wright, L. T., *Arch. Int. M.* 96:61, 1955. [9] Eichorn, P. A., Huffman, K. V., Oleson, J. J., Halliday, S. L., and Williams, J. H., *Ann. N. York Acad. Sc.* 58:1172, 1954. [10] Pizzi, T. P., Prager, S., and Knerim, F. T., *Bol. inform. parasit. chile.* 8:77, 1953. [11] Tobie, E. J., *Am. J. Trop. M. Hyg.* 3:852, 1954. [12] Hewitt, R. I., Gumble, A. R., Wallace, W. S., and Williams, J. H., *Antibiotics and Chemotherapy* 5:139, 1955. [13] Taylor, D. J., Bond, H. W., and Sherman, J. F., "Antibiotics Annual, 1954-55," p 745, New York: Medical Encyclopedia, Inc. [14] Bond, H. W., Sherman, J. F., and Taylor, D. J., *ibid*, p 751. [15] Eyles, D. E., and Coleman, N., *Antibiotics and Chemotherapy* 4:649, 1954. [16] Christen, R. A., and Thiermann, E. I., *Bol. inform. parasit. chile.* 8:49, 1953. [17] Gumble, A. R., Hewitt, R. I., Taylor, L. H., Jr., and Wallace, W. S., "Antibiotics Annual, 1955-56," p 260, New York: Medical Encyclopedia, Inc. [18] Troy, W., et al, "Antibiotics Annual, 1953-54," p 186, New York: Medical Encyclopedia, Inc. [19] Bennett, P. L., Halliday, S. L., Oleson, J. J., and Williams, J. H., "Antibiotics Annual, 1954-55," p 766, New York: Medical Encyclopedia, Inc. [20] Sherman, J. F., Taylor, D. J., and Bond, H. W., *ibid*, p 757. [21] Agosin, M., and Von Brand, T., *Antibiotics and Chemotherapy* 4:624, 1954. [22] Oleson, J. J., Bennett, P. L., Halliday, S. L., and Williams, J. H., *Acta Unio Intern. contra Cancrum* 11:161, 1955. [23] MacKneson, R. G., and Ormsby, H. L., *Am. J. Ophth.* 39:689, 1955. [24] Sonntag, R., and Klotzel, J., *Fol. clin. biol.*, S. Paulo 20:133, 1953. [25] Trincão, C., Nogueira, A., and Franco, A., *Antibiotics and Chemotherapy* 5:505, 1955. [26] Faiguenbaum, J., and Alba, M., *Bol. inform. parasit. chile.* 9:94, 1954. [27] Alves Meira, J., Amato Neto, V., DeAguiar Tartari, J. T., and Sonntag, R., *Rev. brasil. med.* 11:829, 1954. [28] Wilmot, A. J., "Antibiotics Annual, 1955-56," p 319, New York: Medical Encyclopedia, Inc. [29] Trincão, C., Franco, A., Nogueira, A., Pinto, A. R., and Mühlpfordt, H., *ibid*, p 596. [30] Sherman, J. F., *Antibiotics and Chemotherapy* 6:116, 1956. [31] Taylor, A. E., and Godfrey, D. G., *Brit. J. Pharm.* 11:71, 1956. [32] Tarnowski, G. S., *Cancer Res. Sup.* 2:333, 1955. [33] Farber, S., *Am. J. Path.* 31:582, 1955 (abstr.). [34] Echeverria Alvarez, E., and Leon Moreno, A., *Antibiotic M.* 2:327, 1956.

260. PYO COMPOUNDS

- [1] Hays, E. E., et al, *J. Biol. Chem.* 159:725, 1945. [2] Wells, I. C., *ibid* 196:331, 1952. [3] Wells, I. C., Hays, E. E., Thayer, S. A., and Doisy, E. A., *ibid* 196:341, 1952. [4] Wells, I. C., et al, *ibid* 167:53, 1947.

261. PYOCYANINE

- [1] Richter, V., "The Chemistry of the Carbon Compounds" (translated by Taylor, T. W., and Millidge, A. F.). New York: Nordemann, 1939. [2] McCombie, H., and Scarborough, H. A., *J. Chem. Soc.* 1923:3279. [3] Stokes, J. L., Peck, R. L., and Woodward, C. R., Jr., *Proc. Soc. Exp. Biol.* 51:126, 1946. [4] Schoental, R., *Brit. J. Exp. Path.* 22:137, 1941.

262. PYOLIPIC ACID

- [1] Bergstrom, S., Theorell, H., and Davide, H., *Arch. Biochem.*, N. Y. 10:165, 1946. [2] Davide, H., *Nord. med.* 32:2534, 1946.

263. PYRIDOMYCIN

- [1] Maeda, K., Kosaka, H., Okami, Y., and Umezawa, H., *J. Antibiot.*, Tokyo, Ser. A 6:140, 1953. [2] Okami, Y., Maeda, K., and Umezawa, H., *ibid* 7:55, 1954. [3] Kuroya, M., et al, *ibid* 7:58, 1954. [4] Nitta, K., Takeuchi, T., Yamamoto, T., and Umezawa, H., *ibid* 8:120, 1955.

264. QUADRIFIDINS

- [1] Doery, H. M., Gardner, J. F., Burton, H. S., and Abraham, E. P., *Antibiotics and Chemotherapy* 1:409, 1951.

REFERENCES (Continued)

265. QUATRIMYCIN

[1] Doerschuk, A. P., Bitler, B. A., and McCormick, J. R., *J. Am. Chem. Soc.* 77:4687, 1955. [2] Stephens, C. R., et al, *ibid* 78:1515, 1956. [3] McCormick, J. R., et al, *ibid* 78:3547, 1956.

266. RACTINOMYCINS

[1] Utahara, R., et al, *J. Antibiot., Tokyo, Ser. A* 8:132, 1955.

267. RAISNOMYCIN

[1] Barr, F. S., and Carman, P. E., *Antibiotics and Chemotherapy* 6:286, 1956.

268. RAMNACIN

[1] Ahmad, K., and Islam, M. F., *Nature* 176:646, 1955.

269. RESISTOMYCIN

[1] Brockmann, H., and Schmidt-Kastner, G., *Naturwissenschaften* 38:479, 1951. [2] Brockmann, H., and Schmidt-Kastner, G., *Chem. Ber.* 87:1460, 1954.

270. RHODOCIDIN

[1] Charney, J., Machlowitz, R. A., Roberts, W. S., and Fisher, W. P., *Antibiotics and Chemotherapy* 3:788, 1953.

271. RHODOMYCETIN

[1] Shockman, G., and Waksman, S. A., *Antibiotics and Chemotherapy* 1:68, 1951.

272. RHODOMYCINS

[1] Brockmann, H., and Bauer, K., *Naturwissenschaften* 37:492, 1950. [2] Brockmann, H., Bauer, K., and Borchers, I., *Chem. Ber.* 84:700, 1951. [3] Brockmann, H., and Borchers, I., *ibid* 86:261, 1953. [4] Brockmann, H., and Spohler, E., *Naturwissenschaften* 42:154, 1955. [5] Brockmann, H., and Patt, P., *Chem. Ber.* 88:1455, 1955.

273. RIMOCIDIN

[1] Davisson, J. W., Tanner, F. W., Jr., Finlay, A. C., and Solomons, I. A., *Antibiotics and Chemotherapy* 1:289, 1951. [2] Seneca, H., Kane, J. H., and Rockenbach, J., *ibid* 2:435, 1953. [3] Seneca, H., and Ides, D., *Am. J. Trop. M. Hyg.* 2:1045, 1953. [4] Packchianian, A., *ibid* 2:243, 1953. [5] De Mello, G. C., and Kiser, J. S., "Antibiotics Annual, 1954-55," p 678, New York: Medical Encyclopedia, Inc. [6] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952. [7] Seneca, H., and Ides, D., *J. Urol., Balt.* 70:947, 1953. [8] Weber, E. M., Luther, H. G., and Reynolds, W. M., *Bull. World Health Org., N. Y.* 6:149, 1952. [9] Schendel, H. E., and Johnson, B. C., *J. Animal Sc.* 12:84, 88, 1953. [10] Dekker, J., *Nature* 175:689, 1955. [11] Barton, L. V., and MacNab, J., *Contrib. Boyce Thompson Inst.* 17:419, 1954. [12] Melnick, J. L., *Ann. N. York Acad. Sc.* 61:754, 1955. [13] Seneca, H., and Bergendahl, E., *Antibiotics and Chemotherapy* 5:737, 1955.

274. ROSEIN II

[1] Freeman, G. G., Morrison, R. I., and Michael, S. E., *Biochem. J., Lond.* 45:191, 1949.

275. ROSEOMYCIN

[1] Ishida, K., *J. Antibiot., Tokyo* 3:845, 1950. [2] Nagao, I., *ibid, Sup. C* 3:20, 1950. [3] Nagao, I., *J. Antibiot., Tokyo* 4:24, 1951. [4] Miyamori, A., *ibid* 5:163, 1952. [5] Takahashi, T., Matsunaga, M., and Uematsu, K., *ibid, Ser. B* 6:452, 1953.

276. ROSEOTHRICIN

[1] Nakanishi, K., Ito, T., Hirata, Y., *J. Am. Chem. Soc.* 76:2845, 1954. [2] Hosoya, S., et al, *Jap. J. Exp. M.* 20:481, 1950.

277. ROTAVENTIN

[1] Benedict, R. G., *Botan. Rev.* 19:229, 1953 (quoted from Hosoya, et al, *Jap. J. Exp. M.* 21:279, 1951; *ibid* 22:23, 1952). [2] Hosoya, S., Komatsu, N., and Soeda, M., *J. Antibiot., Tokyo* 5:451, 1952. [3] Hosoya, S., et al, *ibid, Ser. A* 6:92, 1953.

REFERENCES (Continued)

278. RUBIDIN

- [1] Banerjee, A. K., Sen, G. P., and Nandi, P., "Antibiotics Annual, 1955-56," p 640, New York: Medical Encyclopedia, Inc.

279. RUBROGLIOCLADIN

- [1] Brian, P. W., Curtis, P. J., Howland, S. R., Jefferys, E. G., and Raudnitz, H., *Experientia*, Basel 7:266, 1951.
[2] Vischer, E. B., *J. Chem. Soc.* 1953:815.

280. RUBROMYCIN

- [1] Brockmann, H., and Renneberg, K., *Naturwissenschaften* 40:59, 1953.

281. RUGULOSIN

- [1] Breen, J., Dacre, J. C., Raistrick, H., and Smith, G., *Biochem. J.*, Lond. 60:618, 1955.

282. RUTICIN

- [1] Fisher, W. P., Charney, J., Machlowitz, R. A., Blair, J. E., and Tytell, A. A., "Antibiotics Annual, 1953-54," p 174, New York: Medical Encyclopedia, Inc.

283. SARCIDIN

- [1] Takeuchi, T., Nitta, K., and Umezawa, H., *J. Antibiot.*, Tokyo, Ser. A 6:31, 1953.

284. SARKOMYCIN

- [1] Umezawa, H., et al, *Antibiotics and Chemotherapy* 4:514, 1954. [2] Umezawa, H., Takeuchi, T., Nitta, K., and Okami, Y., *J. Antibiot.*, Tokyo, Ser. A 6:147, 1953. [3] Takeuchi, T., *ibid* 7:37, 1954. [4] Ishiyama, S., *ibid* 7:82, 1954. [5] Ishiyama, S. et al, *ibid* 8:22, 1955. [6] Hooper, I. R., et al, *Antibiotics and Chemotherapy* 5:585, 1955. [7] Ishiyama, S., Hirayama, H., Takamura, M., and Ohashi, T., *J. Antibiot.*, Tokyo, Ser. A 8:57, 1955. [8] Takeuchi, T., Nitta, K., Yamamoto, T., and Umezawa, H., *ibid* 8:110, 1955. [9] Fujii, R., Onizawa, J., Shima, N., Okuyama, K., and Okamoto, Y., *ibid* 8:83, 1955. [10] Nakatsuka, M., et al, *ibid*, Ser. B 7:343, 1955. [11] Sugiura, K., *Ann. N. York Acad. Sc.* 63:962, 1956. [12] Sugiura, K., and Schmid, M. S., *Proc. Am. Ass. Cancer Res.* 2:151, 1956 (abstr.). [13] Karnofsky, D. A. (cited by Sugiura, K.), *Ann. N. Y. Acad. Sc.* 63:962, 1956. [14] Oboshi, S., Aoki, K., and Sakuraba, T., *J. Antibiot.*, Tokyo, Ser. A 8:153, 1955. [15] Sagawa, E., Asari, S., Miyake, M., and Shigeta, Y., *ibid* 8:168, 1955. [16] Magill, G. B., et al, *Cancer Res.* 16:960, 1956.

285. SELIGOCIDIN

- [1] Nakamura, S., Maeda, K., Okami, Y., and Umezawa, H., *J. Antibiot.*, Tokyo, Ser. A 7:57, 1954.

286. SIMPLEXIN

- [1] Cordon, T. C., and Haenseler, C. M., *Soil Sc.* 47:207, 1939. [2] Katznelson, H., *Canad. J. Res.* 20:169, 1942.
[3] Foster, J. W., and Woodruff, H. B., *J. Bact.*, Balt. 51:363, 1946.

287. SISTOMYCOSIN

- [1] *Brit. Pat.* 712,547, 1954.

288. SPINULOSIN

- [1] Birkinshaw, J. H., and Raistrick, H., *Trans. Roy. Soc., London B* 220:245, 1931. [2] Anslow, W. K., and Raistrick, H., *Biochem. J.*, Lond. 32:687, 1938. [3] Anslow, W. K., and Raistrick, H., *ibid* 32:803, 1938. [4] Anslow, W. K., Raistrick, H., *ibid* 32:2288, 1938. [5] Heatley, N. G., and Philpot, F. J., *J. Gen. Microb.*, Lond. 1:232, 1947. [6] Waksman, S. A., and Geiger, W. B., *J. Bact.*, Balt. 47:391, 1944. [7] Kavanagh, F., *ibid* 54:761, 1947. [8] Oxford, A. E., and Raistrick, H., *Chemistry and Industry* 61:128, 1942.

289. SPIRAMYCIN

- [1] Pinnert-Sindico, S., Ninet, L., Preud'homme, J., and Cosar, C., "Antibiotics Annual, 1954-55," p724, New York: Medical Encyclopedia, Inc. [2] Chabbert, Y., *Ann. Inst. Pasteur, Par.* 89:434, 1955. [3] Hudson, D. G., Yoshihara, G. M., and Kirby, W. M., *Arch. Int. M.* 97:57, 1956. [4] Bogacz, J., *Bull. Soc. path. exot.*, Par. 47:903, 1954; *Trop. Dis. Bull.*, Lond. 53:103, 1956 (abstr.). [5] Ravina, A., Pestel, M., Eloy, P., Duchesnay, G., Albouy, R., and Rey, M., "Antibiotics Annual, 1955-56," p 223, New York: Medical Encyclopedia, Inc. [6] Lepper, M. H., Spies, H. W., Kellow, W. F., Rosenthal, I. M., and Plaut, S., *ibid*, p 658.

REFERENCES (Continued)

290. STREPTOCARDIN

[1] Fisher, W. P., Machlowitz, R. A., Tytell, A. A., and Charney, J., "Antibiotics Annual, 1953-55," p 177, New York: Medical Encyclopedia, Inc.

291. STREPTOCIN

[1] Waksman, S. A., Harris, D. A., Kupferberg, A. B., Singher, H. O., and Styles, H., Proc. Soc. Exp. Biol. 70:308, 1949. [2] Kupferberg, A. B., Styles, H., Singher, H. O., and Waksman, S. A., J. Bact., Balt. 59:523, 1950.

292. STREPTOGRAMIN

[1] Charney, J., Fisher, W. P., Curran, C., Machlowitz, R. A., and Tytell, A. A., "Antibiotics Annual, 1953-54," p 171, New York: Medical Encyclopedia, Inc. [2] Charney, J., Fisher, W. P., Curran, C., Machlowitz, R. A., and Tytell, A. A., Antibiotics and Chemotherapy 3:1283, 1953. [3] Verwey, W. F., West, M. K., and Miller, A. K., Soc. Am. Bact. Bact. Proc., p 79, 1954.

293. STREPTOGRAMIN-LIKE ANTIBIOTIC

[1] De Somer, P., and Van Dijck, P., Antibiotics and Chemotherapy 5:632, 1955.

294. STREPTOLINS

[1] Rivett, R. W., and Peterson, W. H., J. Am. Chem. Soc. 69:3006, 1947. [2] Larson, L. M., Sternberg, H., and Peterson, W. H., *ibid* 75:2036, 1953. [3] Smisson, E. E., Sharpe, R. W., Aycock, B. F., Van Tamelen, E. E., and Peterson, W. H., *ibid* 75:2029, 1953. [4] Van Tamelen, E. E., and Smisson, E. E., *ibid* 75:2031, 1953. [5] Pagano, J. F., Weinstein, M. J., and Donovick, R., Proc. Exp. Biol. 79:359, 1952. [6] Van Tamelen, E. E., et al, J. Am. Chem. Soc. 78:4817, 1956.

295. STREPTOLYDIGIN

[1] De Boer, C., Dietz, A., Silver, W. S., and Savage, G. M., "Antibiotics Annual, 1955-56," p 886, New York: Medical Encyclopedia, Inc. [2] Eble, T. E., et al, *ibid*, p 893. [3] Lewis, C., Wilkins, J. R., Schwartz, D. F., and Nikitas, C. T., *ibid*, p 897.

296. STREPTOMYCIN and DIHYDROSTREPTOMYCIN

[1] Regna, P. P., Wassele, L. A., and Solomons, I. A., J. Biol. Chem. 165:631, 1946. [2] Kuehl, F. A., Jr., Peck, R. L., Hoffhine, C. E., Jr., and Folkers, K., J. Am. Chem. Soc. 70:2325, 1948. [3] Waksman, S. A., "Streptomycin, Its Nature and Practical Application," Baltimore: Williams and Wilkins Co., 1949. [4] Heuser, L. J., Dolliver, M. A., and Stiller, E. T., J. Am. Chem. Soc. 70:2833, 1948. [5] Grundy, W. E., et al, Arch. Biochem., N. Y. 28:150, 1950. [6] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949. [7] Fried, J., and Wintersteiner, O., Science 101:613, 1945. [8] Kuehl, F. A., Jr., et al, *ibid* 102:34, 1945. [9] Ashton, G. C., Foster, M. C., and Fotherley, M., Analyst 78:581, 1953. [10] Schatz, A., Bugie, E., and Waksman, S. A., Proc. Soc. Exp. Biol. 55:66, 1944. [11] Johnstone, D. B., and Waksman, S. A., J. Bact., Balt. 55:317, 1948. [12] Sawazaki, T., et al, J. Antibiot., Tokyo, Ser. A 8:44, 1955.

General References

Pratt, R., and Dufrenoy, J., "Antibiotics," Philadelphia: J. B. Lippincott Co., 1953. Welch, H., et al, "Principles and Practice of Antibiotic Therapy," New York: Medical Encyclopedia, Inc., 1954. Am. M. Ass. Council on Pharmacy and Chemistry, "New and Nonofficial Remedies," Philadelphia: J. B. Lippincott Co., 1956. Valentine, F. C., and Shooter, R. A., "Recent Advances in Chemotherapy, Vol. II, Antibiotics," New York: Blakiston Co., 1954. Waksman, S. A., "The Literature of Streptomycin, 1944-52," New Brunswick: Rutgers Univ. Press, 1953. Meyler, L., "Side Effects of Drugs," New York: Elsevier Pub. Co., 1952. Waksman, S. A., Antibiotics and Chemotherapy 3:333, 1953. Kitchen, H. B., and Waksman, S. A., J. Am. Pharm. Ass., Sci. Ed. 45:522, 1953. Am. M. Ass. Council on Pharmacy and Chemistry, J. Am. M. Ass. 154:52, 1954. Riddell, M. I., Am. J. M. Sc. 223:301, 1952. Kutscher, A. H., Lane, S. L., and Segall, R., J. Allergy 25:135, 1954. Scheidy, S. F., J. Am. Vet. M. Ass. 118:213, 1951. Uvarov, O., Vet. Rec., Lond. 67:67, 1955. Waksman, S. A., "Streptomycin, Its Nature and Practical Application," Baltimore: Williams and Wilkins Co., 1949. Braude, R., Kon, S. K., and Porter, J. W., Nutrit. Abstr., Aberdeen: 23:473, 1953. Anderson, H. W., and Gottlieb, D., Econ. Botany 6:294, 1952. Zaumeyer, W. J., J. Agr. Food Chem. 3:112, 1955. Finland, M., N. England J. M. 353:909, 1955. Ebert, R. H., Am. J. M. 5:738, 1955. Kitchen, H. B., and Waksman, S. A., J. Am. Vet. M. Ass. 127:261, 1955. Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949.

297. STREPTOTHRICIN

[1] Peck, R. L., et al, J. Am. Chem. Soc. 68:772, 1946. [2] Fried, J., and Wintersteiner, O., Science 101:613, 1945. [3] Kuehl, F. A., Jr., et al, *ibid* 102:34, 1945. [4] Peck, R. L., and Lyons, J. E., Annual Rev. Biochem. 20:367, 1951. [5] Carter, H. E., et al, J. Am. Chem. Soc. 76:566, 1954. [6] Waksman, S. A., and Woodruff, H. B., Proc. Soc. Exp.

297. STREPTOTHRICIN (Concluded)

- Biol. 49:207, 1942. [7] Foster, J. W., and Woodruff, H. B., Arch. Biochem., N. Y. 3:241, 1943. [8] Woodruff, H. B., and Foster, J. W., Proc. Soc. Exp. Biol. 57:88, 1944. [9] Smith, D. G., and Robinson, H. J., J. Bact., Balt. 50:613, 1945. [10] Waksman, S. A., *ibid* 46:299, 1943. [11] Metzger, H. J., Waksman, S. A., and Pugh, L. H., Proc. Soc. Exp. Biol. 51:251, 1942. [12] Robinson, H. J., and Smith, D. G., J. Pharm. Exp. Ther. 81:390, 1944. [13] Robinson, H. J., Graessle, O. E., and Smith, D. G., Science 99:540, 1944. [14] Meyer, E., and Ordal, Z. J., J. Infect. Dis. 79:199, 1946. [15] Hamre, D., and Rake, G., *ibid* 81:175, 1947. [16] Feldman, W. H., and Hinshaw, H. C., Am. Rev. Tuberc. 52:299, 1945. [17] Steenken, W., Jr., and Wagley, P. F., *ibid* 56:41, 1947. [18] Meyer, K. F., Quan, S. F., McCrumb, F. R., and Larson, A., Ann. N. York Acad. Sc. 55:1228, 1952. [19] Geiling, E. M., and Taliaferro, W. H., "A Survey of Antimalarial Drugs, 1941-1945," Ann Arbor: J. W. Edwards, 1946. [20] Rake, G., Kavanagh, F., Koerber, W. L., and Donovan, R., Am. J. M. Sc. 210:61, 1945. [21] Robinson, H. J., Graessle, O. E., Gundel, M., and Silber, R. H., J. Pharm. Exp. Ther. 86:22, 1946. [22] Mushett, C. W., and Martland, H. S., Fed. Proc. 5:194, 1946. [23] Moore, P. R., et al, J. Biol. Chem. 165:437, 1946. [24] Price, C. W., Randall, W. A., Chandler, V. L., and Reedy, R. J., J. Bact., Balt. 53:481, 1947. [25] Pagano, J. F., Weinstein, M. J., and Donovan, R., Proc. Soc. Exp. Biol. 79:359, 1952. [26] Seneca, H., and Ides, D., Am. J. Trop. M. Hyg. 2:1045, 1953. [27] Chapman, S. S., Downs, C. M., Coriell, L. L., and Kowall, S. L., J. Infect. Dis. 84:25, 1949. [28] De Ropp, R. S., Phytopathology 39:822, 1949. [29] Trussell, P. C., Fulton, C. O., and Grant, G. A., J. Bact., Balt. 53:769, 1947. [30] Peterson, D. H., Colingsworth, D. R., Reineke, L. M., and De Boer, C., J. Am. Chem. Soc. 69:3145, 1947. [31] Gray, R. A., Sup. to Proc. of 6th Plant Physiol. Meet., Plant Physiol. 30:vi, 1955. [32] Van Tamelen, E. E., et al, J. Am. Chem. Soc. 78:4817, 1956. [33] Umezawa, H., et al, J. Antibiot., Tokyo 3:833, 1950. [34] Maeda, K., et al, *ibid* 5:343, 1952.

298. STREPTOTHRICIN TYPE 3

- [1] Inoue, M., J. Antibiot., Tokyo, Ser. A 6:122, 1953.

299. SUBTENOLIN

- [1] Hirschhorn, H. N., Bucca, M. A., and Thayer, J. D., Proc. Soc. Exp. Biol. 67:429, 1948. [2] Howell, S. F., and Tauber, H., *ibid* 67:432, 1948. [3] Dvonch, W., and Benedict, R. G., Antibiotics and Chemotherapy 3:192, 1952. [4] Coatney, G. R., and Greenberg, J., Ann. N. York Acad. Sc. 55:1075, 1952.

300. SUBTILIN

- [1] Jansen, E. F., and Hirschman, D. J., Arch. Biochem., N. Y. 4:297, 1944. [2] Dimick, K. P., et al, *ibid* 15:1, 1947. [3] Lewis, J. C., and Snell, N. S., J. Am. Chem. Soc. 73:4812, 1951. [4] Salle, A. J., and Jann, G. J., Proc. Soc. Exp. Biol. 60:60, 1945. [5] Steenken, W., Jr., and Wolinsky, E., J. Bact., Balt. 57:453, 1949. [6] Eagle, H., Musselman, A. D., and Fleischman, R., *ibid* 55:347, 1948. [7] Anderson, H. H., Villela, G. G., Hansen, E. L., and Reed, R. Science 103:418, 1946. [8] Packchianian, A., Am. J. Trop. M. Hyg. 2:243, 1953. [9] Dunn, M. C., and Thompson, P. E., J. Infect. Dis. 92:33, 1953. [10] Hall, E. A., Kavanagh, F., and Asheshov, I. N., Antibiotics and Chemotherapy 1:369, 1951. [11] Salle, A. J., and Jann, G. J., J. Clin. Invest. 28:1036, 1949. [12] Schuhardt, V. T., Ann. N. York Acad. Sc. 55:1209, 1952. [13] Goodman, J. J., and Henry, A. W., Science 105:320, 1947. [14] Salle, A. J., Soc. Am. Bact. Bact. Proc., p 72, 1954. [15] Carminati, G. M., and Ercoli, N., Boll. Ist sieroter. milan. 30:97, 1951. [16] Coatney, G. R., and Greenberg, J., Ann. N. York Acad. Sc. 55:1075, 1952. [17] Jackson, E. B., Antibiotics and Chemotherapy 1:231, 1951. [18] Wilson, R. H., De Eds, F., and Rather, L. J., Proc. Soc. Exp. Biol. 78:517, 1951. [19] Sacks, L. E., Antibiotics and Chemotherapy 2:79, 1952. [20] LeBlanc, F. R., Devlin, K. A., and Stumbo, C. R., Chem. Eng. Progr. 49:181, 1953. [21] Williams, O. B., and Fleming, T. C., Antibiotics and Chemotherapy 2:75, 1952. [22] Heuser, G. F., and Norris, L. C., Poultry Sc. 31:857, 1951. [23] Godkin, W. J., and Cathcart, W. H., Food Technol. 6:224, 1952. [24] Godkin, W. J., and Cathcart, W. H., *ibid* 7:282, 1953. [25] Salle, A. J., Jann, G. J., and Molander, C. W., Soc. Am. Bact. Bact. Proc., p 57, 1954. [26] Lewis, J. C., and Jansen, E. F., Fed. Proc. 6:270, 1947. [27] Chin, Y. C., *ibid* 7:211, 1948. [28] Salle, A. J., and Jann, G. J., Proc. Soc. Exp. Biol. 61:23, 1946. [29] Wilson, R. H., Humphreys, E. M., Reynolds, D. M., and Lewis, J. C., *ibid* 71:700, 1949. [30] Heishman, J. O., Am. J. Vet. Res. 11:206, 1950. [31] Salle, A. J., and Jann, G. J., J. Bact., Balt. 55:463, 1948. [32] Levaditi, C., and Henry, J., Presse méd. 56:493, 1948. [33] Carson, J. F., Jansen, E. F., and Lewis, J. C., J. Am. Chem. Soc. 71:318, 1949. [34] Katznelson, H., and Hood, E. G., J. Dairy Sc. 32:961, 1949. [35] Katznelson, H., J. Bact., Balt. 59:471, 1950. [36] Adams, A. T., Ayres, J. C., and Tischer, R. G., Food Technol. 5:82, 1951. [37] Jann, G. J., Streitfeld, M. M., and Salle, A. J., J. Bact., Balt. 63:353, 1952. [38] Sacks, L. E., *ibid* 70:491, 1955.

301. SULFACTIN

- [1] Junowicz-Kocholaty, R., Kocholaty, W., and Kelner, A., J. Biol. Chem. 168:765, 1947. [2] Morton, H. E., Proc. Soc. Exp. Biol. 66:345, 1947.

302. SYNNEMATINS

- [1] Gottshall, R. Y., Roberts, J. M., Portwood, L. M., and Jennings, J. C., Proc. Soc. Exp. Biol. 76:307, 1951. [2] Olson, B. H., Jennings, J. C., and Junek, A. J., Science 117:76, 1953. [3] Gottshall, R. Y., Roberts, J. M., and Portwood, L. M., U. S. Pat. 2,658,018, 1953. [4] Olarte, J., and Figueroa, G., Antibiotics and Chemotherapy 5:162,

REFERENCES (Continued)

302. SYNNEMATINS (Concluded)

1955. [5] Olson, B. H., and Jennings, J. C., *ibid* 4:11, 1954. [6] Palencia, L., González, R., and Varcla, G., *Rev. Inst. salub. enferm. trop.*, Méx. 14:113, 1954. [7] Benavides, V. L., Olson, B. H., Varela, G., and Holt, S. H., *J. Am. M. Ass.* 157:989, 1955. [8] Newton, G. G., and Abraham, E. P., *Nature* 175:548, 1955. [9] Abraham, E. P., et al, *ibid* 176:551, 1955. [10] Varela, G., Palencia, L., González, R., and Vazquez, A., *Rev. Inst. salub. enferm. trop. Méx.* 14:215, 1954.

303. TARDIN

[1] Borodin, N., Philpot, F. J., and Florey, H. W., *Brit. J. Exp. Path.* 28:31, 1947.

304. TERRECIN

[1] Iwata, K., and Yosioka, I., *J. Antibiot.*, Tokyo 3:192, 1950.

305. TERREIC ACID

[1] Florey, H. W., et al, "Antibiotics," London: Oxford Univ. Press, 1949. [2] Kaplan, M. A., Hooper, I. R., and Heinemann, B., *Antibiotics and Chemotherapy* 4:746, 1954.

306. TERTIOMYCIN A

[1] Osato, T., et al, *J. Antibiot.*, Tokyo, Ser. A 8:105, 1955. [2] Osato, T., Yagishita, K., and Umezawa, H., *ibid* 8:161, 1955.

307. TERTIOMYCIN B

[1] Osato, T., Yagishita, K., and Umezawa, H., *J. Antibiot.*, Tokyo, Ser. A 8:161, 1955.

308. TETAINE

[1] Borowski, E., *Bull. Inst. Marine Trop. M.*, Gdańsk 5:294, 1953; *Chem. Abstr.* 48:11000, 1954. [2] Kryński, S., Borowski, E., Kuchta, A., Borowski, J., and Becla, E., *ibid* 4:310, 1952; *Chem. Abstr.* 47:7594, 1953. [3] Kryński, S., et al, *Acta Polon. Pharm.* 12:85, 1955; *Chem. Abstr.* 49:16061, 1955.

309. TETRACYCLINE

[1] Boothe, J. H., Morton, J., Petisi, J. P., Wilkinson, R. G., and Williams, J. H., *J. Am. Chem. Soc.* 75:4621, 1953. [2] Conover, L. H., Moreland, W. T., English, A. R., Stephens, C. R., and Pilgrim, F. J., *ibid* 75:4622, 1953. [3] Minieri, P. P., et al, "Antibiotics Annual, 1953-54," p 81, New York: Medical Encyclopedia, Inc. [4] Conover, L. H., U. S. Pat. 2,699,054, 1955. [5] Finland, M., et al, *J. Am. M. Ass.* 154:561, 1954. [6] Regna, P. P., "Encyclopedia of Chemical Technology," vol. 13, p 803, New York: Interscience Encyclopedia, Inc., 1954. [7] Bohonos, N., Dornbush, A. C., Feldman, L. I., Martin, J. H., Pelcak, E., and Williams, J. H., "Antibiotics Annual, 1953-54," p 49, New York: Medical Encyclopedia, Inc. [8] English, A. R., P'an, S. Y., McBride, T. J., Gardocki, J. F., Van Halsema, G., and Wright, W. A., *ibid*, p 70. [9] Eisenberg, G. M., Foltz, E. L., Palazollo, A. J., and Flippin, H. F., "Antibiotics Annual, 1954-55," p 611, New York: Medical Encyclopedia, Inc. [10] Thayer, J. D., Field, F. W., and Perry, M. I., *Antibiotics and Chemotherapy* 5:132, 1955. [11] Love, B. D., Jr., Wright, S. S., Purcell, E. M., Mou, T. W., and Finland, M., *Proc. Soc. Exp. Biol.* 85:25, 1954. [12] Potce, K. G., Wright, S. S., and Finland, M. J., *Labórat. Clin. M.* 44:463, 1954. [13] Wright, S. S., Potce, K. G., and Finland, M., *Am. J. Clin. Path.* 24:1121, 1954. [14] Reedy, R. J., Randall, W. A., and Welch, H., *Antibiotics and Chemotherapy* 5:115, 1955. [15] Sanford, J. P., Favour, C. B., Harrison, J. H., and Mao, F. H., *N. England J. M.* 251:810, 1954. [16] Seneca, H., and Bergendahl, E., *Am. J. M. Sc.* 228:16, 1954. [17] English, A. R., McBride, T. J., Simon, D. L., and Mullady, H. E., *Antibiotics and Chemotherapy* 4:1082, 1954. [18] Kiser, J. S., et al, "Antibiotics Annual, 1953-54," p 56, New York: Medical Encyclopedia, Inc. [19] Kiser, J. S., and De Mello, G. C., *Proc. 58th Annual Meet.*, Nov. 1954, U. S. Livestock Sanitary Ass., p 81, 1955. [20] Palencia, L., González, R., and Varela, G., *Rev. Inst. salub. enferm. trop.*, Méx. 14:113, 1954. [21] Eyles, D. E., and Coleman, N., *Antibiotics and Chemotherapy* 4:988, 1954. [22] Eaton, M. D., "Antibiotics Annual, 1954-55," p 1046, New York: Medical Encyclopedia, Inc. [23] Dukcs, C. D., and Tettenbaum, I. S., *ibid*, p 674. [24] De Mello, G. C., and Kiser, J. S., *ibid*, p 678. [25] Welch, H., *Antibiotics and Chemotherapy* 4:375, 1954. [26] Welch, H., et al, "Principles and Practice of Antibiotic Therapy," New York: Medical Encyclopedia, Inc., 1954. [27] Am. M. Ass. Council on Pharmacy and Chemistry, *J. Am. M. Ass.* 156:1328, 1954. [28] Milberg, M. B., Kahmi, B., and Banowitch, M. M., *Antibiotics and Chemotherapy* 4:1086, 1954. [29] Wood, W. S., et al, *Arch. Int. M.* 94:351, 1954. [30] Freci, E., III, Auner, C. R., Van Metre, T. E., Jr., and Zubrod, C. G., *N. England J. M.* 252:173, 1955. [31] Trafton, H. M., and Lind, H. E., *Antibiotics and Chemotherapy* 4:697, 1954. [32] Prigot, A., Whitaker, J. C., Shidlovsky, B. A., and Marmell, M., "Antibiotics Annual, 1954-55," p 556, New York: Medical Encyclopedia, Inc. [33] Schiff, I., *ibid*, p 585. [34] Mann, C. H., et al, *ibid*, p 637. [35] Spics, H. W., Lepper, M. H., and Dowling, H. F., *ibid*, p 619. [36] Kent, B., Shoemaker, E. H., Townsend, E. S., Bennett, B., and Yow, E. M., *ibid*, p 632. [37] Buckinger, R. H., and Hookings, C. E., *ibid*, p 574. [38] Gable, G. R., Romansky, M. J., and Taggart, S. R., *ibid*, p 578. [39] Willcox, R. R., *Antibiotic M.* 1:142, 1955. [40] Ruiz Sanchez, F., Ruiz Sanchez, A., Flores, N., Bcerra, A.,

309. TETRACYCLINE (Concluded)

- and Naranjo Granda, E., *ibid* 1:158, 1955. [41] Marmell, M., and Prigot, A., *Antibiotics and Chemotherapy* 4:1117, 1954. [42] Maynard, A. De L., Prigot, A., and Marmell, M., *Am. J. Syph.* 38:606, 1954. [43] Bergsdorf, W., Brinkman, E., *Zschr. ges. inn. Med.* 9:98, 1954. [44] Fitz, R. H., et al, *Am. J. M. Sc.* 229:252, 1955. [45] Ruiz Sanchez, F., Ruiz Sanchez, A., Becerra, A., and Naranjo Granda, E., *Antibiotics and Chemotherapy* 4:402, 1954. [46] Liu, R. S., Adams, C. B., Jr., Snyder, M. J., Gauld, J., and Parker, R. T., "Antibiotics Annual, 1954-55," p 556, New York: Medical Encyclopedia, Inc. [47] Rein, C. R., et al, *ibid*, p 563. [48] Albertson, H. A., and Trout, H. H., Jr., *ibid*, p 599. [49] Elsdon-Dew, R., *ibid*, p 869. [50] Abbott, J. D., and Parry, H. E., *Lancet*, Lond. 268:16, 1955. [51] Ruiz Sanchez, F., Ruiz Sanchez, A., and Naranjo Granda, E., *Antibiotic M.* 1:30, 1955. [52] Welsh, A. L., and Ede, M., *Arch. Dermatol. u. Syphilis* 71:111, 1955. [53] Easterbrooks, H. L., Helmboldt, C. F., and Plastring, W. N., *Vet. M.*, Chic. 50:114, 1955. [54] Downing, H. E., Hardie, W. B., Hawley, G. E., and Price, K. E., "Antibiotics Annual, 1954-55," p 312, New York: Medical Encyclopedia, Inc. [55] Leaming, J. D., *Vet. Bull. Lederle* 13:32, 1954. [56] Tennison, L. B., *ibid* 13:23, 1954. [57] Meyer, K. F., and Eddie, B., "Antibiotics Annual, 1954-55," p 544, New York: Medical Encyclopedia, Inc. [58] Cunningham, R. W., Hines, L. R., Stokey, E. H., Vessey, R. E., and Yuda, N. N., "Antibiotics Annual, 1953-54," p 63, New York: Medical Encyclopedia, Inc. [59] Tisch, D. E., Cull, K. M., and Dickison, H. L., "Antibiotics Annual, 1954-55," p 668, New York: Medical Encyclopedia, Inc. [60] Nelson, A. A., and Radomski, J. L., *Antibiotics and Chemotherapy* 4:1174, 1954. [61] Wright, S. S., et al, "Antibiotics Annual, 1953-54," p 92, New York: Medical Encyclopedia, Inc. [62] Putnam, L. E., Hendricks, F. D., and Welch, H., *ibid*, p 88. [63] Maynard, A. De L., Andriola, J. C., and Prigot, A., *ibid*, p 102. [64] Wood, W. S., and Kipnis, G. P., *ibid*, p 98. [65] Wright, S. S., and Finland, M., *Proc. Soc. Exp. Biol.* 85:40, 1954. [66] Carlson, C. W., and Kohlmeyer, W., *Poultry Sc.* 33:1047, 1954. [67] Horvath, D. J., and Vander Noot, G. W., *J. Animal Sc.* 13:899, 1954. [68] Chavez Max, G., *Antibiotic M.* 1:216, 1955. [69] Seneca, H., *ibid* 1:221, 1955. [70] Mitsui, Y., Yamashita, K., and Hanabusa, J., *ibid* 1:225, 1955. [71] Zegarra Araujo, N., *ibid* 1:201, 1955. [72] MacKneson, R. G., and Ormsby, H. L., *Am. J. Ophth.* 39:689, 1955. [73] Hobby, G. L., and Lenert, T. F., *Am. Rev. Tuberc.* 72:367, 1955. [74] Wodraska, T. W., *Antibiotic M.* 1:327, 1955. [75] Davidson, J. L., Haas, K. B., and Stocking, G. G., *Vet. M.*, Chic. 50:416, 1955. [76] Johnson, W. P., Gouge, H. E., and Alson, M. C., *ibid* 50:448, 1955. [77] Johnson, W. P., and Percival, R. C., *J. Am. Vet. M. Ass.* 127:142, 1955. [78] Kakemi, K., Uno, T., and Samejima, M., *J. Pharm. Soc. Japan* 75:970, 1955. [79] Kakemi, K., Uno, T., and Miyake, T., *ibid* 75:973, 1955. [80] Albert, A., and Rees, C. W., *Nature* 177:433, 1956. [81] Anwar, A. A., and Turner, T. B., *Bull. John Hopkins Hosp.* 98:85, 1956. [82] Kolmer, J. A., "Antibiotics Annual, 1955-56," p 592, New York: Medical Encyclopedia, Inc. [83] Lynch, J. E., and Stephens, C. R., *ibid*, p 466. [84] Katz, E., *J. Infect. Dis.* 98:177, 1956. [85] Katsura, S. et al, *J. Antibiot.*, Tokyo, Ser. A 8:181, 1955. [86] Gold, H., *Arch. Int. M.* 96:387, 1955. [87] Waddington, W. S., Bergy, G. G., Nielsen, R. L., and Kirby, W. M., *Am. J., M. Sc.* 228:164, 1954. [88] Dowling, H. F., "Tetracycline," *Antibiotics Monographs* No. 3, p 40, New York: Medical Encyclopedia, Inc., 1955. [89] Gsell, O., and Kesselring, F., *Schweiz. med. Wschr.* 85:721, 1955. [90] Brock, W. E., Pearson, C. C., and Kliever, I. O., *North Am. Vet.* 36:547, 1955. [91] Lanek, N., and Börnfors, S., *Vet. Rec.*, Lond. 68:53, 1956. [92] Haas, K. B., and Connor, N. D., *Vet. M.*, Chic. 51:80, 1956. [93] Splitter, E. J., Castro, E. R., and Kanawyer, W. L., *ibid* 51:17, 1956. [94] Cosar, C., and Kolsky, M., *C. rend. Soc. biol.* 149:1163, 1955. [95] Am. M. Ass. Council on Pharmacy and Chemistry, *J. Am. M. Ass.* 159:1634, 1955. [96] De Armijo Valenzuela, M., and Wattenberg, J. M., *Arch. inst. farmacol. exptl.*, Madrid 6:77, 1954; *Chem. Abstr.* 49:15070, 1955. [97] Brannick, T. L., Burnett, L. S., Heilman, F. R., Wellman, W. E., and Geraci, J. E., *Proc. Staff Meet. Mayo Clin.* 30:380, 1955. [98] Knothe, H., and Thon, D., *Arzneimittel-Forsch.* 6:16, 1956. [99] Konde, W. N., *Vet. M.*, Chic. 51:123, 1956.

310. THERMOPHILLIN

- [1] Burton, H. S., *Nature* 166:570, 1950.

311. THERMOVIRIDIN

- [1] Schuurmans, D. M., Olson, B. H., and San Clemente, C. L., *Appl. Microbiol.* 4:61, 1956.

312. THIOAURIN

- [1] Bolhofer, W. A., Machlowitz, R. A., and Charney, J., *Antibiotics and Chemotherapy* 3:382, 1953. [2] Eisenman, W., et al, *ibid* 3:385, 1953.

313. THIOLUTIN

- [1] Peck, R. L., and Lyons, J. E., *Annual Rev. Biochem.* 20:367, 1951. [2] Seneca, H., Kane, J. H., and Rockenbach, J., *Antibiotics and Chemotherapy* 2:357, 1952. [3] Celmer, W. D., et al, *J. Am. Chem. Soc.* 74:6304, 1952. [4] Celmer, W. D., and Solomons, I. A., "Antibiotics Annual, 1953-54," p 622, New York: Medical Encyclopedia, Inc. [5] Celmer, W. D., and Solomons, I. A., *abstr. of papers*, 126th Meet., Am. Chem. Soc., p 15N, 1954. [6] Tanner, F. W., Jr., Means, J. A., and Davison, J. W., *abstr. of papers*, 118th Meet., Am. Chem. Soc., p 18A, 1950. [7] Gopalkrishnan, K. S., and Jump, J. A., *Proc. Indiana Acad. Sc.* 61:97, 1952. [8] Seneca, H., and Ides, D., *Am. J. Trop. M. Hyg.* 2:1045, 1953. [9] Seneca, H., and Ides, D., *J. Urol.*, Balt. 70:947, 1953. [10] Packchianian, A., *Am. J. Trop. M. Hyg.* 2:243, 1953. [11] Coatney, G. R., and Greenberg, J., *Ann. N. York Acad. Sc.* 55:1075, 1952. [12] Murneek, A. E., *Phytopathology* 42:57, 1952. [13] Bonde, R., *ibid* 43:463, 1953. [14] Gopalkrishnan, K. S., and Jump, J. A., *ibid*

REFERENCES (Continued)

313. THIOLUTIN (Concluded)

42:338, 1952. [15] Strandkov, F. B., and Bockelmann, J. B., *J. Agr. Food Chem.* 1:1219, 1953. [16] Celmer, W. D., and Solomons, I. A., *J. Am. Chem. Soc.* 77:2861, 1955. [17] Goldberg, H. S., and Logue, J. T., *Antibiotics and Chemotherapy* 6:19, 1956. [18] Barton, L. V., and MacNab, J., *Contrib. Boyce Thompson Inst.* 17:419, 1954. [19] Seneca, H., and Bergendahl, E., *Antibiotics and Chemotherapy* 5:737, 1955.

314. THIOMYCIN

[1] Hinuma, Y., Hamada, S., Yashima, T., and Ishihara, K., *J. Antibiot., Tokyo, Ser. A* 8:118, 1955.

315. THIOSTREPTON

[1] Pagano, J. F., Weinstein, M. J., Stout, H. A., and Donovick, R., "Antibiotics Annual, 1955-56," p 554, New York: Medical Encyclopedia, Inc. [2] Vandeputte, J., and Dutcher, J. D., *ibid*, p 560. [3] Steinberg, B. A., Jambor, W. P., and Suydam, L. O., *ibid*, p 562.

316. TOXIMYCIN

[1] Stessel, G. J., Leben, C., and Keitt, G. W., *Phytopathology* 43:23, 1953. [2] Stessel, G. J., Leben, C., and Keitt, G. W., *ibid* 42:20, 1952.

317. TOYOCAMYCIN

[1] Kikuchi, K., *J. Antibiot., Tokyo, Ser. A* 8:145, 1955. [2] Yajima, T., *ibid* 8:189, 1955.

318. TRICHOMYCIN

[1] Hosoya, S., Komatsu, N., Soeda, M., and Sonoda, Y., *Jap. J. Exp. M.* 22:505, 1952; *Chem. Abstr.* 48:3444, 1954. [2] Yamazaki, S., *J. Antibiot., Tokyo, Ser. A* 7:155, 1954. [3] Hosoya, S., et al, *J. Antibiot., Tokyo* 5:564, 1952. [4] Yagi, K., and Nishimoto, T., *ibid, Ser. B* 7:135, 1954. [5] Magara, M., Yokouti, E., Senda, T., and Amino, E., *Antibiotics and Chemotherapy* 4:433, 1954. [6] Sambe, B., Yamazaki, T., and Ishikawa, K., *J. Antibiot., Tokyo, Ser. A* 7:132, 1954. [7] Hosoya, S., et al, *ibid* 6:98, 1953. [8] Ozaki, M., Kataoka, Y., Maesawa, T., Tashima, A., and Kubo, H., *ibid* 7:159, 1954. [9] Hosoya, S., et al, *ibid* 8:5, 1955. [10] Hosoya, S., Hamamura, N., and Ogata, S., *ibid* 8:48, 1955. [11] Ito, T., Miyamura, S., Yuasa, H., and Miyashita, T., *ibid, Ser. B* 8:57, 1955. [12] Soeda, M., and Soeda, M., *ibid* 7:347, 1954. [13] Hosoya, S., and Nakazawa, S., *ibid, Ser. A* 8:137, 1955. [14] Lynch, J. E., Holley, E. C., and Margison, J. E., *Antibiotics and Chemotherapy* 5:508, 1955. [15] Hosoya, S., et al, *Chemotherapy, Japan* 3:10, 1955; *Chem. Abstr.* 49:9160, 1955. [16] Onoda, Y., *J. Antibiot., Tokyo, Ser. B* 8:65, 1955. [17] Dimmling, T., *Zbl. Bakt. (Abt. I, Orig.)* 163:530, 1955. [18] Okada, K., *Chemotherapy, Japan* 3:215, 1955; *Chem. Abstr.* 50:5085, 1956. [19] Hosoya, S., et al, *J. Antibiot., Tokyo, Ser. A* 6:92, 1953.

319. TRICHOTHECIN

[1] Freeman, G. G., and Morrison, R. I., *Nature* 162:30, 1948. [2] Freeman, G. G., and Morrison, R. I., *Biochem. J., Lond.* 44:1, 1949. [3] Freeman, G. G., and Gill, J. E., *Nature* 166:698, 1950. [4] Freeman, G. G., *J. Gen. Microb., Lond.* 12:213, 1955. [5] Freeman, G. G., and Morrison, R. I., *ibid* 3:60, 1949. [6] Bawden, F. C., and Freeman, G. G., *ibid* 7:154, 1952. [7] Wallen, V. R., *Plant Disease Repr.* 39:124, 1955.

320. TYROCIDINE

[1] Hotchkiss, R. D., and Dubos, R. J., *J. Biol. Chem.* 141:155, 1941. [2] Hotchkiss, R. D., and Dubos, R. J., *ibid* 136:803, 1940. [3] Hotchkiss, R. D., *Advance Enzymol., N. Y.*, 4:153, 1944. [4] Paladini, A., and Craig, L. C., *J. Am. Chem. Soc.* 76:688, 1954. [5] Battersby, A. R., and Craig, L. C., *ibid* 74:4019, 1952. [6] Battersby, A. R., and Craig, L. C., *ibid* 74:4023, 1952. [7] Tishler, M., Stokes, J. L., Trenner, N. R., and Conn, J. B., *J. Biol. Chem.* 141:197, 1941. [8] Stokes, J. L., and Woodward, C. R., Jr., *J. Bact., Balt.* 46:83, 1943. [9] Dubos, R. J., and Hotchkiss, R. D., *J. Exp. M.* 73:629, 1941. [10] Rittenberg, S. C., Sternberg, H. E., and Bywater, W. G., *J. Biol. Chem.* 168:183, 1947. [11] Amrein, Y. U., *Proc. Soc. Exp. Biol.* 76:744, 1951. [12] Robinson, H. J., and Graessle, O. E., *J. Pharm., Lond.* 76:316, 1942. [13] Packchianian, A., *Am. J. Trop. M. Hyg.* 2:243, 1953. [14] Robinson, H. J., and Molitor, H., *J. Pharm., Lond.* 74:75, 1942. [15] Rammelkamp, C. H., and Weinstein, L., *J. Infect. Dis.* 71:166, 1942. [16] King, T. P., and Craig, L. C., *J. Am. Chem. Soc.* 77:6624, 1956. [17] King, T. P., and Craig, L. C., *ibid* 77:6627, 1956.

321. TYROTHRICIN

[1] Dubos, R. J., *J. Exp. M.* 70:1, 1939. [2] Hotchkiss, R. D., *Advance. Enzymol., N. Y.* 4:153, 1944. [3] Fitzgerald, R. J., and Hampp, E. G., *J. Dent. Res.* 31:20, 1952. [4] Weinman, D., *Proc. Soc. Exp. Biol.* 54:38, 1943. [5] Packchianian, A., *Am. J. Trop. M. Hyg.* 2:243, 1953. [6] Gate, J., Bessemans, A., and Derom, R., Antonie van Leeuwenhoek, *J. Microbiol. Serol.* 16:295, 1950. [7] Dubos, R. J., *J. Exp. M.* 70:11, 1939. [8] Robinson, H. J., and

REFERENCES (Continued)

321. TYROTHRICIN (Concluded)

- Graessle, O. E., *J. Pharm.*, Lond. 76:316, 1942. [9] Tillett, W. S., Cambier, M. J., and Harris, W. H., *J. Clin. Invest.* 22:249, 1943. [10] Hoogerheide, J. C., *J. Franklin Inst.* 229:677, 1940. [11] Rammelkamp, C. H., *J. Infect. Dis.* 71:40, 1942. [12] Schoenbach, E. B., Enders, J. F., and Mueller, J. H., *Science* 94:217, 1941. [13] Taliaferro, L. G., Coulston, F., and Silverman, M., *J. Infect. Dis.* 75:179, 1944. [14] Coggeshall, L. T., and Porter, R. J. "A Survey of Antimalarial Drugs, 1941-1945," Ann Arbor: J. W. Edwards, 1946. [15] McKee, C. M., Hamre, D. M., and Rake, G., *Proc. Soc. Exp. Biol.* 54:211, 1943. [16] Hac, L. R., *J. Infect. Dis.* 74:161, 1944. [17] Am. M. Ass. Council on Pharmacy and Chemistry, "New and Nonofficial Remedies," Philadelphia: J. B. Lippincott Co., 1956. [18] Welch, H., et al, "Principles and Practice of Antibiotic Therapy," New York: Medical Encyclopedia, Inc., 1954. [19] Herrell, W. E., "Penicillin and Other Antibiotic Agents," Philadelphia: W. B. Saunders Co., 1945. [20] Rammelkamp, C. H., War M., *Chic.* 2:380, 1942. [21] Kozoll, D. D., Meyer, K. A., Hoffman, W. S., and Levine, S., *Surg. Gyn. Obst.* 83:323, 1946. [22] Lammers, T., and Durner, G., *Arztl. Wschr.* 6:948, 1951. [23] Mehring, A., *Med. Klin., Berl.* 48:1781, 1953. [24] Schweigmann, I., *ibid* 48:1295, 1953. [25] Kupperman, R. B., and Iger, J., "Antibiotics Annual, 1954-55," p 876, New York: Medical Encyclopedia, Inc. [26] Pildes, R. B., *ibid*, p 885. [27] Packard, L. A., *Eye, Ear, Nose, Throat Monthly* 28:75, 1949. [28] Gate, J., Cotte, J., and Coudert, J., *Maroc méd.* 27:335, 1948; *Biol. Abstr.*, Balt. 25:20973, 1951. [29] Ludwick, W. E., Fosdick, L. S., and Schantz, C. W., *J. Am. Dent. Ass.* 43:285, 1951. [30] Biró, L., and Szekeley, A., *Acta Med. Acad. Sci. Hung.* 2:481, 1952. [31] Little, R. B., Dubos, R. J., and Hotchkiss, R. D., *J. Am. Vet. M. Ass.* 98:189, 1941. [32] Schalm, O. W., *ibid* 100:323, 1942. [33] Scheidy, S. F., *ibid* 118:213, 1951. [34] Bachrach, A., *ibid* 114:27, 1949. [35] Fleck, G. J., Guss, S. B., and Royer, H. K., *ibid* 114:83, 1949. [36] Robinson, H. J., and Molitor, H., *J. Pharm.*, Lond. 74:75, 1942. [37] Rammelkamp, C. H., and Weinstein, L., *J. Infect. Dis.* 71:166, 1942. [38] MacLeod, C. M., Mirick, G. S., and Curnen, E. C., *Proc. Soc. Exp. Biol.* 43:461, 1940. [39] Henle, G., and Zittle, C. A., *ibid* 47:193, 1941. [40] Seydell, E. M., and McKnight, W. P., *Arch. Otolaryng.*, *Chic.* 47:465, 1948. [41] Otenasek, F. J., and Fairman, D., *ibid* 47:21, 1948. [42] Rammelkamp, C. H., *Proc. Soc. Exp. Biol.* 49:346, 1942. [43] Gros, F., Macheboeuf, M., and Latterade, C., *Ann. Inst. Pasteur, Par.* 75:411, 1948. [44] Hotchkiss, R. D., and Dubos, R. J., *J. Biol. Chem.* 141:155, 1941. [45] Sévin, A., Beerens, H., and Spy, C., *Ann. Inst. Pasteur, Lille* 1:223, 1948. [46] Am. M. Ass. Council on Pharmacy and Chemistry, *J. Am. M. Ass.* 159:1634, 1955.

322. UNGULINIC ACID

- [1] Birkinshaw, J. H., Morgan, E. N., and Findlay, W. P., *Biochem. J.*, Lond. 50:509, 1952. [2] Marcus, S., *ibid* 50:516, 1952.

323. USNIC ACID

- [1] Marshak, A., *Pub. Health Rept.*, Wash. 62:3, 1947. [2] Curd, F. H., and Robertson, A., *J. Chem. Soc.* 1937:894. [3] Burkholder, P. R., and Evans, A. W., *Bull. Torrey Bot. Club* 72:157, 1945. [4] Stark, J. B., Walter, E. D., and Owerls, H. S., *J. Am. Chem. Soc.* 72:1819, 1950. [5] Jones, F. T., and Palmer, K. J., *ibid* 72:1820, 1950. [6] Barton, D. H., and Bruun, T., *J. Chem. Soc.* 1953:603. [7] Baron, A. L., "Handbook of Antibiotics," New York: Reinhold Pub. Co., 1950. [8] Castle, H., and Kubsch, F., *Arch. Biochem.*, N. Y. 23:158, 1949. [9] Stoll, A., Brack, A., and Renz, J., *Experientia, Basel* 3:115, 1947. [10] Bustinza, F., *An. Jard. Bot. Madrid* 10:151, 1951; *Biol. Abstr.*, Balt. 26:31693, 1952. [11] Suntola, S., Heilala, P., Patiala, J., and Patiala, R., *Suomen Kemistilehti* 21A:179, 1948; *Chem. Abstr.* 43:1353, 1949. [12] Patiala, R., *Acta derm. vener.*, Stockh. 31:36, 1951. [13] Johnson, R. B., Feldott, G., and Lardy, H. A., *Arch. Biochem.*, N. Y. 28:317, 1950. [14] Barton, D. H., Deflorin, A. M., and Edwards, O. E., *Chemistry and Industry* 1955:1039. [15] Zatulovskii, B. G., *Mikrobiol. Zhur.*, Akad. Nauk Ukr. R. S. R. 16:54, 1955; *Chem. Abstr.* 49:10521, 1955. [16] Patiala, J., and Brander, E., *Ann. med. exp. biol. fenn.* 32:282, 1954; *abstr. in Bull. Hyg.* 30:408, 1955. [17] Patiala, J., and Patiala, R., *ibid* 32:408, 1954; *ibid* 30:408, 1955. [18] Mose, J. R., *Arzneimittel-Forsch.* 5:510, 1955. [19] Coatney, G. R., Cooper, W. C., Eddy, N. B., and Greenberg, J., "Survey of Antimalarial Agents," Public Health Mono. No. 9, p 250, Federal Security Agency, Washington, D. C., 1953.

324. USTILAGIC ACID

- [1] Lemieux, R. U., Thorn, J. A., Brice, C., and Haskins, R. H., *Canad. J. Chem.* 29:409, 1951. [2] Haskins, R. H., and Thorn, J. A., *Canad. J. Bot.* 29:585, 1951. [3] Lemieux, R. U., *Canad. J. Chem.* 29:415, 1951. [4] Lemiwux, R. U., *ibid* 31:396, 1953.

325. VALINOMYCIN

- [1] Brockmann, H., and Schmidt-Kastner, G., *Chem. Ber.* 88:57, 1955.

326. VANCOMYCIN

- [1] McCormick, M. H., et al, "Antibiotics Annual, 1955-56," p 606, New York: Medical Encyclopedia, Inc. [2] Griffith, R. S., and Peck, F. B., Jr., *ibid*, p 619. [3] Ziegler, D. W., Wolfe, R. N., and McGuire, J. M., *ibid*, p 612. [4] Pittenger, R. C., and Brigham, R. B., *Antibiotics and Chemotherapy* 6:642, 1956.

REFERENCES (Continued)

327. VINACETIN

[1] Omachi, K., *J. Antibiot.*, Tokyo, Ser. A 6:73, 1953.

328. VIOLACEIN

[1] Richter, V., "The Chemistry of the Carbon Compounds," New York: Nordemann Publ. Co., 1939. [2] Lichstein, H. C., and Van de Sand, V. F., *J. Infect. Dis.* 76:47, 1945. [3] Strong, F. M., *Science* 100:287, 1944. [4] Lichstein, H. C., and Van de Sand, V. F., *J. Bact.*, Balt. 52:145, 1946. [5] Beer, R. J., Clarke, K., Khorana, H. G., Robertson, A., *J. Chem. Soc.* 1949:885, [6] Beer, R. J., Jennings, B. E., and Robertson, A., *ibid* 1954:2679. [7] Singh, B. N., *Nature* 149:168, 1942.

329. VIOLACETIN

[1] Aiso, K., et al, *J. Antibiot.*, Tokyo, Ser. A 8:33, 1955.

330. VIOMYCIN

[1] Haskell, T. H., Fusari, S. A., Frohardt, R. P., and Bartz, Q. R., *J. Am. Chem. Soc.* 74:599, 1952. [2] Finlay, A. C., et al, *Am. Rev. Tuberc.* 63:1, 1951. [3] Bartz, Q. R., et al, *ibid* 63:4, 1951. [4] Jackson, A. W., *Antibiotics and Chemotherapy* 4:1210, 1954. [5] Mayer, R. L., Crane, C., De Boer, C. J., Konopka, E. A., Marsh, W. S., and Eisman, P. C., *Proc. 12th Internat. Congr. Pure and Applied Chem.*, New York, Sept., 1951. [6] Ehrlich, J., Smith, R. M., Penner, M. A., Anderson, L. E., and Bratton, A. C., Jr., *Am. Rev. Tuberc.* 63:7, 1951. [7] Hobby, G. L., Lenert, T. F., Donikian, M., and Pikula, D., *ibid* 63:17, 1951. [8] Youmans, G. P., and Youmans, A. S., *ibid* 63:25, 1951. [9] Steenken, W. J., Jr., and Wolinsky, E., *ibid* 63:30, 1951. [10] Karlson, A. G., and Gainer, J. H., *ibid* 63:36, 1951. [11] Packchianian, A., *Am. J. Trop. M. Hyg.* 2:243, 1953. [12] Mackaness, G. B., *J. Path. Bact.*, Lond. 64:429, 1952. [13] Karlson, A. G., and Gainer, J. H., *Proc. Staff. Meet. Mayo Clin.* 26:53, 1951. [14] Kiser, J. S., and De Mello, G. C., *Proc. 58th Ann. Meet.*, Nov. 1954, U. S. Livestock Sanitary Ass., p 81, 1955. [15] Hobby, G. L., Hanks, J. H., Donikian, M. A., and Backerman, T., *Am. Rev. Tuberc.* 69:173, 1954. [16] Werner, C. A., Tompsett, R., Muschenheim, C., and McDermott, W., *ibid* 63:49, 1951. [17] Hackney, R. L., King, E. Q., Marshall, E. E., Harden, K. A., and Payne, H. M., *Dis. Chest.* 24:591, 1953. [18] *Am. M. Ass. Council on Pharmacy and Chemistry*, *J. Am. M. Ass.* 154:52. [19] Tucker, W. B., *Am. Rev. Tuberc.* 70:812, 1954. [20] King, D. S., *N. England J. M.* 252:135, 1955. [21] *Tr. 12th Conf. on Chemotherapy of Tuberculosis*, Veterans Admin., Washington, D. C., Feb, 1953. [22] P'an, S. Y., Halley, T. V., Reilly, J. C., and Pekich, A. M., *Am. Rev. Tuberc.* 63:44, 1951. [23] Muschenheim, C., *Tr. 10th Conf. on Chemotherapy of Tuberculosis*, Veterans Admin., Washington, D. C., Jan, 1951. [24] Seneca, H., and Bergendahl, E., *Am. J. Digest. Dis.* 22:131, 1955. [25] Mayer, R. L., Eisman, P. C., and Konopka, E. A., *Experientia*, Basel 10:335, 1954. [26] Deom, J., and Mortelmans, J., *Antonie van Leeuwenhoek. J. Microbiol. Serol.* 21:377, 1955. [27] Keller, H., Krüpe, W., Sous, H., and Mückter, H., "Antibiotics Annual, 1955-56," p 35, New York: Medical Encyclopedia, Inc. [28] Metzger, J. F., Fusillo, M. H., and Kuhns, D. M., *Antibiotics and Chemotherapy* 2:227, 1952.

331. VIRIDICATIN

[1] Cunningham, K. G., and Freeman, G. G., *Biochem. J.*, Lond. 53:328, 1953. [2] Bracken, A., Pocker, A., and Raistrick, H., *ibid* 57:587, 1954.

332. VIRIDINS

[1] Brian, P. W., and McGowan, J. C., *Nature* 156:144, 1945. [2] Brian, P. W., Curtis, P. H., Hemming, H. G., and McGowan, J. C., *Ann. Appl. Biol.*, Lond. 33:190, 1946. [3] Vischer, E. B., Howland, S. R., and Raudnitz, H., *Nature* 165:528, 1950. [4] Wallen, V. R., and Skolko, A. J., *Canad. J. Bot.* 29:316, 1951. [5] Packchianian, A., *Am. J. Trop. M. Hyg.* 2:243, 1953. [6] Dahmen, M., and Moutschen, J., *Ann. Inst. Pasteur, Par.* 87:204, 1954. [7] Yajima, T., *J. Antibiot.*, Tokyo, Ser. A 8:189, 1955.

333. VISCOSIN

[1] Groupé, V., Pugh, L. H., Weiss, D. W., and Kochi, M., *Proc. Soc. Exp. Biol.* 78:354, 1951. [2] Kochi, M., Weiss, D. W., Pugh, L. H., and Groupé, V., *Bact. Proc.* 1951:29. [3] Ohno, T., Tajima, S., and Toki, K., *J. Agr. Chem. Soc. Japan* 27:665, 1953; *Chem. Abstr.* 49:3012, 1955.

334. WHITMORIN

[1] Jameson, J. E., *J. Hyg.*, Lond. 47:142, 1949.

335. XANTHELLIN

[1] Wachter, R. F., Bohonos, N., and Quackenbush, F. W., *Antibiotics and Chemotherapy* 1:399, 1951.

REFERENCES (Concluded)

336. XANTHOCILLIN

[1] Beiersdorf, R., and Ahrens, W., *Die Pharmazie* 8:796, 1953. [2] Rothe, W., *ibid* 5:190, 1950. [3] Rothe, W., *Deut. med. Wschr.* 79:1080, 1954. [4] Beiersdorf, R., and Ahrens, W., *Deut. Gesundheitswes.* 9:805, 1954; abstr. in *Excerpta Med., Sect., IV*, 8:337, 1955.

337. XANTHOMYCINS

[1] Thorne, C. B., and Peterson, W. H., *J. Biol. Chem.* 176:413, 1948. [2] Mold, J. D., and Bartz, Q. R., *J. Am. Chem. Soc.* 72:1847, 1950. [3] Rao, K. V., and Peterson, W. H., *ibid* 76:1335, 1954. [4] Rao, K. V., Peterson, W. H., and Van Tamelen, E. E., *ibid* 77:4327, 1955. [5] Dougall, D., and Abraham, E. P., *Nature* 176:256, 1955.

338. XANTHOTHRICIN

[1] Machlowitz, R. A., Fisher, W. P., McKay, B. S., Tytell, A. A., and Charney, J., *Antibiotics and Chemotherapy* 4:259, 1954.

339. XEROSIN

[1] Groupé, V., Pugh, L. H., Levine, A. S., and Herrmann, E. C., Jr., *J. Bact., Balt.* 68:10, 1954. [2] Groupé, V., Pugh, L. H., and Levine, A. S., *Proc. Soc. Exp. Biol.* 80:710, 1952. [3] Ginsberg, H. S., *Fed. Proc.* 13:494, 1954. [4] Groupé, V., and Herrmann, E. C., Jr., *J. Immun., Balt.* 74:249, 1955. [5] Wagner, R. R., *Proc. Soc. Exp. Biol.* 90:214, 1955. [6] Ginsberg, H. S., *J. Immun., Balt.* 75:430, 1955. [7] Groupé, V., Rauscher, F. J., and Bryan, W. R., *Science* 123:1073, 1956. [8] Waksman, B. H., and Groupé, V., *J. Immun., Balt.* 77:47, 1956. [9] Groupé, V., Dougherty, R.M., and Manaker, R. A., *J. Bact., Balt.* 72:604, 1956.

340. ZAOMYCIN

[1] Hinuma, Y., *J. Antibiot., Tokyo, Ser. A* 7:134, 1954.

APPENDIX

APPENDIX 1: ANTIBIOTIC EFFICACY,
A LISTING BY ORGANISM

The organisms listed below appear in the body of the volume, thus this is not a supplementary listing. Alphabetization, rather than taxonomic grouping, has been employed for convenience of the user. Numbers immediately following the name of the organism identify the antibiotics and are in ascending numerical order--not in order of preference or effectiveness. Antibiotics so indicated have, according to the text of this volume, demonstrated moderate to marked efficacy against that organism.

- Absidia glauca, 13, 16, 55, 127, 138
 A. orchidis, 30, 58, 81, 120, 205, 332
 Acetobacter aceti, 36
 Achorion gypseum, 238
 A. schoenleinii, 205, 261
 Actinomyces spp, 144, 217, 237
 A. bovis, 78, 112, 156, 330
 A. israeli, 45
 Aerobacter aerogenes, 7, 10, 11, 47, 84, 105, 144, 151, 166, 178, 193, 212, 214, 223, 224, 233, 235, 244, 249, 267, 289, 294, 309, 312, 313, 320, 324, 326, 329, 330, 335, 337
 Agrobacterium tumefaciens, 17, 77, 159
 Alcaligenes spp, 249, 259
 A. faecalis, 10, 22, 289
 A. viscosa, 337
 Alternaria spp, 36, 54, 198
 A. kikuchiana, 118
 A. solani, 113, 130, 158, 316
 A. tenuis, 324
 Armillaria spp, 36
 A. mellea, 324
 Ascochyta spp, 324
 A. linicola, 130
 A. pinodella, 229
 A. pisi, 96, 140
 Ascomycetes, 53 (See also specific ascomycetes.)
 Aspergillus spp, 36, 54, 56, 93, 120
 A. flavus, 138, 277, 297
 A. fumigatus, 24, 58, 229, 319
 A. niger, 7, 12, 13, 30, 35, 41, 42, 46, 55, 58, 62, 81, 82, 96, 102, 113, 119, 120, 121, 125, 127, 130, 138, 148, 164, 186, 188, 191, 198, 200, 205, 209, 221, 245, 246, 266, 277, 284, 285, 312, 319, 324, 329, 332
 A. oryzae, 114, 148, 200, 277
 A. terreus, 13, 164
 Aspicularis tetraptera, 232, 259
 Bacillus spp, 76, 237
 B. agri, 14, 20, 163, 285, 340
 B. allii, 279
 B. alvei, 17
 B. anthracis, 1, 4, 7, 10, 14, 19, 23, 35, 39, 45, 47, 52, 53, 55, 60, 63, 65, 69, 71, 77, 84, 87, 112, 117, 121, 126, 129, 133, 136, 144, 149, 152, 154, 159, 160, 178, 182, 184, 195, 199, 211-213, 218, 223, 225, 232, 233, 236, 240, 242-244, 254, 256, 260, 261, 263, 266, 267, 284, 285, 288, 296, 298, 300, 301, 304, 306, 307, 309, 314, 328, 330, 340
 B. anthracis-1024-2048, 281
 B. brevis, 166, 326, 337
 B. cereus, 23, 34, 36, 52, 82, 105, 112, 141, 155, 166, 212, 226, 235, 259, 281, 294, 295, 301, 316, 326, 335, 337
 B. cereus phage, 82
 B. cereus var. mycoides, 268
 B. circulans, 108, 301
 B. licheniformis, 326
 B. macerans, 166
 B. megatherium, 6, 25, 36, 124, 172, 207, 235, 266, 294, 301, 306, 307, 326, 328, 337
 Bacillus mesentericus, 17, 71, 77, 144, 155, 178, 179, 221, 301, 328, 329, 337
 B. mycoides, 12, 17, 46, 55, 60, 77, 85, 102, 123, 144, 155, 179, 186, 191, 196, 212, 216, 223, 226, 235, 239, 247, 248, 250, 288, 291, 294, 301, 320, 321, 337
 B. niger, 337
 B. polymyxa, 108, 109, 166, 294, 326, 335
 B. subtilis, 4, 7, 10-12, 14, 20, 21, 23, 33-35, 37, 46, 47, 49, 51, 52, 54, 55, 58-60, 62, 65, 70, 76, 82, 84, 85, 88, 95, 99, 102, 105, 108, 109, 112-114, 117, 121, 123, 126, 129, 133, 136, 139, 141, 148-152, 154, 155, 158, 163, 166, 168, 172-174, 178, 179, 181, 184, 186, 188, 190, 191, 193-196, 198, 203, 204, 209, 210, 212, 214, 216, 218, 221, 223, 226, 228, 233, 235, 239, 240, 243-250, 259, 260, 263, 264, 266-270, 274, 278-280, 282, 284, 285, 288-293, 295, 298, 301, 302, 306, 307, 309, 311-315, 320, 321, 324-326, 328-330, 334, 335, 337, 338, 340
 B. subtilis-256, 281
 B. subtilis phage, 82
 B. vulgatus, 337
 Bacterium stewartii, 159
 Bacteroides spp, 295
 Bartonella muris, 80, 232
 Blastomyces spp, 105
 Bl. brasiliensis, 24, 41, 113, 227, 273
 Bl. dermatitidis, 41, 56, 57, 105, 113, 119, 130, 140, 206, 224, 227, 229, 250, 273, 287, 297, 312, 313, 319
 Borrelia spp, 237
 B. anserina, 78, 232
 B. duttoni, 45, 80, 232, 300, 318
 B. novyi, 78, 80, 232, 326
 B. recurrentis, 78, 80, 212, 232
 B. vincentii, 321
 Botryosphaeria ribis, 130
 Botrytis spp, 30, 56, 58, 120, 205, 332
 B. allii, 13, 16, 17, 33, 59, 93, 97, 98, 127, 138, 140, 142, 158, 164, 316, 332
 B. bassiana, 285
 B. cinerea, 35, 41, 55, 81, 93, 153, 198
 Brucella spp, 296
 Br. abortus, 10, 20, 49, 51, 52, 58, 65, 70, 77, 84, 87, 105, 144, 156, 160, 182, 184, 193, 203, 212, 223, 224, 249, 267, 270, 292, 297, 302, 329, 330
 Br. bronchiseptica, 60, 84, 112, 166, 216, 228, 233, 249, 289, 309, 313, 324, 330, 335
 Br. melitensis, 10, 20, 65, 121, 154, 178, 184, 212, 223, 298, 302
 Br. suis, 20, 47, 77, 112, 156, 184, 212, 302, 330, 335
 Byssoschlamys fulva, 138, 142
 Candida spp, 36, 104, 105, 197
 C. albicans, 1, 7, 24, 27, 30, 41, 56, 57, 64, 90, 93, 105, 112-114, 119, 120, 122, 124, 125, 130, 131, 140, 158, 160, 166, 188, 200, 202, 203, 205, 206, 216, 227, 235, 249, 250, 261, 263, 266, 273, 285, 287, 297, 305, 312, 317-319, 321, 324, 329, 332
 C. guilliermondii, 202

- Candida krusei*, 30, 56, 58, 90, 113, 118, 120, 140, 205, 318, 329, 332
C. parakrusei, 56
C. parapsilosis, 24
C. pseudotropicalis, 24, 56
C. reukaufii, 93
C. stellatoidea, 56, 113, 140, 202, 297
C. tropicalis, 24, 56, 90, 93, 105, 116, 118, 124, 140, 188, 202, 285, 318
Cephalosporium spp, 332
C. longisporum, 138
C. recifei, 24
Ceratostomella fimbriata, 54
C. paradoxa, 198
C. ulmi, 140
Cercospora spp, 36, 56
Chaetomium spp, 324
C. convolutum, 319
C. globosum, 12, 46, 82, 102, 186, 191, 209, 312
Chalara quercina, 28, 229, 316
Chilomonas paramecium, 235
Cholera phage, 82
Chromobacterium violaceum, 55
Cladosporium carrioni, 24
C. cucumerinum, 229
C. fulvum, 96
C. herbarum, 93, 332
C. werneckii, 24, 113
Claviceps purpurea, 204, 235, 324
Clostridia, 45 (See also specific clostridia.)
Clostridium spp, 31, 36, 45, 60, 144, 180, 195, 212, 217, 237, 244, 299
Cl. acetobutylicum, 295
Cl. bifermentans, 232
Cl. botulinum, 60, 177, 295, 329
Cl. butyricum, 329
Cl. fallax, 250
Cl. feseri, 112, 160
Cl. hemolyticum, 112, 156
Cl. histolyticum, 14, 146, 223, 232, 250
Cl. novyi, 68, 112, 159, 224, 232, 295
Cl. perfringens, 14, 52, 53, 60, 70, 77, 112, 144, 146, 159, 160, 173, 187, 212, 232, 233, 249, 250, 295, 304, 309, 320, 321
Cl. septicum, 70, 77, 112, 159, 160, 193, 232, 295, 311, 315
Cl. sporogenes, 14, 53, 68, 77, 112, 224, 228, 329
Cl. tetani, 60, 70, 112, 160, 228, 232, 233, 304, 309, 311, 320, 321
Cl. tetanomorphum, 295
Coccidioides spp, 105
C. brasiliensis, 313
C. immitis, 119, 125, 206, 227, 255, 297, 313, 319
Colletotrichum spp, 28, 158, 313
C. atramentarium, 118
C. circinans, 229
C. lagenarium, 96, 229
C. lindemuthianum, 119
C. lini, 332
C. pisi, 229
Corticium solani, 198
Corynebacterium spp, 144, 212, 217, 237, 240, 316, 334
C. acnes, 112
C. bovis, 60
C. diphtheriae, 10, 14, 19, 20, 22, 25, 35, 39, 45, 47, 50, 60, 77, 99, 108, 109, 112, 115, 117, 124, 133, 136, 155, 156, 159, 162, 166, 177-179, 181, 182, 187, 193, 195, 207, 212, 218, 221, 223, 224, 228, 233, 242, 249, 254, 260, 280, 295, 296, 301-303, 309, 311, 321, 326-330, 336
Corynebacterium diphtheriae-512-4096, 281
C. flaccumfaciens, 324, 326
C. hoffmani, 49, 260
C. michiganense, 159, 204, 326
C. ovis, 70
C. pseudodiphtheriae, 155
C. pseudodiphtheriticum, 22, 169, 222, 224, 233, 289
C. pseudotuberculosis, 224, 293
C. pyogenes, 22, 160, 244
C. renale, 22, 182, 224
C. sepedonicum, 159, 204, 326
C. xerose, 3, 10, 22, 23, 45, 50, 53, 71, 89, 105, 108, 109, 112, 177, 178, 204, 225, 233, 241, 260, 301, 303, 309
Coxiella burnetii, 60
Cryptococcus spp, 30, 105, 200
Cr. neoformans, 7, 24, 27, 56, 90, 96, 105, 113, 116, 119, 131, 188, 197, 202, 203, 205, 206, 212, 227, 238, 273, 284, 285, 312, 319, 324
Cr. parakrusei, 24
Cr. pararoseus, 329
Debaryomyces gruetzii, 205
D. matrucoti, 93
Dendrophoma obscurans, 119
Diaporthe citri, 96
Diplocarpon rosae, 96
Diplococcus spp, 237
D. pneumoniae, 3, 6, 7, 14, 20, 22, 23, 31, 35, 40, 45, 52, 53, 60, 65, 68, 70, 91, 108, 109, 112, 117, 121, 144, 146, 152, 154, 156, 159, 182, 184, 193, 212, 217, 218, 221-224, 228, 232, 233, 235, 240, 242, 244, 247, 250, 254, 260, 267, 286, 289, 293, 295-298, 300-302, 304, 309, 311, 320, 321, 323, 326, 328, 329, 334, 340
D. pneumoniae (type 2), 315
Diplodia spp, 119
D. zeae, 96
Dipodascus uninucleatus, 205, 297
Eastern equine encephalitis virus, 1
Endomyces spp, 105
Endomycopsis spp, 227
Endothia parasitica, 96, 119
Entamoeba histolytica, 25, 27, 36, 78, 80, 108, 109, 112, 125, 128, 212, 227, 232, 255, 259, 273, 300, 309, 313
Enterobius vermicularis, 232
Enterococcus spp, 226
Epidermophyton spp, 93, 131
Ep. cruris, 235
Ep. floccosum, 24, 41, 105, 113, 115, 140, 227, 250, 313
Ep. inguinale, 41, 205
Erwinia amylovora, 224
E. carotovora, 55, 236
Erysipelothrix rhusiopathiae, 60, 87, 112, 156, 217, 224, 228, 232, 233, 295, 309, 330
Escherichia coli, 7, 10, 12, 14, 15, 17, 18, 21, 22, 31-33, 35-37, 39, 40, 46, 47, 51, 52, 55, 58, 60, 69, 82, 84, 85, 87-90, 99, 102, 105, 112, 114, 122-124, 126, 129, 132, 133, 136, 137, 139, 140, 144, 146, 148, 151, 154, 159, 160, 163, 166, 174, 177-179, 181-183, 186, 187, 191, 194, 209, 210, 212, 213, 216, 218, 221, 223-226, 230, 233, 235, 236, 239, 242, 244-250, 252, 259, 260, 263, 264, 266, 267, 270, 275, 279, 280, 281, 284, 286, 288-290, 292, 294, 297-299, 302, 304, 305, 309, 311-314, 320, 321, 323, 324, 327, 329, 330, 335, 337, 338

- Escherichia coli* phage T₂, 82
Euglena gracilis, 96
- Feline pneumonitis virus*, 80, 232, 309
Flavobacterium spp, 326
Fonsecaea compactum, 24
F. pedrosoi, 24
Fungi imperfecti, 153
Fusarium spp, 7, 55, 125, 198
F. bulbigenum, 24
F. caeruleum, 13, 59, 138, 164, 332
F. culmorum, 332
F. graminearum, 13, 59, 138, 319
F. oxysporum, 93, 113, 130
F. oxysporum dianthi, 119
Fusobacterium plauti-vincenti, 294
- Gaffkya tetragena*, 14, 23, 60, 112, 144, 223, 289, 301, 340
Geotrichum spp, 24, 56, 105, 119, 227
G. cutaneum, 319
Gliocladium fimbriatum, 316
G. roseum, 324
Gliomastix convoluta, 82, 102, 186, 191
Glomerella spp, 105
G. cingulata, 81, 229, 316
Gnomonia fragariae, 119
Gram-negative bacteria, 15, 35, 37, 60, 70, 78, 80, 84, 94, 108, 109, 112, 121, 126, 146, 156, 174, 212, 228, 232, 235, 249, 276, 296, 297, 308, 309 (See also specific bacteria.)
Gram-positive bacteria, 5, 15, 21, 23, 25, 32, 34, 35, 37, 45, 53, 60, 68, 70, 75, 76, 78, 80, 83, 85, 94, 105, 108, 109, 112, 121, 126, 133, 144, 156, 174, 212, 216, 220, 232, 233, 235, 236, 253, 271, 276, 296, 297, 307-309, 315 (See also specific bacteria.)
Gray lung virus, 80, 232
- Hansenula anomala*, 73, 205
Helminthosporium spp, 36, 158, 268, 316
H. oryzae, 54, 81
H. sacchari, 319
H. sativum, 55, 119, 324
Hemolytic streptococci, 79, 183, 217
Hemophilus spp, 237, 296
H. aegyptius, 78, 80, 232
H. ducreyi, 166, 309
H. influenzae, 36, 45, 60, 84, 112, 156, 184, 212, 224, 232, 249, 289, 309, 329, 330
H. pertussis, 15, 20, 45, 60, 69, 70, 99, 112, 117, 140, 156, 180, 184, 212, 218, 221, 224, 228, 233, 249, 292, 293, 330
Herpes simplex virus, 239
Heterosporium iridis, 96
Histoplasma spp, 105
H. capsulatum, 24, 27, 30, 41, 56, 105, 113, 119, 125, 197, 206, 227, 229, 238, 250, 273, 284, 287, 312, 313, 319
Hormodendrum spp, 93
H. compactum, 113, 119, 273
H. langeroni, 319
H. pedrosoi, 56, 90, 113, 206
- Infectious bronchitis virus*, 333
Influenza virus, 167, 333
Influenza A virus, 103, 239
Influenza B virus, 103
Influenza FM-1 virus, 62
Influenza PR-8 virus, 62, 128, 247, 300
- Japanese B encephalitis virus*, 2
- Klebsiella* spp, 270, 296
K. pneumoniae, 1, 10, 12, 21, 22, 31, 35, 41, 46, 52, 55, 58, 69, 70, 82, 84, 99, 102, 112, 123, 124, 151, 166, 168, 178-181, 185, 186, 191, 193, 209, 210, 212, 214, 223, 224, 226, 232, 233, 239, 244, 245, 247-250, 259, 288, 289, 298, 302, 305, 309, 312, 313, 323, 327, 329, 330, 335, 337
Kloeckera spp, 227
- Lactobacillus* spp, 108, 109, 144, 166
L. acidophilus, 23, 53, 112, 315, 321
L. casei, 23, 53, 108, 112, 300
L. lactis, 166
L. leichmannii, 23
Leishmania donovani, 212, 255, 273, 313, 318
L. tropica, 255, 273, 313
Leptosphaeria acuta, 38
L. culmifraga, 38
L. culmorum, 38
Leptospira spp, 237
L. canicola, 174, 313
L. grippotyphosa, 313
L. icterohemorrhagiae, 14, 108, 109, 112, 174, 180, 212, 313
L. mitis, 313
L. pomona, 326
Leuconostoc citrovorum, 108, 109, 166, 224
L. mesenteroides, 224
Listeria monocytogenes, 60, 70, 112, 181, 212, 228, 232, 233, 295, 309
Lymphogranuloma venereum virus, 78, 108
- Malleomyces mallei*, 87, 112, 212
M. pseudomallei, 126
Melanospora destruens, 198
Memnoniella echinata, 46, 82, 102, 186, 191, 209
Meningopneumonitis virus, 108, 109, 156
Micrococci, 48 (See also specific micrococci.)
Micrococcus spp, 76, 169, 237, 296, 297
M. albus, 281, 326, 329
M. aurantiacus, 301
M. citreus, 14, 133, 136, 281, 327, 329
M. conglomeratus, 22, 300, 320, 321
M. flavus, 21, 52, 163, 166, 190, 216, 266, 306, 307, 329
M. freudenrichii, 329
M. lysodeikticus, 144, 166, 212, 297, 301, 320, 321
M. pyogenes phage, 102
M. pyogenes var. *albus*, 47, 55, 129, 136, 140, 199, 214, 221, 224
M. pyogenes var. *aureus*, 3, 4, 6, 7, 9, 10, 12-15, 17-23, 25, 31, 34, 35, 37-40, 45-47, 55, 58, 60, 63, 65, 68, 71, 76, 77, 82, 84, 86, 88, 91, 92, 99, 100-102, 105, 111-115, 117, 121-124, 126, 129, 132-138, 140, 141, 144, 146, 148-152, 154, 156, 158-163, 166, 168, 170-174, 176-196, 198, 199, 203, 204, 207, 209-218, 221, 223-226, 228, 230, 232, 233, 235, 236, 239-242, 244-248, 252-254, 256, 258-261, 264, 266-270, 272, 278, 280, 282, 284, 286, 288-293, 295, 297-307, 309-316, 320, 321, 323-330, 334-338, 340
M. pyogenes var. *aureus*-2-1024, 281
M. sphaeroides, 166
M. tetragena, 53
Microsporium spp, 105, 235
M. audouinii, 24, 27, 41, 105, 130, 140, 205, 206, 227, 235, 249, 250, 303, 313, 324
M. canis, 24, 27, 105, 131, 140, 206, 227, 287, 303, 319, 324
M. gypseum, 24, 41, 90, 113, 115, 160, 202, 206, 261, 312, 321

- Microsporium lanosum*, 205, 249
Monascus spp, 54, 81
Monilia spp, 121
M. nigra, 229
Monosporium apiospermum, 24, 41, 113, 119, 224
Moraxella bovis, 112, 156
Mouse pneumonitis virus, 108, 232
Mucor spp, 81, 120
M. erectus, 138, 319
M. javanicus, 35
M. mucedo, 93, 114, 127, 142, 164, 200
M. pusillus, 30, 58, 120, 205, 332
M. sulfa, 297
Mumps virus, 222
Mycobacterium spp, 17, 37, 58, 60, 62, 152, 190, 216, 218, 228, 233, 243, 253, 259, 275, 284, 289, 291, 298, 313
Myc. avium, 20, 21, 35, 51, 54, 55, 65, 84, 95, 99, 108, 115, 121, 141, 149, 166, 181, 184, 194, 208, 211, 212, 221, 291, 297, 323, 326, 327
Myc. butyricum, 266, 324
Myc. lacticola, 155
Myc. leprae, 212
Myc. minetti, 52
Myc. paratuberculosis, 107
Myc. phlei, 1, 12, 17, 19-22, 26, 35, 37, 39, 46, 51, 52, 65, 71, 89, 107, 108, 121, 133, 141, 148-151, 163, 166, 173, 176, 177, 181, 182, 198, 208, 212, 219, 221, 228, 230, 241, 243, 248, 251, 263, 264, 266, 274, 278, 281, 288, 295, 302, 307, 309, 323, 326, 327, 330
Myc. ranae, 52, 58, 168, 181, 182, 212, 214-216, 295, 309, 330
Myc. smegmatis, 12, 20, 21, 35, 46, 55, 58, 65, 82, 102, 121, 123, 133, 136, 155, 168, 177, 178, 185, 186, 191, 209, 210, 216, 226, 228, 233, 239, 243, 247, 248, 251, 281, 288, 293, 295, 297, 309, 323, 326, 330, 335, 340
Myc. tuberculosis, 10, 11, 19, 21, 22, 26, 31, 35, 36, 40, 46, 49-51, 58, 67, 70, 77, 84, 87, 104, 106, 110-112, 114, 115, 144, 148, 151, 152, 155, 156, 159, 166, 168, 173, 177, 178, 181, 182, 185, 187, 195, 203, 209, 210, 212, 215, 217, 240, 243-246, 248, 250, 262-264, 266, 269, 270, 274, 290, 292, 296, 297, 300, 302, 309, 312, 314, 325, 330, 331, 333, 335, 338
Myc. tuberculosis lacticola, 293
Myc. tuberculosis var. *bovis*, 163, 208, 323
Myc. tuberculosis var. *hominis*, 52, 99, 113, 124, 126, 143, 150, 163, 167, 175, 201, 208, 221, 224, 295, 298, 323, 327, 329, 334
Myc. tuberculosis var. *hominis* (strain BCG), 315
Myc. tuberculosis var. *hominis* (strain H37RV), 293
Mycoderma spp, 30, 105, 114, 200
M. valida, 93
Mycotorula spp, 121
Myrothecium verrucaria, 13, 16, 46, 82, 102, 138, 164, 186, 191, 209, 312

Neisseria spp, 155, 217, 237
N. catarrhalis, 36, 60, 77, 84, 112, 140, 144, 156, 166, 178, 223, 228, 233, 235, 242, 249, 261, 289, 295, 309, 321, 326, 330
N. gonorrhoeae, 45, 60, 69, 70, 77, 112, 144, 156, 180, 184, 212, 224, 228, 233, 289, 299, 300, 304, 309, 315, 320, 334
N. meningitidis, 15, 22, 36, 60, 69, 70, 77, 112, 121, 144, 152, 156, 159, 162, 184, 212, 224, 228, 233, 249, 254, 289, 298, 309, 320, 321, 327-330, 334
N. sicca, 301
Nematospora spp, 36
N. coryli, 205

Neurospora ascospora, 297
N. crassa, 55, 319
N. sitophila, 93, 324
Newcastle disease virus, 222, 300, 333
Nigrospora sphaerica, 28
Nocardia sp, 240
N. asteroides, 78, 113, 114, 119, 188, 238, 284, 285, 330
N. coeliaca, 166
N. gardneri, 166
N. mexicana, 114

Oidium lactis, 93, 114, 200
Oospora lactis, 11
Ophiobolus herpotrichus, 38
Ornithosis virus, 329

Paracoccidioides brasiliensis, 56
Paracolobactrum spp, 112
Pasteurella spp, 40, 71, 126, 286, 296, 299, 330
Past. multocida, 22, 36, 60, 70, 80, 87, 160, 181, 182, 187, 212, 224, 232, 244, 249, 258, 267, 289, 295, 309, 330
Past. pestis, 124, 249, 299
Past. tularensis, 232, 275, 297
Penicillium spp, 7, 200, 268, 324
P. brevi-compactum, 13, 59
P. chrysogenum, 17, 81, 93, 114, 116, 148, 188, 238, 266, 277, 284, 285
P. citrinum, 319
P. claviforme, 17
P. digitatum, 59, 119, 138, 142, 235, 319
P. expansum, 13, 59, 138, 164, 229, 319, 332
P. gladioli, 13, 127
P. glaucum, 277
P. italicum, 81
P. janczewski, 138
P. lilacinum, 319
P. meleagrinus, 319
P. notatum, 41, 46, 82, 93, 102, 119, 125, 138, 172, 186, 191, 198, 209, 229, 297, 316, 332
P. oxalicum, 319
P. puberulum, 58
P. roqueforti, 41, 319
P. roseum, 55
P. spinulosum, 30, 319
P. stoloniferum, 59
Phialophora verrucosa, 24, 27, 113, 119, 273
Phoma betae, 119, 142
P. lingam, 28
Phomopsis spp, 119, 313
Photobacterium fischeri, 186, 248, 288
Phycomyces blakesleeanae, 82, 186, 191, 209
Phycomycetes, 53 (See also specific phycomycetes.)
Physalospora tucumanensis, 96
Phytophthora spp, 35
P. erythroseptica, 204, 235
P. infestans, 118
P. palmivora, 142
Piricularia oryzae, 55
Plasmodium spp, 232
P. berghei, 78
P. gallinaceum, 78, 80, 128, 144, 321
P. lophurae, 45
Pleospora spp, 324
Poliomyelitis virus, 1
Poliomyelitis Y-SK virus, 239
Polyporus spp, 36
P. circinatus, 324
Poria spp, 36

- Proteus* spp, 22, 91, 126, 159, 174, 224, 225, 294, 302, 313, 330
Pr. mirabilis, 126, 224
Pr. morgani, 126, 224
Pr. rettgeri, 126, 224
Pr. vulgaris, 1, 14, 17, 20, 52, 65, 84, 99, 112, 121, 122, 126, 133, 146, 154, 166, 178, 179, 193, 194, 212, 216, 218, 221, 223, 224, 233, 235, 236, 246, 259, 263, 266-268, 270, 278, 282, 284, 290, 292, 302, 305, 311, 312, 314, 323, 327, 329, 330, 337, 338
Pseudomonas spp, 126, 226
Ps. aeruginosa, 12, 14, 22, 46, 49, 52, 65, 82, 84, 89, 99, 102, 105, 112, 123, 124, 151, 154, 159, 166, 174, 177, 181, 182, 186, 191, 193, 203, 209, 210, 212, 216, 224, 226, 233, 235, 239, 244-247, 249, 250, 266, 270, 278, 281, 284, 288-290, 294, 295, 298, 302, 305, 312-314, 323, 324, 329, 330
Ps. aeruginosa phage 2A, 239
Ps. fluorescens, 136, 148, 294
Ps. fluorescens-2, 281
Ps. glycinea, 159
Ps. marginalis, 159
Ps. medicaginis, 17
Ps. mori, 17
Ps. syringae, 159
Psittacosis virus, 78, 108, 109, 156
Pullularia spp, 56
Pythium spp, 313
P. intermedium, 281
P. ultimum, 235, 236

Rabies virus, 239
Rhizoctonia spp, 105, 313
R. crocorum, 204, 235
R. solani, 41, 55, 93, 119, 140, 235, 286, 324
Rhizopus spp, 93
R. japonicus, 35
R. nigricans, 30, 41, 55, 81, 114, 297
R. stolonifer, 198
Rhodotorula spp, 131, 227
Rh. glutinis, 24
Rh. mucilaginoso, 24
Rh. rubra, 205, 297
Rickettsiae, 80, 108, 109, 112, 232, 289 (See also specific rickettsiae.)
Rickettsia akari, 60, 108
R. conori, 60
R. prowazekii, 36, 60, 108, 109, 156
R. rickettsi, 60, 108
R. tsutsugamushi, 60, 300
R. typhi, 60, 108

Saccharomyces spp, 8, 55, 93, 227
Sac. carlsbergensis, 205, 319
Sac. cerevisiae, 20, 24, 28, 46, 58, 62, 64, 73, 82, 93, 96, 102, 113, 118, 120, 148, 158, 186, 209, 245, 266, 297, 312, 316, 317, 332
Sac. formosensis, 118
Sac. fragilis, 73
Sac. pastorianus, 11, 73, 118, 119, 166
Sac. saké, 35, 73, 81, 114, 116, 200, 221, 266, 277, 284, 329
Salmonella spp, 10, 71, 84, 89, 144, 146, 147, 151, 178, 193, 211, 226, 244, 249, 296
S. ambigua, 166
S. choleraesuis, 160, 232, 235, 302
S. enteritidis, 31, 63, 70, 85, 99, 133, 159, 166, 174, 177, 223, 225, 232, 235, 236, 249, 254, 263, 264, 281, 302, 303, 314, 326, 329
Salmonella gallinarum, 22, 78, 80, 166, 181, 232, 259, 297, 309, 337
S. hirschfeldii, 329
S. paratyphi, 1, 35, 37, 55, 87, 88, 126, 133, 140, 146, 154, 166, 179, 183, 203, 212, 218, 221, 223, 224, 233, 235, 236, 249, 250, 252, 284, 286, 297, 298, 302, 309, 313, 321, 329, 330, 335
S. pullorum, 22, 55, 151, 212, 214, 224, 259, 267, 302, 335
S. schottmuelleri, 22, 35, 36, 40, 69, 70, 88, 91, 112, 124, 126, 140, 179, 182, 183, 185, 203, 212, 214, 218, 221, 223, 224, 235, 249, 250, 252, 263, 266, 267, 281, 284, 297-299, 302, 309, 312, 329, 330, 337
S. typhimurium, 1, 22, 55, 69, 70, 149, 154, 223, 224, 232, 235, 236, 250, 281, 288, 302, 311, 323, 329
S. typhosa, 13, 35-37, 39, 40, 51, 52, 69, 70, 84, 87, 88, 91, 99, 112, 121, 124, 126, 132, 133, 140, 144, 154, 156, 159, 174, 177-179, 183, 185, 203, 212, 214, 218, 221, 223-225, 232, 233, 235, 236, 242, 245, 246, 249, 250, 252, 259, 263, 264, 267, 270, 275, 278, 280-282, 284, 286, 290, 292, 295, 297-299, 302, 304, 305, 309, 312, 313, 320, 329, 330, 335, 338
Sarcina spp, 71
S. lutea, 2, 4, 7, 17, 20, 34, 45, 48, 52, 55, 58, 70, 76, 77, 99, 108, 111, 129, 144, 151, 166, 172, 190, 196, 212, 216, 223, 224, 235, 240, 259, 266, 268, 283, 289, 293, 297, 302, 307, 309, 311, 320, 321, 326, 335, 337
Schizosaccharomyces spp, 93
S. pomb, 73
Sclerotinia spp, 41, 105, 313
S. americana, 140
S. fructicola, 28, 96, 205, 316
S. fructigena, 198
S. sclerotiorum, 38, 119, 235
Sclerotium rolfsii, 93, 96
Serratia marcescens, 11, 55, 151, 212, 224, 329, 330, 337
Shigella spp, 10, 126, 144, 147, 151, 226, 296, 297
Sh. alkalescens, 302
Sh. dysenteriae, 1, 15, 22, 35, 37, 51, 84, 85, 88, 89, 91, 99, 121, 133, 136, 146, 149, 154, 178, 179, 183, 212, 218, 221, 224, 235, 236, 249, 250, 263, 266, 267, 278, 281, 284, 302, 308, 309, 329
Sh. paradysenteriae, 22, 35, 37, 133, 154, 156, 166, 179, 182, 183, 187, 212, 214, 223, 235, 242, 249, 252, 264, 267, 302, 311, 329, 330
Sh. sonnei, 22, 52, 89, 112, 124, 133, 152, 193, 212, 223, 224, 249, 298, 309, 314, 327, 337
Silkworm jaundice virus, 148
Sphaeropsis spp, 313
Spirillum minus, 80
S. serpens, 181
Spirochaeta sogdianum, 15
Sporobolomyces spp, 227
Sporotrichum spp, 105
S. beurmanni, 188, 285, 319
S. schenckii, 24, 41, 57, 93, 105, 119, 206, 250, 273, 287, 312, 319
S. tropicale, 319
Stachybotrys spp, 324
S. atra, 59, 127, 332
Staphylophage, 82
Stemphylium spp, 59, 138, 332
S. consortiale, 46, 82, 102, 186, 191
S. sarcinaeforme, 28
Stereum purpureum, 204, 235
Streptococcus spp, 7, 40, 60, 71, 112, 146, 154, 156, 166, 180, 182, 195, 215, 223, 226, 237, 240, 270, 280, 296, 299, 336

- Streptococcus agalactiae*, 23, 45, 53, 68, 112, 156, 160, 224, 244, 295
Str. cremoris, 101
Str. dysgalactiae, 23, 53, 68, 112, 160
Str. faecalis, 22, 52, 60, 68, 84, 105, 124, 144, 166, 181, 187, 193, 207, 221, 233, 244, 258, 267, 278, 289, 293, 295, 309, 313, 315, 321, 326, 329
Streptococcus (group D), 22, 144, 280
Str. hemolyticus, 58, 68, 77, 101
Str. lactis, 60, 71, 77, 101, 166, 295
Str. mitis, 60, 108, 109, 124, 166, 207, 295
Str. pyogenes, 3, 6, 14, 15, 17, 19, 20, 22, 23, 25, 31, 34, 35, 45, 49, 52, 53, 60, 63, 65, 69, 70, 85, 87, 99, 112, 117, 121, 124, 133, 136, 144, 155, 156, 159, 162, 166, 170, 173, 174, 177, 179, 184, 187, 193, 198, 199, 207, 212, 218, 221, 223, 224, 225, 228, 230, 232, 233, 235, 242, 244, 247, 250, 252, 254, 256, 258, 260, 261, 267, 268, 289, 292, 293, 295, 298-302, 304, 305, 309, 311, 315, 320, 321, 323, 326-328, 330, 334, 340
Str. pyogenes-2048-4096, 281
Str. salivarius, 166, 242, 321
Str. uberis, 23, 45, 112, 224
Str. viridans, 14, 22, 45, 68, 70, 129, 133, 136, 140, 159, 179, 182, 212, 221, 224, 235, 252, 254, 267, 289, 295, 298, 300, 301, 303, 309, 311, 326-328, 330
Str. viridans-2048, 281
Streptomyces spp, 324
S. antibioticus, 212
S. coelicolor, 212
S. diastaticus, 166
S. fradiae, 212
S. griseus, 114, 166, 221, 285, 324
S. griseus phage, 239
S. lavendulae, 166, 212
S. roseoflavus, 114
S. scabies, 114
S. venezuelae, 166
Syphacia obvelata, 259

Tetrahymena geleii, 96
T. pyriformis (strain W), 259
Thamnidium elegans, 13, 59, 138, 142, 319
Thielaviopsis spp, 119
Tobacco mosaic virus, 319
Tobacco necrosis virus, 319
Tomato bushy stunt virus, 319
Torula spp, 105
T. cremoris, 205
T. rubra, 118, 200, 277, 329
T. utilis, 30, 58, 64, 73, 120, 205, 238, 284, 285, 332
Torulopsis delbruckii, 205
T. neoformans, 93
T. rotundata, 122
T. utilis, 93
Treponema spp, 237
T. pallidum, 45, 78, 300, 318, 321
T. pallidum (Reiter strain), 318
Trichoderma spp, 7, 56, 125, 205
T. viride, 13, 93, 138, 164, 332
Trichomonas foetus, 27, 36, 78, 80, 112, 222, 291, 318, 340
T. vaginalis, 27, 34, 84, 105, 118, 120, 128, 212, 214, 222, 224, 232, 249, 273, 277, 291, 297, 313, 318, 321
Trichophyton spp, 8, 105, 120, 131, 188, 197, 205, 235, 238

Trichophyton equinum, 303
T. gallinae, 24
T. gypseum, 140
T. interdigitale, 30, 58, 81, 114, 120, 200, 205, 297, 319, 329, 332
T. megnini, 24
T. mentagrophytes, 7, 12, 24, 41, 46, 57, 82, 90, 93, 102, 105, 113, 115, 122, 123, 125, 130, 158, 160, 186, 191, 202, 205, 206, 209, 216, 227, 235, 249, 261, 266, 284, 285, 297, 305, 312, 316, 319, 321, 324
T. purpureum, 140, 200, 249
T. rosaceum, 227
T. rubrum, 24, 41, 105, 119, 140, 166, 202, 206, 227, 250, 285, 287, 313, 319, 324
T. schoenleinii, 41, 105, 160, 297, 321
T. sulfureum, 27, 273, 319
T. tonsurans, 24, 90, 105, 140
T. violaceum, 41, 273
Trichosporium rubrum, 93
Trichosporon spp, 93, 227
T. beigelli, 116, 238
T. utilis, 116
Trichothecium roseum, 138, 332
Trypanosoma brucei, 325
T. connorhini, 255
T. cruzi, 80, 105, 125, 212, 255, 259, 273, 300, 313, 318, 320, 321, 332
T. equiperdum, 7, 108, 300
T. gambiense, 259, 318
T. rhodesiense, 112

Ustilago tritici, 96
U. zeae, 81, 96, 118, 205

Vaccinia virus, 45, 214, 239
Venturia inaequalis, 28, 96
Verticillium spp, 93, 158, 198, 324
V. alboatrum, 138, 229
V. dahliae, 204, 235
Vibrio comma, 10, 35, 36, 65, 69, 70, 78, 84, 85, 89, 99, 121, 124, 129, 133, 136, 146, 152, 156, 160, 161, 178, 182-184, 195, 211, 212, 223, 226, 232, 236, 249, 252, 275, 278, 288, 298, 330
V. comma-16, 281
V. comma phage, 102
V. comma phage C, 239
V. foetus, 160

Western equine encephalitis virus, 1
Willia spp, 30, 58, 120, 317, 332
W. anomala, 114, 329
Wojnowicia graminis, 38

Xanthomonas campestris, 17, 55, 159, 236, 316, 324
X. malvacearum, 17, 77, 159, 236
X. phaseoli, 17
X. pruni, 159, 224
X. translucens, 324

Zygosaccharomyces spp, 93
Z. major, 73
Z. prioranus, 119
Z. salsus, 93

APPENDIX II: ANTIBIOTIC SOURCES,
A LISTING BY ORGANISM

Source microorganism(s) for each of the 340 antibiotics are listed in the text. These data have been rearranged here, by organism rather than by antibiotic. The name of each organism is followed by the name(s) of antibiotics for which it is a source. Underscored numbers are the identifying item numbers of antibiotics as they appear in the book.

| | | | |
|----------------------------|-----------------------------|-------------------------------|-------------------------------------|
| Acetobacter spp | Kojic acid, <u>174</u> | Bacillus subtilis (concluded) | Eumycin, <u>115</u> |
| Achromobacter xerosis | Xerosin, <u>339</u> | | Fluvomycin, <u>122</u> |
| Aerobacter aerogenes | Coliformin, <u>90</u> | | Globicin, <u>141</u> |
| Agroclybe dura | Agroclybin, <u>12</u> | | Iturins, <u>172</u> |
| Alternaria solani | Alternaric acid, <u>16</u> | | Mycosubtilin, <u>205</u> |
| | Alternarine, <u>17</u> | | Neocidin, <u>211</u> |
| Alternaria tenuis | Alternariol, <u>18</u> | | Subtenolin, <u>299</u> |
| Aspergillus spp | Citrinin, <u>85</u> | | Subtilin, <u>300</u> |
| | Granegillin, <u>147</u> | | Toximycin, <u>316</u> |
| | Kojic acid, <u>174</u> | | Xanthellin, <u>335</u> |
| | Mycocidin, <u>201</u> | Bacterium antimyceticum | Comirin, <u>93</u> |
| | Patulin, <u>235</u> | | |
| | Penicillic acid, <u>236</u> | Cephalosporium spp | Cephalosporin C, <u>69</u> |
| | Penicillins, <u>237</u> | | Cephalosporin N, <u>70</u> |
| Aspergillus candidus | Candidulin, <u>58</u> | | Cephalosporin P series, <u>71</u> |
| Aspergillus flavus | Aspergillic acid, <u>31</u> | | |
| Aspergillus fumigatus | Fumagillin, <u>128</u> | Cephalosporium salmo- | |
| | Fumigatin, <u>129</u> | synnematum | Synnematin, <u>302</u> |
| | Gliotoxin, <u>140</u> | Cephalothecium sp | Cephalothecin, <u>72</u> |
| | Helvolic acid, <u>159</u> | Chaetomium cochlioides | Chetomin, <u>76</u> |
| | Spinulosin, <u>288</u> | Chromobacterium sp | Chlororaphin, <u>79</u> |
| Aspergillus humicola | Humicolin, <u>164</u> | Chromobacterium iodinum | Iodinin, <u>170</u> |
| Aspergillus melleus | Mellein, <u>189</u> | Chromobacterium violaceum | Violacein, <u>328</u> |
| Aspergillus nidulans | Nidulin, <u>215</u> | Clitocybe candida | Clitocybins, <u>87</u> |
| | Nor-nidulin, <u>215</u> | Clitocybe diatreta | Diatretynes, <u>100</u> |
| Aspergillus ochraceus | Mellein, <u>189</u> | Clitocybe illudens | Illudins, <u>168</u> |
| Aspergillus oryzae | Oryzasazine, <u>231</u> | Clitocybe nebularis | Nebularine, <u>208</u> |
| Aspergillus parasiticus | Aurantidin, <u>32</u> | Coprinus quadrifidus | Quadrifidins, <u>264</u> |
| Aspergillus tamaris-oryzae | Kojic acid, <u>174</u> | Coprinus similis | 5-Methoxy-p-toluquinone, <u>191</u> |
| Aspergillus terreus | Geodin, <u>136</u> | | Cordycepin, <u>95</u> |
| | Terreicin, <u>304</u> | Cordyceps militaris | |
| | Terreic acid, <u>305</u> | Drosophila substrata | Drosophilins, <u>102</u> |
| Bacillus spp | Fungistatin, <u>131</u> | | |
| | Gramicidin S, <u>146</u> | Escherichia coli | Colicines, <u>89</u> |
| Bacillus alvei | Alvein, <u>19</u> | | Coliformin, <u>90</u> |
| Bacillus brevis | Brevin, <u>50</u> | Fomes juniperinus | Fomecin A, <u>123</u> |
| | Brevolin, <u>51</u> | Fusarium spp | Chlamydosporin, <u>77</u> |
| | Gramicidin, <u>144</u> | | Lateritiin group, <u>176</u> |
| | Gramicidin J, <u>145</u> | Fusarium bostrycoides | Bostrycoidin, <u>49</u> |
| | Tyrocidine, <u>320</u> | Fusarium javanicum | Javanicin, <u>173</u> |
| | Tyrothricin, <u>321</u> | Fusarium orthoceras | Enniatin A, <u>106</u> |
| Bacillus cereus | Biocerin, <u>47</u> | | Enniatin B, <u>107</u> |
| Bacillus circulans | Circulin, <u>84</u> | Ganoderma oregonense | Oregonensin, <u>230</u> |
| | Polypeptin, <u>250</u> | Gibberella baccata | Baccatine A, <u>38</u> |
| Bacillus krzemieniewski | Polypeptin, <u>250</u> | Gibberella fujikuroi | Fusaric acid, <u>132</u> |
| Bacillus laterosporus | Laterosporins, <u>177</u> | Gliocladium roseum | Aurantiogliocladin, <u>33</u> |
| Bacillus licheniformis | Bacitracins, <u>45</u> | | Gliorosein, <u>139</u> |
| | Licheniformins, <u>182</u> | | Rubrogliocladin, <u>279</u> |
| Bacillus mesentericus | Esperin, <u>110</u> | Grifola confluens | Grifolin, <u>149</u> |
| Bacillus polymyxa | Polymyxins, <u>249</u> | | |
| Bacillus pumilus | Pumilin, <u>258</u> | Inoloma traganum | Inolomin, <u>169</u> |
| | Tetaine, <u>308</u> | | |
| Bacillus simplex | Simplexin, <u>286</u> | Lactarius deliciosus | Lactaroviolin, <u>175</u> |
| Bacillus subtilis | Bacilipins, <u>39</u> | Lentinus degener | 5-Methoxy-p-toluquinone, <u>191</u> |
| | Bacillin, <u>40</u> | | Lenzitin, <u>179</u> |
| | Bacillomycin, <u>41</u> | Lenzites sepiaria | Thermophilin, <u>310</u> |
| | Bacillomycin B, <u>42</u> | Lenzites thermophila | |
| | Bacilysin, <u>44</u> | | |
| | Bacitracins, <u>45</u> | | |

| | | | |
|------------------------------|--|--------------------------|--|
| Marasmius conigenus | Marasmic acid, <u>186</u> | Polyporus betulina | Polyporenic acid C, <u>251</u> |
| Marasmius graminum | 6-Methyl-1,4-naphtha- quinone, <u>192</u> | Polyporus biforminis | Ungulinic acid, <u>322</u> |
| Metarrhizium glutinosum | Glutinosin, <u>142</u> | Polystictus sanguineus | Biformynes, <u>46</u> |
| Micrococcus sp | Micrococcin, <u>195</u> | Poria corticola | Polyporin, <u>252</u> |
| Micromonospora sp | Microcins, <u>194</u> | | Nemotin, <u>209</u> |
| | Micromonosporin, <u>196</u> | | Nemotinic acid, <u>210</u> |
| Mycobacterium tuberculosis | Phthiocol, <u>242</u> | Poria tenuis | Nemotin, <u>209</u> |
| | | | Nemotinic acid, <u>210</u> |
| Nocardia spp | Azomycin, <u>37</u> | Proactinomyces cyaneus | Litmocidin, <u>183</u> |
| | Cardicin, <u>62</u> | Pseudomonas aeruginosa | Glyco-lipide, <u>143</u> |
| | Nocardamin, <u>219</u> | | Hemipyrocyanine, <u>160</u> |
| | Nocardianin, <u>220</u> | | Pyo compounds, <u>260</u> |
| | Nocardorubin, <u>221</u> | | Pyocyanine, <u>261</u> |
| | Streptocardin, <u>290</u> | | Pyolipic acid, <u>262</u> |
| Nocardia acidophilus | Mycomycin, <u>203</u> | Pseudomonas antimycetica | Comirin, <u>93</u> |
| Nocardia formica | Noformicin, <u>222</u> | Pseudomonas viscosa | Viscosin, <u>333</u> |
| Nocardia gardneri | Proactinomycins, <u>254</u> | | |
| Nocardia kuroishi | Neonocardin, <u>213</u> | | |
| Nocardia mesenterica | Azomycin, <u>37</u> | Serratia marcescens | Marcesin, <u>187</u> |
| | Mesenterin, <u>190</u> | | Prodigiosin, <u>255</u> |
| | | | Hirsutic acids, <u>162</u> |
| Oidiodendron fuscum | Fuscin, <u>133</u> | Stereum hirsutum | Nisins, <u>217</u> |
| | | Streptococcus cremoris | Diplococcin, <u>101</u> |
| | | Streptococcus lactis | Actiduids, <u>3</u> |
| | | Streptomyces spp | Actinomyceline, <u>5</u> |
| Penicillium spp | Gentisyl alcohol, <u>135</u> | | Actinone, <u>8</u> |
| | Griseofulvin, <u>153</u> | | Actinorubin, <u>10</u> |
| | Notatin, <u>223</u> | | Amphotericins, <u>24</u> |
| | Patulin, <u>235</u> | | Anisomycin, <u>27</u> |
| | Penicillic acid, <u>236</u> | | Antimycin A, <u>28</u> |
| | Penicillins, <u>237</u> | | Aureolic acid, <u>34</u> |
| | Puberulic acid, <u>256</u> | | Bromotetracycline, <u>52</u> |
| | Puberulonic acid, <u>257</u> | | Cacaomycetin, <u>54</u> |
| Penicillium albidum | Albidin, <u>13</u> | | Candididins, <u>56</u> |
| Penicillium brevi-compactum | Mycophenolic acid, <u>204</u> | | Carzinocidin, <u>64</u> |
| Penicillium canescens | Canescin, <u>59</u> | | Catenulin, <u>67</u> |
| Penicillium carneo-lutescens | Carneolutescin, <u>63</u> | | Cereviocidin, <u>73</u> |
| Penicillium citrinum | Citrinin, <u>85</u> | | Chartreusin-like antibiotic, <u>75</u> |
| Penicillium cyclopium | Cyclopaldic acid, <u>97</u> | | Chromin, <u>81</u> |
| | Viridicatin, <u>331</u> | | Chrysomycin, <u>82</u> |
| Penicillium daleae | Kojic acid, <u>174</u> | | Dextromycin, <u>99</u> |
| Penicillium frequentans | Citromycetin, <u>86</u> | | Ehrlichin, <u>103</u> |
| | Frequentin, <u>127</u> | | Endomycin, <u>105</u> |
| Penicillium funiculosum | Helenine, <u>157</u> | | Etamycin, <u>112</u> |
| Penicillium gladioli | Gladiolic acid, <u>138</u> | | Eulicin, <u>113</u> |
| Penicillium griseofulvum | Dechlorogriseofulvin, <u>98</u> | | Eumycetin, <u>114</u> |
| | Griseofulvin, <u>153</u> | | Fermicidin, <u>118</u> |
| | Mycelianamide, <u>199</u> | | Flavacid, <u>120</u> |
| Penicillium herquei | Herquein, <u>161</u> | | Flaveolin, <u>121</u> |
| Penicillium janczewski | Dechlorogriseofulvin, <u>98</u> | | Foromacidins, <u>124</u> |
| Penicillium nigricans | Griseofulvin, <u>153</u> | | Framycetin, <u>126</u> |
| Penicillium notatum | Notatin, <u>223</u> | | Grisamine, <u>150</u> |
| | Penicillins, <u>237</u> | | Helixin, <u>158</u> |
| | Xanthocillin, <u>336</u> | | Lavendulin, <u>178</u> |
| Penicillium palitans | Palitantin, <u>234</u> | | Levomycin, <u>181</u> |
| Penicillium patulum | Gentisyl alcohol, <u>135</u> | | Methymycin, <u>193</u> |
| Penicillium paxilli | Estin, <u>111</u> | | Musarin, <u>198</u> |
| Penicillium phoeniceum | Phenicin, <u>241</u> | | Mycolutein, <u>202</u> |
| Penicillium puberulum | Puberulic acid, <u>256</u> | | Neomycins, <u>212</u> |
| | Puberulonic acid, <u>257</u> | | Nigericin, <u>216</u> |
| Penicillium raistrickii | Griseofulvin, <u>153</u> | | Nybomycin, <u>226</u> |
| Penicillium rubrum | Phenicin, <u>241</u> | | Oligomycin, <u>229</u> |
| Penicillium rugulosum | Rugulosin, <u>281</u> | | Pleocidin, <u>245</u> |
| Penicillium spinulosum | Spinulosin, <u>288</u> | | Ramnacin, <u>268</u> |
| Penicillium tardum | Tardin, <u>303</u> | | Rubidin, <u>278</u> |
| Penicillium urticae | Griseofulvin, <u>153</u> | | Ruticin, <u>282</u> |
| Penicillium viridicatum | Viridicatin, <u>331</u> | | Sarkomycin, <u>284</u> |
| Penicillium wortmanni | Rugulosin, <u>281</u> | | Seligocidin, <u>285</u> |
| Pfeifferella whitmori | Whitmorin, <u>334</u> | | Streptocardin, <u>290</u> |
| Pleurotus griseus | Pleurotin, <u>248</u> | | Streptogramin-like anti- biotic, <u>293</u> |
| Pleurotus mutilus | Pleuromutilin, <u>247</u> | | |

| | | | |
|------------------------------|-----------------------------------|-------------------------------|---------------------------------|
| Streptomyces spp (concluded) | Streptolins, <u>294</u> | Streptomyces griseoluteus | Griseoluteins, <u>154</u> |
| | Streptothricin, <u>297</u> | Streptomyces griseoviridus | Etamycin, <u>112</u> |
| | Streptothricin type 3, <u>298</u> | | Griseoviridin, <u>156</u> |
| | Tetracycline, <u>309</u> | Streptomyces griseus | Candididins, <u>56</u> |
| | Thioaurin, <u>312</u> | | Cycloheximide, <u>96</u> |
| | Thiomycin, <u>314</u> | | Dihydrostreptomycin, <u>296</u> |
| | Thiostrepton, <u>315</u> | | Etamycin, <u>112</u> |
| | Vinaceticin, <u>327</u> | | Grisein, <u>151</u> |
| | Violaceticin, <u>329</u> | | Griseoviridin, <u>156</u> |
| | Viomycin, <u>330</u> | | Mannosidostreptomycin, |
| | Xanthomycins, <u>337</u> | | <u>185</u> |
| | Xanthothricin, <u>338</u> | | Phagolessin A-58, <u>239</u> |
| Streptomyces abikoensum | Abikoviromycin, <u>1</u> | | Rhodomycin, <u>271</u> |
| Streptomyces achromogenes | Achromoviromycin, <u>2</u> | | Streptocin, <u>291</u> |
| | Sarcidin, <u>283</u> | | Streptomycin, <u>296</u> |
| | Pyridomycin, <u>263</u> | Streptomyces hachijoensis | Trichomycin, <u>318</u> |
| Streptomyces albidofuscus | Eurocidin, <u>116</u> | Streptomyces halstedii | Carbomycin, <u>60</u> |
| Streptomyces albireticuli | Puromycin, <u>259</u> | | Carbomycin B, <u>61</u> |
| Streptomyces albo-niger | Actinomycetin, <u>6</u> | Streptomyces hawaiiensis | Bryamycin, <u>53</u> |
| Streptomyces albus | Albomycetin, <u>14</u> | Streptomyces hepaticus | Elaiomycin, <u>104</u> |
| | Thiolutin, <u>313</u> | Streptomyces hygrosopicus | Angustimycin, <u>26</u> |
| | Congocidin, <u>94</u> | | Hygromycin, <u>166</u> |
| | Spiramycin, <u>289</u> | | Hygrosopins, <u>167</u> |
| Streptomyces ambofaciens | Actinomycins, <u>7</u> | Streptomyces kentuckensis | Rainomycin, <u>267</u> |
| | Oleandomycin, <u>228</u> | Streptomyces kitasatoensis | Leucomycin, <u>180</u> |
| | Chlortetracycline, <u>80</u> | Streptomyces kitazawaensis | Antimycin A, <u>28</u> |
| | Actinoleukin, <u>4</u> | | Carzinocidin, <u>64</u> |
| Streptomyces aureofaciens | Dihydrostreptomycin, <u>296</u> | Streptomyces lavendulae | Actithiazic acid, <u>11</u> |
| Streptomyces aureus | Streptomycin, <u>296</u> | | p-4-Amino-3-isoxazoli- |
| Streptomyces bikiniensis | Cacaoomycetin, <u>54</u> | | done, <u>22</u> |
| | Celesticetin, <u>68</u> | | Grasseriomycin, <u>148</u> |
| | Ascocin, <u>30</u> | | Streptothricin, <u>297</u> |
| | Amphomycin, <u>23</u> | Streptomyces lydicus | Streptolydigin, <u>295</u> |
| | Aureothricin, <u>35</u> | Streptomyces mashuensis | Dihydrostreptomycin, <u>296</u> |
| | Fungichromin, <u>130</u> | | Streptomycin, <u>296</u> |
| | Chartreusin, <u>74</u> | Streptomyces mediocidicus | Mediocidin, <u>188</u> |
| | Netropsin, <u>214</u> | Streptomyces narbonensis | Narbomycin, <u>207</u> |
| | Actinomycin C, <u>78</u> | Streptomyces netropsis | Netropsin, <u>214</u> |
| | Cinnamycin, <u>83</u> | Streptomyces nitrosporeus | Nitrosporin, <u>218</u> |
| | Actinorhodin, <u>9</u> | Streptomyces niveus | Novobiocin, <u>224</u> |
| | Coelicolorin, <u>88</u> | Streptomyces noboritoensis | Homomycin, <u>163</u> |
| | Collinomycin, <u>92</u> | Streptomyces noursei | Cycloheximide, <u>96</u> |
| | Rubromycin, <u>280</u> | | Nystatin, <u>227</u> |
| | Endomycin, <u>105</u> | Streptomyces olivaceus | Phalamycin, <u>240</u> |
| Streptomyces endus | Erythromycin, <u>108</u> | Streptomyces orchidaceus | Antibiotics PA-114, <u>233</u> |
| Streptomyces erythreus | Erythromycin B, <u>109</u> | | p-4-Amino-3-isoxazoli- |
| | Tertiomycin A, <u>306</u> | | done, <u>22</u> |
| | Tertiomycin B, <u>307</u> | | Vancomycin, <u>326</u> |
| | Angolamycin, <u>25</u> | Streptomyces orientalis | |
| Streptomyces eurocidicus | Exfoliatin, <u>117</u> | Streptomyces phaeochromo- | |
| | Amicetin, <u>21</u> | genus | Moldin, <u>197</u> |
| | Picromycin, <u>244</u> | | Ractinomycins, <u>266</u> |
| | Filipin, <u>119</u> | Streptomyces phaeofaciens | Phaeofacin, <u>238</u> |
| | Luteomycin, <u>184</u> | Streptomyces phoenix | Rhodocidin, <u>270</u> |
| | | Streptomyces pleofaciens | Pleomycin, <u>246</u> |
| | | Streptomyces purpurascens | Isorhodomycins, <u>171</u> |
| | Amaromycin, <u>20</u> | | Rhodomycins, <u>272</u> |
| | Viomycin, <u>330</u> | Streptomyces resistomycificus | Resistomycin, <u>269</u> |
| Streptomyces floridae | Dextromycin, <u>99</u> | Streptomyces reticuli | Rotaventin, <u>277</u> |
| Streptomyces fradiae | Fradicin, <u>125</u> | Streptomyces rimosus | Oxytetracycline, <u>232</u> |
| | Neomycins, <u>212</u> | | Rimocidin, <u>273</u> |
| | Azaserine, <u>36</u> | Streptomyces rochei | Borrelidin, <u>48</u> |
| | Fuscomycin, <u>134</u> | Streptomyces roseochromo- | |
| | p-4-Amino-3-isoxazoli- | genus | Roseomycin, <u>275</u> |
| | done, <u>22</u> | | Roseothricin, <u>276</u> |
| | Elaiomycin, <u>104</u> | Streptomyces roseoflavus | Mycelin, <u>200</u> |
| Streptomyces gelaticus | Streptogramin, <u>292</u> | Streptomyces roseus | Sulfactin, <u>301</u> |
| Streptomyces graminofaciens | Hydroxystreptomycin, <u>165</u> | Streptomyces ruber | Mycoticin, <u>206</u> |
| Streptomyces griseo-carneus | Griseoflavin, <u>152</u> | Streptomyces rubescens | Abikoviromycin, <u>1</u> |
| Streptomyces griseoflavus | Anisomycin, <u>27</u> | Streptomyces rutgersensis | Camphomycin, <u>55</u> |
| Streptomyces griseolus | Argomycin, <u>29</u> | Streptomyces sahachiroi | Carzinophilin, <u>65</u> |
| | Griseomycin, <u>155</u> | | Carzinophilin A, <u>66</u> |
| | Fermicidin, <u>118</u> | Streptomyces sindenensis | Amicetin, <u>21</u> |

| | | | |
|-----------------------------------|-----------------------------|---------------------------|----------------------------|
| Streptomyces spheroides | Novobiocin, <u>224</u> | Streptomyces zaomyceticus | Zaomycin, <u>340</u> |
| Streptomyces subtropicus | Albomycin, <u>15</u> | Thermoactinomyces viridis | Thermoviridin, <u>311</u> |
| Streptomyces tanashiensis | Luteomycin, <u>184</u> | Trichoderma viride | Viridins, <u>332</u> |
| Streptomyces venezuelae | Chloramphenicol, <u>78</u> | Tricholoma nudum | Nudic acids, <u>225</u> |
| Streptomyces vinaceus- drappus | Amicetin, <u>21</u> | Trichothecium roseum | Rosein II, <u>274</u> |
| Streptomyces virginiae | Actithiazic acid, <u>11</u> | Ustilago zeae | Ustilagic acid, <u>324</u> |
| Streptomyces viridoflavus | Candidins, <u>57</u> | | |
| Streptomyces viridosporus | Sistomycosin, <u>287</u> | | |
| Streptomyces xanthophaeus | Geomycins, <u>137</u> | | |

INDEX

INDEX

Antibiotics appearing in this volume are listed here in alphabetical order. In addition, commonly used alternate names, synonyms, proprietary and trade names, and, where available, official designations have been included so that this listing may serve as a cross index.

A term appearing by itself--i.e., not followed by another in parentheses--in the index appears as such in the text. A term followed by another term in parentheses in the index appears in the text as the parenthetical term. Each antibiotic covered in the text is assigned an item number, so that each term in the index is followed by an underscored number--the item number--separated by a colon from a second number or numbers--the page number(s). For example:

ACTINOLEUKIN, 4:3,4

indicates that the antibiotic Actinoleukin is item 4 and is found on pages 3 and 4; and

OCHRACIN, (MELLEIN) 189:109,110

shows that the antibiotic Ochracin is listed in the text as Mellein, item 189 on pages 109 and 110.

- 289, ANTIBIOTIC-, (LUTEOMYCIN) 184:107
 899, ANTIBIOTIC-, (STREPTOGRAMIN-LIKE ANTI-BIOTIC) 293:169,170
 8450, ANTIBIOTIC-, (HELENINE) 157:93,94
 ABIKOVIRIOMYCIN, 1:3
 ACHROMOVIROMYCIN, 2:3
 ACHROMYCIN, (PUROMYCIN) 259:153-155
 ACHROMYCIN, (TETRACYCLINE) 309:179-182
 ACIDOMYCIN, (ACTITHIAZIC ACID) 11:8,9
 ACTIDIONE, (CYCLOHEXIMIDE) 96:60,61
 ACTIDUINS, 3:3
 ACTILINE, (FRAMYCETIN) 126:77,78
 ACTINOCRYSIN, (ACTINOMYCINS) 7:4-7
 ACTINOLEUKIN, 4:3,4
 ACTINOMYCELINE, 5:4
 ACTINOMYCETIN, 6:4
 ACTINOMYCINS, 7:4-7
 ACTINONE, 8:7
 ACTINORHODIN, 9:7,8
 ACTINORUBIN, 10:8
 ACTITHIAZIC ACID, 11:8,9
 AEROSPORIN, (POLYMYXINS) 249:146-148
 AGROCYBIN, 12:9,10
 ALBAMYCIN, (NOVOBIOCIN) 224:127-129
 ALBIDIN, 13:10
 ALBOMYCETIN, 14:10,11
 ALBOMYCIN, 15:11
 ALLOMYCIN, (AMICETIN) 21:14,15
 ALTERNARIC ACID, 16:11,12
 ALTERNARINE, 17:12
 ALTERNARIOL, 18:12,13
 ALVEIN, 19:13
 AMAROMYCIN, 20:13
 AMICETIN, 21:14,15
 AMIMYCIN, (OLEANDOMYCIN) 228:132
 D-4-AMINO-3-ISOXAZOLIDONE, 22:15,16
 AMPHOMYCIN, 23:16,17
 AMPHOTERICINS, 24:17,18
 ANGOLAMYCIN, 25:18
 ANGUSTMYCIN, 26:18,19
 ANISOMYCIN, 27:19,20
 ANTIBIOTIC 289, (LUTEOMYCIN) 184:107
 ANTIBIOTIC 899, (STREPTOGRAMIN-LIKE ANTI-BIOTIC) 293:169,170
 ANTIBIOTIC 8450, (HELENINE) 157:93,94
 ANTIBIOTIC APM, (XEROSIN) 339:199
 ANTIBIOTIC HA-9, (THIOAURIN) 312:183
 ANTIBIOTIC PA-93, (NOVOBIOCIN) 224:127-129
 ANTIBIOTIC PA-105, (OLEANDOMYCIN) 228:132
 ANTIBIOTIC XG, (FUNGISTATIN) 131:80,81
 ANTIBIOTICS PA-114, 233:137,138
 ANTIMYCIN A, 28:20
 ANTIPIRICULLIN, (ANTIMYCIN A) 28:20
 APM, ANTIBIOTIC-, (XEROSIN) 339:199
 ARGOMYCIN, 29:20,21
 ASCOSIN, 30:21
 ASPERGILLIC ACID, 31:21,22
 ASPERGILLIN, (GLIOTOXIN) 140:84,85
 AURANTIDIN, 32:22
 AURANTIOLIOCLADIN, 33:22,23
 AUREOLIC ACID, 34:23
 AUREOMYCIN, (CHLORTETRACYCLINE) 80:49-53
 AUREOTHRICIN, 35:23,24
 AYFIVIN, (BACITRACINS) 45:28-30
 AZASERINE, 36:24,25
 AZOMYCIN, 37:25,26
 BACCATINE A, 38:26
 BACILIPINS, 39:26
 BACILLIN, 40:26
 BACILLOMYCIN, 41:26,27
 BACILLOMYCIN B, 42:27
 BACILLOMYCIN C, 43:27,28
 BACILLOMYCIN R, (BACILLOMYCIN) 41:26,27
 BACILYSIN, 44:28
 BACITRACINS, 45:28-30
 BIFORMIN, (BIFORMYNES) 46:30,31
 BIFORMINIC ACID, (BIFORMYNES) 46:30,31
 BIFORMYNES, 46:30,31
 BIOCERIN, 47:31
 BORRELIDIN, 48:31
 BOSTRYCOIDIN, 49:31,32
 BREVIN, 50:32
 BREVOLIN, 51:32
 BROMOTETRACYCLINE, 52:32,33
 BRYAMYCIN, 53:33,34
 5-n-BUTYLPYRIDINE-2-CARBOXYLIC ACID, 132:81
 CACAOMYCETIN, 54:34
 CAMPHOMYCIN, 55:34
 CANDICIDINS, 56:34,35
 CANDIDINS, 57:35
 CANDIDULIN, 58:35,36
 CANESIN, 59:36
 CANPHOMYCIN, (CAMPHOMYCIN) 55:34
 CARBOMYCIN, 60:36-38
 CARBOMYCIN B, 61:38
 CARDELMYCIN, (NOVOBIOCIN) 224:127-129
 CARDICIN, 62:38,39
 CARNEOLUTESIN, 63:39
 CARZINOCIDIN, 64:39
 CARZINOPHILIN, 65:39,40
 CARZINOPHILIN A, 66:40
 CATENULIN, 67:40,41

CATHOCIN, (NOVOBIOCIN) 224:127-129
CATHOMYCIN, (NOVOBIOCIN) 224:127-129
CELESTICETIN, 68:41
CEPHALOSPORIN C, 69:42
CEPHALOSPORIN N, 70:42, 43
CEPHALOSPORIN P SERIES, 71:43
CEPHALOTHECIN, 72:44
CEREVIACCIDIN, 73:44
CHAETOMIN, (CHETOMIN) 76:45
CHARTREUSIN, 74:44, 45
CHARTREUSIN-LIKE ANTIBIOTIC, 75:45
CHETOMIN, 76:45
CHLAMYDOSPORIN, 77:46
CHLORAMPHENICOL, 78:46-48
CHLOROMYCETIN, (CHLORAMPHENICOL) 78:46-48
CHLORORAPHIN, 79:48, 49
CHLORTETRACYCLINE, 80:49-53
CHROMIN, 81:53
CHRYSOMYCIN, 82:53, 54
CINNAMYCIN, 83:54
CIRCULIN, 84:54, 55
CIRCULIN, (POLYPEPTIN) 250:148, 149
CITRININ, 85:55, 56
CITROMYCETIN, 86:56
CLAVACIN, (PATULIN) 235:138, 139
CLAVATIN, (PATULIN) 235:138, 139
CLAVIFORMIN, (PATULIN) 235:138, 139
CLITOCYBINS, 87:56, 57
COELICOLORIN, 88:57
COLICINES, 89:57
COLIFORMIN, 90:58
COLISTATIN, 91:58
COLLINOMYCIN, 92:58
COMIRIN, 93:58, 59
CONGOCIDIN, 94:59
CORDYCEPIN, 95:59, 60
CYCLOHEXIMIDE, 96:60, 61
CYCLOPALDIC ACID, 97:61, 62
CYCLOSERINE, (D-4-AMINO-3-ISOXAZOLIDONE)
22:15, 16

DECHLOROGRISOFULVIN, 98:62
DEXTROMYCIN, 99:62
DIATRETYNES, 100:62, 63
O-DIAZOACETYL-L-SERINE, (AZASERINE) 36:24, 25
DIHYDROSTREPTOMYCIN, 296:171-173
3, 6-DIHYDROXY-4-METHOXY-2, 5-TOLUQUINONE,
(SPINULOSIN) 288:167
6-DIMETHYLAMINO-9[3'-(p-METHOXY-L-PHENYL-
ALANYLAMINO)- β -D-RIBOFURANOSYL]-PURINE,
(PUROMYCIN) 259:153-155
DIPLOCOCCIN, 101:63
DROSOPHILIN B, (PLEUROMUTILIN) 247:145, 146
DROSOPHILINS, 102:63, 64

EHRLICHIN, 103:64
ELAIOMYCIN, 104:64, 65
ENDOMYCIN, 105:65
ENNIATIN A, 106:65, 66
ENNIATIN B, 107:66, 67
ENTEROMYCIN, (SELIGOCIDIN) 285:166
EPITETRACYCLINE, (QUATRIMYCIN) 265:157, 158
ERYTHROCIN, (ERYTHROMYCIN) 108:67-69
ERYTHROMYCIN, 108:67-69
ERYTHROMYCIN B, 109:69, 70
ESPERIN, 110:70
ESTIN, 111:70
ETAMYCIN, 112:70, 71
EULICIN, 113:71, 72
EUMYCETIN, 114:72

EUMYCIN, 115:72
EUROCIDIN, 116:72, 73
EXFOLIATIN, 117:73
EXPANSINE, (PATULIN) 235:138, 139

FERMICIDIN, 118:73
FILIPIN, 119:73, 74
FLAGECIDIN, (ANISOMYCIN) 27:19, 20
FLAVACID, 120:74, 75
FLAVEOLIN, 121:75
FLAVOMYCIN, (NEOMYCINS) 212:120-122
FLUVOMYCIN, 122:75
FOMECIN A, 123:76
FOROMACIDINS, 124:76, 77
FRADICIN, 125:77
FRAMYCETIN, 126:77, 78
FREQUENTIC ACID, (CITROMYCETIN) 86:56
FREQUENTIN, 127:78
FUGILLIN, (FUMAGILLIN) 128:78, 79
FUMAGILLIN, 128:78, 79
FUMIDIL, (FUMAGILLIN) 128:78, 79
FUMIGACIN, (HELVOLIC ACID) 159:94, 95
FUMIGATIN, 129:79, 80
FUNGICHRONIN, 130:80
FUNGICIDIN, (NYSTATIN) 227:130-132
FUNGISTATIN, 131:80, 81
FUNGOCIN, (BACILLOMYCIN) 41:26, 27
FUSARIC ACID, 132:81
FUSCIN, 133:81, 82
FUSCOMYCIN, 134:82

GENTISYL ALCOHOL, 135:82
GEODIN, 136:82, 83
GEOMYCINS, 137:83
GLADIOLIC ACID, 138:83, 84
GLIOROSEIN, 139:84
GLIOTOXIN, 140:84, 85
GLOBICIN, 141:85
GLUTINOSIN, 142:85, 86
GLYCO-LIPIDE, 143:86
GRAMICIDIN, 144:86, 87
GRAMICIDIN J, 145:87, 88
GRAMICIDIN S, 146:88
GRANEGILLIN, 147:88
GRASSERIOMYCIN, 148:88, 89
GRIFOLIN, 149:89
GRISAMINE, 150:89, 90
GRISEIN, 151:90
GRISEOFLAVIN, 152:90
GRISEOFULVIN, 153:91
GRISEOLUTEINS, 154:91, 92
GRISEOMYCIN, 155:92
GRISEOVIRIDIN, 156:93

HA-9, ANTIBIOTIC-, (THIOAURIN) 312:183
HELENINE, 157:93, 94
HELIXIN, 158:94
HELVOLIC ACID, 159:94, 95
HEMIPYOCYANINE, 160:95
HERQUEIN, 161:95, 96
HIRSUTIC ACIDS, 162:96
HOMOMYCIN, 163:96
HUMICOLIN, 164:97
1- β -HYDROXYDECANOIC ACID, (GLYCO-LIPIDE)
143:86
3-HYDROXY-2-METHYL-1, 4-NAPHTHOQUINONE,
(PHTHIOCOL) 242:143
 α -HYDROXYPHENAZINE, (HEMIPYOCYANINE) 160:95
HYDROXYSTREPTOMYCIN, 165:97
HYGROMYCIN, 166:97, 98

HYGROSCOPINS, 167:98,99

IA 887, (NETROPSIN) 214:122,123
ILLUDINS, 168:99
ILOTYCIN, (ERYTHROMYCIN) 108:67-69
INOLOMIN, 169:99,100
IODININ, 170:100
ISORHODOMYCINS, 171:100,101
ITURINS, 172:101

JAVANICIN, 173:101,102

KOJIC ACID, 174:102

LACTAROVIOLIN, 175:102,103
LATERITIIN GROUP, 176:103,104
LATEROSPORINS, 177:104
LAVENDULIN, 178:104
LENZITIN, 179:104,105
LEUCOMYCIN, 180:105
LEVOMYCIN, 181:105,106
LICHENIFORMINS, 182:106
LITMOCIDIN, 183:107
LOMYCIN, (GRISEOMYCIN) 155:92
LUTEOMYCIN, 184:107

MAGNAMYCIN, (CARBOMYCIN) 60:36-38
MAGNAMYCIN B, (CARBOMYCIN B) 61:38
MANNOSIDOSTREPTOMYCIN, 185:107,108
MARASMIC ACID, 186:108,109
MARCESIN, 187:109
MATROMYCIN, (OLEANDOMYCIN) 228:132
MEDIOCIDIN, 188:109
MELLEIN, 189:109,110
MESENERIN, 190:110
5-METHOXY-p-TOLUQUINONE, 191:110,111
6-METHYL-1,4-NAPHTHAQUINONE, 192:111
METHMYCIN, 193:111,112
MICROCINS, 194:112
MICROCOCCIN, 195:112,113
MICROMONOSPORIN, 196:113
MOLDIN, 197:113
MUSARIN, 198:113,114
MYCELLANAMIDE, 199:114
MYCELIN, 200:114,115
MYCIFRADIN, (NEOMYCINS) 212:120-122
MYCOBACIDIN, (ACTITHIAZIC ACID) 11:8,9
MYCOCIDIN, 201:115
MYCOLUTEIN, 202:115
MYCOMYCIN, 203:115,116
MYCOPHENOLIC ACID, 204:116
MYCOSTATIN, (FUNGICIDIN) 227:130-132
MYCOSUBTILIN, 205:116,117
MYCOTICIN, 206:117

NARBOMYCIN, 207:117,118
NEBULARINE, 208:118
NEMOTIN, 209:119
NEMOTINIC ACID, 210:119
NEOCIDIN, 211:119
NEOMYCINS, 212:120-122
NEONOCARDIN, 213:122
NETROPSIN, 214:122,123
NIDULIN, 215:123
NIGERICIN, 216:123,124
NISINS, 217:124
NITROSPORIN, 218:124,125
NOCARDAMIN, 219:125
NOCARDIANIN, 220:125,126
NOCARDORUBIN, 221:126

NOFORMICIN, 222:126,127
NOR-NIDULIN, 215:123
NOTATIN, 223:127
NOVOBIOCIN, 224:127-129
NUDIC ACIDS, 225:129
NYBOMYCIN, 226:130
NYSTATIN, 227:130-132

OCHRACIN, (MELLEIN) 189:109,110
OLEANDOMYCIN, 228:132
OLIGOMYCIN, 229:132,133
OREGONENSIN, 230:133
OROSOMYCIN, (THIOAURIN) 312:183
ORYZACIDINE, (ORYZASIZINE) 231:133
ORYZASIZINE, 231:133
OXAMYCIN, (p-4-AMINO-3-ISOXAZOLIDONE) 22:15,16
OXYTETRACYCLINE, 232:133-137

PA-93, ANTIBIOTIC-, (NOVOBIOCIN) 224:127-129
PA-94, (p-4-AMINO-3-ISOXAZOLIDONE) 22:15,16
PA-105, ANTIBIOTIC-, (OLEANDOMYCIN) 228:132
PA-114, ANTIBIOTICS-, 233:137,138
PALITANTIN, 234:138
PANMYCIN, (TETRACYCLINE) 309:179-182
PATULIN, 235:138,139
PENATIN, (NOTATIN) 223:127
PENICIDIN, (PATULIN) 235:138,139
PENICILLIC ACID, 236:139,140
PENICILLIN B, (NOTATIN) 223:127
PENICILLINS, 237:140,141
PHAEOFACIN, 238:141
PHAGOLESSIN A-58, 239:142
PHAGOPEDIN SIGMA, (FUMAGILLIN) 128:78,79
PHALAMYCIN, 240:142
PHENICIN, 241:142,143
PHOENICIN, (PHENICIN) 241:142,143
PHTHIACOL, 242:143
PHTHIOMYCIN, 243:143
PICROMYCIN, 244:143,144
PLEOCIDIN, 245:144,145
PLEOMYCIN, 246:145
PLEUROMUTILIN, 247:145,146
PLEUROTIN, 248:146
POLYCYCLINE, (TETRACYCLINE) 309:179-182
POLYMYXINS, 249:146-148
POLYPEPTIN, 250:148,149
POLYPORIN, 252:149,150
POLYPORIN, 252:149,150
PORTAMYCIN, (STREPTOLYDIGIN) 295:170,171
PRIMYCIN, 253:150
PROACTINOMYCINS, 254:150,151
PRODIGIOSIN, 255:151,152
PUBERULIC ACID, 256:152
PUBERULONIC ACID, 257:152,153
PUMILIN, 258:153
PUROMYCIN, 259:153-155
PYO COMPOUNDS, 260:155,156
PYOCYANINE, 261:156
PYOLIPIC ACID, 262:156
PYRIDOMYCIN, 263:156,157

QUADRIFIDINS, 264:157
QUATRIMYCIN, 265:157,158

RACTINOMYCINS, 266:158
RAISNOMYCIN, 267:159
RAMNACIN, 268:159
RESISTOMYCIN, 269:159
RETICULIN, (HYDROXYSTREPTOMYCIN) 165:97
RHODOCIDIN, 270:159,160
RHODOMYCETIN, 271:160

RHODOMYCIN, (RHODOMYCETIN) 271:160
RHODOMYCINS, 272:160,161
9-(β -D-RIBOFURANOSYL)PURINE, (NEBULARINE)
208:118
RIMOCIDIN, 273:161
ROSEIN II, 274:161,162
ROSEOMYCIN, 275:162
ROSEOTHRICIN, 276:162
ROTAVENTIN, 277:162,163
ROVAMYCIN, (SPIRAMYCIN) 289:167,168
RUBIDIN, 278:163
RUBROGLIOCLADIN, 279:163
RUBROMYCIN, 280:163,164
RUGULOSIN, 281:164
RUTICIN, 282:164,165

SACROMYCIN (AMICETIN) 21:14,15
SANAMYCIN, (ACTINOMYCINS) 7:4-7
SARCIDIN, 283:165
SARKOMYCIN, 284:165,166
SELIGOCIDIN, 285:166
SEROMYCIN, (D-4-AMINO-3-ISOXAZOLIDONE)
22:15,16
SIMPLEXIN, 286:166
SISTOMYCOSIN, 287:166,167
SOFRAMYCINE, (FRAMYCETIN) 126:77,78
SPINULOSIN, 288:167
SPIRAMYCIN, 289:167,168
STECLIN, (TETRACYCLINE) 309:179-182
STREPTOCARDIN, 290:168
STREPTOCIN, 291:168,169
STREPTOGRAMIN, 292:169
STREPTOGRAMIN-LIKE ANTIBIOTIC, 293:169,170
STREPTOLINS, 294:170
STREPTOLYDIGIN, 295:170,171
STREPTOMYCIN, 296:171-173
STREPTOMYCIN B, (MANNOSIDOSTREPTOMYCIN)
185:107,108
STREPTONIVICIN, (NOVOBIOCIN) 224:127-129
STREPTOTHRICIN, 297:173,174
STREPTOTHRICIN TYPE 3, 298:174
STYLOMYCIN, (PUROMYCIN) 259:153-155
SUBTENOLIN, 299:174,175
SUBTILIN, 300:175,176
SULFACTIN, 301:176
SYNNEMATIN B, (CEPHALOSPORIN N) 70:42,43
SYNNEMATINS, 302:176,177

TARDIN, 303:177
TERRAMYCIN, (OXYTETRACYCLINE) 232:133-137
TERRECIAN, 304:177,178
TERREIC ACID, 305:178
TERTIOMYCIN, (TERTIOMYCIN A) 306:178,179

TERTIOMYCIN A, 306:178,179
TERTIOMYCIN B, 307:179
TETAINE, 308:179
TETRACYCLINE, 309:179-182
TETRACYCIN, (TETRACYCLINE) 309:179-182
THERMOPHILLIN, 310:182
THERMOVIRIDIN, 311:182,183
THIOAURIN, 312:183
THIOLUTIN, 313:183,184
THIOMYCIN, 314:184
THIOSTREPTON, 315:184,185
TOXIMYCIN, 316:185
TOYOCAMYCIN, 317:185,186
TOYOKAMYCIN, (TOYOCAMYCIN) 317:185,186
TRICHOMYCIN, 318:186,187
TRICHOTHECIN, 319:187
TYROCIDINE, 320:187,188
TYROTHRICIN, 321:188,189 (See also GRAMICIDIN,
144; TYROCIDINE, 320.)

UNGULINIC ACID, 322:189,190
USNIC ACID, (USNIC ACID) 323:190,191
USNEIN, (USNIC ACID) 323:190,191
USNIC ACID, 323:190,191
USTILAGIC ACID, 324:191
USTIN, (NOR-NIDULIN) 215:123

VALINOMYCIN, 325:191,192
VANCOCIN, (VANCOMYCIN) 326:192
VANCOMYCIN, 326:192
VINACETIN, 327:192,193
VINACTANE, (VIOMYCIN) 330:194,195
VINACTIN A, (VIOMYCIN) 330:194,195
VIOCIN, (VIOMYCIN) 330:194,195
VIOLACEIN, 328:193
VIOLACETIN, 329:193-194
VIOMYCIN, 330:194,195
VIRIDICATIN, 331:195
VIRIDINS, 332:196
VIRIDOGRISEIN, (ETAMYCIN) 112:70,71
VIROSIN, (ANTIMYCIN A) 28:20
VISCOSIN, 333:196,197

WHITMORIN, 334:197

XANTHELLIN, 335:197
XANTHOCILLIN, 336:197,198
XANTHOMYCINS, 337:198
XANTHOTHRICIN, 338:198,199
XEROSIN, 339:199
XG, ANTIBIOTIC-, (FUNGISTATIN) 131:80,81

ZAOMYCIN, 340:199,200