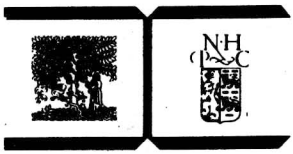
New Trends in Antibiotics: Research and Therapy

G. Gialdroni Grassi and L. D. Sabath
Editors

NEW TRENDS IN ANTIBIOTICS: RESEARCH AND THERAPY

Proceedings of the International Symposium on New Trends in Antibiotics: Research and Therapy held in Milan, Italy, October 29-31, 1980.

Editors:
G. Gialdroni Grassi
and
L.D. Sabath



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PREFACE

The lectures and the papers that are collected in this volume were presented at the Symposium on "NEW TRENDS IN ANTIBIOTICS:Research and Therapy", held in Milano (Italy), on October 29-31,1980.

The Symposium, sponsored also by the Italian Society of Chemotherapy and the Italian Society of Hospital Pharmacists, was organized by Fondazione Lorenzini to celebrate the 10^{th} anniversary of its foundation, a decade in which its initiatives have contributed a great deal to the scientific progress in many fields of biological and medical sciences.

The subject chosen for this Symposium was quite ambitious:it intendend to cover the present status and to indicate the future development of antibacterial chemotherapy. But this task did not seem to be too hard for the specialists who convened here from all over the world. Their reports show how the present knowledges and experiences are open to new perspectives for the future : a sign of the vitality of this branch of science.

Giuliana Gialdroni Grassi

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TETRACYCLINES: CHEMICAL ASPECTS AND SOME STRUCTURE-ACTIVITY RELATIONSHIPS

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INTRODUCTION

Tetracyclines are one of the oldest family of antibiotics (in fact, they appeared in the late 40's), nevertheless they are still widely used. This long and good life of tetracyclines is the result of the characteristics of these antibiotics: broad antimicrobial spectrum, low toxicity, few allergic reactions (only low incidence of phototoxicity), good oral absorption, low cost. The major drawbacks of tetracyclines are the deposition in calcified tissues with stains and impairments of bone and teeth (therefore, tetracyclines are not recommended in pregnancy and in children younger than 12 years) and sometimes development of resistance.

From 1950 so far a great deal of work was performed in the field of tetracyclines: their structure was cleared in 1953-1954 (by the combined effort of R.B. Woodward group and Pfizer Research Laboratories), stereochemistry was elucidated in 1963 through X-ray crystallography, absolute configuration was confirmed, total synthesis of various tetracyclines (even though not economical) was performed, biosynthesis has been very carefully elucidated, mechanism of action is now clear, about one thousand derivatives of tetracyclines have been prepared (of these about 20 by fermentation processes).

In conclusion, few classes of drugs have been so deeply and thoroughly studied as the tetracycline family.

Seven tetracyclines are to-day clinically used (see table 1).

This table shows that there are two generations of tetracyclines: the first-generation tetracyclines (from 1948 to 1957) are produced by fermentation, whereas the second-generation tetracyclines (from 1965 to 1972) are produced by semi-synthesis.

Tetracycline itself remains the most used member of the family, whereas doxycycline (which induces sustained blood levels) is the first "one-day" tetracycline. Some of the most interesting properties of tetracyclines clinically used to-day are shown in table 2.

TABLE 1

			Product	Year of discovery	Produced by
Cl	HO CH_3	H	Chlorotetracycline	1948	Streptomyces aureofaciens
H	HO CH_3	HO	Oxytetracycline	1948	Streptomyces rimosus
H	HO CH_3	H	Tetracycline	1953	Chemically from chlorotetracycline or Streptomyces aureofaciens
Cl	HO H	H	Demethylchlorotetracycline	1957	Mutant of Streptomyces aureofaciens
H	CH_2	HO	Methacycline	1965	chemically
H	H CH_3	HO	Doxycycline	1967	chemically
CH_3 CH_3 N	H H	H	Minocycline	1972	chemically

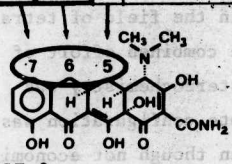


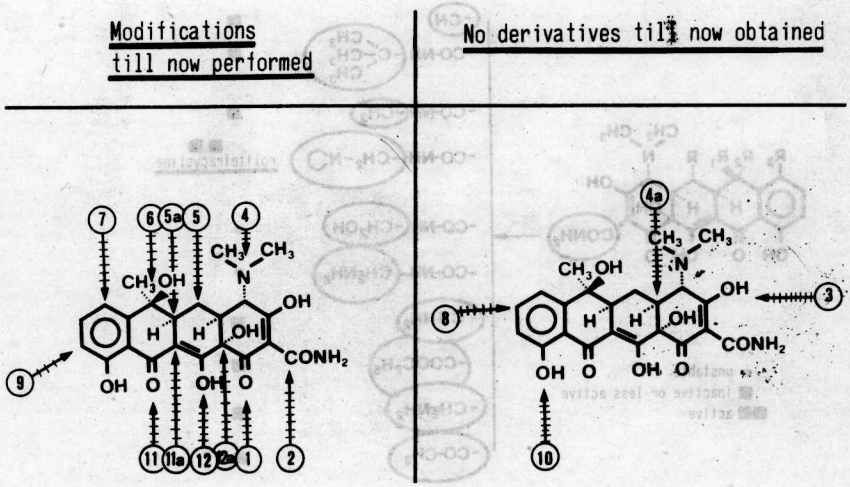
TABLE 2

Product	In vitro relative potency against S. aureus	ED50 oral in infected mice S. aureus mg/kg	Recommended daily-dose mg/day	% of oral absorption	half-life hrs	protein binding %
Tetracycline	100	5.8	500	77-80%	8.2	55-64%
Chlorotetracycline	130-200	7.6	500	25-30%	5.6	43-55%
Oxytetracycline	80	7.2	500	58%	9.2	20-35%
Demethylchlorotetracycline	150	6.0	300	66%	12	75-91%
Methacycline	150	4.5	300	88%	14	78%
Doxycycline	110	2.6	150	95%	17	82-93%
Minocycline	200	3.5	150	95%	16	76%

CHEMICAL TRANSFORMATION OF TETRACYCLINES FAMILY

Many chemical changes were performed on tetracyclines. In figure 1 the numbers and arrows denote the centers for which relevant derivatives are available.

Fig. 1



Till now no changes are performed at carbons 3, 4 a, 8 and 10 (without altering the whole structure of the molecule).

In the following reports we describe only the most relevant modifications, and (for simplification) only "active" or "non-active" (but the accurate data of activity may be found in the pertinent literature).

Some derivatives were obtained from tetracycline, others from doxycycline, others from 6-deoxy-6-demethyltetracycline and few from minocycline.

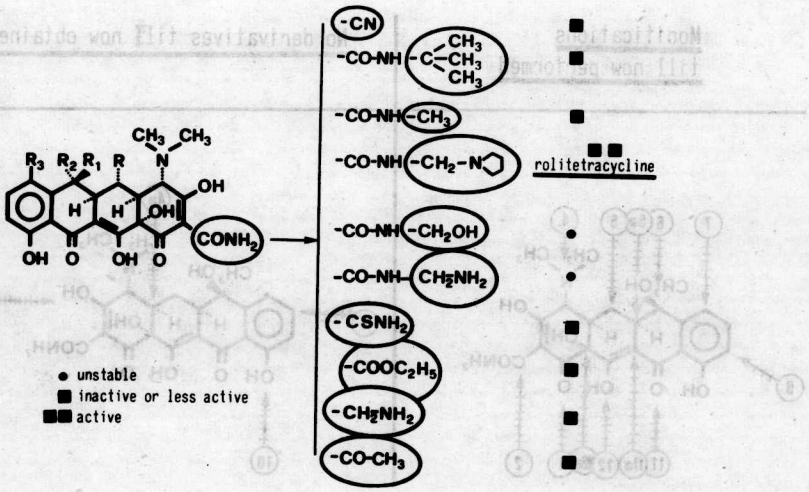
a) Chemistry in position 2

The most interesting derivatives of carbon 2 are shown in figure 2: the last product (2-acetyl-2-decarboxamido-tetracycline) was obtained by fermentation, all the others by chemical reactions.

All the products are inactive or less active than the parent antibiotics (only rolitetracycline is active because in water it reverts into the parent tetracycline).

In conclusion, carboxamide group is very important for bioactivity and no important changes are possible in position 2.

Fig. 2



b) Chemistry in position 4

Some of the most important derivatives in position 4 are shown in figure 3

No useful changes were performed in position 4: the orientation of dimethylamino group below the plane of ring A is essential for bioactivity (4-epitetracycline has a weak activity in-vitro and none in-vivo), also the basicity of dimethylamino group (with pKa 9.3) is important because more or less substituted amino-groups are less active; steric phenomena are also important because derivatives with higher dialkylamino groups have a lower bioactivity.

c) Chemistry in position 5

Some of the most interesting derivatives in position 5 are shown in figure 4.

Position 5 appears to be not very critical for bioactivity.

It is interesting to note that, whereas 5,5a-didehydro compound is inactive, 5,5a-didehydro-6-epioxytetracycline is surprisingly highly active both in-vitro and in-vivo.

Fig. 3

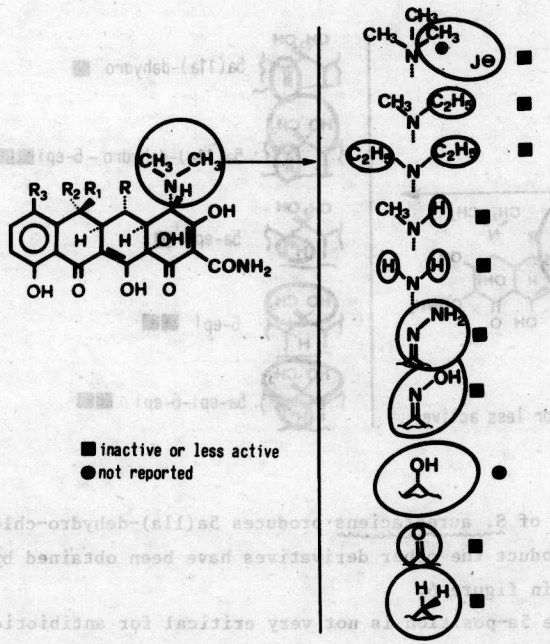
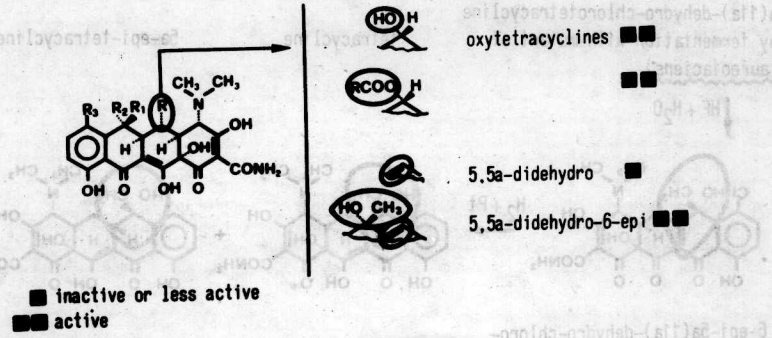

■ inactive or less active
● not reported

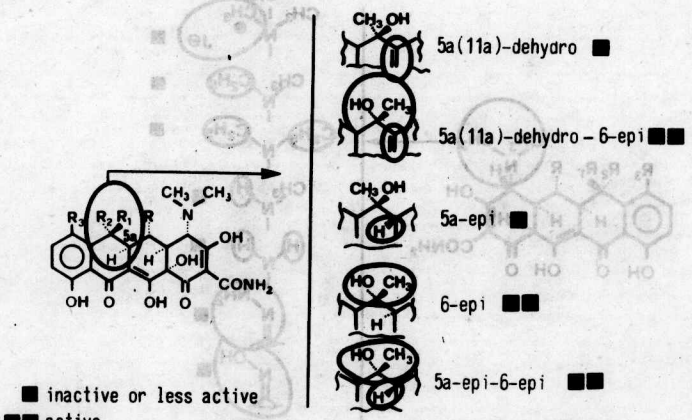
Fig. 4


oxytetracyclines ■■
■■
5,5a-didehydro ■
5,5a-didehydro-6-epi ■■
■ inactive or less active
■■ active

d) Chemistry in position 5a

Some of the most interesting derivatives in position 5a are shown in figure 5.

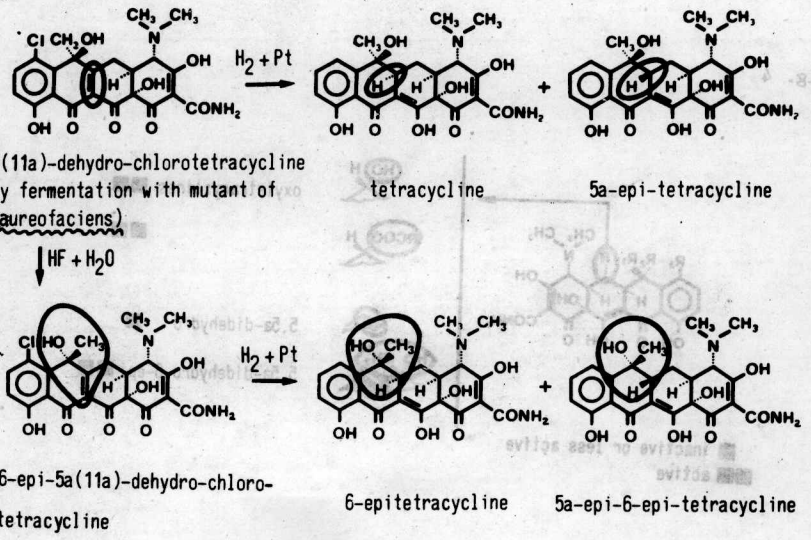
Fig. 5



A blocked mutant of S. aureofaciens produces 5a(11a)-dehydro-chlorotetracycline and from this product the other derivatives have been obtained by chemical steps, as depicted in figure 6.

It seems that the 5a-position is not very critical for antibiotic activity, but natural tetracyclines are still the best compounds and no improvements were obtained so far with modifications in position 5a.

Fig. 6



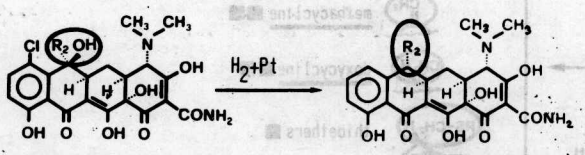
e) Chemistry in position 6

Some 6-epi compounds have been described above.

Position 6 is not critical for antibiotic activity and some of the most interesting, and clinically used tetracyclines have been obtained through changes in position 6: in fact 6-demethylchlorotetracycline, methacycline, doxycycline, are products modified in position 6.

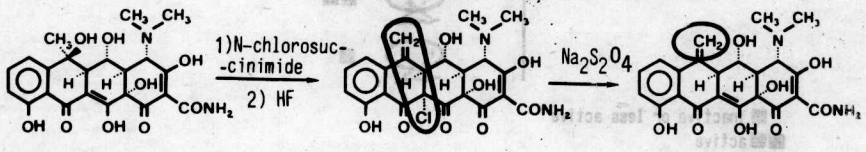
Some of the most interesting chemical reactions in position 6 are shown in figures 7 and 8.

Fig. 7



$R_2 = CH_3$ chlorotetracycline $R_2 = CH_3$ 6-desoxy-tetracycline

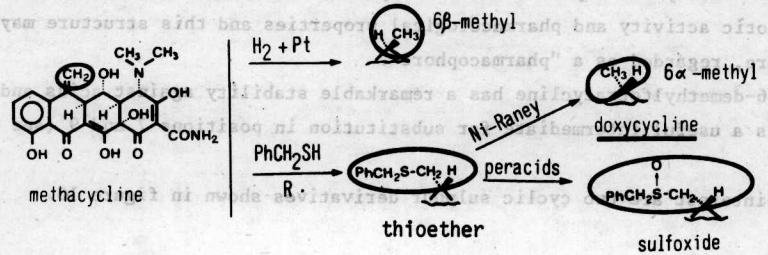
$R_2 = H$ 6-demethylchlorotetracycline $R_2 = H$ 6-desoxy-6-demethyltetracycline

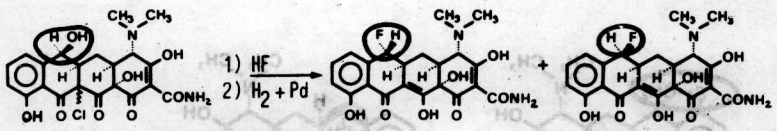


oxytetracycline

methacycline

Fig. 8





11a-chloro-6-demethyltetracycline