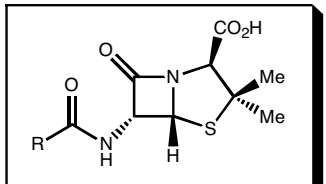
**Massachusetts Institute of Technology**

*5.13: Organic Chemistry II* *Fall 2003*

# Outline & Study Guide for Unit V. Carboxylic Acids & Derivatives

## Penicillin: The Wonder Drug

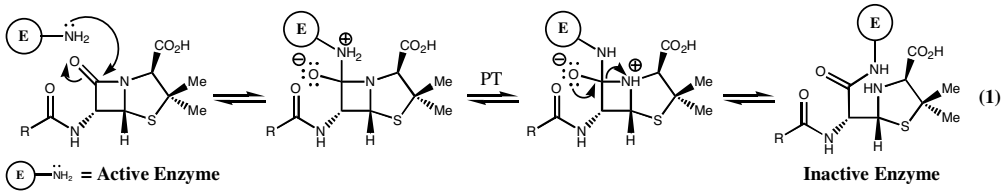
In the late 1800s, Louis Pasteur proposed the ground-breaking hypothesis that diseases were caused by microorganisms. This theory prompted numerous scientists to begin the search for substances that could kill the microorganisms causing the disease without also killing the patient. In the late 1920s, at St. Mary's Hospital in London, Alexander Fleming found that his bacterial culture plates were contaminated with an airborne fungus. More importantly, he noticed that the fungus inhibited the growth of bacteria on the plate. The fungus was *Penicillium notatum*, and Fleming named the extract of the fungus penicillin.



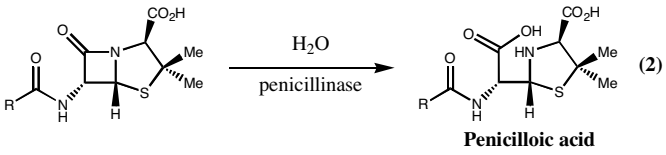
**Penicillin V (R = $CH_2OPh$)**
**Penicillin G (R = $CH_2Ph$)**

By the late 1930s, enough penicillin had been extracted to perform successful clinical trials with humans, but British scientists were unable to generate useful amounts of the drug. With World War II raging in Europe, the scientists turned to the United States for assistance. The United States government declared the production of penicillin a war project, and by the end of the war, enough penicillin was being produced to treat seven million patients per year.

Penicillin was successfully used to treat pneumonia, strep throat, scarlet fever, syphilis, gonorrhea, meningitis, and many other diseases. The cooperative wartime project between the British and the Americans also led to the proposed β-lactam structure for penicillin. Research into the bioactivity of penicillin indicated that penicillin interferes with the synthesis of bacterial cell walls by acylating an essential enzyme in the cell wall biosynthetic pathway. This acylation opens the strained β-lactam ring and renders the enzyme inactive (eq 1).




Unfortunately, Fleming was correct in his prediction that bacteria would soon develop resistance to penicillin through genetic modification. Penicillin-resistant bacteria produce an enzyme called penicillinase that hydrolyzes the β-lactam ring to form Penicilloic acid, an ineffective acylating agent unable to block cell wall synthesis (eq 2). By the early 1950s, nearly 60% of all staph infections were penicillin-resistant. As a result, the vital search for newer and more effective antibiotics continues today.




As a side note, the first total synthesis of natural penicillin (penicillin V) was completed in 1959 by Professor John C. Sheehan at MIT. In the course of his work, he developed one of the most widely used methods for forming amide bonds. You can check out the details in his paper: "The Total Synthesis of Penicillin V" *J. Am. Chem. Soc.* **1959**, *81*, 3089–3094.

**V. Carboxylic Acids and Derivatives (Chapters 20 & 21)**

A. Introduction
1. Structure
2. Acidity
3. Synthesis (Review)
   a) Oxidation of Primary Alcohols and Aldehydes
   b) Oxidative Cleavage of Alkenes and Alkynes
   c) Carboxylation of Grignard Reagents
   d) Hydrolysis of Nitriles
3. Acyl Derivatives

B. Acyl Transfer Reactions
1. Relative Reactivity of Acyl Derivatives
2. Mechanism: Addition-Elimination
3. Acyl Chlorides and Anhydrides
4. Esters
   a) Hydrolysis
   b) Transesterification
   c) Amide Formation
5. Carboxylic Acids
   a) Acid-Catalyzed Esterification
   b) Base-Catalyzed Esterification
   c) Formation of Acyl Chlorides
6. Amides
   a) Acidic Hydrolysis
   b) Basic Hydrolysis
7. Evidence for a Tetrahedral Intermediate
   a) Labeling Study: Ester Hydrolysis
   b) Labeling Study: Acyl Chloride Hydrolysis
   c) Labeling Study: Amide Hydrolysis
8. Reactions with $NaBH_4$, $LiAlH_4$, RMgBr, and RLi
9. Chemistry of Nitriles

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| **Suggested Reading:** | Chapter 20 (pp. 900–933)<br>Chapter 21 (pp. 940–992) |
| **Recommended Problems:** | Chapter 20-3,11,13,16,20,22,23,35,36<br>Chapter 21-7,8,9,15,16,22,24,27,28,35,48 |
| **Extra Problems:**<br>**(for more practice)** | Chapter 20-29,30,34,38,39,42,46<br>Chapter 21-10,14,17,18,26,32,34,49,50,60 |