

**Lec 1**

**4th stage**

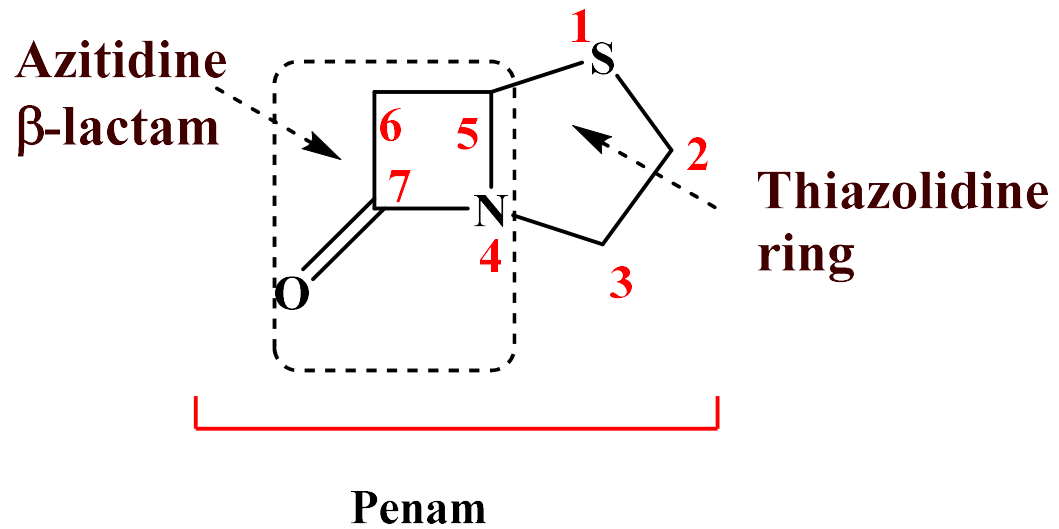
**Organic Pharmaceutical Chemistry III  
2018-2019**

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College of Pharmacy, university of Basrah**

**Textbook of Organic medicinal and  
pharmaceutical chemistry**

**Wilson and Gisvold's**

## *Stereo chemical aspect of penicillin*



# According to CA

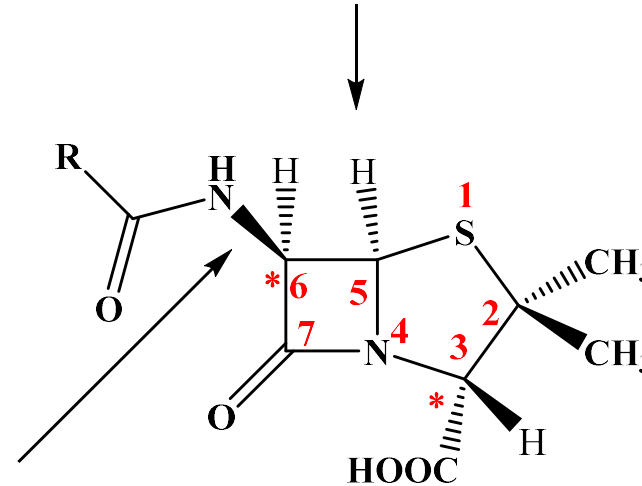
3 carbon chiral atom are present

C3

C5

C6

Cis stereochemistry  
Cis orientation of hydrogen are very essential



Trans orientation of amino group  
present at 6<sup>th</sup> position

The carbon atom bearing the acylamino group (C-6) has the L-configuration, whereas the carbon to which the carboxyl group is attached has the D-configuration. Thus, the acyl amino and carbonyl groups are trans to each other, with the former in the  $\alpha$  and the latter in the orientation relative to the penam ring system. The absolute stereochemistry of the penicillins is designated 3S:5R:6R.

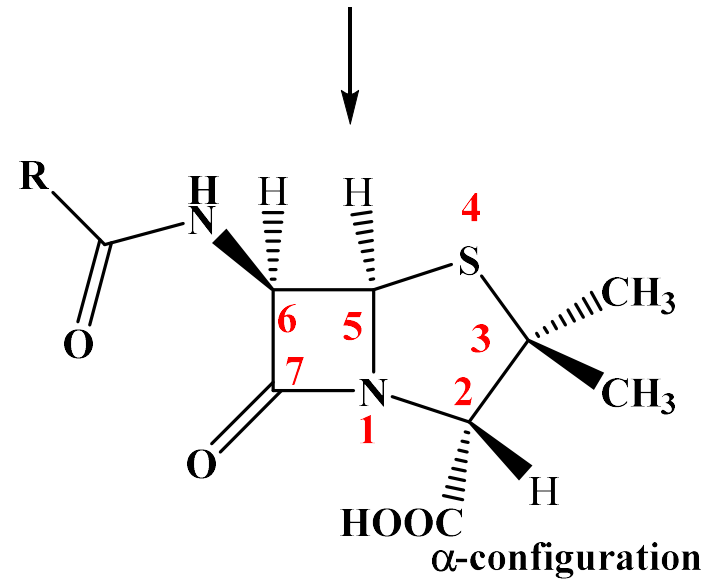
# According to USP

3 carbon chiral atom are present

C2

C5

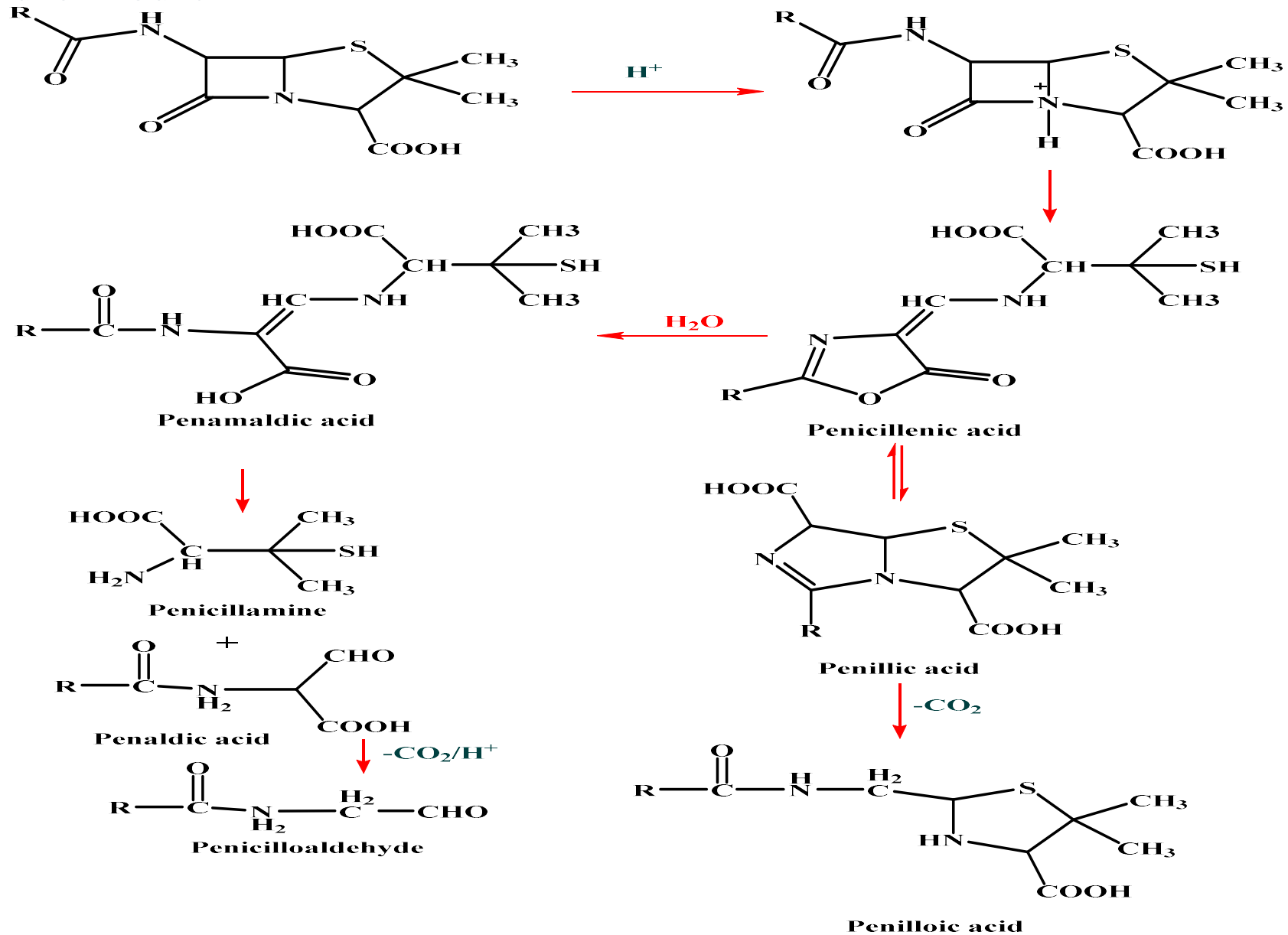
C6



The overall shape of the molecule is like a half-open book. acyl amino group and corboxyl group are treans to one another.

# Penicillin hydrolysis in acidic and basic medium

## Acidic medium



In strongly acidic solutions (pH <3), penicillin undergoes a complex series of reactions leading to various inactive degradation products .

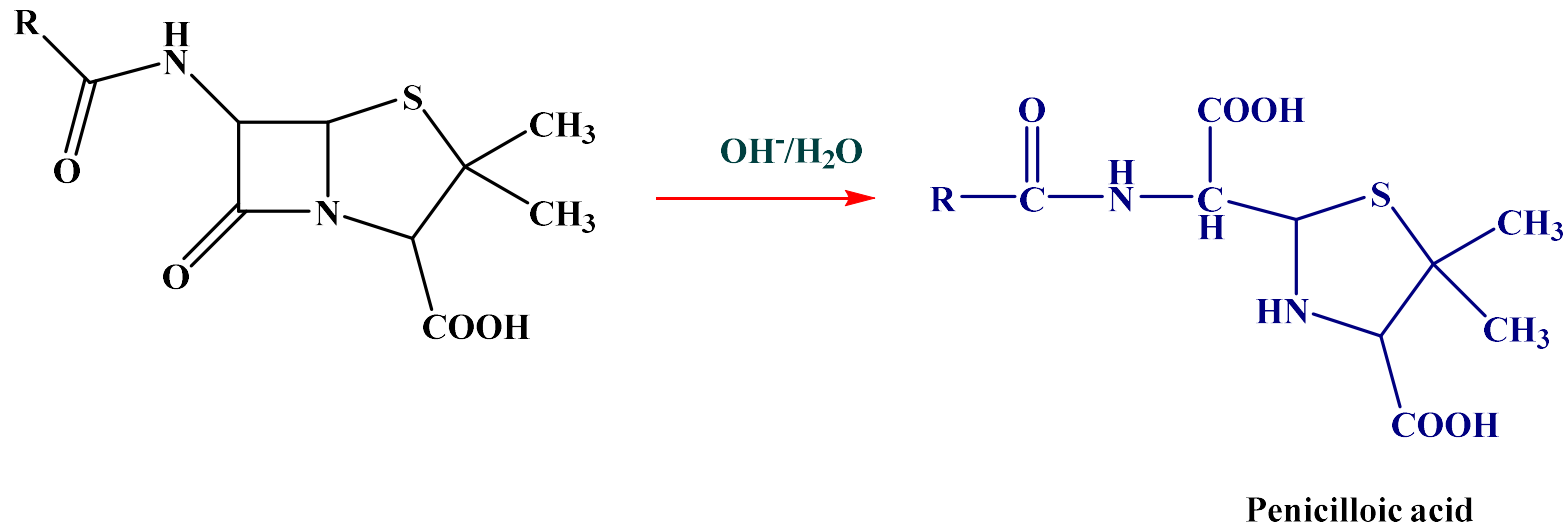
The first step appears to involve rearrangement to the penicillenic acid. This process is initiated by protonation of the  $\beta$ -lactam nitrogen, followed by nucleophilic attack of the acyl oxygen atom on the  $\beta$ -lactam carbonyl carbon. The subsequent opening of the  $\beta$ -lactam ring destabilizes the thiazolidine ring, which then also suffers acid-catalyzed ring opening to form the penicillenic acid.

The latter is very unstable and experiences two major degradation pathways. The most easily understood path involves hydrolysis of the oxazolone ring to form the unstable penamaldic acid. Because it is an enamine, penamaldic acid easily hydrolyzes to penicillamine (a major degradation product) and penaldic acid.

The second path involves a complex rearrangement of penicillanic acid to a penillic acid through a series of intramolecular processes that remain to be elucidated completely. Penillic acid (an imidazolidine-2-carboxylic acid) readily decarboxylates and suffers hydrolytic ring opening under acidic conditions to form a second major end product of acid-catalyzed penicillin degradation—penilloic acid.

## Basic medium

Penicilloic acid, the major product formed under weakly acidic to alkaline (as well as enzymatic) hydrolytic conditions, cannot be detected as an intermediate under strongly acidic conditions.



It exists in equilibrium with penamaldic acid, however, and undergoes decarboxylation in acid to form penilloic acid. The third major product of the degradation is penicilloaldehyde, formed by decarboxylation of penaldic acid (a derivative of malonaldehyde).

## **Bacterial Resistance**

The most important biochemical mechanism of penicillin resistance is the bacterial elaboration of enzymes that inactivate penicillins.

Such enzymes, which have been given the nonspecific name

- penicillinases, are of two general types:-

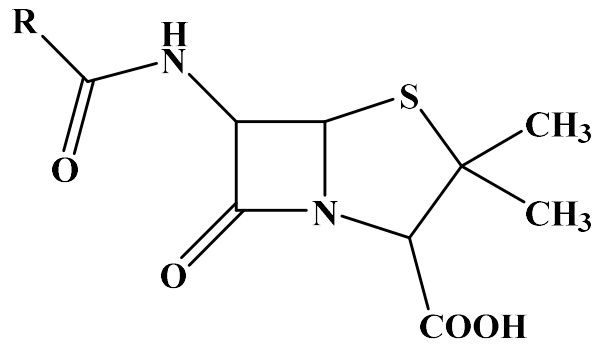
**1-  $\beta$ -lactamases.**

**2- acylases.**

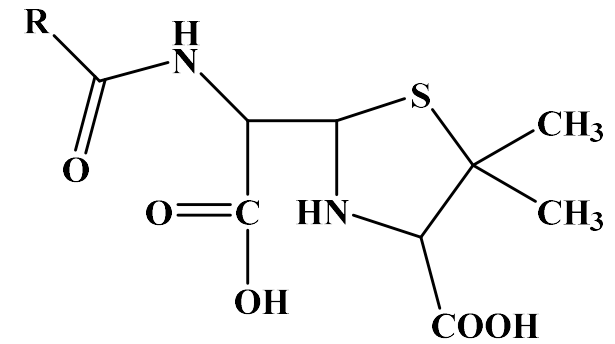
The more important of these are the  $\beta$ -lactamases, enzymes that catalyze the hydrolytic opening of the  $\beta$ -lactam ring of penicillins to produce inactive penicilloic acids.



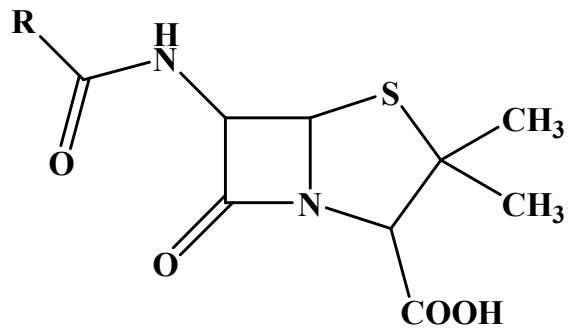
## *$\beta$ -lactamases*



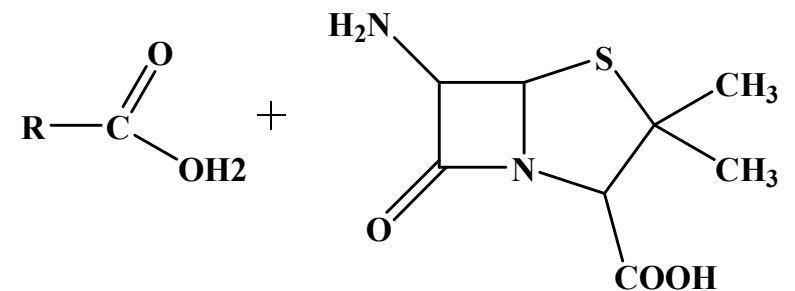
Attack at  $\beta$ -lactam carbonyl



## *Acylases*

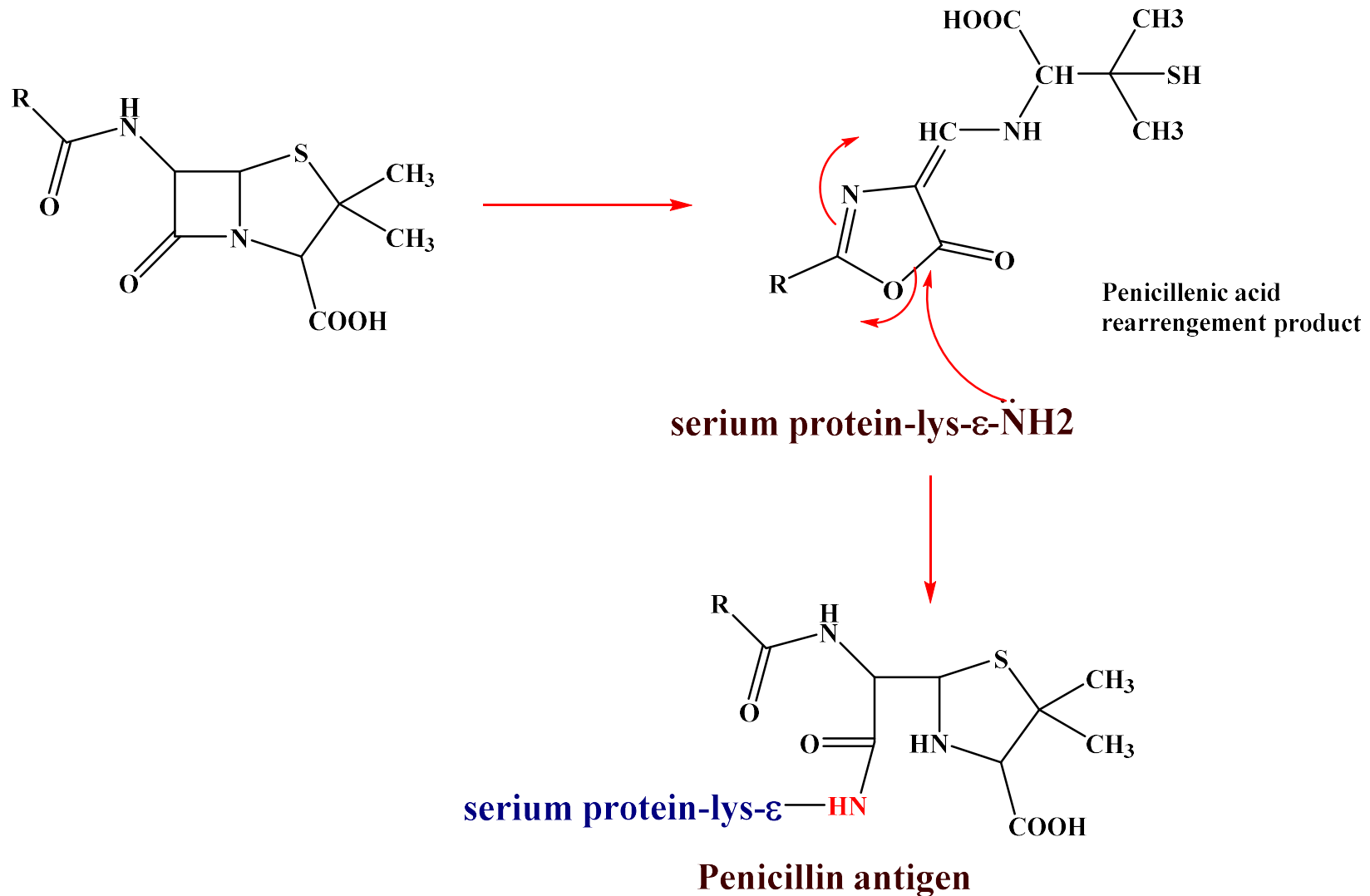


Attack at carbonyl side chain



## **Allergy to Penicillins**

rashes to penicillin, fever and anaphylaxis, constitute the major problem associated with the use of this class of antibiotics. 1-10% of the population show signs of this allergic response, this may be due to the formation of penicillin antigen as outline below.



Evidence suggests that rearrange product (penicillenic acid ) formed in vivo react with lysine  $\epsilon$ -amino group of serum proteins to form antigenic penicilloyl protein.

