Lecture 6

Organic Pharm. Chemistry for Pharmacy Students

By

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Functional Group Approaches to Prodrugs: Functional Groups in Peptides

- Functional Group Approaches to Prodrugs: Functional Groups **in Peptides**.
- peptides play critical roles in various biological processes. many of which are clinically used pharmaceutical agents.
- The high polarity and hydrogen-bonding potential, and the presence of charged functional groups, all of which are significant contributing factors to the generally poor permeation properties of peptides across membrane barriers.
- In addition, peptides typically undergo rapid metabolism, which leads to short half-lives *in vivo* (<30 min).

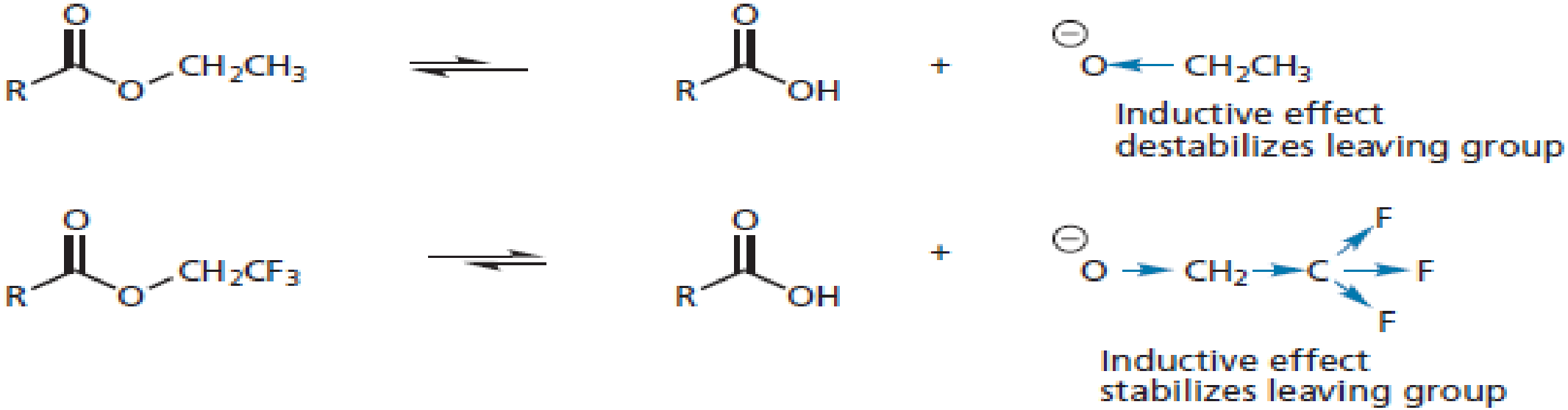
- Consequently, peptides are generally considered poor candidates for development as orally and CNS-active pharmaceutical agents.
- One way to overcome this problem is the prodrug approach, *i.e.*, to temporarily and bioreversibly mask those functional groups responsible for the undesirable physicochemical and pharmaceutical properties of peptides ,
- Therefore, prodrug derivatization of peptides has been focused on bioreversibly **derivatizing carboxyl, amino, guanidino, and hydroxyl groups**. The derivatization of such individual functional groups on small molecules through ester and amide formation and N-oxidation.
- Examples of prodrugs that exist naturally or were produced unintentionally during drug development include **aspirin, parathion, codeine, heroin, L-dopa, and various antiviral nucleosides.**

Prodrugs to improve membrane permeability

- **A carboxylic acid** functional group may have an important role to play in binding a drug to its binding site via ionic or hydrogen bonding
- However, the very fact that it is an ionizable group may prevent it from crossing a fatty cell membrane
- The answer is to protect the acid function as an ester
- The less polar ester can cross fatty cell membranes and, once it is in the bloodstream, it is hydrolysed back to the free acid by esterases in the blood

Ester prodrugs

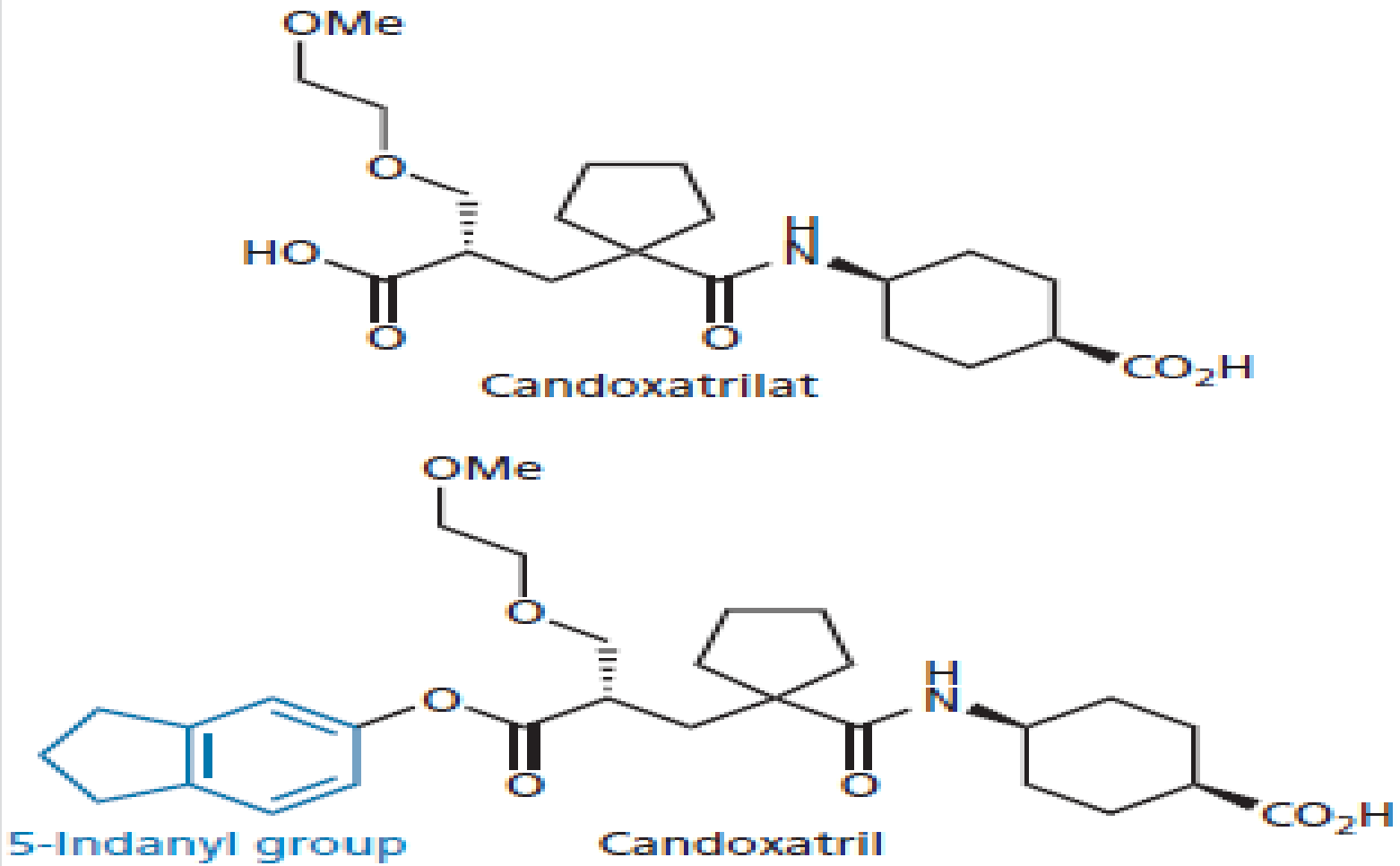
- It is possible to make esters more susceptible to hydrolysis by introducing electron-withdrawing groups to the alcohol moiety (e.g. OCH_2CF_3, OCH_2CO_2R, $OCONR_2$, OAr)
- The inductive effect of these groups aids the hydrolytic mechanism by stabilizing the alkoxide leaving group



Ester prodrugs

- The protease inhibitor **candoxatrilat** has to be given intravenously because it is too polar to be absorbed from the gastro intestinal tract
- Different esters were tried as prodrugs to get round this problem
- It was found that an ethyl ester was absorbed but was inefficiently hydrolysed
- A more activated ester was required and a 5-indanyl ester proved to be the best
- The 5-indanol released on hydrolysis is non-toxic

Ester prodrugs

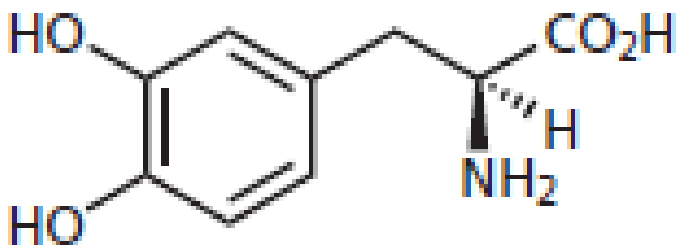


Ester prodrugs

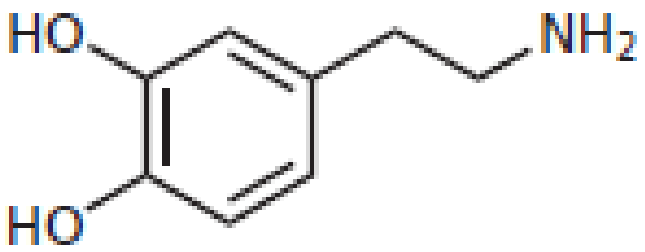
- Another way round the problem of membrane permeability is to design a prodrug which can take advantage of transport proteins in the cell membrane, such as the ones responsible for carrying amino acids into a cell
- **Levodopa** is a prodrug for the neurotransmitter **dopamine** and has been used in the treatment of Parkinson's disease—a condition due primarily to a deficiency of that neurotransmitter in the brain
- **Dopamine** itself cannot be used as it is too polar to cross the blood–brain barrier

Ester prodrugs

- **Levodopa** is even more polar and seems an unlikely prodrug, but it is also an amino acid, and so it is recognized by the transport proteins for amino acids which carry it across the cell membrane
- Once in the brain, a decarboxylase enzyme removes the acid group and generates dopamine



Levodopa



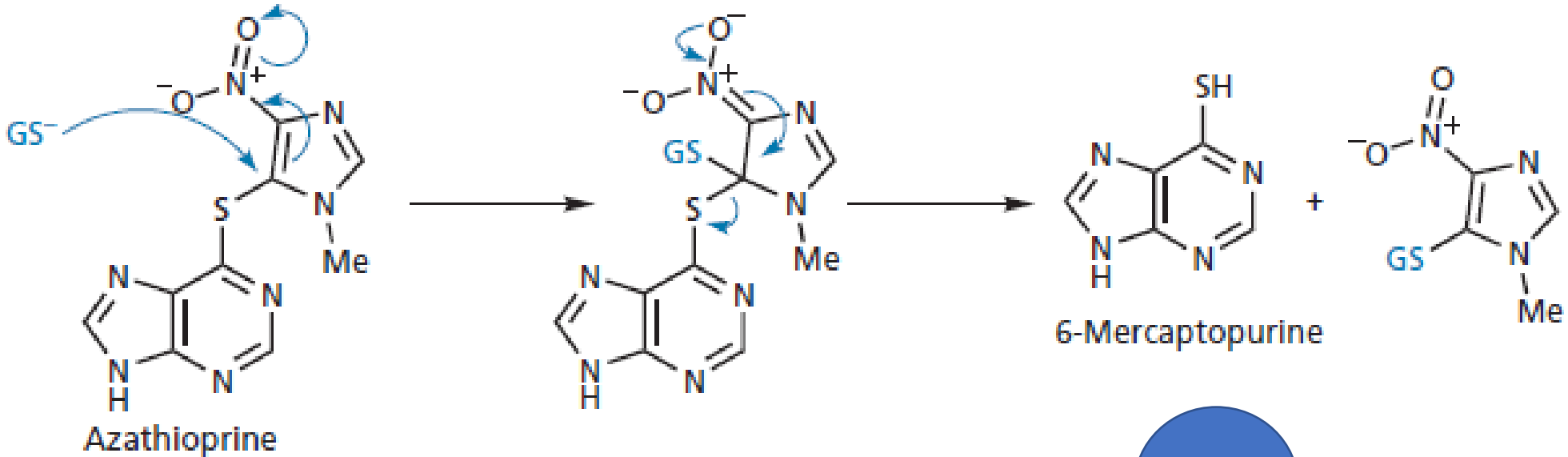
Dopamine

Prodrugs to prolong drug activity

- prodrugs are also designed to be converted slowly to the active drug, thus prolonging a drug's activity
- **6-mercaptopurine** suppresses the body's immune response and is, therefore, useful in protecting donor grafts
- Unfortunately, the drug tends to be eliminated from the body too quickly
- The prodrug **azathioprine** has the advantage that it is slowly converted to **6-mercaptopurine** by being attacked by **glutathione** allowing a more sustained activity.

Prodrugs to prolong drug activity

Ex,

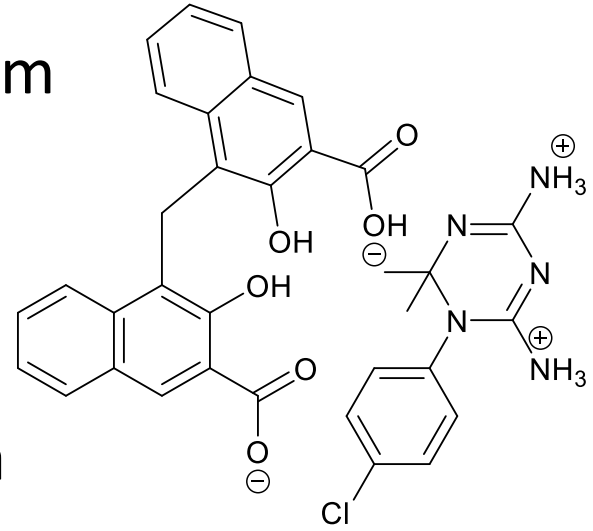


Prodrug

Drug

Prodrugs to prolong drug activity

- Another approach to maintaining a sustained level of drug over long periods is to deliberately associate a very lipophilic group to the drug
- This means that most of the drug is stored in fat tissue from where it is steadily and slowly released into the bloodstream
- The antimalarial agent **cycloguanil pamoate** is one such agent
- The active drug is bound ionically to an anion containing a large lipophilic group and is only released into the blood supply following slow dissociation of the ion complex



Prodrugs masking drug toxicity and side effects

- Prodrugs can be used to mask the side effects and toxicity of drugs
- **LDZ** is an example of a diazepam prodrug which avoids the drowsiness side effects associated with **diazepam**
- These side effects are associated with the high initial plasma levels of diazepam following administration
- The use of a prodrug avoids this problem. An aminopeptidase enzyme hydrolyses the prodrug to release a non-toxic lysine moiety, and the resulting amine spontaneously cyclizes to the diazepam

Prodrugs masking drug toxicity and side effects

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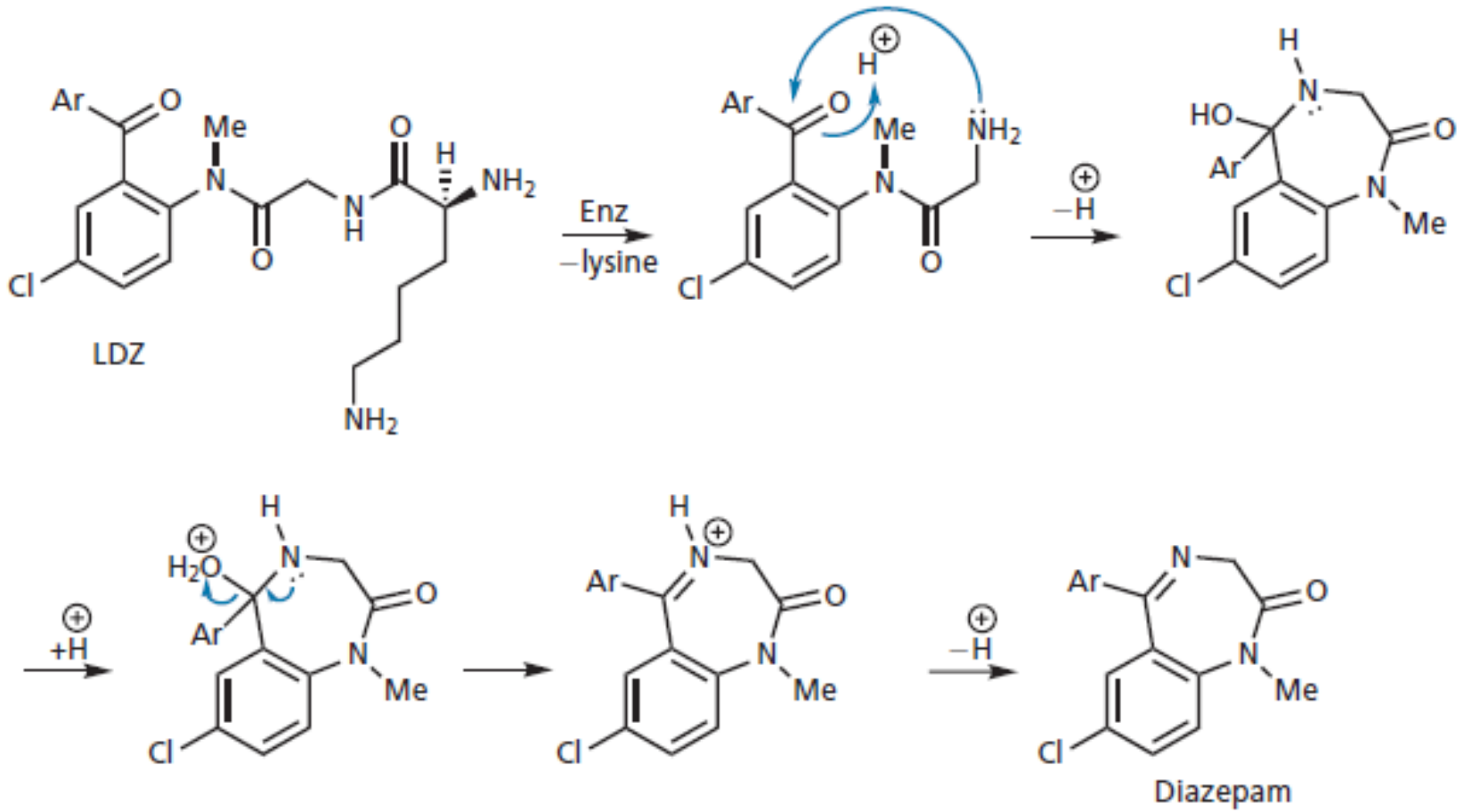
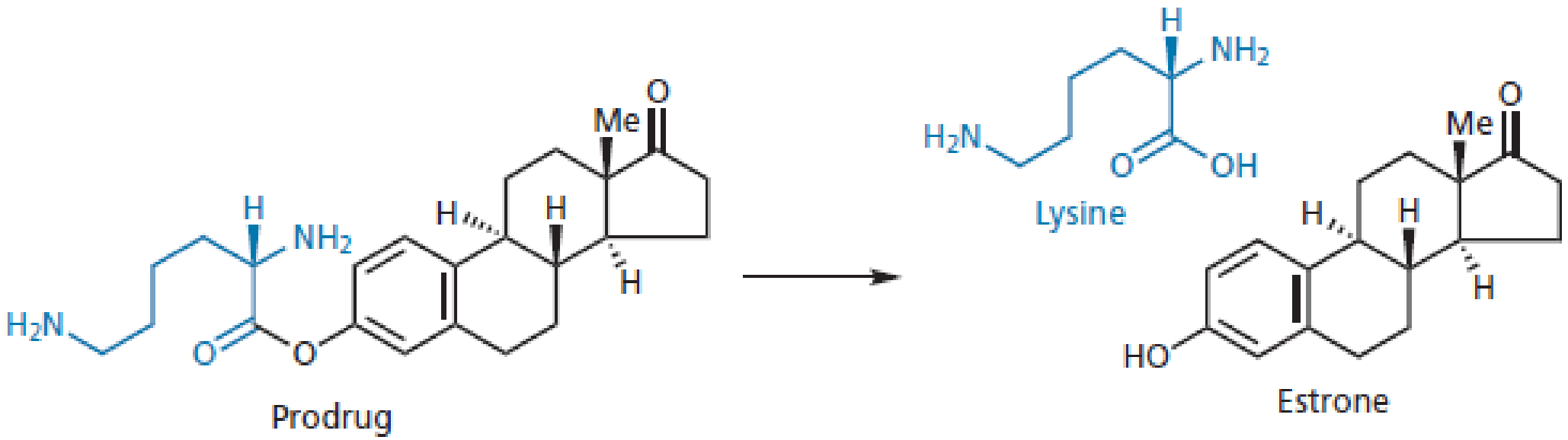


Prodrugs to improve water solubility

- Polar prodrugs have been used to improve the absorption of non-polar drugs from the gut (الامعاء)
- Drugs have to have some water solubility if they are to be absorbed, otherwise they dissolve in fatty globules and fail to interact effectively with the gut wall
- The steroid **estrone** is one such drug. By using a lysine ester prodrug, water solubility and absorption is increased
- Hydrolysis of the prodrug releases the active drug and the amino acid lysine as a non-toxic by-product

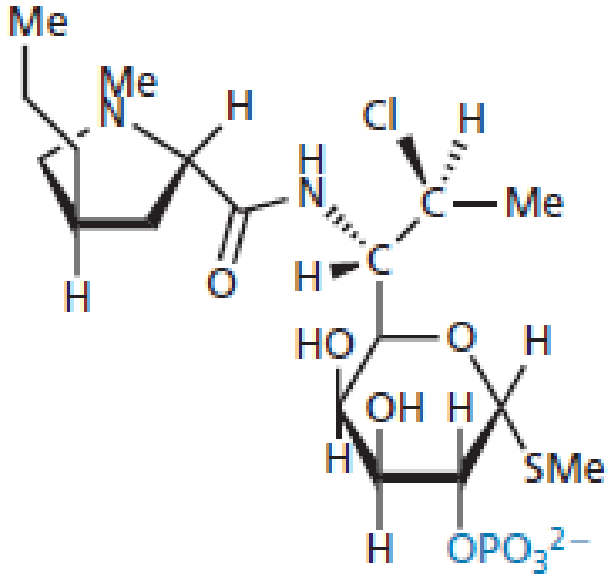
Prodrugs to improve water solubility

- Ex.



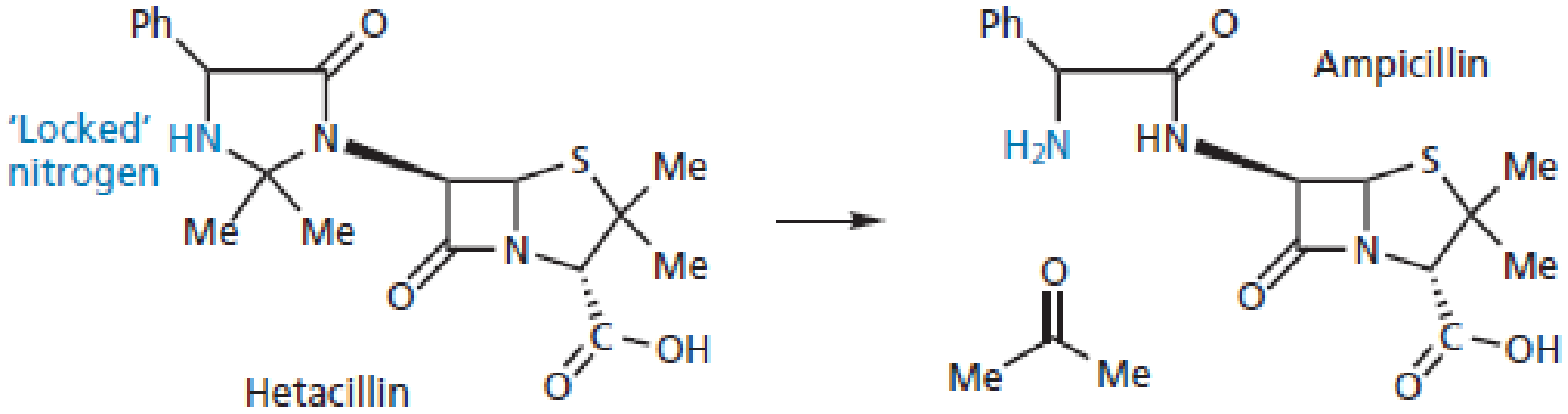
Prodrugs to improve water solubility

- Prodrugs designed to increase water solubility have proved useful in preventing the pain associated with some injections, which is caused by the poor solubility of the drug at the site of injection
- The antibacterial agent **clindamycin** is painful when injected, but this is avoided by using a phosphate ester prodrug which has much better solubility because of the ionic phosphate group



Prodrugs to increase chemical stability

- The antibacterial agent **ampicillin** decomposes in concentrated aqueous solution as a result of intramolecular attack of the side chain amino group on the lactam ring
- **Hetacillin** is a prodrug which locks up the off ending nitrogen in a ring and prevents this reaction. Once the prodrug has been administered, hetacillin slowly decomposes to release ampicillin and acetone



Photodynamic therapy (PDT)

- A variation of the prodrug approach is the concept of a sleeping agent
- This is an inactive compound which is converted to the active drug by some form of external influence
- The best example of this approach is the use of photosensitizing agents such as **porphyrins** or **chlorins** in cancer treatment— photodynamic therapy (PDT)
- Porphyrins occur naturally in chlorophyll in plants and haemoglobin in red blood cells
- They usually complex a metal ion in the centre of the molecule(magnesium in chlorophyll and iron in haemoglobin)

Photodynamic therapy

- In this form, they are non-toxic but if they lack the central ion, they have the potential to do great damage
- Given intravenously, these agents accumulate within cells and have some selectivity for tumour cells
- By themselves, the agents have little effect, but if the cancer cells are irradiated with red light or a red laser, the **porphyrins** are converted to an excited state and react with molecular oxygen to produce highly toxic singlet oxygen
- Singlet oxygen can then attack proteins and unsaturated lipids in the cell membrane leading to the formation of hydroxyl radicals which further react with DNA leading to cell destruction

Photodynamic therapy

- **Temoporfin** is an example of a chlorin photosensitizing agent which is used to treat advanced head and neck tumours that do not respond to other treatments