الكيمياء الصيدلية 1

المحاضرة الاولى

introduction

د. يوسف الأحمد

ما هي الكيمياء الصيدلية ؟
البحث في المركبات الكيميائية الفعالة

- **Physicochemical properties**
- **Physical chemistry**

- العزل
- التنقية

- ***Organic chemistry***
- ***Medicinal chemistry***
- ***Analytical chemistry***

- تحديد الصيغة العامة والفراغية
- استنباط طرق اصطناع عالية المردود واقتصادية
- دراسة ثبات وتخرب ومقايسات

- **Pharmacology**

- تحديد المقادير العلاجية
- التوافر الحيوي
- الاستقلاب داخل العضوية

ما هي الكيمياء الصيدلية

- *Stereochemistry*
- *SAR &QSAR*
- *Synthesis*
- *combinatorial chemistry*

- ***Organic chemistry***
- ***Medicinal chemistry***
- ***Computational chemistry***

- Physicochemical properties
- Identification
- Assay

- **Pharmacopoeia**
- **Analytical chemistry**
- **Physical chemistry**

- **indications**

- **Pharmacology**
- **Molecular biology**
- **Molecular pharmacology**
- **receptors**

ما هي الكيمياء الصيدلية ؟
البحث في المركبات الكيميائية الفعالة

- القسم اللاعضوي
- المركبات المعدنية

- المركبات الصيدلانية العضوية
- التصنيف الكيميائي

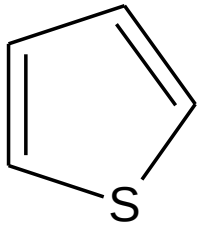
- المجموعات الدوائية

- مراجع مهمة:

- wilson and gisvold's textbook of organic medicinal and pharmaceutical chemistry 12th 2011
- British pharmacopoeia
- USP
- An introduction to medicinal chemistry patrick 2009
- Synthesis of Essential Drugs 2006, *Vardanyan and V.J. Hruby*
- *UMD*
- *الكيمياء الصيدلية 1 منشورات جامعة دمشق 2011/2012 د. الجندي , د. حيدر*

تذكرة 1

Heterocycles



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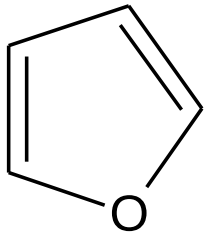

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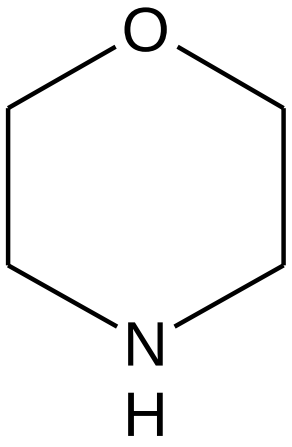

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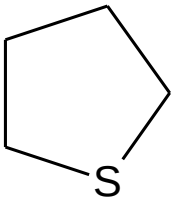

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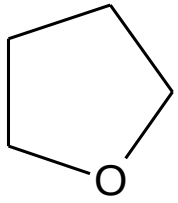
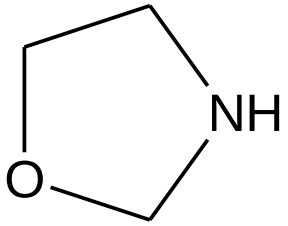
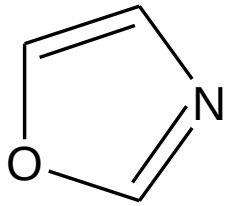


tetrahydrofuran



1,3-oxazolidine



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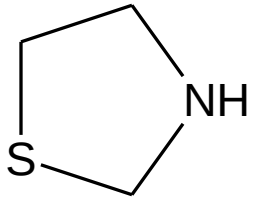

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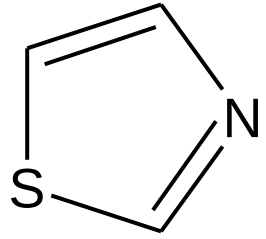
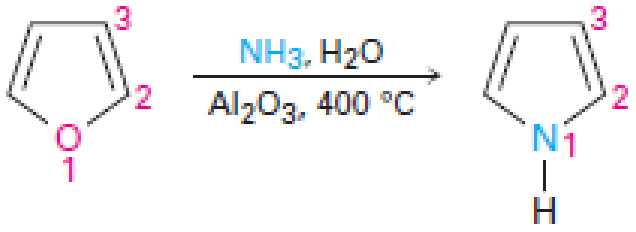
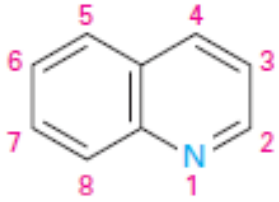


1,3-thiazole

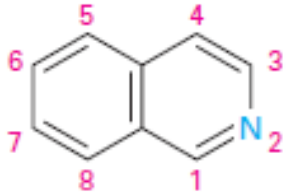
Heterocycles



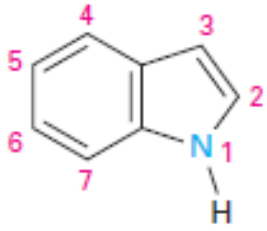
Furan **Pyrrole**



Quinoline

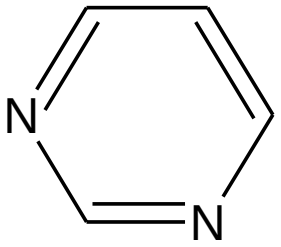


Isoquinoline

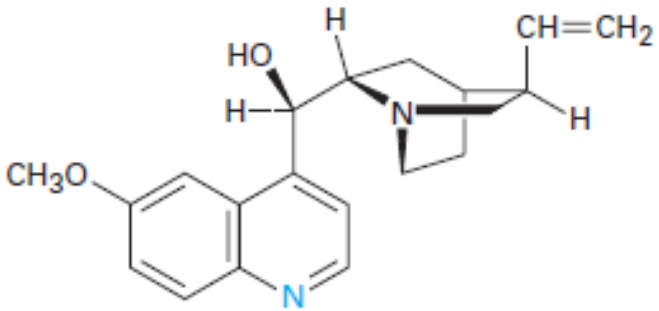


Indole

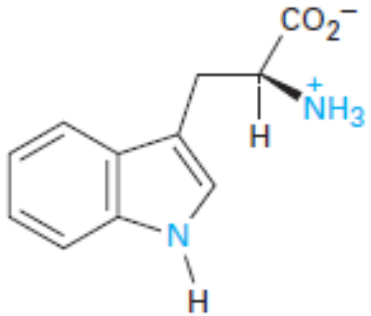
Purine



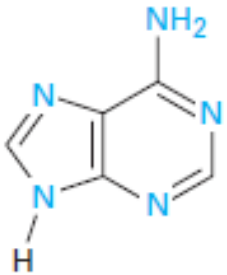
pyrimidine



Quinine
(antimalarial)

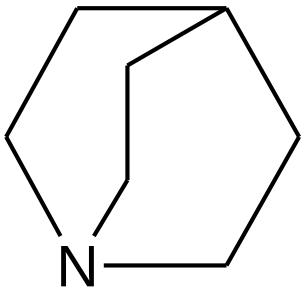


Tryptophan
(amino acid)

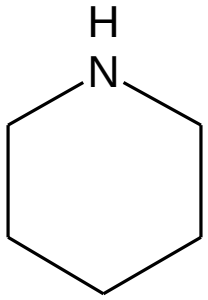


Adenine
(DNA constituent)

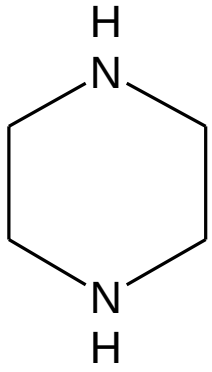
Heterocycles



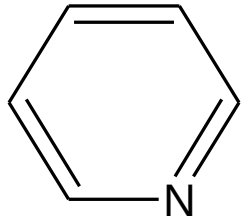
quinuclidine



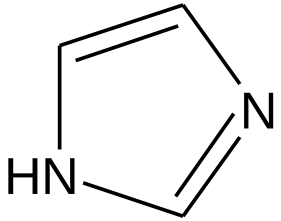
piperidine



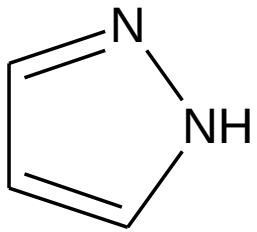
piperazine



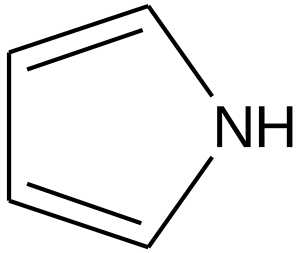
pyridine



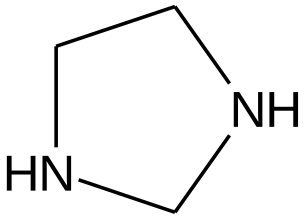
1*H*-imidazole



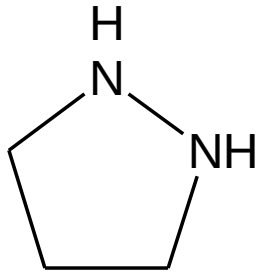
1*H*-pyrazole



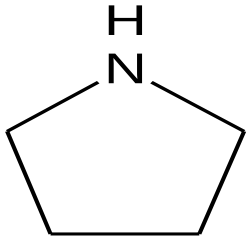
1*H*-pyrrole



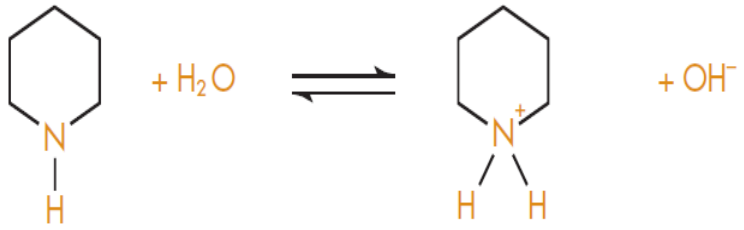
imidazolidine



pyrazolidine



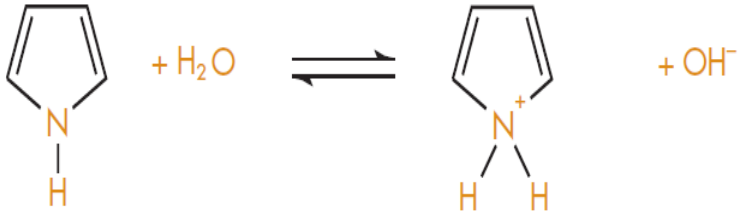
pyrrolidine



Piperidine
pK_a = 11·2

aliphatic heterocyclic compounds

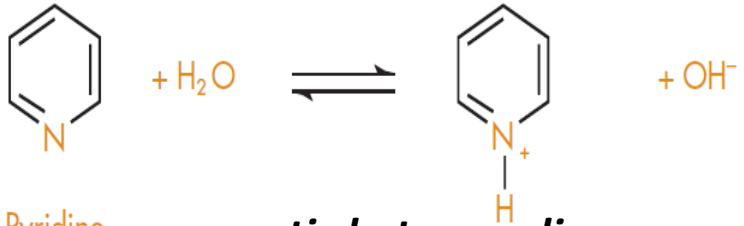
- saturated heterocyclic ring and the lone pair of electrons is available for eaction with protons. So, similar in base strength to their open-chain aliphatic counterparts



Pyrrole
pK_a = − 0·27

aromatic heterocyclic compounds,

- *lone pairs on the nitrogen atoms* are involved in interaction with electrons of the aromatic ring.
- the lone pair contributes to the aromatic sextet and is not available for reaction with protons. So, pyrrole is a very weak base with a p*Ka value* .



Pyridine
pK_a = 5·2

aromatic heterocyclic compounds,

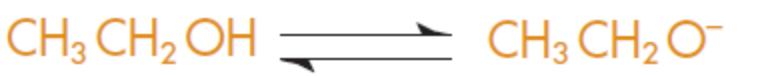
- only one electron from the nitrogen contributes to the aromatic sextet. This leaves an unshared pair of electrons, which can accept a proton, so that pyridine is measurably basic with a p*Ka value of 5.2.*
- *This value is similar to that found in aromatic*
- amines such as aniline (aminobenzene)

Figure 3.19 The ionisation of some nitrogen-containing heterocyclics.

تذكرة 2

- **Physicochemical properties of drugs**

$pK_a = 4{\cdot}7$

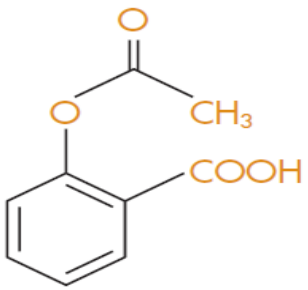


$pK_a \sim 16$

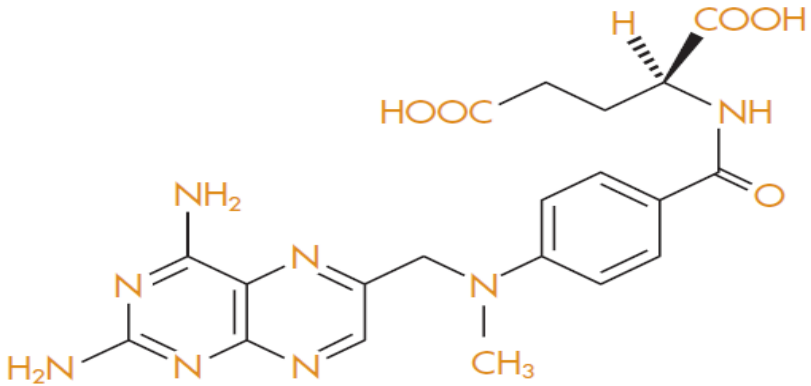
The ionisations of acetic acid and ethanol

- The ionisations of acetic acid and ethanol
- This means that acetic acid is almost a hundred thousand million (or 1011) times more acidic than ethanol.
- the anion formed on ionisation of acetic acid is resonancestabilised.

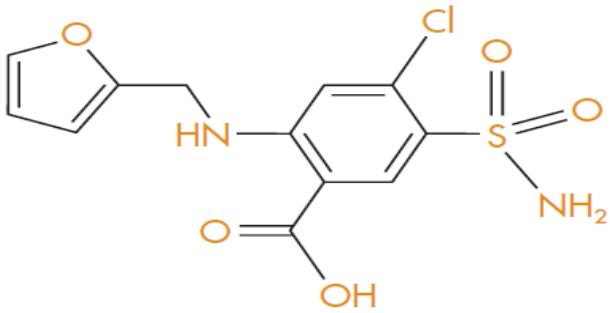
- **Physicochemical properties of drugs**



Aspirin



Methotrexate



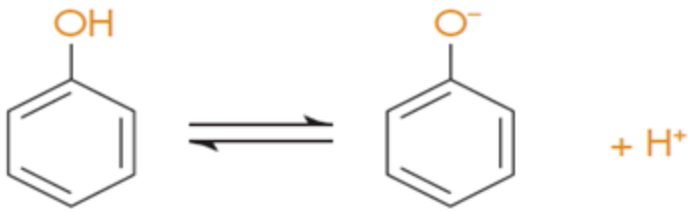
Furosemide

Exemples:

•aspirin (p*Ka 3.5), the anticancer compound methotrexate* (**p*Ka 3.8, 4.8 and 5.6)*** *and the diuretic furosemide*, p*Ka 3.9).*

• ***ionisied in biological fluides***

- **Physicochemical properties of drugs**



Phenols are weak acids that liberate protons to give the phenoxide anion.
This anion is resonance-stabilised and four canonical forms may be drawn

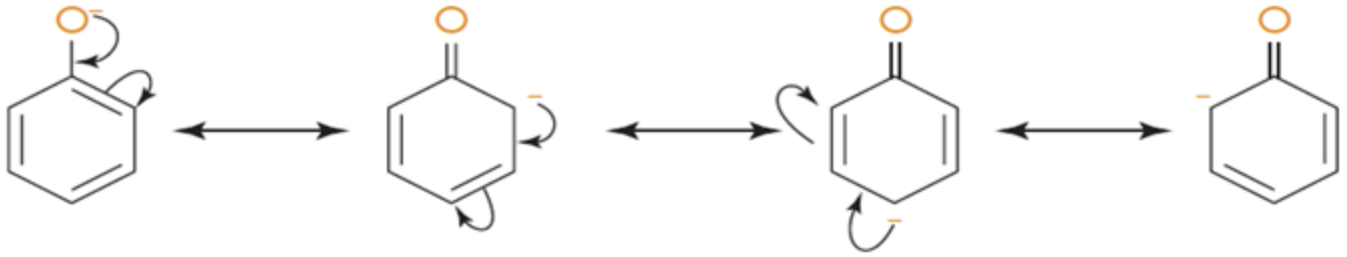
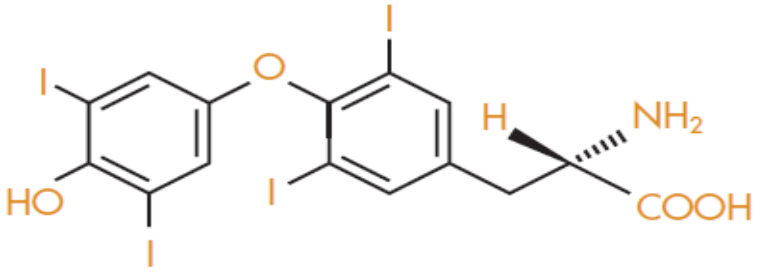


Figure 3.5 Resonance stabilisation of the phenoxide anion.



Levothyroxine

CHARACTERS

An almost white or slightly brownish-yellow powder, or a fine, crystalline powder, very slightly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

Warfarin

- Warfarin is an anticoagulant that inhibits the clotting action of blood through an action on vitamin K-derived clotting factors.
- **deep-vein thrombosis or pulmonary embolism**.
- **Warfarin is used in the UK as the sodium salt, (acid)**

- The acidic hydrogen is located between two electron-withdrawing carbonyl groups.
- resonance-stabilised anion.
- This enhanced stability of the anion allows warfarin to lose a proton and renders the drug acidic with a **p*Ka of* 5.0**.
- Warfarin in the free acid form is not very soluble in water and is therefore always administered (and is official in the *B P) as* the sodium salt.

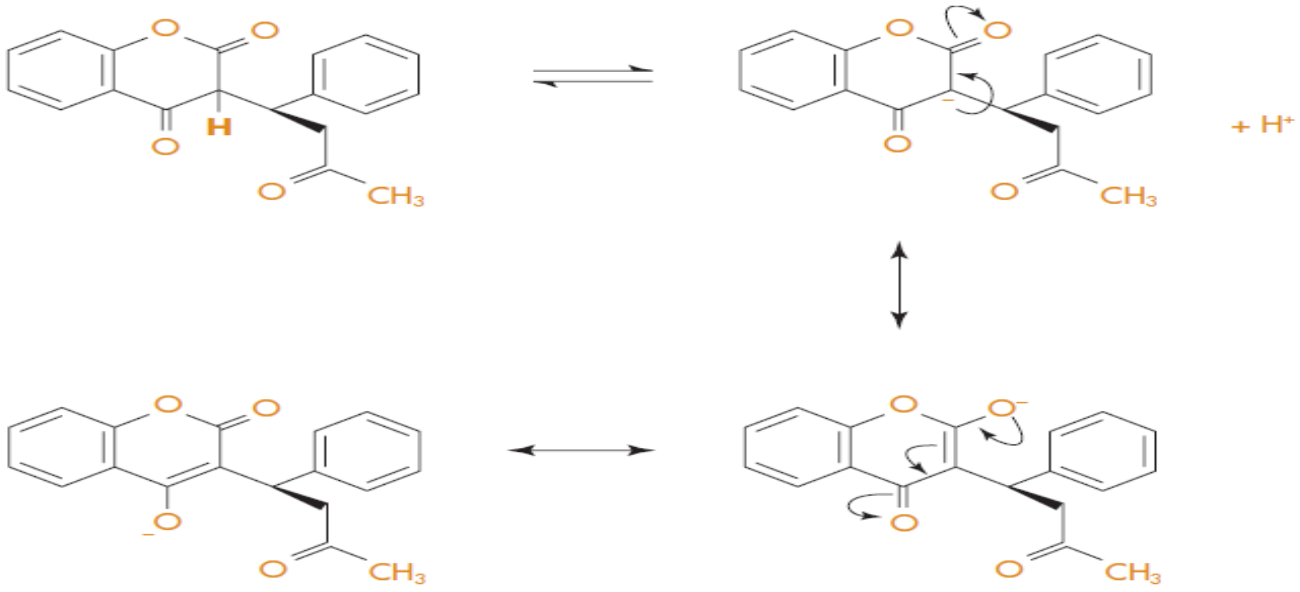
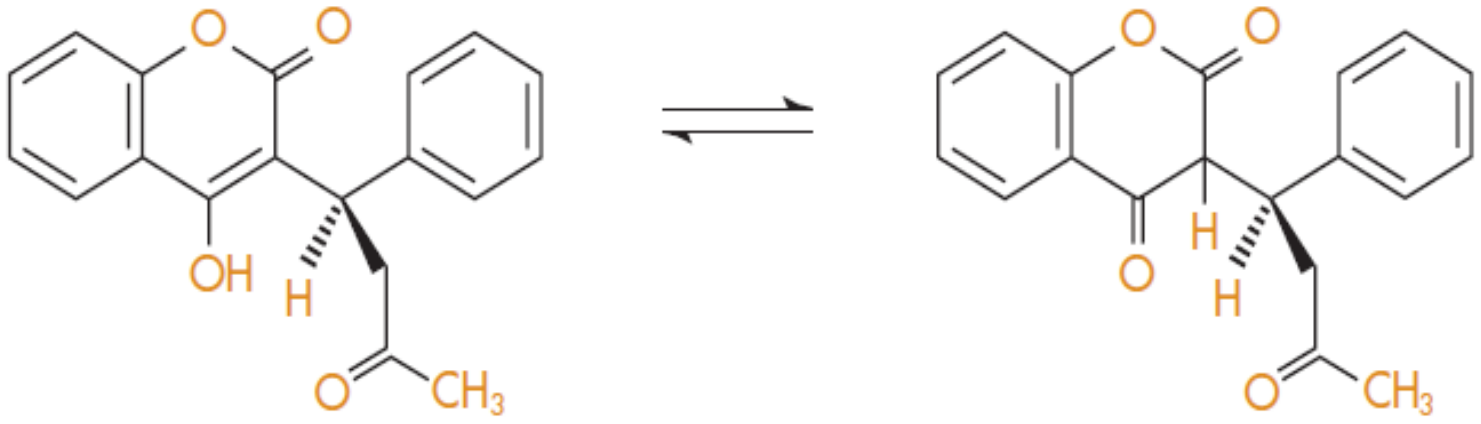


Figure 3.7 The ionisation of warfarin.

Warfarin

- **keto–enol *tautomerism.* This means that warfarin exists in two constitutional isomeric forms (tautomers) that are in equilibrium with each other, although one of the forms is usually present to a much higher degree than the other.**



Enol form

Keto form

Figure 3.8 The tautomerism of warfarin.

Comparison of resonance and tautomerism

Resonance forms of a drug[a]	*Tautomeric forms of a drug*[b]
Same compound	Different compounds
Differ only in position of *electrons*	Differ in position of *atoms* (usually hydrogen)
Each canonical form contributes to a single resonance structure	Each form exists in equilibrium
Canonical forms cannot be isolated	Each tautomer may be isolated

[a]Represented by a double-headed arrow ⟷.

[b]Represented by an equilibrium arrow ⇌.

Phenylbutazone

- **popular misconception that:** because amines are basic and amines contain a nitrogen atom, then all drugs that contain nitrogen will be basic.

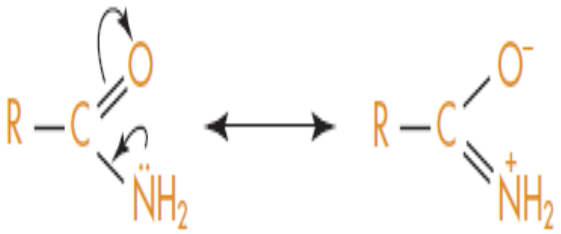
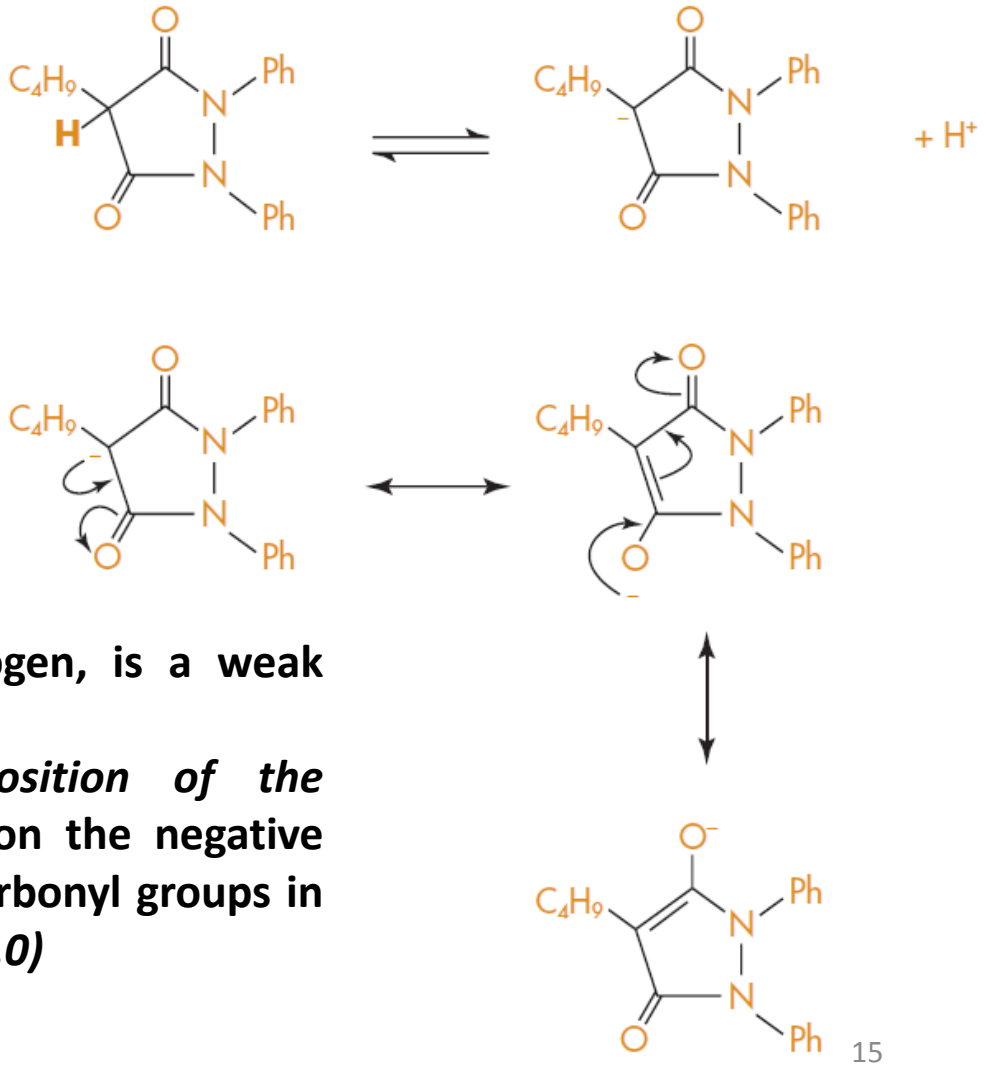


Figure 3.10 Resonance effects of the amide group.



Phenylbutazone, despite containing nitrogen, is a weak acid with a p*Ka of 4.4.*

The acidic hydrogen is on the 4-position of the **pyrazolidinedione ring and upon ionisation the negative charge is delocalised onto the adjacent carbonyl groups in a similar manner to that in warfarin (p*Ka 5.0)***

sulfonamides

- Sulfonamides are a class of antibacterial compounds, all of which contain the sulfonamido group a SO2NH. Sulfonamides are all weakly acidic (p*Ka approximately 5–8) due to the powerful electron-withdrawing effect of the –SO2-substituent*and stabilisation of the resulting anion by resonance.
- Sulfonamides are usually administered in the form of the sodium salt to increase their water solubility

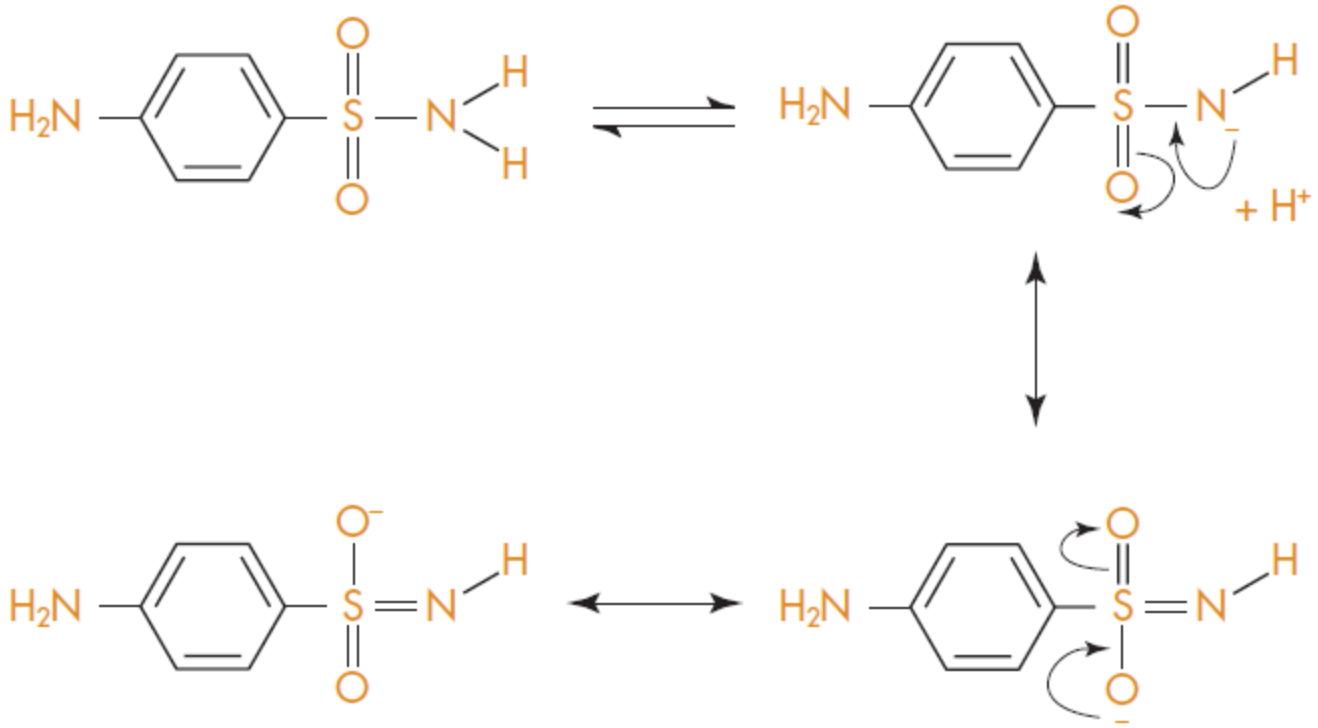


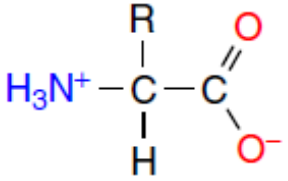
Figure 3.17 The ionisation of a sulfonamide.

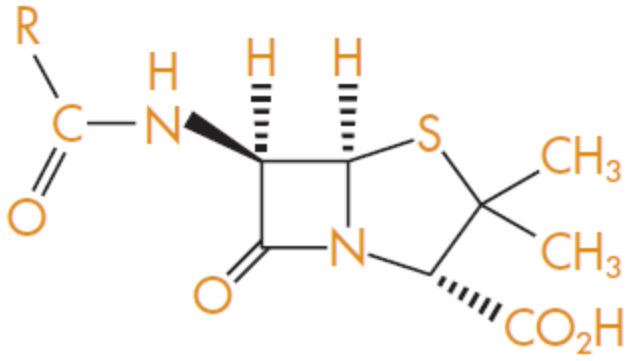
تذكرة 3

الكيمياء الفراغية Stereochemistry

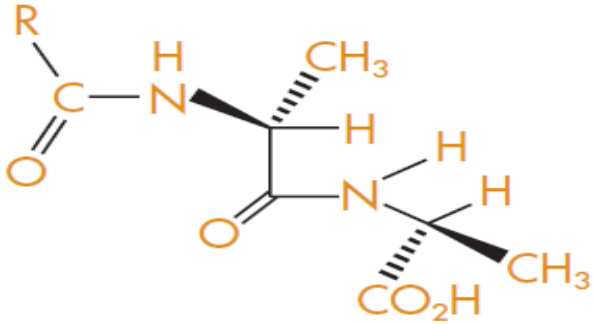
Amino Acids & their Derivatives

- Substituted Carboxylic acid, αAA
- L-Configuration





Penicillin



Acyl-D-Ala-D-Ala

Acyl-D-Ala-D-Ala

- يوجد في الجراثيم وهو ضروري لتشكيل الجدار الخلوي
- يتشابه فراغياً مع البنسلين
- عدم وجود حموض أمينية D لدى الإنسان يفسر عدم سمية البنسلين للخلية البشرية

آلية تأثير البيتالاكتامات

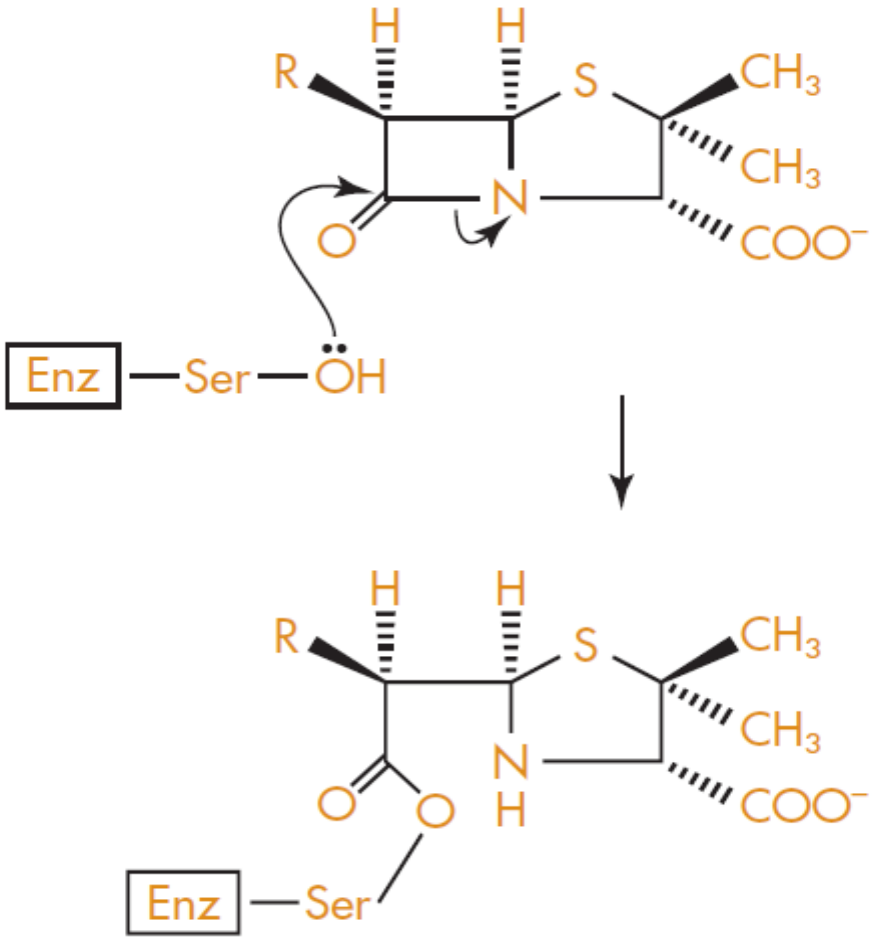
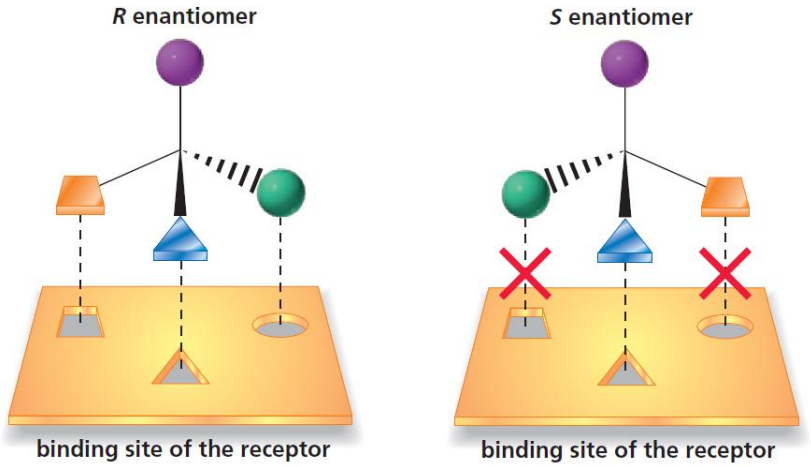
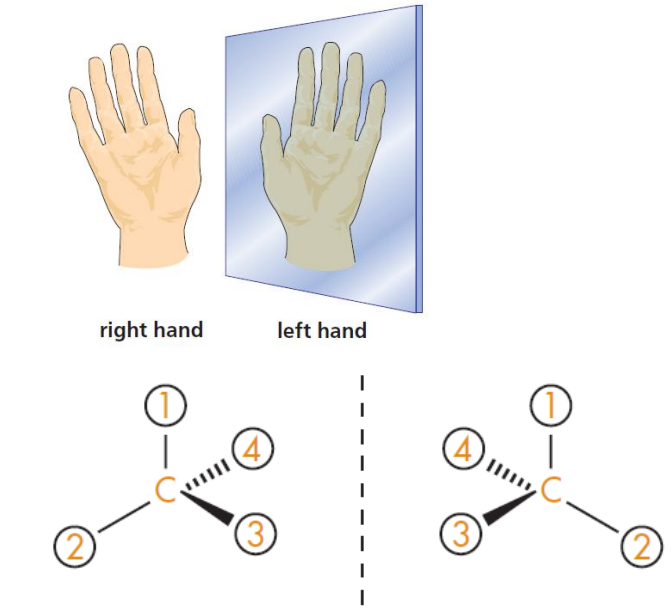


Figure 4.11 Mode of action of β-lactam antibiotics.

chirality

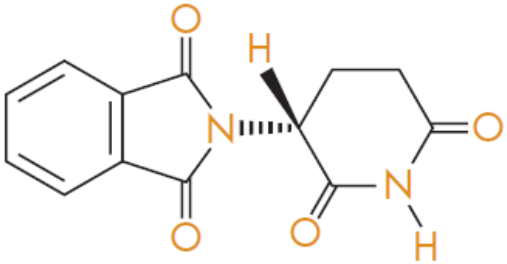
- كربون مرتبط بأربع متبادلات مختلفة
- نمط التهجين SP^3
- تدعى المماكبات في حال وجود مركز عدم تناظر واحد المتصاوغات المرآتية enantiomers



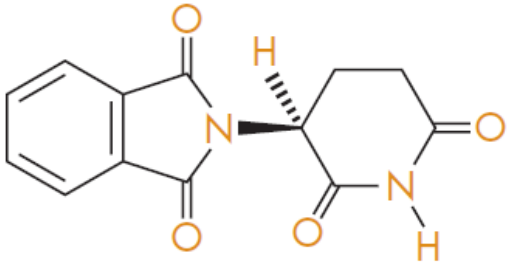


- اختلاف بالتأثير العلاجي

sedative



(*R*)-Thalidomide

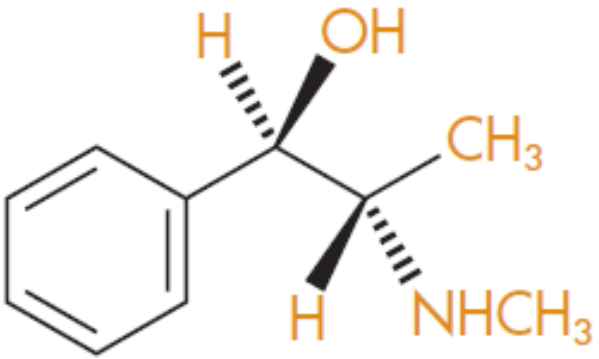


(*S*)-Thalidomide

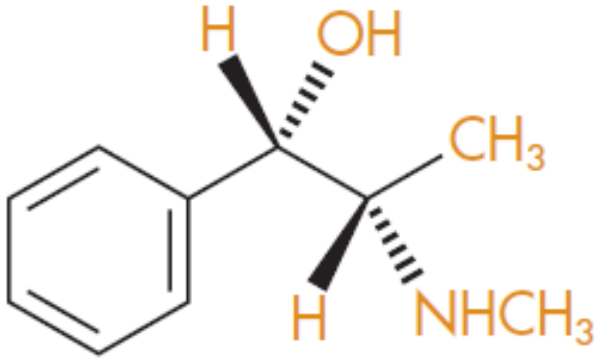
teratogenic

المتصاوغات الفراقية diastereoisomers

وجود اكثر من مركز عدم تناظر وبالتالي فإن عدد المماكبات الفراغية يعطى بالعلاقة 2^n حيث n عدد مراكز عدم التناظر.



Ephedrine



Pseudoephedrine

الخصائص الفيزيائية والكيميائية للمتصاوغات

Enantiomers

تمتلك المتصاوغات المرآتية (enantiomers) خصائص كيميائية وفيزيائية متطابقة ما عدا حرفها للضوء المستقطب.

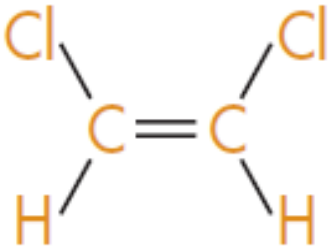
Diastereomers

بينما تمتلك المتصاوغات الفراقية (Diastereomers) خصائص فيزيائية وكيميائية مختلفة عن بعضها البعض.

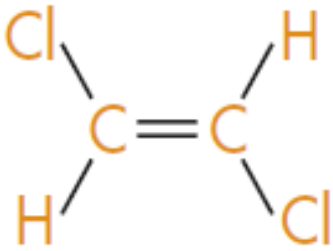
Geometrical isomerism

•the term *cis is : describes the* molecule If the substituents around the double bond are similar and both are on the same side of the double bond,.

• the term *trans:* the same groups are on opposite sides of the double bond.



cis-Dichloroethene



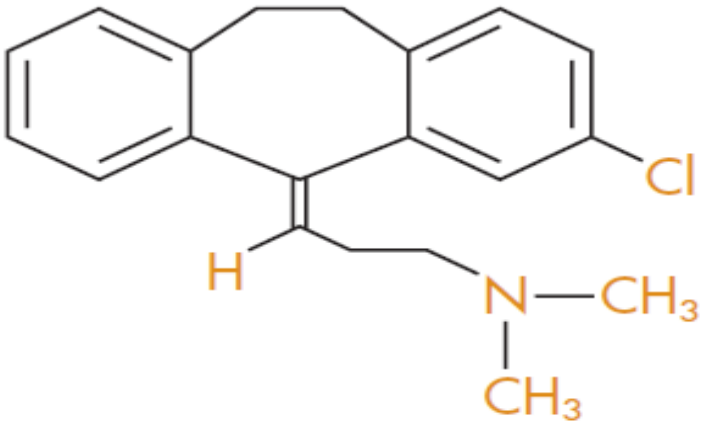
trans-Dichloroethene

Figure 4.15 Examples of *cis* and *trans* isomerism.

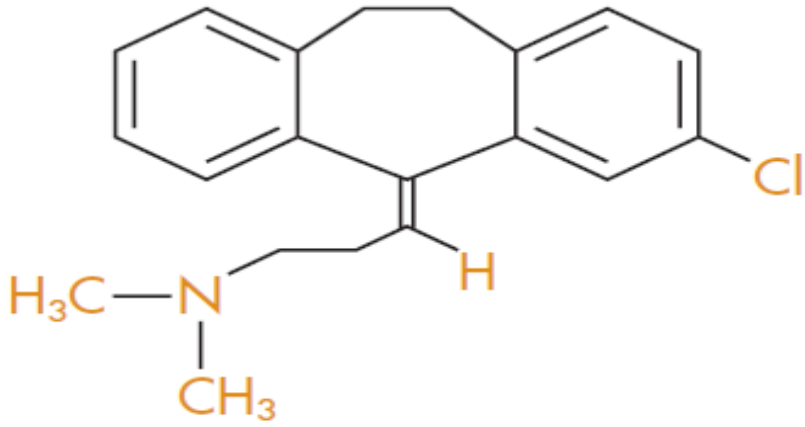
Geometrical isomerism

• the (*Z) isomer:* the high-priority substituents are on the same side of the double bond is *(from the German zusammen meaning* together).

•The alternative configuration, with the high-priority groups on opposite sides of the double bond, is described as (*E) (also from the* German, *entgegen or opposite).*



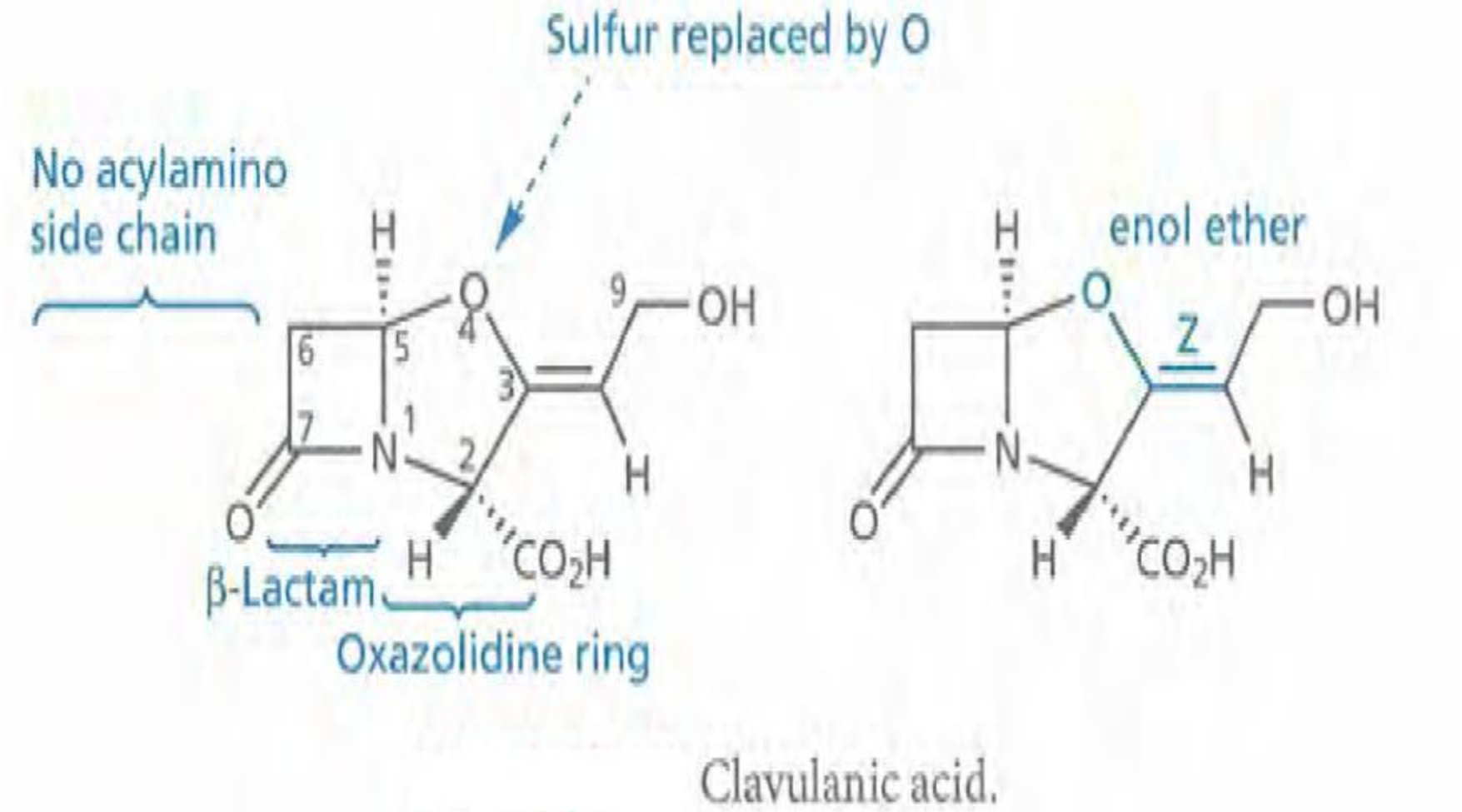
Chloroamitriptyline
(*Z*) isomer



Chloroamitriptyline
(*E*) isomer

Figure 4.16 Examples of (*Z*) and (*E*) isomers.

مثال هام


Sulfur replaced by O
No acylamino side chain
enol ether
β-Lactam
Oxazolidine ring
Clavulanic acid.

Identification test

الهدف من اختبارات الاستعراف هو تأكيد بنية الجوهر الفعال و ذلك بأكثر من اختبار (تفاعلات كيميائية كيفية او قياسات خاصة بالثوابت الكيميائية أو الفيزيائية أو الفيزيوكيميائية).

- Organic compound
- Inorganic compound
- Salts (cation + Anion-)

الماء الأوكسجيني
Hydrogen peroxide

- **Identification:**
- To 2 ml add 0.2 ml of *dilute sulphuric acid R*)and 0.2 ml of *0.02 M potassium permanganate*. The solution becomes colourless or slightly pink within 2 min
- To 0.5 ml add 1 ml of *dilute sulphuric acid R*, 2 ml of *ether R* and 0.1 ml of *potassium dichromate solution R* (5%)and shake. The ether layer is blue

- $4H_2O_2 + Cr_2O_7^{2-} + 2\ H^+ \longrightarrow 2CrO(O_2)_2 + 5\ H_2O$

$2CrO(O_2)_2$ /ether blue

الماء الأوكسجيني مطهر موضعي يحرر الاوكسجين بملامسة الجروح بفعل خميرة الكاتلاز. كما و يستخدم لفك الأربطة

Assay:

Hydrogen peroxide: H2O2 3% (BP 2007)

Dilute 10.0 g to 100.0 ml with *water R*. To 10.0 ml of this solution add 20 ml of *dilute sulphuric acid R*. Titrate with *0.02 M potassium permanganate* until a pink colour is obtained.

1 ml of *0.02 M potassium permanganate* is equivalent to 1.701 mg of H_2O_2 or 0.56 ml of oxygen.

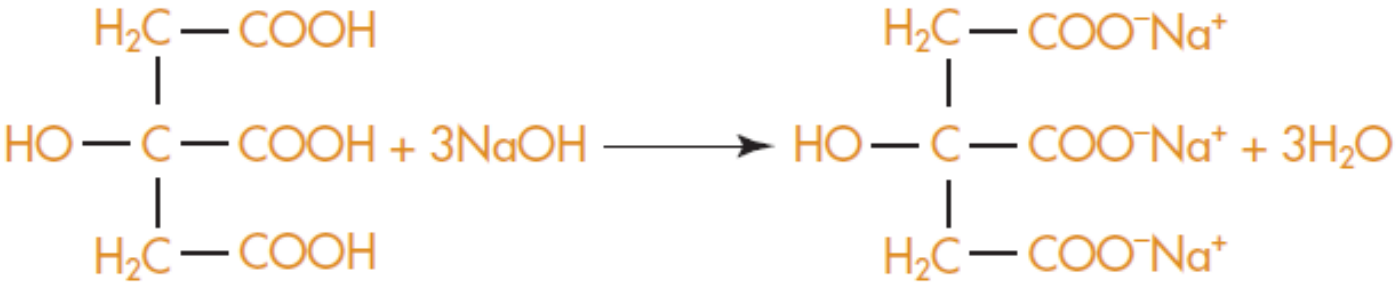
Hydrogen peroxide: H2O2 30 % (Bp 2007)

Dilute 1.00 g to 100.0 ml with *water R*. To 10.0 ml of this solution add 20 ml of *dilute sulphuric acid R*. Titrate with *0.02 M potassium permanganate* until a pink colour is obtained.

1 ml of *0.02 M potassium permanganate* is equivalent to 1.701 mg of H_2O_2 or 0.56 ml of oxygen.

$$2KMnO_4 + 5H_2O_2 + 3H_2SO_4 \longrightarrow 2MnSO_4 + 2K_2SO4 + 8H_2O + 5O_2$$

Assay & calculations



1 mole citric acid ≡ 3 moles NaOH

and

192.1 g citric acid ≡ 3 litres 1 M NaOH

or

192.1 g citric acid ≡ 3000 mL 1 M NaOH

Therefore,

(192.1/3000) g citric acid ≡ 1 mL 1 M NaOH

or

0.06403 g citric acid ≡ 1 mL 1 M NaOH

Argentiric titration

$Cl^- + Ag+ \longrightarrow AgCl$

$2\ Ag+ + CrO_4^{2-} \longrightarrow Ag_2CrO_4$ (yellow- brown/red)

الطريقة الأكثر شيوعاً هي المعايرة بالرجوع back titration حيث تضاف زيادة من نترات الفضة AgNO3إلى العينة الحاوية على أيونات الكلوريد او البروميد ثم تعاير زيادة نترات الفضة بثيوسيانات الأمونيوم Ammonium Thiocyanateو يستخدم مؤشر امونيوم سلفات الحديدوز لكشف زيادة SCN^-حيث يعطي لوناً احمرحسب المعادلتين:

$Ag+ + NH_4SCN \longrightarrow AgSCN + NH_4NO_3$

$Fe^{3+} + 3SCN^- \longrightarrow Fe(SCN)_3 + 3SCN^-$ $[Fe(SCN)_6]^{3-}$

قبل إجراء المعايرة بالرجوع يجب ترشيح راسب AgCl أو تلبيسه Coating يواسطة مركب ثنائي ايتيل فتالات و ذلك لإبعاد أيونات ثيوسيانات التي تشرد dissociation كلوريد الفضة.

Kcl

Sodium Cobaltinitrite: Sodium hexanitritocobaltate(III); $Na_3Co(NO_2)_6$

محاليل التوازن الشاردي (رينغر مثلاً)

KCl:

Dissolve 1.300 g in *water R and dilute to 100.0 ml with the same solvent. To 10.0 ml of the solution add 50 ml of water R, 5 ml of dilute nitric acid R, 25.0 ml of 0.1 M silver nitrate and 2 ml of* ***dibutyl phthalate*** *R. Shake. Titrate with 0.1 M ammonium thiocyanate, using 2 ml of ferric ammonium sulphate solution R2 as indicator and shaking vigorously towards the end-point.*

1 ml of *0.1 M silver nitrate is equivalent to 7.46 mg of* ***KCl****.*

H_3BO_3 حمض البور (مطهر ومضاد تعفن)

- Dissolve 0.1 g by gently heating in 5 ml of *methanol R*, add 0.1 ml of *sulphuric acid R* and ignite the solution. The flame has a green border.

- **ASSAY**

  Dissolve 1.000 g with heating in 100 ml of *water R* containing 15 g of *mannitol R*. Titrate with *1 M sodium hydroxide*, using 0.5 ml of *phenolphthalein solution R* as indicator, until a pink colour is obtained.

1 ml of *1 M sodium hydroxide* is equivalent to 61.8 mg of H_3BO_3

محتوى المحاضرات القادمة

- القسم اللاعضوي
- القسم العضوي :
  - الكحولات والايترات والالدهيدات والكيتونات ومشتقاتها
  - الحموض الكاربوكسيلية و الأمينات والأميدات ومشتقاتها
  - الفينولات ومشتقاتها
  - الحموض الامينية ومشتقاتها
  - الحمموض السولفونية الدورية ومشتقاتها
- المجموعات الدوائية :
  - أدوية الجهاز القلبي الوعائي
  - المخدرات الموضعية
  - الادوية التنفسية
  - أدوية الجهاز الهضمي