**Lecture 1.**

**Pharmaceutical chemistry**

Quinoline and isoquinoline derivatives. Quinoline derivatives. 4 and 8substituted syuthetic analogues. Quinulidine derivatives.

N

O

H

N

N

H

2

8-oxyquinoline 4-aminoquinoline



quinolon-4 fluorquinonons

**Table:**

|  |  |  |  |
| --- | --- | --- | --- |
| **R1** | **R2** | **l-isomer** | **d-isomer** |
| CH3O | CH2 = CH | Quinine | Quinidine |
| H | CH2 = CH | Cinchonidine | Cinchomine |
| CH3O | CH3CH2 | Hydroquinine | Hydroquinidine |
| H | CH3CH2 | Hydrocinchonidine | Hydrocinchonine |
| H | CH2CH | Cupreine |  |

**QUINOLINE ALKALOIDS**

Cinchona bark contains 30—60 % of alkaloids of the qulnine group, are the derivatives of quinoline. The principal alkaloids are and quinidine (dextro-rotatory stereoisomer of quinine) and 6'-demethoxyderivatives cinchonidine and cinchonine.

**In** addition to the antimalarial action, cinchona alkaloids are antic. The action of quinine on the central temperature-regulating causes peripheral vasodilation. This effect accounts for use of quinine in cold remedies and fever treatments.

Quinine has been used as a diagnostic agent for myasthenia gravis accentuating the symptoms). The antimalarial action of cinchona may be obtained by oral, intravenous, or intramuscular administration. Administration by injection, particularly intravenous injection, is not without hazard and should be used cautiously. Quinine hydrochloride is usually used for intramuscular injection.

Quinine

1

2

3

4

5

6

7

8

N

C

H

C

H

2

1

2

3

4

5

6

7

8

O

C

3

H

N

\*

C

H

O

H

\*

\*

.

3

H

2

O

Quinine occurs as a levorotatory, odourless, white crystalline pow-  
possessing an intensely bitter taste. It is only slightly soluble in water (1:1,500), but it is quite soluble in alcohol (1:1), chloroform (1:1), or ether.

Quinine behaves as a diacidlc base and forms salts readily. These may be of two types, the acid, or bi - salts and the neutral salts. Neutral salts are formed by involvement of only the tertiary nitrogen in the qumuehdme nucleus, and acid salts are the result of involvement of both basic nitrogens. Inasmuch as the quinoline nitrogen is very much less basic than the quinuclidine nitrogen, involvement of both nitrogens results in a definitely acidic compound.

Quinine Sulphate

(Chinini sulfas). Ph, Eur

H

2

S

O

4

2

H

2

O

1

C

H

N

O

H

C

H

N

O

C

3

H

C

H

2

.

.

2

Quinine hydrochloride

(Chinini hydrochloridum), Ph. Eur.

H

C

l

2

H

2

O

1

C

H

N

O

H

C

H

N

O

C

3

H

C

H

2

.

Properties. Fine, silky needles, often in clusters, colourless, solu­ble in water, freely soluble in alcohol.

Identification. 1. Examine by thin-layer chromatography

1. The Talleioquin test. After interaction with bromine water and dilute ammonia a green colour develops:

O

C

3

H

C

H

2

C

H

N

O

H

N

B

r

2

H

3

C

O

C

H

2

C

H

N

O

H

N

B

r

B

r

+

4

N

H

4

O

H

O

N

H

C

H

2

C

H

N

O

H

N

O

H

O

H

+

2

N

H

4

B

r

+

4

H

2

O

N

H

Some authors propose such structure as:

N

N

2

H

C

3

H

C

H

C

O

H

N

O

H

N

O

H

N

N

N

O

H

N

C

H

C

H

2

C

H

3

1. Dissolve the substance in dilute sulphuric acid. When examined in ultraviolet light at 366 nm, an intense blue fluorescence appears, which disappears almost completely on addition of 1 mL of hydro­chloric acid.
2. It gives reactions of sulphatesr (or reactions of chlorides for qui­nine hydrochloride).
3. It complies with the test for pH.

**Non-Pharmacopoeial reactions:** a) with iodine alkaline solution — appeare green crystals of ((C2pH2402N2)2 • (H2S04)2 • (HI)2 • I4 • 6H20);

1. with general precipitative reagents.

Assay. For for quinine sulphate, non-aqueous titration in the medi­um of chloroform and anhydrous acetic acid determining the end­point potentiometrically; s=1/3.

H

3

C

O

C

H

2

C

H

N

O

H

N

C

H

S

O

4

2

-

+

3

H

C

l

O

4

.

C

H

3

C

O

O

H

;

C

H

C

l

3

2

+

H

3

C

O

C

H

2

C

H

N

O

H

N

C

H

2

C

l

O

4

+

+

+

.

H

-

H

3

C

O

C

H

2

C

H

N

O

H

N

C

H

C

l

O

4

+

+

.

H

-

.

H

S

O

4

-

+

For quinine hydrochloride'. 1. Alkalimetry in the medium of alcohol determining the end-point potentiometrically; **s=**1.

H

3

C

O

C

H

2

C

H

2

N

O

H

N

+

N

a

C

l

+

H

2

O

C

H

H

C

l

+

N

a

O

H

O

H

N

.

C

H

N

C

H

3

O

2. Gravimetry method can be used after quinine sedimentation with NaOH.

3. Alkalimetry in the medium of chloroform and ethanol; **s =** 1/2.

C

H

2

N

+

N

a

2

S

O

4

+

2

H

2

O

C

H

O

H

N

2

C

H

3

O

Usage. Antimalarial.

Storage. Store protected from light.

DERIVATIVES OF QUINOLINE  
Derivatives of 8-Oxyquinoline

Nitroxolinum

N

O

2

N

O

H

5-nitro-8-oxyquinoline

O

H

H

N

O

3

N

O

2

O

H

H

N

H

2

O

H

C

O

H

C

H

C

H

2

a

c

r

a

l

d

e

h

y

d

e

phenol o-nitrophenol 0-aminophenol

O

H

N

H

N

O

2

O

H

N

N

a

N

O

2

;

H

C

l

N

O

O

H

N

O

N

O

2

O

H

N

**Properties**. A yellow or greyish-yellow microcrystalline powder.

**Identification.** 1. UV-spectrum (0.001 % alcoholic solution has max at 242 356 and 455 nm). j

2. With ferric choride solution — a black-green colouring develops.

3. Reduce nitro-group to aminogroup and carry out the determi­nation of the primary aromatic amino group — an orange colouring is produced:

N

O

2

O

H

N

H

N

H

2

O

H

N

H

C

l

N

a

N

O

2

;

N

O

H

N

N

C

l

-

O

H

N

a

O

H

N

O

H

N

N

**Assay.** 1. Alkalimetry in the non-aqueous medium. The substance is dissolved in dimethylformamide and titrated with 0.1 M sodium methylate from yellow to blue-green colouring (the indicator is the solution of thymol blue in dimethylformamide); s = 1. Carry out a blank titration.

N

O

2

O

H

N

+

C

H

3

O

N

a

D

M

E

A

N

O

2

O

N

a

N

+

C

H

3

O

H

2. Non-aqueous titration. The substance is dissolved in the formic acid and titrated with 0.1 M perchloric acid until a yellow colour is produced (the indicator is malachite green); s= 1.

N

O

2

O

H

N

+

H

C

l

O

4

C

l

O

4

N

O

2

O

H

N

H

C

O

O

H

H

+

-

3. Nitritometry (after reducing of nitro-group to aminogroup); s= 1.

Usage. Urinary antibacterial.

Storage. Protected from light.

Derivatives of 4-Aminoquinoline

Chloroquine Phosphate, Ph. Eur.  
(Chingaminum)

l

C

N

H

N

C

H

C

H

2

C

H

2

C

H

2

N

C

2

H

5

C

2

H

5

C

H

3

.

2

H

3

P

O

4

N4- (7 - Chloroquinolin-4-y 1) - N1,N1 -diethylpentane-1,4-diamine bis

(dihydrogen phosphate)

**Properties.**

l

C

N

H

2

H

2

C

C

H

C

O

O

C

H

3

l

C

N

C

C

C

O

O

C

H

3

H

2

H

2

H

m-Chloroamine methyl ester of 3-chlorophenyl- aminopropionic acid

l

C

O

N

H

(C

H

)3

N

(C

2

H

5

)2

H

2

N

C

3

H

C

H

7-chloroquinolone-4

l

C

N

N

H

C

H

C

H

2

C

H

2

C

H

2

N

(C

2

H

5

)2

chloroquine base

**Properties.** A white or almost white, crystalline powder, hydroscopic freely soluble in water, very slightly soluble in alcohol and in methanol.

Identification. 1. UV-spectrum.

1. IR-spectrum.
2. Determination of the melting point.
3. Dissolve the substance in water, add the dilute sodium hydroxide solution and shake with methylene chloride. The aqueous layer acidified by the addition of nitric acid gives reactions of phos­phates.

**Assay.** Non-aqueous titration in the medium of the anhydrous acetic acid. Thrate with 0.1 M perchloric acid determining the end­point potentiometrically;

s =1/2:

l

C

N

N

H

C

H

C

H

2

C

H

2

C

H

2

N

C

H

3

C

2

H

5

C

2

H

5

.

2

H

3

P

O

4

+2

H

C

l

O

4

C

H

3

C

O

O

H

l

C

N

H

N

C

H

C

H

2

C

H

2

C

H

2

N

C

H

3

C

2

H

5

C

2

H

5

H

2

C

l

O

4

+

2

H

3

P

O

4

.

-

+

**Usage.** Antimalarial.

**Storage.** In airtight containers protected fromlight.

Derivatives of 8-Aminoquinoline

**Chinocidum**

.

O

C

3

H

N

H

(C

H

2

3

C

H

N

H

2

C

H

3

2

H

C

l

)

6-Methoxy-8-(4-aminopentyl)-aminoquinoline dihydrogen chloride

**Properties.** An orange-yellow, crystalline powder. Very soluble in water, slightly soluble in alcohol, practically insoluble in ether, in ben­zene and in acetone.

**Identification.** 1. With potassium dichromate — a light-brown pre­cipitate developed becomes dark under the actioii of light (the reaction of quinoline nucleus).

2. The reactions of chlorides.

**Assay.** 1. Dissolve the substance in water and titrate with AgN03 in the presence of barium chloride. Determining the end-point potentiometrically or with the absorption indicator; s=1.

2. Non-aqueous in the presence of mercuric acetate determining the end-point potentiometrically; s=1.

**Usage.** Antimalarial.

**Storage.** Store protected from light.

Fluoroquinolones

This group of the substances includes fluoroderivatives of 3-quinonecarboxylic acid with the antimicrobial activity. The structure-actity studies have shown that the 1,4-dihydro-4-oxo-3-pyridine- irboxylic acid moiety is essential for the antibacterial activity.

The quinolones comprise a series of synthetic antibacterial agents itterned after nalidixic acid, a naphthyridine derivative introduced r the treatment of urinary tract infections in 1963.

Isosteric heterocyclic groupings in this class include the quinolines. g., norfloxacin, ciprofloxacin, and lomefloxacin), the naphthy- lines (e.g., nalidixic acid and enoxacin), and the cinnolines g., cinoxacin). Up to- the present time, the clinical usefulness of qumolones has been largely confined to the treatment of urinary ct infections. For this, good oral absorption, activity against comm gram-negative urinary pathogens, and comparatively higher nary (compared with plasma and tissue) concentrations are useful iperties.

However, as a result of extensive structure-activity investigations ding to compounds with enhanced'potency, extended spectrum of ivity, and improved absorption and distribution properties, the class evolved to the point that certain newer members have utility for treatment of a variety of serious systemic infections.

In fact, these more potent analogues are sometimes classified irately (from the urinary, tract-specific agents) as the fluoroqui- ones because all members of the group have a 6-fluoro substituent ommon.

Ofloxacin

(Ofloxacinum), Ph. Eur.

N

C

3

H

N

F

O

O

C

O

H

N

C

H

3

O

9- Fluoro- 2,3 -dihydro- 3 -methyl-10- (4-methyl-1 -piperasinyl)-  
7-oxo-7 H-pyrido/1,2,3-de/1,4-benzoxazinecarboxylic acid

Properties. A pale yellow or bright yellow, crystalline powderly soluble in water, soluble in the glacial acetic acid, slightly soluble methylene chloride, slightly soluble in methanol.

Identification. IR-spectrum.

Assay. Non-aqueous titration in the anhydrous acetic acid, rate with 0.1 M perchloric acid determining the end-point metrically; s=1.

Usage. Antibiotic.

Storage. Store in airtight containers protected from light.

Norfloxacin

(Norfloxacinum), Ph. Eur.

H

N

N

N

F

O

O

C

O

H

C

2

H

5

l-Ethyl-6-fluoro-4-oxo-7-(piperazin-l-yl)-l,4-dihydro-  
quinoline-3-carboxylic acid

Properties. A white or pale-yellow, hygroscopic, photosensitive, crystalline powder, very slightly soluble in water, slightly soluble in acetone and in alcohol.

Identification. IR-spectrum.

Assay. Non-aqueous titration in the anhydrous acetic acid. Tit­rate with 0.1 M perchloric acid determining the end-point potentio- metrically; s=1.

Usage Antibiotic.

Storage. Store in airtight containers protected from light.

**Ciprofloxacin hydrochloride**

**(Ciprofloxacini hydrochloridum),**

**Ph.Eur.**

**Ph.Eur.**

**Ciprofloxacin**

**(Ciprofloxacinum)**

**Ph.Eur.**

H

N

N

N

F

O

O

C

O

H

.

C

C

H

2

C

2

H

H

H

N

N

N

F

O

O

C

O

H

C

C

H

2

C

2

H

H

H

C

l

**1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride**

**1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-(1-piperazinyl)-3-quinolinecarboxylic acid**

## Preparation

Ethyl ester of 1-cyclopropyl-6-fluoro-dihydro-4-oxo-7(piperazine-1-yl) quinoline-3-carboxilic

Ethyl ester of 1-cyclopropyl-6,7-dihydro-1,4-oxoquinoline-3-carboxilic acid

N

H

N

H

N

F

O

O

E

t

F

O

H

N

N

N

F

O

O

E

t

O

H

C

l

N

a

O

H

;

H

N

N

N

F

O

C

O

O

H

ciprofloxacin

**Properties.** Almost white or pale yellow, crystalline powder, slightly hygroscopic. Practically insoluble in water, very slightly soluble in etha­nol and in methylene chloride.

Identification: 1. IR spectrum.

2. Reactions of chlorides (for ciprofloxacin).

Non-Pharmacopoeial reactions: a) heterocyclic nitrogen is deter­mined with alkaloid reagents;

b) fluorine is determined after mineralization (see Phthorafurum).

Assay. Ciprofloxacin. Non-aqueous titration. Titrate in the medi­um of the glacial acetic acid with 0.1 M perchloric acid determining the end-point potentiometrically; 5=1.

Ciprofloxacin hydrochloride. Liquid chromatography.

Usage. Antibiotic.

Storage. Store in airtight containers protected from light.

**Lomefloxacin**

H

N

N

N

F

O

F

C

C

3

H

C

2

H

5

O

H

O

1 -Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl) -  
4-oxo-3-quinolinecarboxylic acid

All the flouroquinolones are very active antibiotics. Their activity increases from ofloxacine to lomefloxacin.

The substitution of ethyl radical of norfloxacin by cyclopropyl in­creases the activity (for about 3—8 times).

**Derivatives of acridine**

N

N

N

H

2

acridine 9­aminoacridine

A simple acridine derivative of pharmaceutical interest is 3,6 –diaminoderivative, which was used as an antiseptic in ophthalmic surgery under the name proflavine hemisulphate, or simply “proflavine”.

O

C

3

H

O

C

3

H

N

C

H

2

O

C

3

H

O

C

3

H

.

H

C

l

N

a

O

H

C

2

H

5

O

H

+

O

C

3

H

O

C

3

H

N

C

H

2

O

C

3

H

O

C

3

H

N

a

C

l

H

2

O

+

+

2. Non-aqueous titration;s=1.

C

H

3

C

O

O

H

O

C

3

H

O

C

3

H

N

C

H

2

O

C

3

H

O

C

3

H

H

C

l

2

H

C

l

O

4

H

g

C

H

3

C

O

O

.

O

C

3

H

O

C

3

H

N

C

H

2

O

C

3

H

O

C

3

H

H

C

l

2

H

C

l

O

4

H

g

(C

H

3

C

O

O

)2

.

C

H

3

C

O

O

H

+

+

O

C

3

H

O

C

3

H

N

C

H

2

O

C

3

H

O

C

3

H

H

C

l

O

4

H

g

C

l

2

2

C

H

3

C

O

O

H

.

2

+

+

3. Alkalimetry in the water-alcoholic medium; the indicator is phepthalein;s=1

4. Spectrophotometry (for medicinal forms).

Usage. Antispasmodic. Its main effect is as antispasmodic on smooth muscle acting as a direct, nonspecific relaxant on vascular, diac, and other smooth muscle.

Storage. In well-closed containers protected from light.

**Drotaverine hydrochloride**

**Nospanium**

O

2

C

5

H

O

2

C

5

H

N

C

H

O

2

C

5

H

O

2

C

5

H

H

C

l

.

H

1-(3,4-Diethoxybenzyliden) -6,7-diethoxy-1,2,3,4-tetra-hydroisoquinoline hydrochloride

It is the synthetic analogue of papaverine.

Usage. Antispasmodic.

Morphine is obtained from optium, which is the partly dried latex from incised unripe capsules of Papaver somniferum. It was the firstalcoloid to be isolated in the crystalline from by Sertrner in 1806.

Before 1929, the derivatives of morpine that had been made were primarly the result of simple changes on the molecule, such as esterification of the phenolic or alcoholic hydroxyl group, etherification of the phenolic hydroxyl group, and similar minor changes. The net result was the discovery of some compounds with greater activity than morphine, but also with greater toxicities and addiction tendencies. No compounds were found that did not prossess in some measure the addiction liabilities of morphine.

It differs from most of the other common alkaloids in having phenolic as well as basic properties. The other hydroxyl group is a secondary alcohol. Morphine can be presented as a derivative of morphinane.

N

H

N

O

H

O

1

2

3

4

5

6

7

8

9

1

0

1

1

1

2

1

3

1

4

1

5

1

6

O

H

\*

\*

\*

\*

\*

C

H

3

morphinane morphine

The molecule of morphine has five asymmetric carbon atoms and due to phenanthrene nucleus it show the sterochemical structure.