**Lecture 2**

**Pharmaceutical chemestry**

**Topic:**

Isoquinolin derivatives, Benzylisoquinolin derivatives, Phenantrenisoquinoline derivatives, Morphine, codeine and other preparations, Aprophen derivatives



 **quinoline isoquynoline**

morphine aprophine 1-benzylisoquinoline



 meconic acid lactic acid

Papaverine Hydrochloride
(Papaverini hydrochloridum), Ph. Eur.



1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline hydrochloride

This alkaloid was isolated by Merck in 1848 from opium, in which it osccurs to the extent of about 1% and was synthesized in 1909. Although its natural origin is closely related to morphine, the pharmacological actions of papaverine hydrochloride are unlike those of morphine.

**Propertions.** A white or almost white, crystalline powder or white or almost white crystals. Sparingly soluble in water, slightly soluble in alcohol.

Identification. 1. IR -, UV-spectroscopy.

1. Thin-layer chromatography
2. With ammonium solution a precipitate appears; it melts at 146 to 1490C

O

C

3

H

O

C

3

H

N

C

H

2

O

C

3

H

O

C

3

H

H

C

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N

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H

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O

C

3

H

O

C

3

H

N

C

H

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O

C

3

H

O

C

3

H

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e

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i

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i

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**DEMO**

1. It gives reactions of chlorides.

Non-Pharmacopoeial reactions: a) with concentrated H2SO — a violet colour appears;

1. with cone. HN03.— a yellow colour appears; it becomes orange when heating;
2. with the Marquis reagent —a red colour appears; it becomes yellow and bright orange. Under the action of bromine water a violet precipitate appeares, it becomes a violet-red in alcohol:

C

H

2

O

C

3

H

O

C

H

3

C

H

2

N

H

O

C

3

H

O

C

3

H

O

C

3

H

O

C

H

3

N

H

C

H

2

O

C

H

3

O

C

H

3

+

+

S

O

4

2

-

This reaction can be used for assay by the spectrophotometric method.

1. with general precipitative reagents.

**Assay.** 1. Direct alkalimetry in the mixture of 0.01 M hydrochlo­ric acid and alcohol. Carry out a potentiometric titration using 0.1 M so­dium hydroxide solution. Read the volume added between the two points of inflexion; s=1.

HC1 + NaOH NaCl + H20

Morphine has high enough reactive abilities and its relationship shown by the followed scheme:

O

2

C

5

H

C

H

3

N

O

H

O

e

t

h

y

l

a

t

i

o

n

C

H

3

N

O

H

O

H

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H

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H

O

H

N

C

H

3

O

H

N

C

H

3

O

2

C

5

H

m

o

r

p

h

i

n

e

d

i

o

n

i

n

e

c

o

d

e

i

n

e

a

p

o

m

o

r

p

h

i

n

e

Morphine Hydrochloride

(Morphini hydrochloridum), Ph. Eur.

O

O

H

N

C

H

3

O

H

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H

C

l

8-Didehydro-4,5a-epoxy-17-methylmorphinane-3,6a-diol hydrochloride

**Poperties.** A white or almost white, crystalline powder or colourless, silky needles or cubical masses, efflorescent in a dry atmosphere, soluble in water and in glycerol, slightly soluble in alcohol.

**Identification.** 1. UV-spectrum in water.

2. UV-spectrum in 0.1 M sodium hydroxide.

3. With sulphuric acid—formaldehyde reagent (the Marquis re-agent) a purple colour develops and becomes violet.

4. Wiith freshly prepared solution of potassium ferricyanide and ferric chloride solution a blue colour is produced immediately:

N

C

H

3

O

H

O

H

O

4

+

4

K

3

F

e

(

C

N

)

6

N

C

H

3

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H

O

H

O

N

C

H

3

O

H

O

H

O

+

+

3

K

4

F

e

(

C

N

)

6

H

4

F

e

(

C

N

)

6

+

K

4

F

e

(

C

N

)

6

+

F

e

C

l

3

K

F

e

F

e

(

C

N

)

6

+

3

K

C

l

5.After interaction with dilute hydrogen- peroxide solution, dilute ammonia solution and solution of copper sulphate a red colour develops.

6.It gives reactions of chlorides.

7.It gives reactions of alkaloids.

Non-Pharmacopoeial reactions: a) with amonium molibdate andconcentrated H2S04 a violet colour appears; becomes blue and green:

b) with ammonium hydroxide solution a white crystalline precipitate is formed, which is soluble in NaOH sollution;

c) optical rotation: -97 to -99° (2 % water solution);

d) with ferric chloride solution a blue violetcolour appears (the reaction of phenol hydroxyl);

e) the reaction of azo-dye formation:

N

N

C

H

3

O

H

O

H

O

S

O

3

H

-

N

C

H

3

O

H

O

H

O

-

S

O

3

H

O

H

H

S

O

4

N

N

+

+

N

1. reactions with general precipitative reagents.

Assay. 1. Non-aqueous titration; in the medium of acetic acid, in the presence of mercuric acetate solution using crystal violet solu­tion as an indicator; **s=** 1.

2. Argentometry; **s = 1.**

Usage. Analgesic (narcotic).

Storage. Store protected from light.

Codeine

(Codeinum), Ph. Eur.

N

C

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4,5a-Epoxy-3-methoxy-17-methyl-7,8-didehydrorhorphinan-6a-ol hydrochloride

**Properties.** A white, crystalline powder or colourless crystals, soluble in boiling water, freely soluble in alcohol, soluble in ether.

**Identification.** 1. The melting point is 155—159 °C.

1. UV-spectrophotometry.
2. Examine by infrared absorption spectrophotometry.
3. With sulphuric acid and ferric chloride solution when heating on
a water-bath a blue colour develops, which changes to red after nitric
acid addition.
4. It gives the reaction of alkaloids.

Non-Pharamacopoeial reactions: a) after interaction with nitric acid an orange colouring appeares;

1. with the Marquis reagent a blue-violet colouring appears;
2. reactions with general precipitative reagents.

Assay. 1. Non-aqueous titration using crystal violet solution as an indicator; s= 1.

2. Codeine is a strong enough base, so it can be determined by the method of acidimetry in the water-alcoholic medium using methyl. Red solution as an indicator; s=1:

N

C

H

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H

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H

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H

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H

N

C

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Usage. Antidiarrhoeal, cough suppressant, analgesic.

Storage. Store protected from light.

Codeine Hydrochloride Dihydrate

(Codeini hydrochloridum dihydricum), Ph. Eur.

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H

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4,5a-Epoxy-3-methoxy-17-methyl-7,8-didehydromorphinan-6a-ol

hydrochloride

Properties. A white, crystalline powder or small, colourless crys­tals, soluble in water, slightly soluble in ethanol, practically insoluble in cyclohexane.

Identification. 1. Examine by infrared absorption spectrophoto­metry.

1. After interaction with strong sodium hydroxide solution the pre­cipitate obtained melts at 155 to 159 °C.
2. With sulphuric acid and ferric chloride solution when heating on a water-bath a blue colour develops, which changes to red after nitric acid addition.
3. Reactions of chlorides.
4. It gives reactions of alkaloids.

Non-Pharamacopoeial reactions (see Codeine).

**Assay.** 1. Alkalimetry in the water-alcoholic medium. Carry out a potentiometric titration, using 0.1 M sodium hydroxide. Read the volume added between the two points of inflexion; s = 1.

1. Non-aqueous titration in the presence of mercuric acetate; s=1.
2. Argentometry; s=1.

Usage. Analgesic.

Storage. Store protected from light.

Codeine Phosphate Hemihydrate (Sesquihydrate) odeini phosphas hemihydricus (sesquihydricus)), Ph. Eur.

4,5a-Epoxy- 3 - methoxy-17-methyl -7,8- didehydromorphinan-6a-ol phosphate

Properties. A white, crystalline powder or small, colourless crystals freely soluble in water, slightly soluble in alcohol, practically in soluble in ether.

Identification. 1. UV-spectrophotometry.

2. Examine by infrared absorption spectrophotometry.

3. After interaction with strong sodium hydroxide solution the precipitate obtained melts at 155 to 159 °C.

4. With sulphuric acid and ferric chloride solution when heating on a water-bath a blue colour develops, which changes to red after nitric acid addition.

5. It gives reaction of phosphates.

6. It gives reactions of alkaloids.

Non-Pharamacopoeial reactions (see Codeine).

Assey. 1. Non-aqueous titration in the mixture of anhydrous acetic acid and dioxan. Titrate with 0.1 M perchloric acid using crystal violet soution as an indicator; s= 1.

2. Alkalimetry in the water-chloroform (1:2) medium, using phenolphthalein solution as an indicator; 5= 1/2.

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Epoxy-3-methoxy-17-methyl-7,7-didehdromorphinan-6α-ol-phosphate

**Ethylmorphine Hydrochloride**

**(Ethylraorphini hydrochloridum), Ph. Eur.
(Dionine)**

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7,8-Didehydro-4,5a-epoxy-3-ethoxy-17-methylmorphinan-6α-ol
hydrochloride dihydrate

**Properties.** A white or almost white, crystalline powder. Soluble in water and in alcohol, insoluble in cyclohexane.

**Identification.** 1. Infrared absorption spectrophotometry.

1. Determination of the melting point of the ethylmorphine base after interaction with sodium hydroxide solution (85—89 °C).
2. With sulphuric acid and ferric chloride solution a blue colour develops. Add nitric acid — the colour becomes red.
3. Reactions of chlorides.

Non-Pharmacopoeial reactions: a) iodoform test (for ethanol, which is obtained after hydrolysis):

R-OC2H5+NaOH R-ONa+C2H5OH
C2H5OH + 4I2 + 6NaOH CHI3 + 5NaI + HCOONa + 5H20

A yellow precipitate with a specific odour is obtained.

b) reactions with general precipitative reagents.

Assay. 1. Alkalimetry in the mixture of water and alcohol after hydrochloric acid addition. Carry out a potentiometric titration, using 0.1 M sodium hydroxide. Read the volume added between the two points of inflexion; **s=** 1.

2. Non-aqueous titration determining the end-point by potentio metry; **s=1.**

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3. UV-spectrophotometry.

Usage. Opioid analgesic.The systemic action of this morphine native is intermediate between those of codeine and morphine, is analgesic properties and sometimes is used for the relief of pain.

As a depressant of the cough reflex, it is as effective as codeine and, equently, is found in some commercial cough syrups. However, hief use of this compound was in ophthalmology, storage. Store protected from light

Apomorphine Hydrochloride

(Apomorphini hydrochloridum), Ph. Eur.

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$∙$HCl

6aR(-6-Methyl-5,6,6a,7-tetrahydro-4H-dibenzo [de,g] quinolone-10,11-diol hydrochloride hemihydrate

Apomorphine can be shown as derivative of the aporphine cycle.

Properties. A white or slightly yellowish-brown or green-tinged greyish crystalline powder or crystals; on exposure to air and light, the green tinge becomes more pronounced. Sparingly soluble in water and in alcohol, practically insoluble in toluene

identification. 1. UV-spectrophotometry.

1. Infrared absorption spectrophotometry.
2. With sodium hydrogen carbonate solution a white precipitate is formed. The precipitate slowly becomes greenish. After iodine addition the precipitate becomes greyish-green. It dissolves in ether giving a purple solution, in methylene chloride giving a violet-blue solution and in alcohol giving a blue solution.
3. Reactions of chlorides.

Non-Pharmacopoeial reactions: a) with concentrated HN03 — a bright-red colounng is formed;

1. specific optical rotation: from —46 to —52° (1.5 % solution in 0.02 M HC1);
2. reactions with general precipitative reagents.

**Assay.** 1. Alkalimetry in the mixture of water and alcohol after hydrochloric acid addition. Carry out a potentiometric titration, using 0.1 M sodium hydroxide. Read the volume added between the two points of inflexion; s=1.

1. Non-aqueous titration; s=1.
2. Argentometry; s=1.

Usage. Emetic.

Storage. Store protected from light.

**PURINE ALKALOIDS (XANTHINES,)**

The naturally occurring xanthines are caffeine, theophylline, and theobromine.

Caffeine enjoys wide use as a CNS stimulant. Theophylline has some use as a CNS stimulant (as will be discussed later); its CNS-stimulant properties are encountered more often as side effects, sometimes severe and potentially life-threatening, of its use in bronchial asthma therapy. Theobromine has very little CNS activity and will not be discussed further as a CNS stimulant. Its I-[5-oxohexyl] derivative pentoxifylline (Trental) is useful in intermittent claudication, presumably in part by improving red blood cell deformability. Its potential use in other occlu­sive disorders, such as acute stroke, is under investigation.

Caffeine is used often as it occurs in brewed coffee (~85 mg/cup), brewed tea (~ 60 mg/cup), and cola beverages (~50 mg/12 Cl oz). In most subjects 85 to 250 mg of caffeine acts as a cortical stimulant and facilitates clear thinking and wakefulness, promotes an ability to con­centrate on the task at hand, and lessens fatigue. As the dose is increased, side effects indicative of excessive stimulation.