**Pharmaceutical chemisty IV**

**Lecture 6**

**Topic: Pteridin and isoalloxazine derivatives Folic acid and its analogues. Phenothiazine derivatives. Alkyl and acyl derivatives of phenothiazine**

DERIVATIVES OF PHENOTHIAZINE

Phenothiazine itself has a helminthicide and local anaesthetic activity.

S

N

H

1

2

3

4

5

6

7

8

9

1

0

The general formula of phenothiazine derivatives is:

S

N

R

R

.

H

C

l

Many potentially useful phenothiazine derivatives have been synthesized and pharmacologically evaluated. Consequently, there is a large body of information permitting accurate statements about the structural features associated with activity. The best position for substitution is the 2-position. Activity increases (with some exceptions) as the electron-withdrawing ability of the substituent increases.

Depending on a substituent of nitrogen (10) atom phenothiazines
have various pharmacological actions: 10-alkylderivatives (chloropro-
mazine (aminazinum), promethazine (diprazinum), promazine, perphenazine (aethaperazinum)) are used as antipsychotic and antihista mine substances, 10-acylderivatives (aethmozinum) are effective for treating of cardiac diseases.

Chloropromazine Hydrochloride

**(Aminazinum), Ph. Eur.**

S

N

C

H

2

C

l

.

H

C

l

C

H

2

C

H

2

N

C

H

3

C

H

3

3-(2-Choloro-10/T-phenothiazin-10-yl)-N,N-dimethylpropan-1-amine hydrochloride

Preparation. Chlorpromazine hydrochloride (aminazinum) is synthesized by the flowing scheme:

H

N

S

+

C

l

C

H

2

C

H

2

C

H

2

N

C

H

3

C

H

3

+

N

a

N

H

2

l

C

c

h

l

o

r

o

p

h

e

n

o

t

h

i

a

z

i

n

e

3

-

d

i

m

e

t

h

y

l

a

m

i

n

o

p

r

o

p

y

l

c

h

l

o

r

i

d

e

s

o

d

i

u

m

a

m

i

d

e

C

H

3

N

S

l

C

C

H

3

C

H

2

C

H

2

C

H

2

N

H

C

l

c

h

l

o

r

o

p

r

o

m

a

z

i

n

e

C

H

3

N

S

l

C

C

H

3

C

H

2

C

H

2

C

H

2

N

H

C

l

.

chloropromazine hydrochloride

Properties. A white or almost white, crystalline powder, very soluble in water, freely soluble in alcohol and practically insoluble in ether. It decomposes on the exposure to air and light.

Identification. 1. UV-spectrum. Prepare the solution protected from light and measure the absorbances immediately.

2. IR-spectrum.

3. Thin-layer chromatography (the solution for detection — 10% sulphtıric acid in ethanol).

4. The reactions of chlorides.

Non-Pharmacopoeial reactions: a) with oxidizers (concentrated H2S04, bromine water, HN03, FeCl3 and others):

R

R

N

S

O

R

R

N

O

O

S

R

R

N

S

O

O

— the reaction with bromine water (more specific). The substance gives a transparent red colour of the solution. The probable structure of the product obtained is:

R

+

N

S

(

B

r

B

r

2

)

-

.

— the reaction with concentrated H2S04 — a red colour appears;

1. reactions with alkaloid reagents (due to tertiary nitrogen) — the substance forms precipitates;
2. after the interaction with NaOH the base of the substance ex- amined is obtained;
3. sulphur is detected after mineralization with KN03 and K^COj by the forming of a precipitate with BaCl2.

Assay. 1. Alkalimetry in the medium of alcohol and in the pre- sence of 0.01 M hydrochloric acid. Titrate with 0.1 M sodium hydro- xide solution determining the end-point potentiometrically. Read the volume added between the points of inflexion; **5=1.**

1. Non-aqueous titration. Titrate with perchloric acid in the pre- sence of (CH3COO)2Hg using methyl orange as an indicator in the acetone medium and crystal violet in the medium of the anhydrous acetic acid; **5=1.**
2. Alkalimetry in the presence of chloroform, **5=1.**
3. Determination of nitrogen by sulphuric acid digestion (the Kjel- dahl’s method).
4. Cerimetry.
5. Iodometry.
6. Iodine-chlorimetry.
7. Spectrophotometry.
8. Photocolorimetry.

Usage. Antipsychotic, antiemetic.

Storage. In an airtight Container protected from light.

Promethazine Hydrochloride, Ph. Eur.

**(Diprazinum)**

N

S

C

H

2

C

H

N

C

H

3

H

C

l

C

H

3

C

H

3

.

(2 RS)-N. N - Dimethyl-1 -(1O/Tphenothiazin-10-yl)propan-2-amine

hydrochloride

Properties. A white or faintly yellowish, crystalline powder, very oluble in water, freely soluble in alcohol and in methylene chloride. ı melts at about 222 °C with decomposition.

Identification. 1. IR-spectrum.

1. Thin-layer chromatography (see Chloropromazıne).
2. Dissolve the substance in water, add nitric acid dropwise. A precipitate is formed; it rapidly dissolves giving a red solution, be-corning orange and then yellow. Heat to boiling. The solution becomes orange and an orange-red precipitate is formed.
3. The reactions of chlorides.,

Non-Pharmacopoeial reactions (see Chloropromazine): a) with bromine water — a turbid dark-red solution with a precipitate;

1. with the concentrated H2S04 — a red or orange-red colouring;
2. reactions with alkaloid reagents (due to tertiary nitrogen) — the substance forms precipitates;
3. after the interaction with NaOH the base of the substance ex-amined is obtaıned;
4. sulphur is detected äfter mineralization with KN03 and K2 CO3 by forming a precipitate with BaCl2.

Assay. Alkalimetry in alcohol and in the presence of 0.1 M hydrochloric acid. itrate with 0.1 M sodium hydroxide determining the and-point potentiometrically; s— 1.

Usage. Antihistaminic, neuroleptic.

Storage. In an airtight Container protected from light.

Promazine Hydrochloride, Ph. Eur.

**(Propazinum)**

N

S

.

H

C

l

(

C

H

2

)

3

N

(

C

H

3

)

2

3 - (10 H- Phenothiazin-10 -yl) - N ,N -dimethylpropan- 1-arnıne
hydrochloride

Properties. A white or almost white, crystalline powder, slightly hygroscopic, very soluble in water, in alcohol and in methylene chlo- ride. It melts at about 179 °C.

Identification. 1. IR-spectrum.

1. Thin-layer chromatography (see Chloropromazine).
2. Dissolve the substance in sulphuric acid and allow it to stand for 5 min — an orange colour is produced.
3. The reactions of chlorides.

Non-Pharmacopoeial reactions: a) with bromine water — a trans- parent brown-red colouring appears;

1. reactions with alkaloid reagents (due to tertiary nitrogen) — the substance forms precıpitates;
2. after the interaction with NaOH the base of the substance examined is obtained;
3. sulphur is detected after mineralisation with KN03 and K2C03 by forming a precipitate with BaCl2.

Assay. Alkalimetry in alcohol and in the presence of 0.1 M hydro- chloric acid. Titrate with 0.1 M sodium hydroxide determining the end-point potentiometrically; **s=1.**

Usage. Antihistaminic, neuroleptic.

Storage. In an airtight Container protected from light.

Perphenazine

(Aethaperazinum), Ph.Eur.

N

S

(

C

H

2

)

3

C

l

N

N

(

C

H

2

)

2

O

H

2-[4-[3-(2-Chk>rophenothiazin- 10-yl)propyl)piperazin-l-yl]ethanol

1. The solution gives the reactions of chlorides.

Assay. Alkalimetry in aleohol and'in the presence of 0.1 M hydro- chloric acid. Titrate with 0.1 M sodium hydroxide determining the end-point potentiometrically; s = 1/2.

Usage. Antihistaminic, neuroleptic.

Storage. In an airtight Container protected from light.

DERIVATIVES OF BENZODİAZEPİNE

Benzodiazepine is a heterocyclic system, includes nuclei of benzene and 7-membered heteroeyele — 1,4-diazepine:

N

N

H

1

2

3

4

5

6

7

8

9

The electron oetet of azepines is less delocalizated than the benzene sextet; so that azepines would be expected to have üttle aromatic character and show high reactivity.

The presence of an electron-attracting substituçnt at position 7 is required for activity, and the more electron attractipg it is, the higher the activity is. Positions 6, 8, and 9 should not be substituted.

Alkyl substitution at the 3-position decreases activity, whereas substitution with a hydroxy does not. The presence or absence of the 3-hydroxyl is important pharmacokinetically. Compounds without the hydroxyl are nonpolar, have long half-lives and undergo hepatic oxidation. Compounds with the hydroxyl are much more polar and are readily converted to the excreted glucu\_ronide (see the overall metabolic relationship seheme). The 2-carbonyl funetion is optimal for activity, as is the nitrögen atom at position 1. The N-substituent should be small.
1,4-benzodiazepines have weak-basic properties due to the nitrogen atom (4). Compounds with the lactam group — NH—CO— have weak-acidic properties and can form salts with alkaline metals (amphoteric compounds).

Benzodiazepines and benzodiazepine-like drugs bind to a benzo-diazepine recognition site or benzodiazepine receptor.

Medicinal substances, derivatives of benzodiazepine, are used as tranquillisers (have a sedative effect).

N

S

.

2

H

C

l

(

C

H

2

)

3

C

F

3

N

N

C

H

3

C

3

H

N

N

H

2

.

S

C

H

3

C

H

2

C

H

2

O

H

N

B

r

H

B

r

1

/

H

2

O

2

-

.

N

+

+

C

3

H

N

N

H

2

N

S

C

H

3

C

H

2

C

H

2

O

H

N

B

r

H

B

r

+

C

H

3

C

O

O

H

-

.

N

2

H

C

l

O

4

+

2

H

g

(

C

H

3

C

O

O

)

2

H

C

O

O

H

;

+

C

3

H

N

N

H

2

.

S

C

H

3

C

H

2

C

H

2

O

H

N

C

l

O

4

-

H

C

l

O

4

+

H

g

B

r

2

+

2

C

H

C

O

O

H

+

C

3

H

N

N

H

2

N

S

C

H

3

C

H

2

C

H

2

O

H

N

B

r

H

B

r

+

N

a

B

r

+

H

2

O

-

.

N

N

a

O

H

-

+

C

3

H

N

N

H

2

+

S

C

H

3

C

H

2

C

H

2

O

H

N

B

r

+

C

3

H

N

N

H

2

N

S

C

H

3

C

H

2

C

H

2

O

H

N

B

r

N

a

H

B

r

+

N

a

N

O

3

+

2

A

g

B

r

-

+

N

N

O

-

+

C

3

H

N

N

H

2

+

S

C

H

3

C

H

2

C

H

2

O

H

N

2

A

g

N

O

3

3

A

g

N

O

3

+

F

e

(

S

C

N

)

3

3

A

g

S

C

N

+

F

e

(

N

O

3

)

3

**Pharmaceutical chemisty IV**

**Lecture 6**

**Topic: Pteridin and isoalloxazine derivatives Folic acid and its analogues. Phenothiazine derivatives. Alkyl and acyl derivatives of phenothiazine**

DERIVATIVES OF PHENOTHIAZINE

Phenothiazine itself has a helminthicide and local anaesthetic activity.

S

N

H

1

2

3

4

5

6

7

8

9

1

0

The general formula of phenothiazine derivatives is:

S

N

R

R

.

H

C

l

Many potentially useful phenothiazine derivatives have been synthesized and pharmacologically evaluated. Consequently, there is a large body of information permitting accurate statements about the structural features associated with activity. The best position for substitution is the 2-position. Activity increases (with some exceptions) as the electron-withdrawing ability of the substituent increases.

Depending on a substituent of nitrogen (10) atom phenothiazines
have various pharmacological actions: 10-alkylderivatives (chloropro-
mazine (aminazinum), promethazine (diprazinum), promazine, perphenazine (aethaperazinum)) are used as antipsychotic and antihista mine substances, 10-acylderivatives (aethmozinum) are effective for treating of cardiac diseases.

Chloropromazine Hydrochloride

**(Aminazinum), Ph. Eur.**

S

N

C

H

2

C

l

.

H

C

l

C

H

2

C

H

2

N

C

H

3

C

H

3

3-(2-Choloro-10/T-phenothiazin-10-yl)-N,N-dimethylpropan-1-amine hydrochloride

Preparation. Chlorpromazine hydrochloride (aminazinum) is synthesized by the flowing scheme:

H

N

S

+

C

l

C

H

2

C

H

2

C

H

2

N

C

H

3

C

H

3

+

N

a

N

H

2

l

C

c

h

l

o

r

o

p

h

e

n

o

t

h

i

a

z

i

n

e

3

-

d

i

m

e

t

h

y

l

a

m

i

n

o

p

r

o

p

y

l

c

h

l

o

r

i

d

e

s

o

d

i

u

m

a

m

i

d

e

C

H

3

N

S

l

C

C

H

3

C

H

2

C

H

2

C

H

2

N

H

C

l

c

h

l

o

r

o

p

r

o

m

a

z

i

n

e

C

H

3

N

S

l

C

C

H

3

C

H

2

C

H

2

C

H

2

N

H

C

l

.

chloropromazine hydrochloride

Properties. A white or almost white, crystalline powder, very soluble in water, freely soluble in alcohol and practically insoluble in ether. It decomposes on the exposure to air and light.

Identification. 1. UV-spectrum. Prepare the solution protected from light and measure the absorbances immediately.

2. IR-spectrum.

3. Thin-layer chromatography (the solution for detection — 10% sulphtıric acid in ethanol).

4. The reactions of chlorides.

Non-Pharmacopoeial reactions: a) with oxidizers (concentrated H2S04, bromine water, HN03, FeCl3 and others):

R

R

N

S

O

R

R

N

O

O

S

R

R

N

S

O

O

— the reaction with bromine water (more specific). The substance gives a transparent red colour of the solution. The probable structure of the product obtained is:

R

+

N

S

(

B

r

B

r

2

)

-

.

— the reaction with concentrated H2S04 — a red colour appears;

1. reactions with alkaloid reagents (due to tertiary nitrogen) — the substance forms precipitates;
2. after the interaction with NaOH the base of the substance ex- amined is obtained;
3. sulphur is detected after mineralization with KN03 and K^COj by the forming of a precipitate with BaCl2.

Assay. 1. Alkalimetry in the medium of alcohol and in the pre- sence of 0.01 M hydrochloric acid. Titrate with 0.1 M sodium hydro- xide solution determining the end-point potentiometrically. Read the volume added between the points of inflexion; **5=1.**

1. Non-aqueous titration. Titrate with perchloric acid in the pre- sence of (CH3COO)2Hg using methyl orange as an indicator in the acetone medium and crystal violet in the medium of the anhydrous acetic acid; **5=1.**
2. Alkalimetry in the presence of chloroform, **5=1.**
3. Determination of nitrogen by sulphuric acid digestion (the Kjel- dahl’s method).
4. Cerimetry.
5. Iodometry.
6. Iodine-chlorimetry.
7. Spectrophotometry.
8. Photocolorimetry.

Usage. Antipsychotic, antiemetic.

Storage. In an airtight Container protected from light.

Promethazine Hydrochloride, Ph. Eur.

**(Diprazinum)**

N

S

C

H

2

C

H

N

C

H

3

H

C

l

C

H

3

C

H

3

.

(2 RS)-N. N - Dimethyl-1 -(1O/Tphenothiazin-10-yl)propan-2-amine

hydrochloride

Properties. A white or faintly yellowish, crystalline powder, very oluble in water, freely soluble in alcohol and in methylene chloride. ı melts at about 222 °C with decomposition.

Identification. 1. IR-spectrum.

1. Thin-layer chromatography (see Chloropromazıne).
2. Dissolve the substance in water, add nitric acid dropwise. A precipitate is formed; it rapidly dissolves giving a red solution, be-corning orange and then yellow. Heat to boiling. The solution becomes orange and an orange-red precipitate is formed.
3. The reactions of chlorides.,

Non-Pharmacopoeial reactions (see Chloropromazine): a) with bromine water — a turbid dark-red solution with a precipitate;

1. with the concentrated H2S04 — a red or orange-red colouring;
2. reactions with alkaloid reagents (due to tertiary nitrogen) — the substance forms precipitates;
3. after the interaction with NaOH the base of the substance ex-amined is obtaıned;
4. sulphur is detected äfter mineralization with KN03 and K2 CO3 by forming a precipitate with BaCl2.

Assay. Alkalimetry in alcohol and in the presence of 0.1 M hydrochloric acid. itrate with 0.1 M sodium hydroxide determining the and-point potentiometrically; s— 1.

Usage. Antihistaminic, neuroleptic.

Storage. In an airtight Container protected from light.

Promazine Hydrochloride, Ph. Eur.

**(Propazinum)**

N

S

.

H

C

l

(

C

H

2

)

3

N

(

C

H

3

)

2

3 - (10 H- Phenothiazin-10 -yl) - N ,N -dimethylpropan- 1-arnıne
hydrochloride

Properties. A white or almost white, crystalline powder, slightly hygroscopic, very soluble in water, in alcohol and in methylene chlo- ride. It melts at about 179 °C.

Identification. 1. IR-spectrum.

1. Thin-layer chromatography (see Chloropromazine).
2. Dissolve the substance in sulphuric acid and allow it to stand for 5 min — an orange colour is produced.
3. The reactions of chlorides.

Non-Pharmacopoeial reactions: a) with bromine water — a trans- parent brown-red colouring appears;

1. reactions with alkaloid reagents (due to tertiary nitrogen) — the substance forms precıpitates;
2. after the interaction with NaOH the base of the substance examined is obtained;
3. sulphur is detected after mineralisation with KN03 and K2C03 by forming a precipitate with BaCl2.

Assay. Alkalimetry in alcohol and in the presence of 0.1 M hydro- chloric acid. Titrate with 0.1 M sodium hydroxide determining the end-point potentiometrically; **s=1.**

Usage. Antihistaminic, neuroleptic.

Storage. In an airtight Container protected from light.

Perphenazine

(Aethaperazinum), Ph.Eur.

N

S

(

C

H

2

)

3

C

l

N

N

(

C

H

2

)

2

O

H

2-[4-[3-(2-Chk>rophenothiazin- 10-yl)propyl)piperazin-l-yl]ethanol

1. The solution gives the reactions of chlorides.

Assay. Alkalimetry in aleohol and'in the presence of 0.1 M hydro- chloric acid. Titrate with 0.1 M sodium hydroxide determining the end-point potentiometrically; s = 1/2.

Usage. Antihistaminic, neuroleptic.

Storage. In an airtight Container protected from light.

DERIVATIVES OF BENZODİAZEPİNE

Benzodiazepine is a heterocyclic system, includes nuclei of benzene and 7-membered heteroeyele — 1,4-diazepine:

N

N

H

1

2

3

4

5

6

7

8

9

The electron oetet of azepines is less delocalizated than the benzene sextet; so that azepines would be expected to have üttle aromatic character and show high reactivity.

The presence of an electron-attracting substituçnt at position 7 is required for activity, and the more electron attractipg it is, the higher the activity is. Positions 6, 8, and 9 should not be substituted.

Alkyl substitution at the 3-position decreases activity, whereas substitution with a hydroxy does not. The presence or absence of the 3-hydroxyl is important pharmacokinetically. Compounds without the hydroxyl are nonpolar, have long half-lives and undergo hepatic oxidation. Compounds with the hydroxyl are much more polar and are readily converted to the excreted glucu\_ronide (see the overall metabolic relationship seheme). The 2-carbonyl funetion is optimal for activity, as is the nitrögen atom at position 1. The N-substituent should be small.
1,4-benzodiazepines have weak-basic properties due to the nitrogen atom (4). Compounds with the lactam group — NH—CO— have weak-acidic properties and can form salts with alkaline metals (amphoteric compounds).

Benzodiazepines and benzodiazepine-like drugs bind to a benzo-diazepine recognition site or benzodiazepine receptor.

Medicinal substances, derivatives of benzodiazepine, are used as tranquillisers (have a sedative effect).

N

S

.

2

H

C

l

(

C

H

2

)

3

C

F

3

N

N

C

H

3

C

3

H

N

N

H

2

.

S

C

H

3

C

H

2

C

H

2

O

H

N

B

r

H

B

r

1

/

H

2

O

2

-

.

N

+

+

C

3

H

N

N

H

2

N

S

C

H

3

C

H

2

C

H

2

O

H

N

B

r

H

B

r

+

C

H

3

C

O

O

H

-

.

N

2

H

C

l

O

4

+

2

H

g

(

C

H

3

C

O

O

)

2

H

C

O

O

H

;

+

C

3

H

N

N

H

2

.

S

C

H

3

C

H

2

C

H

2

O

H

N

C

l

O

4

-

H

C

l

O

4

+

H

g

B

r

2

+

2

C

H

C

O

O

H

+

C

3

H

N

N

H

2

N

S

C

H

3

C

H

2

C

H

2

O

H

N

B

r

H

B

r

+

N

a

B

r

+

H

2

O

-

.

N

N

a

O

H

-

+

C

3

H

N

N

H

2

+

S

C

H

3

C

H

2

C

H

2

O

H

N

B

r

+

C

3

H

N

N

H

2

N

S

C

H

3

C

H

2

C

H

2

O

H

N

B

r

N

a

H

B

r

+

N

a

N

O

3

+

2

A

g

B

r

-

+

N

N

O

-

+

C

3

H

N

N

H

2

+

S

C

H

3

C

H

2

C

H

2

O

H

N

2

A

g

N

O

3

3

A

g

N

O

3

+

F

e

(

S

C

N

)

3

3

A

g

S

C

N

+

F

e

(

N

O

3

)

3