**Parmaceutical chemisty IV**

**Lecture 7**

**Topic: Azepine derivatives. Benzodiazepine derivatives. Dibenzodiazepine derivatives. Oxazine derivatives**

7

N

H

6

5

1

2

3

4

5

6

7

N

4

1

2

3

H

H

b

a

d

c

g

e

f

7

6

1

1

b

4

1

2

3

8

9

0

1

f

N

H

7

6

5

4

1

2

3

N

H

7

6

5

4

1

2

3

N

H

N

7

6

5

4

1

2

3

N

H

S

a

z

e

p

i

n

e

d

i

a

z

e

p

i

n

e

t

i

a

z

e

p

i

n

e

**Trifluoperazine Hydrochloride, Ph.Eur.**

**(Triphthazinum)**

N

C

F

3

S

(C

H2

N

N

C

H

3

.

2

H

C

l

)3

Methylpiperazin-1 –yl propyl -2-(trifluoromethyl)-10 H-phenothiazine dihydrochloride

**Properties.** A white or pale-yellow, crystalline powder, hygroscopic, frelly
esoluble in water, soluble in alcohol. It melts at about 242 °C, with decomposition.

**Identification.** 1. UV-spectrum.

2. Thin-layer chromatography (see Chloropromazine).

3. Place in a separating funnel, add water and dilute sodium hydrpxide solution. Shake vigorously with ether. Wash the ether layer with water, add maleic acid and evaporate the ether. The residue is recrystallized from alcohol and dried, it melts at about 192 °C.

4. Dissolve the substance in water, add bromine water and shake. Add sulphuric acid dropwise — a red colour develops.

5. Dissolve the substance in water, add the nitric acid — a dark-red colour develops, it turns to pale yellow.

6. The solution gives the reactions of chlorides.

Assay. Alkalimetry in alcohol and’ in the presence of 0.1 M hydrochloric 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 BENZODIAZEPINE**

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

2

1

8

9

7

6

5

4

3

N

N

H

The electron octet of azepines is less delocalizated than the ben-
zene sextet; so that azepines would be expected to have little aromatic
character and show high reactivity.

The presence of an electron-attracting substituent at position 7 is
required for activity, and the more electron attracting 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 metabo-
lic relationship scheme). Tire 2-carbonyl function is optimal for activity,
as is the nitrogen atom at position 1. The N-substituent should be small.

1,4-benzodiazepines have weak-basic properties due to the nitro-
gen atom (4). Compounds with the lactam group —NH—CO— have
weak-acidic properties and can form salts with alkaline metals (am-
photeric 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).

**Oxazepam, Ph. Eur.**

**Nozepanum**

N

N

l

C

O

O

H

H

 (3 RS) - 7-Chloro- 3-hydroxy- 5 -phenyl-1, 3-dihydro-
2 H-1,4-enzodiazepin-2-one

**Preparation.** The synthesis of benzodiazepines can be described in
the example of oxazepam:

N

O

2

l

C

+

C

H

2

C

N

C

H

3

O

H

l

C

N

O

F

e

p

­

n

i

t

r

o

c

h

l

o

r

o

b

e

n

z

e

n

e

b

e

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y

l

c

y

a

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O

N

H

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C

C

N

H

2

O

H

N

N

H

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C

C

O

H

C

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C

C

H

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c

h

l

o

r

o

b

e

n

z

o

p

h

e

n

o

n

e

H

O

H

O

l

C

N

N

**Properties.** A white or almost white, crystalline powder, practically
insoluble in water, slightly soluble in alcohol and in methylene chloride.

**Identification.** 1. UV-spectrum.

2. IR-spectrum.

3. Thin-layer chromatography.

4. Dissolve the substance in the mixture of hydrochloric acid and
water. Heat to boiling for 5 min and cool. Add the solution of sodium
nitrite and the solution of sulphamic acid, mix and allow it to stand for 1 min. Add solution of naphthylethylenediamine dihydrochloride- a red colour develops:

o

H

O

H

l

C

O

l

C

N

a

N

O

2

;

H

C

l

N

H

C

l

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C

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C

N

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N

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N

N

H

(C

H

2

N

H

2

)2

Nort-Pharmacopoeial reactions: a) when heating with H3P04 and
adding fuchsinsulphuric acid — a violet colour develops (the reaction of formaldehid):

C

S

O

3

H

N

2

H

N

2

H

N

H

S

O

2

C

H

R

O

H

H

C

O

H

N

H

N

2

H

C

N

H

S

O

2

C

H

R

O

H

C

O

H

H

H

O

S

O

2

H

+

1. with alkaloids reagents it forms precipitates;
2. chlorine can be determined with silver nitrate solution after
mineralization.

1.Non-aqueous titration in the mixture of the anhydrous and acetic anhydride. Titrate with 0.1 M perchloric acid ling the end-point potentiometrically; s— 1.

 rophotometry.

Pllotocolorimetry.

Tranquilliser.

fMge. Store protected from light.

**Chlorodiazepoxide, Ph. Eur.**

**(Chlordiazepoxidum)**

N

N

l

C

N

H

C

H

3

O

7-Chloro-N-methyl-5-phenyl-3£f-l,4-benzodiazepin-2-amine 4-oxide

**Properties.** Almost white or light yellow, crystalline powder. Practically insoluble in water, sparingly soluble in alcohol.

**Identification.** IR-spectrum.

Non-Pharmacopoeial reactions (see Oxazepam).

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

1. Spectrophotometry.
2. Photocolorimetry.

**Usage.** Tranquilliser.

**Storage.** Store protected from

**Fenazepam**

**(phenazepamum), Ph. Eur.**

N

N

r

B

H

O

C

l

7-Bromo-2,3-dihydro-5-(2-chlorophenyl) 1H-1,4-benzodiazepin-2-one

**Properties.** A white or almost white powder. Slightly soluble in
I alcohol, practically insoluble in water.

When heating with mineral acids it is hydrolysed.

**Identification.** 1. With the concentrated acids (H2S04, HC1, HC104)
it forms coloured salts with fluorescence in UV-light.

1. The tertiary nitrogen causes forming the precipitates with alkaloid reagents.
2. The coloured product of melting is characteristic for fenazepam. Depending on the pH medium various colours are produced: in the alkaline one is blue-violet, in acidic one is blue-green, which turns yellow.
3. After the hydrolysis the azo-dye is developed (see Oxazepam).
5. Beilstein test is carried out of halogens.

**Assay.** 1. Non-aqueous titration; s=1.

2. Spectrophotometry.
3. Photocolorimetry.
**Usage.** Tranquillisers.

**Storage.** Protected from light.

**Diazepam**

**(Sibazonum), Ph. Eur.**

N

N

l

C

C

H

3

O

1 7-Chloro- l-methyl-5-phenyl- l,3-dihydro-2//-1,4-benzodiazepin-2-one

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

**Identification.** 1. The melting point is 131—135 °C.

1. UV-spectrum.
2. Dissolve the substance in sulphuric acid —the solution gives greenish-yellow fluorescence in UV-light at 365 nm.
3. To the substance in a porcelain crucible add the anhydrous sodium carbonate. Heat over an open flame for 10 min. Take up the residue
with dilute nitric acid and filter. To the filtrate add water — the solution
gives the reaction (a) of chlorides (see Pharmacopoeia, 2.3.1).

Non-Pharmacopoeial reactions: a) with alkaloids reagents it forms\
precipitates;

b) after the hydrolysis it becomes yellow:

N

N

l

C

C

H

3

O

o

H

C

l

;

t

C

l

C

O

C

N

H

C

H

3

Purity. The related substances are determined by the thin-layer chromatography.

Assay. 1. Non-aqueous titration in the medium of acetic anhydride using the Nile blue solution as an indicator, titrate with perchloric acid until a yellowish-green colour is obtained; s= 1.

1. Spectrophotometry.
2. Photocolorimetry.

**Usage.** Tranquilliser.

**Storage.** Store protected from light.

**Nitrazepam**

**(Nitrazepamum), Ph. Eur.**

N

N

N

2

O

H

O

7-Nitro-5-phenyl-.l,3-dihydro-2//- l,4-benzodiazepin-2-one

**Properties.** A yellow, crystalline powder, practically insoluble irf
water, slightly soluble in alcohol and in ether.

**Identification.** 1. The melting point is 226—230 °C.

1. UV-spectrum.
2. IR-spectrum.
3. Dissolve the substance in a mixture of the hydrochloric acid and
water. Boil for 5 min, cool and add the solution of sodium nitrite.

Allow it to stand for 1 min and add the solution of sulphamic acid and
mix. Add the solution of naphthylethylenediamine dihydrochloride —
a red colour is produced (see Oxazepam).

1. Dissolve the substance in methanol warming, if necessary, and
add the dilute solution of NaOH — an intense yellow colour is produced:

N

N

N

2

O

H

O

N

a

O

H

N

N

O

N

O

a

N

O

+

-

The non-Pharmacopoeial reaction: with alkaloids reagents it forms
precipitates.

**Assay.** 1. Non-aqueous titration in the medium of acetic anhy-
dride. Titrate with 0.1 M perchloric acid determining the end-point
potentiometrically; s = 1.

1. Spectrophotometry.
2. Photocolorimetry.

**Usage.** Tranquilliser.

**Storage.** Store protected from light.

**DERIVATES OF PURINE**

Purine is a condensed heterocyclic system, it consists of two cycles:
pyrimidine and imidazole:

N

N

N

N

H

**Aciclovir**

**(Aciclovirum), Ph.Eur.**

O

H

N

N

2

H

N

N

N

C

H

2

O

C

H

2

C

H

2

O

H

20-Amino-9-[(2-hydroxyethoxyl)methyl]-1,9-dihydro-6H-purin-6-one