**Pharmaceetical cheistry IV**

**Lecture 4**

**Topic:** Pyrimidine -2,4,6-trion (barbituric acid) derivatives. Pyriidine-thiazole derivatives (B1 group Vitamines) and their coenzi preparations (cocarboxylase, phosphothiamine, benphothiamine).

**MEDICINAL SUBSTANCES,**

**WHICH ARE DERIVATIVES OF BARBITURIC ACID**

Pyrimidine is in the base of the structure of barbituric acid. Deri­vatives of the barbituric acid-barbiturates are used in medical prac­tice as hypnotic and sedative substances:

C

N

H

2

N

H

2

O

+

C

C

C

O

O

R

1

O

5

H

2

C

O

5

H

2

C

R

2

1

2

3

4

5

6

N

H

N

H

O

O

R

1

R

2

O

$-$2C2H5OH

The acidic properties of barbituric acid are caused by the presence of mobile hydrogen atoms of methylene and imide groups. Barbituric acid has two types of isomerism:

1. keto-enol caused by mobile hydrogens of methylene group (bar­bituric

acid is 5-6 times more strong than acetic acid);

O

R

2

R

1

O

O

N

H

N

H

+

N

a

O

H

-

H

2

O

O

R

2

R

1

O

O

N

H

N

N

a

+

2) lactam-lactim is caused by mobile hydrogens of imide group:

1

2

3

4

5

6

N

H

N

O

O

R

1

R

2

O

R

3

1

2

3

4

5

6

N

N

O

O

R

1

R

2

R

3

O

a

N

5-Mono substitued barbituric acid are also strong enough acids (e. g. 5-diethylbarbituric acid), but 5,5-disubstitued (e. g. 5,5-diethylbar- bituric acid) are very weak acids. Due to mobile hydrogen atoms the salts of barbiturates, which are soluble in water can be obtained:

**Preparation.** The synthesis of barbituric acid derivatives consists of two stages:

 1) obtaining of an appropriate ester of malonic acid;

 2) the condensation of the ester with urea (in the presence of sodi­um

alcoholate in the medium of anhydrous alcohol).

The scheme of the synthesis of barbital:



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

In barbital and in phénobarbital the appropriate impurities of 5-ethyl- or 5-phenylbarbituric acid are determined: boil the substance, cool and filter. To the filtrate add methyl red solution. The solution is orange-yellow. Not more than 0.1 mL of 0.1 M sodium hydroxide is required to produce a pure yellow colour.

**Assay.** 1. Acid-base titration: a) indirect alkalimetry after the in­teraction with AgN03 (see Barbital);

b) alkalimetric titraton in the non-aqueous medium for the acidic forms of barbiturates. The substance is dissolved in dimethylformamide or in a mixture of dimethylformamide and benzene, which are neutra­lised with thymol blue (for increasing the acidic properties). Titrate with sodium methoxide, lithium methoxide or .with NaOH in the mixture of methanol and benzene using thymol blue as an indicator; s = 1

c) alkalimetry in the water-alcoholic medium for acidic fori barbiturates. The substance is dissolved in alcohol, neutralised thymolphthalein (for increasing solubility and decreasing hydroh the salts); s= 1:

d) acidimetry in the aqueous medium for sodium salts of barlut rates. The indicator is methyl orange; s=1:

A free alkali is also titrated. Calculate the content of sodium sail > barbiturate (a dry condition) using the formula



where % alkali is % content of a free alkali in the substance examined C1 is the coefficient calculated as a ratio M. m. of a salt to M. m. NaOH.

2. Gravimetry. Acidic forms of barbiturates are extracted with the ether from acidic solutions. The ether is evaporated; the substance obtained is dried and weighted. This method is used for quantification of thiopental sodium (Na is also determined by acidimetry).

3. Argentometry. The substance examined is dissolved in 5 % solu­tion of anhydrous sodium carbonate and titrated with silver nitrate solution (without an indicator) to the appearance of turbidity (disub- stituted salt); s=1:



O

R

2

R

1

N

N

O

A

g

O

N

a

The first sedative-hypnotic barbiturate, 5,5-diethylbarbituric acid, was introduced in 1903. With time, many members were added, and the barbiturates dominated the sedative-hypnotic field until the advent of the benzodiazepines, which for reasons outlined earlier, but most notably a much greater margin of safety, displaced the barbiturates as the most broadly useful agents in sedative-hypnotic applications.

Beginning with lower alkyls, there is an increase in onset and a decrease in duration of action with increasing hydrocarbon content up to about seven to nine total carbon atoms substituted on the 5-position.

Lipophilicity and the ability to penetrate the brain in the first case and the ability to penetrate liver microsomes in the second one may be involved. Also, for more hydrophobic compounds partitioning out of the brain to other sites can be involved in the second instance.

There is an inverse correlation between the total number of carbon atoms substituted on the 5-position and the duration of action, which N even better when the character of these substituents is taken into ac­count. for example, the relatively polar character of a phenyl substituent (approximates a three- to four-carbon aliphatic chain), branching of alkyls, presence of an isolated double or triple bond, and so on. Addi­tionally, these groups can influence the ease of oxidative metabolism by effects on bond strengths, as well as by influencing partitioning.

**Barbital**

**(Barbitalum), Ph. Eur. H**

O

C

2

H

5

C

2

H

5

O

O

N

H

N

H

M.k.184,2

5,5-Diethylbarbituruc acid

**Properties.** A white, crystalline powder or colourless crystals, slightly soluble in water, soluble in boiling water, in alcohol and in ether. It forms water-soluble , compounds with alkali, carbonates solutions and with ammonia.

**Identification.** 1. Determination of the melting point.

2. IR-spectrum.

3. Thin-layer chromatography.

4. It gives the reaction of non-nitrogen substituted barbiturates. Dissolve the substance to be examined in methanol, add the solution of cobalt nitrate and calcium chloride. Mix and add with shaking dilute sodium hydroxide solution. A violet-blue colour and precipitate are formed:

N

R

2

R

1

O

O

N

O

R

3

2

C

o

v

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y

a

C

u

Non-Pharmacopoeial reactions: a) with AgNO3 – a white precipitate;

b) with CuS04 in the presence of potassium carbonate and hydrogen carbonate- a blue colouring and precipitate are produced.

It is necessary to carry out such reactions in the neutal medimum avoid forming precipitates of heavy metals hydroxides). Acidic froms the previously neutralised with NaOH.

The probable structure of the complexes:

O

R

2

C

H

2

O

O

N

H

N

H

C

H

3

+

O

H

O

C

H

3

C

H

O

 vanilin

O

R

2

C

O

O

N

H

N

H

O

C

H

3

C

H

O

H

C

H

3

c) melt with NaOH - the salts of disubstituted derivs of acetic acid, ammonia and sodium carbonate are formed:

O

R

2

R

1

O

O

N

H

N

H

+

5

N

a

O

H

C

H

1

R

2

R

C

O

O

N

a

+

2

N

H

3

+

2

N

a

2

C

O

3

Na2CO3 + 2HCl → 2NaCl + CO2↑ + H2O

C

O

O

N

a

+

H

C

l

2

R

1

R

C

H

N

a

C

l

+

C

H

1

R

2

R

C

O

O

H

When adding an acid carbon dioxide and acetic acid derivatives (with a characteristic odour) are educed.

d) the reaction with *p*-dimethylaminobenzaldehyde and concen­trated sulphuric acid - a yellow colour develops.

**Assay.** Dissolve the substance in pyridine. Add thymolphthalein solution and add silver nitrate solution in pyridine. Titrate with ethanolic sodium hydroxide until a pure blue colour appears; s= 1/2. Carry out a blank titration.

N

C

2

H

5

C

2

H

5

O

O

N

H

O

H

+

H

C

O

N

(

C

H

3

)

2

N

C

2

H

5

C

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H

5

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C

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H

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N

a

+

N

C

2

H

5

C

2

H

5

O

O

N

H

O

a

N

**Usage.** Hypnotic.

**Storage.** In well-closed containers protected from light.

**Phénobarbital**

**Phenobarbitalum), Ph. Eur. H**

O

C

6

H

5

C

2

H

5

O

O

N

H

N

H

M.k.232,24

5-Ethyl-5-phenylbarbituric acid

Properties. Awhite, crystalline powder or colourless crystals, very slightly soluble in water, freely soluble in alcohol, soluble in ether It forms water-soluble compounds with alkali, carbonates and with ammonia.

**Identification.** 1. Determination of the melting point.

2. IR-spectrum.

3. Thin-layer chromatography.

4. The reaction of non-nitrogen substances (see Barbital).

Non-Pharmacopoeial reactions: a) with AgN03 - a white precipitate;

b) with CuS04 — a dull lilac precipitate;

c) melt with NaOH {see Barbital);

d) with NaN03 and concentrated H2S04 -a yellow colouring appears (the reaction of phenyl radical):



fenilmalon turşusunun

dietil efiri

oksalilfenilsirkə turşusunun dietil efiri

fenilsirkə turşusunun

etil efiri

 feniletilmalon turşusunun

 dietil efiri

e) with formaldehyde and concentrated sulphuric acid - a pink colour develops.

**Assay.** Dissolve the substance in pyridine; add thyrnolphthalem solution and silver nitrate in pyridine. Titrate with ethanolic sodium hydroxide until a pure blue colour appears; s= 1/2. Carry out a blank titration (see Barbital).

**Usage.** Sedative, hypnotic, anticonvulsant.

**Storage.** In well-closed containers protected from light.

**Benzobarbital**

**(Benzonalum)**

O

C

6

H

5

C

2

H

5

O

O

N

N

H

C

C

6

H

5

O

M.k. 336,34

1 -Benzoyl-5-ethyl-5-phenylbarbituric acid

**Properties.** A white, crystalline powder, very slightly soluble in water, freely soluble in chloroform, soluble in ether, slightly soluble in alcohol.

**Identification.** 1. With AgN03 -a white precipitate develops.

2. With Co(N03)2 in the presence of CaCl2 and NaOH - a violet colouring develops.

3. With CuS04, NaOH in the presence of potassium carbonate and hydrocarbonate - a grey-blue colouring appears.

4. Melt with NaOH - see Barbital.

5. With sodium nitrate and concentrated sulphuric acid - a yel­low colouring develops (see Phenobarbitalum).

6. The specific reaction -after alkaline hydrolysis the substance gives reaction of benzoates. A dull-yellow precipitate is formed:

O

C

6

H

5

C

2

H

5

O

O

N

N

H

C

C

6

H

5

O

N

H

2

O

H

H

C

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N

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H

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C

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N

H

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H

5

H

6

C

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F

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C

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p

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+

C

O

N

H

O

5

H

6

C

3

F

e

**Assay.** See Methods mentioned above.

**Usage.** Anticonvulsant. Unlike phénobarbital it shows less hypnosedative effect.

**Storage.** In well-closed containers protected from light.

**Pentobarbital Sodium**

**(Aethaminalum-natricum), Ph. Eur.**

**Properties.** A white, crystalline powder, hygroscopic, very soluble in water.

**Identification.** 1. Determination of the melting point.

2. Thin-layer chromatography.

3. With vanillin and sulphuric acid a reddish-brown colour deve­lops. After ethanol addition the colour becomes violet and then blue.

4. After ignition the residue gives reactions of sodium.

Non-Pharmacopoeial reactions: a) with AgN03 - a white preci­pitate appears;

b) with Co(N03)? in the presence of CaCl2 - a violet colouring develops;

1. with CuS04 in the presence of potassium carbonate and hydro­carbonate - a blue precipitate appears;
2. melt with NaOH (see Barbital);
3. with *p*-dimethylaminobenzaldehyde and concentrated sulphuric acid- a red colour appears.

**Assay.** Dissolve the substance in the solution of silver nitrate in pyridine. Titrate with ethanolic sodium hydroxide solution until a pure blue colour is produced using thymolphthalein solution as an indica­tor; s- 1. Carry out a blank titration:

**Storage**. In well-closed containers.

**Hexobarbital**

**(Hexenalum), Ph. Eur. H**

N

N

C

H

3

O

O

O

a

N

C

H

3

M.k.258,25

1,5-Dimethyl-5-(cyclohexane- l'-yl)-barbiturat

Properties. A white, crystalline powder, very slightly soluble in water, sparingly soluble in alcohol and in ether. It forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

**Identification.** 1. Determination of the melting point.

2. IR-spectrum.

1. Thin-layer chromatography.
2. With vanillin alcoholic solution and a cooled mixture of water with

sulphuric acid a greenish-yellow colour develops; after heating the colour becomes dark red.

Non-Pharmacopoeial reactions: a) with AgN03 and NaOH - a white precipitate develops;

b) with Co(N03), in the presence of CaCl2and NaOH - a violet colour

appears;

1. with CuS04 in the alkaline medium - a blue colouring deve­lops, which

becomes an intense blue and then a white precipitate develops;

1. with formaldehyde and concentrated sulphuric acid - a dark- red colour

with a green fluorescence appears;

1. the substance discharges bromine water and potassium perman­ganate

solution:



**Assay.** Dissolve the substance in pyridine, add thymolphthalein solution and silver nitrate solution in pyridine. Titrate with 0.1 moI/L ethanolic sodium hydroxide solution until a pure blue colour is pro­duced; s=l. Carry out a blank titration.



**Hypnotic**. Sodium salt (hexenalum) is used for intrave­nous narcosis.

**Storage.** In well-closed containers protected from light.

**Thiopental Sodium and Sodium Carbonate**

**(Thiopentalum natricum et natrii carbonas), Ph. Eur.**

N

H

N

C

2

H

5

O

O

S

a

N

C

H

C

H

3

C

H

2

C

H

2

C

H

3

+

N

a

2

C

O

3

M.k.264,32 + 105,99

Mixture of sodium 5-ethyl-5-(2'-amyl)-2-thiobarbiturate

with anhydrous sodium carbonate

**Properties.** A yellowish-white powder, hygroscopic, freely soluble in water, partly soluble in ethanol, practically insoluble in ether.

**Identification.** 1. Determination of the melting point after acid addition.

2. IR-spectrum.

1. Thin-layer chromatography.
2. The reaction of non-nitrogen substituted barbiturates (see barbital).
3. It gives reactions of sodium.

Non-Pharmacopoeial reactions: a) with CuS04 - a yellow-green colouring with a precipitate;



b) sulphur is detected when heating with lead acetate in the presence of NaOH:





c) sulphur is detected after mineralisation with NaNO3 and Na2C3 (as a sulphate).

**Assay.** Assay for this medicine consists of two stages: quantifica tion of sodium (by acidimetry with hydrochloric acid using methyl red solution as an indicator) and quantification of thiopental (by alkali­metry with lithium methoxide).,

Alkalimetry with lithium methoxide after acid addition (to decom­pose sodium carbonate). Dissolve the residue in a previously neutra­lised dimethylformamide, add solution of thymol blue in methanol and titrate immediately with 0.1 M lithium methoxide solution until a blue colour is obtained. Protect from atmospheric carbon dioxide during titration; s=1:

**Usage.** For intravenous narcosis.

**Storage.** Store in airtight containers protected from light.

**MEDICINAL SUBSTANCES, WHICH ARE DERIVATIVES OF HEXAHYDROPYRIMIDINEDIONE**

In medical practice the structural analogue of barbiturates - pri­midone (hexamidinum or mysoline) is used. It is a diketone derived from hexahydropyrimidine. The chemical nature of primidone is that of a cyclic diamide, and it has none of the acidic character of barbitu­ric acid and the barbiturates.

**Primidone**

**(Hexamidiuum), Ph. Eur.**

N

H

N

H

C

2

H

5

O

O

C

6

H

5

1

2

3

4

5

6

M.k.218,16

5-Ethyl-5-phenylhexahydropyrimidinedione-4,6

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

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

2. IR-spectrum.

1. Dissolve the substance in the solution of the chromotropic acid, sodium

salt in the mixture of water and sulphuric acid. A pinkish-blue colour develops when heating:



The formaldehyde educed is detected with chromotropic acid in the presence of concentrated sulphuric acid (violet colour):

:

H

e

k

s

a

m

i

d

i

n

[

O

]

+

C

H

2

O

C

5

H

2

C

5

H

6

C

C

O

N

H

2

C

O

N

H

2

 feniletilmalon

 turşusunun diamidi

S

O

3

H

S

O

3

H

C

O

H

H

+

O

H

O

H

H

2

S

O

4

-

H

2

O

2

O

H

O

H

O

H

O

H

S

3

O

H

S

3

O

H

S

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H

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H

C

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[

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H

O

H

O

H

S

3

O

H

S

3

O

H

S

O

3

H

S

O

3

H

C

H

1. Mix the substance with anhydrous sodium carbonate. Heat until the

mixture is melted. Ammaonia is evolved, it is detectable by its odour and the alkaline reaction:

P

r

i

m

i

d

o

n

K

2

S

O

4

;

C

u

S

O

4

;

H

2

S

O

4

[

O

]

2

N

H

3

$$\uparrow $$

+

1

2

C

O

2

+

4

H

2

O

2NH3 + H2SO4 → (NH4)2SO4

(NH4)2SO4 + 2NaOH → 2NH3$\uparrow $+Na2SO4 + 2H2O

NH3 + H3BO3 → NH4BO2 + H2O

NH4BO2 + HCl $\rightarrow $ NH4Cl + HBO2

**Assay.** 1. UV-spectrophotometry.

2. Determination of nitrogen by sulphuric acid digestion (the Kjeldahls method).

**Usage.** Anticonvulsant.

**Storage**. In well-closed container.

Pyrimidine-thiazole Derivatives

(Vitamins of B1 group)

The termolabile, anti-beri-beri substance, now known as vitamin B1 aneurine, or thiamine, was first obtained in the crystalline form from rice polishings and later from yeast. The vitamin is a compound of the basic character, and the molecule contains a pyrimidine ring *(A)* and ahthiazole (B) ring linked by a methylene group. The nitrogen atom of the thiazole ring forms a strongly basic cation in association with a chloride ion. The crystalline hydrochloride, which is a salt formed the weakly basic – NH2 group, has the following structure:

N

N

N

S

This substance was synthesized in 1936, and the synthetic com­pound is now produced commercially.

**Thiamine Hydrochloride**

**(Thiamini hydrochloridum). Ph. Eur.**

2

1

3

4

5

6

N

3

H

C

N

N

H

2

C

H

2

+

0

C

H

3

C

H

2

C

H

2

S

N

2

1

3

4

5

1

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0

C

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3-Metil-5-β-oksietil-N-(2-metil-4-amin-5-metilpirimidil)-tiazolium xlorid (bromid)-hidroxlorid (hidrobromid)

**Identification.** 1. UV-spectra. With dilute acetic acid and 1 M sodium hydroxide heat the solution of substance on for 30 min. Add dilute sodium hydroxide solution, ( cyanide solution and butanol; shake. The upper alcoholic layer shows an intense light-blue fluorescence, especially in ultraviolet light at 365 nm.

T

i

a

m

i

n

N

a

O

H

N

N

3

H

C

N

H

2

N

C

O

H

S

H

C

C

H

2

C

C

H

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C

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R3Fe(CN)6

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H

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C

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C

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S

N

N

N

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Repeat the test using 1 M sodium hydroxide and sodium sulphite. Practically no fluorescence is seen.

2. IR-spectrum.

3. It goes reactions of chlorides.

Assay. 1. Non-aqueous titration in the medium of anhydrous formic acid and acetic anhydride. Titrate immediately with 0.1 M perchloric acid, determining the end-point potentioimetrically and carry-ins out the titration within 2 min. Carry out a hi.ml un lion; s = 1/2.

Tiamin-xlorid + Hg(CH3COO)2 + 2HClO4→

(və ya (C12H17N4OS)+Cl- $∙$ HCl)

H

g

C

l

2

+

2

C

H

3

C

O

O

H

+

C

H

2

N

S

H

C

H

2

C

H

3

N

3

H

C

N

H

2

N

C

H

2

O

H

2

C

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O

4

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+

+

2. Alkalimetry in the mixture of 0.1 M hydrochloric acid solution and 96% ethanol. Titrate with 0.1 M sodium hydroxide; s=1/2.

**Usage**. Used in prevention and treatment of vitamin B1 deficiencies.

**Storage.** In a non-metallic container, protected from light.

**Thiamine Hydrochloride**

**(Thiamini hydrochloridum). SPU**

Then add nitric acid and indicator - ferric ammonia sulphate so­lution and 0.1 mL of 0.1 M ammonia thiocyanate solution:

The content of thiamine bromine is calculated by the difference between volumes of AgN03, NaOH and NH4SCN; s=1.

Usage. It is used in prevention and treatment of vitamin B, defi­ciencies.

Storage. In a non-metallic container, protected from light.