Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

SPECIAL PHARMACEUTICAL CHEMISTRY

Chromane and phenylchromane vitamins

Lesson 13

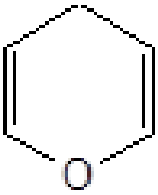
VII term

Volgograd, 2023

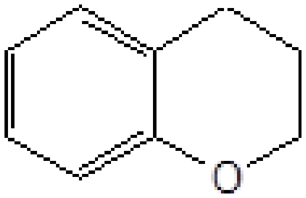
Tocopherols

Tocopherols are natural antioxidants and play an important role in metabolism.

To date, seven different substances with E-vitamin activity (tocopherols) have been isolated from natural sources or synthetically produced. According to their chemical structure, they are derivatives of chromane (benzo-γ-dihydropyran), which includes a benzene nucleus condensed with a hydrogenated γ-pyran nucleus:

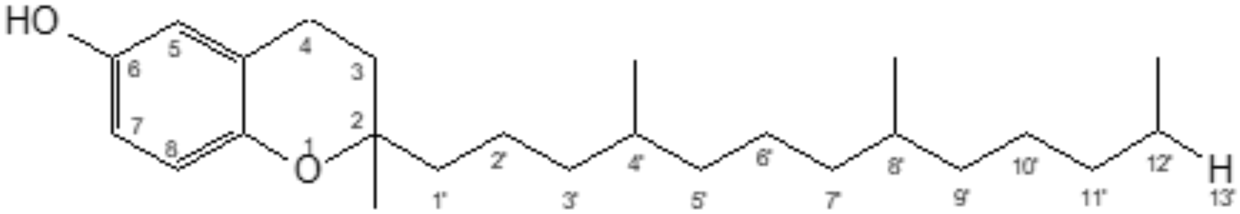


γ-pyran



Chromane (benzo-γ-dihydropyran)

The basic chemical structure of all seven tocopherols is tocol, which is 2-methyl-2-(4', 8', 12'-trimethyltridecyl)-6-oxychromane:



The side chain in tocopherol formulas is usually written abbreviated:

Tocopherols are distinguished by the number of methyl groups, which are located at positions 5, 7 and 8

Tocopherols	Position		
	5	7	8
α-Tocopherol	$-CH_3$	$-CH_3$	$-CH_3$
β-Tocopherol	$-CH_3$	–	$-CH_3$
γ-Tocopherol	–	$-CH_3$	$-CH_3$
ζ-Tocopherols	$-CH_3$	$-CH_3$	–
8-Methyltocol (δ-Tocopherol)	–	–	$-CH_3$
5-Methyltocol (ε-Tocopherol)	$-CH_3$	–	–
7-Methyltocol (η-Tocopherol)	–	$-CH_3$	–

The number of methyl groups in the tocopherol molecule has a significant effect on biological activity. α-Tocopherol containing three methyl groups in the benzene nucleus has the highest activity. Substitution of the phytol radical with another, shortening or complete removal of the side chain leads to complete loss of activity.

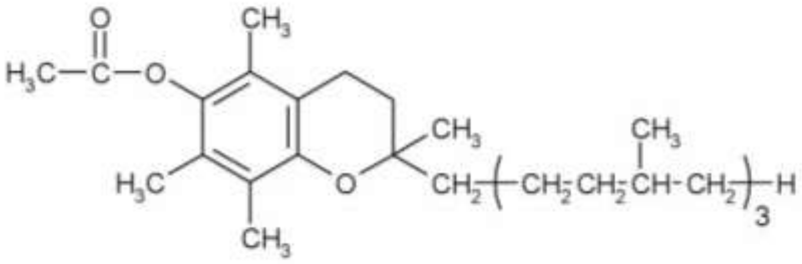
Sources of vitamin E

The best plant sources of vitamin E include: green peas, wheat and rye germ, soybeans, beans, green salad, lentils, oats, corn, soybean, olive oil.

Animal products also contain some vitamin: animal fat, meat, beef liver.

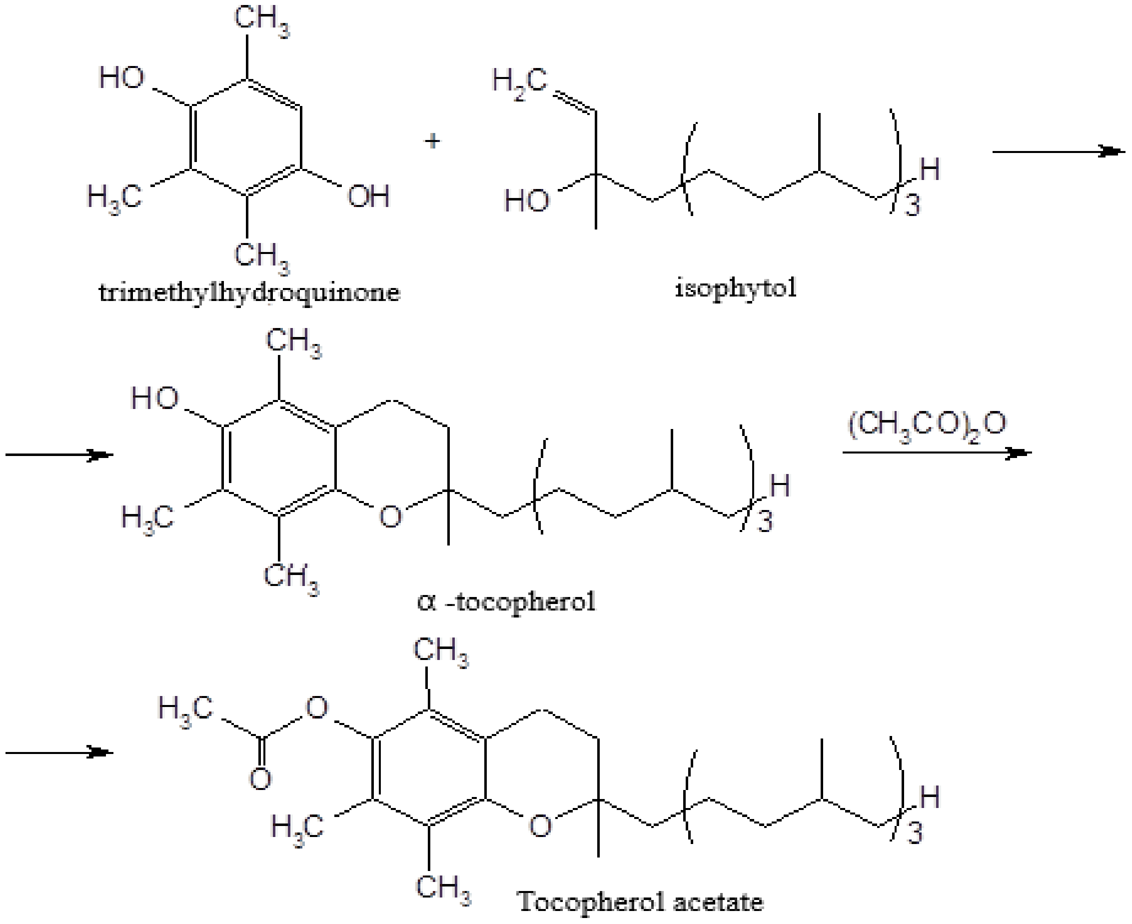
α-Tocopherol acetate is used as a drug.

Tocopherol acetate



OBTAINING

It is synthesized by condensation of trimethylhydroquinone and isophytol followed by acetylation with acetic anhydride of the resulting α -tocopherol:



PHYSICAL PROPERTIES

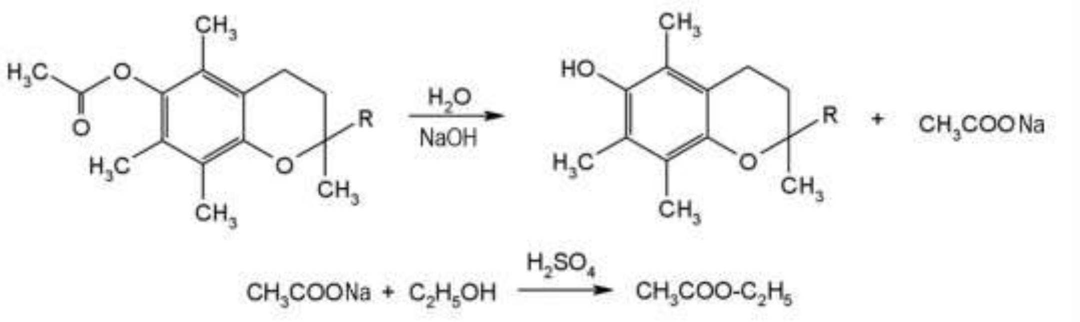
Colorless or light yellow transparent, viscous, oily liquid with a faint odor. Under the influence of light and air it turns yellow. Refractive index 1.4950-1.4985

Practically insoluble in water, easily soluble in ethanol, very easily soluble in ether and vegetable oils.

IDENTIFICATION

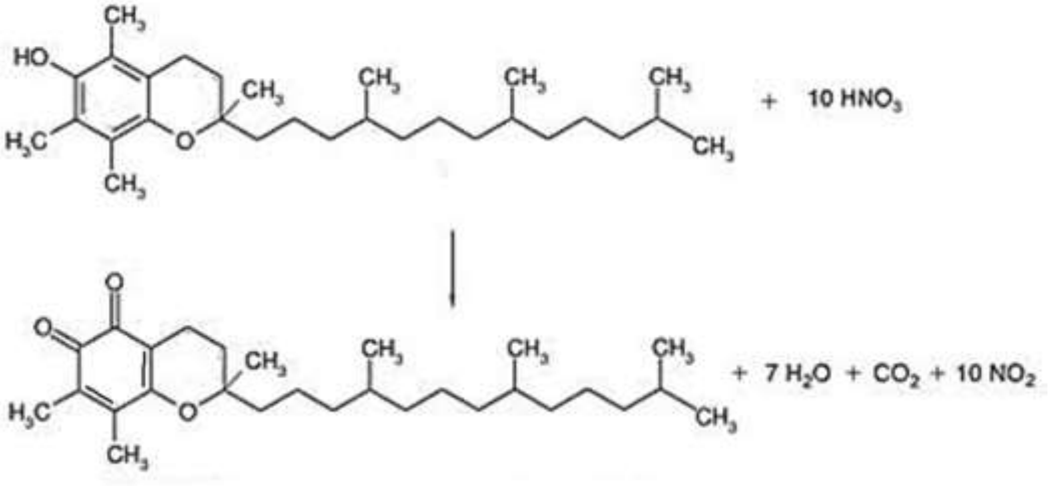
1. ***Infrared spectroscopy***
2. ***UV spectrophotometry***
3. ***Alkaline hydrolysis followed by detection of acetic acid***

   Preliminary tocopherol acetate is subjected to alkaline hydrolysis (with reflux condenser) in the presence of absolute ethanol, and then add concentrated sulfuric acid and pour the resulting mixture into a flask with water. The sodium acetate formed during hydrolysis in the presence of concentrated sulfuric acid is converted first into acetic acid, which with ethanol forms ethyl acetate:



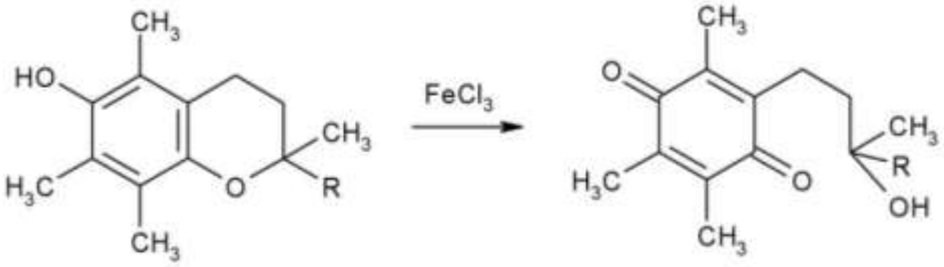
4. ***Interaction with concentrated nitric acid on heating***

   When heated to 80°C with concentrated nitric acid, a red-orange colored o-tocopherylquinone is formed:



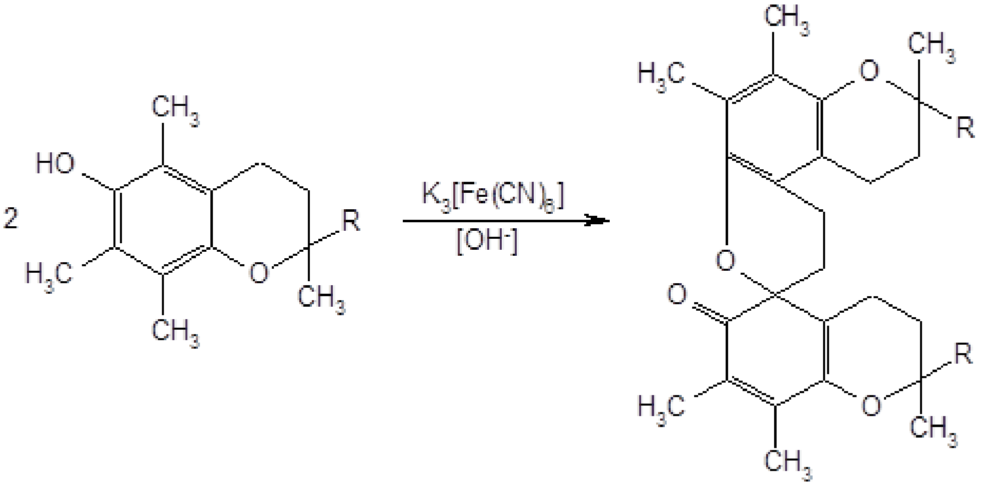
5. ***Interaction with ferric chloride.***

   When tocopherol is oxidized with ferric chloride solution, the pyran ring is broken to form a yellow colored compound:



6. ***Interaction with potassium hexacyanoferrate in alkaline medium***

   When potassium hexacyanoferrate (III) is used as an oxidizing agent in an alkaline medium, colored di-α-tocopherol is formed:



7. ***Interaction with a reagent containing iron (III) chloride and*** α,α***-dipyridyl in a mixture of ethanol and benzene.***

   A red coloration appears, having a maximum of light absorption at a wavelength of 500 nm.

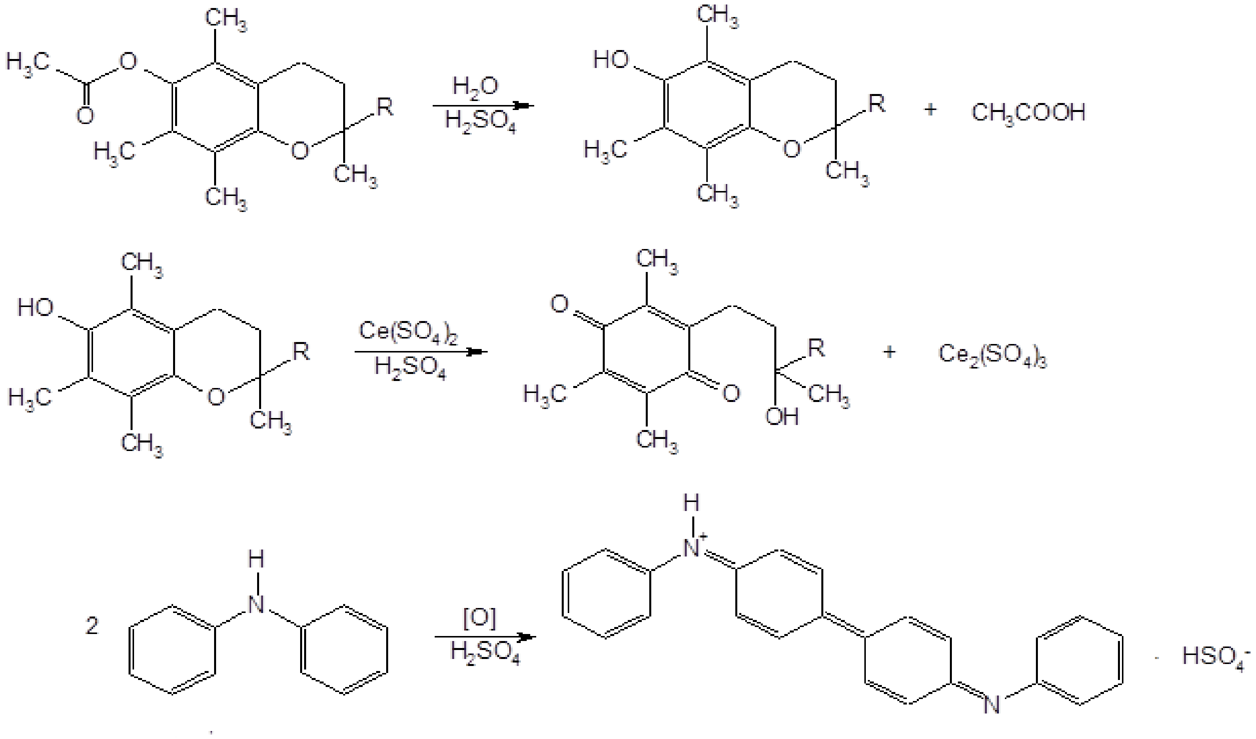
PURITY TEST

When testing for purity determine the transparency, color of the solution, acid number (not more than 0.5 from a sample of 2.0 g). Determine the sum of extraneous impurities (up to 1%) and impurity α-tocopherol (not more than 4%) by HPLC. Detection of the total content of impurities is performed at a wavelength of 210 nm, and α-tocopherol - at 292 nm. Calculations are made by comparing the peak areas of the test substance and the state standard sample of tocopherol acetate.

QUANTIFICATION

1. ***Cerimetry***

   Determination is based on acid hydrolysis (by boiling with reflux in the presence of sulfuric acid). Then the released tocopherol is titrated with cerium (IV) sulfate (indicator diphenylamine) until blue-violet coloration appears:



2. ***Gas-liquid chromatography***

   This method is used to quantify tocopherol oil solutions

3. ***HPLC***

STORAGE

During storage it is necessary to take into account the influence of UV radiation. Tocopherol acetate is stored in hermetically sealed, filled to the top in dark glass jars in a cool place protected from light (at a temperature not exceeding +10°C).

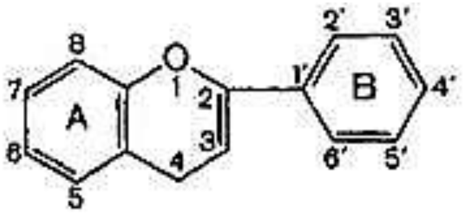
MEDICAL USE

Tocopherol acetate is used in the form of solutions in oil 5, 10 and 30% for ingestion and intramuscular injection. It is prescribed for diseases of the neuromuscular system, peripheral vessels, atherosclerosis, threatened abortion, dysfunction of the sex glands in men and other diseases.

Phenylchroman vitamins.

BIOFLAVONOIDS (P VITAMINS)

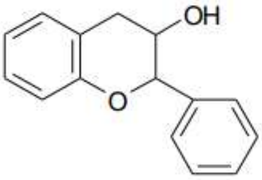
The structure of bioflavanoids is based on 2 - phenylchroman, or flavan:



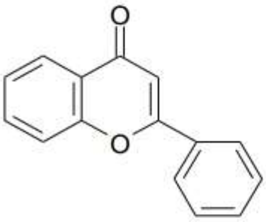
There is a large variety of oxyflavans in nature, which have a polyphenolic character and give many derivatives .

Three groups of flavan derivatives are of interest for medicine.

1. ***3-Oxy derivatives of flavan (2 - phenylchroman)*** are catechins with tannin property:



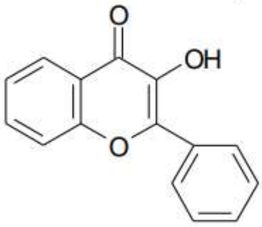
2. ***Derivatives of 4 - oxoflavan (4 - oxo - 2 - phenylchroman) - Flavanones***, which cause coloration of fruits and berries:



   This group includes eriodictin and hesperidin.

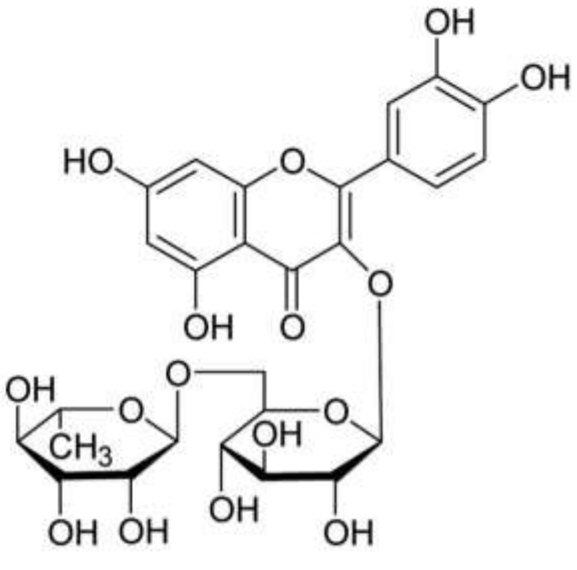
3. ***The oxysubstituted flavones are flavonols:***

   Rutin belongs to this group. All these compounds have P - vitamin activity, therefore, "vitamin P" is a conditional term that unites a large group of bioflavanoids with capillary-strengthening properties.

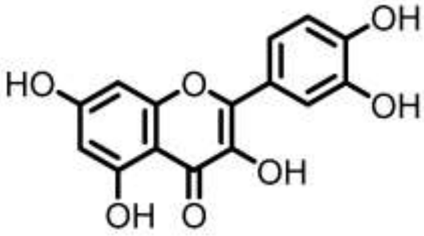


Rutin and quercetin are used in medicine. According to its chemical structure, rutin belongs to glycosides. The sugar part of its molecule - disaccharide - includes

D-glucose and L-rhamnose. The aglycon is quercetin, which is used as an individual drug substance with P-vitamin activity.



Rutin



Quercetin

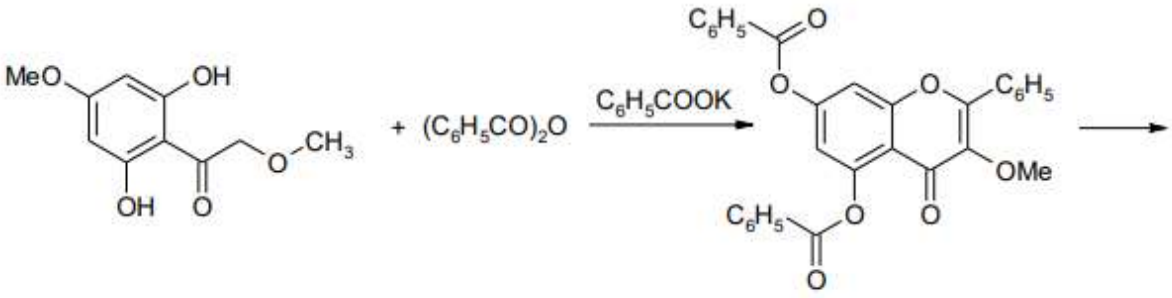
Rutin was first isolated by the Nuremberg pharmacologist Weiss (1842) from a semi-shrubby plant of the ruta family (Ruta graveolems). Later, it was isolated from the green mass of buckwheat, where its content, depending on the variety of buckwheat, ranges from 1.5 to 6% of the dry matter. Rutin is also found in the leaves of Eucaliptus nacror (about 24% per dry matter) and in the leaves of the Chinese tree Sophorica japonica with a content of up to 44.5% per dry matter.

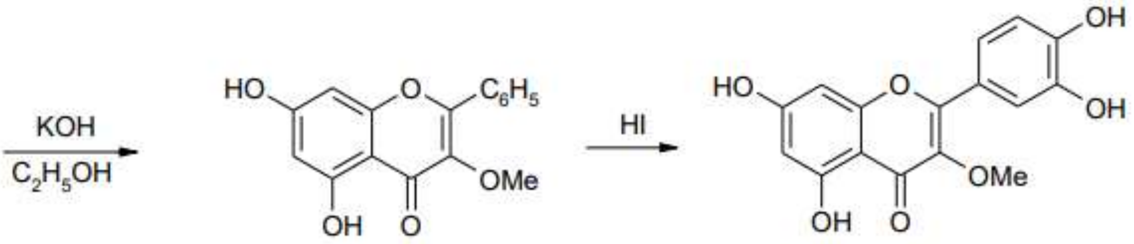
As a substance with P - vitamin activity rutin was recognized in medicine in 1944 and is used not only for the treatment of diseases associated with impaired capillary function, but also in the treatment of frostbite.

OBTAINING

Obtaining quercetin

1. Scheme of quercetin synthesis





2. Quercetin can be obtained from rutin by hydrolysis.

Obtaining rutin

Rutin is extracted with water from plant material, then separate proteins by precipitation, and rutin recrystallized. When obtaining should be taken into account that rutin in an acidic environment, especially when heated, is easily hydrolyzed to form quercetin, rhamnose and glucose.

PHYSICAL PROPERTIES

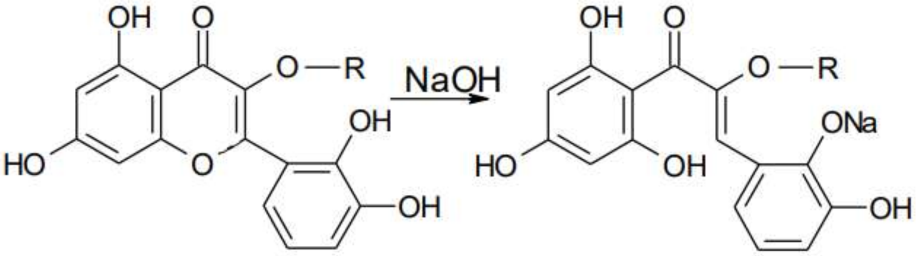
Rutin is a greenish-yellow odorless fine-crystalline powder. Practically insoluble in water and chloroform, soluble in boiling ethanol. Being a polyatomic phenol, rutin is soluble in dilute solutions of caustic alkali.

Quercetin is a yellow, fine-crystalline, odorless powder. Practically insoluble in water and chloroform, slightly soluble in ethanol. Being a polyatomic phenol, quercetin is soluble in dilute solutions of caustic alkali.

IDENTIFICATION

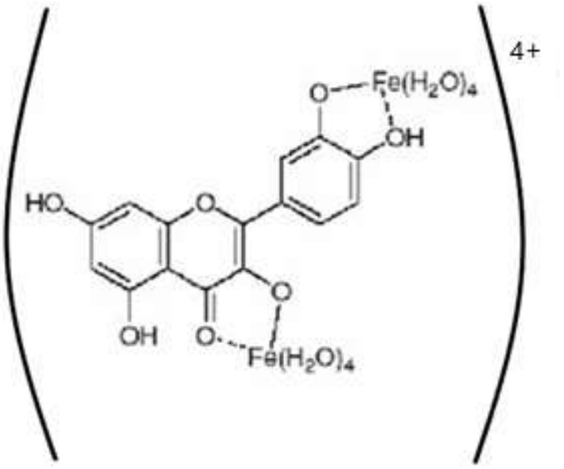
1. ***IR, UV spectrophotometry, PMR spectroscopy are used to test the authenticity of flavonoids.***
2. ***Alkaline hydrolysis***

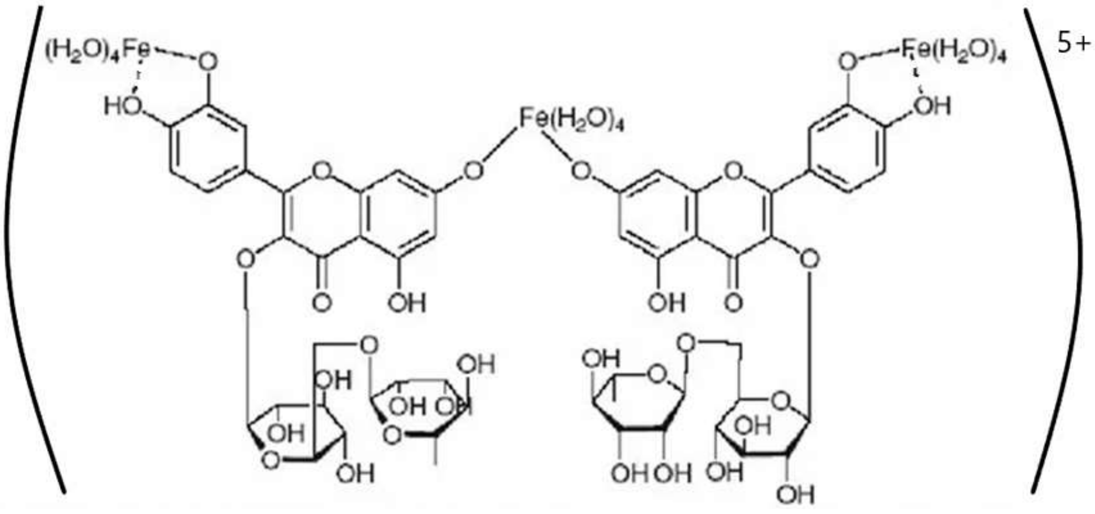
   Reaction with alkali is characteristic of all flavanoids having polyphenolic character. Rutin when dissolved in alkali solution gives yellow-orange coloring. The coloration is intensified during standing due to the transition of the flavonoid to chalcone with the opening of the heterocyclic ring:



3. *Interaction with iron chloride*

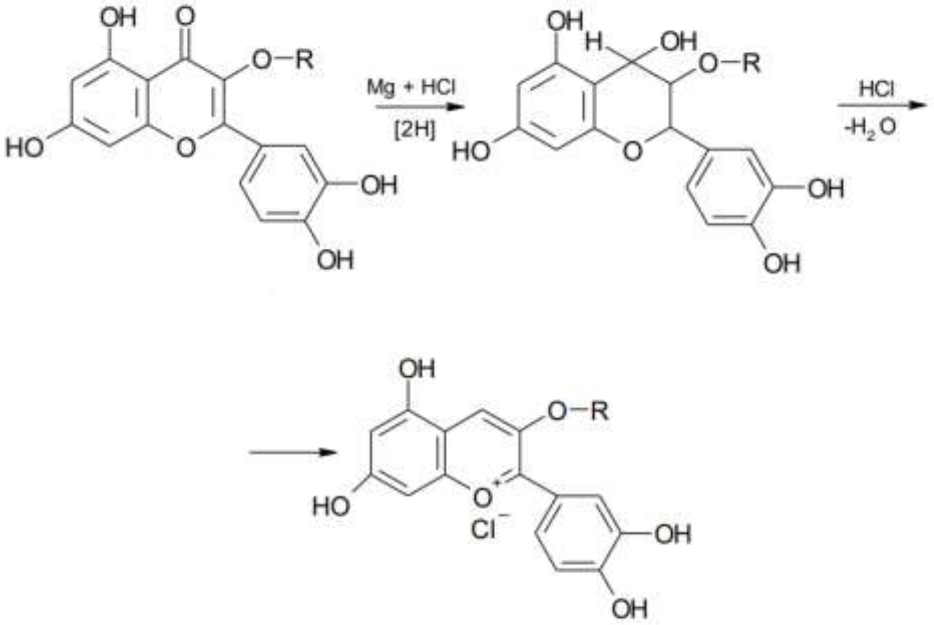
Phenolic hydroxyls in the rutin molecule cause a positive reaction with FeCl3 solution. In this case, a dark green coloring is formed, and with the subsequent addition of a few drops of alkali solution, the coloring of the solution changes to red-brown.





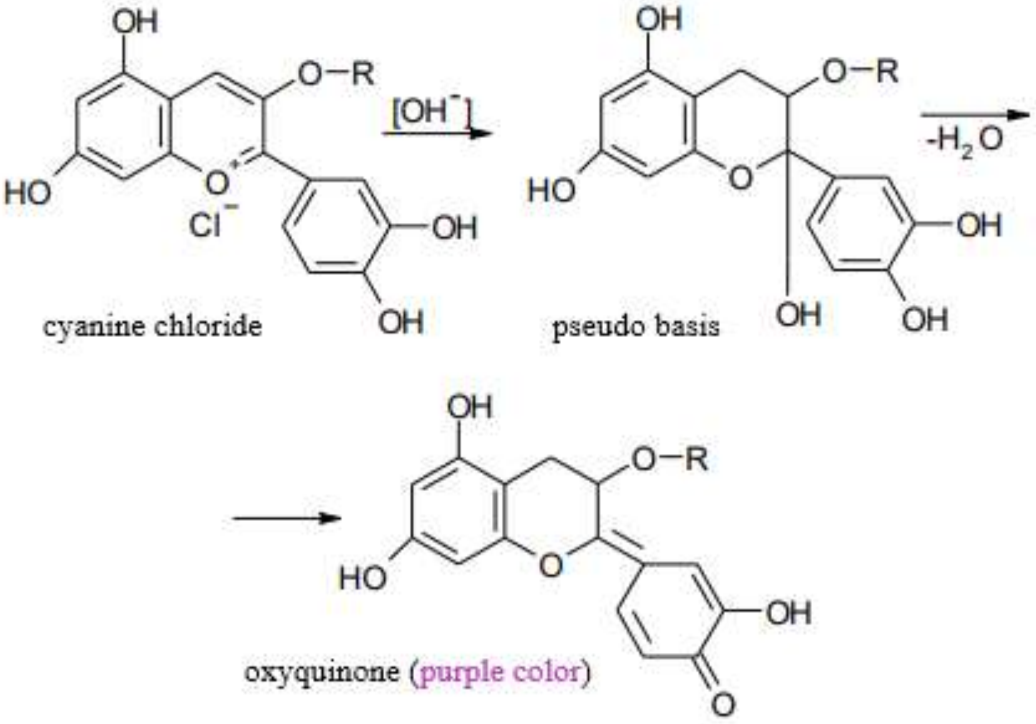
4. *Cyanine reaction*

The reaction occurs when rutin and quercetin are exposed to magnesium powder and concentrated hydrochloric acid in an alcoholic medium (red staining). It is based on the formation of colored pyrylium salts by hydrogen reduction of flavonoids, including rutin:



5. *Formation of oxyquinone and its salts*

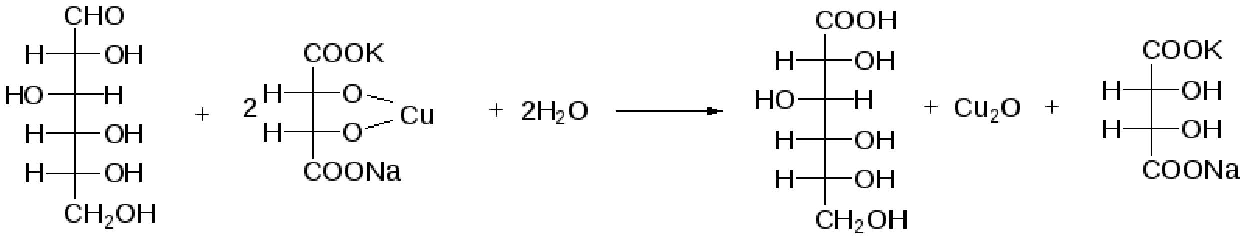
The coloration increases if an alkaline solution is added to the reaction mixture to neutral reaction of the medium. In this case, first a pseudo-base is formed, which very quickly detaches water and transforms into a quinone derivative, which causes a brighter coloring of the solution:



With excess alkali, an oxyquinone salt is formed that can dissociate, and the coloration will be deepe.

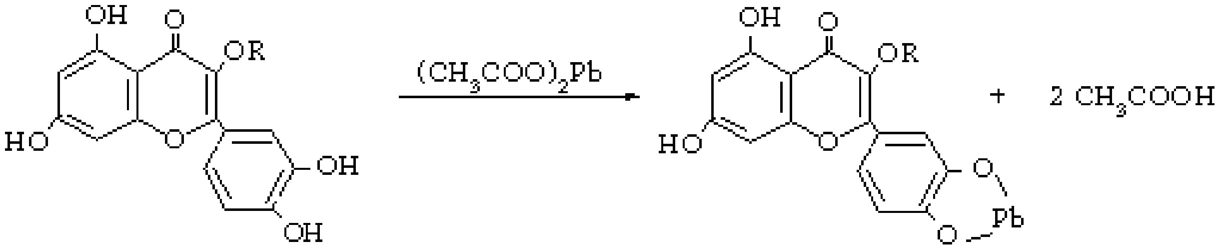
6. ***Detection of sugars after hydrolysis.***

   Being a glycoside, rutin is easily hydrolyzed under the action of dilute acids when heated. In this case, either rutinose or glucose and rhamnose are detached, which have reducing properties and give a positive reaction with Fehling's liquid (red coloring due to copper oxide).



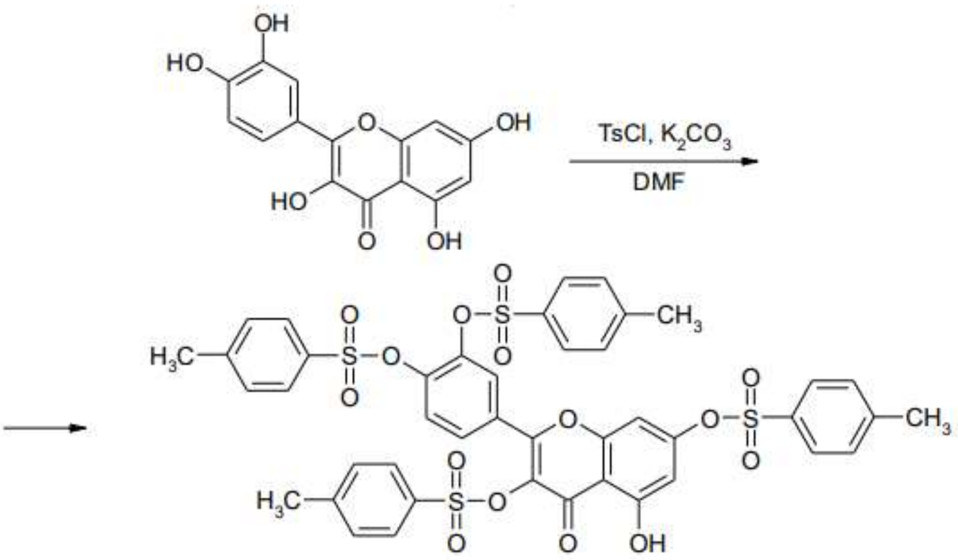
7. ***Formation of complex salts.***

   Many flavanoids are able to form complex compounds with salts of heavy metals, for example, with lead. The resulting complex compounds differ from each other in persistence, solubility, coloring, which is used both for identification and to clarify the structure of unknown compounds. For example, the interaction of rutin with lead acetate produces a precipitate of complex compounds colored yellow or orange.



8. ***Obtaining a tosyl derivative of quercetin.***

   The reaction of quercetin with p-toluenesulfochloride was carried out in DMF, in the presence of K2CO3 (room temperature; 4.5 hours). After extraction with ethyl acetate, washing and concentration, yellow crystals of tetratosylflavone have a melting point of 191.5 °C.



QUANTIFICATION

1. ***Spectrophotometric determination***
2. ***Colorimetric determination.***

   The method is based on the reactions of

   - ✓ with alkali;
   - ✓ formation of colored complex compounds.

STORAGE

Rutin and quercetin are stored in well sealed containers, in a dry place, protected from light.

MEDICAL USE

The main effect of rutin, especially in combination with ascorbic acid, is to resist capillaries and reduce vascular permeability. In addition, it takes part in the oxidative-reductive processes of metabolism, normalizes the activity of the thyroid gland, enhances the effect of ascorbic acid and promotes its accumulation in various organs.

There is information about the favorable effect of rutin in radiation sickness. Often rutin is prescribed together with ascorbic acid.