Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

SPECIAL PHARMACEUTICAL CHEMISTRY

Quinoline derivatives

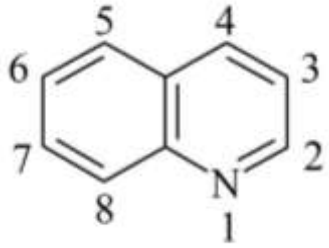
Lesson 3

VII term

Volgograd, 2023

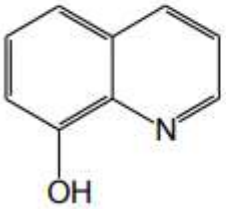
GENERAL CHARACTERISTIC

Quinoline is a condensed system formed by an aromatic benzene core and a pyridine cycle:

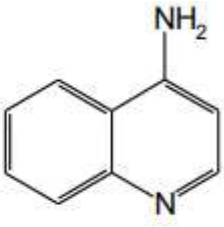


Quinoline was first isolated in 1834 from coal tar, and somewhat later A.M. Butlerov and A.N. Vyshnegradsky proved its presence in the quinine molecule. This was the impetus for research into the development of antimalarial agents in the series of quinoline derivatives.

The study of the relationship between the chemical structure and pharmacological action of various compounds has led to the production of active antiprotozoal and immunosuppressive agents among 4-aminoquinoline derivatives and effective antibacterial drugs of 8-oxyquinoline derivatives:

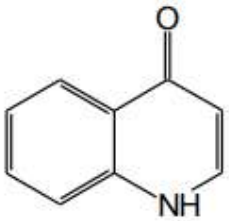


4-aminoquinoline

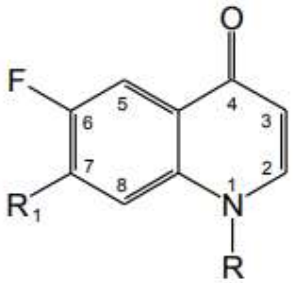


8-oxyquinoline

A major achievement of the last two decades was the creation of new effective synthetic antibacterial drugs of quinolone-4 derivatives - fluoroquinolones. The peculiarity of their chemical structure is the presence of an oxo group at position 4 of the quinoline nucleus and a fluorine atom at position 6:



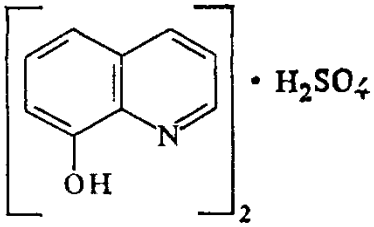
quinolone-4



fluoroquinolones

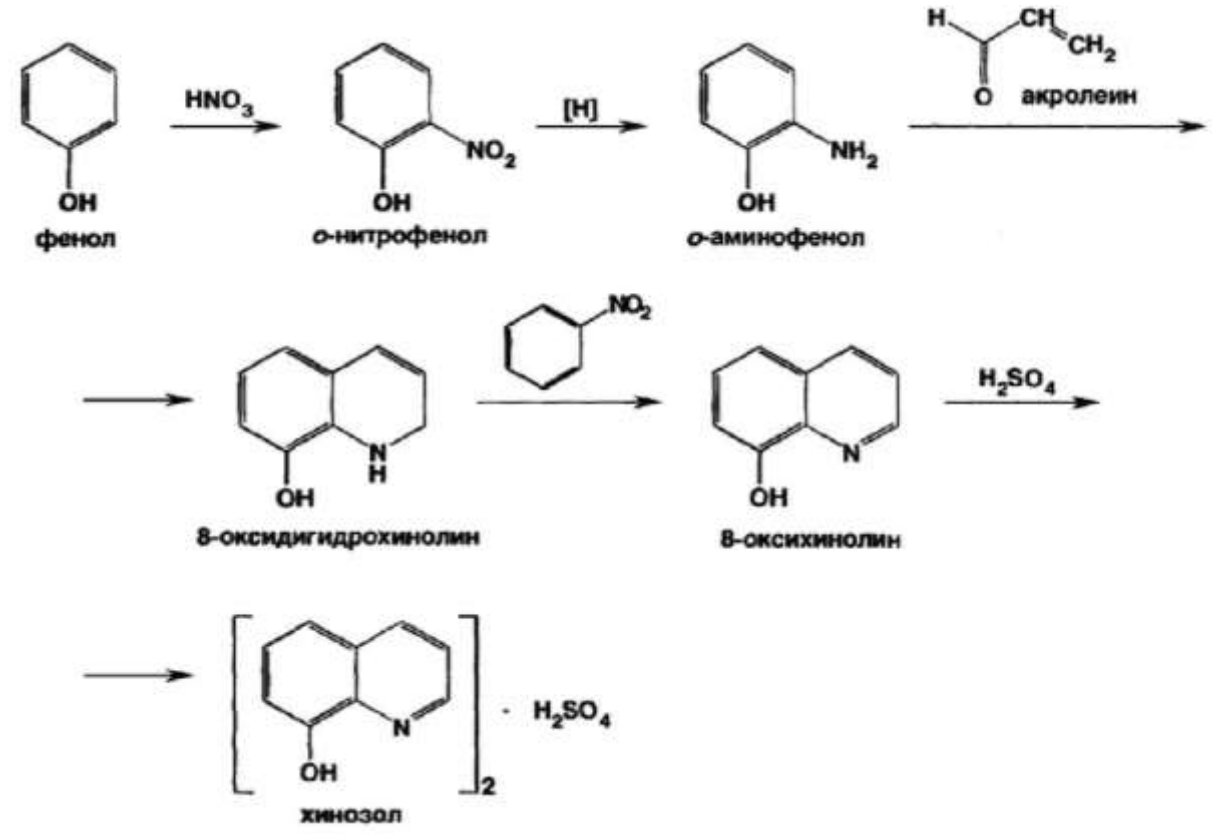
8-OXYQUINOLINE DERIVATIVES

Chinosolum



OBTAINING

For the synthesis of chinosol, phenol is used as a starting product, from which o-nitrophenol and then o-aminophenol are obtained in series. The latter is combined with acrolein according to the Scraup method. The formation of 8-oxydihydroquinoline occurs, which as a result of oxidation with nitrobenzene passes into 8-oxyquinoline. From it chinosol is obtained by acting with dilute sulfuric acid:



PHYSICAL PROPERTIES

Fine crystalline powder with lemon-yellow color and peculiar odor, easily soluble in water and ethanol, practically insoluble in ether and chloroform.

IDENTIFICATION

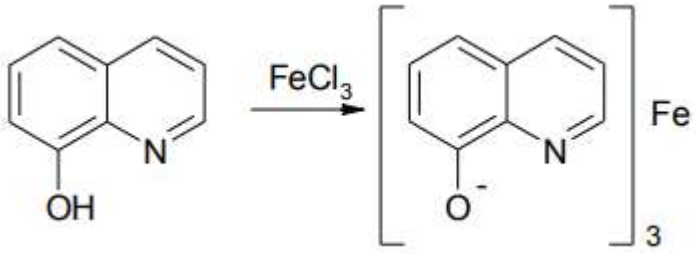
1. Instrumental methods.

IR spectra should have complete coincidence of absorption bands with absorption bands of standard samples in terms of intensity and position of bands.

UV spectra. A solution of chinosol in 0.1 M hydrochloric acid in the region of 220-270 nm should have an absorption maximum at 252 nm, and in the region of 270-400 nm - maximums at 308, 320 and 360 nm.

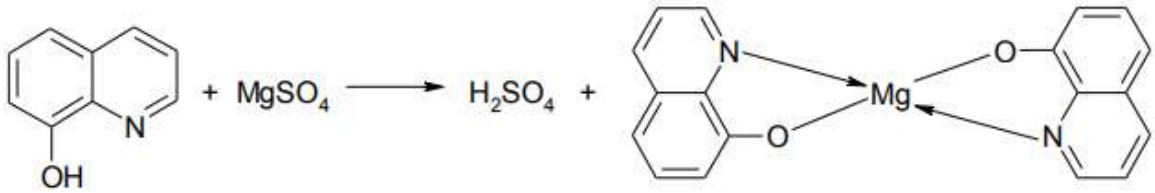
2. Interaction with ferric (III) chloride solution

The solution takes on a green coloration.



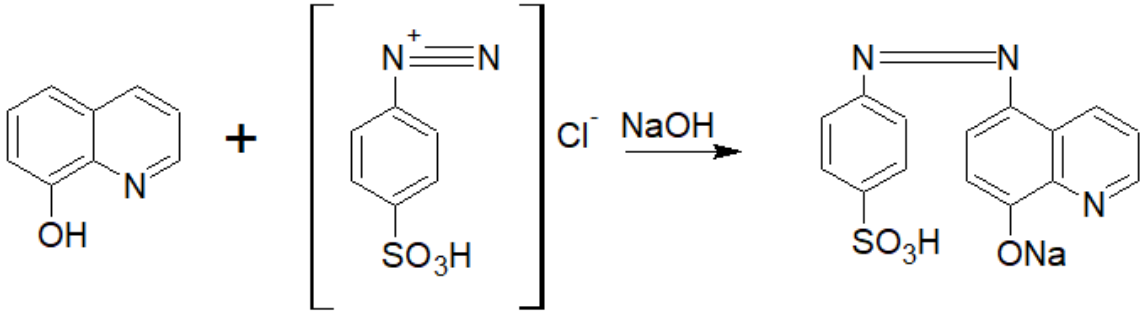
3. Formation of complex salt with metal cations

Chinosol forms colored intra-complex compounds with metal cations: magnesium (white precipitate), cadmium, copper (II), zinc, aluminum.



4. Formation of azo dye

A red-colored azo dye is formed.

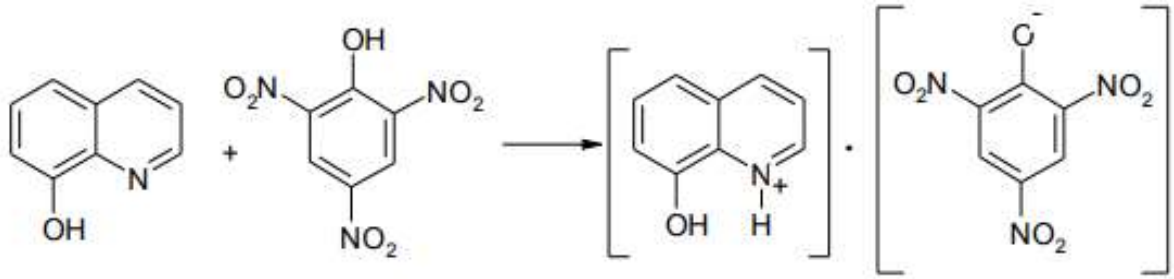


5. *Reaction with citric acid*

When chinosol is heated in a solution of citric acid and acetic anhydride, purplish-red coloring appears (reaction with tertiary nitrogen atom).

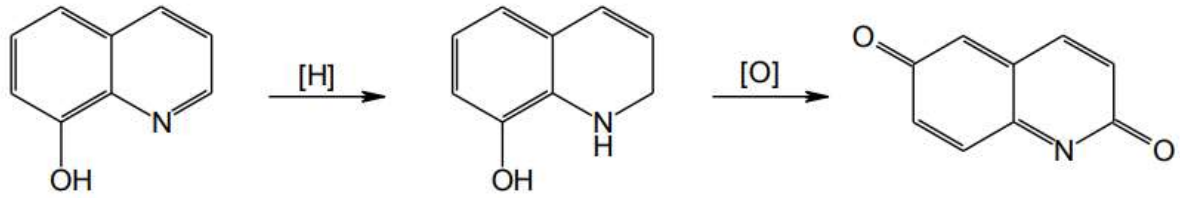
6. Reaction with common alkaloid reagents

The presence of tertiary nitrogen in the quinoline nucleus causes positive reactions of chinosol with precipitating (general alkaloid) reagents: Wagner, Meyer, Dragendorf, picric acid solution (yellow precipitate), as well as with potassium dichromate solution.



7. Formation of a quinoid structure

Chinosol in the presence of zinc dust and dilute hydrochloric acid is hydrogenated to dihydro derivatives. Subsequent addition of a few drops of perhydrol or bromine water to the filtrate leads to the gradual appearance of red-violet coloration due to the formation of a compound of quinoid structure:



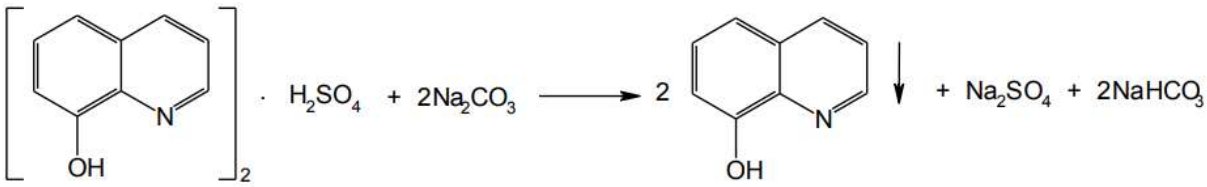
8. Detection of sulfate ion

The sulfate ion in chinosol is discovered using barium chloride solution. A white precipitate is formed.

$$H_2SO_4 + BaCl_2 = BaSO_4\downarrow + 2HCl$$

9. Precipitation of chinosol base

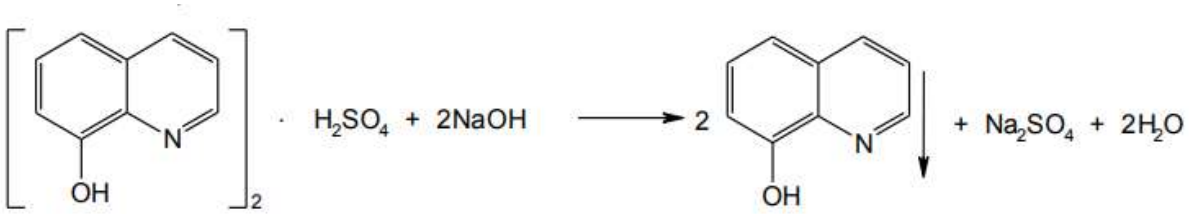
When chinosol solution is exposed to sodium carbonate solution, 8-oxyquinoline precipitates:



QUANTIFICATION

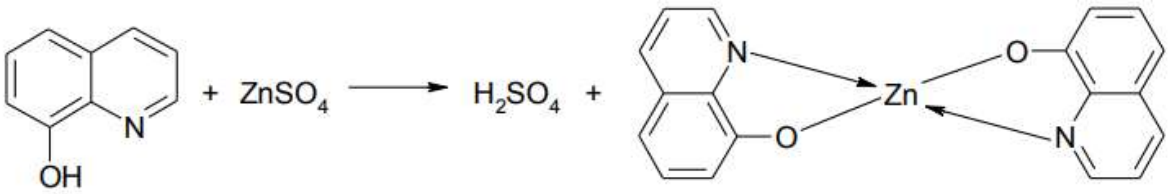
1. Neutralization

Titrated with 0.1 M sodium hydroxide solution (indicator phenolphthalein). Titration is carried out in the presence of chloroform, which is added to extract the released chinosol base (8-oxyquinoline).

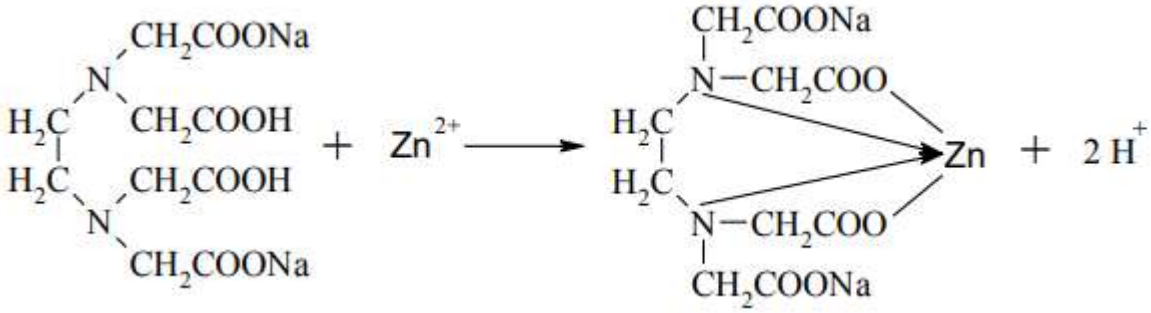


2. Complexometric titration

Chinosol is quantified by the reverse complexometric method (after conversion to base). The base is dissolved in ethanol under heating to 60oC, precipitated with an excess of 0.1 M zinc sulfate solution and buffer solution (pH 10) is added.



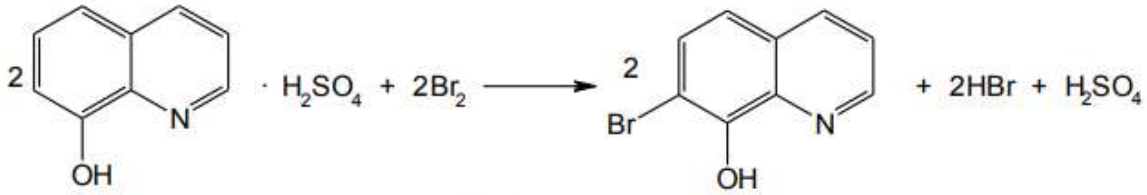
The precipitate is dissolved in chloroform, water is added and excess zinc sulfate is titrated with 0.1 M trilon B solution (indicator Eriochrome black T).



3. Bromatometric determination

The reverse bromatometric method for the determination of chinosol is based on the formation of the 7-bromo derivative. An excess of 0.1 M potassium bromate solution in the presence of potassium bromide is determined by the iodometric method:

$$KBrO_3 + 5KBr + 3H_2SO_4 \longrightarrow 3Br_2 + 3K_2SO_4 + 3H_2O$$



$$Br_2 + 2KI \longrightarrow I_2 + 2KBr$$

$$I_2 + 2Na_2S_2O_3 \longrightarrow 2NaI + Na_2S_4O_6$$

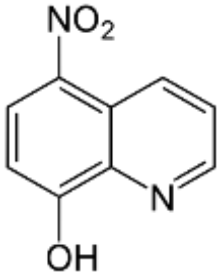
STORAGE

The medicinal substance is stored in a dry place protected from light, in well sealed containers.

MEDICAL USE

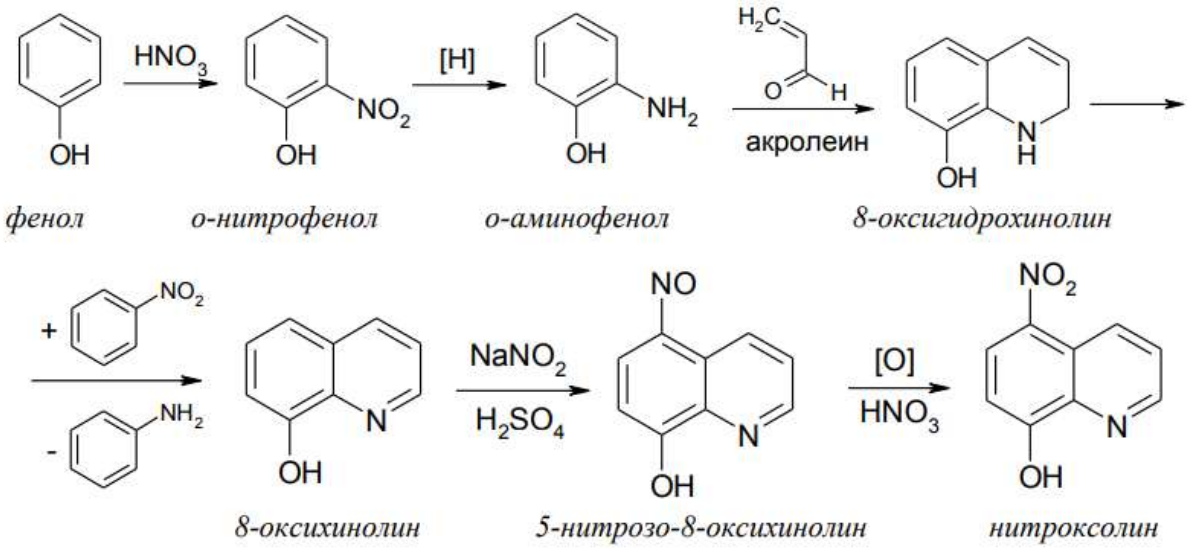
Chinosol has antiseptic properties. It is used for disinfection of hands, rinses, sphincters. It is included in the composition of ointments, powders.

Nitroxoline



OBTAINING

In the synthesis of nitroxoline, 8- oxyquinoline, which is nitrosated with sodium nitrite in acidic medium with subsequent oxidation of the nitroso group to the nitro group:



PHYSICAL PROPERTIES

Fine crystalline powder with yellow coloring and peculiar odor. Nitroxoline is practically insoluble in water, slightly soluble in ethanol. Nitroxoline is slightly soluble in ether and moderately soluble in chloroform.

IDENTIFICATION

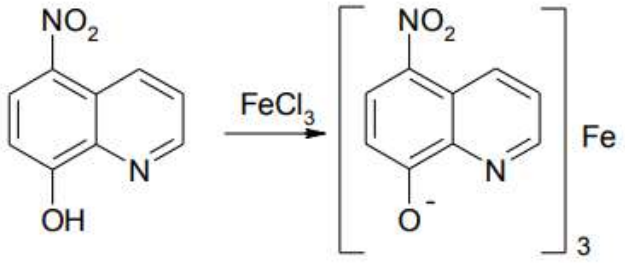
1. Instrumental methods

The IR spectra should completely match in position and relative intensities of the IR bands of the standard sample.

The UV spectrum of 0.0005% solution of nitroxoline in ethanol-buffer solution mixture with pH 9.18 (98:2) in the region of 220-500 nm has absorption maxima at 249, 341, 452.5 nm and two shoulders - from 228 to 238 nm and from 258 to 268 nm.

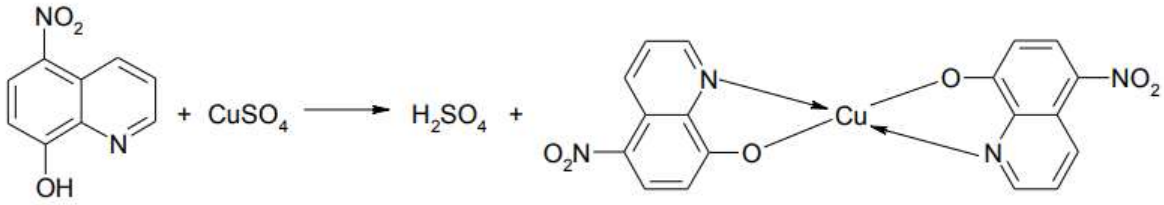
2. Reaction with ferric (III) chloride

Nitroxoline has a phenolic hydroxyl in its molecule, so the FS recommends a general color reaction with iron (III) chloride solution to test its authenticity. The nitroxoline solution turns green:



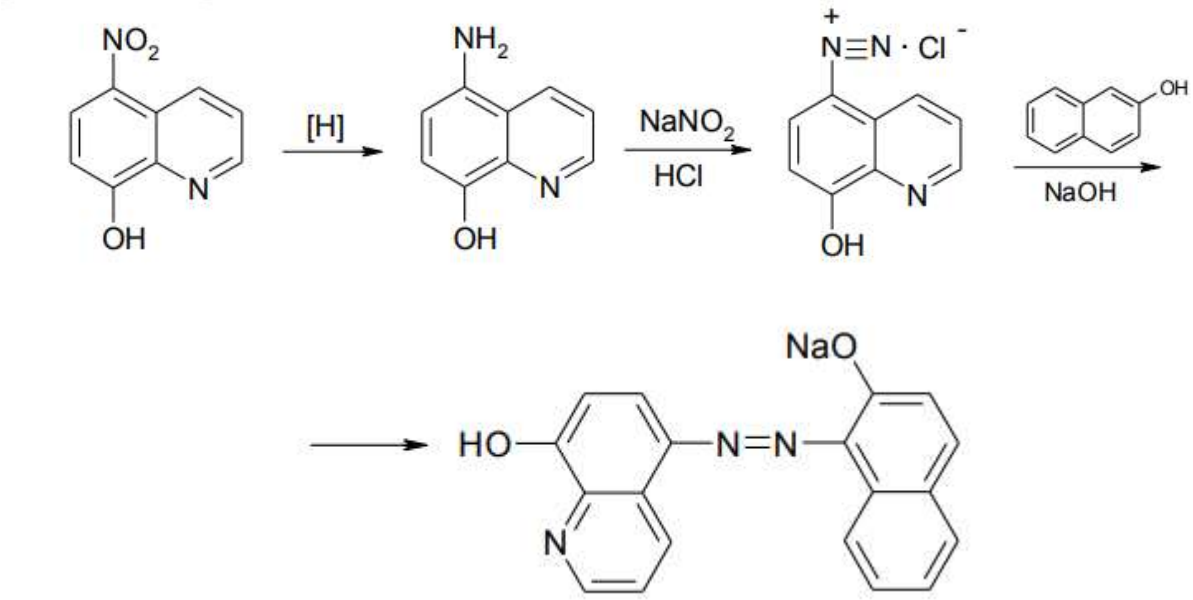
3. Complex salt formation with metal cations

Nitroxoline forms colored intra-complex compounds with metal cations: magnesium, cadmium, copper (II) (green precipitate), zinc, aluminum:



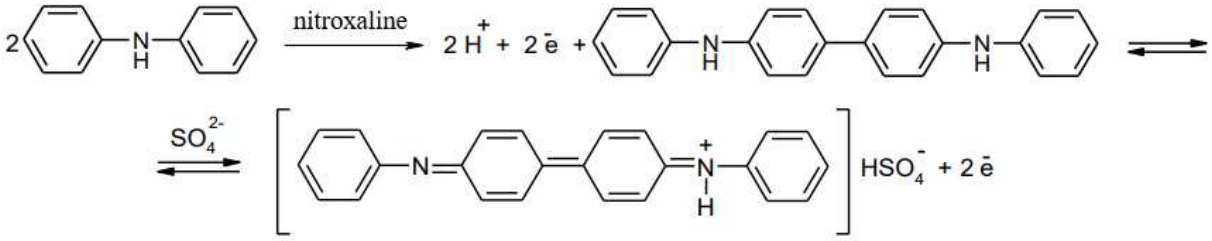
4. Formation of azo dye after reduction

After hydrogenation of the nitro group in the nitroxoline molecule to an aromatic amino group, a diazotization and azo-coupling reaction with an alkaline solution of β-naphthol is performed. A red-orange coloration appears.



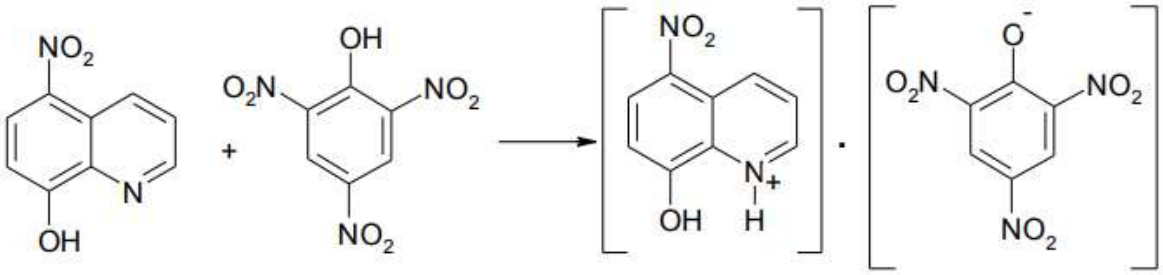
5. Reaction with diphenylamine in sulfuric acid

The presence of a nitro group in the nitroxaline molecule can be confirmed by reaction with diphenylamine in the presence of concentrated sulfuric acid. Initially, in the presence of nitroxoline, irreversible oxidation of diphenylamine to diphenylbenzidine occurs, then reversible oxidation of benzidine to blue-colored diphenyldiphenoquinondiimine occurs:



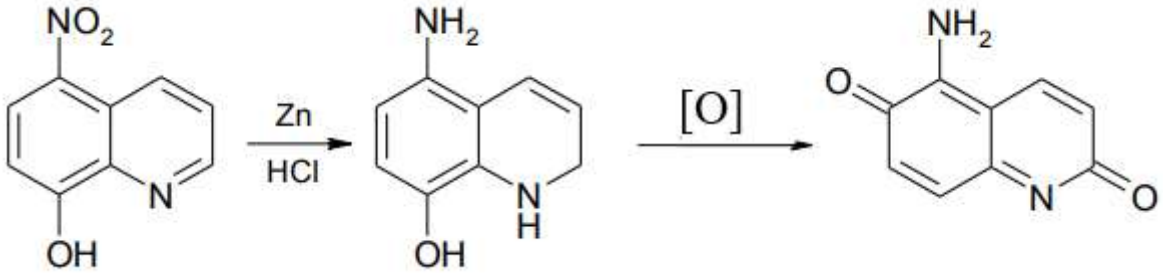
6. *Reaction with general alkaloid reagents*

The presence of tertiary nitrogen in quinoline nucleus causes positive reactions of nitroxoline with precipitating (general alkaloid) reagents: Wagner, Meyer, Dragendorf, picric acid solution (yellow precipitate).



7. Oxidation with perhydrol after hydrogenation

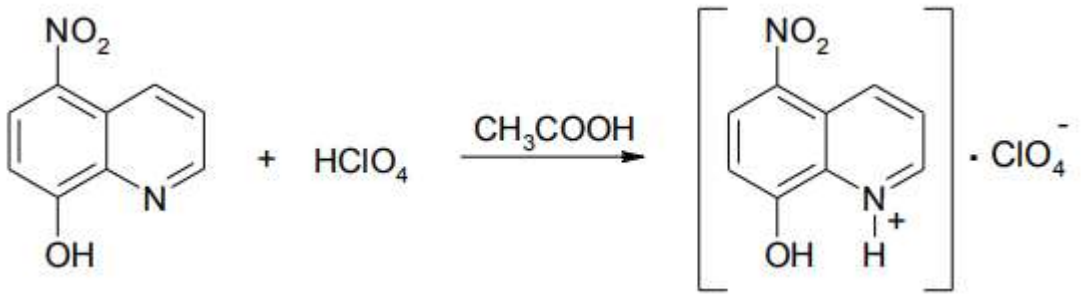
Nitroxoline in the presence of zinc dust and dilute hydrochloric acid is hydrogenated to a dihydro derivative. Subsequent addition of a few drops of perhydrol or bromine water to the filtrate leads to the gradual appearance of red-violet coloration due to the formation of a compound of quinoid structure:



QUANTIFICATION

Non-aqueous titration

Nitroxoline is quantitatively determined by non-aqueous titration using acetic anhydride as solvent and 0.1 M chloric acid solution as titrant. Determination is performed in the presence of formic acid and malachite green indicator.



STORAGE

The medicinal substance is stored in a dry place protected from light, in well sealed containers.

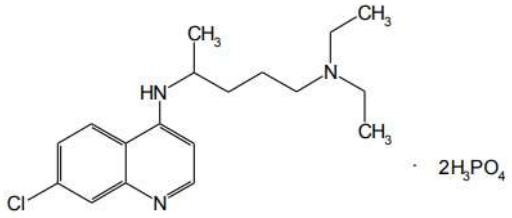
MEDICAL USE

Nitroxoline belongs to the number of antibacterial drugs. Nitroxoline is used as an antimicrobial agent for the prevention and treatment of genitourinary tract infections orally in the form of tablets of 0.05 grams.

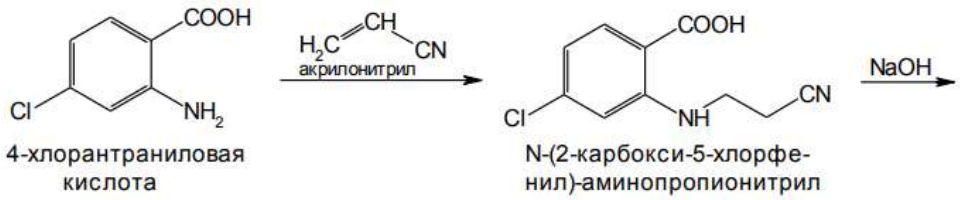
4-AMINOQUINOLINE DERIVATIVES

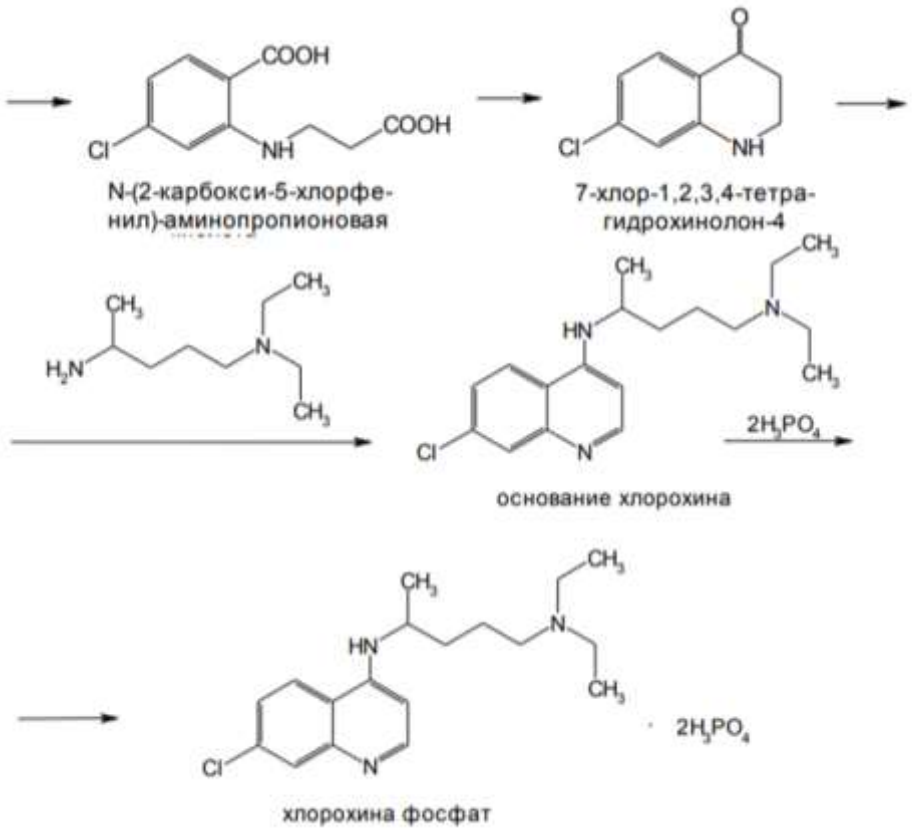
Among the 4-aminoquinoline derivatives, the drugs chloroquine phosphate (hingamine) and hydroxychloroquine sulfate (plaquenil) are used.

Hingamin



OBTAINING





PHYSICAL PROPERTIES

White or white with a slight creamy tinge, odorless or almost odorless crystalline powder. T.pl. 214,5-218°C (with decomposition). Easily soluble in water and very slightly soluble in organic solvents: ethanol, ether, chloroform.

IDENTIFICATION

1. UV spectrophotometry

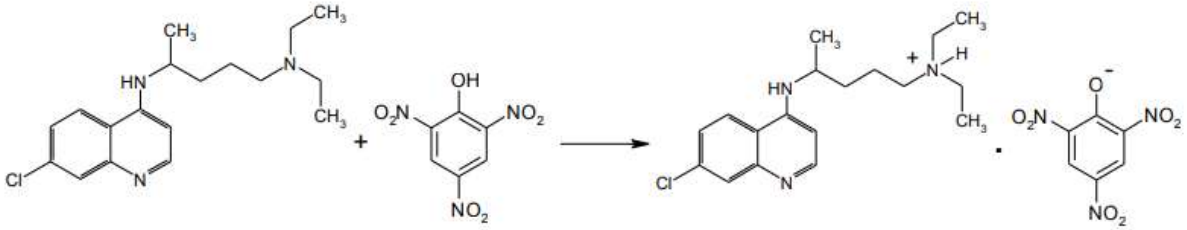
Chloroquine phosphate (hingamine) has three absorption maxima in the UV region (240-360 nm): at 257, 329, 343 nm (0.001% solution in 0.01 M hydrochloric acid solution) with optical densities of about 0.29, 0.32, and 0.37. The ratios of these values at 257 and 329 nm to the absorbance at 343 nm should be in the range 0.86-0.95.

2. Precipitation of the bases of chingamine

A number of precipitation reactions are known by which the authenticity of chloroquine phosphate and hydroxychloroquine sulfate can be confirmed. Bases precipitate from solutions of salts under the action of alkali. (*Write the reaction in your notebook*).

3. Action of common alkaloid reagents

Being nitrogen-containing organic bases, they give positive reactions with precipitating (general alkaloid) reagents: Wagner, Meyer, Dragendorf. With picric acid they form picrates (yellow precipitates). Chloroquine phosphate picrate has a melting point of 204-207°C.



4. Detection of phosphate ion

- Phosphate ion is precipitated from solutions by silver nitrate to form a yellow precipitate soluble in dilute nitric acid and ammonia solution.

$$PO_4^{3-} + 3\,Ag^+ \longrightarrow Ag_3PO_4\downarrow$$

- Phosphate ion in the presence of ammonium chloride, forms with magnesium salts a white crystalline precipitate of magnesium-ammonium phosphate, soluble in acetic acid:

$$MgSO_4 + Na_2HPO_4 + NH_4Cl \longrightarrow MgNH_4PO_4\downarrow + Na_2SO_4 + HCl$$

- Solutions of phosphates in dilute nitric acid give with ammonium molybdate on heating yellow coloring, when standing yellow crystalline precipitate of ammonium phosphoromolybdate is released:

$$H_3PO_4 + 12\,(NH_4)_2MO_4 + 21HNO_3 \longrightarrow 21\,NH_4NO_3 + 12\,H_2O + \\ + (NH_4)_3PO_4 \cdot 12\,MoO_3\downarrow$$

QUANTIFICATION

1. Non-aqueous titration

The quantitative determination of chloroquine phosphate is performed by the non-aqueous titration method. MF recommends the use of glacial acetic acid (heated with reflux condenser) and dioxane as solvent. The titrant is 0.1 M chloric acid solution.

Crystal violet indicator - for visual or calomel electrode - for potentiometric determination of the end point of titration. Chloroquine phosphate is determined in the medium of glacial acetic acid only, using the same titrant and indicator.

2. UV-visible spectrophotometry

The US Pharmacopeia recommends UV-visible spectrophotometry for the quantitative determination of hydroxychloroquine sulfate. The measurement is performed at a wavelength of 343 nm relative to the solvent - hydrochloric acid (1:100). Calculations are carried out according to a standard sample.

STORAGE

Chloroquine phosphate and hydroxychloroquine sulfate are stored according to List B, in well-closed containers of orange glass, protected from light. They gradually color in the light.

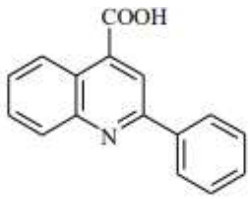
MEDICAL USE

Chloroquine phosphate and hydroxychloroquine sulfate are effective antiprotozoal and immunosuppressive agents. They have therapeutic and prophylactic antimalarial effect on both sexless and sexual forms of malarial plasmodia. They are also prescribed in the treatment of arthritis, lupus erythematosus and others. Produced chloroquine phosphate in tablets of 0.25 g and as a 5% solution in ampoules of 5 ml for injection, and hydroxychloroquine sulfate in tablets of 0.2 g.

4-CARBOXYQUINOLINE DERIVATIVES

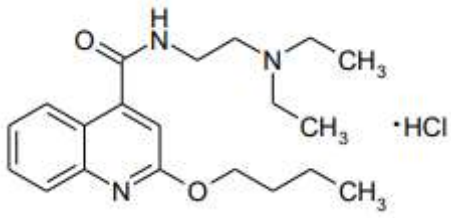
(CINCHONINIC ACID)

Cinchophthene (Cinchophtnum) 2-phenyl-cinchoninic acid



Used for gout, rheumatism, neuralgia.

Sovcain (Sovcainum) β-diethylamino-ethylamide 2-butoxycinchoni new acid hydrochloride

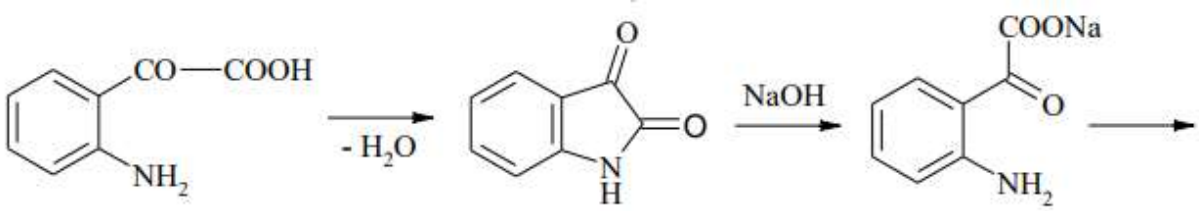


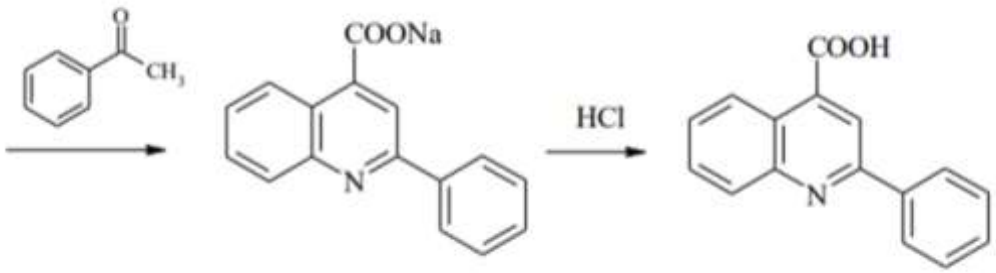
In surgery for local Anesthesia and spinal anesthesia.

Cinchophthene

OBTAINING

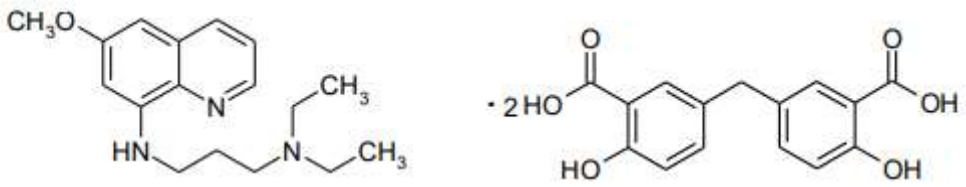
It was first obtained in 1887. It has been used in medicine since 1908. There are various methods of obtaining cinchofen, but the most common method is from isatin.





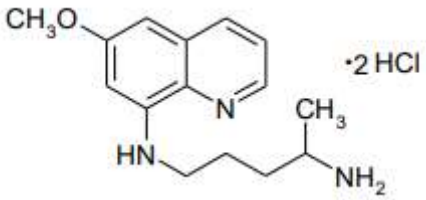
8-AMINOQUINOLINE DERIVATIVES

Plasmocid (Plasmocidum) 6-methoxy-8-(3'-diethylaminopropylamino)-quinoline di- (methylene bis-salicylate)



For the treatment of three-day and tropical malaria.

Chinocid (Chinocium) 6-methoxy-8-(4-aminopentyl)-aminoquinoline dihydrochloride



For the treatment of three-day and four-day malaria.