Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical, Toxicological Chemistry
Pharmacognosy and Botany

SPECIAL PHARMACEUTICAL CHEMISTRY

Hydroxyphenylalkylamines

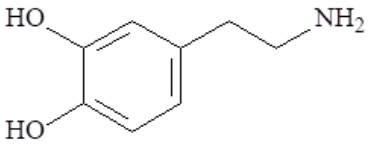
Lesson 3

IX term

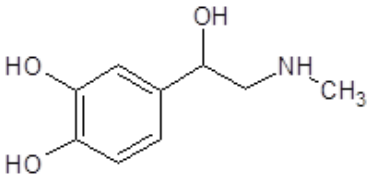
Volgograd, 2024

HORMONES OF THE ADRENAL MEDULA

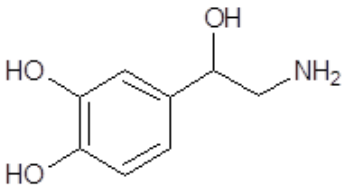
Adrenal medullary hormones, like thyroid hormones, are derivatives of aromatic amino acids. Hormones such as epinephrine, norepinephrine and dopamine are collectively known as catecholamines and are synthesised from a single precursor, tyrosine. Tyrosine is formed from phenylalanine by the phenylalanine hydroxylase reaction. This reaction is catalysed by a polyfunctional complex that includes phenylalanine hydroxylase and folate and dihydropterin reductases.



Dopamine



Epinephrine

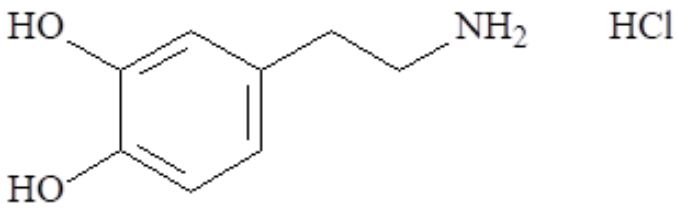


Norepinephrine

Dopamine, epinephrine (adrenaline), epinephrine hydrotartrate, norepinephrine hydrotartrate are used as drugs.

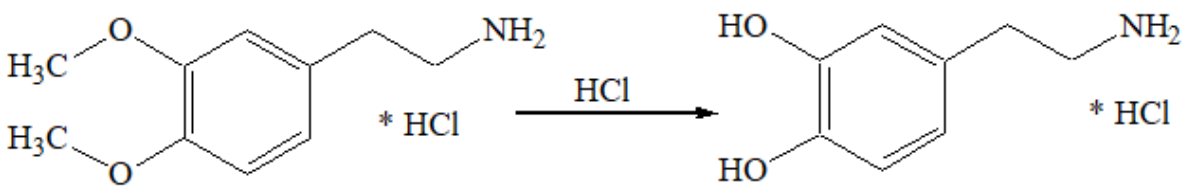
DOPAMINE HYDROCHLORIDE

Dopamini hydrochloridum



Obtaining

Dopamine is obtained by treating homoveratrilamine hydrochloride with hydrochloric acid at 100-115°C:



Physical properties

White or cream-coloured, odourless, crystalline powder. Melting point 245-259°C (with decomposition). Freely soluble in water, slightly soluble or soluble in 96 % alcohol, moderately soluble in acetone.

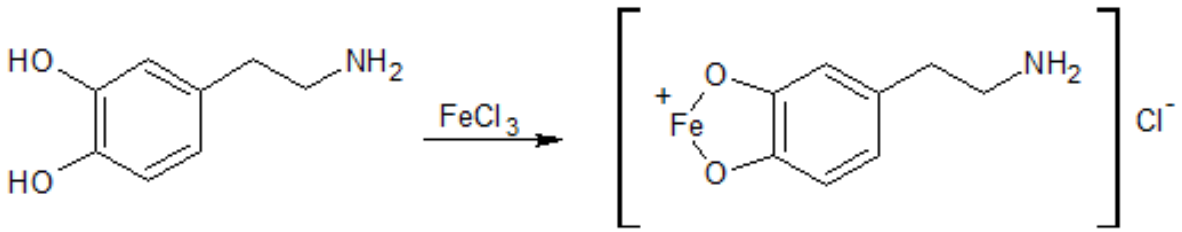
Identification

1. ***IR and UV spectrometry***

   The absorption bands of the IR spectrum should be fully consistent with the spectral figure in the pharmacopoeia monograph.

   The UV spectrum of a 0.005% solution of dopamine in 0.1M hydrochloric acid in the 230-300 nm region should have an absorption maximum at 280 nm and an absorption minimum at 250 nm in methanol.

2. ***Interaction with iron (III) chloride***



   An emerald green colour appears. If 1 drop of ammonia solution is added to the test tube, the colour changes to cherry red.

3. ***Formation of azo dye***

4. ***Interaction with ninhydrin***

   Yellow stains appear.

5. ***Detection of chloride ion***

   The chloride ion is detected with silver nitrate solution. A white, curdled precipitate is formed.

$$HCl + AgNO_3 \rightarrow AgCl\downarrow + HNO_3$$

Purity test

1. Determine the presence of impurity of the starting product of synthesis - homoveratrilamine (not more than 0.8%). The test is carried out by TLC on plates with powdered cellulose in the system n-butanol - glacial acetic acid - water (40:10:50). After drying and exposure, the impurity stain should not exceed the witness stain (in size and colour intensity). The HPLC method is also used to detect this impurity.

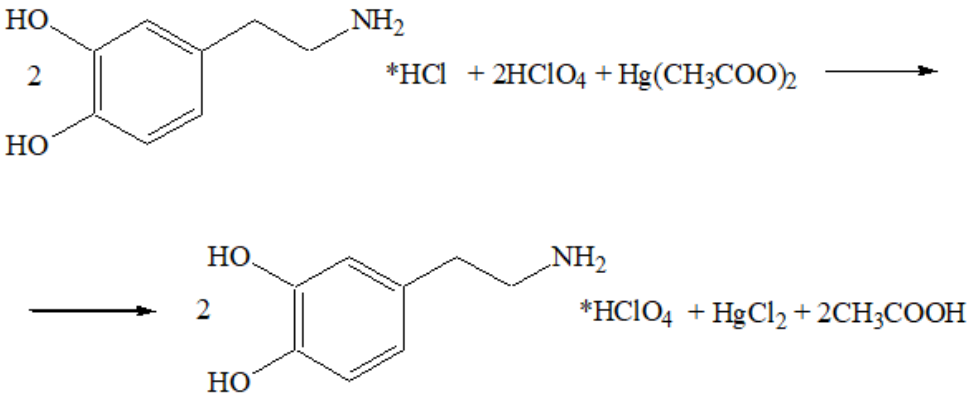
2. Determine the content of sulphates and heavy metals.
3. Determine microbiological purity and bacterial endotoxins (for parenteral drugs).

Assay

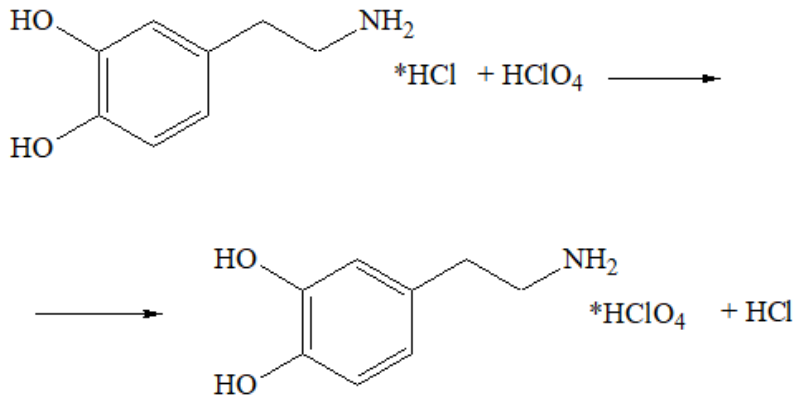
Non-aqueous titration

Dopamine is quantified by non-aqueous titration in glacial acetic acid with mercury acetate (A). A mixture of formic acid and acetic anhydride can be used as a medium (B). Titrate with 0.1M perchloric acid solution (indicator methyl violet or crystal violet). The end point of the titration can be determined potentiometrically.

Scheme A



Scheme B



Storage

As dopamine is easily oxidised by light and atmospheric oxygen, it should be stored away from light in hermetically sealed orange glass containers or in sealed ampoules.

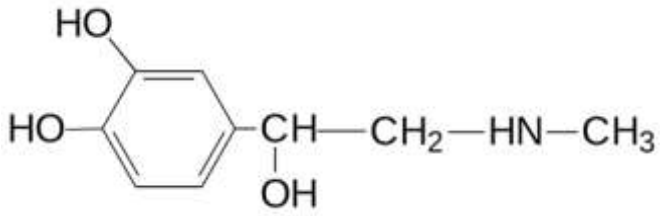
Medical use

Dopamine hydrochloride is used as a cardiac stimulant in shock. It is also used to improve haemodynamics in acute heart failure, renal failure, etc. It is usually given as a 0.5% or 4% solution (0.025 or 0.2 g).

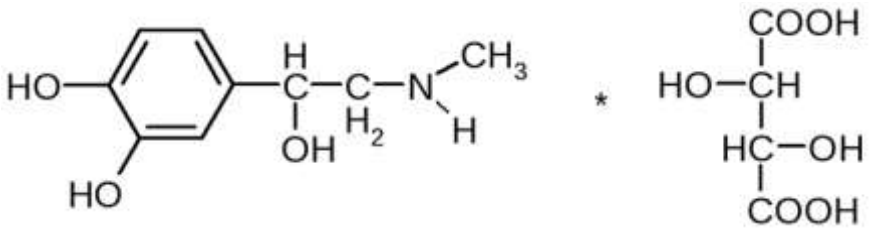
Dopamine hydrochloride is available as 0.5%, 1%, 4% solutions in ampoules.

ADRENALINE (EPINEPHRINE)

ADRENALINE (EPINEPHRINE) HYDROTARTRATE



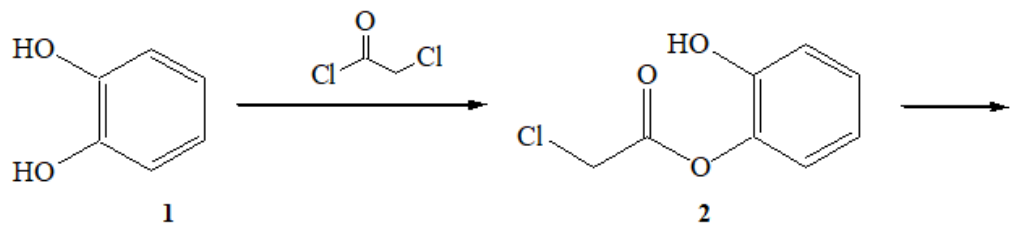
Adrenaline



Adrenaline hydrotartrate

Obtaining

Adrenaline intended for medical purposes is obtained synthetically. The initial product of the synthesis is pyrocatechin (1), which is heated with monochloroacetic acid chlorohydride in alkaline medium. This yields pyrocatechin-monochloroacetate (2), which is rearranged into chloromethyl -3,4-dioxiphenyl ketone (3). On interaction of the resulting compound (3) with methylamine, adrenalone (4) is obtained. When adrenalone is reduced, adrenaline (5) is obtained.



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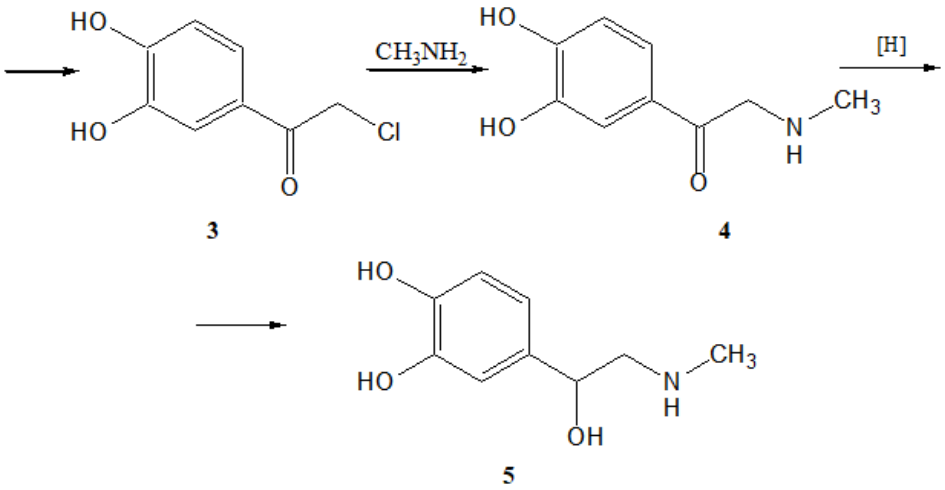


Adrenaline is optically active. Natural adrenaline is a left-handed isomer, synthetic adrenaline is a racemate. The racemates obtained during synthesis are separated with tartaric acid.

Physical properties

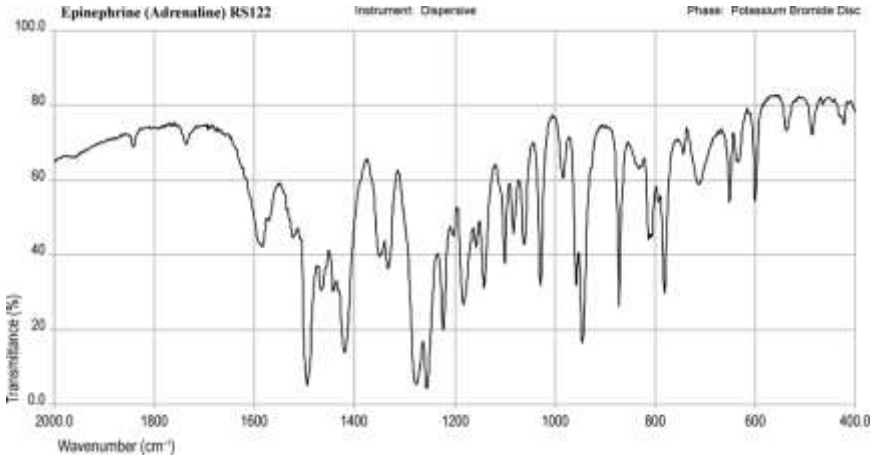
Adrenaline is a white or creamy-white odourless fine crystalline powder. Changes colour under the influence of air and light. Specific rotation from -50 to -54° (4% solution in 1 M hydrochloric acid). Epinephrine is very slightly soluble in water, moderately soluble in 0.1 M hydrochloric acid, practically insoluble in ethanol and chloroform.

Adrenaline hydrotartrate is white or white with greyish tinge, odourless crystalline powder. Melting point is 147-152°C (with decomposition). Easily changed under the action of light and air oxygen. Easily soluble in water, slightly or very slightly soluble in 96% alcohol, practically insoluble in chloroform.

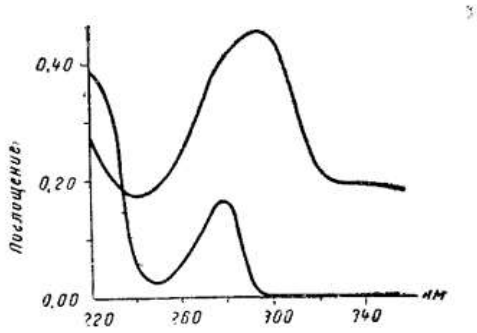
Identification

1. IR and UV spectrometry

The absorption bands of the IR spectrum should be fully consistent with the spectral figure in the pharmacopoeia monograph.



The UV spectrum of a 0.005% solution of adrenaline in 0.1 M hydrochloric acid in the 230-300 nm region should have an absorption maximum at 279 nm.

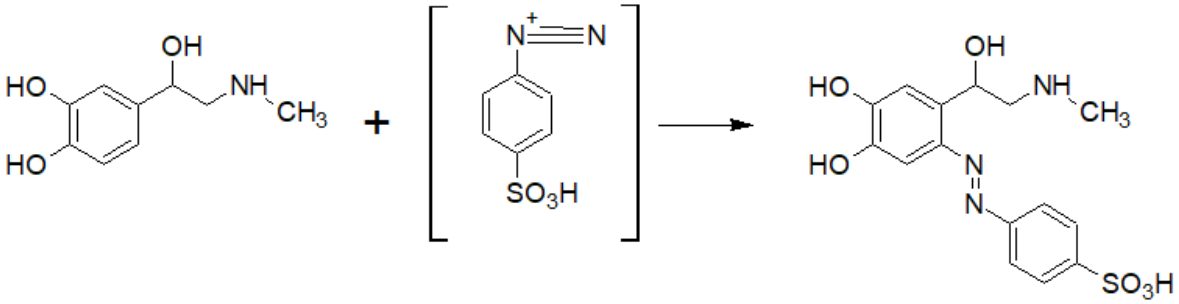


Ультрафиолетовый спектр адреналина
а — раствор в 0,1 н. соляной кислоте;
б — раствор в 0,1 н. едком натре.

2. ***Determine the specific rotation***

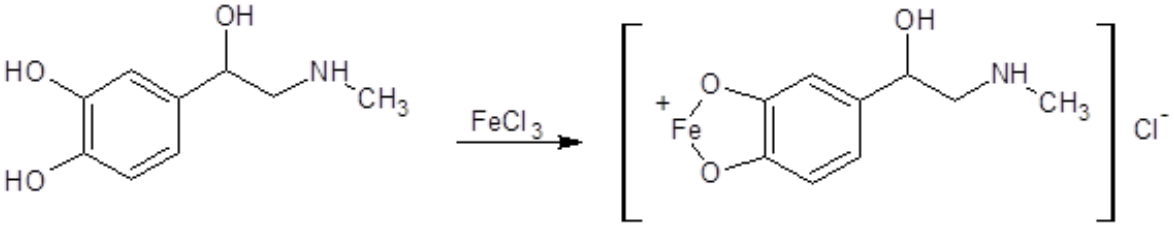
   Specific rotation in 0.5N hydrochloric acid solution should be -48° to -54°

3. ***Formation of azo dye***



4. ***Interaction with iron chloride***

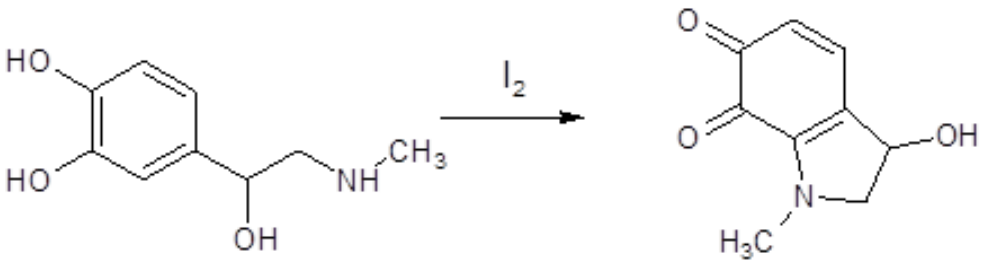
   With iron (III) chloride an emerald green colouring is formed, which on addition of 1 drop of ammonia solution changes to cherry-red and then orange-red.



5. ***Oxidation reaction with iodine solution (formation of coloured adrenochrome)***

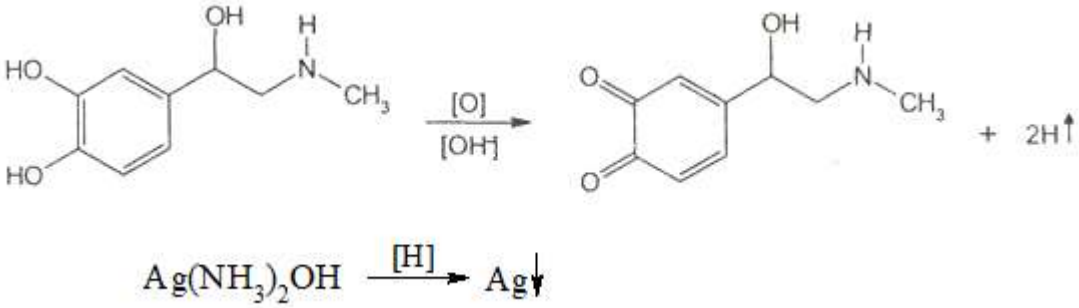
   When iodine solution is added to the drug solution in the presence of hydrotartrate buffer solution with pH 3.56, it forms adrenochrome of dark

red colour, at pH 6.5 - red-violet colour. The colouring is retained (at pH 3.56) after addition of 0.1 m sodium thiosulphate solution.



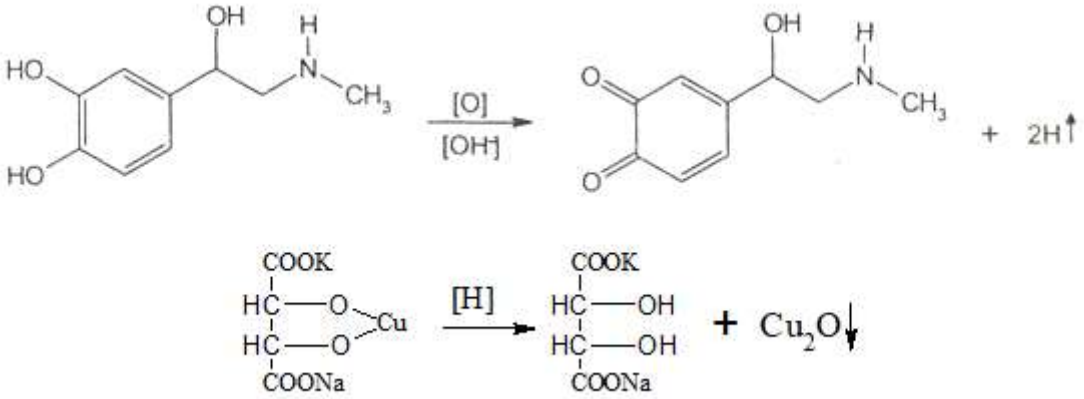
6. *The 'silver mirror' reaction*

A black precipitate is formed



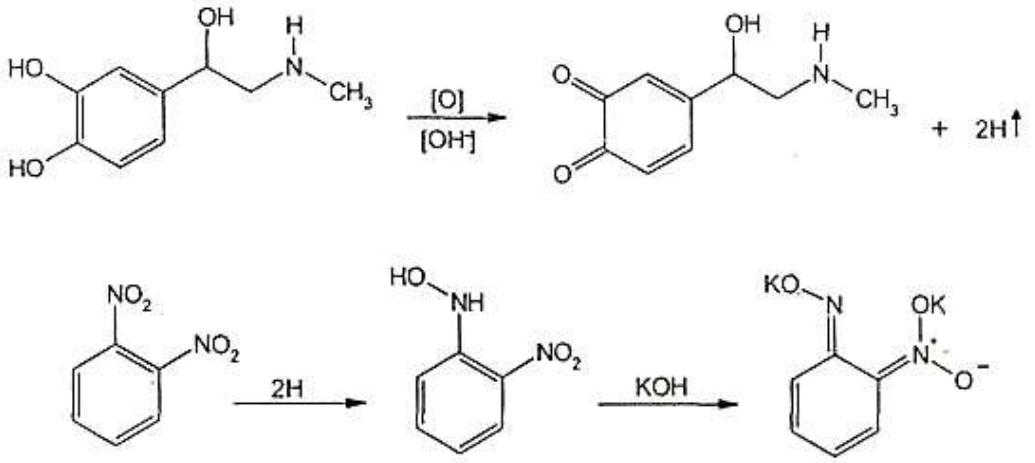
7. *Reaction with Fehling's reagent*

A brick-red precipitate is formed



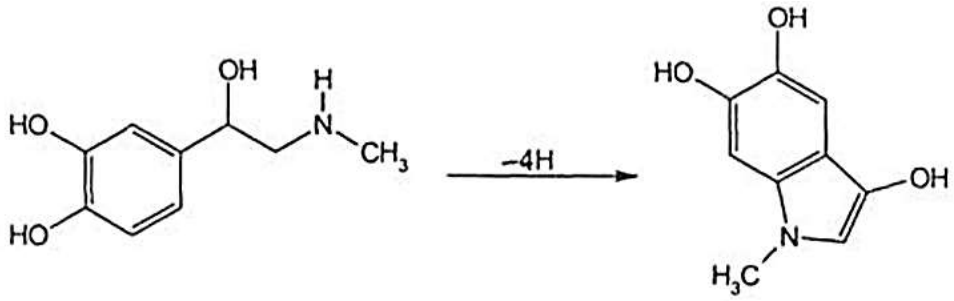
8. *Interaction with 1,2-dinitrobenzene*

The reduction of 1,2-dinitrobenzene to blue-violet coloured compounds of o-quinoid structure takes place:



9. Adrenolutine formation

When a small amount of alkali is added to a solution of adrenaline, its oxidation products (adrenolutin) fluoresce yellow-green:



10. Colour reactions:

- With a-nitroso-b-naphthol gives a reddish brown colour;

- with ninhydrin gives a yellow colour;

- if the adrenaline bitartrate solution is mixed with a 4% solution of mercuric sulphate, it gradually turns pink;

- Specific for adrenalin is the reaction with a reagent prepared by rubbing yellow mercuric oxide and potassium thiocyanate in dilute nitric acid. When the reagent and adrenalin are brought to the boil, an intense red or purple colour appears.

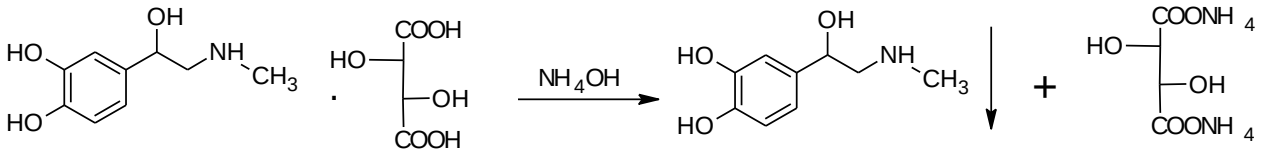
- With ammonium molybdate, sodium nitrite in the presence of diethylene-triaminepentaacetic acid has been used for the photometric determination of adrenalin at a wavelength of 465 nm.

- The addition of concentrated sulphuric acid and resorcinol produces a cherry red colour.

11. Interaction with common alkaloid reagents (Write reactions)

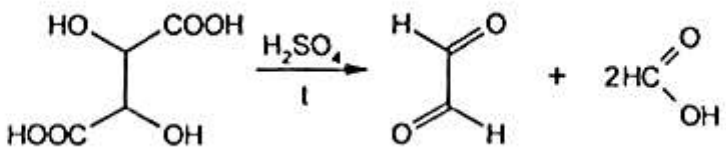
12. Base isolation reaction

Ammonia solution is used to perform this test, as alkalis produce soluble phenoxides.

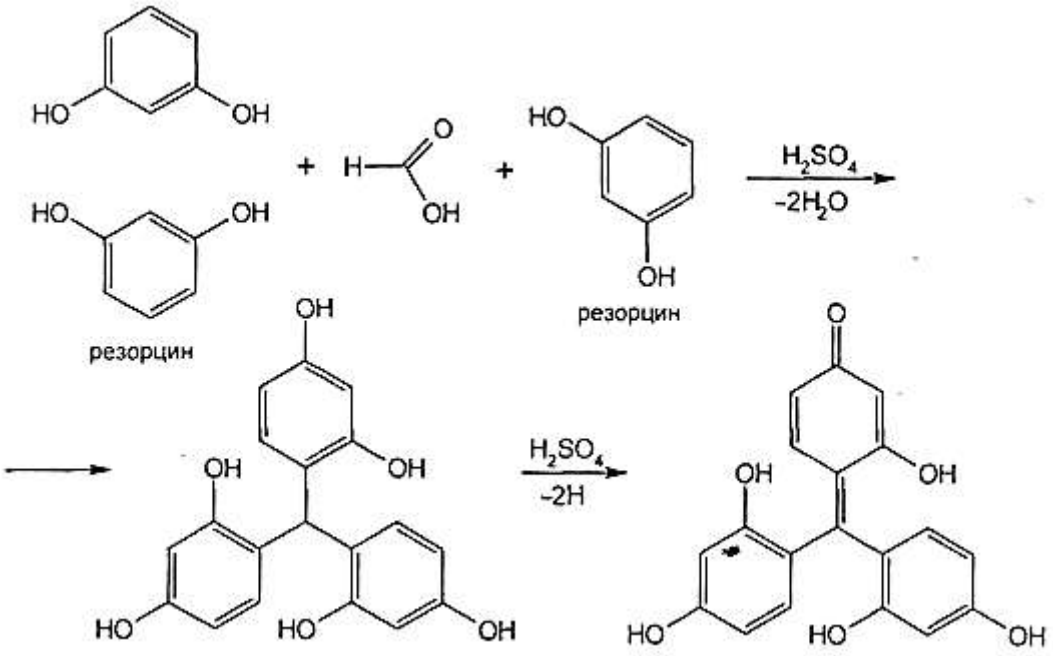


13. Tartrate ion detections

A reaction based on dehydration followed by oxidation by heating with concentrated sulphuric acid in the presence of resorcinol is used. Glyoxal and formic acid are formed first:



The formic acid then undergoes a condensation reaction with three resorcinol molecules. The result is an auric dye with a quinoid structure:



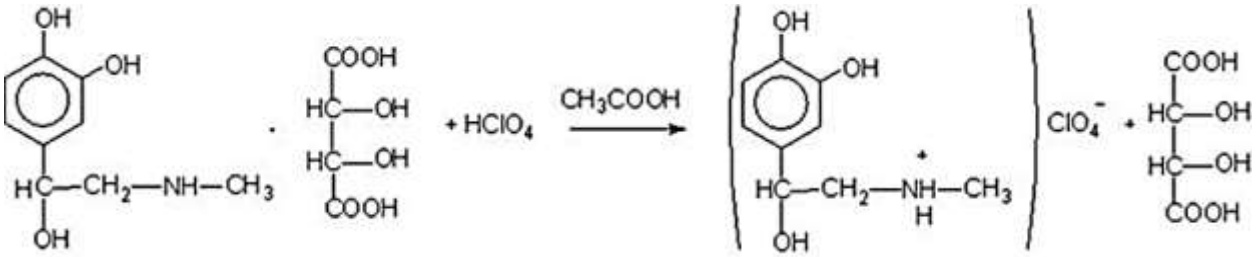
Purity test

The main test for the purity of adrenaline hydrotartrate is the detection of acceptable limits of impurities in synthesis intermediates. Adrenaline is detected by measuring the optical density of a solution in 0.01 M hydrochloric acid at 310 nm.

The presence of the impurity norepinephrine is also determined. The colour reaction with 1,2-naphthoquinone-4-potassium sulphonate and the TLC method on Silufol plates are used for detection, and the HPLC method in the mobile phase: water-methanol (85:15) is used for quantitative determination (maximum 0.0018 %). Calculate the norepinephrine content from the peak areas.

Assay

1. ***Non-aqueous titration***
   Dissolve the exact quantity in glacial acetic acid, titrate with 0,1H HClO4 in the presence of methyl violet to a bluish-green colour. Crystal violet may be used.



2. ***UV spectrophotometry***
3. ***Photocolorimetry based on colour reactions***

Storage

As adrenalin is easily oxidised, especially in the presence of alkali, sodium chloride is added to its solutions, as well as stabilisers, most commonly sodium metabisulphite. However, even under these conditions, prolonged storage causes the solutions to turn brown and the physiological activity of the drug is greatly reduced.

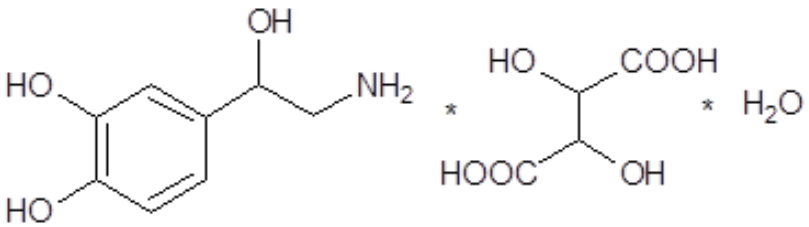
Alkaline glass vials or ampoules, high external temperature, sunlight, contact with air contribute to the decrease in activity. Therefore, the medicine should be stored in vials filled to the top and sealed ampoules made of neutral glass in a place protected from light. Shelf life is 1 year.

Medical use

Sympathomimetic (vasoconstrictor, bronchodilator). It is used in hypotension, urticaria, bronchial asthma.

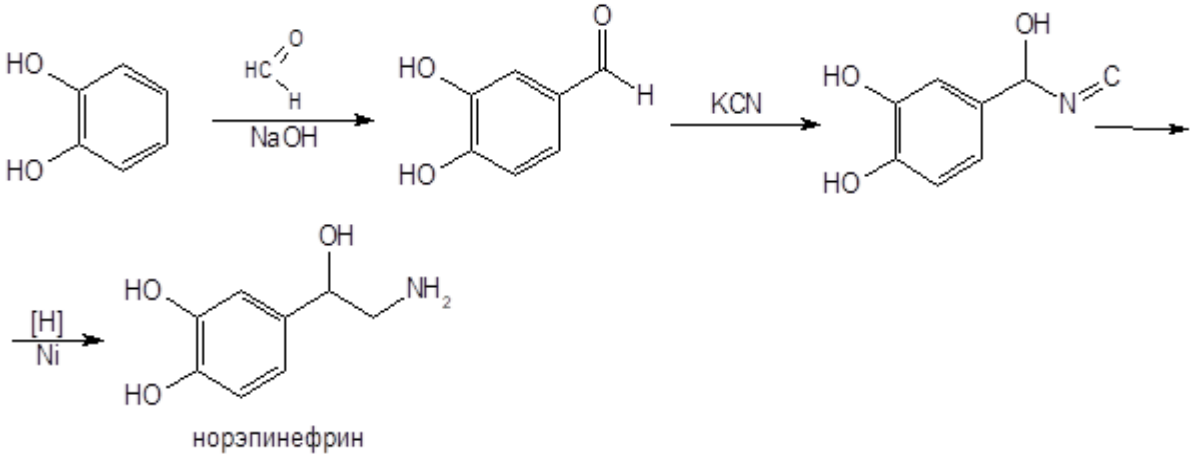
Adrenalin hydrotartrate solution 0.18% for injection; 0.1% for subcutaneous injection.

NORADRENALINE (NOREPINEPHRINE) HYDROTARTRATE



Obtaining

Noradrenaline is synthesised from pyrocatechin by sequential formylation, cyanidation and hydrogenation:



The racemate obtained from the synthesis is separated with tartaric acid.

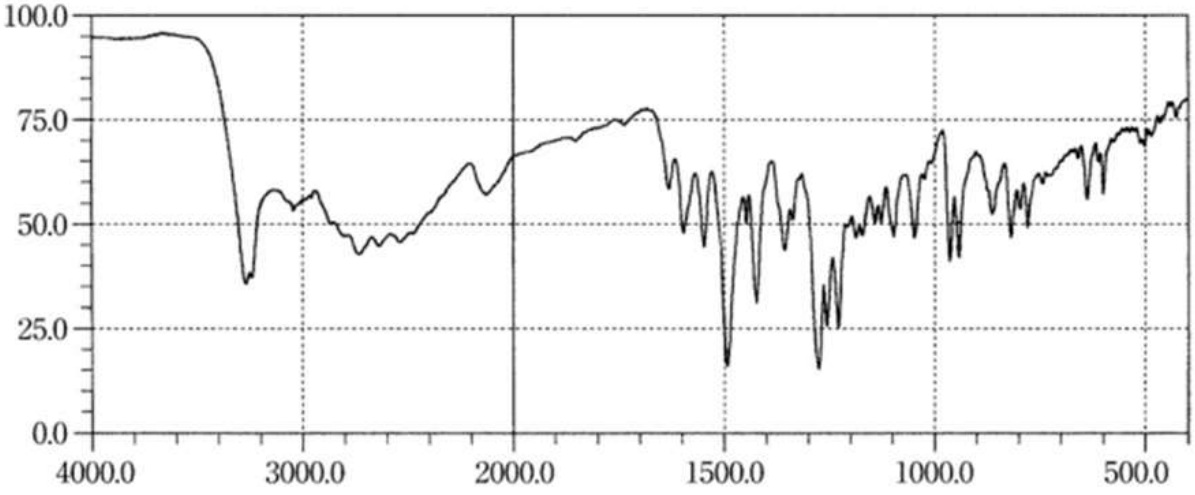
Physical properties

White or almost white crystalline powder, odourless, bitter in taste. Easily changes under the influence of light and air oxygen. Melting point is 100-106° (the melting point is cloudy; the drug is not dried beforehand). Easily soluble in water, slightly soluble in alcohol, practically insoluble in ether and chloroform.

Identification

1. ***IR spectroscopy***

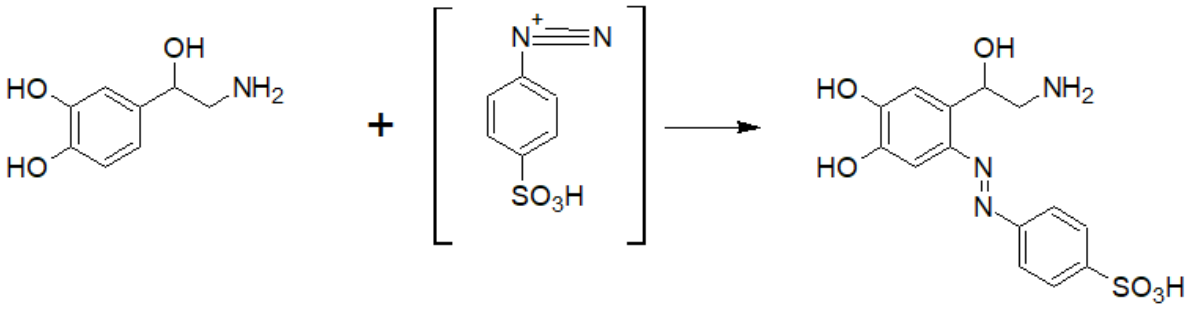
   The absorption bands should coincide completely with the spectrum figure attached to the pharmacopoeial monograph.



2. ***UV spectrophotometry***

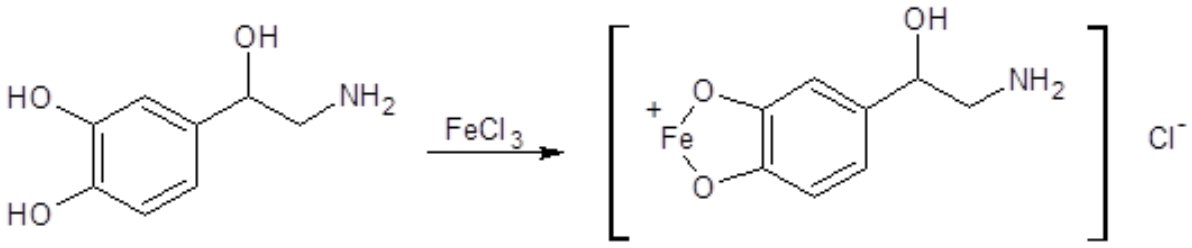
The UV spectrum of noradrenaline hydrotartrate in 0.1 M hydrochloric acid has absorption maxima at 279 nm. The FS recommends that the specific absorbance at 279 nm be determined to confirm identity.

3. ***Formation of azo dye***



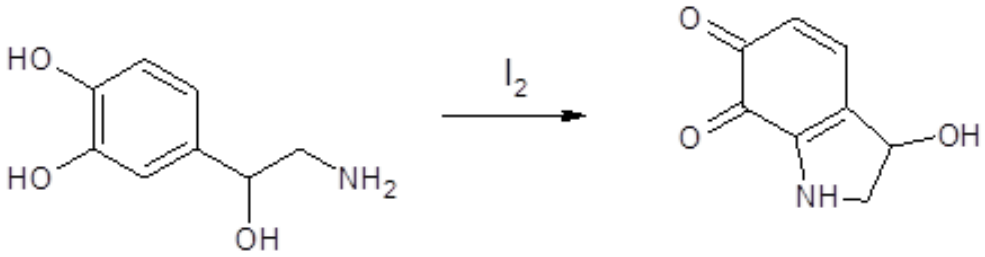
4. ***Interaction with iron chloride***

With iron (III) chloride an emerald green colouring is formed, which on adding 1 drop of ammonia solution changes to cherry-red and then orange-red.



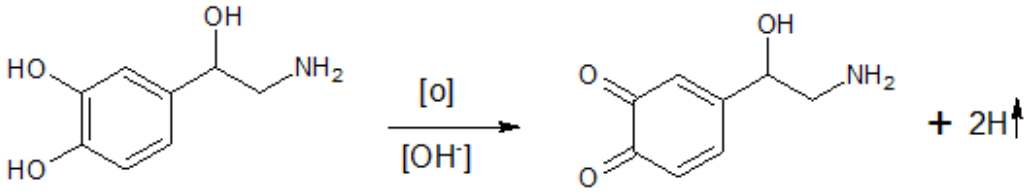
5. ***The formation of noradrenochrome***

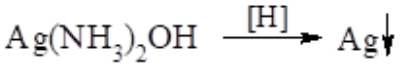
Adrenaline and noradrenaline can be distinguished by an oxidation reaction with 0.1 M iodine solution in two buffer solutions of pH 3.56 and 6.5. Noradrenaline forms noradrenochrome (red-violet colour) only in solutions of pH 6.5:



6. ***The 'silver mirror' reaction***

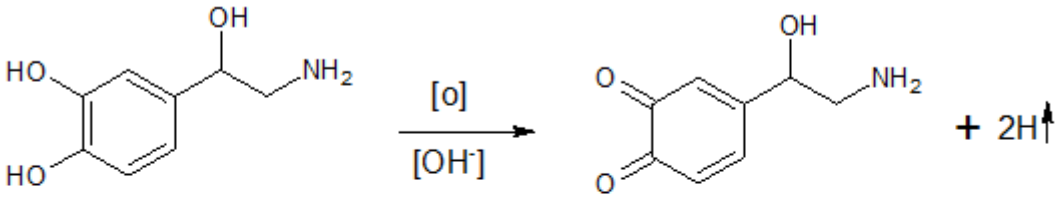
A black precipitate is formed

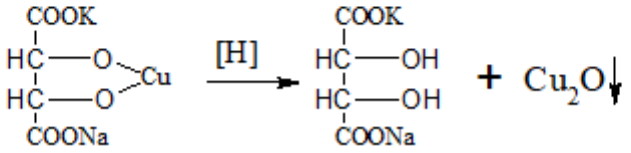




7. *Reaction with Fehling's reagent*

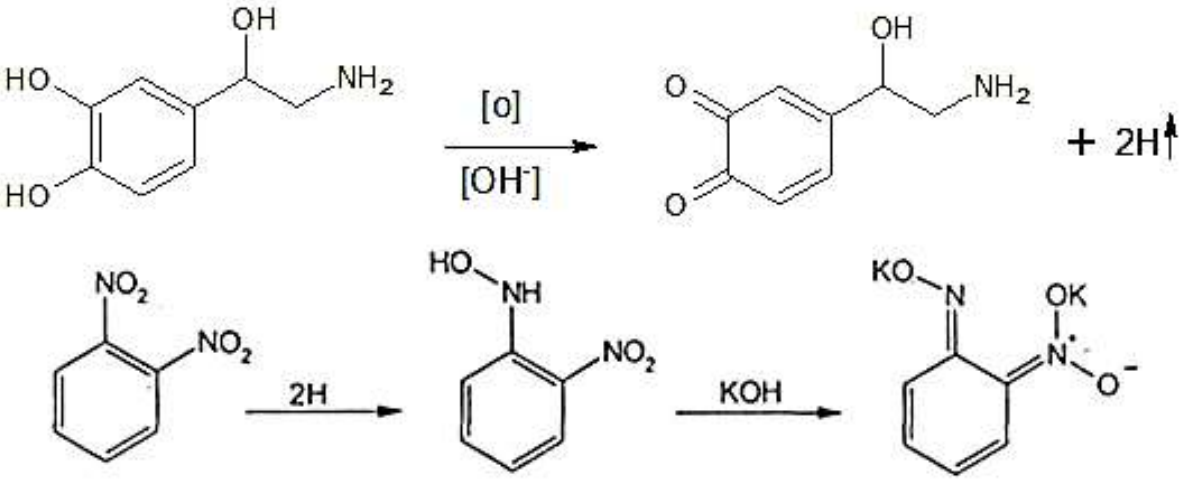
A brick-red precipitate is formed





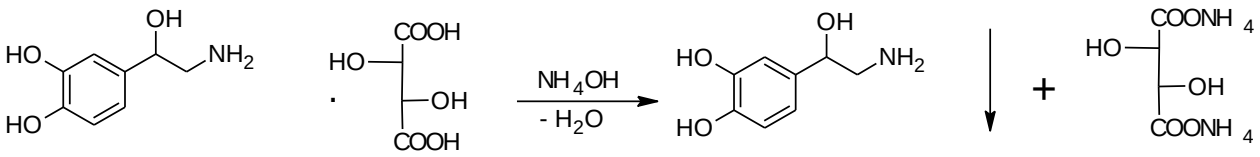
8. *Interaction with 1,2-dinitrobenzene*

The reduction of 1,2-dinitrobenzene to blue-violet coloured compounds of o-quinoid structure takes place:



9. *Base isolation reaction*

Ammonia solution is used to perform this test, as alkalis produce soluble phenoxides.



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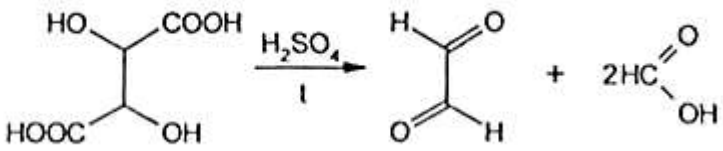
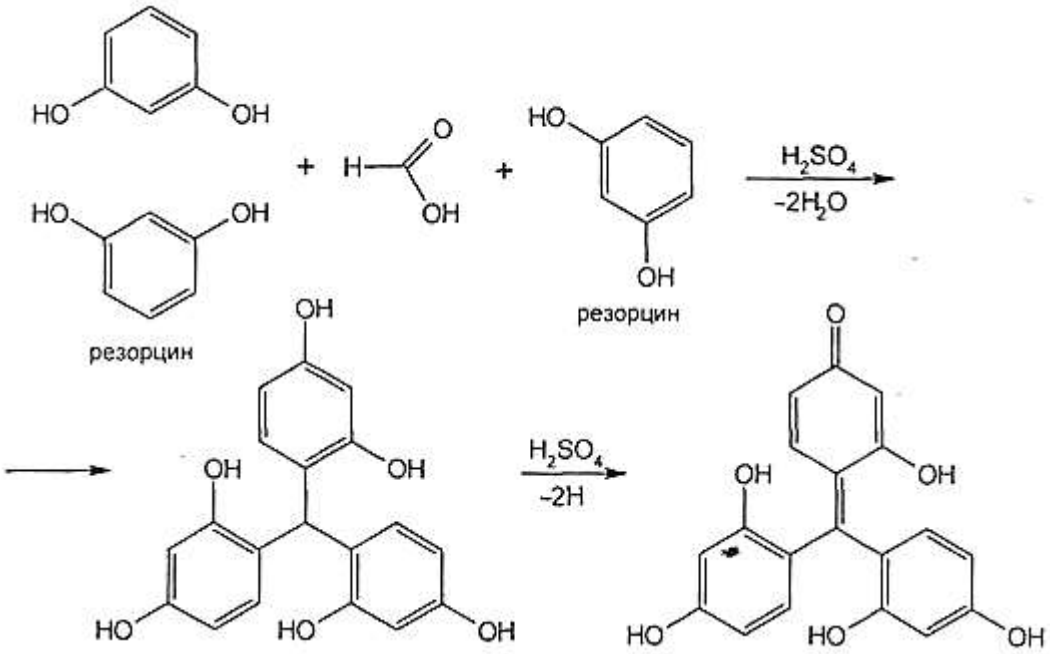


The formic acid then undergoes a condensation reaction with three resorcinol molecules. The result is an auric dye with a quinoid structure:



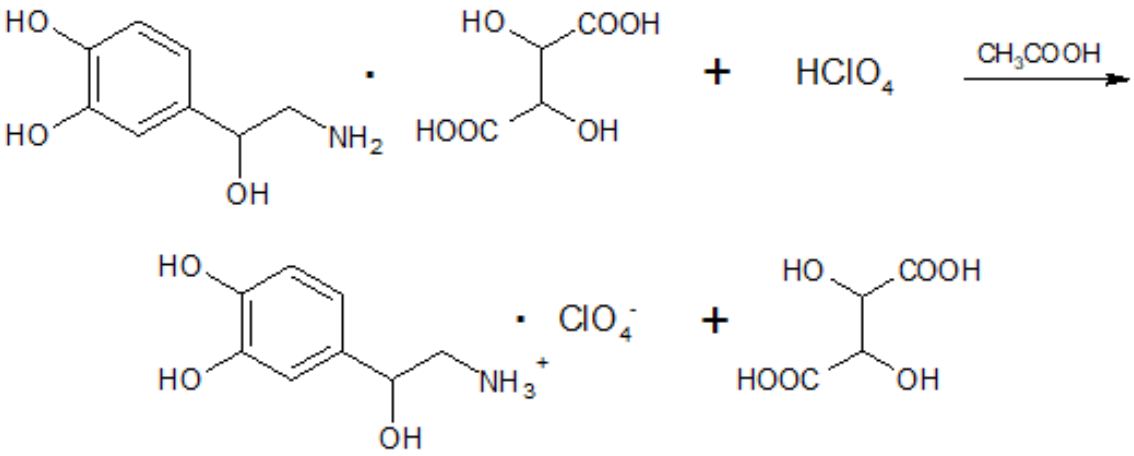
Purity test

Detection of the permissible limits of noradrenalone impurity is carried out by determining the optical density of the solution in 0.01 M hydrochloric acid at 310 nm.

Assay

1. ***Non-aqueous titration***

   Quantitative determination of noradrenaline hydrotartrate is performed by non-aqueous titration in glacial acetic acid, titrating with 0.1 M chloric acid solution (indicator methyl violet or crystal violet):



2. ***UV-visible spectrophotometry at 279 nm light absorption maximum.***
3. ***Photocolorimetry based on colour reactions***

Storage

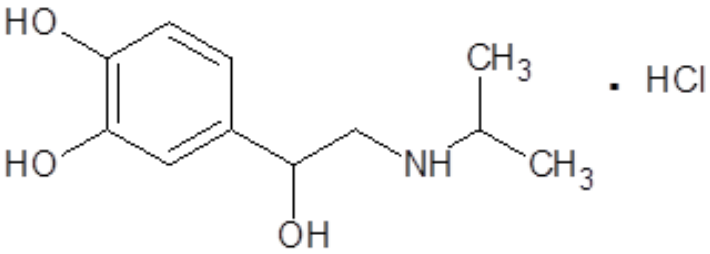
As norepinephrine is easily oxidised by light and atmospheric oxygen, it should be stored away from light in hermetically sealed orange glass containers or in sealed ampoules. For stabilisation, 0.1% sodium metabisulphite [sodium pentaoxodisulphate (IV)], which has reducing properties, is added to injectable solutions.

Medical use

Norepinephrine is used in collapse, acute hypotension due to trauma, poisoning, to reduce haemorrhage and blood loss. It is administered intravenously as a 0.2% solution.

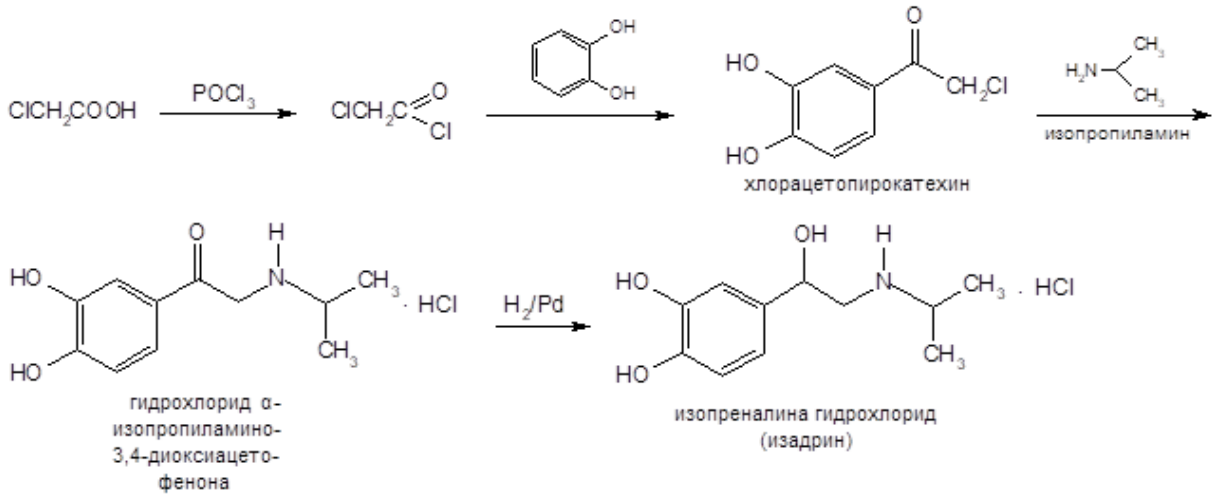
SYNTHETIC ANALOGUES OF CATECHOLAMINES

ISOPRENALINE HYDROCHLORIDE (ISADRINE)



Obtaining

Scheme of industrial method of obtaining it from chloroacetic acid and pyrocatechin:



Physical properties

White crystalline powder without odour. Melting point1 66-172°C. Easily soluble in water, moderately in alcohol, easily in alkalis.

Identification

1. ***IR spectroscopy***

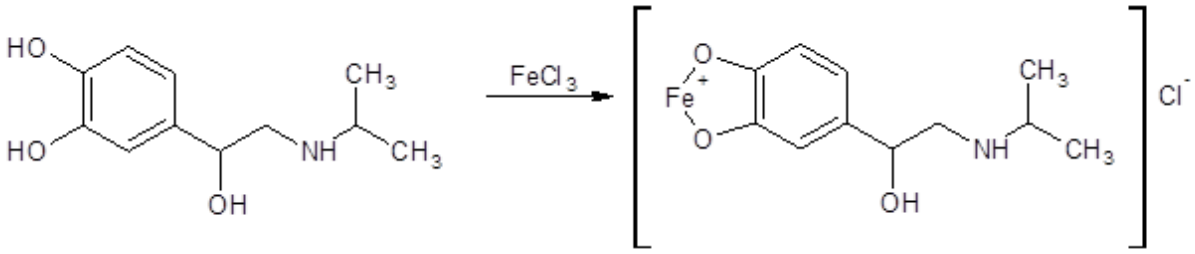
   The absorption bands should coincide completely with the spectrum figure attached to the pharmacopoeial monograph.

2. ***UV spectrophotometry***

   The UV spectrum of a solution of isoprenaline hydrochloride in 0.1 M hydrochloric acid is characterised by the presence of two absorption maxima - in the region of 223 and 279 nm.

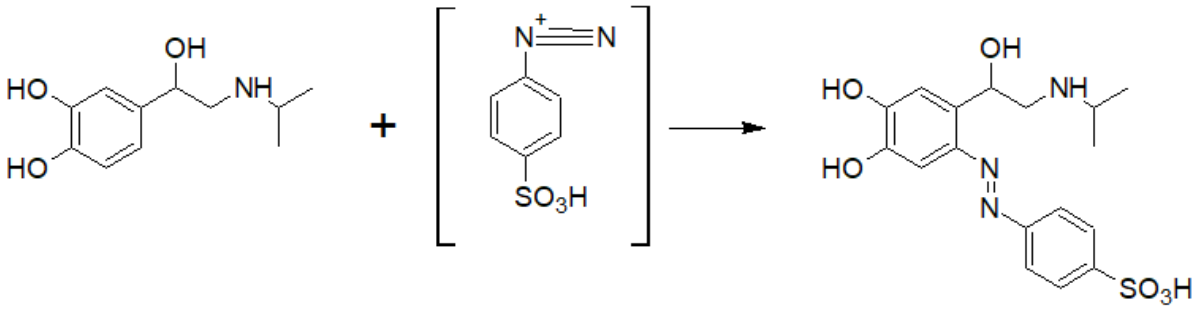
3. *Interaction with ferric chloride*

When interacting with iron (III) chloride solution, it forms emerald green colouring, changing from a drop of ammonia solution to cherry red and then to orange-red.



4. *Formation of azo dye*

A cherry-red coloured azo compound is formed.



5. *Colour reactions:*

- with nitrous acid, dirty purple;

- with alpha-nitroso-beta-naphthol, reddish brown colour;

- with ninhydrin yellow colouring;

- with potassium iodate in acid medium, cherry red colour;

- with phosphoric molybdenum acid, green colour;

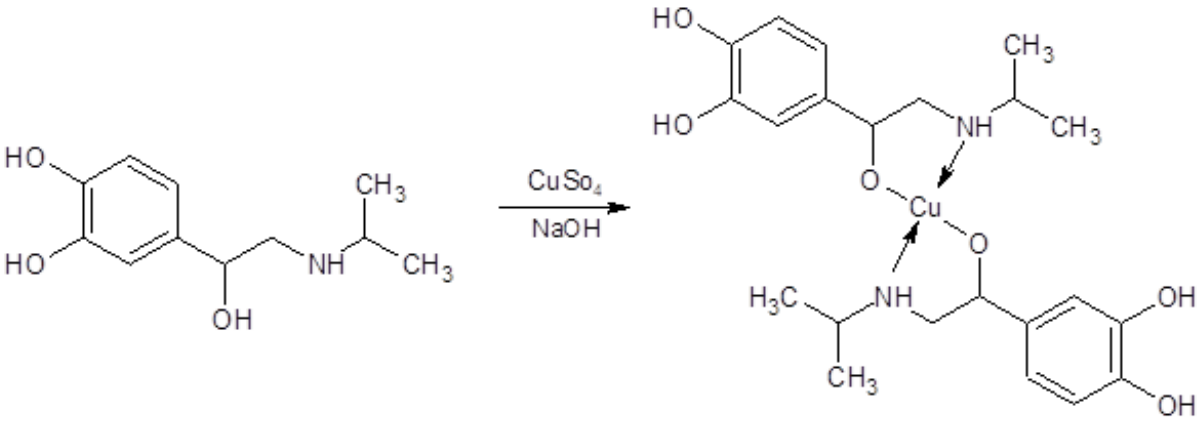
- with chloramine, isoprenaline hydrochloride gives a purple colour, which changes to red after the addition of 4-aminoantipyrine;

- with selenic acid it forms a brown amorphous precipitate;

- with cerium (IV) sulphate, a red-orange coloured product is obtained.

6. *Complex formation with copper (II) ions*

In the presence of sodium hydroxide, isoprenaline forms a complex with copper ions, which, unlike ephedrine and mesaton, has a dark green colouring.

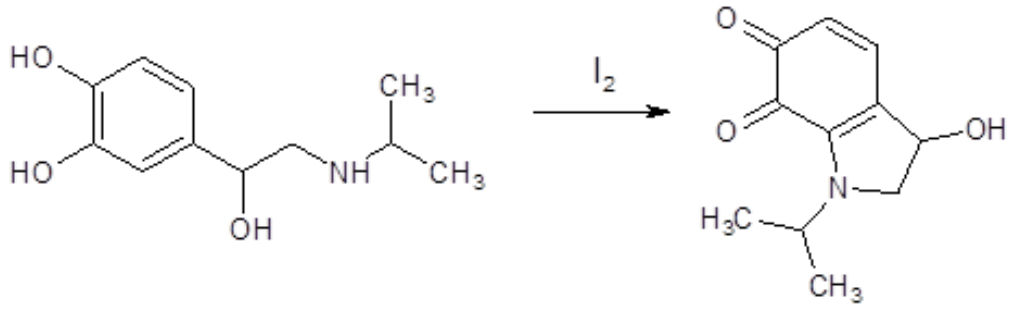


7. ***Interaction with phosphorus-tungstic acid***

   When interacting with phosphorus-tungstic acid, unlike adrenaline, isoprenaline hydrochloride forms a white precipitate, which turns brown on standing.

8. ***Formation of aminochrome***

   The oxidation reaction with 0.1M iodine solution is used to distinguish isoprenaline from norepinephrine. The required pH is achieved with 0.1 M hydrochloric acid solution. After 5 minutes, an excess of 0.1 M sodium thiosulphate solution is added. The iodine is decoloured and the solution becomes pink.



9. ***Reaction for chlorides in aqueous solution***

   A white curd-like sludge is formed.

$$HCl + AgNO_3 \rightarrow AgCl\downarrow + HNO_3$$

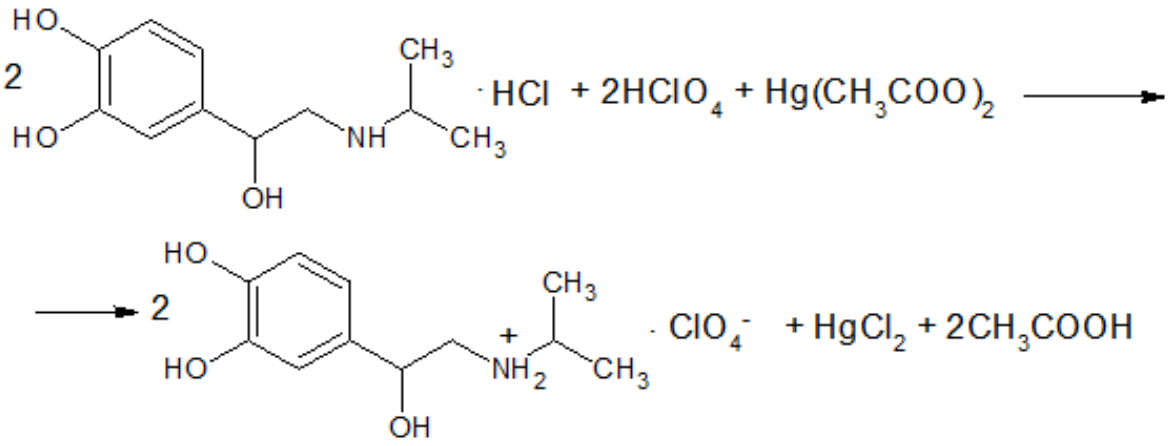
Purity test

When testing the purity of isoprenaline hydrochloride to detect impurities of isoprenalone (intermediate product of synthesis), the optical density of a 0.2% solution in 0.01 M hydrochloric acid (not more than 0.2) is measured at 310 nm.

Assay

Non-aqueous titration

Isoprenaline hydrochloride, like other hydrochlorides of organic bases, is titrated in the presence of mercuric acetate. The solvent is glacial acetic acid, the titrant is 0.1 M perchloric acid solution and the indicator is crystal violet or 1-naphtholbenzene.



Storage

Isoprenaline hydrochloride oxidises even in the dark, especially when the temperature rises and in a humid atmosphere. It is therefore stored in tightly closed orange glass bottles. Aqueous solution of isoprenaline hydrochloride turns pink when standing. Do not freeze.

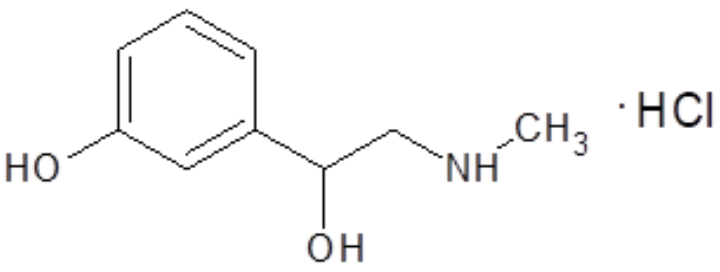
Medical use

The action of isoprenaline is explained by its stimulating effect on beta-adrenergic receptors. It is a potent bronchodilator, increases heart rate and contractions, and increases cardiac output and myocardial oxygen consumption.

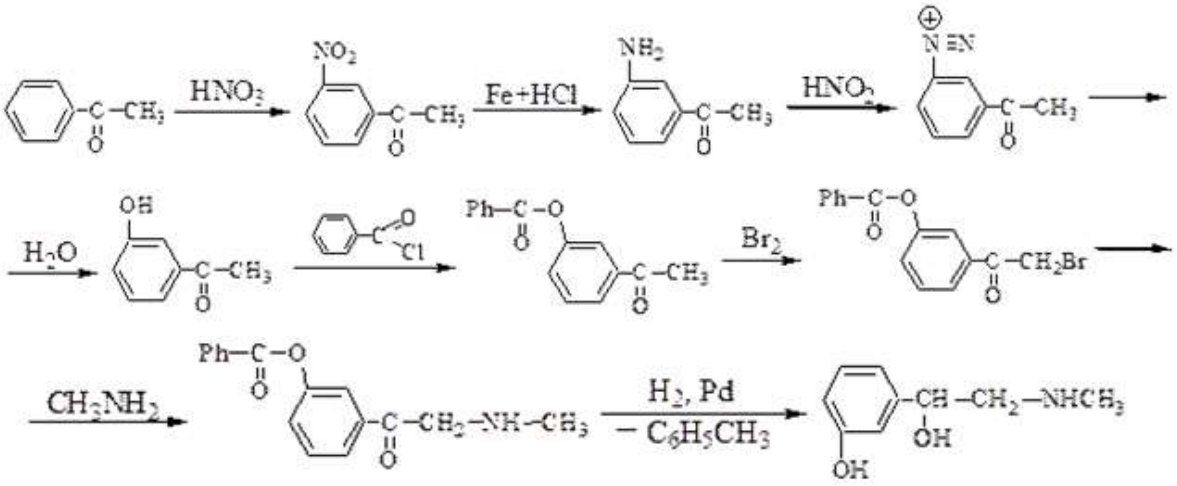
Isoprenaline hydrochloride is most commonly prescribed as a bronchodilator in the form of 0.5% and 1% solutions for inhalation or as sublingual tablets.

It is available in vials of 25 and 100 ml of 0.5% and 1% solutions and in tablets of 0.005 g.

MESATONE



Obtaining



Physical properties

White or white with slightly yellowish tinge, odourless crystalline powder. Easily soluble in water, 95% alcohol and dilute solutions of alkalis and acids, practically insoluble in ether.

Identification

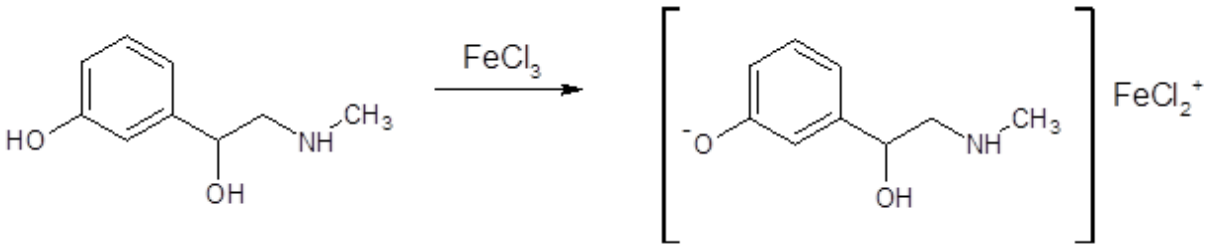
1. ***IR spectroscopy***

   The absorption bands should coincide completely with the spectrum figure attached to the pharmacopoeial monograph.

2. ***UV spectrophotometry***

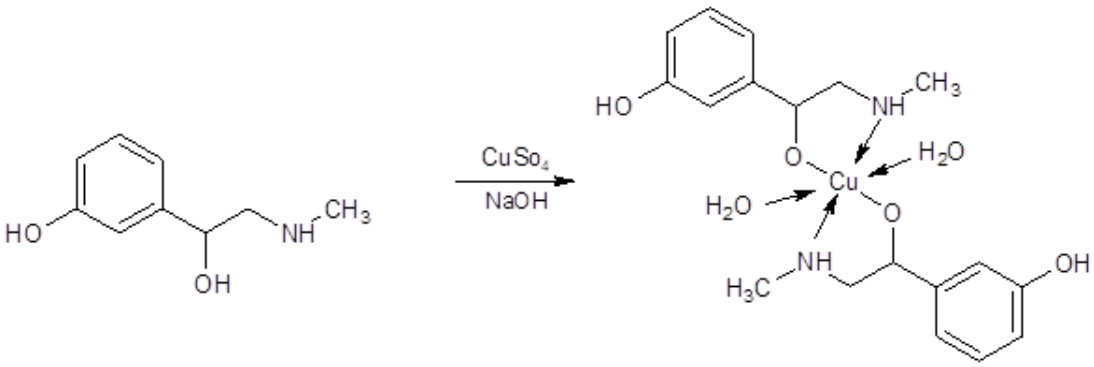
3. ***Interaction with iron (III) chloride solution***

   A violet colouration appears.



4. ***Reaction with copper sulphate solution in the presence of sodium hydroxide***

   A complex coloured blue-violet, insoluble in ether, is formed.



5. ***Reaction for chlorides with silver nitrate solution.***

   A white curd-like sludge is formed.

$$HCl + AgNO_3 \rightarrow AgCl\downarrow + HNO_3$$

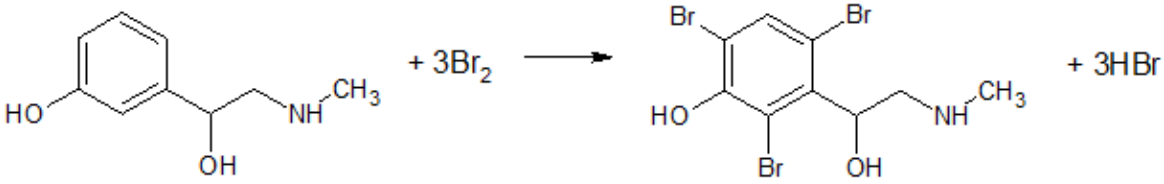
Assay

Bromatometry

Dissolve the exact weight of the drug in water and add potassium bromate solution, potassium bromide and concentrated hydrochloric acid.

Then potassium iodide solution is added and the released iodine is titrated with 0.1 n sodium thiosulfate solution (indicator - starch).

$$KBrO_3 + 5\ KBr + 6HCl \rightarrow 3Br_2 + 6KCl + 3H_2O$$



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

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

A control experiment is carried out in parallel.

Storage

In well corked orange glass jars, away from light.

Medical use

Mesatone acts selectively on α-receptors. It is used to increase blood pressure (hypotension). Its structure is characterised by the presence of a hydroxyl group in the aromatic nucleus. Mesatone is much less effective than adrenaline, but it lasts much longer (due to slow degradation by enzymes).