МЕДИЦИНСКИ УНИВЕРСИТЕТ – ПЛЕВЕН
ФАКУЛТЕТ „ФАКУЛТЕТ ФАРМАЦИЯ“
ЦЕНТЪР ЗА ДИСТАНЦИОННО ОБУЧЕНИЕ

Лекция №05

Анализ на антиинфекциозни лекарства. Производни на имидазола, фурана, индола и акридина – 2 част

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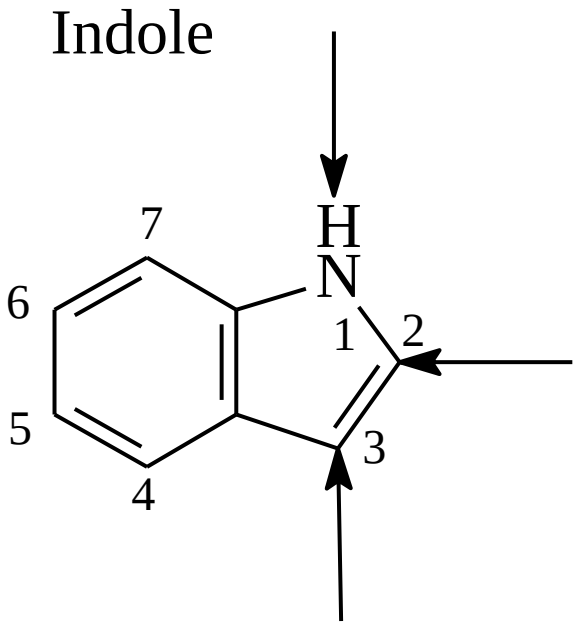
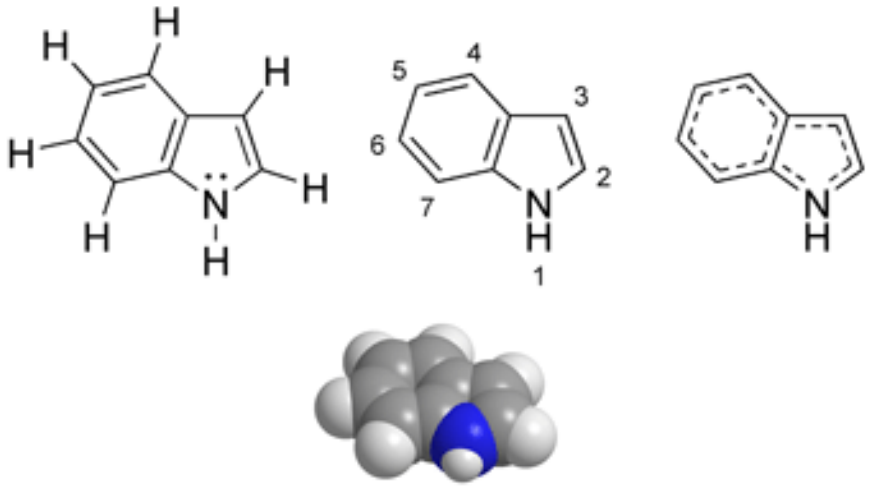
АНАЛИЗ НА ИНДОЛОВИ ПРОИЗВОДНИ

1*H*-бензо[*b*]пирол (1*H*-бензо[*b*]азол)

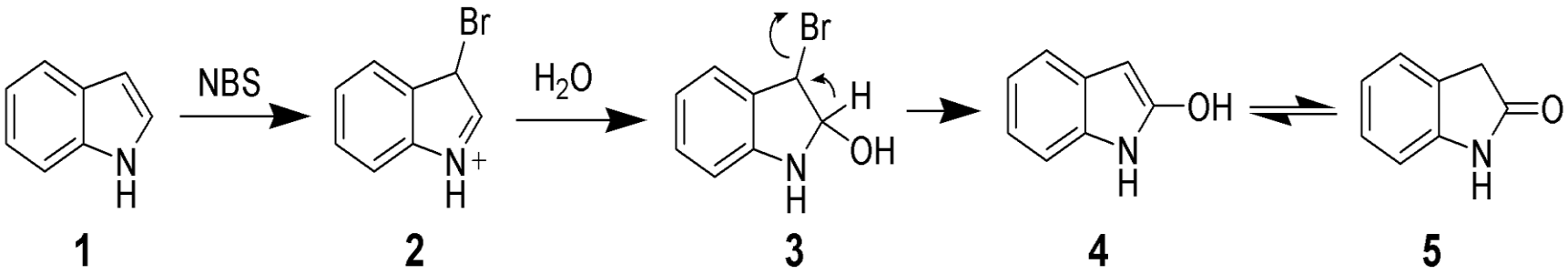




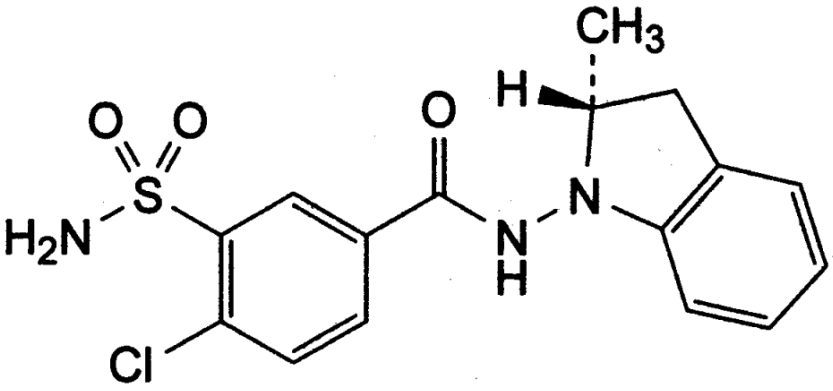
Basicity

Unlike most amines, indole is not basic. The bonding situation is completely analogous to that in pyrrole. Very strong acids such as hydrochloric acid are required to protonate indole. The protonated form has an pKa of −3.6. The sensitivity of many indolic compounds (e.g., tryptamines) under acidic conditions is caused by this protonation. The most reactive position on indole for electrophilic aromatic substitution is C-3, which is 10-13 times more reactive than benzene.

Due to the electron-rich nature of indole, it is easily oxidized. Simple oxidants such as *N*-bromosuccinimide will selectively oxidize indole 1 to oxindole (4 and 5).



Indapamide

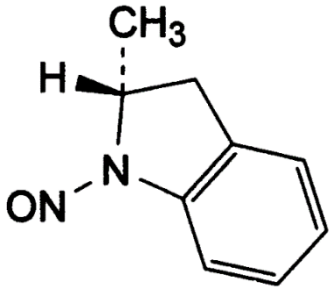


and enantiomer

4-chloro-*N*-[(2*RS*)-2-methyl-2,3-dihydro-1*H*-indol-1-yl]-3-sulphamoylbenzamide

Methylnitrosoindoline

Not more than 5 ppm, determined by liquid chromatography *(2.2.29)*. *Carry out the test protected from light.*



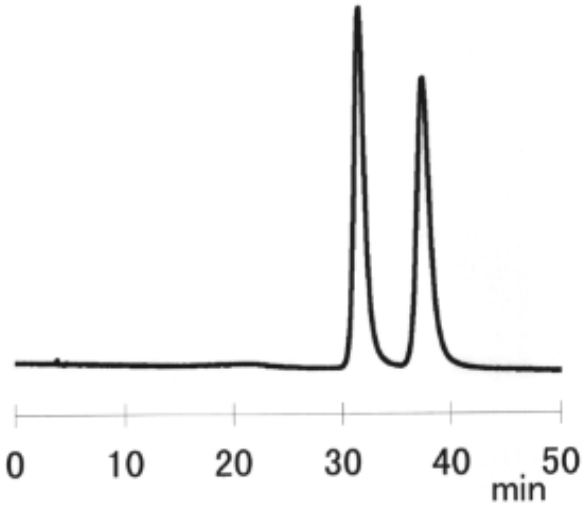
and enantiomer

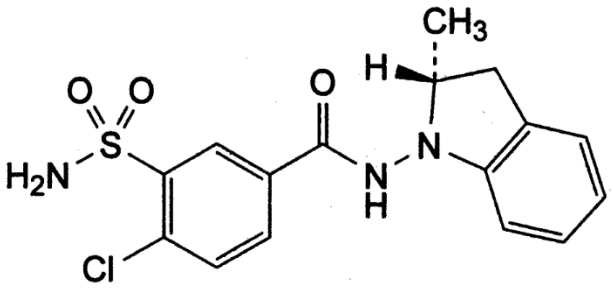
ASSAY

Examine by liquid chromatography *(2.2.29)*. *Carry out the assay protected from light and prepare the solutions immediately before use or maintain them at 4 °C.*

Optical rotation *(2.2.7)*

Dissolve 0.250 g in *anhydrous ethanol R* and dilute to 25.0 ml with the same solvent. The angle of optical rotation is - 0.02° to + 0.02°.



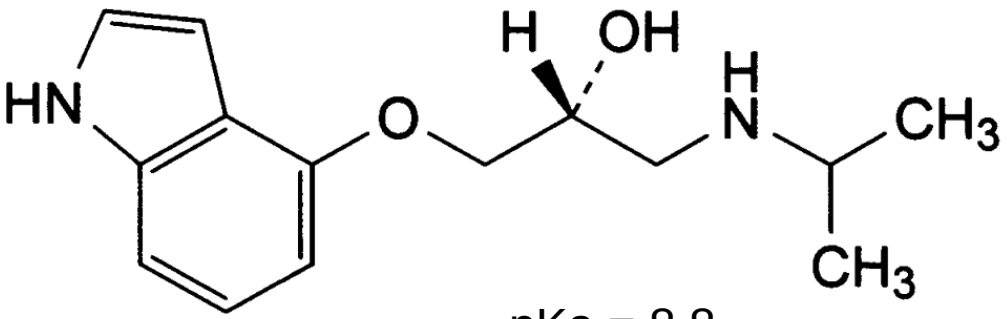


and enantiomer

Column :	Циклодекстрин (4.6 mm ID x 150 mm)
Eluent :	10% CH3CN + 90% (1.4% CH3COOH + 0.7% $(C_2H_5)_3N$ + 0.2M NaCl) in H_2O
Flow rate :	0.5mL/min
Detector :	Shodex UV(254nm)
Column temp. :	10 ^{0}C

Pindolol

(2*RS*)-1-(1*H*-indol-4-yloxy)-3-[(1-methylethyl)amino]propan-2-ol



and enantiomer

pKa = 8.8

ASSAY

Dissolve 0.200 g in 80 ml of *methanol R*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically *(2.2.20)*.

1 ml of *0.1 M hydrochloric acid* is equivalent to 24.83 mg of $C_{14}H_{20}N_2O_2$.

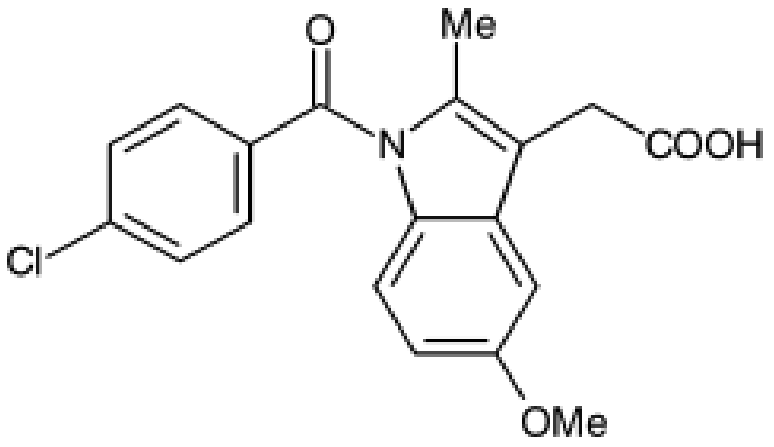
STORAGE

Store protected from light.

Indometacin

Indometacin contains not less than 98.5 per cent and not more than the equivalent of 100.5 per cent of [1-(4-chlorobenzoyl)- 5 - methoxy-2-methylindol-3-yl] acetic acid, calculated with reference to the dried substance.

A white or yellow, crystalline powder, practically insoluble in water, sparingly soluble in alcohol.



Indometacin

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D, E.

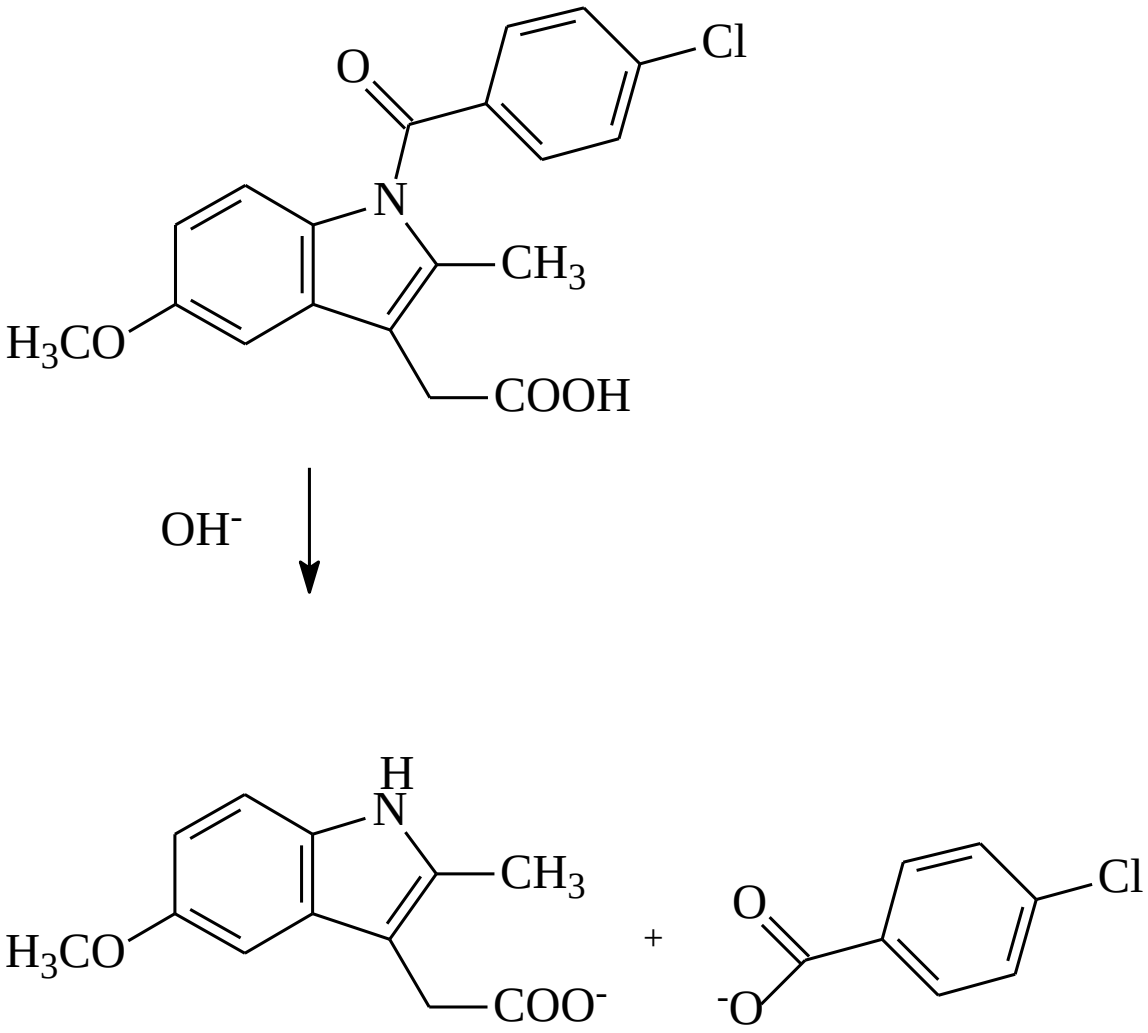
A. Melting point *(2.2.14*): 158°C to 162°C.

B. Dissolve 25 mg in a mixture of 1 volume of *1*M *hydrochloric acid* and 9 volumes of *methanol R* and dilute to 100.0 ml with the same mixture of solvents. Dilute 10.0 ml of the solution to 100.0 ml with a mixture of 1 volume of *1*M *hydrochloric acid* and 9 volumes of *methanol R*. Examined between **300 nm and 350 nm** *(2.2.25*), the solution shows an absorption maximum at 318 nm. The specific absorbance at the maximum is 170 to 190.

C. Examine by infrared absorption spectrophotometry *(2.2.24),* comparing with the spectrum obtained with *indometacin CRS*. Examine the substances in the solid state without recrystallisation.

D. Dissolve 0.1 g in 10 ml of *alcohol R*, heating slightly if necessary. To 0.1 ml of the solution add 2 ml of a freshly prepared mixture of 1 volume of a 250 g/l solution of *hydroxylamine hydrochloride R* and 3 volumes of *dilute sodium hydroxide solution R*. Add 2 ml of *dilute hydrochloric acid R* and 1 ml of *ferric chloride solution R2* and mix. A violet-pink colour develops.

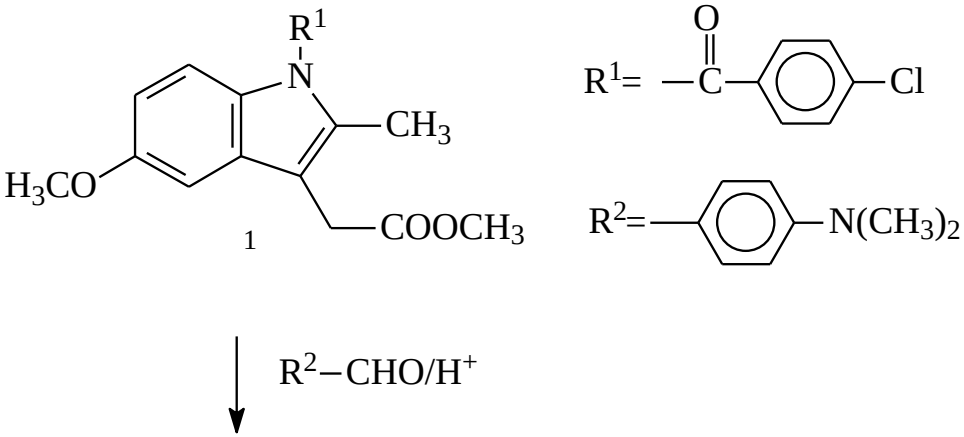
Indomethacin



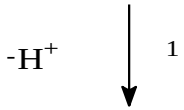
E. To 0.5 ml of the solution in alcohol prepared in identification test D, add 0.5 ml of *dimethylaminobenzaldehyde solution R2*. A precipitate is formed that dissolves on shaking. Heat on a water- bath. A bluish-green colour is produced. Continue to heat for 5 min and cool in iced water for 2 min. A precipitate is formed and the colour changes to light greyish-green. Add 3 ml of *alcohol R*. The solution is clear and violet-pink in colour.

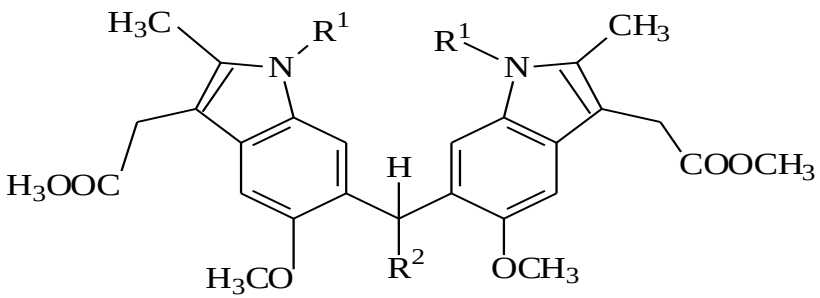
Indometacin

Indomethacin methyl ester



Indometacin





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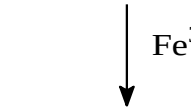

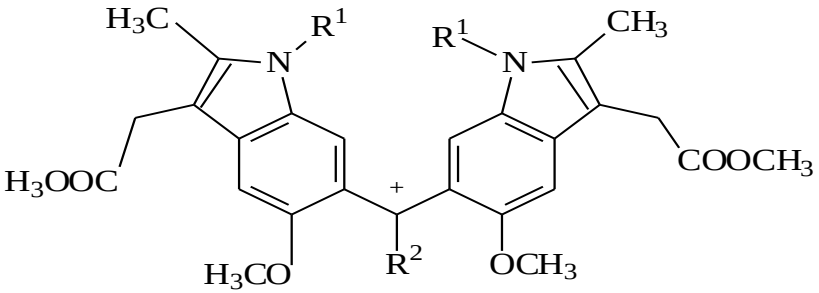

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ASSAY

Dissolve 0.300 g in 75 ml of *acetone R*, through which *nitrogen R*, free from carbon dioxide, has been passed for 15 min. Maintain a constant stream of nitrogen through the solution. Add 0.1 ml of *phenolphthalein solution R.* Titrate with *0.1* M *sodium hydroxide*. Carry out a blank titration.

1 ml of *0.1* M *sodium hydroxide* is equivalent to 35.78 mg of $C_{19}H_{16}ClNO_4$.

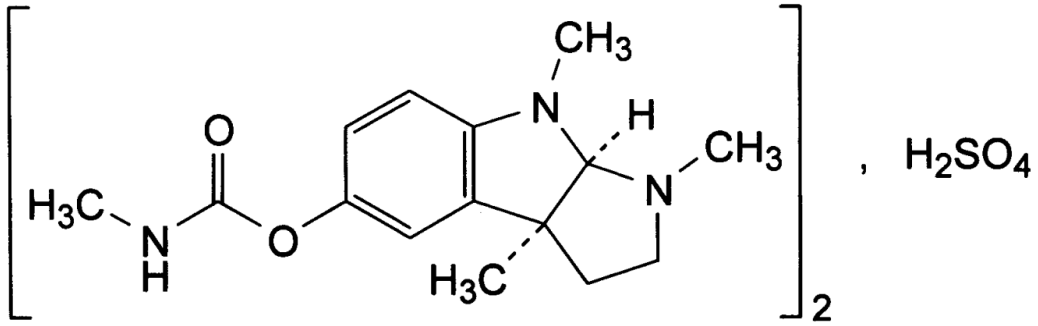
STORAGE

Store in a well-closed container, protected from light.

IMPURITIES

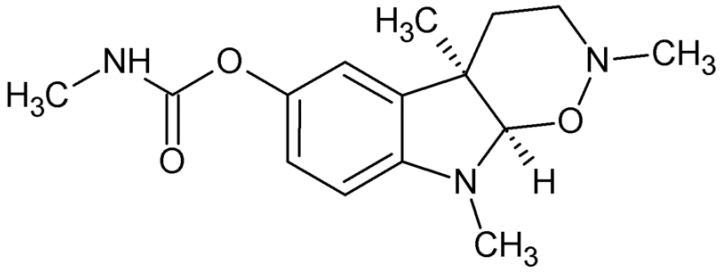
A. 4-chlorobenzoic acid.

Physostigmine Sulphate



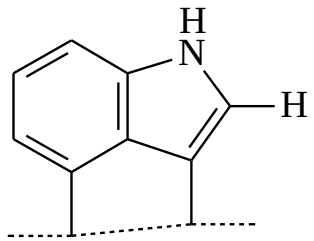
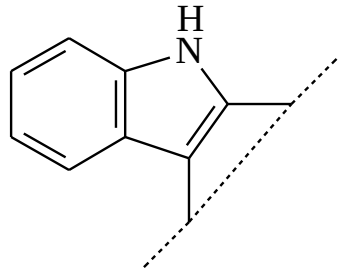
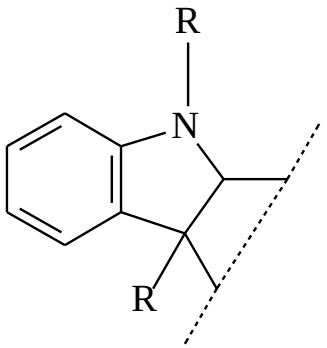
di[(3a*S*,8a*R*)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indol-5-yl methylcarbamate] sulphate

1,2-Oxazino[6,5-b]indol-6-ol, 2,3,4,4a,9,9a-hexahydro-2,4a,9-trimethyl-,methylcarbamate

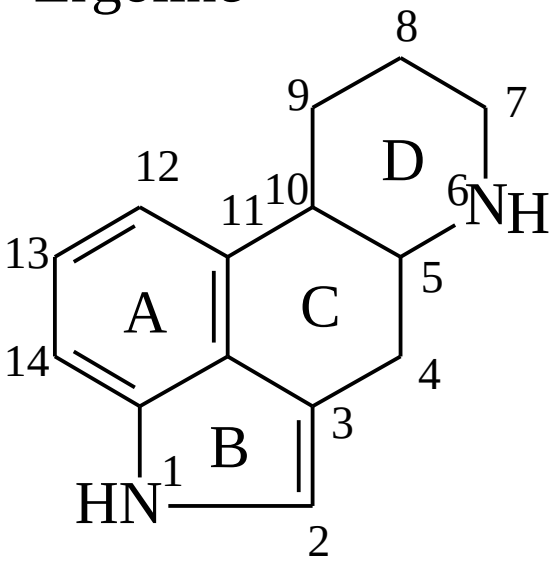


Eseridine

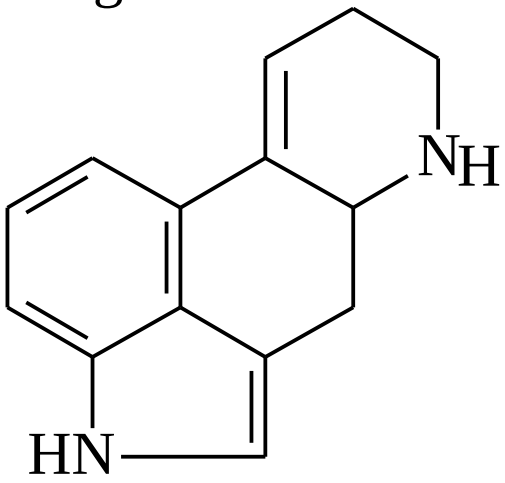
To 5 ml of solution S add a few crystals of *potassium iodate R*, 0.05 ml of *dilute hydrochloric acid R* and 2 ml of *chloroform R* and shake. After 1 min, the chloroform layer is not more intensely coloured than a reference solution prepared at the same time in the same manner using 5 ml of *water R* instead of solution S.

Type		Example
2		ergotamine ergometrine
3		yohimbine reserpine
4		ajmaline strychnine physostigmine

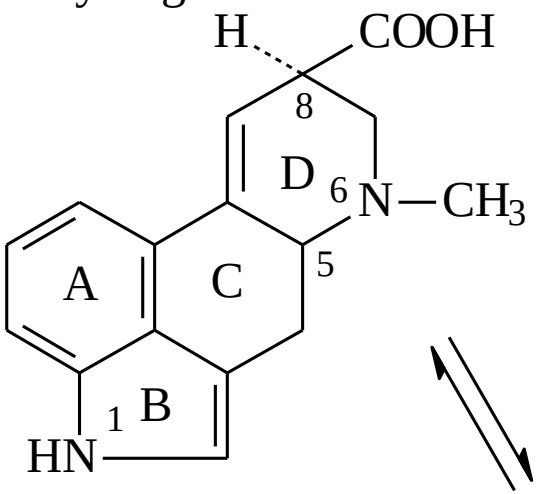
Ergoline



Ergolene

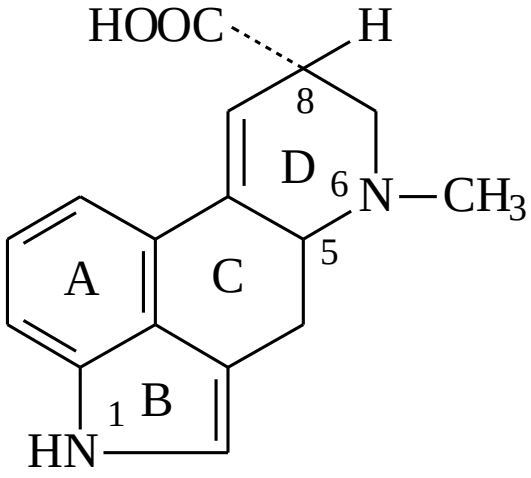


Lysergic acid

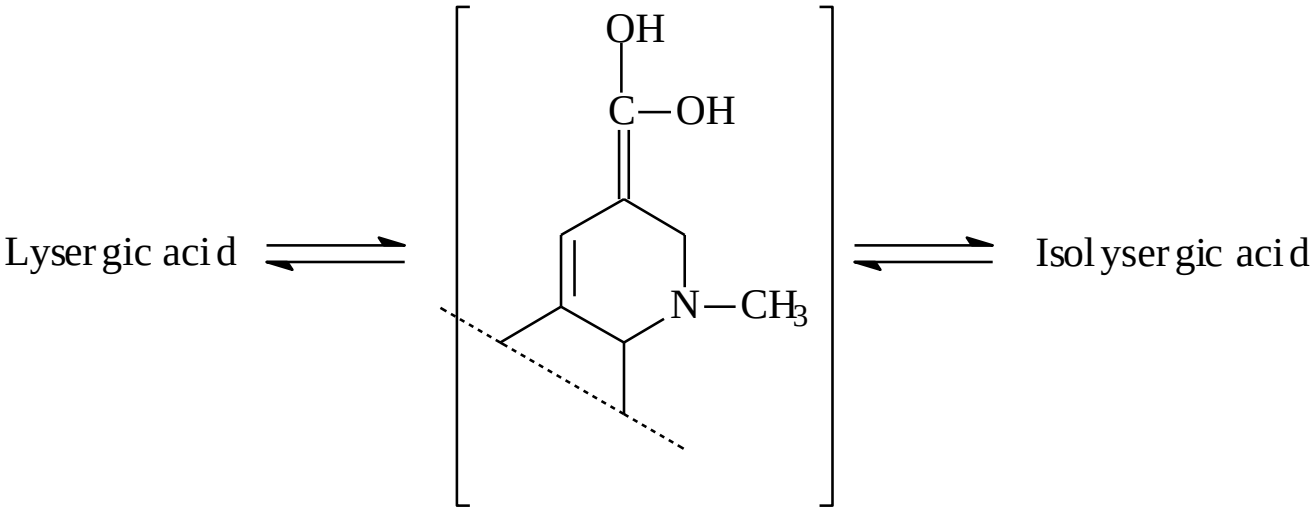


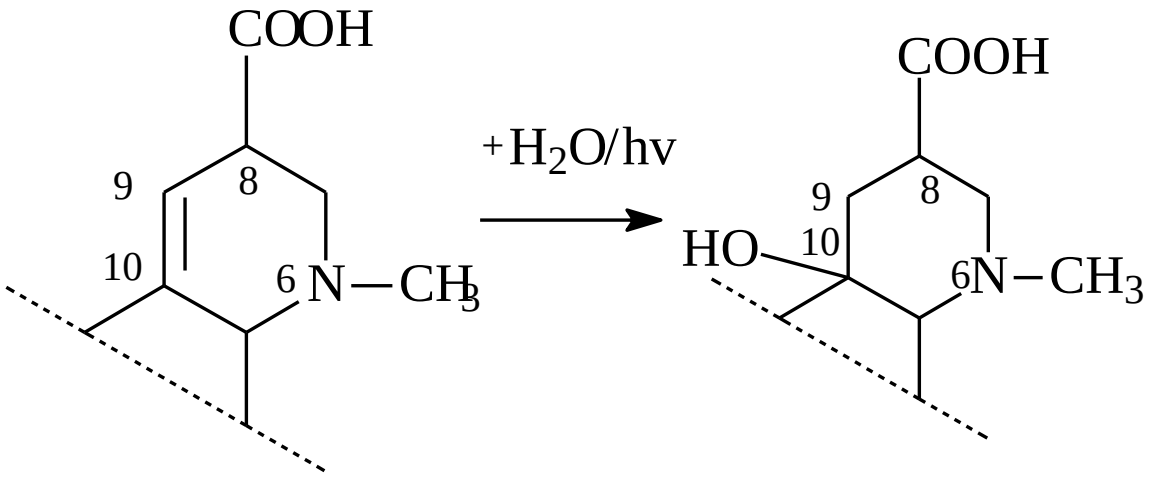
$^{5}R : {}^{8}R$

Isolysergic acid

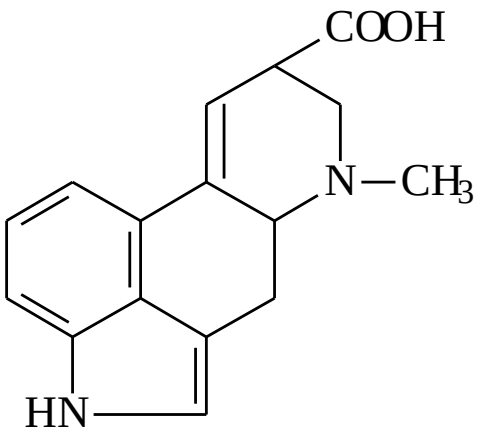


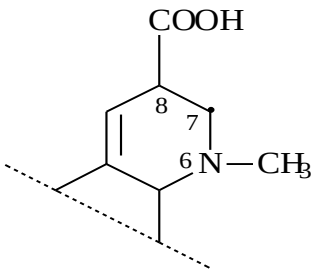
$^{5}R : {}^{8}S$

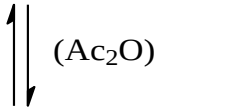

Lysergic acid
OH
C—OH
N—CH3
Isolysergic acid

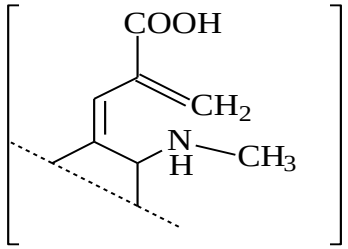

COOH
9
8
10
6
N—CH3
+H2O/hv
COOH
9
8
HO
10
6
N—CH3

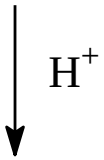
Lysergic acid

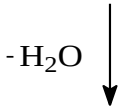


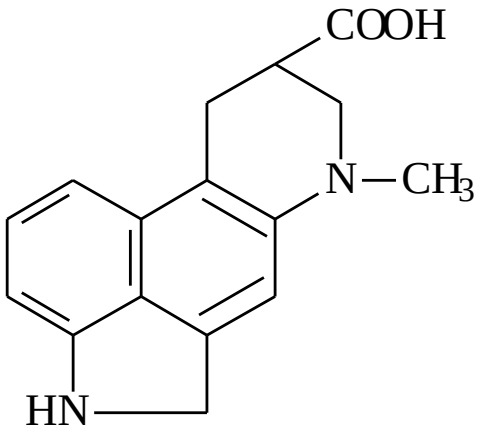


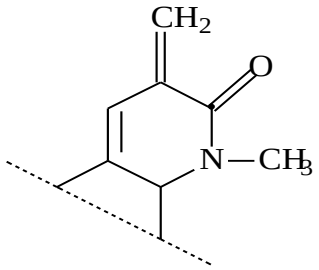




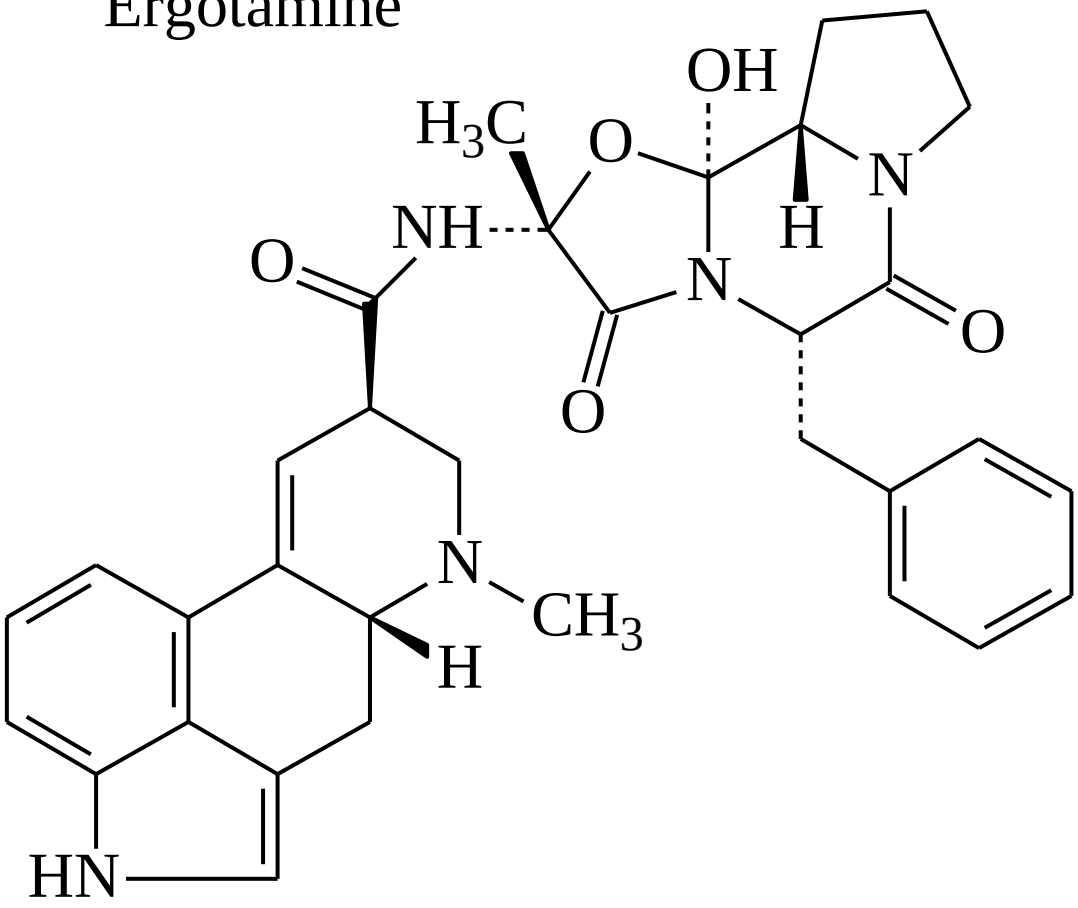




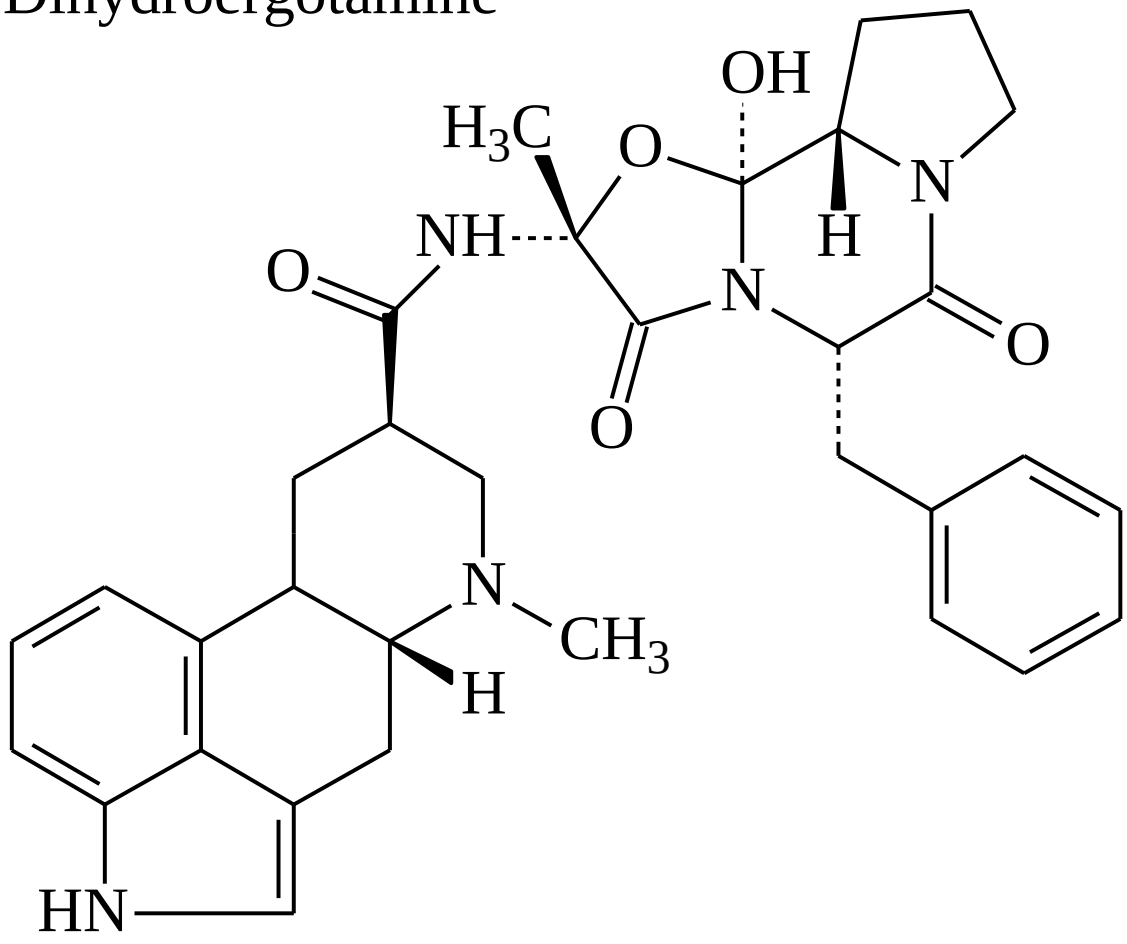




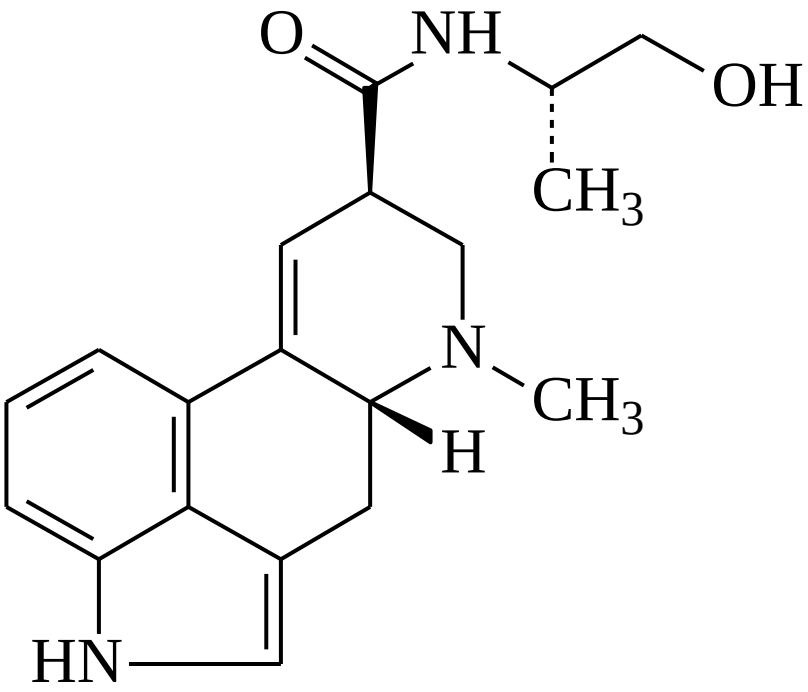
Ergotamine



Dihydroergotamine

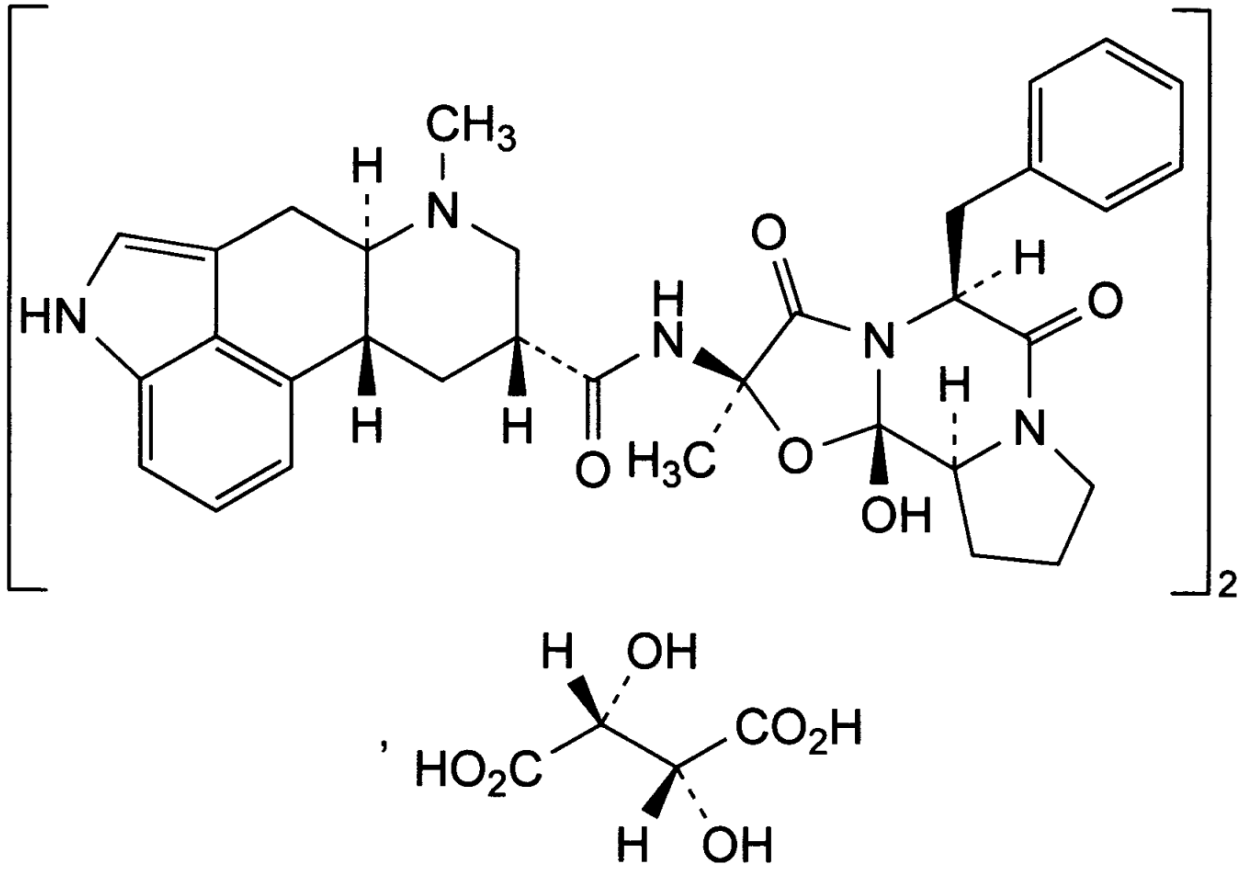


Ergometrine



Ph Eur

Dihydroergotamine Tartrate



mesilate, tartrate

bis[(6a*R*,9*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-methyl-3,6-dioxo-octahydro-8*H*-oxazolo[3,2-*a*]pyrrolo [2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide] tartrate

Appearance of solution

Dissolve 0.1 g in *alcohol (85 per cent V/V) R* warming carefully in a water-bath at 40 °C and dilute to 50 ml with the same solvent.
The solution is clear *(2.2.1)* and not more intensely coloured than reference solution Y7 or BY7 *(2.2.2, Method II)*.

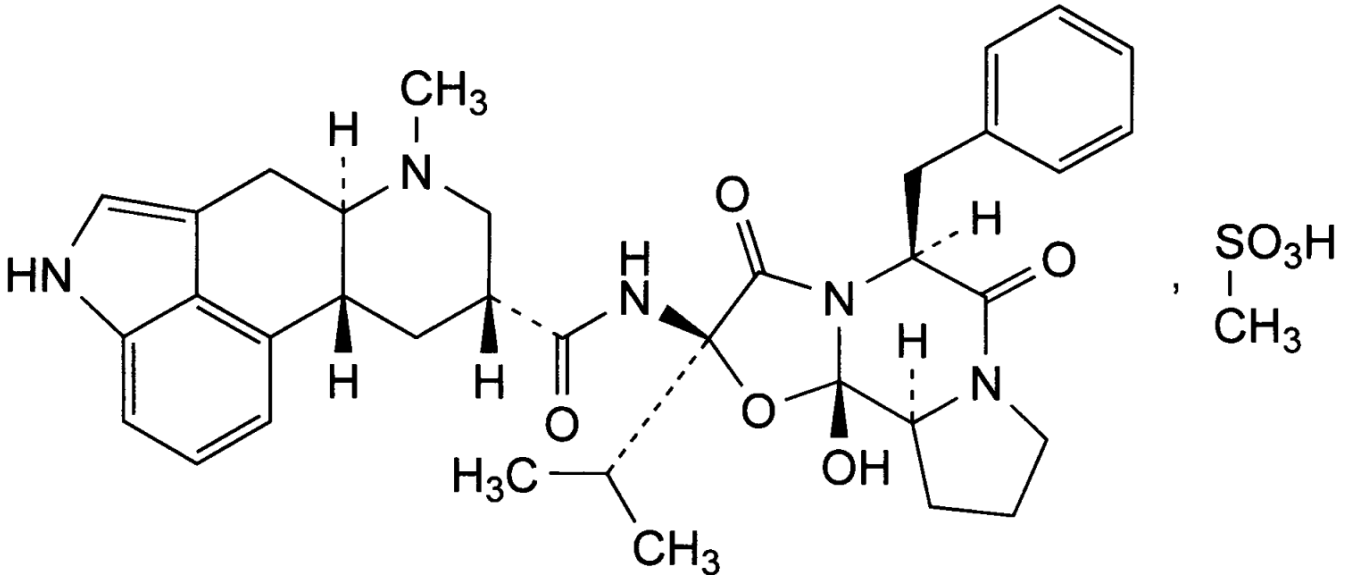
ASSAY

Dissolve 0.250 g in 50 ml of *anhydrous acetic acid R*. Titrate with *0.05 M perchloric acid*, determining the end-point potentiometrically *(2.2.20)*.

1 ml of *0.05 M perchloric acid* is equivalent to 32.93 mg of $C_{70}H_{80}N_{10}O_{16}$.

STORAGE

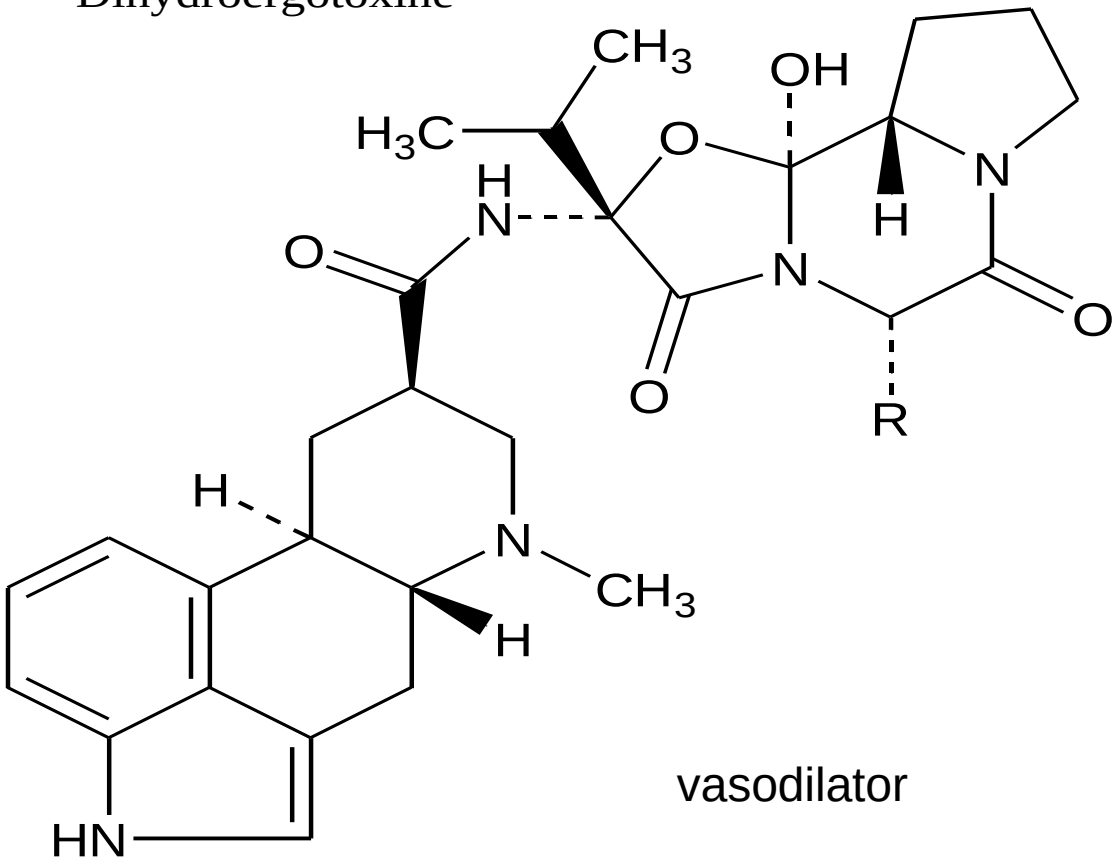
Protected from light.



Ph Eur

Dihydroergocristine Mesilate

Dihydroergotoxine



- CH_3SO_3H

Ph Eur

vasodilator

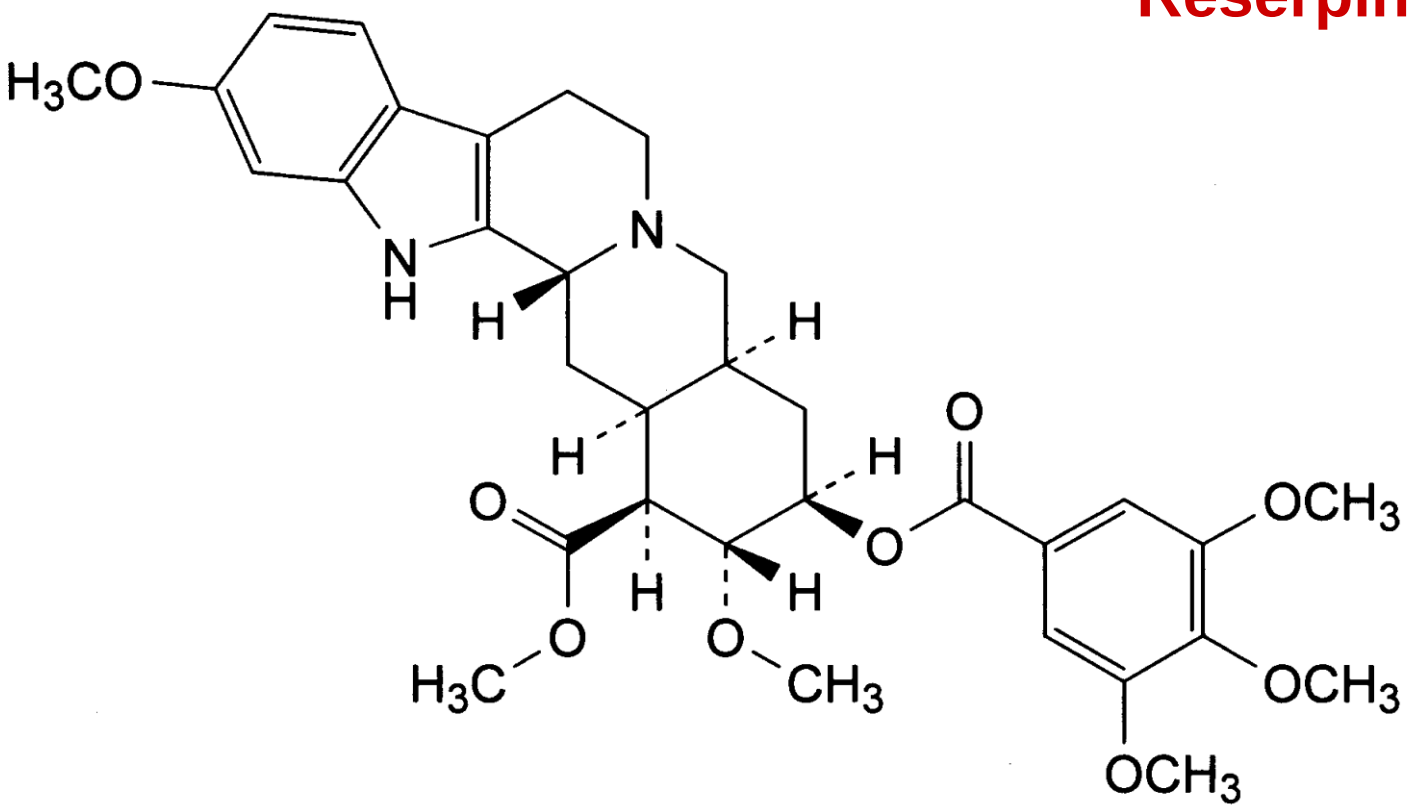
Dihydroergocornine	R = $CH(CH_3)_2$
Dihydroergocristine	R = $CH_2C_6H_5$
Dihydro-α-ergocryptine	R = $CH_2CH(CH_3)_2$
Dihydro-β-ergocryptine	R = $CH(CH_3)CH_2CH_3$

ASSAY

Dissolve 0.300 g in 60 ml of *pyridine R*. Pass a stream of *nitrogen R* over the surface of the solution and titrate with *0.1 M tetrabutylammonium hydroxide*, determining the end-point potentiometrically *(2.2.20)*. Note the volume used at the second point of inflexion.

1 ml of *0.1 M tetrabutylammonium hydroxide* is equivalent to 35.39 mg of $C_{36}H_{45}N_5O_8S$.

Reserpine



Oxidation products

Dissolve 20 mg in *glacial acetic acid R* and dilute to 100.0 ml with the same acid. The absorbance *(2.2.25)* measured immediately at 388 nm is not greater than 0.10.

ASSAY

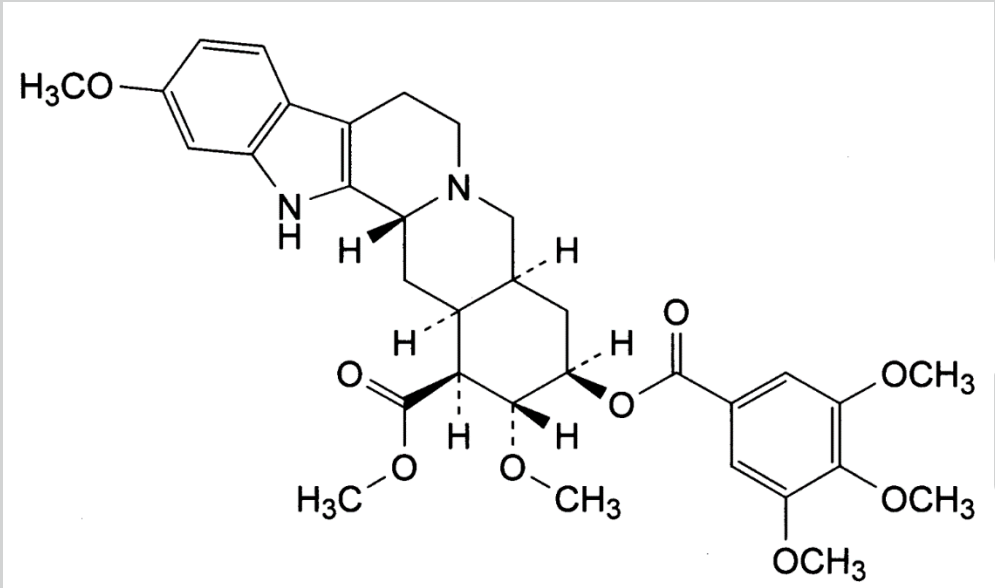
Total alkaloids

Dissolve 0.500 g in a mixture of 6 ml of *acetic anhydride R* and 40 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically *(2.2.20)*.

Reserpine

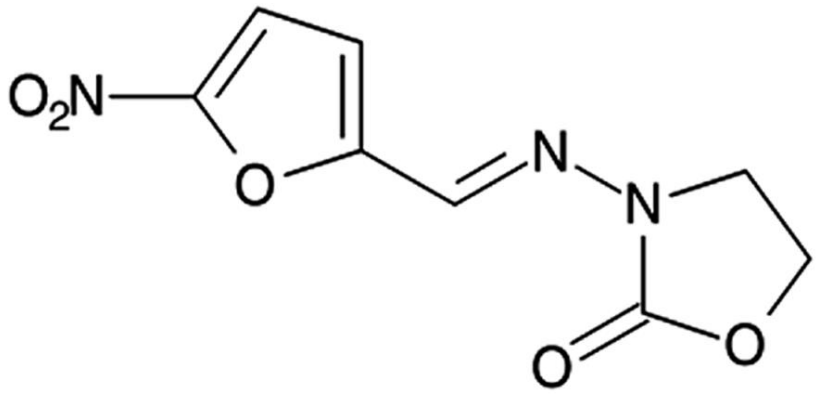
Protect the solutions from light. Moisten 25.0 mg with 2 ml of *alcohol R*, add 2 ml of *0.25 M sulphuric acid* and 10 ml of *alcohol R*, and warm gently to effect solution. Cool and dilute to 100.0 ml with *alcohol R*. Dilute 5.0 ml of this solution to 50.0 ml with *alcohol R*. Prepare a reference solution in the same manner using 25.0 mg of *reserpine CRS*. Place 10.0 ml of each solution separately in two boiling-tubes, add 2.0 ml of *0.25 M sulphuric acid* and 2.0 ml of a freshly prepared 3 g/l solution of ***sodium nitrite R*.** Mix and heat in a water-bath at 55 °C for 35 min. Cool, add 1.0 ml of a freshly prepared 50 g/l solution of *sulphamic acid R* and dilute to 25.0 ml with *alcohol R*. Measure the absorbance *(2.2.25)* of each solution at the maximum at 388 nm, using as the compensation liquid 10.0 ml of the same solution treated at the same time in the same manner, but omitting the sodium nitrite.

Electrochemical (anodic) oxidation of reserpine in an acidic medium results in the formation of 3,4-dehydroreserpine instead of the reported 10-hydroxy-reserpine. Electrochemical and chemical oxidation by sodium nitrite lead quantitatively to the same product; few by-products or consecutive products are formed if protected from light. The validity of the conditions of the spectrophotometric assay of the European Pharmacopoeia were confirmed by following the reaction using HPLC with a photodiode-array detector.



АНАЛИЗ НА ЛЕКАРСТВА, ПРОИЗВОДНИ НА ФУРАН

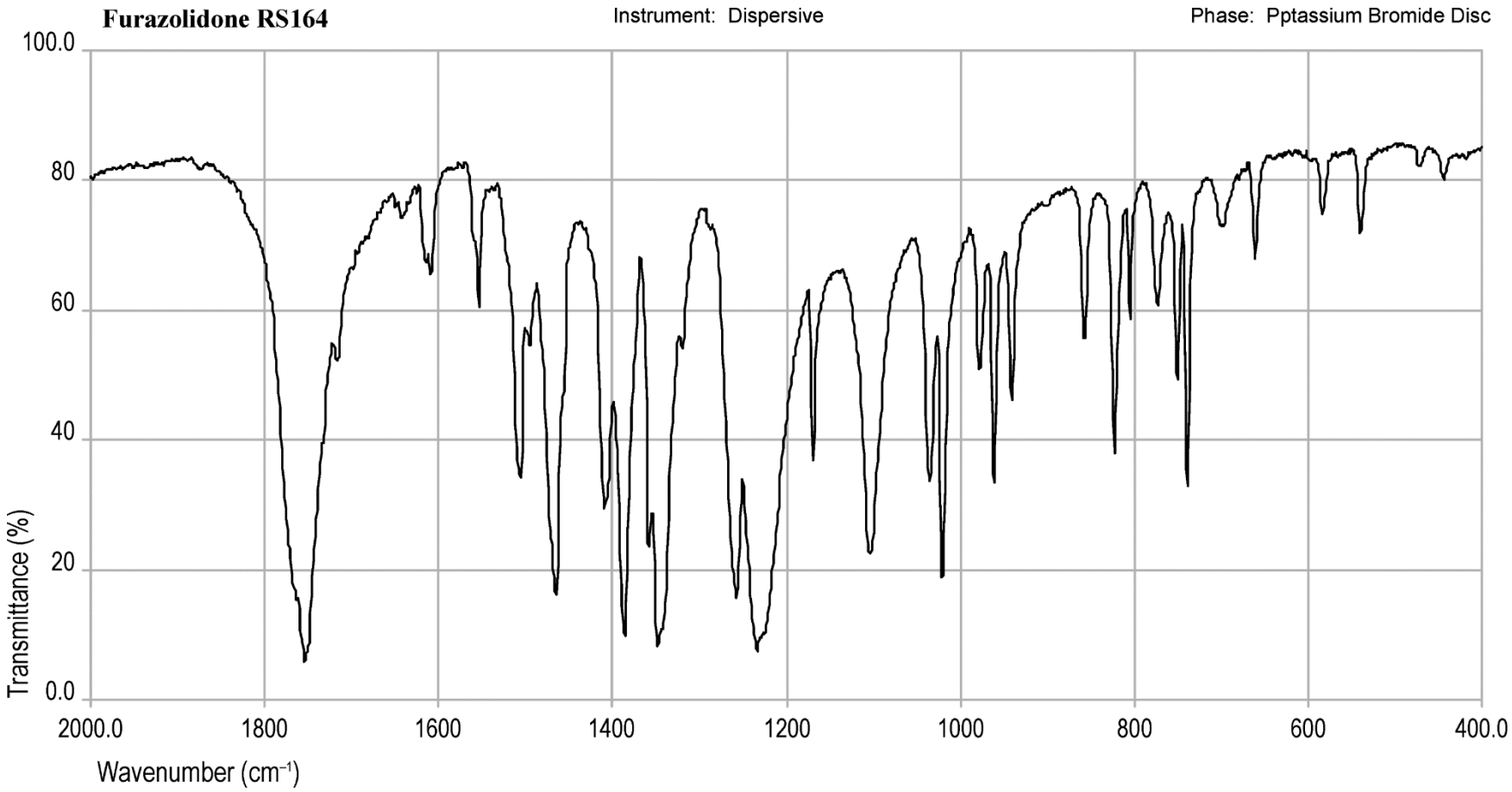
3-(5-nitrofurfurylideneamino)oxazolidin-2-one



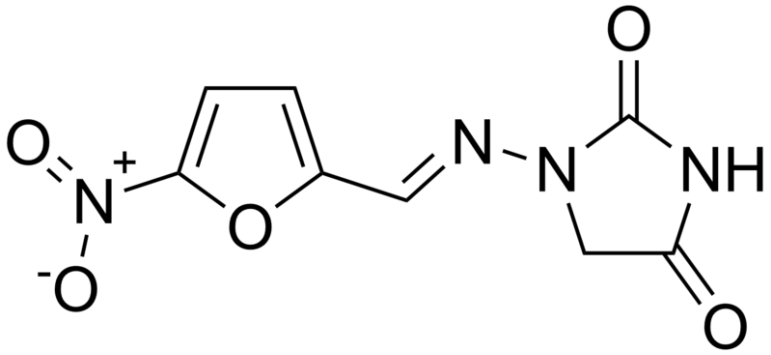
Furazolidone

ИЧ-тест за идентичност

–C–NO_2	- 1550 и 1350 cm^{-1}
–C–N	– валентно при 900 – 1300 cm^{-1}
–C=N	– валентно при 1580 – 1700 cm^{-1}


Furazolidone RS164
Instrument: Dispersive
Phase: Pptassium Bromide Disc
100.0
80
60
40
20
0.0
Transmittance (%)
2000.0
1800
1600
1400
1200
1000
800
600
400.0
Wavenumber (cm-1)

Nitrofurantoin

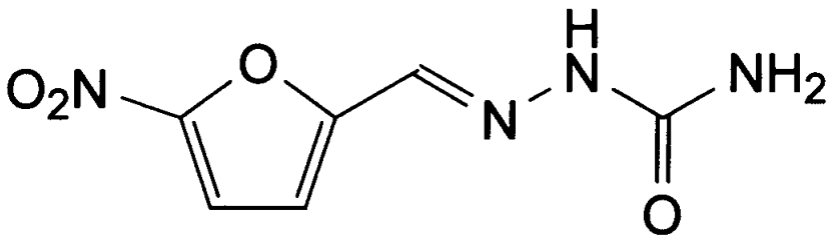


1-[[(5-nitrofuran-2-yl)methylene]amino] imidazolidine-2,4-dione

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 220 to 400 nm of the final solution obtained in the Assay exhibits two maxima, at 266 nm and 367 nm.

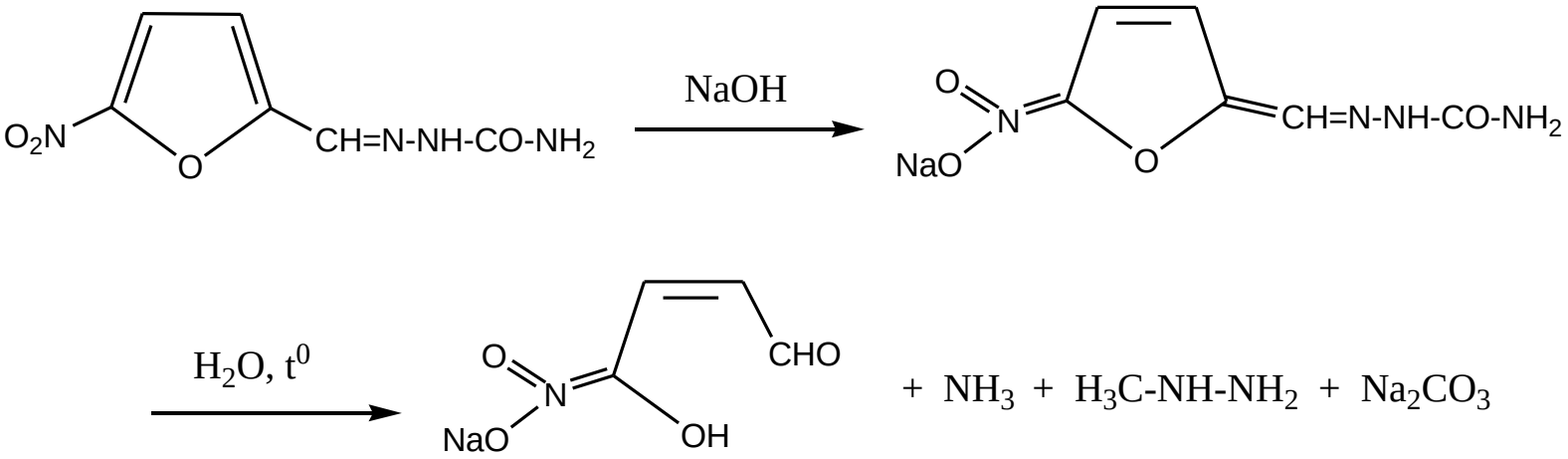
B. Dissolve 5 mg of the residue obtained by centrifuging a quantity of the oral suspension containing 50 mg of Nitrofurantoin in 5 ml of 0.1M *sodium hydroxide*. A deep yellow solution is produced, which changes to deep orange-red.



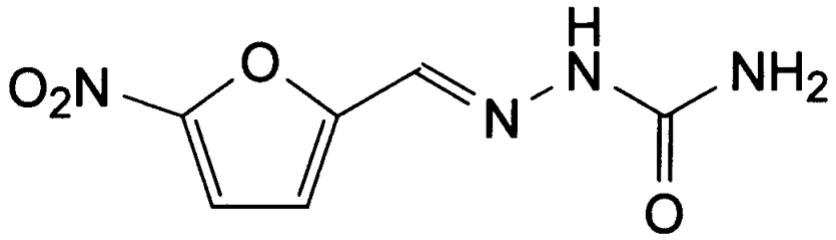
Nitrofurazone

2-[(5-nitrofuran-2-yl)methylene]diazanecarboxamide

Идентичност: 1. Реакция с натриев хидроксид:



оранжевочервено оцветяване



Semicarbazone derivative

With ketones:

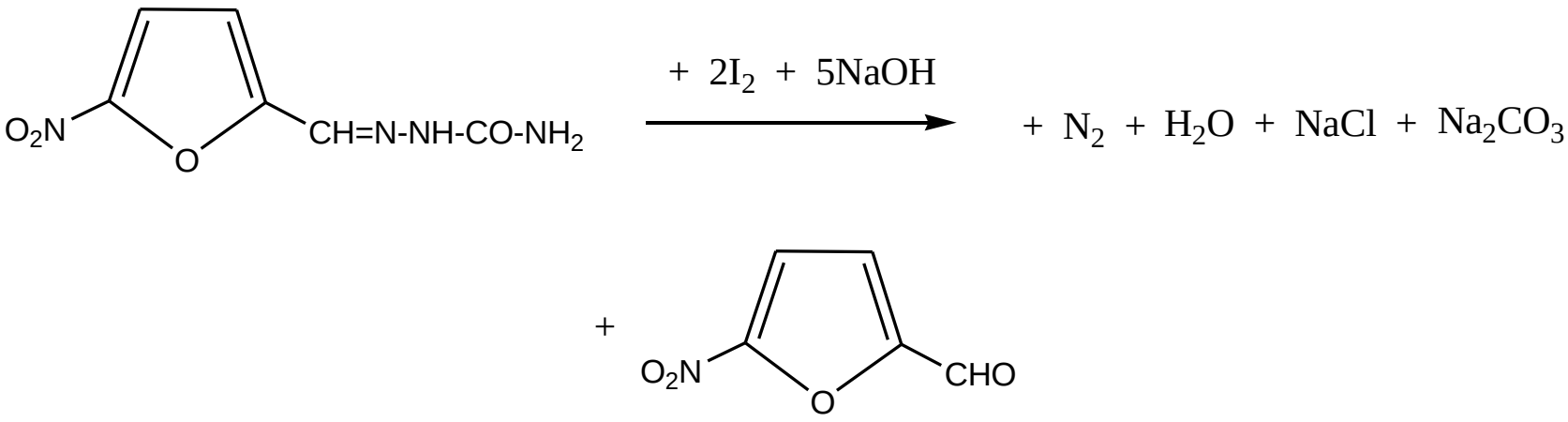
$$H_2NNHC(=O)NH_2 + RC(=O)R \rightarrow R_2C=NNHC(=O)NH_2$$

semicarbazide

With aldehydes:

$$H_2NNHC(=O)NH_2 + RCHO \rightarrow RCH=NNHC(=O)NH_2$$

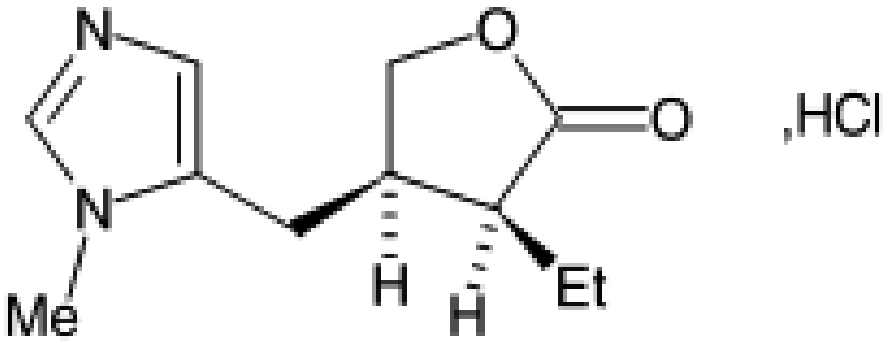
Semicarbazones are crystalline solids, useful for the identification of the parent aldehydes/ketones by melting point analysis.



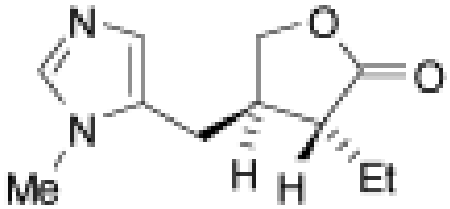
2. Реакция за доказване на нитрогрупа, която има свойства на ароматна - образуват се цветни нитрониеви соли. Нитрогрупата е причина и слабокиселите им свойства – разтварят се в основни разтворители – диметилформамид, пиридин като дават цветни солвати.

Pilocarpine HCl

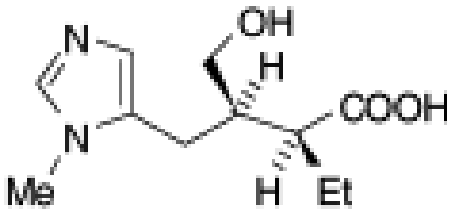
(3*S*,4*R*)-3-ethyl-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]dihydrofuran-2(3*H*)one



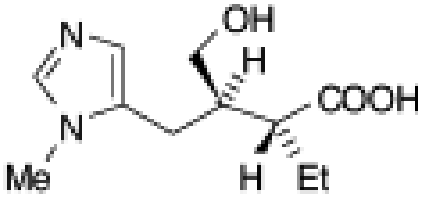
isopilocarpine



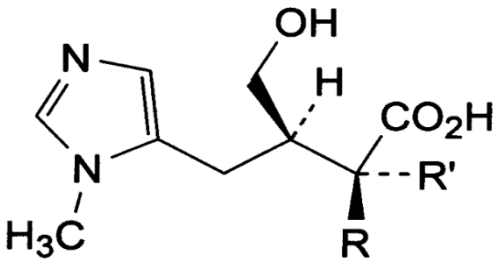
pilocarpic acid



isopilocarpic acid



Pilocarpine



Examine by liquid chromatography *(2.2.29)*.

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 100.0 ml with the same solvent.

Reference solution (a) Dilute 5.0 ml of the test solution to 100.0 ml with *water R*. Dilute 2.0 ml of the solution to 20.0 ml with *water R*.

Reference solution (b) Dissolve 5.0 mg of *pilocarpine nitrate for system suitability CRS* in *water R* and dilute to 50.0 ml with the same solvent.

Reference solution (c) To 5 ml of the test solution, add 0.1 ml of *ammonia R* and heat the solution on a water-bath for 30 min, cool and dilute to 25 ml with *water R*. Take 3 ml of this solution and dilute to 25 ml with *water R*. Mainly **pilocarpic acid** is formed.