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

Лекция №06

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

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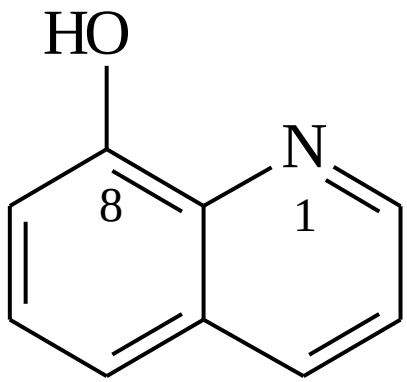
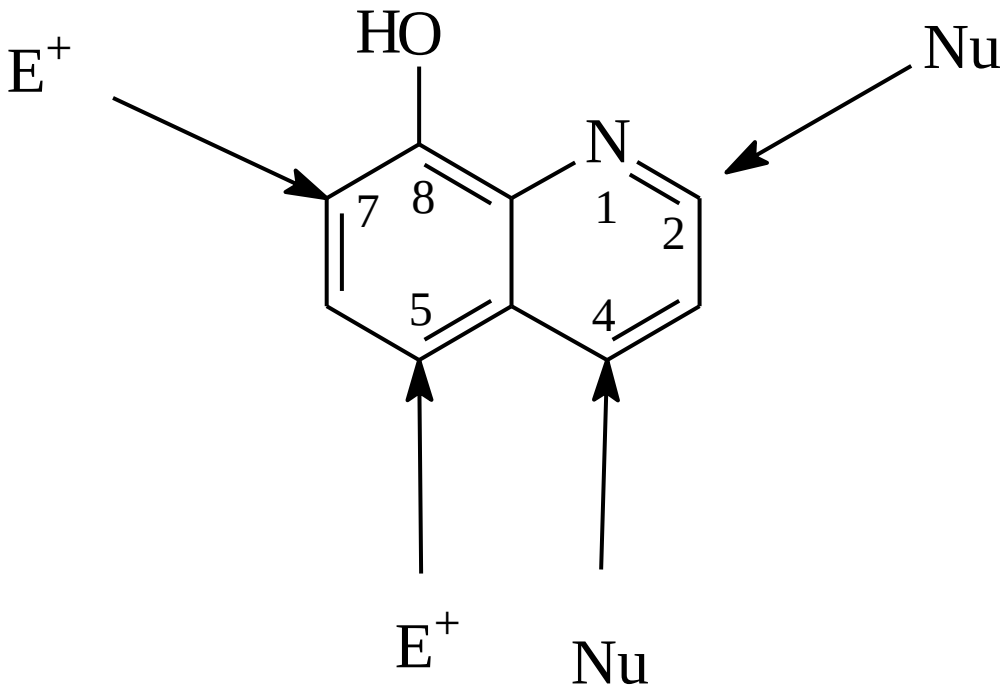
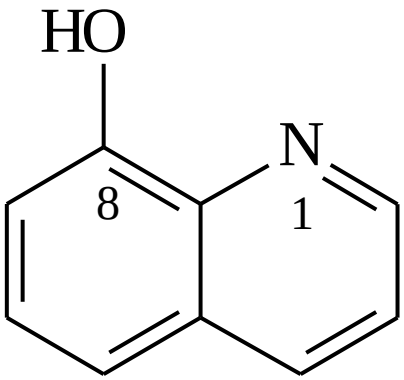
АНАЛИЗ НА ХИНОЛИНОВИ И ИЗОХИНОЛИНОВИ ПРОИЗВОДНИ

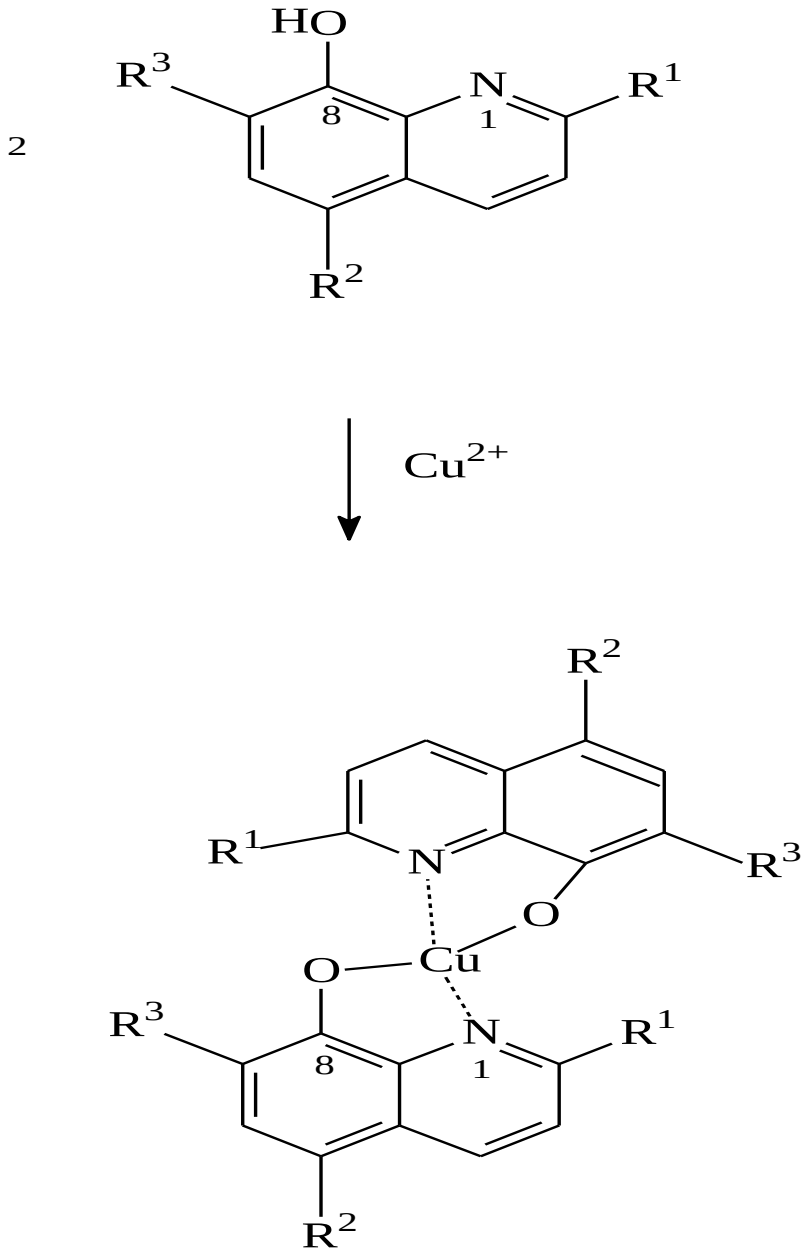


8 – ХИДРОКСИХИНОЛИН
pKa1 = 5,05 (база)
pKa2 = 9,81 (киселина)

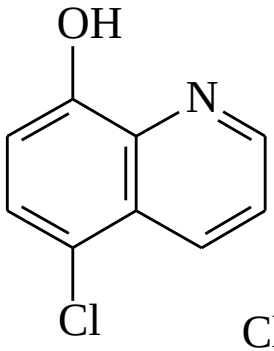


8-Hydroxyquinoline is a monoprotic bidentate chelating agent. Related ligands are the Schiff bases derived from salicylaldehyde, such as salicylaldoxime and salen. In neutral solution, the hydroxyl is in the protonated form (pKa=9.89) and the nitrogen is not protonated (pKa=5.13). However, an excited-state zwitterionic isomer exists in which H+ is transferred from the oxygen (giving an oxygen anion) to the nitrogen (giving a protonated nitrogen cation).



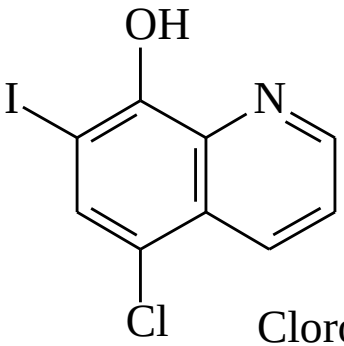

2
HO
R3
N
R1
8
1
R2
Cu2+
R2
R1
N
R3
O
O
Cu
R3
N
R1
8
1
R2

Cloxiquin



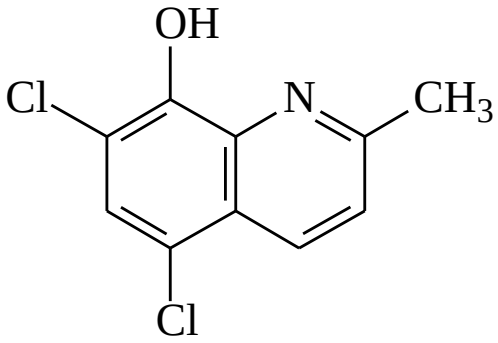
5-Chloroquinolin-8-ol

Clioquinol



5-Chloro-7-iodoquinolin-8-ol

Cloroquinaldol



5,7-dichloro-2-methyl-8-quinolinol

Appearance

Almost white, light yellow, brownish-yellow or yellowish-grey powder.

Solubility

Practically insoluble in water, sparingly soluble in methylene chloride, very slightly soluble or slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification *B.*

Second identification *A, C, D.*

A. Dissolve 40.0 mg in *methanol R* and dilute to 100.0 ml with the same solvent. Dilute 10.0 ml to 100.0 ml with *methanol R* (solution A). Examined between 280 nm and 350 nm *(2.2.25)*, solution A shows an absorption maximum at 321 nm. Dilute 10.0 ml of solution A to 100.0 ml with *methanol R* (solution B). Examined between 230 nm and 280 nm, solution B shows an absorption maximum at 255 nm. The specific absorbance at this absorption maximum is 1530 to 1660.

B. Infrared absorption spectrophotometry *(2.2.24)*.

Preparation Discs of *potassium bromide R*.

Comparison *clioquinol CRS*.

C. When heated, violet fumes are produced.

D. Dissolve about 1 mg in 5 ml of *ethanol (96 per cent) R*. Add 0.05 ml of *ferric chloride solution R1*. A dark green colour develops.

Halides

Maximum 140 ppm, expressed as chlorides.

Shake 0.5 g with 25 ml of *water R* for 1 min and filter. To the filtrate add 0.5 ml of *dilute nitric acid R* and 0.5 ml of *silver nitrate solution R2*. Allow to stand for 5 min. Any opalescence is not more intense than that in a standard prepared at the same time by adding 0.5 ml of *silver nitrate solution R2* to 25 ml of *water R* containing 0.2 ml of *0.01 M hydrochloric acid* and 0.5 ml of *dilute nitric acid R*.

ASSAY

Dissolve 0.200 g in 20 ml of *acetic anhydride R* and add 30 ml of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically *(2.2.20)*.

1 ml of *0.1 M perchloric acid* is equivalent to 30.55 mg of total quinolines, calculated as clioquinol.

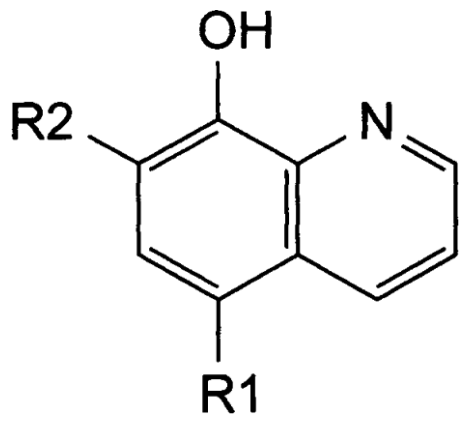
STORAGE

Protected from light.

clioquinol

IMPURITIES

Specified impurities *A, B, C.*



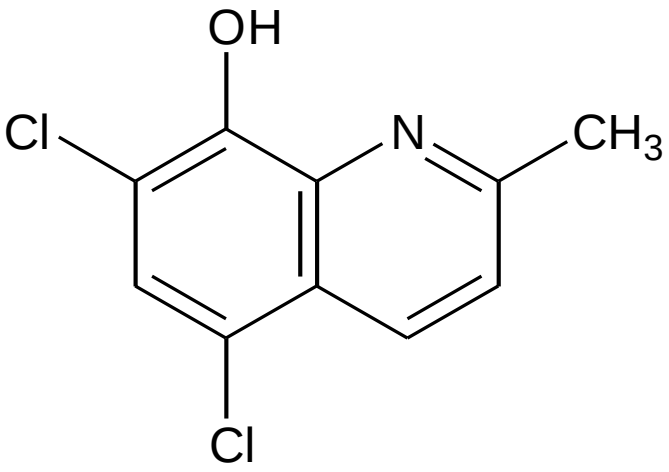
A. R1 = Cl, R2 = H: 5-chloroquinolin-8-ol,

B. R1 = R2 = Cl: 5,7-dichloroquinolin-8-ol,

C. R1 = R2 = I: 5,7-diiodoquinolin-8-ol.

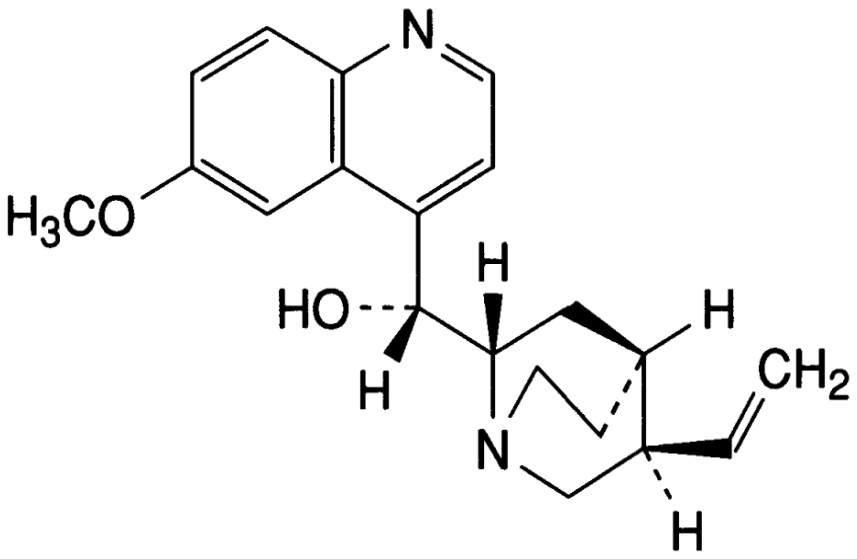
Ph Eur

Chloroquinaldol



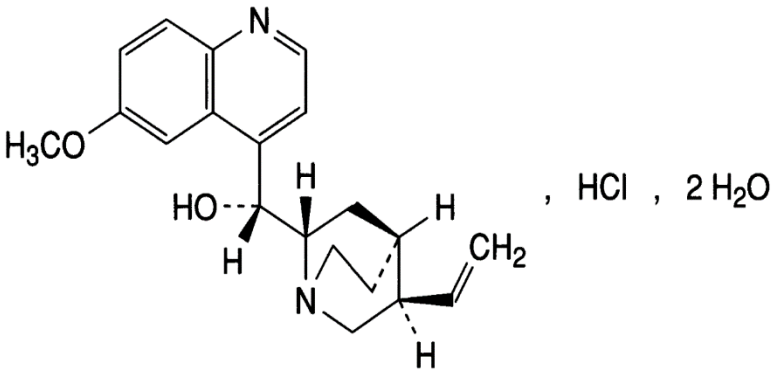
Literature references: Prepd by chlorination of 8-hydroxyquinaldine with or without formic acid as solvent: Senn, U.S. pat. 2,411,670 (1946 to Geigy).
Properties: Yellow needles from alc, mp 114-115degrees (slight decompn) . Medicinal odor. uv max (ethanol): 316 nm (A 1% 1cm 170) ; min 280 nm. Practically insol in water. Soly (25degrees) in ethanol 1.0 g/100 ml of soln; chloroform 5.0 g; acetone 4.0 g; ether 3.0 g; 0.1 N NaOH 1.4 g. Also sol in benzene, glacial acetic acid.
Melting Point: 114-115 degrees (slight decomp.) UV Maxima: 316
THERAP CAT: Antibacterial.
THERAP CAT (VET): Antibacterial; antifungal.

Quinine Hydrochloride



, HCl , 2 H_2O

Quinine Hydrochloride



(*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol hydrochloride

Other cinchona alkaloids

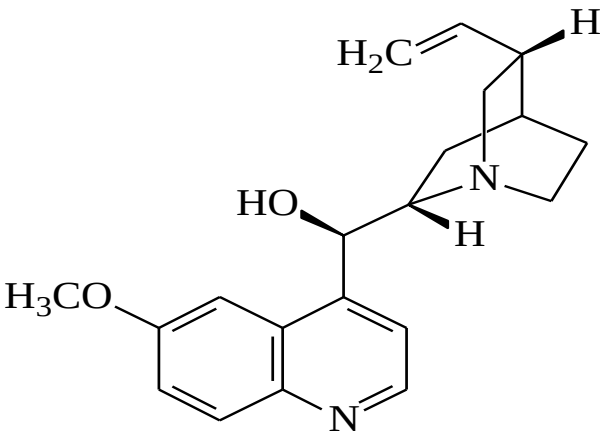
Examine by liquid chromatography *(2.2.29)*.

Test solution Dissolve 20 mg of the substance to be examined, with gentle heating if necessary, in 5 ml of the mobile phase and dilute to 10 ml with the mobile phase.

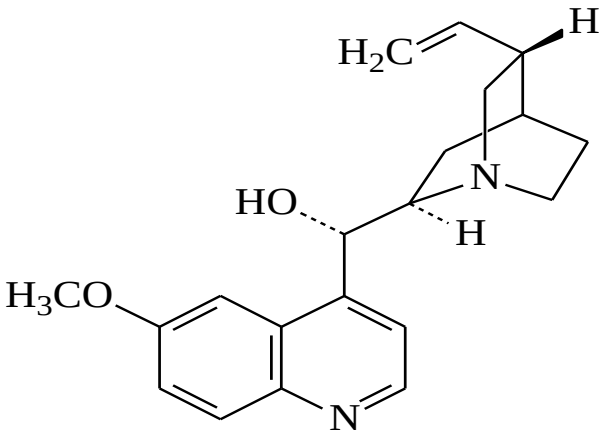
Reference solution (a) Dissolve 20 mg of *quinine sulphate CRS*, with gentle heating if necessary, in 5 ml of the mobile phase and dilute to 10 ml with the mobile phase.

Reference solution (b) Dissolve 20 mg of ***quinidine sulphate*** *CRS*, with gentle heating if necessary, in 5 ml of the mobile phase and dilute to 10 ml with the mobile phase.

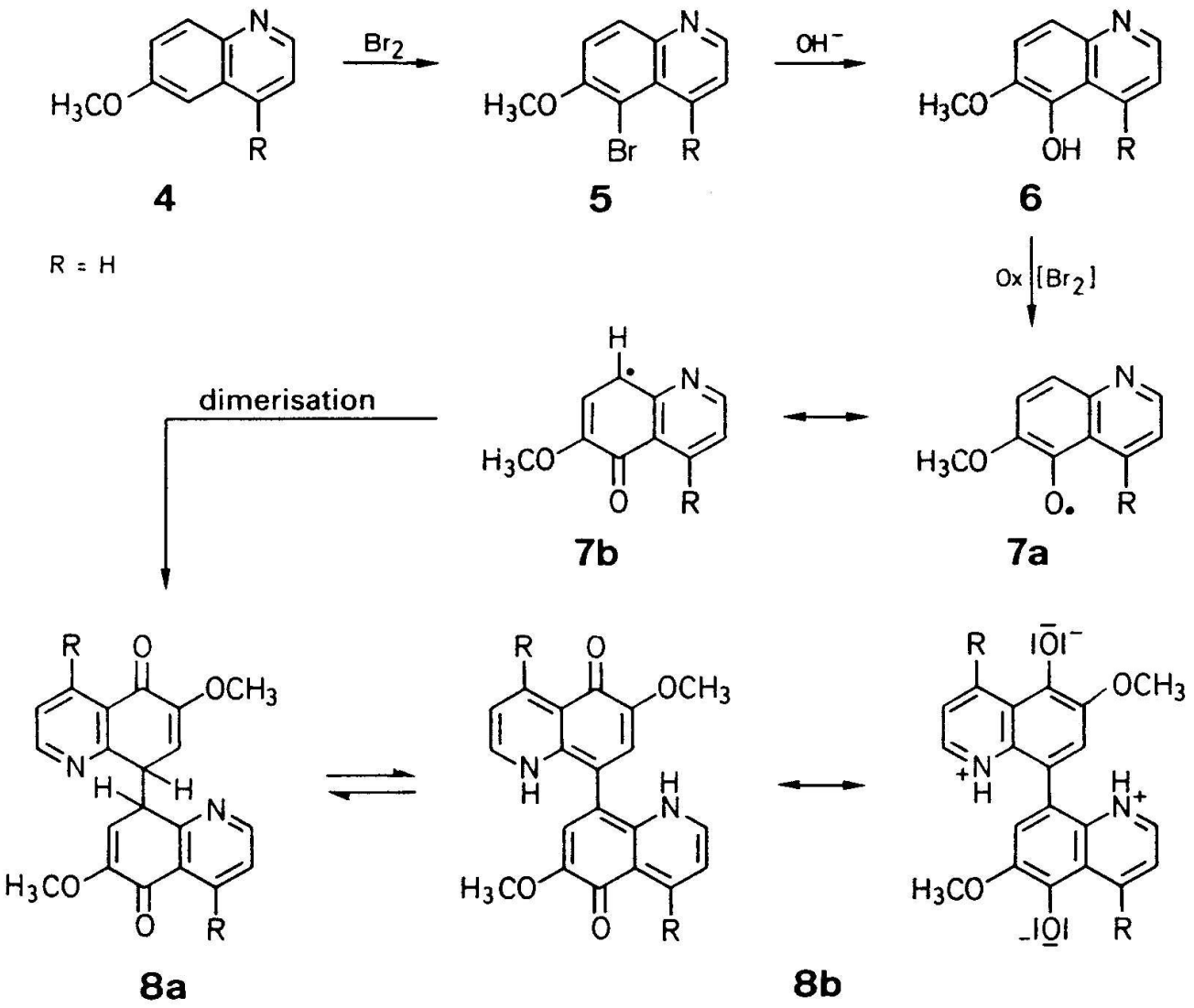
Quinine



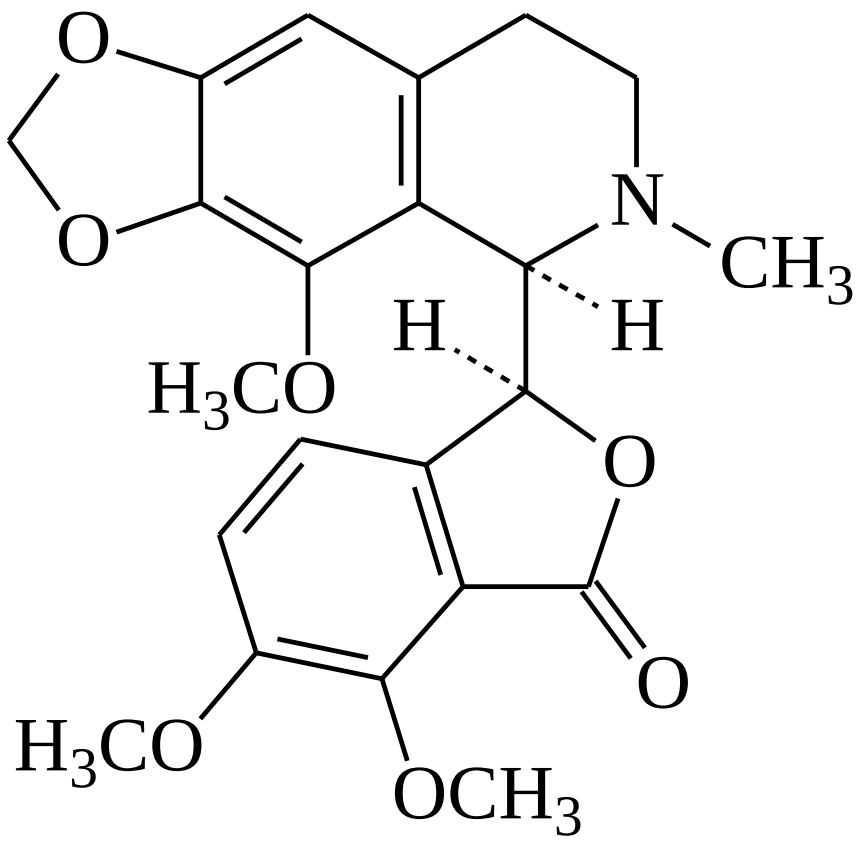
Quinidine



Summary: A high-performance liquid chromatographic method with fluorescence detection is described for the simultaneous measurement of quinine and quinidine in plasma, whole blood, and erythrocytes. The compounds were separated on an Ultrasphere C18 reversed-phase column (25 cm x 4.6 mm inside diameter, 5 μm particle size) using a mobile phase of acetonitrile/ water/triethylamine (11:88:1, vol/vol) at pH 2.5. The method, simple, accurate, and selective, requires only a single-step liquid-liquid extraction and uses the structurally similar alkaloid, cinchonine, as the internal standard. The commercial impurities, dihydroquinine and dihydroquinidine, and unknown metabolites were well resolved from the parent drugs. The assay is precise, with interassay coefficients of variation 7.0% and an accuracy of 7.3% over a concentration range of 0.125 to 4.0 μg/0.25 ml. The extraction recoveries of the two drugs were similar, averaging 82.9% for quinine and 79.3% for quinidine from the three biological fluids. The clinical application of the method for routine drug monitoring and for estimating the pharmacokinetics of quinine and quinidine in man are discussed.


Br2
OH⁻
H3CO
R
Br
OH
4
5
6
R = H
Ox [Br2]
dimerisation
H
O
O.
7b
7a
OCH3
H
8a
8b

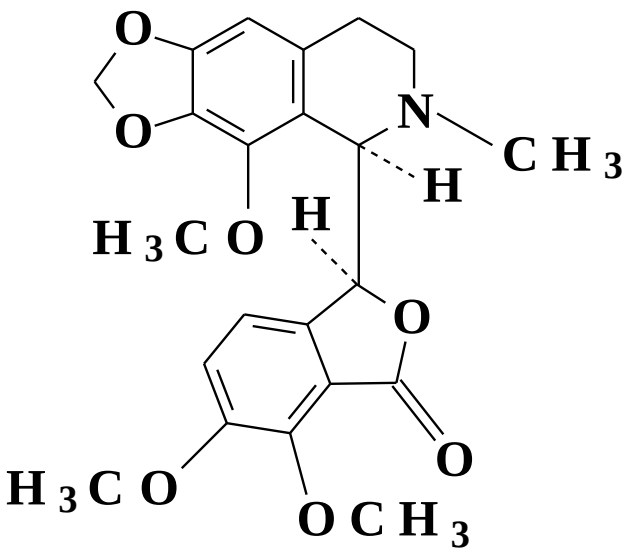
Noscapine



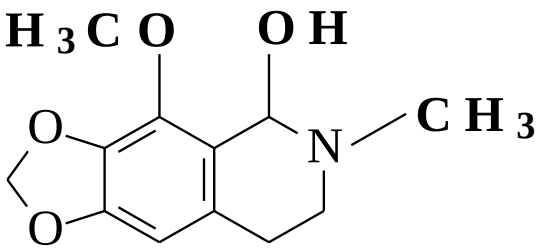
(3*S*)- 6,7-Dimethoxy-3-[(5*R*)-5,6,7,8-tetrahydro- 4-methoxy- 6-methyl-1,3-dioxolo(4,5-g)isoquinolin-5-yl]-1(3H)-isobenzofuranone

Naturally it occurs as the alpha enantiomer. It can be converted into the beta enantiomer when it is dissolved in alkaline water-ethanol solutions. The lactone ring is unstable and opens in basic media. The opposite reaction is presented in acidic media. The bond C1-C3' is also unstable. This is the bond connecting the two optically active carbon atoms. In aqueous solution of sulphuric acid and heating it dissociates into Cotarnine (4-methoxy- 6-methyl- 5,6,7,8-tetrahydro- [1,3]dioxolo [4,5-g]isoquinoline) and Opic acid (6-formyl- 2,3-dimethoxybenzoic acid). When Noscapine is reduced with Zn/HCl the bond C1-C3' saturates and the molecule dissociates into (2-hydroxycotarnine) and (6,7-dimethoxyisobenzofuran -1(3H)-one).

Noscapine

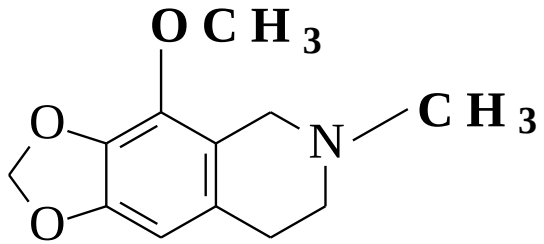


H_2SO_4 Zn/HCl



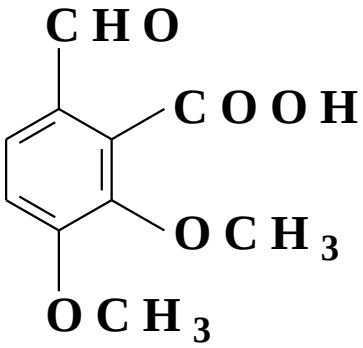
(2)

+

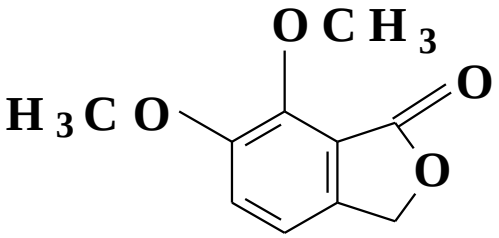


(4)

+



(3)

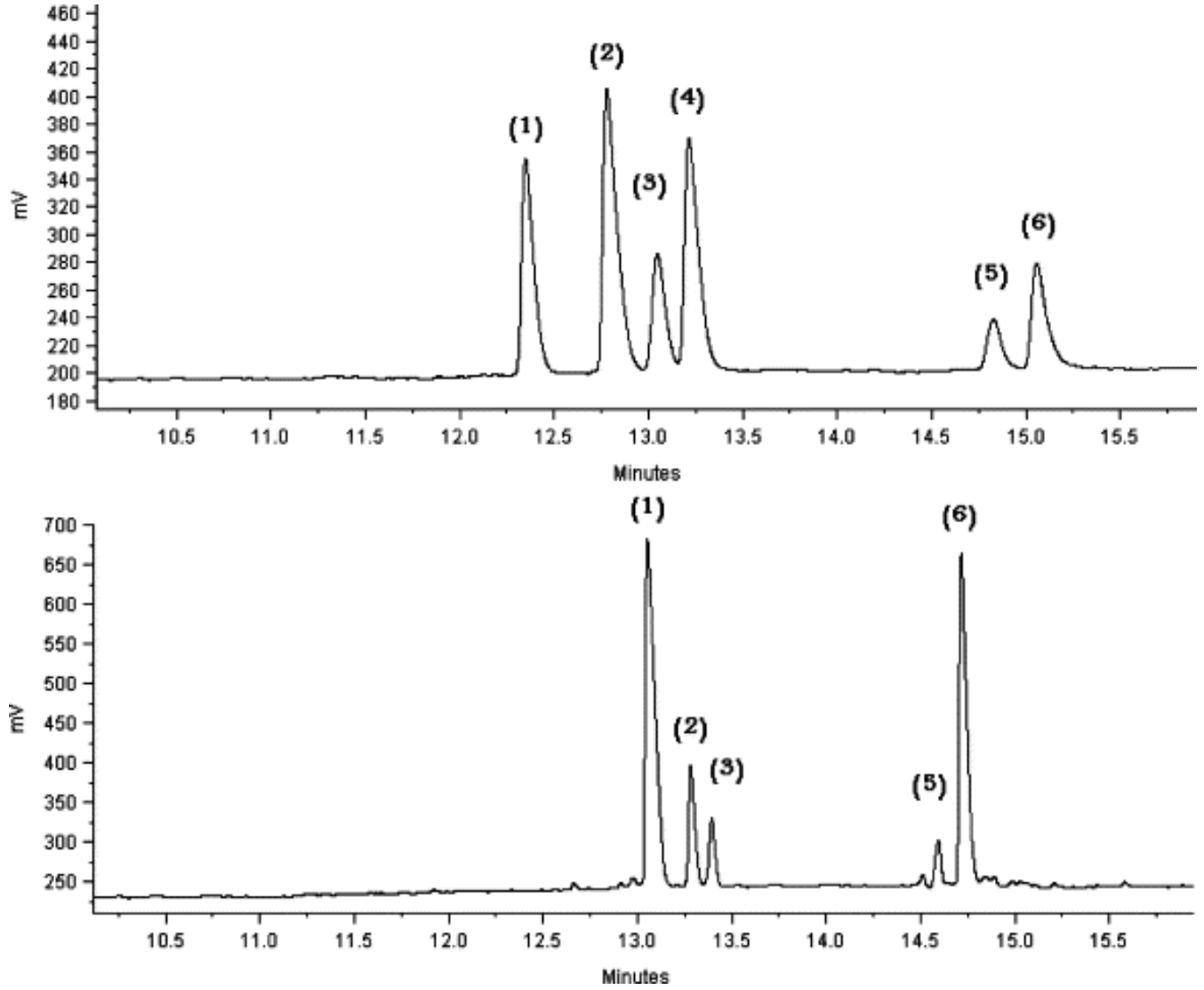


(5)

Cotarnine (4); Opic acid (3); 2-hydroxycotarnine (2); meconine (5)

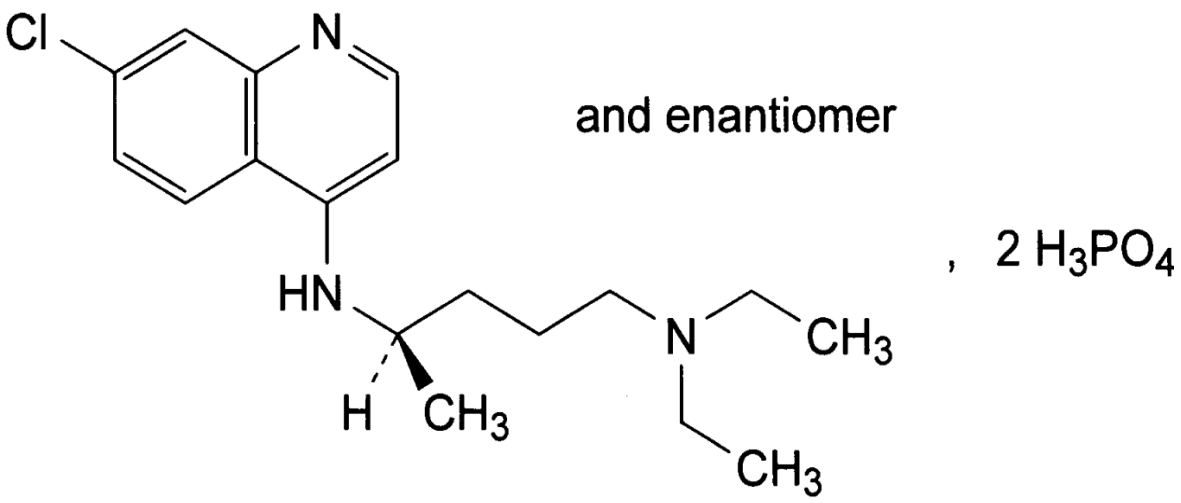
The fully automated commercially available capillary electrophoresis (CE) systems has presented as analytical alternative to HPLC and TLC. The modern CE instruments are capable of the required sensitivity and precision, with similar characteristics to HPLC. In addition, CE offers several advantages, including highly efficient and fast separations, relatively inexpensive and long lasting capillary columns, very small sample size requirements, and low reagent consumption.

A variety of detectors have been used in CE, including: UV-visible absorbance and, fluorescence, chemiluminescence, mass spectrometric, conductivity , radiometric detection. Of these, the most widely used are UV-visible absorbance detectors.



Typical electropherogram of (a) 500 ng/ml mixture of (1) morphine; (2) codeine; (3) thebaine; (4) 1000 ng/ml nalorphine (IS); (5) papaverine and (6) noscapin; (b) prepared opium sample

Chloroquine Phosphate



***N*⁴-(7-chloroquinolin-4-yl)-*N*¹,*N*¹-diethylpentane-1,4-diamine bis(dihydrogen phosphate)**

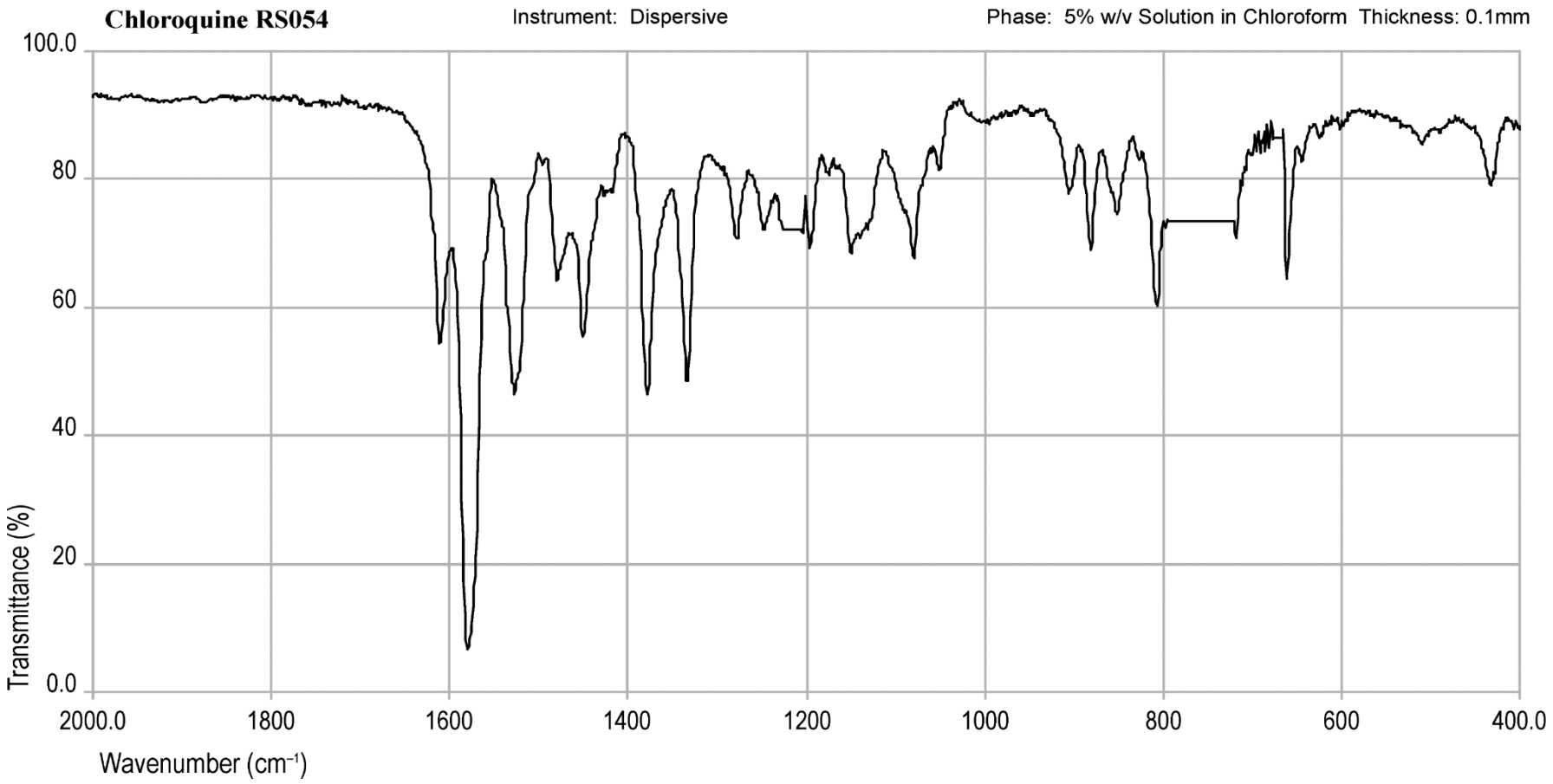
IDENTIFICATION

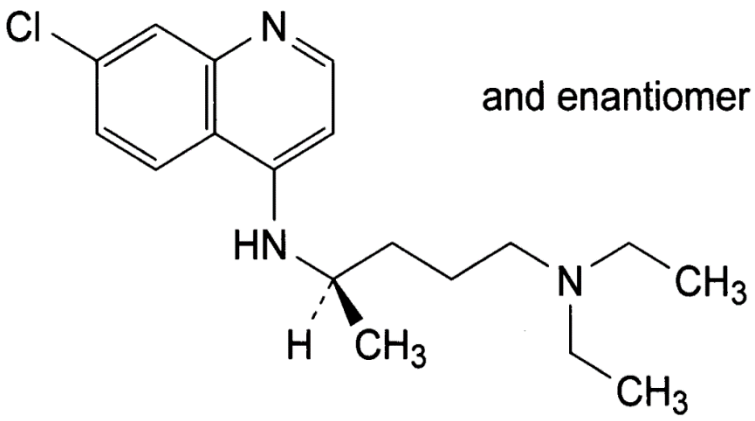
A. Dissolve 0.100 g in *water R* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of this solution to 100.0 ml with *water R*. Examined between 210 nm and 370 nm *(2.2.25)*, the solution shows **absorption maxima at 220 nm, 235 nm, 256 nm, 329 nm and 342 nm**. The specific absorbances at the maxima are respectively 600 to 660, 350 to 390, 300 to 330, 325 to 355 and 360 to 390.

B. Examine by **infrared absorption spectrophotometry** *(2.2.24)*, comparing with the spectrum obtained with the base isolated from *chloroquine sulphate CRS*. Record the spectra using solutions prepared as follows: dissolve separately 0.1 g of the substance to be examined and 80 mg of the reference substance in 10 ml of *water R*, add 2 ml of *dilute sodium hydroxide solution R* and shake with 2 quantities, each of 20 ml, of *methylene chloride R*; combine the organic layers, wash with *water R*, dry over *anhydrous sodium sulphate R*, evaporate to dryness and dissolve the residues separately, each in 2 ml of *methylene chloride R*.

C. Dissolve 25 mg in 20 ml of *water R* and add 8 ml of *picric acid solution R1*. The precipitate, washed with *water R*, with *alcohol R* and finally with *methylene chloride R*, melts *(2.2.14)* at 206-209 °C.

D. Dissolve 0.1 g in 10 ml of *water R*, add 2 ml of *dilute sodium hydroxide solution R* and shake with 2 quantities, each of 20 ml, of *methylene chloride R*. The aqueous layer, acidified by the addition of *nitric acid R*, gives reaction (b) of phosphates *(2.3.1)*.


Chloroquine RS054
Instrument: Dispersive
Phase: 5% w/v Solution in Chloroform Thickness: 0.1mm
100.0
80
60
40
20
0.0
Transmittance (%)
2000.0
1800
1600
1400
1200
1000
800
600
400.0
Wavenumber (cm⁻¹)



and enantiomer

, 2 H_3PO_4

ASSAY

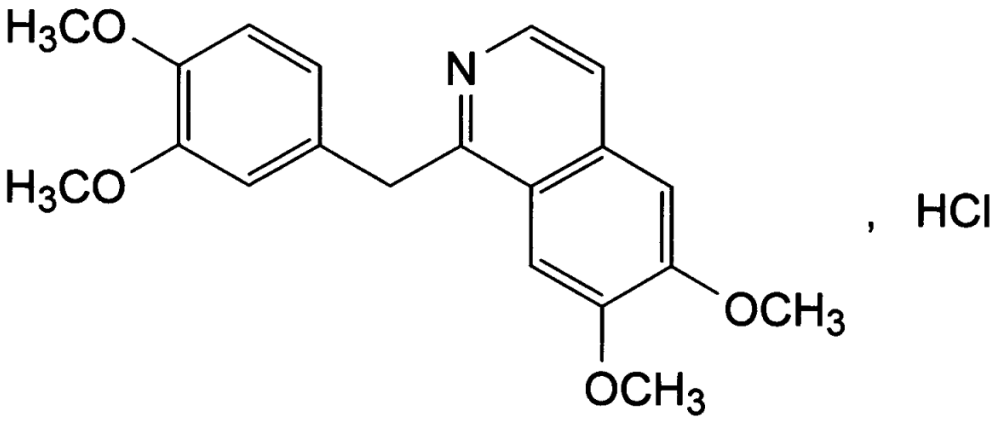
Dissolve 0.200 g in 50 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically *(2.2.20)*.

1 ml of *0.1 M perchloric acid* is equivalent to 25.79 mg of $C_{18}H_{32}ClN_3O_8P_2$.

STORAGE

In an airtight container , protected from light.

Papaverine Hydrochloride



1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline hydrochloride

White or almost white, crystalline powder or white or almost white crystals.

Solubility

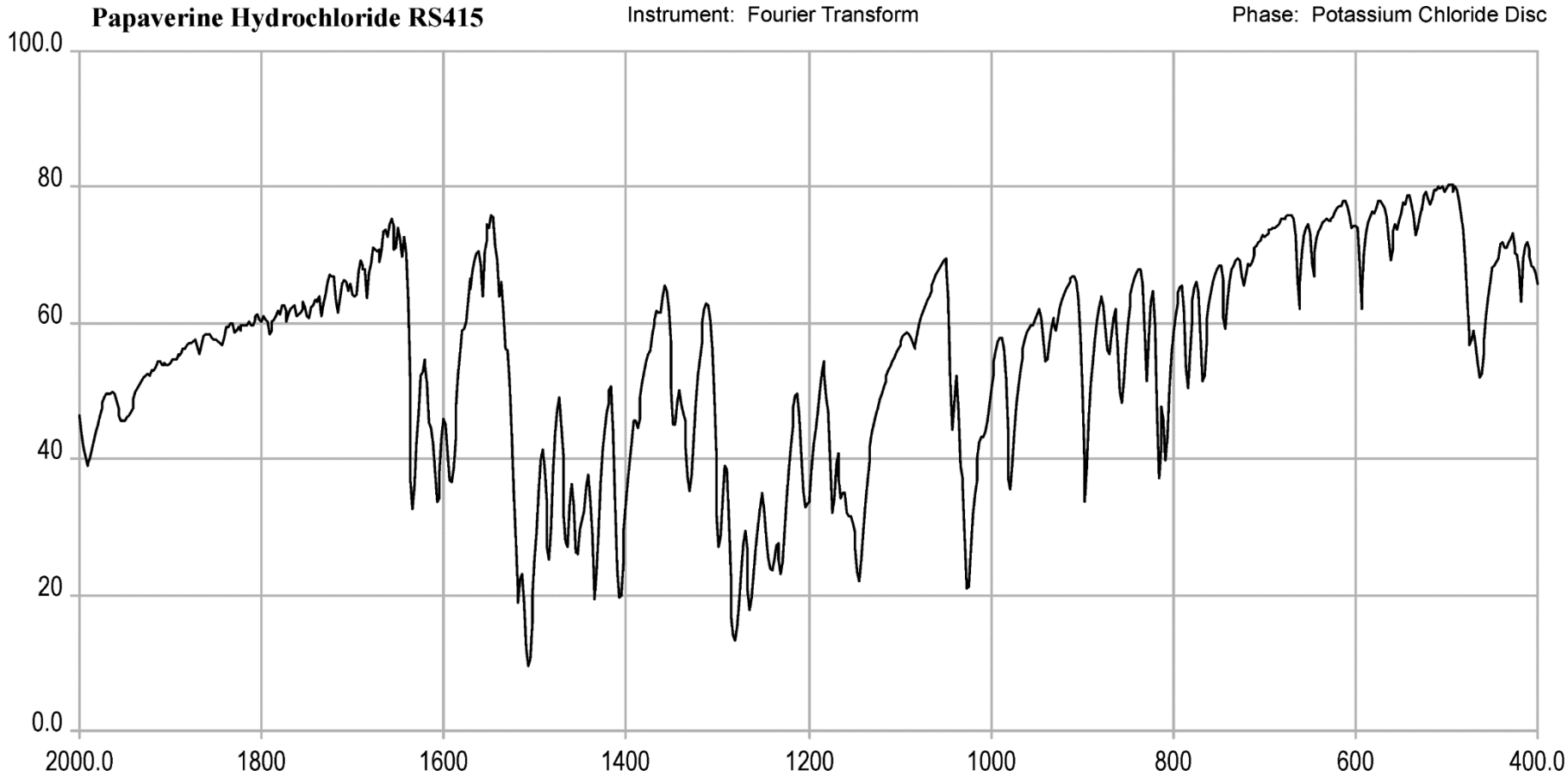
Sparingly soluble in water, slightly soluble in alcohol.

IDENTIFICATION

A. **Infrared absorption spectrophotometry** *(2.2.24)*.

Comparison papaverine hydrochloride CRS.

B. **Thin-layer chromatography** *(2.2.27)*.


Papaverine Hydrochloride RS415
Instrument: Fourier Transform
Phase: Potassium Chloride Disc
100.0
80
60
40
20
0.0
2000.0
1800
1600
1400
1200
1000
800
600
400.0

ASSAY

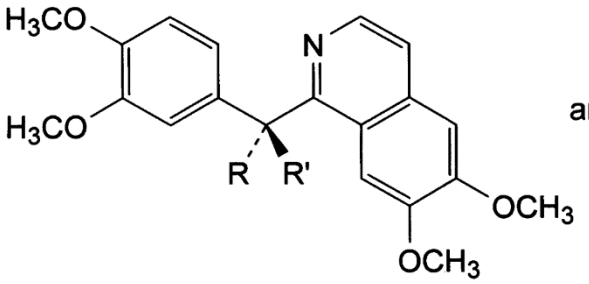
Papaverine Hydrochloride

Dissolve 0.300 g in a mixture of 5.0 ml of *0.01 M hydrochloric acid* and 50 ml of *alcohol R*. Carry out a potentiometric titration *(2.2.20)*, using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 ml of *0.1 M sodium hydroxide* is equivalent to 37.59 mg of $C_{20}H_{22}ClNO_4$.

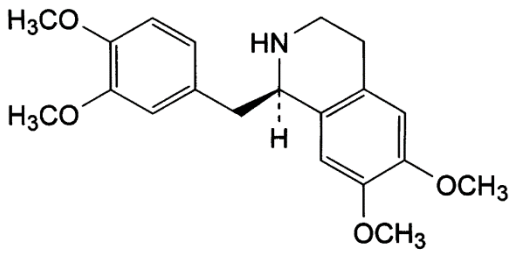
IMPURITIES

A. noscapine,



and enantiomer

B. 1-(3,4–dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (dihydropapaverine)



and enantiomer

Papaverine Injection

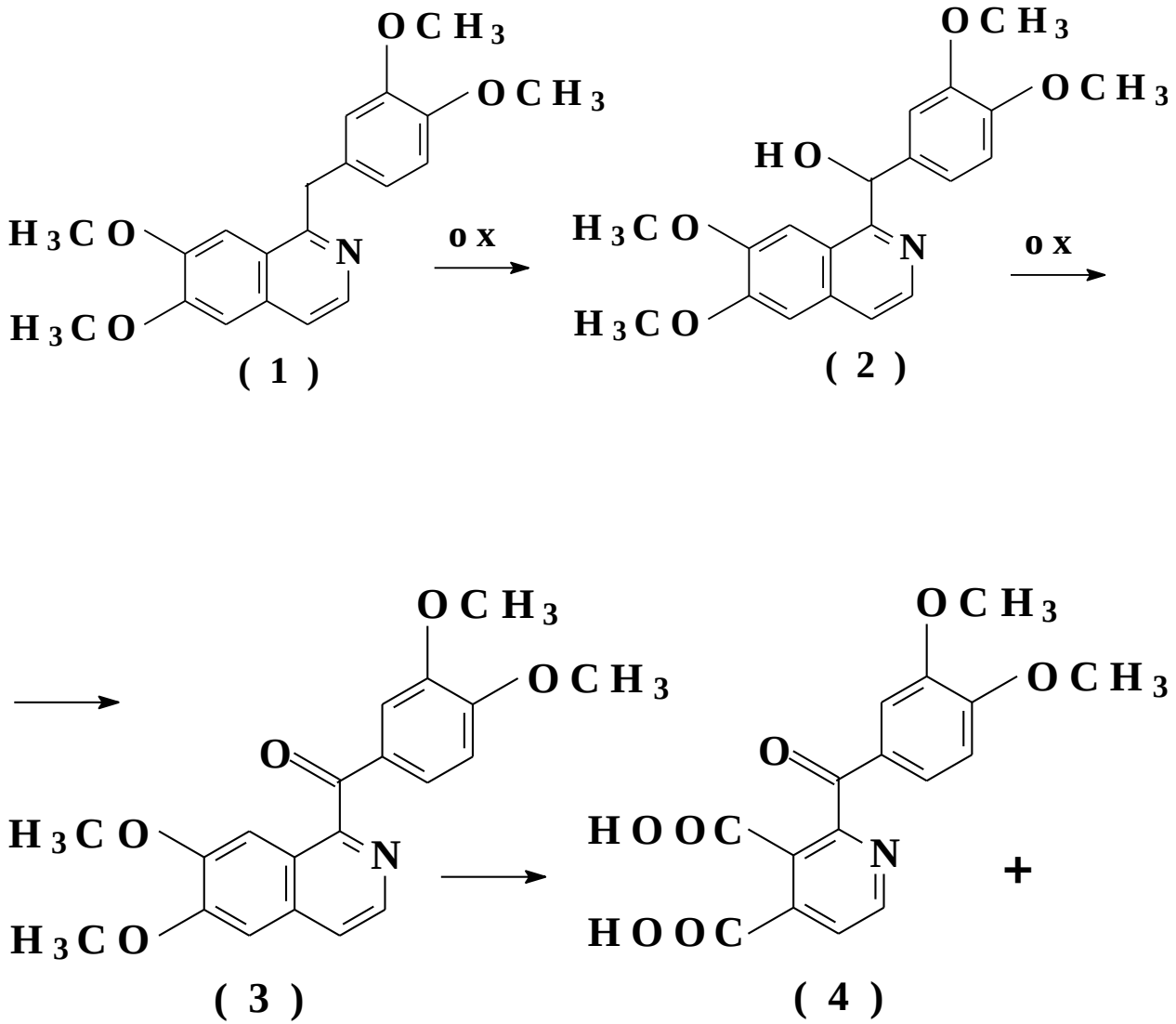
Related substances

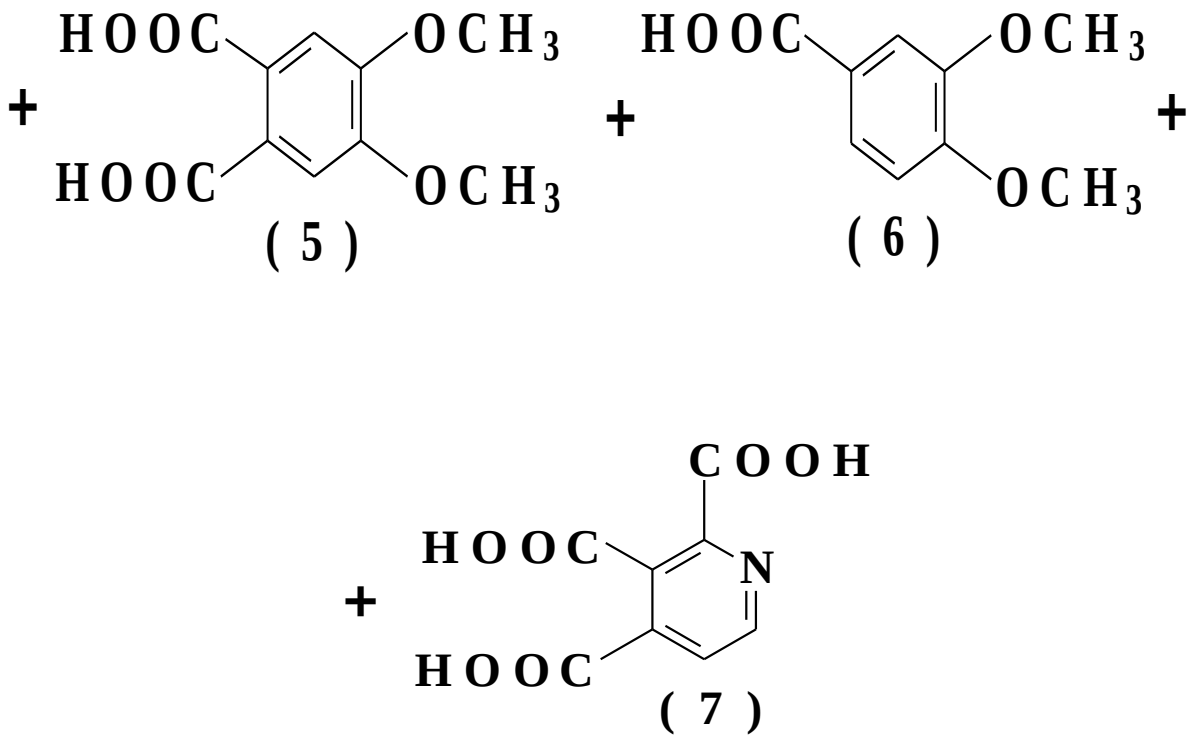
Carry out the method for ***liquid chromatography***, Appendix III D, using the following solutions. For solution (1) dilute a volume of the injection, if necessary, with *methanol (50%)* to produce a solution containing 0.06% w/v of Papaverine Hydrochloride. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *methanol* (50%). Solution (3) contains 0.0005% w/v of *papaverine hydrochloride BPCRS* and 0.005% w/v of *noscapine* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *endcapped octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C(18)2 is suitable), (b) as the mobile phase with a flow rate of 1 ml per minute a mixture prepared by adding 700 ml of *methanol* containing 2.22 g of *dioctyl sodium sulphosuccinate* to 100 ml of *water* containing 1.36 g of *sodium acetate*, diluting to 1 litre with *water* and adjusting the pH to 5.5 with *glacial acetic acid* and (c) a detection wavelength of 250 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the ***resolution factor*** between the peaks due to papaverine hydrochloride and noscapine is at least 3.0.

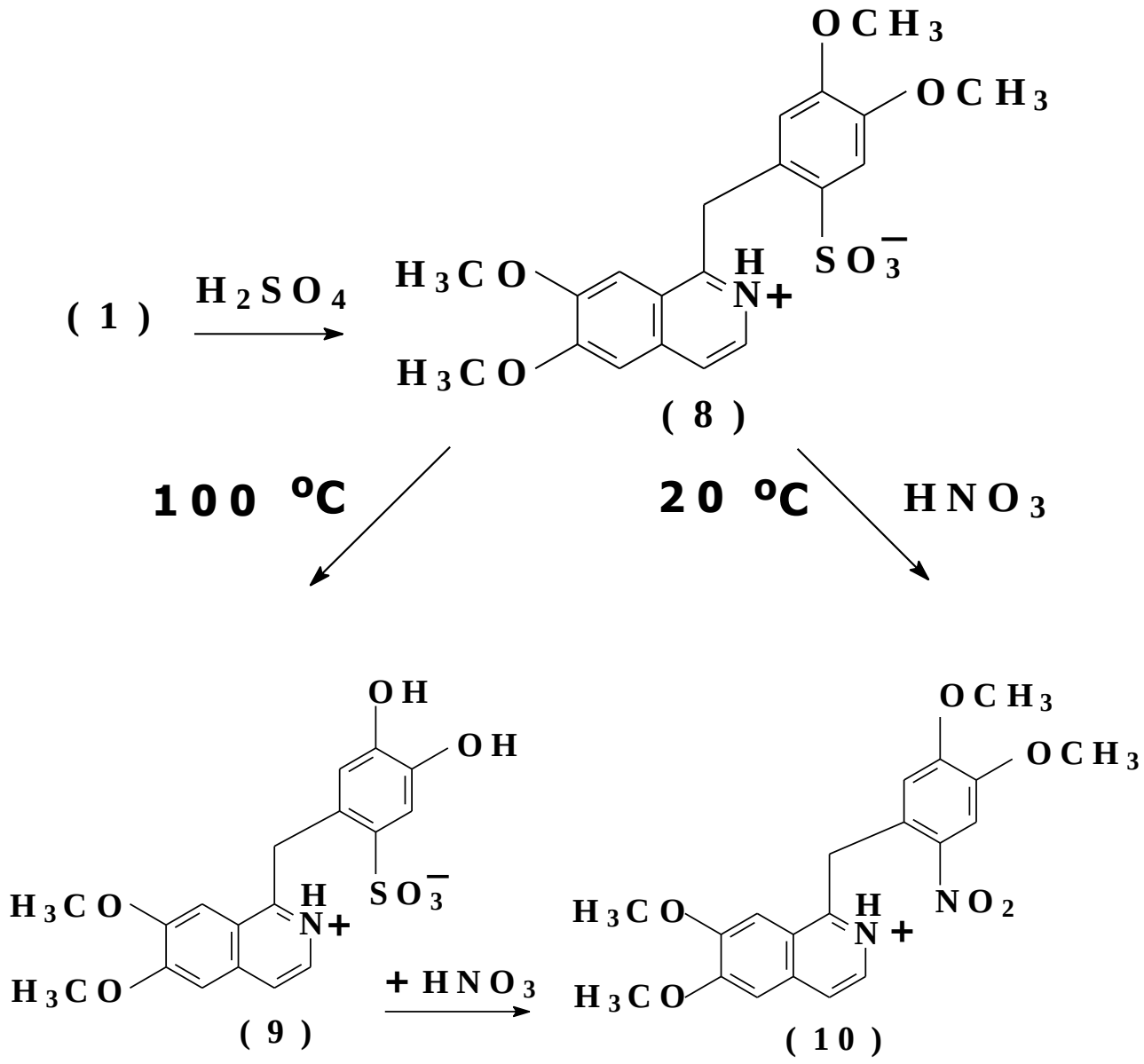
In the chromatogram obtained with solution (1), the sum of the areas of any *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).


O C H 3
O C H 3
H 3 C O
H 3 C O
N
o x
(1)
H O
(2)
O
H O O C
H O O C
+
(3)
(4)

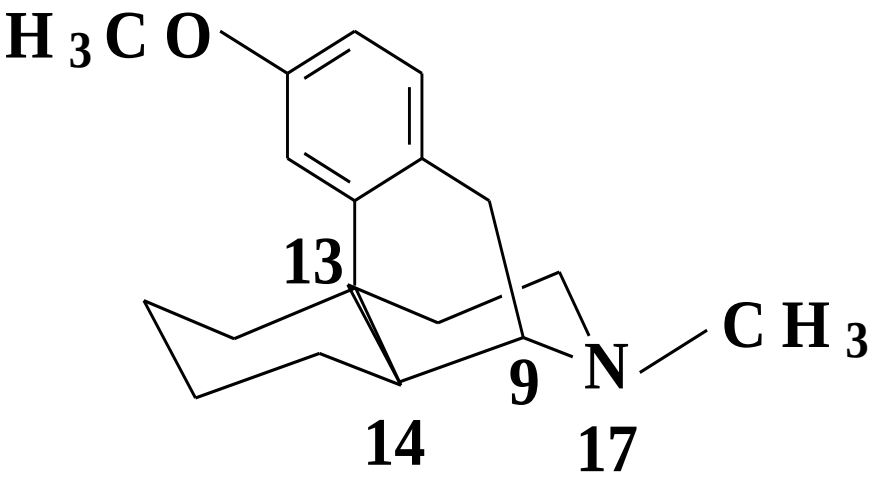


papaverinic acid (4); m-hemipinic acid (5); veratric acid (6);

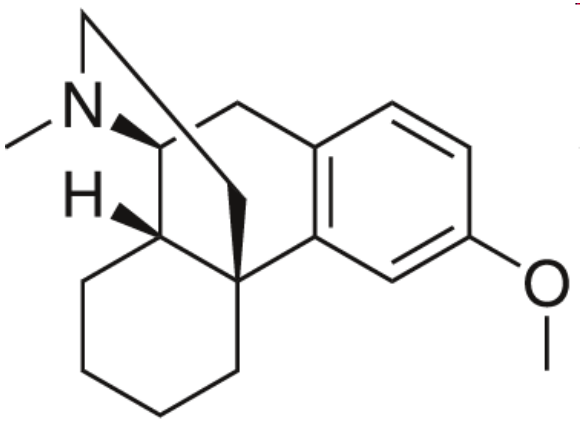
pyridine-2,3,4-carboxylic acid (7)


(1)
H2SO4
H3CO
H3CO
OCH3
OCH3
H
N+
SO3−
(8)
100 ºC
20 ºC
HNO3
OH
OH
SO3−
(9)
+ HNO3
NO2
(10)

Dextromethorphan

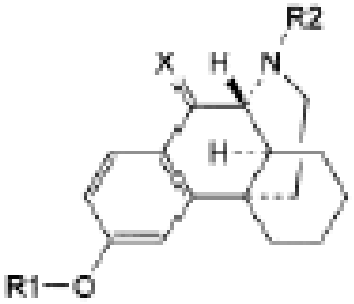


((+)-3-methoxy-17-methyl- (9α,13α,14α)-morphinan)



Dextromethorphan is the dextrorotatory enantiomer of the methyl ether of levorphanol, an opioid analgesic. It is also a stereoisomer of levomethorphan, an opioid analgesic. It is named according to IUPAC rules as (+)-3-methoxy-17-methyl-9α,13α,14α-morphinan. As the pure free base, dextromethorphan occurs as an odorless, white to slightly yellow crystalline powder. It is freely soluble in chloroform and essentially insoluble in water. Dextromethorphan is commonly available as the monohydrated hydrobromide salt, however some newer extended-release formulations contain dextromethorphan bound to an ion exchange resin based on polystyrene sulfonic acid. Dextromethorphan's specific rotation in water is +27.6° (20°C, Sodium D-line).

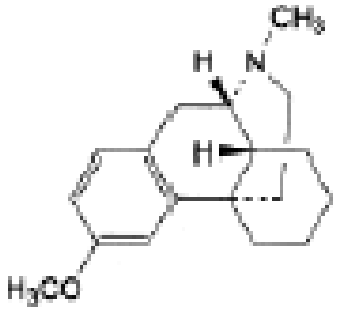
IMPURITIES



A. R1 = CH_3, R2 = H, X = H_2: *ent*-3-methoxymorphinan,

B. R1 = H, R2 = CH_3, X = H_2: *ent*-17-methylmorphinan-3-ol,

C. R1 = R2 = CH_3, X = O: *ent*-3-methoxy-17-methylmorphinan-10-one,



D. *ent*-(14*S*)-3-methoxy-17-methylmorphinan.