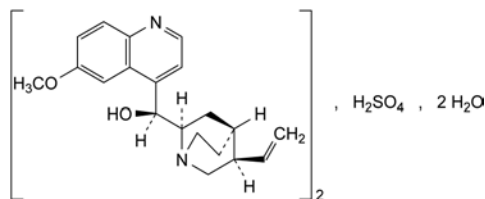


01/2008:0017 pH (2.2.3): 6.0 to 6.8.

QUINIDINE SULFATE

Chinidini sulfas



$C_{40}H_{50}N_4O_8S \cdot 2H_2O$
[6591-63-5]

 M_r 783

DEFINITION

Content: 99.0 per cent to 101.0 per cent of alkaloid monosulfates, expressed as bis[(S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl]-(6-methoxyquinolin-4-yl)methanol] sulfate (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or silky, colourless needles.

Solubility: slightly soluble in water, soluble in boiling water and in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution. Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 0.10 g of *quinidine sulfate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate: TLC silica gel G plate R.

Mobile phase: diethylamine R, ether R, toluene R (10:24:40 V/V/V).

Application: 5 µL.

Development: twice over a path of 15 cm; dry in a current of air for 15 min between the 2 developments.

Drying: at 105 °C for 30 min and allow to cool.

Detection: spray with iodoplatinate reagent R.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Dissolve about 5 mg in 5 mL of *water R*. Add 0.2 mL of *bromine water R* and 1 mL of *dilute ammonia R2*. A green colour develops.C. Dissolve 0.1 g in 3 mL of *dilute sulfuric acid R* and dilute to 100 mL with *water R*. When examined in ultraviolet light at 366 nm, an intense blue fluorescence appears which disappears almost completely on addition of 1 mL of *hydrochloric acid R*.D. Dissolve about 50 mg in 5 mL of hot *water R*, cool, add 1 mL of *silver nitrate solution R1* and stir with a glass rod. After a few minutes, a white precipitate is formed that dissolves on the addition of *dilute nitric acid R*.

E. It gives reaction (a) of sulfates (2.3.1).

F. pH (see Tests).

TESTS

Solution S. Dissolve 0.500 g in 0.1 M *hydrochloric acid* and dilute to 25.0 mL with the same acid.

Appearance of solution. Solution S is clear (2.2.1) and not more intensely coloured than reference solution GY₆ (2.2.2, Method II).

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7): + 275 to + 290 (dried substance), determined on solution S.

Other cinchona alkaloids. Liquid chromatography (2.2.29): use the normalisation procedure.

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

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

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

Reference solution (c). To 1 mL of reference solution (a) add 1 mL of reference solution (b).

Reference solution (d). Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (e). Dissolve 10 mg of *thiourea R* in the mobile phase and dilute to 10 mL with the mobile phase.

Column:

- size: $l = 0.15\text{--}0.25$ m, $\varnothing = 4.6$ mm;
- stationary phase: octadecylsilyl silica gel for chromatography R (5–10 µm).

Mobile phase: dissolve 6.8 g of *potassium dihydrogen phosphate R* and 3.0 g of *hexylamine R* in 700 mL of *water R*, adjust to pH 2.8 with *dilute phosphoric acid R*, add 60 mL of *acetonitrile R* and dilute to 1000 mL with *water R*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 250 nm for reference solution (e) and at 316 nm for the other solutions.

Injection: 10 µL.

Run time: 2.5 times the retention time of quinidine.

Identification of peaks: use the chromatogram obtained with reference solution (a) to identify the peaks due to impurity A and dihydroquinine; use the chromatogram obtained with reference solution (b) to identify the peaks due to quinidine and impurity C; the chromatogram obtained with reference solution (c) shows 4 peaks due to quinidine, impurity A, impurity C and dihydroquinine which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with reference solutions (a) and (b).

Relative retention with reference to impurity A: dihydroquinine = about 1.4.

Relative retention with reference to quinidine: impurity C = about 1.5.

System suitability:

- resolution: minimum 3.0 between the peaks due to impurity A and quinidine and minimum 2.0 between the peaks due to impurities C and A in the chromatogram obtained with reference solution (c);
- signal-to-noise ratio: minimum 4 for the principal peak in the chromatogram obtained with reference solution (d);
- mass distribution ratio: 3.5 to 4.5 for the peak due to quinidine in the chromatogram obtained with reference solution (b), t_R being calculated from the peak due to thiourea in the chromatogram obtained with reference solution (e); if necessary, adjust the concentration of acetonitrile in the mobile phase.

Limits:

- impurity C: maximum 15 per cent;
- any impurity eluted before quinidine: for each impurity, maximum 5 per cent;

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corrected 6.0

- *any other impurity*: for each impurity, maximum 2.5 per cent;
- *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent).

Boron: maximum 5 ppm. *Avoid where possible the use of glassware.*

Test solution. Dissolve 1.00 g in a mixture of 0.5 mL of *hydrochloric acid R* and 4.0 mL of *water R*.

Reference solution. Dissolve 0.572 g of *boric acid R* in *water R* and dilute to 1000.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *water R*. To 1.0 mL of this solution add 3.0 mL of *water R* and 0.5 mL of *hydrochloric acid R*.

Blank solution. Add 0.5 mL of *hydrochloric acid R* to 4.0 mL of *water R*.

Add 3.0 mL of a 100 g/L solution of *2-ethylhexane-1,3-diol R* in *methylene chloride R* to the test solution, to the reference solution and to the blank solution, then shake for 1 min. Allow to stand for 6 min. To 1.0 mL of the lower layer, add 2.0 mL of a 3.75 g/L solution of *curcumin R* in *anhydrous acetic acid R* and 0.3 mL of *sulfuric acid R*. Mix and after 20 min add 25.0 mL of *ethanol (96 per cent) R*. Mix. The blank solution is yellow. Any red colour in the test solution is not more intense than that in the reference solution.

Loss on drying (2.2.32): 3.0 per cent to 5.0 per cent, determined on 1.000 g by drying in an oven at 130 °C.

Sulfated ash (2.4.14): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

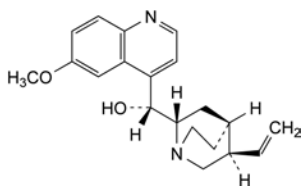
Dissolve 0.200 g in 20 mL of *acetic anhydride R*. Titrate with 0.1 M *perchloric acid*, using 0.15 mL of *naphtholbenzein solution R* as indicator.

1 mL of 0.1 M *perchloric acid* is equivalent to 24.90 mg of $C_{20}H_{25}N_2O_2 \cdot 2H_2O$.

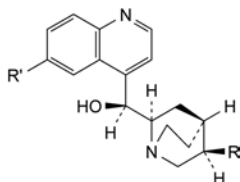
STORAGE

Protected from light.

IMPURITIES



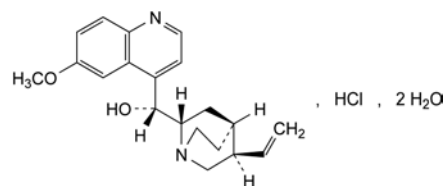
- A. (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol (quinine),



- B. $R = CH=CH_2$, $R' = H$: (*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](quinolin-4-yl)methanol (cinchonine),
- C. $R = C_2H_5$, $R' = OCH_3$: (*S*)-[(2*R*,4*S*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol (dihydroquinidine).

QUININE HYDROCHLORIDE

Chinini hydrochloridum



$C_{20}H_{25}ClN_2O_2 \cdot 2H_2O$
[6119-47-7]

M_r 396.9

DEFINITION

Content: 99.0 per cent to 101.0 per cent of alkaloid monohydrochlorides, expressed as (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol hydrochloride (dried substance).

CHARACTERS

Appearance: white or almost white or colourless, fine, silky needles, often in clusters.

Solubility: soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution. Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 0.10 g of *quinine sulfate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate: TLC silica gel G plate *R*.

Mobile phase: *diethylamine R*, *ether R*, *toluene R* (10:24:40 V/V/V).

Application: 5 µL.

Development: twice over a path of 15 cm; dry in a current of air for 15 min between the 2 developments.

Drying: at 105 °C for 30 min and allow to cool.

Detection: spray with *iodoplatinate reagent R*.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

- B. Dissolve about 10 mg in *water R* and dilute to 10 mL with the same solvent. To 5 mL of this solution add 0.2 mL of *bromine water R* and 1 mL of *dilute ammonia R2*. A green colour develops.
- C. Dissolve 0.1 g in 3 mL of *dilute sulfuric acid R* and dilute to 100 mL with *water R*. When examined in ultraviolet light at 366 nm, an intense blue fluorescence appears which disappears almost completely on the addition of 1 mL of *hydrochloric acid R*.
- D. It gives the reactions of chlorides (2.3.1).
- E. pH (see Tests).

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution. Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

pH (2.2.3): 6.0 to 6.8.

Dilute 10 mL of solution S to 20 mL with *carbon dioxide-free water R*.