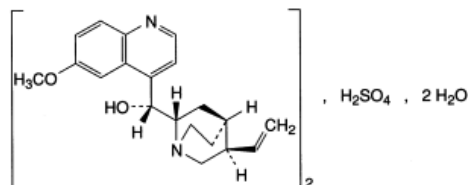


Quinine Sulphate



(Ph Eur monograph 0019)



$(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ 783 6119-70-6

Action and use

Antiprotozoal (malaria).

Preparation

Quinine Sulphate Tablets

Ph Eur

DEFINITION

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder or fine, colourless needles.

Solubility

Slightly soluble in water, sparingly soluble in boiling water and 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 sulphate 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 sulphuric 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. Dissolve about 45 mg in 5 ml of *dilute hydrochloric acid R*. The solution gives reaction (a) of sulphates (2.3.1).

E. 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*).

pH (2.2.3)

5.7 to 6.6 for a 10 g/l suspension in *water R*.

Specific optical rotation (2.2.7)

– 237 to – 245 (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 sulphate CRS* 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 sulphate 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 (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:* $l = 0.15\text{--}0.25\text{ m}$, $\varnothing = 4.6\text{ mm}$;

— *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 quinine.

Identification of peaks use the chromatogram obtained with reference solution (a) to identify the peaks due to quinine and impurity C; use the chromatogram obtained with reference solution (b) to identify the peaks due to impurity A and dihydroquinidine; the chromatogram obtained with reference solution (c) shows 4 peaks due to impurity A, quinine, dihydroquinidine and impurity C 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 quinine: impurity C = about 1.4.

Relative retention with reference to impurity A: dihydroquinidine = about 1.5.

System suitability:

- *resolution*: minimum 3.0 between the peaks due to quinine and impurity A and minimum 2.0 between the peaks due to dihydroquinidine and quinine 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 impurity A 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 10 per cent;
- *any impurity eluted before quinine*: for each impurity, maximum 5 per cent;
- *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).

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 105°C.

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

ASSAY

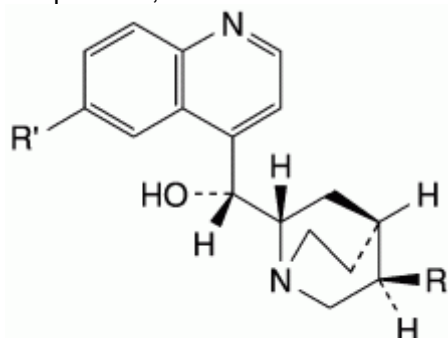
Dissolve 0.300 g in a mixture of 10 ml of *chloroform R* and 20 ml of *acetic anhydride R*. Titrate with 0.1 M *perchloric acid*, determining the end-point potentiometrically (2.2.20). 1 ml of 0.1 M *perchloric acid* is equivalent to 24.90 mg of $C_{40}H_{50}N_4O_8S$.

STORAGE

Protected from light.

IMPURITIES

A. quinidine,



B. $R = CH=CH_2$, $R' = H$: (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](quinolin-4-yl)methanol (cinchonidine),

C. $R = C_2H_5$, $R' = OCH_3$: (*R*)-[(2*S*,4*S*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol (dihydroquinine).