– *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;
– *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 *sulphuric 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.

Sulphated 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.

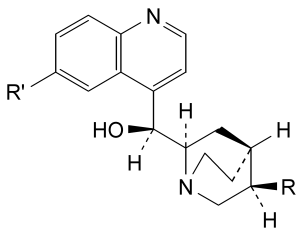
1 ml of *0.1 M perchloric acid* is equivalent to 24.90 mg of $C_{40}H_{50}N_4O_8S$.

STORAGE

Protected from light.

IMPURITIES

A. quinine,



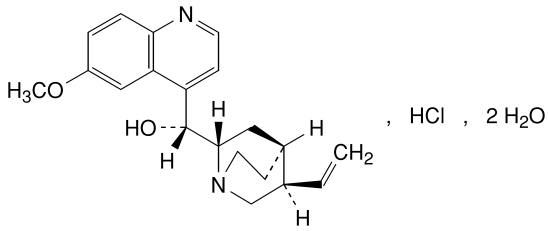
B. R = $CH{=}CH_2$, R′ = H: (*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](quinolin-4-yl)methanol (cinchonine),

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).

01/2008:0018
corrected 6.0

QUININE HYDROCHLORIDE

Chinini hydrochloridum



, HCl , 2 H_2O

$C_{20}H_{25}ClN_2O_2,2H_2O$ M_r 396.9
[6119-47-7]

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 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 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 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. 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*.

Specific optical rotation (*2.2.7*): – 245 to – 258 (dried substance).

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

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* = 0.15-0.25 m, Ø = 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 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).

Sulphates (*2.4.13*): maximum 500 ppm, determined on solution S.

Barium. To 15 ml of solution S add 1 ml of *dilute sulphuric acid R*. Allow to stand for 15 min. Any opalescence in the solution is not more intense than that in a mixture of 15 ml of solution S and 1 ml of *distilled water R*.

Loss on drying (*2.2.32*): 6.0 per cent to 10.0 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 0.250 g in 50 ml of *ethanol (96 per cent) R* and add 5.0 ml of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 inflexion points.

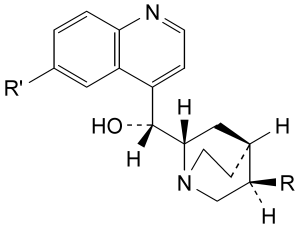
1 ml of *0.1 M sodium hydroxide* is equivalent to 36.09 mg of $C_{20}H_{25}ClN_2O_2$

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).