

$(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ : 782.94  
(8*R*,9*S*)-6'-Methoxycinchonan-9-ol hemisulfate  
monohydrate [6591-63-5]

Quinidine Sulfate, when dried, contains not less than 98.5% of  $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$ : 746.91.

**Description** Quinidine Sulfate occurs as white crystals. It is odorless, and has a very bitter taste.

It is freely soluble in ethanol (95) and in boiling water, sparingly soluble in water, and practically insoluble in diethyl ether. Quinidine Sulfate, previously dried, is freely soluble in chloroform.

It darkens gradually by light.

Specific rotation  $[\alpha]_D^{20}$ : +275 – +287° (after drying, 0.5 g, 0.1 mol/L hydrochloric acid VS, 25 mL, 100 mm).

**Identification (1)** Dissolve 0.01 g of Quinidine Sulfate in 10 mL of water and 2 to 3 drops of dilute sulfuric acid: a blue fluorescence is produced.

(2) To 5 mL of an aqueous solution of Quinidine Sulfate (1 in 1000) add 1 to 2 drops of bromine TS, then add 1 mL of ammonia TS: a green color develops.

(3) To 5 mL of an aqueous solution of Quinidine Sulfate (1 in 100) add 1 mL of silver nitrate TS, stir with a glass rod, and allow to stand for a short interval: a white precipitate is produced, and it dissolves on addition of nitric acid.

(4) Dissolve 0.4 g of Quinidine Sulfate in 20 mL of water and 1 mL of dilute hydrochloric acid: the solution responds to the Qualitative Tests for sulfate.

**pH** Dissolve 1.0 g of Quinidine Sulfate in 100 mL of freshly boiled and cooled water: the pH of this solution is between 6.0 and 7.0.

**Purity (1)** Chloroform-ethanol-insoluble substances—Warm 2.0 g of Quinidine Sulfate with 15 mL of a mixture of chloroform and ethanol (99.5) (2:1) at about 50°C for 10 minutes. After cooling, filter through a tared glass filter (G4) by gentle suction. Wash the residue with five 10-mL portions of a mixture of chloroform and ethanol (99.5) (2:1), and dry at 105°C for 1 hour: the mass of the residue is not more than 2.0 mg.

(2) Related substances—Dissolve 0.020 g of Quinidine Sulfate in the mobile phase to make exactly 100 mL, and use this solution as the sample solution. Separately, dissolve 0.025 g of cinchonine in the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50  $\mu$ L each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of the sample solution by the automatic integration method, and calculate their amount by the area percentage method: the amount of hydroquinidine sulfate is not more than 15.0%, and those of quinine sulfate and dihydroquinine sulfate are not more than 1.0%. The total area of the peaks other than the principal peak and the above peaks is not larger than the peak area of cinchonine from the standard solution.

**Operating conditions—**

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A column about 4 mm in inside diameter and about 25 cm in length, packed with octadecylsilanized silica gel (10  $\mu$ m in particle diameter).

Temperature: Room temperature.

Mobile phase: A mixture of water, acetonitrile, methanesulfonic acid TS and a solution of diethylamine (1 in 10) (43:5:1:1).

Flow rate: Adjust the flow rate so that the retention time of quinidine is about 10 minutes.

Selection of column: Dissolve 0.01 g each of Quinidine Sulfate and quinine sulfate in 5 mL of methanol, and add the mobile phase to make 50 mL. Proceed with 50  $\mu$ L of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of quinidine, quinine, dihydroquinidine and dihydroquinine in this order with a resolution between quinidine and quinine and that between quinine and dihydroquinidine being not less than 1.2, respectively.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of cinchonine obtained from 50  $\mu$ L of the standard solution is between 5 mm and 10 mm.

Time span of measurement: About twice as long as the retention time of quinidine after the solvent peak.

(3) Readily carbonizable substances—Take 0.20 g of Quinidine Sulfate and perform the test: the solution has no more color than Matching fluid M.

**Loss on drying** Not more than 5.0% (1 g, 130 °C, 3 hours).

**Residue on ignition** Not more than 0.10% (1 g).

**Assay** Weigh accurately about 0.5 g of Quinidine Sulfate, previously dried, dissolve in 20 mL of acetic acid (100), and add 80 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS until the color of the solution changes from purple through blue to blue-green (indicator: 3 drops of crystal violet TS). Perform a blank determination, and make any necessary correction.

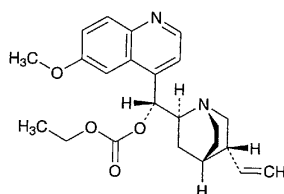
Each mL of 0.1 mol/L perchloric acid VS  
= 24.898 mg of  $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$

**Containers and storage** Containers—Well-closed containers.

Storage—Light-resistant.

## Quinine Ethyl Carbonate

エチル炭酸キニーネ



$C_{23}H_{28}N_2O_4$ : 396.48

Ethyl (8*S*,9*R*)-6'-methoxycinchonan-9-yl carbonate  
[83-75-0]

Quinine Ethyl Carbonate contains not less than

98.5% of  $C_{23}H_{28}N_2O_4$ , calculated on the dehydrated basis.

**Description** Quinine Ethyl Carbonate occurs as white crystals. It is odorless, and tasteless at first but slowly develops a bitter taste.

It is very soluble in methanol, freely soluble in ethanol (95) and in ethanol (99.5), soluble in diethyl ether, and practically insoluble in water.

It dissolves in dilute hydrochloric acid.

**Identification (1)** Determine the absorption spectrum of a solution of Quinine Ethyl Carbonate in methanol (1 in 20,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Quinine Ethyl Carbonate as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

**Optical rotation**  $[\alpha]_D^{20}$ :  $-42.2 - -44.0^\circ$  (0.5 g, calculated on the dehydrated basis, methanol, 50 mL, 100 mm).

**Melting point**  $91 - 95^\circ C$

**Purity (1) Chloride**—Dissolve 0.30 g of Quinine Ethyl Carbonate in 10 mL of dilute nitric acid and 20 mL of water. To 5 mL of the solution add 2 to 3 drops of silver nitrate TS: no color develops.

(2) **Sulfate**—Dissolve 1.0 g of Quinine Ethyl Carbonate in 5 mL of dilute hydrochloric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid VS, 5 mL of dilute hydrochloric acid and water to make 50 mL (not more than 0.048%).

(3) **Heavy metals**—Proceed with 2.0 g of Quinine Ethyl Carbonate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(4) **Related substances**—Dissolve 0.020 g of Quinine Ethyl Carbonate in the mobile phase to make exactly 100 mL, and use this solution as the sample solution. Separately, dissolve 0.025 g of quinine sulfate in the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10  $\mu$ L each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of these solutions by the automatic integration method, and calculate the amount of a main impurity in the sample solution which appears at about 1.2 times of the retention time of quinine ethyl carbonate by the area percentage method: it is not more than 10.0%. The total peak area other than the principal peak and above mentioned peak from the sample solution is not larger than the peak area of Quinine from the standard solution.

**Operating conditions**—

**Detector:** An ultraviolet absorption photometer (wavelength: 235 nm).

**Column:** A stainless steel column about 4 mm in inside di-

ameter and about 15 cm in length, packed with octadecylsilylated silica gel for liquid chromatography (5  $\mu$ m in particle diameter).

**Column temperature:** A constant temperature of about  $40^\circ C$ .

**Mobile phase:** Dissolve 1.2 g of sodium 1-octanesulfonate in 1000 mL of a mixture of water and methanol (1:1), and adjust to pH 3.5 with diluted phosphoric acid (1 in 20).

**Flow rate:** Adjust the flow rate so that the retention time of the peak of quinine ethyl carbonate is about 20 minutes.

**Selection of column:** Dissolve 5 mg each of Quinine Ethyl Carbonate and quinine sulfate in the mobile phase to make 50 mL. Proceed with 10  $\mu$ L of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of quinine, dihydroquinine, quinine ethyl carbonate and the main impurity of quinine ethyl carbonate in this order with the resolution between the peaks of quinine and dihydroquinine being not less than 2.7, and between the peaks of quinine and quinine ethyl carbonate being not less than 5.

**Detection sensitivity:** Adjust the detection sensitivity so that the peak height of quinine obtained from 10  $\mu$ L of the standard solution is between 5 mm and 10 mm.

**Time span of measurement:** About 2 times as long as the retention time of quinine ethyl carbonate.

**Water** Not more than 3.0% (0.5 g, direct titration).

**Residue on ignition** Not more than 0.10% (1 g).

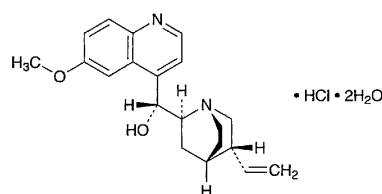
**Assay** Weigh accurately about 0.3 g of Quinine Ethyl Carbonate, dissolve in 60 mL of acetic acid (100), add 2 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS  
= 19.824 mg of  $C_{23}H_{28}N_2O_4$

**Containers and storage** Containers—Well-closed containers.

## Quinine Hydrochloride

塩酸キニーネ



$C_{20}H_{24}N_2O_2 \cdot HCl \cdot 2H_2O$ : 396.91  
(8*S*,9*R*)-6'-Methoxycinchonan-9-ol monohydrochloride dihydrate [6119-47-7]

Quinine Hydrochloride, when dried, contains not less than 98.5% of  $C_{20}H_{24}N_2O_2 \cdot HCl$  (mol. wt.: 360.88).

**Description** Quinine Hydrochloride occurs as white crys-