

the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

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

**Assay** Weigh accurately about 0.5 g of Diphenhydramine, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid (100) (7:3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

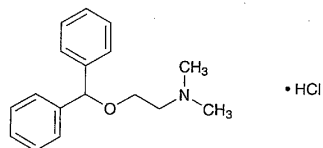
Each mL of 0.1 mol/L perchloric acid VS  
= 25.536 mg of  $C_{17}H_{21}NO$

**Containers and storage** Containers—Tight containers.

Storage—Light-resistant, and almost well-filled.

## Diphenhydramine Hydrochloride

塩酸ジフェンヒドรามミン



$C_{17}H_{21}NO \cdot HCl$ : 291.82

*N*-(2-Benzhydryloxyethyl)-*N,N*-dimethylamine monohydrochloride [147-24-0]

Diphenhydramine Hydrochloride, when dried, contains not less than 98.0% of  $C_{17}H_{21}NO \cdot HCl$ .

**Description** Diphenhydramine Hydrochloride occurs as white crystals or crystalline powder. It is odorless, and has a bitter taste, followed by a sensation of numbness on the tongue.

It is very soluble in methanol and in acetic acid (100), freely soluble in water and in ethanol (95), sparingly soluble in acetic anhydride, and practically insoluble in diethyl ether.

It is gradually affected by light.

**Identification** (1) Determine the absorption spectrum of a solution of Diphenhydramine Hydrochloride in methanol (1 in 2000) 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 Diphenhydramine Hydrochloride as directed in the potassium chloride 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.

(3) A solution of Diphenhydramine Hydrochloride (1 in 50) responds to the Qualitative Tests for chloride.

**pH** Dissolve 1.0 g of Diphenhydramine Hydrochloride in 10 mL of water: the pH of this solution is between 4.0 and 5.0.

**Melting point** 166 – 170°C

**Purity** (1) Clarity and color of solution—Dissolve 1.0 g

of Diphenhydramine Hydrochloride in 10 mL of water: the solution is clear and colorless.

(2) Heavy metals—Proceed with 1.0 g of Diphenhydramine Hydrochloride according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Related substances—Dissolve 0.20 g of Diphenhydramine Hydrochloride in 10 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 5  $\mu$ L each of the sample solution and the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of hexane, ethyl acetate, methanol and ammonia solution (28) (10:4:2:1) to a distance of about 10 cm, and air-dry the plate. Spray evenly iodine TS on the plate: the spots other than the principal spot from the sample solution and the spot on the original point are not more intense than the spot from the standard solution.

**Loss on drying** Not more than 0.5% (2 g, 105°C, 3 hours).

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

**Assay** Weigh accurately about 0.4 g of Diphenhydramine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid (100) (7:3). 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  
= 29.182 mg of  $C_{17}H_{21}NO \cdot HCl$

**Containers and storage** Containers—Tight containers.

Storage—Light-resistant.

## Diphenhydramine Tannate

タンニン酸ジフェンヒドรามミン

Diphenhydramine Tannate is a compound of diphenhydramine and tannic acid, and contains not less than 25.0% and not more than 35.0% of diphenhydramine ( $C_{17}H_{21}NO$ : 255.35).

**Description** Diphenhydramine Tannate occurs as a grayish white to light brown powder. It is odorless or has a slight, characteristic odor. It is tasteless.

It is slightly soluble in ethanol (95), and practically insoluble in water and in diethyl ether.

**Identification** (1) To 1 g of Diphenhydramine Tannate add 15 mL of water and 0.3 mL of dilute hydrochloric acid, shake thoroughly for 1 minute, filter, and use this filtrate as the sample solution. Transfer 10 mL of the sample solution to a separator, extract with two 20-mL portions of chloroform, combine the chloroform extracts, and evaporate on a water bath to dryness. To 5 mL of a solution of the residue (1 in 100) add 5 drops of Reinecke salt TS: a light red precipitate is produced.

(2) To 10 mL of a solution of the residue obtained in (1) (1 in 100) add 10 mL of 2,4,6-trinitrophenol TS dropwise, and allow to stand for 30 minutes. Collect the precipitate by filtration, recrystallize from dilute ethanol, and dry at 105°C for 30 minutes: the crystals melt between 128°C and 133°C.

(3) To 1 mL of the sample solution obtained in (1) add 1 drop of iron (III) chloride TS: a dark blue-purple color develops.

**Purity** Heavy metals—Proceed with 1.0 g of Diphenhydramine Tannate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

**Loss on drying** Not more than 7.0% (1 g, 105°C, 5 hours).

**Residue on ignition** Not more than 1.0% (1 g).

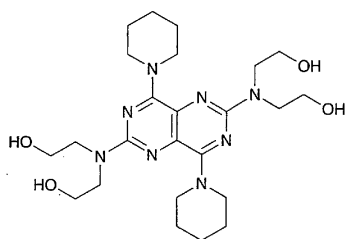
**Assay** Transfer about 1.7 g of Diphenhydramine Tannate, accurately weighed, to a separator, dissolve in 20 mL of water and 3.0 mL of dilute hydrochloric acid with thorough shaking, add 20 mL of a solution of sodium hydroxide (1 in 10) and exactly 25 mL of isooctane, shake vigorously for 5 minutes, dissolve 2 g of sodium chloride with shaking, and allow to stand. To 20 mL of the isooctane layer add exactly 80 mL of acetic acid (100), 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  
= 25.536 mg of C<sub>17</sub>H<sub>21</sub>NO

**Containers and storage** Containers—Tight containers.  
Storage—Light-resistant.

## Dipyridamole

ジピリダモール



C<sub>24</sub>H<sub>40</sub>N<sub>8</sub>O<sub>4</sub>: 504.63  
2,2',2'',2'''-[4,8-Di(piperidin-1-yl)pyrimido[5,4-d]-  
pyrimidine-2,6-diyl]dinitrilo}tetraethanol [58-32-2]

Dipyridamole, when dried, contains not less than 98.5% of C<sub>24</sub>H<sub>40</sub>N<sub>8</sub>O<sub>4</sub>.

**Description** Dipyridamole occurs as yellow crystals or crystalline powder. It is odorless, and has a slightly bitter taste.

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

**Identification** (1) Dissolve 5 mg of Dipyridamole in 2 mL of sulfuric acid, add 2 drops of nitric acid, and shake: a

deep purple color develops.

(2) Determine the absorption spectrum of a solution of Dipyridamole in a mixture of methanol and hydrochloric acid (99:1) (1 in 100,000) 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.

(3) Determine the infrared absorption spectrum of Dipyridamole, previously dried, 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.

**Melting point** 165 - 169°C

**Purity** (1) Clarity and color of solution—Dissolve 0.5 g of Dipyridamole in 10 mL of chloroform: the solution is clear, and shows a yellow color.

(2) Heavy metals—Proceed with 2.0 g of Dipyridamole 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).

(3) Arsenic—Prepare the test solution with 1.0 g of Dipyridamole according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

(4) Related substances—Dissolve 0.050 g of Dipyridamole in 50 mL of the mobile phase, and use this solution as the sample solution. Pipet 0.5 mL of the sample solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL 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: the total area of the peaks other than the peak of dipyridamole from the sample solution is not larger than the peak area of dipyridamole from the standard solution.

**Operating conditions**—

**Detector:** An ultraviolet absorption photometer (wavelength: 280 nm).

**Column:** A stainless steel column about 4 mm in inside diameter and 15 to 25 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

**Column temperature:** A constant temperature of about 40°C.

**Mobile phase:** Dissolve 0.2 g of potassium dihydrogenphosphate in 200 mL of water, and add 800 mL of methanol.

**Flow rate:** Adjust the flow rate so that the retention time of dipyridamole is about 4 minutes.

**Selection of column:** Dissolve 7 mg of Dipyridamole and 3 mg of terphenyl in 50 mL of methanol. Proceed with 20 μL of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of dipyridamole and terphenyl in this order with the resolution between these peaks being not less than 5.

**Detection sensitivity:** Adjust the detection sensitivity so that the peak height of dipyridamole obtained from 20 μL of the standard solution is between 2 mm and 6 mm.

**Time span of measurement:** About 5 times as long as the retention time of dipyridamole.

**Loss on drying** Not more than 0.2% (1 g, 105°C, 3 hours).