horizontally, put a sterilized flame (200 mm × 200 mm, 5 mm in flame width, 5 to 20 mm in depth) on the plate, pour 150 mL of agar medium for seed into the flame, and incubate the medium after harden the agar at 37°C for 16 to 20 hours. Measure the diameter at the developing direction of each zone of inhibition near *Rf* of 0.1 to the nearest 0.1 mm accuracy, and calculate the averages of the diameter obtained by the sample solution and the standard solution.

(4) Iodine adsorption substances—When the test is run according to the following conditions, the amount of iodine adsorption substances is not more than 8.0%. Weigh accurately about 0.20 g of Ticarcillin Sodium, dissolve in water to make exactly 100 mL, and use this solution as the sample solution. Pipet 0.5 mL of 1 mol/L hydrochloric acid TS and 10 mL of 0.01 mol/L iodine VS in a glass-stoppered conical flask, add exactly 10 mL of the sample solution, mix, and titrate immediately with 0.02 mol/L sodium thiosulfate VS (indicator: 1 mL of starch TS). Designate the consumed amount of 0.02 mol/L sodium thiosulfate VS for the test as *A* mL. Perform a blank determination in the same manner and designate the consumed amount for the blank as *B* mL.

$$\text{Amount (\%) of the iodine absorption substances} = \frac{(B - A) \times 446.4 \times 0.02 \times f}{\text{amount (g) of the sample} \times 10.4}$$

f: Factor of 0.02 mol/L sodium thiosulfate VS

Water Not more than 6.0% (0.4 g, volumetric titration, direct titration).

Assay Weigh accurately an amount of Ticarcillin Sodium and Ticarcillin Sodium Reference Standard, equivalent to about 0.075 g (potency), dissolve each in a suitable amount of water, add exactly 10 mL of the internal standard solution and water to make 100 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of ticarcillin to that of the internal standard of each solution. Both the sample solution and the standard solution are keep at not exceeding 5°C and use within 24 hours.

$$\text{Amount [μg (potency)] of ticarcillin } (C_{15}H_{16}N_2O_6S_2) = \text{amount [mg (potency)] of Ticarcillin Sodium Reference Standard} \times \frac{Q_T}{Q_S} \times 1000$$

Internal standard solution—Dissolve 0.63 g of *o*-toluic acid in 100 mL of a solution of sodium hydrogen carbonate (21 in 5000), and add water to make 250 mL.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

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

Column temperature: A constant temperature of about 30°C.

Mobile phase: Dissolve 3.9 g of sodium dihydrogenphosphate dihydrate and 1.61 g of tetra *n*-butylammonium bromide in 750 mL of water, adjust to pH 3.0 with phosphoric acid, and add water to make 1000 mL. To this solution add 225 mL of acetonitlile and 2.5 mL of aceteic acid (100).

Flow rate: Adjust the flow rate so that the retention time of *o*-toluic acid is about 10 minutes.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the internal standard and ticarcillin are eluted in this order with the resolution between these peaks being not less than 3.7.

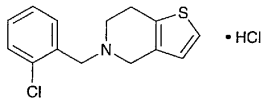
System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak area of ticarcillin to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Storage—In a cold place.

Ticlopidine Hydrochloride

塩酸チクロピジン



$C_{14}H_{14}ClNS.HCl$: 300.25

5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine monohydrochloride [*53885-35-1*]

Ticlopidine Hydrochloride contains not less than 99.0% of $C_{14}H_{14}ClNS.HCl$, calculated on the anhydrous basis.

Description Ticlopidine Hydrochloride occurs as a white to pale yellowish white crystalline powder.

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

Identification **(1)** Determine the infrared absorption spectrum of Ticlopidine Hydrochloride 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.

(2) A solution of Ticlopidine Hydrochloride (1 in 20) responds to the Qualitative Tests (2) for chloride.

Purity **(1)** Heavy metals—Proceed with 2.0 g of Ticlopidine Hydrochloride according to Method 3, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(2) Arsenic—Prepare the test solution with 1.0 g of Ticlopidine Hydrochloride according to Method 4, and perform the test using Apparatus B (not more than 2 ppm).

(3) Related substances—Dissolve 0.5 g of Ticlopidine Hydrochloride in 20 mL of a solution of hydrochloric acid in methanol (1 in 20,000), and use this solution as the sam-

ple solution. To exactly 5 mL of the sample solution add a solution of hydrochloric acid in methanol (1 in 20,000) to make exactly 200 mL, and use this solution as the standard solution (1). Separately, pipet 1 mL of the sample solution, add a solution of hydrochloric acid in methanol (1 in 20,000) to make exactly 50 mL, and use this solution as the standard solution (2). Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 10 μL each of the sample solution and the standard solution (1) on a plate of silica gel for thin-layer chromatography (Plate 1), and spot 10 μL each of the sample solution and the standard solution (2) on another plate of silica gel for thin-layer chromatography (Plate 2). Develop the plates with an upper layer of a mixture of water, 1-butanol and acetic acid (100) (5:4:1) to a distance of about 15 cm, and air-dry the plates. Spray evenly a solution of ninhydrin in acetone (1 in 50) on Plate 1, and heat at 100°C for 20 minutes: the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution (1). Allow Plate 2 to stand in an iodine vapor for 30 minutes: the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution (2).

(4) Formaldehyde—Dissolve 0.80 g of Ticlopidine Hydrochloride in 19.0 mL of water, add 1.0 mL of 4 mol/L sodium hydroxide TS, shake well, centrifuge, and filter the supernatant liquid. To 5.0 mL of the filtrate add 5.0 mL of acetylacetone TS, mix, and warm at 40°C for 40 minutes: the solution has no more color than the following control solution.

Control solution: Weigh accurately 0.54 g of formaldehyde solution, and add water to make exactly 1000 mL. To exactly 10 mL of this solution add water to make exactly 1000 mL. Prepare before use. To 8.0 mL of this solution add water to make 20.0 mL, and filter. To 5.0 mL of the filtrate add 5.0 mL of acetylacetone TS, and proceed in the same manner.

Water Not more than 1.0% (0.3 g, direct titration).

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

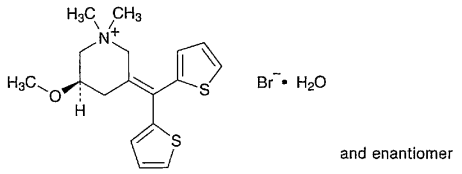
Assay Weigh accurately about 0.4 g of Ticlopidine Hydrochloride, dissolve in 20 mL of acetic acid (100), add 40 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 30.025 mg of $C_{14}H_{14}ClNS.HCl$

Containers and storage Containers—Well-closed containers.

Timepidium Bromide

臭化チメピジウム



and enantiomer

$C_{17}H_{22}BrNOS_2.H_2O$: 418.41
(*RS*)-3-(Dithien-2-ylmethylene)-5-methoxy-1,1-dimethylpiperidinium bromide monohydrate
[*35035-05-3*, anhydride]

Timepidium Bromide contains not less than 98.5% of $C_{17}H_{22}BrNOS_2$ (mol. wt.: 400.40), calculated on the anhydrous basis.

Description Timepidium Bromide occurs as white crystals or crystalline powder.

It is very soluble in methanol and in acetic acid (100), freely soluble in ethanol (99.5), sparingly soluble in water and in acetic anhydride, and practically insoluble in diethyl ether.

The pH of a solution of Timepidium Bromide in freshly boiled and cooled water (1 in 100) is between 5.3 and 6.3.

A solution of Timepidium Bromide in methanol (1 in 20) shows no optical rotation.

Identification (1) To 1 mL of a solution of Timepidium Bromide (1 in 100) add 1 mL of ninhydrin-sulfuric acid TS: a red purple color develops.

(2) Determine the absorption spectrum of a solution of Timepidium Bromide (1 in 50,000) 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 Timepidium Bromide as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhitit similar intensities of absorption at the same wave numbers.

(4) A solution of Timepidium Bromide (1 in 100) responds to the Qualitative Tests (1) for Bromide.

Purity (1) Clarity and color of solution—Dissolve 0.10 g of Timepidium Bromide in 10 mL of water: the solution is clear and colorless.

(2) Heavy metals—Proceed with 1.0 g of Timepidium Bromide 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).

(3) Related substances—Dissolve 0.10 g of Timepidium Bromide in 10 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add methanol to make exactly 100 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 10 μL each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for