

thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol, water, acetic acid (100) and ethyl acetate (5:4:1:1:1) to a distance of about 13 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

**Water** 3.5 – 5.0% (0.4 g, direct titration).

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

**Assay** Weigh accurately about 0.6 g of Timepidium Bromide, dissolve in 60 mL of a mixture of acetic anhydride and acetic acid (100) (2:1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

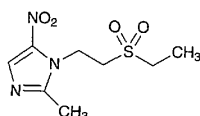
Each mL of 0.1 mol/L perchloric acid VS  
= 40.04 mg of  $C_{17}H_{22}BrNOS_2$

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

Storage—Light-resistant.

## Tinidazole

チニダゾール



$C_8H_{13}N_3O_4S$ : 247.27

Ethyl 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl sulfone  
[19387-91-8]

Tinidazole, when dried, contains not less than 98.5% of  $C_8H_{13}N_3O_4S$ .

**Description** Tinidazole occurs as a light yellow, crystalline powder. It is odorless or has a slight, characteristic odor. It has a bitter taste.

It is soluble in acetic anhydride and in acetone, sparingly soluble in methanol and in ethanol (95), and very slightly soluble in water and in diethyl ether.

**Identification** (1) Dissolve 0.01 g of Tinidazole in 2 mL of methanol, and add 1 mL of a solution of *N,N*-dimethylaniline in methanol (1 in 10): a yellow-green color develops.

(2) Determine the absorption spectrum of a solution of Tinidazole in methanol (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 Tinidazole as directed in the paste 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** 125 – 129°C

**Purity** (1) Sulfate—To 2.0 g of Tinidazole add 100 mL

of water, boil for 5 minutes, cool, add water to make 100 mL, and filter. Take 25 mL of the filtrate, and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution, and perform the test. Prepare the control solution with 0.45 mL of 0.005 mol/L sulfuric acid VS (not more than 0.043%).

(2) Heavy metals—Proceed with 1.0 g of Tinidazole 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) Arsenic—Prepare the test solution with 2.0 g of Tinidazole according to Method 3, and perform the test using Apparatus B (not more than 1 ppm).

(4) Related substances—Dissolve 0.050 g of Tinidazole in 2 mL of acetone, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add acetone 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 10  $\mu$ L each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and diethylamine (19:1) to a distance of about 10 cm, air-dry the plate, heat at 100°C for 5 minute, and cool. Examine under ultraviolet light (main wavelength: 254 nm): the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

**Loss on drying** Not more than 1.0% (1 g, 105°C, 2 hours).

**Residue on ignition** Not more than 0.1% (1 g).

**Assay** Weigh accurately about 0.35 g of Tinidazole, previously dried, dissolve in 50 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.

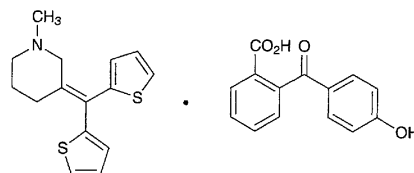
Each mL of 0.1 mol/L perchloric acid VS  
= 24.728 mg of  $C_8H_{13}N_3O_4S$

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

Storage—Light-resistant.

## Tipepidine Hibenazate

ヒベンズ酸チペピジン



$C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$ : 517.66

3-(Dithien-2-ylmethylene)-1-methylpiperidine mono[2-(4-hydroxybenzoyl)benzoate] [31139-87-4]

Tipepidine Hibenazate, when dried, contains not less than 98.5% of  $C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$ .

**Description** Típepidine Hibenzate occurs as a white to light yellow, crystalline powder. It is odorless and tasteless.

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

**Identification** (1) Dissolve 0.01 g of Típepidine Hibenzate in 5 mL of sulfuric acid: an orange-red color develops.

(2) Dissolve 0.3 g of Típepidine Hibenzate in 10 mL of sodium hydroxide TS and 5 mL of water, and extract with two 20-mL portions of chloroform. Wash the chloroform extracts with 10 mL of water, and filter the chloroform layer. Evaporate the filtrate on a water bath to dryness, and dissolve the residue in 0.5 mL of 1 mol/L hydrochloric acid TS and 5 mL of water. To 2 mL of this solution add 5 mL of Reinecke salt TS: a light red precipitate is formed.

(3) Determine the absorption spectrum of a solution of Típepidine Hibenzate in ethanol (99.5) (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.

(4) Determine the infrared absorption spectrum of Típepidine Hibenzate, 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** 189 – 193°C

**Purity** (1) Clarity of solution—Dissolve 1.0 g of Típepidine Hibenzate in 10 mL of acetic acid (100): the solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectrophotometry: its absorbance at 400 nm is not more than 0.16.

(2) Heavy metals—Proceed with 2.0 g of Típepidine Hibenzate 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 Típepidine Hibenzate according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

(4) Related substances—(i) Dissolve 0.010 g of Típepidine Hibenzate in 20 mL of the mobile phase, and use this solution as the sample solution. Pipet 1 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  $\mu$ 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 both solutions by the automatic integration method: the total area of all peaks other than the area of the hibenzic acid and típepidine from the sample solution is not larger than the peak area of the típepidine from the standard solution.

**Operating conditions**—

**Detector:** An ultraviolet absorption photometer (wavelength: 254 nm).

**Column:** A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5  $\mu$ m in particle diameter).

**Column temperature:** A constant temperature of about 50°C.

**Mobile phase:** A mixture of a solution of ammonium acetate (1 in 100) and tetrahydrofuran (32:13).

**Flow rate:** Adjust the flow rate so that the retention time of típepidine is about 12 minutes.

**Time span of measurement:** As long as the retention time of típepidine after the solvent peak.

**System suitability**—

**Test for required detection:** To exactly 2 mL of the standard solution add the mobile phase to make exactly 20 mL. Confirm that the peak area of típepidine obtained from 20  $\mu$ L of this solution is equivalent to 7 to 13% of that of típepidine obtained from 20  $\mu$ L of the standard solution.

**System performance:** Dissolve 0.010 g of Típepidine Hibenzate and 3 mg of propyl parahydroxybenzoate in 100 mL of the mobile phase. When the procedure is run with 20  $\mu$ L of this solution under the above operating conditions, hibenzic acid, típepidine and propyl parahydroxybenzoate are eluted in this order with the resolution between the peaks of típepidine and propyl parahydroxybenzoate being not less than 3.

**System repeatability:** When the test is repeated 6 times with 20  $\mu$ L of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of típepidine is not more than 1.5%.

(ii) Dissolve 0.010 g of Típepidine Hibenzate in 20 mL of the mobile phase, and use this solution as the sample solution. Pipet 1 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  $\mu$ 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 both solutions by the automatic integration method: the total area of all peaks other than the area of the hibenzic acid and típepidine from the sample solution is not larger than 1/2 of the peak area of the típepidine from the standard solution.

**Operating conditions**—

**Detector:** An ultraviolet absorption photometer (wavelength: 254 nm).

**Column:** A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5  $\mu$ m in particle diameter).

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

**Mobile phase:** A mixture of methanol and a solution of ammonium acetate (1 in 500) (13:7).

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

**Time span of measurement:** As long as the retention time of típepidine after the solvent peak.

**System suitability**—

**Test for required detection:** To exactly 2 mL of the standard solution add the mobile phase to make exactly 20 mL. Confirm that the peak area of típepidine obtained from 20  $\mu$ L of this solution is equivalent to 7 to 13% of that of típepidine obtained from 20  $\mu$ L of the standard solution.

**System performance:** Dissolve 0.012 g of Típepidine Hibenzate and 4 mg of xanthene in 50 mL of the mobile phase. When the procedure is run with 10  $\mu$ L of this solution under the above operating conditions, hibenzic acid, típepidine and xanthene are eluted in this order with the resolution between the peaks of típepidine and xanthene being

not less than 3.

**System repeatability:** When the test is repeated 6 times with 20  $\mu$ L of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of tipepidine is not more than 3.0%.

**Loss on drying** Not more than 0.5% (1 g, 60°C, in vacuum, phosphorus (V) oxide, 3 hours).

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

**Assay** Weigh accurately about 1 g of Tipepidine Hibenzate, previously dried, dissolve in 40 mL of acetic acid (100), and titrate with 0.1 mol/L perchloric acid VS until the color of the solution changes from purple through blue to 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  
= 51.77 mg of  $C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$

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

Storage—Light-resistant.

## Tipepidine Hibenzate Tablets

ヒベンズ酸チペピジン錠

Tipepidine Hibenzate Tablets contain not less than 95% and not more than 105% of the labeled amount of tipepidine hibenzate ( $C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$ ; 517.66).

**Method of preparation** Prepare as directed under Tablets, with Tipepidine Hibenzate.

**Identification (1)** To a quantity of powdered Tipepidine Hibenzate Tablets, equivalent to 0.044 g of Tipepidine Hibenzate according to the labeled amount, add 5 mL of water, shake for 1 minute, add 10 mL of sodium hydroxide TS, and extract with two 20-mL portions of chloroform. Combine the extracts, wash with 10 mL of water, and filter the chloroform layer. Evaporate the filtrate on a water bath to dryness, dissolve the residue in 0.2 mL of 1 mol/L hydrochloric acid TS and 2 mL of water, and add 5 mL of Reinecke salt TS: a light red precipitate is formed.

**(2)** To a quantity of powdered Tipepidine Hibenzate Tablets, equivalent to 0.011 g of Tipepidine Hibenzate according to the labeled amount, add 30 mL of ethanol (99.5), and warm for 10 minutes with occasional shaking. After cooling, add ethanol (99.5) to make 50 mL, and filter. To 1 mL of the filtrate add ethanol (99.5) to make 20 mL, and determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectrophotometry: it exhibits a maximum between 282 nm and 286 nm.

**Dissolution test** Perform the test with 1 tablet of Tipepidine Hibenzate Tablets at 50 revolutions per minute according to Method 2 under the Dissolution Test, using 900 mL of water as the test solution. Use the dissolved solution 30 minutes after starting the test as the sample solution. Separately, weigh accurately about 0.11 g of tipepidine hibenzate for assay, previously dried in a desiccator (in vacuum, phosphorus (V) oxide, 60°C) for 3 hours, and dissolve

in 80 mL of diluted ethanol (99.5) (3 in 4) by warming occasionally. After cooling, add diluted ethanol (99.5) (3 in 4) to make exactly 100 mL, then pipet 20 mL of this solution, add water to make exactly 900 mL, and use this solution as the standard solution. Determine the absorbances,  $A_{T1}$  and  $A_{S1}$ , at 286 nm, and  $A_{T2}$  and  $A_{S2}$ , at 360 nm of the sample solution and the standard solution as directed under the Ultraviolet-visible Spectrophotometry.

The dissolution rate of Tipepidine Hibenzate Tablets in 30 minutes is not less than 80%.

Dissolution rate (%) with respect to the labeled amount of tipepidine hibenzate ( $C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$ )

$$= W_S \times \frac{A_T - A_{T2}}{A_S - A_{S2}} \times \frac{20}{C}$$

$W_S$ : Amount (mg) of tipepidine hibenzate for assay.

$C$ : Labeled amount (mg) of tipepidine hibenzate ( $C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$ ) in 1 tablet.

**Assay** Weigh accurately and powder not less than 20 Tipepidine Hibenzate Tablets. Weigh accurately a portion of the powder, equivalent to about 0.022 g of tipepidine hibenzate ( $C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$ ), add 10 mL of diluted acetic acid (100) (1 in 2) and 30 mL of methanol, and warm for 10 minutes with occasional shaking. After cooling, add diluted methanol (1 in 2) to make exactly 50 mL, and filter. Discard the first 10 mL of the filtrate, pipet the subsequent 5 mL, add exactly 5 mL of the internal standard solution, then add diluted methanol (1 in 2) to make 25 mL, and use this solution as the sample solution. Separately, weigh accurately about 0.022 g of tipepidine hibenzate for assay, previously dried in a desiccator (in vacuum, phosphorus (V) oxide, 60°C) for 3 hours, dissolve in 10 mL of diluted acetic acid (100) (1 in 2) and 30 mL of methanol, and add diluted methanol (1 in 2) to make exactly 50 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, then add diluted methanol (1 in 2) to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 20  $\mu$ L each of the sample solution and the standard solution 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 tipepidine to that of the internal standard, respectively.

Amount (mg) of tipepidine hibenzate

( $C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$ )

= amount (mg) of tipepidine hibenzate for assay

$$\times \frac{Q_T}{Q_S}$$

**Internal standard solution**—A solution of dibucaine hydrochloride in methanol (1 in 2000).

**Operating conditions**—

**Detector:** An ultraviolet absorption photometer (wavelength: 254 nm).

**Column:** A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5  $\mu$ m in particle diameter).

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

**Mobile phase:** A mixture of a solution of sodium lauryl sulfate in diluted phosphoric acid (1 in 1000) (1 in 500), acetonitrile and 2-propanol (3:2:1).

**Flow rate:** Adjust the flow rate so that the retention time