

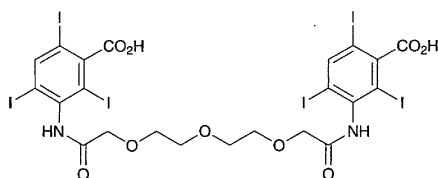
in 40 mL of sodium hydroxide TS, add 1 g of zinc powder, and heat for 30 minutes under a reflux condenser. Cool, filter, wash the flask and the filter paper with 50 mL of water, and combine the washings and the filtrate. Add 5 mL of acetic acid (100) to this solution, and titrate with 0.1 mol/L silver nitrate VS, until the color of the precipitate changes from yellow to green (indicator: 1 mL of tetrabromophenolphthalein ethyl ester TS).

Each mL of 0.1 mol/L silver nitrate VS
= 20.464 mg of $C_{11}H_9I_3N_2O_4$

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

Iotroxic Acid

イオトロクス酸



$C_{22}H_{18}I_6N_2O_9$; 1215.81
3,3'-(3,6,9-Trioxaundecanedioyl)diiminobis-(2,4,6-triiodobenzoic acid) [51022-74-3]

Iotroxic Acid contains not less than 98.5% of $C_{22}H_{18}I_6N_2O_9$, calculated on the anhydrous basis.

Description Iotroxic Acid occurs as a white crystalline powder.

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

It is gradually colored by light.

Identification (1) Heat 0.1 g of Iotroxic Acid over a flame: a purple gas evolves.

(2) Dissolve a suitable amount of Iotroxic Acid in a suitable amount of methanol, evaporate the methanol under reduced pressure, and determine the infrared absorption spectrum of the residue so obtained 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.

Purity (1) Clarity and color of solution—Dissolve 1.0 g of Iotroxic Acid in 10 mL of diluted sodium hydroxide TS (1 in 5): the solution is clear and colorless.

(2) Primary aromatic amines—Dissolve 0.20 g of Iotroxic Acid in 5 mL of water and 1 mL of sodium hydroxide TS, add 4 mL of a solution of sodium nitrite (1 in 100) and 10 mL of 1 mol/L hydrochloric acid TS, mix, and allow to stand for 2 minutes. Add 5 mL of ammonium amidosulfate TS, shake well, allow to stand for 1 minute, then add 0.4 mL of a solution of α -naphthol in ethanol (95) (1 in 10), 15 mL of sodium hydroxide TS and water to make exactly 50 mL. Read the absorbance of this solution at 485 nm as directed under the Ultraviolet-visible Spectrophotometry,

using a blank solution obtained in the same manner as above: the absorbance is not more than 0.22.

(3) Iodine—Dissolve 0.20 g of Iotroxic Acid in 2.0 mL of sodium hydrogen carbonate TS, add 5 mL of toluene, mix well, and allow to stand: the toluene layer is colorless.

(4) Free iodine ion—Weigh accurately about 5.0 g of Iotroxic Acid, dissolve in 12 mL of a solution of meglumine (3 in 20), add water to make 70 mL, and adjust the pH to about 4.5 with acetic acid (100). To this solution add 2 mL of 0.1 mol/L sodium chloride TS, and titrate with 0.001 mol/L silver nitrate VS (potentiometric titration).

Each mL of 0.001 mol/L silver nitrate
= 0.12690 mg of I

Content of iodine ion in Iotroxic Acid, calculated on the anhydrous basis, is not more than 0.004%.

(5) Heavy metals—Heat strongly 1.0 g of Iotroxic Acid as directed under the Residue on Ignition Test, then proceed according to Method 2, and perform the test. Prepare the control solution with 1.0 mL of Standard Lead Solution (not more than 10 ppm).

(6) Related substances—Dissolve 0.15 g of Iotroxic Acid 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 10 μ 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 toluene, acetone and formic acid (6:4:1) to a distance of about 15 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 1.0 – 2.0% (0.5 g, direct titration).

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

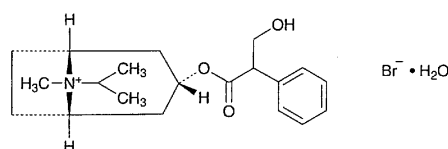
Assay Weigh accurately about 0.5 g of Iotroxic Acid, dissolve in 40 mL of sodium hydroxide TS in a saponification flask, add 1 g of zinc powder, and boil for 30 minutes under a reflux condenser. After cooling, filter, wash the flask and the filter paper with 50 mL of water, and combine the washings to the filtrate. To this solution add 5 mL of acetic acid (100), and titrate with 0.1 mol/L silver nitrate VS (potentiometric titration).

Each mL of 0.1 mol/L silver nitrate VS
= 20.264 mg of $C_{22}H_{18}I_6N_2O_9$

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

Ipratropium Bromide

臭化イプラトロピウム



$C_{20}H_{30}BrNO_3 \cdot H_2O$: 430.38

(1*R*,3*r*,5*S*)-3-[(*RS*)-3-Hydroxy-2-phenylpropanoyloxy]-8-isopropyl-8-methyl-8-azoniabicyclo[3.2.1]octane bromide monohydrate [66985-17-9]

Ipratropium Bromide, when dried, contains not less than 99.0% of $C_{20}H_{30}BrNO_3$ (mol. wt.: 412.36).

Description Ipratropium Bromide occurs as a white, crystalline powder.

It is freely soluble in water, soluble in ethanol (99.5), slightly soluble in acetonitrile and in acetic acid (100), and practically insoluble in diethyl ether.

The pH of a solution of Ipratropium Bromide (1 in 20) is between 5.0 and 7.5.

Melting point: about 223°C (with decomposition, after drying).

Identification (1) To 5 mg of Ipratropium Bromide add 0.5 mL of fuming nitric acid, and evaporate on a water bath to dryness. After cooling, dissolve the residue in 5 mL of acetone, and add 2 drops of potassium hydroxide-ethanol TS: a purple color develops.

(2) Determine the absorption spectrum of a solution of Ipratropium Bromide in 0.01 mol/L hydrochloric acid TS (3 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.

(3) Determine the infrared absorption spectrum of Ipratropium Bromide 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.

(4) The solution of Ipratropium Bromide (1 in 100) responds to the Qualitative Tests for bromide.

Purity (1) Clarity and color of solution—Dissolve 1.0 g of Ipratropium Bromide in 20 mL of water: the solution is clear and colorless.

(2) Sulfate—Perform the test with 1.0 g of Ipratropium Bromide. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid VS (not more than 0.024%).

(3) Heavy metals—Proceed with 2.0 g of Ipratropium Bromide according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(4) Arsenic—Prepare the test solution with 2.0 g of Ipratropium Bromide according to Method 3, and perform the test using Apparatus B. Use a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 10) (not more than 1 ppm).

(5) Isopropylatropine bromide—Dissolve 0.025 g of Ipratropium Bromide in the mobile phase to make exactly 100 mL, and use this solution as the sample solution. Perform the test with 25 μ L of the sample solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area, A_a , of ipratropium and the peak area, A_b , having a ratio of the retention time to ipratropium about 1.3 by the automatic integration method: $A_b/(A_a + A_b)$ is not more than 0.01, and no peak other than the peak of ipratropium and the peak having a ratio of the retention time to ipratropium about 1.3 appears within

about 14 minutes of the retention time after the solvent peak.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

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

Column temperature: Room temperature.

Mobile phase: A mixture of diluted phosphoric acid (1 in 200), acetonitrile and methanesulfonic acid (1000:120:1).

Flow rate: Adjust the flow rate so that the retention time of ipratropium is about 7 minutes.

Selection of column: Heat a solution of Ipratropium Bromide in 1 mol/L hydrochloric acid TS (1 in 100) at 100°C for 1 hour, and cool. To 2.5 mL of this solution add the mobile phase to make 100 mL. Proceed with 25 μ L of this solution under the above operating conditions, and calculate the resolution. Use a column showing a resolution not less than 3 between the peak of ipratropium and the peak having a ratio of the retention time to ipratropium about 0.6.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of ipratropium obtained from 25 μ L of the sample solution composes 50 to 80% of the full scale.

(6) Apo-compounds—Dissolve 0.14 g of Ipratropium Bromide in 0.01 mol/L hydrochloric acid TS to make 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectrophotometry, and determine the absorbances, A_1 and A_2 , at 246 nm and 263 nm, respectively: A_1/A_2 is not more than 0.91.

Loss on drying 3.9 – 4.4% (1 g, 105°C, 4 hours).

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

Assay Weigh accurately about 0.3 g of Ipratropium Bromide, previously dried, dissolve in 40 mL of acetic acid (100), add 40 mL of 1,4-dioxane and 2.5 mL of bismuth nitrate TS, 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
= 41.24 mg of $C_{20}H_{30}BrNO_3$

Containers and storage Containers—Tight containers.