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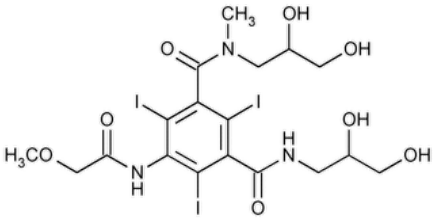
Iopromide



$C_{18}H_{24}I_3N_3O_8$ 791.11

1,3-Benzenedicarboxamide, *N*,*N*'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino]-*N*-methyl-.

N,*N*'-Bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(2-methoxyacetamido)-*N*-methylisophthalamide CAS RN®: 73334-07-3; UNII: 712BAC33MZ.

» Iopromide contains not less than 97.0 percent and not more than 102.5 percent of $C_{18}H_{24}I_3N_3O_8$, calculated on the anhydrous and solvent-free basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

USP Reference standards ⟨11⟩—

USP Iopromide RS
USP Iopromide Related Compound A RS
USP Iopromide Related Compound B RS

5-(Acetylamino)-*N*,*N*'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-*N*-methyl-1,3-benzenedicarboxamide.

Identification—

Change to read:

A: ▲*Spectroscopic Identification Tests* ⟨197⟩, *Infrared Spectroscopy: 197K*▲ (CN 1-May-2020) ·

B: The R_F value of the principal spot in the chromatogram, developed with the *Basic eluant*, obtained from the *Test solution* corresponds to that obtained from the *Standard solution* in the *Ordinary impurities* test.

Water Determination, *Method I* ⟨921⟩: not more than 1.5%.

Residue on Ignition ⟨281⟩: not more than 0.1%.

Free iodine—Transfer 2.0 g of Iopromide to a glass-stoppered test tube, and dissolve in 20 mL of water. Add 2 mL of toluene and 2 mL of diluted sulfuric acid, and shake vigorously: the toluene layer shows no red color.

Limit of free iodide—Transfer 10.0 g of Iopromide to a 150-mL conical flask, and dissolve in 70 mL of water. Adjust with 0.1 N sulfuric acid to a pH of 3.5 ± 0.5. Titrate with 0.001 N silver nitrate VS, determining the endpoint potentiometrically, using a silver or platinum electrode in combination with an appropriate reference electrode (see *Titrimetry* ⟨541⟩). Each mL of 0.001 N silver nitrate is equivalent to 126.9 µg of I: the limit is 0.002%.

Limit of free aromatic amine—

Test solution—Transfer 500 mg of Iopromide to a 25-mL volumetric flask, add 20 mL of water, and mix.

Standard solution—Dissolve a suitable quantity of USP Iopromide Related Compound A RS in water, and dilute with water to obtain a stock solution having a known concentration of 0.25 mg per mL. Transfer 2.0 mL of this stock solution to a 25-mL volumetric flask, add 18.0 mL of water, and mix.

Blank solution—Transfer 20 mL of water to a 25-mL volumetric flask.

Procedure—Treat each flask as follows. Place the flasks in an ice bath, and protect from light. Add slowly 1.0 mL of 8 N hydrochloric acid, mix, and allow to stand for 5 minutes. Add 1.0 mL of sodium nitrite solution (1 in 50), mix, and allow to stand for 5 minutes. Add 0.50 mL of freshly prepared sulfamic acid solution, (8 in 100). Shake each flask vigorously several times within the next 5 minutes, venting off the gas that evolves. [**Caution—**Considerable pressure is produced.] Add 1.0 mL of freshly prepared *N*-(1-naphthyl) ethylenediamine dihydrochloride solution, (1 in 1000) in a mixture of propylene glycol and water (70:30), and shake. Remove the flasks from the ice bath, and allow to stand in a water bath at about 25° for 10 minutes. Dilute with water to volume, mix, and degas with the aid of sonication for 1 minute. Concomitantly determine the absorbances of the *Test solution* and the *Standard solution* in 1-cm cells at the wavelength of maximum absorbance at about 495 nm, with a suitable spectrophotometer, using the *Blank solution,* treated in the same manner. The absorbance of the *Standard solution* is not less than 0.40. Calculate the percentage of free aromatic amine in the portion of Iopromide taken by the formula:

$$10(W_S/W_U)(A_U/A_S)$$

in which W_S is the quantity, in mg, of USP Iopromide Related Compound A RS taken to prepare the *Standard solution*; W_U is the quantity, in mg, of the Iopromide taken to prepare the *Test solution*; and A_U and A_S are the absorbances of the *Test solution* and the *Standard solution*, respectively: not more than 0.1% is found.

Limit of alcohol—

Standard solution—Prepare a solution of alcohol in dimethylformamide to obtain a solution having a known concentration of about 0.050 mg of alcohol (C_2H_5OH) per mL.

Test solution—Dissolve an accurately weighed portion of Iopromide in dimethylformamide to obtain a concentration of about 50 mg per mL.

Blank solution—Use dimethylformamide.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector, a flame-ionization detector, and a 0.25-mm × 30-m capillary column, the internal wall of which is coated with a 1.4-µm film of liquid phase G43. The column temperature is programmed according to the following steps: it is held at 40° for 10 minutes, then increased at a rate of 5° per minute to 70°; it is then increased at a rate of 30° per minute to 220°. The injector port is maintained at 160°; the headspace sampler is maintained at 80°; and the detector is maintained at 250°. Helium is used as the carrier gas at a flow rate of about 27 cm per second. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the retention time for alcohol is about 3 minutes; and the relative standard deviation for three injections of the *Standard solution* is not more than 4.0%. Chromatograph the *Blank solution*, and record the peak responses as directed for *Procedure:* the chromatogram shows no peak at the retention time for alcohol.

Procedure—[NOTE—Use peak areas where peak responses are indicated.] Transfer 2.0 mL each of the *Test solution*, the *Standard solution*, and the *Blank solution* to separate headspace vials, add 10 µL of 1 N hydrochloric acid to each vial, then seal the vials using a flanged cap so that the cap can no longer be turned. Record the chromatograms, and measure the responses for the alcohol peak. Calculate the concentration of alcohol in the portion of Iopromide taken by the formula:

$$(C/I)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of alcohol (C_2H_5OH) in the *Standard solution*; I is the quantity, in mg per mL, of Iopromide in the *Test solution*; and r_U and r_S are the alcohol peak responses in the chromatograms obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.4% of alcohol (C_2H_5OH) is found. Use the percentage obtained to calculate the *Assay* result on the solvent-free basis.

Limit of *N*-acetyl compound (iopromide related compound B)—Using the chromatograms obtained in the *Assay*, calculate the percentage of N-acetyl compound in the Iopromide taken by the formula:

$$20(W_B/W_I)[(A_{Y1} + A_{Y2})/(R_{Y1} + R_{Y2})]$$

in which W_B is the quantity, in mg, of USP Iopromide Related Compound B RS taken to prepare the *Related compound B standard solution*; W_I is the quantity, in mg, of Iopromide taken to prepare the *Assay preparation*; A_{Y1} and A_{Y2} are the peak responses for the iopromide related compound B *Y*1- and *Y*2-isomers, respectively, in the chromatogram obtained from the *Assay preparation*; and R_{Y1} and R_{Y2} are the peak responses for the iopromide related compound B *Y*1- and *Y*2-isomers, respectively, in the chromatogram obtained from the *Related compound B standard solution:* not more than 1.5% of N-acetyl compound is found.

ORDINARY IMPURITIES ⟨466⟩—

Test solution: a mixture of methanol and water (1:1).

Standard solutions: a mixture of methanol and water (1:1).

Visualization solution—

SOLUTION A—Dissolve 2.7 g of ferric chloride in 100 mL of 2.4 N hydrochloric acid. Store this solution in a refrigerator.

SOLUTION B—Dissolve 3.5 g of potassium ferricyanide in 100 mL of water. Store this solution in a refrigerator.

SOLUTION C—Dissolve 5.0 g of sodium arsenite in 30 mL of 1 N sodium hydroxide solution that has been cooled to 0°. While stirring, mix with 65 mL of 2.4 N hydrochloric acid, and store at room temperature. Use the clear supernatant.

Procedure—Mix 10 mL of *Solution A*, 10 mL of *Solution B*, and 2.0 mL of *Solution C*. Use within 30 minutes.

Basic eluant: a mixture of dioxane, water, and ammonium hydroxide (85:15:4).

Acidic eluant: a mixture of chloroform, methanol, water, and 96 percent formic acid (62:32:6:2).

Procedure—Apply 1 µL and 2 µL of the *Test solution* and 1 µL of each of the *Standard solutions* to two separate thin-layer chromatographic plates. Place one plate in a development chamber containing the *Acidic eluant*, and the second plate in a development chamber containing the *Basic eluant*. After the chromatograms have developed, remove the plates from the chambers, and allow to dry at room temperature.

Visualization—

DETECTION 1—Observe both plates under 254-nm UV light.

DETECTION 2—The plate developed with the *Acidic eluant* is exposed to ammonia vapors for 10 to 30 minutes and is air dried. Both plates are exposed to unfiltered 254-nm UV light for several minutes until the principal spots appear yellow. Overspray with *Visualization solution*, and examine the plates under ambient light. Determine the percentage of all secondary spots, except those due to free aromatic amine and to the *N*-acetyl compound.

Limit—The sum of all secondary spots observed in the chromatograms of the *Test solution*, except those due to the free aromatic amine and to the *N*-acetyl compound in addition to the percentage of *N*-acetyl compound obtained in the test for *Limit of N-Acetyl compound*, corresponds to not more than 3.0%.

Isomer distribution—Using the chromatogram of the *Assay preparation* obtained in the *Assay*, calculate the percentage of iopromide *E*1- and *Z*1-isomers in the Iopromide taken by the formula:

$$100(r_{E1} + r_{Z1})/(r_{E1} + r_{E2} + r_{Z1} + r_{Z2})$$

in which r_{E1}, r_{E2}, r_{Z1}, and r_{Z2} are the peak responses for iopromide *E*1-, *E*2-, *Z*1-, and *Z*2-isomers, respectively, in the chromatogram obtained from the *Assay preparation:* between 40.0% and 51.0% of *E*1- and *Z*1-isomers is found. Calculate the percentages of iopromide *E*2- and *Z*2-isomers in the Iopromide taken by the formula:

$$100(r_{E2} + r_{Z2})/(r_{E1} + r_{E2} + r_{Z1} + r_{Z2}):$$

between 49.0% and 60.0% *E*2- and *Z*2-isomers is found.

Assay—

Diluent—Prepare a mixture of methanol and water (1:1).

Mobile phase—

[Note—Use chloroform, methanol, and water that have been filtered and degassed.]

Mix 6 g of chloroform with 59 g of methanol, then add 900 g of water. Store in a sealed container, and do not stir or sparge the *Mobile phase* during use.

Standard preparation—Transfer an accurately weighed quantity of about 38 mg of USP Iopromide RS, to a 20-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Related compound B standard solution—Transfer about 1.9 mg of USP Iopromide Related Compound B RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Assay preparation—Transfer about 38 mg of Iopromide, accurately weighed, to a 20-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.2 mL per minute. The temperature is maintained at a constant temperature of about 20°. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative retention times for iopromide *E*1-isomer, iopromide *E*2-isomer, iopromide *Z*1-isomer, and iopromide *Z*2-isomer are about 0.70, 0.75, 0.85, and 1.0, respectively; the resolution, *R,* between iopromide isomers *Z*1 and *Z*2 is not less than 2.0; and the relative standard deviation for replicate injections for total iopromide area is not more than 2.0%. Chromatograph the *Related compound B standard solution*, and measure the area of the peak responses: the relative retention times for the iopromide related compound B *Y*1- and *Y*2-isomers are about 0.28 and 0.31, respectively; and the signal-to-noise ratio for the iopromide related compound B *Y*2-isomer is not less than 20.

Determine which peaks in the chromatograms correspond to the *E*-isomers as follows. Transfer a portion of the *Standard preparation* to a vial, seal with a crimp-top, and heat to 121° for 15 minutes. Inject the cooled solution. Compare the chromatogram obtained with that of the unheated *Standard preparation*, and note the retention times of the two *E*-isomer peaks, which increase in size after heating.

Procedure—[Note—Use peak areas where peak responses are indicated.] Separately inject equal volumes (about 10 µL) of the *Standard preparation,* the *Related compound B standard solution*, and the *Assay preparation* into the chromatograph, and measure the responses for the major peaks. Allow the *Mobile phase* to flow for not less than 60 minutes between each injection to prevent interference from late-eluting amine peaks. Calculate the quantity of $C_{18}H_{24}I_3N_3O_8$ in the portion of Iopromide taken by the formula:

$$C(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Iopromide RS in the *Standard preparation*; and r_U and r_S are the sums of the peak responses for iopromide *E*1-isomer, iopromide *E*2-isomer, iopromide *Z*1-isomer, and iopromide *Z*2-isomer in the chromatograms obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
IOPROMIDE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. Information currently unavailable

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