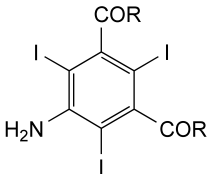


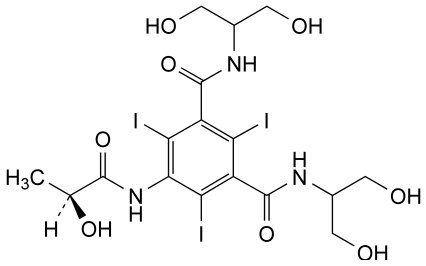
K. R = OH: 5-amino-2,4,6-triiodobenzene-1,3-dicarboxylic acid,

L. R = Cl: 5-amino-2,4,6-triiodobenzene-1,3-dicarbonyl dichloride.

01/2008:1115
corrected 6.0

IOPAMIDOL

Iopamidolum



$C_{17}H_{22}I_3N_3O_8$ M_r 777
[60166-93-0]

DEFINITION

N,N'-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodobenzene-1,3-dicarboxamide.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: freely soluble in water, very slightly soluble in methanol, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *iopamidol CRS*.

B. It complies with the test for loss on drying (see Tests).

C. It complies with the test for specific optical rotation (see Tests).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 1 g in *water R* and dilute to 50 ml with the same solvent.

Acidity or alkalinity. Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 ml with the same solvent. Not more than 0.75 ml of *0.01 M hydrochloric acid* or 1.4 ml of *0.01 M sodium hydroxide* is required to adjust to pH 7.0 (*2.2.3*).

Specific optical rotation (*2.2.7*): −4.6 to −5.2 (dried substance), determined at 436 nm.

Dissolve 10.0 g, with heating if necessary, in *water R* and dilute to 25.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.50 g of the substance to be examined in *water R* and dilute to 50.0 ml with the same solvent.

Reference solution (a). Dissolve 5.0 mg of *iopamidol impurity H CRS* in *water R* and dilute to 100.0 ml with the same solvent.

Reference solution (b). Dilute 2.0 ml of the test solution to 20.0 ml with *water R*. Dilute 1.0 ml of this solution to 50.0 ml with *water R*.

Reference solution (c). Add 0.1 ml of the test solution to 20 ml of reference solution (a) and dilute to 50 ml with *water R*.

Column: 2 columns coupled in series,
- *size*: *l* = 0.25 m, Ø = 4.6 mm,
- *stationary phase*: *phenylsilyl silica gel for chromatography R* (5 µm),
- *temperature*: 60 °C.

Mobile phase:
- *mobile phase A*: *water R*,
- *mobile phase B*: *acetonitrile R, water R* (50:50 *V/V*),

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 18	100	0
18 - 40	100 - 62	0 - 38
40 - 45	62 - 50	38 - 50
45 - 50	50 - 100	50 - 0
50 - 60	100	0

Flow rate: 2.0 ml/min.

Detection: spectrophotometer at 240 nm.

Injection: 20 µl.

Relative retention with reference to iopamidol (retention time = about 14.6 min): impurity D = about 0.1; impurity B = about 0.6; impurities I and H = about 0.9; impurity G = about 1.1; impurity K = about 1.2; impurity C = about 1.3; impurity J = about 1.5; impurity A = about 1.8; impurity E = about 2.2; impurity F = about 2.3.

System suitability: reference solution (c):
- *resolution*: minimum 2.0 between the peaks due to impurity H and iopamidol.

Limits:
- *sum of impurities H and I*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
- *impurities A, B, C, D, E, F, G, J, K*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *any other impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *sum of impurities other than H and I*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),
- *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

Free aromatic amines: maximum 200 ppm.

Keep the solutions and reagents in iced water, protected from bright light.

Test solution. In a 25 ml volumetric flask, dissolve 0.500 g of the substance to be examined in 20.0 ml of *water R*.

Reference solution. In a 25 ml volumetric flask, mix 4.0 ml of a 25.0 mg/l solution of *iopamidol impurity A CRS* with 16.0 ml of *water R*.

Blank solution. Place 20.0 ml of *water R* in a 25 ml volumetric flask.

Place the flasks in iced water, protected from light, for 5 min. Add 1.0 ml of *hydrochloric acid R* to each flask, mix and allow to stand for 5 min. Add 1.0 ml of a 20 g/l solution of *sodium nitrite R* prepared immediately before use, mix and allow to stand for 5 min. Add 1.0 ml of a 120 g/l solution of *ammonium sulphamate R*, swirl gently until gas liberation has ceased, and allow to stand for 5 min. *(CAUTION: considerable pressure is produced).* Add 1.0 ml of a freshly prepared 1 g/l solution of *naphthylethylenediamine dihydrochloride R* and mix. Remove the flasks from the iced water and allow to stand for 10 min. Dilute to 25.0 ml with *water R* and mix. Measure immediately the absorbance (*2.2.25*) at 500 nm of the solutions obtained from the test solution and the reference solution using, as the compensation liquid, the solution obtained from the blank solution.

The absorbance of the test solution is not greater than that of the reference solution.

Free iodine: maximum 10 ppm.

Dissolve 2.0 g in 25 ml of *water R* in a ground-glass stoppered centrifuge tube. Add 5 ml of *toluene R* and 5 ml of *diluted sulphuric acid R*. Shake and centrifuge. Any red colour of the upper layer is not more intense than that of the upper phase obtained in the same way from 22 ml of *water R*, 2 ml of *iodide standard solution (10 ppm I) R*, 5 ml of *dilute sulphuric acid R*, 1 ml of *concentrated hydrogen peroxide solution R* and 5 ml of *toluene R*.

Iodide: maximum 10 ppm.

Dissolve 6.000 g in *water R* and dilute to 20 ml with the same solvent. Add 2.0 ml of *0.001 M potassium iodide*. Carry out a potentiometric titration (*2.2.20*) with *0.001 M silver nitrate* using a silver indicator electrode and an appropriate reference electrode. Subtract the volume of titrant corresponding to the 2.0 ml of *0.001 M potassium iodide*, determined by titrating a blank to which is added 2.0 ml of *0.001 M potassium iodide* and use the residual value to calculate the iodide content.

1 ml of *0.001 M silver nitrate* is equivalent to 126.9 µg of iodide.

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with limit test C. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*): less than 1.4 IU/g, if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

To 0.300 g in a 250 ml round-bottomed flask add 5 ml of *strong sodium hydroxide solution R*, 20 ml of *water R*, 1 g of *zinc powder R* and a few glass beads. Boil under a reflux condenser for 30 min. Allow to cool and rinse the condenser with 20 ml of *water R*, adding the rinsings to the flask. Filter through a sintered-glass filter (*2.1.2*) and wash the filter with several quantities of *water R*. Collect the filtrate and washings. Add 5 ml of *glacial acetic acid R* and titrate immediately with *0.1 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*) using a suitable electrode system such as silver-silver chloride.

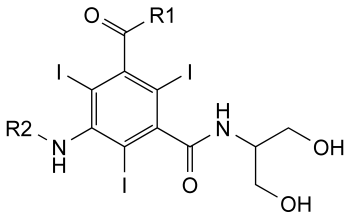
1 ml of *0.1 M silver nitrate* is equivalent to 25.90 mg of $C_{17}H_{22}I_3N_3O_8$.

STORAGE

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

IMPURITIES

Specified impurities: A, B, C, D, E, F, G, H, I, J, K.



A. R1 = NH-CH(CH_2OH)$_2$, R2 = H: 5-amino-*N*,*N*'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodobenzene-1,3-dicarboxamide,

B. R1 = NH-CH(CH_2OH)$_2$, R2 = CO-CH_2OH: 5-[(hydroxyacetyl)amino]-*N*,*N*'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodobenzene-1,3-dicarboxamide,

C. R1 = NH-CH(CH_2OH)$_2$, R2 = CO-CH_3: 5-(acetylamino)-*N*,*N*'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodobenzene-1,3-dicarboxamide,

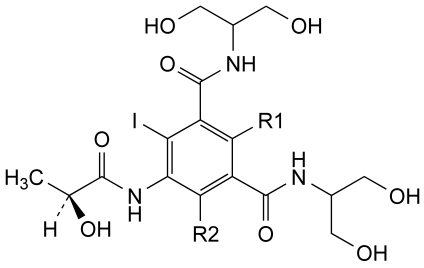
D. R1 = OH, R2 = CO-CHOH-CH_3: 3-[[2-hydroxy-1-(hydroxymethyl)ethyl]carbamoyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodobenzoic acid,

E. R1 = NH-CH(CH_2OH)$_2$, R2 = CO-CH(CH_3)-O-CO-CH_3: (1*S*)-2-[[3,5-bis[[2-hydroxy-1-(hydroxymethyl)ethyl]carbamoyl]-2,4,6-triiodophenyl]amino]-1-methyl-2-oxoethyl acetate,

F. R1 = N(CH_3)$_2$, R2 = CO-CHOH-CH_3: *N*'-[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodo-*N*,*N*-dimethylbenzene-1,3-dicarboxamide,

G. R1 = NH-CH_2-CHOH-CH_2OH, R2 = CO-CHOH-CH_3: *N*-(2,3-dihydroxypropyl)-*N*'-[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodobenzene-1,3-dicarboxamide,

J. R1 = NH-CH_2-CH_2OH, R2 = CO-CHOH-CH_3: *N*-(2-hydroxyethyl)-*N*'-[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodobenzene-1,3-dicarboxamide,



H. R1 = I, R2 = Cl: 4-chloro-*N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,6-diiodobenzene-1,3-dicarboxamide,

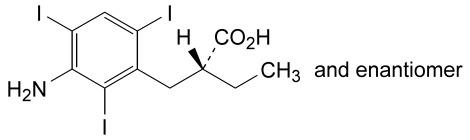
I. R1 = Cl, R2 = I: 2-chloro-*N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-4,6-diiodobenzene-1,3-dicarboxamide,

K. R1 = I, R2 = H: *N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4-diiodobenzene-1,3-dicarboxamide.

01/2008:0700
corrected 6.0

IOPANOIC ACID

Acidum iopanoicum



$C_{11}H_{12}I_3NO_2$ M_r 571
[96-83-3]

DEFINITION

Iopanoic acid contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (*RS*)-2-(3-amino-2,4,6-tri-iodobenzyl)butanoic acid, calculated with reference to the dried substance.

CHARACTERS

A white or yellowish-white powder, practically insoluble in water, soluble in ethanol and in methanol. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): about 155 °C, with decomposition.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *iopanoic acid CRS*.

C. Examine the chromatograms obtained in the test for related substances (see Tests). Spray the plate with a 1 g/l solution of *4-dimethylaminocinnamaldehyde R* in a mixture of 1 volume of *hydrochloric acid R* and 99 volumes of *alcohol R*. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Heat 50 mg carefully in a small porcelain dish over a flame. Violet vapour is evolved.

TESTS

Appearance of solution. Dissolve 1.0 g in *1 M sodium hydroxide* and dilute to 20 ml with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_3 (*2.2.2, Method II*).

Related substances. Examine by thin-layer chromatography (*2.2.27*), using *silica gel* GF_{254} *R* as the coating substance.

Test solution (a). Dissolve 1.0 g of the substance to be examined in a mixture of 3 volumes of *ammonia R* and 97 volumes of *methanol R* and dilute to 10 ml with the same mixture of solvents.

Test solution (b). Dilute 1 ml of test solution (a) to 10 ml with a mixture of 3 volumes of *ammonia R* and 97 volumes of *methanol R*.

Reference solution (a). Dissolve 50 mg of *iopanoic acid CRS* in a mixture of 3 volumes of *ammonia R* and 97 volumes of *methanol R* and dilute to 5 ml with the same mixture of solvents.

Reference solution (b). Dilute 1 ml of test solution (b) to 50 ml with a mixture of 3 volumes of *ammonia R* and 97 volumes of *methanol R*.

Apply separately to the plate 5 µl of each solution. Develop over a path of 10 cm using a mixture of 10 volumes of *concentrated ammonia R*, 20 volumes of *methanol R*, 20 volumes of *toluene R* and 50 volumes of *dioxan R*. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

Halides. To 0.46 g add 10 ml of *nitric acid R* and 15 ml of *water R*. Shake for 5 min and filter. 15 ml of the filtrate complies with the limit test for chlorides (*2.4.4*) (180 ppm, expressed as chloride).

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 1 h.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

To 0.150 g in a 250 ml round-bottomed flask add 5 ml of *strong sodium hydroxide solution R*, 20 ml of *water R*, 1 g of *zinc powder R* and a few glass beads. Boil under a reflux condenser for 60 min. Allow to cool and rinse the condenser with 20 ml of *water R*, adding the rinsings to the flask. Filter through a sintered-glass filter (*2.1.2*) and wash the filter with several quantities of *water R*. Collect the filtrate and washings. Add 40 ml of *dilute sulphuric acid R* and titrate immediately with *0.1 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*), using a suitable electrode system such as silver-mercurous sulphate.

1 ml of *0.1 M silver nitrate* is equivalent to 19.03 mg of $C_{11}H_{12}I_3NO_2$.

STORAGE

Store protected from light.