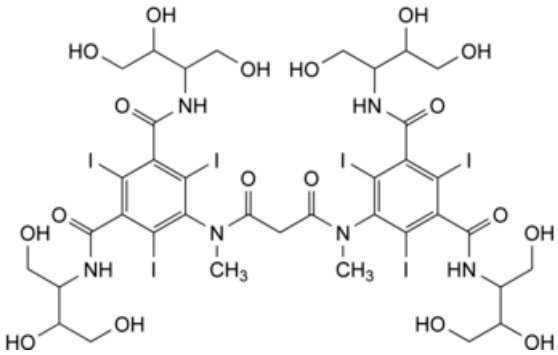
Edition: BP 2025 (Ph. Eur. 11.6 update)

Iotrolan

General Notices

(Ph. Eur. monograph 1754)



$C_{37}H_{48}I_6N_6O_{18}$ 1626 *79770-24-4*

Action and use

Iodinated contrast medium.

Ph Eur

DEFINITION

Mixture of stereoisomers of 5,5′-[propanedioylbis(methylimino)]bis[*N*,*N*′-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]2,4,6-triiodobenzene-1,3-dicarboxamide].

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white powder, hygroscopic.

Solubility

Very soluble in water, freely soluble in dimethyl sulfoxide, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *iotrolan CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Dissolve 18.0 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Conductivity (2.2.38)

Maximum 25 $\mu S \cdot cm^{-1}$.

Dissolve 1.000 g in *water R* and dilute to 50.0 mL with the same solvent.

Primary aromatic amines

Protect the solutions from light throughout the test. All given times are critical for the test results. The test solution, the reference solution and the blank solution must be processed in parallel.

Test solution Dissolve 0.500 g of the substance to be examined in 20.0 mL of *water R* in a 25 mL volumetric flask.

Reference solution Dissolve 5.0 mg of *iopamidol impurity A CRS* in *water R* and dilute to 20.0 mL with the same solvent. Transfer 1.0 mL of this solution to a 25 mL volumetric flask and add 19.0 mL of *water R*.

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

Procedure Cool the test solution, reference solution and blank solution in a bath of iced water for 5 min. Add 1.0 mL of *hydrochloric acid R1* to each solution and cool again for 5 min in a bath of iced water. Add 1.0 mL of a 20 g/L solution of *sodium nitrite R*, shake vigorously and cool for another 5 min in a bath of iced water. To each solution add 0.50 mL of an 80 g/L solution of *sulfamic acid R*. Over the next 5 min, shake vigorously several times, raising the stoppers to vent the gas that evolves. Afterwards add to each solution 1.0 mL of a 1 g/L solution of *naphthylethylenediamine dihydrochloride R* in a mixture of 300 volumes of *water R* and 700 volumes of *propylene glycol R*, shake, allow to cool to room temperature for 10 min and dilute to 25.0 mL with *water R*. Degas the solutions in an ultrasonic bath for 1 min and measure the absorbance (2.2.25) of the test solution and the reference solution at 495 nm against the blank, within 5 min.

System suitability:

— *absorbance of the reference solution*: minimum 0.40.

Limit:

— *absorbance of the test solution*: not more than the absorbance of the reference solution (0.05 per cent).

Related substances

Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use*.

Test solution Dissolve 1.0 g of the substance to be examined in a mixture of equal volumes of *methanol R* and *water R* and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with a mixture of equal volumes of *methanol R* and *water R*.

Reference solution (b) Dilute 2.0 mL of reference solution (a) to 10.0 mL with a mixture of equal volumes of *methanol R* and *water R*.

Reference solution (c) Dissolve the contents of a vial of *iotrolan for system suitability CRS* (containing about 0.05 per cent of each of impurities A and B) in 50 µL of a mixture of equal volumes of *methanol R* and *water R*.

Plate *TLC silica gel F_{254} plate R*.

Pretreatment Over 3/4 of the plate with *methylene chloride R*.

Mobile phase *concentrated ammonia R*, *water R*, *dioxan R* (4:20:80 *V/V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying In a current of air until the solvents have evaporated.

Detection Examine in ultraviolet light at 254 nm. Expose the plate to the ultraviolet light for 2-5 min until the principal spots appear clearly as yellow spots. Spray with *ferric chloride-ferricyanide-arsenite reagent R* and examine in daylight.

R_F values Iotrolan = about 0.25; impurity A = about 0.4; impurity B = about 0.5.

System suitability Reference solution (c):

— the chromatogram shows 3 clearly separated spots.

Limits:

— *impurities A, B*: any spot due to impurity A or B is not more intense than the principal spot in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: any other spot is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (0.10 per cent).

Isomer distribution

Liquid chromatography (*2.2.29*) as described under Assay. Use the normalisation procedure.

Identification of peaks Use the chromatogram supplied with *iotrolan CRS* and the chromatogram obtained with the reference solution to identify the peaks due to the 3 isomer groups.

Calculate the percentage content of each of the isomer groups G1, G2 and G3, with reference to the total area of all of the peaks due to the 3 isomer groups, using the chromatogram obtained with the test solution.

Limits:

— *isomer group G1*: 53.0 per cent to 70.0 per cent;

— *isomer group G2*: 3.0 per cent to 11.0 per cent;

— *isomer group G3*: 25.0 per cent to 39.0 per cent.

Free iodine

Dissolve 0.20 g in 1 mL of *water R* in a glass-stoppered test tube. Add 4 mL of a 370 g/L solution of *sulfuric acid R* and 5 mL of *toluene R*, close and shake vigorously. The upper layer remains colourless (*2.2.2, Method II*).

Iodide

Maximum 20 ppm.

Dissolve 10.0 g in 50 mL of *carbon dioxide-free water R*. Adjust to pH 3-4 adding about 0.15 mL of *dilute sulfuric acid R*. Titrate with *0.001 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*). Not more than 1.5 mL of *0.001 M silver nitrate* is required to reach the end-point.

Water (*2.5.12*)

Maximum 3.5 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.7 IU/g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 40.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution Dissolve 40.0 mg of *iotrolan CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *methanol R*, *water for chromatography R* (10:90 *V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 40 min.

Retention time Isomer group G1 = about 8 min to 12 min; isomer group G2 = about 15 min to 22 min; isomer group G3 = about 22 min to 32 min.

System suitability Reference solution:

— the chromatogram obtained is similar to the chromatogram supplied with *iotrolan CRS*.

Calculate the percentage content of iotrolan from the total area of all of the peaks of the 3 isomer groups G1, G2 and G3 and the declared content of *iotrolan CRS*.

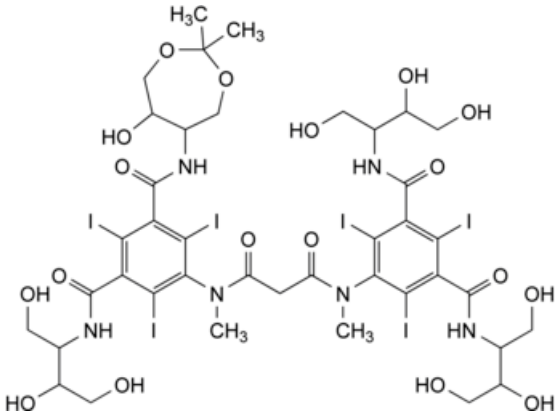
STORAGE

In an airtight container, protected from light.

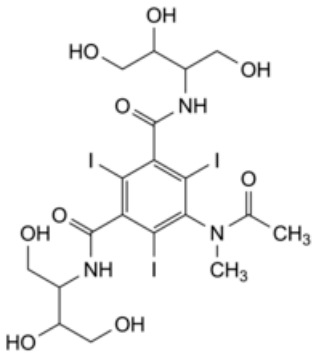
IMPURITIES

Specified impurities *A, B.*

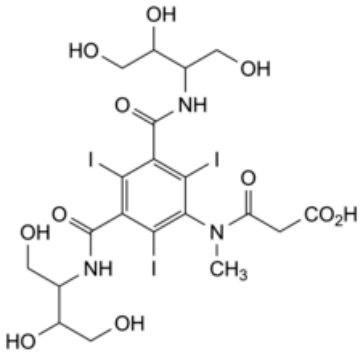
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, F, G, H, I, J.*



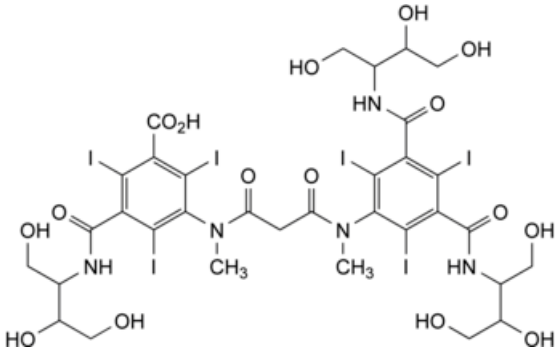
A. *N*,*N*′-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-5-[[3-[[3-[[2,3-dihydroxy-1-(hydroxymethyl)propyl]carbamoyl]-5-[(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)carbamoyl]-2,4,6-triiodophenyl]methylamino]-3-oxopropanoyl]methylamino]-2,4,6-triiodobenzene-1,3-dicarboxamide,



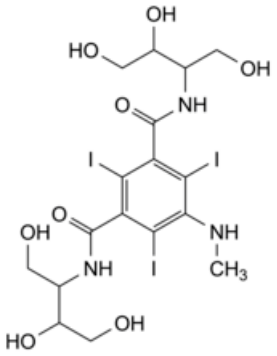
B. 5-(acetylmethylamino)-*N*,*N*′-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-2,4,6-triiodobenzene-1,3-dicarboxamide,



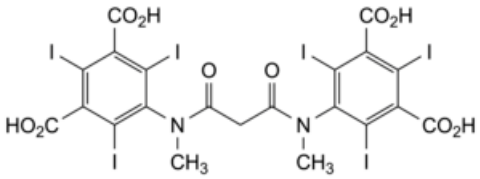
C. 3-[[3,5-bis[[2,3-dihydroxy-1-(hydroxymethyl)propyl]carbamoyl]-2,4,6-triiodophenyl]methylamino]-3-oxopropanoic acid,



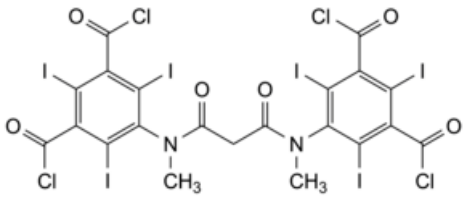
D. 3-[[3-[[3,5-bis[[2,3-dihydroxy-1-(hydroxymethyl)propyl]carbamoyl]-2,4,6-triiodophenyl]methylamino]-3-oxopropanoyl]methylamino]-5-[[2,3-dihydroxy-1-(hydroxymethyl)propyl]carbamoyl]-2,4,6-triiodobenzoic acid,



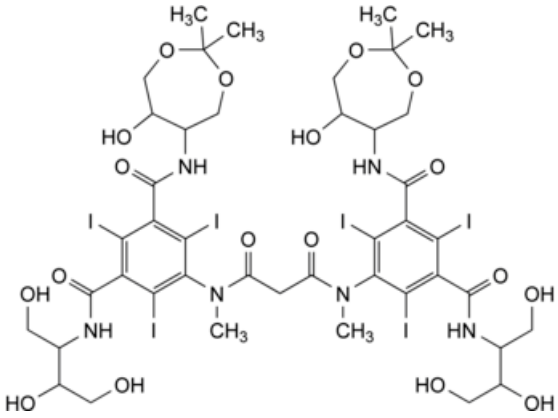
E. *N*,*N*′-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-2,4,6-triiodo-5-(methylamino)benzene-1,3-dicarboxamide,



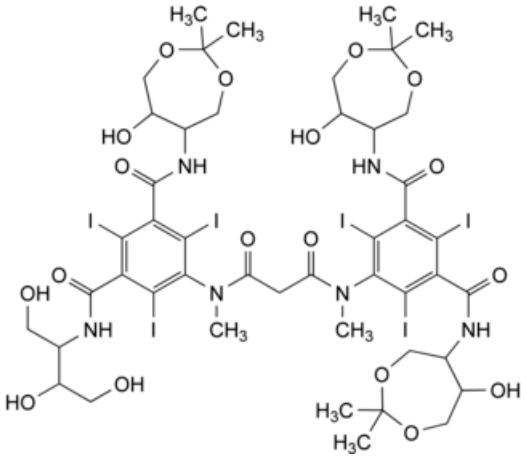
F. 5,5′-[propanedioylbis(methylimino)]bis[2,4,6-triiodobenzene-1,3-dicarboxylic] acid,



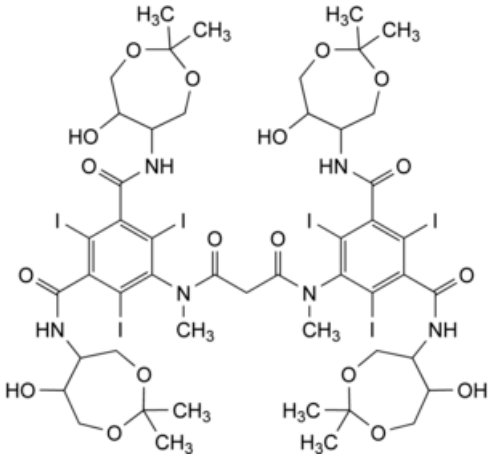
G. 5,5′-[propanedioylbis(methylimino)]bis[2,4,6-triiodobenzene-1,3-dicarbonyl] tetrachloride,



H. 5,5′-[propanedioylbis(methylimino)]bis[*N*-[2,3-dihydroxy-1-(hydroxymethyl)propyl]-*N*′-(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-2,4,6-triiodobenzene-1,3-dicarboxamide],



I. 5-[[3-[[3-[[2,3-dihydroxy-1-(hydroxymethyl)propyl]carbamoyl]-5-[(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)carbamoyl]-2,4,6-triiodophenyl]methylamino]-3-oxopropanoyl]methylamino]-*N*,*N*′-bis(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-2,4,6-triiodobenzene-1,3-dicarboxamide,



J. 5,5′-[propanedioylbis(methylimino)]bis[*N*,*N*′-bis(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-2,4,6-triiodobenzene-1,3-dicarboxamide].

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