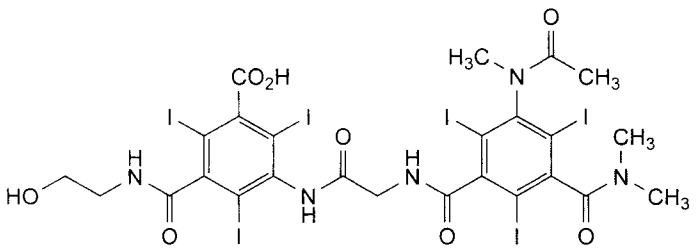
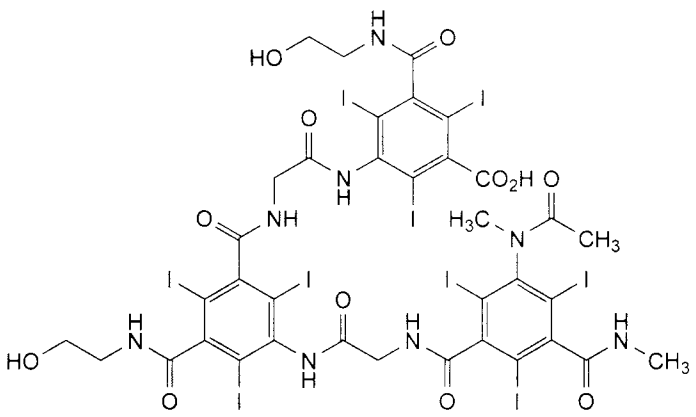
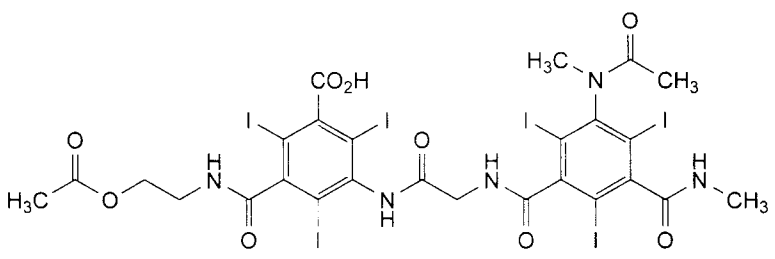


D. D1, D2, D3 and D4: 3-[[[[3-(acetylmethylamino)-5-(dimethylcarbamoyl)-2,4,6-triiodobenzoyl]amino]acetyl]amino]-5-[(2-hydroxyethyl)carbamoyl]-2,4,6-triiodobenzoic acid,

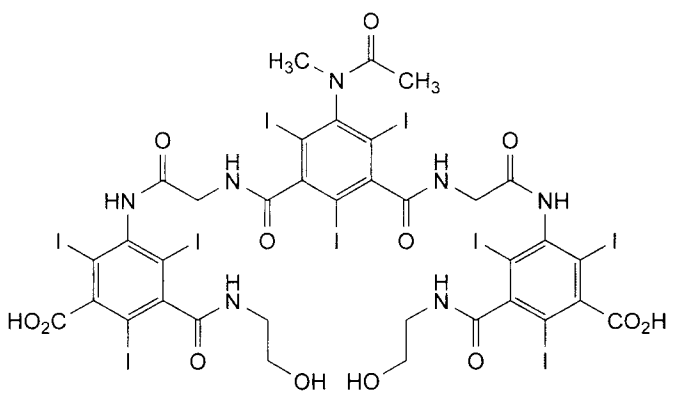


E. 3-[[[[3-[[[[3-(acetylmethylamino)-2,4,6-triiodo-5-(methylcarbamoyl)benzoyl]amino]acetyl]amino]-5-[(2-hydroxyethyl)carbamoyl]-2,4,6-triiodobenzoic acid,

F. unknown structure,



G. 3-[[[[3-(acetylmethylamino)-2,4,6-triiodo-5-(methylcarbamoyl)benzoyl]amino]acetyl]amino]-5-[[2-(acetyloxy)ethyl]carbamoyl]-2,4,6-triiodobenzoic acid,

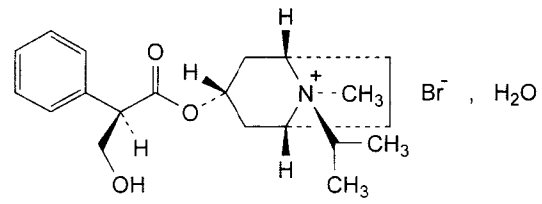


H. 3,3′-[[5-(acetylmethylamino)-2,4,6-triiodo-1,3-phenylene]bis(carbonyliminomethylenecarbonylimino)]bis[5-[(2-hydroxyethyl)carbamoyl]-2,4,6-triiodobenzoic] acid.

01/2008:0919
corrected 9.6

IPRATROPIUM BROMIDE

Ipratropii bromidum



and enantiomer

$C_{20}H_{30}BrNO_3,H_2O$ M_r 430.4
[66985-17-9]

DEFINITION

(1*R*,3*r*,5*S*,8*r*)-3-[[(2*RS*)-3-Hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide monohydrate.

Content: 99.0 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: soluble in water, freely soluble in methanol, slightly soluble in ethanol (96 per cent).

mp: about 230 °C, with decomposition.

IDENTIFICATION

First identification: A, E.

Second identification: B, C, D, E.

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

B. Examine the chromatograms obtained in the test for impurity A.
Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. To 5 mL of solution S (see Tests), add 2 mL of *dilute sodium hydroxide solution R*. No precipitate is formed.

D. To about 1 mg add 0.2 mL of *nitric acid R* and evaporate to dryness on a water-bath. Dissolve the residue in 2 mL of *acetone R* and add 0.1 mL of a 30 g/L solution of *potassium hydroxide R* in *methanol R*. A violet colour develops.

E. It gives reaction (a) of bromides (*2.3.1*).

TESTS

Solution S. Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution GY_7 (*2.2.2, Method II*).

pH (*2.2.3*): 5.0 to 7.5 for solution S.

Impurity A. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 1.0 mL with the same solvent.

Reference solution (a). Dissolve 20 mg of *ipratropium bromide CRS* in *methanol R* and dilute to 1.0 mL with the same solvent.

Reference solution (b). Dissolve 20 mg of *methylatropine bromide CRS* in 1.0 mL of reference solution (a).

Reference solution (c). Dissolve 5 mg of *ipratropium impurity A CRS* in 100.0 mL of *methanol R*. Dilute 2.0 mL of the solution to 5.0 mL with *methanol R*.

Plate: *TLC silica gel plate R* (2-10 µm).

Mobile phase: *anhydrous formic acid R, water R, ethanol (96 per cent) R, methylene chloride R* (1:3:18:18 *V/V/V/V*).

Application: 1 µL.

Development: over a path of 6 cm.

Drying: at 60 °C for 15 min.

Detection: spray with *potassium iodobismuthate solution R5*, allow the plate to dry in air, spray with a 50 g/L solution of *sodium nitrite R* and protect immediately with a sheet of glass.

System suitability: the chromatogram obtained with reference solution (b) shows 2 clearly separated principal spots.

Limit:

- *impurity A*: any spot due to impurity A is not more intense than the principal spot in the chromatogram obtained with reference solution (c) (0.1 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.200 g of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a). Dissolve 10.0 mg of *ipratropium bromide CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *ipratropium bromide CRS* and 5 mg of *ipratropium impurity B CRS* in 1 mL of *methanol R* and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Column:

- *size*: *l* = 0.15 m, Ø = 3.9 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 30 °C.

Mobile phase: dissolve 12.4 g of *sodium dihydrogen phosphate R* and 1.7 g of *tetrapropylammonium chloride R* in 870 mL of *water for chromatography R*; adjust to pH 5.5 with a 180 g/L solution of *disodium hydrogen phosphate dodecahydrate R* and add 130 mL of *methanol R1*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 5 µL.

Run time: 6 times the retention time of ipratropium.

Relative retention with reference to ipratropium (retention time = about 4.9 min): impurity C = about 0.7; impurity B = about 1.2; impurity D = about 1.8; impurity E = about 2.3; impurity F = about 5.1.

System suitability: reference solution (b):

- *resolution*: minimum 3.0 between the peaks due to impurity B and ipratropium;
- *symmetry factor*: maximum 2.5 for the principal peak.

Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.3; impurity D = 0.2; impurity F = 0.5;
- *impurity D*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);
- *impurities B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);
- *disregard limit*: one-third of the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent); disregard the peak due to the bromide ion.

Water (*2.5.12*): 3.9 per cent to 4.4 per cent, determined on 0.50 g.

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

ASSAY

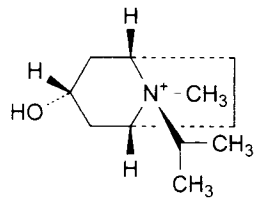
Dissolve 0.350 g in 50 mL of *water R* and add 3 mL of *dilute nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 41.24 mg of $C_{20}H_{30}BrNO_3$.

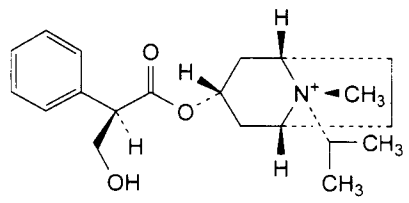
IMPURITIES

Specified impurities: *A, B, C, D.*

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*): *E, F.*

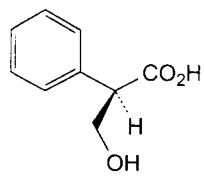


A. (1*R*,3*r*,5*S*,8*r*)-3-hydroxy-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane,



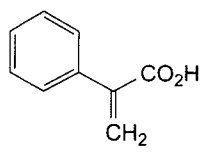
and enantiomer

B. (1*R*,3*r*,5*S*,8*s*)-3-[[(2*RS*)-3-hydroxy-2-phenylpropanoyl]-oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo-[3.2.1]octane,

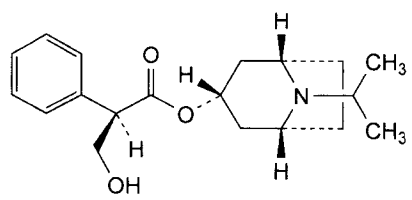


and enantiomer

C. (2*RS*)-3-hydroxy-2-phenylpropanoic acid (DL-tropic acid),



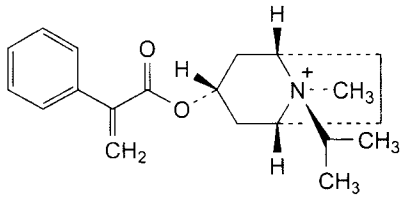
D. 2-phenylpropenoic acid (atropic acid),



and enantiomer

E. (1*R*,3*r*,5*S*)-8-(1-methylethyl)-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate,

Monographs

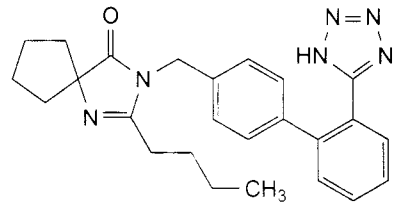


F. (1*R*,3*r*,5*S*,8*r*)-8-methyl-8-(1-methylethyl)-3-[(2-phenylpropenoyl)oxy]-8-azoniabicyclo[3.2.1]octane.

01/2020:2465

IRBESARTAN

Irbesartanum



$C_{25}H_{28}N_6O$ M_r 428.5
[138402-11-6]

DEFINITION

2-Butyl-3-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

As *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) are classified as probable human carcinogens, manufacturers must ensure that their manufacturing process does not generate such impurities and develop appropriate control strategies. To allow manufacturers to make the necessary changes to their process, a transition period has been agreed by competent authorities and strict temporary limits on levels of these impurities introduced in the Test section.

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, sparingly soluble in methanol, slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *irbesartan CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness at 60 °C and record new spectra using the residues.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

Dissolve 0.50 g in a mixture of 1 volume of *2 M sodium hydroxide R* and 9 volumes of *methanol R2* and dilute to 10 mL with the same mixture of solvents.

Impurity B. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution. Dissolve 25.0 mg of *sodium azide R* (sodium salt of impurity B) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 0.25 mL of the solution to 200.0 mL with the mobile phase.

Precolumn (used to prevent saturation of the column with irbesartan):

- *size*: *l* = 0.05 m, Ø = 4 mm;
- *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (8.5 µm).

Column:

- *size*: *l* = 0.25 m, Ø = 4 mm;
- *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (8.5 µm).

Mobile phase: 4.2 g/L solution of *sodium hydroxide R* in *carbon dioxide-free water R*.

Flow rate: 1.0 mL/min.

Detection: conductivity detector with a sensitivity of 3 µS; use a self-regenerating anion suppressor.

Neutralisation of the eluent: either chemical or electrochemical:

- *chemical*: by continuous countercurrent circulation in a neutralising micromembrane, performed before detection:
  - *neutralising solvent*: *0.025 M sulfuric acid*;
  - *flow rate*: 10 mL/min;
  - *pressure*: about 100 kPa.
- *electrochemical*: 300 mA (for example).

Injection: 200 µL; after each injection of the test solution, rinse the precolumn with a mixture of mobile phase and *methanol R* (40:60 *V/V*) for 10 min; equilibrate to initial conditions as necessary; a switch valve can be used to avoid disconnecting the precolumn from the column.

Run time: 25 min.

Retention time: impurity B = about 14 min.

System suitability: reference solution:

- *signal-to-noise ratio*: minimum 10 for the peak due to impurity B.

Limit:

- *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (10 ppm).

Related substances. Liquid chromatography (*2.2.29*).

Buffer solution pH 3.2. Mix 5.5 mL of *phosphoric acid R* and 950 mL of *water for chromatography R* and adjust to pH 3.2 with *triethylamine R*.

Test solution. Dissolve 50 mg of the substance to be examined in *methanol R2* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R2*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R2*.

Reference solution (b). Dissolve 5 mg of the substance to be examined and 5 mg of *irbesartan impurity A CRS* in *methanol R2* and dilute to 10 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *methanol R2*.

Column:

- *size*: *l* = 0.25 m, Ø = 4 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *acetonitrile R1*, buffer solution pH 3.2 (33:67 *V/V*).

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 µL.

Run time: 1.4 times the retention time of irbesartan.

Identification of impurities: use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.