ASSAY

Transfer 10.00 g of the tincture to be examined to a chromatography column about 0.2 m long and about 15 mm in internal diameter, filled with 8 g of *basic aluminium oxide R*. After infiltration into the aluminium oxide layer rinse the internal wall of the column with 3 quantities, each of 2 ml, of *ethanol (70 per cent V/V) R*. Elute in portions, with 40 ml of *ethanol (70 per cent V/V) R*. Avoid whirling or drying of the surface of the aluminium oxide layer. Collect the whole of the eluate. Evaporate the eluate on a water-bath to about 10 ml. Allow to cool. Add 10.0 ml of *0.02 M hydrochloric acid* and 20 ml of *carbon dioxide-free water R*. Titrate the excess acid with *0.02 M sodium hydroxide* using 0.15 ml of *methyl red mixed solution R* as indicator.

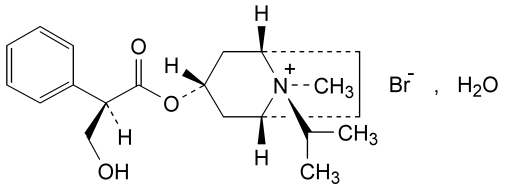
Perform a blank assay replacing the tincture to be examined with 10.0 ml of alcohol of the strength stated on the label.

1 ml of *0.02 M hydrochloric acid* is equivalent to 4.807 mg of total alkaloids, calculated as emetine.

01/2008:0919

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 R*, 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.

Limits:

– *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 R*; adjust to pH 5.5 with a 180 g/l solution of *disodium hydrogen phosphate R* and add 130 ml of *methanol R*.

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);

– *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.

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

ASSAY

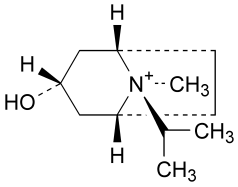
Dissolve 0.350 g in 50 ml of *water R* and add 3 ml of *dilute nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

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

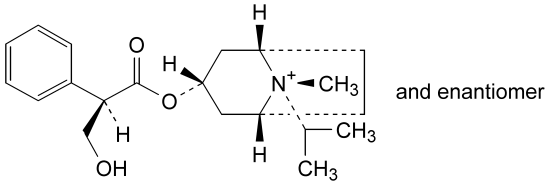
IMPURITIES

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

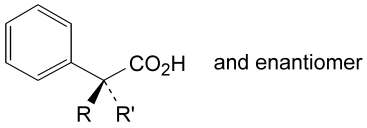
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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,

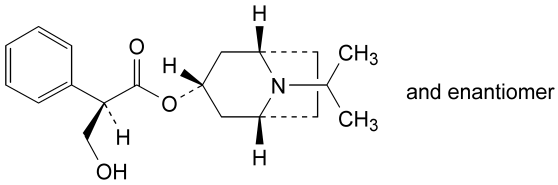


B. (1*R*,3*r*,5*S*,8*s*)-3-[[(2*RS*)-3-hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane,

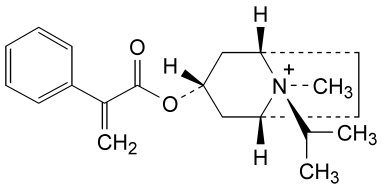


C. R = CH_2-OH, R′ = H: (2*RS*)-3-hydroxy-2-phenylpropanoic acid (DL-tropic acid),

D. R + R′ = CH_2: 2-phenylpropenoic acid (atropic acid),



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

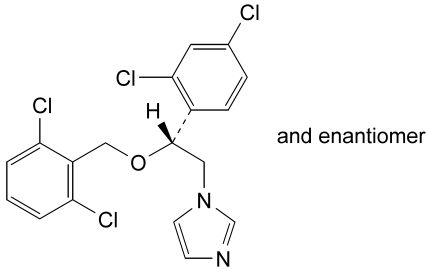


F. (1*R*,3*r*,5*S*,8*r*)-8-methyl-8-(1-methylethyl)-3-[(2-phenylpropenoyl)oxy]-8-azoniabicyclo[3.2.1]octane.

01/2008:1018
corrected 6.0

ISOCONAZOLE

Isoconazolum



$C_{18}H_{14}Cl_4N_2O$ M_r 416.1
[27523-40-6]