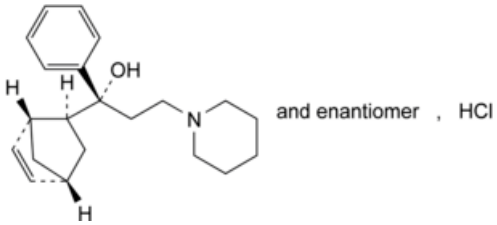
Edition: BP 2025 (Ph. Eur. 11.6 update)

Biperiden Hydrochloride

General Notices

(Ph. Eur. monograph 1074)



$C_{21}H_{30}ClNO$ 347.9 *1235-82-1*

Action and use

Anticholinergic.

Ph Eur

DEFINITION

(1*RS*)-1-[(1*RS*,2*SR*,4*RS*)-Bicyclo[2.2.1]hept-5-en-2-yl]-1-phenyl-3-(piperidin-1-yl)propan-1-ol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water and in ethanol (96 per cent), very slightly soluble in methylene chloride.

mp

About 280 °C, with decomposition.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *biperiden hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of *biperiden hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *biperiden impurity A CRS* in reference solution (a) and dilute to 2 mL with the same solution.

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

Mobile phase *diethylamine R*, *methanol R*, *toluene R* (1:1:20 *V/V/V*).

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with *dilute potassium iodobismuthate solution R* and then with *sodium nitrite solution R* and examine in daylight.

Results B 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).

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

C. To about 20 mg add 5 mL of *phosphoric acid R*. A green colour develops.
D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.10 g in *carbon dioxide-free water R*, heating gently if necessary, and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (2.2.1) and is colourless (2.2.2, *Method II*).

pH (2.2.3)

5.0 to 6.5 for solution S.

Related substances

Gas chromatography (2.2.28).

Test solution Dissolve 0.10 g of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 0.5 mL of the test solution to 100 mL with methanol R. Dilute 10 mL of this solution to 50 mL with methanol R.

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

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.25 mm;

— *stationary phase*: phenyl(5)methyl(95)polysiloxane R (film thickness 0.25 µm).

Carrier gas nitrogen for chromatography R.

Flow rate 0.4 mL/min.

Split ratio 1:250.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	200
	5 - 40	200 → 270
Injection port		250
Detector		300

Detection Flame ionisation.

Injection 2 µL.

Run time Twice the retention time of biperiden.

Relative retention With reference to biperiden: impurities A, B and C = between 0.95 and 1.05.

System suitability:

— resolution: minimum 2.5 between the peak due to biperiden (1st peak) and the peak due to impurity A (2nd peak) in the chromatogram obtained with reference solution (b);

— signal-to-noise ratio: minimum 6 for the principal peak in the chromatogram obtained with reference solution (a).

Limits:

— *impurities A, B, C*: for each impurity, maximum 0.50 per cent of the area of the principal peak;

— *any other impurity*: for each impurity, maximum 0.10 per cent of the area of the principal peak;

— *total of impurities A, B and C*: maximum 1.0 per cent of the area of the principal peak;

— *total of impurities other than A, B and C*: maximum 0.50 per cent of the area of the principal peak;

— *disregard limit*: 0.05 per cent of the area of the principal peak.

Impurity F (2.4.24)

Maximum 2 ppm.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 60 mL of *ethanol (96 per cent) R*. In a closed vessel, titrate with *0.1 M alcoholic potassium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M alcoholic potassium hydroxide* is equivalent to 34.79 mg of $C_{21}H_{30}ClNO$.

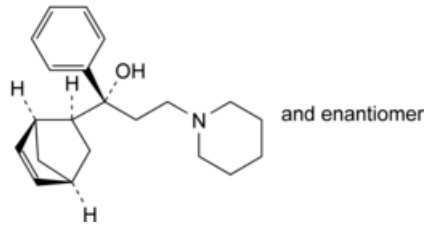
STORAGE

In an airtight container, protected from light.

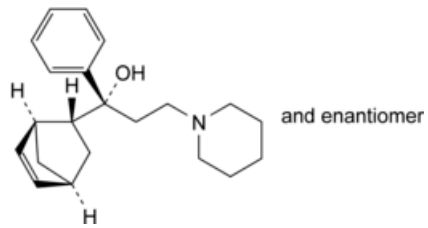
IMPURITIES

Specified impurities *A, B, C, F.*

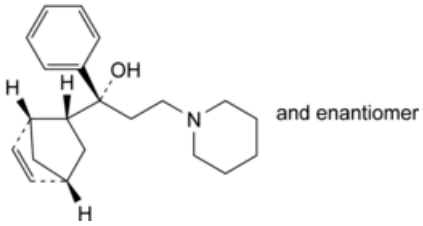
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



A. (1*RS*)-1-[(1*SR*,2*SR*,4*SR*)-bicyclo[2.2.1]hept-5-en-2-yl]-1-phenyl-3-(piperidin-1-yl)propan-1-ol (*endo* form),

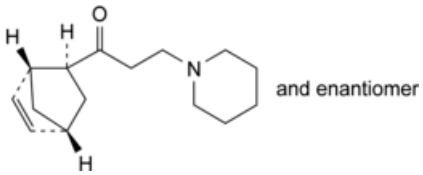


B. (1*RS*)-1-[(1*SR*,2*RS*,4*SR*)-bicyclo[2.2.1]hept-5-en-2-yl]-1-phenyl-3-(piperidin-1-yl)propan-1-ol,



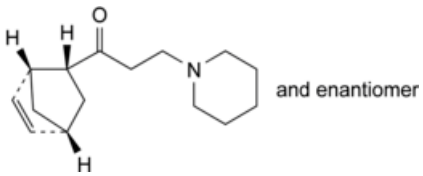
and enantiomer

C. (1*RS*)-1-[(1*RS*,2*RS*,4*RS*)-bicyclo[2.2.1]hept-5-en-2-yl]-1-phenyl-3-(piperidin-1-yl)propan-1-ol,



and enantiomer

D. 1-[(1*RS*,2*SR*,4*RS*)-bicyclo[2.2.1]hept-5-en-2-yl]-3-(piperidin-1-yl)propan-1-one,



and enantiomer

E. 1-[(1*RS*,2*RS*,4*RS*)-bicyclo[2.2.1]hept-5-en-2-yl]-3-(piperidin-1-yl)propan-1-one,

F. benzene.

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