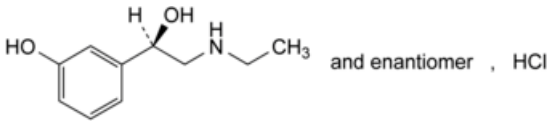
Edition: BP 2025 (Ph. Eur. 11.6 update)

Etilefrine Hydrochloride

General Notices

(Ph. Eur. monograph 1205)



$C_{10}H_{16}ClNO_2$ 217.7 *943-17-9*

Action and use

Adrenoceptor agonist.

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DEFINITION

(1*RS*)-2-(Ethylamino)-1-(3-hydroxyphenyl)ethanol hydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Melting point (2.2.14): 118 °C to 122 °C.
B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs of *potassium chloride R*.

Comparison *etilefrine hydrochloride CRS*.

C. Thin-layer chromatography (*2.2.27*).

Prepare the solutions protected from bright light and develop the chromatograms protected from light.

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 *etilefrine hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *phenylephrine hydrochloride CRS* in 2 mL of reference solution (a) and dilute to 10 mL with *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *methylene chloride R* (5:25:70 *V/V/V*).

Application 5 µL.

Development Over a path of 15 cm.

Drying In a current of warm air.

Detection Spray with a 10 g/L solution of *potassium permanganate R*; examine in daylight after 15 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

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).

D. To 0.2 mL of solution S (see Tests), add 1 mL of *water R*, 0.1 mL of *copper sulfate solution R* and 1 mL of *strong sodium hydroxide solution R*. A blue colour is produced. Add 2 mL of *ether R* and shake. The upper layer is colourless.
E. Dilute 1 mL of solution S to 10 mL with *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

Dilute 4 mL of solution S to 10 mL with *carbon dioxide-free water R*. Add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

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

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

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 50.0 mL with *water R*.

Reference solution (b) Dissolve 10.0 mg of *etilefrine impurity A CRS* in *water R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *water R*.

Reference solution (c) To 10.0 mL of reference solution (a) add 5.0 mL of reference solution (b) and dilute to 20.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 35 volumes of *acetonitrile R* and 65 volumes of a 1.1 g/L solution of *sodium laurilsulfate R* adjusted to pH 2.3 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time 5 times the retention time of etilefrine.

Relative retention With reference to etilefrine (retention time = about 9 min): impurity E = about 0.5; impurity C = about 0.8; impurity B = about 0.9; impurity A = about 1.2; impurity F = about 1.7; impurity D = about 4.5.

System suitability Reference solution (c):

— *resolution*: minimum 2.5 between the peaks due to etilefrine and impurity A.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent),

— *impurities B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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 (a) (0.1 per cent),

— *sum of impurities other than A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent),

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent); disregard any peak due to the solvent.

Sulfates (*2.4.13*)

Maximum 200 ppm, determined on 15 mL of solution S.

Loss on drying (*2.2.32*)

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

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in a mixture of 20 mL of *anhydrous acetic acid R* and 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 21.77 mg of $C_{10}H_{16}ClNO_2$.

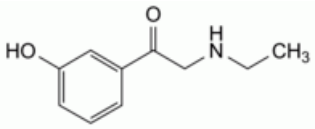
STORAGE

In an airtight container, protected from light.

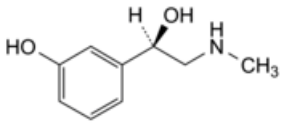
IMPURITIES

Specified impurities A, B, C, D, E.

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) F.

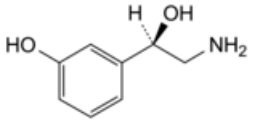


A. 2-(ethylamino)-1-(3-hydroxyphenyl)ethanone (etilefrone),



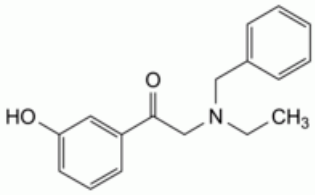
and enantiomer

B. (1*RS*)-1-(3-hydroxyphenyl)-2-(methylamino)ethanol (phenylephrine),

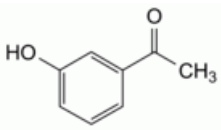


and enantiomer

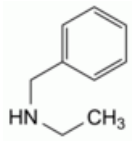
C. (1*RS*)-2-amino-1-(3-hydroxyphenyl)ethanol (norfenefrine),



D. 2-(benzylethylamino)-1-(3-hydroxyphenyl)ethanone (benzyletilefrone),



E. 1-(3-hydroxyphenyl)ethanone (3-hydroxyacetophenone),



F. *N*-benzylethanamine (benzylethylamine).

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