Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	70	30
10 - 20	70 → 40	30 → 60
20 - 35	40	60
35 - 40	40 → 70	60 → 30

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 240 nm.

Injection: 20 µl; inject the test solution and reference solutions (a) and (b).

Relative retentions with reference to phenylbutazone (retention time = about 13 min): impurity E = about 0.2; impurity A = about 0.5; impurity B = about 1.2; impurity C = about 1.3; impurity D = about 1.7.

System suitability: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to phenylbutazone and to impurity B.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.55,
– *impurities A, B*: for each impurity, not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent),
– *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.20 per cent),
– *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.025 per cent); disregard any peak due to impurity E.

Impurity E. Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Detection: spectrophotometer at 280 nm.

Injection: test solution and reference solution (c).

System suitability: reference solution (c):

– *signal-to-noise ratio*: minimum 10 for the principal peak.

Limit:

– *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (5 ppm).

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with limit test C. Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.2 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 4 h.

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

ASSAY

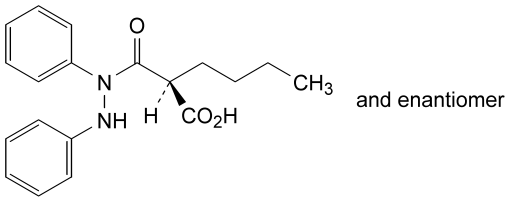
Dissolve 0.250 g in 25 ml of *acetone R* and add 0.5 ml of *bromothymol blue solution R1*. Titrate with *0.1 M sodium hydroxide* until a blue colour is obtained which persists for 15 s. Carry out a blank titration.

1 ml of *0.1 M sodium hydroxide* is equivalent to 30.84 mg of $C_{19}H_{20}N_2O_2$.

STORAGE

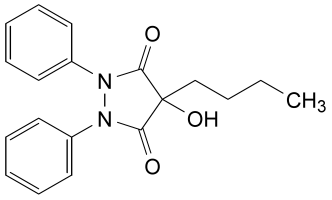
Protected from light.

IMPURITIES



and enantiomer

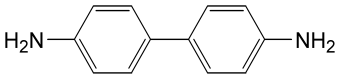
A. (2*RS*)-2-[(1,2-diphenyldiazanyl)carbonyl]hexanoic acid,



B. 4-butyl-4-hydroxy-1,2-diphenylpyrazolidine-3,5-dione,

C. C_6H_5-NH-NH-C_6H_5: 1,2-diphenyldiazane, (1,2-diphenylhydrazine),

D. C_6H_5-N=N-C_6H_5: 1,2-diphenyldiazene,



E. biphenyl-4,4′-diamine (benzidine).

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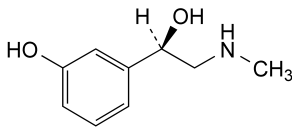
corrected 6.0

PHENYLEPHRINE

Phenylephrinum



$C_9H_{13}NO_2$ M_r 167.2

[59-42-7]

DEFINITION

(1*R*)-1-(3-Hydroxyphenyl)-2-(methylamino)ethanol.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

mp: about 174 °C.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *phenylephrine CRS*.

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

Solvent mixture. A mixture of equal volumes of *methylene chloride R* and methanolic hydrochloric acid (*hydrochloric acid R* diluted to 10 volumes with *methanol R*).

Test solution. Dissolve 0.1 g of the substance to be examined in the solvent mixture and dilute to 5 ml with the solvent mixture.

Reference solution. Dissolve 20 mg of *phenylephrine CRS* in the solvent mixture and dilute to 1 ml with the solvent mixture.

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

Mobile phase: *concentrated ammonia R, methanol R, methylene chloride R* (0.5:25:70 *V/V/V*).

Application: 10 µl.

Development: over a path of 15 cm.

Drying: in a current of cold air.

Detection: examine in ultraviolet light at 254 nm; spray with a 1 g/l solution of *fast red B salt R* in a 50 g/l solution of *sodium carbonate R* and examine in daylight.

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 the reference solution.

D. Dissolve about 10 mg in 1 ml of *1 M hydrochloric acid*, add 0.05 ml of *copper sulphate solution R* and 1 ml of a 200 g/l solution of *sodium hydroxide R*. A violet colour develops. Add 1 ml of *ether R* and shake. The upper layer remains colourless.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Dissolve 1 g in *1 M hydrochloric acid* and dilute to 10 ml with the same acid.

Specific optical rotation (*2.2.7*): −53 to −57 (dried substance).

Dissolve 1.250 g in *1 M hydrochloric acid* and dilute to 25.0 ml with the same acid.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *dilute hydrochloric acid R*, mobile phase B, mobile phase A (5:200:800 *V/V/V*).

Buffer solution pH 2.8. Dissolve 3.25 g of *sodium octanesulphonate R* in 1000 ml of *water R* by stirring for 30 min and adjust to pH 2.8 with *dilute phosphoric acid R*.

Test solution. Dissolve 41.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). Dilute 5.0 ml of the test solution to 100.0 ml with the solvent mixture. Dilute 2.0 ml of this solution to 100.0 ml with the solvent mixture.

Reference solution (b). Dissolve the contents of a vial of *phenylephrine hydrochloride for peak identification CRS* (containing impurities C and E) in 2.0 ml of the solvent mixture.

Column:

– *size*: *l* = 0.055 m, Ø = 4.0 mm;
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);
– *temperature*: 45 °C.

Mobile phase:

– *mobile phase A*: *acetonitrile R1*, buffer solution pH 2.8 (10:90 *V/V*);
– *mobile phase B*: buffer solution pH 2.8, *acetonitrile R1* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	93	7
3 - 13	93 → 70	7 → 30
13 - 14	70 → 93	30 → 7

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 215 nm.

Injection: 10 µl.

Relative retention with reference to phenylephrine (retention time = about 2.8 min): impurity C = about 1.3; impurity E = about 3.6.

System suitability:

– *symmetry factor*: maximum 1.9 for the principal peak in the chromatogram obtained with the test solution;
– *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to phenylephrine in the chromatogram obtained with reference solution (b).

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.5; impurity E = 0.5;
– *impurities C, E*: 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 twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.150 g in 60 ml of *anhydrous acetic acid 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 16.72 mg of $C_9H_{13}NO_2$.

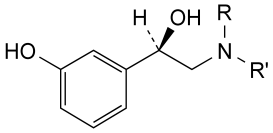
STORAGE

In an airtight container, protected from light.

IMPURITIES

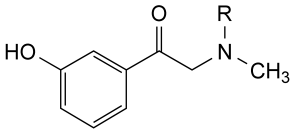
Specified impurities: *C, E.*

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*): *A, D.*



A. R = R′ = H: (1*R*)-2-amino-1-(3-hydroxyphenyl)ethanol (norphenylephrine),

D. R = CH_2-C_6H_5, R′ = CH_3: (1*R*)-2-(benzylmethylamino)-1-(3-hydroxyphenyl)ethanol (benzylphenylephrine),



C. R = H: 1-(3-hydroxyphenyl)-2-(methylamino)ethanone (phenylephrone),

E. R = CH_2-C_6H_5: 2-(benzylmethylamino)-1-(3-hydroxyphenyl)ethanone (benzylphenylephrone).

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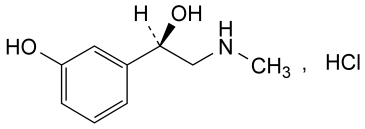
corrected 6.0

PHENYLEPHRINE HYDROCHLORIDE

Phenylephrini hydrochloridum



$C_9H_{14}ClNO_2$ M_r 203.7
[61-76-7]

DEFINITION

(1*R*)-1-(3-Hydroxyphenyl)-2-(methylamino)ethanol hydrochloride.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water and in ethanol (96 per cent).

mp: about 143 °C.

IDENTIFICATION

First identification: A, C, E.

Second identification: A, B, D, E.

A. Specific optical rotation (see Tests).

B. Melting point (*2.2.14*): 171 °C to 176 °C.

Dissolve 0.3 g in 3 ml of *water R*, add 1 ml of *dilute ammonia R1* and initiate crystallisation by scratching the wall of the tube with a glass rod. Wash the crystals with iced *water R* and dry at 105 °C for 2 h.

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *phenylephrine hydrochloride CRS.*

D. Dissolve about 10 mg in 1 ml of *water R* and add 0.05 ml of a 125 g/l solution of *copper sulphate R* and 1 ml of a 200 g/l solution of *sodium hydroxide R*. A violet colour is produced. Add 1 ml of *ether R* and shake; the upper layer remains colourless.

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

TESTS

Solution S. Dissolve 2.00 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 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. To 10 ml of solution S 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.

Specific optical rotation (*2.2.7*): – 43 to – 47 (dried substance), determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: mobile phase B, mobile phase A (20:80 *V/V*).

Buffer solution pH 2.8. Dissolve 3.25 g of *sodium octanesulphonate R* in 1000 ml of *water R* by stirring for 30 min and adjust to pH 2.8 with *dilute phosphoric acid R*.

Test solution. Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). Dilute 5.0 ml of the test solution to 100.0 ml with the solvent mixture. Dilute 2.0 ml of this solution to 100.0 ml with the solvent mixture.

Reference solution (b). Dissolve the contents of a vial of *phenylephrine hydrochloride for peak identification CRS* (containing impurities C and E) in 2.0 ml of the solvent mixture.

Column:

– *size*: *l* = 0.055 m, Ø = 4.0 mm;
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);
– *temperature*: 45 °C.

Mobile phase:

– *mobile phase A*: *acetonitrile R1,* buffer solution pH 2.8 (10:90 *V/V*);
– *mobile phase B*: buffer solution pH 2.8, *acetonitrile R1* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	93	7
3 - 13	93 → 70	7 → 30
13 - 14	70 → 93	30 → 7

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 215 nm.

Injection: 10 µl.

Relative retention with reference to phenylephrine (retention time = about 2.8 min): impurity C = about 1.3; impurity E = about 3.6.

System suitability:

– *symmetry factor*: maximum 1.9 for the principal peak in the chromatogram obtained with the test solution;
– *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to phenylephrine in the chromatogram obtained with reference solution (b).