Limits:

– *total*: calculate the ratio (*R*) of the area of the peak due to cineole to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (a); from the chromatogram obtained with test solution (b), calculate the ratio of the sum of the areas of any peaks, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to internal standard: this ratio is not greater than *R* (2 per cent),

– *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

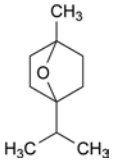
Residue on evaporation: maximum 0.1 per cent.

To 2.0 g add 5 mL of *water R*, evaporate to dryness on a water-bath and dry at 100-105 °C for 1 h. The residue weighs a maximum of 2 mg.

STORAGE

In an airtight container, protected from light.

IMPURITIES

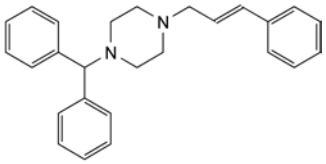


A. 1-methyl-4-(1-methylethyl)-7-oxabicyclo[2.2.1]heptane (1,4-cineole).

07/2011:0816

CINNARIZINE

Cinnarizinum



$C_{26}H_{28}N_2$ M_r 368.5

[298-57-7]

DEFINITION

(*E*)-1-(Diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine.

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

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, slightly soluble in ethanol (96 per cent) and in methanol.

IDENTIFICATION

First identification: *A, B.*

Second identification: *A, C, D.*

A. Melting point (*2.2.14*): 118 °C to 122 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *cinnarizine CRS.*

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

Test solution. Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (a). Dissolve 10 mg of *cinnarizine CRS* in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (b). Dissolve 10 mg of *cinnarizine CRS* and 10 mg of *flunarizine dihydrochloride CRS* in *methanol R* and dilute to 20 mL with the same solvent.

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

Mobile phase: 58.4 g/L solution of *sodium chloride R*, *methanol R*, *acetone R* (20:30:50 *V/V/V*).

Application: 5 µL.

Development: in an unsaturated tank, over 3/4 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

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 and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve 0.2 g of *anhydrous citric acid R* in 10 mL of *acetic anhydride R* in a water-bath at 80 °C and maintain the temperature of the water-bath at 80 °C for 10 min. Add about 20 mg of the substance to be examined. A purple colour develops.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 0.5 g in *methylene chloride R* and dilute to 20 mL with the same solvent.

Acidity or alkalinity. Suspend 0.5 g in 15 mL of *water R*. Boil for 2 min. Cool and filter. Dilute the filtrate to 20 mL with *carbon dioxide-free water R*. To 10 mL of this solution add 0.1 mL of *phenolphthalein solution R* and 0.25 mL of *0.01 M sodium hydroxide*. The solution is pink. To 10 mL of the solution add 0.1 mL of *methyl red solution R* and 0.25 mL of *0.01 M hydrochloric acid*. The solution is red.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 12.5 mg of *cinnarizine CRS* and 15.0 mg of *flunarizine dihydrochloride CRS* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 20.0 mL with *methanol R*.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 5.0 mL of this solution to 20.0 mL with *methanol R*.

Column:

– *size*: *l* = 0.1 m, Ø = 4.0 mm;

– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

– *mobile phase A*: 10 g/L solution of *ammonium acetate R*;

– *mobile phase B*: 0.2 per cent *V/V* solution of *glacial acetic acid R* in *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	75 → 10	25 → 90
20 - 25	10	90

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 10 µL.

Relative retention with reference to cinnarizine (retention time = about 11 min): impurity A = about 0.4; flunarizine = about 1.05; impurity B = about 1.1; impurity C = about 1.2; impurity D = about 1.6; impurity E = about 1.8.

System suitability: reference solution (a):

– *resolution*: minimum 5.0 between the peaks due to cinnarizine and flunarizine.

Limits:

– *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);
– *unspecified impurities*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

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

Dissolve 1.0 g in a mixture of 15 volumes of *water R* and 85 volumes of *acetone R*. Add *dilute hydrochloric acid R* until dissolution is complete. Dilute to 20 mL with a mixture of 15 volumes of *water R* and 85 volumes of *acetone R*. 12 mL of the solution complies with test B. Prepare the reference solution using 10 mL of lead standard solution (1 ppm Pb) obtained by diluting *lead standard solution (100 ppm Pb) R* with a mixture of 15 volumes of *water R* and 85 volumes of *acetone R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven *in vacuo* at 60 °C for 4 h.

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

ASSAY

Dissolve 0.150 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator.

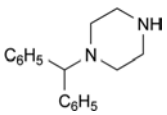
1 mL of *0.1 M perchloric acid* is equivalent to 18.43 mg of $C_{26}H_{28}N_2$.

STORAGE

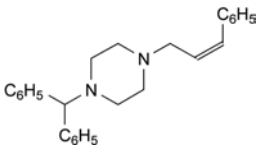
Protected from light.

IMPURITIES

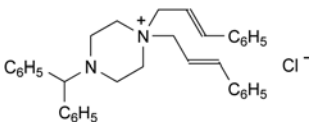
Specified impurities: A, B, C, D, E.



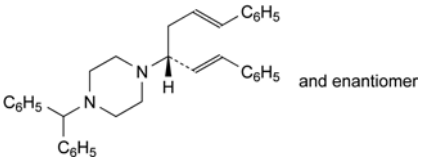
A. 1-(diphenylmethyl)piperazine,



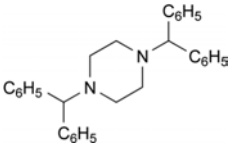
B. (*Z*)-1-(diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine,



C. 4-(diphenylmethyl)-1,1-bis[(*E*)-3-phenylprop-2-enyl]piperazinium chloride,



D. 1-(diphenylmethyl)-4-[(1*RS*,3*E*)-4-phenyl-1-[(*E*)-2-phenylethenyl]but-3-enyl]piperazine,

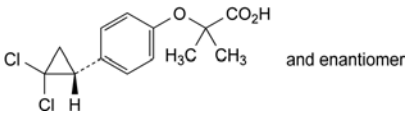


E. 1,4-bis(diphenylmethyl)piperazine.

01/2008:2013

CIPROFIBRATE

Ciprofibratum



$C_{13}H_{14}Cl_2O_3$ M_r 289.2
[52214-84-3]

DEFINITION

2-[4-[(1*RS*)-2,2-Dichlorocyclopropyl]phenoxy]-2-methylpropanoic acid.

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

CHARACTERS

Appearance: white or slightly yellow, crystalline powder.

Solubility: practically insoluble in water, freely soluble in anhydrous ethanol, soluble in toluene.

mp: about 115 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *ciprofibrate CRS*.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_4 (*2.2.2, Method II*).

Dissolve 1.0 g in *anhydrous ethanol R* and dilute to 10.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.125 g of the substance to be examined in a mixture of equal volumes of *acetonitrile R* and *water R* and dilute to 50 mL with the same mixture of solvents.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*. Dilute 1.0 mL of this solution to 10.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*.

Reference solution (b). Dissolve the contents of a vial of *ciprofibrate for system suitability CRS* in 2.0 mL of a mixture of equal volumes of *acetonitrile R* and *water R*.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm,
– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

– *mobile phase A*: 1.36 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 2.2 with *phosphoric acid R*,