

– *stationary phase*: macrogol 20 000 R (film thickness 0.25 µm).

Carrier gas: helium for chromatography R.

Linear velocity: 45 cm/s.

Split-ratio: 1:70.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 10	50
	10 - 35	50 → 100
	35 - 45	100 → 200
	45 - 55	200
Injection port		220
Detector		250

Detection: flame ionisation.

Injection: 1 µL.

System suitability: reference solution (b):

– *resolution*: minimum 10 between the peaks due to impurity A and to cineole.

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).

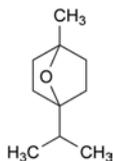
Residue on evaporation: maximum 0.1 per cent.

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

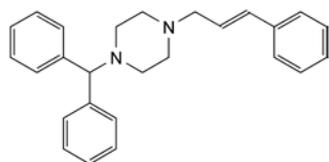


- A. 1-methyl-4-(1-methylethyl)-7-oxabicyclo[2.2.1]heptane (1,4-cineole).

01/2008:0816
corrected 6.0

CINNARIZINE

Cinnarizinum



C₂₆H₂₈N₂
[298-57-7]

M_r 368.5

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).

Preparation: discs.

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 F₂₅₄ plate R.

Mobile phase: 1 M sodium chloride, *methanol R*, *acetone R* (20:30:50 V/V/V).

Application: 5 µL.

Development: in an unsaturated tank, over a path of 15 cm.

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 BY₇ (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, $\varnothing = 4.0$ mm;
- stationary phase: base-deactivated octadecylsilyl silica gel for chromatography R (3 μ m).

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

If necessary, adjust the concentration of glacial acetic acid in mobile phase B to obtain a horizontal baseline in the chromatogram.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 230 nm.

Equilibration: with the mobile phase at the initial composition for at least 30 min.

Injection: 10 μ L; inject methanol R as a blank.

Retention time: cinnarizine = about 11 min; flunarizine = about 11.5 min.

System suitability: reference solution (a):

- resolution: minimum 5.0 between the peaks due to cinnarizine and flunarizine; if necessary, adjust the time programme for the gradient elution.

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);
- 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); disregard any peak due to the blank.

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 ethyl methyl ketone R. Titrate with 0.1 M perchloric acid, using 0.2 mL of naphtholbenzein solution R as indicator.

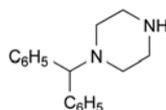
1 mL of 0.1 M perchloric acid is equivalent to 18.43 mg of $C_{26}H_{28}N_2$.

STORAGE

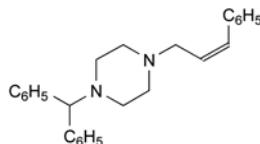
Protected from light.

IMPURITIES

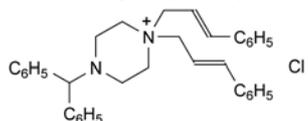
Specified impurities: A, B, C, D, E.



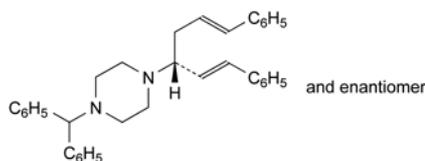
A. 1-(diphenylmethyl)piperazine,



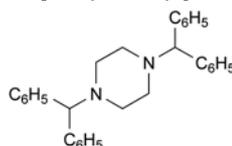
B. (Z)-1-(diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine,



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



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

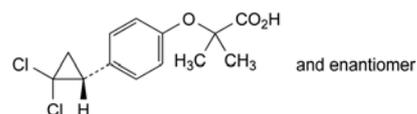


E. 1,4-bis(diphenylmethyl)piperazine.

01/2008:2013

CIPROFIBRATE

Ciprofibratum



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

M_r 289.2

DEFINITION

2-[4-[(1R,2S)-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 BY₄ (2.2.2, Method II).

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