Reference solution (d). Dilute 0.5 mL of reference solution (b) to 25 mL with reference solution (a).

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *silica gel OD for chiral separations R.*

Mobile phase: *diethylamine R, anhydrous ethanol R, hexane R* (0.2:5:95 *V/V/V*).

Flow rate: 0.8 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL of the test solution and reference solutions (a), (c) and (d).

Elution order: impurity A, levodropropizine.

System suitability:

– *retention times*: the retention times of the principal peaks in the chromatograms obtained with the test solution and reference solution (a) are similar;

– *resolution*: minimum 1.3 between the peaks due to impurity A and levodropropizine in the chromatogram obtained with reference solution (d).

Limit:

– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (2 per cent).

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 0.500 g by drying *in vacuo* at 60 °C over *diphosphorus pentoxide R* at a pressure of 0.15-0.25 kPa for 4 h.

Sulfated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 50 mL of *anhydrous acetic acid R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M perchloric acid*. Read the volume added at the 2nd point of inflexion.

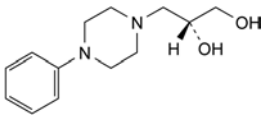
1 mL of *0.1 M perchloric acid* is equivalent to 11.82 mg of $C_{13}H_{20}N_2O_2$.

STORAGE

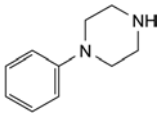
Protected from light.

IMPURITIES

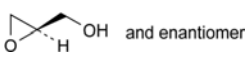
Specified impurities: *A, B, C.*



A. (2*R*)-3-(4-phenylpiperazin-1-yl)propane-1,2-diol (dextrodropropizine),



B. 1-phenylpiperazine,

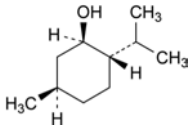


C. [(2*RS*)-oxiran-2-yl]methanol (glycidol).

01/2008:0619

LEVOMENTHOL

Levomentholum



$C_{10}H_{20}O$ M_r 156.3
[2216-51-5]

DEFINITION

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexanol.

CHARACTERS

Appearance: prismatic or acicular, colourless, shiny crystals.

Solubility: practically insoluble in water, very soluble in ethanol (96 per cent) and in light petroleum, freely soluble in fatty oils and in liquid paraffin, very slightly soluble in glycerol.

mp: about 43 °C.

IDENTIFICATION

First identification: A, C.

Second identification: B, D.

A. Specific optical rotation (see Tests).

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. Dissolve 25 mg of *menthol CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate: *TLC silica gel G plate R.*

Mobile phase: *ethyl acetate R, toluene R* (5:95 *V/V*).

Application: 2 µL.

Development: over a path of 15 cm.

Drying: in air, until the solvents have evaporated.

Detection: spray with *anisaldehyde solution R* and heat at 100-105 °C for 5-10 min.

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.

C. Examine the chromatograms obtained in the test for related substances.

Results: the principal peak in the chromatogram obtained with test solution (b) is similar in position and approximate dimensions to the principal peak in the chromatogram obtained with reference solution (c).

D. Dissolve 0.20 g in 0.5 mL of *anhydrous pyridine R*. Add 3 mL of a 150 g/L solution of *dinitrobenzoyl chloride R* in *anhydrous pyridine R*. Heat on a water-bath for 10 min. Add 7.0 mL of *water R* in small quantities with stirring and allow to stand in iced water for 30 min. A precipitate is formed. Allow to stand and decant the supernatant liquid. Wash the precipitate with 2 quantities, each of 5 mL, of iced *water R*, recrystallise from 10 mL of *acetone R*, wash with iced *acetone R* and dry at 75 °C at a pressure not exceeding 2.7 kPa for 30 min. The crystals melt (*2.2.14*) at 154 °C to 157 °C.

TESTS

Solution S. Dissolve 2.50 g in 10 mL of *ethanol (96 per cent) R* and dilute to 25.0 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. Dissolve 1.0 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent. Add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Specific optical rotation (*2.2.7*): – 48 to – 51, determined on solution S.

Related substances. Gas chromatography (*2.2.28*).

Test solution (a). Dissolve 0.20 g of the substance to be examined in *methylene chloride R* and dilute to 50.0 mL with the same solvent.

Test solution (b). Dilute 1.0 mL of test solution (a) to 10.0 mL with *methylene chloride R*.

Reference solution (a). Dissolve 40.0 mg of the substance to be examined and 40.0 mg of *isomenthol R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Reference solution (b). Dilute 0.10 mL of test solution (a) to 100.0 mL with *methylene chloride R*.

Reference solution (c). Dissolve 40.0 mg of *menthol CRS* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Column:
- *material*: glass;
- *size*: *l* = 2.0 m, Ø = 2 mm;
- *stationary phase*: *diatomaceous earth for gas chromatography R* impregnated with 15 per cent *m/m* of *macrogol 1500 R*.

Carrier gas: *nitrogen for chromatography R*.

Flow rate: 30 mL/min.

Temperature:
- *column*: 120 °C;
- *injection port*: 150 °C;
- *detector*: 200 °C.

Detection: flame ionisation.

Injection: 1 µL.

Run time: twice the retention time of menthol.

System suitability:
- *resolution*: minimum 1.4 between the peaks due to menthol and isomenthol in the chromatogram obtained with reference solution (a);
- *signal-to-noise ratio*: minimum 5 for the principal peak in the chromatogram obtained with reference solution (b).

Limits: test solution (a):
- *total*: not more than 1 per cent of the area of the principal peak;
- *disregard limit*: 0.05 per cent of the area of the principal peak.

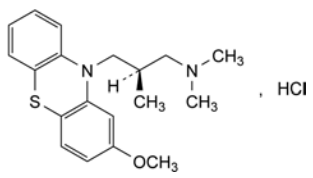
Residue on evaporation: maximum 0.05 per cent.

Evaporate 2.00 g on a water-bath and heat in an oven at 100-105 °C for 1 h. The residue weighs not more than 1.0 mg.

01/2008:0505
corrected 6.0

LEVOMEPROMAZINE HYDROCHLORIDE

Levomepromazini hydrochloridum



$C_{19}H_{25}ClN_2OS$ M_r 364.9
[1236-99-3]

DEFINITION

Levomepromazine hydrochloride contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (2*R*)-3-(2-methoxy-10*H*-phenothiazin-10-yl)-*N*,*N*,2-trimethylpropan-1-amine hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or very slightly yellow, crystalline powder, slightly hygroscopic, freely soluble in water and in alcohol. It deteriorates when exposed to air and light. It exists in two forms, one melting at about 142 °C and the other at about 162 °C.

IDENTIFICATION

A. *Prepare the solution protected from bright light and carry out the measurements immediately.* Dissolve 50.0 mg in *water R* and dilute to 500.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with *water R*. Examined between 230 nm and 340 nm (*2.2.25*), the solution shows two absorption maxima, at 250 nm and 302 nm. The specific absorbance at the maximum at 250 nm is 640 to 700.

B. It complies with the identification test for phenothiazines by thin-layer chromatography (*2.3.3*): use *levomepromazine hydrochloride CRS* to prepare the reference solution.

C. Introduce 0.2 g into a 100 mL separating funnel. Add 5 mL of *water R* and 0.5 mL of *strong sodium hydroxide solution R*. Shake vigorously with two quantities, each of 10 mL, of *ether R*. Combine the ether layers, dry over *anhydrous sodium sulfate R* and evaporate to dryness. Keep the residue at 100 °C to 105 °C for 15 min and allow to crystallise in iced water. Initiate crystallisation if necessary by scratching the wall of the flask with a glass rod. Dry the crystals at 60 °C for 2 h. The crystals melt (*2.2.14*) at 122 °C to 128 °C.

D. It gives reaction (b) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Acidity or alkalinity. To 10 mL of solution S add 0.1 mL of *bromocresol green solution R*. Not more than 0.5 mL of *0.01 M sodium hydroxide* or 1.0 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Specific optical rotation (*2.2.7*): + 9.5 to + 11.5, determined on solution S and calculated with reference to the dried substance.

Related substances. *Carry out the test protected from bright light.* Examine by thin-layer chromatography (*2.2.27*), using *silica gel* GF_{254} *R* as the coating substance.

Test solution. Dissolve 0.2 g of the substance to be examined in a mixture of 5 volumes of *diethylamine R* and 95 volumes of *methanol R* and dilute to 10 mL with the same mixture of solvents. Prepare immediately before use.

Reference solution. Dilute 0.5 mL of the test solution to 100 mL with a mixture of 5 volumes of *diethylamine R* and 95 volumes of *methanol R*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 10 volumes of *acetone R*, 10 volumes of *diethylamine R* and 80 volumes of *cyclohexane R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

Loss on drying (*2.2.32*). Not more than 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.