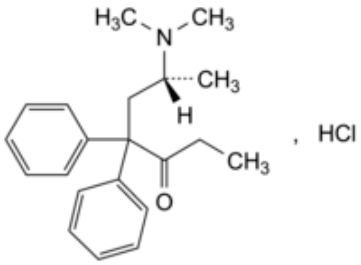
Edition: BP 2025 (Ph. Eur. 11.6 update)

Levomethadone Hydrochloride

General Notices

(Ph. Eur. monograph 1787)



$C_{21}H_{28}ClNO$ 345.9 *5967-73-7*

Action and use

Opioid analgesic.

Ph Eur

DEFINITION

(6*R*)-6-(Dimethylamino)-4,4-diphenylheptan-3-one hydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C, D.

Second identification: A, B, D.

A. Specific optical rotation (see Tests).
B. Melting point (2.2.14): 239 °C to 242 °C.
C. Infrared absorption spectrophotometry (2.2.24).

Comparison Ph. Eur. reference spectrum of methadone hydrochloride.

D. Dilute 1 mL of solution S (see Tests) to 5 mL with water R and add 1 mL of dilute ammonia R1. Mix, allow to stand for 5 min and filter. The filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in carbon dioxide-free 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 10 mL of solution S to 25 mL with carbon dioxide-free water R. To 10 mL of the solution add 0.2 mL of methyl red solution R and 0.2 mL of 0.01 M sodium hydroxide. The solution is yellow. Add 0.4 mL of 0.01 M hydrochloric acid. The solution is red.

Specific optical rotation (2.2.7)

-125 to -135 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 12.0 mg of imipramine hydrochloride CRS in the mobile phase and dilute to 10 mL with the mobile phase. To 1 mL of the solution add 5 mL of the test solution and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase Mix 35 volumes of *acetonitrile R* and 65 volumes of an 11.5 g/L solution of *phosphoric acid R* adjusted to pH 3.6 with *tetraethylammonium hydroxide solution R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Equilibration About 30 min.

Injection 10 µL.

Run time 7 times the retention time of levomethadone.

Retention time Levomethadone = about 5 min.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to imipramine and levomethadone.

Limits:

— *any 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);

— *total*: not more than 2.5 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) (0.05 per cent).

Dextromethadone

Liquid chromatography (*2.2.29*).

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *2-hydroxypropylbetadex for chromatography R* (5 µm);

— *temperature*: 10 °C.

Mobile phase Mix 1 volume of *triethylamine R* adjusted to pH 4.0 with *phosphoric acid R*, 15 volumes of *acetonitrile R* and 85 volumes of a 13.6 g/L solution of *potassium dihydrogen phosphate R*.

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 210 nm.

Equilibration About 30 min.

Injection 10 µL.

Relative retention With reference to levomethadone: dextromethadone = about 1.4.

System suitability Test solution:

— *number of theoretical plates*: minimum 2000, calculated for the peak due to levomethadone;

— *tailing factor*: maximum 3 for the peak due to levomethadone.

Limit:

— *dextromethadone*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.5 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.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 40 mL of *water R* and 5 mL of *acetic acid R*. Titrate with *0.1 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*), using a silver electrode.

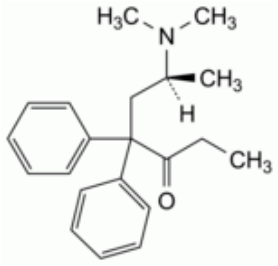
1 mL of *0.1 M silver nitrate* is equivalent to 34.59 mg of $C_{21}H_{28}ClNO$.

STORAGE

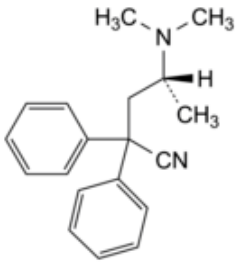
Protected from light.

IMPURITIES

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

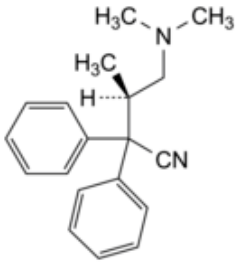


A. (6*S*)-6-(dimethylamino)-4,4-diphenylheptan-3-one,



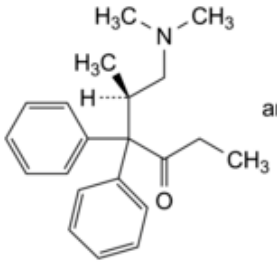
and enantiomer

B. (4*RS*)-4-(dimethylamino)-2,2-diphenylpentanenitrile,



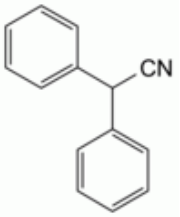
and enantiomer

C. (3*RS*)-4-(dimethylamino)-3-methyl-2,2-diphenylbutanenitrile,

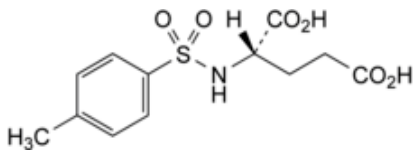


and enantiomer

D. (5*RS*)-6-(dimethylamino)-5-methyl-4,4-diphenylhexan-3-one,



E. diphenylacetonitrile,



F. (2*S*)-2-[[(4-methylphenyl)sulfonyl]amino]pentanedioic acid (*N*-*p*-tosyl-L-glutamic acid).

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