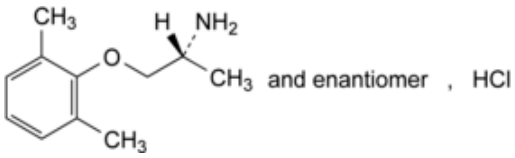
Edition: BP 2025 (Ph. Eur. 11.6 update)

Mexiletine Hydrochloride

General Notices

(Ph. Eur. monograph 1029)



$C_{11}H_{18}ClNO$ 215.7 *5370-01-4*

Action and use

Class I antiarrhythmic.

Preparation

Mexiletine Capsules

Ph Eur

DEFINITION

(2*RS*)-1-(2,6-Dimethylphenoxy)propan-2-amine hydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, sparingly soluble in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *mexiletine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Dilute 1.5 mL of solution S (see Tests) to 15 mL with *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dilute 5 mL of solution S to 10 mL with *water R*.

pH (2.2.3)

4.0 to 5.5 for solution S.

Impurity D Liquid chromatography (2.2.29)

Buffer solution To 1790 mL of *water for chromatography R* add 15 mL of *triethylamine R* and 1 mL of *glacial acetic acid R*.

Solvent mixture *acetonitrile R*, *water R* (20:80 *V/V*).

Test solution Dissolve 0.200 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5.0 mg of *mexiletine impurity D CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Mix 1 mL of reference solution (a) and 1 mL of the test solution and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R (5 µm);

— *temperature*: 40 °C.

Mobile phase acetonitrile R, buffer solution (18:82 *V/V*); adjust to pH 11.5 with triethylamine R.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 262 nm.

Injection 30 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of mexiletine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identifiy the peak due to impurity D.

Relative retention With reference to mexiletine (retention time = about 26 min): impurity D = about 0.9.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity D and mexiletine.

Calculation of percentage content:

— for impurity D, use the concentration of impurity D in reference solution (b).

Limit:

— *impurity D*: maximum 0.10 per cent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.200 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

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

Reference solution (b) Dissolve 2.0 mg of mexiletine impurity C CRS in the mobile phase and transfer the solution quantitatively to a volumetric flask containing 16.0 mg of mexiletine impurity A CRS, then dilute to 20.0 mL with the mobile phase. Mix 1.0 mL of this solution with 2.0 mL of reference solution (a) and dilute the mixture to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 65 volumes of methanol R2 and 35 volumes of a solution prepared as follows: dissolve 11.5 g of anhydrous sodium acetate R in 500 mL of water for chromatography R, add 3.2 mL of glacial acetic acid R, mix and allow to cool; adjust to pH 4.8 with glacial acetic acid R and dilute to 1000 mL with water for chromatography R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 262 nm.

Injection 20 µL.

Run time 5.5 times the retention time of mexiletine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C.

Relative retention With reference to mexiletine (retention time = about 4 min): impurity C = about 0.7; impurity A = about 1.8.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity C and mexiletine.

Limits:

— *impurity A*: not more than 2.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *impurity C*: not more than 20 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to mexiletine in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 2.5 times the area of the peak due to mexiletine in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the peak due to mexiletine in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

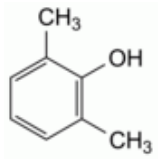
Dissolve 0.150 g in 50 mL of a mixture of equal volumes of *acetic anhydride R* and *anhydrous acetic acid R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*) and completing the titration within 2 min.

1 mL of *0.1 M perchloric acid* is equivalent to 21.57 mg of $C_{11}H_{18}ClNO$.

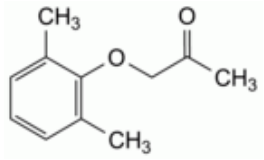
IMPURITIES

Specified impurities *A, C, D.*

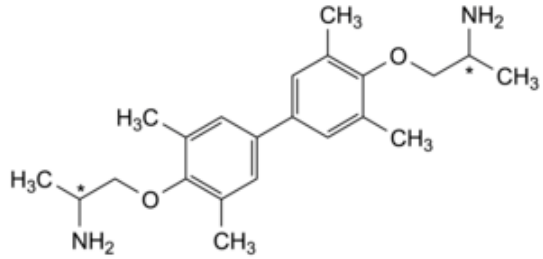
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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) *B.*



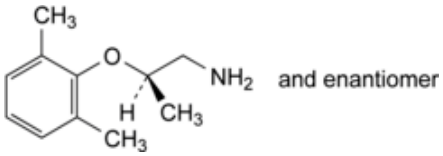
A. 2,6-dimethylphenol,



B. 1-(2,6-dimethylphenoxy)propan-2-one,



C. 1,1′-[(3,3′,5,5′-tetramethyl[1,1′-biphenyl]-4,4′-diyl)bis(oxy)]di(propan-2-amine),



D. (2*RS*)-2-(2,6-dimethylphenoxy)propan-1-amine.

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