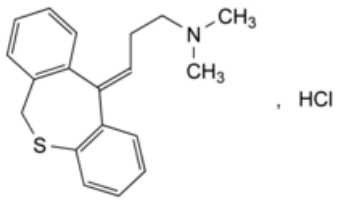
Edition: BP 2025 (Ph. Eur. 11.6 update)

Dosulepin Hydrochloride

General Notices

(Ph. Eur. monograph 1314)



$C_{19}H_{22}ClNS$ 331.9 *897-15-4*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

Preparations

Dosulepin Capsules

Dosulepin Oral Solution

Dosulepin Tablets

Ph Eur

DEFINITION

(*E*)-3-(Dibenzo[*b*,*e*]thiepin-11(6*H*)-ylidene)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

Content

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

CHARACTERS

Appearance

White or faintly yellow, crystalline powder.

Solubility

Freely soluble in water, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 25.0 mg in a 1 g/L solution of *hydrochloric acid R* in *methanol R* and dilute to 100.0 mL with the same solution. Dilute 2.0 mL to 50.0 mL with a 1 g/L solution of *hydrochloric acid R* in *methanol R*.

Spectral range 220-350 nm.

Absorption maxima 231 nm and 306 nm.

Shoulder About 260 nm.

Specific absorbance at the absorption maximum at 231 nm 660 to 730.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dosulepin hydrochloride CRS*.

C. Dissolve about 1 mg in 5 mL of *sulfuric acid R*. A dark red colour is produced.
D. Dissolve 19 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, *Method II*).

Dissolve 1 g in *water R* and dilute to 20 mL with the same solvent.

pH (2.2.3)

4.2 to 5.2.

Dissolve 1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 50.0 mg of the substance to be examined in 5 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 12.5 mg of *dosulepin impurity A CRS* in 5 mL of *methanol R* and dilute to 50.0 mL with the mobile phase. Dilute 0.5 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *dosulepin for system suitability CRS* (containing impurity E) in 5 mL of *methanol R* and dilute to 20 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

— *temperature*: 35 °C.

Mobile phase 0.83 per cent *V/V* solution of *perchloric acid R*, *propanol R*, *methanol R1*, *water for chromatography R* (1:10:30:60 *V/V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 229 nm.

Injection 5 µL.

Run time 2.5 times the retention time of dosulepin.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *dosulepin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity E.

Relative retention With reference to dosulepin (retention time = about 14 min): impurity A = about 0.3; impurity E = about 0.92.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to dosulepin.

Limits:

— *impurity E*: not more than 5 per cent of the sum of the areas of the peak due to impurity E and the principal peak in the chromatogram obtained with the test solution (5 per cent);

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

— *sum of impurities other than E*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 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 0.250 g in a mixture of 5 mL of *anhydrous acetic acid R* and 35 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 33.19 mg of $C_{19}H_{22}ClNS$.

STORAGE

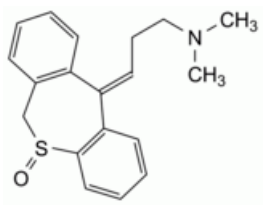
Protected from light.

IMPURITIES

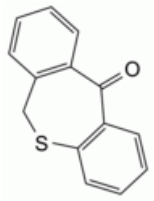
Specified impurities *A, E.*

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

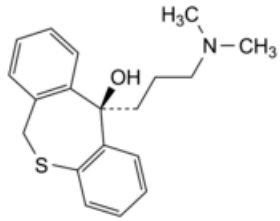
the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D.



A. (*E*)-11-[3-(dimethylamino)propylidene]-6,11-dihydro-5*H*-5λ^4-dibenzo[*b*,*e*]thiepin-5-one,

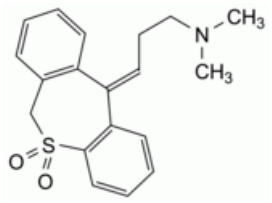


B. dibenzo[*b*,*e*]thiepin-11(6*H*)-one,

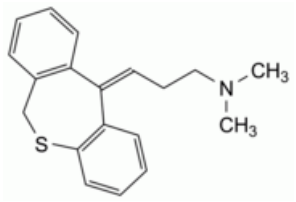


and enantiomer

C. (11*RS*)-11-[3-(dimethylamino)propyl]-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol,



D. (*E*)-11-[3-(dimethylamino)propylidene]-6,11-dihydro-5*H*-5λ^6-dibenzo[*b,e*]thiepin-5,5-dione,



E. (*Z*)-3-(dibenzo[*b*,*e*]thiepin-11(*6H*)-ylidene)-*N*,*N*-dimethylpropan-1-amine.

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