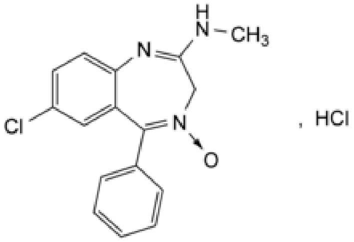
Edition: BP 2025 (Ph. Eur. 11.6 update)

Chlordiazepoxide Hydrochloride

General Notices

(Ph. Eur. monograph 0474)



$C_{16}H_{15}Cl_2N_3O$ 336.2 *438-41-5*

Action and use

Benzodiazepine.

Preparations

Chlordiazepoxide Capsules

Chlordiazepoxide Tablets

Ph Eur

DEFINITION

7-Chloro-*N*-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-amine 4-oxide hydrochloride.

Content

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

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

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

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison chlordiazepoxide hydrochloride CRS.

If the spectra obtained in the solid state show differences, dissolve 100 mg in 9 mL of water R and add 1 mL of dilute sodium hydroxide solution R. Extract with 10 mL of methylene chloride R in a separating funnel. Evaporate the organic layer and dry the residue obtained at 100-105 °C. Proceed in the same way with the reference substance. Record new spectra using the residues.

B. Dissolve 50 mg in 5 mL of water R, add 1 mL of dilute ammonia R1, mix, allow to stand for 5 min and filter. Acidify the filtrate with dilute nitric acid 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 GY_6 (2.2.2, Method II).

Dissolve 2.5 g in water R and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the following operations protected from bright light and prepare the solutions immediately before use.*

Test solution Dissolve 20.0 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 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of chlordiazepoxide impurity A CRS in the mobile phase, add 25.0 mL of the test solution and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (c) Dissolve 4.0 mg of aminochlorobenzophenone R in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

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

Mobile phase acetonitrile R, water R (50:50 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 μL.

Run time 6 times the retention time of chlordiazepoxide.

Relative retention With reference to chlordiazepoxide (retention time = about 3.6 min): impurity A = about 0.7; impurity B = about 2.3; impurity C = about 3.9.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and chlordiazepoxide.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent),

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 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).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *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 0.250 g in 50 mL of *water R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

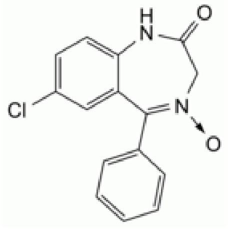
1 mL of *0.1 M silver nitrate* is equivalent to 33.62 mg of $C_{16}H_{15}Cl_2N_3O$.

STORAGE

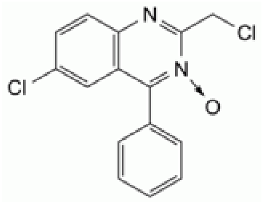
Protected from light.

IMPURITIES

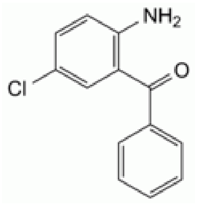
Specified impurities   *A, B, C*.



A.   7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide,



B.   6-chloro-2-(chloromethyl)-4-phenylquinazoline 3-oxide,



C. (2-amino-5-chlorophenyl)phenylmethanone (aminochlorobenzophenone).

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