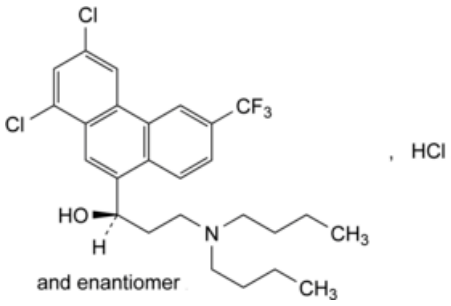
Edition: BP 2025 (Ph. Eur. 11.6 update)

Halofantrine Hydrochloride

General Notices

(Ph. Eur. monograph 1979)



$C_{26}H_{31}Cl_3F_3NO$ 536.9 *36167-63-2*

Action and use

Antiprotozoal (malaria).

Ph Eur

DEFINITION

(1*RS*)-3-(Dibutylamino)-1-[1,3-dichloro-6-(trifluoromethyl)phenanthren-9-yl]propan-1-ol hydrochloride.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methanol, sparingly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison halofantrine hydrochloride CRS.

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

B. Dissolve about 30 mg in 2 mL of methanol R. The solution gives reaction (a) of chlorides (2.3.1); use methanol R instead of water R to wash the precipitate.

TESTS

Optical rotation (2.2.7)

-0.10° to + 0.10°.

Dissolve 1.00 g in ethanol (96 per cent) R and dilute to 100.0 mL with the same solvent.

Absorbance (2.2.25)

Maximum 0.085 at 450 nm.

Dissolve 0.200 g in methanol R and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

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

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 40.0 mg of halofantrine hydrochloride CRS in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (d) Dissolve 10 mg of halofantrine impurity C CRS in the mobile phase and dilute to 25 mL with the mobile phase. To 5 mL of the solution, add 5 mL of reference solution (a) and dilute to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.30 m, Ø = 3.9 mm;

— *stationary phase*: irregular end-capped octadecylsilyl silica gel for chromatography R (10 µm).

Mobile phase Mix 250 mL of a 2.0 g/L solution of sodium hydroxide R, previously adjusted to pH 2.5 with perchloric acid R, and 750 mL of acetonitrile R.

Flow rate 1 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL; inject test solution (a) and reference solutions (c) and (d).

Run time 5 times the retention time of halofantrine.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C.

Relative retention With reference to halofantrine (retention time = about 6 min): impurity C = about 1.2.

System suitability:

— *resolution*: minimum 3.3 between the peaks due to halofantrine and impurity C in the chromatogram obtained with reference solution (d).

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (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 for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (b).

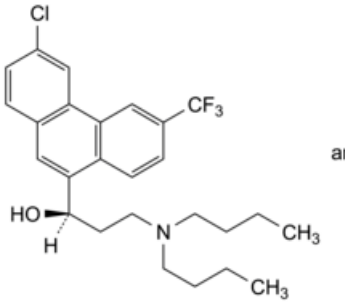
Calculate the percentage content of $C_{26}H_{31}Cl_3F_3NO$ taking into account the assigned content of *halofantrine hydrochloride CRS*.

STORAGE

Protected from light.

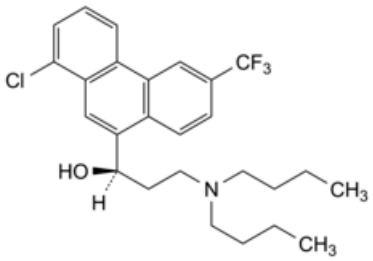
IMPURITIES

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) A, B, C.



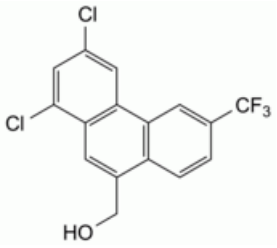
and enantiomer

A. (1*RS*)-1-[3-chloro-6-(trifluoromethyl)phenanthren-9-yl]-3-(dibutylamino)propan-1-ol (1-dechlorohalofantrine),



and enantiomer

B. (1*RS*)-1-[1-chloro-6-(trifluoromethyl)phenanthren-9-yl]-3-(dibutylamino)propan-1-ol (3-dechlorohalofantrine),



C. [1,3-dichloro-6-(trifluoromethyl)phenanthren-9-yl]methanol.

Ph Eur