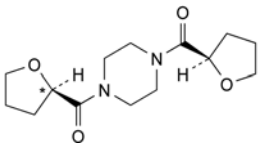
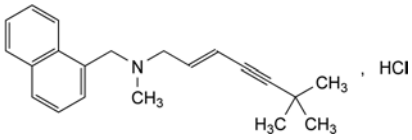


O. 1,4-bis[(tetrahydrofuran-2-yl)carbonyl]piperazine.

01/2010:1734

TERBINAFINE HYDROCHLORIDE

Terbinafini hydrochloridum



$C_{21}H_{26}ClN$ M_r 327.9
[78628-80-5]

DEFINITION

(2*E*)-*N*,6,6-Trimethyl-*N*-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine hydrochloride.

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

CHARACTERS

Appearance: white or almost white powder.

Solubility: very slightly or slightly soluble in water, freely soluble in anhydrous ethanol and in methanol, slightly soluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *terbinafine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*) using *anhydrous ethanol R* as solvent.

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture A: *acetonitrile R, water R* (50:50 *V/V*).

Solvent mixture B: *acetonitrile R, methanol R* (40:60 *V/V*).

Buffer solution. Dilute 2.0 mL of *triethylamine R1* to 950 mL with *water R*. Adjust to pH 7.5 with a mixture of 5 volumes of *glacial acetic acid R* and 95 volumes of *water R* and dilute to 1000.0 mL with *water R*.

Test solution. Dissolve 25 mg of the substance to be examined in solvent mixture A and dilute to 50.0 mL with solvent mixture A.

Reference solution (a). Dissolve 5 mg of *terbinafine for system suitability CRS* (containing impurities B and E) in 10.0 mL of solvent mixture A.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with solvent mixture A. Dilute 1.0 mL of this solution to 10.0 mL with solvent mixture A.

Column:

– *size*: *l* = 0.15 m, Ø = 3.0 mm;
– *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: buffer solution, solvent mixture B (30:70 *V/V*);
– *mobile phase B*: buffer solution, solvent mixture B (5:95 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	100	0
4 - 25	100 → 0	0 → 100
25 - 30	0	100

Flow rate: 0.8 mL/min.

Detection: spectrophotometer at 280 nm.

Injection: 20 µL.

Identification of impurities: use the chromatogram supplied with *terbinafine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and E.

Relative retention with reference to terbinafine (retention time = about 15 min): impurity B = about 0.9; impurity E = about 1.7.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the peaks due to impurity B and terbinafine.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity E by 0.5;
– *impurity B*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);
– *impurity E*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (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 50 mL of *ethanol (96 per cent) R*, add 5 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide* determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 32.79 mg of $C_{21}H_{26}ClN$.

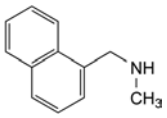
STORAGE

Protected from light.

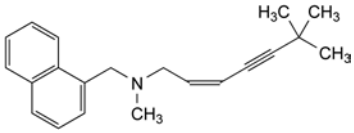
IMPURITIES

Specified impurities: B, E.

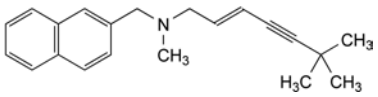
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



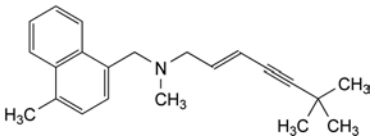
A. *N*-methyl-*C*-(naphthalen-1-yl)methanamine,



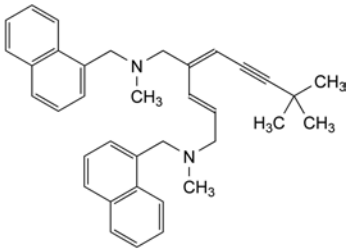
B. (2*Z*)-*N*,6,6-trimethyl-*N*-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine (*cis*-terbinafine),



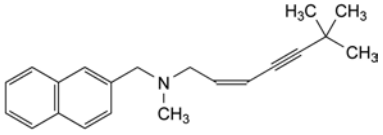
C. (2*E*)-*N*,6,6-trimethyl-*N*-(naphthalen-2-ylmethyl)hept-2-en-4-yn-1-amine (*trans*-isoterbinafine),



D. (2*E*)-*N*,6,6-trimethyl-*N*-[(4-methylnaphthalen-1-yl)methyl]hept-2-en-4-yn-1-amine (4-methylterbinafine),



E. (2*E*,4*E*)-4-(4,4-dimethylpent-2-yn-1-ylidene)-*N*,*N*′-dimethyl-*N*,*N*′-bis(naphthalen-1-ylmethyl)pent-2-ene-1,5-diamine,

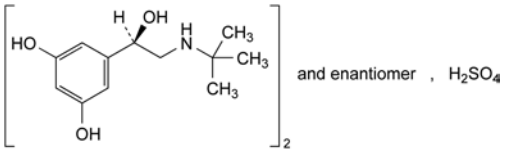


F. (2*Z*)-*N*,6,6-trimethyl-*N*-(naphthalen-2-ylmethyl)hept-2-en-4-yn-1-amine (*cis*-isoterbinafine).

01/2008:0690
corrected 6.0

TERBUTALINE SULFATE

Terbutalini sulfas



$C_{24}H_{40}N_2O_{10}S$ M_r 548.7
[23031-32-5]

DEFINITION

Bis[(1*RS*)-1-(3,5-dihydroxyphenyl)-2-[(1,1-dimethylethyl)-amino]ethanol] sulfate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water, slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *terbutaline sulfate CRS*.

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

B. 5 mL of solution S (see Tests) gives reaction (a) of sulfates (*2.3.1*).

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and its absorbance (*2.2.25*) at 400 nm in a 2 cm cell is not greater than 0.11.

Acidity. To 10 mL of solution S add 0.05 mL of *methyl red solution R*. Not more than 1.2 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Optical rotation (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 75.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a). Dissolve 7.5 mg of *terbutaline impurity C CRS* and 22.5 mg of *terbutaline sulfate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 20.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;
– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 4.23 g of *sodium hexanesulfonate R* in 770 mL of 0.050 M ammonium formate solution prepared as follows: dissolve 3.15 g of *ammonium formate R* in about 980 mL of *water R*; adjust to pH 3.0 by adding about 8 mL of *anhydrous formic acid R* and dilute to 1000 mL with *water R*; then add 230 mL of *methanol R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 276 nm.

Injection: 20 µL.

Run time: 6 times the retention time of terbutaline.

Retention time: impurity C = about 9 min; terbutaline = about 11 min.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the peaks due to impurity C and terbutaline; if necessary adjust the composition of the mobile phase, decrease the content of methanol to increase the retention time.

Limits:

– *impurity C*: not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *impurities A, B, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
– *sum of impurities other than C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);