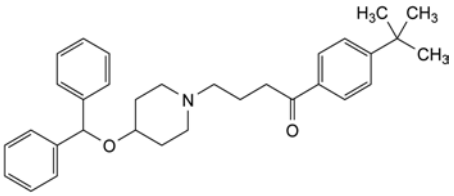
01/2008:2015

EBASTINE

Ebastinum



$C_{32}H_{39}NO_2$ M_r 469.7
[90729-43-4]

DEFINITION

1-[4-(1,1-Dimethylethyl)phenyl]-4-[4-(diphenylmethoxy)piperidin-1-yl]butan-1-one.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, very soluble in methylene chloride, sparingly soluble in methanol.

mp: about 86 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *Ph. Eur. reference spectrum of ebastine.*

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Keep the solutions protected from light.*

Solution A. Mix 65 volumes of *acetonitrile R* and 35 volumes of a 1.1 g/L solution of *phosphoric acid R* adjusted to pH 5.0 with a 40 g/L solution of *sodium hydroxide R*.

Test solution. Dissolve 0.125 g of the substance to be examined in solution A and dilute to 50.0 mL with the same solution.

Reference solution (a). Dissolve 5.0 mg of *ebastine impurity C CRS* and 5.0 mg of *ebastine impurity D CRS* in solution A and dilute to 20.0 mL with the same solution. Dilute 1.0 mL of the solution to 100.0 mL with solution A.

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

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm,
- *stationary phase*: *nitrile silica gel for chromatography R* (5 µm).

Mobile phase: mix 35 volumes of *acetonitrile R* and 65 volumes of a 1.1 g/L solution of *phosphoric acid R* adjusted to pH 5.0 with a 40 g/L solution of *sodium hydroxide R*. Adjust the percentage of acetonitrile to between 30 per cent *V/V* and 40 per cent *V/V* so that the retention time of ebastine is about 110 min.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µL.

Run time: 1.4 times the retention time of ebastine.

Relative retention with reference to ebastine: impurity A = about 0.04; impurity B = about 0.05; impurity D = about 0.20; impurity C = about 0.22; impurity F = about 0.42; impurity G = about 0.57; impurity E = about 1.14.

System suitability: reference solution (a):

- *resolution*: minimum 2.0 between the peaks due to impurity D and impurity C.

Limits:

- *impurities A, B, C, D, E, F, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 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).

Sulfates (*2.4.13*): maximum 100 ppm.

Suspend 2.5 g in 25 mL of *dilute nitric acid R*. Boil under a reflux condenser for 10 min. Cool and filter. 15 mL of the filtrate complies with the limit test for sulfates.

Water (*2.5.12*): maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

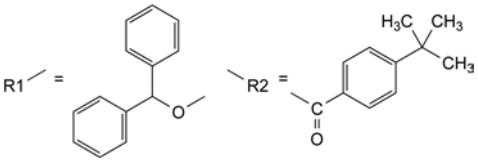
Dissolve 0.350 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 46.97 mg of $C_{32}H_{39}NO_2$.

STORAGE

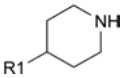
Protected from light.

IMPURITIES

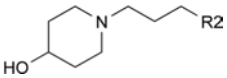


A. R1−H: diphenylmethanol (benzhydrol),

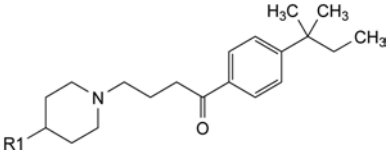
B. R2−CH_3: 1-[4-(1,1-dimethylethyl)phenyl]ethanone,



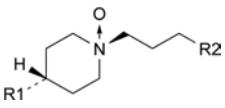
C. 4-(diphenylmethoxy)piperidine,



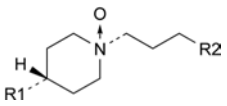
D. 1-[4-(1,1-dimethylethyl)phenyl]-4-(4-hydroxypiperidin-1-yl)butan-1-one,



E. 1-[4-(1,1-dimethylpropyl)phenyl]-4-[4-(diphenylmethoxy)piperidin-1-yl]butan-1-one,



F. 1-[4-(1,1-dimethylethyl)phenyl]-4-[*cis*-4-(diphenylmethoxy)-1-oxidopiperidin-1-yl]butan-1-one,

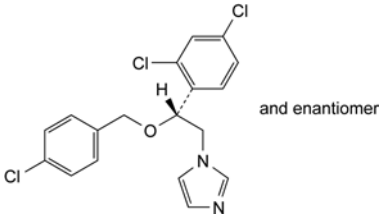


G. 1-[4-(1,1-dimethylethyl)phenyl]-4-[*trans*-4-(diphenylmethoxy)-1-oxidopiperidin-1-yl]butan-1-one.

07/2010:2049
corrected 7.0

ECONAZOLE

Econazolum



$C_{18}H_{15}Cl_3N_2O$ M_r 381.7
[27220-47-9]

DEFINITION

1-[(2*RS*)-2-[(4-Chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole.

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

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, very soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Melting point (*2.2.14*): 88 °C to 92 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *econazole CRS*.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 10 mg of *econazole for system suitability CRS* (containing impurities A, B and C) in *methanol R* and dilute to 1.0 mL with the same solvent.

Reference solution (b). Dilute 1.0 mL of the test solution to 20.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 25.0 mL with *methanol R*.

Column:
- *size*: *l* = 0.10 m, Ø = 4.6 mm;
- *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm);
- *temperature*: 35 °C.

Mobile phase:
- *mobile phase A*: *methanol R*, 0.77 g/L solution of *ammonium acetate R* (20:80 *V/V*);
- *mobile phase B*: *methanol R, acetonitrile R* (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	60 → 10	40 → 90
25 - 27	10	90

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 225 nm.

Injection: 10 µL.

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

Relative retention with reference to econazole (retention time = about 15 min): impurity A = about 0.2; impurity B = about 0.6; impurity C = about 1.1.

System suitability: reference solution (a):
- *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to econazole.

Limits:
- *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.4;
- *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (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 (b) (0.10 per cent);
- *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
- *disregard limit*: 0.25 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 vacuo* at 60 °C for 4 h.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 75 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

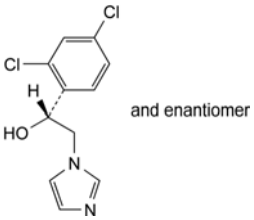
1 mL of *0.1 M perchloric acid* is equivalent to 38.17 mg of $C_{18}H_{15}Cl_3N_2O$.

STORAGE

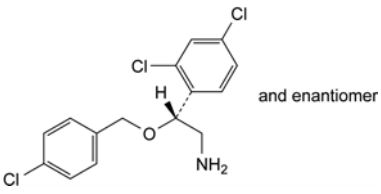
Protected from light.

IMPURITIES

Specified impurities: A, B, C.



A. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol,



B. (2*RS*)-2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)-ethanamine,