Reference solution (a). Dissolve 2 mg of *betamethasone 17-valerate CRS* and 2 mg of *betamethasone 21-valerate CRS* in solution A and dilute to 50.0 ml with solution A.

Reference solution (b). Dilute 1.0 ml of the test solution to 50.0 ml with solution A.

The chromatographic procedure may be carried out using:

– a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm);

– as mobile phase at a flow rate of 1 ml/min a mixture prepared as follows: mix 350 ml of *water R* with 600 ml of *acetonitrile R* and allow to equilibrate; adjust the volume to 1000 ml with *water R* and mix again;

– as detector a spectrophotometer set at 254 nm.

Equilibrate the column with the mobile phase for about 45 min.

Adjust the sensitivity so that the height of the principal peak in the chromatogram obtained with reference solution (b) is 70 per cent to 90 per cent of the full scale of the recorder.

Inject 20 µl of reference solution (a). When the chromatograms are recorded in the prescribed conditions, the retention times are: betamethasone 17-valerate, about 7 min; betamethasone 21-valerate, about 9 min. The test is not valid unless the resolution between the peaks due to betamethasone 17-valerate and betamethasone 21-valerate is at least 5.0; if necessary, adjust the concentration of acetonitrile in the mobile phase.

Inject 20 µl of the test solution and 20 µl of reference solution (b). Continue the chromatography for 2.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution: the area of any peak apart from the principal peak is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent) and not more than one such peak has an area greater than half the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent); the sum of the areas of all the peaks, apart from the principal peak, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent). Disregard any peak with an area less than 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (b).

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 ml with the same solvent. Dilute 2.0 ml of the solution to 50.0 ml with *ethanol (96 per cent) R* . Measure the absorbance (*2.2.25*) at the maximum at 240 nm.

Calculate the content of $C_{27}H_{37}FO_6$ taking the specific absorbance to be 325.

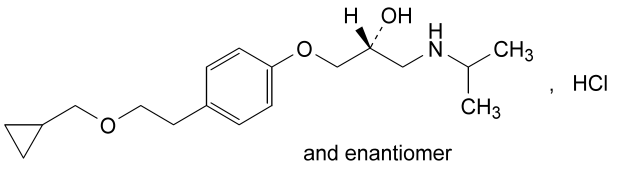
STORAGE

Protected from light.

01/2008:1072
corrected 6.0

BETAXOLOL HYDROCHLORIDE

Betaxololi hydrochloridum



$C_{18}H_{30}ClNO_3$ M_r 343.9
[63659-19-8]

DEFINITION

(2*RS*)-1-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]propan-2-ol hydrochloride.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 113 °C to 117 °C.

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

C. Thin-layer chromatography (*2.2.27*).
Test solution. Dissolve 10 mg of the substance to be examined in 1 ml of *methanol R.*
Reference solution (a). Dissolve 20 mg of *betaxolol hydrochloride CRS* in 2 ml of *methanol R.*
Reference solution (b). Dissolve 10 mg of *oxprenolol hydrochloride CRS* in 1 ml of reference solution (a).
Plate: *TLC octadecylsilyl silica gel F_{254} plate R.*
Mobile phase: *perchloric acid R, methanol R, water R* (0.5:50:50 *V/V/V*).
Application: 2 µl.
Development: over a path of 10 cm.
Drying: in air.
System suitability: reference solution (b):
– the chromatogram shows 2 clearly separated spots.
Detection A: examine in ultraviolet light at 254 nm.
Results A: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).
Detection B: spray with a 50 g/l solution of *vanillin R* in a mixture of 5 volumes of *sulphuric acid R,* 10 volumes of *glacial acetic acid R* and 85 volumes of *methanol R.* Heat at 100-105 °C until the colour of the spots reaches maximum intensity (10-15 min). Examine in daylight.
Results B: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.5 g in *water R* and dilute to 25 ml with the same solvent.

Acidity or alkalinity. Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 20 ml with the same solvent. Add 0.2 ml of *methyl red solution R* and 0.2 ml of *0.01 M hydrochloric acid*. The solution is red. Add 0.4 ml of *0.01 M sodium hydroxide*. The solution is yellow.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 5.0 ml with the mobile phase.

Reference solution (a). Dissolve 8 mg of the substance to be examined and 4 mg of *betaxolol impurity A CRS* in 20.0 ml of the mobile phase.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4 mm;
– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 175 ml of *acetonitrile R* with 175 ml of *methanol R* and dilute the mixture to 1 litre with a 3.4 g/l solution of *potassium dihydrogen phosphate R*, previously adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 273 nm.

Injection: 20 µl.

Run time: 4 times the retention time of betaxolol.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the peaks due to impurity A and betaxolol.

Limits:

– *impurities A, B, C, D, E*: for each impurity, not more than 0.3 times the area of the peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
– *total*: not more than the area of the peak in the chromatogram obtained with reference solution (b) (1.0 per cent);
– *disregard limit*: 0.025 times the area of the peak in the chromatogram obtained with reference solution (b) (0.025 per cent).

Heavy metals (*2.4.8*): maximum 10 ppm.

Dissolve 2.0 g in 20 ml of *water R*. 12 ml of the solution complies with test A. Prepare the reference solution using 10 ml of *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.300 g in a mixture of 10.0 ml of *0.01 M hydrochloric acid* and 50 ml of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

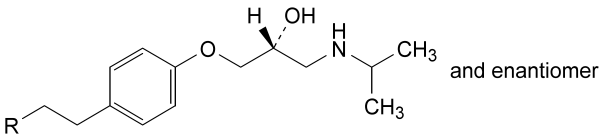
1 ml of *0.1 M sodium hydroxide* is equivalent to 34.39 mg of $C_{18}H_{30}ClNO_3$.

STORAGE

Protected from light.

IMPURITIES

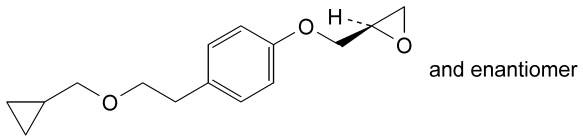
Specified impurities: *A, B, C, D, E.*



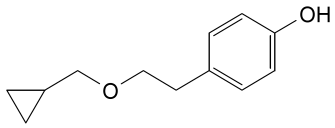
A. R = H: (2*RS*)-1-(4-ethylphenoxy)-3-[(1-methylethyl)-amino]propan-2-ol,

B. R = OH: (2*RS*)-1-[4-(2-hydroxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,

E. R = O-CH_2-CH_2-CH_2-CH_3: (2*RS*)-1-[4-(2-butoxyethyl)-phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,



C. 2-[[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]methyl]-oxirane,

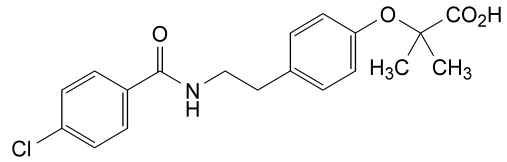


D. 4-[2-(cyclopropylmethoxy)ethyl]phenol.

01/2008:1394
corrected 6.0

BEZAFIBRATE

Bezafibratum



$C_{19}H_{20}ClNO_4$ M_r 361.8

[41859-67-0]

DEFINITION

2-[4-[2-[(4-Chlorobenzoyl)amino]ethyl]phenoxy]-2-methylpropanoic acid.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white crystalline powder.

Solubility: practically insoluble in water, freely soluble in dimethylformamide, sparingly soluble in acetone and in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

A. Melting point (*2.2.14*): 181 °C to 185 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).