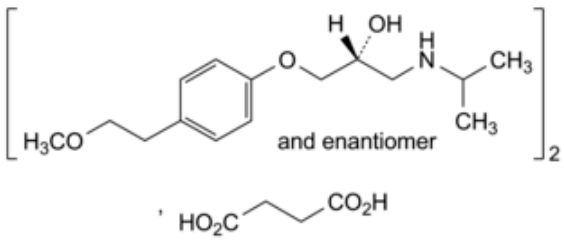
Edition: BP 2025 (Ph. Eur. 11.6 update)

Metoprolol Succinate

General Notices

(Ph. Eur. monograph 1448)



$C_{34}H_{56}N_2O_{10}$ 653 *98418-47-4*

Action and use

Beta-adrenoceptor antagonist.

Ph Eur

DEFINITION

Bis[(2*RS*)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol] butanedioate.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in methanol, slightly soluble in ethanol (96 per cent), very slightly soluble in ethyl acetate.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of metoprolol succinate*.

TESTS

Solution S

Dissolve 0.500 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

pH (*2.2.3*)

7.0 to 7.6 for solution S.

Impurities M, N, O

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.50 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dilute 1 mL of the test solution to 50 mL with *methanol R*. Dilute 5 mL of this solution to 50 mL with *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase Place 2 beakers, each containing 30 volumes of *concentrated ammonia R*, at the bottom of a chromatographic tank containing a mixture of 20 volumes of *methanol R* and 80 volumes of *ethyl acetate R*.

Application 10 µL.

Development Over 2/3 of the plate in a tank saturated for at least 1 h.

Drying In air for at least 3 h.

Detection Expose the plate to iodine vapour for at least 15 h.

Limits:

— *any impurity*: any spot, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.2 per cent);

— *disregard* any spot on the line of application.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 1.5 mg of *metoprolol impurity A CRS* and 2.5 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

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

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

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

Mobile phase Dissolve 3.9 g of *ammonium acetate R* in 810 mL of *water R*, add 2.0 mL of *triethylamine R*, 3.0 mL of *phosphoric acid R*, 10.0 mL of *glacial acetic acid R* and 146 mL of *acetonitrile R* and mix.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 3 times the retention time of metoprolol.

Relative retention With reference to metoprolol (retention time = about 7 min): impurity C = about 0.4; impurity A = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 6.0 between the peaks due to impurity A and metoprolol.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.1;

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 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 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 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); disregard any peak due to succinic acid.

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 40 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 32.64 mg of $C_{34}H_{56}N_2O_{10}$.

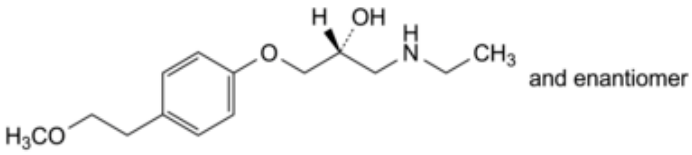
STORAGE

Protected from light.

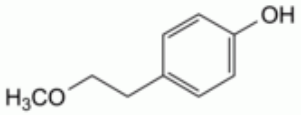
IMPURITIES

Specified impurities C, M, N, O.

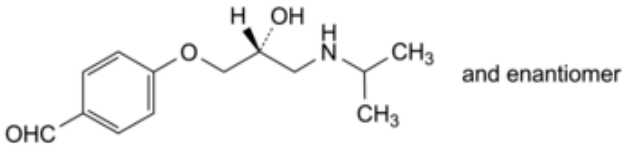
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



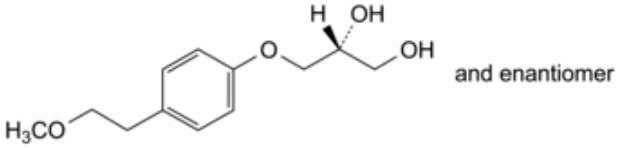
A. (2*RS*)-1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol,



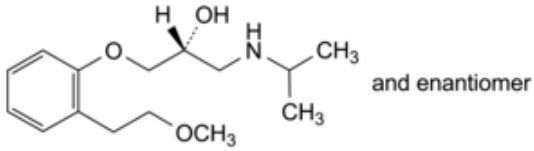
B. 4-(2-methoxyethyl)phenol,



C. 4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]benzaldehyde,

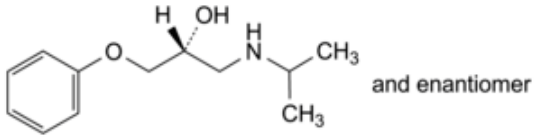


D. (2*RS*)-3-[4-(2-methoxyethyl)phenoxy]propane-1,2-diol,



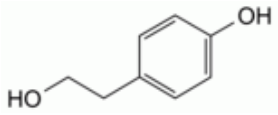
and enantiomer

E. (2*RS*)-1-[2-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,

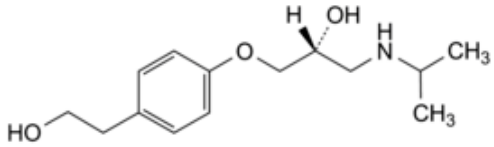


and enantiomer

F. (2*RS*)-1-[(1-methylethyl)amino]-3-phenoxypropan-2-ol,

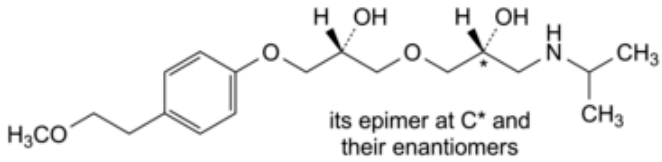


G. 2-(4-hydroxyphenyl)ethanol,

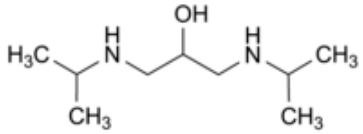


and enantiomer

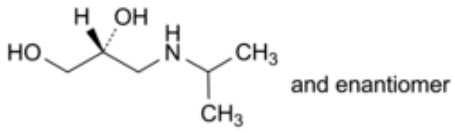
H. (2*RS*)-1-[4-(2-hydroxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,



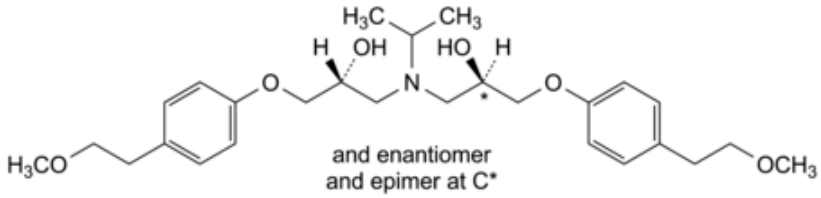
J. mixture of the 4 stereoisomers of 1-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol,



M. 1,3-bis[(1-methylethyl)amino]propan-2-ol,



N. (2*RS*)-3-[(1-methylethyl)amino]propane-1,2-diol,



O. mixture of the 3 stereoisomers of 1,1′-[(1-methylethyl)imino]bis[3-[4-(2-methoxyethyl)phenoxy]propan-2-ol].

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