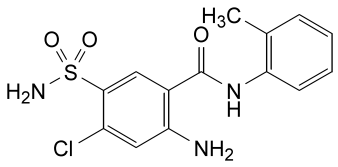
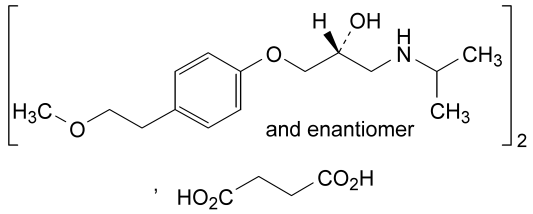


E. 2-amino-4-chloro-*N*-(2-methylphenyl)-5-sulphamoylbenzamide.

01/2008:1448
corrected 6.0

METOPROLOL SUCCINATE

Metoprololi succinas



$C_{34}H_{56}N_2O_{10}$ M_r 653
[98418-47-4]

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 alcohol, 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 it is colourless (*2.2.2, Method II*).

pH (*2.2.3*): 7.0 to 7.6 for solution S.

Related substances

A. 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 a path of 12 cm 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 starting line.

B. 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 5.0 mg of the substance to be examined and 3.0 mg of *metoprolol impurity A CRS* in the mobile phase and dilute to 100.0 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 the solution to 10.0 ml with the mobile phase.

Reference solution (c). If this solution is required (see below), it is to be prepared in a fume cupboard. This solution is used only to identify the peak due to impurity C. Dissolve 10 mg of the substance to be examined in 10 ml of *0.1 M hydrochloric acid*. Transfer this solution to an evaporating dish 10 cm in diameter. Place the dish so that the surface of the solution is 5 cm from a lamp emitting ultraviolet light (*2.1.3*) at 254 nm for 6 h. Dilute 0.5 ml of this solution to 25 ml with the mobile phase.

Column:

– *size*: *l* = 0.15 m, Ø = 3.9 mm,

– *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent.

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

Flow rate: 1 ml/min.

Detection: spectrophotometer at 280 nm.

Injection: 20 µl; inject the test solution and reference solutions (a) and (b).

Run time: 3 times the retention time of metoprolol.

Relative retention with reference to metoprolol (retention time = about 7 min): impurity C = about 0.3; impurity A = about 0.7.

System suitability: reference solution (a):

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

Limits:

- *any 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 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.

If a peak occurs with a retention time of about 2.3 min (impurity C) which has an area greater than the area of the principal peak in the chromatogram obtained with reference solution (b), prepare and inject reference solution (c). For the chromatogram obtained with the test solution, multiply the peak area of impurity C by a correction factor of 0.1.

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 limit test A. Prepare the standard using *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 0.250 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 $C_{34}H_{56}N_2O_{10}$.

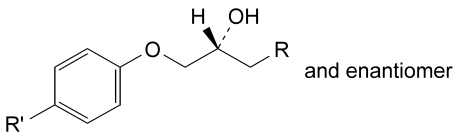
STORAGE

Protected from light.

IMPURITIES

By liquid chromatography: A, B, C, D, E, F, G, H, J.

By thin-layer chromatography: M, N, O.



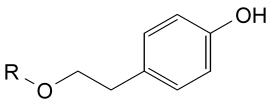
A. R = NH-CH_2-CH_3, R′ = CH_2-CH_2-OCH_3: (2*RS*)-1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol,

C. R = NH-$CH(CH_3)_2$, R′ = CHO: 4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]benzaldehyde,

D. R = OH, R′ = CH_2-CH_2-OCH_3: (2*RS*)-3-[4-(2-methoxyethyl)phenoxy]propane-1,2-diol,

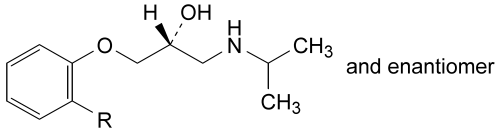
H. R = NH-$CH(CH_3)_2$, R′ = CH_2-CH_2-OH: (2*RS*)-1-[4-(2-hydroxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,

J. R = O-CH_2-CHOH-CH_2-NH-$CH(CH_3)_2$, R′ = CH_2-CH_2-OCH_3: 1-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol,



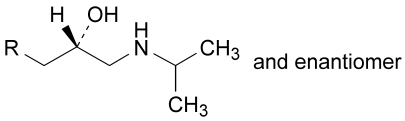
B. R = CH_3: 4-(2-methoxyethyl)phenol,

G. R = H: 2-(4-hydroxyphenyl)ethanol,



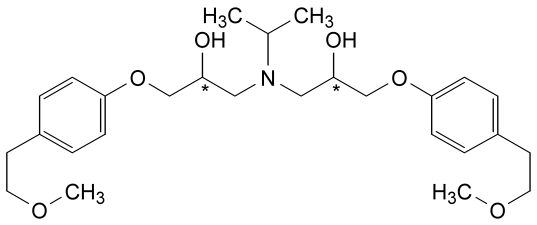
E. R = CH_2-CH_2-OCH_3: (2*RS*)-1-[2-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,

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



M. R = NH-$CH(CH_3)_2$: 1,3-bis[(1-methylethyl)amino]propan-2-ol,

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

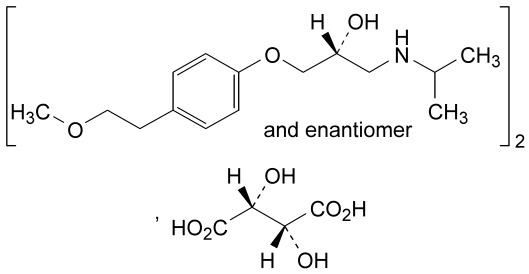


O. 1,1′-[(1-methylethyl)imino]bis[3-[4-(2-methoxyethyl)phenoxy]propan-2-ol].

01/2008:1028
corrected 6.0

METOPROLOL TARTRATE

Metoprololi tartras



$C_{34}H_{56}N_2O_{12}$ M_r 685

[56392-17-7]

DEFINITION

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

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