Mobile phase: mix 1 volume of *methanol R2*, 20 volumes of *acetonitrile R* and 79 volumes of a 2.82 g/l solution of *sodium hexanesulphonate R*.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 252 nm.

Injection: 20 µl.

System suitability:

- the chromatogram obtained with reference solution (c) is similar to the chromatogram provided with *carteolol for system suitability CRS*; the peaks due to impurity H and carteolol show base-line separation,
- *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (d),
- *number of theoretical plates*: minimum 6000, calculated for the principal peak in the chromatogram obtained with reference solution (a).

Limits: locate impurity H by comparison with the chromatogram provided with *carteolol for system suitability CRS*,

- *impurity H*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),
- *any other 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 half the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
- *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 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 for 3 h.

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

ASSAY

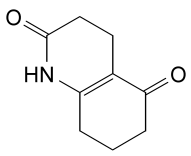
Dissolve 0.250 g in 60 ml of *alcohol R*. Add 5.0 ml of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 ml of *0.1 M sodium hydroxide* is equivalent to 32.88 mg of $C_{16}H_{25}N_2O_3Cl$.

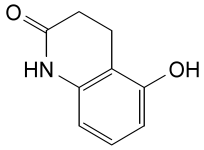
STORAGE

In an airtight container.

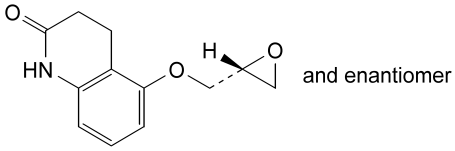
IMPURITIES



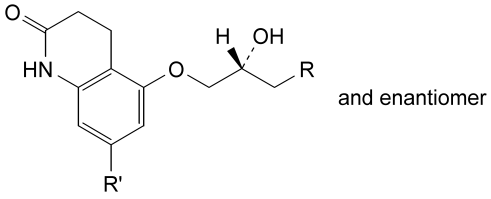
A. 4,6,7,8-tetrahydroquinoline-2,5(1*H*,3*H*)-dione,



B. 5-hydroxy-3,4-dihydroquinolin-2(1*H*)-one,



C. 5-[[(2*RS*)-oxiran-2-yl]methoxy]-3,4-dihydroquinolin-2(1*H*)-one,

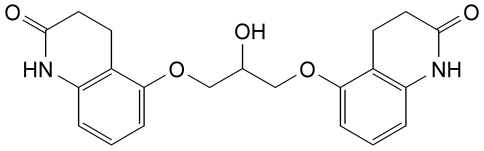


D. R = Cl, R′ = H: 5-[(2*RS*)-3-chloro-2-hydroxypropoxy]-3,4-dihydroquinolin-2(1*H*)-one,

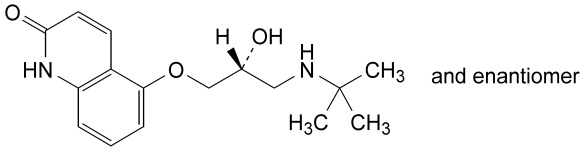
F. R = OCH_3, R′ = H: 5-[(2*RS*)-2-hydroxy-3-methoxypropoxy]-3,4-dihydroquinolin-2(1*H*)-one,

G. R = OH, R′ = H: 5-[(2*RS*)-2,3-dihydroxypropoxy]-3,4-dihydroquinolin-2(1*H*)-one,

I. R = NH-$C(CH_3)_3$, R′ = Br: 7-bromo-5-[(2*RS*)-3-[(1,1-(dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydroquinolin-2(1*H*)-one,



E. 5,5′-[(2-hydroxypropan-1,3-diyl)bis(oxy)]bis(3,4-dihydroquinolin-2(1*H*)-one),

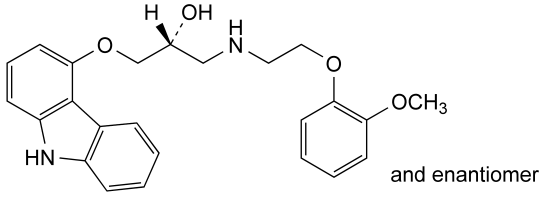


H. 5-[(2*RS*)-3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]quinolin-2(1*H*)-one.

01/2008:1745
corrected 6.0

CARVEDILOL

Carvedilolum



$C_{24}H_{26}N_2O_4$ M_r 406.5
[72956-09-3]

DEFINITION

(2*RS*)-1-(9*H*-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, slightly soluble in alcohol, practically insoluble in dilute acids.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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

If the spectrum obtained shows differences, dissolve the substance to be examined in *2-propanol R*, evaporate to dryness and record a new spectrum using the residue.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 ml with the mobile phase.

Reference solution (a). 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.

Reference solution (b). Dissolve 5.0 mg of *carvedilol impurity C CRS* in 5.0 ml of the test solution and dilute to 100.0 ml with the mobile phase.

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 100.0 ml with the mobile phase. Dilute 2.0 ml of this solution to 10.0 ml with the mobile phase.

Column:

- *size*: *l* = 0.125 m, Ø = 4.6 mm,
- *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm),
- *temperature*: 55 °C.

Mobile phase: dissolve 1.77 g of *potassium dihydrogen phosphate R* in *water R* and dilute to 650 ml with the same solvent; adjust to pH 2.0 with *phosphoric acid R* and add 350 ml of *acetonitrile R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 240 nm.

Injection: 20 µl.

Run time: 8 times the retention time of carvedilol.

Relative retention with reference to carvedilol (retention time = about 4 min): impurity A = about 0.6; impurity C = about 3.5; impurity B = about 6.7.

System suitability: reference solution (b):

- *resolution*: minimum 17 between the peaks due to carvedilol and to impurity C.

Limits:

- *correction factor*: for the calculation of content, multiply the peak area of impurity A by 2,
- *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),
- *impurity C*: not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent),
- *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
- *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
- *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.01 per cent).

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

2.0 g complies with limit test C. Prepare the standard using 2.0 ml of *lead standard solution (10 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.

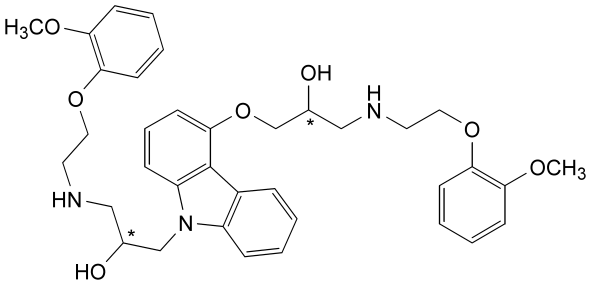
Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

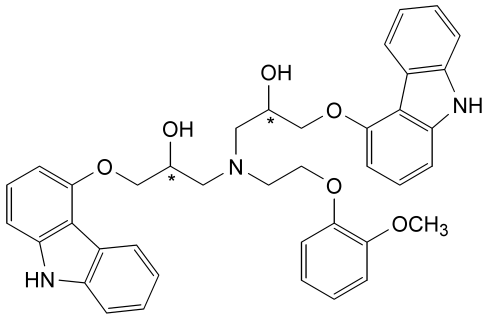
Dissolve 0.350 g in 60 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 40.65 mg of $C_{24}H_{26}N_2O_4$.

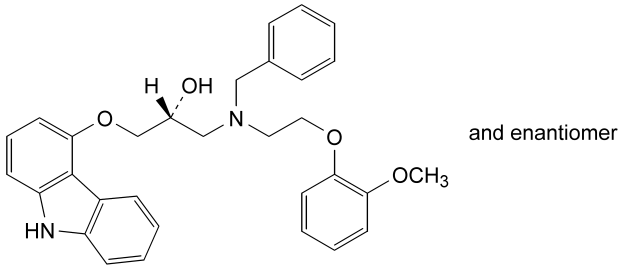
IMPURITIES



A. 1-[[9-[2-hydroxy-3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]-9*H*-carbazol-4-yl]oxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol,



B. 1,1′-[[2-(2-methoxyphenoxy)ethyl]nitrilo]bis[3-(9*H*-carbazol-4-yloxy)propan-2-ol],



C. (2*RS*)-1-[benzyl[2-(2-methoxyphenoxy)ethyl]amino]-3-(9*H*-carbazol-4-yloxy)propan-2-ol.