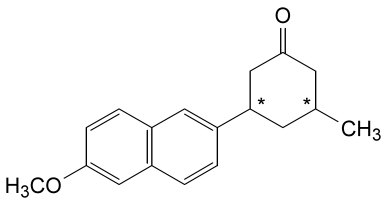
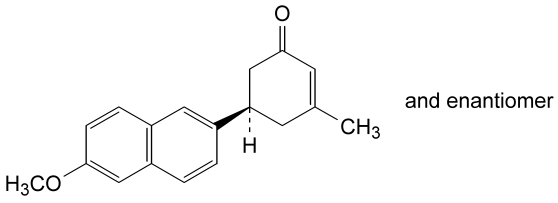
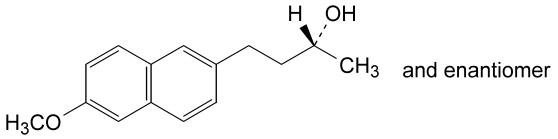


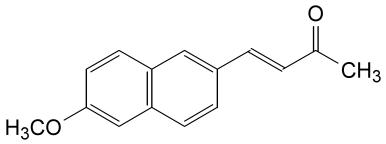
A. 3-(6-methoxynaphthalen-2-yl)-5-methylcyclohexanone,



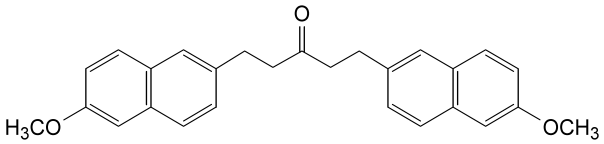

B. (5*RS*)-5-(6-methoxynaphthalen-2-yl)-3-methylcyclohex-2-enone,



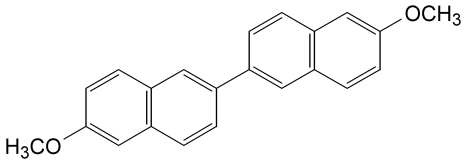

C. (2*RS*)-4-(6-methoxynaphthalen-2-yl)butan-2-ol,



D. (*E*)-4-(6-methoxynaphthalen-2-yl)but-3-en-2-one,



E. 1,5-bis(6-methoxynaphthalen-2-yl)pentan-3-one,

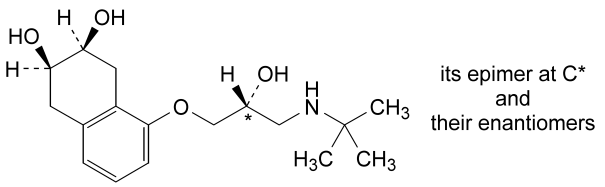


F. 6,6′-dimethoxy-2,2′-binaphthalenyl.

**01/2008:1789**

# NADOLOL

## Nadololum




$C_{17}H_{27}NO_4$ $M_r$ 309.4

[42200-33-9]

DEFINITION

*cis*-5-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydronaphthalene-2,3-diol.

It consists of 2 pairs of enantiomers which are present as 2 racemic compounds: racemate A and racemate B.

*Content*: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

*Appearance*: white or almost white, crystalline powder.

*Solubility*: slightly soluble in water, freely soluble in alcohol, practically insoluble in acetone.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *nadolol CRS*.

TESTS

**Racemate content**. Infrared absorption spectrophotometry (*2.2.24*).

Prepare a mull in *liquid paraffin R* of the substance to be examined (dried substance), adjusting the thickness of the mull to give an absorbance reading of 0.6 ± 0.1 at 1587 $cm^{-1}$. Record the spectrum from 1667 to 1111 $cm^{-1}$, using *liquid paraffin R* as reference. Measure the absorbance $A_a$, corresponding to racemate A, at the maximum at 1266 $cm^{-1}$ and the absorbance $A_b$, corresponding to racemate B, at the maximum at 1250 $cm^{-1}$. The ratio $A_a/A_b$ is 0.72 to 1.08 (corresponding to racemate A content of between 40 per cent and 60 per cent).

**Related substances**. Liquid chromatography (*2.2.29*).

*Test solution*. Dissolve 0.100 g of the substance to be examined in 4.0 ml of *methanol R* and dilute to 100.0 ml with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

*Reference solution (a)*. Dilute 1.0 ml of the test solution to 50.0 ml with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*. Dilute 5.0 ml of the solution to 50.0 ml with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

*Reference solution (b)*. Dissolve 20 mg of *pindolol CRS* and 20 mg of the substance to be examined in 20 ml of *methanol R* and dilute to 100.0 ml with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*. Dilute 1.0 ml of the solution to 100.0 ml with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

*Reference solution (c)*. Dilute 5.0 ml of reference solution (a) to 20.0 ml with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

*Column*:

– *size*: *l* = 0.30 m, Ø = 3.9 mm,

– *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm), with a specific surface area of 700 $m^2/g$, a pore size of 0.9 nm and a carbon loading of 12 per cent.

– *temperature*: 40 °C.

*Mobile phase*:

– *mobile phase A*: 5.6 g/l solution of *sodium octanesulphonate R* adjusted to pH 3.5 with a 300 g/l solution of *phosphoric acid R*,

– *mobile phase B*: *acetonitrile R*,

| Time (min) | Mobile phase A (per cent *V/V*) | Mobile phase B (per cent *V/V*) |
|---|---|---|
| 0 - 7 | 77 | 23 |
| 7 - 30 | 77 → 65 | 23 → 35 |
| 30 - 45 | 65 | 35 |
| 45 - 50 | 65 → 77 | 35 → 23 |
| 50 - 60 | 77 | 23 |

*Flow rate*: 1 ml/min.

*Detection*: spectrophotometer at 206 nm.

*Injection*: 20 µl.

*Relative retention* with reference to nadolol (retention time = about 18 min): impurity A = 0.25; impurity B = 0.4; impurity C (doublet) = 0.6 and 0.7; impurity D = 1.4; impurity E = 1.6; impurity F = 2.2; impurity G = 2.6.

*System suitability*: reference solution (b):

– *resolution*: minimum of 8.0 between the peaks due to nadolol and to pindolol.

*Limits*:

– *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.7; impurity B = 1.7; impurity C = 1.7 (multiply the sum of the areas of the 2 peaks);
– *impurity 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 (a) (0.2 per cent);
– *any other impurity*: not more than half the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
– *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

**Heavy metals** (*2.4.8*): maximum 30 ppm.

1.0 g complies with limit test D. Prepare the standard using 3 ml of *lead standard solution (10 ppm Pb) R*.

**Loss on drying** (*2.2.32*): maximum 2.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

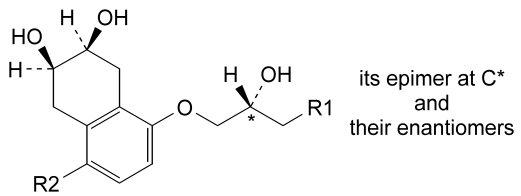
**Sulphated ash** (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 100 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 30.94 mg of $C_{17}H_{27}NO_4$.

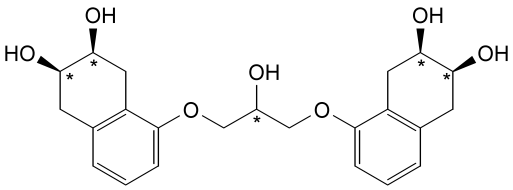
IMPURITIES



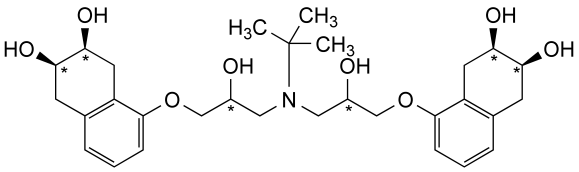

A. R1 = OH, R2 = H: *cis*-5-[(2*RS*)-2,3-dihydroxypropoxy]-1,2,3,4-tetrahydronaphtalene-2,3-diol (tetraol),

B. R1 = $OCH_3$, R2 = H: *cis*-5-[(2*RS*)-2-hydroxy-3-methoxypropoxy]-1,2,3,4-tetrahydronaphtalene-2,3-diol,

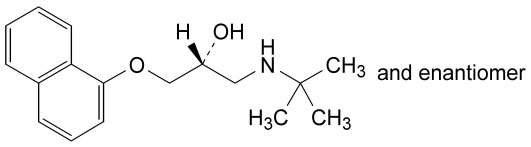
E. R1 = NH-C$(CH_3)_3$, R2 = I: *cis*-5-[(2*RS*)-3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-8-iodo-1,2,3,4-tetrahydronaphtalene-2,3-diol,



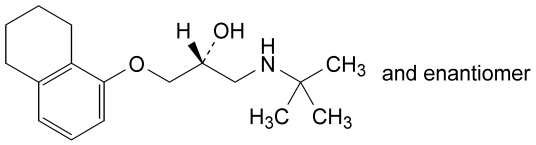
C. 5,5′-[(2-hydroxypropane-1,3-diyl)bis(oxy)]bis(*cis*-1,2,3,4-tetrahydronaphthalene-2,3-diol),



D. 5,5′-[[(1,1-dimethylethyl)imino]bis[(2-hydroxypropane-1,3-diyl)oxy]]bis(*cis*-1,2,3,4-tetrahydronaphthalene-2,3-diol),




F. (2*RS*)-1-[(1,1-dimethylethyl)amino]-3-(naphthalen-1-yloxy)propan-2-ol,




G. (2*RS*)-1-[(1,1-dimethylethyl)amino]-3-[(5,6,7,8-tetrahydronaphtalen-1-yl)oxy]propan-2-ol.

**01/2008:1134**

# NADROPARIN CALCIUM

## Nadroparinum calcicum