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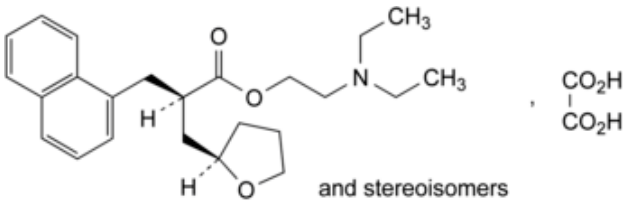
Edition: BP 2025 (Ph. Eur. 11.6 update)

Naftidrofuryl Oxalate

General Notices

(Naftidrofuryl Hydrogen Oxalate, Ph. Eur. monograph 1594)



$C_{26}H_{35}NO_7$ 473.6 *3200-06-4*

Action and use

Vasodilator.

Preparation

Naftidrofuryl Capsules

Ph Eur

DEFINITION

Mixture of 4 stereoisomers of 2-(diethylamino)ethyl 2-[(naphthalen-1-yl)methyl]-3-(tetrahydrofuran-2-yl)propanoate hydrogen oxalate.

Content

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

CHARACTERS

Appearance

White or almost white powder.

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Solubility

Freely soluble in water, freely soluble or soluble in ethanol (96 per cent), slightly or sparingly soluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Dissolve 1.0 g in *water R* and dilute to 50 mL with the same solvent. Add 2 mL of *concentrated ammonia R* and shake with 3 quantities, each of 10 mL, of *methylene chloride R*. To the combined lower layers, add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate by suitable means at a temperature not exceeding 30 °C. Use the residue obtained.

Comparison *Ph. Eur. reference spectrum of naftidrofuryl*.

B. Dissolve 0.5 g in *water R* and dilute to 10 mL with the same solvent. Add 2.0 mL of *calcium chloride solution R*. A white precipitate is formed. The precipitate dissolves after the addition of 3.0 mL of *hydrochloric acid R*.

TESTS

Absorbance (*2.2.25*)

Maximum 0.1 at 430 nm.

Dissolve 1.5 g in *water R* and dilute to 10 mL with the same solvent. If necessary use an ultrasonic bath.

Related substances

A. Liquid chromatography (*2.2.29*).

Test solution Dissolve 80.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase. Sonicate for 10 s. A precipitate is formed. Filter through a membrane filter (nominal pore size 0.45 µm), discarding the first 5 mL. *Use a freshly prepared solution.*

Reference solution (a) Dissolve 5.0 mg of *naftidrofuryl impurity A CRS* in *acetonitrile R* and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *naftidrofuryl impurity B CRS* and 5 mg of the substance to be examined in *acetonitrile R* and dilute to 50 mL with the same solvent. Dilute 1 mL of the solution to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

Mobile phase Mix 60 mL of *methanol R* with 150 mL of *tetrabutylammonium buffer solution pH 7.0 R* and dilute to 1000 mL with *acetonitrile R*.

Flow rate 1 mL/min.

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Detection Spectrophotometer at 283 nm.

Injection 20 µL.

Run time 2.3 times the retention time of naftidrofuryl.

Relative retention With reference to naftidrofuryl (retention time = about 7 min): impurity A = about 0.5; impurity B = about 0.8; impurity C = about 1.8.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity B and naftidrofuryl.

Limits:

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *any other impurity*: for each 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 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

B. Gas chromatography (2.2.28).

Test solution (a) Dissolve 1.0 g of the substance to be examined in *water R* and dilute to 50 mL with the same solvent. Add 2 mL of *concentrated ammonia R* and shake with 3 quantities, each of 10 mL, of *methylene chloride R*. To the combined lower layers, add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate by suitable means at a temperature not exceeding 30 °C. Take up the residue with *methylene chloride R* and dilute to 20.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *methylene chloride R*.

Reference solution Dissolve 5 mg of *naftidrofuryl impurity F CRS* in *methylene chloride R* and dilute to 50 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.45 µm).

Carrier gas *helium for chromatography R*.

Splitter flow rate 25 mL/min.

Flow rate 2.9 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 4	210
	4 - 8	210 → 230
	8 - 18	230 → 260

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	Time (min)	Temperature (°C)
	18 - 30	260
Injection port		290
Detector		290

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to the second eluting peak of naftidrofuryl: impurity D = about 0.14; impurity B = about 0.55 (for the second eluting peak); impurity E = about 0.86; impurity F = about 1.04 (for the second eluting peak).

System suitability Test solution (b):

— *resolution*: minimum 1.0 between the 2 peaks due to the diastereoisomers of naftidrofuryl.

Limits Test solution (a):

— *impurity F*: for the sum of the areas of the 2 peaks, maximum 0.20 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl (0.20 per cent);

— *impurity E*: maximum 0.20 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl (0.20 per cent);

— *impurity D*: maximum 0.10 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl (0.10 per cent);

— *any other impurity*: for each impurity, maximum 0.10 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl (0.10 per cent);

— *total*: maximum 0.50 per cent of the sum of the areas of the 2 peaks due to naftidroduryl (0.50 per cent);

— *disregard limit*: 0.02 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl (0.02 per cent); disregard any peaks due to impurity B.

Diastereoisomer ratio

Gas chromatography (*2.2.28*) as described in test B for related substances.

Limits Test solution (b):

— *first eluting naftidrofuryl diastereoisomer*: minimum 30 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl.

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.

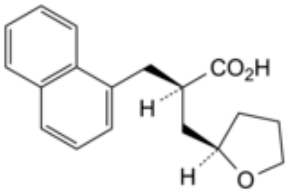
ASSAY

Dissolve 0.350 g in 50 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 47.36 mg of $C_{26}H_{35}NO_7$.

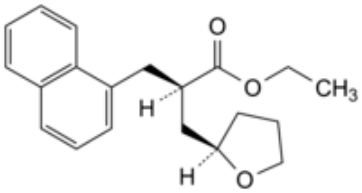
IMPURITIES

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



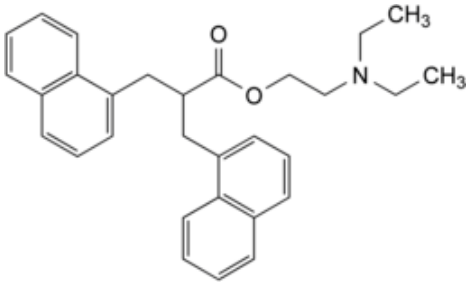
and stereoisomers

A. 2-[(naphthalen-1-yl)methyl]-3-(tetrahydrofuran-2-yl)propanoic acid,

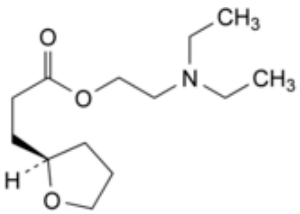


and stereoisomers

B. ethyl 2-[(naphthalen-1-yl)methyl]-3-(tetrahydrofuran-2-yl)propanoate,



C. 2-(diethylamino)ethyl 3-(naphthalen-1-yl)-2-[(naphthalen-1-yl)methyl]propanoate,



and enantiomer

D. 2-(diethylamino)ethyl 3-[(2*RS*)-tetrahydrofuran-2-yl]propanoate,

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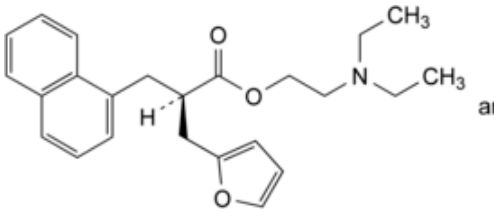
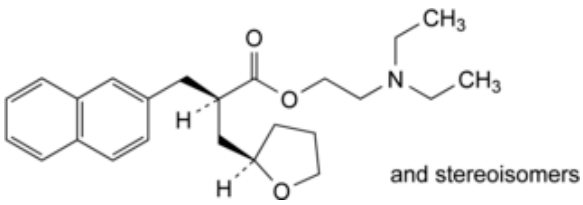


E. 2-(diethylamino)ethyl (2*RS*)-2-[(furan-2-yl)methyl]-3-(naphthalen-1-yl)propanoate,



F. 2-(diethylamino)ethyl 2-[(naphthalen-2-yl)methyl]-3-(tetrahydrofuran-2-yl)propanoate.

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