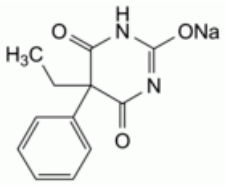
Edition: BP 2025 (Ph. Eur. 11.6 update)

Phenobarbital Sodium

General Notices

(Ph. Eur. monograph 0630)



$C_{12}H_{11}N_2NaO_3$ 254.2 *57-30-7*

Action and use

Barbiturate.

Preparations

Phenobarbital Injection

Paediatric Phenobarbital Oral Solution

Phenobarbital Sodium Tablets

Ph Eur

DEFINITION

Sodium derivative of 5-ethyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

Solubility

Freely soluble in carbon dioxide-free water (a small fraction may be insoluble), soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

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It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, B, E.

Second identification: A, C, D, E.

A. Acidify 10 mL of solution S (see Tests) with *dilute hydrochloric acid R* and shake with 20 mL of *ether R*. Separate the ether layer, wash with 10 mL of *water R*, dry over *anhydrous sodium sulfate R* and filter. Evaporate the filtrate to dryness and dry the residue at 100-105 °C (test residue). Determine the melting point (2.2.14) of the test residue. Mix equal parts of the test residue and *phenobarbital CRS* and determine the melting point of the mixture. The difference between the melting points (which are about 176 °C) is not greater than 2 °C.
B. Infrared absorption spectrophotometry (2.2.24).

Preparation Use the test residue obtained in identification test A.

Comparison *phenobarbital CRS*.

If the spectra obtained in the solid state show differences, dissolve the test residue and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *ethanol (50 per cent V/V) R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 9 mg of *phenobarbital CRS* in *ethanol (50 per cent V/V) R* and dilute to 10.0 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *ethanol (96 per cent) R*, *methylene chloride R* (5:15:80 *V/V/V*); use the lower layer.

Application 10 µL.

Development Over 2/3 of the plate.

Detection Examine immediately in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives the reaction of non-nitrogen substituted barbiturates (2.3.1).
E. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *ethanol (50 per cent V/V) R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

pH (2.2.3)

Maximum 10.2.

Dissolve 5.0 g as completely as possible in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

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Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 55.0 mg of the substance to be examined in 2.0 mL of *methanol R* and dilute to 10.0 mL with the mobile phase.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in 10.0 mL of *methanol R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Mix 1.0 mL of test solution (b) and 20.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *phenobarbital impurity A CRS* and 5.0 mg of *phenobarbital impurity B CRS* in 2.0 mL of *methanol R* and dilute to 10.0 mL with the mobile phase. Mix 1.0 mL of the solution and 20.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 25.0 mg of *phenobarbital CRS* in 10.0 mL of *methanol R* and dilute to 50.0 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 Dissolve 6.6 g of *sodium acetate R* in 900 mL of *water R*, add 3 mL of *glacial acetic acid R*, adjust to pH 4.5 with *glacial acetic acid R* and dilute to 1000 mL with *water R*. Mix 60 volumes of this solution and 40 volumes of *methanol R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 2.5 times the retention time of phenobarbital.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to phenobarbital (retention time = about 13 min): impurity A = about 0.29; impurity B = about 0.32.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B.

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (b);

— for impurity B, use the concentration of impurity B in reference solution (b);

— for impurities other than A and B, use the concentration of phenobarbital sodium in reference solution (a).

Limits:

— *impurities A, B*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 7.0 per cent, determined on 0.500 g by drying in an oven at 150 °C for 4 h.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection 10 µL of test solution (b) and reference solution (c).

Run time 1.5 times the retention time of phenobarbital.

Calculate the percentage content of $C_{12}H_{11}N_2NaO_3$ taking into account the assigned content of *phenobarbital CRS* and a conversion factor of 1.095.

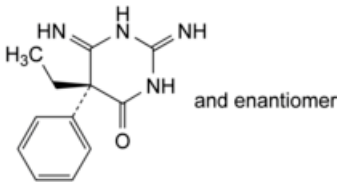
STORAGE

In an airtight container.

IMPURITIES

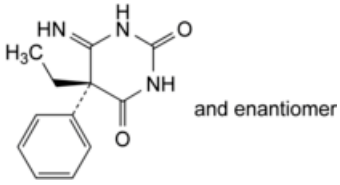
Specified impurities *A, B*.

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) *C, E*.



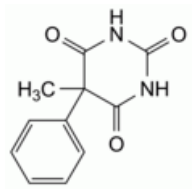
and enantiomer

A. (5*RS*)-5-ethyl-2,6-diimino-5-phenyltetrahydropyrimidin-4(1*H*)-one,



and enantiomer

B. (5*RS*)-5-ethyl-6-imino-5-phenyldihydropyrimidine-2,4(1*H*,3*H*)-dione,



C. 5-methyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione,

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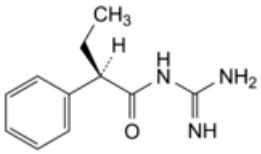

and enantiomer

E. (2*RS*)-*N*-carbamimidoyl-2-phenylbutanamide.

Ph Eur