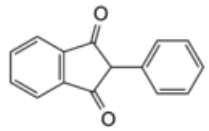
Edition: BP 2025 (Ph. Eur. 11.6 update)

Phenindione

General Notices



$C_{15}H_{10}O_2$ 222.2 *83-12-5*

Action and use

Oral anticoagulant (indanedione).

Preparation

Phenindione Tablets

DEFINITION

Phenindione is 2-phenylindane-1,3-dione. It contains not less than 98.0% and not more than 102.0% of $C_{15}H_{10}O_2$, calculated with reference to the dried substance.

CHARACTERISTICS

Soft, white or creamy white crystals.

Very slightly soluble in *water*; slightly soluble in *ethanol (96%)* and in *ether*. Solutions are yellow to red.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of phenindione *(RS 268)*.

TESTS

Melting point

148° to 151°, Appendix V A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) 0.25% w/v of the substance being examined in *methanol*.
(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.
(3) 0.0005% w/v each of *phenindione BPCRS*, *phenylacetic acid* (impurity 3), *benzalphthalide* (impurity 4) and *phthalic acid* (impurity 5) in *methanol*.
(4) Dilute 1 volume of solution (2) to 10 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (X-bridge shield C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a chilled auto-sampler temperature of 4°.
(f) Use a detection wavelength of 220 nm.
(g) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes *acetonitrile*, 10 volumes of a 1.36% w/v *dipotassium hydrogen phosphate* solution previously adjusted to pH 3.0 with *orthophosphoric acid*, and 80 volumes of *water*.

Mobile phase B 10 volumes *water* and 90 volumes *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-0.5	80	20	isocratic
0.5-10	80→50	20→50	linear gradient
10-13	50	50	isocratic
13-21	50→30	50→70	linear gradient
21-22	30→80	70→20	linear gradient
22-25	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to phenindione (retention time about 7 minutes) are: impurity 5, about 0.2; impurity 3, about 0.4; impurity 1, about 0.6; impurity 4, about 1.8 and impurity 2, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks due to impurity 5 and impurity 3 is at least 4.6.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity 1 or 2 is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

Loss on drying

When dried at 105° for 2 hours, loses not more than 1.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solution A 2% v/v *glacial acetic acid* in *acetonitrile*.

(1) Mix with the aid of ultrasound 25 mg of Phenindione in 20 mL of 0.01M *sodium hydroxide* and add 50 mL of solution A. Dilute to 100 mL with solution A.
(2) 25 mg of *phenindione BPCRS* in 20 mL of 0.01M *sodium hydroxide* and 30 mL of solution A. Make up to 100 mL with solution A.
(3) 5 mg each of *phenindione BPCRS* and *phenylacetic acid* (impurity 3) in 5 mL of 0.01M *sodium hydroxide* and 5 mL of solution A. Make up to 20 mL with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use an autosampler temperature of 4°.
(f) Use a detection wavelength of 250 nm.
(g) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes *acetonitrile* and 60 volumes of 0.68 % w/v *potassium dihydrogen phosphate* previously adjusted to pH 3.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

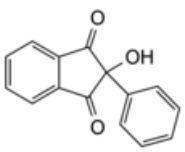
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity 3 and phenindione is at least 6.0.

DETERMINATION OF CONTENT

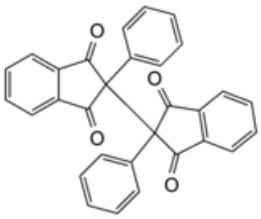
Calculate the content of $C_{15}H_{10}O_2$ using the declared content of $C_{15}H_{10}O_2$ in *phenindione BPCRS*.

IMPURITIES

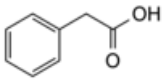
The impurities limited by the requirements of this monograph include:



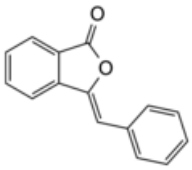
1. 2-hydroxy-2-phenyl-1*H*-indene-1,3(2*H*)-dione



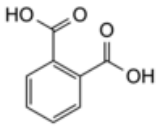
2. 2′-diphenyl-1*H*,1′*H*-[2,2′-bi-indene]-1,1′,3,3′(2*H*,2′*H*)-tetrone



3. phenylacetic acid



4. 3-benzylidene-2-benzofuran-1(3*H*)-one (benzalphthalide)



5. phthalic acid