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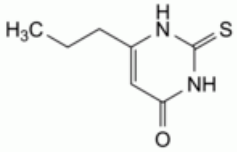
Propylthiouracil

General Notices

(Ph. Eur. monograph 0525)



$C_7H_{10}N_2OS$ 170.2 *51-52-5*

Action and use

Thiourea antithyroid drug.

Preparation

Propylthiouracil Tablets

Ph Eur

DEFINITION

6-Propyl-2-sulfanylidene-2,3-dihydropyrimidin-4(1*H*)-one.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder or crystals.

Solubility

Very slightly soluble in water, sparingly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (2.2.14): 217 °C to 221 °C.
B. Infrared absorption spectrophotometry (2.2.24).

Comparison *propylthiouracil CRS*.

C. To about 20 mg add 8 mL of *bromine water R* and shake for a few minutes. Boil until the mixture is decolourised, allow to cool and filter. To the filtrate add 2 mL of *barium chloride solution R1*. A white precipitate is formed whose colour does not become violet on the addition of 5 mL of *dilute sodium hydroxide solution R*.

TESTS

Impurity A

Liquid chromatography (2.2.29).

Solvent mixture *water R*, *acetonitrile R* (30:70 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution Dissolve 2.5 mg of *propylthiouracil impurity A CRS* in 70 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography, alkyl-bonded for use with highly aqueous mobile phases R* (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: to 1000 mL of *water for chromatography R*, add 1 mL of *phosphoric acid R* and mix. Mix 900 mL of this solution and 100 mL of *acetonitrile for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 15	100 → 70	0 → 30
15 - 25	70	30

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

Run time 1.5 times the retention time of propylthiouracil.

Identification of impurities Use the chromatogram obtained with the reference solution to identify the peak due to impurity A.

Relative retention With reference to propylthiouracil (retention time = about 16 min): impurity A = about 0.27.

Calculation of percentage content:

— for impurity A, use the concentration of impurity A in the reference solution.

Limit:

— *impurity A*: maximum 0.05 per cent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in 20 mL of *methanol R*, sonicate to dissolve and dilute to 100.0 mL with *methanol R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with *methanol R*. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*.

Reference solution (b) Dissolve 25 mg of the substance to be examined and 25 mg of *methylthiouracil R* (impurity B) in 50 mL of *methanol R* and dilute to 100 mL with the same solvent. Dilute 0.5 mL of the solution to 50 mL with *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

— *temperature*: 30 °C.

Mobile phase To 1000 mL of *water for chromatography R*, add 1 mL of *phosphoric acid R* and mix. Mix 900 mL of this solution and 100 mL of *acetonitrile R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL.

Run time 1.5 times the retention time of propylthiouracil.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to propylthiouracil (retention time = about 19 min): impurity B = about 0.3.

System suitability Reference solution (b):

— *resolution*: minimum 20 between the peaks due to impurity B and propylthiouracil.

Calculation of percentage contents:

— for each impurity, use the concentration of propylthiouracil in reference solution (a).

Limits:

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

— *total*: maximum 0.2 per cent;

— *reporting threshold*: maximum 0.05 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.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

To 0.300 g add 30 mL of *water R* and 30.0 mL of *0.1 M sodium hydroxide*. Boil and shake until dissolution is complete. Add 50 mL of *0.1 M silver nitrate* while stirring, boil gently for 5 min and cool. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). The volume of *0.1 M sodium hydroxide* used is equal to the sum of the volume added initially and the volume used in the final titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 8.511 mg of $C_7H_{10}N_2OS$.

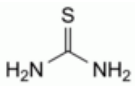
STORAGE

Protected from light.

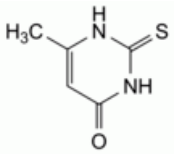
IMPURITIES

Specified impurities *A*.

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) *B*.



A. thiourea,



B. 6-methyl-2-sulfanylidene-2,3-dihydropyrimidin-4(1*H*)-one (methylthiouracil).

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