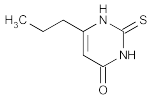
Propylthiouracil



$C_7H_{10}N_2OS$ 170.23
4(1*H*)-Pyrimidinone, 2,3-dihydro-6-propyl-2-thioxo-.
6-Propyl-2-thiouracil [51-52-5].

» Propylthiouracil contains not less than 98.0 percent and not more than 100.5 percent of $C_7H_{10}N_2OS$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

USP Reference standards ⟨11⟩**—**
USP Propylthiouracil RS

Identification, *Infrared Absorption* ⟨197K⟩.

Melting range ⟨741⟩: between 218° and 221°.

Loss on drying ⟨731⟩**—**Dry it at 105° for 2 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Selenium ⟨291⟩: 0.003%, a 200-mg specimen being used.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Ordinary impurities ⟨466⟩**—**

Test solution: methanol.

Standard solution: methanol.

Application volume: 10 µL.

Eluant: a mixture of toluene, ethyl acetate, and formic acid (50:45:5), in a nonequilibrated chamber.

Visualization: 1.

Assay—Weigh accurately about 300 mg of Propylthiouracil, transfer to a 500-mL conical flask, and add 30 mL of water. Add from a buret about 30 mL of 0.1 N sodium hydroxide VS, heat to boiling, and agitate until solution is complete. Wash down any particles on the wall of the flask with a few mL of water, then add about 50 mL of 0.1 N silver nitrate while mixing, and boil gently for 7 minutes. Cool to room temperature, and continue to titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically, using a glass-calomel electrode system. Each mL of 0.1 N sodium hydroxide is equivalent to 8.512 mg of $C_7H_{10}N_2OS$.

Propylthiouracil Tablets

» Propylthiouracil Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_7H_{10}N_2OS$.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩**—**
USP Propylthiouracil RS

Identification—

A: Boil a quantity of finely powdered Tablets, equivalent to about 100 mg of propylthiouracil, with 10 mL of alcohol under a reflux condenser for 20 minutes. Filter while hot, and evaporate the filtrate on a steam bath to dryness: a portion of the residue responds to the *Identification* tests under *Propylthiouracil.*

B: The chromatogram of the *Assay preparation* obtained as directed in the *Assay* exhibits a major peak, the retention time of which corresponds to that exhibited in the chromatogram of the *Standard preparation*.

Dissolution ⟨711⟩**—**

Medium: water; 900 mL.

Apparatus 1: 100 rpm.

Time: 30 minutes.

Procedure—Determine the amount of $C_7H_{10}N_2OS$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 274 nm of filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, in comparison with a Standard solution having a known concentration of USP Propylthiouracil RS in the same medium.

Tolerances—Not less than 85% *(Q)* of the labeled amount of $C_7H_{10}N_2OS$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

0.025 M Phosphate buffer—Transfer an accurately weighed quantity of 3.40 g of monobasic potassium phosphate to a 1000-mL beaker. Add 500 mL of water, and stir until dissolved. Adjust the resulting solution with phosphoric acid or 0.1 N sodium hydroxide to a pH of 4.6. Add 500 mL of water to this solution, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.025 M Phosphate buffer* and acetonitrile (80:20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer an accurately weighed quantity of about 25 mg of USP Propylthiouracil RS to a 50-mL volumetric flask, add 5 mL of methanol, and sonicate for 5 minutes. Add 25 mL of water, and shake by mechanical means for 15 minutes. Dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having a known concentration of about 50 µg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder equivalent to about 50 mg of propylthiouracil to a 100-mL volumetric flask, add 10 mL of methanol, and sonicate for 5 minutes. Add 50 mL of water, and shake by mechanical means for 20 minutes. Dilute with water to volume, mix, and filter. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 272-nm detector and a 4.6-mm × 10-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as described for *Procedure:* the column efficiency, determined from the analyte peak, is not less than 3500 theoretical plates, the tailing factor, *T*, for the propylthiouracil peak is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak area responses for the major peaks. Calculate the quantity, in mg, of $C_7H_{10}N_2OS$ in the portion of Tablets taken by the formula:

$$1000C(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of USP Propylthiouracil RS in the *Standard preparation*, and r_U and r_S are the peak area responses of propylthiouracil obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Protamine Sulfate

DEFINITION

Protamine Sulfate is a purified mixture of simple protein principles obtained from the sperm or testes of suitable species of

fish, which has the property of neutralizing heparin. Each mg of Protamine Sulfate, calculated on the dried basis, neutralizes NLT 100 USP Heparin Units.

ASSAY

- **PROCEDURE**

Sample solution A: 0.15 mg/mL of Protamine Sulfate in water

Sample solution B: Dilute 2.0 mL of *Sample solution A* with water to 3.0 mL.

Sample solution C: Dilute 1.0 mL of *Sample solution A* with water to 3.0 mL.

Titrant: USP Heparin Sodium for Assays RS in water (about 80–120 USP Heparin Units/mL)

Analysis: [NOTE—Titrate each *Sample solution* in duplicate.] Transfer a volume of the *Sample solution* to the analytical cell of a suitable colorimeter, and set the apparatus for measurement at a suitable wavelength (none is critical) in the visible range. Add *Titrant* in small volumes until there is a sharp increase in the absorbance, and note the volume of *Titrant* added. Perform the entire *Assay* in triplicate for a total of 18 determinations.

Calculate the number of USP Heparin Units in the volume of *Titrant* added at the endpoint per mg of Protamine Sulfate. Calculate the USP Heparin Units neutralized per mg of Protamine Sulfate taken:

$$\text{Result} = (V_T \times C_T)/(V_S \times C_S)$$

V_T = volume of *Titrant* added (mL)
C_T = concentration of *Titrant* (USP Heparin Units/mL)
V_S = volume of the *Sample solution* (mL)
C_S = concentration of Protamine Sulfate (mg/mL)

Calculate the potency of the Protamine Sulfate as the average of the 18 values. Calculate the 3 standard deviations for the results obtained with each of the *Sample solutions*. Calculate the 3 standard deviations for the results obtained with each of the 3 independent assays. The *Assay* is valid if each of the 6 standard deviations is NMT 5% of the average result.

Acceptance criteria: Each mg of Protamine Sulfate neutralizes NLT 100 USP Heparin Units on the dried basis.

OTHER COMPONENTS

- **NITROGEN DETERMINATION,** *Method II* ⟨**461**⟩

Acceptance criteria: 22.5%–25.5% of N on the dried basis

SPECIFIC TESTS

- **LOSS ON DRYING** ⟨**731**⟩**:** Dry a sample at 105° for 3 h: it loses NMT 5% of its weight.
- **ULTRAVIOLET ABSORBANCE**

Sample solution: 1.0% solution of Protamine Sulfate in water

Spectrometric conditions

(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)

Mode: UV

Wavelength range: 260–280 nm

Blank: Water

Acceptance criteria: The difference in absorbance of the *Sample solution* at 260–280 nm against the *Blank* is NMT 0.1.

- **SULFATE**

Sample: 150 mg

Analysis: Dissolve the *Sample* in 75 mL of water, add 5 mL of 3 N hydrochloric acid, heat to boiling, and while maintaining at the boiling point, slowly add 10 mL of barium chloride TS. Cover the vessel, and allow the mixture to stand on a steam bath for 1 h. Filter, wash the precipitate with several portions of hot water, dry, and ignite to constant weight. The weight of the barium sulfate, multiplied by 0.4117, represents the weight of sulfate in the portion of Protamine Sulfate taken.

Acceptance criteria: 16%–22% on the dried basis

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers in a refrigerator.
- **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Heparin Sodium for Assays RS

Protamine Sulfate Injection

DEFINITION

Protamine Sulfate Injection is a sterile, isotonic solution of Protamine Sulfate. Each mg of Protamine Sulfate, used in the manufacture of the Injection, neutralizes NLT 100 USP Heparin Units, calculated on the dried basis. It contains NLT 90.0% and NMT 120.0% of the labeled amount of protamine sulfate.

IDENTIFICATION

- **IDENTIFICATION TESTS—GENERAL,** *Sulfate* ⟨**191**⟩**:** Meets the requirements

ASSAY

- **PROCEDURE**

Sample solution: 0.15 mg/mL of protamine sulfate in Water for Injection from a measured volume of Injection

Analysis: [NOTE—Titrate the *Sample solution* in duplicate.] Transfer the same volume of the *Sample solution* to the analytical cell as used in the *Assay* for the drug substance. Proceed as directed in the *Assay* under *Protamine Sulfate*, using the same concentration of *Titrant* and the same wavelength as used in the *Assay* for the drug substance. The concentration of the *Sample solution* of the drug substance should also be 0.15 mg/mL. Perform the entire *Assay* in triplicate, and calculate the average of the triplicate determinations. The percentage of the label claim is given as follows:

$$\text{Result} = (v/V) \times 100$$

v = volume of *Titrant* added to the Injection *Sample solution* (mL)
V = volume of *Titrant* added to the drug substance *Sample solution* (mL)

Acceptance criteria: 90.0%–120.0%

SPECIFIC TESTS

- **BACTERIAL ENDOTOXINS TEST** ⟨**85**⟩**:** It contains NMT 7.0 USP Endotoxin Units/mg of protamine sulfate.
- **OTHER REQUIREMENTS:** It meets the requirements under *Injections* ⟨1⟩.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in single-dose containers, preferably of Type I glass. Store at controlled room temperature.
- **LABELING:** Label it to indicate the approximate neutralization capacity in USP Heparin Units.
- **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Endotoxin RS
USP Heparin Sodium for Assays RS

Protamine Sulfate for Injection

DEFINITION

Protamine Sulfate for Injection is a sterile mixture of Protamine Sulfate with one or more suitable, dry diluents. Each mg of Protamine Sulfate, used in the manufacture of the Protamine Sulfate for Injection, neutralizes NLT 100 USP Heparin Units, calculated on the dried basis. It contains NLT 90.0% and NMT 120.0% of the labeled amount of protamine sulfate.