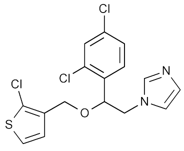
Standard solution 4 and *Standard solution 5*, respectively; any spot, other than the principal spot, obtained from *Test solution 1* is not more intense than the spot obtained from *Standard solution 2;* and not more than one such spot is more intense than the spot obtained from *Standard solution 3*.

Assay—Dissolve 150 mg of Tinidazole, accurately weighed, in 25.0 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically with suitable electrodes (see *Titrimetry* ⟨541⟩). Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 24.73 mg of $C_8H_{13}N_3O_4S$.

Tioconazole



$C_{16}H_{13}Cl_3N_2OS$ 387.71

1*H*-Imidazole, 1-[2-[(2-chloro-3-thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-;

1-[2,4-Dichloro-[*β*-(2-chloro-3-thenyl)-oxy]phenethyl]imidazole [65899-73-2].

DEFINITION

Tioconazole contains NLT 97.0% and NMT 103.0% of $C_{16}H_{13}Cl_3N_2OS$.

IDENTIFICATION

- **A. Infrared Absorption ⟨197M⟩**
- **B. Procedure**

Standard solution: 50 mg/mL of USP Tioconazole RS in methanol

Sample solution: 50 mg/mL of Tioconazole in methanol

Developing solvent system: Chloroform, methanol, and glacial acetic acid (40:5:1)

Visualizing solution: Dissolve 0.85 g of bismuth subnitrate in 10 mL of glacial acetic acid, and dilute with water to 50 mL. Mix 10 mL of this solution, 50 mL of potassium iodide solution (2 in 25), and 20 mL of glacial acetic acid, and dilute to 100 mL.

Chromatographic system

(See *Chromatography* ⟨621⟩, *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 10 µL

Analysis

Samples: *Standard solution* and *Sample solution*

Develop the chromatogram until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber and locate the spots on the plate by viewing under short- and long-wavelength UV light after drying the plate at 80° for 5 min. Spray the plate with *Visualizing solution*, air-dry for 2 min, and overspray with sodium nitrite solution (1 in 20). Air-dry the plate for 5 min, and examine it for brown spots on a pale yellow background.

Acceptance criteria: The R_F value of the principal spot from the *Sample solution* corresponds to that from the *Standard solution.*

- **C.** The retention time of the major peak for tioconazole of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**

Mobile phase: Acetonitrile, methanol, and water (44:40:28). Degas the solution, and add 2.0 mL of ammonium hydroxide. [Note—Prepare the *Mobile phase* fresh daily.]

Standard solution: 200 µg/mL of USP Tioconazole RS in methanol

Sample solution: 200 µg/mL of Tioconazole in methanol

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 219 nm

Column: 5-mm × 25-cm; packing L1 with a precolumn containing packing L4 installed between the pump and the injector. [Note—Replace the precolumn daily.]

Flow rate: Adjust to obtain a retention time of between 12 and 17 min for tioconazole.

Injection size: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1000 theoretical plates, determined from the analyte peak

Tailing factor: NMT 2.0 for the analyte peak

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{16}H_{13}Cl_3N_2OS$ in the Tioconazole taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Tioconazole RS in the *Standard solution* (mg/mL)
C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 97.0%–103.0%

IMPURITIES

Inorganic Impurities

- **Residue on Ignition ⟨281⟩:** NMT 0.2%
- **Chloride and Sulfate,** *Chloride* **⟨221⟩:** A 0.7-g portion dissolved in methanol shows no more chloride than corresponds to 0.50 mL of 0.020 N hydrochloric acid (0.05%).
- **Heavy Metals,** *Method II* **⟨231⟩:** NMT 50 ppm

Organic Impurities

- **Procedure**

Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay.*

Standard solution: Dissolve 1 mg each of USP Tioconazole Related Compound A RS, USP Tioconazole Related Compound B RS, and USP Tioconazole Related Compound C RS in 15.0 mL of methanol, and shake until the contents are completely dissolved.

Sample solution: Dissolve 100 mg of Tioconazole in 15.0 mL of methanol, and shake until the substance is completely dissolved.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate, in turn, the percentages of 1-[2,4-dichloro-*β*-[(3-thenyl)-oxy]phenethyl]imidazole hydrochloride (tioconazole related compound A), 1-[2,4-dichloro-*β*-[(2,5-dichloro-3-thenyl)-oxy]phenethyl]imidazole hydrochloride (tioconazole related compound B), and 1-[2,4-dichloro-*β*-[(5-bromo-2-chloro-3-thenyl)-oxy]phenethyl]imidazole hydrochloride (tioconazole related compound C) in the portion of Tioconazole taken:

$$\text{Result} = (r_U/r_S) \times (W_I/W_U) \times 100$$

r_U = peak response of the related compound from the *Sample solution*

r_S = peak response of the related compound from the *Standard solution*
W_I = weight of the respective USP Reference Standard taken to prepare the *Standard solution* (mg)
W_U = weight of Tioconazole taken to prepare the *Sample solution* (mg)

Acceptance criteria: The limit of each related compound is NMT 1.0%.

SPECIFIC TESTS

- **Water Determination,** *Method I* ⟨**921**⟩**:** NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers.
- **USP Reference Standards** ⟨**11**⟩
  USP Tioconazole RS
  USP Tioconazole Related Compound A RS
  1-[2,4-Dichloro-β-[(3-thenyl)-oxy]phenethyl]imidazole hydrochloride.
  $C_{16}H_{14}Cl_2N_2OS \cdot HCl$ 389.73
  USP Tioconazole Related Compound B RS
  1-[2,4-Dichloro-β-[(2,5-dichloro-3-thenyl)oxy]phenethyl] imidazole hydrochloride.
  $C_{16}H_{12}Cl_4N_2OS \cdot HCl$ 458.62
  USP Tioconazole Related Compound C RS
  1-[2,4-Dichloro-β-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]imidazole hydrochloride.
  $C_{16}H_{13}BrCl_2N_2OS \cdot HCl$ 468.63

Titanium Dioxide

TiO_2 79.87
Titanium oxide (TiO_2).
Titanium oxide (TiO_2) [13463-67-7].

» Titanium Dioxide contains not less than 99.0 percent and not more than 100.5 percent of TiO_2, calculated on the dried basis. If labeled as attenuation grade, then Titanium Dioxide contains not less than 99.0 percent and not more than 100.5 percent of TiO_2, calculated on the ignited basis. Attenuation grade material may contain suitable coatings, stabilizers, and treatments to assist formulation.

NOTE—If labeled as attenuation grade, then all tests and assays are conducted on uncoated, untreated material. For UV attenuation grade, the test for *Loss on drying* does not apply. The FDA requires the content of lead to be not more than 10 ppm, that of antimony to be not more than 2 ppm, and that of mercury to be not more than 1 ppm (21 CFR 73.1575).

Packaging and storage—Preserve in well-closed containers.

Labeling—If intended for UV-attenuation, the material must be labeled as attenuation grade. If intended for UV-attenuation, and any added coatings, stabilizers, or treatments are used, the labeling shall include the name and amount of the additives.

Identification—To 500 mg add 5 mL of sulfuric acid, and heat gently. After fumes of sulfur trioxide appear, continue heating for a minimum of 10 seconds. Cool the suspension, and cautiously dilute with water to 100 mL. Filter, and to 5 mL of the clear filtrate add a few drops of hydrogen peroxide TS: a yellow-red to orange-red color develops immediately.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 0.5% of its weight.

Loss on ignition ⟨733⟩—Ignite 2 g, previously dried and accurately weighed, at 800 ± 25° to constant weight: it loses not more than 0.5% of its weight. If labeled as attenuation grade, ignite 4 g of titanium dioxide, accurately weighed, at 800 ± 25° to constant weight: it loses not more than 13% of its weight.

Water-soluble substances—Suspend 4.0 g in 50 mL of water, mix, and allow to stand overnight. Transfer to a 200-mL volumetric flask, add 2 mL of ammonium chloride TS, and mix. If the Titanium Dioxide does not settle, add another 2-mL portion of ammonium chloride TS. Allow the suspension to settle, dilute with water to volume, mix, and filter through a double thickness of fine-porosity filter paper, discarding the first 10 mL of the filtrate. Collect 100 mL of the clear filtrate, transfer to a tared platinum dish, evaporate on a hot plate to dryness, and ignite at a dull red heat to constant weight: the residue weighs not more than 5 mg (0.25%).

Acid-soluble substances—Suspend 5.0 g in 100 mL of 0.5 N hydrochloric acid, and heat on a steam bath for 30 minutes, with occasional stirring. Filter through an appropriate filter medium until clear. Wash with three 10-mL portions of 0.5 N hydrochloric acid. Evaporate the combined filtrate and washings to dryness, and ignite at a dull red heat to constant weight: the residue weighs not more than 25 mg (0.5%).

Arsenic, *Method I* ⟨211⟩—Prepare the *Test Preparation* as follows. Add 3.0 g to a 250-mL conical flask fitted with a thermometer and a vapor outlet. Add 50 mL of water, 500 mg of hydrazine sulfate, 500 mg of potassium bromide, 20 g of sodium chloride, and 25 mL of sulfuric acid. Arrange to collect the evolved vapors in 52 mL of water contained in the arsine generator flask, then heat the test specimen to 90°, and maintain the temperature at 90° to 100° for 15 minutes. Add 3 mL of hydrochloric acid to the solution in the generator flask: the resulting solution meets the requirements of the test, the addition of 20 mL of 7 N sulfuric acid specified for *Procedure* being omitted. The limit is 1 ppm.

Assay—Accurately weigh about 300 mg of Titanium Dioxide, transfer to a 250-mL beaker, and add 20 mL of sulfuric acid and 7 to 8 g of ammonium sulfate. Mix, heat on a hot plate until fumes of sulfur trioxide appear, and continue heating over a strong flame until solution is complete or it is apparent that the undissolved residue is siliceous matter. Cool, cautiously dilute with 100 mL of water, stir, heat carefully to boiling while stirring, and allow the insoluble matter to settle. Filter, transfer the entire residue to the filter, and wash thoroughly with cold 2 N sulfuric acid. Dilute the filtrate with water to 200 mL, and cautiously add about 10 mL of ammonium hydroxide.

Prepare a zinc amalgam column in a 25-cm Jones reductor tube, placing a pledget of glass wool in the bottom of the tube, and filling the constricted portion of the tube with zinc amalgam prepared as follows. Add 20- to 30-mesh zinc to mercuric chloride solution (1 in 50), using about 100 mL of the solution for each 100 g of zinc, and after about 10 minutes, decant the solution from the zinc, then wash the zinc by decantation. Wash the zinc amalgam column with 100-mL portions of 2 N sulfuric acid until 100 mL of the washing does not decolorize 1 drop of 0.1 N potassium permanganate.

Place 50 mL of ferric ammonium sulfate TS in a 1000-mL suction flask, and add 0.1 N potassium permanganate until a faint pink color persists for 5 minutes. Attach the Jones reductor tube to the neck of the flask, and pass 50 mL of 2 N sulfuric acid through the reductor at a rate of about 30 mL per minute. Pass the prepared titanium solution through the reductor at the same rate, and follow with 100 mL each of 2 N sulfuric acid and of water. During these operations, keep the reductor filled with solution or water above the upper level of the amalgam. Taking precautions against the admission of atmospheric oxygen, gradually release the suction, wash down the outlet tube of the reductor and the sides of the receiver, and titrate immediately with 0.1 N potassium permanganate VS. Perform a blank determination, substituting 200 mL of 2 N sulfuric acid for the assay solution, and make any necessary correction. Each mL of 0.1 N potassium permanganate is equivalent to 7.988 mg of TiO_2.