Saccharin

$C_7H_5NO_3S$ 183.18
1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide;
1,2-Benzisothiazolin-3-one 1,1-dioxide [81-07-2].

DEFINITION
Saccharin contains NLT 99.0% and NMT 101.0% of $C_7H_5NO_3S$, calculated on the dried basis.

IDENTIFICATION
- **INFRARED ABSORPTION** ⟨197K⟩

ASSAY
- **PROCEDURE**
  Sample: 500 mg
  Analysis: Dissove the *Sample* in 40 mL of alcohol. Add 40 mL of water and phenolphthalein TS. Titrate with 0.1 N sodium hydroxide. Perform a blank titration, if necessary, and make the appropriate correction. Each mL of 0.1 N sodium hydroxide is equivalent to 18.32 mg of $C_7H_5NO_3S$.
  Acceptance criteria: 99.0%–101.0% on the dried basis

IMPURITIES
Inorganic Impurities
- **RESIDUE ON IGNITION** ⟨281⟩: NMT 0.2%. The ignition temperature is 600 ± 50°.
- **HEAVY METALS**, *Method II* ⟨231⟩: NMT 10 ppm

Organic Impurities
- **PROCEDURE 1: LIMIT OF TOLUENESULFONAMIDES**
  Internal standard solution: 0.25 mg/mL of caffeine in methylene chloride
  Standard stock solution: 20.0 µg/mL of USP *o*-Toluenesulfonamide RS and 20.0 µg/mL of USP *p*-Toluenesulfonamide RS in methylene chloride
  Standard solution: Evaporate 5.0 mL of the *Standard stock solution* to dryness in a stream of nitrogen. Dissolve the residue in 1 mL of the *Internal standard solution*.
  Sample solution: Suspend 10 g of Saccharin in 20 mL of water, and dissolve using 5–6 mL of 10 N sodium hydroxide. If necessary, adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 7–8, and dilute with water to 50 mL. Shake the solution with four quantities each of 50 mL of methylene chloride. Combine the lower layers, dry over anhydrous sodium sulfate, and filter. Wash the filter and the sodium sulfate with 10 mL of methylene chloride. Combine the solution and the washings, and evaporate almost to dryness in a water bath at a temperature not exceeding 40°. Using a small quantity of methylene chloride, quantitatively transfer the residue into a suitable 10-mL tube, evaporate to dryness in a stream of nitrogen, and dissolve the residue in 1.0 mL of the *Internal standard solution*.
  Blank solution: Evaporate 200 mL of methylene chloride to dryness in a water bath at a temperature not exceeding 40°. Dissolve the residue in 1 mL of methylene chloride.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: GC
  Detector: Flame ionization
  Column: 0.53-mm × 10-m fused silica column, coated with G3 phase (film thickness 2 µm)
  Temperature
  Injector: 250°
  Detector: 250°
  Column: 180°
  Carrier gas: Nitrogen
  Flow rate: 10 mL/min
  Injection size: 1 µL
  Split ratio: 2:1
  System suitability
  Samples: *Standard solution* and *Blank solution*
  [NOTE—The substances are eluted in the following order: *o*-toluenesulfonamide, *p*-toluenesulfonamide, and caffeine.]
  Suitability requirements: No peaks at the retention times for the internal standard, *o*-toluenesulfonamide, or *p*-toluenesulfonamide; *Blank solution*
  Resolution: NLT 1.5 between *o*-toluenesulfonamide and *p*-toluenesulfonamide, *Standard solution*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Acceptance criteria: If any peaks due to *o*-toluenesulfonamide and *p*-toluenesulfonamide appear in the chromatogram obtained with the *Sample solution*, the ratio of their areas to that of the *Internal standard solution* is NMT the corresponding ratio in the chromatogram obtained with the *Standard solution*.
  Individual impurities: See *Impurity Table 1*.

Impurity Table 1

Name	Acceptance Criteria (ppm)
o-Toluenesulfonamide	10
p-Toluenesulfonamide	10

- **PROCEDURE 2: LIMIT OF BENZOATE AND SALICYLATE**
  Sample solution: 10 mL of a hot, saturated solution of saccharin
  Analysis: Add ferric chloride TS dropwise to the *Sample solution*.
  Acceptance criteria: No precipitate or violet color appears in the liquid.

SPECIFIC TESTS
- **MELTING RANGE OR TEMPERATURE** ⟨741⟩: 226°–230°
- **LOSS ON DRYING** ⟨731⟩: Dry a sample at 105° for 2 h: it loses NMT 1.0% of its weight.
- **READILY CARBONIZABLE SUBSTANCES TEST** ⟨271⟩
  Sample solution: 40 mg/mL in sulfuric acid (94.5%–95.5% [w/w] of H_2SO_4), maintained at 48°–50° for 10 min
  Acceptance criteria: The *Sample solution* has no more color than *Matching Fluid A*, when viewed against a white background.
- **CLARITY OF SOLUTION**
  [NOTE—The *Sample solution* is to be compared to *Reference suspension A* and to water in diffused daylight 5 min after preparation of *Reference suspension A*.]
  Diluent: 200-g/L solution of sodium acetate
  Hydrazine solution: 10.0 mg/mL of hydrazine sulfate. [NOTE—Allow to stand for 4–6 h.]
  Methenamine solution: Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.
  Primary opalescent suspension: Transfer 25.0 mL of *Hydrazine solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 h. [NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use. Allow the suspension to stand for 24 h.]
  Opalescence standard: Dilute 15.0 mL of the *Primary opalescent suspension* with water to 1000 mL. [NOTE—This suspension should not be used beyond 24 h after preparation.]
  Reference suspension A: *Opalescence standard* and water (1 in 20)

Temperature . Injector: 250° Saccharin

Detector: 250° Column: 180° Carrier gas: Nitrogen Flow rate: 10 mL/min Injection size: 1 µL Split ratio: 2:1

System suitability

C 1,2-Benzisothiazol-3(2H)-one, 7

H

5

NO

3

S 183.18 Samples: Standard solution and Blank solution 1,1-dioxide; 1,2-Benzisothiazolin-3-one 1,1-dioxide [81-07-2]. [NOTE—The substances are eluted in the following order:

o-toluenesulfonamide, p-toluenesulfonamide, and caffeine.]

DEFINITION Saccharin contains calculated on NLT 99.0% and the dried basis.

NMT 101.0% of C

7

H

5

NO

3

S,

Suitability requirements: No peaks at the retention

times for the internal standard, o-toluenesulfonamide, or p-toluenesulfonamide; Blank solution Resolution: NLT 1.5 between o-toluenesulfonamide and IDENTIFICATION

• INFRARED ABSORPTION ⟨197K⟩

p-toluenesulfonamide, Standard solution Analysis

Samples: Standard solution and Sample solution ASSAY

• PROCEDURE Sample: 500 mg Analysis: Dissove the Sample in 40 mL of alcohol. Add 40

mL of water and phenolphthalein TS. Titrate with 0.1 N so- dium hydroxide. Perform a blank titration, if necessary, and make the appropriate correction. Each mL of 0.1 N sodium

Acceptance criteria: If any peaks due to o-toluenesulfona- mide and p-toluenesulfonamide appear in the chromatogram obtained with the Sample solution, the ratio of their areas to that of the Internal standard solution is NMT the corresponding ratio in the chromatogram obtained with the Standard solution.

Individual impurities: See Impurity Table 1.

hydroxide Acceptance is equivalent to criteria: 99.0%–101.0% 18.32 mg of on C

the 7 H

5

NO dried 3 S.

basis

Impurity Table 1

IMPURITIES Inorganic Impurities Acceptance Criteria Name (ppm) • RESIDUE ON IGNITION ⟨281⟩: NMT 0.2%. The ignition temper-

o-Toluenesulfonamide 10 ature is 600 ± 50°.

• HEAVY METALS, Method II ⟨231⟩: NMT 10 ppm

p-Toluenesulfonamide 10

Organic Impurities

• PROCEDURE 2: LIMIT OF BENZOATE AND SALICYLATE • PROCEDURE 1: LIMIT OF TOLUENESULFONAMIDES

Sample solution: 10 mL of a hot, saturated solution of Internal standard solution: 0.25 mg/mL of caffeine in

saccharin methylene chloride Analysis: Add ferric chloride TS dropwise to the Sample Standard stock solution: 20.0 µg/mL of USP o-Toluenesul-

solution. fonamide RS and 20.0 µg/mL of USP p-Toluenesulfonamide Acceptance criteria: No precipitate or violet color appears RS in methylene chloride in the liquid. Standard solution: Evaporate 5.0 mL of the Standard stock

solution to dryness in a stream of nitrogen. Dissolve the residue in 1 mL of the Internal standard solution. Sample solution: Suspend 10 g of Saccharin in 20 mL of

water, and dissolve using 5–6 mL of 10 N sodium hydrox- ide. If necessary, adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 7–8, and dilute with water to 50 mL. Shake the solution with four quanti-

SPECIFIC TESTS

• MELTING RANGE OR TEMPERATURE ⟨741⟩: 226°–230°

• LOSS ON DRYING ⟨731⟩: Dry a sample at 105° for 2 h: it loses

NMT 1.0% of its weight.

• READILY CARBONIZABLE SUBSTANCES TEST ⟨271⟩ Sample solution: 40 mg/mL in sulfuric acid (94.5%–95.5%

[w/w] of H

2

SO ties each of 50 mL of methylene chloride. Combine the lower layers, dry over anhydrous sodium sulfate, and filter. Wash the filter and the sodium sulfate with 10 mL of meth- ylene chloride. Combine the solution and the washings, and evaporate almost to dryness in a water bath at a tem- perature not exceeding 40°. Using a small quantity of methylene chloride, quantitatively transfer the residue into a suitable 10-mL tube, evaporate to dryness in a stream of nitrogen, and dissolve the residue in 1.0 mL of the Internal standard solution. Blank solution: Evaporate 200 mL of methylene chloride to

dryness in a water bath at a temperature not exceeding 40°. Dissolve the residue in 1 mL of methylene chloride. Chromatographic system

(See Chromatography ⟨621⟩, System Suitability.)

Mode: GC Detector: Flame ionization Column: 0.53-mm × 10-m fused silica column, coated

with G3 phase (film thickness 2 µm)

Acceptance criteria: 4

), maintained at 48°–50° for 10 min

The Sample solution has no more color than Matching Fluid A, when viewed against a white background.

• CLARITY OF SOLUTION [NOTE—The Sample solution is to be compared to Reference suspension A and to water

in diffused daylight 5 min after preparation of Reference suspension A.] Diluent: 200-g/L solution of sodium acetate Hydrazine solution: 10.0 mg/mL of hydrazine sulfate.

[NOTE—Allow to stand for 4–6 h.] Methenamine solution: Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve. Primary opalescent suspension: Transfer 25.0 mL of Hydra-

zine solution to the Methenamine solution in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 h. [NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use. Allow the suspension to stand for 24 h.] Opalescence standard: Dilute 15.0 mL of the Primary opal- escent suspension with water to 1000 mL. [NOTE—This sus- pension should not be used beyond 24 h after preparation.] Reference suspension A: Opalescence standard and water (1

in 20)

Reference suspension B: *Opalescence standard* and water (1 in 10)
Sample solution: 200 mg/mL in *Diluent*
Analysis
Samples: *Diluent, Reference suspension A, Reference suspension B, Sample solution,* and water
Transfer a sufficient portion of the *Sample solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Reference suspension A, Reference suspension B,* water, and *Diluent* to separate matching test tubes. Compare the solutions in diffused daylight, viewing vertically against a black background (see *Spectrophotometry and Light-Scattering* ⟨851⟩, *Visual Comparison*). [NOTE—The diffusion of light must be such that *Reference suspension A* can readily be distinguished from water, and that *Reference suspension B* can readily be distinguished from *Reference suspension A.*]
Acceptance criteria: The *Sample solution* shows the same clarity as that of water, or *Diluent,* or its opalescence is NMT that of *Reference suspension A.*

- **COLOR OF SOLUTION**

Diluent A: 200-g/L solution of sodium acetate
Diluent B: 10-g/L solution of hydrochloric acid
Standard stock solution: Ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and *Diluent B* (3.0:3.0:2.4:1.6)
Standard solution: *Standard stock solution* and *Diluent B* (1 in 100). [NOTE—Prepare the *Standard solution* immediately before use.]
Sample solution: Use the *Sample solution* from the test for *Clarity of Solution.*
Analysis
Samples: *Diluent A, Standard solution, Sample solution,* and water
Transfer a sufficient portion of the *Sample solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm to obtain a depth of 40 mm. Similarly transfer portions of the *Standard solution, Diluent A,* and water to separate, matching test tubes. Compare the solutions in diffused daylight, viewing vertically against a white background (see *Spectrophotometry and Light-Scattering* ⟨851⟩, *Visual Comparison*).
Acceptance criteria: The *Sample solution* has the appearance of water or *Diluent A,* or is not more intensely colored than the *Standard solution.*

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at room temperature.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Saccharin RS
  USP *o*-Toluenesulfonamide RS
  USP *p*-Toluenesulfonamide RS

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Reference suspension B: Opalescence standard and water (1 Sample solution: Use the Sample solution from

the test for

in 10) Clarity of Solution. Sample solution: 200 mg/mL in Diluent Analysis Analysis Samples: Diluent A, Standard solution, Sample solution, and

Samples: Diluent, Reference suspension A, Reference suspen- water

sion B, Sample solution, and water Transfer a sufficient portion of the Sample solution to a test Transfer a sufficient portion of the Sample solution to a test tube of colorless, transparent, neutral glass with a flat base tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm to obtain a depth and an internal diameter of 15–25 mm to obtain a depth of 40 mm. Similarly transfer portions of the Standard solu- of 40 mm. Similarly transfer portions of Reference suspen- tion, Diluent A, and water to separate, matching test tubes. sion A, Reference suspension B, water, and Diluent to sepa- Compare the solutions in diffused daylight, viewing verti- rate matching test tubes. Compare the solutions in dif- cally against a white background (see Spectrophotometry fused daylight, viewing vertically against a black and Light-Scattering ⟨851⟩, Visual Comparison). background (see Spectrophotometry and Light-Scattering Acceptance criteria: The Sample solution has the appear- ⟨851⟩, Visual Comparison). [NOTE—The diffusion of light ance of water or Diluent A, or is not more intensely colored must be such that Reference suspension A can readily be than the Standard solution. distinguished from water, and that Reference suspension B

ADDITIONAL REQUIREMENTS can readily be distinguished from Reference suspension A.]

• PACKAGING AND STORAGE: Preserve in well-closed containers. Acceptance criteria: The Sample solution shows the same

Store at room temperature. clarity as that of water, or Diluent, or its opalescence is NMT

• USP REFERENCE STANDARDS ⟨11⟩ that of Reference suspension A.

USP Saccharin RS

• COLOR OF SOLUTION

USP o-Toluenesulfonamide RS Diluent A: 200-g/L solution of sodium acetate

USP p-Toluenesulfonamide RS Diluent B: 10-g/L solution of hydrochloric acid Standard stock solution: Ferric chloride CS, cobaltous chlo-

ride CS, cupric sulfate CS, and Diluent B (3.0:3.0:2.4:1.6) Standard solution: Standard stock solution and Diluent B (1 in 100). [NOTE—Prepare the Standard solution immediately before use.]