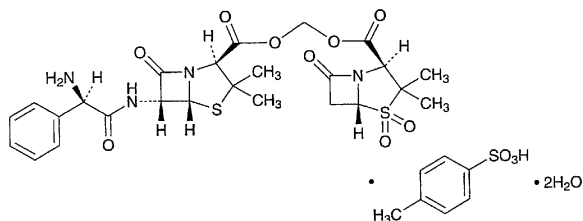


Sultamicillin Tosilate

トシル酸スルタミシリン



$C_{25}H_{30}N_4O_9S_2 \cdot C_7H_8O_3S \cdot 2H_2O$: 802.89
 (2*S*,5*R*)-(3,3-Dimethyl-4,4,7-trioxo-4-thia-1-azabicyclo[3.2.0]hept-2-ylcarbonyloxy)methyl (2*S*,5*R*,6*R*)-6-[(2*R*)-2-amino-2-phenylacetyl-amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monotosylate dihydrate [83105-70-8, anhydride]

Sultamicillin Tosilate contains not less than 698 μ g (potency) per mg, calculated on the anhydrous basis and corrected by the amount of ethyl acetate. The potency of Sultamicillin Tosilate is expressed as mass (potency) of sultamicillin ($C_{25}H_{30}N_4O_9S_2$: 594.66).

Description Sultamicillin Tosilate occurs as a white to yellowish white crystalline powder.

It is freely soluble in acetonitrile, in methanol and in ethanol (99.5), and very slightly soluble in water.

Identification Determine the infrared absorption spectrum of Sultamicillin Tosilate as directed in the paste method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of Sultamicillin Tosilate Reference Standard: both spectra exhibit similar intensities of absorption at the same wave numbers.

Optical rotation $[\alpha]_D^{20}$: +173 – +187° (0.5 g calculated on the anhydrous bases, a mixture of water and acetonitrile (3:2), 25 mL, 100 mm).

Purity (1) Heavy metals—Proceed with 1.0 g of Sultamicillin Tosilate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL Standard Lead Solution (not more than 20 ppm).

(2) **Arsenic**—Prepare the test solution with 1.0 g of Sultamicillin Tosilate, according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

(3) **Ampicillin**—Perform the procedure rapidly. Weigh accurately about 0.020 g of Sultamicillin Tosilate, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the sample solution. Separately, weigh accurately about 0.02 g (potency) of Ampicillin Reference Standard, dissolve in the mobile phase to make exactly 100 mL. Pipet 6 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μ L each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the area of the peak of ampicillin by the automatic integration method: the peak area from the sample solution is not more than that from the standard solution.

Operating conditions—

Detector, column, and column temperature: Proceed as directed in the operating conditions in the Assay.

Mobile phase: Dissolve 3.12 g of sodium dihydrogenphosphate in about 750 mL of water, adjust to pH 3.0 with diluted phosphoric acid (1 in 10), and add water to make 1000 mL. To 80 mL of acetonitrile for liquid chromatography add this solution to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of ampicillin is about 14 minutes.

System suitability—

System performance: Dissolve 0.012 g of Ampicillin Reference Standard, 4 mg of Sulbactam Reference Standard and 4 mg of *p*-toluenesulfonic acid monohydrate in 1000 mL of the mobile phase. When the procedure is run with 25 μ L of this solution under the above operating conditions, sulbactam, *p*-toluenesulfonic acid and ampicillin are eluted in this order with the resolution between these peaks being not less than 2.0.

System repeatability: When the test is repeated 6 times with 25 μ L of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of ampicillin is not more than 1.0%.

(4) **Sulbactam**—Perform the procedure rapidly. Weigh accurately about 0.020 g of Sultamicillin Tosilate, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the sample solution. Separately, weigh accurately an amount of Sulbactam Reference Standard, equivalent to about 0.02 g (potency), dissolve in the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μ L each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the area of the peak of sulbactam by the automatic integration method: the peak area from the sample solution is not more than that from the standard solution.

Operating conditions—

Proceed as directed in the operating conditions in the Purity (3).

System suitability—

Proceed as directed in the system suitability in the Purity (3).

(5) **Penicilloic acids**—Weigh accurately about 0.025 g of penicilloic acid, dissolve in 1 mL of acetonitrile, and add 25 mL of 0.02 mol/L phosphate buffer solution, pH 3.0, in a 100-mL flask with stopper. Add exactly 5 mL of 0.005 mol/L iodine VS, and allow to stand the stoppered flask for 5 minutes. Titrate with 0.005 mol/L sodium thiosulfate VS (indicator: 1.0 mL of starch TS). Perform a blank determination in the same manner, and make any necessary correction. Calculate the amount of penicilloic acid ($C_{25}H_{34}N_4O_{11}S_2$: 630.70) by using the following equation: it is not more than 3.0%.

$$\text{Each mL of 0.005 mol/L sodium thiosulfate VS} \\ = 0.25848 \text{ mg of } C_{25}H_{34}N_4O_{11}S_2$$

(6) **Ethyl acetate**—Weigh accurately about 0.1 g of Sultamicillin Tosilate, dissolve in 2 mL of methanol, add water to make exactly 20 mL, and use this solution as the sample solution. Separately, weigh accurately about 1 g of ethyl acetate, and mix with water to make exactly 200 mL. Pipet

2 mL of this solution, add 10 mL of methanol and water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 5 μ L each of the sample solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and determine the peak areas, A_T and A_S , of ethyl acetate of these solutions. Calculate the amount of ethyl acetate by the following equation: not more than 2.0%.

Amount (%) of ethyl acetate

$$= \frac{\text{amount (mg) of ethyl acetate}}{\text{amount (mg) of the sample}} \times \frac{A_T}{A_S} \times \frac{1}{5}$$

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A column 3 mm in inside diameter and 1 m in length, packed with porous styrene-divinylbenzene copolymer for gas chromatography (0.0085 μ m in average pore size and 300 – 400 m²/g in specific surface area) (150 to 180 μ m in particle diameter).

Column temperature: A constant temperature of about 155°C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of ethyl acetate is about 6 minutes.

System suitability—

System performance: When the procedure is run with 5 μ L of the standard solution under the above operating conditions, the number of theoretical steps and the symmetry coefficient of the peak of ethyl acetate are not less than 500 steps and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 5 μ L of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of ethyl acetate is not more than 5%.

Water 4.0 – 6.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition Not more than 0.20% (1 g).

Assay Perform the procedure rapidly. Weigh accurately an amount of Sultamicillin Tosilate and Sultamicillin Tosilate Reference Standard, equivalent to about 0.05 g (potency), dissolve each in the mobile phase to make exactly 50 mL. Pipet 5 mL each of these solutions, add exactly 5 mL of the internal standard solution, add the mobile phase to make 25 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 10 μ L each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S , of the peak area of sultamicillin to that of the internal standard of each solution.

$$\begin{aligned} &\text{Amount } [\mu\text{g (potency)}] \text{ of sultamicillin (C}_{25}\text{H}_{30}\text{N}_4\text{O}_9\text{S}_2) \\ &= \text{amount [mg (potency)] of Sultamicillin Tosilate} \\ &\quad \text{Reference Standard} \\ &\quad \times \frac{Q_T}{Q_S} \times 1000 \end{aligned}$$

*Internal standard solution—*A solution of isopropyl-4-aminobenzoate in the mobile phase (1 in 2500).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column 3.9 mm in inside di-

ameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μ m in particle diameter).

Column temperature: A constant temperature of about 35°C.

Mobile phase: Dissolve 3.12 g of sodium dihydrogenphosphate in about 750 mL of water, adjust to pH 3.0 with diluted phosphoric acid (1 in 10), and add water to make 1000 mL. To 400 mL of acetonitrile for liquid chromatography add this solution to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of sultamicillin is about 4 minutes.

System suitability—

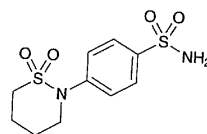
System performance: When the procedure is run with 10 μ L of the standard solution under the above operating conditions, *p*-toluenesulfonic acid, sultamicillin and the internal standard are eluted in this order with the resolution between these peaks being not less than 2.0.

System repeatability: When the test is repeated 6 times with 10 μ L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sultamicillin is not more than 2.0%.

Containers and storage Containers—Tight containers.

Sultiamе

スルチアム



C₁₀H₁₄N₂O₄S₂: 290.36

4-(Tetrahydro-2H-1,2-thiazin-2-yl)benzenesulfonamide S,S-dioxide [61-56-3]

Sultiamе, when dried, contains not less than 98.5% of C₁₀H₁₄N₂O₄S₂.

Description Sultiamе occurs as white crystals or crystalline powder. It is odorless, and has a slightly bitter taste.

It is very soluble in *N,N*-dimethylformamide, freely soluble in *n*-butylamine, slightly soluble in methanol and in ethanol (95), very slightly soluble in water, and practically insoluble in diethyl ether.

It dissolves in sodium hydroxide TS.

Identification (1) Dissolve 0.02 g of Sultiamе in 5 mL of water and 1 mL of *n*-butylamine, add 2 to 3 drops of copper (II) sulfate TS, and shake well. To this solution add 5 mL of chloroform, shake, and allow to stand: a green color develops in the chloroform layer.

(2) Mix 0.1 g of Sultiamе with 0.5 g of sodium carbonate decahydrate, and melt carefully: the gas evolved changes moistened red litmus paper to blue. After cooling, crush the fused substance with a glass rod, stir with 10 mL of water, and filter. To 4 mL of the filtrate add 2 drops of hydrogen peroxide (30), 5 mL of diluted hydrochloric acid (1 in 5) and 2 to 3 drops of barium chloride TS: a white precipitate is formed.