

4-(Dipropylaminosulfonyl)benzoic acid [57-66-9]

Probenecid, when dried, contains not less than 98.0% of  $C_{13}H_{19}NO_4S$ .

**Description** Probenecid occurs as white crystals or crystalline powder. It is odorless, and has a slightly bitter taste, followed by unpleasant bitter.

Probenecid is sparingly soluble in ethanol (95), slightly soluble in diethyl ether, and practically insoluble in water.

It dissolves in sodium hydroxide TS and in ammonia TS. Melting point: 198 – 200°C

**Identification (1)** Heat Probenecid strongly: the odor of sulfur dioxide is perceptible.

(2) Determine the absorption spectrum of a solution of Probenecid in ethanol (95) (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Probenecid Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

**Purity (1) Acid**—To 2.0 g of Probenecid add 100 mL of water, heat on a water bath with occasional shaking for 30 minutes, cool, and filter. To the filtrate add 1 drop of phenolphthalein TS and 0.50 mL of 0.1 mol/L sodium hydroxide VS: a red color develops.

(2) Chloride—To 1.0 g of Probenecid add 100 mL of water and 1 mL of nitric acid, and heat on a water bath with occasional shaking for 30 minutes. After cooling, add, if necessary, water to make 100 mL, and filter. Perform the test using 50 mL of the filtrate as the test solution. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid VS (not more than 0.021%).

(3) Sulfate—To 1.0 g of Probenecid add 100 mL of water and 1 mL of hydrochloric acid, and heat on a water bath with occasional shaking for 30 minutes. After cooling, add, if necessary, water to make 100 mL, and filter. Perform the test using 50 mL of the filtrate as the test solution. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS (not more than 0.038%).

(4) Heavy metals—Proceed with 2.0 g of Probenecid according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

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

**Loss on drying** Not more than 0.5% (1 g, 105°C, 4 hours).

**Residue on ignition** Not more than 0.10% (1 g).

**Assay** Weigh accurately about 0.5 g of Probenecid, previously dried, and dissolve in 50 mL of neutralized ethanol. Titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS  
= 28.536 mg of  $C_{13}H_{19}NO_4S$

**Containers and storage** Containers—Well-closed containers.

## Probenecid Tablets

プロベネシド錠

Probenecid Tablets contain not less than 95% and not more than 105% of the labeled amount of probenecid ( $C_{13}H_{19}NO_4S$ : 285.36).

**Method of preparation** Prepare as directed under Tablets, with Probenecid.

**Identification (1)** Weigh a quantity of powdered Probenecid Tablets, equivalent to 0.5 g of Probenecid according to the labeled amount, add 50 mL of ethanol (95) and 1 mL of 1 mol/L hydrochloric acid TS, shake, and filter. Evaporate the filtrate on a water bath to about 20 mL. After cooling, collect produced crystals, recrystallize with 50 mL of dilute ethanol, and dry at 105°C for 4 hours: it melts between 198°C and 200°C. With the crystals so obtained, proceed as directed in the Identification (1) under Probenecid.

(2) Determine the absorption spectrum of a solution of the dried crystals obtained in (1) in ethanol (95) (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry: it exhibits maxima between 224 nm and 226 nm and between 247 nm and 249 nm, and a minimum between 234 nm and 236 nm.

**Dissolution test** Perform the test with 1 tablet of Probenecid Tablets at 50 revolutions per minute according to Method 2 under the Dissolution Test, using 900 mL of diluted phosphate buffer solution, pH 6.8, (1 in 2) as the test solution. Take 30 mL or more of the dissolved solution 30 minutes after start of the test, and filter through a membrane filter with pore size of not more than 0.8  $\mu$ m. Discard the first 10 mL of the filtrate, pipet the subsequent  $V$  mL, add diluted phosphate buffer solution, pH 6.8, (1 in 2) to make exactly  $V'$  mL so that each mL contains about 14  $\mu$ g of probenecid ( $C_{13}H_{19}NO_4S$ ) according to the labeled amount, and use this solution as the sample solution. Separately, weigh accurately about 0.07 g of Probenecid Reference Standard, previously dried at 105°C for 4 hours, and dissolve in diluted phosphate buffer solution, pH 6.8, (1 in 2) to make exactly 100 mL. Pipet 1 mL of this solution, add diluted phosphate buffer solution, pH 6.8, (1 in 2) to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances,  $A_T$  and  $A_S$ , of the sample solution and the standard solution at 244 nm as directed under the Ultraviolet-visible Spectrophotometry.

The dissolution rate of Probenecid Tablets in 30 minutes is not less than 80%.

Dissolution rate (%) with respect to the labeled amount of probenecid ( $C_{13}H_{19}NO_4S$ )

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 18$$

$W_S$ : Amount (mg) of Probenecid Reference Standard.

$C$ : Labeled amount (mg) of probenecid ( $C_{13}H_{19}NO_4S$ ) in 1 tablet.

**Assay** Weigh accurately, and powder not less than 20 Probenecid Tablets. Weigh accurately a portion of the powder, equivalent to about 0.15 g of probenecid ( $C_{13}H_{19}NO_4S$ ), add 200 mL of ethanol (95) and 5 mL of 1 mol/L

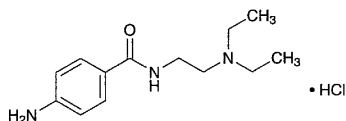
hydrochloric acid TS, and heat on a water-bath at 70°C for 30 minutes with occasional shaking. After cooling, add ethanol (95) to make exactly 250 mL, and filter. Discard the first 20 mL of the filtrate. To 5 mL of the subsequent filtrate, exactly measured, add 5 mL of 0.1 mol/L hydrochloric acid TS, dilute with ethanol (95) to exactly 250 mL, and use this solution as the sample solution. Separately, weigh accurately about 0.15 g of Probenecid Reference Standard, previously dried at 105°C for 4 hours, dissolve in 5 mL of 1 mol/L hydrochloric acid TS, and add ethanol (95) to make exactly 250 mL. Pipet 5 mL of the solution, add 5 mL of 0.1 mol/L hydrochloric acid TS and ethanol (95) to make exactly 250 mL, and use this solution as the standard solution. Determine the absorbances,  $A_T$  and  $A_S$ , of the sample solution and the standard solution at 248 nm as directed under the Ultraviolet-visible Spectrophotometry, using a solution prepared by mixing 5 mL of 0.1 mol/L hydrochloric acid TS and ethanol (95) to make exactly 250 mL as the blank.

$$\begin{aligned} & \text{Amount (mg) of probenecid (C}_{13}\text{H}_{19}\text{NO}_4\text{S)} \\ &= \text{amount (mg) of Probenecid Reference Standard} \\ & \quad \times \frac{A_T}{A_S} \end{aligned}$$

**Containers and storage** Containers—Well-closed containers.

## Procainamide Hydrochloride

塩酸プロカインアミド



$\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}\cdot\text{HCl}$ : 271.79  
4-Amino-*N*-(2-diethylaminoethyl)benzamide  
monohydrochloride [614-39-1]

Procainamide Hydrochloride, when dried, contains not less than 98.0% of  $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}\cdot\text{HCl}$ .

**Description** Procainamide Hydrochloride occurs as a white to light yellow, crystalline powder. It is odorless.

It is very soluble in water, freely soluble in methanol, in acetic acid (100) and in ethanol (95), slightly soluble in acetic anhydride, and practically insoluble in diethyl ether.

It is hygroscopic.

**Identification (1)** Dissolve 1 g of Procainamide Hydrochloride in 10 mL of water, add 10 mL of sodium hydroxide TS, and extract with two 10-mL portions of a mixture of diethyl ether and chloroform (1:1). Combine the extracts, add calcium chloride for drying, and dry the extracts for 30 minutes. Decant the solution into a small flask, add 5 mL of pyridine, and slowly add dropwise 1 mL of benzoyl chloride. Heat the mixture on a water bath for 30 minutes, add 20 mL of a mixture of diethyl ether and chloroform (1:1), shake, and pour the mixture into 100 mL of sodium hydroxide TS, then shake. Separate the organic solvent lay-

er, wash it with 20 mL of water, cool to 10°C, and allow the crystals to separate. Collect the separated crystals, recrystallize from 10 mL of dilute ethanol, and dry at 105°C for 1 hour: the crystals so obtained melt between 180°C and 187°C.

(2) Dissolve 0.01 g of Procainamide Hydrochloride in 1 mL of dilute hydrochloric acid and 4 mL of water: the solution responds to the Qualitative Tests for primary aromatic amines.

(3) A solution of Procainamide Hydrochloride (1 in 20) responds to the Qualitative Tests for chloride.

**pH** Dissolve 1.0 g of Procainamide Hydrochloride in 10 mL of water: the pH of this solution is between 5.0 and 6.5.

**Melting point** 165 – 169°C

**Purity (1)** Clarity of solution—Dissolve 1.0 g of Procainamide Hydrochloride in 10 mL of water: the solution is clear.

(2) Heavy metals—Proceed with 2.0 g of Procainamide Hydrochloride according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(3) Arsenic—Prepare the test solution with 1.0 g of Procainamide Hydrochloride according to Method 1, and perform the test using Apparatus B (not more than 2 ppm).

(4) Related substances—Dissolve 0.20 g of Procainamide Hydrochloride in 10 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 10  $\mu\text{L}$  each of the sample solution and the standard solution on a plate of silica gel for thin-layer chromatography. Then spot 10  $\mu\text{L}$  each of a solution of ammonia solution (28) in methanol (11 in 50) on each of the above spots. Develop the plate with a mixture of chloroform, methanol and ammonia solution (28) (700:300:7) to a distance of about 10 cm, and air-dry the plate. Spray evenly 4-dimethylaminobenzaldehyde TS for spray on the plate: the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

**Loss on drying** Not more than 0.30% (2 g, 105°C, 4 hours).

**Residue on ignition** Not more than 0.10% (2 g).

**Assay** Weigh accurately about 0.5 g of Procainamide Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid (100) (7:3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

$$\begin{aligned} & \text{Each mL of 0.1 mol/L perchloric acid VS} \\ &= 27.179 \text{ mg of } \text{C}_{13}\text{H}_{21}\text{N}_3\text{O}\cdot\text{HCl} \end{aligned}$$

**Containers and storage** Containers—Tight containers.