$C_7H_8ClN_3O_4S_2$: 297.74
6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide [*58-93-5*]

Hydrochlorothiazide, when dried, contains not less than 99.0% of $C_7H_8ClN_3O_4S_2$.

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

It is freely soluble in acetone, sparingly soluble in acetonitrile, very slightly soluble in water and in ethanol (95), and practically insoluble in diethyl ether.

It dissolves in sodium hydroxide TS.

Melting point: about 267°C (with decomposition).

Identification (1) To 5 mg of Hydrochlorothiazide add 5 mL of disodium chlomotropate TS, and allow to stand for 5 minutes: a purple color develops.

(2) Fuse a mixture of 0.1 g of Hydrochlorothiazide and 0.5 g of sodium carbonate decahydrate cautiously: the gas evolved changes moistened red litmus paper to blue. After cooling, crush with a glass rod, add 10 mL of water, stir, 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 produced.

(3) To 4 mL of the filtrate obtained in (2) add 5 mL of dilute nitric acid and 3 drops of silver nitrate TS: a white precipitate is produced.

(4) Dissolve 0.012 g of Hydrochlorothiazide in 100 mL of sodium hydroxide TS. Dilute 10 mL of the solution with water to make 100 mL. Determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Hydrochlorothiazide Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) Chloride—Dissolve 1.0 g of Hydrochlorothiazide in 30 mL of acetone, add 6 mL of dilute nitric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution as follows: to 1.0 mL of 0.01 mol/L hydrochloric acid VS add 30 mL of acetone, 6 mL of dilute nitric acid and water to make 50 mL (not more than 0.036%).

(2) Sulfate—Dissolve 1.0 g of Hydrochlorothiazide in 30 mL of acetone, add 1 mL of dilute hydrochloric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution as follows: to 1.0 mL of 0.005 mol/L sulfuric acid VS add 30 mL of acetone, 1 mL of dilute hydrochloric acid and water to make 50 mL (not more than 0.048%).

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

(4) Primary aromatic amines—Dissolve 0.08 g of Hydrochlorothiazide in acetone to make exactly 100 mL. Measure exactly 1 mL of the solution, add 3.0 mL of dilute hydrochloric acid, 3.0 mL of water and 0.15 mL of sodium nitrite TS, shake, and allow to stand for 1 minute. Shake this solution with 1.0 mL of ammonium amidosulfate TS, allow to stand for 3 minutes, then add 1.0 mL of *N*-(1-naphthyl)-*N'*-diethylethylenediamine oxalate TS, shake, and allow to stand for 5 minutes. Perform the test with this solution as directed under the Ultraviolet-visible Spectrophotometry, using a solution prepared with 1.0 mL of acetone in the same manner as the blank: the absorbance at 525 nm is not more than 0.10.

Loss on drying Not more than 1.0% (1 g, 105°C, 2 hours).

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

Assay Weigh accurately about 0.03 g each of Hydrochlorothiazide and Hydrochlorothiazide Reference Standard, previously dried, and dissolve in 150 mL of the mobile phase, add exactly 10 mL each of the internal standard solution, then add the mobile phase to make 200 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 20 μL each of the sample solution and the standard solution 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 hydrochlorothiazide to that of the internal standard.

$$\text{Amount (mg) of } C_7H_8ClN_3O_4S_2 = \text{amount (mg) of Hydrochlorothiazide Reference Standard} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of 4-aminoacetophenone in acetonitrile (9 in 2000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in inside diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: A mixture of 0.1 mol/L sodium dihydrogenphosphate TS, pH 3.0 and acetonitrile (9:1).

Flow rate: Adjust the flow rate so that the retention time of hydrochlorothiazide is about 10 minutes.

Selection of column: Proceed with 20 μL of the standard solution under the above operating conditions, and calculate the resolution. Use a column giving elution of hydrochlorothiazide and the internal standard in this order with the resolution between these peaks being not less than 4.

Containers and storage Containers—Well-closed containers.

Hydrocortisone

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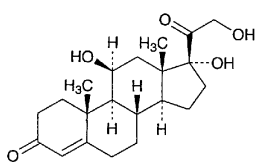

$C_{21}H_{30}O_5$: 362.46
11β,17,21-Trihydroxypregn-4-ene-3,20-dione [*50-23-7*]

Hydrocortisone, when dried, contains not less than 97.0% and not more than 102.0% of $C_{21}H_{30}O_5$.

Description Hydrocortisone occurs as a white, crystalline powder. It is odorless.

It is sparingly soluble in methanol, in ethanol (95) and in 1,4-dioxane, slightly soluble in chloroform, and very slightly soluble in diethyl ether and in water.

Melting point: 212 - 220°C (with decomposition).

Identification (1) Add 2 mL of sulfuric acid to 2 mg of Hydrocortisone: the solution shows a yellow-green fluorescence immediately, and the color of the solution changes gradually from orange to dark red. Dilute carefully the solution with 10 mL of water: the color changes through yellow to orange-yellow with green fluorescence, and a small amount of a flocculent precipitate is formed.

(2) Dissolve 0.01 g of Hydrocortisone in 1 mL of methanol, add 1 mL of Fehling's TS, and heat: a red precipitate is formed.

(3) Determine the infrared absorption spectrum of Hydrocortisone, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of previously dried Hydrocortisone Reference Standard: both spectra exhibit similar intensities of absorption at the same wave numbers. If any difference appears between the spectra, dissolve Hydrocortisone and Hydrocortisone Reference Standard in ethanol (95), respectively, then evaporate the ethanol to dryness, and repeat the test on the residues.

Optical rotation $[\alpha]_D^{20}$: +150 - +156° (after drying, 0.1 g, 1,4-dioxane, 10 mL, 100 mm).

Purity Other steroids—Dissolve 0.020 g of Hydrocortisone in 10 mL of a mixture of chloroform and methanol (9:1), and use this solution as the sample solution. Pipet 1 mL of this solution, add a mixture of chloroform and methanol (9:1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 10 μL each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and ethanol (95) (17:3) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): 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 1.0% (0.5 g, 105°C, 3 hours).

Residue on ignition Not more than 0.1% (0.5 g).

Assay Dissolve about 0.02 g each of Hydrocortisone and Hydrocortisone Reference Standard, previously dried and accurately weighed, in 20 mL each of a mixture of chloroform and methanol (9:1), add 10 mL each of the internal standard solution, then add a mixture of chloroform and methanol (9:1) to make 50 mL, and use these solutions as the sample solution and the standard solution. Perform the test with 5 μL 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 hydrocortisone to that of the internal standard, respectively.

Amount (mg) of $C_{21}H_{30}O_5$
= amount (mg) of Hydrocortisone Reference Standard

$$\times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of prednisone in a mixture of chloroform and methanol (9:1) (9 in 10,000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 20°C.

Mobile phase: A mixture of chloroform, methanol and acetic acid (100) (1000:20:1).

Flow rate: Adjust the flow rate so that the retention time of hydrocortisone is about 15 minutes.

System suitability—

System performance: When the procedure is run with 5 μL of the standard solution under the above operating conditions, the internal standard and hydrocortisone are eluted in this order with the resolution between these peaks being not less than 7.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak area of hydrocortisone to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Hydrocortisone Acetate

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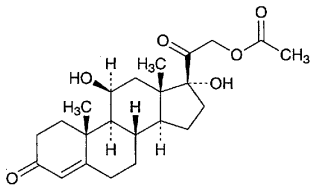

$C_{23}H_{32}O_6$: 404.50
11β,17,21-Trihydroxypregn-4-ene-3,20-dione 21-acetate
[*50-03-3*]

Hydrocortisone Acetate, when dried, contains not less than 97.0% and not more than 102.0% of $C_{23}H_{32}O_6$.

Description Hydrocortisone Acetate occurs as white crystals or crystalline powder. It is odorless.

It is sparingly soluble in 1,4-dioxane, slightly soluble in methanol, in ethanol (95) and in chloroform, very slightly soluble in diethyl ether, and practically insoluble in water.

Melting point: about 220°C (with decomposition).