

10 mL of 1 mol/L hydrochloric acid TS, and add water to make exactly 100 mL. Pipet 5 mL of the solution, and add water to make exactly 100 mL. To 2.0 mL of the solution add 2 mL of formic acid, 15 mL of 1 mol/L hydrochloric acid TS and 20 mL of water, and proceed in the same manner.

**Loss on drying** Not more than 2.0% (1 g, 130°C, 2 hours).

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

**Assay** Weigh accurately about 0.2 g of Chlorhexidine Hydrochloride, previously dried, dissolve in 2.0 mL of formic acid, add 60 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

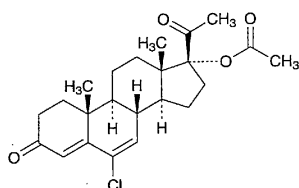
Each mL of 0.1 mol/L perchloric acid VS  
= 14.459 mg of  $C_{22}H_{30}Cl_2N_{10} \cdot 2HCl$

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

Storage—Light-resistant.

## Chlormadinone Acetate

酢酸クロルマジノン



$C_{23}H_{29}ClO_4$ : 404.93

6-Chloro-3,20-dioxopregna-4,6-dien-17-yl acetate  
[302-22-7]

Chlormadinone Acetate, when dried, contains not less than 98.0% of  $C_{23}H_{29}ClO_4$ .

**Description** Chlormadinone Acetate occurs as white to light yellow crystals or crystalline powder. It is odorless.

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

**Identification** (1) Dissolve 2 mg of Chlormadinone Acetate in 1 mL of ethanol (95), and add 1 mL of 1,3-dinitrobenzene TS and 1 mL of a solution of potassium hydroxide (1 in 5): a red-purple color develops.

(2) To 0.05 g of Chlormadinone Acetate add 2 mL of potassium hydroxide-ethanol TS, and boil on a water bath for 5 minutes. After cooling, add 2 mL of diluted sulfuric acid (2 in 7), and boil gently for 1 minute: the odor of ethyl acetate is perceptible.

(3) Determine the infrared absorption spectrum of Chlormadinone Acetate, 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 Chlormadinone Acetate Reference Standard: both spectra exhibit similar intensities of absorption at the same wave numbers.

(4) Perform the test with Chlormadinone Acetate as

directed under the Flame Coloration Test (2): a green color appears.

**Optical rotation**  $[\alpha]_D^{20}$ :  $-10.0 - -14.0^\circ$  (after drying, 0.2 g, acetonitrile, 10 mL, 100 mm).

**Melting point** 211 – 215°C

**Purity** (1) Heavy metals—Proceed with 1.0 g of Chlormadinone Acetate 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).

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

(3) Other steroids—Dissolve 0.020 g of Chlormadinone Acetate in 10 mL of acetonitrile, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add acetonitrile to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10  $\mu$ L each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of these solutions by the automatic integration method: the total area of peaks other than the peak of chlormadinone acetate from the sample solution is not larger than the peak area of chlormadinone acetate from the standard solution.

**Operating conditions**—

**Detector:** An ultraviolet absorption photometer (wavelength: 236 nm).

**Column:** A stainless steel column about 6 mm in inside diameter and about 15 cm in length, packed with octadecylsilylated silica gel for liquid chromatography (5  $\mu$ m in particle diameter).

**Column temperature:** A constant temperature of about 30°C.

**Mobile phase:** A mixture of acetonitrile and water (13:7).

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

**Selection of column:** Dissolve 8 mg of Chlormadinone Acetate and 2 mg of butyl parahydroxybenzoate in 100 mL of acetonitrile. Proceed with 10  $\mu$ L of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of butyl parahydroxybenzoate and chlormadinone acetate in this order with the resolution between these peaks being not less than 8.

**Time span of measurement:** About 1.5 times as long as the retention time of chlormadinone acetate after the solvent peak.

**Loss on drying** Not more than 0.5% (0.5 g, in vacuum, phosphorus (V) oxide, 4 hours).

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

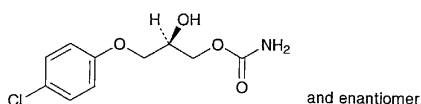
**Assay** Weigh accurately about 0.02 g each of Chlormadinone Acetate and Chlormadinone Acetate Reference Standard, previously dried, and dissolve in ethanol (95) to make exactly 100 mL. Pipet 5 mL each of these solutions, to each add ethanol (95) to make exactly 100 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with these solutions as directed under the Ultraviolet-visible Spectrophotometry, and determine the absorbances,  $A_T$  and  $A_S$ , at 285 nm.

$$\begin{aligned} & \text{Amount (mg) of } C_{23}H_{29}ClO_4 \\ & = \text{amount (mg) of Chlormadinone Acetate} \\ & \quad \text{Reference Standard} \\ & \quad \times \frac{A_T}{A_S} \end{aligned}$$

**Containers and storage** Containers—Tight containers.  
Storage—Light-resistant.

## Chlorphenesin Carbamate

カルバミン酸クロルフェネシン



$C_{10}H_{12}ClNO_4$ : 245.66  
(*RS*)-3-(4-Chlorophenoxy)-2-hydroxypropyl carbamate  
[886-74-8]

Chlorphenesin Carbamate, when dried, contains not less than 98.0% and not more than 102.0% of  $C_{10}H_{12}ClNO_4$ .

**Description** Chlorphenesin Carbamate occurs as white crystals or crystalline powder. It is odorless, and has a slight bitter taste.

It is freely soluble in methanol, in ethanol (95) and in pyridine, soluble in 2-propanol, sparingly soluble in diethyl ether, slightly soluble in water, and practically insoluble in hexane.

A solution of Chlorphenesin Carbamate in ethanol (95) (1 in 20) shows no optical rotation.

**Identification** (1) Determine the absorption spectrum of a solution of Chlorphenesin Carbamate in ethanol (95) (3 in 200,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Chlorphenesin Carbamate, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Perform the test with Chlorphenesin Carbamate as directed under the Flame Coloration Test (2): a green color appears.

**Melting point** 88 – 91°C

**Purity** (1) Heavy metals—Dissolve 2.0 g of Chlorphenesin Carbamate in 20 mL of ethanol (95), and add 2 mL of dilute acetic acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution as follows: to 2.0 mL of Standard Lead Solution add 20 mL of ethanol (95), 2 mL of dilute acetic acid and water to make 50 mL (not more than 10 ppm).

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

(3) Related substances—(i) Chlorphenesin-2-carba-

mate: Dissolve 0.10 g of Chlorphenesin Carbamate in 20 mL of a mixture of hexane for liquid chromatography and 2-propanol (7:3), and use this solution as the sample solution. Perform the test with 10  $\mu$ L of the sample solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area,  $A_a$ , of chlorphenesin carbamate and the peak area,  $A_b$ , of chlorphenesin-2-carbamate by the automatic integration method: the ratio,  $A_b/(A_a + A_b)$ , is not larger than 0.007.

**Operating conditions**—

**Detector:** An ultraviolet absorption photometer (wavelength: 280 nm).

**Column:** A stainless steel column about 4 mm in inside diameter and about 30 cm in length, packed with silica gel for liquid chromatography (5  $\mu$ m in particle diameter).

**Column temperature:** A constant temperature of about 40°C.

**Mobile phase:** A mixture of hexane for liquid chromatography, 2-propanol and acetic acid (100) (700:300:1).

**Flow rate:** Adjust the flow rate so that the retention time of chlorphenesin carbamate is about 9 minutes.

**Detection sensitivity:** Pipet 1 mL of the sample solution, add a mixture of *n*-hexane for liquid chromatography and 2-propanol (7:3) to make exactly 100 mL. Adjust the detection sensitivity so that the peak height of chlorphenesin carbamate from 10  $\mu$ L of this solution is about 20 to 40% of the full scale.

**Selection of column:** Dissolve 0.1 g of Chlorphenesin Carbamate in methanol to make 50 mL. To 25 mL of this solution add 25 mL of sodium hydroxide TS, and warm at 60°C for 20 minutes. To 20 mL of this solution add 5 mL of 1 mol/L hydrochloric acid TS, shake well with 20 mL of ethyl acetate, and allow to stand to separate the ethyl acetate layer. Proceed with 10  $\mu$ L of this layer under the above operating conditions, and calculate the resolution. Use a column giving elution of chlorphenesin, chlorphenesin carbamate and chlorphenesin-2-carbamate in this order, with the ratios of the retention time of chlorphenesin and chlorphenesin-2-carbamate to chlorphenesin carbamate are about 0.7 and about 1.2, respectively, and with the resolution between the peaks of chlorphenesin and chlorphenesin carbamate being not less than 2.0.

(ii) Other related substances: Dissolve 0.10 g of Chlorphenesin Carbamate in 10 mL of ethanol (95), and use this solution as the sample solution. Pipet 1 mL of the sample solution, add ethanol (95) to make exactly 20 mL. Pipet 2 mL of this solution, add ethanol (95) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 50  $\mu$ L each of the sample solution and the standard solution on a plate of silica gel for liquid chromatography. Develop the plate with a mixture of ethyl acetate, methanol and ammonia solution (28) (17:2:1) to a distance of about 10 cm, and air-dry the plate. Allow to stand in iodine vapor for 20 minutes: 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 0.20% (1 g, in vacuum, silica gel, 4 hours).

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

**Assay** Weigh accurately about 0.5 g of Chlorphenesin Carbamate, previously dried, dissolve in 20 mL of pyridine, add exactly 50 mL of 0.1 mol/L potassium hydroxide-ethanol