Related substances. Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution. Dissolve 25 mg of the substance to be examined in *acetone R* and dilute to 5 mL with the same solvent.

Reference solution. Dilute 1 mL of the test solution to 100 mL with *acetone R*.

Apply to the plate 5 µL of each solution. Develop over a path of 15 cm using a mixture of 15 volumes of *2-propanol R* and 85 volumes of *ethyl acetate R*. Dry the plate in a current of air until the solvents have evaporated (about 10 min) and spray with a mixture of equal volumes of *alcoholic solution of sulfuric acid R* and *alcohol R*; use about 10 mL for a plate 200 mm square and spray in small portions, allowing the solvent to evaporate each time to avoid excessive wetting. Heat at 100-105 °C for 30 min and immediately place the plate above, but not in contact with, 10 mL of a saturated solution of *sodium nitrite R* in a glass tank. Carefully add 0.5 mL of *sulfuric acid R* to the sodium nitrite solution, close the tank, and allow to stand for 15 min. Remove the plate, heat in a ventilated oven at 40 °C for 15 min and spray with 3 quantities, each of 5 mL, of a freshly prepared 5 g/L solution of *naphthylethylenediamine dihydrochloride R* in *alcohol R*. Examine the plate by transmitted light. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (1.0 per cent).

Chlorides (*2.4.4*). 15 mL of solution S complies with the limit test for chlorides (160 ppm).

Heavy metals (*2.4.8*). 1.0 g complies with limit test C for heavy metals (20 ppm). Prepare the standard using 2 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *dimethylformamide R*. Titrate with *0.1 M tetrabutylammonium hydroxide in 2-propanol* determining the end-point potentiometrically (*2.2.20*) at the first point of inflexion. Carry out a blank titration.

1 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol* is equivalent to 29.57 mg of $C_7H_6ClN_3O_4S_2$.

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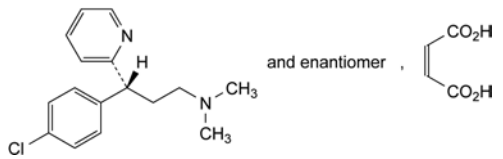
CHLORPHENAMINE MALEATE

Chlorphenamini maleas



$C_{20}H_{23}ClN_2O_4$ M_r 390.9
[113-92-8]

DEFINITION

(3*RS*)-3-(4-Chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine hydrogen (*Z*)-butenedioate.

Content: 98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.14*): 130 °C to 135 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *chlorphenamine maleate CRS*.

C. Optical rotation (see Tests).

TESTS

Solution S. Dissolve 2.0 g in *water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Optical rotation (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a). Dilute 0.5 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c). Dissolve 5 mg of *chlorphenamine impurity C CRS* in 5 mL of the test solution and dilute to 50.0 mL with the mobile phase. Dilute 2 mL of this solution to 20 mL with the mobile phase.

Reference solution (d). Dissolve 5 mg of *2,2′-dipyridylamine R* (impurity B) in the mobile phase and dilute to 100 mL with the mobile phase.

Reference solution (e). Dissolve the contents of a vial of *chlorphenamine impurity A CRS* in 2 mL of the test solution. Sonicate for 5 min.

Column:

– *size*: *l* = 0.30 m, Ø = 3.9 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase: mix 20 volumes of *acetonitrile R* and 80 volumes of a 8.57 g/L solution of *ammonium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 225 nm.

Injection: 20 µL.

Run time: 3.5 times the retention time of chlorphenamine.

Relative retention with reference to chlorphenamine (retention time = about 11 min): maleic acid = about 0.2; impurity A = about 0.3; impurity B = about 0.4; impurity C = about 0.9; impurity D = about 3.0.

System suitability: reference solution (c):

– *resolution*: minimum 1.5 between the peaks due to impurity C and chlorphenamine.

Limits:

– *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.5; impurity B = 1.4;
– *impurity A*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *impurities B, C, D*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

– *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

– *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peaks due to the blank and maleic acid.

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test C. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 25 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

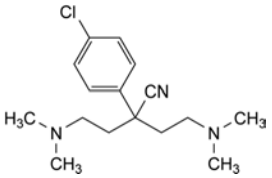
1 mL of *0.1 M perchloric acid* is equivalent to 19.54 mg of $C_{20}H_{23}ClN_2O_4$.

STORAGE

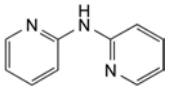
Protected from light.

IMPURITIES

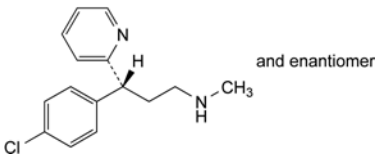
Specified impurities: A, B, C, D.



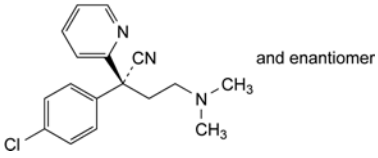
A. 2-(4-chlorophenyl)-4-(dimethylamino)-2-[2-(dimethylamino)ethyl]butanenitrile,



B. *N*-(pyridin-2-yl)pyridin-2-amine (2,2′-dipyridylamine),



C. (3*RS*)-3-(4-chlorophenyl)-*N*-methyl-3-(pyridin-2-yl)propan-1-amine,

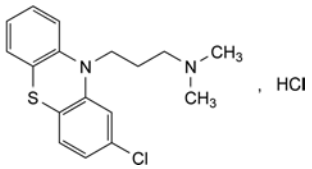


D. (2*RS*)-2-(4-chlorophenyl)-4-(dimethylamino)-2-(pyridin-2-yl)butanenitrile.

01/2008:0475
corrected 7.0

CHLORPROMAZINE HYDROCHLORIDE

Chlorpromazini hydrochloridum



$C_{17}H_{20}Cl_2N_2S$ M_r 355.3
[69-09-0]

DEFINITION

3-(2-Chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: very soluble in water, freely soluble in ethanol (96 per cent).

It decomposes on exposure to air and light.

mp: about 196 °C.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*). *Prepare the solutions protected from bright light and measure the absorbances immediately.*

Test solution. Dissolve 50.0 mg in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 500.0 mL with the same solution. Dilute 5.0 mL of the solution to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Spectral range: 230-340 nm.

Absorption maximum: at 254 nm and 306 nm.

Specific absorbance at the absorption maximum:

– *at 254 nm*: 890 to 960.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *chlorpromazine hydrochloride CRS*.

C. Identification test for phenothiazines by thin-layer chromatography (*2.3.3*): use *chlorpromazine hydrochloride CRS* to prepare the reference solution.

D. It gives reaction (b) of chlorides (*2.3.1*).

TESTS

pH (*2.2.3*): 3.5 to 4.5. *Carry out the test protected from light and use freshly prepared solutions.*

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light and use freshly prepared solutions.*

Test solution. Dissolve 40 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a). Dissolve 4 mg of *chlorpromazine impurity D CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. To 1 mL of this solution add 1 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.