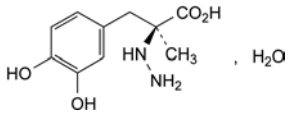
01/2008:0755
corrected 6.0

CARBIDOPA

Carbidopum



$C_{10}H_{14}N_2O_4,H_2O$ M_r 244.2
[38821-49-7]

DEFINITION

(2*S*)-3-(3,4-Dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid monohydrate.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or yellowish-white powder.

Solubility: slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute solutions of mineral acids.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D, E.

A. Specific optical rotation (see Tests).

B. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 50.0 mg in a 8.5 g/L solution of *hydrochloric acid R* in *methanol R* and dilute to 100.0 mL with the same solution. Dilute 10.0 mL of this solution to 100.0 mL with a 8.5 g/L solution of *hydrochloric acid R* in *methanol R*.

Spectral range: 230-350 nm.

Absorption maximum: at 283 nm.

Specific absorbance at the absorption maximum: 135 to 150 (dried substance).

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *carbidopa CRS*.

D. Shake vigorously about 5 mg with 10 mL of *water R* for 1 min and add 0.3 mL of *ferric chloride solution R2*. An intense green colour is produced, which quickly turns to reddish-brown.

E. Suspend about 20 mg in 5 mL of *water R* and add 5 mL of *cupri-tartaric solution R*. On heating, the colour of the solution changes to dark brown and a red precipitate is formed.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 or B_6 (*2.2.2, Method II*).

Dissolve 0.25 g in 25 mL of *1 M hydrochloric acid*.

Specific optical rotation (*2.2.7*): – 22.5 to – 26.5 (dried substance).

With the aid of an ultrasonic bath, dissolve completely 0.250 g in *aluminium chloride solution R* and dilute to 25.0 mL with the same solution.

Hydrazine. Thin-layer chromatography (*2.2.27*).

Test solution (a). Dissolve 0.50 g in *dilute hydrochloric acid R* and dilute to 2.0 mL with the same acid.

Test solution (b). Place 25 g of *strongly basic anion exchange resin R* into each of 2 conical flasks with ground-glass stoppers. To each, add 150 mL of *carbon dioxide-free water R* and shake from time to time during 30 min. Decant the liquid from both flasks and repeat the process with further quantities, each of 150 mL, of *carbon dioxide-free water R*.

Take two 100 mL measuring cylinders 3.5-4.5 cm in internal diameter and label these A and B. Into cylinder A, transfer as completely as possible the resin from 1 conical flask using 60 mL of *carbon dioxide-free water R*; into cylinder B, transfer the 2nd quantity of resin, this time using 20 mL of *carbon dioxide-free water R*.

Into each cylinder, insert a gas-inlet tube, the end of which has an internal diameter of 2-3 mm and which reaches almost to the bottom of the cylinder. Pass a rapid stream of *nitrogen for chromatography R* through each mixture so that homogeneous suspensions are formed. After 30 min, without interrupting the gas flow, add 1.0 mL of test solution (a) to cylinder A; after 1 min stop the gas flow into cylinder A and transfer the contents, through a moistened filter paper, into cylinder B. After 1 min, stop the gas flow to cylinder B and pour the solution immediately through a moistened filter paper into a freshly prepared mixture of 1 mL of a 200 g/L solution of *salicylaldehyde R* in *methanol R* and 20 mL of *phosphate buffer solution pH 5.5 R* in a conical flask; shake thoroughly for 1 min and heat in a water-bath at 60 °C for 15 min. The liquid becomes clear. Allow to cool, add 2.0 mL of *toluene R* and shake vigorously for 2 min. Transfer the mixture into a centrifuge tube and centrifuge.

Separate the toluene layer in a 100 mL separating funnel and shake vigorously with 2 quantities, each of 20 mL, of a 200 g/L solution of *sodium metabisulfite R* and finally with 2 quantities, each of 50 mL, of *water R*. Separate the toluene layer.

Reference solution (a). Dissolve 10 mg of *hydrazine sulfate R* in *dilute hydrochloric acid R* and dilute to 50 mL with the same acid. Dilute 1.0 mL of this solution to 10.0 mL with *dilute hydrochloric acid R*.

Reference solution (b). Prepare the solution at the same time and in the same manner as described for test solution (b) using 1.0 mL of reference solution (a) instead of 1.0 mL of test solution (a).

Plate: *TLC silanised silica gel plate R*.

Mobile phase: *water R, methanol R* (10:20 *V/V*).

Application: 10 µL of test solution (b) and reference solution (b).

Development: over a path of 10 cm.

Drying: in air.

Detection: examine in ultraviolet light at 365 nm.

Limit:

– *hydrazine*: any spot showing a yellow fluorescence is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (20 ppm).

Methyldopa and methylcarbidopa. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in *0.1 M hydrochloric acid* and dilute to 10.0 mL with the same acid.

Reference solution (a). Dissolve the contents of a vial of *methylcarbidopa CRS* in *0.1 M hydrochloric acid*, add 1 mg of *methyldopa CRS* and dilute to 20.0 mL with the same acid.

Reference solution (b). Dissolve 5 mg of *carbidopa CRS* and 5 mg of *methyldopa CRS* in *0.1 M hydrochloric acid* and dilute to 10.0 mL with the same acid.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *methanol R*, 14 g/L solution of *potassium dihydrogen phosphate R* (2:98 *V/V*).

Flow rate: 1 mL/min.

Detection: spectrophotometer at 282 nm.

Injection: 20 µL.

System suitability: reference solution (b):

– *resolution*: minimum 4.0 between the peaks due to methyldopa and carbidopa.

Limits:

– *methyldopa and methylcarbidopa*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

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*): 6.9 per cent to 7.9 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.150 g with gentle heating in 75 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 22.62 mg of $C_{10}H_{14}N_2O_4$.

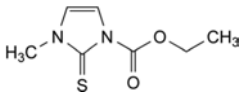
STORAGE

Protected from light.

01/2008:0884

CARBIMAZOLE

Carbimazolum



$C_7H_{10}N_2O_2S$ M_r 186.2
[22232-54-8]

DEFINITION

Ethyl 3-methyl-2-thioxo-2,3-dihydro-1*H*-imidazole-1-carboxylate.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or yellowish-white, crystalline powder.

Solubility: slightly soluble in water, soluble in acetone and in alcohol.

IDENTIFICATION

First identification: *B*.

Second identification: *A, C, D*.

A. Melting point (*2.2.14*): 122 °C to 125 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *carbimazole CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 10 mg of *carbimazole CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel* GF_{254} *plate R*.

Mobile phase: *acetone R, methylene chloride R* (20:80 *V/V*).

Application: 10 µL.

Development: over a path of 15 cm.

Drying: in air for 30 min.

Detection: examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 10 mg in a mixture of 50 mL of *water R* and 0.05 mL of *dilute hydrochloric acid R*. Add 1 mL of *potassium iodobismuthate solution R*. A red precipitate is formed.

TESTS

Impurity A and other related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 5.0 mg of the substance to be examined in 10.0 mL of a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*. Use this solution within 5 min of preparation.

Reference solution (a). Dissolve 5 mg of *thiamazole R* and 0.10 g of *carbimazole CRS* in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 100.0 mL with the same mixture of solvents. Dilute 1.0 mL of this solution to 10.0 mL with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Reference solution (b). Dissolve 5.0 mg of *thiamazole R* in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 10.0 mL with the same mixture of solvents. Dilute 1.0 mL of this solution to 100.0 mL with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Column:

– *size*: *l* = 0.15 m, Ø = 3.9 mm,

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *acetonitrile R, water R* (10:90 *V/V*).

Flow rate: 1 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µL.

Run time: 1.5 times the retention time of carbimazole.

Retention time: carbimazole = about 6 min.

System suitability: reference solution (a):

– *resolution*: minimum 5.0 between the peaks due to impurity A and carbimazole.

Limits:

– *impurity A*: not more than half the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

– *any other impurity*: not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

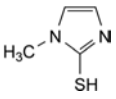
Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator over *diphosphorus pentoxide R* at a pressure not exceeding 0.7 kPa for 24 h.

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

ASSAY

Dissolve 50.0 mg in *water R* and dilute to 500.0 mL with the same solvent. To 10.0 mL add 10 mL of *dilute hydrochloric acid R* and dilute to 100.0 mL with *water R*. Measure the absorbance (*2.2.25*) at the maximum at 291 nm. Calculate the content of $C_7H_{10}N_2O_2S$ taking the specific absorbance to be 557.

IMPURITIES



A. 1-methyl-1*H*-imidazole-2-thiol (thiamazole).