ASSAY

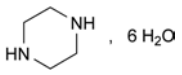
Dissolve 0.100 g in 10 mL of *anhydrous acetic acid R* with gentle heating and dilute to 70 mL with the same acid. Titrate with *0.1 M perchloric acid* using 0.25 mL of *naphtholbenzein solution R* as indicator until the colour changes from brownish-yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 10.71 mg of $C_{24}H_{46}N_6O_{14}$.

01/2008:0425

PIPERAZINE HYDRATE

Piperazinum hydricum



$C_4H_{10}N_2,6H_20$ M_r 194.2
[142-63-2]

DEFINITION

Piperazine hydrate contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of piperazine hexahydrate.

CHARACTERS

Colourless, deliquescent crystals, freely soluble in water and in alcohol.

It melts at about 43 °C.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *piperazine hydrate CRS*. Dry the substance to be examined and the reference substance over *diphosphorus pentoxide R in vacuo* for 48 h, powder the substances avoiding uptake of water, prepare discs and record the spectra without delay.

B. Examine the chromatograms obtained in the test for related substances after spraying with the ninhydrin solutions. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.5 g in 5 mL of *dilute sodium hydroxide solution R*. Add 0.2 mL of *benzoyl chloride R* and mix. Continue to add *benzoyl chloride R* in portions of 0.2 mL until no further precipitate is formed. Filter and wash the precipitate with a total of 10 mL of *water R* added in small portions. Dissolve the precipitate in 2 mL of hot *alcohol R* and pour the solution into 5 mL of *water R*. Allow to stand for 4 h, filter, wash the crystals with *water R* and dry at 100 °C to 105 °C. The crystals melt (*2.2.14*) at 191 °C to 196 °C.

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_8 (*2.2.2, Method II*).

pH (*2.2.3*). The pH of solution S is 10.5 to 12.0.

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

Test solution (a). Dissolve 1.0 g of the substance to be examined in 6 mL of *concentrated ammonia R* and dilute to 10 mL with *ethanol R*.

Test solution (b). Dilute 1 mL of test solution (a) to 10 mL with a mixture of 2 volumes of *ethanol R* and 3 volumes of *concentrated ammonia R*.

Reference solution (a). Dissolve 0.1 g of *piperazine hydrate CRS* in a mixture of 2 volumes of *ethanol R* and 3 volumes of *concentrated ammonia R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (b). Dissolve 25 mg of *ethylenediamine R* in a mixture of 2 volumes of *ethanol R* and 3 volumes of *concentrated ammonia R* and dilute to 100 mL with the same mixture of solvents.

Reference solution (c). Dissolve 25 mg of *triethylenediamine R* in a mixture of 2 volumes of *ethanol R* and 3 volumes of *concentrated ammonia R* and dilute to 100 mL with the same mixture of solvents.

Reference solution (d). Dissolve 12.5 mg of *triethylenediamine R* in 5.0 mL of test solution (a) and dilute to 50 mL with a mixture of 2 volumes of *ethanol R* and 3 volumes of *concentrated ammonia R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 15 cm using a freshly prepared mixture of 20 volumes of *concentrated ammonia R* and 80 volumes of *acetone R*. Dry the plate at 105 °C and spray successively with a 3 g/L solution of *ninhydrin R* in a mixture of 3 volumes of *anhydrous acetic acid R* and 100 volumes of *butanol R* and a 1.5 g/L solution of *ninhydrin R* in *ethanol R*. Dry the plate at 105 °C for 10 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent). Spray the plate with *0.05 M iodine* and allow to stand for about 10 min. Any spot corresponding to triethylenediamine in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.25 per cent). The test is not valid unless the chromatogram obtained with reference solution (d) shows two clearly separated spots.

Heavy metals (*2.4.8*). 12 mL of solution S complies with limit test A for heavy metals (20 ppm). Prepare the standard using *lead standard solution (1 ppm Pb) R*.

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

ASSAY

Dissolve 80.0 mg in 10 mL of *anhydrous acetic acid R* with gentle heating and dilute to 70 mL with the same acid. Titrate with *0.1 M perchloric acid* using 0.25 mL of *naphtholbenzein solution R* as indicator until the colour changes from brownish-yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 9.705 mg of $C_4H_{10}N_2,6H_20$.

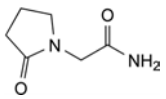
STORAGE

Store in an airtight container, protected from light.

01/2008:1733
corrected 6.0

PIRACETAM

Piracetamum



$C_6H_{10}N_2O_2$ M_r 142.2
[7491-74-9]

DEFINITION

2-(2-Oxopyrrolidin-1-yl)acetamide.

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

CHARACTERS

Appearance: white or almost white, powder.

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

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *piracetam CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *ethanol (96 per cent) R*, evaporate to dryness on a water-bath and record new spectra using the residues.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 10 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R* and dilute to 100.0 mL with the same mixture of solvents.

Test solution (b). Dilute 10.0 mL of test solution (a) to 50.0 mL with a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R*.

Reference solution (a). Dissolve 5 mg of the substance to be examined and 10 µL of *2-pyrrolidone R* in a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R* and dilute to 100.0 mL with the same mixture of solvents.

Reference solution (b). Dilute 1.0 mL of test solution (a) to 100.0 mL with a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R*. Dilute 5.0 mL of this solution to 50.0 mL with a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R*.

Reference solution (c). Dissolve 50.0 mg of *piracetam CRS* in a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R* and dilute to 100.0 mL with the same mixture of solvents. Dilute 10.0 mL of this solution to 50.0 mL with a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 10 volumes of *acetonitrile R1* and 90 volumes of a 1.0 g/L solution of *dipotassium hydrogen phosphate R*; adjust to pH 6.0 with *dilute phosphoric acid R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 205 nm.

Injection: 20 µL of test solution (a) and reference solutions (a) and (b).

Run time: 8 times the retention time of piracetam.

Relative retention with reference to piracetam (retention time = about 4 min): impurity D = about 0.8; impurity A = about 1.15; impurity B = about 2.8; impurity C = about 6.3.

System suitability: reference solution (a):

– *resolution*: minimum 3.0 between the peaks due to piracetam and impurity A,
– *symmetry factor*: maximum 2.0 for the peak due to piracetam.

Limits:

– *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 10 ppm.

Dissolve 2.0 g in 20 mL of *water R*. 12 mL of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 1.0 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

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection: test solution (b) and reference solution (c).

Calculate the percentage content of $C_6H_{10}N_2O_2$ from the areas of the peaks and the declared content of *piracetam CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities: A, B, C, D.

A. R = H: pyrrolidin-2-one (2-pyrrolidone),

B. R = CH_2-CO-O-CH_3: methyl (2-oxopyrrolidin-1-yl)acetate,

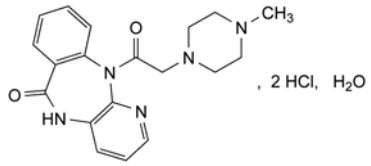
C. R = CH_2-CO-O-C_2H_5: ethyl (2-oxopyrrolidin-1-yl)acetate,

D. R = CH_2-CO_2H: (2-oxopyrrolidin-1-yl)acetic acid.

01/2008:2001
corrected 7.0

PIRENZEPINE DIHYDROCHLORIDE MONOHYDRATE

Pirenzepini dihydrochloridum monohydricum



$C_{19}H_{23}Cl_2N_5O_2,H_2O$ M_r 442.3

DEFINITION

11-[(4-Methylpiperazin-1-yl)acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one dihydrochloride monohydrate.

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

CHARACTERS

Appearance: white or yellowish, crystalline powder.

Solubility: freely soluble in water, slightly soluble in methanol, very slightly soluble in ethanol, practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.