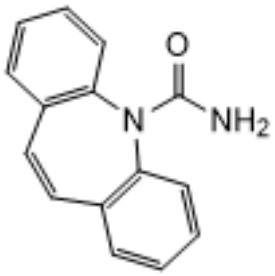
Carbamazepine (Carbamazepinum)

2016-01

Molecular formula. $C_{15}H_{12}N_2O$

Relative molecular mass. 236.3

Graphic formula



Chemical name. 5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide; 5*H*-dibenz[*b*,*f*]azepine-5-carboxamide; CAS Reg. No. 298-46-4.

Description. A white to almost white, crystalline powder.

Solubility. Very slightly soluble in water; sparingly soluble in acetone; soluble in ethanol (~750 g/L) TS; freely soluble in dichloromethane.

Category. Antiepileptic.

Additional information. Carbamazepine exhibits polymorphism.

Storage. Carbamazepine should be kept in a tightly closed container.

Requirements

Definition. Carbamazepine is anhydrous polymorph form III, the crystal form of carbamazepine RS. Carbamazepine contains not less than 98.0% and not more than 102.0% of $C_{15}H_{12}N_2O$, calculated with reference to the dried substance.

Identity tests

-Either test A or any two of tests B, C and D may be applied.

A. Carry out the examination as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum obtained from the test substance without pretreatment is concordant with the spectrum obtained from carbamazepine RS or with the *reference spectrum* of carbamazepine.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1 Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 µL of each of the following three solutions, prepared using a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the test substance per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam R per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

B.2 Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3, then heat it at 105 °C for 15 minutes. Examine the chromatogram in daylight.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution

(C) shows 2 clearly separated spots.

C. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the conditions given under “Assay”, Method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).

D. Heat 0.1 g with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

Chlorides. For the preparation of the test solution boil 3.57 g in 50 mL of water for 10 minutes, cool, again adjust the volume, filter. To 25 mL of the filtrate add 10 mL of nitric acid (~130 g/L) TS and proceed as described under *2.2.1 Limit test for chlorides*; the chloride content is not more than 0.14 mg/g.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under *2.2.3 Limit test for heavy metals*, Procedure 3; determine the heavy metals content according to Method A; not more than 10 µg/g.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry to constant weight at 105 °C; it loses not more than 5.0 mg/g.

Acidity or alkalinity. To 1.0 g add 20 mL of carbon-dioxide-free water R, shake for 15 minutes and filter. To 10 mL of the filtrate add 0.05 mL of phenolphthalein/ethanol TS and 0.5 mL of carbonate-free sodium hydroxide (0.01 mol/L) VS; the solution is red. Add 1.0 mL of hydrochloric acid (0.01 mol/L) VS; the solution is colourless. Add 0.15 mL of methyl red/ethanol TS; the solution is red.

Related substances. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the chromatographic conditions given under “Assay”, method B.

Prepare the following solutions. For solution (1) dissolve about 75 mg of the test substance in 25 mL of methanol R, sonicate and dilute to 50 mL with water R. For solution (2) dilute 1 volume of solution (1) to 1000 volumes with a mixture of equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A RS per mL of a mixture of equal volumes of methanol R and water R. For solution (4) use a solution containing 10 µg of iminodibenzyl R (impurity E) per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A is not less than 1.7.

Inject alternately 20 µL each of solution (1), (2) and (4). Record the chromatograms for eight times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity A about 0.9; impurity D about 2.1; and impurity E about 3.5. Use the chromatogram obtained with solution (3) to identify the peak due to impurity A and the chromatogram obtained with solution (4) to identify the peak due to impurity E.

In the chromatogram obtained with solution (1):

- -the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.8, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);
- -the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- -the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);
- -the area of any other impurity peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.10%);
- -the sum of the corrected areas of the peaks corresponding to impurity A, impurity D and impurity E and the areas of all other peaks, other than the principal peak, is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (2) (0.05%).

Assay

-Either method A or B may be applied.

A. Dissolve about 0.1 g, accurately weighed, in sufficient ethanol (~750 g/L) TS to produce 100.0 mL. Dilute 10.0 mL of this solution to 100.0 mL with the same solvent, and again dilute 10.0 mL of this dilution to 100.0 mL with ethanol (~750 g/L) TS. Measure the absorbance *(1.6)* of a 1 cm layer of the resulting solution at the maximum at about 285 nm. Calculate the percentage content of $C_{15}H_{12}N_2O$ in the substance being tested, using the

absorptivity value of 49.0 ($A^{1\%}_{1cm}$ = 490).

B. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded cyanopropyl groups (10 µm). As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

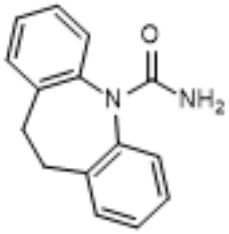
Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1) dissolve about 10 mg of the test substance, accurately weighed, in 25 mL of methanol R, sonicate and dilute to 50.0 mL with water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

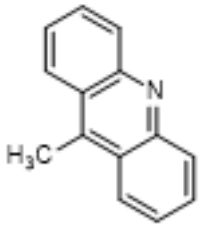
Inject alternately 20 µL each of solution (1) and (2). The assay is not valid unless the column efficiency (N) is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

Measure the areas of the peaks corresponding to carbamazepine obtained in the chromatograms from solution (1) and (2) and calculate the percentage content of carbamazepine ($C_{15}H_{12}N_2O$) in the samples using the declared content of $C_{15}H_{12}N_2O$ in carbamazepine RS.

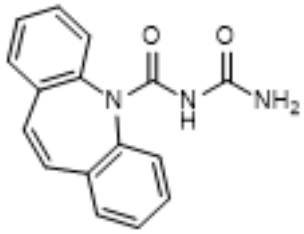
Impurities



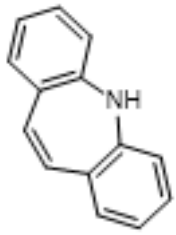
A. 10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide (10,11-dihydrocarbamazepine), (synthesis impurity)



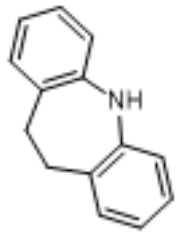
B. 9-methylacridine



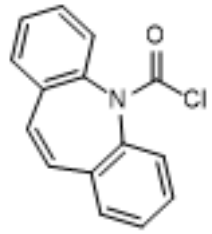
C. *N*-(5*H*-dibenzo[*b*,*f*]azepine-5-carbonyl)urea (*N*-carbamoylcarbamazepine)



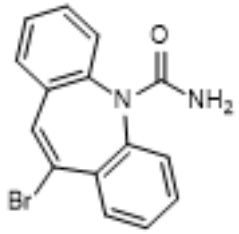
D. 5*H*-dibenzo[*b*,*f*]azepine (iminostilbene) (synthesis impurity / degradation product)



E: 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine (iminodibenzyl) (synthesis impurity)



F. 5H-dibenzo[b,f]azepine-5-carbonyl chloride (synthesis impurity)



G. 10-bromo-5*H*-dibenzo[*b,f*]azepine-5-carboxamide (10-bromocarbamazepine) (synthesis impurity)