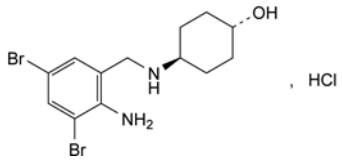
01/2011:1489

AMBROXOL HYDROCHLORIDE

Ambroxoli hydrochloridum



$C_{13}H_{19}Br_2ClN_2O$ M_r 414.6
[23828-92-4]

DEFINITION

trans-4-[(2-Amino-3,5-dibromobenzyl)amino]cyclohexanol hydrochloride.

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

CHARACTERS

Appearance: white or yellowish, crystalline powder.

Solubility: sparingly soluble in water, soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

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

Test solution. Dissolve 20.0 mg in *0.05 M sulfuric acid* and dilute to 100.0 mL with the same acid. Dilute 2.0 mL of the solution to 10.0 mL with *0.05 M sulfuric acid.*

Spectral range: 200-350 nm.

Absorption maxima: at 245 nm and 310 nm.

Absorbance ratio: A_{245}/A_{310} = 3.2 to 3.4.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *ambroxol hydrochloride CRS.*

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

Test solution. Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution. Dissolve 50 mg of *ambroxol hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

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

Mobile phase: *concentrated ammonia R, propanol R, ethyl acetate R, hexane R* (1:10:20:70 *V/V/V/V*).

Application: 10 µL.

Development: over 2/3 of the plate.

Drying: in air.

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 25 mg in 2.5 mL of *water R*, mix with 1.0 mL of *dilute ammonia R1* and allow to stand for 5 min. Filter and acidify the filtrate with *dilute nitric acid R*. The filtrate gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 0.75 g in *methanol R* and dilute to 15 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*): 4.5 to 6.0.

Dissolve 0.2 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 50 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). In order to prepare impurity B *in situ*, dissolve 5 mg of the substance to be examined in 0.2 mL of *methanol R*, add 0.04 mL of a mixture of 1 volume of *formaldehyde solution R* and 99 volumes of *water R*. Heat at 60 °C for 5 min. Evaporate to dryness under a current of nitrogen. Dissolve the residue in 5 mL of *water R* and dilute to 20.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: a mixture of equal volumes of *acetonitrile R* and a solution prepared as follows: dissolve 1.32 g of *ammonium phosphate R* in 900 mL of *water R*, adjust to pH 7.0 with *phosphoric acid R* and dilute to 1000 mL with *water R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 248 nm.

Injection: 20 µL.

Run time: 3 times the retention time of ambroxol.

Identification of impurities: use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention with reference to ambroxol (retention time = about 9 min): impurity B = about 0.6.

System suitability: reference solution (b):

– *resolution*: minimum 4.0 between the peaks due to impurity B and ambroxol.

Limits:

– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent),
– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 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*): maximum 0.5 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 0.300 g in 70 mL of *ethanol (96 per cent) R* and add 5 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

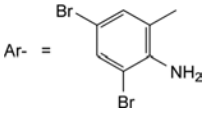
1 mL of *0.1 M sodium hydroxide* is equivalent to 41.46 mg of $C_{13}H_{19}Br_2ClN_2O$.

STORAGE

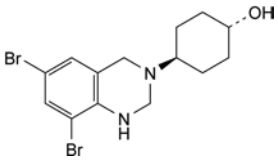
Protected from light.

IMPURITIES

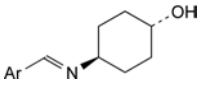
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities for substances for pharmaceutical use*): *A, B, C, D, E.*



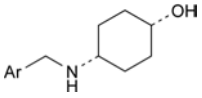
A. Ar-CH_2OH: (2-amino-3,5-dibromophenyl)methanol,



B. *trans*-4-(6,8-dibromo-1,4-dihydroquinazolin-3(2*H*)-yl)cyclohexanol,



C. *trans*-4-[[(*E*)-2-amino-3,5-dibromobenzyliden]amino]cyclohexanol,



D. *cis*-4-[(2-amino-3,5-dibromobenzyl)amino]cyclohexanol,

E. Ar-CH=O: 2-amino-3,5-dibromobenzaldehyde.

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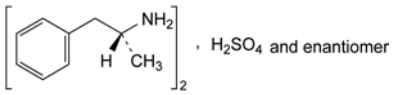
corrected 6.0

AMFETAMINE SULFATE

Amfetamini sulfas



$C_{18}H_{28}N_2O_4S$ M_r 368.5
[60-13-9]

DEFINITION

Bis[(2*RS*)-1-phenylpropan-2-amine] sulfate.

Content: 99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

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

IDENTIFICATION

First identification: A, B, E.

Second identification: A, C, D, E.

A. Optical rotation (*2.2.7*): – 0.04° to + 0.04° (measured in a 2 dm tube), determined on solution S (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).
Preparation: mulls in *liquid paraffin R*.
Comparison: *Ph. Eur. reference spectrum of amfetamine sulfate*.

C. To 50 mL of solution S add 5 mL of *strong sodium hydroxide solution R* and 0.5 mL of *benzoyl chloride R* and shake. Continue to add *benzoyl chloride R* in portions of 0.5 mL until no further precipitate is formed. Filter, wash the precipitate with *water R*, recrystallise twice from a mixture of equal volumes of *ethanol (96 per cent) R* and *water R*, then dry at 100-105 °C. The crystals melt (*2.2.14*) at 131 °C to 135 °C.

D. To about 2 mg add 1 mL of *sulfuric acid-formaldehyde reagent R*. An orange colour develops and quickly becomes dark-brown.

E. Solution S gives reaction (a) of sulfates (*2.3.1*).

TESTS

Solution S. Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

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

Acidity or alkalinity. To 25 mL of solution S add 0.1 mL of *methyl red solution R*. Not more than 0.1 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 1.00 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 0.300 g in 30 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 36.85 mg of $C_{18}H_{28}N_2O_4S$.

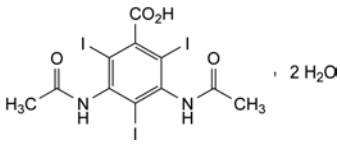
STORAGE

Protected from light.

01/2008:0873
corrected 6.0

AMIDOTRIZOIC ACID DIHYDRATE

Acidum amidotrizoicum dihydricum



$C_{11}H_9I_3N_2O_4,2H_2O$ M_r 650
[50978-11-5]

DEFINITION

Amidotrizoic acid dihydrate contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of 3,5-bis(acetylamino)-2,4,6-triiodobenzoic acid, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, very slightly soluble in water and in alcohol. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *amidotrizoic acid dihydrate CRS*.