– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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).

Loss on drying (*2.2.32*): maximum 0.2 per cent, determined on 1.000 g by drying at 80 °C at a pressure not exceeding 2.7 kPa for 4 h.

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

ASSAY

Dissolve 0.250 g in 20 mL of *anhydrous acetic acid R*. Add 50 mL of *acetic anhydride 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 31.62 mg of $C_{14}H_{10}BrN_3O$.

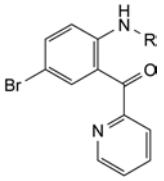
STORAGE

Protected from light.

IMPURITIES

Specified impurities: *A, B, E.*

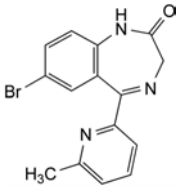
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



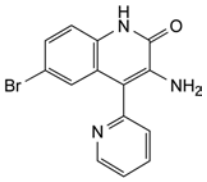
A. R = H: (2-amino-5-bromophenyl)(pyridin-2-yl)methanone,

B. R = CO-CH_2-Cl: *N*-[4-bromo-2-(pyridin-2-ylcarbonyl)phenyl]-2-chloroacetamide,

E. R = CO-CH_2-Br: 2-bromo-*N*-[4-bromo-2-(pyridin-2-ylcarbonyl)phenyl]acetamide,



C. 7-bromo-5-(6-methylpyridin-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one,



D. 3-amino-6-bromo-4-(pyridin-2-yl)quinolin-2(1*H*)-one.

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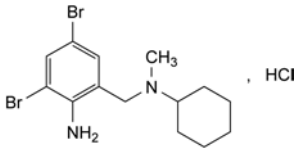
corrected 6.0

BROMHEXINE HYDROCHLORIDE

Bromhexini hydrochloridum



$C_{14}H_{21}Br_2ClN_2$ M_r 412.6
[611-75-6]

DEFINITION

N-(2-Amino-3,5-dibromobenzyl)-*N*-methylcyclohexanamine hydrochloride.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: very slightly soluble in water, slightly soluble in alcohol and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: *A, E.*

Second identification: *B, C, D, E.*

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *bromhexine hydrochloride CRS.*

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

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

Test solution. Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 20 mg of *bromhexine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

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

Mobile phase: *glacial acetic acid R, water R, butanol R* (17:17:66 *V/V/V*).

Application: 20 µL.

Development: over 3/4 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.

C. Dissolve about 25 mg in a mixture of 1 mL of *dilute sulfuric acid R* and 50 mL of *water R*. Add 2 mL of *methylene chloride R* and 5 mL of *chloramine solution R* and shake. A brownish-yellow colour develops in the lower layer.

D. Dissolve about 1 mg in 3 mL of *0.1 M hydrochloric acid*. The solution gives the reaction of primary aromatic amines (*2.3.1*).

E. Dissolve about 20 mg in 1 mL of *methanol R* and add 1 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

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

Dissolve 0.6 g in *methanol R* and dilute to 20 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 5 mg of *bromhexine impurity C CRS* in *methanol R*, add 1.0 mL of the test solution and dilute to 10.0 mL with the same solvent.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

– *size*: *l* = 0.12 m, Ø = 4.6 mm,
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase: mix 0.50 mL of *phosphoric acid R* in 950 mL of *water R*, adjust to pH 7.0 with *triethylamine R* (about 1.5 mL) and dilute to 1000 mL with *water R*; mix 20 volumes of this solution with 80 volumes of *acetonitrile R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 248 nm.

Injection: 10 µL.

Run time: 2.5 times the retention time of bromhexine.

Relative retention with reference to bromhexine (retention time = about 11 min): impurity A = about 0.1; impurity B = about 0.2; impurity C = about 0.4; impurity D = about 0.5.

System suitability: reference solution (a):

– *resolution*: minimum 12.0 between the peaks due to impurity C and bromhexine.

Limits:

– *any impurity*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), and not more than 1 such peak has an area greater 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).

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

Dissolve 0.300 g in 70 mL of *alcohol R* and add 1 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 41.26 mg of $C_{14}H_{21}Br_2ClN_2$.

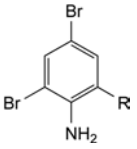
STORAGE

Protected from light.

IMPURITIES

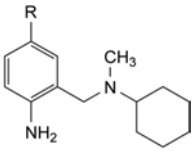
Specified impurities: A, B, C, D.

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 in substances for pharmaceutical use*): *E.*



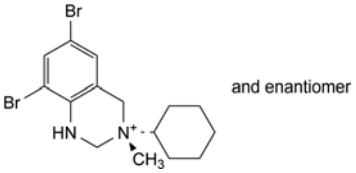
A. R = CH_2OH: (2-amino-3,5-dibromophenyl)methanol,

B. R = CHO: 2-amino-3,5-dibromobenzaldehyde,



C. R = H: *N*-(2-aminobenzyl)-*N*-methylcyclohexanamine,

D. R = Br: *N*-(2-amino-5-bromobenzyl)-*N*-methylcyclohexanamine,



E. (3*RS*)-6,8-dibromo-3-cyclohexyl-3-methyl-1,2,3,4-tetrahydroquinazolin-3-ium.

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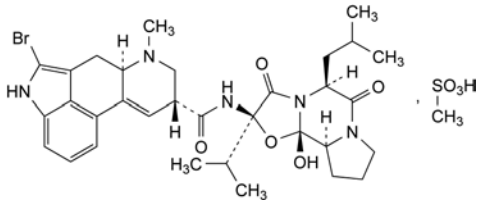
BROMOCRIPTINE MESILATE

Bromocriptini mesilas



$C_{33}H_{44}BrN_5O_8S$ M_r 751

[22260-51-1]

DEFINITION

(6a*R*,9*R*)-5-Bromo-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-10b-hydroxy-2-(1-methylethyl)-5-(2-methylpropyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide monomethanesulfonate.

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

PRODUCTION

The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.

CHARACTERS

Appearance: white or slightly coloured, fine crystalline powder.

Solubility: practically insoluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), sparingly soluble in methylene chloride.