Injection: 20 µl of the test solution and reference solutions (b), (c), (d) and (e).

Run time: twice the retention time of mannitol.

Relative retention with reference to mannitol (retention time = about 22 min): impurity C (eluted in 2 peaks) = about 0.7; impurity B = about 0.8; impurity A = about 1.2.

System suitability: reference solution (d):

– *resolution*: minimum 2 between the peaks due to mannitol and impurity A.

Limits:

– *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

– *impurity C*: for the sum of the areas of the 2 peaks, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

– *unspecified impurities*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

– *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

– *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Lead (*2.4.10*): maximum 0.5 ppm.

Dissolve the substance to be examined in 150.0 ml of the prescribed mixture of solvents.

Nickel (*2.4.15*): maximum 1 ppm.

Dissolve the substance to be examined in 150.0 ml of the prescribed mixture of solvents.

Water (*2.5.12*): maximum 0.5 per cent, determined on 1.00 g. Use as solvent 40 ml of a mixture of equal volumes of *anhydrous methanol R* and *formamide R* at about 50 °C.

Microbial contamination: if intended for use in the manufacture of parenteral dosage forms: the total viable aerobic count (*2.6.12*) is not more than 10^2 bacteria and 10^2 fungi per gram, determined by plate count; it complies with the tests for *Escherichia coli* and *Salmonella* (*2.6.13*).

Bacterial endotoxins (*2.6.14*): if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins: less than 4 IU/g for parenteral dosage forms having a concentration of 100 g/l or less of mannitol, and less than 2.5 IU/g for parenteral dosage forms having a concentration of more than 100 g/l of mannitol.

ASSAY

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

Injection: test solution and reference solution (a).

Calculate the percentage content of D-mannitol from the areas of the peaks and the declared content of *mannitol CRS*.

LABELLING

The label states:

– where applicable, the maximum concentration of bacterial endotoxins;

– where applicable, that the substance is suitable for use in the manufacture of parenteral dosage forms.

IMPURITIES

Specified impurities: A, B, C.

A. sorbitol,

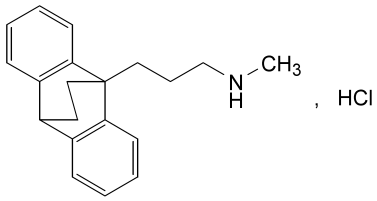
B. maltitol,

C. isomalt.

01/2008:1237

MAPROTILINE HYDROCHLORIDE

Maprotilini hydrochloridum



$C_{20}H_{24}ClN$ M_r 313.9

[10347-81-6]

DEFINITION

3-(9,10-Ethanoanthracen-9(10*H*)-yl)-*N*-methylpropan-1-amine hydrochloride.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: slightly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), sparingly soluble in methylene chloride, very slightly soluble in acetone.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

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

Test solution. Dissolve 10 mg in *1 M hydrochloric acid* and dilute to 100 ml with the same acid.

Spectral range: 250-300 nm.

Absorption maxima: at 265 nm and 272 nm.

Absorption minimum: at 268 nm.

Absorbance ratio: A_{272}/A_{265} = 1.1 to 1.3.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *maprotiline hydrochloride CRS*.

If the spectra obtained 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.

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

Test solution. Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 ml with the same solvent.

Reference solution (a). Dissolve 25 mg of *maprotiline hydrochloride CRS* in *methanol R* and dilute to 5 ml with the same solvent.

Reference solution (b). Dissolve 10 mg of *maprotiline impurity D CRS* in reference solution (a) and dilute to 2 ml with reference solution (a).

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

Mobile phase: *ethyl acetate R, dilute ammonia R1, 2-butanol R* (4:5:14 *V/V/V*).

Application: 5 µl.

Development: over a path of 10 cm.

Drying: in a current of warm air.

Detection: examine in ultraviolet light at 254 nm.

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated principal spots.

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 reference solution (a).

D. Dilute 0.5 ml of solution S (see Tests) to 2 ml with *methanol R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 1.0 g in *methanol 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 BY_6 (*2.2.2, Method II*).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.10 g of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (a). Dilute 1.0 ml of the test solution to 10.0 ml with the mobile phase. Dilute 2.0 ml of this solution to 100.0 ml with the mobile phase.

Reference solution (b). Dissolve 1.0 mg of *maprotiline impurity D CRS* in the test solution and dilute to 10.0 ml with the test solution.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

Mobile phase: dissolve about 0.580 g of *ammonium acetate R* in 200 ml of *water R* and add 2 ml of a 70 g/l solution of *concentrated ammonia R*; add 150 ml of *2-propanol R* and 650 ml of *methanol R*; the resulting apparent pH value is between 8.2 and 8.4.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 272 nm.

Injection: 20 µl.

Run time: 1.5 times the retention time of maprotiline.

Relative retention with reference to maprotiline (retention time = about 10.3 min): impurity A = about 0.3; impurity B = about 0.47; impurity C = about 0.74; impurity D = about 0.81; impurity E = about 1.26.

System suitability: reference solution (b):

– *resolution*: 1.8 to 3.2 between the peaks due to impurity D and maprotiline; if necessary, adjust the pH of the mobile phase, in steps of 0.1 pH unit, by adding a 50 per cent *V/V* solution of *acetic acid R* if the resolution is less than 1.8, or by adding a 70 g/l solution of *concentrated ammonia R* if the resolution is greater than 3.2.

Limits:

– *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 80 °C at a pressure not exceeding 2.5 kPa for 6 h.

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

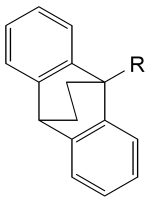
ASSAY

Dissolve 0.250 g in a mixture of 5 ml of *0.1 M hydrochloric acid* and 50 ml of *ethanol (96 per cent) R*. 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 31.39 mg of $C_{20}H_{24}ClN$.

IMPURITIES

Specified impurities: *A, B, C, D, E.*

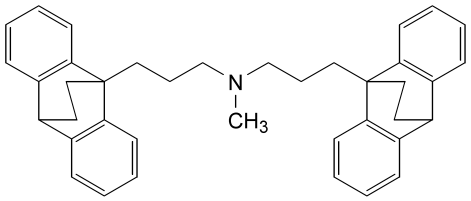


A. R = CH=CH-CH=O: 3-(9,10-ethanoanthracen-9(10*H*)-yl)prop-2-enal,

C. R = CH_2-CH_2-CH_2-NH_2: 3-(9,10-ethanoanthracen-9(10*H*)-yl)propan-1-amine,

D. R = CH=CH-CH_2-NH-CH_3: 3-(9,10-ethanoanthracen-9(10*H*)-yl)-*N*-methylprop-2-en-1-amine (dehydromaprotiline),

E. R = CH_2-CH_2-CH_2-N(CH_3)$_2$: 3-(9,10-ethanoanthracen-9(10*H*)-yl)-*N*,*N*-dimethylpropan-1-amine,



B. 3-(9,10-ethanoanthracen-9(10*H*)-yl)-*N*-[3-(9,10-ethanoanthracen-9(10*H*)-yl)propyl]-*N*-methylpropan-1-amine.

01/2008:1856
corrected 6.0

MARSHMALLOW LEAF

Althaeae folium

DEFINITION

Whole or cut dried leaf of *Althaea officinalis* L.