– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm),

– *temperature*: 40 °C.

Mobile phase: mix 33 volumes of *methanol R2* and 67 volumes of a solution prepared as follows: dissolve 6.8 g of *potassium dihydrogen phosphate R* and 7.0 g of *sodium heptanesulphonate monohydrate R* in 1000 ml of *water R* and adjust to pH 2.7 with a 330 g/l solution of *phosphoric acid R*.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µl.

Run time: 3 times the retention time of homatropine.

Relative retention with reference to homatropine (retention time = about 6.8 min): impurity C = about 0.2; impurity A = about 0.9; impurity B = about 1.1; impurity D = about 1.9.

System suitability: reference solution (c):

– *resolution*: minimum 1.5 between the peaks due to homatropine and impurity B,

– *symmetry factor*: maximum 2.5 for the peak due to homatropine.

Limits:

– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

– *impurities 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),

– *any other impurity*: 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 twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent); disregard the peak due to the bromide ion which appears close to the peak due to the solvent,

– *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 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.300 g in a mixture of 5.0 ml of *0.01 M hydrochloric acid* and 50 ml of *alcohol 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.

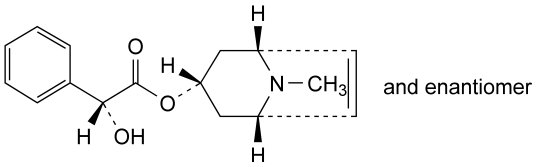
1 ml of *0.1 M sodium hydroxide* is equivalent to 35.63 mg of $C_{16}H_{22}BrNO_3$.

STORAGE

Protected from light.

IMPURITIES

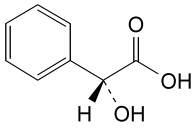
Specified impurities: A, B, C, D.



and enantiomer

A. (1*R*,3*s*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-6-en-3-yl (2*RS*)-2-hydroxy-2-phenylacetate (dehydrohomatropine),

B. hyoscine,



and enantiomer

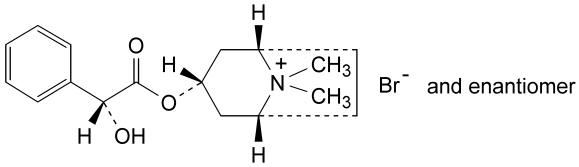
C. (2*RS*)-2-hydroxy-2-phenylacetic acid (mandelic acid),

D. atropine.

01/2008:0720
corrected 6.0

HOMATROPINE METHYLBROMIDE

Homatropini methylbromidum



and enantiomer

$C_{17}H_{24}BrNO_3$ M_r 370.3
[80-49-9]

DEFINITION

(1*R*,3*r*,5*S*)-3-[[(2*RS*)-2-hydroxy-2-phenylacetyl]oxy]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: freely soluble in water, soluble in alcohol.

mp: about 190 °C.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*), *Comparison*: *homatropine methylbromide CRS*.

B. Dissolve 50 mg in 1 ml of *water R* and add 2 ml of *dilute acetic acid R*. Heat and add 4 ml of *picric acid solution R*. Allow to cool, shaking occasionally. The crystals, washed with 2 quantities, each of 3 ml, of iced *water R* and dried at 100-105 °C melt (*2.2.14*) at 132 °C to 138 °C.

C. It gives reaction (a) of bromides (*2.3.1*).

TESTS

Solution S. Dissolve 1.25 g in *carbon dioxide-free water R* and dilute to 25 ml with the same solvent.

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

pH (*2.2.3*): 4.5 to 6.5 for solution S.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile R*, mobile phase A (9:41 *V/V*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 ml with the solvent mixture.

Reference solution (a). Dilute 5.0 ml of the test solution to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 25.0 ml with the solvent mixture.

Reference solution (c). Dissolve 5.0 mg of *homatropine hydrobromide CRS* in the solvent mixture and dilute to 50.0 ml with the solvent mixture. To 10.0 ml of the solution add 0.5 ml of the test solution and dilute to 100.0 ml with the solvent mixture.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm,
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm),
- *temperature*: 25 °C.

Mobile phase:

- *mobile phase A*: dissolve 3.4 g of *potassium dihydrogen phosphate R* and 5.0 g of *sodium heptanesulphonate monohydrate R* in 1000 ml of *water R*, and adjust to pH 3.0 with a 330 g/l solution of *phosphoric acid R*,
- *mobile phase B*: mix 400 ml of mobile phase A and 600 ml of *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	70	30
2 - 15	70 → 30	30 → 70
15 - 20	30 → 70	70 → 30

Flow rate: 1.4 ml/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µl.

Relative retention with reference to homatropine methylbromide (retention time = about 4.8 min): impurity C = about 0.7; impurity A = about 0.9; impurity B = about 1.2; impurity D = about 1.3; impurity E = about 1.4; impurity F = about 1.7.

System suitability: reference solution (c):

- *resolution*: minimum 2.5 between the peaks due to homatropine methylbromide and impurity B,
- *symmetry factor*: maximum 2.5 for the peak due to homatropine methylbromide.

Limits:

- *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
- *impurities C, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *any other impurity*: 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 twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent); disregard the peak due to the bromide ion which appears close to the peak due to the solvent,
- *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 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.300 g in 10 ml of *water R*. Titrate with *0.1 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*), using a silver indicator electrode and a silver-silver chloride reference electrode.

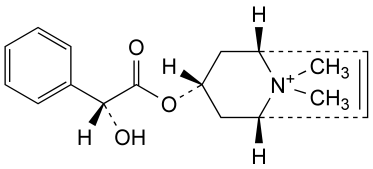
1 ml of *0.1 M silver nitrate* is equivalent to 37.03 mg of $C_{17}H_{24}BrNO_3$.

STORAGE

Protected from light.

IMPURITIES

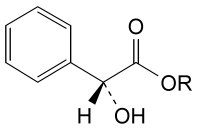
Specified impurities: A, B, C, D, E, F.



and enantiomer

A. (1*R*,3*s*,5*S*)-3-[[(2*RS*)-2-hydroxy-2-phenylacetyl]oxy]-8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-6-ene (methyldehydrohomatropine),

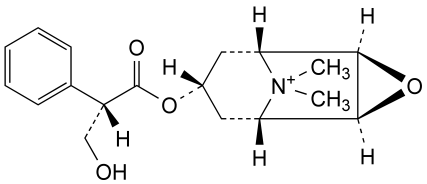
B. homatropine,



and enantiomer

C. R = H: (2*RS*)-2-hydroxy-2-phenylacetic acid (mandelic acid),

F. R = CH_3: methyl (2*RS*)-2-hydroxy-2-phenylacetate (methyl mandelate),



D. (1*R*,2*R*,4*S*,5*S*,7*s*)-7-[[(2*S*)-3-hydroxy-2-phenylpropanoyl]oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane (methylhyoscine),

E. methylatropine.