– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 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).

Water (*2.5.12*): maximum 0.5 per cent, determined on 1.000 g.

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

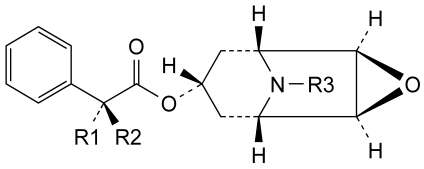
ASSAY

Dissolve 0.250 g in 60 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 30.34 mg of $C_{17}H_{21}NO_4$.

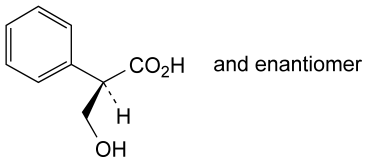
IMPURITIES

Specified impurities: A, B, C, D.



A. R1 = CH_2OH, R2 = R3 = H: (1*R*,2*R*,4*S*,5*S*,7*s*)-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate (norhyoscine),

B. R1 + R2 = CH_2, R3 = CH_3: (1*R*,2*R*,4*S*,5*S*,7*s*)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl 2-phenylprop-2-enoate (apohyoscine),



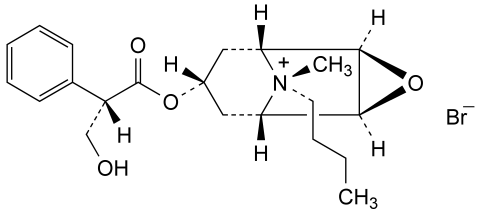
C. (2*RS*)-3-hydroxy-2-phenylpropanoic acid (DL-tropic acid),

D. hyoscyamine.

01/2008:0737
corrected 6.0

HYOSCINE BUTYLBROMIDE

Hyoscini butylbromidum
Scopolamini butylbromidum



$C_{21}H_{30}BrNO_4$ M_r 440.4
[149-64-4]

DEFINITION

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

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water and in methylene chloride, sparingly soluble in anhydrous ethanol.

IDENTIFICATION

First identification: A, C, F.

Second identification: A, B, D, E, F.

A. It complies with the test for specific optical rotation (see Tests).

B. Melting point (*2.2.14*): 139 °C to 141 °C.

C. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *hyoscine butylbromide CRS*.

D. To about 1 mg add 0.2 ml of *nitric acid R* and evaporate to dryness on a water-bath. Dissolve the residue in 2 ml of *acetone R* and add 0.1 ml of a 30 g/l solution of *potassium hydroxide R* in *methanol R*. A violet colour develops.

E. To 5 ml of solution S (see Tests) add 2 ml of *dilute sodium hydroxide solution R*. No precipitate is formed.

F. 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 25.0 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*): 5.5 to 6.5 for solution S.

Specific optical rotation (*2.2.7*): – 18 to – 20 (dried substance), determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution (a). Dilute 1.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 5.0 ml of this solution to 50.0 ml with the mobile phase.

Reference solution (b). Dilute 10.0 ml of reference solution (a) to 20.0 ml with the mobile phase.

Reference solution (c). Dissolve 5.0 mg of *hyoscine butylbromide impurity E CRS* in the mobile phase, add 1.0 ml of the test solution and dilute to 10.0 ml with the mobile phase. Dilute 5.0 ml of this solution to 50.0 ml with the mobile phase.

Column:
– *size*: *l* = 0.125 m, Ø = 4.0 mm,
– *stationary phase*: *octylsilyl silica gel for chromatography R* (4 µm),
– *temperature*: 25 ± 1 °C.

Mobile phase: dissolve 5.8 g of *sodium dodecyl sulphate R* in a mixture of 410 ml of *acetonitrile R* and 605 ml of a 7.0 g/l solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.3 with *0.05 M phosphoric acid*.

Flow rate: 2.0 ml/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µl.

Run time: 3.5 times the retention time of butylhyoscine.

Relative retention with reference to butylhyoscine (retention time = about 7.0 min): impurity B = about 0.1; impurity A = about 0.36; impurity C = about 0.40; impurity D = about 0.7; impurity E = about 0.8; impurity F = about 0.9; impurity G = about 3.0.

System suitability: reference solution (c):

– *resolution*: minimum 1.5 between the peaks due to butylhyoscine and impurity E,

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

Limits:

– *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.3; impurity G = 0.6;

– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

– *impurities B, C, D, E, F, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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) (0.4 per cent); disregard any peak due to the bromide ion which appears close to the solvent peak;

– *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 2.5 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 0.5 g.

ASSAY

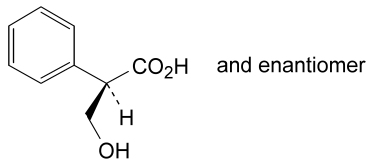
Dissolve 0.400 g in 50 ml of *water R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*) using a silver indicator electrode and a silver-silver chloride reference electrode.

1 ml of *0.1 M silver nitrate* is equivalent to 44.04 mg of $C_{21}H_{30}BrNO_4$.

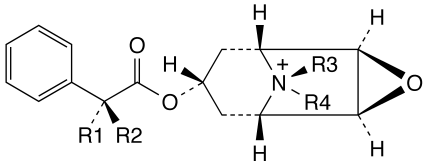
IMPURITIES

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

A. hyoscine,



B. (2*RS*)-3-hydroxy-2-phenylpropanoic acid (DL-tropic acid),

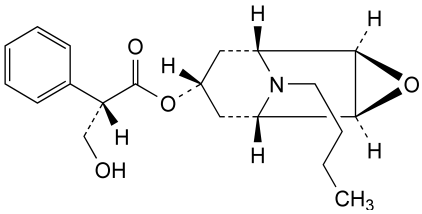


C. R1 = CH_2OH, R2 = H, R3 = R4 = CH_3: (1*R*,2*R*,4*S*,5*S*,7*s*)-7-[[(2*S*)-3-hydroxy-2-phenylpropanoyl]oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane (methylhyoscine),

D. R1 = CH_2OH, R2 = H, R3 = CH_3, R4 = CH_2-CH_2-CH_3: (1*R*,2*R*,4*S*,5*S*,7*s*,9*r*)-7-[[(2*S*)-3-hydroxy-2-phenylpropanoyl]oxy]-9-methyl-9-propyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane (propylhyoscine),

F. R1 = CH_2OH, R2 = H, R3 = CH_2-CH_2-CH_2-CH_3, R4 = CH_3: (1*R*,2*R*,4*S*,5*S*,7*s*,9*s*)-9-butyl-7-[[(2*S*)-3-hydroxy-2-phenylpropanoyl]oxy]-9-methyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane (pseudo-isomer),

G. R1 + R2 = CH_2 , R3 = CH_3, R4 = CH_2-CH_2-CH_2-CH_3: (1*R*,2*R*,4*S*,5*S*,7*s*,9*r*)-9-butyl-9-methyl-7-[(2-phenylprop-2-enoyl)oxy]-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane (apo-*N*-butylhyoscine);

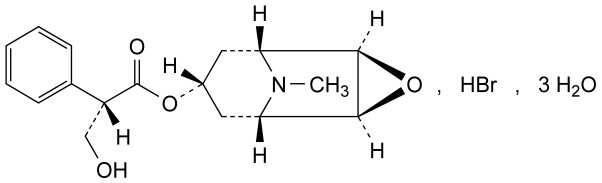


E. (1*R*,2*R*,4*S*,5*S*,7*s*)-9-butyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]nonan-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate (*N*-butylhyoscine).

01/2008:0106

HYOSCINE HYDROBROMIDE

Hyoscini hydrobromidum
Scopolamini hydrobromidum



$C_{17}H_{22}BrNO_4,3H_2O$ M_r 438.3
[6533-68-2]

DEFINITION

(1*R*,2*R*,4*S*,5*S*,7*s*)-9-Methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate hydrobromide trihydrate.

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

CHARACTERS

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

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

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. It complies with the test for specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *hyoscine hydrobromide CRS*.

If the spectra obtained in the solid state show differences, proceed as follows: dissolve 3 mg of the substance to be examined in 1 ml of *ethanol (96 per cent) R* and evaporate to dryness on a water-bath; dissolve the residue in 0.5 ml of *methylene chloride R* and add 0.2 g of *potassium bromide R* and 15 ml of *ether R*; allow to stand for 5 min shaking frequently; decant; dry the residue on a water-bath until the solvents have evaporated; using the