C. To about 1 mg add 0.5 mL of *sulfuric acid R*. A stable red-orange colour develops.

D. Dissolve about 1 mg in 0.25 mL of *perchloric acid R* and warm gently until the solution becomes turbid. Add 5 mL of *glacial acetic acid R*; a pink colour with an intense green fluorescence appears.

E. To about 5 mg add 1 mL of *acetic anhydride R* and 5 mL of *pyridine R*. A purple colour develops.

TESTS

pH (*2.2.3*). Suspend 0.25 g in *carbon dioxide-free water R*, dilute to 25 mL with the same solvent and filter. The pH of the solution is 3.7 to 4.5.

Related substances. Examine by thin-layer chromatography (*2.2.27*), using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

Test solution (a). Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b). Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a). Dilute 1.0 mL of test solution (a) to 100.0 mL with *methanol R*.

Reference solution (b). Dissolve 20 mg of *deptropine citrate CRS* in *methanol R* and dilute to 2 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *methanol R*.

Reference solution (c). Dissolve 5 mg of *tropine CRS* in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (d). Dissolve 10 mg of *deptropine citrate CRS* and 10 mg of *tropine CRS* in *methanol R* and dilute to 25 mL with the same solvent.

Apply to the plate 40 µL of each solution. Develop over a path of 10 cm using a mixture of 8 volumes of *concentrated ammonia R* and 92 volumes of *butanol R*. Dry the plate at 100 °C to 105 °C until the ammonia has completely evaporated. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (1 per cent). Spray with *dilute potassium iodobismuthate solution R* and then with a 10 g/L solution of *sodium nitrite R*. Expose the plate to iodine vapours. Examine in daylight and in ultraviolet light at 254 nm. In the chromatogram obtained with test solution (a): any spot corresponding to tropine is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.5 per cent); any spot, apart from the principal spot and any spot corresponding to tropine, is not more intense than the spot in the chromatogram obtained with reference solution (a) (1 per cent). The test is not valid unless the chromatogram obtained with reference solution (d) shows two clearly separated spots.

Heavy metals (*2.4.8*). 1.0 g complies with limit test C for heavy metals (20 ppm). Prepare the standard using 2 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

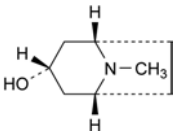
Dissolve 0.400 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 52.56 mg of $C_{29}H_{35}NO_8$.

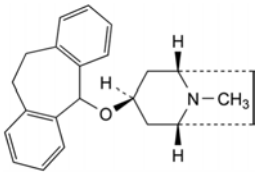
STORAGE

Store protected from light.

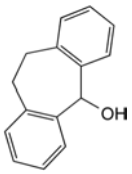
IMPURITIES



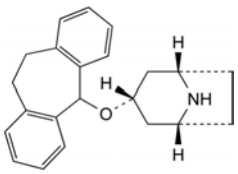
A. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (tropine),



B. (1*R*,3*s*,5*S*)-3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane (pseudodeptropine),



C. 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ol (dibenzocycloheptadienol),

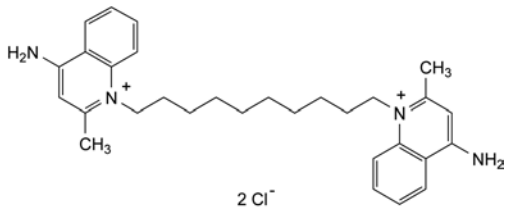


D. (1*R*,3*r*,5*S*)-3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-yloxy)-8-azabicyclo[3.2.1]octane (demethyldeptropine).

01/2008:1413
corrected 6.0

DEQUALINIUM CHLORIDE

Dequalinii chloridum



$C_{30}H_{40}Cl_2N_4$ M_r 527.6
[522-51-0]

DEFINITION

1,1′-(decane-1,10-diyl)bis(4-amino-2-methylquinolinium) dichloride (dried substance).

Content: 95.0 per cent to 101.0 per cent.

CHARACTERS

Appearance: white or yellowish-white powder, hygroscopic.

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

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

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

Test solution. Dissolve about 10 mg in *water R* and dilute to 100 mL with the same solvent. Dilute 10 mL of the solution to 100 mL with *water R*.

Spectral range: 230-350 nm.

Absorption maxima: at 240 nm and 326 nm.

Shoulder: at 336 nm.

Absorbance ratios:

- A_{240}/A_{326} = 1.56 to 1.80;
- A_{326}/A_{336} = 1.12 to 1.30.

B. Infrared absorption spectrophotometry (*2.2.24*).

Spectral range: 600-2000 cm^{-1}.

Comparison: *dequalinium chloride CRS*.

C. To 5 mL of solution S (see Tests) add 5 mL of *potassium ferricyanide solution R*. A yellow precipitate is formed.

D. To 10 mL of solution S add 1 mL of *dilute nitric acid R*. A white precipitate is formed. Filter and reserve the filtrate for identification test E.

E. The filtrate from identification test D gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 0.2 g in 90 mL of *carbon dioxide-free water R*, heating if necessary, 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 5 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.2 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Related substances. Liquid chromatography (*2.2.29*).

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

Reference solution (a). Dissolve 10.0 mg of *dequalinium chloride for performance test CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 10.0 mg of *dequalinium chloride CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R*.

Mobile phase: dissolve 2 g of *sodium hexanesulfonate R* in 300 mL of *water R*; adjust to pH 4.0 with *acetic acid R* and add 700 mL of *methanol R*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 240 nm.

Injection: 10 µL.

Run time: 5 times the retention time of dequalinium chloride.

System suitability: reference solution (a):

- *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to dequalinium chloride. If necessary, adjust the concentration of methanol in the mobile phase.

Limits:

- *impurity A*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);
- *total of impurities other than A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (10 per cent);
- *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Readily carbonisable substances. Dissolve 20 mg in 2 mL of *sulfuric acid R*. After 5 min the solution is not more intensely coloured than reference solution BY_4 (*2.2.2, Method I*).

Loss on drying (*2.2.32*): maximum 7.0 per cent, determined on 1.000 g by drying at 105 °C at a pressure not exceeding 0.7 kPa.

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

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.200 g in 5 mL of *anhydrous formic acid R* and 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 26.38 mg of $C_{30}H_{40}Cl_2N_4$.

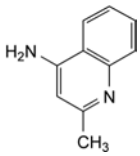
STORAGE

In an airtight container.

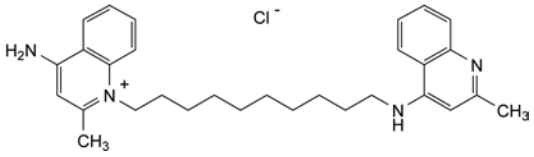
IMPURITIES

Specified impurities: A.

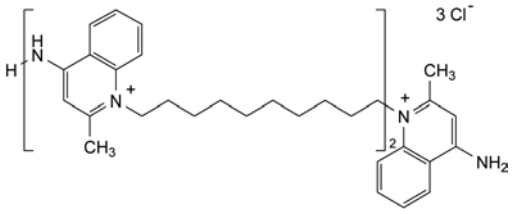
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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*): *B, C.*



A. 2-methylquinolin-4-amine,



B. 4-amino-1-[10-[(2-methylquinolin-4-yl)amino]decyl]-2-methylquinolinium chloride,

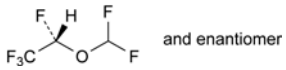


C. 1-[10-(4-amino-2-methylquinolinio)decyl]-4-[[10-(4-amino-2-methylquinolinio)decyl]amino]-2-methylquinolinium trichloride.

04/2008:1666
corrected 7.0

DESFLURANE

Desfluranum



$C_3H_2F_6O$ M_r 168.0
[57041-67-5]

DEFINITION

(2*RS*)-2-(Difluoromethoxy)-1,1,1,2-tetrafluoroethane.

CHARACTERS

Appearance: clear, colourless, mobile, heavy liquid.

Solubility: practically insoluble in water, miscible with anhydrous ethanol.

Relative density: 1.47, determined at 15 °C.

bp: about 22 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: examine the substance in the gaseous state.

Comparison: *Ph. Eur. reference spectrum of desflurane.*

TESTS

The substance to be examined must be cooled to a temperature below 10 °C and the tests must be carried out at a temperature below 20 °C.

Acidity or alkalinity. To 20 mL add 20 mL of *carbon dioxide-free water R*, shake for 3 min and allow to stand. Collect the upper layer and add 0.2 mL of *bromocresol purple solution R*. Not more than 0.1 mL of *0.01 M sodium hydroxide* or 0.6 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Related substances. Gas chromatography (*2.2.28*).

Test solution. The substance to be examined.

Reference solution (a). Introduce 25 mL of the substance to be examined into a 50 mL flask fitted with a septum, and add 0.50 mL of *desflurane impurity A CRS* and 1.0 mL of *isoflurane CRS* (impurity B). Add 50 µL of *acetone R* (impurity H), 10 µL of *chloroform R* (impurity F) and 50 µL of *methylene chloride R* (impurity E) to the solution, using an airtight syringe, and dilute to 50.0 mL with the substance to be examined. Dilute 5.0 mL of this solution to 50.0 mL with the substance to be examined. Store at a temperature below 10 °C.

Reference solution (b). Dilute 5.0 mL of reference solution (a) to 50.0 mL with the substance to be examined. Store at a temperature below 10 °C.

Reference solution (c). Dilute 5.0 mL of reference solution (b) to 25.0 mL with the substance to be examined. Store at a temperature below 10 °C.

Column:

- *material*: fused silica;
- *size*: *l* = 105 m, Ø = 0.32 mm;
- *stationary phase*: *poly[methyl(trifluoropropylmethyl)-siloxane] R* (film thickness 1.5 µm).

Carrier gas: *helium for chromatography R*.

Flow rate: 2.0 mL/min.

Split ratio: 1:25.

Temperature:

- *column*: 30 °C;
- *injection port*: 150 °C;
- *detector*: 200 °C.

Detection: flame ionisation.

Injection: 2.0 µL.

Run time: 35 min.

Relative retention with reference to desflurane (retention time = about 11.5 min): impurity C = about 1.06; impurity D = about 1.09; impurity A = about 1.14; impurity G = about 1.39; impurity E = about 1.5; impurity B = about 1.7; impurity F = about 2.2; impurity H = about 2.6.

System suitability: reference solution (a):

- *number of theoretical plates*: minimum 20 000, calculated for the peak due to impurity A;
- *symmetry factor*: maximum 2.0 for the peak due to impurity B.

Limits:

- *impurity B*: not more than the difference between the area of the corresponding peak in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution (0.2 per cent *V/V*);
- *impurity A*: not more than the difference between the area of the corresponding peak in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution (0.1 per cent *V/V*);
- *impurities C, D, G*: for each impurity, not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (b) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.01 per cent *V/V*);
- *impurities E, H*: for each impurity, not more than the difference between the area of the corresponding peak in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution (0.01 per cent *V/V*);
- *impurity F*: not more than the difference between the area of the corresponding peak in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution (0.002 per cent *V/V*);
- *unspecified impurities*: for each impurity, not more than 0.5 times the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (b) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.005 per cent *V/V*);
- *sum of impurities other than A, B, C, D, E, F, G and H*: not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (b) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.01 per cent *V/V*);
- *disregard limit*: the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (c) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.002 per cent *V/V*).

Fluorides: maximum 10 ppm.

Potentiometry (*2.2.36, Method I*).

Test solution. To 10.0 mL in a separating funnel, add 10 mL of a mixture of 30.0 mL of *dilute ammonia R2* and 70.0 mL of *distilled water R*. Shake for 1 min and collect the upper layer. Repeat this extraction procedure twice, collecting the upper layer each time. Adjust the combined upper layers to pH 5.2 with *dilute hydrochloric acid R*. Add 5.0 mL of *fluoride standard solution (1 ppm F) R* and dilute to 50.0 mL with *distilled water R*. To 20.0 mL of this solution add 20.0 mL of *total-ionic-strength-adjustment buffer R* and dilute to 50.0 mL with *distilled water R*.